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Second-line olaparib maintenance therapy is associated with poor response to subsequent chemotherapy in *BRCA1/2*-mutated epithelial ovarian cancer: A multicentre retrospective study

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HIGHLIGHTS

- Although second-line olaparib significantly improved PFS1, olaparib did not prolong PFS2.
- Relapsed patients despite 2 L-olaparib maintenance show poor response to subsequent chemotherapy.
- The negative effects were more pronounced in patients with PFS1 > 12 months.

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ABSTRACT

Introduction. With expanded use of poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi), there is a potential impact of PARPi resistance on platinum resistance. A post-hoc analysis of SOLO2 demonstrated a reduction in response to subsequent platinum-based therapy among patients who received prior olaparib but not placebo. The present multicentre, retrospective, observational study was conducted to determine the effects of olaparib on subsequent therapy for recurrent epithelial ovarian cancer (EOC).

Materials and methods. Data on EOC patients with *BRCA1/2*-mutated tumours who received second-line platinum-based chemotherapy between January 2012 and June 2020, at three South Korean institutions ($n = 197$) were collected. Patients who received olaparib as maintenance therapy after second-line chemotherapy were assigned to the olaparib group ($n = 105$), and subjects who did not receive olaparib maintenance therapy were assigned to the control group ($n = 92$). The primary endpoint was time intervals from the date of second disease progression (PFS1) to the date of third disease progression (PFS2), expressed as PFS2 − PFS1.

Results. As expected, PFS1 in the olaparib group was longer than the control group. However, PFS2 – PFS1 in the olaparib group was significantly shorter than that of the control group (median 7.9 vs. 13.6 m; $p = 0.0005$). Even when the third-line PARPi maintenance (cross-over) patients were excluded from the control group, the response to subsequent therapy in the olaparib group remained poor (median 7.7 vs. 11.5; $p = 0.0422$).

Discussions. Patients with platinum-sensitive *BRCA1/2* mutated tumours who progressed during olaparib maintenance after second-line chemotherapy were less likely to respond to third-line chemotherapy compared to controls who did not receive olaparib, suggesting that resistance to olaparib may contribute to chemotherapy resistance.

1. Introduction

Poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors (PARPi) represent and important breakthrough in the management of

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ovarian cancer. PARPi as maintenance therapy for recurrent ovarian cancer have been investigated using olaparib in Study 19 [1] and SOLO-2 [2], niraparib in NOVA [3], and rucaparib in ARIEL3 [4]. Taken together, the greatest benefit has been observed in tumours that have mutations in *BRCA1/2* or related genes in the homologous recombination (HR) DNA repair pathway, as well as tumours with evidence of HR deficiency. Since 2018, there has also been a paradigm shift in the management of newly diagnosed ovarian cancer due to the substantial benefits of PARPi, demonstrated in four randomised phase III trials (SOLO-1 [5], PAOLA-1 [6], PRIMA [7] and VELIA [8]) in a front-line setting. Based on these data, the American Society of Clinical Oncology recommend all patients with newly diagnosed, advanced, platinum-sensitive epithelial ovarian cancer (EOC) should be offered PARPi maintenance therapy [9].

As more patients receive PARPi as maintenance therapy, the number of recurrent patients previously exposed (and potentially resistant) to PARPi will increase. However, optimal management of patients relapsing after PARPi maintenance therapy remains to be determined. Although subsequent chemotherapy is offered based on projected platinum sensitivity, with a prolonged platinum-free interval (PFI), few data are available on post-progression outcome for patients after PARPi maintenance.

In an exploratory post-hoc analysis of the SOLO2 trial, unexpected results were found. The efficacy of subsequent chemotherapy (particularly platinum-based chemotherapy) assessed based on time to second progression (PFS2 - PFS1) was lower in patients who received olaparib maintenance compared with those receiving placebo [10]. It has been hypothesized that olaparib resistance could be correlated with induction of platinum resistance, due to overlapping pathways associated with the DNA damage response (DDR) and subsequent DNA repair.

The current multicentre, retrospective, observational study was conducted to investigate the durability of clinical benefit of olaparib maintenance therapy following disease progression, and to compare the post-progression outcomes according to the use of olaparib maintenance after second-line chemotherapy.

2. Materials and methods

This multicentre retrospective cohort study was reviewed and approved by the institutional review boards of the participating centres (YUHS, 4–2021-0733; SNUH, H-2107-103-1234; SMC, 2022–01-122). This study was conducted in accordance with the Declaration of Helsinki.

2.1. Study population

From three tertiary institutional hospitals in Korea, patients who met the following inclusion criteria were identified: (1) pathologically confirmed high-grade serous ovarian, fallopian tube, and primary peritoneal carcinoma (collectively termed ovarian cancer); (2) germline or somatic *BRCA1/2* mutation; (3) completed second-line platinum-based chemotherapy between March 2012 and December 2020, and showed an objective response of complete remission (CR) or partial response

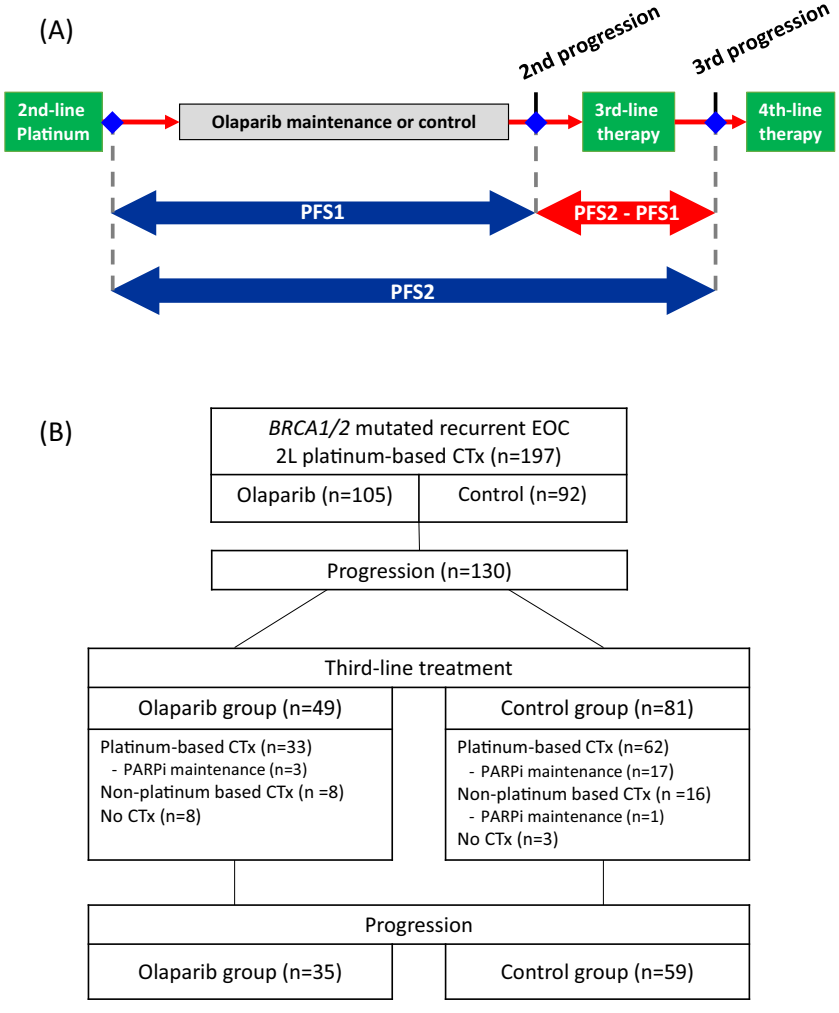

Fig. 1. Study scheme. (A) Study flow and endpoint diagram. (B) Patients enrolment and treatment.

Table 1
Patient demographics and baseline characteristics.

Group	Olaparib ($n = 105$)	Control ($n = 92$)	Total ($n = 197$)	p-value
Age (years) at diagnosis				
Median (range)	55 (32–79)	54 (28–77)	54 (28–79)	0.544
Primary tumour location, n (%)				0.835
Ovary	94 (89.5)	80 (87.0)	174 (88.3)	
Fallopian tube	5 (4.8)	6 (6.5)	11 (5.6)	
Peritoneum	6 (5.7)	6 (6.5)	12 (6.1)	
BRCA1/2 status, n (%)				0.245
g*BRCA1* mutation	55 (52.4)	58 (63.0)	113 (57.4)	
g*BRCA2* mutation	33 (31.4)	15 (16.3)	48 (24.4)	
g*BRCA1*and *2* mutation	3 (2.9)	3 (3.3)	6 (3.0)	
s*BRCA1* mutation	6 (5.7)	8 (8.7)	13 (6.6)	
s*BRCA2* mutation	6 (5.7)	7 (7.6)	13 (6.6)	
s*BRCA1* and *2* mutation	2 (1.9)	1 (1.1)	3 (1.5)	
Bevacizumab use in first-line therapy, n (%)	11 (10.5)	6 (6.5)	17 (8.6)	0.324
Progression-free survival				0.945
Median (months, range)	19.7 (9.9–88.1)	19.4 (3.1–90.2)		
Platinum-free interval				0833
Median (months, range)	13.9 (5.8–53.6)	14.1 (0.7–85.9)		
Objective response to second-line platinum-based regimen, n (%)				0.781
CR	51 (48.6)	49 (53.3)	100 (50.8)	
PR	54 (50.9)	43 (46.7)	97 (49.2)	

* Abbreviations: BRCA, breast cancer antigen; gBRCA, germline BRCA; sBRCA, somatic BRCA; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

(PR) according to the Response Evaluation Criteria In Solid Tumour (RECIST) version 1.1 [11] or a response based on the Gynecology Cancer InterGroup (GCIG) CA-125 response criteria [12]; and (4) no treatment with PARPi prior to second-line therapy (PARPi naïve at second-line therapy).

2.2. Data collection

From the medical records, patient clinicopathologic data, including age at diagnosis, *BRCA1/2* mutational status, objective response to second-line platinum-based chemotherapy, third-line therapy modalities, and chemotherapy regimen were collected.

During surveillance, patients underwent computed tomography (CT) scans approximately every 12 weeks until 2 years after chemotherapy and then every 6 months or based on clinical symptoms. Disease progression was determined according to the RECIST version 1.1 or GCIG CA-125 response criteria.

In the current study, the primary endpoint was time intervals from the date of second progression (PFS1) to the date of third progression (PFS2), expressed as PFS2 − PFS1. (Fig. 1A). For this endpoint, patients were censored if they had not experienced second disease progression or death at the last date known to be alive. Duration of PFS2 − PFS1 was set to 1 day for patients who were censored for PFS1 and did not have any further follow-up information. The date of the second event of progression or censoring was used to calculate PFS2 − PFS1 for patients who were censored for PFS1 but received subsequent anticancer treatment or had other follow-up data [13]. As a secondary endpoint, objective response rate (ORR) to third-line chemotherapy was investigated based on the RECIST version 1.1 or GCIG CA-125 response criteria. Overall survival (OS) was calculated as the time from the end of second-line chemotherapy to death from any cause.

2.3. Statistical analysis

Descriptive statistics were used for demographic data and are summarised as medians (ranges) or frequencies (percentages). Differences in patient characteristics between groups were compared using Chi-square or Mann-Whitney *U* tests. Survival analyses were conducted using the Kaplan-Meier method and log-rank test. For multivariate analyses, Cox proportional hazard regression analyses were conducted, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Statistical analyses were performed using IBM SPSS statistics software (version 21.0; IBM Corp., Armonk, NY, USA) and Prism software (GraphPad, La Jolla, CA, USA). A p-value <0.05 was considered to indicate statistical significance.

Table 2
Details of third-line therapy and responses.

	Olaparib ($n = 49$)	No olaparib ($n = 81$)	Total ($n = 130$)	p-value
Third-line therapy				
Platinum-based chemotherapy	33 (67.3)	62 (76.6)	95 (73.1)	0.971
Paclitaxel+Cisplatin	0 (0.0)	1 (1.2)	1 (0.8)	
Paclitaxel+Carboplatin	4 (8.2)	12 (14.8)	16 (12.3)	
Gemcitabin+Carboplatin	7 (14.3)	2 (2.5)	9 (6.9)	
Docetaxel+Cisplatin	0 (0.0)	3 (3.7)	3 (2.3)	
Docetaxel+Carboplatin	2 (4.1)	7 (8.6)	9 (6.9)	
Belotecan+Cisplatin	3 (6.1)	5 (6.2)	8 (6.2)	
Belotecan+Carboplatin	1 (2.0)	1 (1.2)	2 (1.5)	
PLD + carboplatin	6 (12.2)	28 (34.6)	34 (26.2)	
Topotecan+Cisplatin	0 (0.0)	1 (1.2)	1 (0.8)	
Topotecan+Carboplatin	6 (12.2)	1 (1.2)	7 (5.4)	
Other*	4 (8.2)	1 (1.2)	5 (3.8)	
Non-platinum-based chemotherapy	8 (16.3)	16 (19.7)	24 (18.5)	0.971
PLD	3 (6.1)	9 (11.1)	12 (9.2)	
Belotecan	1 (2.0)	1 (1.2)	2 (1.5)	
Topotecan	4 (8.2)	4 (4.8)	8 (6.2)	
Docetaxel	0 (0.0)	0 (0.1)	1 (0.8)	
Paclitaxel	0 (0.0)	0 (0.1)	1 (0.8)	
Third-line maintenance therapy	4 (8.1)	19 (23.4)	23 (17.7)	0.052
Bevacizumab	1 (2.0)	1 (1.2)	2 (1.5)	
PARP inhibitors	3 (6.1)	18 (22.2)	21 (16.2)	
Third-line No maintenance	45 (91.9)	62 (76.6)	107 (82.3)	0.052
Debulking operation only	2 (4.1)	0 (0.0)	2 (1.5)	
Radiation therapy only	2 (4.1)	3 (3.7)	5 (3.8)	
Other†	4 (8.2)	0 (0.0)	4 (3.1)	
Response to third-line therapy				<0.001
CR	2 (4.1)	23 (34.6)	30 (23.1)	
PR	8 (16.3)	26 (32.1)	34 (26.2)	
SD	8 (16.3)	5 (6.2)	13 (10.0)	
PD	21 (42.9)	17 (21.0)	38 (29.2)	
Unknown	10 (20.4)	5 (6.2)	15 (11.5)	

*Carboplatin ($n = 2$), Cyclophosphamide+Carboplatin (n = 2), Vinorelbine+Cisplatin (n = 1), †Pembrolizumab (n = 2), Nivolumab (n = 1), Prexasertib (n = 1).

3. Results

The present analysis included 197 patients; 105 patients who received olaparib maintenance after second-line platinum-based chemotherapy were assigned to the olaparib group, and 92 patients who received second-line platinum-based chemotherapy without olaparib maintenance were assigned to the control group (Fig. 1B). As shown in Table 1, the olaparib and control groups showed similar baseline characteristics in terms of age, primary tumour location, *BRCA1/2* status, bevacizumab use in first-line therapy, progression-free survival, platinum-free interval and ORR of second-line chemotherapy.

Second progression was observed in 45.3% (49/105) and 88.0% (81/92) of patients in the olaparib and control groups, respectively. Among the patients who relapsed a second time, 119 (91.5%) received third-line subsequent chemotherapy, 2 (1.5%) underwent surgery, and 5 (3.8%) were treated with radiation only. The other 4 (3.1%) patients received salvage treatment (Table 2). Platinum-based chemotherapy was administered to 33/49 (67.3%) patients in the olaparib group and 62/81 (76.6%) patients in the control group. Pegylated liposomal doxorubicin (PLD) + carboplatin doublet was the most frequently administered platinum-based regimen (26.2%, Table 2). Among patients who received third-line chemotherapy, 21 (3 and 18 patients in the olaparib and control group, respectively) were treated with PARPi maintenance after third-line chemotherapy (Table 2).

Patients in the olaparib group showed significantly longer PFS1 than did subjects in the control group (median, 15.4 months vs. 9.2 months; $p < 0.001$; Fig. 2A). At the time of analysis, 79 (75.2%) patients had received olaparib for at least 6 months, 53 (50.5%) patients for at least 12 months, and 16 (15.2%) more >2 years. Approximately 50% of patients were still receiving treatment at time of analysis.

When comparing PFS2 between the olaparib group and control group, significant difference was not observed (median 27.2 months vs. 26.1 months, HR 0.88, $p = 0.5030$, Fig. 2B). However, when excluding patients who received PARPi maintenance after third-line chemotherapy, the olaparib group ($n = 102$) showed significantly longer PFS2 than did the control group ($n = 74$) (median, 27.2 months vs. 23.3 months, HR 0.65, $p = 0.0331$, **Supplementary Fig. S1A**).

PFS2 − PFS1, representing the response to third-line chemotherapy, was worse in the olaparib group than in the control group (Fig. 2C; median 7.9 months vs. 13.6 months, HR 1.97, $p = 0.005$). Even after excluding patients who received PARPi after third-line chemotherapy, PFS2 − PFS1 in the olaparib group remained shorter than that in the control group (**Supplementary Fig. S1A**; median 7.7 months vs. 11.5 months, HR 1.52, $p = 0.0422$). Furthermore, when only patients with PFS1 > 12 months were compared, the differences of PFS1 and PFS2 − PFS1 between the two groups were more pronounced (**Supplementary Fig. S1B**, median PFS1 undefined vs. 19.8 months, $p = 0.0319$; median PFS2 − PFS1 7.9 months vs. 12.7 months, $p = 0.0059$).

In terms of responses to third-line chemotherapy, only 2 patients (4.1%) achieved CR in the olaparib group and 23 patients (34.6%) in the control group. ORR to third-line chemotherapy was poorer in the olaparib group than in the control group (Tables 2, 20.4% vs. 66.7%, $p < 0.001$).

Next, PFS2 − PFS1 was analysed based on third-line chemotherapy regimen in patients who experienced second recurrence ($n = 119$) to elucidate whether post-progression outcome differed due to subsequent chemotherapy regimen. As shown in Fig. 3, platinum-based chemotherapy showed better PFS2 − PFS1 than did non-platinum chemotherapy in the olaparib group (median 8.9 months vs. 4.4 months, HR 0.31, $p = 0.0017$) and in the control group (median 14.8 months vs. 8.1, HR 0.27, $p < 0.0001$). Among the patients who received platinum-based chemotherapy for third-line chemotherapy, the olaparib group showed poorer PFS2 − PFS1 than the control group (median PFS2 − PFS1 8.9 months vs. 14.8 months, HR 2.4 $p = 0.0002$). Among the patients who received non-platinum-based chemotherapy for third-line chemotherapy, the

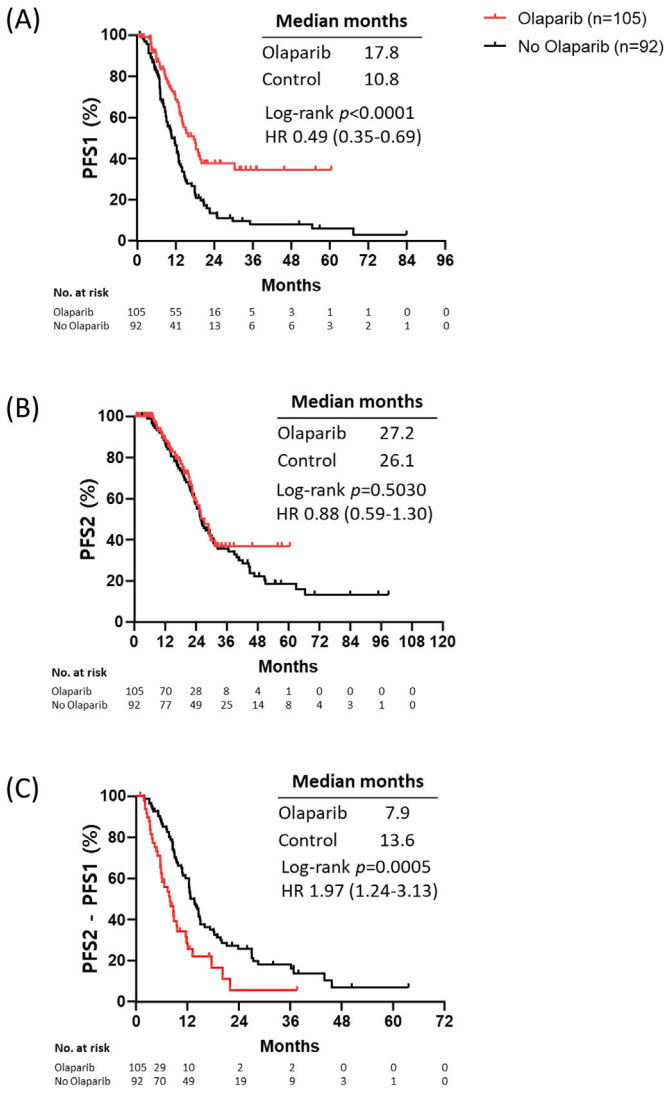

Fig. 2. Kaplan-Meier estimates of PFS1, PFS2, and PFS2 − PFS1 in all enrolled patients. The retrospective cohort included 105 patients in the olaparib group and 92 patients in the control group.
PFS1: time from the end of second-line chemotherapy to second disease progression or death.
PFS2: time to date of third disease progression or death.

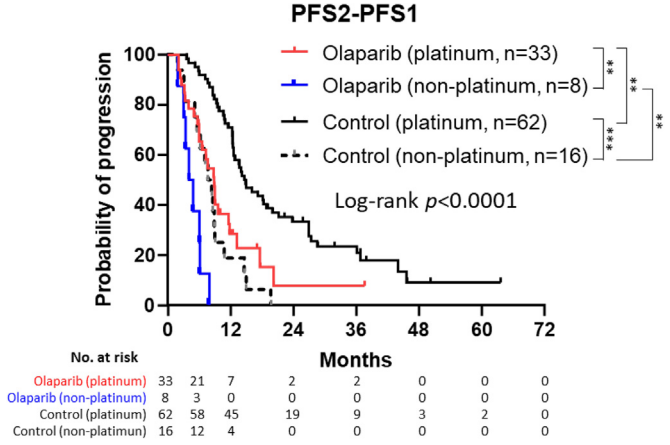

Fig. 3. Kaplan-Meier estimates of PFS2 − PFS1 based on subsequent third-line chemotherapy in patients who relapsed a second time.

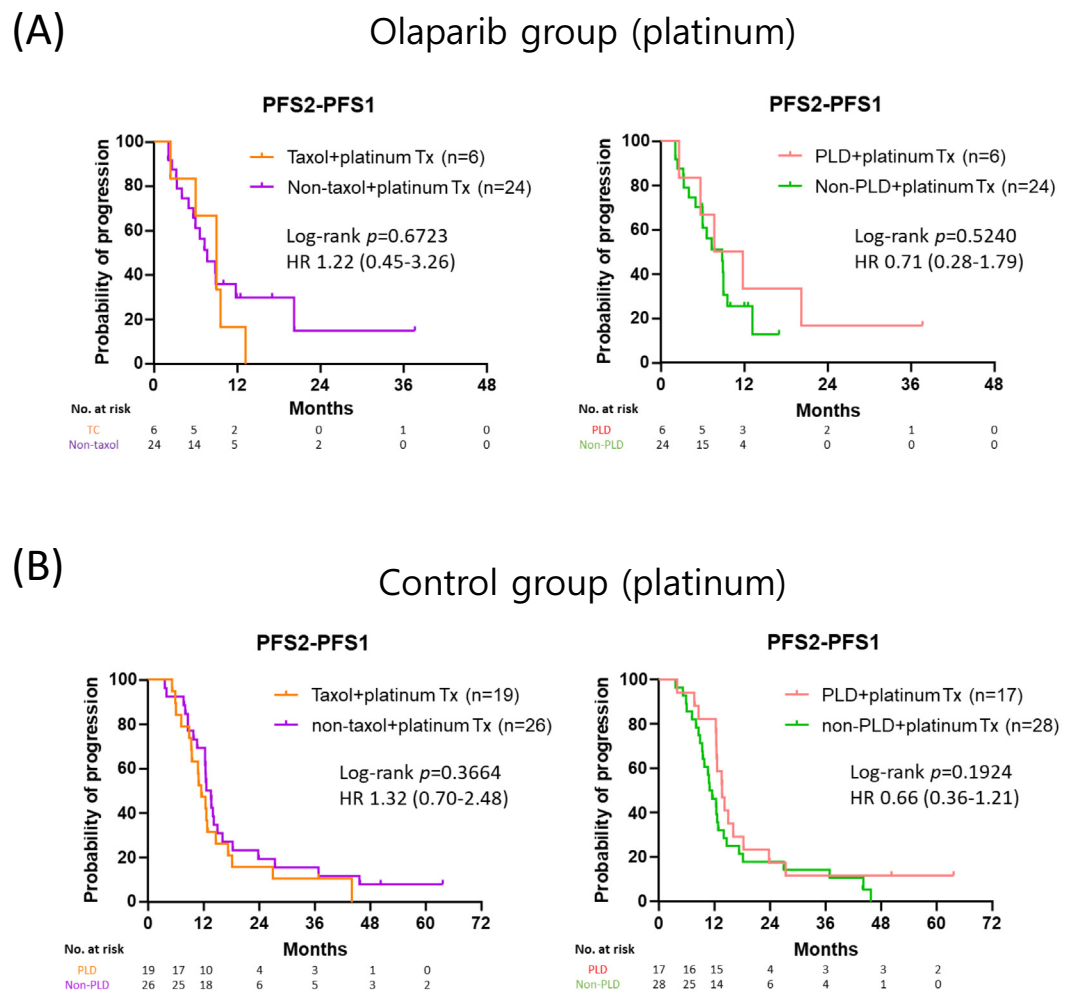

Fig. 4. Kaplan-Meier estimates of PFS2-PFS1 in patients who relapsed a second time based on a regimen of third-line platinum-based chemotherapy. (A) Olaparib group. (B) Control group.
PFS1: time from the end of second-line chemotherapy to second disease progression or death.
PFS2: time to date of third disease progression or death.
PLD: pegylated liposomal doxorubicin.

olaparib group showed poorer PFS2 — PFS1 than the control group (median PFS2-PFS1 4.4 months vs. 8.1 months, HR 2.9 $p = 0.0054$; Fig. 3). Even after excluding third-line PARPi maintenance (cross-over) patients, the results of PFS2 — PFS1 based on chemotherapy regimen remained unchanged (**Supplementary Fig. S2**).

Next, to explore the most effective third-line platinum-based chemotherapy regimen, Taxol- or PLD-containing chemotherapy regimens were analysed. However, significant difference was not observed based on use of PLD in platinum-based chemotherapy. In addition, difference was not observed regarding the use of paclitaxel (Fig. 4A, olaparib; Fig. 4B, control). Furthermore, in order to investigate the effect of PARPi on platinum sensitivity, the third-line platinum-based chemotherapy response by PFS2 - PFS1 was analysed in the "olaparib group", and there was no significant difference according to the duration of use of olaparib (12 months) (**Supplementary Fig. S3).**

Multivariate analysis using Cox regression showed that second-line olaparib maintenance was a significant determinant for PFS2-PFS1 when all other prognostic variables were considered (HR 2.1, 95% CI = 1.1–4.0, $p = 0.023$). Advanced initial cancer stage ($p = 0.005$) was another significant determinant (Table 3). However, *BRCA1/2* status, PFS1, age, and third-line chemotherapy regimen were not significant.

Table 3
Multivariate analysis using potential covariates for PFS2 — PFS1.

List of covariates	HR	95% CI	*p*-value
Second-line olaparib maintenance			
Control	1		
Olaparib	2.105	1.111–3.990	0.023
BRCA1/2 status			
Germline mutation	1		
Somatic mutation	1.371	0.816–2.305	0.233
BRCA1 mutation	1		
BRCA2 mutation	0.883	0.530–1.470	0.632
BRCA1 and *BRCA2* mutation	1.322	0.544–3.210	0.538
Stage			
I–II	1		
III–IV	5.957	1.710–20.756	0.005
PFS1 (months)			
≤12	1		
>12	0.658	0.396–1.092	0.106
Age (years)[a]			
≤54	1		
>54	0.905	0.553–1.482	0.692
Third-line chemotherapy regimen			
Platinum-based	1		
Non-platinum-based	0.775	0.379–1.586	0.486

a. median age: 54 years (28–79 years) *Abbreviations: HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.

4. Conclusions

In the present multicentre, retrospective cohort study, inclusion of olaparib in second-line treatment was associated with a reduction in efficacy of subsequent treatments in recurrent, *BRCA1/2*-mutated, EOC patients. Although the inclusion of olaparib in second-line treatment significantly improved PFS1 (as expected), olaparib did not prolong PFS2, which can serve as a surrogate for OS. Excluding third line PARPi maintenance (cross-over) patients, we noted that the olaparib group showed significantly prolonged PFS2, however, patients in the olaparib group showed shorter PFS2 − PFS1 than subjects in the control group. Notably, the negative effects were more pronounced in patients with PFS1 > 12 months

For patients with recurrent ovarian cancer associated with a *BRCA1/2* mutation or HRD and who respond to second-line platinum-based chemotherapy, PARPi have become a standard of care [1–3]. In the SOLO2 trial, the final analysis confirmed the use of olaparib for maintenance in patients with platinum-sensitive, relapsed ovarian cancer and *BRCA1/2* mutation; olaparib provided a median progression-free survival benefit of 13.6 months compared with placebo (19.1 months vs. 5.5 months) [14]. Maintenance therapy is intended to delay disease progression without negative side effects.

Few data are available on post-progression outcome for women with platinum-sensitive recurrent EOC who received PARPi maintenance treatment [10,13,15]. Therefore, the present study is significant because results showed that olaparib had a negative effect on subsequent therapy. This is the first report using real-world data of post-progression treatment and response in which olaparib maintenance therapy and no maintenance therapy were compared in terms of PFS2 − PFS1.

Our results were consistent with previous studies. In the SOLO2 trial, the post-hoc analysis showed lower efficacy of subsequent chemotherapy in patients who received olaparib maintenance versus placebo [10]. In addition, real-world data on post-progression showed a lower response rate to subsequent treatment with ORR of 22.2% even in patients with platinum-free interval > 12 months [15]. This indicates cross-resistance to chemotherapy after olaparib resistance and requires further clarification regarding the resistance mechanism for subsequent treatment.

However, other findings were observed with other PARPi (niraparib and rucaparib) without negatively affecting post-progression therapy. In the NOVA trial, maintenance niraparib significantly improved median chemotherapy-free interval (CFI) and median time to start of first subsequent therapy (TFST) compared with placebo in patients with/without germline *BRCA1/2* mutation [3]. In addition, niraparib did not negatively affect subsequent therapy (PFS2 − PFS1) [16]. In ARIEL3, rucaparib showed clinically meaningful delay of disease progression (CFI) without negative effects on post-progression (TFST, PFS2, and PFS2 − PFS1) [13]. However, the NOVA and ARIEL3 trials included *BRCA1/2* wild-type patients. The SOLO2 trial and the current study only included *BRCA1/2* mutant patients. Therefore, we must be careful with direct comparisons of these studies. Furthermore, real-world data on post-progression outcomes for niraparib and rucaparib are lacking. Further research is needed to clarify this issue.

Overall survival is the gold standard measure in oncology trials, including those for ovarian cancer. However, PARPi has not been found to hold significant OS benefit. As in the final analysis of the SOLO2 trial [14], olaparib did not show a statistically significant OS benefit in the current study (**Supplementary fig. S4**). In the NOVA trial, niraparib also did not demonstrate a long-term benefit in terms of OS [17]. The discrepancy between progression-free survival and OS is becoming an issue in the treatment of patients with EOC. Demonstrating OS improvement in EOC patients has been difficult due to crossover between groups and longer post-progression survival associated with subsequent therapies [18–20]. However, the poorer efficacy of subsequent chemotherapy after olaparib maintenance, which was consistent with the post-hoc analysis of the SOLO2 trial, could be a major reason. The exact mechanisms need to be explored in detail.

In this study, we had no data to suggest an optimal time-point at which to introduce olaparib for maintenance treatment of *BRCA1/2*-mutated, EOC patients. A number of changes in the genetic context and reversion mutations during PARPi maintenance could substantially influence treatment responsiveness, and these changes could be related with chemotherapy resistance. The poorer response to third-line chemotherapy after olaparib maintenance (especially if PFS1 > 12 months) could be evidence. However, we need further translational studies to elucidate this issue.

The optimal management of patients after progression despite PARPi is uncertain. Recently, the survival benefit for cytoreductive surgery in recurrent EOC has been reported [21]. In this study, a longer PFS2 - PFS1 was also found in recurrent patients who underwent secondary cytoreductive surgery (SCS) as third-line therapy. Although there was no significance due to the small sample size, SCS appears to be beneficial for patients who experience recurrence after olaparib maintenance (supplementary fig. S5). In general, treatment typically is guided by patient platinum sensitivity, with a platinum doublet used for sensitive patients with recurrent disease. In the current study, PFS2 − PFS1 was compared based on third-line chemotherapy regimen to explore effective chemotherapy agents for olaparib-resistant relapsed patients. Platinum-based chemotherapy showed better response than non-platinum-based chemotherapy in the olaparib and control groups. The study evaluated the best platinum-based regimen based on PFS2 − PFS1. Because PLD has shown enhanced response in *BRCA1/2*-mutated EOC patients [22,23], PFS2 − PFS1 was compared based on use of PLD in platinum-based chemotherapy; however, significant difference was not observed. Furthermore, significant difference was not observed regarding use of paclitaxel (Fig. 4). In addition to optimal subsequent chemotherapy, important issues remain regarding maintenance therapy after such treatment.

PARPi re-treatment as maintenance therapy is an ongoing strategy in the OReO trial (NCT03106987) [13], and PARPi re-treatment with anti-angiogenic agents and/or immunotherapy is underway in OPEB-01 (NCT04361370) [24] and NIRVANA-R (NCT04734665) [25] trials. To overcome PARPi resistance, various mechanisms have been suggested in preclinical and translational research [26]. The most common PARPi resistance mechanism is restoration of homologous recombination (HR). In particular, somatic reversion mutations have been shown to be clinically relevant in *BRCA1/2*-mutated ovarian cancer [27]. Furthermore, preclinical evidence of epigenetic reversion and reacquisition of DNA end resection to restore HR capacity has been shown in recent studies [28]. In addition to HR restoration, stabilisation of replication forks, diminished trapping of PARP-1, and drug efflux mechanism were suggested as other resistance mechanisms of PARPi [29,30]. However, further studies are required to reveal clinically relevant evidence other than somatic reversion. Accordingly, clinical trials are encouraged. Novel agents targeting DNA damage response are being investigated in ongoing clinical trials such as EFFORT (Wee1 kinase inhibitor, NCT03579316) [31] and CAPRI (ATR inhibitor, NCT03462342) [32].

The present study had several limitations including the retrospective, observational design and selection biases. Chemotherapy regimens, doses, and treatment modalities varied by physician and institution. Because focus in the current study was on *BRCA1/2*-mutated recurrent EOC patients, post-progression outcomes of *BRCA1/2* wild-type and/or front-line EOC patients were not evaluated and could be another limitation of this study.

In this retrospective, multicentre, observational study, a decrease in ORR and PFS with subsequent chemotherapy was observed among patients with *BRCA1/2* mutated tumours who relapsed after olaparib maintenance compared to a control group that did not receive maintenance olaparib. This tendency was more pronounced in patients who received olaparib >12 months. These findings need to be confirmed in larger studies due to the importance of decisions in clinical practice.

The broad utilization of PARPi maintenance therapy may contribute to the early emergence of chemotherapy resistance, limiting the efficacy of subsequent chemotherapy, and future prospective trials should address more innovative and selective treatment strategies.

Authors' contributions

1. Conceptualization: Jung-Yun Lee.
2. Data curation: Junsik Park, Se Ik Kim, Soo Young Jeong, Yup Kim.
3. Formal analysis: Junsik Park.
4. Funding acquisition: Jung-Yun Lee.
5. Investigation: Junsik Park.
6. Methodology: Se Ik Kim, Junsik Park, Jung-Yun Lee.
7. Project administration: Jung-Yun Lee.
8. Resources: Jung-Yun Lee, Jae-Weon Kim, Byoun-Gie Kim.
9. Software: Junsik Park.
10. Supervision: Jung-Yun Lee, Jae-Weon Kim, Byoun-Gie Kim.
11. Validation: Jung-Yun Lee.
12. Visualization: Junsik Park.
13. Writing – original draft: Junsik Park.
14. Writing – review & editing: Jung-Yun Lee, Se Ik Kim, Michael A. Bookman.
15. Approval of final manuscript: all authors.

Declaration of Competing Interest

Jung-Yun Lee reported institutional financial interest (clinical trials/contracted research) from AstraZeneca, Beigene, Bergenbio, Clovis Oncology, Eutilex, Immunogen, Janssen, Merck, MSD, Synthon, and TAKEDA; advisory board of AstraZeneca, Eisai, Merck, MSD, and TAKEDA. Jae-Weon Kim reported personal fee from Astra Zeneca, CMIC, and Janssen; advisory board of Boryung, GSK Korea, LG Pharma, MSD Korea, Takeda Korea, and Vifor Pharma. Byung-Gie Kim reported research fund from AstraZeneca, Cellid, and Utilex; advisory board of AstraZeneca, MSD, Esai, and Cellid. Michael A. Bookman reported participation on a Data Safety Monitoring Board or Advisory Board of Immunogen, AbbVie, Genetech-Roche, and Merk (Sharp & Dohme). All remaining authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary figures to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.02.002.

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