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Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial

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ABSTRACT

Objective In the PAOLA-1/ENGOT-ov25 trial (NCT02477644), adding maintenance olaparib to bevacizumab provided a substantial progression-free survival benefit in patients with newly diagnosed advanced ovarian cancer and homologous recombination deficiency (HRD)-positive tumors, irrespective of clinical risk. Subsequently, a clinically meaningful improvement in overall survival was reported with olaparib plus bevacizumab in the HRD-positive subgroup. We report updated progression-free survival and overall survival by clinical risk and HRD status.

Methods Patients in clinical response after first-line platinum-based chemotherapy plus bevacizumab received maintenance olaparib (up to 24 months) plus bevacizumab (up to 15 months in total) or placebo plus bevacizumab. This *post hoc* analysis evaluated 5-year progression-free survival and mature overall survival in patients classified by clinical risk and HRD status.

Results Of 806 randomized patients, 74% were higher-risk and 26% were lower-risk. In higher-risk HRD-positive patients, the hazard ratio (HR) for progression-free survival was 0.46 (95% confidence interval (95% CI) 0.34 to 0.61), with 5-year progression-free survival of 35% with olaparib plus bevacizumab versus 15% with bevacizumab alone; and the HR for overall survival was 0.70 (95% CI 0.50 to 1.00), with 5-year overall survival of 55% versus 42%, respectively. In lower-risk HRD-positive patients, the HR for progression-free survival was 0.26 (95% CI 0.15 to 0.45), with 5-year progression-free survival of 72% with olaparib plus bevacizumab versus 28% with bevacizumab alone; and the HR for overall survival was 0.31 (95% CI 0.14 to 0.66), with 5-year overall survival of 88% versus 61%, respectively. No benefit was seen in HRD-negative patients regardless of clinical risk.

Conclusion This *post hoc* analysis indicates that in patients with newly diagnosed advanced HRD-positive ovarian cancer, maintenance olaparib plus bevacizumab should not be limited to those considered at higher risk of disease progression. Five-year progression-free survival rates support long-term remission and suggest an increased potential for cure with particular benefit suggested in lower-risk HRD-positive patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ After 2 years' follow-up, combination therapy with maintenance olaparib plus bevacizumab provided a progression-free survival benefit in patients with newly diagnosed advanced ovarian cancer whose tumors tested positive for homologous recombination deficiency (HRD), irrespective of clinical risk; a clinically meaningful improvement in overall survival was subsequently shown at 5 years in the HRD-positive subgroup.

INTRODUCTION

Cure is the ultimate goal of treatment in patients with newly diagnosed ovarian cancer. However, patients often have advanced disease at the time of diagnosis and experience relapse[1]; once relapse has occurred, advanced ovarian cancer is considered to be incurable in most patients. Factors such as disease stage and surgical outcome impact the risk of relapse and survival, with improved overall survival seen in patients with complete surgical resection, compared with residual disease, after primary cytoreductive surgery.[2]

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WHAT THIS STUDY ADDS

⇒ The majority of patients with ovarian cancer relapse within 3 years of diagnosis, meaning that patients who remain relapse-free at 5 years are potentially cured. Five-year progression-free survival results in PAOLA-1 indicate that maintenance olaparib plus bevacizumab may have the potential to enhance cure in a substantial proportion of HRD-positive patients. A clinically meaningful overall survival benefit was seen with olaparib plus bevacizumab over bevacizumab alone in patients whose tumors tested HRD-positive regardless of whether they were considered at higher risk or lower risk of disease progression, with particular benefit suggested in lower-risk patients. The incidence of myelodysplastic syndrome, acute myeloid leukemia, or aplastic anemia was balanced between treatment arms in both higher-risk and lower-risk patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This analysis indicates that, regardless of clinical risk, maintenance olaparib plus bevacizumab should be considered one of the standards of care in patients with newly diagnosed advanced ovarian cancer whose tumors test HRD-positive, with the greatest potential for cure seen in lower-risk HRD-positive patients.

The phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644) demonstrated that the addition of maintenance olaparib to bevacizumab significantly improved progression-free survival versus bevacizumab alone (hazard ratio (HR) 0.59, 95% confidence interval (95% CI) 0.49 to 0.72, p<0.001) in patients with newly diagnosed advanced ovarian cancer who were in clinical response after first-line platinum-based chemotherapy plus bevacizumab.[3] A substantial progression-free survival benefit was observed with olaparib plus bevacizumab over bevacizumab alone in patients whose tumors tested positive for homologous recombination deficiency (HRD; defined as a *BRCA1* and/or *BRCA2* (BRCA) mutation and/or genomic instability) (HR 0.33, 95% CI 0.25 to 0.45),[3] leading to its approval in this patient population. A clinically meaningful overall survival benefit was also seen after 5 years of follow-up in patients with HRD-positive tumors (HR 0.62, 95% CI 0.45 to 0.85), with 5-year overall survival rates of 66% versus 48%, respectively.[4]

All patients with newly diagnosed advanced ovarian cancer are at risk for disease progression and death,[1] including patients who may be considered 'lower-risk' such as those with International Federation of Gynecology and Obstetrics (FIGO) stage III disease and no residual macroscopic disease following upfront cytoreductive surgery. Importantly, entry into PAOLA-1 was not restricted by surgical outcome, with 'lower-risk' patients eligible for enrollment.[3] In PAOLA-1 analyses by clinical risk, the definition of higher-risk was modified from the ICON7[5] criteria to include neoadjuvant chemotherapy. A previous *post hoc* analysis at the primary analysis data cut-off (March 22, 2019) demonstrated that maintenance olaparib plus bevacizumab provided a progression-free survival benefit over bevacizumab alone in patients with HRD-positive tumors irrespective of clinical risk.[6] A greater treatment effect was seen for olaparib plus bevacizumab versus bevacizumab alone in lower-risk patients (HR 0.15, 95% CI 0.07 to 0.30; 2-year progression-free survival, 90% vs 43%) than in higher-risk patients (HR 0.39, 95% CI 0.28 to 0.54; 2-year progression-free survival, 56% vs 23%).[6] We conducted this *post hoc* subgroup analysis of PAOLA-1 to evaluate overall survival with maintenance olaparib plus bevacizumab versus bevacizumab alone in patients considered at higher and lower risk for disease progression and by HRD status. Median progression-free survival had not been reached in lower-risk HRD-positive patients at the primary analysis data cut-off; we also report updated progression-free survival at 5 years by clinical risk and HRD status.

METHODS

Patients

As reported previously,[3] eligible patients had newly diagnosed FIGO stage III or IV, high-grade serous or high-grade endometrioid ovarian, primary peritoneal and/or fallopian tube cancer, or other epithelial non-mucinous ovarian cancer with a germline BRCA mutation, and no evidence of disease or clinical complete or partial response after surgery and first-line treatment with platinum-based chemotherapy plus bevacizumab. Patients were eligible irrespective of surgical outcome. In this analysis, patients with stage III disease who had undergone upfront surgery and had residual disease or who had received neoadjuvant chemotherapy, or who had stage IV disease, were considered higher risk, and patients with stage III disease who had undergone upfront surgery and had complete resection were considered lower risk. Tumor BRCA mutation status was determined centrally. Full eligibility criteria have been published previously.[3] PAOLA-1/ENGOT-ov25 was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, under the auspices of an independent data monitoring committee, and was approved by the appropriate institutional review boards (affirmed by Isabelle Ray-Coquard, principal investigator). All patients provided written informed consent.

Study Design and Treatments

PAOLA-1/ENGOT-ov25 was a randomized, double-blind, multicenter phase III trial conducted in 11 countries. The trial was designed by the European Network of 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 Gynecologiques (ARCAGY) Research, according to the ENGOT model A.[7 8]

Randomization occurred at least 3 weeks and no more than 9 weeks after the last dose of chemotherapy and was stratified according to the outcome of first-line treatment at screening and tumor BRCA mutation status. Patients were randomized to receive olaparib tablets 300 mg twice daily or placebo. Study treatment continued for up to 24 months or until investigator-assessed objective radiological disease progression (modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[9]) or unacceptable toxicity, whichever occurred first, as long as the patient experienced benefit and did not meet other discontinuation criteria. Crossover between the treatment arms was not planned. Further information is provided in Online Supplemental File 1.

All patients received intravenous bevacizumab 15 mg/kg every 3 weeks for a total duration of 15 months (including when administered in combination with chemotherapy).

Endpoints

Progression-free survival (primary endpoint; investigator assessed using modified RECIST version 1.1),[3] time to first subsequent

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therapy or death,[3] and overall survival (key secondary endpoint)[4] have been reported previously.

In this *post hoc* analysis, progression-free survival, time to first subsequent therapy or death, and overall survival were evaluated according to clinical risk and biomarker profile. HRD-positive was defined as a tumor BRCA mutation and/or a genomic instability score (GIS) ≥42 (MyChoice HRD Plus assay; Myriad Genetic Laboratories, Inc, Salt Lake City, UT), HRD-positive without a BRCAm was defined as GIS ≥42 and no tumor BRCA mutation, and HRD-negative was defined as GIS <42 and no tumor BRCA mutation. The incidence of myelodysplastic syndrome, acute myeloid leukemia, and aplastic anemia was also evaluated according to clinical risk and biomarker profile; monitoring for these adverse events continued during follow-up for overall survival.

Statistical Analysis

The final overall survival analysis was planned for ~60% data maturity or 3 years after the primary progression-free survival analysis and has been reported previously.[4]

Efficacy data were summarized and analyzed in the intent-to-treat population (all randomized patients; full analysis set) using the electronic case report form data set, apart from the HRD analysis, which used Myriad data to determine HRD status.

Progression-free survival, time to first subsequent therapy or death, and overall survival were estimated using the Kaplan-Meier method. In the full analysis set, the treatment groups were compared using the stratified log-rank test and HRs and 95% CIs were calculated using a stratified Cox proportional hazards model. For the higher-risk and lower-risk subgroups, HRs and 95% CIs were calculated from a single Cox proportional hazards model performed on the overall population, including a term for treatment, the subgroup covariate, and the treatment by subgroup interaction term. The treatment effect HR was obtained for each level of the subgroup from this model. The Cox model was fitted with the Efron method[10] to handle ties. For the biomarker subgroups, the same method mentioned above was applied to both the higher-risk and lower-risk subgroups (Online Supplemental File 1). Overall survival analyses were unadjusted for subsequent therapy.

Safety data were analyzed descriptively in the safety analysis set (all randomized patients who received at least one dose of olaparib or placebo).

RESULTS

As reported previously, of the 806 patients who underwent randomization, 595 (74%) were higher risk and 211 (26%) were lower risk (Online Supplemental Figure S1).[6] Patient baseline characteristics were generally well balanced between the higher-risk and lower-risk subgroups, although differences were seen in FIGO stage, timing of surgery, and residual disease status, reflecting the clinical risk definitions (Online Supplemental Table S1).[6]

Overall, the median (IQR) follow-up was 61.7 (57.6–66.8) months (data cut-off: March 22, 2022). Five-year progression-free survival, time to first subsequent therapy and death, and overall survival by clinical risk in the intent-to-treat population, as well as the proportion of patients receiving a poly(ADP-ribose) polymerase (PARP) inhibitor during subsequent therapy, are reported in Online Supplemental Table S2.

Five-year progression-free survival in patients whose tumors tested HRD-positive has been reported previously.[4] In higher-risk HRD-positive patients, median progression-free survival was 31.3 months with olaparib plus bevacizumab and 15.9 months with placebo plus bevacizumab; the HR for progression-free survival was 0.46 (95% CI 0.34 to 0.61) and 5-year progression-free survival was 35% versus 15%, respectively (Kaplan-Meier estimates) (figure 1A). In lower-risk HRD-positive patients, median progression-free survival was unstable in the olaparib plus bevacizumab group due to lack of events and was 22.3 months with placebo plus bevacizumab; the HR for progression-free survival was 0.26 (95% CI 0.15 to 0.45) and 5-year progression-free survival was 72% versus 28%, respectively (Kaplan-Meier estimates) (figure 1B). The time to first subsequent therapy or death also favored olaparib plus bevacizumab over placebo plus bevacizumab in both higher-risk and lower-risk HRD-positive patients (Online Supplemental Figure S3A and S3B).

Overall survival in patients whose tumors tested HRD-positive has been reported previously.[4] In higher-risk HRD-positive patients, median overall survival was unstable in the olaparib plus bevacizumab group due to lack of events and was 54.0 months with placebo plus bevacizumab; the HR for overall survival was 0.70 (95% CI 0.50 to 1.00) and 5-year overall survival was 55% versus 42%, respectively (Kaplan-Meier estimates). Analysis did not account for subsequent PARP inhibitor therapy; 19% of olaparib plus bevacizumab patients versus 56% of placebo plus bevacizumab patients received subsequent PARP inhibitor therapy (figure 2A). In lower-risk HRD-positive patients, median overall survival was not reached in either treatment group; the HR for overall survival for olaparib plus bevacizumab versus placebo plus bevacizumab was 0.31 (95% CI 0.14 to 0.66) and 5-year overall survival was 88% versus 61%, respectively (Kaplan-Meier estimates). Analysis did not account for subsequent PARP inhibitor therapy; 14% of olaparib plus bevacizumab patients versus 40% of placebo plus bevacizumab patients received subsequent PARP inhibitor therapy (figure 2B).

Benefit was seen with olaparib plus bevacizumab over bevacizumab in patients with a tumor BRCA mutation (figure 1C,D, figure 2C,D, Online Supplemental Figures S3C and S3D) and in patients with HRD-positive tumors without a BRCA mutation (figure 1E,F, figure 2E, Online Supplemental Figures S3E and S3F) regardless of clinical risk.

No benefit was seen in higher-risk or lower-risk patients with HRD-negative tumors who received olaparib plus bevacizumab versus bevacizumab alone (table 1 and Online Supplemental Figures S2, S3G, S3H, and S4).

The incidence of myelodysplastic syndrome, acute myeloid leukemia, or aplastic anemia at the March 22, 2022 data cut-off has been reported previously.[4] The incidence of these events was balanced between treatment arms in both higher-risk and lower-risk patients, including in the HRD-positive subgroups (table 2).

DISCUSSION

Summary of Main Results

In PAOLA-1, the addition of maintenance olaparib to bevacizumab provided a clinically meaningful overall survival benefit in patients

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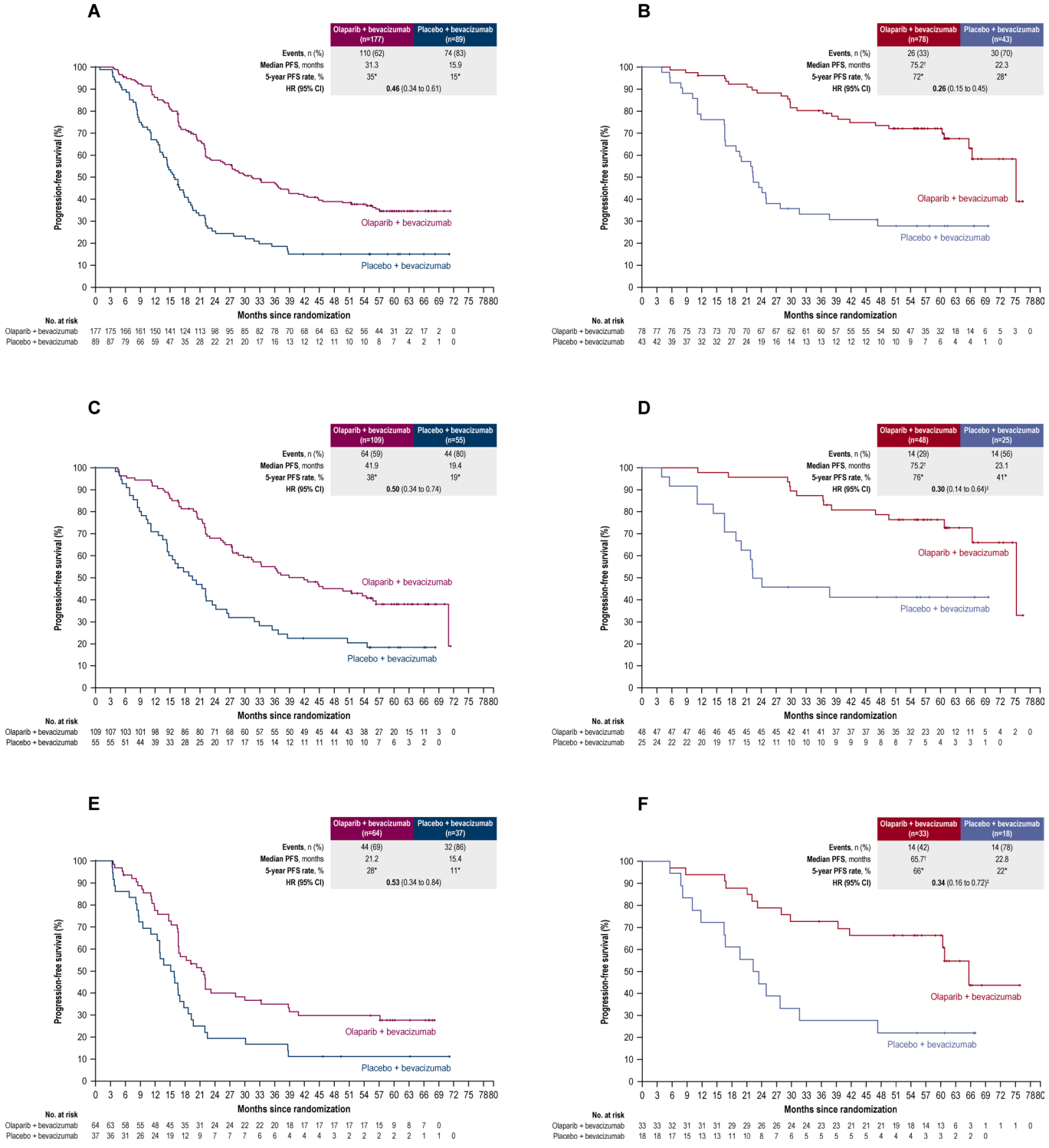

Figure 1 Kaplan-Meier estimate of progression-free survival in (A) higher-risk patients with HRD-positive tumors, (B) lower-risk patients with HRD-positive tumors, (C) higher-risk patients with a BRCA mutation, (D) lower-risk patients with a BRCA mutation, (E) higher-risk patients with HRD-positive tumors without a BRCA mutation, and (F) lower-risk patients with HRD-positive tumors without a BRCA mutation. Five-year progression-free survival data from the final overall survival data cut-off (March 22, 2022). The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points. Tumor BRCAm status was determined by one of five central French academic laboratories before trial entry, and HRD status was determined retrospectively by the MyChoice HRD Plus assay. HRD-positive defined as a tumor BRCA mutation and/or GIS ≥42; HRD-positive without a BRCAm defined as GIS ≥42 and no tumor BRCA mutation. The number of patients in the tumor BRCAm and HRD-positive without tumor BRCAm subgroups does not equal the total number of patients in the HRD-positive subgroup because of these different testing methods. *Kaplan-Meier estimates. †Unstable median due to lack of events. ‡Too few events and/or survival curves cross; interpret HRs with caution. BRCA, *BRCA1* and/or *BRCA2*; GIS, genomic instability score; HRD, homologous recombination deficiency; PFS, progression-free survival.

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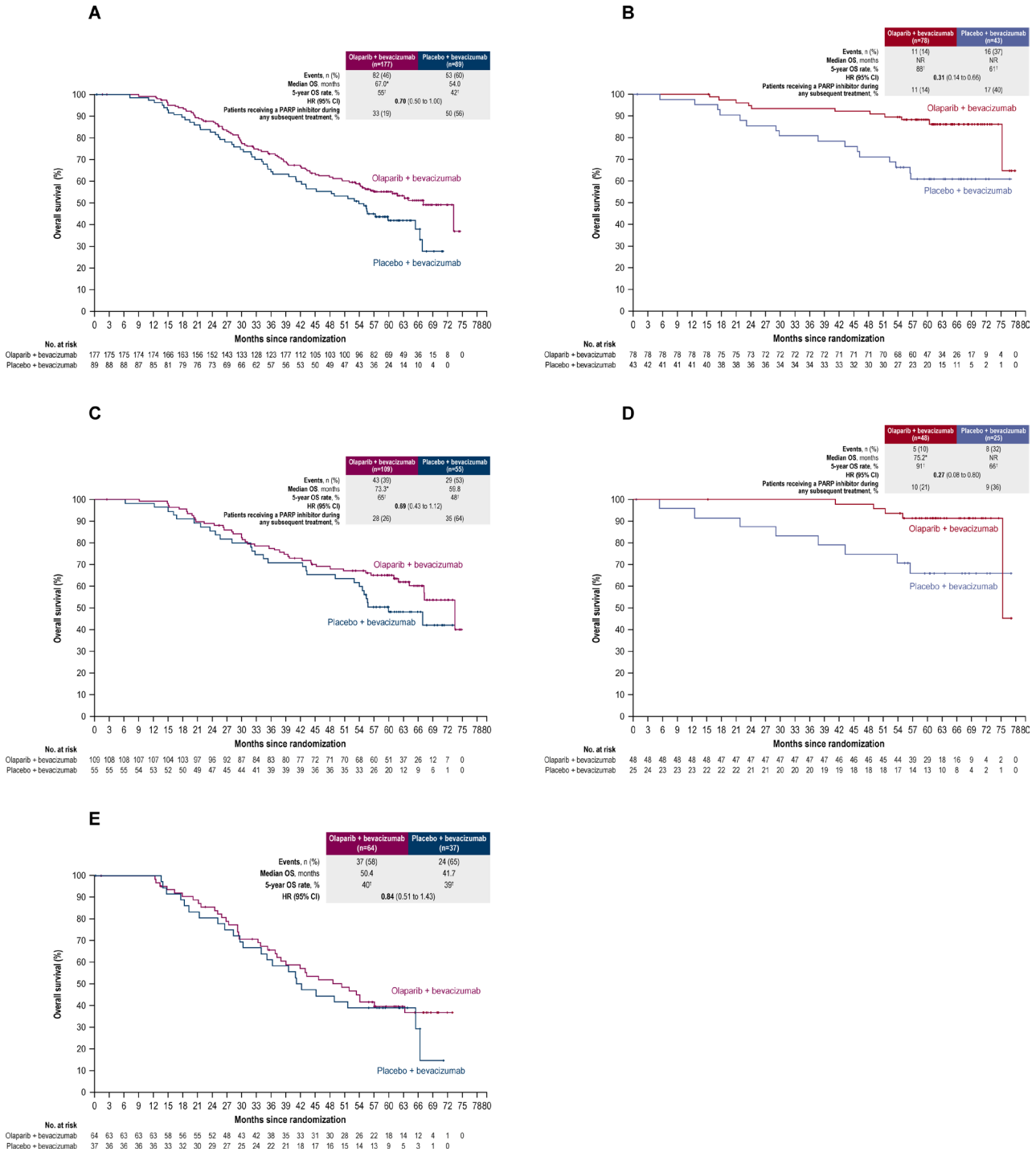

Figure 2 Kaplan-Meier estimate of overall survival in (A) higher-risk patients with HRD-positive tumors, (B) lower-risk patients with HRD-positive tumors, (C) higher-risk patients with a BRCA mutation, (D) lower-risk patients with a BRCA mutation, and (E) higher-risk patients with HRD-positive tumors without a BRCA mutation. Data in panel E are shown for higher-risk patients with HRD-positive tumors without a BRCA mutation; in lower-risk patients with HRD-positive tumors without a BRCA mutation, median overall survival was not reached in either treatment group, and the HR was not reported because of too few events; 5-year overall survival was 82% in the olaparib plus bevacizumab group versus 54% in the bevacizumab group (Kaplan-Meier estimates). The end of the curves should be interpreted with caution because of the small number of patients at risk at these time points. Tumor BRCAm status was determined by one of five central French academic laboratories before trial entry and HRD status was determined retrospectively by the MyChoice HRD Plus assay. HRD-positive defined as a tumor BRCA mutation and/or GIS ≥42; HRD-positive without a BRCA mutation defined as GIS ≥42 and no tumor BRCA mutation. The number of patients in the tumor BRCAm and HRD-positive without tumor BRCAm subgroups does not equal the total number of patients in the HRD-positive subgroup because of these different testing methods. *Unstable median due to lack of events. †Kaplan-Meier estimates. BRCA, *BRCA1* and/or *BRCA2*; GIS, genomic instability score; HRD, homologous recombination deficiency; NR, not reached; OS, overall survival.

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Table 1 Outcomes in higher-risk and lower-risk patients in the HRD-negative subgroup

	Higher risk		Lower risk	
	Olaparib + bevacizumab (n=144)	**Placebo + bevacizumab (n=62)**	**Olaparib + bevacizumab (n=48)**	**Placebo + bevacizumab (n=23)**
PFS*				
Events, n (%)	130 (90)	57 (92)	37 (77)	17 (74)
Median PFS, months	15.2	13.8	23.8	22.9
HR (95% CI)	0.92 (0.68 to 1.27)		1.12 (0.64 to 2.03)†	
5-year PFS rate,‡ %	6	7	15	26
TFST*				
Events, n (%)	135 (94)	55 (89)	37 (77)	19 (83)
Median TFST, months	16.5	14.1	27.3	26.3
HR (95% CI)	0.97 (0.71 to 1.34)		1.00 (0.58 to 1.77)†	
5-year TFST rate,‡ %	5	10	20	18
OS				
Events, n (%)	116 (81)	46 (74)	24 (50)	12 (52)
Median OS, months	31.6	28.5	59.3	56.2
HR (95% CI)	1.15 (0.82 to 1.63)		1.14 (0.58 to 2.38)	
5-year OS rate,‡ %	18	26	48	49
Patients receiving a PARP inhibitor during any subsequent treatment, n (%)	32 (22)	21 (34)	14 (29)	13 (57)

HRD-negative defined as GIS < 42 and no tumor BRCA mutation (MyChoice HRD Plus).
*5-year PFS and TFST data from the final overall survival data cut-off (March 22, 2022).
†Survival curves cross; interpret HRs with caution.
‡Kaplan-Meier estimates.
BRCAm, *BRCA1* and/or *BRCA2* mutation; GIS, genomic instability score; HRD, homologous recombination deficiency; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; TFST, time to first subsequent therapy or death.

with HRD-positive tumors irrespective of whether they were considered at higher or lower risk of disease progression. Approximately one-half of HRD-positive patients in the placebo plus bevacizumab group received subsequent PARP inhibitor therapy, with a higher rate of crossover seen in higher-risk than in lower-risk patients. Overall survival analyses were unadjusted for subsequent PARP inhibitor therapy and the overall survival benefit was seen in the HRD-positive subgroup, despite 56% of higher-risk patients and 40% of lower-risk patients in the placebo plus bevacizumab group receiving subsequent PARP inhibitor therapy. These findings show that the improvement in progression-free survival seen with olaparib plus bevacizumab in the HRD-positive subgroup[6] translates into an overall survival benefit regardless of clinical risk and support the upfront use of olaparib plus bevacizumab.

Overall survival favored maintenance olaparib plus bevacizumab over bevacizumb alone in higher-risk and lower-risk patients with HRD-positive tumors with or without a BRCA mutation or with BRCA-mutated tumors, emphasizing the importance of biomarker testing to guide decision-making in the first-line setting.

Maintenance olaparib plus bevacizumab may provide particular benefit in lower-risk patients with stage III disease and complete resection after upfront surgery, although results in the biomarker subgroups should be interpreted with caution because of small numbers of patients.

Table 2 MDS/AML/AA in higher-risk and lower-risk patients in the intent-to-treat population and HRD-positive subgroup in the safety analysis set

	Higher risk		Lower risk	
	Olaparib + bevacizumab	**Placebo + bevacizumab**	**Olaparib + bevacizumab**	**Placebo + bevacizumab**
Intent-to-treat population	n=398	n=194	n=137	n=73
Patients with MDS/AML/AA, n (%)	7 (1.8)	4 (2.1)	2 (1.5)	2 (2.7)
HRD-positive subgroup	n=177	n=88	n=78	n=43
Patients with MDS/AML/AA, n (%)	4 (2.3)	2 (2.3)	2 (2.6)	2 (4.7)

HRD-positive defined as a tumor BRCAm and/or GIS ≥42 (MyChoice HRD Plus).
AA, aplastic anemia; AML, acute myeloid leukemia; BRCAm, *BRCA1* and/or *BRCA2* mutation; GIS, genomic instability score; HRD, homologous recombination deficiency; ITT, intent-to-treat; MDS, myelodysplastic syndrome.

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Results in the Context of Published Literature

It remains unclear why lower-risk patients might have experienced particular benefit in PAOLA-1. The possibility that combination therapy has an additive effect due to an undetermined biological mechanism cannot be excluded and possible mechanisms relating to underlying pathophysiology[11] have been discussed previously.[6] Although comparisons across trials should be made with caution because of differences in trial design and study populations, a greater treatment effect was not observed in patients considered lower risk than in those considered higher risk in phase III trials evaluating bevacizumab (GOG-0218,[12] ICON7[5]) or PARP inhibitor maintenance monotherapy (SOLO1,[13] ATHENA-MONO[14]) in the first-line setting (Online Supplemental Table S3).

There remains a high unmet need in patients with newly diagnosed advanced ovarian cancer whose tumors test HRD-negative. Consistent with earlier results,[6] no overall survival benefit was seen with olaparib plus bevacizumab over placebo plus bevacizumab in higher- or lower-risk patients with HRD-negative tumors in PAOLA-1. A progression-free survival benefit was seen in newly diagnosed patients with HRD-negative advanced ovarian cancer who received maintenance niraparib versus placebo in PRIMA/ENGOT-ov26 (which only enrolled higher-risk patients)[15 16] and maintenance rucaparib versus placebo in ATHENA-MONO.[17] Whether the progression-free survival benefit seen in HRD-negative patients receiving maintenance niraparib or rucaparib will translate into an overall survival advantage is still unknown. Recently reported results from an interim progression-free survival analysis of the DUO-O study showed a progression-free survival benefit in a newly diagnosed all-comers population for paclitaxel/carboplatin plus bevacizumab and the anti-programmed death-ligand 1 antibody durvalumab followed by maintenance olaparib plus durvalumab and bevacizumab compared with paclitaxel/carboplatin plus bevacizumab followed by maintenance bevacizumab. A progression-free survival benefit was also observed in the HRD-negative subgroup.[18] Results of other studies[19–21] evaluating combination regimens including PARP inhibitors and immuno-oncology agents are awaited with interest.

Strengths and Weaknesses

PAOLA-1 was a well-designed, randomized, double-blind, placebo-controlled study and was the first trial of PARP inhibitor maintenance therapy in the first-line setting to include an active control arm. The PAOLA-1 population was generally representative of real-world patients with newly diagnosed advanced ovarian cancer as patient selection was not restricted by surgical outcome or biomarker status. Potential limitations of PAOLA-1 are that only patients with no evidence of disease or clinical complete or partial response after standard first-line treatment were included, and that HRD status was not a stratification factor in the study. Interpretation of the presented data are limited by the *post hoc* nature of the analyses, the definition of 'high risk' was modified from that used in ICON7, and the small number of patients in the biomarker subgroups.

Implications for Practice and Future Research

The first-line setting provides the main opportunity for cure in advanced ovarian cancer. The majority of patients relapse within 3 years of diagnosis,[1] meaning that patients who remain relapse-free at 5 years are potentially cured. Results of 5-year progression-free survival analyses support long-term remission with maintenance olaparib plus bevacizumab, and suggest that combination therapy may enhance the potential for cure in a substantial proportion of patients with HRD-positive tumors, with particular benefit suggested in lower-risk patients. At 5 years in the lower-risk HRD-positive subgroup, 72% of patients who received olaparib plus bevacizumab were alive and free from relapse (vs 28% in the placebo plus bevacizumab arm) and 88% (vs 61%) of patients were alive, with a plateau seen in the survival curve in the olaparib plus bevacizumab group. These results showing the enhanced potential for cure, especially in lower-risk patients with HRD-positive tumors, emphasize the importance of providing optimal first-line treatment to this patient population rather than reserving such treatment for the relapsed setting. Combination therapy with maintenance olaparib plus bevacizumab should not be limited to those considered at higher risk of disease progression in the first-line setting.

Further insight into the benefit of first-line treatment with a PARP inhibitor plus bevacizumab versus a PARP inhibitor alone will be provided by the phase II NIRVANA-1/ENGOT-ov63 trial in lower-risk patients with stage III ovarian cancer and complete resection after upfront surgery,[22] and by the phase III AGO-OVAR 28/ENGOT-ov57 trial in an all-comers population.[23]

CONCLUSIONS

Results of this *post hoc* analysis indicate that maintenance olaparib plus bevacizumab should be considered one of the standards of care for all patients with newly diagnosed advanced ovarian cancer whose tumors test positive for HRD, regardless of whether they are considered at higher or lower risk of disease progression. Five-year progression-free survival rates support long-term remission and suggest an increased potential for cure with the addition of olaparib to platinum-based chemotherapy plus bevacizumab, with particular benefit suggested in lower-risk patients.

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Data availability statement Data are available upon reasonable request. ARCAGY-GINECO has a long history of academic data sharing for research purposes. The process is similar for every trial sponsored by ARCAGY-GINECO (or ARCAGY Research). Researchers have to submit a request to the sponsor directly or through the principal investigator. The request should be written in a predefined format of a short synopsis indicating the objective of the research, the methodology intended to be used, including the statistical analysis plan, and the variables within the database required for the research. A scientific board will review and approve the requests on a case-by-case basis. Only encoded datasets will be used, which enables us to fulfil legal and ethical obligations to protect our patients while at the same time utilizing patient data in progressing medical research to its full potential in the best interests of public health. A specific agreement between the sponsor and the researcher is requested for data transfer. This data transfer agreement details both parts responsibilities to ensure the required level of data integrity and legal and ethical obligations. In the case of sharing encoded patient-level data, please note that the full dataset may not be shared in view of the following: clinical consent for some countries prohibits secondary use of the data; patients may withdraw their consent for participation in the trial at any point; other aspects might also be taken into consideration to protect patient privacy (eg, review of rare clinical events where information is aggregated to a higher level before sharing).

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REFERENCES

1 Ledermann JA, Raja FA, Fotopoulou C, *et al*. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24 Suppl 6:vi24–32.
2 du Bois A, Reuss A, Pujade-Lauraine E, *et al*. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe D'Investigateurs Nationaux pour LES Etudes des cancers de L'Ovaire (GINECO). *Cancer* 2009;115:1234–44.
3 Ray-Coquard I, Pautier P, Pignata S, *et al*. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med* 2019;381:2416–28.
4 Ray-Coquard I, Leary A, Pignata S, *et al*. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-Ov25 trial. *Ann Oncol* 2023;34:681–92.
5 Oza AM, Cook AD, Pfisterer J, *et al*. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol* 2015;16:928–36.
6 Harter P, Mouret-Reynier MA, Pignata S, *et al*. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-Ov25 trial. *Gynecol Oncol* 2022;164:254–64.
7 Vergote I, Pujade-Lauraine E, Pignata S, *et al*. European Network of Gynaecological Oncological Trial groups' requirements for trials between academic groups and pharmaceutical companies. *Int J Gynecol Cancer* 2010;20:476–8.
8 du Bois A, Reuss A, Pujade-Lauraine E, *et al*. European Network of Gynaecological Oncological Trial groups' requirements for trials between academic groups and industry partners--first update 2015. *Int J Gynecol Cancer* 2015;25:1328–30.
9 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
10 Efron B. The efficiency of Cox's likelihood function for censored data. *J Am Stat Assoc* 1977;72:557–65.
11 Covens AL. A critique of surgical cytoreduction in advanced ovarian cancer. *Gynecol Oncol* 2000;78(3 Pt 1):269–74.
12 Tewari KS, Burger RA, Enserro D, *et al*. Final overall survival of a randomized trial of bevacizumab for primary treatment of ovarian cancer. *J Clin Oncol* 2019;37:2317–28.
13 Banerjee S, Moore KN, Colombo N, *et al*. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (Solo1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2021;22:1721–31.
14 Kristeleit R, Ghamande S, Lim M-C, *et al*. Rucaparib maintenance treatment in patients (Pts) with newly diagnosed ovarian cancer (OC): defining benefit according to disease risk subgroups within the phase 3 ATHENA–MONO study. *Ann Oncol* 2022;33(Suppl):S786–7.
15 González-Martín A, Pothuri B, Vergote I, *et al*. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019;381:2391–402.
16 González-Martín A, Pothuri B, Vergote I, *et al*. Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-Ov26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. *Eur J Cancer* 2023;189.
17 Monk BJ, Parkinson C, Lim MC, *et al*. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-Ov45). *J Clin Oncol* 2022;40:3952–64.
18 Harter P, Trillsch F, Okamoto A, *et al*. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (BEV), followed by maintenance durvalumab, BEV, and olaparib in patients (Pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): results from the randomized, placebo (Pbo)-controlled phase III DUO-O trial. *J Clin Oncol* 2023;41(17_suppl):LBA5506.
19 Monk BJ, Coleman RL, Fujiwara K, *et al*. ATHENA (GOG-3020/ENGOT-Ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. *Int J Gynecol Cancer* 2021;31:1589–94.
20 Hardy-Bessard A-C, Moore KN, Mirza MR, *et al*. ENGOT-Ov44/FIRST study: a randomized, double-blind, adaptive, phase III study of platinum-based therapy with dostarlimab (TSR-042) + niraparib versus standard-of-care (SOC) platinum-based therapy as first-line treatment of stage 3/4 non-mucinous epithelial ovarian cancer (OC). *J Clin Oncol* 2019;37(15_suppl):TPS5600.
21 Coleman RL, Fujiwara K, Sehouli J, *et al*. ENGOT-Ov43/Keylynk-001: a phase III, placebo- and active-controlled trial of pembrolizumab plus chemotherapy with olaparib maintenance for first-line treatment of advanced BRCA-nonmutated epithelial ovarian cancer. *Gynecol Oncol* 2020;159:89–90.
22 Freyer G, Gonzalez Martin AJ, Raspagliesi F, *et al*. NIRVANA-1: a multicentre randomized study comparing carboplatin-paclitaxel (CP) followed by niraparib (Nira) to CP–bevacizumab (BEV) followed by Nira-BEV in patients with FIGO stage III ovarian high-grade epithelial cancer and no residual disease after upfront surgery. *Ann Oncol* 2022;33:S826.
23 Heitz F, Marth C, Henry S, *et al*. AGO-OVAR 28/ENGOT-Ov57: niraparib versus niraparib in combination with bevacizumab in patients with carboplatin-taxane based chemotherapy in advanced ovarian cancer—a multicenter, randomized, phase III trial. *J Clin Oncol* 2022;40(16_suppl):TPS5612.

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