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Maintenance olaparib monotherapy in patients with platinum-sensitive relapsed ovarian cancer without a germline *BRCA1* and/or *BRCA2* mutation: Final overall survival results from the OPINION trial☆

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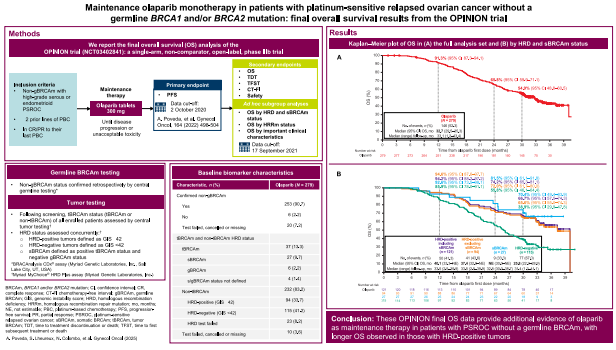
HIGHLIGHTS

- OPINION investigated maintenance olaparib in platinum-sensitive relapsed ovarian cancer patients without a germline BRCAm.
- In this final OS analysis, the overall median OS was 32.7 months (95 % CI 29.5–35.3), with a 24-month OS rate of 65.8 %.
- Longer OS was observed in patients with homologous recombination deficiency-positive tumors.
- The safety profile of maintenance olaparib was consistent with the primary analysis, with no new safety findings.
- Our findings provide additional evidence of olaparib as maintenance therapy in PSROC patients without a germline BRCAm.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. Maintenance olaparib demonstrated clinical activity for progression-free survival in patients without a germline *BRCA1* and/or *BRCA2* mutation (non-gBRCAm) who had platinum-sensitive relapsed ovarian cancer in the phase IIIb, open-label, single-arm, non-comparator, international OPINION trial (NCT03402841). We report final overall survival (OS; secondary endpoint), prespecified secondary endpoint updates and *ad hoc* OS analysis by homologous recombination deficiency (HRD) and somatic BRCAm (sBRCAm) status.

Methods. Patients with non-gBRCAm platinum-sensitive relapsed ovarian cancer, ≥2 prior lines of platinum-based chemotherapy, and in response following their last platinum-based chemotherapy received 300 mg olaparib tablets twice daily until disease progression or unacceptable toxicity.

Results. 279 patients were enrolled and treated. With a median follow-up in patients censored for OS of 33.1 months (data cut-off September 17, 2021), median OS was 32.7 months (95 % CI 29.5–35.3); the 24-month OS rate was 65.8 %. In *ad hoc* subgroup analyses, OS rates tended to be higher in patients with HRD-positive tumors; 24-month OS rates were 81.5 %, 74.2 %, 72.0 % and 55.8 % in the sBRCAm, HRD-positive including sBRCAm, HRD-positive excluding sBRCAm, and HRD-negative subgroups, respectively. Grade ≥ 3 treatment-emergent adverse events were reported in 82 patients (29.4 %), most commonly anemia (13.6 %). Overall, two cases of myelodysplastic syndrome were reported (no new cases since the primary analysis).

Conclusion. These data provide additional evidence of olaparib as maintenance therapy in patients with non-gBRCAm platinum-sensitive relapsed ovarian cancer, with longer OS observed in those with HRD-positive tumors. The safety profile was consistent with the primary analysis and known safety profile of olaparib, with no new safety findings.

1. Introduction

Poly(ADP-ribose) polymerase (PARP) plays a key role in the repair of single-strand DNA breaks during DNA replication [1,2]. PARP inhibitors, such as olaparib, inhibit PARP enzyme activity and trap the inactivated enzyme at the site of the single-strand DNA break, preventing its repair [1,2]. This can lead to the generation of a more deleterious double-strand DNA break which would normally be fixed *via* the homologous recombination repair (HRR) pathway; however, cancer cells with homologous recombination deficiency (HRD), such as those harboring a *BRCA1* and/or *BRCA2* mutation (BRCAm), rely on less accurate DNA repair pathways, resulting in genomic instability and tumor cell death [1,2].

Olaparib is globally approved as maintenance monotherapy for patients with platinum-sensitive relapsed ovarian cancer (PSROC). In the USA, olaparib is approved in patients with a germline or somatic BRCAm (sBRCAm) [3], and in Europe, it is approved irrespective of BRCAm status [4]. In both the USA and Europe, patients must meet the clinical biomarker criterion of being in response to platinum-based chemotherapy (PBC). Approval was based on two randomized trials in PSROC: the phase III SOLO2/ENGOT-Ov21 trial (NCT01874353) in patients with a germline BRCAm (gBRCAm) and the phase II Study 19 trial (NCT00753545) in patients with any BRCA status [5–7].

In ovarian cancer, PARP inhibitors have shown greater efficacy in patients with a BRCAm than those without a BRCAm; however, a subset of patients without a BRCAm who have HRD-positive tumors may also derive significant benefit [8]. HRD can be determined by screening for germline or somatic mutations in genes involved in HRR such as *BRCA1* and *BRCA2* (among others), or by assessing genomic instability with assays that evaluate loss of heterozygosity, telomeric allelic imbalance and large-scale transitions [9–11].

OPINION (NCT03402841) was the first trial to assess prospectively olaparib maintenance monotherapy in 279 patients with PSROC in response to PBC and without a gBRCAm (non-gBRCAm) [12]. The primary analysis (data cut-off [DCO] October 2, 2020) of the single-arm, non-comparator, phase IIIb OPINION trial reported clinical activity with olaparib in patients with non-gBRCAm PSROC [12], relative to historical placebo data from published studies in patients with similar clinical characteristics (median progression-free survival [PFS] ranging from 3.7 to 5.5 months) [5,7,13,14]. In OPINION, median PFS was 9.2 months (95 % CI 7.6–10.9) in the overall non-gBRCAm population [12]. These findings support those of a preplanned exploratory analysis of Study 19 by BRCAm status, in which median PFS was 7.4 *versus* 5.5 months with maintenance olaparib *versus* placebo in patients with non-BRCAm PSROC (albeit including patients with no known BRCAm or with a BRCA variant of unknown significance) and two or more prior lines of PBC [15].

The OPINION primary analysis also demonstrated clinical activity with olaparib relative to historical placebo controls across predefined biomarker subgroups, with a trend towards longer PFS in patients with HRD-positive tumors (assessed by measuring genomic instability) than in patients with HRD-negative tumors. Median PFS was 16.4 months in patients with an sBRCAm, 11.1 months in patients with HRD-positive tumors including sBRCAm, 9.7 months in patients with HRD-positive tumors excluding sBRCAm and 7.3 months in patients with HRD-negative tumors [12]. In a further exploratory biomarker analysis of the OPINION study, clinical activity with olaparib was observed in patients with a non-BRCA HRR mutation (HRRm), who experienced longer PFS relative to patients without a HRRm (median PFS 14.8 and 7.6 months, respectively) [16].

In the OPINION primary analysis, median time to treatment discontinuation or death (TDT), time to first subsequent treatment or death (TFST) and chemotherapy-free interval (CT-FI) was 9.6, 13.9 and 17.3 months, respectively, in the overall population, supporting the overall PFS outcome [12]. Overall survival (OS) was not mature (data maturity, 30.5 %) at the time of the primary analysis.

Here we report final OS (secondary endpoint), prespecified secondary endpoint updates, *ad hoc* subgroup analyses of OS by HRD/BRCAm status, HRRm status and by important clinical characteristics, and updated safety data for OPINION.

2. Methods

2.1. Study design and participants

The OPINION study design has been previously described [12]. Briefly, OPINION is a phase IIIb, single-arm, non-comparator, open-label, international study which enrolled patients in 17 countries. The study was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines and the AstraZeneca policy on bioethics [17]. Eligible patients were aged 18 years or older with histologically diagnosed relapsed high-grade serous or high-grade endometrioid

ovarian cancer (including primary peritoneal and/or fallopian tube cancer), and without a deleterious or suspected deleterious gBRCAm according to local testing (or central testing in exceptional circumstances) performed at or before screening. Patients must have had two or more prior lines of PBC; were platinum-sensitive (disease progression >6 months after completion of last PBC dose) following their penultimate PBC regimen before enrolment; were in partial response, complete response or had no evidence of disease (NED; if optimal cytoreductive surgery was conducted prior to chemotherapy) following their last PBC before enrolment; and had no evidence of rising cancer antigen-125. Patients were not permitted to have received bevacizumab during their last PBC regimen and must have received olaparib within 8 weeks of their last chemotherapy dose. All patients provided informed consent.

Non-gBRCAm status was confirmed retrospectively by central germline testing using the BRACAnalysis CDx® assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA). Following screening, the tumor BRCAm status (tBRCAm or non-tBRCAm) of all enrolled patients was assessed by central tumor testing using the Myriad MyChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc.). The same assay was used to assess HRD status concurrently, with HRD-positive and HRD-negative tumors defined as those with a genomic instability score (GIS) of ≥42 and <42, respectively. sBRCAm status was defined as a positive tBRCAm status and negative gBRCAm status. Patients with non-tBRCAm status were further subdivided into those with a GIS of ≥42 (HRD-positive excluding sBRCAm subgroup) and those with a GIS <42 (HRD-negative). Patients with sBRCAm tumors and those with HRD-positive excluding sBRCAm status were combined to create an HRD-positive including sBRCAm subgroup. HRRm status was assessed using the Myriad MyChoice® HRD Plus assay, and positive HRRm status was defined as the presence of a qualifying mutation in *BRCA1* or *BRCA2,* or any of 13 other prespecified genes involved in HRR (*ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L*).

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 they met other protocol-specified discontinuation criteria. Patients could continue to receive olaparib beyond progression if, in the investigator's opinion, they were benefiting from treatment and did not meet any other discontinuation criteria.

2.2. Endpoints and assessments

The primary endpoint of investigator-assessed PFS, and prespecified secondary endpoints of PFS by HRD/BRCAm status, and of TDT, TFST and CT-FI, have been previously reported [12].

Here, we report OS (prespecified secondary endpoint), as well as updated TDT, TFST, CT-FI and safety. *Ad hoc* OS subgroup analyses are also reported.

Adverse events (AEs) were collected from informed consent, throughout the treatment period up to and including 30 days after the last dose of olaparib. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and graded using Common Terminology Criteria for AEs (CTCAE) version 5.0. Events of myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), new primary malignancy (NPM) and pneumonitis were considered AEs of special interest (AESIs) for olaparib; AESIs were actively solicited throughout the survival follow-up period, including beyond the 30-day post-treatment follow-up period. An important change to the study protocol after trial commencement was revision of OS from an exploratory endpoint to a secondary endpoint; this update was made on October 26, 2018 at the request of the Committee for Medicinal Products for Human Use.

Table 1
Baseline demographics and clinical characteristics (FAS).

Characteristic	Olaparib ($N = 279$)
Median (range) age at enrolment, years	65.0 (40–85)
Age at enrolment, years, *n* (%)	
<65	132 (47.3)
≥65	147 (52.7)
Median (range) prior lines of PBC	2.0 (2–7)
Objective response to last PBC, *n* (%)	
Complete response or NED	92 (33.0)
Partial response	184 (65.9)
Stable disease[a]	3 (1.1)
Confirmed non-gBRCAm,[b] n (%)	
Yes	253 (90.7)
No	6 (2.2)
Test failed, cancelled or missing[c]	20 (7.2)
tBRCAm and non-tBRCAm HRD status, *n* (%)	
tBRCAm	37 (13.3)
sBRCAm	27 (9.7)
gBRCAm	6 (2.2)
s/gBRCAm status not defined[d]	4 (1.4)
Non-tBRCAm	232 (83.2)
HRD-positive (GIS ≥42)[e]	94 (33.7)
HRD-negative (GIS <42)[e]	115 (41.2)
HRD test failed	23 (8.2)
Test failed, cancelled or missing[c]	10 (3.6)
HRRm status, *n* (%)	
HRRm	71 (25.4)
Non-tBRCAm HRRm	34 (12.2)[f]
Non-HRRm	198 (71.0)
Test failed, cancelled or missing[c]	10 (3.6)
Histology type, *n* (%)	
Serous	260 (93.2)
Endometrioid	12 (4.3)
Other	7 (2.5)
Platinum sensitivity, *n* (%)[g]	
Partial (6–12 months PFS)	88 (31.5)
Full (≥12 months PFS)	185 (66.3)
Missing	6 (2.2)

FAS, full analysis set; gBRCAm, germline BRCA mutation; GIS, genomic instability score; HRD, homologous recombination deficiency; HRRm, homologous recombination repair mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS, progression-free survival; sBRCAm, somatic BRCA mutation; tBRCAm, tumor BRCA mutation.
[a] Protocol violators.
[b] Absence of gBRCAm by central Myriad testing.
[c] Reasons include no sample data, low tumor content, poor DNA quality, and issues with tissue quality and/or quantity.
[d] tBRCAm by Myriad testing but no Myriad gBRCAm test result.
[e] HRD status assessed using the Myriad MyChoice® HRD Plus assay.
[f] Of 34 patients with non-tBRCAm HRRm, 8 patients had a mutation in *RAD51C*, 7 in *BRIP1*, 7 in *RAD51D*, 3 in *CDK12*, 2 in *FANCL*, 2 in *PALB2*, 1 in *ATM*, 1 in *BARD1*, 1 in *RAD51B*, 1 in *CHEK2* and *RAD51D*, and 1 in *PPP2R2A* and *RAD51C* [16].
[g] PFS from last dose of penultimate platinum-based chemotherapy.

2.3. Statistical methods

OS, TDT, TFST and CT-FI were summarized using the Kaplan–Meier (KM) method, and 95 % confidence intervals (CIs) for the median calculated using the Brookmeyer–Crowley method [18].

OS was defined as the time from the date of the first dose of olaparib to the date of death from any cause. *Ad hoc* OS subgroup analyses were performed using subgroups prespecified for PFS analyses: Myriad HRD and sBRCAm status subgroups; HRRm status subgroups (including and excluding tBRCAm); and important clinical characteristics (response to latest PBC; prior use of bevacizumab with penultimate PBC; number of prior PBC regimens; degree of sensitivity to penultimate PBC; extent of disease at baseline; age at enrolment).

TDT was defined as the time from the date of the first olaparib dose to the date of olaparib discontinuation or death by any cause, whichever

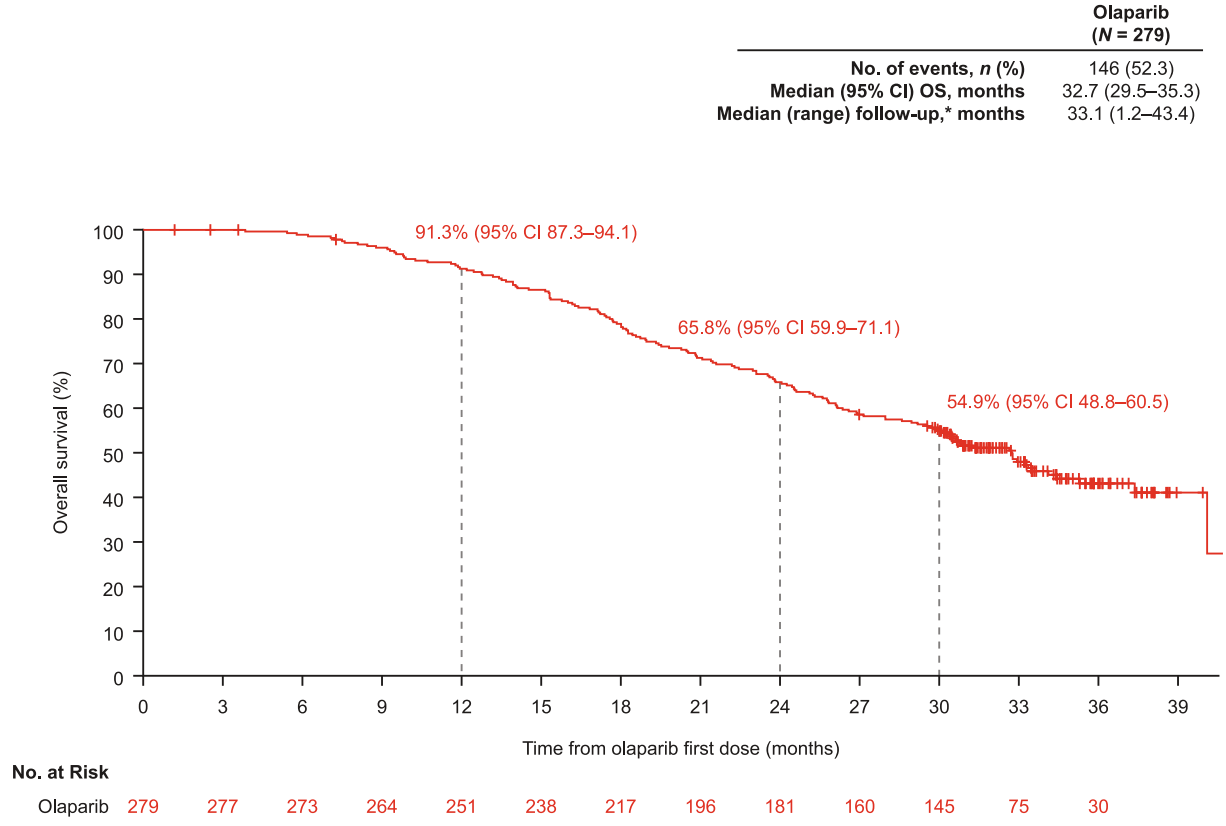


Fig. 1. Kaplan–Meier estimates of OS in the FAS.
Tick mark indicates a censored observation.
*In patients censored for OS.
CI, confidence interval; FAS, full analysis set; OS, overall survival.

occurred first. TFST was defined as the time from the first olaparib dose to the date of the first subsequent anticancer therapy or death by any cause, whichever occurred first. CT-FI was defined as the time from the date of the last dose of PBC immediately prior to enrolment until the date of the first subsequent anticancer therapy.

Efficacy analyses were performed on the full analysis set (FAS; all enrolled patients assigned to olaparib) and safety analyses were performed in the safety analysis set (all enrolled patients who received at least one dose of olaparib).

3. Results

3.1. Patient disposition and baseline characteristics

Of the 279 patients enrolled and assigned to olaparib (FAS), all received at least one dose of olaparib and were included in the safety analysis. The final OS analysis was performed after 146/279 patients had died (52.3 % data maturity; final DCO September 17, 2021). At the final DCO, 233 patients (83.5 %) had discontinued treatment, most commonly due to objective disease progression (**Supplementary Table S1**).

Median (range) age was 65.0 (40–85) years, with 52.7 % (147/279) of patients aged 65 years or older. Absence of gBRCAm was confirmed by central testing in 253 (90.7 %) patients, while test results were undetermined or missing for 20 (7.2 %) patients; six (2.2 %) patients were confirmed by central testing as positive for gBRCAm and, with regards to biomarker subgroup analyses, were only included in the HRRm (including tBRCAm) subgroup analysis. Patients had received a median (range) of two (2–7) prior lines of PBC (Table 1) [12].

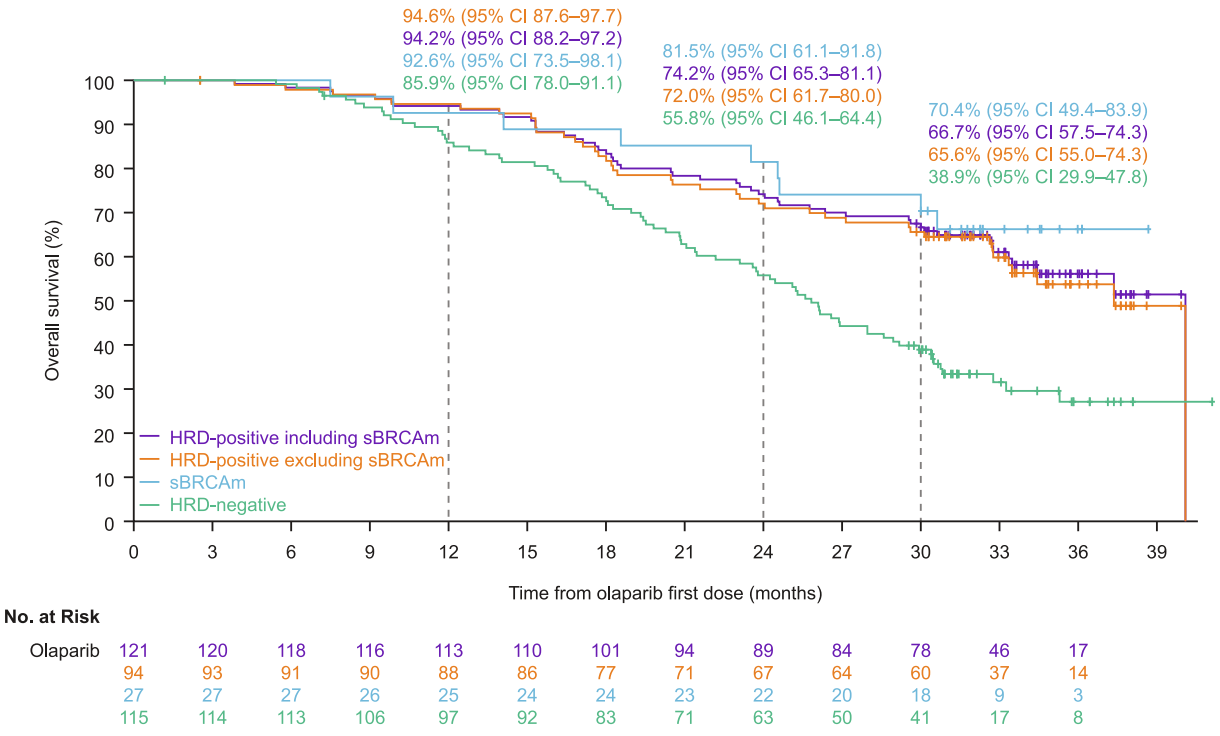
3.2. Overall survival

The median duration of follow-up in patients censored for OS was 33.1 months (range 1.2–43.4). In the FAS ($N = 279$), overall median OS was 32.7 months (95 % CI 29.5–35.3), and OS rates at 12, 24 and 30 months were 91.3 % (95 % CI 87.3–94.1), 65.8 % (95 % CI 59.9–71.1) and 54.9 % (95 % CI 48.8–60.5), respectively (Fig. 1).

In *ad hoc* Myriad HRD and sBRCAm status subgroup analyses, OS rates at 12, 24 and 30 months were consistently numerically higher in the HRD-positive subgroups than the HRD-negative subgroup. At 24 months, OS rates were 81.5 % (95 % CI 61.1–91.8) in the sBRCAm subgroup ($n = 27$), 74.2 % (95 % CI 65.3–81.1) in the HRD-positive including sBRCAm subgroup ($n = 121$), 72.0 % (95 % CI 61.7–80.0) in the HRD-positive excluding sBRCAm subgroup ($n = 94$) and 55.8 % (95 % CI 46.1–64.4) in the HRD-negative subgroup ($n = 115$) (Fig. 2).

In *ad hoc* OS analyses by HRRm status, consistently numerically higher OS rates at 12, 24 and 30 months were estimated for patients in the HRRm subgroup (both when including and excluding tBRCAm) than in the non-HRRm subgroup (Table 2; **Supplementary Figs. S1 and S2**). In *ad hoc* OS analyses by important clinical characteristics, OS tended towards numerically higher survival rates in patients with complete response to last PBC, NED at baseline or full sensitivity to the penultimate PBC regimen relative to patients without these characteristics (Table 2). No notable difference in OS rates was observed for other important clinical characteristics, including age at enrolment, prior use of bevacizumab with penultimate PBC or number of prior PBC regimens (2 or >2) (Table 2 and **Supplementary Table S2**).

	HRD-positive including sBRCAm (*n* = 121)	HRD-positive excluding sBRCAm (*n* = 94)	sBRCAm (*n* = 27)	HRD-negative (*n* = 115)
No. of events, *n* (%)	50 (41.3)	41 (43.6)	9 (33.3)	77 (67.0)
Median (95% CI) OS, months	40.1 (33.3–NE)	37.4 (32.8–NE)	NE (30.0–NE)	25.8 (22.2–28.9)
Median (range) follow-up,† months	33.5 (2.5–39.9)	33.5 (2.5–39.9)	32.8 (30.0–38.7)	31.4 (1.2–41.1)



No. at Risk

Olaparib	121	120	118	116	113	110	101	94	89	84	78	46	17
	94	93	91	90	88	86	77	71	67	64	60	37	14
	27	27	27	26	25	24	24	23	22	20	18	9	3
	115	114	113	106	97	92	83	71	63	50	41	17	8

Fig. 2. Kaplan–Meier estimates of OS by HRD and sBRCAm status* (FAS).
Tick mark indicates a censored observation.
*Determined by central Myriad MyChoice® HRD Plus assay.
†In patients censored for OS.
BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; FAS, full analysis set; HRD, homologous recombination deficiency; NE, not estimable; OS, overall survival; sBRCAm, somatic BRCA mutation.

3.3. Other secondary endpoints

At the final DCO in the FAS, median TDT was 9.6 months (95 % CI 7.8–11.1; 83.5 % data maturity) and KM estimates of the proportion of patients who were still alive and had not yet discontinued treatment at 12, 24 and 30 months were 40.9 % (95 % CI 35.1–46.6), 22.2 % (95 % CI 17.5–27.3) and 18.6 % (95 % CI 14.3–23.4), respectively (**Supplementary Fig. S3A**). Median TFST was 13.9 months (95 % CI 11.5–16.6; 69.9 % data maturity), with KM estimates of the proportion of patients who were still alive and yet to receive a first subsequent therapy at 12, 24 and 30 months of 54.2 % (95 % CI 48.1–59.9), 35.9 % (95 % CI 30.2–41.6) and 31.5 % (95 % CI 26.1–37.0), respectively (**Supplementary Fig. S3B**). Median CT-FI was 17.9 months (95 % CI 13.8–23.3; 55.9 % data maturity) and KM estimates of the proportion of patients yet to reach the end of the CT-FI at 12, 24 and 30 months were 62.2 % (95 % CI 56.1–67.7), 43.7 % (95 % CI 37.6–49.7) and 41.5 % (95 % CI 35.4–47.5), respectively (**Supplementary Fig. S3C**).

Overall, a subsequent anticancer therapy was received by 55.9 % (156/279) of patients, and the most common first subsequent therapy was PBC (78 [28.0 %] patients); PARP inhibitors were received as a first subsequent therapy by two (0.7 %) patients (Table 3).

3.4. Safety

At the final DCO, the median total treatment duration was 9.6 months (range 0.0–43.4), and the updated safety results were consistent with the primary DCO. In the safety analysis set, 268/279 (96.1 %) patients reported at least one treatment-emergent AE (TEAE). TEAEs that occurred in at least 10 % of patients are reported in Table 4. The most common any-grade TEAEs were nausea (136 patients [48.7 %]), fatigue/asthenia (125 patients [44.8 %]), anemia (113 patients [40.5 %]), neutropenia (45 patients [16.1 %]) and vomiting (45 patients [16.1 %]). At least one grade ≥ 3 TEAE was reported in 82 (29.4 %) patients, most frequently anemia (38 patients [13.6 %]); all other grade ≥ 3 TEAEs occurred in less than 4 % of patients (Table 4). A serious AE (SAE) was experienced by 58 (20.8 %) patients, including two (0.7 %) fatalities (one each of aspiration pneumonia and COVID-19; neither considered related to olaparib). The most frequent SAEs were in blood and lymphatic system disorders (23 patients [8.2 %]), including anemia (22 patients [7.9 %]) and thrombocytopenia (one patient [0.4 %]). TEAEs leading to dose interruption were reported in 139 (49.8 %) patients, dose reduction in 65 (23.3 %) patients and treatment discontinuation in 23 (8.2 %) patients. The most common TEAE leading to treatment discontinuation was anemia (six patients [2.2 %]).

Since the start of enrolment, a total of nine AESIs have been reported in eight patients (2.9 %; including events reported beyond the 30-day post-treatment follow-up period): NPMs were reported in three (1.1 %) patients (two with breast cancer [0.7 %], one with rectal adenocarcinoma [0.4 %]) and pneumonitis (including lung infiltration) was reported in four (1.4 %) patients. MDS was reported in two (0.7 %) patients (239 and 491 days after starting olaparib). Of the nine AESIs reported, seven (in six patients) were reported at the primary analysis

Table 2
OS by HRRm status and important clinical characteristics.

Characteristic	Subgroup	Deaths, *n* (%)	Kaplan–Meier OS estimates, % (95 % CI)			
			12-month	18-month	24-month	30-month
FAS ($n = 279$)	N/A	146 (52.3)	91.3 (87.3–94.1)	78.9 (73.6–83.3)	65.8 (59.9–71.1)	54.9 (48.8–60.5)
HRRm status (including tBRCAm)	HRRm ($n = 71$)	26 (36.6)	94.3 (85.5–97.8)	88.6 (78.4–94.1)	80.0 (68.6–87.6)	71.4 (59.2–80.5)
	Non-HRRm ($n = 198$)	117 (59.1)	90.3 (85.2–93.7)	75.5 (68.9–80.9)	60.7 (53.5–67.2)	48.5 (41.3–55.2)
HRRm status (excluding tBRCAm)	HRRm ($n = 34$)	12 (35.3)	93.9 (77.9–98.4)	93.9 (77.9–98.4)	84.8 (67.4–93.4)	75.8 (57.3–87.1)
	Non-HRRm ($n = 198$)	117 (59.1)	90.3 (85.2–93.7)	75.5 (68.9–80.9)	60.7 (53.5–67.2)	48.5 (41.3–55.2)
Response to latest PBC	Complete response or NED ($n = 92$)	33 (35.9)	93.5 (86.1–97.0)	88.0 (79.5–93.2)	81.5 (72.0–88.1)	73.9 (63.6–81.7)
	Partial response ($n = 184$)	111 (60.3)	90.0 (84.6–93.6)	75.0 (68.0–80.7)	58.3 (50.8–65.1)	45.5 (38.1–52.6)
Degree of sensitivity to penultimate PBC	Partial (6–12 months PFS) ($n = 88$)	55 (62.5)	88.5 (79.7–93.6)	71.3 (60.5–79.6)	54.0 (43.0–63.8)	40.2 (29.9–50.3)
	Full (≥12 months PFS) ($n = 185$)	87 (47.0)	93.4 (88.7–96.2)	83.5 (77.3–88.2)	72.5 (65.4–78.4)	62.6 (55.1–69.2)
Extent of disease at baseline	Measurable disease ($n = 108$)	73 (67.6)	86.8 (78.7–92.0)	72.6 (63.1–80.1)	50.0 (40.2–59.1)	35.7 (26.7–44.8)
	Non-measurable disease ($n = 77$)	38 (49.4)	94.7 (86.4–98.0)	77.3 (66.1–85.2)	69.3 (57.6–78.4)	58.7 (46.7–68.8)
	NED ($n = 94$)	35 (37.2)	93.6 (86.3–97.1)	87.2 (78.6–92.5)	80.9 (71.3–87.5)	73.4 (63.2–81.2)
Age at enrolment	<65 years ($n = 132$)	66 (50.0)	93.8 (88.0–96.8)	84.5 (77.0–89.7)	69.8 (61.0–76.9)	59.7 (50.7–67.6)
	≥65 years ($n = 147$)	80 (54.4)	89.1 (82.8–93.1)	74.0 (66.1–80.3)	62.3 (54.0–69.6)	50.6 (42.2–58.4)

HRRm status was determined using Myriad MyChoice® HRD Plus assay.
CI, confidence interval; FAS, full analysis set; HRRm, homologous recombination repair mutation; N/A, not applicable; NED, no evidence of disease; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; tBRCAm, tumor BRCA mutation.

DCO, with two new AESIs (in two new patients) reported at the final DCO: lung infiltration in one patient (0.4 %) and NPM in one patient (0.4 %; breast cancer). There were no new events of MDS after the primary analysis DCO. Additionally, AML was reported as the cause of death for one patient during the final survival status update; however, this was not reported as an AESI by the site.

4. Discussion

The final OS analysis of the single-arm, non-comparator OPINION study demonstrated a median OS of 32.7 months (95 % CI 29.5–35.3) with maintenance olaparib in patients with PSROC without a gBRCAm. In *ad hoc* subgroup analyses by tumor HRD and sBRCAm status, longer survival was observed in patients with HRD-positive tumors, both including and excluding sBRCAm, relative to those with HRD-negative tumors, consistent with PFS findings from the primary analysis [12].

Direct comparison of survival in OPINION with that reported in other studies is challenging due to key differences in study design and patient population. Furthermore, as PARP inhibitors become more widely used, the increasing likelihood of subsequent PARP inhibitor therapy in placebo patients may confound OS findings [19]. Study 19 [7] and ARIEL3 [13] have reported OS in similar patient populations (patients with PSROC, in complete or partial response to their last PBC, and with two or more prior lines of PBC), and included patients with non-BRCAm tumors among the study participants. In the final OS analysis of Study 19, a subgroup of patients with non-BRCAm PSROC (with no known gBRCAm or tBRCAm or with a variant of unknown significance) reported a median OS of 24.5 months (95 % CI 19.8–35.0) with maintenance olaparib and 26.6 months (95 % CI 23.1–32.5) with placebo (hazard ratio [HR] 0.84; 95 % CI 0.57–1.25; nominal $p = 0.39749$) in 57 and 61 patients, respectively [19]. While median OS favored placebo, separation of KM curves in favor of olaparib after approximately 3 years of follow-up suggested that a subset of patients with non-BRCAm PSROC may derive durable benefit from maintenance olaparib [19]. In Study 19, only 13 % of patients in the overall placebo group, and 5 % in the non-BRCAm placebo group, received subsequent PARP inhibitors through participation in later trials, simplifying interpretation of OS findings in that trial [19]. The final OS analysis of the phase III ARIEL3 trial reported a median OS of 40.5 months (95 % CI 36.6–48.4) with maintenance rucaparib and 47.8 months (95 % CI 42.7–53.0) with placebo (HR 1.005; 95 % CI 0.766–1.320; $p = 0.97$) in 236 and 118 patients, respectively, with HRD-positive tumors (defined as a BRCAm or non-BRCAm with high loss of heterozygosity) [13,20]; however, subsequent PARP inhibitor therapy was high in ARIEL3, used by ~45 % of all placebo patients overall [20]. Although not powered to assess differences in OS between groups [13], final OS analyses from ARIEL3 (BRCAm, HRD-positive and intent-to-treat cohorts) led to restriction of maintenance rucaparib in the USA to patients with PSROC harboring a BRCAm [21,22]. Moreover, based on these OS results from ARIEL3, the final OS results from NOVA (a phase III randomized controlled trial of maintenance niraparib *versus* placebo in patients with PSROC with or without a gBRCAm) [23,24] and the potential class-effect, maintenance olaparib was restricted to patients with BRCAm PSROC in the USA [25].

In OPINION, *ad hoc* subgroup analyses showed that patients with a HRRm (including and excluding tBRCAm) had numerically higher OS estimates than patients without a HRRm at 12, 24 and 30 months. Interestingly, OS estimates were similar in patients with a HRRm regardless of whether they had a tBRCAm, with OS rates at 24 months of 80.0 % (95 % CI 68.6–87.6) in the HRRm including tBRCAm group ($n = 71$) and 84.8 % (95 % CI 67.4–93.4) in the non-tBRCAm HRRm group ($n = 34$). However, the HRRm subgroups were small, and caution should be applied when interpreting the results. In ORZORA, a phase IV single-arm trial in patients with PSROC in response after two or more prior lines of PBC, similar clinical activity was observed with maintenance olaparib in an exploratory cohort of 33 patients with a non-BRCA HRRm, 55 patients with a sBRCAm and 87 patients with a gBRCAm (36-month OS rates of 56.6 % [95 % CI 36.8–72.4], 56.8 % [95 % CI 42.4–68.8] and 62.6 % [95 % CI 51.0–72.2], respectively) [26]. Although

Table 3
First subsequent anticancer therapy (FAS).

Anticancer therapy	Patients, *n* (%) (*N* = 279)
Received anticancer therapy	156 (55.9)
Anthracyclines and related substances[a]	52 (18.6)
Platinum compounds	78 (28.0)
Carboplatin	67 (24.0)
Cisplatin	11 (3.9)
Taxanes	29 (10.4)
Docetaxel	2 (0.7)
Paclitaxel	27 (9.7)
PARP inhibitors	2 (0.7)
Niraparib	1 (0.4)
Olaparib	1 (0.4)

Table shows classes of anticancer therapy received by ≥10 % of patients, and any PARP inhibitor use. Patients could receive more than one first subsequent therapy.
FAS, full analysis set; PARP, poly(ADP-ribose) polymerase.
[a] Including doxorubicin, liposomal doxorubicin hydrochloride, liposomal doxorubicin, pegylated liposomal doxorubicin hydrochloride and pegylated liposomal doxorubicin.

the ORZORA non-BRCA HRRm and sBRCAm subgroups were small, together with OPINION they provide additional evidence of olaparib as maintenance therapy in patients with PSROC other than BRCAm [26].

Other important clinical characteristics that numerically favored higher OS estimates in the OPINION population included being in complete response relative to partial response to latest PBC; exhibiting full sensitivity relative to partial sensitivity to penultimate PBC; and having NED relative to either non-measurable or measurable disease at baseline. No notable difference in KM OS estimates was observed when patients were stratified by number of prior lines of PBC (two or more than two). Observed activity with maintenance olaparib across a range of clinical and molecular characteristics will help inform treatment decisions.

In this updated analysis, median TDT, TFST and CT-FI with maintenance olaparib remained consistent with the OPINION primary analysis [12] at 9.6 (95 % CI 7.8–11.1), 13.9 (95 % CI 11.5–16.6) and 17.9 (95 % CI 13.8–23.3) months, respectively, and, as such, median TFST remained consistent with that observed in the non-BRCAm subgroup in Study 19 (12.9 months [95 % CI 7.8–15.3] with olaparib *vs* 6.9 months [95 % CI 5.7–9.3] with placebo) [15]. Potential postponement of further lines of chemotherapy is of particular benefit to patients given the cumulative toxicity of chemotherapy and potential detrimental effects on health-related quality of life [27–29], and, together, these surrogate measures of PFS following further data maturity support the PFS findings demonstrated in the OPINION primary analysis [12].

Table 4
Summary of TEAEs in ≥10 % of patients.

	Patients, *n* (%) (*N* = 279)	
	Any grade	Grade ≥ 3
Any	268 (96.1)	82 (29.4)
Nausea	136 (48.7)	1 (0.4)
Fatigue/asthenia[a]	125 (44.8)	9 (3.2)
Anemia[a]	113 (40.5)	38 (13.6)
Neutropenia[a]	45 (16.1)	5 (1.8)
Vomiting	45 (16.1)	3 (1.1)
Abdominal pain	43 (15.4)	–
Dysgeusia	40 (14.3)	–
Diarrhea	40 (14.3)	–
Thrombocytopenia[a]	36 (12.9)	6 (2.2)
Decreased appetite	32 (11.5)	–
Cough	31 (11.1)	–
Increased blood creatinine	30 (10.8)	–
Urinary tract infection	28 (10.0)	–

For TEAEs, the safety follow-up period was during study treatment and up to and including 30 days after the last dose. AEs of special interest (MDS/AML, new primary malignancy, pneumonitis) were required to be reported even if they occurred after the 30-day post-treatment follow-up period.
AE, adverse event; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.
[a] Grouped term.

The updated safety data presented here further consolidate the previously characterized safety profile of olaparib, with no new safety findings reported [12]. In the 11.5 months since the primary DCO, the rate of treatment discontinuation due to TEAEs remained low (7.5 % [12] and 8.2 % for the primary and final DCOs, respectively), despite 16.5 % of patients still receiving olaparib at the final DCO. After a median (range) duration of olaparib treatment of 9.6 (0.0–43.4) months at the final DCO (compared with 9.4 [0.0–31.9] months at the primary DCO [12]), no additional cases of MDS have been reported since the primary analysis, while AML was reported as the cause of death for one patient in long-term follow-up but was not reported as an AESI. With the inclusion of this additional patient, the incidence of MDS/AML would remain low (1.1 %), in line with other olaparib studies [26,30].

Limitations of the OPINION study have been fully described in the primary analysis [12], including the absence of a control arm on ethical grounds in light of the established PFS benefit of PARP inhibitors, and PFS detriment with placebo, in patients both with and without a BRCAm [7,12–15]. Lack of a control arm is particularly relevant for the subgroup analyses presented here. Specifically, without a comparator arm, greater survival in one subgroup may be due to the presence of confounding clinicopathological prognostic features (*i.e.* increased survival in that subgroup regardless), predictive features (*i.e.* increased efficacy of olaparib in that subgroup) or both. Together with the high degree of data censoring around the median OS estimates for the HRD and sBRCAm subgroups, and small sample size of the non-tBRCAm HRRm subgroup, results should therefore be interpreted with caution when inferring any relative benefit of olaparib between subgroups. Furthermore, updated PFS was not available as RECIST progression was not assessed after the primary analysis DCO; however, the secondary endpoints of TDT, TFST and CT-FI can act as proxy measures of PFS.

These OPINION final OS data, updated secondary endpoint data and *ad hoc* subgroup OS analyses provide additional evidence of olaparib as maintenance therapy in patients with non-gBRCAm PSROC, with longer OS observed in patients with HRD-positive tumors. However, given the absence of a control arm, the extent of the activity observed in the different subgroups should be interpreted with caution. The updated safety data remained consistent with the primary analysis and the known safety profile of olaparib, with no new safety findings, building on existing evidence for the benefit of maintenance olaparib therapy for patients with ovarian cancer whose disease has relapsed.

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CRediT authorship contribution statement

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Declaration of competing interest

A. Poveda: Honoraria: AstraZeneca.

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A. Oaknin: Consulting fees and Participation on a Data Safety Monitoring Board or Advisory Board: AbbVie Inc. Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Deciphera Pharmaceuticals, Daïichi Sankyo, Debiopharm International, Eisai, Exelisis, F. Hoffmann-La Roche, Genmab, GlaxoSmithKline, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncoXerna Therapeutics, Inc., PharmaMar, Regeneron, Sattucklabs, Seagen/Pfizer, Sutro Biopharma, TORL Therapeutics, Zentalis, Zymeworks; Honoraria/Speakers' Bureau: NSGO, Peerview, Peervoice, Medscape, Asociación Colombiada de Ginecológos Oncólogos, ESO, AstraZeneca, GlaxoSmithKline; Travel/other expenses: AstraZeneca, PharmaMar, Roche; Leadership Role: Gynecologic Cancer Intergroup, European Society for Medical Oncology (ESMO); Other: Gynecologic Cancer Intergroup, ESMO, American Society of Clinical Oncology, Spanish Society of Medical Oncology, GOG Foundation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2025.04.580.

Data availability

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.

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