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ORIGINAL ARTICLE

Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OReO/ENGOT-ov38): a phase IIIb trial

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Background: Poly(ADP-ribose) polymerase (PARP) inhibitor maintenance therapy is the standard of care for some patients with advanced ovarian cancer. We evaluated the efficacy and safety of PARP inhibitor rechallenge.

Patients and methods: This randomized, double-blind, multicenter trial (NCT03106987) enrolled patients with platinum-sensitive relapsed ovarian cancer who had received one prior PARP inhibitor therapy for ≥18 and ≥12 months in the BRCA-mutated and non-BRCA-mutated cohorts, respectively, following first-line chemotherapy or for ≥12 and ≥6 months, respectively, following a second or subsequent line of chemotherapy. Patients were in response following their last platinum-based chemotherapy regimen and were randomized 2 : 1 to maintenance olaparib tablets 300 mg twice daily or placebo. Investigator-assessed progression-free survival (PFS) was the primary endpoint.

Results: Seventy four patients in the BRCA-mutated cohort were randomized to olaparib and 38 to placebo, and 72 patients in the non-BRCA-mutated cohort were randomized to olaparib and 36 to placebo; >85% of patients in both cohorts had received ≥3 prior lines of chemotherapy. In the BRCA-mutated cohort, the median PFS was 4.3 months with olaparib versus 2.8 months with placebo [hazard ratio (HR) 0.57; 95% confidence interval (CI) 0.37-0.87; $P = 0.022$]; 1-year PFS rates were 19% versus 0% (Kaplan–Meier estimates). In the non-BRCA-mutated cohort, median PFS was 5.3 months for olaparib versus 2.8 months for placebo (HR 0.43; 95% CI 0.26-0.71; $P = 0.0023$); 1-year PFS rates were 14% versus 0% (Kaplan–Meier estimates). No new safety signals were identified with olaparib rechallenge.

Conclusions: In ovarian cancer patients previously treated with one prior PARP inhibitor and at least two lines of platinum-based chemotherapy, maintenance olaparib rechallenge provided a statistically significant, albeit modest,

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PFS improvement over placebo in both the BRCA-mutated and non-BRCA-mutated cohorts, with a proportion of patients in the maintenance olaparib rechallenge arm of both cohorts remaining progression free at 1 year.
Key words: olaparib, PARP inhibitor, rechallenge, platinum-sensitive relapsed ovarian cancer, OReO/ENGOT-ov38

INTRODUCTION

Maintenance therapy with a poly(ADP-ribose) polymerase (PARP) inhibitor (PARPi) is a standard of care for patients with ovarian cancer in the platinum-sensitive relapsed disease setting[1-3] and also more recently for newly diagnosed patients with advanced disease,[4-8] particularly for those newly diagnosed patients with a *BRCA1* and/or *BRCA2* mutation (BRCAm) or whose tumors test homologous recombination deficiency (HRD)-positive.

In PARPi-naive patients with platinum-sensitive relapsed ovarian cancer (PSROC), PARPi maintenance therapy provided a statistically significant progression-free survival (PFS) benefit,[1-3] with a clinically meaningful overall survival (OS) benefit seen with maintenance olaparib in patients with a BRCAm in this setting.[9] Although the greatest PFS benefit occurred in patients with BRCAm,[1-3] PFS benefit was also observed in patients without a BRCAm regardless of their HRD status.[2,3,10-13] In patients with newly diagnosed advanced ovarian cancer, PARPi maintenance therapy also provided a substantial PFS benefit,[4-7,14] with a clinically meaningful OS benefit seen with maintenance olaparib in patients with BRCAm[15] and with maintenance olaparib plus bevacizumab in patients with HRD-positive tumors.[16] The patients showing the greatest PFS prolongation were those with BRCAm[4,14] or whose tumors tested HRD-positive with or without BRCAm.[5-7] However, it is unknown if patients will benefit from rechallenge with PARPi maintenance therapy at relapse.

The randomized, double-blind, placebo-controlled OReO/ENGOT-ov38 study (NCT03106987) is the first phase III trial to address the question of whether rechallenge with maintenance olaparib provides benefit to patients with PSROC who are in response to platinum-based chemotherapy and have previously received a PARPi.

METHODS

Study design and participants

OReO/ENGOT-ov38 was a randomized, double-blind, placebo-controlled, multicenter phase IIIb trial. Eligible patients had relapsed histologically diagnosed non-mucinous epithelial ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer. Patients were eligible if they had serous, endometrioid, or transitional cell tumors or mixed histology if one of these subtypes was predominant.

There was no limit to the number of prior lines of chemotherapy patients could have received. The most recent line of chemotherapy had to comprise at least four cycles of platinum-based chemotherapy, and bevacizumab was not permitted as part of this regimen. Patients were platinum sensitive and in complete or partial radiological response to their most recent platinum-based chemotherapy regimen. Eligibility criteria were amended to permit inclusion of patients with no evidence of disease following cytoreductive surgery (if optimal cytoreductive surgery was conducted before chemotherapy) and without evidence of rising serum CA-125 levels.

Based on their previously documented BRCAm status, patients were enrolled in one of two cohorts: a BRCAm cohort (defined as a confirmed germline or somatic BRCAm by local testing) or a non-BRCAm cohort (defined as BRCAm-negative by local germline testing, recognizing some of these patients could have undetected somatic BRCAm).

Patients were required to have received one prior course of maintenance therapy with any PARPi in any prior line of therapy. The required duration of prior PARPi exposure differed between the two cohorts, with a minimum duration of prior PARPi exposure of $\geq$18 months following first-line chemotherapy or $\geq$12 months following a second or subsequent line of chemotherapy for the BRCAm cohort and $\geq$12 months following first-line chemotherapy or $\geq$6 months following a second or subsequent line of chemotherapy for the non-BRCAm cohort (see the Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.09.3110, for further information).

The trial was carried out in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and the AstraZeneca policy of bioethics,[17] and according to ENGOT Model C,[18] under the auspices of an independent data monitoring committee. All patients provided written informed consent.

Treatment

Randomization occurred within 8 weeks of the last dose of platinum-based chemotherapy and was stratified by use of bevacizumab before the most recent line of chemotherapy (yes versus no) and the number of prior lines of platinum-based chemotherapy ($\leq$3 versus $\geq$4 lines). Patients were randomized (2 : 1) to olaparib tablets 300 mg twice daily or placebo. Patients known to be unable to tolerate olaparib 300 mg twice daily, based on prior use, could start on a dosage of 250 mg twice daily.

Treatment continued until objective radiological disease progression (RECIST version 1.1) or as long as the patient experienced benefit and did not meet other discontinuation criteria.

Outcomes

The primary endpoint was PFS, defined as the time from randomization to the date of investigator-assessed objective radiological disease progression according to RECIST version 1.1, or death.

A prespecified exploratory subgroup analysis evaluated PFS according to HRD status in the non-BRCAm cohort based on retrospective testing of archival tissue from the primary tumor carried out at Myriad Genetic Laboratories, Inc., Salt Lake City, USA using the MyChoice® HRD Plus assay.

Prespecified subgroup analyses evaluated PFS according to relevant clinical factors, and prespecified sensitivity analyses assessed the possible effects of time assessment bias, attrition bias, and adjustment for prognostic factors on PFS.

Secondary endpoints included time from randomization to first subsequent therapy or death (TFST); time from randomization to second subsequent therapy or death (TSST); OS (defined as time from randomization to death from any cause); health-related quality of life (HRQoL); and safety and tolerability.

The HRQoL endpoint was the change from baseline in the Functional Assessment of Cancer Therapy—Ovarian (FACT-O) Trial Outcome Index (TOI) score.[19] TOI scores range from 0 to 100, with higher scores indicating better HRQoL; a difference of 10 points indicates a clinically significant difference.[20]

Adverse events (AEs) were monitored throughout the treatment period and for 30 days after discontinuation of study treatment until resolution (National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03). Patients were actively followed for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and other new primary malignancies beyond the 30-day post-treatment safety follow-up period.

Statistical analysis

Publication of SOLO2 data[1] resulted in an amendment to the expected median PFS in the placebo arm to 4.5 months, with sample sizes recalculated to support detection of a hazard ratio (HR) of 0.5 in both cohorts; the target number of randomly assigned patients was reduced from 416 to 228 (see Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.09.3110, for further information).

Sample sizes were calculated assuming an HR of 0.5 for both cohorts, based on an expected median PFS of ∼4.5 months with placebo[1,2,10] with an additional 4.5-month increase in median PFS with olaparib. In the BRCAm cohort, 85 progression or death events from 120 patients had 85% power to demonstrate a significant PFS benefit at the two-sided 5% level, and in the non-BRCAm cohort, 74 progression or death events from 108 patients had 80% power to demonstrate a significant PFS benefit at the two-sided 5% level.

Data cut-off (DCO) for the primary PFS analysis was to occur when both the 85 PFS events had occurred in the BRCAm cohort and 74 PFS events had occurred in the non-BRCAm cohort. The final DCO was planned ∼60 months after the first patient was enrolled or after 50% of deaths had occurred in either cohort, whichever occurred first.

The BRCAm and non-BRCAm cohorts were analyzed separately. Efficacy data were analyzed in the full analysis set (all randomized patients), safety data were summarized in the safety analysis set (all patients receiving at least one dose of randomized treatment), and HRQoL data were summarized in all randomized patients with a baseline HRQoL assessment.

The Kaplan—Meier method was used to analyze PFS, including median PFS and PFS rates at prespecified clinically relevant time points (6 months and 1 year), with the difference between olaparib and placebo assessed using a stratified log-rank test at the two-sided 5% significance level [strata were use of prior bevacizumab (yes versus no) and number of prior regimens of platinum-based chemotherapy ($\leq$3 versus $\geq$4)]. The HRs and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. The same methodology was used to assess secondary efficacy endpoints.

HRQoL was analyzed using a mixed model for repeated measures analysis of the change from baseline in TOI scores for each on-treatment visit.

AEs were analyzed descriptively.

SAS® version 9.3 (SAS Institute, Inc., Cary, NC) was used for the analyses.

RESULTS

One hundred and twelve patients underwent randomization from 3 October 2017 to 15 April 2020 in the BRCAm cohort and 108 patients underwent randomization from 28 June 2017 to 10 February 2021 in the non-BRCAm cohort (Figure 1). Instead of the planned 120, 112 patients were randomized in the BRCAm cohort because the required number of PFS events (85 PFS events) had been reached.

DCO occurred per-protocol on 15 February 2021 (5 days after the last patient was randomized in the non-BRCAm cohort) when the predefined number of PFS events had been reached in both cohorts; the median duration of follow-up was 4.1 months [interquartile range (IQR) 2.7-8.5 months] for olaparib versus 2.8 months (IQR 2.7-5.5 months) for placebo in the BRCAm cohort and 2.9 months (IQR 2.6-5.5 months) for olaparib versus 2.8 months for placebo (IQR 2.6-2.9 months) in the non-BRCAm cohort (Supplementary Material, available at https://doi.org/10.1016/j.annonc.2023.09.3110). At the time of DCO, the BRCAm cohort had also reached 50% data maturity for OS.

Within each cohort, baseline characteristics were generally balanced between the treatment arms, although numerically more placebo than olaparib patients were in complete response, particularly in the BRCA-mutated cohort (Table 1; additional data are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.09.3110, including histology type). Patients were heavily pretreated with >85% of patients in both cohorts having received $\geq$3 prior lines of any chemotherapy (Table 1); some patients had received prior non-platinum chemotherapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.09.3110). Only 7% of BRCAm patients and 14% of non-BRCAm patients were included at first relapse after having

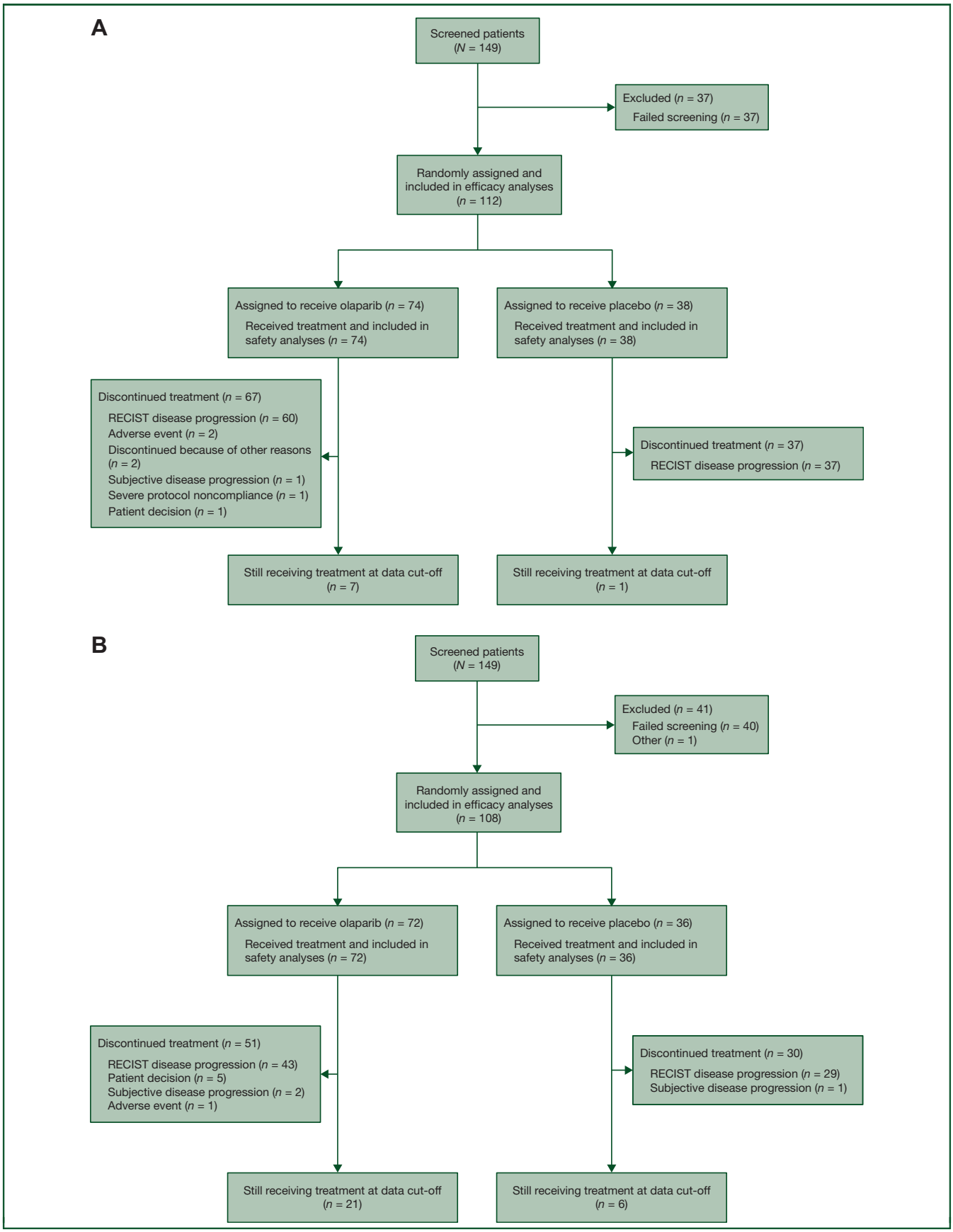

Figure 1. Trial profile in the (A) BRCA-mutated and (B) non-BRCA-mutated cohorts.
RECIST, Response Evaluation Criteria in Solid Tumors.

Table 1. Patient characteristics at baseline[a]

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib ($N = 74$)	Placebo ($N = 38$)	Olaparib ($N = 72$)	Placebo ($N = 36$)
Median (range) age, years	58.5 (37-80)	61.5 (44-87)	66.5 (29-81)	62.5 (43-77)
ECOG performance status, *n* (%)				
0	56 (76)	26 (68)	52 (72)	21 (58)
1	18 (24)	12 (32)	20 (28)	15 (42)
Primary tumor location, *n* (%)				
Ovary	65 (88)	34 (89)	61 (85)	29 (81)
Fallopian tube	4 (5)	2 (5)	6 (8)	2 (6)
Primary peritoneal	4 (5)	2 (5)	5 (7)	4 (11)
Other	1 (1)	0	0	1 (3)
Number of prior lines of any chemotherapy, *n* (%)				
2[b]	5 (7)	3 (8)	10 (14)	5 (14)
3	31 (42)	16 (42)	31 (43)	17 (47)
4	21 (28)	11 (29)	11 (15)	6 (17)
>4	17 (23)	8 (21)	20 (28)	8 (22)
Median (range) duration of previous PARP inhibitor therapy, months	21.2 (12-58)	18.3 (12-55)	12.6 (6-102)	12.4 (3-36)
Duration of previous PARP inhibitor exposure, *n* (%)				
<12 months	1 (1)[c]	1 (3)[c]	31 (43)	17 (47)
≥12 to <18 months	26 (35)	15 (39)	20 (28)	12 (33)
≥18 months	47 (64)	22 (58)	21 (29)	7 (19)
Type of previous maintenance PARP inhibitor, *n* (%)				
Olaparib	69 (93)	34 (89)	15 (21)	8 (22)
Niraparib	3 (4)	2 (5)	46 (64)	21 (58)
Rucaparib	1 (1)	2 (5)	7 (10)	6 (17)
Veliparib	0	0	3 (4)	0
Other	1 (1)[d]	0	1 (1)[e]	1 (3)[e]
Response after most recent chemotherapy before randomization, *n* (%)				
Complete response[f]	15 (20)	13 (34)	19 (26)	11 (31)
Partial response	58 (78)	25 (66)	53 (74)	25 (69)
Missing	1 (1)	0	0	0
BRCAm category at screening, *n* (%)				
Deleterious or suspected deleterious mutation	72 (97)	37 (97)	0	1 (3)[g]
No deleterious or suspected deleterious mutation detected	0	0	71 (99)	34 (94)
Missing[h]	2 (3)	1 (3)	1 (1)	1 (3)
BRCAm type at screening, *n* (%)				
*BRCA1*m	51 (69)	29 (76)	0	1 (3)[g]
*BRCA2*m	20 (27)	7 (18)	0	0
*BRCA1*m and *BRCA2*m	2 (3)	1 (3)	0	0
Missing[h]	1 (1)	1 (3)	0	0
HRD status,[i] *n* (%)				
HRD-positive	—	—	29 (40)[j]	16 (44)[j]
HRD-negative	—	—	30 (42)	11 (31)
HRD-unknown	—	—	13 (18)[k]	9 (25)[k]

BRCAm, *BRCA1* and/or *BRCA2* mutation; ECOG, Eastern Cooperative Oncology Group; GIS, genomic instability score; HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase.

[a]Percentages may not total 100 because of rounding.

[b]Patients had received prior PARP inhibitor therapy in the first-line setting. Following relapse, their second line of chemotherapy was administered before enrollment in OReO/ENGOT-ov38.

[c]These patients are protocol deviations.

[d]Patient had previously received placebo and was PARP inhibitor naive.

[e]Patient had previously received blinded therapy and was potentially PARP inhibitor naive, as permitted in OReO/ENGOT-ov38.

[f]Patients with no evidence of disease were recorded as complete response.

[g]This patient is a protocol deviation.

[h]Patients classified as 'missing' did not have information on their BRCAm category or type recorded on their electronic case report form at screening.

[i]HRD status based on retrospective tumor testing carried out at Myriad Genetic Laboratories, Inc. (myChoice® HRD Plus assay). HRD-positive defined as a GIS ≥42 and/or the presence of a qualifying tumor BRCAm, HRD-negative defined as GIS <42 and the absence of a qualifying tumor BRCAm, and HRD-unknown defined as a missing/canceled/failed test.

[j]Eight (11%) of 72 patients in the olaparib group and 4 (11%) of 36 patients in the placebo group were found to have a qualifying tumor BRCAm on retrospective tumor testing.

[k]In the olaparib group, tests were missing in five (7%) patients and canceled/failed in eight (11%) patients. In the placebo arm, tests were missing in three (8%) patients and canceled/failed in six (17%) patients.

received a maintenance PARPi as part of first-line therapy. In the non-BRCAm cohort, 40% of olaparib patients and 44% of placebo patients had HRD-positive tumors.

In the BRCAm cohort, 103 PFS events had occurred in 112 patients at DCO (data maturity 92%), with an HR for PFS of 0.57 (95% CI 0.37-0.87; $P = 0.0220$) and a median PFS of 4.3 months for olaparib versus 2.8 months for placebo; 6-month PFS rates were 35% versus 13%, respectively, and 1-year PFS rates were 19% versus 0%, respectively (Kaplan–Meier estimates) (Figure 2A).

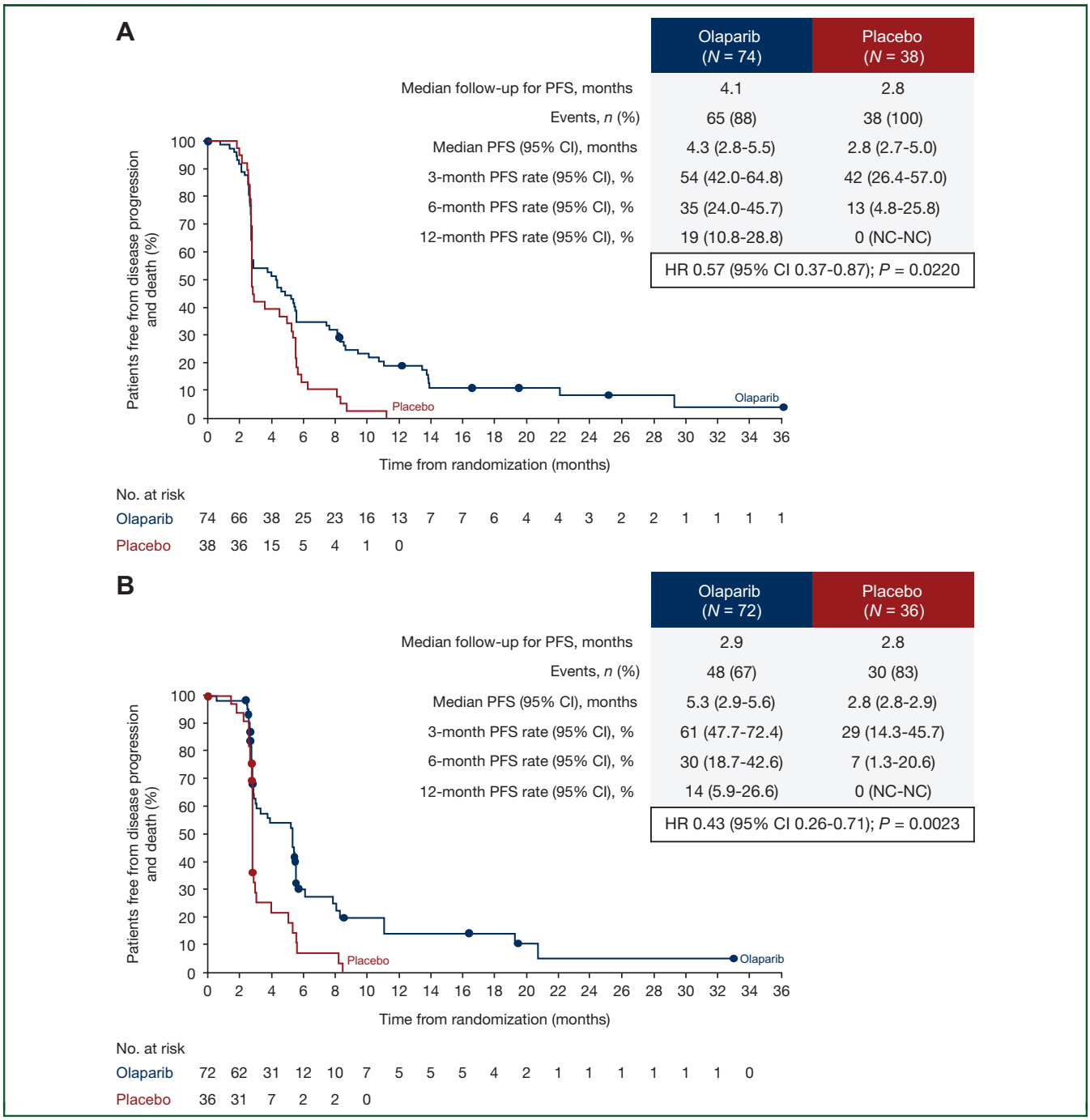

Figure 2. Kaplan–Meier estimates of progression-free survival in (A) BRCA-mutated patients and (B) non-BRCA-mutated patients.
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival.

In the non-BRCAm cohort, 78 PFS events had occurred in 108 patients at DCO (data maturity 72%), with an HR for PFS of 0.43 (95% CI 0.26-0.71; $P = 0.0023$) and a median PFS of 5.3 months for olaparib versus 2.8 months for placebo; 6-month PFS rates were 30% versus 7%, respectively, and 1-year PFS rates were 14% versus 0%, respectively (Kaplan–Meier estimates) (Figure 2B).

In HRD-positive non-BRCAm patients, the HR for PFS was 0.52 (95% CI 0.26-1.10); median PFS was 5.3 months with olaparib versus 2.8 months with placebo (Supplementary Figure S1A, available at https://doi.org/10.1016/j.annonc.2023.09.3110). In HRD-negative non-BRCAm patients, the HR for PFS was 0.49 (95% CI 0.21-1.23); median PFS was 5.4 months with olaparib versus 2.8 months with placebo (Supplementary Figure S1B, available at https://doi.org/10.1016/j.annonc.2023.09.3110).

PFS data in prespecified subgroups (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.09.3110) and sensitivity analyses (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.09.3110) are provided in the Supplementary Material.

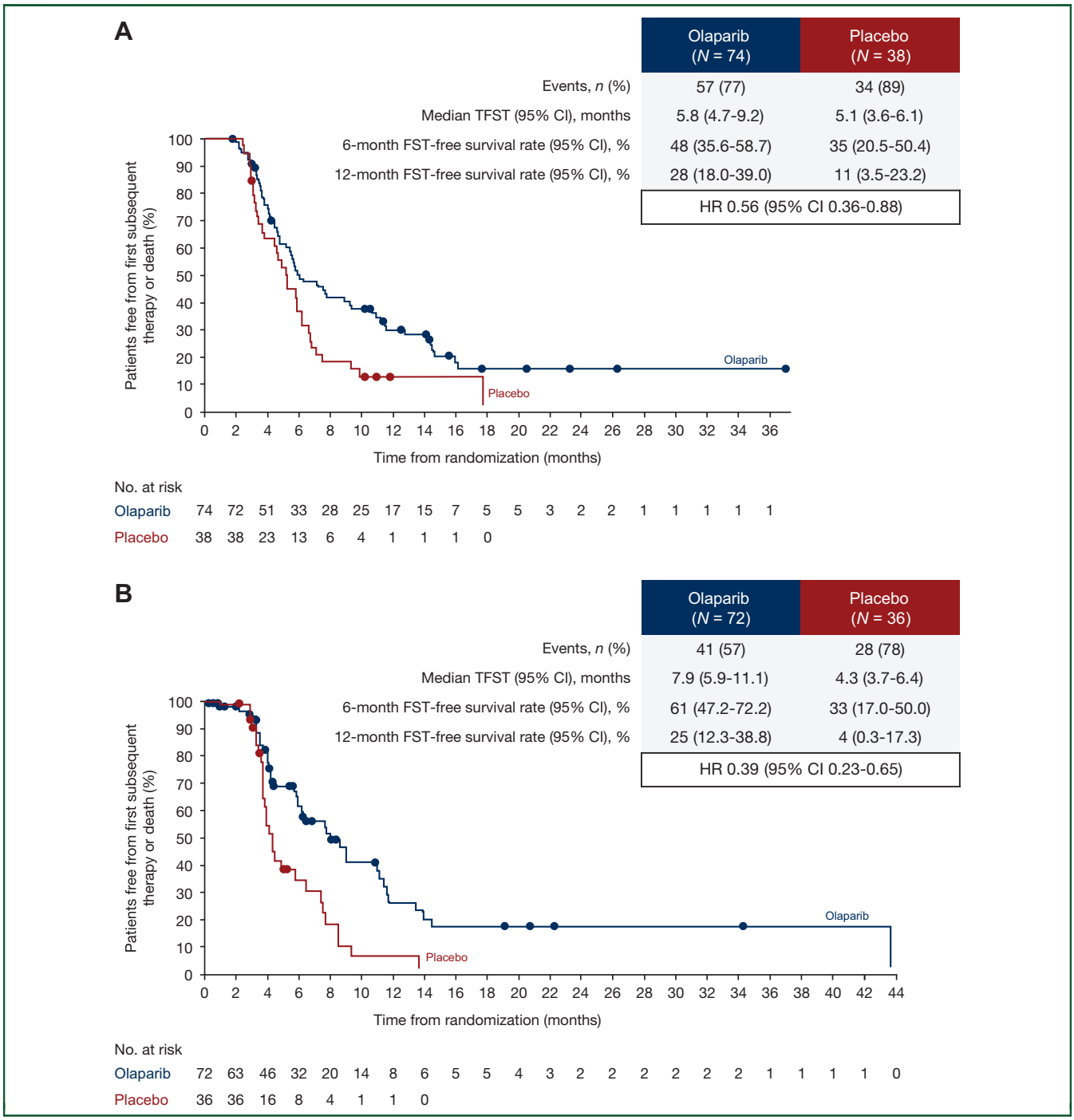

Figure 3. Kaplan–Meier estimates of time to first subsequent therapy or death in (A) BRCA-mutated patients and (B) non-BRCA-mutated patients.
CI, confidence interval; FST, first subsequent therapy; HR, hazard ratio; TFST, time from randomization to first subsequent therapy or death.

TFST was significantly improved with olaparib versus placebo in both the BRCAm cohort (HR 0.56; 95% CI 0.36-0.88; $P = 0.0117$; median TFST 5.8 versus 5.1 months) (Figure 3A) and non-BRCAm cohort (HR 0.39; 95% CI 0.23-0.65; $P = 0.0011$; median TFST 7.9 versus 4.3 months) (Figure 3B).

In the BRCAm cohort, the HR for TSST was 0.70 (95% CI 0.45-1.13; $P = 0.1798$) (median TSST 13.1 months with olaparib versus 11.7 months with placebo) (Supplementary Figure S3A, available at https://doi.org/10.1016/j.annonc.2023.09.3110). In the non-BRCAm cohort, the HR for TSST was 0.56 (95% CI 0.28-1.11; $P = 0.1189$) (median TSST 15.4 months with olaparib versus 12.7 months with placebo) (Supplementary Figure S3B, available at https://doi.org/10.1016/j.annonc.2023.09.3110).

The OS analysis in the BRCAm cohort was conducted at 54% data maturity. Median OS in the BRCAm cohort was 20.1 months with olaparib and 20.9 months with placebo

Table 2. Summary of adverse events[a]

Patients with adverse event, *n* (%)	Olaparib		Placebo	
	Any grade	Grade ≥3	Any grade	Grade ≥3
BRCA-mutated cohort	***N* = 74**		***N* = 38**	
Any	64 (86)	11 (15)	33 (87)	2 (5)
Fatigue or asthenia	31 (42)	0	8 (21)	0
Nausea	29 (39)	0	4 (11)	0
Anemia[b]	13 (18)	2 (3)	2 (5)	0
Diarrhea	10 (14)	0	5 (13)	0
Constipation	9 (12)	0	6 (16)	0
Abdominal pain	8 (11)	0	11 (29)	0
Vomiting	8 (11)	0	4 (11)	0
Dyspnea	7 (10)	0	2 (5)	0
Upper abdominal pain	7 (10)	0	0	0
Neutropenia[c]	6 (8)	2 (3)	4 (11)	1 (3)
Thrombocytopenia[d]	4 (5)	1 (1)	0	0
Urinary tract infection	2 (3)	0	4 (11)	0
Decreased appetite	2 (3)	0	1 (3)	0
Arthralgia	0	0	3 (8)	0
Leading to dose modification	18 (24)	—	6 (16)	—
Leading to treatment discontinuation	2 (3)	—	0	—
Non-BRCA-mutated cohort	***N* = 72**		***N* = 36**	
Any	66 (92)	15 (21)	31 (86)	3 (8)
Nausea	30 (42)	0 (0)	3 (8)	0
Fatigue or asthenia	28 (39)	2 (3)	4 (11)	0
Anemia[b]	17 (24)	1 (1)	1 (3)	0
Diarrhea	12 (17)	0	2 (6)	0
Neutropenia[c]	9 (13)	3 (4)	4 (11)	0
Constipation	9 (13)	0	2 (6)	1 (3)
Decreased appetite	7 (10)	0	1 (3)	0
Dyspnea	7 (10)	0	0	0
Thrombocytopenia[d]	7 (10)	0	0	0
Abdominal pain	6 (8)	0	6 (17)	0
Vomiting	6 (8)	0	1 (3)	0
Upper abdominal pain	4 (6)	0	2 (6)	0
Urinary tract infection	3 (4)	0	0	0
Arthralgia	2 (3)	0	4 (11)	0
Leading to dose modification	18 (24)	—	6 (16)	—
Leading to treatment discontinuation	2 (3)	—	0	—

[a]Data are shown for treatment-emergent adverse events that occurred in at least 10% of patients in either treatment group in either cohort during study treatment or up to 30 days after discontinuation of the intervention. The adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).
[b]The data include patients with anemia, decreased hemoglobin level, decreased hematocrit, decreased red blood cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.
[c]The data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, or agranulocytosis.
[d]Thrombocytopenia occurred in <10% of the patients in each trial group in the BRCA-mutated cohort, but the data are provided to complete the profile of hematological adverse events. The data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

(HR 0.88; 95% CI 0.52-1.53; $P = 0.44$). OS data were immature in the non-BRCAm cohort; 21% of patients had died at the time of the DCO.

The overall adjusted mean change in TOI score from baseline was −1.27 points in the olaparib group ($n = 64$) and 1.67 points in the placebo group ($n = 35$) (difference −2.94; 95% CI −4.99 to −0.90) in the BRCAm cohort, and −2.08 points in the olaparib group ($n = 55$) and 0.58 points in the placebo group ($n = 35$) (difference −2.66; 95% CI −4.75 to −0.58) in the non-BRCAm cohort; these differences were not considered clinically meaningful in either cohort. Compliance with the FACT-O questionnaire was ≥75% in both treatment arms of both cohorts (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.09.3110).

The median duration of treatment was 4.73 months (IQR 2.8-9.5 months) for olaparib and 3.35 months (IQR 2.8-5.6 months) for placebo in the BRCAm cohort and 3.98 months (IQR 2.8-6.1 months) for olaparib and 2.86 months (IQR 2.8-4.1 months) for placebo in the non-BRCAm cohort.

The most commonly reported AEs in patients receiving maintenance olaparib rechallenge were fatigue/asthenia, nausea, and anemia; most AEs were grade 1-2 (Table 2). In the BRCAm cohort, serious AEs were reported in five (7%) patients in the olaparib group and no patients in the placebo group, with treatment-related serious AEs reported in one (1%) patient in the olaparib group (anemia and neutropenia) and no patients in the placebo group. In the non-BRCAm cohort, serious AEs were reported in 11 (15%) patients in the olaparib group and 2 (6%) patients in the placebo group, with treatment-related serious AEs reported in 3 (4%) patients in the olaparib group [anemia ($n = 1$), neutropenia ($n = 1$), and general physical health

deterioration ($n = 1$)] and no patients in the placebo group. There were no AEs resulting in death in either cohort.

Data on MDS/AML and new primary malignancies were collected beyond the 30-day safety follow-up period up to DCO (15 February 2021). No cases of MDS/AML were reported in the olaparib group. MDS was reported in one (3%) patient in the placebo group from the BRCAm cohort (onset of MDS was 292 days after the last dose of placebo). New primary malignancies occurred in one (1%) patient in the olaparib group (esophageal squamous cell carcinoma) and one (3%) patient in the placebo group (breast neoplasm) in the BRCAm cohort, and in one (1%) patient in the olaparib group (basal cell carcinoma) and no patients in the placebo group in the non-BRCAm cohort. No cases of pneumonitis were reported during the treatment or safety follow-up periods.

AEs were usually managed by dose modification, with few patients requiring treatment discontinuation because of AEs in either cohort (Table 2).

DISCUSSION

OReO/ENGOT-ov38 is the first randomized placebo-controlled trial to report data for rechallenge with a PARPi in patients with PSROC. In meeting its primary endpoint, OReO demonstrated that rechallenge with maintenance olaparib provided a statistically significant, albeit modest, improvement in PFS compared with placebo in both the BRCAm and non-BRCAm cohorts. PARPi maintenance therapy has typically provided a greater benefit in patients with BRCAm versus non-BRCAm tumors in the PARPi-naive PSROC setting;[2,3,10] however, in the OReO post-PARPi population, a similar beneficial effect was observed across the biomarker populations. Although the study was not designed to compare these subgroups, as comparisons may be confounded by differences in the patient populations (inclusion criteria differed between the two cohorts, which were randomized separately) and by limitations due to a small subgroup size, this observation is intriguing and warrants further investigation in future clinical trials. In addition, patients in OReO were globally more heavily pretreated than patients in other maintenance trials of olaparib in the relapsed setting[1,11] and few patients had received prior PARPi therapy in the first-line setting, which contributed to a shorter median PFS in the placebo arm of both OReO cohorts than anticipated. In this patient population, which has few treatment options and a poor prognosis, the HRs for PFS seen with maintenance olaparib rechallenge versus placebo translated to a modest improvement in median PFS of ∼2 months. However, a proportion of the OReO population was still progression free at 1 year. The statistically significant improvements in PFS seen with maintenance olaparib rechallenge were achieved without detrimental effects on patients' HRQoL or TSST. No difference in OS was observed between treatment arms in the BRCAm cohort, whereas OS data were immature (21%) in the non-BRCAm cohort.

Prespecified subgroup analyses did not identify any consistent clinical or biological factor that predicted long-term benefit (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.09.3110), although small patient numbers make interpretation of these subgroup analyses difficult. A similar HR for PFS was seen in the HRD-positive and HRD-negative subgroups in the non-BRCAm cohort.

OReO selected patients who were platinum sensitive and had previously demonstrated sensitivity to a PARPi. Though the number of patients in each subgroup is small, a trend was observed for patients with a long duration of previous PARPi maintenance therapy to get the greatest benefit from olaparib rechallenge. However, it should be noted that a proportion of patients in the relapsed disease setting do not experience progression (e.g. 28% of patients in the olaparib arm of SOLO2 had still not experienced a TFST event at 5 years after randomization[9]), and so the very best PARPi responders may not have been included in OReO.

The initial rapid drop in the Kaplan—Meier PFS curves seen in both treatment arms and both cohorts of OReO was not unexpected given that the population was heavily pretreated. The low complete response rate to the platinum-based regimen before patient entry into the trial and the short duration of disease control seen in the placebo arm of OReO could suggest a decrease in platinum sensitivity. This decrease in platinum sensitivity may partly explain the median PFS of 4.3 months seen in patients receiving maintenance olaparib rechallenge in the BRCAm cohort of OReO. The rapid disease progression seen in some OReO patients also suggests the development of PARPi resistance[21] during previous PARPi maintenance therapy. However, screening biopsies were not carried out in OReO, meaning it was not possible to analyze how the presence or absence of PARPi resistance mechanisms influenced outcomes. Patients typically continue PARPi maintenance therapy until disease progression in the relapsed disease setting and, given that most OReO patients had received prior PARPi maintenance therapy for relapsed disease, it is probable that some of these patients experienced disease progression because they developed PARPi resistance. The reason for discontinuation of prior PARPi therapy was not captured in the OReO study. By contrast, many patients who receive maintenance PARPi therapy for a fixed duration in the first-line setting will experience disease progression after they have finished maintenance therapy and may be less likely to have developed PARPi resistance, potentially improving outcomes of rechallenge.

PARPi resistance mechanisms may also impact the efficacy of subsequent chemotherapy. A *post hoc* exploratory analysis of the phase III SOLO2 trial in PSROC suggested that following disease progression in patients receiving PARPi maintenance therapy, the efficacy of subsequent platinum-based chemotherapy was reduced, although this was a postbaseline analysis based on a comparison of non-randomized subgroups of patients with loss of key stratification factors such as response status.[22] In addition, a *post hoc* exploratory analysis of the phase III PAOLA-1 study

suggested that in patients whose disease progressed, the efficacy of subsequent chemotherapy was reduced when relapse occurred during first-line PARPi maintenance therapy rather than after PARPi maintenance therapy had ended.[23] However, given their limitations, results of these analyses should be treated with caution and further research is needed, including prospective analyses to determine the impact of prior PARPi therapy on the efficacy of subsequent therapy and any impact this could have on median PFS.

The safety profile of maintenance olaparib rechallenge was as expected and no new safety signals were identified. Most AEs were grade 1-2 and AEs were usually manageable with dose modification. Few patients in OReO ($\leq$3%) discontinued maintenance olaparib rechallenge because of AEs.

Selection for patients who previously tolerated PARPi maintenance therapy may have contributed to the favorable tolerability profile of maintenance olaparib rechallenge. Although the duration of olaparib therapy was relatively short in OReO, other studies indicate that the AEs most commonly reported in patients receiving maintenance olaparib (i.e. nausea, fatigue/asthenia, anemia) tend to occur early.[24]

In the BRCAm population of PARPi-naive patients with platinum-sensitive relapsed disease, the phase III SOLO2 trial demonstrated a clinically meaningful OS prolongation in the maintenance olaparib arm versus the placebo arm.[9] In the same setting, Study 19, in which approximately half of the patients were BRCAm, also showed an apparent OS advantage in the maintenance olaparib arm versus the placebo arm.[11] In the OReO BRCAm population, maintenance olaparib rechallenge in patients who had received prior PARPi therapy did not show a significant OS difference in favor of the olaparib arm versus the placebo arm (HR 0.88; 95% CI 0.52-1.53; $P = 0.44$). This suggests a trend for less activity of maintenance PARPis in the rechallenge setting, in which a proportion of patients with BRCAm will have experienced disease progression during prior PARPi therapy and may have developed PARPi resistance, compared with PARPi-naive patients. However, there was no evidence of a deleterious effect of maintenance PARPi rechallenge on OS in the OReO BRCAm population.

By contrast, in patients with PSROC without BRCAm, the potentially unfavorable OS outcome seen in the phase III NOVA[25-27] and ARIEL3[28] trials has led to restriction of maintenance niraparib to patients with a germline BRCAm[29] and maintenance rucaparib to those with BRCAm in the USA,[30] and subsequently, on the basis of these data and a potential class effect, maintenance olaparib was also restricted to those with BRCAm in the USA.[31] In the non-BRCAm cohort of OReO, the OS data were immature and will not be evaluated further as the criteria for the final DCO in OReO have been met. Further research is needed to evaluate if maintenance PARPi rechallenge has the potential to improve OS in patients who relapse after completing maintenance PARPi therapy for a fixed duration such as in the first-line setting.

In terms of study limitations, the OReO population had a poor prognosis, contributing to a shorter-than-planned median PFS. In addition, the slower recruitment to the non-BRCAm cohort (primarily reflecting PARPi therapy for non-BRCAm relapsed disease being available much later than for BRCAm relapsed disease in most participating countries) resulted in early censoring and a shorter duration of follow-up than the BRCAm cohort. As the final DCO criteria were met, outcomes data with a longer duration of follow-up, including median OS in the non-BRCAm cohort, will not be available. Recruitment to OReO started before PARPis became available in the first-line setting, and therefore very few patients received maintenance olaparib rechallenge as part of second-line therapy. The absence of information concerning reasons for discontinuation of prior PARPi therapy also represents a study limitation. The short duration of follow-up means that data on longer-term safety, including MDS/AML events, are limited.

Future research points relevant to PARPi rechallenge are discussed in the Supplementary Material.

In conclusion, OReO is the first study to demonstrate that in a heavily pretreated ovarian cancer population, maintenance olaparib rechallenge provided a statistically significant, albeit modest, improvement in PFS compared with placebo, regardless of BRCAm status. A proportion of patients in the maintenance olaparib rechallenge arm in both the BRCAm and non-BRCAm cohorts remained progression free at 1 year. Further investigation may reveal identifiable characteristics of those patients deriving the most clinical benefit.

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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