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ORIGINAL ARTICLE

Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial☆

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Background: The phase III PRIMA/ENGOT-OV26/GOG-3012 trial met its primary endpoint. Niraparib first-line maintenance significantly prolonged progression-free survival (PFS) among patients with newly diagnosed advanced ovarian cancer that responded to first-line platinum-based chemotherapy, regardless of homologous recombination deficiency (HRD) status. Final overall survival (OS) results are reported.

Patients and methods: Patients were randomized 2:1 to niraparib or placebo, stratified by response to first-line treatment, receipt of neoadjuvant chemotherapy, and tumor HRD status. After reaching 60% target maturity, OS was evaluated via a stratified log-rank test using randomization stratification factors and summarized using Kaplan—Meier methodology. OS testing was hierarchical [overall population first, then the homologous recombination-deficient (HRd) population]. Other secondary outcomes and long-term safety were assessed; an updated, *ad hoc* analysis of investigator-assessed PFS was also conducted (cut-off date, 8 April 2024).

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☆Note: This study was presented at the 2024 meeting of the European Society for Medical Oncology, 13-17 September 2024, Barcelona, Spain.

Results: The median follow-up was 73.9 months. In the overall population, the OS hazard ratio was 1.01 [95% confidence interval (CI) 0.84-1.23; $P = 0.8834$] for niraparib ($n = 487$) versus placebo ($n = 246$). In the HRd ($n = 373$) and homologous recombination-proficient ($n = 249$) populations, the OS hazard ratios were 0.95 (95% CI 0.70-1.29) and 0.93 (95% CI 0.69-1.26), respectively. Subsequent poly(ADP-ribose) polymerase inhibitor therapy was received by 11.7% and 15.8% of niraparib patients and 37.8% and 48.4% of placebo patients in the overall and HRd populations, respectively. The 5-year PFS rate numerically favored niraparib in the overall (niraparib, 22%; placebo, 12%) and HRd populations (niraparib, 35%; placebo, 16%). Myelodysplastic syndromes/acute myeloid leukemia incidence was <2.5% (niraparib, 2.3%; placebo, 1.6%). No new safety signals were observed.

Conclusions: In patients with newly diagnosed advanced ovarian cancer at high risk of recurrence, there was no difference in OS between treatment arms. In the HRd population, patients alive at 5 years were two times as likely to be progression free with niraparib treatment than placebo. Long-term safety remained consistent with the established niraparib safety profile.

Key words: ovarian cancer, niraparib, PARP inhibitor, maintenance, overall survival

INTRODUCTION

Ovarian cancer (OC) is the sixth most common cause of cancer mortality among women in the United States and the eighth worldwide,[1,2] and the estimated 5-year survival rate for patients with distant disease at diagnosis is ≈30%.[2] The standard treatment for patients with newly diagnosed advanced OC is surgical resection combined with first-line platinum-based chemotherapy either alone or in combination with bevacizumab.[3] In patients who experience a complete or partial response to first-line treatment, maintenance therapy with poly(ADP)-ribose polymerase (PARP) inhibitors is recommended, with or without bevacizumab.[3,4] Niraparib is a PARP inhibitor approved for the first-line maintenance treatment of patients with newly diagnosed advanced OC regardless of homologous recombination deficiency (HRD) status[5-7] after showing significant improvements in progression-free survival (PFS) compared with placebo.[8-10]

The PRIMA/ENGOT-OV26/GOG-3012 trial was a randomized, double-blind, placebo-controlled, phase III trial that evaluated the safety and efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced OC at high risk for recurrence that responded to first-line platinum-based chemotherapy.[8] In the primary analysis (data cut-off date, 17 May 2019), niraparib maintenance therapy was shown to significantly extend PFS compared with placebo in both the homologous recombination-deficient [HRd; median PFS 21.9 versus 10.4 months; hazard ratio 0.43, 95% confidence interval (CI) 0.31-0.59; $P < 0.001$] and overall populations (median PFS 13.8 versus 8.2 months; hazard ratio 0.62, 95% CI 0.50-0.76; $P < 0.001$).[8] At the time of the primary analysis, overall survival (OS) data were immature (10.8% of the overall population).[8] The safety findings for niraparib were consistent with the known drug safety profile, and the most common grade ≥3 treatment-emergent adverse events (TEAEs) were hematologic in nature.[8] Subsequent *ad hoc* analyses carried out with 3.5 years of follow-up confirmed the sustained PFS benefit of niraparib maintenance across biomarker populations, and the niraparib safety profile remained consistent.[10] Reported herein are the results of the planned final analysis of OS.

METHODS

Trial design and patients

Details of the double-blind, placebo-controlled phase III PRIMA/ENGOT-OV26/GOG-3012 trial have been published previously.[8] Briefly, eligible patients were aged ≥18 years with histologically confirmed advanced cancer of the ovary, fallopian tube, or peritoneum (collectively referred to as OC) with high-grade serous or endometrioid tumors classified as stage III-IV per the International Federation of Gynecology and Obstetrics. Patients must have received first-line platinum-based chemotherapy that resulted in a complete or partial response per investigator assessment. All patients were required to provide tumor samples for HRD testing (MyChoice CDx HRD test; Myriad Genetics, Inc., Salt Lake City, UT) and were eligible regardless of test results.

Patients were randomized 2:1 to receive oral niraparib or placebo once daily within 12 weeks after the last dose of first-line chemotherapy. Randomization was stratified according to response to first-line treatment (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and tumor HRD status [HRd or homologous recombination-proficient (HRp)/homologous recombination status not determined (HRnd)]. Patients were treated until progressive disease or intolerable toxicity with a planned duration of study treatment of 3 years; patients who were benefitting from treatment per investigator assessment were eligible to continue receiving treatment beyond 3 years. At study start, all patients received a fixed starting dose ($n = 475$) of 300 mg. In November 2017, the protocol was amended to include individualized dosing (200 mg for patients with baseline body weight <77 kg or platelet count <150 000/μl; 300 mg for patients with body weight ≥77 kg and ≥150 000/μl) for newly enrolled patients [individualized starting dose (ISD); $n = 258$]. Crossover between treatment arms was not permitted. Patients who discontinued from study treatment for any reason could receive subsequent therapies during follow-up, including PARP inhibitors, at the investigator's discretion. This trial is registered with ClinicalTrials.gov, NCT02655016, and with EudraCT, 2015-000952-11.

Endpoints and assessments

Results for the primary endpoint, PFS assessed by a blinded independent central review, were previously reported.[8] Prespecified secondary efficacy endpoints were OS, PFS2, and time to first subsequent therapy (TFST) and were assessed in all randomized patients. OS was defined as the time from randomization to the date of death by any cause. PFS2 was defined as the time from randomization to the earliest date of assessment of progression on the next anticancer therapy after study treatment or death by any cause. TFST was defined as the time from randomization to the date of the first subsequent anticancer therapy or death by any cause. Follow-up anticancer therapies and patient-reported outcomes were also assessed as part of the final OS analysis. An updated, descriptive *ad hoc* PFS analysis by investigator assessment was also conducted. Adverse events were continuously monitored throughout the trial and were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Safety outcomes were evaluated in all patients who received one or more doses of the study treatment.

Statistical analysis

The final OS analysis was planned after ≈440 deaths in the overall population (60% maturity). Per protocol, a hierarchical testing strategy was used to control the overall type I error at the two-sided 0.05 level. In the primary analysis, PFS was tested first in the HRd population, followed by the overall population. Interim OS was tested in the overall population using a Lan—DeMets alpha-spending function with O'Brien—Fleming stopping boundaries, per the defined OS testing hierarchy (overall population tested first, followed by the HRd population if testing continued). As OS results were not statistically significant at the interim analysis, testing proceeded to the final analysis using the same hierarchical structure. The trial had 80% power to detect a statistically significant difference between treatment arms for OS if the true hazard ratio was ≤0.75 in the overall population. The median OS follow-up time was calculated using a time-to-censoring analysis.

OS was evaluated by a stratified log-rank test using randomization stratification factors and summarized using the Kaplan—Meier methodology. A stratified Cox proportional hazards model was used to calculate the hazard ratios and associated 95% CIs for the populations described above plus additional prespecified exploratory subgroups, unless otherwise specified (eg, if a subgroup level had at least one stratum with less than five events, unstratified models were used for all levels within the subgroup; HRd models were stratified regardless). Formal statistical testing was not carried out for exploratory subgroups. No adjustments were made for subsequent PARP inhibitor therapy. PFS2 and TFST were analyzed in the same manner as OS. The statistical methodology for the *ad hoc* analysis of investigator-assessed PFS followed the primary analysis specification, as defined in the PRIMA statistical analysis plan. The detailed methodology has been previously published.[10] Because of the substantial receipt of subsequent PARP inhibitor therapy in the placebo arm, prespecified OS sensitivity analyses adjusting for second-line PARP inhibitor use were conducted using a rank-preserving structural failure time model (RPSFTM), two-stage accelerated failure time model (2-stage AFT), and inverse probability of censoring weighting (IPCW) model methodologies. See the 'Supplemental Methods' section in the Supplementary Materials, available at https://doi.org/10.1016/j.annonc.2024.08.2241 for full details on the models and their key limitations.

Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[11-14] and were analyzed as previously described.[8,15] All analyses were conducted using data from the clinical cut-off date of 8 April 2024, and were carried out using SAS 9.4 (Cary, NC).

Trial oversight

The trial was carried out in accordance with the principles of the Declaration of Helsinki, Good Clinical Practices, and all local laws under the auspices of an independent data and safety monitoring committee. All patients provided written informed consent. The trial was designed and sponsored by GSK in collaboration with the authors and academic groups under the European Network of Gynaecological Oncological Trial groups (ENGOT) and the Gynecologic Oncology Group (GOG) Foundation, according to the ENGOT model C.[16] The sponsor was responsible for overseeing data collection, analysis, and interpretation. The manuscript was written by the authors, all of whom had full access to the study data, with medical writing support funded by the sponsor. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol.

RESULTS

Patients

From July 2016 to June 2018, 733 patients were enrolled and randomized to study treatment (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2024.08.2241). Baseline demographic and clinical characteristics have been previously published.[8,10,17] In brief, PRIMA enrolled patients with known risk factors for disease progression or death: 35.1% of patients had stage IV disease at diagnosis, 66.7% received neoadjuvant chemotherapy, 30.6% had a partial response to first-line platinum-based chemotherapy, and 47.5% had post-operative visible residual disease or did not undergo debulking surgery.

At the time of the data cut-off (8 April 2024), the median duration of follow-up was 6.2 years (niraparib, 73.9 months; placebo, 73.8 months). The median duration of treatment exposure was 11.3 (range 0-80) months in the niraparib arm and 8.3 (range 0-77) months in the placebo arm. The number of patients continuing to receive the assigned study

treatment at the time of the data cut-off date was 27 in the niraparib arm and 11 in the placebo arm.

In the overall population, subsequent anticancer therapy was received by 325 patients (66.7%) in the niraparib arm and 180 patients (73.2%) in the placebo arm (Table 1). Subsequent PARP inhibitor therapy was received by 57 patients (11.7%) in the niraparib arm and 93 patients (37.8%) in the placebo arm in the overall population and by 39 patients (15.8%) in the niraparib arm and 61 patients (48.4%) in the placebo arm in the HRd population (Table 1). Subsequent PARP inhibitor receipt was most predominant and imbalanced between treatment arms in patients with HRd/*BRCA*-mutated (*BRCA*m) tumors (niraparib, 19.1%; placebo, 57.7%), with therapy mostly initiated in the second-line setting (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.08.2241).

Efficacy

At the time of the data cut-off, 458 deaths had occurred (62.5% maturity). In the overall population, the OS hazard ratio was 1.01 (95% CI 0.84-1.23; $P = 0.8834$) for niraparib compared with placebo (median OS 46.6 versus 48.8 months, respectively; Figure 1A). OS in the overall population was not statistically significant; therefore formal testing did not proceed to the HRd population. In the HRd and HRp populations, OS hazard ratios were 0.95 (95% CI 0.70-1.29) and 0.93 (95% CI 0.69-1.26), respectively (Figure 1B and C). OS results by tumor HRD and *BRCA* status were consistent with those of the overall population (Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2024.08.2241); results for other subgroups are shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2024.08.2241. Among patients with HRd/*BRCA*m tumors, for which second-line subsequent PARP inhibitor use in the placebo arm was most pronounced, adjusted OS analyses resulted in hazard ratios of 0.89 (95% CI 0.38-1.93), 0.87 (0.50-1.50), and 0.77 (95% CI 0.47-1.26) for the RPSFTM (recensored), 2-stage AFT (recensored), and IPCW models, respectively (unadjusted hazard ratio 0.94, 95% CI 0.63-1.41).

To further contextualize the OS findings, updated investigator-assessed PFS was also evaluated. In these descriptive analyses, the PFS benefit of niraparib was sustained with additional follow-up in the overall (hazard ratio 0.66, 95% CI 0.55-0.78), HRd (hazard ratio 0.51, 95% CI 0.40-0.66), and HRp (hazard ratio 0.67, 95% CI 0.50-0.89; Table 2 and Figure 2) populations. In contrast to 5-year OS rates that were similar between treatment arms in the overall (niraparib, 42%; placebo, 44%) and HRd (niraparib, 55%; placebo, 56%) populations, 5-year PFS rates numerically favored niraparib, with a higher percentage of patients remaining progression free compared with placebo. The 5-year PFS rate was 22% in the niraparib arm versus 12% in the placebo arm in the overall population and 35% versus 16% in the HRd population (Table 2 and Figure 2). In the HRp subgroup, almost all patients had disease progression by the 3-year mark. Results by tumor HRD and *BRCA* status are shown in Table 2 and Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2024.08.2241.

In the overall population, the hazard ratios for TFST and PFS2 were 0.74 (95% CI 0.62-0.89) and 0.96 (95% CI 0.79-1.17) for niraparib compared with placebo, respectively; see Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.08.2241 for additional details and results by tumor HRD and *BRCA* status.

Table 1. Subsequent anticancer therapies by treatment arm in the overall and HRd populations

Any subsequent anticancer therapy	Niraparib		Placebo	
	HRd ($n = 247$)	Overall ($n = 487$)	HRd ($n = 126$)	Overall ($n = 246$)
Total, *n* (%)	141 (57.1)	325 (66.7)	94 (74.6)	180 (73.2)
Number of lines of subsequent therapy during follow-up, *n* (%)				
1	44 (17.8)	94 (19.3)	39 (31.0)	60 (24.4)
2	37 (15.0)	90 (18.5)	18 (14.3)	46 (18.7)
3	24 (9.7)	58 (11.9)	20 (15.9)	34 (13.8)
≥4	36 (14.6)	83 (17.0)	16 (12.7)	37 (15.0)
Surgery, *n* (%)	41 (16.6)	77 (15.8)	19 (15.1)	37 (15.0)
Radiotherapy, *n* (%)	20 (8.1)	41 (8.4)	11 (8.7)	19 (7.7)
Platinum-based chemotherapy[a], *n* (%)	126 (51.0)	285 (58.5)	81 (64.3)	153 (62.2)
Bevacizumab or bevacizumab biosimilar, *n* (%)	77 (31.2)	189 (38.8)	35 (27.8)	88 (35.8)
Taxane[b], *n* (%)	83 (33.6)	203 (41.7)	42 (33.3)	84 (34.1)
Doxorubicin[c], *n* (%)	91 (36.8)	223 (45.8)	60 (47.6)	130 (52.8)
Gemcitabine[d], *n* (%)	82 (33.2)	172 (35.3)	40 (31.7)	89 (36.2)
PARP inhibitor, *n* (%)	39 (15.8)	57 (11.7)	61 (48.4)	93 (37.8)
Niraparib	12 (4.9)	16 (3.3)	19 (15.1)	35 (14.2)
Niraparib tosylate monohydrate	1 (0.4)	1 (0.2)	0 (0)	0 (0)
Olaparib	24 (9.7)	34 (7.0)	38 (30.2)	53 (21.5)
Rucaparib	3 (1.2)	7 (1.4)	5 (4.0)	8 (3.3)
Talazoparib	0 (0)	0 (0)	1 (0.8)	1 (0.4)

HRd, homologous recombination deficient; PARP, poly(ADP)-ribose polymerase.
[a]Includes carboplatin, cisplatin, and oxaliplatin.
[b]Includes docetaxel and paclitaxel.
[c]Includes doxorubicin, doxorubicin hydrochloride, liposomal doxorubicin, liposomal doxorubicin hydrochloride, pegylated liposomal doxorubicin, and pegylated liposomal doxorubicin hydrochloride.
[d]Includes gemcitabine and gemcitabine hydrochloride.

Safety

Safety findings were consistent with those of the primary analysis,[8] and no new safety signals were identified (Table 2). The most common TEAEs that occurred throughout the trial are listed in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2241; compared with the primary analysis, with an additional ≈5 years of follow-up, five additional patients experienced grade ≥3 thrombocytopenia, five additional patients experienced grade ≥3 anemia, and four additional patients experienced grade ≥3 neutropenia in the niraparib arm. Consistent with the primary analysis results,[10,18] the safety profile of niraparib improved with the use of the ISD (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2241).

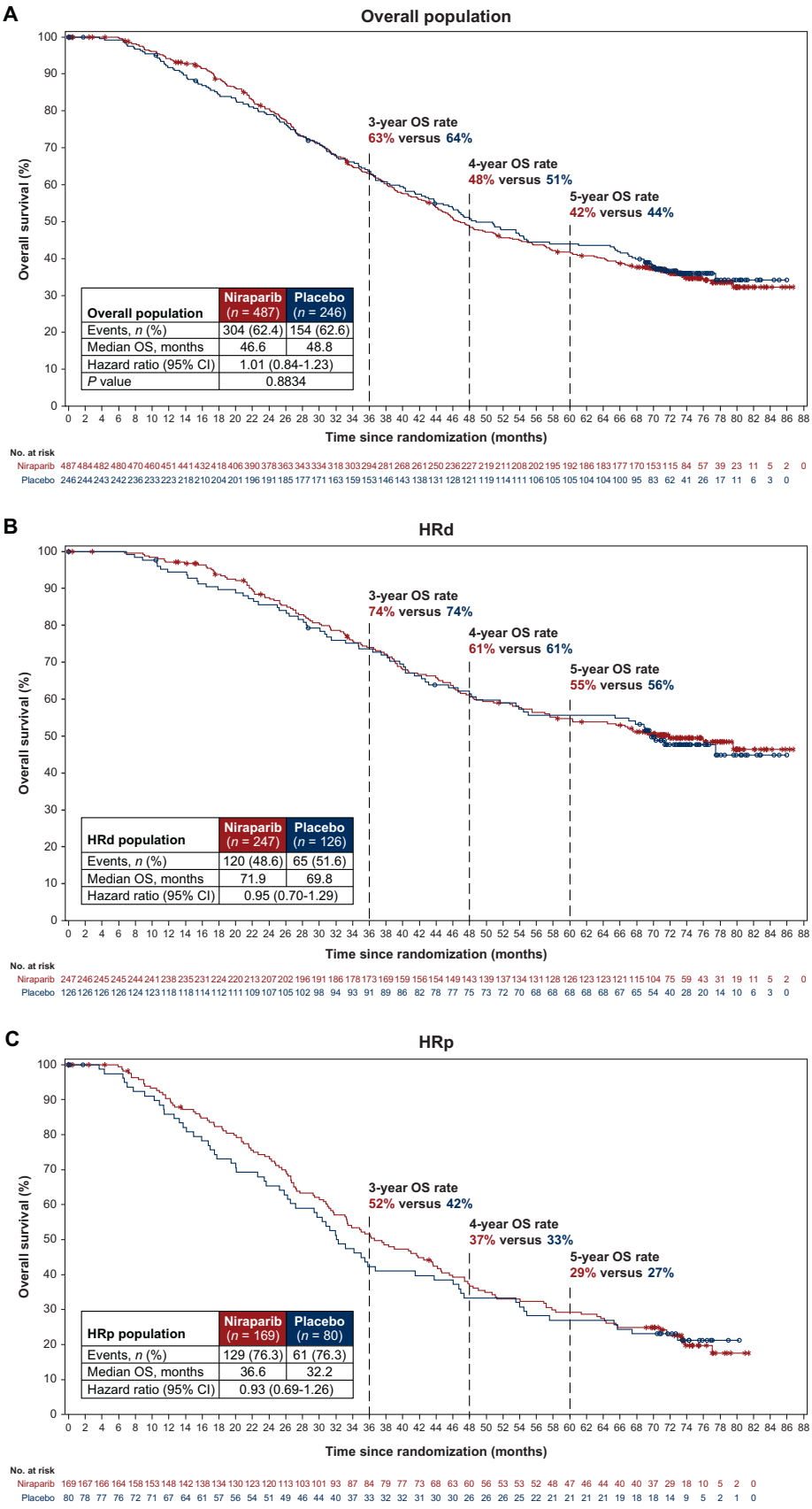

Figure 1. Overall survival. Kaplan–Meier estimates of overall survival in the (A) overall, (B) HRd, and (C) HRp populations. Hazard ratio and 95% CI for HRp were calculated using unstratified Cox proportional hazards models.
CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival.

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Table 2. Updated investigator-assessed PFS in the overall population and by tumor HRD/*BRCA* status

Updated investigator-assessed PFS	Overall population		All HRd		HRd/*BRCA*m		HRd/*BRCA*wt		HRp	
	Nir ($n = 487$)	PBO ($n = 246$)	Nir ($n = 247$)	PBO ($n = 126$)	Nir ($n = 152$)	PBO ($n = 71$)	Nir ($n = 94$)	PBO ($n = 55$)	Nir ($n = 169$)	PBO ($n = 80$)
Events, *n* (%)	352 (72.3)	209 (85.0)	150 (60.7)	105 (83.3)	90 (59.2)	60 (84.5)	59 (62.8)	45 (81.8)	147 (87.0)	71 (88.8)
Progression	347 (71.3)	209 (85.0)	146 (59.1)	105 (83.3)	89 (58.6)	60 (84.5)	56 (59.6)	45 (81.8)	147 (87.0)	71 (88.8)
Death	5 (1.0)	0 (0)	4 (1.6)	0 (0)	1 (0.7)	0 (0)	3 (3.2)	0 (0)	0 (0)	0 (0)
Median PFS (months)	13.8	8.2	24.5	11.2	30.1	11.5	19.4	10.4	8.4	5.4
Hazard ratio (95% CI)	0.66 (0.55-0.78)		0.51 (0.40-0.66)		0.43 (0.31-0.59)		0.67 (0.45-1.00)		0.67 (0.50-0.89)	
5-year PFS rate[a], %	22	12	35	16	37	14	30	18	8	7

*BRCA*m, *BRCA*-mutated; *BRCA*wt, *BRCA* wild-type; CI, confidence interval; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; Nir, niraparib; PBO, placebo; PFS, progression-free survival.
[a]Kaplan–Meier estimates.

In patients who received one or more doses of study treatment, myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) events were reported in 11 patients (2.3%) in the niraparib arm and 4 patients (1.6%) in the placebo arm. In patients who developed MDS/AML, the duration of study treatment ranged from 3.7 to 60.1 months in the niraparib arm and from 4.9 to 22.1 months in the placebo arm. Of the patients in the niraparib arm who developed MDS/AML, three patients received subsequent platinum-based chemotherapy, including one patient who also received a PARP inhibitor during follow-up; seven patients had no evidence of subsequent therapy receipt. Three out of four patients in the placebo arm who developed MDS/AML received subsequent platinum-based chemotherapy, and four out of four patients received subsequent PARP inhibitor treatment. Additional details, including HRD and *BRCA* status, are included in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.08.2241. Excluding MDS/AML, 18 patients developed new malignancies (niraparib, 2.5%; placebo, 2.5%). In total, 12 patients (2.5%) in the niraparib arm and 4 patients (1.6%) in the placebo arm experienced TEAEs leading to death (Table 3 and Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.08.2241).

Patient-reported outcomes

Consistent with the primary analysis,[8,15] completion rates of patient-reported outcome assessment forms were high, and health-related quality of life (HRQOL) was similar between treatment arms overall (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2024.08.2241).

DISCUSSION

The phase III PRIMA trial evaluated the safety and efficacy of niraparib first-line maintenance therapy in patients with newly diagnosed advanced OC that responded to first-line platinum-based chemotherapy and who were at high risk for disease progression or death based on multiple negative prognostic factors. In the final prespecified OS analysis reported here, there was no difference between treatment arms in the overall population. TFST results were consistent with the primary analysis PFS results[8] and showed a benefit with niraparib treatment. PFS2 results were more closely aligned with the OS findings, with no difference observed between treatment arms.

OS was also evaluated by HRD and *BRCA* status, with no notable differences observed between treatment arms in patients with HRd, HRd/*BRCA*m, HRd/*BRCA* wild-type (*BRCA*wt), and HRp tumors. OS results for other subgroups were generally consistent, with hazard ratios close to 1.0 and 95% CI at or crossing 1.0 in all cases. Some variation across subgroups was observed, with hazard ratios >1.0 in several subgroups, including in patients with HRnd tumors and stage IV disease. However, these results should be interpreted with caution because the study was not designed to evaluate treatment effects specifically in these subgroups, and no formal testing was carried out. In addition, it is difficult to evaluate the effects of individual factors in isolation. For example, stage IV disease at diagnosis is independently prognostic of poor long-term outcomes[2] and is also known to be associated with other risk factors for disease progression and death, including the use of neoadjuvant chemotherapy and post-operative residual disease.[3,19] Furthermore, in the PRIMA trial, variations were observed in the number and location of new lesions in patients with stage III and IV disease at diagnosis who experienced disease progression, potentially leading to differences in the overall prognoses of these patient subgroups.[20]

Although improved OS is a key goal of all anticancer treatments, quality of life is also important to consider. As previously documented in the PRIMA trial, disease progression negatively affected HRQOL regardless of treatment.[21] Accordingly, PFS is a clinically meaningful endpoint, and any extension of PFS can help preserve HRQOL in patients. As reported here, *ad hoc* evaluation of investigator-assessed PFS at the time of the final analysis found that the PFS benefit observed with niraparib first-line maintenance therapy was sustained, with PFS hazard ratios maintained across the overall, HRd, and HRp populations with additional follow-up. Patients in the HRd population who were alive at 5 years were two times as likely to be progression free if they received niraparib first-line maintenance than if they received a placebo. Given the close association between being progression free and preserving HRQOL, this observation underscores the long-term clinical benefit of niraparib, particularly in patients with HRd tumors.

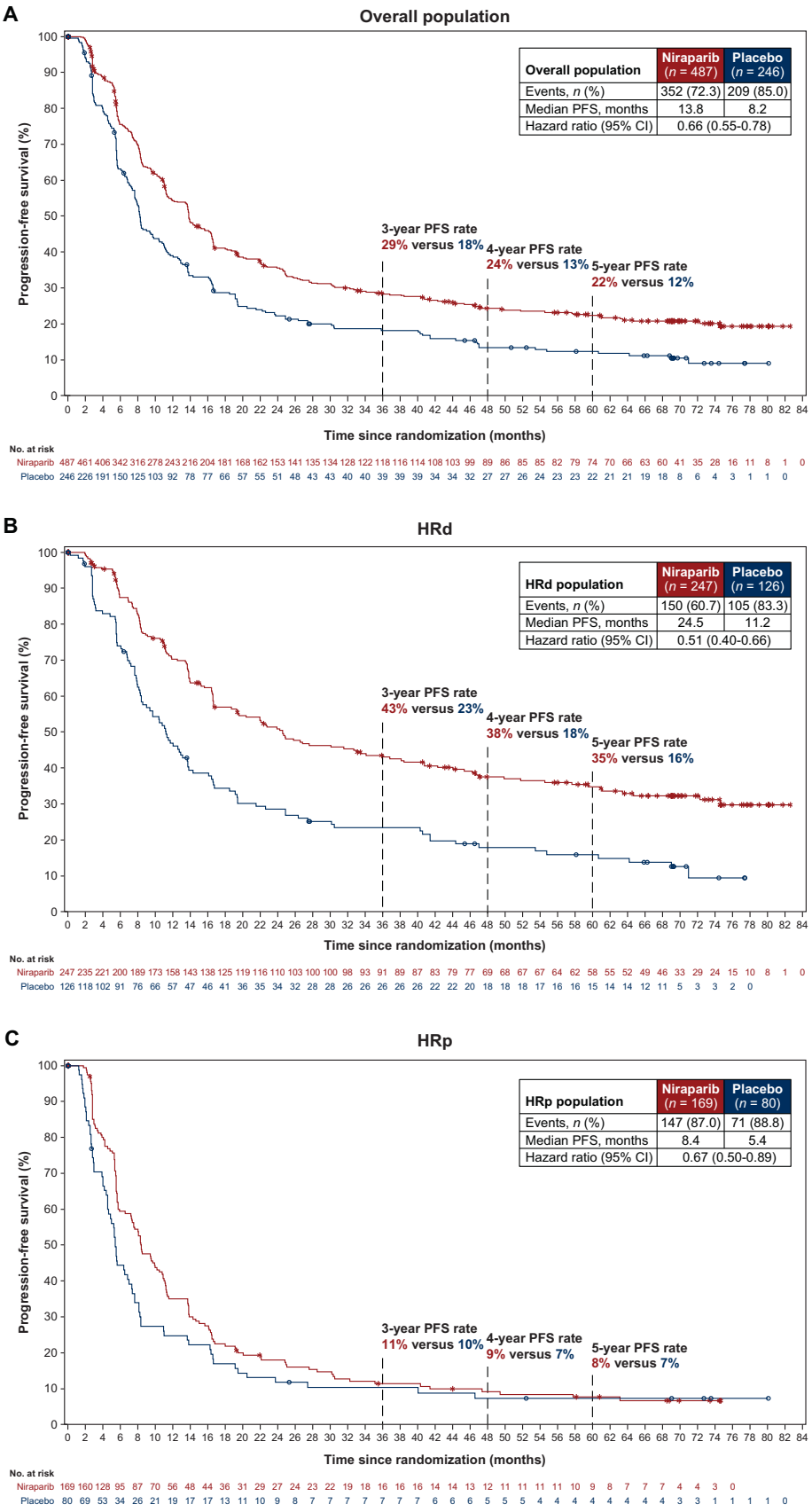

Figure 2. Investigator-assessed PFS. Kaplan–Meier estimates of updated *ad hoc* investigator-assessed PFS in the (A) overall, (B) HRd, and (C) HRp populations. CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PFS, progression-free survival.

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Table 3. Overall safety in randomized patients who received one or more doses of the study drug

Adverse events	Niraparib (n = 484), n (%)	Placebo (n = 244), n (%)
TEAE		
Any	479 (99.0)	229 (93.9)
Grade ≥3	357 (73.8)	58 (23.8)
TRAE		
Any	467 (96.5)	175 (71.7)
Grade ≥3	324 (66.9)	21 (8.6)
Serious TEAE, any grade	198 (40.9)	43 (17.6)
Any TEAE leading to		
Dose interruption	391 (80.8)	56 (23.0)
Dose reduction	347 (71.7)	25 (10.2)
Treatment discontinuation	79 (16.3)	9 (3.7)
Death	12 (2.5)	4 (1.6)

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Assessment of the long-term efficacy of first-line interventions in advanced OC is complicated by the length of follow-up required and the multiple lines of treatment patients can receive after recurrence.[22] In the PRIMA trial, almost 70% of patients in the overall population went on to receive subsequent anticancer therapy, with ≈12% of patients in the niraparib arm and 38% of patients in the placebo arm receiving subsequent PARP inhibitor therapy. To investigate the potential impact of this confounding factor, OS analyses adjusting for subsequent PARP inhibitor therapy use in the placebo arm were carried out using multiple statistical models. The results of these analyses should be interpreted with caution given the limitations of post-progression data collection, and the complexities associated with model fitting and covariate selection. As reported in patients with HRd/*BRCA*m tumors, the subgroup in which subsequent PARP inhibitor therapy in the placebo arm was most pronounced (≈60%), the lower adjusted hazard ratios compared with the unadjusted hazard ratio support the premise that subsequent PARP inhibitor use may have affected OS results.

Within the advanced OC maintenance therapy landscape, niraparib is one of three PARP inhibitors currently approved/recommended for use in the first-line setting.[3,4] Comparisons across the four main registration trials for niraparib (PRIMA/ENGOT-OV26/GOG-3012),[8] rucaparib (ATHENA-MONO/GOG-3020/ENGOT-ov45),[23] olaparib (SOLO1),[24] and olaparib plus bevacizumab (PAOLA-1/ENGOT-ov25)[25] maintenance therapy are complicated by marked differences in trial design and patient populations. In particular, differences in eligibility criteria resulted in patient populations with different risk profiles for disease progression and death based on established prognostic factors. For example, one of the greatest negative prognostic indicators for both PFS and OS is post-operative residual disease.[19] Although the specific definitions varied across trials, the percentage of patients with post-operative residual disease or no surgery ranged from a low of 23% in SOLO1 to a high of 48% in PRIMA.[17,23-25] Trial populations also varied by *BRCA* status, with the PRIMA, PAOLA-1, and ATHENA-MONO trials all having >65% of patients with *BRCA*wt disease, known to be associated with worse outcomes, whereas the SOLO1 trial exclusively enrolled patients with *BRCA*m disease, known to be associated with improved clinical outcomes.[10,23-26] Similar differences were also observed for the risk factors of stage IV disease at diagnosis and receipt of neoadjuvant chemotherapy, with the PRIMA patient population having the highest percentages of patients with these characteristics across the trials.[8,23-25]

The long-term efficacy data for first-line PARP inhibitor maintenance therapy in advanced OC are emerging, with results from >5 years of follow-up available from SOLO1 and PAOLA-1.[27,28] Although the SOLO1 OS data remained immature with 7 years of follow-up, an OS benefit was observed with olaparib first-line maintenance monotherapy compared with placebo in patients with *BRCA*m disease (5-year OS rate 73.1% versus 63.4%). In PAOLA-1, fully mature OS results in the intention-to-treat population numerically favored the addition of olaparib to bevacizumab compared with bevacizumab alone, but results failed to meet statistical significance (hazard ratio 0.92, 95% CI 0.76-1.12; P = 0.4118); 5-year OS rates were higher with olaparib plus bevacizumab than bevacizumab alone in patients with HRd tumors (65.5% versus 48.4%), regardless of *BRCA* status but not in patients with HRp tumors (25.7% versus 32.3%).[28] Contextualization of these findings, however, remains complex because of the differences in patient populations outlined above. Available real-world evidence suggests that the presence of one or more factors associated with an increased risk of disease progression or death can affect long-term outcomes regardless of treatment,[29,30] indicating that the differences in patient populations and risk profiles across the PRIMA, SOLO1, and PAOLA-1 trials should be taken into account when interpreting long-term efficacy data. Consistent with this, subsequent *post hoc* analyses of the PAOLA-1 OS data cut found that the PFS and OS benefit observed with combination olaparib plus bevacizumab maintenance treatment in patients with HRd tumors varied based on clinical risk status.[31] In addition, earlier *post hoc* analyses of the SOLO1 and PRIMA primary analysis data cuts found that PFS outcomes were affected differently by the presence of post-operative residual disease in patients with *BRCA*m tumors (SOLO1 trial) versus a mixed *BRCA*m/*BRCA*wt population (PRIMA trial), further underscoring the potential for interplay across multiple risk factors for disease progression and death.[17,32] Accordingly, these results caution against direct cross-trial comparisons and support further evaluation of how the high-risk patient population in the PRIMA trial may have affected long-term clinical outcomes.

With ≈5 years of additional follow-up, long-term safety findings from the PRIMA trial remained consistent with previously published observations from the study[8,10,33] and with the known safety profile of niraparib.[34,35] In addition, long-term follow-up confirmed that the use of an ISD improved the safety profile of niraparib compared with a fixed starting dose.[10,18] Similar to other anticancer therapies, PARP inhibitor therapy is known to be a risk factor for

MDS/AML in patients with OC.[36,37] At the time of the final OS analysis in the PRIMA trial, 11 patients in the niraparib arm and 4 patients in the placebo arm developed MDS/AML. Of these patients, 4 out of 11 patients in the niraparib arm received some type of follow-up therapy; in the placebo arm, all 4 patients received subsequent PARP inhibitor therapy, and 3 out of 4 received subsequent platinum-based chemotherapy. Overall, 7 out of the 15 total patients who developed MDS/AML had tumors that were HRd/*BRCA*m. In patients who receive PARP inhibitor maintenance therapy, additional work is needed to better understand how the interplay among different treatments, treatment durations, and genetic factors influences MDS/AML risk.

Several potential limitations should be considered when interpreting these results. The PRIMA trial was designed to evaluate the efficacy of niraparib first-line maintenance therapy using a primary endpoint of PFS, with OS as a prespecified key secondary endpoint.[8] Although PFS and OS are both favored as primary endpoints for OC trials per consensus recommendations from the sixth Gynecologic Cancer InterGroup (GCIG) Ovarian Cancer Consensus Conference, intrinsic differences between PFS and OS generally preclude their use as dual primary endpoints.[38] Accordingly, the inherent limitations of OS analyses, including the requirement for longer-term patient follow-up and the larger patient populations needed to draw definitive conclusions,[39] must be taken into account when considering the PRIMA OS findings. Subsequent therapy may also influence OS results,[39] especially in first-line settings with long post-progression survival like OC.[22] In this study, adjusted analyses were implemented in an effort to understand the impact of subsequent therapy on OS. However, these analyses rely on underlying assumptions that may not all be validated and require complex model fitting across multiple parameters. In addition, results from the prespecified exploratory subgroup analyses should be interpreted with caution because of the small sample sizes in several of the subgroups (particularly the HRnd and HRd/*BRCA*wt subgroups). The trial was not designed to evaluate OS in these subgroups, and results from such small numbers of patients may not be generalizable to other patient groups with similar characteristics. Although beyond the scope of this analysis, future studies that explore how PARP inhibitor first-line maintenance therapy may affect the sequence and outcomes of subsequent therapies may be of interest.

In summary, in patients with newly diagnosed advanced OC at high risk for recurrence, no difference in OS was observed between the niraparib first-line maintenance and placebo treatment arms in the overall population and by tumor HRD/*BRCA* status. Receipt of subsequent therapy was common across treatment arms, with a notably higher percentage of patients in the placebo arm going on to receive subsequent PARP inhibitor therapy as a standard of care than patients in the niraparib arm, which may have confounded OS results. The PFS benefit observed with niraparib treatment was sustained with additional follow-up, with reductions in the overall risk for disease progression or death maintained in the overall, HRd, and HRp populations. In addition, among patients who were alive at 5 years in the HRd population, those who received niraparib were two times as likely to be progression free as patients who received a placebo. Long-term safety remained consistent with the established safety profile for niraparib. Taken together, the long-term data support the benefit of niraparib first-line maintenance therapy in patients with newly diagnosed advanced OC regardless of HRD status.

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DATA SHARING

Please refer to the GSK weblink to access GSK's data sharing policies and as applicable seek anonymized subject-level data via the link https://www.gsk-studyregister.com/en/.

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