Olaparib Maintenance Monotherapy in Asian Patients with Platinum-Sensitive Relapsed Ovarian Cancer: Phase III Trial (L-MOCA)

Qinglei Gao[1], Jianqing Zhu[2], Weidong Zhao[3], Yi Huang[4], Ruifang An[5], Hong Zheng[6], Pengpeng Qu[7], Li Wang[8], Qi Zhou[9], Danbo Wang[10], Ge Lou[11], Jing Wang[12], Ke Wang[13], John Low[14], Beihua Kong[15], Abdul Malik Rozita[16], Lim Chun Sen[17], Rutie Yin[18], Xing Xie[19], Jihong Liu[20], Wei Sun[3], Jingya Su[21], Chunyi Zhang[21], Rongyu Zang[22], and Ding Ma[1]

ABSTRACT

Purpose: In patients with platinum-sensitive relapsed (PSR) ovarian cancer, olaparib maintenance monotherapy significantly improves progression-free survival (PFS) versus placebo. However, evidence in the Asian population is lacking. This is the first study to evaluate olaparib efficacy and tolerability exclusively in Asian patients with PSR ovarian cancer.

Patients and Methods: Considering the limited placebo effect and significant clinical benefit of olaparib in previous trials, and the rapid approval of olaparib in China, this phase III study was designed as an open-label, single-arm trial. Patients with high-grade epithelial PSR ovarian cancer were enrolled from country-wide clinical centers across China and Malaysia. Patients received oral olaparib (300 mg) twice daily until disease progression or unacceptable toxicity. Primary endpoint was median PFS (mPFS). Primary analysis of PFS using the Kaplan–Meier method was performed when data reached 60% maturity (clinicaltrials.gov NCT03534453).

Results: Between 2018 and 2020, 225 patients were enrolled, and 224 received olaparib; 35.7% had received ≥3 lines of chemotherapy, 35.3% had achieved complete response to their last line of platinum-based chemotherapy, and 41.1% had a platinum-free interval ≤12 months. At primary data cut-off (December 25, 2020), overall mPFS was 16.1 months; mPFS was 21.2 and 11.0 months in *BRCA*-mutated and wild-type *BRCA* subgroups, respectively. Adverse events (AE) occurred in 99.1% of patients (grade ≥3, 48.7%); 9.4% discontinued therapy due to treatment-related AEs.

Conclusions: Olaparib maintenance therapy was highly effective and well tolerated in Asian patients with PSR ovarian cancer, regardless of *BRCA* status. This study highlights the promising efficacy of olaparib in this Asian population.

See related commentary by Nicum and Blagden, p. 2201

Introduction

Most patients (80%) with ovarian cancer of any stage respond to platinum-based chemotherapy (first-line therapy), although the majority will eventually relapse (1). For patients with platinum-sensitive relapsed (PSR) advanced disease, chemotherapy effectiveness is limited and prognosis is poor (2–4). An alternative approach to enable consolidation and prolongation of tumor responses is to use an effective and well-tolerated oral antitumor agent; PARP inhibitors (PARPi) are a class of antitumor therapy that target cells defective in homologous recombination repair (HRR), leading to cell death via apoptosis following suppression of the DNA repair pathway (5, 6).

[1]Department of Gynecological Oncology, Tongji Hospital, Tongji Medical College Huazhong University of Science and Technology, Wuhan, China. [2]Department of Gynecologic Oncology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China. [3]Department of Gynecologic Oncology, Anhui Provincial Cancer Hospital, Hefei, China. [4]Department of Gynecologic Oncology, Hubei Cancer Hospital, Wuhan, China. [5]Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China. [6]Department of Gynecology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Beijing Cancer Hospital, Beijing, China. [7]Department of Gynecology Oncology, Tianjin Central Hospital of Gynecology Obstetrics, Tianjin, China. [8]Department of Gynecologic Oncology, Affiliated Cancer Hospital of Zhengzhou University, (Henan Cancer Hospital), Zhengzhou, China. [9]Department of Gynecologic Oncology, Chongqing University Cancer Hospital, Chongqing, China. [10]Department of Gynecologic Oncology, Liaoning Cancer Hospital, Shenyang, China. [11]Department of Gynecologic Oncology, Harbin Medical University Cancer Hospital, Harbin, China. [12]Department of Gynecologic Oncology, Hunan Cancer Hospital, Changsha, China. [13]Department of Gynecologic Oncology, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China. [14]Cancer Centre @ PHKL, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia. [15]Department of Obstetrics and Gynecology, Qilu Hospital of Shandong University, Jinan, China. [16]Clinical Oncology Unit, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. [17]Oncology Department, Hospital Sultan Ismail, Johor Bahru, Malaysia. [18]Department of Obstetrics and Gynecology, West China Second University Hospital, Chengdu, China. [19]Department of Gynecologic Oncology, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, China. [20]Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China. [21]Department of Medical Affairs, AstraZeneca, Shanghai, China. [22]Department of Gynaecologic Oncology, Zhongshan Hospital, Fudan University, Shanghai, China.

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

Current address for W. Zhao: Department of Obstetrics and Gynecology, The First Affiliated Hospital of UTSC, Anhui Provincial Hospital, Hefei, China.

Prior presentations: At the time of submission, this study had been accepted for presentation at the American Society of Clinical Oncology (ASCO) 2021 and the Chinese Society of Clinical Oncology (CSCO) 2021.

Corresponding Authors: Ding Ma, Department of Gynecological Oncology, Tongji Hospital, 1095 Jie Fang Avenue, Hankou, Wuhan 430030, China. Phone: 138-860-90620; E-mail: dma@tjh.tjmu.edu.cn; and Rongyu Zang, Department of Gynaecologic Oncology, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Xuhui District, Shanghai 200032, China. Phone: 139-016-13103; E-mail: zang.rongyu@zs-hospital.sh.cn

Clin Cancer Res 2022;28:2278–85

doi: 10.1158/1078-0432.CCR-21-3023

Translational Relevance

Olaparib, a PARP inhibitor, has shown encouraging efficacy in patients with platinum-sensitive relapsed (PSR) ovarian cancer in global phase III trials. However, evidence in the Asian population is lacking. In this phase III, open-label, single-arm trial, olaparib maintenance monotherapy was highly effective and well tolerated in Asian patients (>90% Chinese) with PSR ovarian cancer, regardless of their *BRCA* status. These results reinforce the current global evidence and strongly support use of olaparib in patients with PSR ovarian cancer in Asian clinical practice. This study also demonstrates good safety in the Asian population and shows that predictors of survival may include age at first dose, response to last chemotherapy, number of prior lines of therapy, and time to disease progression after second-to-last platinum-based chemotherapy; these prognostic factors require validation in subsequent clinical studies.

Olaparib is a potent, orally available PARPi that targets PARP-1, -2, and -3 to mediate this synthetic lethality in cells with homologous recombination deficiency (HRD), including those with *BRCA*1/2 mutations (7, 8). Previous PARPi clinical trials have demonstrated their efficacy in patients with PSR ovarian cancer (Supplementary Table S1; refs. 2, 9–13), and a meta-analysis of randomized controlled trials comprising patients with PSR ovarian cancer receiving PARPi maintenance treatment demonstrated a 74%, 76%, 66%, and 51% reduced risk of progression in patients with *BRCA* mutation (*BRCA*m), somatic *BRCA*m (s*BRCA*m), HRD, and wild-type status, respectively (14). Olaparib was the first PARPi approved by the European Medicines Agency (2014) for PSR disease due to the positive efficacy observed in the phase II Study19 trial, where patients receiving olaparib had a 65% reduction in risk of progression or death (2). Subsequent approval by the Food and Drug Administration (2017) was based on results from Study19, as well as the phase III SOLO2 trial (9), which corroborated the benefit of olaparib maintenance monotherapy in patients with *BRCA*1/2-mutated PSR ovarian cancer. In SOLO2, patients randomized to olaparib achieved a median progression-free survival (mPFS) of 19.1 months [95% confidence interval (CI), 16.3–25.7], compared with 5.5 months with placebo (95% CI, 5.2–5.8; ref. 9). In addition, treatment with olaparib was associated with a tolerable safety profile (2, 9).

In Study19, mPFS in the placebo arm was 4.8 months (2), while in the phase III NOVA trial of niraparib versus placebo in patients with/without g*BRCA*m, mPFS with placebo was 5.5 months in the g*BRCA*m cohort, and 3.9 months in the non-g*BRCA*m cohort (10). Together, these results demonstrated the poor outcomes achieved with placebo in patients with PSR ovarian cancer. Subsequent studies of niraparib and fuzuloparib in Chinese patients were consistent with observations from global studies (mPFS in placebo arm, 5.4–5.5 months; refs. 10, 12, 15). Due to the limited placebo effect and significant clinical benefit of olaparib in patients with PSR ovarian cancer, in addition to improved access to olaparib in China following express approval by the National Medical Products Administration, this phase III trial, L-MOCA, was designed as a single-arm study. The study aimed to evaluate the efficacy and tolerability of olaparib in Asian patients with PSR ovarian cancer, and as such was carried out exclusively in Asia. Here, we report the primary analysis of efficacy and safety from the L-MOCA study.

Patients and Methods

Patients and sites

Patients were recruited from 28 centers in China ($n = 22$) and Malaysia ($n = 6$), from which 267 patients were screened. Patients were eligible for inclusion if they were 18 years of age or older, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1, and had relapsed, high-grade serous or high-grade endometrioid epithelial ovarian cancer, including primary peritoneal and/or fallopian tube cancer. Patients had to have received at least two previous lines of platinum-based chemotherapy and achieved objective response [partial response (PR) or complete response (CR), according to modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1], with no evidence of rising cancer antigen 125 levels following the last platinum-based therapy prior to study enrollment. Patients were also required to have platinum-sensitive relapsed disease, defined as disease progression occurring at least 6 months after the last dose of platinum-based chemotherapy. For subgroup analysis of the primary endpoint, we grouped patients into partially platinum-sensitive (platinum-free interval of 6–12 months) and fully platinum-sensitive (platinum-free interval of more than 12 months; ref. 16). Patients gave consent to provide blood and/or tumor samples to confirm *BRCA*/HRR status as part of screening procedures. The limitation for detection of *BRCA* single-nucleotide variant or insertion/deletion was 5%, and HRR status was determined using next-generation sequencing on a panel of 72 genes (Supplementary Table S2). Samples were collected at any time following diagnosis, but prior to study entry. Normal organ and bone marrow function was required within 28 days prior to administration of study treatment. Patients were excluded if they had previously received PARPi treatment. Informed written consent was obtained from all study participants. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and any amendments were approved by the national regulatory authority and the respective ethics committees at each participating institution.

Design and treatment

In this open-label, single-arm, phase III study, eligible patients with high-grade epithelial PSR ovarian cancer received oral olaparib 300 mg (tablet formulation) twice daily. Olaparib treatment was initiated within 8 weeks after the last dose of chemotherapy until investigator-assessed disease progression or unacceptable toxicity. Patients could receive treatment beyond progression if the investigator deemed that the patient was experiencing benefit and did not meet other criteria for discontinuation. If required, toxicities could be managed by treatment interruptions and dose reductions. Repeat dose interruptions were permitted, as needed, for a maximum of 28 days on each occasion. Dose reduction [to 250 mg twice daily and then, if needed, to 200 mg twice daily (minimum dose)] was permitted, and permanent discontinuation of study treatment also allowed if the reduced dose was not tolerated. Dose escalation following a dose reduction was not permitted. After discontinuation of study treatment, patients were managed as per local clinical practice, and were followed until objective disease progression as defined by RECIST 1.1.

Study endpoints and assessments

The primary endpoint was investigator-assessed mPFS, defined as the time from date of first olaparib dose to date of disease progression or death. Clinical and objective radiologic tumor assessments were conducted according to RECIST 1.1 at baseline, every 12 weeks until Week 72, and every 24 weeks thereafter until objective disease progression.

After disease progression, patients were followed every 12 weeks for additional disease progression and survival analyses.

The primary endpoint was further examined by type of *BRCA* mutation [*BRCA*m; somatic (s*BRCA*m), g*BRCA*m, or wild-type (*BRCA*wt)]; HRR mutation status (HRRwt vs. HRRm); age group at first dose (<65 vs. ≥65 years); time to progression following last platinum-based therapy (>12 vs. 6–12 months); previous line of anticancer therapy (second- vs. third-line); and response to most recent platinum-based chemotherapy (CR vs. PR). Secondary endpoints included overall survival (OS), time to study treatment discontinuation, time to first subsequent treatment, time to second progression, and time to second subsequent treatment. Safety endpoints were assessed in terms of adverse events (AE) and serious AEs, laboratory analyses, and vital signs. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Hematology and biochemistry parameters were assessed on Day 1, 8, 15, 22, and 29, every 4 weeks until Week 72, and every 12 weeks thereafter.

Statistical analyses

The target sample size was 220 patients. Based on the *BRCA*m rate of 21%, an estimated 46 patients with *BRCA*m ovarian cancer were expected to be enrolled (17). The primary analysis was performed when the data reached approximately 60% maturity (i.e., 132 events of disease progression or death). Assuming an mPFS of 8.4 months (2), 132 progression events provide a 95% CI of 7.1 to 10.0 months, and assuming an mPFS of 19.1 months in patients with *BRCA*m (9), 27 progression events (60% of 46 patients with *BRCA*m) provide a 95% CI of 13.1 to 27.9 months. Data were summarized by descriptive statistics, while time-to-event endpoints were analyzed using the Kaplan–Meier method. All statistical analyses were conducted using SAS (version 9.4).

Data availability

The data underlying this article will be shared on reasonable request.

Results

Patients

Between March 2018 and December 2020, 225 patients were enrolled. At primary analysis data cut-off (December 25, 2020), 224 patients had received oral olaparib twice daily (full analysis set); one enrolled patient chose not to receive olaparib treatment (**Fig. 1**). Demographic and baseline characteristics are shown in **Table 1**. Briefly, all patients were female, median age was 54.0 years [interquartile range (IQR), 50.0–61.5], and most patients were from China [91.5% ($n = 205$), Malaysia 8.5% ($n = 19$)]. There were 31 (13.8%) patients with stage IV, and 152 (67.9%) with stage III disease at diagnosis. More than one third (35.7%) of patients had received ≥3 lines of chemotherapy, and 15 (6.7%) patients had received prior treatment with bevacizumab. To their last line of chemotherapy, 145 (64.7%) and 79 (35.3%) patients achieved PR and CR, respectively. More than half (58.9%) the patients had a platinum-free interval >12 months, while 40.2% and 0.9% of patients had a platinum-free interval of 6 to 12 months and <6 months, respectively (**Table 1**). There were 60 (26.8%) patients who had undergone secondary cytoreductive surgery. Overall, 47.3% ($n = 106$) were positive for *BRCA*m [s*BRCA*m 6.3% ($n = 14$); g*BRCA*m 41.1% ($n = 92$)], while 52.2% ($n = 117$) were *BRCA*wt, and one patient's *BRCA* status was unknown. For HRRm status, there were 128 (57.1%) patients with HRRm, 95 (42.4%) patients with HRRwt, and one patient's HRR status was unknown.

Efficacy

After a median follow-up of 15.5 months, we performed the primary efficacy analysis upon 139 (62.1%) investigator-assessed events of

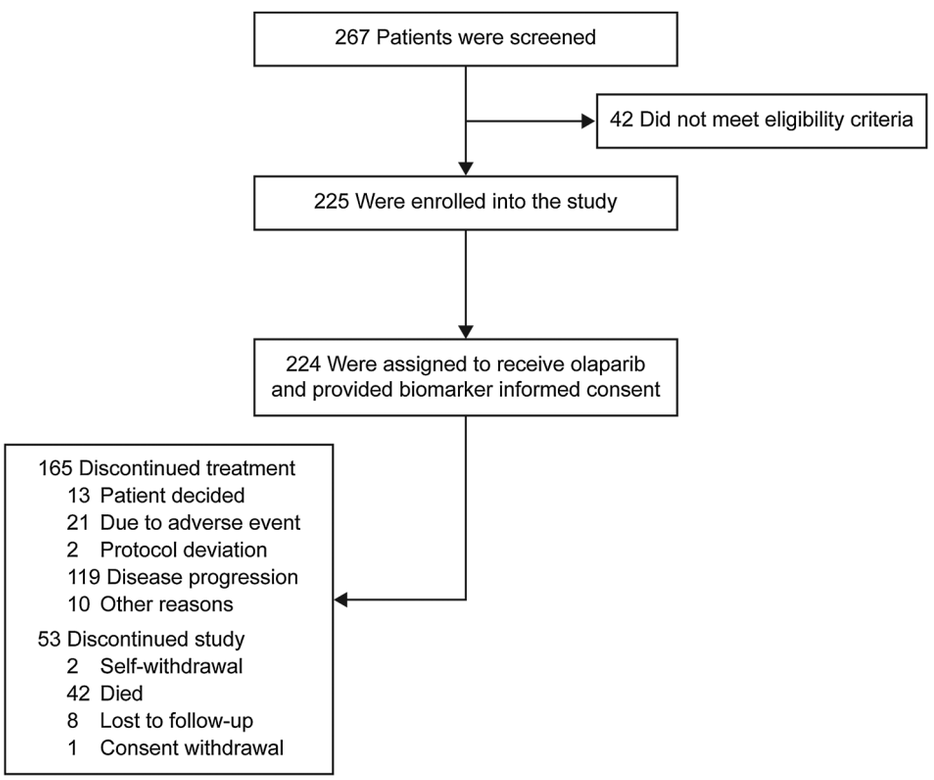

Figure 1.
Patient disposition.

Table 1. Baseline characteristics and patient demographics[a].

	Olaparib ($n = 224$)
Age, years, median (IQR)	54.0 (50.0–61.5)
Female, *n* (%)	224 (100.0)
Country, *n* (%)	
China	205 (91.5)
Malaysia	19 (8.5)
Body mass index (kg/m^2), mean (SD)	23.86 (3.7)
Body mass index groups, *n* (%)	
≤24 kg/m^2	121 (54.0)
>24 kg/m^2	103 (46.0)
ECOG performance status score, *n* (%)	
0	154 (68.8)
1	70 (31.3)
Primary tumor location, *n* (%)	
Ovary	203 (90.6)
Fallopian tube	10 (4.5)
Peritoneum	5 (2.2)
Other	6 (2.7)
FIGO stage at initial diagnosis, *n* (%)	
Stage I	9 (4.0)
Stage II	26 (11.6)
Stage III	152 (67.9)
Stage IV	31 (13.8)
Unknown	6 (2.7)
Histology type, *n* (%)	
Serous	215 (96.0)
Endometrioid	7 (3.1)
Other	2 (0.9)
BRCA mutation status, *n* (%)	
wt	117 (52.2)
Germline	92 (41.1)
*BRCA*1	64 (28.6)
*BRCA*2	28 (12.5)
Somatic	14 (6.3)
*BRCA*1	9 (4.0)
*BRCA*2	5 (2.2)
Unknown[b]	1 (0.4)
HRR mutation status, *n* (%)	
HRRm	128 (57.1)
HRRwt	95 (42.4)
Unknown	1 (0.4)
Age group at first dose, *n* (%)	
<65 years	187 (83.5)
≥65 years	37 (16.5)
Last line of anticancer therapy, *n* (%)	
2nd line	144 (64.3)
3rd line	52 (23.2)
4th line and beyond	28 (12.5)
Prior bevacizumab use, *n* (%)	15 (6.7)
Response to last line of platinum therapy, *n* (%)	
CR	79 (35.3)
PR	145 (64.7)
Platinum-free interval, *n* (%)	
<6 months	2 (0.9)
6–12 months	90 (40.2)
>12 months	132 (58.9)
Cytoreductive surgery (prior to enrollment), *n* (%)	60 (26.8)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, The International Federation of Gynecology and Obstetrics; HRR, homologous recombination repair; IQR, interquartile range; m, mutation; PR, partial response; SD, standard deviation; wt, wild type.
[a]Data presented for patients in full analysis set.
[b]Status unknown due to test failure in both blood and tumor samples.

disease progression or death [$n = 136$ (60.7%) patients had disease progression, $n = 3$ (1.3%) died prior to disease progression). Overall mPFS was 16.1 months (95% CI, 13.3–18.3; **Fig. 2A**), and the estimated 6-month and 12-month PFS rates were 76.0% (95% CI, 69.8–81.2) and 57.1% (95% CI, 50.2–63.5), respectively. Subgroup analysis showed that mPFS was 21.2 months (95% CI, 16.4–24.9) and 11.0 months (95% CI, 8.3–15.8) in patients with *BRCA*m and *BRCA*wt, respectively. Analysis by *BRCA*m subgroup (**Table 2**) revealed that mPFS was 16.1 months (95% CI, 5.9–not evaluable) and 21.4 months (95% CI, 16.5–24.9) in patients with s*BRCA*m and g*BRCA*m, respectively (**Fig. 2B**). Patients with HRRm versus those with HRRwt status had an mPFS of 18.3 (95% CI, 14.5–24.1) versus 13.3 months (95% CI, 8.3–16.5; **Table 2**).

Subgroup analysis of the primary endpoint by other baseline clinical characteristics (**Table 2**) showed that patients who were aged <65 years at first dose had an mPFS of 15.8 months (95% CI, 11.0–18.2), and those who were ≥65 years of age had an mPFS of 19.7 months (95% CI, 11.1–22.2). Patients who achieved CR to last chemotherapy prior to study enrollment had an mPFS of 19.7 months (95% CI, 15.8–22.2), compared with 13.9 months (95% CI, 11.0–16.6) in patients who achieved PR. In patients who were previously treated with second- and third-line anticancer treatment, mPFS was 18.0 months (95% CI, 15.8–22.1) and 8.8 months (95% CI, 6.8–13.9), respectively. Patients who progressed after 12 months versus 6–12 months after second-to-last platinum-based chemotherapy had an mPFS of 20.9 months (95% CI, 16.2–24.1) versus 9.3 months (95% CI, 8.3–14.1).

Secondary endpoint analyses ($N = 224$) showed that median time to first subsequent treatment or death was 19.0 months (95% CI, 16.7–21.8); at 12 months, 89.1% (95% CI, 84.2–92.6) of patients were free from subsequent treatment or death. Median time from first dose to second progression was 26.2 months (95% CI, 23.6–not reached), and the 12-month second progression-free rate was 87.1% (95% CI, 81.8–91.0). Median time to study treatment discontinuation was 13.8 months (95% CI, 9.8–16.2). The percentage of patients remaining on treatment at 12 months was 50.8% (95% CI, 44.1–57.1). At primary data cut-off, median time to second subsequent treatment or death and median OS had not been reached.

Safety

The incidence of AEs of any CTCAE grade was 99.1%; the most common AEs of any grade were anemia (76.4%), nausea (54.0%), and leukopenia (24.1%; **Table 3**). AEs of grade 3 or higher were reported in 48.7% of patients; among these, anemia (25.0%), decreased neutrophil count (14.3%), and decreased platelet count (4.9%) were most common. Serious AEs occurred in 57 (25.4%) patients, of which 39 (17.4%) cases were treatment-related. There were three cases (1.3%) of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), two of which occurred during the treatment period (Supplementary Table S3).

Median duration of olaparib exposure was 300.5 days (IQR, 169.0–552.0), and median daily dose of olaparib was 589.5 mg (IQR, 508.1–596.5). Treatment-related AEs led to dose reduction in 100 (44.6%) patients, and to treatment discontinuation in 21 (9.4%) patients.

Discussion

In this open-label, single-arm, phase III study, oral olaparib monotherapy in Asian patients (91.5% Chinese) with PSR ovarian cancer led to a promising duration of PFS per investigator assessment of the primary endpoint (overall mPFS 16.1 months; 95% CI, 13.3–18.3).

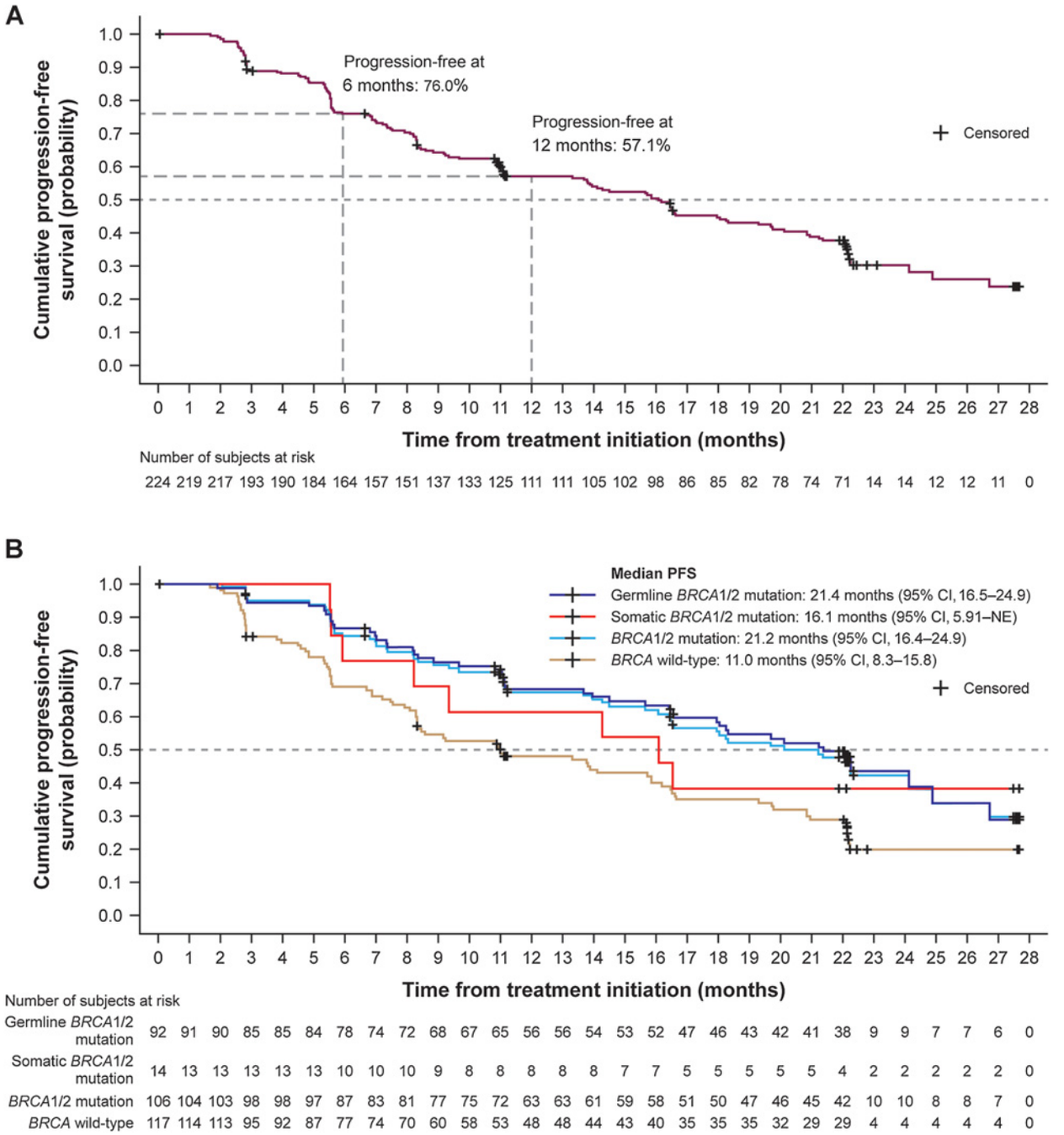

Figure 2.

Kaplan–Meier estimates of PFS (full analysis set). **A,** Overall analysis and **B,** subgroup analysis of *BRCA* mutation type. Primary efficacy analysis was performed after 139 investigator-assessed events of disease progression or death (60.7% of patients had disease progression, $n = 136$; 1.3% died prior to disease progression, $n = 3$). CI, confidence interval; NE, not evaluable.

Furthermore, oral olaparib monotherapy was well tolerated in this patient population. In Study19, overall mPFS in patients with PSR ovarian cancer (with/without g*BRCA*m) randomized to olaparib was 8.4 months (2). It is worth noting that an olaparib capsule was used in Study19, and we speculate that this discrepancy may explain some of the differences observed between these two studies, but data directly comparing olaparib treatment formulations are not currently available. Future studies should investigate the role olaparib formulation plays in patient outcomes, allowing better interpretation of these clinical data. We also note the higher proportion of patients with germline *BRCA*2 mutations in L-MOCA compared with Study19 (12.5% vs. 4.4%, respectively). While evidence in the PSR ovarian

Table 2. Subgroup analysis of mPFS.

	Patients with event, *n* (%)	mPFS (95% CI)
BRCA mutation status		
*BRCA*m	56 (25.0)	21.2 (16.4–24.9)
Germline *BRCA*m	48 (21.4)	21.4 (16.5–24.9)
Somatic *BRCA*m	8 (3.6)	16.1 (5.9–NE)
*BRCA*wt	82 (36.6)	11.0 (8.3–15.8)
HRR mutation status		
HRRm	69 (30.8)	18.3 (14.5–24.1)
HRRwt	69 (30.8)	13.3 (8.3–16.5)
Age group at first dose		
<65 years	117 (52.2)	15.8 (11.0–18.2)
≥65 years	22 (9.8)	19.7 (11.1–22.2)
Last line of previous anticancer therapy		
2nd line	82 (36.6)	18.0 (15.8–22.1)
3rd line	38 (17.0)	8.8 (6.8–13.9)
4th line and beyond	19 (8.5)	13.3 (5.5–20.1)
Time to disease progression on second to last platinum-based chemotherapy		
>12 months	70 (31.3)	20.9 (16.2–24.1)
6–12 months	67 (29.9)	9.3 (8.3–14.1)
Best response		
CR	43 (19.2)	19.7 (15.8–22.2)
PR	96 (42.9)	13.9 (11.0–16.6)

Abbreviations: CI, confidence interval; m, mutation; CR, complete response; HRR, homologous recombination repair; NE, not evaluable; PR, partial response; wt, wild type.

cancer population is lacking, a sub-analysis of the SOLO1 trial (olaparib maintenance in newly diagnosed ovarian cancer) demonstrated increased PARPi sensitivity among *BRCA*2 compared with *BRCA*1 patients (18). The reason for the higher proportion of patients with *BRCA*2 in L-MOCA compared with Study19 may be due to a higher rate of *BRCA*2 among Asian patients (19); however, the rate of germline *BRCA*2 mutation in L-MOCA did not exceed that reported for the international NOVA (37.0%) and SOLO2 (29.6%) trials (9, 10). In the NORA trial (Chinese patients with PSR, 2 prior lines, with/without g*BRCA*m), overall investigator-assessed mPFS was 18.3 months in the niraparib arm (12), and in an interim analysis of the phase III FZOCUS-2 trial, Chinese patients with PSR ovarian cancer (with/without g*BRCA*m) randomized to fuzuloparib achieved an mPFS of 12.9 months (Supplementary Table S1; ref. 15). Head-to-head studies are needed in order to draw direct comparisons between the efficacy of different PARPis overall, and in patient subpopulations.

Table 3. Summary of AEs.

n (%)[a]	Olaparib (*n* = 224)	
Any AE	222 (99.1)	
Grade ≥3	109 (48.7)	
Treatment-related AE	220 (98.2)	
Grade ≥3	96 (42.9)	
Any serious AE	57 (25.4)	
Treatment-related serious AE	39 (17.4)	
Any AE leading to treatment discontinuation	22 (9.8)	
Treatment-related AE leading to treatment discontinuation	21 (9.4)	
Any AE occurring in >10% of patients	**Grade 1 or 2**	**Grade 3 or 4**
Anemia	115 (51.4)	56 (25.0)
Nausea	120 (53.6)	1 (0.4)
Leukopenia	46 (20.5)	8 (3.6)
Vomiting	52 (23.2)	5 (2.2)
Neutropenia	30 (13.4)	12 (5.4)
Decreased appetite	41 (18.3)	0 (0.0)
Cough	26 (11.6)	0 (0.0)
Nasopharyngitis	26 (11.6)	0 (0.0)
Thrombocytopenia	18 (8.1)	6 (2.7)

Abbreviation: AE, adverse event.
[a]Percentages are based on the number of subjects in the full analysis set.

In L-MOCA, investigator-assessed mPFS in patients with *BRCA*m was 21.2 months. In SOLO2, mPFS among patients with *BRCA*m randomized to olaparib was 19.1 months (9). Among patients in the g*BRCA*m subgroup of L-MOCA, mPFS was 21.4 months, while in the phase II and III fuzuloparib studies, mPFS in patients with g*BRCA*m randomized to fuzuloparib was 10.3 and 12.9 months, respectively (15, 20). mPFS in s*BRCA*m and *BRCA*wt subgroups of the current study (i.e., non-g*BRCA*m) were 16.1 and 11.0 months, respectively. In the phase IIIb, single-arm OPINION study, in which patients with non-g*BRCA*m PSR ovarian cancer received olaparib maintenance therapy, mPFS was 9.2 months (21). The NORA study reported mPFS of 11.1 months following niraparib treatment in a non-g*BRCA*m (including s*BRCA*m) population (12); however, this was assessed by a blinded and independent central review (22). Overall, patients with *BRCA*m in the L-MOCA study achieved a greater PFS benefit compared with patients with *BRCA*wt (21.2 months vs. 11.0 months, respectively). While our study was designed as a single-arm study in part due to the proven efficacy of olaparib compared with placebo (2, 6, 9), previous randomized controlled trials in patients with PSR ovarian cancer have shown superior outcomes in patients receiving PARPi treatment compared with placebo, regardless of *BRCA* status (2, 10, 12, 15). The clinical benefit of olaparib seen in this study reinforces that observed in global studies, and supports its use in patients with PSR ovarian cancer, including Asian patients, regardless of *BRCA* status. Another subgroup analysis revealed that patients with HRRm had a numerically longer mPFS (18.3 months) than patients with HRRwt (13.3 months). There is limited evidence supporting the accuracy of HRR as a biomarker for response to olaparib treatment, and so an exploratory analysis of the association between HRD status and olaparib efficacy will be performed to investigate HRD biomarker status in PSR ovarian cancer.

The baseline demographics and clinical characteristics reported here show that this study population is largely representative of the PSR ovarian cancer population seen in clinical practice. We performed subgroup analyses of mPFS according to certain baseline characteristics to better understand predictors of survival in this population, particularly in those with poor prognosis. Patients who achieved CR following previous platinum-based chemotherapy had a longer mPFS than those whose best response was PR. In Study19, CR was found to be a significant prognostic factor for longer PFS (HR, 0.46; $P < 0.001$; ref. 2). This trend was also observed in the NORA trial (Chinese patients), where those who achieved CR and PR to last platinum-based therapy had a 74% and 66% reduction in risk of progression from niraparib (versus placebo), respectively (12). We also found that patients who received second-line treatment prior to study enrollment appeared to have a longer mPFS than those who had received three previous lines of therapy (18.0 vs. 8.8 months). All patients in NORA had previously received second-line therapy (12), thus, together, showing that this patient subgroup may derive substantial PFS benefit from PARPi therapy. Finally, we showed that platinum-free interval may be an important factor in patient selection and for determining

prognosis. A previous study demonstrated that a platinum-free interval >12 months was associated with improved treatment outcomes (23). In our study, patients who had a platinum-free interval >12 months versus 6 to 12 months had a longer mPFS. While a substantial proportion of patients enrolled in L-MOCA had potentially negative prognostic factors, the promising overall mPFS achieved in this study suggests that patients with PSR ovarian cancer treated in real-world clinical practice (24, 25) can gain substantial PFS benefit with olaparib.

The toxicity profile of olaparib in this study was largely consistent with previous international studies (2, 9). The majority of patients (99.1%) in L-MOCA had ≥1 AEs (Study19, 95.6%; SOLO2, 98.0%; refs. 2, 9). In the current study, the most common AEs of any grade were anemia, nausea, and leukopenia; in Study19 and SOLO2 these were nausea, fatigue, and vomiting (2, 9). Consistent with previous global olaparib trials (2, 9), the majority of AEs in L-MOCA were grade 1 or 2. Comparison of PARPi trials (not head-to-head) suggests grade 3/4 hematologic AEs, in particular thrombocytopenia, are more likely to occur with niraparib or rucaparib than with olaparib (26). Headache, dizziness, and insomnia were infrequently reported in our study (8.5%, 10.3%, and 6.3%, respectively). In contrast, these neurologic toxicities were more common with niraparib (up to 25.9%, 16.6%, and 28.8%, respectively; refs. 10, 12) and rucaparib (18%, 15%, and 14%, respectively; ref. 11). The incidence of MDS and AML in this study (1.3%) was lower than in SOLO2 (2%; ref. 9), and consistent with other PARPi trials (NOVA, 1.4%; ARIAL3, 1.0%; refs. 10, 11). Notably, in L-MOCA, MDS was regularly monitored after treatment discontinuation. In addition, dose reduction was required for 44.6% of patients; this was higher than in Study19 and SOLO2, where 22.8% and 25% of patients treated with olaparib, respectively, required a dose reduction (2, 9). However, these data were lower than those reported in the NORA trial, in which 93.8% of patients had individualized niraparib dosing, and 60% of patients required a dose reduction due to treatment-emergent AEs (12). Moreover, 67% of patients in the NOVA trial required a dose reduction (10).

In SOLO2, median OS in olaparib-treated patients was 51.7 months (95% CI, 41.5–59.1), suggesting there may be potential long-term survival benefits associated with olaparib in PSR ovarian cancer (27). We are looking forward to reporting the long-term survival benefit of olaparib in Asian patients with PSR ovarian cancer in L-MOCA, as well as reporting results of an exploratory mPFS analysis in HRD subgroups in this Asian PSR ovarian cancer population.

The study had two key limitations. First, the single-arm study design prevented comparison of the primary endpoint to a control. Second, the data may not be fully representative of the Asian population, because the study only enrolled patients in China and Malaysia.

Conclusion

The findings from this open-label, phase III study demonstrate that olaparib maintenance monotherapy is associated with promising efficacy and is well tolerated in an Asian population with advanced PSR ovarian cancer, independent of *BRCA* status. These data reinforce global evidence that strongly support the use of olaparib in the treatment of PSR ovarian cancer in Asian clinical practice.

Authors' Disclosures

A.M. Rozita reports grants from Novartis, Zeria Pharmaceutical Co. Ltd, and AstraZeneca outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

Q. Gao: Conceptualization, resources, writing–original draft, project administration, writing–review and editing. **J. Zhu:** Resources, data curation, writing–original draft, writing–review and editing. **W. Zhao:** Resources, data curation, writing–original draft, writing–review and editing. **Y. Huang:** Resources, data curation, writing–original draft, writing–review and editing. **R. An:** Resources, data curation, writing–original draft, writing–review and editing. **H. Zheng:** Resources, data curation, writing–original draft, writing–review and editing. **P. Qu:** Resources, data curation, writing–original draft, writing–review and editing. **L. Wang:** Resources, data curation, writing–original draft, writing–review and editing. **Q. Zhou:** Resources, data curation, writing–original draft, writing–review and editing. **D. Wang:** Resources, data curation, writing–original draft, writing–review and editing. **G. Lou:** Resources, data curation, writing–original draft, writing–review and editing. **J. Wang:** Resources, data curation, writing–original draft, writing–review and editing. **K. Wang:** Resources, data curation, writing–original draft, writing–review and editing. **J. Low:** Resources, data curation, writing–original draft, writing–review and editing. **B. Kong:** Resources, data curation, writing–original draft, writing–review and editing. **A.M. Rozita:** Resources, data curation, writing–original draft, writing–review and editing. **L.C. Sen:** Resources, data curation, writing–original draft, writing–review and editing. **R. Yin:** Resources, data curation, writing–original draft, writing–review and editing. **X. Xie:** Resources, data curation, writing–original draft, writing–review and editing. **J. Liu:** Resources, data curation, writing–original draft, writing–review and editing. **W. Sun:** Resources, data curation, writing–original draft, writing–review and editing. **J. Su:** Methodology, writing–original draft, project administration, writing–review and editing. **C. Zhang:** Formal analysis, methodology, writing–original draft, writing–review and editing. **R. Zang:** Resources, methodology, writing–original draft, project administration, writing–review and editing. **D. Ma:** Conceptualization, resources, investigation, methodology, writing–original draft, project administration, writing–review and editing.

Acknowledgments

This work was supported by AstraZeneca China, who provided funding for study design, data collection, analysis, interpretation, medical writing, and decision to submit the manuscript. The authors would like to thank the participants, the collaborating general practitioners, and other clinical staff. Editorial assistance in manuscript preparation was provided by Tim Stentiford, BSc (Hons), PGDip SciComm, CMPP; Anita Abeygoonesekera, BSc (Hons), BPharm (Hons); and Alice Carruthers BSc (Hons), PhD, of Nucleus Global, Shanghai, China, funded by AstraZeneca in accordance with Good Publication Practice 3 guidelines.

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.

Received August 24, 2021; revised October 27, 2021; accepted February 2, 2022; published first February 7, 2022.

References

1. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. Lancet 2009;374:1371–82.
2. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382–92.
3. Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, Vasey PA, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28:3323–9.
4. Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699–707.

5. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly (ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci USA 2011;108:3406–11.
6. Zheng F, Zhang Y, Chen S, Weng X, Rao Y, Fang H. Mechanism and current progress of poly (ADP-ribose) polymerase (PARP) inhibitors in the treatment of ovarian cancer. Biomed Pharmacother 2020;123:109661.
7. Lynparza [package insert]. AstraZeneca. Wilmington, DE: 2014.
8. Bochum S, Berger S, Martens UM. Olaparib. Recent Results Cancer Res 2018; 211:217–33.
9. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomized, placebo-controlled, phase III trial. Lancet Oncol 2017;18:1274–84.
10. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive recurrent ovarian cancer. N Engl J Med 2016;375:2154–64.
11. Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomized, double-blind, placebo-controlled, phase III trial. Lancet 2017;390:1949–61.
12. Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol 2021;32:512–21.
13. Li N, Zhang Y, Wang J, Zhu J, Wang L, Wu X, et al. Fuzuloparib maintenance therapy in patients with platinum-sensitive recurrent ovarian carcinoma: a multicenter, randomized, double blind, placebo-controlled, phase III trial. Presented at: 2021 Society of Gynecologic Oncology Virtual Annual Meeting on Women's Cancer. Abstract 115572021.
14. Tomao F, Bardhi E, Di Pinto A, Sassu CM, Biagioli E, Petrella MC, et al. PARP inhibitors as maintenance treatment in platinum-sensitive recurrent ovarian cancer: an updated meta-analysis of randomized clinical trials according to BRCA mutational status. Cancer Treat Rev 2019;80:101909.
15. Li N, Zhang Y, Wang J, Zhu J, Wang L, Wu X, et al. Fuzuloparib maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer: a multicenter, randomized, double-blind, placebo-controlled, phase III trial. Presented at: 2021 Society of Gynecologic Oncology Virtual Annual Meeting on Women's Cancer Abstract115572021. Gynecol Oncol 2021;162:S57–8.
16. Wilson MK, Pujade-Lauraine E, Aoki D, Mirza MR, Lorusso D, Oza AM, et al. Fifth ovarian cancer consensus conference of the gynecologic cancer intergroup: recurrent disease. Ann Oncol 2017;28:727–32.
17. Madariaga A, Lheureux S, Oza AM. Tailoring ovarian cancer treatment: implications of BRCA1/2 mutations. Cancers 2019;11:416.
18. DiSilvestro P, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Efficacy of maintenance olaparib for patients with newly diagnosed advanced ovarian cancer with a BRCA mutation: subgroup analysis findings from the SOLO1 trial. J Clin Oncol 2020;38:3528–37.
19. Kim H, Choi DH. Distribution of BRCA1 and BRCA2 mutations in Asian patients with breast cancer. J Breast Cancer 2013;16:357–65.
20. Li N, Bu H, Liu J, Zhu J, Zhou Q, Wang L, et al. An open-label, multicenter, single-arm, phase II study of fluzoparib in patients with germline BRCA1/2 mutation and platinum-sensitive recurrent ovarian cancer. Clin Cancer Res 2021;27: 2452–8.
21. Poveda A, Lheureux S, Colombo N, Cibula D, Lindemann K, Weberpals JI, et al. Olaparib maintenance monotherapy for non-germline BRCA1/2-mutated (non-gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): phase IIIb OPINION primary analysis. J Clin Oncol 2021;39:5545.
22. Stone A, Gebski V, Davidson R, Bloomfield R, Bartlett JW, Sabin A. Exaggeration of PFS by blinded, independent, central review (BICR). Ann Oncol 2019;30: 332–8.
23. Rodriguez-Freixinos V, Fariñas-Madrid L, Gil-Martin M, Barretina-Ginesta P, Romeo M, Villacampa G, et al. Chemotherapy and PARP inhibitors in heavily pretreated BRCA1/2 mutation ovarian cancer (BMOC) patients. Gynecol Oncol 2019;152:270–7.
24. Agarwal A, Baghmar S, Dodagoudar C, Qureshi S, Khurana A, Vaibhav V, et al. PARP inhibitor in platinum-resistant ovarian cancer: single-center real-world experience. JCO Glob Oncol 2021;7:506–11.
25. Ledermann JA, Raja FA, 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 2018;29:iv259.
26. LaFargue CJ, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol 2019;20:e15–28.
27. Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomized, placebo-controlled, phase III trial. Lancet Oncol 2021;22:620–31.