Cediranib in Combination with Olaparib in Patients without a Germline BRCA1/2 Mutation and with Recurrent Platinum-Resistant Ovarian Cancer: Phase IIb CONCERTO Trial

Jung-Min Lee[1], Richard G. Moore[2], Sharad Ghamande[3], Min S. Park[4], John P. Diaz[5], Julia Chapman[6], James Kendrick[7], Brian M. Slomovitz[8], Krishnansu S. Tewari[9], Elizabeth S. Lowe[10], Tsveta Milenkova[11], Sanjeev Kumar[11], Mike Dymond[11], Jessica Brown[11], and Joyce F. Liu[12]

ABSTRACT

Purpose: The efficacy, safety, and tolerability of cediranib plus olaparib (cedi/ola) were investigated in patients with nongermline–BRCA-mutated (non-gBRCAm) platinum-resistant recurrent ovarian cancer.

Patients and Methods: PARP inhibitor–naïve women aged ≥18 years with platinum-resistant non-gBRCAm ovarian cancer, ECOG performance status of 0–2, and ≥3 prior lines of therapy received cediranib 30 mg once daily plus olaparib 200 mg twice daily in this single-arm, multicenter, phase IIb trial. The primary endpoint was objective response rate (ORR) by independent central review (ICR) using RECIST 1.1. Progression-free survival (PFS), overall survival (OS), and safety and tolerability were also examined.

Results: Sixty patients received cedi/ola, all of whom had confirmed non-gBRCAm status. Patients had received a median of four lines of chemotherapy; most (88.3%) had received prior bevacizumab. ORR by ICR was 15.3%, median PFS was 5.1 months, and median OS was 13.2 months. Forty-four (73.3%) patients reported a grade ≥3 adverse event (AE), with one patient experiencing a grade 5 AE (sepsis), considered unrelated to the study treatment. Dose interruptions, reductions, and discontinuations due to AEs occurred in 55.0%, 18.3%, and 18.3% of patients, respectively. Patients with high global loss of heterozygosity (gLOH) had ORR of 26.7% [4/15; 95% confidence interval (CI), 7.8–55.1], while ORR was 12.5% (4/32; 95% CI, 3.5–29.0) in the low gLOH group.

Conclusions: Clinical activity was shown for the cedi/ola combination in heavily pretreated, non-gBRCAm, platinum-resistant patients with ovarian cancer despite failing to meet the target ORR of 20%, highlighting a need for further biomarker studies.

Introduction

Ovarian cancer is the fifth leading cause of cancer-related death among women, with 5-year survival of less than 50% (1). Cytoreductive surgery and chemotherapy are the mainstay of first-line therapy, but approximately 80% of women with advanced ovarian cancer experience a recurrence within 3 years of diagnosis (2) and almost all patients with recurrent disease ultimately develop platinum resistance (3). In this setting, approved treatment options include non–platinum-based chemotherapy, the vascular endothelial growth factor (VEGF) inhibitor bevacizumab in combination with chemotherapy, and poly(ADP-ribose) polymerase (PARP) inhibitors in tumors with a BRCA mutation (4). Outcomes are poor for patients who subsequently relapse, with a response rate of less than 10% to late-line chemotherapy or small-molecule targeted therapy after progression on bevacizumab plus chemotherapy (5–9). Single-digit response rates to PARP inhibitor monotherapy have been observed in relapsed platinum-resistant patients with non–BRCA-mutated tumors (10). Therefore, an unmet need remains for more effective therapies in platinum-resistant patients who have received ≥3 lines of prior chemotherapy and who do not carry a deleterious germline BRCA1/2 mutation (gBRCAm).

Cediranib is a potent, oral, once-daily, small-molecule tyrosine kinase VEGF inhibitor that targets all three VEGF receptors (VEGFR-1, -2, -3) and stem cell factor receptor tyrosine kinase (c-kit; refs. 11, 12). Olaparib, an inhibitor of PARP 1 and PARP 2, is approved for several ovarian cancer indications: as monotherapy for the treatment of gBRCAm ovarian cancer patients who have received ≥3 prior lines of treatment (U.S. Food and Drug Administration only); as first-line maintenance therapy in newly diagnosed BRCA-mutated patients; as maintenance therapy in platinum-sensitive relapsed patients regardless of BRCAm status; and in combination with bevacizumab as first-line maintenance therapy for patients with advanced ovarian

[1]Center for Cancer Research, National Cancer Institute, Bethesda, Maryland. [2]Wilmot Cancer Institute, Department of Obstetrics and Gynecology, University of Rochester, Rochester, New York. [3]Cancer Center, Medical College of Georgia, Augusta University, Augusta, Georgia. [4]Swedish Cancer Institute, Swedish Medical Center, Seattle, Washington. [5]Miami Cancer Institute, Baptist Health South Florida, Miami, Florida. [6]Obstetrics and Gynecology, University of Kansas Medical Center, Kansas City, Kansas. [7]Advent Health Orlando, Orlando, Florida. [8]Broward Health, Fort Lauderdale, Florida, and Department of Obstetrics and Gynecology, Florida International University, Miami, Florida. [9]Ovarian Cancer Center, UCI Health, Irvine, California. [10]AstraZeneca, Gaithersburg, Maryland. [11]AstraZeneca, Cambridge, United Kingdom. [12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

Current address for B.M. Slomovitz: Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, Florida, and Sylvester Comprehensive Cancer Center, University of Miami, Miami, Florida.

Trial Registration: ClinicalTrials.gov, NCT02889900

Corresponding Author: Jung-Min Lee, Center for Cancer Research, National Cancer Institute, 10 Center Drive, Building 10, Room 4B54, Bethesda, MD 20892-1906. Phone: 240-760-6128; E-mail: leej6@mail.nih.gov

Clin Cancer Res 2022;28:4186–93

doi: 10.1158/1078-0432.CCR-21-1733

Translational Relevance

This open-label, phase IIb, single-arm, multicenter trial investigated the safety and efficacy of cediranib in combination with olaparib in heavily pretreated, platinum-resistant, nongermline–BRCA-mutated (non-gBRCAm) ovarian cancer. The 60 patients who received treatment had received a median of four previous lines of chemotherapy, and most (88.3%) had received prior bevacizumab before entering the study. The objective response rate by independent radiological review was 15.3%. Median progression-free survival was 5.1 months, and overall survival was 13.2 months. Cediranib plus olaparib showed activity in subsets of heavily pretreated, non-gBRCAm, platinum-resistant ovarian cancer, which is a difficult-to-treat population for which there is a significant unmet need for new treatment options.

cancer whose cancer is associated with homologous recombination deficiency (HRD)-positive status (13).

Limited responses have been shown with cediranib monotherapy in platinum-resistant ovarian cancer (11, 14). However, in combination with olaparib, clinical activity has been shown in platinum-resistant, non-gBRCAm ovarian cancer in previous phase II trials (15, 16), including at the recommended phase II dose (17) of cediranib 30 mg once daily plus olaparib 200 mg twice daily (16). Therefore, the objective of this study was to further investigate the safety, tolerability and efficacy of cediranib (30 mg once daily) plus olaparib (200 mg twice daily) in heavily pretreated patients with recurrent, platinum-resistant, non-gBRCAm ovarian cancer, who represent a particularly difficult-to-treat population.

Patients and Methods

Study design and oversight

This was an open-label, phase IIb, single-arm, multicenter trial to assess the efficacy and safety of cediranib plus olaparib in patients with recurrent platinum-resistant (defined as disease progression within 6 months of the last receipt of platinum-based chemotherapy) ovarian cancer in women without a gBRCAm. The study is registered with ClinicalTrials.gov, NCT02889900.

The trial was conducted across 25 study centers in the United States, with oversight provided by the steering committee; a data monitoring committee was not considered necessary as this was an open-label study and the safety profiles of olaparib and cediranib as monotherapies and in combination have been previously established. The Institutional Review Boards of all participating sites approved the study, and patients were enrolled following written informed consent.

The study was performed in accordance with the Declaration of Helsinki, Good Clinical Practice (as defined by the International Conference on Harmonisation), applicable regulatory requirements, and the AstraZeneca policy on bioethics and human biological samples.

Patients

Women aged ≥18 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and histologically proven high-grade ovarian/fallopian tube and primary peritoneal cancer with no evidence of a deleterious or suspected deleterious gBRCAm, as defined by a test conducted in an appropriately accredited laboratory (e.g., Clinical Laboratory Improvement Amendments certified), were eligible for inclusion. Patients were included if their life expectancy was ≥12 weeks, they had recurrent disease with evidence of progression after a platinum-free interval (PFI) of ≤6 months after their most recent line of platinum therapy prior to study enrollment (i.e., platinum resistant), and they had received ≥3 prior lines of therapy as follows: platinum chemotherapy, ≥2 prior lines required, and non-platinum chemotherapy, up to two prior lines allowed but not required. Prior antiangiogenic treatment such as bevacizumab, in either a first-line or a recurrent setting, was initially required for study entry, but the protocol was subsequently amended to make this optional to allow for timelier accrual. Hormonal therapy (e.g., tamoxifen, aromatase inhibitors), bevacizumab (or other angiogenesis inhibitor), or other immunotherapy used as a single agent was not counted as a line of cytotoxic therapy. CT/MRI evidence of measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) was required for inclusion.

Patients who had a gBRCAm, were previously treated with a PARP inhibitor, had disease progression during or within 6 months of completing first-line platinum-based chemotherapy (i.e., primary platinum resistant/refractory), or were platinum refractory (defined as disease progression during the last receipt of platinum-based therapy) were ineligible.

Study procedures and assessments

Eligible patients received the recommended phase II dose (17) of cediranib tablets (30 mg daily) plus olaparib tablets (200 mg twice daily) until objective radiologic disease progression (defined by RECIST 1.1), unacceptable toxicity, or withdrawal of consent for treatment. Dose reductions for toxicity were permitted for either or both therapies at the discretion of the investigator, although no dose reescalation was allowed.

The primary outcome was objective response rate (ORR) in the evaluable-for-response (EFR) analysis set [i.e., complete response (CR) plus partial response (PR; ref. 18); confirmed responses only as described below]. ORR was established by independent central review (ICR) using RECIST 1.1. All patients had RECIST 1.1 tumor assessments at screening (within 28 days prior to the start of study treatment) and every 8 weeks (±1 week) after start of treatment until objective radiologic disease progression or withdrawal of consent. Objective responses had to be confirmed during the next RECIST 1.1 visit assessment to ensure that identified responses were not a result of measurement error.

Additional efficacy outcome measures, including duration of response (DoR), progression-free survival (PFS), time to treatment discontinuation or death (TDT), overall survival (OS), and disease control rate (DCR), were assessed by ICR. Categorization of objective tumor response assessment was based on RECIST 1.1. Efficacy was also evaluated according to the presence of predicted loss-of-function tumor variants in BRCA1/2 or predefined homologous recombination repair (HRR)-associated genes determined from archival tissue samples by testing with the DX1 bait set, utilized by the FoundationOne CDx assay (19). Planned *post hoc* subgroup analyses included efficacy evaluation according to the presence of high-percentage genome-wide loss of heterozygosity (gLOH). For further details on the assay methodology, see the Supplementary Methods. Adverse events (AE) and treatment-emergent changes in vital signs and laboratory parameters were also evaluated throughout the study. Details of permitted dose modifications to manage toxicity are described in the Supplementary Methods.

Statistical analysis

Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables were summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated out of the full analysis set (FAS; i.e., all patients who received ≥1 dose of either therapy). Secondary efficacy and safety outcome measures were also assessed in the FAS.

Posterior distribution [modeled with binomial distribution and neutral beta (1/3, 1/3) prior distribution on the rate] of ORR was calculated. A futility analysis of ORR took place after 20 evaluable patients (i.e., with measurable disease at baseline and ≥1 dose of study drugs) had received their first dose of study drugs and had been observed for at least 4 months. Evaluation was based on investigator assessment. The criterion for declaring futility was based on predictive probability within a Bayesian design framework. As four or more patients had an objective response, the study continued to the final analysis.

Originally, 100 patients were planned to be recruited over approximately 12 months. The study design was formulated within a Bayesian framework based on dual criteria to show improvement over the expected response rate under current standard treatments (20% response rate targeted as an improvement versus an expected <15% response rate based on chemotherapy; ref. 20), and to have a response rate of a relevant size (approximately 30%). The latter was defined as having >90% confidence that the true ORR is at least 20% or probability (ORR ≥20%) >0.9 and an observed rate of 30/100 is seen at the final analysis. Assuming a median PFS of 6 months and OS of 12 months, 73% of PFS events and 59% of OS events were expected to occur at the time of the analysis.

However, slower-than-projected recruitment as a result of the emerging availability and uptake of PARP inhibitors in earlier lines of treatment, as well as the requirement of prior antiangiogenics, that is, bevacizumab, restricted the population available for this study. Therefore, the study plan was amended to recruit approximately 60 treated patients, with final analysis of OS at 8 months after the last patient had received her first dose of the study drugs. For 60 treated patients, a response rate of 30% would also give >90% confidence that the true ORR is ≥20%. Based on the duration of recruitment and assuming a median PFS of 6 months as originally planned and a median OS of 12 months, 80% of PFS events and 57% of OS events were expected to occur at the time of the analysis.

Data availability

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Anonymized datasets may be available on request. Requests for access to data may be submitted at https://vivli.org/. The request will undergo an internal review process and, if approved, data will be prepared and shared with specified accessors named on the request form for 12 months via SAS Multi-Sponsor Environment.

Results

Patient disposition

In total, 95 patients were screened, of whom 62 were enrolled in the study and 60 received cediranib plus olaparib (**Fig. 1**). Median total treatment duration was 15.4 weeks for cediranib and 15.3 weeks for

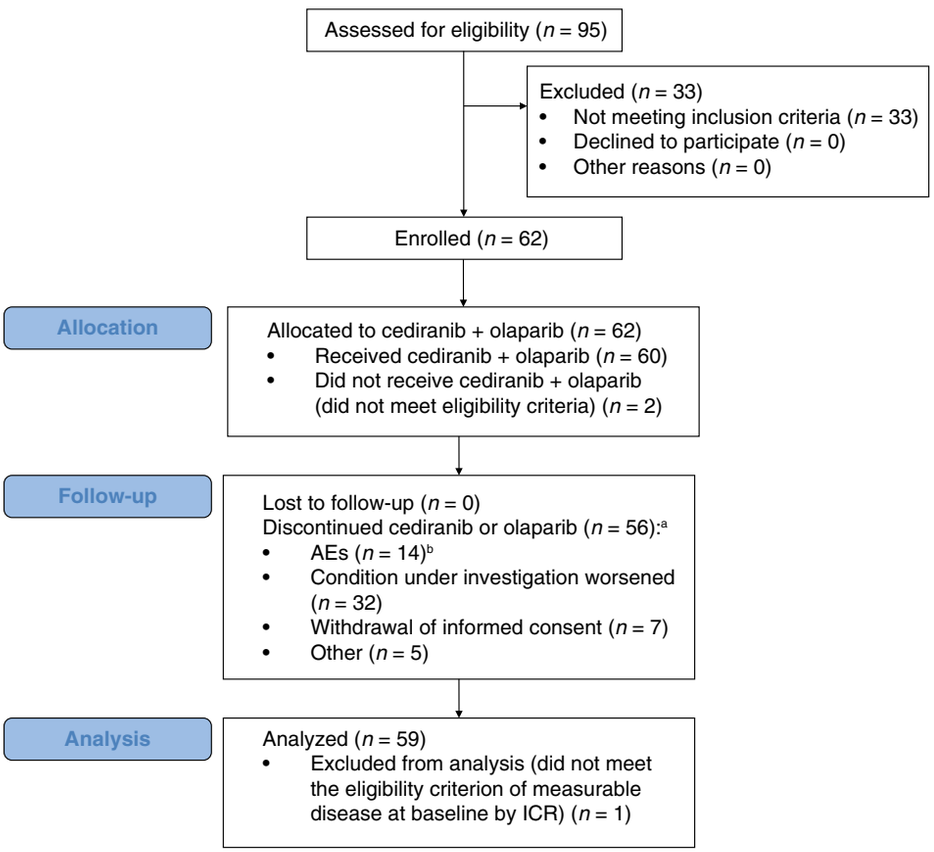

Figure 1.
Patient disposition. [a]The reasons for withdrawal are not mutually exclusive as some patients have specified different reasons for withdrawal; [b]Includes 3 patients who discontinued cediranib but not olaparib and 1 patient who discontinued olaparib but not cediranib.

olaparib. At the time of data cutoff (August 27, 2019), 5 (8.3%) patients were still receiving study treatment [4 (6.7%) receiving cediranib plus olaparib, 1 (1.7%) receiving olaparib only].

Baseline characteristics

Patient baseline characteristics are presented in **Table 1**. All patients had epithelial ovarian carcinoma, including high-grade serous (HGSOC; 54/60, 90.0%), high-grade endometrioid (2/60, 3.3%), clear cell (2/60, 3.3%), and other histologies (2/60, 3.3%; including adenocarcinoma and mixed serous + clear cell histology). Non-gBRCAm status was documented for all patients at study entry.

Based on tumor testing: 4 of 60 (6.7%) patients had a tumor BRCAm (all concluded to be somatic in origin based on a negative germline BRCA result at screening), 5 of 60 (8.3%) carried a tumor non-BRCAm HRR mutation (HRRm; 2 *CDK12*m, 1 *CHEK2*m, 1 *PPP2R2A*m, 1 *BRIP1*m), 43 of 60 (71.7%) were non-BRCAm/non-HRRm, and 8 of 60 (13.4%) had unknown tumor BRCA/HRR status (because of failed or canceled tests/missing results). Further details regarding the 9 patients with a somatic *BRCA2*m or non-BRCA HRR mutations are provided in Supplementary Table S1.

Patients had received a median of four previous lines of chemotherapy (range 3–10), and most (88.3%) had received prior bevacizumab, including 41.7% who received prior bevacizumab in combination with chemotherapy, in either the upfront or the recurrent setting. A total of 52 (86.7%) patients had a PFI of ≤6 months after their most recent line of platinum therapy prior to study enrollment. Eight (13.3%) patients with initial platinum-resistant/refractory disease deviated from the eligibility requirements. In addition, 2 (3.3%) patients entered the study as platinum sensitive (i.e., PFI >6 months after completion of the last platinum chemotherapy) and 3 (5.0%) patients had disease progression during their last platinum treatment, both deviations from eligibility criteria.

Median time from diagnosis to entering the study was 49.5 months. Median time from completion of last previous anticancer therapy to start of study treatment was 1.9 months.

Table 1. Demographics and baseline characteristics.

Demographic characteristics	Cediranib + olaparib (*N* = 60)
Median age, years (range)	64.5 (42–80)
ECOG performance status, *n* (%)	
0	41 (68.3)
1	18 (30.0)
2	1 (1.7)
Primary tumor location, *n* (%)	
Ovary	49 (81.7)
Peritoneum	4 (6.7)
Fallopian tube	7 (11.7)
Tumor grade, *n* (%)	
High	60 (100.0)
Histology type, *n* (%)	
High-grade serous	54 (90.0)
Clear cell	2 (3.3)
High-grade endometrioid	2 (3.3)
Other	2 (3.3)
All regimens of previous chemotherapy, *n* (%)	
3	28 (46.7)
4	16 (26.7)
5	10 (16.7)
6	4 (6.7)
>6	2 (3.3)
Median	4.0
Minimum	3
Maximum	10
Number of regimens of previous platinum chemotherapy, *n* (%)	
1	4 (6.7)
2	34 (56.7)
3	13 (21.7)
4	6 (10.0)
5	3 (5.0)
Median	2.0
Minimum	1
Maximum	5
Platinum sensitivity	
Platinum-free interval of ≤6 months after completion of last line of platinum treatment	52 (86.7)

Response to treatment

ORR by ICR was 15.3% [95% confidence interval (CI), 7.2–27.0], based on 9 patients with a response (1 CR, 8 PR; **Table 2**). When assessed by posterior distribution, mean ORR by ICR was 15.6% (95% CI, 7.0–24.9; Supplementary Table S2), with 52.2% confidence that the true response rate was >15% by posterior distribution. ORR by investigator assessment was 16.7% (95% CI, 8.3–28.5). Median PFS was 5.1 months (95% CI, 3.5–5.5; **Fig. 2**). Median DoR was 8.3 months (95% CI, 5.6–10.3), and 4 of 9 (44.4%) responders had a measurable response for >9 months. The time course of response in the 9 responding patients is provided in Supplementary Fig. S1. Onset of response was observed within 18 weeks in 8 of 9 (88.9%) responding patients. Fourteen of 59 (23.7%) patients evaluable for DCR remained in disease control at 6 months. Median OS was 13.2 months (95% CI, 9.4–16.4), and median TDT was 3.5 months (95% CI, 2.7–5.1).

Tumor BRCA and HRR mutations

Nine (15.3%) patients were classified as BRCAm or non-BRCAm HRRm based on tumor testing: 4 harbored a somatic *BRCA2*m and 5 were non-BRCAm HRRm (Supplementary Table S1). ORR in the BRCAm/HRRm subgroup was 2/9 (22.2%). Both patients had a somatic *BRCA2*m and a PR. In the non-BRCAm/non-HRRm subgroup, ORR was 6/42 (14.3%).

Table 2. Response to treatment.

Cediranib + olaparib	Analysis set	Number of patients	Result	95% CI
ORR, *n* (%)	EFR	59	9 (15.3)	7.2–27.0
	FAS	60	9 (15.0)	7.1–26.6
CR, *n* (%)	EFR	59	1 (1.7)	NC
PR, *n* (%)	EFR	59	8 (13.6)	NC
Median DoR, months[a]	EFR	59	8.3	5.6–10.3
DCR, *n* (%)	EFR	59	14 (23.7)	13.6–36.6
Median PFS, months	FAS	60	5.1	3.5–5.5
Median OS, months	FAS	60	13.2	9.4–16.4
Median TDT, months[b]	FAS	60	3.5	2.7–5.1

Abbreviation: NC, not calculated.
[a]Calculated using the Kaplan–Meier technique.
[b]Defined as the time from the date of first doses of cediranib and olaparib to the earlier of the date of discontinuation of both drugs, or death date.

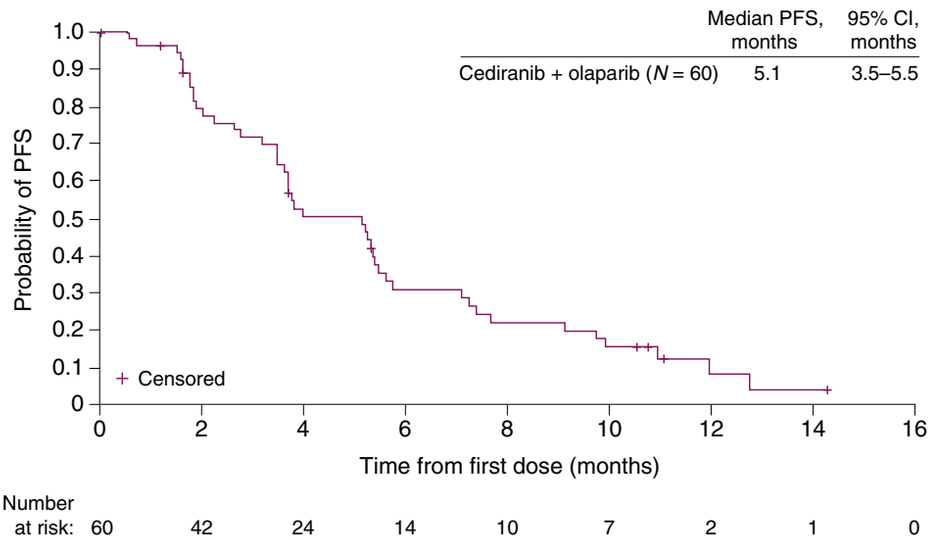

Figure 2.
Kaplan–Meier plot of PFS.

The PFS and OS results were generally similar regardless of mutation status. Percentage gLOH was available for 47 HGSOC patients in the EFR analysis set. Of these, 15 had a tumor BRCAm and/or gLOH score of ≥16% ($gLOH^{high}$), and 32 had a gLOH score of <16% ($gLOH^{low}$). ORR was 26.7% (4/15; 95% CI, 7.8–55.1) in the $gLOH^{high}$ group and 12.5% (4/32; 95% CI, 3.5–29.0) in the $gLOH^{low}$ group.

Safety

Median treatment duration (excluding dose interruptions and planned "no-dose" periods for intermittent dosing) was 3.5 months for cediranib and 3.4 months for olaparib. Forty-four (73.3%) patients reported a grade ≥3 AE [patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) definition]; the most common (in >10% of patients) were hypertension (30.0%), fatigue (21.7%), diarrhea (13.3%), and nausea (11.7%; **Table 3**). Twenty-four (40.0%) patients reported a grade ≥3 AE that was considered related to cediranib and olaparib by the investigator. Twenty-two (36.7%) patients reported a serious AE, the most common of which were nausea in 4 (6.7%) and vomiting in 2 (3.3%) patients. Three (5.0%) patients reported a serious AE causally related to cediranib and olaparib (anemia, ataxia, and decreased appetite, respectively), and 3 (5.0%) patients met predefined criteria for potential Hy's law, of whom 1 (1.7%) was reported to be a case of drug-induced liver injury. All 3 patients had confounding factors associated with the elevation in liver enzymes.

The most common AEs of special interest considered related to cediranib and olaparib were fatigue [31 (51.7%) patients], nausea [20 (33.3%) patients], diarrhea [17 (28.3%) patients], and hypertension [6 (10.0%) patients]. Although not a predefined AE of special interest, one serious AE of enterocutaneous fistula was observed that was considered related to cediranib.

Deaths were reported in 36 (60.0%) patients; most reported deaths (33 patients, 91.7% of deaths) were a result of disease progression. One (1.7%) patient experienced an AE of sepsis with an outcome of death, which was considered unrelated to study treatment; 2 (3.3%) patients died several months after discontinuing from the study, with cause of death reported as "other". There were no events of myelodysplastic syndrome/acute myeloid leukemia reported during the course of the study.

Tolerability

Overall, 47 (78.3%) patients experienced dose interruption, including 33 (55.0%) with interruption to both drugs. The most common AEs leading to dose interruption of cediranib or olaparib were fatigue [12 (20.0%) patients], diarrhea [11 (18.3%) patients], and hypertension [9 (15.0%) patients]. In addition, 29 (48.3%) patients had dose reduction, including 11 (18.3%) with reduction in dose of both drugs. The most common AEs leading to dose reduction in cediranib or olaparib were fatigue [9 (15.0%) patients], diarrhea [8 (13.3%) patients], anemia [3 (5.0%) patients], dyspnea [3 (5.0%) patients], and nausea [3 (5.0%) patients].

Fourteen (23.3%) patients discontinued cediranib or olaparib due to AEs, including 11 (18.3%) patients who discontinued both cediranib

Table 3. Most common AEs (overall frequency of 15%) and corresponding grade ≥3 incidence (safety analysis set).

Cediranib + olaparib (*N* = 60)	**Any grade, *n* (%)**	**PRO-CTCAE grade ≥3, *n* (%)**
Fatigue	41 (68.3)	13 (21.7)
Nausea	41 (68.3)	7 (11.7)
Diarrhea	40 (66.7)	8 (13.3)
Hypertension	40 (66.7)	18 (30.0)
Vomiting	25 (41.7)	4 (6.7)
Decreased appetite	22 (36.7)	1 (1.7)
Abdominal pain	21 (35.0)	3 (5.0)
Headache	21 (35.0)	1 (1.7)
Constipation	18 (30.0)	1 (1.7)
Hypomagnesemia	15 (25.0)	3 (5.0)
Dyspnea	14 (23.3)	1 (1.7)
Anemia	12 (20.0)	4 (6.7)
Hyponatremia	12 (20.0)	2 (3.3)
Dehydration	11 (18.3)	2 (3.3)
Dysgeusia	11 (18.3)	0
Urinary tract infection	11 (18.3)	1 (1.7)
Cough	10 (16.7)	0
Dysphonia	10 (16.7)	0
Hypokalemia	10 (16.7)	0

and olaparib. The most common AEs leading to dose discontinuation of cediranib or olaparib were fatigue [3 (5.0%) patients], nausea [3 (5.0%) patients], vomiting [2 (3.3%) patients], and thrombocytopenia [2 (3.3%) patients].

Discussion

Cediranib plus olaparib showed evidence of antitumor activity, with an ORR by ICR of 15.3% and ORR by posterior distribution of 15.6%, in this heavily pretreated population with non-gBRCAm, platinum-resistant ovarian cancer. This is indicative of limited efficacy based on the posterior probability calculations that did not meet the target of 20%. Importantly, clinically meaningful OS and PFS was observed with the combination in a disease setting in which patients have few treatment options available and most are expected to have disease progression or succumb to the disease within 12 months (2, 20–22).

These findings add to the existing evidence base for the activity of this combination in ovarian cancer. The combination was well tolerated in a previous phase I study (NCT01116648), with an ORR of 44% and evidence of activity regardless of platinum sensitivity or BRCAm status (23). In a parallel phase II study (NCT01116648), PFS was significantly extended versus olaparib alone (17.7 vs. 9.0 months) in relapsed platinum-sensitive patients (17); prominent improvements were observed in women with wild-type/unknown gBRCAm (16.5 vs. 5.7 months with olaparib alone; ref. 17). In a recent phase III trial (NRG GY004), the combination did not significantly improve median PFS (10.4 vs. 10.3 months) or ORR (69.4% vs. 71.3%) relative to platinum-based chemotherapy in recurrent platinum-sensitive patients, although substantial activity was observed in the subgroup of patients with gBRCAm (PFS 18.0 vs. 10.5 months, ORR 89% vs. 71%; ref. 24).

CONCERTO was the first trial to specifically examine cediranib in combination with olaparib in women with platinum-resistant ovarian cancer who had received ≥3 lines of therapy. In the randomized BAROCCO study, which allowed a mixed population of platinum-resistant cancer patients of whom 11% had a known BRCA mutation and 41% had received ≤2 prior lines of therapy, median PFS for the continuous (olaparib 300 mg twice daily plus cediranib 20 mg daily) and the intermittent (olaparib 300 mg twice daily plus cediranib 20 mg 5 days/week) schedules were 5.7 and 3.8 months, respectively (15). In a separate platinum-resistant cohort in a biomarker-driven study sponsored by the National Cancer Institute (NCT02345265), which included 14% of patients with a known BRCA mutation, with only 23% of patients having received ≤3 lines of therapy, ORR was 20%, median duration of response was 6 months, and DCR was 43% (16).

Most patients in CONCERTO (88.3%) had prior exposure to bevacizumab at baseline. Bevacizumab is known to modulate the baseline tumor microenvironment in other cancers (25); however, this has been understudied in ovarian cancer, so it is unclear how previous bevacizumab use may have affected response to therapy in the present study. To date, targeted therapy as either monotherapy or in combination has shown only modest clinical activity in a bevacizumab-exposed population (5, 6). Moreover, PARP inhibitor monotherapy has previously shown activity mainly in patients with BRCA-mutated, recurrent, platinum-sensitive disease and has extremely limited activity in the setting of platinum-resistant ovarian cancer in non-BRCAm tumors (10, 24, 26).

To date, standard-of-care therapies have shown only limited activity in the platinum-resistant setting, with an ORR of 7% to 28%, median OS of 12.2 to 16.6 months, and median PFS of 3.4 to 6.8 months (27–35). Most recent trials in this setting have shown low ORRs and failed to achieve their primary endpoints. In the CLIO trial, olaparib monotherapy showed an ORR (unconfirmed) of 18% in patients with platinum-resistant recurrent ovarian cancer who had received ≥1 prior line of chemotherapy (36). In the QUADRA trial, ORR was 27% with the PARP inhibitor niraparib in patients with relapsed platinum-resistant/refractory ovarian cancer and BRCAm tumors, 10% in those with HRD-positive tumors, and 3% in those with HRD-negative/unknown tumors (10). In the JAVELIN ovarian 200 trial, avelumab in combination with pegylated liposomal doxorubicin (PLD) showed an ORR of 13.3% in patients with platinum-resistant refractory ovarian cancer; the combination failed to meet the PFS and OS endpoints and was not beneficial compared with PLD alone (37). In FORWARD I, ORR was 24% with mirvetuximab soravtansine versus 10% with chemotherapy in patients with folate receptor alpha–positive advanced ovarian cancer who had received 2 to 4 lines of prior therapy; the trial failed to meet its PFS and OS endpoints (18).

It is therefore important to interpret the results of CONCERTO and previous trials in the context of the challenges associated with treating recurrent platinum-resistant ovarian cancer. Treatment responses in this substantially pretreated and treatment-resistant population are often variable, particularly with antiangiogenic therapy, and onset of resistance to therapy can be rapid (38). Thus, any improvements in PFS and survival are valuable, even in lieu of low response rates.

Future research efforts are likely to focus on identifying predictive biomarkers for antiangiogenic therapy (38, 39). The small number of patients with somatic BRCAm, tumor HRRm, or available gLOH data precluded a firm conclusion on the utility of these biomarkers in differentiating patient treatment response in the present study. However, there was a trend for better ORR in patients with gLOH ≥16%. Not all observed responses could be explained by BRCA or HRR mutation status; therefore, further research is needed to understand why some patients respond while others do not.

The most common grade ≥3 AEs observed in the current study (hypertension, fatigue, diarrhea, nausea) are consistent with those observed in previous phase I/II trials (17, 23). The combination has shown an increased incidence of grade ≥3 AEs compared with olaparib alone, specifically nausea, fatigue, diarrhea, and hypertension (17, 23, 24), Although hypertension was the most common grade ≥3 AE in this study, blood pressure elevations were generally asymptomatic for most patients, except for the 1 (2%) patient with grade 4 hypertension. Overlapping toxicity has not been explored for cediranib plus olaparib versus cediranib alone; nevertheless, two cediranib monotherapy studies previously reported high incidence of hypertension, fatigue, and diarrhea (11, 14). Although a significant percentage of patients receiving cediranib plus olaparib experienced AEs in the current trial, most were able to continue treatment with effective management, including dose interruptions, dose reductions, and supportive care.

This open-label, single-arm study has some clear limitations. The lack of a comparator means that it is not possible to ascertain the efficacy and safety of cediranib plus olaparib compared with the monotherapies or the current standard of care in this heavily pretreated population. The 62 patients enrolled offered a limited sample size, so ongoing larger studies will further determine whether the findings of this trial are applicable to the overall population with recurrent platinum-resistant ovarian cancer. The trial was originally designed based on recruitment of 100 patients; however, slower-than-projected recruitment due to the emerging availability and uptake of PARP inhibitors led to an amended target of approximately 60

patients. All patients in this study were PARP inhibitor naïve; the results therefore offer no insight into the clinical activity of combination cediranib and olaparib in patients with prior exposure to PARP inhibitors. In a previous proof-of-concept study in 34 heavily pretreated patients with ovarian cancer who were PARP inhibitor resistant, cediranib (20 mg once daily) plus olaparib (300 mg twice daily) met the predefined bar for efficacy, although activity varied according to genomic mechanism of PARP inhibitor resistance (40). Further studies to characterize the utility of cediranib plus olaparib in PARP inhibitor–resistant or –exposed tumors are warranted.

In conclusion, cediranib plus olaparib showed limited evidence of clinical activity regardless of mutation status, as measured by ORR, in recurrent, platinum-resistant, pretreated ovarian cancer. Despite the study failing to meet its primary endpoint, clinically meaningful OS and PFS were observed with this chemotherapy-free regimen in the subsets of patients in whom current therapy options offer little clinical benefit. These results support further exploration of the combination in platinum-resistant ovarian cancer, and an ongoing phase II/III study is examining cediranib plus olaparib versus their respective monotherapies and versus standard chemotherapy (NRG GY-005, NCT02502266) in the hope of offering a nonchemotherapy, noninfusion-center–dependent doublet treatment option.

Authors' Disclosures

J.-M. Lee reports nonfinancial support from AstraZeneca during the conduct of the study. S. Ghamande reports personal fees from Eisai and GSK outside the submitted work. J.P. Diaz reports grants and other support from AstraZeneca outside the submitted work. B.M. Slomovitz reports personal fees from AbbVie, AstraZeneca, Clovis, GSK, Genentech, Incyte, Myriad, Merck, Genmab, Seagen, and Novartis outside the submitted work. K.S. Tewari reports grants from U.C. Irvine during the conduct of the study, as well as personal fees from Merck, AstraZeneca, AbbVie, Genentech, Eisai, GSK/Tesaro, Seagen/Genmab, and Clovis outside the submitted work. E.S. Lowe reports other support from AstraZeneca Pharmaceuticals during the conduct of the study, as well as other support from AstraZeneca Pharmaceuticals outside the submitted work. T. Milenkova reports other support from AstraZeneca during the conduct of the study, as well as other support from AstraZeneca (employee) outside the submitted work. M. Dymond reports being a paid contractor to AstraZeneca. J. Brown reports other support from AstraZeneca during the conduct of the study, as well as other support from AstraZeneca (employee and shareholder) outside the submitted work. J.F. Liu reports personal fees from AstraZeneca, Clovis Oncology, Eisai, EpsilaBio, Genentech, Regeneron Therapeutics, and GlaxoSmithKline outside the submitted work, as well as funding to institution for study conduct as site Principal Investigator on trials sponsored by 2X Oncology, Aravive, Arch Oncology, AstraZeneca, Bristol Myers Squibb, Clovis Oncology, CytomX Therapeutics, GlaxoSmithKline, Regeneron Therapeutics, Surface Oncology, Vigeo Therapeutics, and Zentalis. No disclosures were reported by the other authors.

Authors' Contributions

J.-M. Lee: Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **R.G. Moore:** Investigation, writing–original draft, writing–review and editing. **S. Ghamande:** Investigation, writing–original draft, writing–review and editing. **M.S. Park:** Investigation, writing–original draft, writing–review and editing. **J.P. Diaz:** Investigation, writing–original draft, writing–review and editing. **J. Chapman:** Investigation, writing–original draft, writing–review and editing. **J. Kendrick:** Investigation, writing–original draft, writing–review and editing. **B.M. Slomovitz:** Investigation, writing–original draft, writing–review and editing. **K.S. Tewari:** Investigation, writing–original draft, writing–review and editing. **E.S. Lowe:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **T. Milenkova:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **S. Kumar:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **M. Dymond:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **J. Brown:** Formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **J.F. Liu:** Investigation, writing–original draft, writing–review and editing.

Acknowledgments

This study was funded by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA.

Medical writing assistance was provided by Manca Povsic, PhD, and Ben Drever, PhD, of AMICULUM, funded by AstraZeneca. The authors would like to thank all participating patients and their families.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received May 19, 2021; revised May 11, 2022; accepted July 29, 2022; published first August 2, 2022.

References

1. American Cancer Society. Cancer facts & figures 2020. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf.
2. Ledermann J, Raja F, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi24–32.
3. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol 2019;30:672–705.
4. Pujade-Lauraine E, Banerjee S, Pignata S. Management of platinum-resistant, relapsed epithelial ovarian cancer and new drug perspectives. J Clin Oncol 2019;37:2437–48.
5. Secord A, McCollum M, Davidson B, Broadwater G, Squatrito R, Havrilesky L, et al. Phase II trial of nintedanib in patients with bevacizumab-resistant recurrent epithelial ovarian, tubal, and peritoneal cancer. Gynecol Oncol 2019;153:555–61.
6. Lee J-M, Annunziata C, Hays J, Cao L, Choyke P, Yu M, et al. Phase II trial of bevacizumab and sorafenib in recurrent ovarian cancer patients with or without prior-bevacizumab treatment. Gynecol Oncol 2020;159:88–95.
7. Hoskins PJ, Le N. Identifying patients unlikely to benefit from further chemotherapy: a descriptive study of outcome at each relapse in ovarian cancer. Gynecol Oncol 2005;97:862–9.
8. Hanker LC, Loibl S, Burchardi N, Pfisterer J, Meier W, Pujade-Lauraine E, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012;23:2605–12.
9. Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2013;166:94–8.
10. Moore K, Secord A, Geller M, Miller D, Cloven N, Fleming G, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2019;20:636–48.
11. Matulonis U, Berlin S, Ivy P, Tyburski K, Krasner C, Zarwan C, et al. Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009;27:5601–6.

12. Kaplan AR, Gueble SE, Liu Y, Oeck S, Kim H, Yun Z, et al. Cediranib suppresses homology-directed DNA repair through down-regulation of BRCA1/2 and *RAD51*. Sci Transl Med 2019;11:eaav4508.
13. FDA. Olaparib highlights of prescribing information. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208558s000lbl.pdf.
14. Hirte H, Lheureux S, Fleming G, Sugimoto A, Morgan R, Biagi J, et al. A phase 2 study of cediranib in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: a trial of the Princess Margaret, Chicago and California Phase II Consortia. Gynecol Oncol 2015;138:55–61.
15. Colombo N, Nicoletto M, Benedetti Panici P, Tognon G, Bologna A, Lissoni A, et al. BAROCCO: a randomized phase II study of weekly paclitaxel vs. cediranib-olaparib combination given with continuous or intermittent schedule in patients with recurrent platinum resistant ovarian cancer (PROC). Ann Oncol 2019;30: V896 (abst 2560).
16. Liu J, Barry W, Wenham R, Hendrickson A, Armstrong D, Chan N, et al. A phase 2 biomarker trial of combination cediranib and olaparib in relapsed platinum (plat) sensitive and plat resistant ovarian cancer (ovca). J Clin Oncol 2018;36:15s (suppl; abst 5519).
17. Liu J, Barry W, Birrer M, Lee J-M, Buckanovich R, Fleming G, et al. A randomized phase 2 study of combination cediranib and olaparib versus olaparib alone as recurrence therapy in platinum-sensitive ovarian cancer. Lancet Oncol 2014;15: 1207–14.
18. Moore K, Oza A, Colombo N, Oaknin A, Scambia G, Lorusso D, et al. FORWARD I (GOG 3011): a phase III study of mirvetuximab soravtansine, a folate receptor alpha (FRa)-targeting antibody-drug conjugate (ADC), versus chemotherapy in patients (pts) with platinum-resistant ovarian cancer (PROC). Ann Oncol 2019;30:v403 (abst 9920).
19. Foundation Medicine Inc. FoundationOne® CDx technical information. 2020. Available from: https://assets.ctfassets.net/w98cd481qyp0/41rJj28gFwtxCwHQxopaEb/2725881bbc67d6f323ab893851344c4a/FoundationOne_CDx_Label_Technical_Info.pdf.
20. Davis A, Tinker A, Friedlander M. "Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? Gynecol Oncol 2014;133:624–31.
21. ESMO. eUpdate – relapsed epithelial ovarian carcinoma treatment recommendations. 2020. Available from: https://www.esmo.org/guidelines/gynaecological-cancers/newly-diagnosed-and-relapsed-epithelial-ovarian-carcinoma/eupdate-ovarian-cancer-treatment-recommendations.
22. Armstrong D, Alvarez R, Bakkum-Gamez J, Barroilhet L, Behbakht K, Berchuck A, et al. NCCN guidelines insights: ovarian cancer version 1.2019. J Natl Compr Canc Netw 2019;17:896–909.
23. Liu J, Tolaney S, Birrer M, Fleming G, Buss M, Dahlberg S, et al. A phase 1 trial of the PARP inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer 2013;49:2972–8.
24. Liu J, Brady M, Matulonis U, Miller A, Kohn E, Swisher E, et al. A phase III study comparing single-agent olaparib or the combination of cediranib and olaparib to standard platinum-based chemotherapy in recurrent platinum sensitive ovarian cancer (NRG oncology GY004). J Clin Oncol 2020;38: 15s (suppl; abst 6003).
25. Lieu C, Tran H, Jiang Z-Q, Mao M, Overman M, Lin E, et al. The association of alternate VEGF ligands with resistance to anti-VEGF therapy in metastatic colorectal cancer. PLoS One 2013;8:e77117.
26. Swisher E, Lin K, Oza A, Scott C, Giordano H, Sun J, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. Lancet Oncol 2017;18: 75–87.
27. FDA. Doxorubicin HCl highlights of prescribing information. 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050718s029lbl.pdf.
28. FDA. Topotecan highlights of prescribing information. 2007. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020671s023lbl.pdf.
29. FDA. Bevacizumab highlights of prescribing information. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125085s319lbl.pdf.
30. Coleman R, Brady W, McMeekin D, Rose P, Soper J, Lentz S, et al. A phase II evaluation of nanoparticle, albumin-bound (nab) paclitaxel in the treatment of recurrent or persistent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a Gynecologic Oncology Group study. Gynecol Oncol 2011; 122:111–5.
31. Gynecologic Oncology Group, Markman M, Blessing J, Rubin S, Connor J, Hanjani P, et al. Phase II trial of weekly paclitaxel (80 mg/m^2) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. Gynecol Oncol 2006;101:436–40.
32. Gynecologic Oncology Group. NCT00993616. Belinostat and carboplatin in treating patients with recurrent or persistent ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer that did not respond to carboplatin or cisplatin. 2019. Available from: https://clinicaltrials.gov/ct2/show/results/NCT00993616?cond=NCT00993616&draw=2&rank=1&view=results.
33. Miller D, Blessing J, Krasner C, Mannel R, Hanjani P, Pearl M, et al. Phase II evaluation of pemetrexed in the treatment of recurrent or persistent platinum-resistant ovarian or primary peritoneal carcinoma: a study of the Gynecologic Oncology Group. J Clin Oncol 2009;27:2686–91.
34. Kunos C, Radivoyevitch T, Abdul-Karim F, Fanning J, Abulafia O, Bonebrake A, et al. Ribonucleotide reductase inhibition restores platinum-sensitivity in platinum-resistant ovarian cancer: a Gynecologic Oncology Group study. J Transl Med 2012;10:79.
35. De Geest K, Blessing J, Morris R, Yamada S, Monk B, Zweizig S, et al. Phase II clinical trial of ixabepilone in patients with recurrent or persistent platinum- and taxane-resistant ovarian or primary peritoneal cancer: a Gynecologic Oncology Group study. J Clin Oncol 2010;28:149–53.
36. Vanderstichele A, Van Nieuwenhuysen E, Han S, Concin N, Van Gorp T, Berteloot P, et al. Randomized phase II CLIO study on olaparib monotherapy versus chemotherapy in platinum-resistant ovarian cancer. J Clin Oncol 2019;37: 15s (abst 5507).
37. Pujade-Lauraine E, Fujiwara K, Ledermann JA, Oza AM, Kristeleit RS, Ray-Coquard IL, et al. Avelumab alone or in combination with pegylated liposomal doxorubicin versus pegylated liposomal doxorubicin alone in platinum-resistant or refractory epithelial ovarian cancer: primary and biomarker analysis of the phase III JAVELIN Ovarian 200 trial. Gynecol Oncol 2019;154: 21–2.
38. Wehland M, Bauer J, Magnusson N, Infanger M, Grimm D. Biomarkers for anti-angiogenic therapy in cancer. Int J Mol Sci 2013;14:9338–64.
39. Pircher A, Hilbe W, Heidegger I, Drevs J, Tichelli A, Medinger M. Biomarkers in tumor angiogenesis and anti-angiogenic therapy. Int J Mol Sci 2011;12:7077–99.
40. Lheureux S, Oaknin A, Garg S, Bruce JP, Madariaga A, Dhani NC, et al. EVOLVE: a multicenter open-label single-arm clinical and translational phase II trial of cediranib plus olaparib for ovarian cancer after PARP inhibition progression. Clin Cancer Res 2020;26:4206–15.