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## Original Article



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# Comparisons of survival outcomes between bevacizumab and olaparib in *BRCA*-mutated, platinum-sensitive relapsed ovarian cancer: a Korean Gynecologic Oncology Group study (KGOG 3052)

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## ABSTRACT

**Objective:** To compare survival outcomes between bevacizumab (BEV) and olaparib (OLA) maintenance therapy in *BRCA*-mutated, platinum-sensitive relapsed (PSR) high-grade serous ovarian carcinoma (HGSOC).


**Methods:** From 10 institutions, we identified HGSOC patients with germline and/or somatic *BRCA1/2* mutations, who experienced platinum-sensitive recurrence between 2013 and 2019, and received second-line platinum-based chemotherapy. Patients were divided into BEV (n=29), OLA (n=83), and non-BEV/non-OLA users (n=36). The OLA and non-BEV/non-OLA users were grouped as the OLA intent group. We conducted 1:2 nearest neighbor-matching between the BEV and OLA intent groups, setting the proportion of OLA users in the OLA intent group from 65% to 100% at 5% intervals, and compared survival outcomes among the matched groups.


**Results:** Overall, OLA users showed significantly better progression-free survival (PFS) than BEV users (median, 23.8 vs. 17.4 months; p=0.004). Before matching, PFS improved in the


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### Synopsis

We conducted a matching study to compare survival between bevacizumab (BEV) and olaparib (OLA) in BRCA-mutated, platinum-sensitive relapsed high-grade serous ovarian carcinoma. OLA was superior to BEV in improving progression-free survival, but no difference in overall survival was observed. The use of OLA might be prioritized in this setting.

### Presentation

This work was presented at 36th Annual Meeting of the Korean Society of Gynecologic Oncology on April 17, 2021.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

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S.S.J., S.S.H., K.M.K., K.K.; Methodology:

K.S.I., H.S., K.K.; Resources: K.K.; Supervision:

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OLA intent group but marginal statistical significance ( $p=0.057$ ). After matching, multivariate analyses adjusting confounders identified intention-to-treat OLA as an independent favorable prognostic factor for PFS in the OLA 65P (adjusted hazard ratio [aHR]=0.505; 95% confidence interval [CI]=0.280–0.911;  $p=0.023$ ) to OLA 100P (aHR=0.348; 95% CI=0.184–0.658;  $p=0.001$ ) datasets. The aHR of intention-to-treat OLA for recurrence decreased with increasing proportions of OLA users. No differences in overall survival were observed between the BEV and OLA intent groups, and between the BEV and OLA users.

**Conclusion:** Compared to BEV, intention-to-treat OLA and actual use of OLA maintenance therapy were significantly associated with decreased disease recurrence risk in patients with BRCA-mutated, PSR HGSOV.

**Keywords:** Cystadenocarcinoma, Serous; Genes, BRCA1; Genes, BRCA2; Mutation

## INTRODUCTION

Epithelial ovarian cancer (EOC) is a profound public health concern as it is one of the deadliest female cancers [1]. Despite the standard primary treatment consisting of cytoreductive surgery (CRS) and platinum-based chemotherapy, disease relapse is common [2]. Treatment in recurrent EOC largely depends on the platinum-free interval (PFI), defined as time from the last platinum-based chemotherapy [3]. For cases with PFI >6 months, so-called “platinum-sensitive relapsed (PSR),” the current guidelines recommend retreatment with platinum-based combination chemotherapy as a second-line treatment [4,5].

Advent of targeted anti-cancer agents have improved PSR EOC treatments [6]. Two phase III randomized controlled trials (RCTs), OCEANS and GOG-213, proved that incorporation of bevacizumab (BEV), a humanized anti-vascular endothelial growth factor monoclonal antibody to platinum-based doublets and maintenance therapy significantly improved progression-free survival (PFS) in PSR EOC [7,8]. A series of phase III RCTs proved PFS benefit from maintenance therapy with various poly (ADP-ribose) polymerase (PARP) inhibitors in PSR EOC, especially for BRCA-mutated, high-grade serous or endometrioid ovarian carcinoma [9-11].

Currently, both BEV and PARP inhibitors are treatment options for patients with BRCA-mutated PSR EOC. However, no studies have directly compared survival outcomes between BEV and PARP inhibitors. Recently, Bartoletti et al. [12] conducted a network meta-analysis of 8 RCTs and suggested PARP inhibitor maintenance therapy, rather than BEV, as a better option for BRCA-mutated, PSR EOC, but these findings were derived from the indirect comparisons. Without a new clinical trial, it seems unfeasible to make direct head-on-head comparisons of the 2 due to complexities related to differences in the timing of treatment: BEV is used concomitantly with second-line platinum-based chemotherapy, while OLA is initiated after confirmation of either complete response (CR) or partial response (PR) to second-line chemotherapy.

To overcome these issues, we conducted this multicenter, matched cohort study, comparing survival outcomes between BEV and PARP inhibitor maintenance therapy for the treatment of BRCA-mutated, PSR EOC. Furthermore, considering the approval history of BEV and PARP inhibitors and the sequential medical environment changes in Korea, we confined the PARP inhibitors to OLA capsules and the histologic type of EOC to high-grade serous ovarian carcinoma (HGSOV).

## MATERIALS AND METHODS

This study was approved by the Korean Gynecologic Oncology Group (No. KGOG 3052) and Institutional Review Boards of the participating institutions and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived.

### 1. Study population

From 10 institutions in Korea, we included patients with the following conditions: (1) aged  $\geq 18$  years; (2) histologically confirmed HGSOc, including primary peritoneal or fallopian tube cancer; (3) received CRS and platinum-based chemotherapy as primary treatment; (4) identified to have a deleterious/suspected deleterious *BRCA1/2* mutation at germline/somatic testing; (5) experienced PSR between January 2013 and December 2019; and (6) received 4–9 cycles of second-line platinum-based combination chemotherapy. Patients were excluded if they: (1) received BEV or PARP inhibitor as primary treatment; (2) received BEV and PARP inhibitor sequentially (change maintenance) or simultaneously (dual maintenance) as second-line treatment; (3) received maintenance therapy other than BEV and PARP inhibitors (e.g., paclitaxel or carboplatin only); (4) were lost to follow-up during chemotherapy or had insufficient clinicopathologic data; or (5) received niraparib or OLA tablets, rather than OLA capsules.

Based on these criteria, 148 patients were selected and classified as BEV users, OLA users, and non-BEV/non-OLA users. We collected clinicopathologic characteristics and treatment-related and survival data from patient medical records.

### 2. *BRCA1/2* gene testing, treatment, and surveillance

All patients underwent either the germline *BRCA1/2* gene test using Sanger sequencing or next-generation sequencing (NGS), the somatic *BRCA1/2* gene test using targeted NGS-based multi-gene panels, or both. Secondary CRS was conducted at the physician's discretion; only selected patients underwent the surgery for macroscopic tumor removal.

BEV users received BEV (15 mg/kg) intravenously with paclitaxel (175 mg/m<sup>2</sup> of body surface area) and carboplatin (area under the curve 5) or with gemcitabine (1,000 mg/m<sup>2</sup> of body surface area) on days 1 and 8 and carboplatin (area under the curve 4) every 3 weeks (main chemotherapy phase). If secondary CRS was performed, BEV was started on cycle 2. After the main chemotherapy phase, patients entered the maintenance phase, in which BEV (15 mg/kg) was administered intravenously every 3 weeks until disease progression, unacceptable toxicity, or patient refusal.

All OLA users responded (CR/PR) to the second-line platinum-based chemotherapy, and underwent OLA maintenance therapy (capsules; 400 mg bid) orally. Dose reduction/interruption of OLA was allowed at the physicians' discretion, and was continued until disease progression, unacceptable toxicity, or patient refusal.

During maintenance therapy, BEV and OLA users routinely underwent computed tomography (CT) scans every 3 cycles of BEV and every 3 months, respectively. After completion of maintenance, CT scans were routinely performed every 3–4 months for the first 2 years, every 6 months for the next 2 years, and annually thereafter, or whenever recurrence was suspected.

### 3. Survival outcomes and treatment response

PFS was defined as the time interval between the start date of the second-line treatment and the date of disease progression, confirmed by the Response Evaluation Criteria in Solid Tumors version 1.1 [13] or the Gynecologic Cancer InterGroup cancer antigen 125 (CA-125) criteria [14]. OS was defined as the time interval between the start date of the second-line treatment and death from any cause, or last follow-up. We also evaluated the best overall response during maintenance therapy, categorized as CR, progressive disease (PD), and non-CR/non-PD. CR was defined when there was no evidence of disease (NED) on CT scans at maintenance therapy initiation and NED remained during maintenance therapy. Patients with non-measurable disease at maintenance therapy initiation, but whose lesions disappeared with normalized serum CA-125 levels, were also regarded as CR.

### 4. Sample matching

Considering that (1) BEV and OLA are prescribed mutually exclusively in *BRCA*-mutated, PSR HGSO, and (2) BEV starts during second-line chemotherapy, whereas OLA starts in some patients who achieved CR/PR after second-line main chemotherapy, we assumed that OLA users and non-BEV/non-OLA users had potentially intention-to-treat OLA from the beginning of second-line treatment. We regarded them collectively as the “OLA intent group” (n=119).

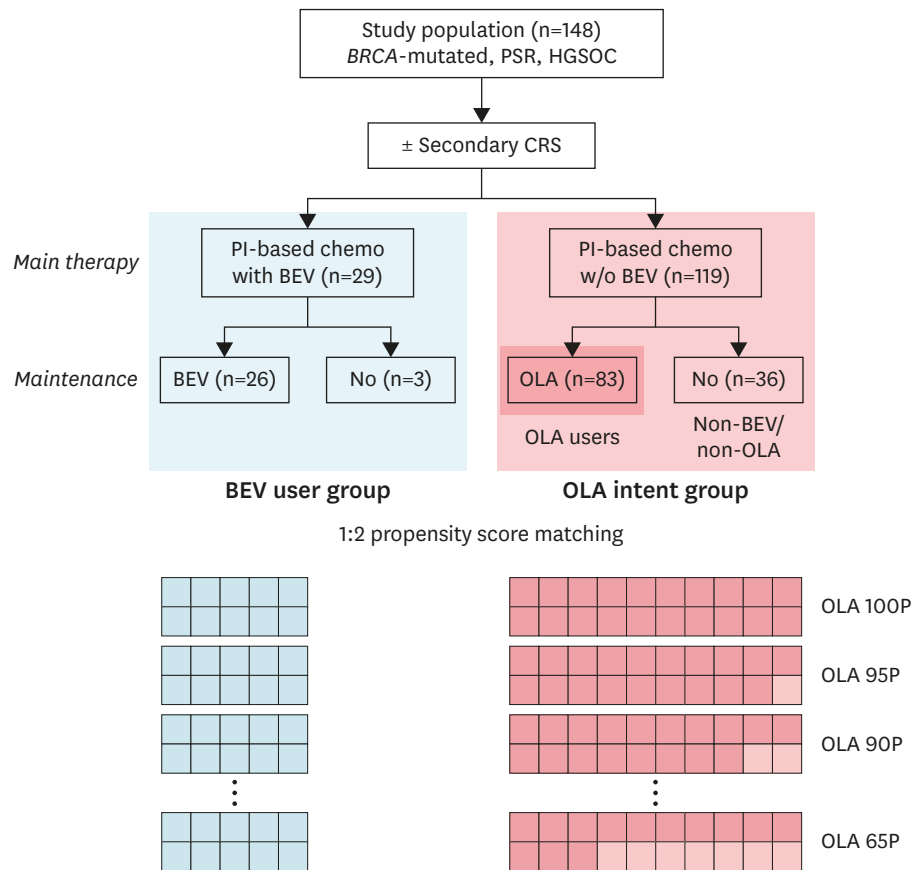
To overcome imbalance in the sample size and baseline characteristics between the BEV and OLA intent groups and the proportional variability of OLA users in the OLA intent group, we conducted 1:2 nearest neighbor matching, considering the proportion of OLA users in the OLA intent group. PFI (6–12 vs. >12 months), serum CA-125 levels at recurrence, secondary CRS, and response to second-line main chemotherapy (CR vs. non-CR) were used for matching. For each patient in the BEV group, we identified patients whose propensity score was within the caliper distance of 0.1 in the OLA intent group. Setting the proportion of OLA users in the OLA intent group from 65% to 100% at 5% intervals, we generated 8 datasets, as follows: first, we constructed a matched dataset, consisting of 100% of OLA users (OLA 100P), randomly selected from those with a propensity score within the specified caliper distance. As the proportion decreased from 100% to 65%, 5% of the matched OLA users were replaced with the randomly matched non-BEV/non-OLA users per step. R statistical software version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria; ISBN3-900051-07-0; <http://www.R-project.org>) was used for matching.

### 5. Statistical analysis

Differences in clinicopathologic characteristics were evaluated between the 2 groups. We used the Student's t-test and Mann-Whitney U test for continuous variables, and the Pearson's chi-squared test and Fisher's exact test for categorical variables. Survival outcomes were compared using Kaplan-Meier analysis with the log-rank test. In multivariate analyses, we used Cox proportional hazards regression models to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Statistical analyses were performed using the SPSS statistical software (version 25.0; IBM Corp., Armonk, NY, USA). A  $p < 0.05$  indicated statistical significance.

## RESULTS

The composition of the study population and consecutive processes of sample matching are depicted in **Fig. 1**. Of 148 included patients, 29 (19.6%), 83 (56.1%), and 36 (24.3%) were BEV users, OLA users, and non-BEV/non-OLA users, respectively.



**Fig. 1.** Flow diagrams depicting the composition of the study population and consecutive processes of sample matching. BEV, bevacizumab; CRS, cytoreductive surgery; HGSOC, high-grade serous ovarian carcinoma; OLA, olaparib; PSR, platinum-sensitive relapsed.

### 1. Analysis in all patients

**Table S1** presents patients' clinicopathologic characteristics. Of 148 patients, 142 (95.9%) and 31 (20.9%) received germline and somatic gene tests, respectively; 25 (16.9%) received both tests. Germline *BRCA1/2* mutations and somatic *BRCA1/2* mutations were identified in 87.8% (130/148) and 20.3% (30/148) of patients, respectively; 12 (8.1%) had both germline and somatic *BRCA1/2* mutations.

Patient age at initial diagnosis, *BRCA* mutational status, FIGO stage, and residual tumor at the first CRS were similar between the BEV (n=29) and OLA intent (n=119) groups. At recurrence, no differences in patient age, serum CA-125 levels, and proportion of secondary CRS were observed between the 2 groups. However, the OLA intent group showed better response to second-line main chemotherapy, compared to the BEV group ( $p < 0.001$ ). The proportion of patients who achieved CR was higher in the OLA intent group with a trend towards statistical significance (46.2% vs. 27.6%;  $p = 0.069$ ). Consistent results were also observed in comparisons between BEV and OLA users. Herein, the proportion of patients who achieved CR after second-line main chemotherapy was significantly higher in the OLA users (49.4% vs. 27.6%;  $p = 0.042$ ) (**Table S1**).

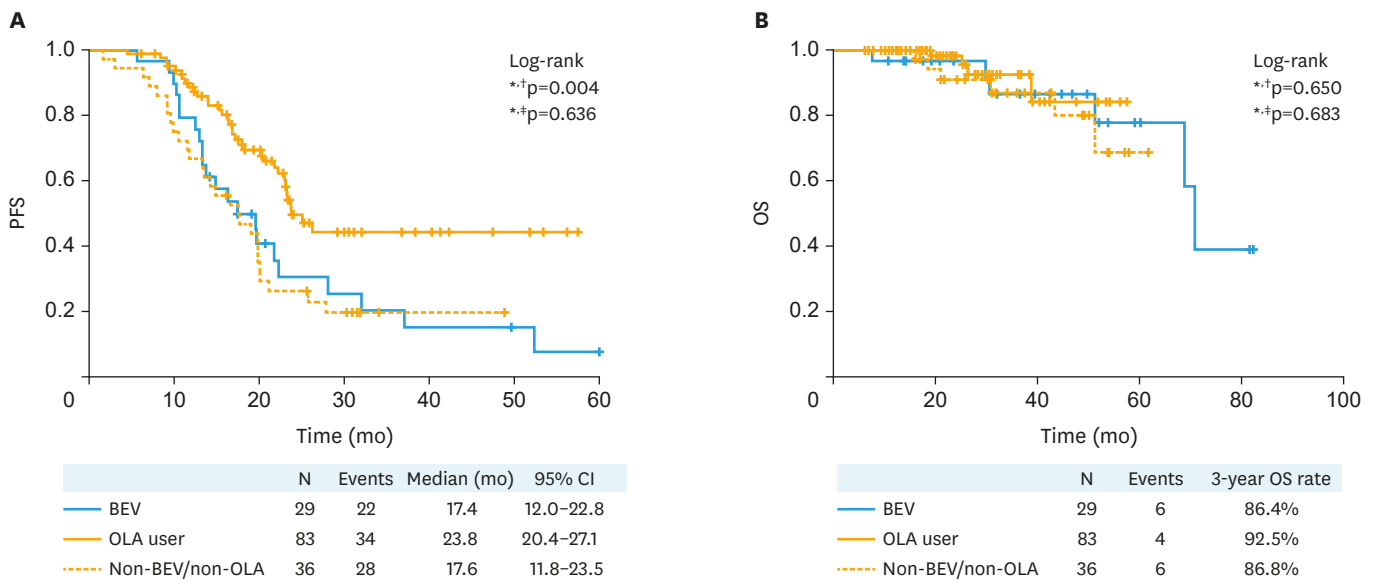
Details of treatment of the BEV group are presented in **Table S2**. Of 29 patients, 23 (79.3%) received BEV with paclitaxel-carboplatin, 6 (20.7%) received BEV with gemcitabine-carboplatin, and 26 (89.7%) received BEV maintenance therapy. The median cycles of BEV maintenance was 13.5 (range, 1–73). During BEV maintenance, 38.5% of the patients achieved or maintained CR. Disease progression was the most common reason for discontinuation of BEV maintenance (n=16, 61.5%).

Details of treatment in the OLA users group are presented in **Table S3**. Pegylated liposomal doxorubicin-carboplatin was the most common second-line chemotherapy regimen (n=56, 67.5%), followed by paclitaxel-carboplatin (n=18, 21.7%). Approximately half of the patients achieved CR to second-line chemotherapy. Of 83 patients, 53 (63.9%) received OLA maintenance for >6 months; 6 patients (7.2%) continued OLA for >24 months. During OLA maintenance, 56.6% of the patients achieved or maintained CR. Dose reduction and interruption occurred in 30 (36.1%) and 9 (10.8%) patients, respectively. Disease progression was the most common reason for discontinuation of OLA maintenance (n=32, 38.6%).

The median observation period for all patients was 26.3 months. The OLA intent group showed improved PFS (marginal statistical significance) compared to the BEV group (median, 22.2 vs. 17.4 months; p=0.057), but similar OS (3-year OS rate, 90.2% vs. 86.4%; p=0.999). OLA users showed significantly better PFS than the BEV group (median, 23.8 vs. 17.4 months; p=0.004). However, no difference in OS was observed between the BEV and OLA users (p=0.650). The non-BEV/non-OLA and BEV users showed similar PFS (median, 17.6 vs. 17.4 months; p=0.636) and OS (p=0.683) (**Fig. 2**).

**2. Analysis in matched patients**

Of the 8 matched datasets, we selected OLA 65P, OLA 80P, and OLA 95P as the representative datasets. Patients in the 3 matched datasets showed similar clinicopathologic characteristics compared to those in the BEV group, except for response to second-line main chemotherapy. However, there were no differences in the proportion of patients who achieved CR (**Table 1**).



**Fig. 2.** Comparisons of survival outcomes in all patients. (A) PFS; (B) OS. BEV, bevacizumab; OLA, olaparib; OS, overall survival; PFS, progression-free survival. \*BEV; †OLA user; ‡Non-BEV/non-OLA.

**BEV vs. OLA in platinum-sensitive ovarian cancer**
**Table 1.** Patients' clinicopathologic characteristics after matching

Characteristics	BEV (n=29)	OLA 65P (n=58, %)	p-value*†	OLA 80P (n=58)	p-value*‡	OLA 95P (n=58)	p-value*§
Age at initial diagnosis, years							
Median (range)	50.0 (36.0–66.0)	50.5 (32.7–77.0)	0.573	52.0 (32.7–77.0)	0.215	52.5 (32.7–77.0)	0.295
FIGO stage			0.105		0.185		0.185
I–III	23 (79.3)	36 (62.1)		38 (65.5)		38 (65.5)	
IV	6 (20.7)	22 (37.9)		20 (34.5)		20 (34.5)	
Residual tumor at first CRS			0.892		0.552		0.219
No residual	12 (41.4)	27 (46.6)		29 (50.0)		33 (56.9)	
<1 cm	14 (48.3)	26 (44.8)		21 (36.2)		17 (29.3)	
≥1 cm	3 (10.3)	5 (8.6)		8 (13.8)		8 (13.8)	
Platinum-free interval			0.241		0.854		0.485
6–12 mo	6 (20.7)	19 (32.8)		13 (22.4)		16 (27.6)	
>12 mo	23 (79.3)	39 (67.2)		45 (77.6)		42 (72.4)	
Age at recurrence, years							
Median (range)	52.0 (38.0–68.0)	53.0 (34.0–79.0)	0.395	55.0 (34.0–79.0)	0.189	55.0 (34.0–79.0)	0.319
CA-125 at recurrence (IU/mL)							
Median (range)	69.8 (8.7–660.0)	64.5 (2.2–1,588.0)	0.978	61.4 (2.2–1,588.0)	0.921	70.8 (2.2–1,588.0)	0.801
Secondary CRS	7 (24.1)	18 (31.0)	0.503	23 (39.7)	0.151	18 (31.0)	0.503
Response to second-line main chemotherapy							
Four categories			0.001		0.001	0	<0.001
CR	8 (27.6)	18 (31.0)		22 (37.9)		21 (36.2)	
PR	14 (48.3)	36 (62.1)		34 (58.6)		37 (63.8)	
SD	7 (24.1)	0		0		0	
PD	0	4 (6.9)		2 (3.4)		0	
Two categories			0.740		0.339		0.421
CR	8 (27.6)	18 (31.0)		22 (37.9)		21 (36.2)	
Non-CR	21 (72.4)	40 (69.0)		36 (62.1)		37 (63.8)	
Maintenance therapy			N/A		N/A		N/A
No	3 (10.3)	20 (34.5)		12 (20.7)		3 (5.2)	
BEV	26 (89.7)	0		0		0	
OLA	0	38 (65.5)		46 (79.3)		55 (94.8)	

Values are presented as number (%).

BEV, bevacizumab; CA-125, cancer antigen 125; CR, complete response; CRS, cytoreductive surgery; FIGO, International Federation of Gynecology and Obstetrics; N/A, not applicable; OLA, olaparib; PD, progressive disease; PR, partial response; SD, stable disease.

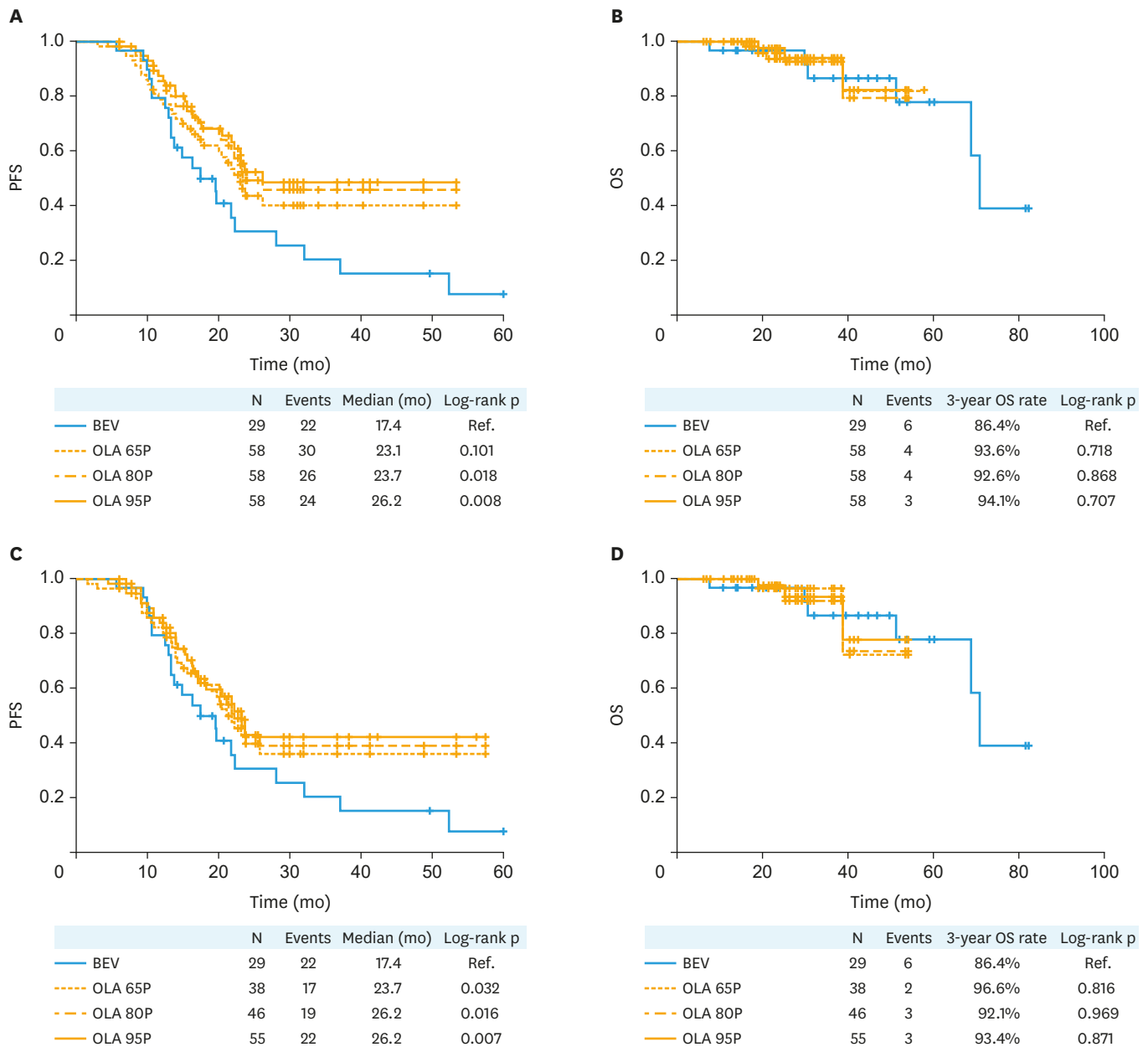
\*BEV; †OLA 65P; ‡OLA 80P; §OLA 95P.

While the OLA 65P dataset showed similar PFS compared with the BEV group ( $p=0.101$ ), the OLA 80P dataset (median, 23.7 vs. 17.4 months;  $p=0.018$ ) and OLA 95P dataset (median, 26.2 vs. 17.4 months;  $p=0.008$ ) showed significantly improved PFS (**Fig. 3A**). In multivariate analyses adjusting for PFI, serum CA-125 levels at the time of recurrence, secondary CRS, and response to second-line main chemotherapy, intention-to-treat OLA was identified as an independent favorable prognostic factor for PFS in all the OLA datasets: OLA 65P (aHR=0.505; 95% CI=0.280–0.911;  $p=0.023$ ) to OLA 100P (aHR=0.348; 95% CI=0.184–0.658;  $p=0.001$ ) (**Table 2**). As the proportion of OLA users increased from 65% to 100%, the aHR of the intention-to-treat OLA for recurrence decreased with stronger statistical significance (**Fig. 4A**). However, no differences in OS were observed (**Fig. 3B**).

Next, we compared survival outcomes of OLA users in the matched OLA datasets with those of BEV users. OLA users in the OLA 65P, OLA 80P, and OLA 95P datasets showed significantly better PFS than the BEV users ( $p=0.032$ ,  $p=0.016$ , and  $p=0.007$ , respectively) (**Fig. 3C**). Multivariate analyses revealed that the OLA use was significantly associated with improved PFS in all the OLA datasets from OLA 65P (aHR=0.336; 95% CI=0.168–0.674;  $p=0.002$ ) to OLA 100P (aHR=0.348; 95% CI=0.184–0.658;  $p=0.001$ ) (**Table 2**). The use of OLA, rather than BEV, consistently showed significant associations with improved PFS, regardless of the matched datasets (**Fig. 4B**). However, the OLA and BEV users showed similar OS in each matched dataset (**Fig. 3D**).



**BEV vs. OLA in platinum-sensitive ovarian cancer**



**Fig. 3.** Comparisons of survival outcomes after matching. (A, B) BEV vs. OLA intent groups; (C, D) BEV vs. OLA users. (A, C) PFS; (B, D) OS. BEV, bevacizumab; OLA, olaparib; OS, overall survival; PFS, progression-free survival.

**DISCUSSION**

In this multicenter study, we conducted matching analyses to compare the survival outcomes of BEV and OLA treatments in *BRCA*-mutated, PSR HGSO. Overall, intention-to-treat OLA was associated with a significantly lower recurrence rate than BEV. Comparisons between BEV and OLA users in the various matched datasets revealed that OLA use, rather than BEV, significantly improved PFS, though OS was comparable.

The Korean Ministry of Food and Drug Safety approved BEV for PSR EOC with the regimens used in the OCEANS (December, 2013) and GOG-213 (May, 2017) [7,8]. The OLA capsule was

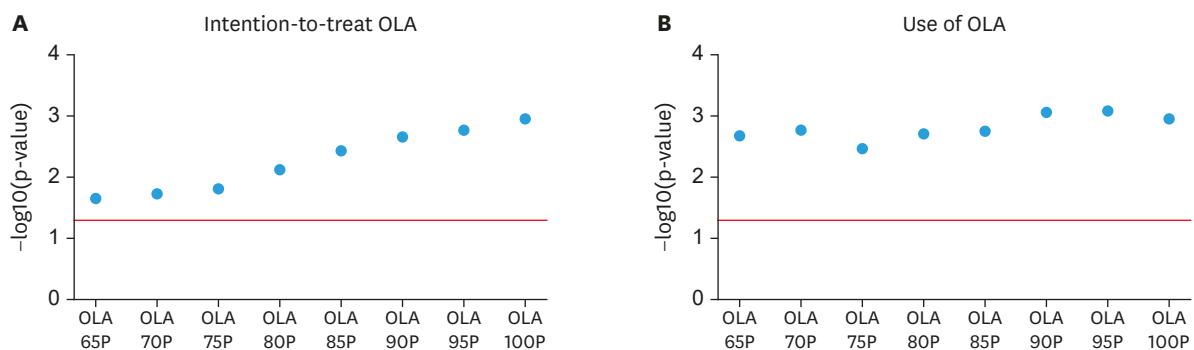
**BEV vs. OLA in platinum-sensitive ovarian cancer**

**Table 2.** Factors associated with progression-free survival in matched patients

Characteristics	Number			OLA intent vs. BEV*			OLA users vs. BEV*		
	BEV user	OLA user	Non-BEV/non-OLA user	aHR	95% CI	p-value	aHR	95% CI	p-value
BEV	29	0	0	1	-	-	1	-	-
OLA 65P	0	38	20	0.505	0.280–0.911	0.023	0.336	0.168–0.674	0.002
OLA 70P	0	40	18	0.491	0.271–0.891	0.019	0.331	0.165–0.662	0.002
OLA 75P	0	43	15	0.475	0.260–0.870	0.016	0.364	0.185–0.717	0.003
OLA 80P	0	46	12	0.435	0.235–0.804	0.008	0.348	0.178–0.680	0.002
OLA 85P	0	49	9	0.399	0.214–0.744	0.004	0.350	0.181–0.677	0.002
OLA 90P	0	52	6	0.372	0.197–0.702	0.002	0.324	0.167–0.630	0.001
OLA 95P	0	55	3	0.368	0.196–0.689	0.002	0.332	0.174–0.634	0.001
OLA 100P	0	58	0	0.348	0.184–0.658	0.001	0.348	0.184–0.658	0.001

aHR, adjusted hazard ratio; BEV, bevacizumab; CI, confidence interval; CR, complete response; OLA, olaparib.

\*Multivariate analysis adjusting for serum cancer antigen 125 levels at recurrence, platinum-free interval (6–12 mo. >12 mo), secondary cytoreductive surgery, and response to second-line main chemotherapy (CR vs. non-CR).



**Fig. 4.** Impact of (A) intention-to-treat OLA and (B) use of OLA on progression-free survival of patients. A dot indicates the negative log<sub>10</sub>-transformed p-value calculated in the corresponding matched OLA dataset. The red line indicates a p-value of 0.05. OLA, olaparib.

the first approved PARP inhibitor for maintenance therapy in *BRCA*-mutated, PSR HGSOc, based on Study 19 [15] and SOLO2 [11] (August, 2015). OLA has been more widely used than BEV since its approval because of more convenient administration, and acceptable side effects and toxicity. This was also evident in our study: OLA users outnumbered BEV users, but had shorter observation periods. The recent publication of OS analysis from SOLO2 is expected to accelerate further use of OLA in Korea [16].

In real-world clinical practice, physicians tend to prescribe BEV and OLA mutually exclusively to patients with *BRCA*-mutated, PSR HGSOc as dual maintenance and switching from BEV to OLA are not recommended in this population [4,5]. Especially, whether to start OLA maintenance therapy is only considered when the patients responded to the second-line main chemotherapy. However, even if patients achieved CR/PR, not all undergo OLA maintenance therapy, influenced by patients' own or sociomedical environmental factors. Therefore, a simple comparison of survival outcomes between BEV users and OLA users is inadequate in a retrospective study. Instead, adopting the concept of intention-to-treat, we conducted nearest neighbor matching between the BEV and OLA intent groups, setting the various proportion of OLA users in the OLA intent group.

In terms of effectiveness, the OLA users in the current study showed better PFS (median, 23.8 vs. 19.1 vs. 14.6 months), compared to those in SOLO2 [11] and a previous real-world Korean study [17]. This may be because our study only included patients who relapsed for the first time, whereas SOLO2 also included patients with multiple recurrences. The BEV users in the

current study showed better PFS (median, 17.4 vs. 12.4 vs. 13.8 months), compared to those in OCEANS and GOG-213 [7,8,18]. However, the 2 studies have not reported the proportions of HGSOc and the patients' *BRCA1/2* mutational status. We also observed no difference in PFS between BEV users and non-BEV/non-OLA users in this study. Similarly, in GOG 218, germline or somatic mutations in *BRCA1/2* genes were not predictive of first-line BEV in advanced EOC [19]. Another retrospective multicenter study also reported that there were no PFS/OS benefits from first-line BEV in EOC patients with *BRCA* mutations [20]. The increased chemosensitivity of *BRCA*-mutated HGSOc may be more influential than the survival benefit from BEV, which may explain our results [21].

If BEV is not part of second-line chemotherapy, OLA use is decided based on the response to the second-line platinum-based chemotherapy. In GOG-213, the investigator-assessed objective response rate of the chemotherapy-only arm was 58.5% (152/260) [8]; this rate is expected to be higher in *BRCA*-mutated PSR HGSOc, as GOG-213 also included non-high grade serous and *BRCA1/2* wild-type tumors. As the original proportion of OLA users in the OLA intent group was 69.7%, we generated matched datasets with proportions of OLA users ranging from 65% to 100%, and found that intention-to-treat OLA, rather than BEV, was an independent favorable prognostic factor for PFS in all the OLA datasets. Such associations were stronger when the proportion of OLA users increased. Therefore, keeping the proportion of OLA users as high as possible might be important and may be achieved by increasing objective response rates or eliminating factors that hinder OLA use (e.g., lowering drug prices and introducing patient support programs for coping with toxicity). Developing a model to predict objective responses to platinum-based chemotherapy would also be valuable.

Interestingly, OS was comparable between the BEV and OLA intent groups, and between the BEV and OLA users. This may be because PARP inhibitor therapy was the third-line treatment or more in BEV users (similar to a crossover as in many RCTs). In addition, OLA use may increase resistance to subsequent platinum and non-platinum chemotherapy as shown in post-hoc analysis of SOLO2 [22]. Nevertheless, we did not investigate post-BEV and post-OLA management and time to second progression in this study; these may be presented in our subsequent studies.

Three phase III RCTs resulted in conflicting results on secondary CRS in EOC patients [23-25]. In addition to the differences in patient selection methods, complete cytoreduction rate, and maintenance therapy, the role of secondary CRS in *BRCA*-mutated EOC and the optimal maintenance therapy after secondary CRS remain to be clarified. In the current study, secondary CRS was identified as an independent favorable prognostic factor for PFS, and was used for propensity score calculation. However, further subgroup analysis by secondary CRS was not feasible owing to the small number of patients who received secondary CRS, especially in the BEV group.

Our study has limitations. First, due to the retrospective nature, issues such as selection bias cannot be ruled out. Second, the sample size was small and the observation period was short. Third, although we matched the proportion of patients who achieved CR after second-line main chemotherapy, the matched groups still differed in detailed responses to the chemotherapy. Besides the small sample size, the inherent difference in start times of the BEV and OLA seems to contribute to such an imbalance between the 2 groups. Fourth, subgroup analyses by the mutated gene and the cumulative dose were not conducted. Lastly, we did

not compare quality-of-life issues, toxicity and adverse events, and cost-effectiveness. Such information may guide decision-making in the management of *BRCA*-mutated, PSR HGSOc.

Currently, OLA and niraparib are recommended as first-line maintenance in EOC patients with specific conditions, based on the SOLO1 [26] and PRIMA [27] studies; dual maintenance with BEV and OLA is also available in homologous-recombination deficient, primary high-grade EOC, based on the PAOLA-1 study [28]. However, the current practice guidelines advise against PARP inhibitor retreatment in ovarian cancer [29]. Therefore, comparing BEV and OLA in *BRCA*-mutated, PSR HGSOc as in our study would become more difficult. Instead, as per a phase II RCT (AVANOVA2) that proved significantly better PFS from BEV and niraparib compared to niraparib alone [30], dual maintenance with BEV and PARP inhibitors might become a new treatment option in this population.

In conclusion, in patients with *BRCA*-mutated, PSR HGSOc, intention-to-treat OLA, rather than BEV, was significantly associated with PFS improvement. As the proportion of OLA users increased, the risk of disease progression decreased significantly. Compared to BEV users, OLA users showed consistently better PFS. Our study results suggest that the use of OLA might be considered at the beginning of second-line treatment in this population.

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## SUPPLEMENTARY MATERIALS

### Table S1

Patients' clinicopathologic characteristics

[Click here to view](#)

### Table S2

Additional characteristics of BEV users

[Click here to view](#)

### Table S3

Additional characteristics of OLA users

[Click here to view](#)

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