

Olaparib maintenance monotherapy in platinum-sensitive relapsed ovarian cancer patients without a germline *BRCA1/BRCA2* mutation: OPINION primary analysis

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HIGHLIGHTS

- OPINION investigated maintenance olaparib in platinum-sensitive relapsed ovarian cancer patients without a germline BRCAm.
- In this primary analysis, median PFS was 9.2 months overall, demonstrating clinical benefit versus historical controls.
- Median PFS was prolonged across predefined biomarker subgroups based on BRCAm and HRD status.
- The safety profile of maintenance olaparib was generally consistent with previous reports.
- Our findings support maintenance olaparib as a standard of care in PSROC, irrespective of BRCAm or HRD status.

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ABSTRACT

Objective. The phase IIIb OPINION trial (NCT03402841) investigated olaparib maintenance monotherapy in patients without a deleterious or suspected deleterious germline *BRCA1/BRCA2* mutation (gBRCAm) who had platinum-sensitive relapsed ovarian cancer (PSROC) and had received ≥ 2 previous lines of platinum-based chemotherapy.

Methods. In this single-arm, open-label, international study, patients who had responded to platinum-based chemotherapy received maintenance olaparib tablets (300 mg twice daily) until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed progression-free survival (PFS) (modified RECIST version 1.1). A key secondary endpoint was PFS by homologous recombination deficiency (HRD) and somatic BRCAm (sBRCAm) status. The primary analysis of PFS was planned for 18 months after the last patient received their first dose.

Results. Two hundred and seventy-nine patients were enrolled and received olaparib. At data cutoff (October 2, 2020), 210 PFS events had occurred (75.3% maturity) and median PFS was 9.2 months (95% confidence interval [CI], 7.6–10.9) in the overall population. At 12 and 18 months, 38.5% and 24.3% of patients were progression-free, respectively. In the predefined biomarker subgroups, median PFS was 16.4, 11.1, 9.7, and 7.3 months in sBRCAm,

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HRD-positive including sBRCAm, HRD-positive excluding sBRCAm, and HRD-negative patients, respectively. The most common treatment-emergent adverse events (TEAEs) were nausea (48.4%) and fatigue/asthenia (44.1%). TEAEs led to dose interruption, dose reduction, and treatment discontinuation in 47.0%, 22.6%, and 7.5% of patients, respectively.

Conclusion. Maintenance olaparib demonstrated clinical benefit in patients without a gBRCAm, and across all subgroups, compared with historical placebo controls. There were no new safety signals.

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1. Introduction

The treatment goals of relapsed ovarian cancer include delaying symptomatic disease progression, postponing the need for subsequent chemotherapy with its associated toxicities, and prolonging survival [1]. Treatment also aims to control disease symptoms and maintain patient quality of life. Therapeutic advances, including poly(ADP-ribose) polymerase (PARP) inhibitors, alone or in combination with vascular endothelial growth factor (VEGF) inhibitors, have greatly improved patient outcomes in these areas.

Olaparib is a PARP inhibitor, which traps PARP at sites of DNA single-strand breaks, preventing their repair and generating double-strand breaks. Double-strand breaks cannot be accurately repaired in tumors with homologous recombination deficiency (HRD), such as those with *BRCA1* and *BRCA2* (BRCA) mutation, as error-prone pathways (primarily non-homologous end joining) lead to chromosomal instability and tumor cell death [2,3]. HRD can be determined by germline or somatic mutation screening of genes involved in homologous recombination repair, or by measuring genomic instability via assays that can evaluate loss of heterozygosity (LOH), telomeric allelic imbalance, and large-scale state transitions [4–6].

Olaparib is approved as maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer (PSROC), regardless of BRCA mutation status, in the USA, Europe, China, and Japan [7–10]. In newly diagnosed patients in response to platinum-based chemotherapy, maintenance olaparib is approved globally as monotherapy for those with a deleterious or suspected deleterious germline or somatic BRCA mutation, and in combination with bevacizumab for HRD-positive (deleterious or suspected deleterious BRCA mutation and/or genomic instability) patients [7,11]. Olaparib is generally well tolerated long term and has an established safety profile [12,13]. The most common adverse events (AEs) observed with olaparib include nausea, fatigue/asthenia, and vomiting [12,14].

Although the greatest benefits of PARP inhibitor treatment in PSROC patients have been observed in those with germline BRCA mutations (gBRCAms), PARP inhibitors have also shown a benefit in PSROC populations without BRCA mutations. In a retrospective analysis, the BRCA wild-type subgroup ($n = 118$) in the phase II Study 19 trial (NCT00753545) [15] showed that a 46% reduction in the risk of progression or death was observed with olaparib compared with placebo (median investigator-assessed progression-free survival [PFS] 7.4 vs. 5.5 months; hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.34–0.85; $P = 0.0075$). PFS benefit was also reported in patients without a gBRCAm for niraparib and rucaparib in the phase III NOVA (NCT01847274) and the phase III ARIEL3 (NCT01968213) trials, respectively (Table S1) [16,17].

Although PARP inhibitors have shown a PFS benefit in PSROC patients regardless of their biomarker status, the presence of HRD-positive tumors defined by high levels of genomic instability or high percentage of genome-wide LOH predicts for greater clinical benefit beyond BRCA mutation (Table S1) [17–20].

Long-term follow-up from Study 19 and the phase III SOLO2 trial (NCT01874353) demonstrated that patients with PSROC can benefit from olaparib for several years. In SOLO2, in patients with a BRCA mutation, a 12.9-month difference in median overall survival was observed

in the olaparib arm relative to the placebo arm (51.7 vs. 38.8 months; HR, 0.74; 95% CI, 0.54–1.00; $P = 0.054$), and 22% of patients had received olaparib for ≥ 5 years [13]. Moreover, in Study 19, 12% ($n = 7/57$) of BRCA wild-type patients were still receiving olaparib for ≥ 5 years [12]. In the NOVA study, improvement in PFS did not translate into an overall survival benefit at the final analysis: median overall survival time for niraparib versus placebo, respectively, was 43.6 versus 41.6 months (HR, 0.93; 95% CI, 0.63–1.36) in the gBRCAm cohort, and 31.1 versus 36.5 months (HR, 1.10; 95% CI, 0.83–1.46) in the non-gBRCAm cohort [21].

The phase IIIb OPINION study (NCT03402841) investigated olaparib (tablet formulation) maintenance monotherapy in PSROC patients without a gBRCAm who had received ≥ 2 previous lines of platinum-based chemotherapy. It is the first study to prospectively evaluate olaparib maintenance monotherapy in a patient population without a gBRCAm, in the relapsed setting.

2. Methods

2.1. Study design and patients

OPINION is a phase IIIb, single-arm, open-label, multicenter, international study. Eligible patients were ≥ 18 years old with histologically diagnosed relapsed high-grade serous or high-grade endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer. Upon study entry, confirmation of an absent deleterious or suspected deleterious gBRCAm was required. Inclusion criteria included receipt of ≥ 2 previous lines of platinum-based chemotherapy and, after the penultimate platinum-based chemotherapy regimen before enrollment, patients must have been platinum-sensitive (disease progression > 6 months after completion of last platinum-based chemotherapy dose). For the platinum-based chemotherapy regimen before enrollment, patients were required to have received ≥ 4 cycles of treatment (bevacizumab during this treatment course was not permitted), and olaparib must have been initiated within 8 weeks of their last chemotherapy dose. Patients must have been in partial response (PR), complete response (CR), or had no evidence of disease (NED) (if optimal cytoreductive surgery was conducted prior to chemotherapy), and had to have no evidence of rising cancer antigen-125 (CA-125). They were required to have one or more lesions (measurable and/or non-measurable) that could be assessed at baseline and was suitable for repeated assessment or NED following CR to platinum-based chemotherapy. Full eligibility criteria are provided in the clinical study protocol [22]. Patients with lesions > 2 cm at baseline were allowed to participate.

Patients received olaparib tablets 300 mg twice daily until investigator-assessed objective radiological disease progression (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), unacceptable toxicity, or another protocol-specified withdrawal criterion. Patients could continue to receive olaparib beyond progression if deemed by the investigator to be benefiting from treatment and they did not meet any other discontinuation criteria. The single-arm design of OPINION was based on the expectation that olaparib would benefit patients without a

gBRCAm, given previous trial results demonstrating PFS benefits of PARP inhibitors in non-BRCAM PSROC patients [15–17,23].

All patients provided informed consent. The study was performed according to the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics [24].

Patients were enrolled based on results of local (blood, saliva/scraping, or tumor) BRCA mutation testing or, for patients without a local test result, a blood sample was sent for central testing using the BRACAnalysis CDx[®] assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA) to determine that patients did not have a gBRCAm at screening.

A blood sample was provided to Myriad to retrospectively confirm that enrolled patients did not have a gBRCAm using the BRACAnalysis CDx[®] assay. Following screening, retrospective central tumor testing was also performed at Myriad to assess somatic BRCA mutation (sBRCAm) status and HRD status using the myChoice[®] HRD Plus assay for all patients enrolled. Patients were categorized as having an HRD-positive tumor if their genomic instability score was ≥ 42 , whereas patients with a score of < 42 were classified as HRD-negative as validated previously in ovarian cancer [16,25]. Patients were categorized as having an sBRCAm if they had positive tumor BRCA mutation (tBRCAm) status based on central tumor testing, and negative gBRCAm status based on central germline testing (Fig. S1).

2.2. Endpoints and assessments

The primary endpoint was investigator-assessed PFS (time from date of first olaparib dose to date of objective radiological disease progression [modified RECIST version 1.1] or death by any cause in the absence of progression).

Secondary endpoints assessed at the primary analysis included investigator-assessed PFS by predefined Myriad HRD and BRCAM status subgroups (sBRCAm; HRD-positive including sBRCAm; HRD-positive excluding sBRCAm; and HRD-negative; Fig. S1), time to first subsequent treatment or death (TFST) (time from date of first olaparib dose to date of first subsequent treatment or death by any cause if this occurred before initiation of first subsequent treatment), time to study treatment discontinuation or death (TDT) (time from date of first olaparib dose to date of discontinuation of study treatment or death by any cause if this occurred before treatment discontinuation), chemotherapy-free interval (CT-FI) (time from the date of last platinum-based chemotherapy dose prior to olaparib to date of first subsequent treatment or death by any cause if this occurred before initiation of first subsequent treatment), and the safety and tolerability of olaparib maintenance monotherapy.

Planned exploratory endpoints assessed at the primary analysis included investigator-assessed PFS by the number of prior platinum-based chemotherapy regimens (2 vs. > 2), objective response to latest platinum-based chemotherapy (CR/NED vs. PR), and by age at enrollment (< 65 vs. ≥ 65 years).

Tumor assessments were performed every 8 weeks for the first 12 months, then every 12 weeks thereafter until disease progression. Safety assessments were performed every 4 weeks for the first 12 months, then every 12 weeks thereafter until olaparib discontinuation.

Treatment-emergent AEs (TEAEs) were defined as AEs with onset between the date of first olaparib dose and 30 days after the last olaparib dose or worsening of a pre-existing AE. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded using the Medical Dictionary for Regulatory Activities version 23.1. AEs of special interest, including myelodysplastic syndrome, acute myeloid leukemia, new primary malignancies, and pneumonitis, were actively solicited throughout the study follow-up period for overall survival.

2.3. Statistical analyses

OPINION was designed to estimate PFS rather than test a formal hypothesis. A sample size of ~ 250 patients was proposed, providing

adequate precision in the primary endpoint of PFS. Simulations were performed assuming 250 patients were enrolled over 12 months, with 50% of patients enrolled after 8 months, a median PFS of 8.5 months, and a piecewise exponential model for PFS.

The primary analysis of PFS was planned to be performed ~ 30 months after the first patient started treatment and ~ 18 months after the last patient started treatment, when ~ 180 PFS events had occurred ($\sim 72\%$ maturity), providing an estimated 95% CI width of 3.27 months for median PFS. Assessments for survival will continue until 135 deaths ($\sim 54\%$ maturity) have been recorded.

Efficacy data (including PFS, PFS by Myriad HRD and BRCAM status subgroups, TFST, TDT, and CT-FI) were reported using the full analysis set, which included all enrolled patients who were assigned to olaparib. Safety data were reported using the safety analysis set, which included all patients in the full analysis set who received one or more olaparib dose.

PFS was summarized using the Kaplan–Meier method, with survival curves presenting the percentage of patients alive and without a PFS event, and estimates of median PFS and the associated 95% CI, using the Brookmeyer–Crowley method [26]. PFS by HRD and BRCAM status subgroups, TFST, TDT, and CT-FI were summarized using the same methodology as for PFS.

3. Results

From February 2018 to April 2019, 371 patients were screened, and 279 patients were enrolled in 17 countries. At primary data cutoff (DCO) on October 2, 2020, 71 patients (25.4%) were still receiving olaparib and 85 patients (30.5%) had died.

Baseline demographic and disease characteristics are shown in Table 1. Overall, 264 patients (94.6%) were enrolled based on a blood or saliva test that did not contain a deleterious or a suspected deleterious gBRCAm (non-gBRCAm); 15 patients (5.4%) had unconfirmed gBRCAm status (14 were enrolled based on a negative tumor BRCA test result and one patient with missing test data was an important protocol deviation) (Table 1). The majority of patients ($n = 241$; 86.4%) were enrolled based on a local gBRCA test, the remainder ($n = 38$; 13.6%) based on a central BRACAnalysis CDx[®] assay performed by Myriad Genetics.

Based on retrospective central germline testing (BRACAnalysis CDx[®]) of all enrolled patients, 253 (90.7%) had a confirmed negative gBRCAm result. Six patients (2.2%) had a gBRCAm (not included in biomarker subgroup analyses), and for 20 patients (7.2%), no result was obtained.

The median follow-up duration in patients censored for PFS was 19.2 months (range, 0.0–30.4). There were 210 PFS events (75.3% maturity), with one death (0.4%) in the absence of progression.

Overall, median PFS was 9.2 months (95% CI, 7.6–10.9) (Fig. 1). The percentage of patients who were progression-free at 12 and 18 months was 38.5% (95% CI, 32.7–44.3) and 24.3% (95% CI, 19.2–29.7), respectively. Consistent with results in the overall study population, a median PFS of 9.1 months (95% CI, 7.4–10.3) was observed in a sensitivity analysis including only the patients who were confirmed not to have a gBRCAm by central biomarker testing ($n = 253$) (Table S1).

For the Myriad HRD and BRCAM status subgroups, median PFS (95% CI) was 16.4 (12.8 to not evaluable [NE]) months in the sBRCAm subgroup, 11.1 (9.2–14.6) months in the HRD-positive including sBRCAm subgroup, 9.7 (8.1–13.6) months in the HRD-positive excluding sBRCAm subgroup, and 7.3 (5.5–9.0) months in the HRD-negative subgroup (Table 2 and Fig. 2). Median PFS (95% CI) was 9.2 (7.4–11.1) and 9.0 (7.2–10.9) months in patients who had received two and > 2 prior platinum-based chemotherapy regimens, respectively (Table 2 and Fig. S2). Median PFS (95% CI) was 13.7 (9.3–16.4) months for patients in CR (or who had NED) and 7.4 (5.6–9.1) months for patients in partial response (PR) to their latest platinum-based chemotherapy (Table 2 and Fig. S3). Median PFS (95% CI) was 9.2 (7.8–12.8) and 9.0

Table 1
Patient demographic and disease characteristics at baseline (full analysis set).

Characteristic	Olaparib (N = 279)
Mean age (SD) [range], years	64.0 (9.2) [40–85]
Age at enrollment, years, n (%)	
<65	132 (47.3)
≥65	147 (52.7)
Race, n (%)	
White	273 (97.8)
Black or African American	1 (0.4)
Asian	2 (0.7)
Other	2 (0.7)
Missing	1 (0.4)
Absence of gBRCAm at screening, n (%)	
Yes	264 (94.6)
No	0
Unknown ^a	15 (5.4)
Absence of gBRCAm by central Myriad testing, n (%)	
Yes	253 (90.7)
No	6 (2.2)
Test failed, canceled, or missing ^b	20 (7.2)
Biomarker status, n (%)	
tBRCAm	37 (13.3)
sBRCAm	27 (9.7)
gBRCAm	6 (2.2)
sBRCAm/gBRCAm status not defined ^c	4 (1.4)
Non-tBRCAm	232 (83.2)
HRD-positive (GIS ≥42)	94 (33.7)
HRD-negative (GIS <42)	115 (41.2)
HRD failed (GIS not calculated)	23 (8.2)
Test failed, canceled, or missing ^b	10 (3.6)
Primary tumor location, n (%)	
Ovary	219 (78.5)
Fallopian tube	41 (14.7)
Primary peritoneal	19 (6.8)
Histology type, n (%)	
Serous	260 (93.2)
Endometrioid	12 (4.3)
Other	7 (2.5)
Number of prior platinum-based chemotherapy regimens, n (%)	
2	165 (59.1)
3	84 (30.1)
>3	30 (10.8)
Objective response to latest platinum-based chemotherapy, n (%)	
Complete response or NED	92 (33.0)
Partial response	184 (65.9)
Stable disease ^d	3 (1.1)
Platinum sensitivity, n (%) ^e	
Partial (6–<12 months PFS)	88 (31.5)
Full (≥12 months PFS)	185 (66.3)
Missing	6
ECOG performance status, n (%)	
0	191 (68.5)
1	88 (31.5)

ECOG, Eastern Cooperative Oncology Group; gBRCAm, germline BRCA mutation; GIS, genomic instability score; HRD, homologous recombination deficiency; NED, no evidence of disease; PFS, progression-free survival; sBRCAm, somatic BRCA mutation; SD, standard deviation; tBRCAm, tumor BRCA mutation.

Percentages may not total 100% because of rounding.

- ^a 14 patients were enrolled based on a negative local tumor BRCA test result.
- ^b Reasons for inconclusive test results include no sample data, low tumor content, poor DNA quality, and issues with tissue quality and/or quantity.
- ^c Four patients could not be classified as having an sBRCAm as they had a tBRCAm by Myriad testing but did not have a Myriad gBRCAm test result.
- ^d Protocol violators.
- ^e PFS from last dose of the penultimate platinum-based chemotherapy.

(7.2–10.8) months in patients who were aged <65 and ≥65 years, respectively (Table 2 and Fig. S4).

Overall, median TFST (95% CI) was 13.9 (11.5–16.4) months (Fig. S5). The percentage of patients (95% CI) who were alive and had not received a first subsequent treatment at 12 and 18 months was 54.1% (48.0–59.8) and 40.4% (34.5–46.1), respectively. The median

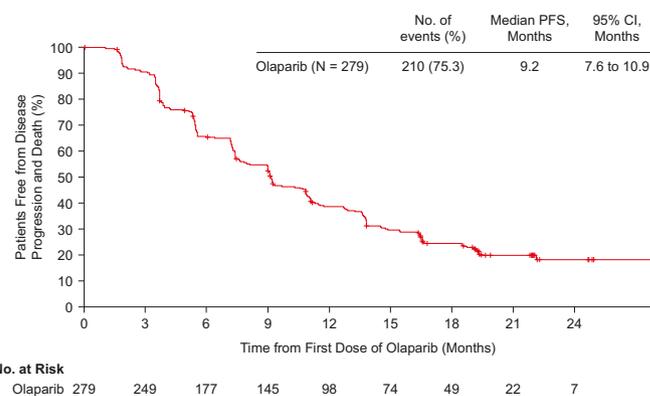


Fig. 1. Kaplan–Meier plot of PFS (full analysis set). Tick mark indicates a censored observation. CI, confidence interval; PFS, progression-free survival.

TDT (95% CI) was 9.6 (7.8–11.1) months (Fig. S6). The percentage (95% CI) of patients who were alive and had not discontinued treatment at 12 and 18 months was 40.9% (35.1–46.6) and 28.0% (22.8–33.3), respectively. The median CT-FI (95% CI) was 17.3 months (13.9–23.3) (Fig. S7). The percentage (95% CI) of patients who were alive and had not received a subsequent treatment at 12 and 18 months was 62.5% (56.4–68.0) and 49.5% (43.3–55.4), respectively.

The median (range) total treatment duration was 9.4 (0.0–31.9) months. TEAEs of all grades and CTCAE grade ≥3 TEAEs were reported in 95.7% and 29.0% of patients, respectively (Table 3). The most common TEAEs of all grades were nausea (48.4%) and fatigue/asthenia (44.1%); the most common CTCAE grade ≥3 TEAEs were anemia (13.6%) and fatigue/asthenia (3.2%). Serious TEAEs occurred in 19.7% of patients, of which the most common was anemia (7.9%); all other serious TEAEs occurred in <2% of patients each.

TEAEs led to dose interruption, dose reduction, and treatment discontinuation in 131 (47.0%), 63 (22.6%), and 21 (7.5%) patients, respectively. The most common TEAEs that led to treatment discontinuation were anemia in five patients (1.8%) and decreased platelet count, depression, fatigue/asthenia, and thrombocytopenia, which all occurred in two patients each (0.7%). One fatal TEAE (aspiration pneumonia) was reported but not considered related to treatment by the investigator.

AEs of special interest included AEs that occurred >30 days after the last olaparib dose. Myelodysplastic syndrome occurred in two patients (0.7%), new primary malignancies occurred in two patients (0.7%) (rectal adenocarcinoma and breast cancer), and pneumonitis and lung infiltration occurred in two (0.7%) and one patient (0.4%), respectively.

4. Discussion

In this analysis of the primary endpoint of PFS, maintenance olaparib demonstrated activity in patients without a gBRCAm, with a median investigator-assessed PFS of 9.2 months in the total study population. This was consistent with a sensitivity analysis in which a median investigator-assessed PFS of 9.1 months was observed in the study participants confirmed not to have a deleterious gBRCAm. This finding expands on the results of Study 19 [15], supporting the activity of maintenance olaparib in non-BRCAm PSROC patients, and is consistent with results from other PARP inhibitor trials [16,21]. Before PARP inhibitor therapy was introduced, chemotherapy plus bevacizumab was the standard treatment for patients without a gBRCAm; in the phase III OCEANS trial (NCT00434642) of patients with PSROC regardless of biomarker status, median PFS (measured from the start of chemotherapy treatment instead of the start of maintenance treatment, as in OPINION) was 12.4 months with bevacizumab plus chemotherapy followed by

Table 2
PFS in key subgroups (full analysis set).

	No. of events (%)	Median PFS, months (95% CI)	PFS rate at 12 months, % (95% CI)	PFS rate at 18 months, % (95% CI)
Myriad HRD and BRCAm status				
sBRCAm	13/27 (48.1)	16.4 ^a (12.8–NE)	73.9 (52.9–86.6)	49.3 (28.9–66.7)
HRD-positive including sBRCAm	80/121 (66.1)	11.1 (9.2–14.6)	49.0 (39.7–57.7)	36.3 (27.6–45.1)
HRD-positive excluding sBRCAm	67/94 (71.3)	9.7 (8.1–13.6)	41.8 (31.6–51.7)	32.5 (23.1–42.3)
HRD-negative	96/115 (83.5)	7.3 (5.5–9.0)	27.0 (19.1–35.6)	11.3 (5.9–18.6)
Number of prior platinum-based chemotherapy regimens				
2	127/165 (77.0)	9.2 (7.4–11.1)	40.1 (32.4–47.6)	23.7 (17.2–30.7)
>2	83/114 (72.8)	9.0 (7.2–10.9)	36.3 (27.3–45.3)	25.3 (17.5–33.9)
Objective response to latest platinum-based chemotherapy ^b				
CR/NED	60/92 (65.2)	13.7 (9.3–16.4)	53.0 (42.2–62.7)	36.3 (26.3–46.4)
PR	147/184 (79.9)	7.4 (5.6–9.1)	31.2 (24.5–38.2)	18.7 (13.2–25.0)
Age at enrollment, years				
<65	100/132 (75.8)	9.2 (7.8–12.8)	43.3 (34.6–51.7)	26.2 (18.9–34.2)
≥65	110/147(74.8)	9.0 (7.2–10.8)	34.0 (26.3–41.9)	22.6 (15.9–30.1)

BRCAm, BRCA mutation; CI, confidence interval; CR, complete response; HRD, homologous recombination deficiency; NE, not evaluable; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; sBRCAm, somatic BRCA mutation.

^a This median is unreliable due to the number of PFS events, with less than 50% maturity.

^b Three patients were excluded from this analysis as they were protocol violators.

maintenance bevacizumab [27]. Our finding supports the use of maintenance olaparib for patients without a gBRCAm.

As shown in Table S1, PFS for placebo groups has been reported in published studies with similar populations (Study 19, SOLO2, NOVA, and ARIEL3; median PFS 3.7–5.5 months) [14,16,17,23]. In each of these studies, participants had high-grade platinum-sensitive relapsed ovarian cancer, were in complete or partial response to their most recent platinum-based regimen after two or more such regimens and were randomized to receive PARP inhibitor maintenance or placebo. Although no statistical comparison was performed, when compared with these placebo groups, olaparib activity was seen across all patient subgroups in OPINION, regardless of HRD and BRCAm status, objective response to latest platinum-based chemotherapy, number of prior platinum-based chemotherapy regimens, or age at enrollment. Across the subgroups, the magnitude of benefit differed. The HRD-positive subgroups, both including and excluding sBRCAm, had longer median PFS than the HRD-negative subgroup. This is consistent with a meta-analysis of PARP inhibitors in PSROC that found that although patients with a gBRCAm or sBRCAm derived greatest benefit, the absence of

the BRCAm or HRD was not grounds for excluding patients from receiving maintenance PARP inhibitor therapy in the relapsed setting [28]. Patients in CR to their last platinum-based therapy had longer median PFS than those in PR. However, this analysis was exploratory, and should be interpreted as such. The incrementally greater benefit in HRD-positive patients is generally consistent with other PARP inhibitor trials [16–19]. NOVA demonstrated longer median PFS in the niraparib arm of the non-BRCAm HRD-positive subgroup (9.3 months) versus the niraparib arm of the HRD-negative subgroup (6.9 months) [16]; the exploratory ARIEL3 analysis showed longer median PFS in the rucaparib arm of the non-BRCAm high-percentage genome-wide LOH cohort (9.7 months) versus the rucaparib arm of the non-BRCAm low-percentage genome-wide LOH cohort (6.7 months) [17]. It is important to note that genomic instability assessment based on high and low genome-wide LOH (as performed in ARIEL3) is determined with a different assay to that used in OPINION, and therefore cannot be compared directly to HRD-positive and -negative status when assessing levels of genomic instability. One-third of OPINION patients were in CR to their last platinum regimen, a proportion similar to ARIEL3 (34%), but lower than Study 19 (42%), SOLO2 (46%), and NOVA (50–51%) [14,16,17,23].

The key secondary endpoints of TFST and TDT supported the overall PFS outcome, with medians of 13.9 and 9.6 months, respectively. The

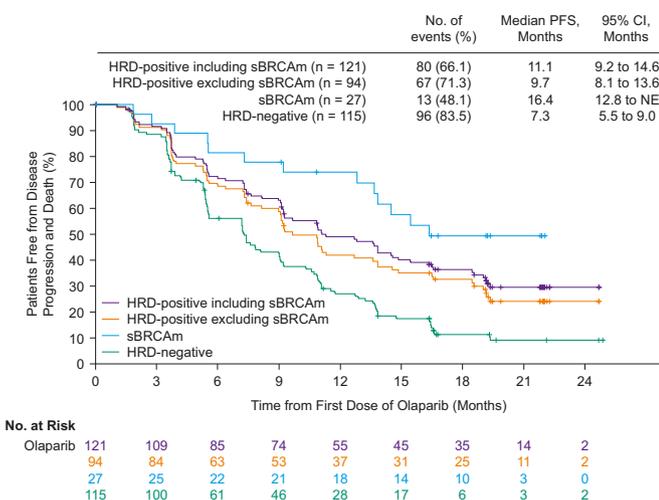


Fig. 2. Kaplan–Meier plot of PFS by Myriad HRD and BRCAm status subgroups (full analysis set).

Tick mark indicates a censored observation. BRCAm, BRCA mutation; CI, confidence interval; HRD, homologous recombination deficiency; NE, not evaluable; PFS, progression-free survival; sBRCAm, somatic BRCA mutation.

Table 3
Summary of TEAEs in ≥10% of patients (safety analysis set).

TEAE	All grades, n (%) ^a (N = 279)	CTCAE grade ≥3, n (%) ^a (N = 279)
Any	267 (95.7)	81 (29.0)
Nausea	135 (48.4)	1 (0.4)
Fatigue/asthenia ^b	123 (44.1)	9 (3.2)
Anemia ^b	109 (39.1)	38 (13.6)
Vomiting	45 (16.1)	3 (1.1)
Neutropenia ^b	44 (15.8)	5 (1.8)
Dysgeusia	39 (14.0)	0
Diarrhea	40 (14.3)	0
Thrombocytopenia ^b	35 (12.5)	6 (2.2)
Abdominal pain	36 (12.9)	0
Decreased appetite	32 (11.5)	0
Cough	29 (10.4)	0

CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

The TEAEs were graded using CTCAE version 5.0 and coded to preferred terms using the Medical Dictionary for Regulatory Activities version 23.1.

^a TEAEs (n, %) are presented at the patient level.

^b Grouped term.

TFST result is consistent with the median TFST (12.9 months in the olaparib arm) of the non-BRCam subgroup in Study 19 [15]. In OPINION, patients could continue olaparib beyond progression as long as, in the investigator's opinion, they were receiving clinical benefit; the comparable TDT rate at 18 months (28.0%) and percentage of patients who were progression-free at 18 months (24.3%) suggest that all patients on treatment were receiving PFS benefit.

Analyses with over 5 years of follow-up in Study 19 and SOLO2 have demonstrated clinically meaningful long-term benefit of olaparib in patients with PSROC. In the SOLO2 final analysis, maintenance olaparib improved median overall survival by 12.9 months over placebo ($P = 0.054$) in gBRCam PSROC patients, with 22% of patients receiving olaparib for ≥ 5 years [13]. Moreover, in Study 19, 12% of patients without a BRCA mutation were still receiving olaparib after ≥ 5 years [12]. At OPINION's primary DCO, overall survival data were immature (85 deaths; 30.5% maturity); this will be assessed at the final analysis to show the effect of maintenance olaparib on overall survival in PSROC patients without a gBRCam.

The safety profile of maintenance olaparib tablets in this analysis was generally consistent with that reported previously [14,18,29]. There was a low treatment-discontinuation rate (7.5%) due to TEAEs at a median total treatment duration of 9.4 months. At the time of the primary analysis, in SOLO2, TEAEs led to a treatment-discontinuation rate of 11% in the olaparib group at a median total treatment duration of 19.4 months [14]. The treatment discontinuation rate due to TEAEs was slightly lower in OPINION; however, there was a longer treatment duration in SOLO2.

A limitation of OPINION is the lack of a placebo comparator group, making it difficult to determine the magnitude of PFS benefit that olaparib provides in patients without a gBRCam. The single-arm design of OPINION was based on previous trial results demonstrating PFS benefits of PARP inhibitors in non-BRCam PSROC patients [15–17,23]. PARP inhibitor trials in PSROC have shown consistent PFS outcomes indicative of rapid disease progression in patients with or without a BRCA mutation who received placebo. Given the expectation that olaparib would benefit patients without a gBRCam, a placebo control was not considered appropriate.

The OPINION study is the largest dataset to demonstrate activity of maintenance olaparib in a population without a gBRCam, in the context of PSROC. In this primary analysis of the study, benefit was observed across all patient subgroups when viewed alongside historical placebo data. Although there was greater magnitude of effect in HRD-positive, both including and excluding sBRCam, versus HRD-negative patients, the benefit in HRD-negative patients suggests that PARP inhibitors should be considered as a standard of care following response to platinum-based chemotherapy, irrespective of BRCA mutation or HRD status.

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 Provision of study material or patients: All authors.
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 Data analysis and interpretation: All authors.
 Manuscript writing: All authors.
 Final approval of manuscript: All authors.
 Accountable for all aspects of the work: All authors.

Prior presentation

Results from the primary analysis of the OPINION study were presented as a poster at the 2021 American Society of Clinical Oncology Annual Meeting.

Data availability statement

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>.

Authors' disclosures of potential conflicts of interest

A. Poveda: Consulting/advisory role: AstraZeneca, Clovis Oncology, GlaxoSmithKline; Travel/other expenses: AstraZeneca.

S. Lheureux: Consulting/advisory role: AstraZeneca, Eisai, GlaxoSmithKline, Merck, Novocure; Honoraria: AstraZeneca, Eisai, GlaxoSmithKline; Research funding (inst): AstraZeneca, GlaxoSmithKline, Merck, Regeneron, Repare, Roche.

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J. Bennett: Consulting/advisory role: AstraZeneca.

E. Škof: Nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ygyno.2021.12.025>.

References

- [1] A. Gadducci, V. Guarneri, F.A. Peccatori, et al., Current strategies for the targeted treatment of high-grade serous epithelial ovarian cancer and relevance of BRCA mutational status, *J Ovarian Res.* 12 (1) (2019) 9.

- [2] H. Farmer, N. McCabe, C.J. Lord, et al., Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, *Nature*. 434 (7035) (2005) 917–921.
- [3] M.J. O'Connor, Targeting the DNA damage response in cancer, *Mol. Cell* 60 (4) (2015) 547–560.
- [4] V. Abkevich, K.M. Timms, B.T. Hennessy, et al., Patterns of genomic loss of heterozygosity predict homologous recombination repair defects in epithelial ovarian cancer, *Br. J. Cancer* 107 (10) (2012) 1776–1782.
- [5] N.J. Birkbak, Z.C. Wang, J.Y. Kim, et al., Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents, *Cancer Discov.* 2 (4) (2012) 366–375.
- [6] T. Popova, E. Manie, G. Rieunier, et al., Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation, *Cancer Res.* 72 (21) (2012) 5454–5462.
- [7] Food and Drug Administration (FDA), Lynparza prescribing information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s013lbl.pdf 2020 (accessed 30 June 2020).
- [8] European Medicines Agency (EMA), Lynparza summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf 2020 (accessed 16 November 2020).
- [9] A. Parker, China approves Lynparza in ovarian cancer, <https://www.biocentury.com/article/297563/china-approves-lynparza-in-ovarian-cancer> 2019 (accessed 30 June 2020).
- [10] AstraZeneca, Lynparza receives approval in Japan for the treatment of advanced ovarian cancer, <https://www.astrazeneca.com/media-centre/press-releases/2018/lynparza-receives-approval-in-japan-for-the-treatment-of-advanced-ovarian-cancer-19012018.html#> 2018 (accessed 30 June 2020).
- [11] AstraZeneca, Lynparza approved in the EU as 1st-line maintenance treatment with bevacizumab for HRD-positive advanced ovarian cancer, <https://www.astrazeneca.com/content/azstraz/media-centre/press-releases/2020/lynparza-approved-in-the-eu-for-wider-ovarian-use.html> 2020 (accessed 5 November 2020).
- [12] M. Friedlander, U. Matulonis, C. Gourley, et al., Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy, *Br. J. Cancer* 119 (9) (2018) 1075–1085.
- [13] A. Poveda, A. Floquet, J.A. Ledermann, 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, randomised, placebo-controlled, phase 3 trial, *Lancet Oncol.* 22 (5) (2021) 620–631.
- [14] E. Pujade-Lauraine, J.A. Ledermann, F. Selle, 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, randomised, placebo-controlled, phase 3 trial, *Lancet Oncol.* 18 (9) (2017) 1274–1284.
- [15] J. Ledermann, P. Harter, C. Gourley, et al., Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial, *Lancet Oncol.* 15 (8) (2014) 852–861.
- [16] M.R. Mirza, B.J. Monk, J. Herrstedt, et al., Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, *N. Engl. J. Med.* 375 (22) (2016) 2154–2164.
- [17] R.L. Coleman, A.M. Oza, D. Lorusso, et al., Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial, *Lancet.* 390 (10106) (2017) 1949–1961.
- [18] I. Ray-Coquard, P. Pautier, S. Pignata, et al., Olaparib plus bevacizumab as first-line maintenance in ovarian cancer, *N. Engl. J. Med.* 381 (25) (2019) 2416–2428.
- [19] A. Gonzalez-Martin, B. Pothuri, I. Vergote, et al., Niraparib in patients with newly diagnosed advanced ovarian cancer, *N. Engl. J. Med.* 381 (25) (2019) 2391–2402.
- [20] K.N. Moore, A.A. Secord, M.A. Geller, et al., Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial, *Lancet Oncol.* 20 (5) (2019) 636–648.
- [21] U.A. Matulonis, J. Herrstedt, A. Oza, et al., Long-term safety and secondary efficacy endpoints in the ENGOT-OV16/NOVA phase 3 trial of niraparib in recurrent ovarian cancer, Presented at: Society of Gynecological Oncology 2021 Virtual Annual Meeting on Women's Cancer; March 19–21; Virtual. Abstract 37, 2021.
- [22] Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed Non gBRCAm Ovarian Cancer Patients, <https://ClinicalTrials.gov/show/NCT03402841> (accessed 18 October 2021).
- [23] J. Ledermann, P. Harter, C. Gourley, et al., Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer, *N. Engl. J. Med.* 366 (15) (2012) 1382–1392.
- [24] AstraZeneca, Code of Ethics, <https://www.astrazeneca.com/content/dam/az/PDF/Sustainability/code-of-ethics-2018/AZ%20Code%20of%20Ethics%20-%20English.pdf> 2018 (accessed 25 June 2020).
- [25] M.L. Telli, K.M. Timms, J. Reid, et al., Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer, *Clin. Cancer Res.* 22 (15) (2016) 3764–3773.
- [26] R. Brookmeyer, J. Crowley, A confidence interval for the median survival time, *Biometrics.* 38 (1) (1982) 29–41.
- [27] C. Aghajanian, S.V. Blank, B.A. Goff, et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, *J. Clin. Oncol.* 30 (17) (2012) 2039–2045.
- [28] C.K. Lee, M.L. Friedlander, A. Tjokrowidjaja, et al., Molecular and clinical predictors of improvement in progression-free survival with maintenance PARP inhibitor therapy in women with platinum-sensitive, recurrent ovarian cancer: a meta-analysis, *Cancer.* 127 (14) (2021) 2432–2441.
- [29] K. Cadoo, F. Simpkins, C. Mathews, N. Kabil, J. Bennett, C. Aghajanian, Olaparib treatment in patients (pts) with platinum-sensitive relapsed (PSR) ovarian cancer (OC) by BRCA mutation (BRCAm) and homologous recombination deficiency (HRD) status: phase II LIGHT study, *J. Clin. Oncol.* 38 (15 Suppl) (2020) (abstr 6013).