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ORIGINAL ARTICLE

Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial

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Background: In the PAOLA-1/ENGOT-ov25 primary analysis, maintenance olaparib plus bevacizumab demonstrated a significant progression-free survival (PFS) benefit in newly diagnosed advanced ovarian cancer patients in clinical response after first-line platinum-based chemotherapy plus bevacizumab, irrespective of surgical status. Prespecified, exploratory analyses by molecular biomarker status showed substantial benefit in patients with a *BRCA1/BRCA2* mutation (BRCAm) or homologous recombination deficiency (HRD; BRCAm and/or genomic instability). We report the prespecified final overall survival (OS) analysis, including analyses by HRD status.

Patients and methods: Patients were randomized 2 : 1 to olaparib (300 mg twice daily; up to 24 months) plus bevacizumab (15 mg/kg every 3 weeks; 15 months total) or placebo plus bevacizumab. Analysis of OS, a key secondary endpoint in hierarchical testing, was planned for ∼60% maturity or 3 years after the primary analysis.

Results: After median follow-up of 61.7 and 61.9 months in the olaparib and placebo arms, respectively, median OS was 56.5 versus 51.6 months in the intention-to-treat population [hazard ratio (HR) 0.92, 95% confidence interval (CI) 0.76-1.12; $P = 0.4118$]. Subsequent poly(ADP-ribose) polymerase inhibitor therapy was received by 105 (19.6%) olaparib patients versus 123 (45.7%) placebo patients. In the HRD-positive population, OS was longer with olaparib plus bevacizumab (HR 0.62, 95% CI 0.45-0.85; 5-year OS rate, 65.5% versus 48.4%); at 5 years, updated PFS also showed a higher proportion of olaparib plus bevacizumab patients without relapse (HR 0.41, 95% CI 0.32-0.54; 5-year PFS rate, 46.1% versus 19.2%). Myelodysplastic syndrome, acute myeloid leukemia, aplastic anemia, and new primary malignancy incidence remained low and balanced between arms.

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Conclusions: Olaparib plus bevacizumab provided clinically meaningful OS improvement for first-line patients with HRD-positive ovarian cancer. These prespecified exploratory analyses demonstrated improvement despite a high proportion of patients in the placebo arm receiving poly(ADP-ribose) polymerase inhibitors after progression, confirming the combination as one of the standards of care in this setting with the potential to enhance cure.
Key words: advanced ovarian cancer, olaparib, bevacizumab, overall survival

INTRODUCTION

Newly diagnosed advanced ovarian cancer is treated with curative intent with cytoreductive surgery and systemic therapy.[1] The addition of the antiangiogenic agent bevacizumab to carboplatin plus paclitaxel, followed by maintenance bevacizumab, is one of the standards of care for systemic therapy in these patients.[2-7] Most ovarian cancer patients are diagnosed at an advanced stage, however, and the majority still relapse despite standard treatments.[3,8]

The phase III PAOLA-1/ENGOT-ov25 (NCT02477644) trial evaluated maintenance therapy with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib plus bevacizumab, compared with placebo plus bevacizumab, in patients with newly diagnosed advanced ovarian cancer, irrespective of biomarker or surgical status, who were in clinical response after first-line platinum-based chemotherapy plus bevacizumab.[9] A statistically significant progression-free survival (PFS) benefit was observed in the intention-to-treat (ITT) population with addition of olaparib to bevacizumab [median PFS 22.1 versus 16.6 months; hazard ratio (HR) 0.59; 95% confidence interval (CI) 0.49-0.72; $P < 0.001$]. In prespecified exploratory subgroup analyses, the PFS benefit was observed in patient subgroups with a tumor *BRCA1* and/or *BRCA2* mutation (BRCAm; HR 0.31; 95% CI 0.20-0.47), and in those who tested positive for homologous recombination deficiency (HRD, defined as a tumor BRCAm and/or genomic instability) (HR 0.33; 95% CI 0.25-0.45), including the subset without a BRCAm (HR 0.43; 95% CI 0.28-0.66).[9] This established the combination of olaparib plus bevacizumab as one of the standards of care for patients with HRD-positive tumors in this setting and confirmed HRD as an important biomarker beyond BRCAm that can inform clinical decisions regarding PARP inhibitor use.[10-12]

The pre-defined analysis of time from randomization to second progression or death (PFS2; data cut-off: 22 March 2020) demonstrated continued benefit beyond first progression for maintenance olaparib plus bevacizumab in PAOLA-1, with statistically significant improvement observed versus placebo plus bevacizumab in the ITT population (HR 0.78; 95% CI 0.64-0.95; $P = 0.0125$), mainly in patients with HRD-positive tumors (HR 0.56; 95% CI 0.41-0.77).[13] At the PFS2 data cut-off, overall survival (OS) data were immature (38% maturity).

Here, we report the final OS analysis of PAOLA-1, including preplanned subgroup analyses by BRCAm and HRD status, updated descriptive analysis for the primary endpoint (PFS), and long-term safety data for maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer.

METHODS

Trial design and patients

PAOLA-1 was a randomized, double-blind, phase III trial conducted in 11 countries. Detailed methodology, including eligibility criteria, has been published previously.[9] Briefly, enrolled patients were aged ≥18 years with newly diagnosed advanced stage [International Federation of Gynecology and Obstetrics (FIGO) stage III or IV] high-grade serous or endometrioid ovarian cancer, and had complete or partial response or no evidence of disease following first-line platinum-based chemotherapy plus bevacizumab. Patients were eligible irrespective of surgical or biomarker status. All patients provided written informed consent. Full eligibility criteria are provided in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2023.05.005.

Tumor BRCAm (tBRCAm) status was determined by central French academic laboratories before trial entry. Prespecified tumor HRD status was determined retrospectively before the primary analysis by MyChoice® HRD Plus assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT; a positive test was defined as a tBRCAm and/or genomic instability score ≥42).

Patients were randomized 2 : 1 to olaparib (300 mg twice daily) or placebo in combination with bevacizumab, stratified by first-line treatment outcome and BRCAm status at screening. Trial interventions continued up to 24 months or until investigator-assessed objective radiologic disease progression (modified Response Evaluation Criteria in Solid Tumors version 1.1)[14] or unacceptable toxicity, or while the patient experienced benefit and did not meet other discontinuation criteria (Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2023.05.005). All patients received intravenous bevacizumab 15 mg/kg every 3 weeks for 15 months (including when administered in combination with platinum-based chemotherapy).

Endpoints

Primary and some key secondary endpoints were reported previously.[9,13] OS was a key secondary endpoint. Prespecified subgroup analyses assessed OS by HRD and BRCAm status. Adverse events (AEs) were monitored throughout treatment (graded according to Common Terminology Criteria for Adverse Events, version 4.03). Monitoring for AEs of special interest (AESIs) [myelodysplastic syndrome (MDS), acute myeloid leukemia (AML), and aplastic anemia (AA); new primary malignancies; pneumonitis] continued during follow-up for OS.

Trial oversight

This trial was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, under the auspices of an independent data monitoring committee. The trial was designed by the European Network for Gynecological Oncological Trial groups (ENGOT) lead group Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) and sponsored by Association de Recherche Cancers Gynécologiques (ARCAGY) Research, according to the ENGOT model A (academic sponsor; details are provided in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2023.05.005).[15,16] ARCAGY Research was responsible for overseeing the collection, analysis, and interpretation of the data. AstraZeneca, Merck Sharp & Dohme (a subsidiary of Merck), and F. Hoffmann—La Roche were given the opportunity to review drafts of the manuscripts but not asked to approve the final content because this was an academic-sponsored trial. The authors wrote the manuscript, with medical writing assistance funded by ARCAGY Research, AstraZeneca, and Merck Sharp & Dohme. The authors attest to the accuracy and completeness of the data and adherence of the trial to the protocol (available at annalsofoncology.org).

Statistical analysis

The final OS analysis was planned for ∼60% data maturity or 3 years after the primary PFS analysis, whichever occurred first. Efficacy data were summarized and analyzed in the ITT population, which included all the patients who had undergone randomization, regardless of the intervention received. In this analysis, we used the electronic case report form data set, except for the prespecified HRD analysis, which used the Myriad MyChoice® HRD Plus test. OS was not adjusted for subsequent PARP inhibitor therapy.

OS was estimated using the Kaplan—Meier method and compared between arms by stratified log-rank tests, and HRs and CIs were estimated from stratified Cox proportional hazards models; stratification factors were first-line treatment outcome and BRCAm status at screening. In accordance with the primary analysis of the ITT population, stratification factors were analyzed 'as randomized' and no reallocations were made for errant assignments of the stratification factors. For the subgroup analyses, we considered these variables as per the electronic case report form. A hierarchical testing procedure controlled for type 1 error at 5%, with PFS, PFS2, and OS tested in that order (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.05.005). PFS was tested first using the full alpha, and PFS2 and OS were tested using a recycling strategy if the previous end-point's null hypothesis was rejected. Patients for whom only year of death was reported were included as censored at their last known alive date. Subgroup analyses by biomarker status were exploratory and not part of the multiple testing procedure so no alpha was assigned to test for statistical significance. Safety data were analyzed descriptively in the safety analysis set, comprising all randomized patients receiving one or more olaparib or placebo dose.

RESULTS

Patients and treatment

From July 2015 through September 2017, 806 patients were randomized: 535/537 patients assigned to olaparib plus bevacizumab and 267/269 patients assigned to placebo plus bevacizumab received the trial intervention (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.05.005).

Baseline characteristics were generally well balanced between arms (Table 1). The patient population included 30% with stage IV disease. A total of 50% of patients had upfront surgery, of whom ∼40% in each arm had post-operative disease. Some 27% of patients had a partial response following platinum-based chemotherapy. Because patient selection was not restricted by surgical outcome or biomarker status, the PAOLA-1 population is representative of real-world newly diagnosed advanced ovarian cancer patients (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.05.005).

Efficacy

The final OS analysis was carried out 3 years after the primary PFS analysis, at 55% data maturity (data cut-off: 22 March 2022). The median duration of follow up for OS was 61.7 months [interquartile range (IQR): 57.5-67.0 months] versus 61.9 months (IQR 58.1-66.8 months) in the olaparib and placebo groups, respectively.

In the ITT population, OS numerically favored olaparib plus bevacizumab over placebo plus bevacizumab, but was not statistically significant [median, 56.5 versus 51.6 months; HR 0.92; 95% CI 0.76-1.12; $P = 0.4118$; 5-year OS rates (Kaplan—Meier estimates): 47.3% versus 41.5%] (Figure 1). This analysis was unadjusted for subsequent therapy, during which 19.6% in the olaparib arm and 45.7% in the placebo arm received a PARP inhibitor (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.05.005).

In patients with HRD-positive tumors, the median duration of OS was prolonged with olaparib plus bevacizumab versus placebo plus bevacizumab and a greater proportion of patients were alive at 5 years (5-year OS rates, 65.5% versus 48.4%; median 75.2 versus 57.3 months; HR 0.62; 95% CI 0.45-0.85) (Figure 2A), despite 50.8% of patients in the placebo arm receiving a PARP inhibitor during subsequent therapy (versus 17.3% in the olaparib arm).

An OS benefit with olaparib plus bevacizumab was observed in patients with HRD-positive tumors regardless of BRCAm status. In the BRCAm population (by central laboratories), 73.2% versus 53.8% were alive at 5 years, respectively [median OS, 75.2 months (unstable; data maturity: 30.6%) versus 66.9 months; HR 0.60; 95% CI 0.39-0.93] (Figure 2B), and in patients with HRD-positive tumors excluding BRCAm (by Myriad), 54.7% versus 44.2% were

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

Characteristic	Olaparib plus bevacizumab (n = 537)	Placebo plus bevacizumab (n = 269)
Age, median, years (range)	61 (32-87)	60 (26-85)
ECOG performance, *n* (%)		
0	378 (70)	189 (70)
1	153 (28)	76 (28)
Primary tumor location, *n* (%)		
Ovary	456 (85)	238 (88)
Fallopian tubes	39 (7)	11 (4)
Primary peritoneal	42 (8)	20 (7)
Histology, *n* (%)		
Serous	519 (97)	253 (94)
Endometrioid	12 (2)	8 (3)
Other	6 (1)	8 (3)
HRD status[a,b], *n* (%)		
HRD-positive	255 (47)	132 (49)
tBRCA mutation	157 (29)	80 (30)
HRD-positive excluding tBRCAm	97 (18)	55 (20)
HRD-negative	192 (36)	85 (32)
HRD unknown	90 (17)	52 (19)
FIGO stage, *n* (%)		
III	378 (70)	186 (69)
IV	159 (30)	83 (31)
History of cytoreductive surgery, *n* (%)		
Upfront surgery	271 (50)	138 (51)
Residual macroscopic disease	111 (41)	53 (38)
No residual macroscopic disease	160 (59)	85 (62)
Interval cytoreductive surgery	228 (42)	110 (41)
Residual macroscopic disease	65 (29)	35 (32)
No residual macroscopic disease	163 (71)	75 (68)
No surgery	38 (7)	21 (8)
Response after surgery/platinum-based chemotherapy, *n* (%)[c]		
NED	290 (54)	141 (52)
CR	106 (20)	53 (20)
PR	141 (26)	75 (28)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; NED, no evidence of disease; PR, partial response; tBRCAm, tumor BRCAm.

[a]BRCAm status by central labs and HRD status by Myriad MyChoice® HRD Plus (Myriad Genetic Laboratories, Salt Lake City, UT); patients in tBRCAm and HRD-positive excluding tBRCAm subgroups do not equal the total number of patients in the HRD-positive subgroup because of different testing methods.

[b]HRD-positive was defined as a tumor BRCA mutation or an HRD score of ≥42 on the MyChoice® HRD Plus assay. HRD-negative was defined as an HRD score of <42. 'Unknown' was defined as an inconclusive, missing, or failed test.

[c]NED was defined as no measurable or assessable disease after cytoreductive surgery plus no radiologic evidence of disease and a normal CA-125 level after chemotherapy. Clinical CR was defined as the disappearance of all measurable or assessable disease and normalization of CA-125 levels. PR was defined as radiologic evidence of disease, an abnormal CA-125 level, or both.

alive at 5 years, respectively (median OS, not reached versus 52 months; HR 0.71; 95% CI 0.45-1.13) (Figure 2C).

In patients with HRD-negative tumors, 25.7% in the olaparib plus bevacizumab group and 32.3% in the placebo plus bevacizumab group were alive at 5 years (median OS, 36.8 versus 40.4 months; HR 1.19; 95% CI 0.88-1.63) (Figure 2E). Some 40.0% of these patients in the placebo arm and 24.0% in the olaparib arm had received a PARP inhibitor as subsequent therapy. Data for patients whose tumor HRD status was unknown (such as those with failed tests or insufficient tumor samples), or negative/unknown, are shown in Supplementary Figures S3 and S4, available at https://doi.org/10.1016/j.annonc.2023.05.005.

An updated, descriptive analysis demonstrated prolonged PFS with olaparib plus bevacizumab versus placebo plus bevacizumab in patients with HRD-positive tumors (data maturity, 53.3%; median PFS: 46.8 versus 17.6 months; HR 0.41; 95% CI 0.32-0.54), and a greater proportion of patients who were alive and had not progressed at 5 years (46.1% versus 19.2%) (Figure 3). PFS results in other molecular subgroups are reported in Table 2.

Safety

All patients had discontinued treatment by the data cut-off for PFS2 and safety data were reported previously.[13] No new safety signals were observed. Data on MDS/AML/AA, new primary malignancies, and pneumonitis were collected up to the OS data cut-off (Table 3): in total, nine (1.7%) versus six (2.2%) cases of MDS/AML/AA were reported in the olaparib versus placebo groups, respectively. New primary malignancies were reported in 22 (4.1%) and 8 (3.0%) patients, respectively, and pneumonitis occurred in 7 (1.3%) versus 2 (0.7%), respectively.

DISCUSSION

The phase III PAOLA-1/ENGOT-ov25 trial evaluated the addition of olaparib to bevacizumab in patients with newly diagnosed advanced ovarian cancer after response to first-line standard-of-care treatment including bevacizumab.

The final, prespecified OS analysis reported here demonstrates that the PFS advantage in the primary analysis, which established the combination of olaparib plus bevacizumab as one of the standards of care for patients with HRD-positive tumors in this setting,[10-13] also translates to a clinically meaningful OS benefit for first-line patients with HRD-positive tumors. In preplanned, exploratory analyses the HRD-positive population (which included patients with a tumor BRCAm and patients without a tumor BRCAm who had genomic instability) demonstrated a 38% reduction in the risk of death with olaparib plus bevacizumab versus bevacizumab alone (HR 0.62; 95% CI 0.45-0.85), with 65.5% of patients in the olaparib group (versus 48.4% in the placebo group) alive at 5 years.

The OS benefit observed in patients with HRD-positive tumors was, in part, driven by the BRCAm subgroup (HR 0.60; 95% CI 0.39-0.93). Recently, a 7-year descriptive analysis of the SOLO1 trial also reported a clinically meaningful OS advantage with maintenance olaparib versus placebo in newly diagnosed advanced ovarian cancer patients with a BRCAm (HR 0.55; 95% CI 0.40-0.76), with 67.0% of patients in the olaparib group (versus 46.5% in the placebo group) alive at 7 years.[17] Although 5-year landmark OS rates in the olaparib arm of SOLO1 and the PAOLA-1 BRCAm subgroup were similar (SOLO1: 73.1% alive; PAOLA-1 BRCAm subgroup: 73.2% alive), in these olaparib arms, the PAOLA-1 BRCAm subgroup had a higher proportion of patients with prognostic features that have historically been considered unfavorable [more stage IV disease

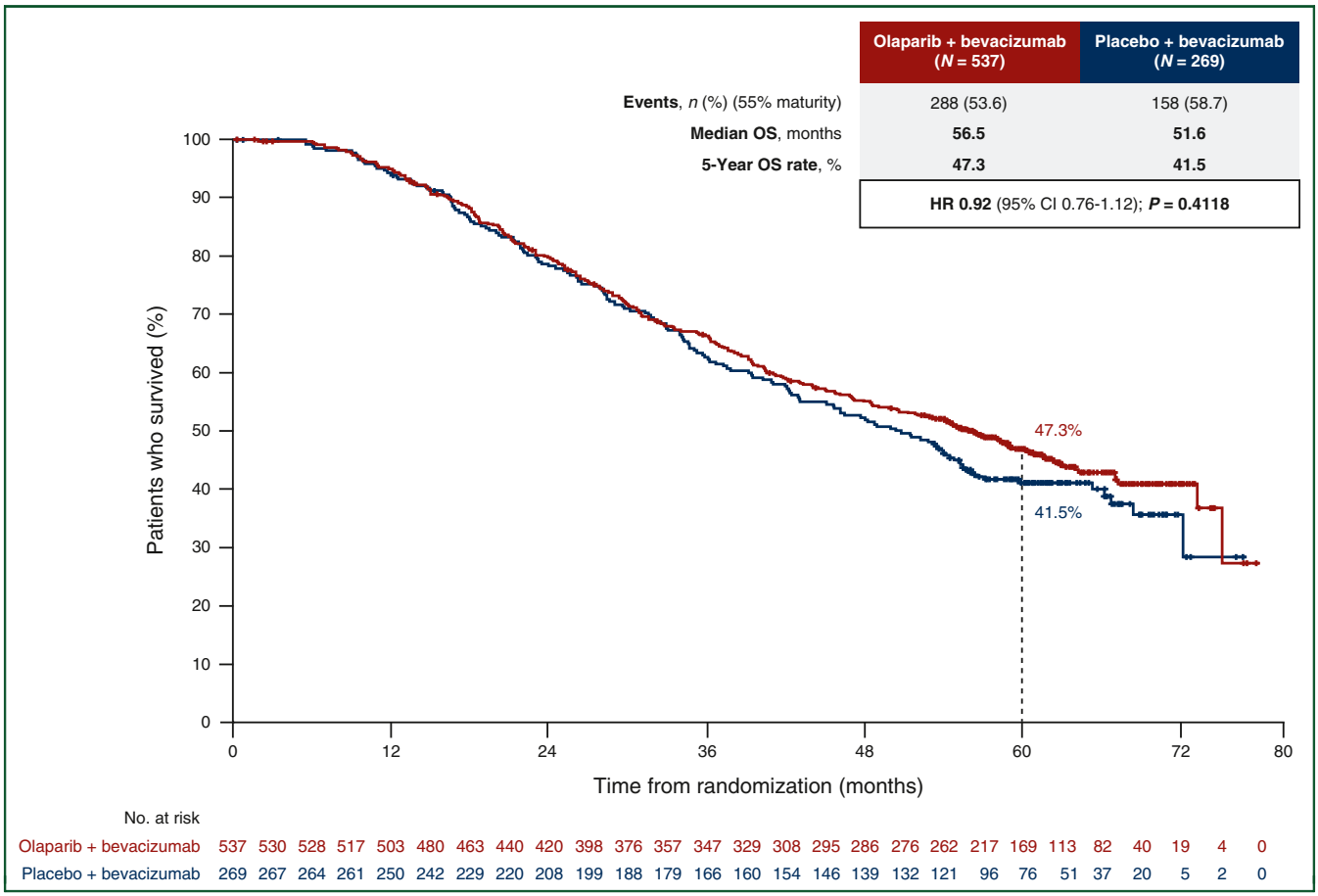

Figure 1. Kaplan–Meier estimates of overall survival in the intention-to-treat population. Shown are Kaplan–Meier estimates of the rate of freedom from death. CI, confidence interval; HR, hazard ratio; OS, overall survival.

(28% versus 15% in SOLO1), more residual macroscopic disease after cytoreductive surgery (30% versus 21%), and more patients undergoing interval cytoreductive surgery (41% versus 36%)].[9,18,19] Caution, however, should be used when comparing trials.

Because PAOLA-1 lacked an olaparib monotherapy arm, it is difficult to draw conclusions on the effect of combining olaparib and bevacizumab versus olaparib alone; however, the value of combination versus single-agent PARP inhibitor therapy is under investigation in the ongoing AGO-OVAR 28/ENGOT-ov57 (NCT05183984) and NIRVANA-1 (NCT05183984) trials.

In PAOLA-1, a numerical OS benefit was also observed in patients with HRD-positive tumors excluding BRCAm (HR 0.71; 95% CI 0.45-1.13). The small subgroup size ($n = 97$ and $n = 55$ in the olaparib plus bevacizumab and placebo plus bevacizumab arms, respectively) may explain the large CIs observed. OS analyses in patients with HRD-positive tumors with newly diagnosed ovarian cancer in other PARP inhibitor trials (ATHENA, PRIMA, VELIA) are awaited with interest.[20-22]

For those patients classified as HRD-negative, there was no benefit observed with the addition of olaparib to bevacizumab (HR 1.19; 95% CI 0.88-1.63). Although the HR is above 1 and the Kaplan–Meier curve for the olaparib plus bevacizumab arm is slightly below the placebo plus bevacizumab curve, there is no statistical evidence of a deleterious effect on OS in the HRD-negative population as the CIs are broad and the lower CI (0.88) clearly crosses 1. In the ITT population, the OS benefit from the HRD-positive population was diluted by the inclusion of the HRD-negative and unknown populations, which together comprised over half the ITT population. This may explain in part why OS was numerically longer with the combination versus bevacizumab alone but the difference did not reach statistical significance (median, 56.5 versus 51.6 months; HR 0.92; 95% CI 0.76-1.12; $P = 0.4118$). These findings are broadly consistent with previous PFS and PFS2 analyses, where benefit was also observed mainly in the HRD-positive population.

Improvements in OS are difficult to demonstrate in ovarian cancer trials, because of the long post-progression survival period during which patients typically receive several lines of post-progression cancer therapy, and particularly when PFS2 extends beyond 1 year.[3,13,17,23-25] In PAOLA-1, OS analyses were not adjusted for subsequent PARP inhibitor therapy, and this likely decreased the magnitude of benefit observed with study treatment. In the ITT population, >45% of placebo patients ($n = 123/269$), versus 20% of olaparib patients ($n = 105/537$), received

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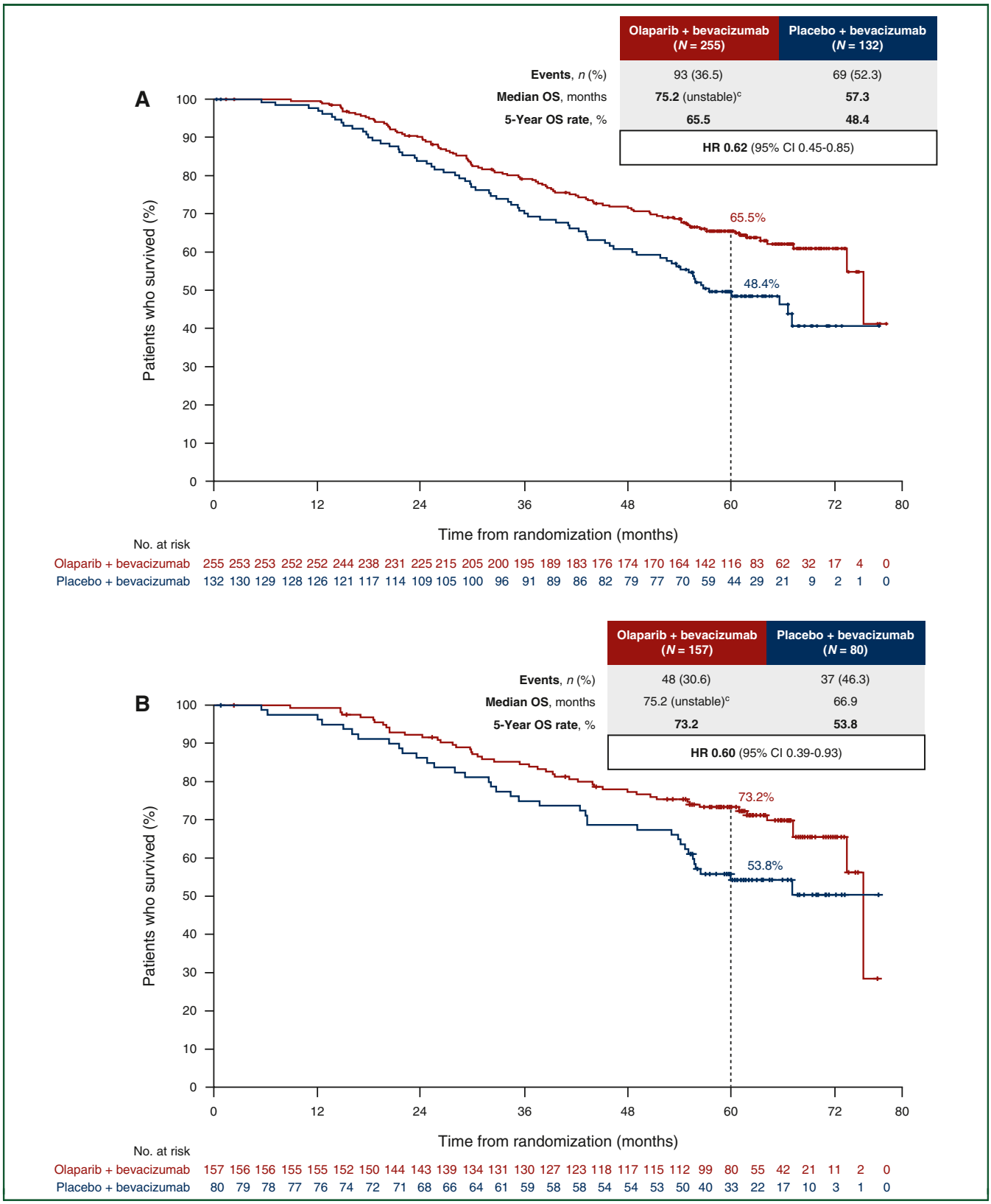

Figure 2. Kaplan–Meier estimates of overall survival according to tumor BRCA mutation status and homologous recombination deficiency status. (A) Patients with HRD-positive tumors including those with a tumor BRCA mutation[a]. (B) Patients with a BRCA mutation[b]. (C) Patients with HRD-positive tumors excluding those with a tumor BRCA mutation[a]. (D) Patients with HRD-negative tumors[a] (excluding unknown).

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; OS, overall survival.

[a]Myriad MyChoice® HRD Plus.

[b]By central labs.

[c]Unstable median; <50% data maturity. The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points.

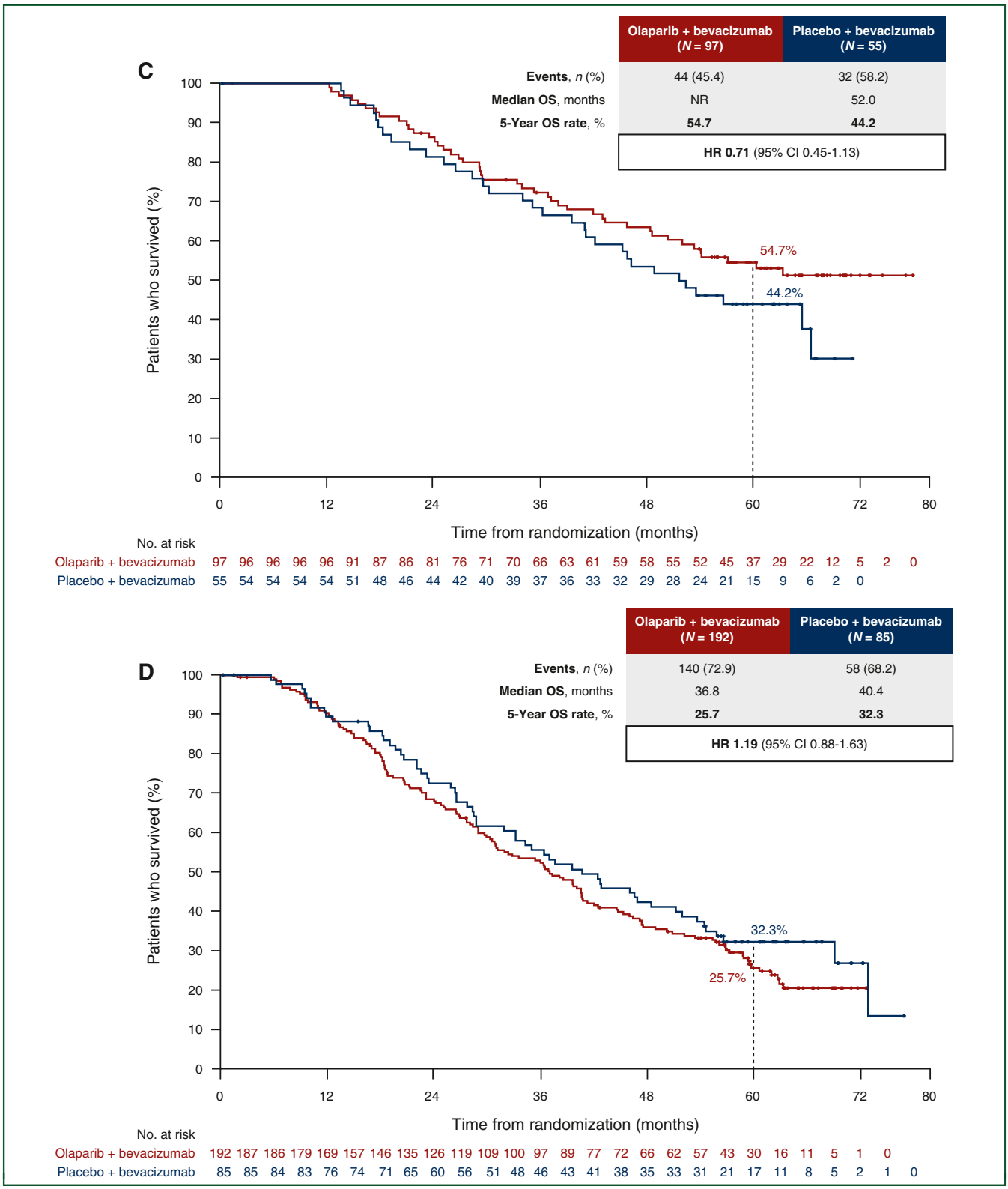

Figure 2. Continued.

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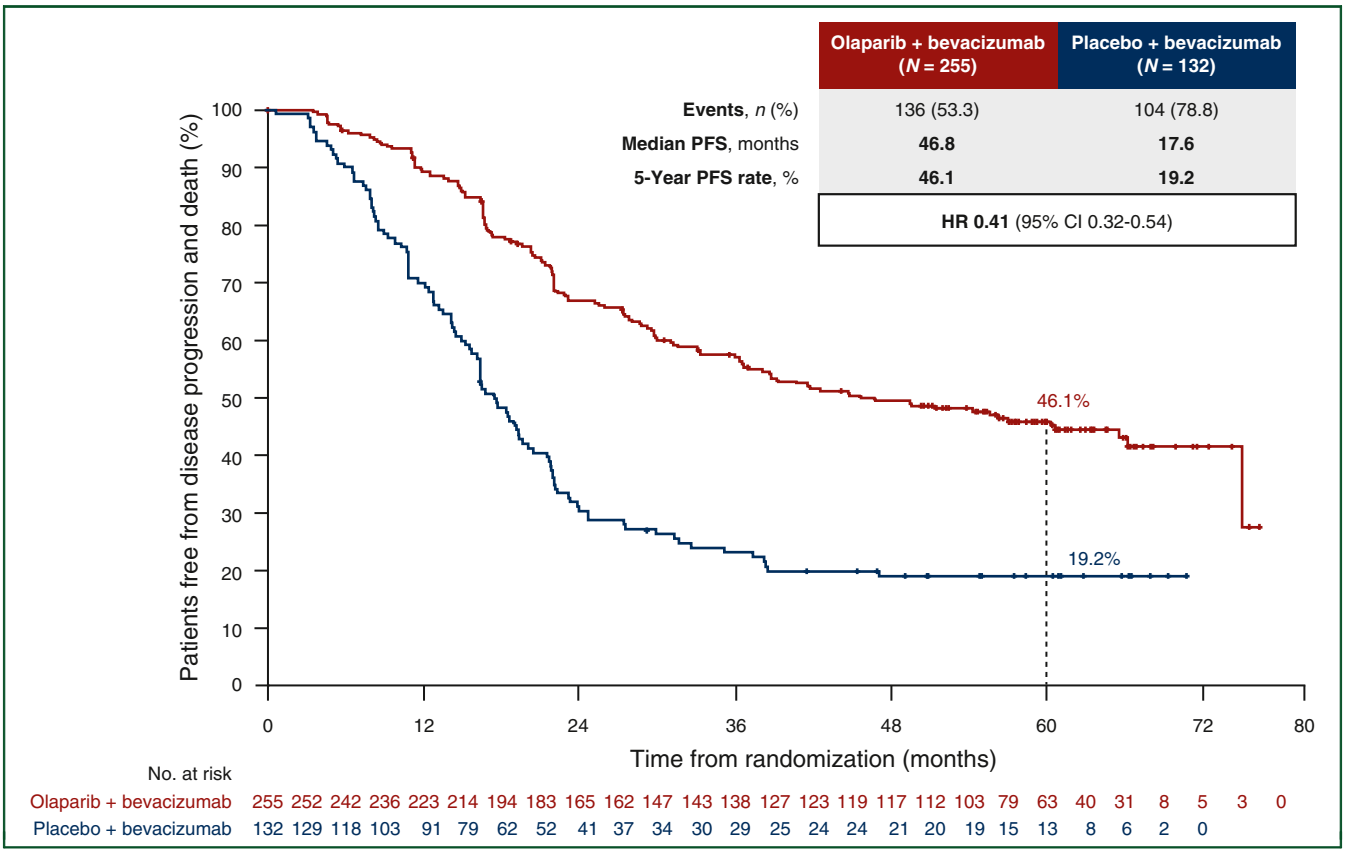

Figure 3. Kaplan–Meier estimates of updated progression-free survival in patients with a homologous recombination deficiency-positive tumor[a].
CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.
[a]Descriptive analysis; PFS by investigator-assessment [modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1].

PARP inhibitors as subsequent treatment and the OS benefit in patients with HRD-positive tumors was observed despite >50% in the placebo arm ($n = 67/132$), versus 17% with olaparib ($n = 44/255$), receiving PARP inhibitors as subsequent therapy.

The first-line setting in advanced ovarian cancer represents a key opportunity for cure, so it is noteworthy that, in PAOLA-1, with a median duration of follow-up for OS of 61.7 months, updated PFS analysis in patients with HRD-positive tumors at the current data cut-off showed a 59% reduction in risk of disease progression or death with the addition of maintenance olaparib to bevacizumab. The percentage of HRD-positive patients in the olaparib group who were still alive and yet to relapse after 5 years was more than twice that in the placebo arm for the HRD-positive population (46% versus 19%), and almost three times greater in the subset of these patients without a BRCAm (41% versus 15%). This is broadly consistent with

Table 2. Updated analysis of progression-free survival by molecular subgroups

PFS[a]	No. of events/no. of patients (%)		Median PFS, months (95% CI)		HR (95% CI)	5-Year PFS rate (%)	
	Olaparib plus bevacizumab	Placebo plus bevacizumab	Olaparib plus bevacizumab	Placebo plus bevacizumab		Olaparib plus bevacizumab	Placebo plus bevacizumab
ITT	366/537 (68.2)	222/269 (82.5)	22.9 (21.9-27.0)	16.6 (15.4-18.6)	0.63 (0.53-0.74)	29.3	15.8
HRD-positive	136/255 (53.3)	104/132 (78.8)	46.8 (36.4-65.7)	17.6 (15.8-20.3)	0.41 (0.32-0.54)	46.1	19.2
tBRCAm	78/157 (49.7)	58/80 (72.5)	60.7 (42.6-NE)	21.7 (16.6-24.1)	0.45 (0.32-0.64)	50.0	25.1
HRD-positive excluding tBRCAm	58/97 (59.8)	46/55 (83.6)	30.0 (21.9-60.3)	16.6 (12.9-19.5)	0.47 (0.32-0.7)	41.1	14.6
HRD-negative/unknown	230/282 (81.6)	118/137 (86.1)	17.3 (16.4-19.3)	16.0 (13.8-18.2)	0.9 (0.72-1.13)	13.4	12.6
HRD-negative	167/192 (87.0)	74/85 (87.1)	16.6 (14.9-18.0)	16.2 (13.8-18.6)	1.01 (0.77-1.33)	8.0	11.7
HRD unknown	63/90 (70.0)	44/52 (84.6)	22.1 (16.7-31.7)	14.6 (10.8-26.2)	0.69 (0.47-1.03)	24.4	14.3

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention-to-treat; NE, not estimated; PFS, progression-free survival; tBRCAm, tumor *BRCA1/BRCA2* mutation.
[a]Descriptive analysis; PFS by investigator-assessment [modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1].

Table 3. Adverse events of special interest in the safety analysis set

	PFS analysis DCO: 22 March 2019[9]		PFS2 analysis DCO: 22 March 2020[13]		Final OS analysis DCO: 22 March 2022	
	Olaparib plus bevacizumab ($N = 535$)	Placebo plus bevacizumab ($N = 267$)	Olaparib plus bevacizumab ($N = 535$)	Placebo plus bevacizumab ($N = 267$)	Olaparib plus bevacizumab ($N = 535$)	Placebo plus bevacizumab ($N = 267$)
MDS/AML/AA, *n* (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)[b]
New primary malignancies,[a] *n* (%)	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/ bronchiolitis, *n* (%)	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

AA, aplastic anemia; AML, acute myeloid leukemia; DCO, data cut-off; ILD, interstitial lung disease; MDS, myelodysplastic syndromes; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PFS2, time from randomization to second progression or death.

[a]New primary malignancies reported in olaparib patients were plasma cell myeloma ($n = 1$), basal cell carcinoma ($n = 2$), breast cancer ($n = 11$), bronchial carcinoma ($n = 1$), colon cancer ($n = 1$), glioblastoma ($n = 1$), malignant neoplasm ($n = 1$), pancreatic carcinoma ($n = 1$), squamous cell carcinoma ($n = 2$), and ureteric cancer ($n = 1$) and in placebo patients were papillary thyroid cancer ($n = 1$), breast cancer ($n = 4$), diffuse large B-cell lymphoma ($n = 1$), malignant lung neoplasm ($n = 1$), and malignant neoplasm ($n = 1$).

[b]Of six patients in the placebo arm who had experienced an MDS/AML/AA event by the OS DCO, four received a PARP inhibitor as subsequent therapy and two did not; in all four patients who received a PARP inhibitor as subsequent therapy, the MDS/AML/AA event occurred within 35 days after the end of the subsequent treatment (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.05.005).

time to first subsequent therapy results in a recent descriptive 7-year analysis of the SOLO1 trial, which were evaluated as a proxy for updated PFS data and showed that 45.3% of olaparib patients with a BRCAm (versus 20.6% of placebo patients) were alive and still to receive a first subsequent therapy after 7 years of follow-up. The PAOLA-1 data now suggest that the addition of olaparib to bevacizumab may enhance the potential for cure in a substantial proportion of patients with HRD-positive tumors, including those without a BRCAm.

The safety profile of olaparib has been well characterized previously, and no new safety signals were observed.[9,13] It is reassuring that, after 5 years of active follow-up in PAOLA-1, MDS/AML/AA, pneumonitis, and new primary malignancy incidence remained low. It should be noted that the high proportion of patients in the placebo arm who received PARP inhibitors as subsequent therapy may have contributed to the balanced rate of AESIs observed between arms. Indeed, while it is difficult to draw firm conclusions due to low event numbers, four of the six patients in the placebo arm who experienced an MDS/AML/AA event had received a PARP inhibitor as subsequent therapy, and in all four patients, the onset of MDS/AML/AA occurred soon after the end of the subsequent therapy. The low risk of MDS/AML/AA observed in PAOLA-1, however, is consistent with reports from other PARP inhibitor maintenance trials in the newly diagnosed setting, reaffirming their use as first-line, fixed duration maintenance therapy, particularly given the potential pre-existing risk of MDS/AML with prior chemotherapy.[17,18,21,26-28]

The PAOLA-1 results highlight the importance of refining biomarker testing to better distinguish patient populations likely to respond to PARP inhibitors. Future analyses of PAOLA-1 data evaluating OS by location and type of BRCA mutation may provide clearer assessment of individuals most likely to derive benefit.[29,30] The absence of benefit observed in patients with HRD-negative tumors in PAOLA-1 also underlines an important unmet need in this population with a high rate of disease progression observed during PARP inhibitor treatment, emphasizing the importance of refining HRD testing to better detect all patients with HRD, and highlighting the need for research into treatment options for patients with HRD-negative disease.[31]

In conclusion, in the final OS analysis of PAOLA-1, the addition of maintenance olaparib to bevacizumab modestly numerically prolonged OS versus bevacizumab alone in patients with newly diagnosed advanced ovarian cancer (ITT population). However, in the subset of patients with HRD-positive tumors, where PARP inhibitors are expected to be biologically active, olaparib plus bevacizumab provided a clinically meaningful, numerical OS advantage at 5 years, despite 50% of patients in the control arm receiving PARP inhibitors after progression. Updated PFS data reinforce the PFS advantage of this first-line maintenance combination in patients with HRD-positive tumors, which previously led to wide approval, and demonstrate that the advantage is maintained at 5 years. Taken together, these results confirm the addition of olaparib to bevacizumab as one of the standards of care for patients with HRD-positive tumors in this setting and highlight the importance of precision medicine and biomarker testing to guide treatment decisions in newly diagnosed advanced ovarian cancer patients.

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