Olaparib and niraparib as maintenance therapy in patients with newly diagnosed and platinum-sensitive recurrent ovarian cancer: A single-center study in China

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Abstract

Background: Poly adenosine-diphosphate-ribose polymerase (PARP) inhibitors (PARPi) have been approved to act as first-line maintenance (FL-M) therapy and as platinum-sensitive recurrent maintenance (PSR-M) therapy for ovarian cancer in China for >5 years. Herein, we have analyzed the clinical-application characteristics of olaparib and niraparib in ovarian cancer-maintenance therapy in a real-world setting to strengthen our understanding and promote their rational usage.

Methods: A retrospective chart review identified patients with newly diagnosed or platinum-sensitive recurrent ovarian cancer, who received olaparib or niraparib as maintenance therapy at Sichuan Cancer Hospital between August 1, 2018, and December 31, 2021. Patient medical records were reviewed. We grouped and analyzed patients based on the type of PARPi they used (the olaparib group and the niraparib group) and the line of PARPi maintenance therapy (the FL-M setting and the PSR-M setting). The primary endpoint was the 24-month progression-free survival (PFS) rate.

Results: In total, 131 patients (olaparib: n = 67, 51.1%; niraparib: n = 64, 48.9%) were enrolled. Breast cancer susceptibility genes (*BRCA*) mutations (*BRCA*m) were significantly less common in the niraparib group than in the olaparib group [9.4% (6/64) *vs*. 62.7% (42/67), P <0.001], especially in the FL-M setting [10.4% (5/48) *vs*. 91.4% (32/35), P <0.001]. The 24-month progression-free survival (PFS) rates in the FL-M and PSR-M settings were 60.4% and 45.7%, respectively. In patients with *BRCA*m, the 24-month PFS rates in the FL-M and PSR-M settings were 62.2% and 72.7%, respectively.

Conclusions: Olaparib and niraparib were effective in patients with ovarian cancer without any new safety signals except for skin pigmentation. In patients with *BRCA*m, the 24-month PFS of the PARPi used in the PSR-M setting was even higher than that used in the FL-M setting.

Keywords: PARP inhibitor; Ovarian cancer; *BRCA* mutation; Real-world study; First-line maintenance therapy; Platinum-sensitive recurrent maintenance therapy; PFS

Introduction

Ovarian cancer remains the leading cause of fatal gynecologic malignancy, with 80% of the cases being diagnosed at an advanced stage (III or IV) with distant metastases.[1,2] Standard treatments include optimal debulking surgery and platinum-based chemotherapy with a response rate of approximately 80%. Despite a favorable initial response to platinum and taxane therapy, effectiveness wanes over time, and 70–80% of the patients relapse within 2 years.[3] It is rare to achieve a clinical cure for recurrent ovarian cancer, with fatality usually occurring due to treatment toxicities and acquired drug resistance.[4,5]

The clinical management of recurrent ovarian cancers depends on diverse factors, including platinum-free interval (PFI), adverse events (AEs), performance status, histology, and disease burden.[6] Novel Poly adenosine-diphosphate-ribose polymerase (PARP) inhibitors (PARPi) have been widely recognized for their antitumor activity in various types of cancers. When used as maintenance

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therapy, PARPi substantially prolongs remission and prevents disease progression in newly diagnosed advanced and platinum-sensitive recurrent (PSR) ovarian cancer.[7,8] In 2017, The United States Food and Drug Administration (FDA) approved the PARPi, olaparib and niraparib, as maintenance therapies based on the promising results observed in several phase II and III clinical trials conducted on recurrent ovarian cancer.[9,10] In Augest 2018, China's National Medical Products Administration (NMPA) approved the use of olaparib as a PSR maintenance (PSR-M) therapy in patients with ovarian cancer. In December 2019, NMPA approved olaparib as a first-line maintenance (FL-M) therapy in patients with breast cancer susceptibility genes (*BRCA*) mutations (*BRCA*m) and niraparib as a PSR-M therapy.[11] In September 2020, niraparib was approved as a FL-M therapy, without limitation to *BRCA* status.

Randomized clinical trials (RCTs) on niraparib (NOVA trial, NORA trial) reported a median progression-free survival (mPFS) ranging from approximately 7 months to 21 months, showing efficacy in both patients with germline *BRCA* (g*BRCA*)-mutated and non-g*BRCA*-mutated PSR ovarian cancers.[12,13] RCTs evaluating olaparib as the PSR-M therapy (Study 19 trial and SOLO-2 trial) in patients with ovarian cancer showed mPFS ranging from approximately 8 months to 19 months.[14,15] RCTs such as SOLO-1 trial, PRIMA trial, PRIME trial, PAOLA-1 trial, and ATHENA-mono trial showed longer progression-free survival (PFS) benefits with PARPi as FL-M therapy than with recurrent maintenance therapy. Recent reports have also shown a potential overall survival (OS) benefit trend when PARPi is used as FL-M therapy. Real-world evidence (RWE) for olaparib and niraparib also exhibited similar survival outcomes compared to phase II and III clinical trials.[16–18]

PARPi maintenance therapy is generally well tolerated. Anemia and fatigue are the most common AEs observed with olaparib maintenance therapy, whereas thrombocytopenia is common with niraparib therapy.[12–15] Although the respective regulatory approvals are available based on clinical trials, there have been few prosopective and comparative evaluations between olaparib and niraparib to directly weigh their clinical merits as maintenance agents following chemotherapy in patients with ovarian cancer. Hence, this study was performed to analyze the clinical-application characteristics of PARPi, olaparib and niraparib, as maintenance therapies for ovarian cancer in real-world settings to strengthen our understanding of these drugs and promote their rational clinical usage.

Methods

Study design and patients

This single-center retrospective study was conducted at Sichuan Cancer Hospital, China. The criteria for enrollment were as follows: (1) Inclusion criteria: patients diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who received olaparib or niraparib as maintenance therapy between August 1, 2018, and December 31, 2021. (2) Exclusion criteria: patients with incomplete clinicopathological data and those who did not receive a pathological diagnosis in our hospital. This study was approved by the Institutional Ethics Committee of the Sichuan Cancer Hospital (No. scchec-02-2022-088).

There are many similarities in the indications of olaparib and niraparib. For example, both can be used for the FL-M therapy in *BRCA*m patients and the PSR-M therapy in all patients (not limited to *BRCA* status). The difference is that niraparib can also be used as the FL-M therapy for *BRCA* wide-type (*BRCA*wt) patients. So we grouped and analyzed patients based on the type of PARPi they used (the olaparib group and the niraparib group) and the line of PARPi maintenance therapy (the FL-M setting and the PSR-M setting).

Baseline characteristics of the patients, including age, body mass index (BMI), number of lines of chemotherapy, time from the end of the last chemotherapy session, and duration of maintenance therapy, were collected. Data on the clinical presentation of the patients, such as histological type, International Federation of Gynecology and Obstetrics (FIGO) stage, *BRCA*m status, homologous recombination deficiency (HRD) status, treatment response before maintenance therapy, cancer antigen 125 (CA125) status, and comorbidities, were also collected.

Dosage regimen and clinical evaluation

Patients received niraparib with an individualized starting dose of either 200 mg or 300 mg (only if the body weight >77 kg and baseline platelet count $\geq 150 \times 10^3/\mu L$) once daily orally. Olaparib was orally administered at a standard dose of 300 mg twice daily. Dose reduction of olaparib and niraparib, or dose interruption, was allowed upon the occurrence of drug-related AEs.

Outcome assessment

Disease assessments were conducted at the end of chemotherapy and every 8–12 weeks until disease progression. All enrolled patients were followed up until June 9, 2023, or death. The primary endpoint was PFS, defined as the period from the end of the last chemotherapy session to disease progression or death from any cause. The PFS rates were assessed at 12 months and 24 months. Efficacy indicators were defined and evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) V1.1. AEs were assessed at therapy initiation and every visit until the end of the study and were graded according to Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Statistical analyses

Descriptive statistics were used to describe continuous variables as medians and interquartile ranges (IQRs), or means and standard deviations. Data were compared using the independent *t*-test. Categorical variables are described as numbers and percentages and compared

using the Cochran–Mantel–Haenszel-χ^2 (CMH-χ^2) test or Fisher's exact test. Kaplan–Meier curves with log-rank tests were used to perform survival analysis with a 95% confidence interval (CI). Hazard ratios (HRs) were calculated using the stratified Cox proportional hazards model with stratification factors based on key baseline and clinical characteristics. All reported *P*-values were two-sided, and values <0.05 were considered statistically significant. All statistical analyses were performed using R version 4.2.0 software (R Foundation, Vienna, Austria).

Results

Baseline characteristics

A total of 131 patients were enrolled in this study. Of these, 83 (63.4%) and 48 (36.6%) received FL-M and PSR-M therapy, respectively. According to the PARPi categorization, olaparib and niraparib were prescribed to 67 (51.1%) and 64 (48.9%) patients, respectively. The median patient age was 50 years (IQR 47–56 years) in the olaparib group and 52 years (IQR 48–59 years) in the niraparib group.

In the FL-M setting, 37 patients had *BRCA*m, 43 patients had *BRCA*wt, and 3 patients had unknown *BRCA* status. In the PSR-M setting, 11 patients had *BRCA*m, 22 had *BRCA*wt, and 15 had unknown *BRCA* status. Significantly lower *BRCA*m rate [9.4% (6/64) *vs*. 62.7% (42/67), $\chi^2 = 52.359$, $P < 0.001$] and high-grade serous carcinoma rate [76.6% (49/64) *vs*. 91.0% (61/67), $\chi^2 = 5.100$, $P = 0.024$] were observed in the niraparib group than in the olaparib group. In the FL-M population, the *BRCA*m rate was 10.4%(5/48) in the niraparib group and 91.4% (32/35) in the olaparib group ($\chi^2 = 61.950$, $P < 0.001$). Other demographic and clinical characteristics were well balanced in both groups [Table 1].

Table 1: Pathological, treatment, and mutation characteristics of patients included in the study.

	Total (*N* = 131; Olaparib: 67; Niraparib: 64)				Total (*N* = 131; FL-M: 83; PSR-M: 48)	
Characteristics	**Olaparib**	**Niraparib**	**Statistics**	***P*-value**	**FL-M**	**PSR-M**
Disease diagnosis			0.362*	0.926		
Fallopian tube cancer	4 (6.0)	5 (7.8)			5 (6.0)	4 (8.3)
Ovarian cancer	59 (88.1)	56 (87.5)			75 (90.4)	40 (83.3)
Peritoneal cancer	4 (6.0)	3 (4.7)			3 (3.6)	4 (8.3)
Histopathological type			5.100	0.024		
High-grade serous carcinoma	61 (91.0)	49 (76.6)			71 (85.5)	39 (81.3)
Others†	6 (9.0)	15 (23.4)			12 (14.5)	9 (18.8)
FIGO staging			4.598*	0.107		
I–II	7 (10.4)	11 (17.2)			14 (16.9)	4 (8.3)
III–IV	56 (83.6)	53 (82.8)			67 (80.7)	42 (87.5)
Unknown	4 (6.0)	0 (0)			2 (2.4)	2 (4.2)
Line of PARPi treatment			7.305	0.007		
FL-M	35 (52.2)	48 (75.0)			–	–
Recurrent maintenance	32 (47.8)	16 (25.0)			–	–
BRCA status			52.359	<0.001		
*BRCA*m	42 (62.7)	6 (9.4)			37 (44.6)	11 (22.9)
*BRCA*wt	13 (19.4)	52 (81.3)			43 (51.8)	22 (45.8)
Not checked/status unknown	12 (17.9)	6 (9.4)			3 (3.6)	15 (31.3)
Treatment response before maintenance therapy			3.937*	0.145		
CR	30 (44.8)	35 (54.7)			53 (63.9)	12 (25.0)
PR	36 (53.7)	25 (39.1)			29 (34.9)	32 (66.7)
Others‡	1 (1.5)	4 (6.3)			1 (1.2)	4 (8.3)
CA125 normal before maintenance therapy			2.815*	0.288		
Yes	61 (91.0)	62 (96.9)			82 (98.8)	41 (85.4)
No	3 (4.5)	2 (3.1)			0	5 (10.4)
Not checked/status unknown	3 (4.5)	0 (0)			1 (1.2)	2 (4.2)
Dose adjustment			3.370*	0.180		
No	27 (40.3)	36 (56.3)			40 (48.2)	23 (47.9)
Yes	35 (52.2)	25 (39.1)			41 (49.4)	19 (39.6)
Unknown	5 (7.5)	3 (4.7)			2 (2.4)	6 (12.5)

Data shown as *n* (%). *Fisher's exact test was used for comparing (CMH-χ^2 was used for others). †Four cases of clear cell carcinoma, four cases of low-grade serous carcinoma, two cases of high-grade endometrioid carcinoma, one case of low-grade endometrioid carcinoma, one case of high-grade mucinous carcinoma, one case of hepatoid adenocarcinoma, and eight cases of adenocarcinoma (specific type unknown). ‡After re-evaluation, there were three cases with stable disease and two cases with PD. *BRCA*m: *BRCA* mutation; *BRCA*wt: *BRCA* wide-type; CA125: Cancer antigen 125; CMH-χ^2: Cochran–Mantel–Haenszel-χ^2; CR: Complete response; FIGO: International Federation of Gynecology and Obstetrics; FL-M: First-line maintenance; IDS: Interval debulking surgery; NACT: Neoadjuvant chemotherapy; PARPi: PARP inhibitors; PD: Progressive disease; PDS: Primary debulking surgery; PR: Partial response; PSR-M: Platinum-sensitive recurrent maintenance; SD: Stable disease; –: Not applicable.

The median time from the end of the last chemotherapy to the initiation of PARPi maintenance therapy was 45.5 days (IQR 35.5–56.3 days) and 39.0 days (IQR 31.0–54.5 days), and the median duration of treatment was 19.6 months (IQR 8.0–29.3 months) and 22.6 months (IQR 11.7–29.6 months) for patients treated with niraparib and olaparib, respectively.

Efficacy

The median follow-up time was 29.7 months (IQR 24.9–36.1 months) in the intent-to-treat (ITT) population, 29.1 months (IQR 24.5–36.1 months) in the FL-M setting, and 31.0 months (IQR 26.2–37.2 months) in the PSR-M setting.

The 24-month PFS rates of the FL-M and PSR-M settings were 60.4% (95% CI, 50.6–72.2%) and 45.7% (95% CI, 33.5–62.2%), respectively. In the FL-M setting, the 24-month PFS rates of the olaparib *BRCA*m and niraparib *BRCA*wt subgroups were 65.9% (95% CI, 50.6–85.9%) and 59.7% (95% CI, 46.2–77.1%), respectively. In the PSR-M setting, the 24-month PFS rates of the *BRCA*m and *BRCA*wt subgroups were 72.7% (95% CI, 50.6–100%) and 45.5% (95% CI, 28.8–71.8%), respectively [Table 2].

The immature mPFS of FL-M therapy was 39.7 months [95% CI, 25.7 months–not available (NA)] for ITT [Figure 1], NA (95% CI, 23.3 months–NA) for the niraparib *BRCA*wt subgroup, and 39.7 months (95% CI, 39.7 months–NA) for the olaparib *BRCA*m subgroup [Figure 2A, B]. For recurrent maintenance, the mPFS was 21.0 months (95% CI, 14.5 months–NA) for ITT [Figure 1], NA (95% CI, NA–NA) for the *BRCA*m subgroup, and 22.7 months (95% CI, 14.3 months–NA) for the *BRCA*wt subgroup [Figure 2C].

We analyzed the differences in benefits by initiating FL-M therapy at different time points after the end of the last chemotherapy session. Maintenance therapy was initiated in 34, 30, and 19 patients within 6 weeks, 6–8 weeks, and >8 weeks after the last chemotherapy session, respectively. The mPFS of ≤6 weeks, >6 weeks and ≤8 weeks, and >8 weeks was 37.4 months (95% CI, 23.3 months–NA), 39.7

Table 2: Number of PFS events and PFS rate.

Treatment setting	Group	12-month PFS rate (%)	24-month PFS rate (%)
FL-M	ITT population (n = 83)	79.5	60.4
	Olaparib *BRCA*m (n = 32)	90.6	65.9
	Niraparib *BRCA*wt (n = 40)	72.5	59.7
PSR-M	ITT population (n = 48)	72.9	45.7
	*BRCA*m (n = 11)	90.9	72.7
	*BRCA*wt (n = 22)	77.3	45.5

*BRCA*m: *BRCA* mutation; *BRCA*wt: *BRCA* wild type; FL-M: First-line maintenance; ITT: Intent-to-treat; mPFS: median progression-free survival; PFS: Progression-free survival; PSR-M: Platinum-sensitive recurrent maintenance.

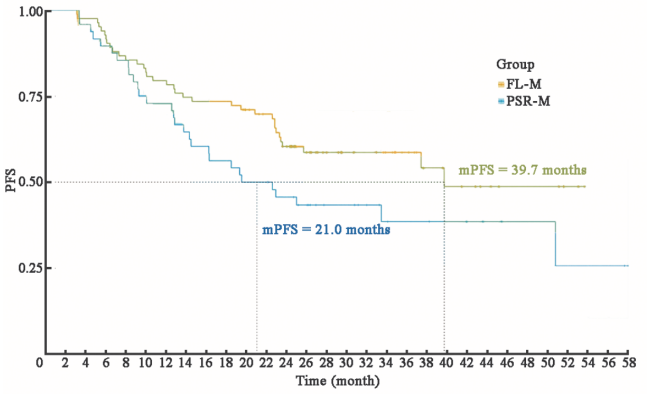

Figure 1: Kaplan–Meier estimates of the mPFS of the intention-to-treat population in FL-M and PSR-M. FL-M: First-line maintenance; mPFS: median progression-free survival; PFS: Progression-free survival; PSR-M: Platinum-sensitive recurrent maintenance.

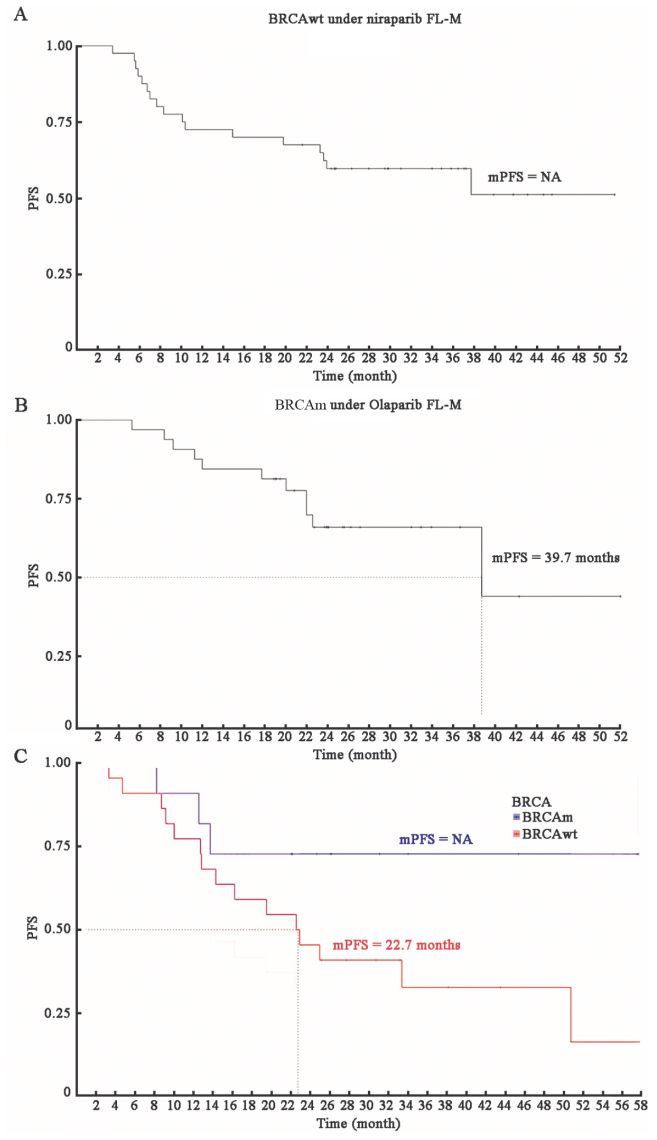

Figure 2: Kaplan–Meier estimates for mPFS of patients with ovarian cancer with (A) *BRCA*wt under niraparib FL-M, (B) *BRCA*m under olaparib FL-M, and (C) PSR-M in the *BRCA* subgroup. *BRCA*m: *BRCA* mutation; *BRCA*wt: *BRCA* wide-type; FL-M: First-line maintenance; mPFS: median progression-free survival; PFS: Progression-free survival; PSR-M: Platinum-sensitive recurrent maintenance.

months (95% CI, 22.8 months–NA), and NA (95% CI, 22.8 months–NA), respectively ($P = 0.62$) [Figure 3].

AEs

Among the hematological AEs, neutropenia of any grade was the most common AE observed in both the olaparib and niraparib groups [53.7% (36/67) *vs.* 68.8% (29/64)]. Anemia was the most common grade 3 or 4 AE in both groups [15.6% (10/64) *vs.* 20.9% (14/67)], followed by thrombocytopenia [14.1% (9/64) *vs.* 7.5% (5/67)] and neutropenia [7.8% (5/64) *vs.* 9.0% (6/67)]. The other most common non-hematological AEs were skin pigmentation [79.7% (51/64)] in patients treated with niraparib and nausea [65.7% (44/67)] in those treated with olaparib [Table 3]. One acute lymphoblastic leukemia, in the FL-M niraparib group, and one acute myeloid leukemia, in the PSR-M olaparib group, were observed during the study. No new safety signals other than skin pigmentation were identified.

Dose interruption occurred in 34.4% (22/64) of the patients in the niraparib group and in 37.3% (25/67) of the patients in the olaparib group. Only a small proportion of the patients were intolerant to olaparib [4.5% (3/67)] or niraparib [4.7% (3/64)].

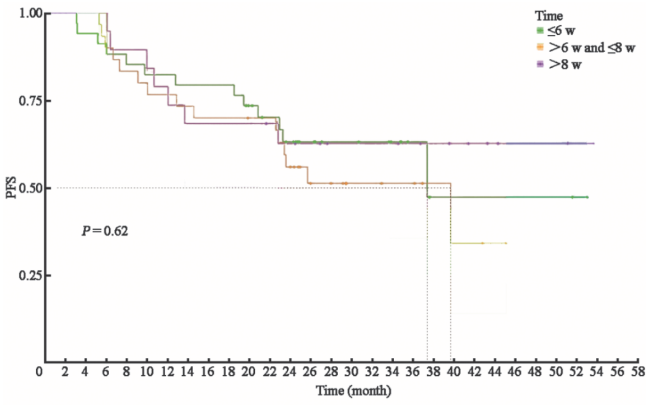

Figure 3: Kaplan–Meier estimates of mPFS of patients with newly diagnosed ovarian cancer with respect to different PARPi initiation time from the end of the last chemotherapy session. mPFS: median progression-free survival; PARPi: PARP inhibitors.

Discussion

This is the first real-world study to include olaparib and niraparib FL-M and PSR-M treatments. Real-world studies are important to generate effective data on the diverse natural conditions that differ from the controlled conditions of RCTs. It is reported that only approximately 31–69% of patients in the actual clinical practice have the same situation as the participants in RCTs.[8] This real-world study assessed olaparib and niraparib as maintenance therapy in patients with ovarian cancer, and the results showed that in the ITT population, both PARPi regimens significantly improved the prognosis of patients with ovarian cancer.

PARPi is recommended by the National Comprehensive Cancer Network (NCCN) guidelines for maintenance therapy in patients with newly diagnosed stage II–IV ovarian cancer.[19] In this study, there were six cases of stage I, of which five were FL-M and one was PSR-M. Five cases receiving FL-M therapy were identified as one case of hepatoid adenocarcinoma (*BRCA*m), one case of adenocarcinoma with unknown specific type (*BRCA*m), two cases of clear cell carcinoma, and one case experienced tumor rupture during the first laparoscopic surgery and underwent re-staging surgery 12 days later. Considering the particularity of the patient's condition, their willingness to choose FL-M, and having no other options other than observation, PARPi maintenance therapy was administered.

PFS improvement by PARPi

Considering the RCTs (SOLO-2 trial/Opinion trial/ARIEL-3 trial/NORA trial) in the PSR setting, current evidence supporting olaparib, niraparib, and rucaparib appears to be largely equivalent, regardless of the *BRCA*m status.[13,15,20] The mPFS for PSR *BRCA*m ovarian cancer is approximately 20 months, which is significantly longer than that of patients with *BRCA*wt (approximately 9 months) in this setting. The baseline characteristics were largely different in the RCTs that evaluated FL-M in ovarian cancer. For instance, the SOLO-1 trial only included patients with *BRCA*m among which 44% received primary debulking

Table 3: Incidence of AEs observed in niraparib and olaparib groups.

	Olaparib ($N = 67$)			Niraparib ($N = 64$)		
AE	**Grade 1**	**Grade 2**	**Grade ≥3**	**Grade 1**	**Grade 2**	**Grade ≥3**
Hematological AEs						
Anemia (Hb <8 g/dL)	11 (16.4)	8 (11.9)	14 (20.9)	10 (15.6)	11 (17.2)	10 (15.6)
Neutropenia (neutrophil count <1500/mm^3)	16 (23.9)	14 (20.9)	6 (9.0)	24 (37.5)	15 (23.4)	5 (7.8)
Thrombocytopenia (platelet count <50,000)	14 (20.9)	4 (6.0)	5 (7.5)	12 (18.8)	8 (12.5)	9 (14.1)
Other adverse reactions						
Nausea	39 (58.2)	4 (6.0)	1 (1.5)	26 (40.6)	10 (15.6)	0
Vomit	25 (37.3)	1 (1.5)	0	13 (20.3)	2 (3.1)	0
Insomnia	20 (29.9)	7 (10.5)	0	20 (31.3)	14 (21.9)	6 (9.4)
Rash	8 (11.9)	0	0	15 (23.4)	1 (1.6%)	1 (1.6)
Skin pigmentation	13 (19.4)	1 (1.5)	–	43 (67.2)	8 (12.5)	–

Data shown as *n* (%). AEs: Adverse events; Hb: Hemoglobin; N: Total number.

surgery and achieved complete resection,[21] whereas the PRIMA trial excluded those patients.[22] The recently published outcomes of the PRIME and ATHENA-MONO trials did not exclude surgical conditions or biomarkers, but both studies showed similar efficacy outcomes.[23,24] After a median follow-up of 26.1 months for rucaparib and 27.5 months for niraparib, the mPFS of patients with ITT were between 20 months and 24 months, while the mPFS of patients with *BRCA*m was NA. Despite variations in the HRD status, the PFS of the placebo arm was similar in both the ATHENA trial (9.9 months) and PRIME trial (11.0 months) trials. Patients with *BRCA*wt with HRD achieved an mPFS of 20.3 months and 24.8 months in the rucaparib and niraparib arms, respectively.[23,24] From the recently published data on RCTs, it can be understood that all the PARPi drugs approved appear to have identical potential in identical patient populations. However, the previous studies of PARPi showed that patients with *BRCA*m have the longest PFS benefit, followed by patients with *BRCA*wt/HRD and HRP. Nevertheless, in our study, the prognosis of the patients in each group appeared to be better than those in the clinical trials mentioned above. This may be because we adopted a full process management mode with dedicated personnel in charge of patients undergoing PARPi maintenance therapy, resulting in relatively lower treatment interruption, dose reduction, and treatment termination rates.

Olaparib and niraparib have different indications for FL-M. Olaparib was the first PARPi recommended by the NCCN guidelines for FL-M, but only for patients with *BRCA*m. Subsequently, niraparib was recommended for FL-M in the entire population, including *BRCA*m and *BRCA*wt. So, in the early stage of the clinical application of PARPi, the olaparib FL-M group was mainly composed of patients with *BRCA*m, while the niraparib group was mainly composed of patients with *BRCA*wt. Although there was a significant difference in baseline *BRCA* status (patients with *BRCA*m receiving niraparib = 10.4%; patients with *BRCA*m receiving olaparib = 91.4%) in the FL-M setting in our study, the PFS rates at 24 months in the olaparib *BRCA*m group (65.9%) and in the niraparib *BRCA*wt group (59.7%) were similar. The follow-up time in this study was not sufficiently long, which could have influenced the similar PFS rates in both the treatment groups. Moreover, most patients with newly diagnosed ovarian cancer were well maintained under treatment, at least during a median follow-up time of 29.1 months. In recurrent settings, a significant difference was observed between the two subgroups, with patients with *BRCA*wt achieving an mPFS of 22.7 months while that in patients with *BRCA*m was not reached. Although the number of patients was small, the observed mPFS was consistent with the trend observed in previous RCTs, and the observed mPFS appears to be longer. Furthermore, this study showed that patients with ovarian cancer gained longer PFS benefits with FL-M than PSR-M. However, in the patients with *BRCA*m, the effectiveness of PARPi used in PSR-M is not inferior to that used in FL-M, and the 24-month PFS rates of the FL-M and PSR-M settings were 62.2% and 72.7%, respectively. According to our analysis, the possible reasons include the high sensitivity to PARPi in patients with *BRCA*m and a relatively low tumor burden before maintenance therapy. Among the 37 cases in the FL-M setting with *BRCA*m, only 2 had tumor lesions larger than 2 cm, which were 3.1 cm and 2.5 cm, respectively. Among the 11 cases in the PSR-M setting with *BRCA*m, only 2 had tumor lesions larger than 2 cm, which were 3.0 cm and 2.5 cm, respectively. However, the sample size was small; so, further prospective studies with larger sample sizes are needed for clarification.

OS controversy of PARPi

The impact of PARPi on OS has been a hot topic in recent years. The OS detriment observed in non-*BRCA*m populations from NOVA trial and ARIEL3 trial have led to the restriction of the label for niraparib and rucaparib in the *gBRCA*m and *tBRCA* PSR settings, respectively, last year in the United States.[25,26] In the NOVA trial, at the final OS analysis, niraparib maintenance treatment showed no OS benefit *vs*. placebo in the non-*gBRCA*m (n = 350) cohort (mOS 31.0 months *vs*. 34.8 months; HR, 1.06, 95% CI, 0.81–1.37).[27] In the ARIEL3 trial, final OS analysis in the *BRCA*wt/loss of heterozygosity (LOH) high (n = 158) and *BRCA*wt/LOH low (n = 161) subgroups reported HR greater than one for rucaparib *vs*. placebo (*BRCA*wt/LOH high median OS 36.8 months *vs*. 44.7 months; HR, 1.28, 95% CI, 0.841–1.948; *BRCA*wt/LOH low median OS 28.6 months *vs*. 32.6 months; HR, 1.15, 95% CI, 0.784–1.695).[28] Based on the OS data seen in the non-*BRCA*m populations from NOVA trial and ARIEL3 trial, the FDA is concerned that all the PARPi represent a class of products associated with increased safety risk when used for the maintenance treatment of ovarian cancer in those without a *BRCA*m in the PSR setting. Therefore, the FDA has restricted the indications for niraparib as PSR-M therapy only for germline *BRCA*m patients and olaparib as PSR-M therapy only for germline or somatic *BRCA*m patients in the United States.[29] At present, the indications of olaparib and niraparib for the PSR-M population have not changed in other countries including China. In future, we will continue to explore the OS of the FL-M and PSR-M settings.

Initiation time of PARPi

In several, large, phase III clinical trials, PARPi maintenance therapy was generally initiated 6–8 weeks after the end of the last chemotherapy. However, there is a lack of consensus regarding its real-world applications. In this study, no significant difference was observed among the three groups that started maintenance therapy at different intervals after chemotherapy, indicating that patients may achieve similar benefits regardless of the initiation time of maintenance therapy.

AEs of PARPi

RCT evidence has shown that hematological AEs are the most commonly observed AEs associated with PARPi. Any grade of thrombocytopenia appears to be more frequent for niraparib than for olaparib.[12,15] After starting the dose adjustment, the NORA study showed a

significant improvement in hematological AEs, especially thrombocytopenia.[13] This is consistent with our observation where most patients were initiated with 200 mg once daily, and only 39.1% of patients in the niraparib group experienced dose reductions, which is lower than that in the olaparib group. In addition, the incidences of some grade 3 or higher AEs were lower than those in the RCTs; for example, grade 3 or higher neutropenia in the niraparib group was 7.8% in our study and 12.8–20.3% in the RCTs,[12,13,22,23] which may be related to not only patient management but also to recall bias in the retrospective study. However, the RWE for olaparib showed anemia and neutropenia as the most frequent AEs resulting in dose interruption (6.8% and 1.6%, respectively) and reduction (8.0% and 1.6%, respectively). Nausea and vomiting (8.4%) were the other AEs frequently reported among patients receiving olaparib.[18] A similar hematological AE profile was observed in this study, with neutropenia and anemia being the most commonly reported AEs. Among non-hematological AEs, skin pigmentation was the most common AE in patients receiving niraparib. The frequency of nausea was higher in those receiving olaparib. It should be noted that in this study, skin pigmentation was higher in patients receiving niraparib; hence, supportive therapy may be recommended for patients with ovarian cancer undergoing niraparib maintenance therapy.

Limitations of the study

The uncontrolled bias over *BRCA*m in the enrolled patients could be a limitation of the present study. Hence, comparative studies on olaparib and niraparib as maintenance therapies with equally comparable numbers of patients according to the *BRCA* subgrouping may be required to determine the differences in efficacy outcomes. Furthermore, a longer follow-up period is needed to observe the long-term survival benefits.

This study portrayed the real-world treatment landscape and was not designed to compare the effects of olaparib and niraparib. Thus, it cannot offer guidance to patients regarding which one to choose, as all medication choices are grounded in the prevailing guidelines.

Similar promising efficacy outcomes and manageable AEs observed in this real-world study signify that both olaparib and niraparib are potential therapeutic agents for the maintenance of patients with ovarian cancer. Both olaparib and niraparib were effective in patients with ovarian cancer without any new safety signals except for skin pigmentation. The interval between the end of chemotherapy and the start of maintenance therapy did not appear to affect the PARPi efficacy. In patients with *BRCA*m, the 24-month PFS of the PARPi used in the PSR-M therapy was even higher than that used in the FL-M.

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Conflicts of interest

None.

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