CEDIRANIB IN COMBINATION WITH OLAPARIB IN PATIENTS WITHOUT A GERMLINE BRCA1/2 MUTATION 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] Iwanka Kozarewa,[11] Joyce Liu[12]

[1]National Cancer Institute, Bethesda, MD, USA; [2]Wilmot Cancer Institute, Rochester, NY, USA; [3]Georgia Cancer Center, Augusta University, GA, USA; [4]Swedish Cancer Institute, Seattle, WA, USA; [5]Miami Cancer Institute, Miami, FL, USA; [6]University of Kansas Medical Center, Westwood, KS, USA; [7]Advent Health Orlando, Orlando, FL, USA; [8]Sylvester Comprehensive Cancer Center, Miami, FL, USA; [9]University of California, Irvine, CA, USA; [10]AstraZeneca, Gaithersburg, MD, USA; [11]AstraZeneca, Cambridge, UK; [12]Dana-Farber Cancer Institute, Boston, MA, USA

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Introduction

- Epithelial ovarian cancer is the fifth most common cause of cancer-related death in women, with particularly poor prognosis in patients resistant to platinum treatment.[1–5]
- Cediranib is a potent, oral, once-daily (qd), small-molecule tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) signaling and angiogenesis that targets all three VEGF receptors (VEGFR-1, -2, -3) and has additional activity against platelet-derived growth factor receptor and stem cell factor receptor dependent tumor growth.[6,7]
- Olaparib is a PARP inhibitor; FDA-approved indications include the treatment of ovarian cancer patients with a germline BRCA1/2 mutation (gBRCAm) who have already received ≥3 lines of chemotherapy, as first-line maintenance therapy in BRCA-mutated newly diagnosed ovarian cancer, and as maintenance therapy in platinum-sensitive relapsed ovarian cancer regardless of BRCAm status.[8,9]
- Limited responses have been shown previously with single-agent olaparib or cediranib in patients with non-BRCA-mutated platinum-resistant ovarian cancer[10] and platinum-resistant ovarian cancer,[6,11] respectively.
- However, the combination of cediranib and olaparib has demonstrated combination benefits in patients with ovarian cancer in previous Phase I (NCT01116648) and II (NCT01116648) trials.[12,13]
- This study (CONCERTO, NCT02889900) investigated the combination of cediranib (30 mg qd) and olaparib (200 mg twice daily) in patients with advanced platinum-resistant ovarian cancer.

Methods

- This was a Phase IIb, single-arm, open-label study. Details of the key study features, including a study design graphic, are provided in the **Supplementary Methods (Supplementary Figure S1)**.
- Patients with recurrent platinum-resistant non-gBRCAm ovarian cancer who had received ≥3 previous lines of therapy and showed disease progression <6 months from the last receipt of platinum-based chemotherapy were included (Table 1).
- The primary endpoint was overall response rate (ORR); secondary endpoints included duration of response (DoR), progression-free survival (PFS), time to treatment discontinuation or death (TDT), overall survival (OS), and disease control rate (DCR; endpoints assessed by independent central review [ICR] using Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1); other outcome measures are listed in the **Supplementary Methods**.
- Archival tumor biopsies were sent for analysis by Foundation Medicine, Inc.

Table 1. Demographics and disease characteristics at baseline

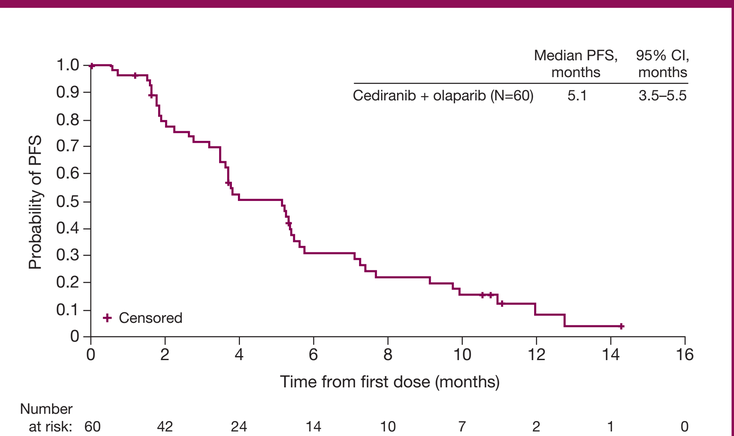
	Cediranib + olaparib (N=60)
Median age, years (range)	64.5 (42–80)
Median body mass index, kg/m² (range)	25.5 (17–58)
ECOG performance status, n (%)	
0	41 (68.3)
1	18 (30.0)
2	1 (1.7)
Primary tumor location, n (%)	
Ovary	49 (81.7)
Peritoneum	4 (6.7)
Fallopian tube	7 (11.7)
Tumor grade, n (%)	
High grade	60 (100.0)
Histology type, n (%)	
Serous	54 (90.0)
Clear cell	2 (3.3)
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

ECOG, Eastern Cooperative Oncology Group

Conclusions

- Cediranib plus olaparib showed evidence of antitumor activity
  - Combination treatment did not meet the target of 20% confirmed ORR in this heavily pretreated (≥4 lines of chemotherapy), non-gBRCAm platinum-resistant ovarian cancer patient population, with 88.3% of the patients already exposed to a VEGF inhibitor, bevacizumab.
- The safety findings of this study were consistent with the known safety profiles of cediranib and olaparib, with some evidence of overlapping toxicity resulting in an increase in grade ≥3 adverse events
  - The toxicity was considered manageable with effective management, including dose interruptions, dose reductions, and/or the use of supportive care, and was considered acceptable for this patient population.
- In patients with available gLOH data, 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
- The small number of patients with somatic BRCAm or tumor HRRm, or with available gLOH data, precluded a firm conclusion on the utility of these potential biomarkers for treatment response.

Figure 1. Progression-free survival (Kaplan–Meier plot)



CI, confidence interval; PFS, progression-free survival

Author contact details: leej6@mail.nih.gov

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Results

- Of 62 American patients enrolled (Table 1), 60 (96.8%) received cediranib plus olaparib (baseline characteristics are provided in the **Supplementary Results**).
- Mean ORR by ICR was 15.6% by posterior distribution; the confirmed number of patients with a response was nine (15.3%; one complete response + eight partial responses [PRs]; Table 2).
- Median DoR was 8.3 months; median PFS was 5.1 months (Figure 1 and Table 2).
- A total of 4/9 (44.4%) responders had a measurable response for >9 months.
- The onset of response was observed within four cycles (18 weeks or fewer, two RECIST scans) in 8/9 (88.9%) responding patients.
- DCR: 14/59 (23.7%) patients evaluable for response remained in disease control at 6 months (Table 2).
- Of the nine patients in the evaluable-for-response analysis set who were positive for somatic *BRCA2*m (four patients) or tumor homologous recombination repair mutation (HRRm; five patients; no somatic *BRCA1*m detected), two (22.2%) with a tumor *BRCA2*m were responders, both of whom had a PR
  - Of the patients with tumor HRRm, two had *CDK12* rearrangements (one accompanied by *CDK12* frameshift), one had *PPP2R2A* loss, one had a *CHEK2* mutation, and one had a *BRIP1* mutation; none were responders
  - In the 42 tumor *BRCA1*m-, *BRCA2*m-, or HRRm-negative patients, six (14.3%) were responders.
- Median PFS was 3.7 months in patients who were positive for *BRCA2*m or HRRm, versus 5.2 months in mutation-negative patients.
- Percentage global LOH (gLOH) measured at Foundation Medicine, Inc. was available for 47 patients in the evaluable-for-response set. Fifteen patients had a tumor BRCAm and/or gLOH score ≥16% (gLOH^{high}), and 32 patients had a gLOH score <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.
- Median OS was 13.2 months and median TDT was 3.5 months (Table 2); OS results were generally similar regardless of whether patients were mutation positive or negative.
- Safety and tolerability data are provided in the **Supplementary Results**.

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*	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	FAS	60	3.5	2.7–5.1

*Calculated using the Kaplan–Meier technique. CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; EFR, evaluable-for-response analysis set; FAS, full analysis set; NC, not calculated; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; TDT, time to treatment discontinuation or death

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