ORIGINAL ARTICLE

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

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ABSTRACT

BACKGROUND

Niraparib, an inhibitor of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP), has been associated with significantly increased progression-free survival among patients with recurrent ovarian cancer after platinum-based chemotherapy, regardless of the presence or absence of *BRCA* mutations. The efficacy of niraparib in patients with newly diagnosed advanced ovarian cancer after a response to first-line platinum-based chemotherapy is unknown.

METHODS

In this randomized, double-blind, phase 3 trial, we randomly assigned patients with newly diagnosed advanced ovarian cancer in a 2:1 ratio to receive niraparib or placebo once daily after a response to platinum-based chemotherapy. The primary end point was progression-free survival in patients who had tumors with homologous-recombination deficiency and in those in the overall population, as determined on hierarchical testing. A prespecified interim analysis for overall survival was conducted at the time of the primary analysis of progression-free survival.

RESULTS

Of the 733 patients who underwent randomization, 373 (50.9%) had tumors with homologous-recombination deficiency. Among the patients in this category, the median progression-free survival was significantly longer in the niraparib group than in the placebo group (21.9 months vs. 10.4 months; hazard ratio for disease progression or death, 0.43; 95% confidence interval [CI], 0.31 to 0.59; P<0.001). In the overall population, the corresponding progression-free survival was 13.8 months and 8.2 months (hazard ratio, 0.62; 95% CI, 0.50 to 0.76; P<0.001). At the 24-month interim analysis, the rate of overall survival was 84% in the niraparib group and 77% in the placebo group (hazard ratio, 0.70; 95% CI, 0.44 to 1.11). The most common adverse events of grade 3 or higher were anemia (in 31.0% of the patients), thrombocytopenia (in 28.7%), and neutropenia (in 12.8%). No treatment-related deaths occurred.

CONCLUSIONS

Among patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy, those who received niraparib had significantly longer progression-free survival than those who received placebo, regardless of the presence or absence of homologous-recombination deficiency. (Funded by GlaxoSmithKline; PRIMA/ENGOT-OV26/GOG-3012 ClinicalTrials.gov number, NCT02655016.)

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Ovarian cancer is a leading cause of death from gynecologic cancers in women worldwide.[1] The standard treatment for newly diagnosed advanced epithelial ovarian cancer is surgical cytoreduction and systemic platinum–taxane combination chemotherapy. Unfortunately, up to 85% of the patients with advanced ovarian cancer have a disease recurrence after completing chemotherapy.

In these patients, bevacizumab can be added to chemotherapy, followed by bevacizumab maintenance therapy. However, the use of bevacizumab is limited because of safety concerns, and data are lacking on its use in the growing number of patients who receive neoadjuvant chemotherapy.[2,3] Olaparib, an inhibitor of poly(adenosine diphosphate [ADP]–ribose) (PARP), has been associated with longer progression-free survival than placebo among patients with *BRCA*-mutated tumors, which includes approximately 15 to 20% of the patients with ovarian cancer, after a response to first-line platinum-based chemotherapy.[4] Therefore, most patients with advanced ovarian cancer do not have an effective treatment option to substantially reduce the risk of death or progressive disease after first-line chemotherapy.[5,6]

Niraparib is an oral, highly selective PARP1 and PARP2 inhibitor that has been approved as maintenance therapy in patients with recurrent ovarian cancer who have had a response to platinum-based chemotherapy. Niraparib has shown efficacy both in patients who have tumors with *BRCA* mutations and in those without *BRCA* mutations.[7,8] In the NOVA (ENGOT-OV16/NOVA) trial,[7] patients who received niraparib had significantly longer progression-free survival than those who received placebo in all the cohorts, including in patients with germline *BRCA* mutations (21.0 months vs. 5.5 months; hazard ratio, 0.27; P<0.001) and in those without germline *BRCA* mutations (9.3 months vs. 3.9 months; hazard ratio, 0.45; P<0.001). The NOVA trial also tested the efficacy of niraparib according to homologous-recombination status in patients without *BRCA* mutations and showed a benefit regardless of homologous-recombination status. (Although a deleterious *BRCA* mutation indicates that a tumor has some form of homologous-recombination deficiency, patterns of genomic instability in the tumor can confer such a phenotype in the absence of a *BRCA* mutation.) The primary objective of the PRIMA (PRIMA/ENGOT-OV26/GOG-3012) trial was to test the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer at high risk for relapse.

Methods

Patients

Eligible patients were at least 18 years of age and had newly diagnosed, histologically confirmed advanced cancer of the ovary, peritoneum, or fallopian tube (collectively defined as ovarian cancer). All the patients had high-grade serous or endometrioid tumors that were classified as stage III or IV, according to the criteria of the International Federation of Gynecology and Obstetrics. Included in this category were patients with stage III disease with visible residual tumor after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy.

Before enrollment, all the patients had received six to nine cycles of first-line platinum-based chemotherapy, which had resulted in a complete or partial response, according to investigator assessment. Tumor samples underwent central testing to identify those with homologous-recombination deficiency (myChoice test, Myriad Genetics). Homologous-recombination deficiency was defined as the presence of a *BRCA* deleterious mutation, a score of at least 42 on the myChoice test,[9-11] or both. Test scores (which range from 1 to 100, with higher scores indicating a greater number of genomic abnormalities) represent a continuum on the basis of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. Additional details regarding testing for homologous-recombination deficiency are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients in whom status regarding homologous-recombination deficiency was not determined were eligible to participate in the trial and were included in the overall population. All the patients provided written informed consent. Further details and eligibility criteria are provided in the Supplementary Appendix.

TRIAL OVERSIGHT

The trial was performed 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. The trial was designed by the sponsor, GlaxoSmithKline, in collaboration with the European Network for Gynecological Oncological Trial (ENGOT) groups and the cooperative group leadership of GOG Partners (a component of the Gynecologic Oncology Group Foundation), according to the ENGOT model C.[12] The sponsor was responsible for overseeing the collection, analysis, and interpretation of the data. All the authors had full access to the trial data. The authors wrote the manuscript, with medical writing assistance funded by the sponsor. All the authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol, available at NEJM.org.

TRIAL DESIGN AND TREATMENT

This randomized, double-blind, placebo-controlled phase 3 trial was conducted in 20 countries at 181 clinical sites. (Details regarding the clinical sites are provided in Table S1 in the Supplementary Appendix.) Within 12 weeks after completion of the last dose of platinum-based chemotherapy, the patients were randomly assigned in a 2:1 ratio to receive oral niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression. In the initial protocol, all the patients started at a fixed dose of 300 mg once daily. The trial was amended on November 27, 2017, to incorporate an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimeter, or both.[13]

Randomization was performed in a double-blind manner with the use of an interactive Web-response system, with stratification according to clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and status regarding tumor homologous recombination (deficient, proficient, or not determined).

Niraparib or placebo was administered continuously until the objective identification of disease progression on imaging, provided that the patient was receiving benefit and did not meet any other criteria for discontinuation, as defined in the protocol. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Indications for treatment interruptions and dose reductions were defined in the protocol. (The schedule of dose reductions is provided in Tables S3 and S4.) Patients receiving placebo were not allowed to cross over to receive niraparib treatment during the trial.

ASSESSMENTS

We performed computed tomography or magnetic resonance imaging to assess progressive disease every 12 weeks until treatment discontinuation. The objective assessment of progressive disease was determined by central radiologic and clinical review in a blinded manner, according to RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1.[14] Clinical progression was reviewed if an increased CA125 level was accompanied by histologic proof or clinical symptoms, as specified in the protocol. We administered the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI),[15] the European Quality of Life five-dimension, five-level questionnaire (EQ-5D-5L),[16] the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC-QLQ-C30),[17] and the EORTC Quality of Life Questionnaire Ovarian Cancer module (EORTC-QLQ-OV28)[18] at the screening visit, throughout treatment, and 4, 8, 12, and 24 weeks after the last dose of niraparib or placebo. (Details regarding the trial assessments, including monitoring of adverse events, are provided in the Supplementary Appendix.)

END POINTS

The primary end point was progression-free survival in patients who had tumors with homologous-recombination deficiency and in those in the overall population, as determined on hierarchical testing. This end point was evaluated in a time-to-event analysis and was assessed by blinded independent central review. Progression-free survival was defined as the time from randomization after completion of platinum-based chemotherapy to the earliest date of objective disease progression on imaging (according to RECIST, version 1.1) or death from any cause. An inde-

pendent radiologic review and central clinician review that were conducted in a blinded manner were used to define the date of disease progression, and an identical schedule of assessments was used for the two trial groups.

Overall survival was a key secondary end point. Other secondary end points were the time until the first subsequent therapy, progression-free survival 2 (defined as time from randomization to progression while the patient was receiving a subsequent anticancer therapy), pharmacokinetic analyses, and patient-reported outcomes (scores on the FOSI, EQ-5D-5L, and EORTC-QLQ-C30/OV28 instruments). Safety was assessed through the monitoring of adverse events, laboratory testing, measurement of vital signs, and physical examination.

STATISTICAL ANALYSIS

We determined that the enrollment of at least 620 patients (including 310 patients who had tumors with homologous-recombination deficiency) would provide a power of more than 90% to detect a significant difference in progression-free survival between niraparib and placebo at a one-sided type I error of 0.025.[19,20] These criteria corresponded to a hazard ratio for disease progression or death of 0.50 in the group with homologous-recombination deficiency and 0.65 in the overall population of all the patients who had undergone randomization.

A hierarchical-testing method was performed for the primary end point in the population with homologous-recombination deficiency, followed by a test in the overall population. At the time of the trial design, consideration of the reported median duration of progression-free survival for patients with ovarian cancer with a *BRCA* mutation who received placebo led to an estimated median duration of progression-free survival of 21 months in the patients with homologous-recombination deficiency and 14 months in the overall population for the sample-size estimation. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From July 2016 through June 2018, a total of 733 patients underwent randomization. Five patients who did not receive either niraparib or placebo after randomization were excluded from the safety analysis. As of the data cutoff on May 17, 2019, a total of 246 patients were still receiving treatment with niraparib or placebo (Fig. 1).

The demographic and clinical characteristics of the patients at baseline were balanced in the two trial groups (Table 1). The overall population included patients at high risk for progressive disease as a result of stage III ovarian cancer with residual disease after primary debulking surgery (23.1%), receipt of neoadjuvant chemotherapy (66.7%), stage IV ovarian cancer (35.0%), or a partial response to first-line platinum-based chemotherapy (30.5%). Of the 733 patients who had undergone randomization, 373 (50.9%) had tumors with homologous-recombination deficiency on myChoice testing; among these patients, 223 had tumors with *BRCA* mutations, and 150 had tumors without *BRCA* mutations (Fig. S1).

EFFICACY

The primary efficacy analysis was performed after disease progression or death had occurred in 154 patients with homologous-recombination deficiency and in 386 patients in the overall population. The median duration of follow-up at the time of the data cutoff was 13.8 months (range, <1.0 to 28.0). The median relative dose intensity (the proportion of administered doses relative to planned doses) was 63% for niraparib and 99% for placebo.

The median duration of progression-free survival in patients with homologous-recombination deficiency was 21.9 months with niraparib and 10.4 months with placebo (hazard ratio for disease progression or death, 0.43; 95% confidence interval [CI], 0.31 to 0.59; P<0.001) (Fig. 2A). In the overall population, the median duration of progression-free survival was 13.8 months with niraparib and 8.2 months with placebo (hazard ratio, 0.62; 95% CI, 0.50 to 0.76; P<0.001) (Fig. 2B).

In the interim analysis of the key secondary end point of overall survival (performed after the deaths of 79 of 733 patients [10.8%] in the overall population), the estimated Kaplan–Meier probability of survival at 24 months was 84% in the niraparib group and 77% in the placebo group (hazard ratio for death, 0.70; 95% CI, 0.44 to 1.11). In the population with homologous-recombination deficiency, the interim analysis

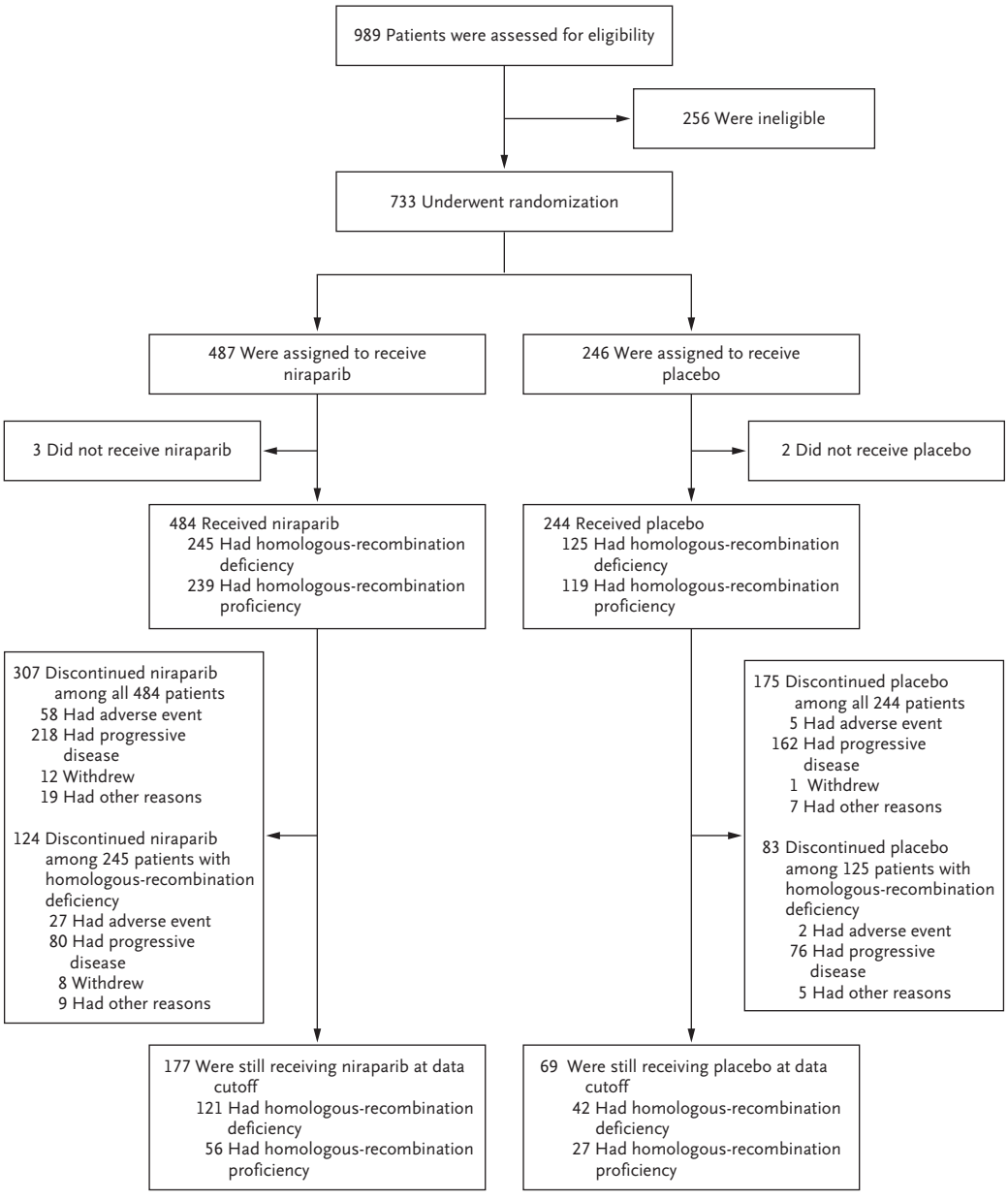

Figure 1. Enrollment and Outcomes in the Two Primary Populations.

In the PRIMA trial, the primary end point was progression-free survival in patients who had tumors with homologous-recombination deficiency and in those in the overall population, as determined on hierarchical testing. The primary end point was first tested in patients who had tumors with homologous-recombination deficiency (who were thought to have an increased benefit with niraparib) and then in the overall population to test the benefit in all the patients. Patients who had undetermined status with regard to homologous recombination were included in the subgroup with homologous-recombination proficiency.

showed an estimated probability of 24-month survival of 91% in the niraparib group and 85% in the placebo group (hazard ratio, 0.61; 95% CI, 0.27 to 1.39). Additional details regarding the secondary end points are provided in Table S5.

The results of prespecified exploratory analyses

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Niraparib		Placebo	
	HRD Population (N=247)	Overall Population (N=487)	HRD Population (N=126)	Overall Population (N=246)
Median age (range) — yr	58 (32–83)	62 (32–85)	58 (33–82)	62 (33–88)
ECOG score — no. (%)†				
0	182 (73.7)	337 (69.2)	97 (77.0)	174 (70.7)
1	65 (26.3)	150 (30.8)	29 (23.0)	72 (29.3)
International FIGO stage — no. (%)‡				
III	161 (65.2)	318 (65.3)	78 (61.9)	158 (64.2)
A	4 (1.6)	7 (1.4)	1 (0.8)	4 (1.6)
B	10 (4.0)	16 (3.3)	9 (7.1)	12 (4.9)
C	140 (56.7)	285 (58.5)	67 (53.2)	138 (56.1)
Not specified	7 (2.8)	10 (2.1)	1 (0.8)	4 (1.6)
IV	86 (34.8)	169 (34.7)	48 (38.1)	88 (35.8)
Primary tumor location — no. (%)				
Ovary	201 (81.4)	388 (79.7)	105 (83.3)	201 (81.7)
Fallopian tube	32 (13.0)	65 (13.3)	13 (10.3)	32 (13.0)
Peritoneum	14 (5.7)	34 (7.0)	8 (6.3)	13 (5.3)
Histologic type — no. (%)§				
Serous	234 (94.7)	465 (95.5)	116 (92.1)	230 (93.5)
Endometrioid	5 (2.0)	11 (2.3)	6 (4.8)	9 (3.7)
Other	8 (3.2)	11 (2.3)	4 (3.2)	6 (2.4)
Receipt of neoadjuvant chemotherapy — no. (%)				
Yes	156 (63.2)	322 (66.1)	80 (63.5)	167 (67.9)
No	91 (36.8)	165 (33.9)	46 (36.5)	79 (32.1)
Clinical response after platinum-based chemotherapy — no. (%)				
Complete response	185 (74.9)	337 (69.2)	93 (73.8)	172 (70.0)
Partial response	62 (25.1)	150 (30.8)	33 (26.2)	74 (30.0)
Cancer antigen 125 level — no. (%)				
≤ULN	236 (95.5)	450 (92.4)	120 (95.2)	226 (91.9)
>ULN	9 (3.6)	34 (7.0)	5 (4.0)	18 (7.3)
Missing data	2 (0.8)	3 (0.6)	1 (0.8)	2 (0.8)
No. of cycles of platinum-based chemotherapy — no. (%)				
6	165 (66.8)	333 (68.4)	84 (66.7)	170 (69.1)
7–9	52 (21.1)	124 (25.5)	28 (22.2)	62 (25.2)
Missing data	30 (12.1)	30 (6.2)	14 (11.1)	14 (5.7)

* Percentages may not total 100 because of rounding. HRD denotes homologous-recombination deficiency, and ULN upper limit of the normal range.

† According to the Eastern Cooperative Oncology Group (ECOG) performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

‡ Details regarding staging criteria according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines are provided in Table S2 in the Supplementary Appendix.

§ Histologic data for one patient were missing, but a serous tumor was identified on cytologic analysis.

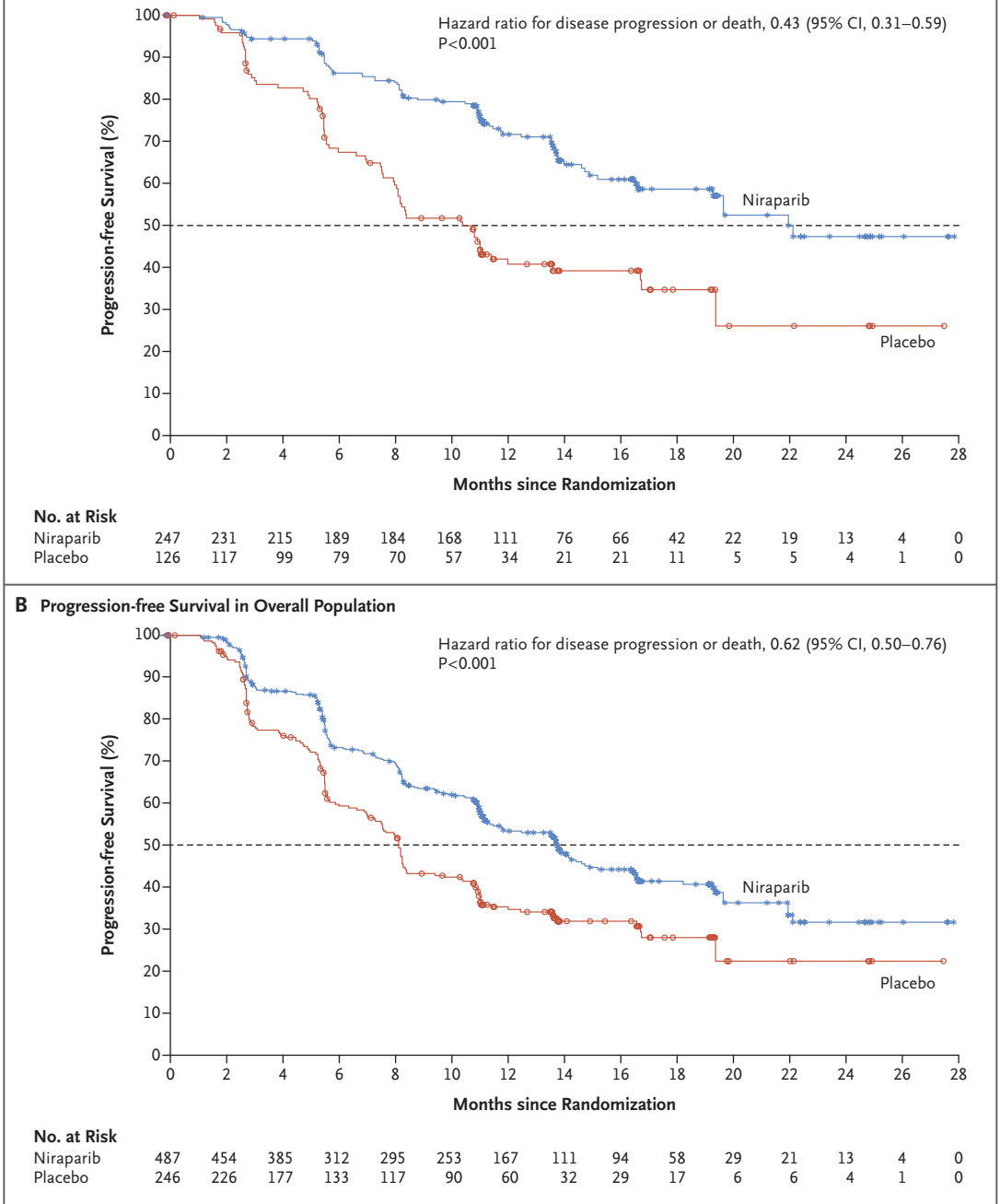

Figure 2. Progression-free Survival in the Two Primary Populations.

Shown are Kaplan–Meier estimates of progression-free survival in the niraparib group and the placebo group among the patients who had tumors with homologous-recombination deficiency (Panel A) and in those in the overall population (Panel B), according to central review. The horizontal dashed line indicates the median value. Asterisks and circles indicate censored data.

are provided in Figure 3 and Table S6. Within the population with homologous-recombination deficiency, the median duration of progression-free survival was 22.1 months in the niraparib group and 10.9 months in the placebo group (hazard ratio, 0.40; 95% CI, 0.27 to 0.62) in the

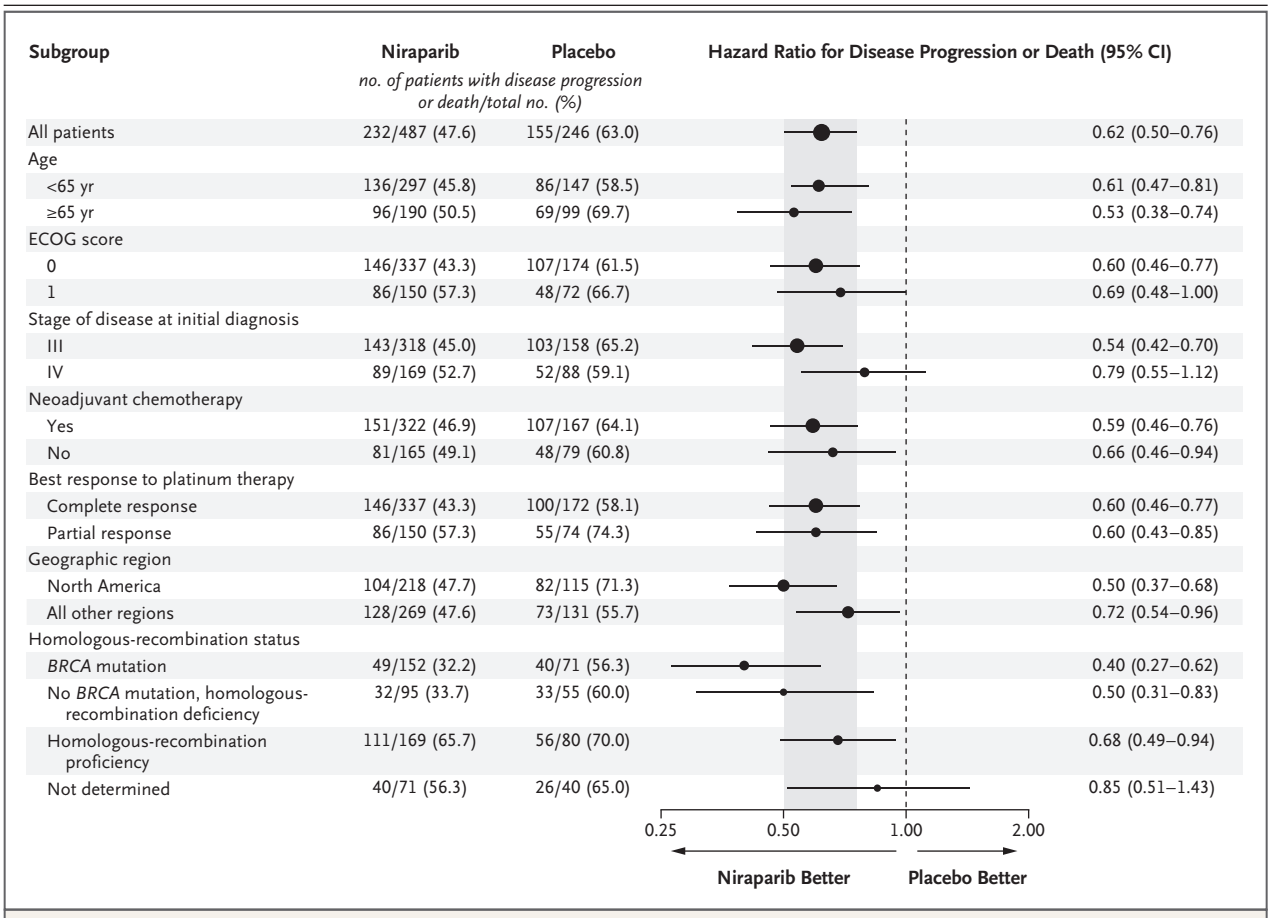

Figure 3. Disease Progression or Death, According to Prespecified Subgroups.

Shown is the incidence of disease progression or death, according to the listed subgroups, in the two trial groups. On the Eastern Cooperative Oncology Group (ECOG) performance-status evaluation, a score of 0 indicates that the patient is fully active and able to carry on all predisease performance without restriction, and a score of 1 indicates that the patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

subgroup with *BRCA* mutations and 19.6 months and 8.2 months, respectively (hazard ratio, 0.50; 95% CI, 0.31 to 0.83), in the subgroup without *BRCA* mutations. In the subgroup of patients with homologous-recombination proficiency, the median duration of progression-free survival was 8.1 months in the niraparib group and 5.4 months in the placebo group (hazard ratio, 0.68; 95% CI, 0.49 to 0.94). In this population, the interim overall survival analysis showed an estimated probability of survival at 24 months of 81% in the niraparib group and 59% in the placebo group (hazard ratio, 0.51; 95% CI, 0.27 to 0.97).

In addition to the subgroup of patients who had tumors with homologous-recombination proficiency, the treatment effect of niraparib extended to patients with advanced ovarian cancer in other subgroups with a poor prognosis, including in those who received neoadjuvant chemotherapy (13.9 vs. 8.2 months; hazard ratio, 0.59; 95% CI, 0.46 to 0.76) and in those with a partial response to platinum-based chemotherapy (8.3 vs. 5.6 months; hazard ratio, 0.60; 95% CI, 0.43 to 0.85). Niraparib was also associated with a longer duration of progression-free survival than placebo in the patients who had a complete response to chemotherapy (16.4 months vs. 9.5 months; hazard ratio, 0.60; 95% CI, 0.46 to 0.77). The results of a sensitivity analysis of progression-free survival were similar to and supported the blinded analysis on independent central review (Table S7).

SAFETY

Common adverse events that occurred during the trial are listed in Table 2 and Table S9. Among the most common grade 3 or higher adverse

events in the niraparib group were anemia (in 31.0% of the patients), thrombocytopenia (in 28.7%), and neutropenia (in 12.8%). Dose reductions were conducted in 70.9% of the patients in the niraparib group. The frequency of treatment discontinuation because of adverse events was 12.0% in the niraparib group and 2.5% in the placebo group. Myelosuppressive adverse events were the main reason for discontinuation but were infrequent (4.3% for thrombocytopenia in the niraparib group) (Table S8). One case of myelodysplastic syndrome was identified in a patient in the niraparib group. Low-grade nausea and fatigue were common in the two groups. No deaths during treatment with niraparib were reported during the trial. Safety improved with the implementation of the individualized dosing regimen (Tables S10 and S11).

PATIENT-REPORTED OUTCOMES

The analysis of patient-reported outcomes did not indicate a between-group difference in health-related quality-of-life scores (Fig. S2). Survey completion rates were high and were similar in the two groups (Table S12).

DISCUSSION

In the PRIMA trial, we found that patients with newly diagnosed advanced ovarian cancer who received niraparib after having a response to first-line platinum-based chemotherapy had significantly longer progression-free survival than those who received placebo in the overall population. No new safety signals were identified for niraparib.

Historically, clinical activity with PARP inhibitors has been associated with the presence of *BRCA* mutations, with most studies conducted in this selected patient population. Recent nonclinical studies,[21] together with the NOVA[7] and QUADRA[8] clinical trials, have shown the effectiveness of niraparib in treating patients with wild-type *BRCA* tumors. In the PRIMA trial, our primary hypothesis was that the clinical benefit of first-line treatment with niraparib could be extended to all patients with advanced ovarian cancer, including those who had tumors with homologous-recombination deficiency (with either mutated or unmutated *BRCA*) and those with homologous-recombination proficiency. Results of this trial confirm the hypothesis that treatment with niraparib provides a longer duration

Table 2. Adverse Events.

Adverse Events	Niraparib (N=484)	Placebo (N=244)
	no. of patients (%)	
Overall Population		
Adverse event		
Any	478 (98.8)	224 (91.8)
Grade ≥3	341 (70.5)	46 (18.9)
Treatment-related adverse event*		
Any	466 (96.3)	168 (68.9)
Grade ≥3	316 (65.3)	16 (6.6)
Serious adverse event		
Any	156 (32.2)	32 (13.1)
Treatment-related	118 (24.4)	6 (2.5)
Leading to treatment discontinuation	58 (12.0)	6 (2.5)
Leading to dose reduction	343 (70.9)	20 (8.2)
Leading to dose interruption	385 (79.5)	44 (18.0)
Leading to death	2 (0.4)	1 (0.4)
Most common adverse events†		
Anemia		
Any grade	307 (63.4)	43 (17.6)
Grade ≥3	150 (31.0)	4 (1.6)
Nausea		
Any grade	278 (57.4)	67 (27.5)
Grade ≥3	6 (1.2)	2 (0.8)
Thrombocytopenia		
Any grade	222 (45.9)	9 (3.7)
Grade ≥3	139 (28.7)	1 (0.4)
Constipation		
Any grade	189 (39.0)	46 (18.9)
Grade ≥3	1 (0.2)	0
Fatigue		
Any grade	168 (34.7)	72 (29.5)
Grade ≥3	9 (1.9)	1 (0.4)
Platelet count decreased		
Any grade	133 (27.5)	3 (1.2)
Grade ≥3	63 (13.0)	0
Neutropenia		
Any grade	128 (26.4)	16 (6.6)
Grade ≥3	62 (12.8)	3 (1.2)
Headache		
Any grade	126 (26.0)	36 (14.8)
Grade ≥3	2 (0.4)	0
Insomnia		
Any grade	119 (24.6)	35 (14.3)
Grade ≥3	4 (0.8)	1 (0.4)
Vomiting		
Any grade	108 (22.3)	29 (11.9)
Grade ≥3	4 (0.8)	2 (0.8)
Abdominal pain		
Any grade	106 (21.9)	75 (30.7)
Grade ≥3	7 (1.4)	1 (0.4)

* The determination of whether an adverse event was related to a trial treatment was made by the investigator.

† The most common adverse events were reported in at least 20% of the patients in the niraparib group and are listed in descending order of frequency.

of progression-free survival than placebo in the overall population. Currently, the most common treatment strategy with these patients is active surveillance. Preliminary results of the interim analysis suggest that overall survival may also be improved, but the data are not sufficiently mature to assess this end point with precision.

The high-risk patients with advanced ovarian cancer who were included in this trial are generally considered to have incurable disease with chemotherapy alone. Niraparib extends treatment beyond chemotherapy and provides a sustained progression-free survival benefit for those at risk for early relapse, including the one third of patients who had a partial response to platinum-based chemotherapy (8.3 months vs. 5.6 months with placebo; hazard ratio, 0.60). Niraparib also prolonged the time without progression or death in the patients who had a complete response after chemotherapy (16.4 months vs. 9.5 months; hazard ratio, 0.60). Notably, at 18 months after randomization and 2 years after the diagnosis of advanced ovarian cancer, Kaplan–Meier analysis estimated that in the niraparib group, 59% of the patients who had tumors with homologous-recombination deficiency and 42% of the overall population were alive without disease progression, as compared with 35% and 25% of patients, respectively, in the placebo group. This treatment effect occurred without a decrement in quality of life, as assessed by patient-reported outcomes.

The clinical benefit of niraparib in the overall population was not driven only by the subgroup of patients with *BRCA* mutations. In the patients who had tumors with homologous-recombination deficiency, niraparib provided a significant clinical benefit over placebo with respect to the median duration of progression-free survival both in patients with *BRCA* mutations (22.1 months vs. 10.9 months; hazard ratio, 0.40) and in those without *BRCA* mutations (19.6 months vs. 8.2 months; hazard ratio, 0.50). In the subgroup of patients with homologous-recombination proficiency, the longer median duration of progression-free survival in the niraparib group than in the placebo group (8.1 months vs. 5.4 months; hazard ratio, 0.68) supports the hypothesis that niraparib has mechanisms of action other than those involved in the repair of DNA damage. Complementary mechanisms of action for niraparib, including PARP-regulated gene transcription, ribosome biogenesis, and immune activation, may explain this clinical observation.[21,22] These analyses suggest that treatment with niraparib after first-line platinum-based chemotherapy extends benefit to all patients. The sensitivity to niraparib is lower in patients who have tumors with homologous-recombination proficiency than in those who have tumors with homologous-recombination deficiency.

The use of olaparib as a first-line treatment is limited to patients with *BRCA* mutations, as it was assessed in the SOLO1 trial.[4] Notable differences exist between the SOLO1 and PRIMA populations. In the PRIMA trial, we enrolled patients who had nonmutated *BRCA* ovarian cancer. Patients in SOLO1 were at lower risk for disease progression or death as evidenced by prognostic factors, since more patients in SOLO1 than in PRIMA had stage III disease (83% vs. 65%) and fewer received neoadjuvant chemotherapy (35% vs. 67%). Most patients with stage III ovarian cancer in SOLO1 underwent primary debulking surgery and had no visible residual disease (44%, vs. 0.4% in PRIMA). These factors influence outcomes and may explain the observed between-trial differences in the median duration of progression-free survival. Subgroup analysis of the data from SOLO1 showed that in the patients with residual disease after debulking surgery, the treatment effect of olaparib (progression-free survival of 29.4 months with olaparib vs. 11.3 months with placebo; hazard ratio, 0.44; 95% CI, 0.25 to 0.77) was similar to that of niraparib in patients with *BRCA* mutations and residual disease in PRIMA (22.1 months with niraparib vs. 10.9 months with placebo; hazard ratio, 0.40; 95% CI, 0.27 to 0.62).[23]

At the time that we designed the PRIMA trial, bevacizumab had not been approved for first-line treatment in all participating countries, and many patients receiving first-line therapy are ineligible to receive bevacizumab because of safety concerns or limited data regarding first-line use. The PRIMA trial provides data on the benefit of niraparib in patients with advanced ovarian cancer who were receiving neoadjuvant chemotherapy, a population of patients who have not been included in the phase 3 trials of bevacizumab (GOG-218 and ICON7)[2,3] and who have limited or no treatment options beyond chemotherapy.

Among the two thirds of patients in the PRIMA trial who received neoadjuvant chemotherapy, the receipt of niraparib was associated with a 41% lower relative risk of disease progression or death than placebo.

Most of the patients receiving niraparib or placebo had an adverse event during the trial. The frequency of adverse events was greater in the niraparib group than in the placebo group, which was consistent with the class effects of PARP inhibitors. Myelosuppression events were managed with treatment interruptions and dose reductions. Treatment discontinuations occurred in 4.3% of the patients in the niraparib group because of thrombocytopenia, a finding that was consistent with the results of the NOVA trial. Other adverse events that have been associated with PARP inhibitors, including nausea and fatigue, were of low grade. One patient in the niraparib group received the diagnosis of myelodysplastic syndrome in the context of bowel perforation, sepsis, and progressive disease.

We found that among patients with newly diagnosed advanced ovarian cancer, those who received daily oral therapy with the PARP inhibitor niraparib after a response to platinum-based chemotherapy had a significantly longer duration of progression-free survival than those who received placebo. There was a higher frequency of myelosuppression and low-grade nausea in the niraparib group than in the placebo group.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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METHODS

STUDY OVERSIGHT

All patients provided written informed consent. The protocol, amendments, and other relevant study documentation were reviewed and approved by an institutional/national review board or independent ethics committee at each study site/country (see Table S1 for a complete list of enrolling sites by country). An independent data monitoring committee provided recommendations for continuation or termination of the trial based on systematic review of the safety data. A blinded independent central review (BICR) committee was established to review efficacy response data and provide an objective, unbiased, independent review that determined efficacy endpoints based on the pertinent radiological and clinical data from the study. The study was designed through a collaboration of the European Network of Gynaecological Oncological Trial groups (ENGOT), academic researchers in the United States and Canada, and the study sponsor, TESARO: A GSK Company. The study was performed according to ENGOT model C. Study data were collected by clinical investigators, and trial conduct was overseen by TESARO: A GSK Company. Statistical analyses were produced by Veristat LLC and overseen by TESARO: A GSK Company according to a statistical analysis plan. Analyses were independently reviewed and approved by a statistician from the Nordic Society of Gynaecological Oncology (ENGOT lead group). This manuscript was developed with full author participation and assistance from a medical writer in accordance with Good Publication Practice 3 guidelines and International Committee of Medical Journal Editors guidelines. All authors had access to full data and analyses presented in this manuscript and approved the final version for submission.

Table S1. Patient Enrollment Sites by Country

Region	Country	Sites, n	Niraparib n=487	Placebo n=246	Overall N=733
North America			**218 (44.8)**	**115 (46.7)**	**333 (45.4)**
	United States	59	164 (33.7)	82 (33.3)	246 (33.6)
	Canada	10	54 (11.1)	33 (13.4)	87 (11.9)
Western Europe			**208 (42.7)**	**104 (42.2)**	**312 (42.6)**
	Spain	18	65 (13.3)	30 (12.2)	95 (13.0)
	Belgium	11	27 (5.5)	13 (5.3)	40 (5.5)
	Italy	7	21 (4.3)	14 (5.7)	35 (4.8)
	France	8	20 (4.1)	11 (4.5)	31 (4.2)
	Denmark	4	17 (3.5)	7 (2.8)	24 (3.3)
	Germany	9	16 (3.3)	8 (3.3)	24 (3.3)
	UK	9	13 (2.7)	8 (3.3)	21 (2.9)
	Israel	6	10 (2.1)	7 (2.8)	17 (2.3)
	Finland	4	10 (2.1)	1 (0.4)	11 (1.5)
	Switzerland	3	5 (1.0)	3 (1.2)	8 (1.1)
	Ireland	2	2 (0.4)	1 (0.4)	3 (0.4)
	Sweden	2	1 (0.2)	1 (0.4)	2 (0.3)
	Norway	1	1 (0.2)	0	1 (0.1)
Eastern Europe			**61 (12.5)**	**27 (11.0)**	**88 (12.0)**
	Russia	12	21 (4.3)	9 (3.7)	30 (4.1)
	Ukraine	8	21 (4.3)	8 (3.3)	29 (4.0)

	Czechia	3	6 (1.2)	6 (2.4)	12 (1.6)
	Poland	3	7 (1.4)	3 (1.2)	10 (1.4)
	Hungary	2	6 (1.2)	1 (0.4)	7 (1.0)

FIGO CANCER STAGING

FIGO cancer staging is shown in Table S2.[1]

Table S2. FIGO Staging Description

FIGO Stage	Stage description
IIIA1	The cancer is in one or both ovaries or fallopian tubes, **or** there is primary peritoneal cancer (T1) and it may have spread or grown into nearby organs in the pelvis (T2). It has spread to the retroperitoneal (pelvic and/or para-aortic) lymph nodes only. It has not spread to distant sites (M0).
IIIA2	The cancer is in one or both ovaries or fallopian tubes, **or** there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. During surgery, no cancer is visible in the abdomen (outside of the pelvis) to the naked eye, but tiny deposits of cancer are found in the lining of the abdomen when it is examined in the lab (T3a). The cancer might or might not have spread to retroperitoneal lymph nodes (N0 or N1), but it has not spread to distant sites (M0).
IIIB	There is cancer in one or both ovaries or fallopian tubes, **or** there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are large enough for the surgeon to see, but are no bigger than 2 cm (about 3/4 inch) across. (T3b). It may or may not have spread to the retroperitoneal lymph nodes (N0 or N1), but it has not spread to the inside of the liver or spleen or to distant sites (M0).

IIIC	The cancer is in one or both ovaries or fallopian tubes, **or** there is primary peritoneal cancer and it has spread or grown into organs outside the pelvis. The deposits of cancer are larger than 2 cm (about 3/4 inch) across and may be on the outside (the capsule) of the liver or spleen (T3c). It may or may not have spread to the retroperitoneal lymph nodes (N0 or N1), but it has not spread to the inside of the liver or spleen or to distant sites (M0).
IVA	Cancer cells are found in the fluid around the lungs (called a malignant pleural effusion) with no other areas of cancer spread such as the liver, spleen, intestine, or lymph nodes outside the abdomen (M1a).
IVB	The cancer has spread to the inside of the spleen or liver, to lymph nodes other than the retroperitoneal lymph nodes, and/or to other organs or tissues outside the peritoneal cavity such as the lungs and bones (M1b).

BIOMARKER TESTING

In the initial PRIMA/ENGOT-OV26/GOG-3012 trial protocol, enrollment was restricted to patients considered to be homologous recombination deficient, and 44 patients were enrolled during this time. Protocol amendment 1 (December 1, 2016) removed the biomarker criteria, and added homologous recombination status as a stratification factor during randomization.

In the PRIMA/ENGOT-OV26/GOG-3012 trial, *BRCA* and homologous recombination status were determined at screening by tumor samples via the myChoice® HRD test (Myriad Genetics, Inc., Salt Lake City, UT). Formalin-fixed paraffin-embedded (archival or fresh) tumor samples were required at screening

centralized homologous recombination testing. Homologous recombination status was a stratification factor during randomization.

The myChoice® HRD test is an integrated genome-based assay for homologous recombination that quantitates genomic instability of the tumor and, in parallel, detects and classifies variants in *BRCA1* and *BRCA2*. It is a next-generation sequencing test that uses DNA extracted from formalin-fixed paraffin-embedded tumor tissue to create libraries that are hybridized to a custom Agilent SureSelect capture array carrying probes for 54,091 single nucleotide polymorphisms distributed across the human genome, as well as 685 probes for *BRCA1* and *BRCA2* exons, exon boundaries, and promoter regions. Three algorithms are used to assess genomic instability and provide a score for each of: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions. The homologous recombination deficiency score is the unweighted sum of the three scores representing a continuum of genomic instability accumulated over time in the tumor. Homologous recombination deficiency is defined by tumor *BRCA* mutation or a composite genomic instability score of greater than or equal to 42. Based on the test results, tumors are classified as homologous recombination deficient or homologous recombination proficient. If test results are inconclusive or the test was not done, tumors are considered as homologous recombination status not determined.

The definitions of the test results are listed below, and the numbers of patients assigned to the various groups and subgroups are shown in Fig. S1 of the Supplementary Appendix.

Germline *BRCA* mutation (g*BRCA*mut) – A g*BRCA*mut is an inherited deleterious mutation in either a *BRCA1* or *BRCA2* tumor suppressor gene. Harmful mutations in

either of these genes may produce a hereditary breast-ovarian cancer syndrome in affected persons. Cells with deleterious or suspected deleterious germline *BRCA1* or *BRCA2* mutations have a defect in the repair of DNA breaks by the error-free mechanism of homologous recombination. This defect results in the repair of such lesions by error-prone mutagenic pathways, such as single-strand annealing and nonhomologous end joining, leading to genomic instability. Women with harmful germline mutations in either *BRCA1* or *BRCA2* have a risk of breast cancer that is approximately five times the normal risk and a risk of ovarian cancer that is about 10 to 30 times the unaffected risk.

Somatic *BRCA* mutation (s*BRCA*mut) – A s*BRCA*mut is a deleterious or suspected deleterious alteration in the *BRCA1* or *BRCA2* genes that is acquired after conception (not hereditary). Somatic mutations can occur in any cell of the body except in germ cells (sperm and egg); therefore, they are not passed on to children. A s*BRCA*mut may also confer an increased risk of cancer in affected cells. These mutations are not present in the germline.

BRCA wild type (*BRCA*wt) – A tumor that does not have either a deleterious or suspected deleterious g*BRCA*mut or s*BRCA*mut.

Homologous recombination deficiency – Unlike the *BRCA*1 and *BRCA*2 mutation test, homologous recombination deficiency score is not based on individual gene mutations, but represents dysregulation in the homologous recombination pathway (due to genetic mutations or alterations) leading to an inability to efficiently repair damaged DNA. Cells deficient in homologous recombination are more susceptible to the effects of

DNA-damaging agents such as platinum agents or poly(ADP-ribose) polymerase inhibitors.

Homologous recombination deficient – homologous recombination deficiency status in this study was determined by the myChoice HRD test. Any tumor that has a score ≥42 or has a deleterious or suspected deleterious *BRCA1/2* mutation was considered homologous recombination deficient.

Homologous recombination proficient – homologous recombination proficiency status in this study was determined by the myChoice HRD test. Any tumor that scored <42 and did not possess a deleterious or suspected deleterious *BRCA1/2* mutation was considered homologous recombination proficient.

STUDY ASSESSMENTS

Tumor samples were sent for centralized homologous recombination testing. To facilitate the screening and enrollment processes, the samples could have been sent in advance of the protocol-defined screening period after patients signed the informed consent for testing. The myChoice test results were required before randomization for patients without a known g*BRCA*mut or s*BRCA*mut. For patients with a documented deleterious g*BRCA*mut or s*BRCA*mut by local results, randomization could have occurred before the homologous recombination test results were available; for stratification purposes, these patients were considered as having homologous recombination deficient tumors. These tumors were still tested by the Myriad test.

Clinic visits (other than cycle 1) were every cycle (28 days ±3 days). Tumor assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

via a computed tomography or magnetic resonance imaging scan of the abdomen/pelvis and other areas as clinically indicated was required at screening, then every 12 weeks (±7 days) from cycle 1/day 1 visit until progression was confirmed by BICR. Positron emission tomography/computed tomography scans could have been used according to RECIST guidelines but were not a study requirement. If a patient discontinued treatment for a reason other than progression or death, withdrawal of consent, or loss to follow-up, scans continued at the specified intervals.

Provision of a tumor sample for exploratory biomarker analyses was optional for patients who discontinued study treatment due to progressive disease. All patients continued to be followed for overall survival (OS) and other secondary objectives.

Adverse events (AEs) were monitored throughout the treatment period, described in detail below, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. All AEs were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system and displayed in tables and data listings using system organ class and preferred term.

Patient-reported outcomes (PROs), assessed using the Functional Assessment of Cancer Therapy-Ovarian Symptoms Index (FOSI), European Quality of Life five-dimension, five-level questionnaire (EQ-5D-5L), European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC-QLQ-C30), and EORTC Quality of Life Questionnaire Ovarian Cancer Model (EORTC-QLQ-OV28), were collected every 8 weeks (±7 days) for 56 weeks beginning on cycle 1/day 1, then every 12 weeks (±7 days) thereafter while the patient received study

treatment. Once a patient discontinued treatment, PRO evaluations were performed at the time of treatment discontinuation and then at 4, 8, 12, and 24 weeks (±1 week for each timepoint) after the end of treatment, regardless of the status of subsequent treatment (see below for additional details).

ADVERSE EVENT MONITORING

AEs and serious AEs were collected from the time of signing the main informed consent form through treatment discontinuation. New serious AEs (including deaths) were collected for 30 days after treatment discontinuation.

AEs could be volunteered spontaneously by the patient or discovered by the study staff during physical examinations or by asking an open, non-leading question such as: “How have you been feeling since you were last asked?” All AEs and any required remedial action were recorded. The nature of the AE, date (and time, if known) of AE onset, date (and time, if known) of AE outcome to date, severity, and action taken of the AE were documented along with the investigator’s assessment of the severity of the AE and causal relationship to the study drug and/or study procedure.

All AEs were recorded individually in the patient’s own words (verbatim) unless, in the opinion of the investigator, the AEs constituted components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome was named rather than each individual symptom. All AEs were coded using MedDRA, and AE severity was assessed using the NCI CTCAE v4.03.

STUDY ENDPOINT DEFINITIONS

- Progression-free survival (PFS): Time from treatment randomization to the earlier date of assessment of progression or death from any cause in the absence of progression
- Overall survival (OS): Time from treatment randomization to the date of death from any cause
- Progression-free survival 2 (PFS2): Time from treatment randomization to the earlier date of assessment of progression on the next anticancer therapy following study treatment or death from any cause
- Time to first subsequent therapy (TFST): Time from treatment randomization to the start date of the first subsequent anticancer therapy or death from any cause

MISSING AND PARTIAL DATA

Methods for handling incomplete PRO instruments are performed according to their scoring manuals. Details are provided in patient-reported outcomes section of this supplement.

Missing and partial dates were queried. Imputed dates were characterized as another numeric variable. Imputed date values were performed according to the most conservative approach. If any date was imputed and requested on a listing, the original non-imputed date was provided on the same listing as reference. In general, imputed dates were only used for analysis purposes. Details are specified in Section 3.10 of the Statistical Analysis Plan.

STATISTICAL ANALYSIS

Patient Disposition

Patient disposition was tabulated and includes the numbers of screened patients (who provided written informed consent for the main study) and randomized patients in each patient population for analysis, the number of patients who discontinued treatment or the study and reason(s) for withdrawal, and the number of patients who died.

Tables were summarized separately for the homologous recombination deficient and overall populations. A by-patient data listing of study completion information including the reasons for treatment discontinuation and/or study discontinuation is presented.

Demographics, Baseline Characteristics, and Medical History

Demographics, baseline characteristics, and medical history information were summarized using descriptive statistics. Tables were summarized separately for the homologous recombination deficient and overall populations.

Efficacy Analyses

Sample Size Determination

The PRIMA/ENGOT-OV26/GOG-3012 trial was sized to evaluate the PFS endpoint and to ensure adequate data to monitor safety and OS. The sample size for the homologous recombination deficient population was determined based on the assumption that niraparib would result in an expected benefit corresponding to a hazard ratio (HR) of 0.5 with 90% power for niraparib relative to placebo. To detect an expected benefit corresponding to an HR of 0.5 with 90% power and 2:1 randomization, at least 99 PFS

events in the homologous recombination deficient population were required in the final analysis of PFS. During the conduct of the study, observations from the reported longer median PFS for placebo patients with *BRCA*mut (~30 months) led to the revised assumption for a median PFS of 21 months in the homologous recombination deficient placebo arm and a median PFS of 14 months in the overall placebo arm. Therefore, the protocol was amended to allow enrollment of approximately 620 patients (~50% homologous recombination deficient) to complete the study in about 44 months. Since this is an event-driven study, if the actual median PFS for the placebo treatment arm is longer or shorter than the assumed median estimate, the time needed to reach the required minimum number of PFS events will be either extended or reduced accordingly.

The PFS analysis in the overall population will include all PFS events observed at the time of the final analysis of PFS. Assuming a median PFS of 14 months for all placebo patients, a total of approximately 270 PFS events are expected for the final analysis of PFS in the overall population. This will provide at least 90% power to detect a true HR of 0.65.

Time-to-Event Analyses

For the homologous recombination deficient and overall populations, PFS was analyzed with a stratified log-rank test using randomization stratification factors and summarized using Kaplan-Meier methodology. HRs with 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with stratification factors used in randomization. Secondary time-to-event endpoints (OS, TFST, PFS2) were analyzed in the same manner as PFS.

Hierarchical testing for the PFS and OS endpoints was used to control for the overall type I error. First, the analysis of PFS was conducted in the homologous recombination deficient population at the one-sided 0.025 type I error. Because this result was positive, PFS analysis was conducted in the overall population at the one-sided 0.025 type I error. Since the PFS analysis was positive in the overall population, the OS analysis was conducted according to the prespecified group sequential design with an interim analysis performed for the overall population at the time of final PFS analysis. A final OS analysis will be performed in the future when the number of OS events is reached. A Lan-DeMets alpha-spending function with the O'Brien-Fleming stopping boundaries was used to determine the significance levels for interim and final OS analyses.[2] The ENGOT statistician independently performed an analysis of the primary endpoint.[3] Analyses of other secondary endpoints were not adjusted for multiple comparisons. All P values are reported at a two-sided significance level of 0.05.

Subgroup analyses of the PFS endpoint were performed using a stratified Cox proportional hazards model in the prespecified subgroups. The stratification factors used in the primary analysis were used in the subgroup analyses when applicable. A statistical test for the presence of a treatment-by-subgroup interaction was performed by including the interaction term in the primary analysis model using Cox regression. If the treatment-by-subgroup interaction was found to be statistically significant at the 10% level ($P<0.10$), this may have been taken as evidence of heterogeneity of the treatment effect across the subgroup categories.

Sensitivity analyses of the PFS endpoint assessed by BICR were performed including:

- The potential impact of informative censoring was assessed by sensitivity analysis using a stratified log-rank test with the investigator-assessed PFS. The stratification factors and censoring rules used in the primary analysis were applied to the investigator data in this sensitivity analysis.
- The PFS endpoint assessed by BICR was assessed using the per-protocol population. The stratification factors were derived based on data from the electronic case report form (eCRF). The censoring rules used in the primary analysis were applied.
- Additional sensitivity analyses are listed in Section 4.3.1 of the Statistical Analysis Plan.

Efficacy data were analyzed in the overall population, defined as all patients who underwent randomization. Safety data were analyzed in the safety population, which included all patients who received at least one dose of niraparib or placebo. An ENGOT statistician performed an independent analysis on pre-defined endpoints.

PROTOCOL-MANDATED DOSE MODIFICATIONS

At the investigator's discretion, dose interruption and/or reduction was implemented at any time for any grade toxicity considered intolerable by the patient. Dose interruptions and/or reductions were mandated for hematologic toxicities and defined in the protocol.

Treatment must have been interrupted for any nonhematologic NCI CTCAE (v4.03) grade 3 or 4 AE that the investigator considered to be related to administration of study treatment. If a grade 3 or 4 nonhematologic toxicity was appropriately resolved to baseline or grade 1 or less within 28 days of interruption, the patient could restart treatment with niraparib at a reduced dose level as outlined in Table S3 if prophylaxis

was not considered feasible. If the event recurred at a similar or worse grade, treatment was interrupted again and, upon resolution, a further dose reduction was made.

Table S3. Dose Reduction Schedule

Dose level	Initial dose: 3 capsules per day	Initial dose: 2 capsules per day
Starting dose	3 capsules once daily (300 mg/day)	2 capsules once daily (200 mg/day)
First dose reduction	2 capsules once daily (200 mg/day)	1 capsule once daily (100 mg/day)
Second dose reduction	1 capsule once daily (100 mg/day)	Patient must discontinue treatment

For patients whose initial dose was 3 capsules once daily (300 mg/day), dose reductions to 2 capsules once daily (200 mg/day) and subsequently to 1 capsule once daily (100 mg/day) were allowed. No further dose reduction was allowed.

For patients whose initial dose was 2 capsules once daily (200 mg/day), dose reduction to 1 capsule once daily (100 mg/day) was allowed. No further dose reduction was allowed without discussion with the medical monitor.

If the toxicity requiring dose interruption was not resolved completely or to NCI CTCAE grade 1 during the maximum 4-week (28-day) dose interruption period, and/or the patient had already undergone the maximum dose reductions, the patient permanently discontinued study treatment.

The dose interruption/modification criteria for hematologic parameters were based on blood counts and are outlined in Table S4.

Table S4. Dose Modifications for Hematologic Adverse Reactions

Monitor complete blood count (CBC) until the AE resolves. To ensure safety of the new dose, CBC weekly blood draws were required for an additional 4 weeks after the AE resolves. Continue monitoring on day 1 of every cycle thereafter. If MDS/AML or secondary cancers (new malignancies other than MDS/AML) is confirmed, discontinue niraparib.	
Platelet count <100,000/μL	First occurrence: Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the medical monitor is required to resume niraparib. Resume study treatment at same or reduced dose per Table S3. If platelet count was <75,000/μL, resume at a reduced dose after recovery. Second occurrence:

	Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/μL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise, discussion with the medical monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table S3. Discontinue study treatment if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone maximum dose reductions per Table S3.
Neutrophil count <1000/μL or hemoglobin <8 g/dL	Withhold study treatment for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1500/μL or hemoglobin returns to ≥9 g/dL. For adverse reactions that do not resolve within 28 days, study treatment should be discontinued. Otherwise,

	discussion with the medical monitor is required to resume niraparib. Resume niraparib at a reduced dose per Table S3. Discontinue study treatment if neutrophil count or hemoglobin level has not returned to acceptable levels within 28 days of the dose interruption period or if the patient has already undergone maximum dose reductions per Table S3.
Hematologic adverse reaction requiring transfusion	For patients with a platelet count ≤10,000/μL, platelet transfusion should be considered. If there are other risk factors, such as coadministration of anticoagulation or antiplatelet drugs, consider interrupting these drugs and/or transfusion at a higher platelet count. Resume study treatment at a reduced dose per Table S3.

AML, acute myeloid leukemia; CBCs, complete blood cell counts; MDS, myelodysplastic syndrome.

If dose interruption or modification was required at any point on study because of hematologic toxicity, weekly blood draws for complete blood cell counts (CBCs) were monitored until the AE resolved. To ensure safety of the new dose, weekly blood draws

for CBCs were also required for an additional 4 weeks after the AE had resolved to the specified levels, after which monitoring every 4 weeks was resumed.

Any patient that required transfusion of platelets or red blood cells (one or more units) or hematopoietic growth factor support must have undergone a dose reduction upon recovery if study treatment was resumed.

If a diagnosis of myelodysplastic syndrome/acute myeloid leukemia or a secondary cancer (new malignancies other than myelodysplastic syndrome/acute myeloid leukemia) was confirmed while on study, the patient permanently discontinued study treatment.

For major surgery while on treatment, up to 28 days of study treatment interruption was allowed.

Once the dose of study treatment had been reduced, any re-escalation was discussed with the medical monitor.

All dose interruptions and reductions (including any missed doses), and the reasons for the reductions/interruptions, were recorded in the eCRF.

PATIENT-REPORTED OUTCOMES

The FOSI is a validated eight-item measure of symptom response to treatment for ovarian cancer based on a subset of questions from the Functional Assessment of Cancer Therapy - Ovarian Cancer questionnaire.[4] For each question, patients responded to their symptom experience over the previous 7 days using a five-point Likert scale of “not at all” (0) to “very much” (4). The FOSI score range is 0 (severely symptomatic) to 32 (asymptomatic).

The FOSI score was derived in accordance with the FOSI scoring manual (SAP appendix 7.1). Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the FOSI score. A higher score indicates a better quality of life (QOL).

If there are missing items, subscale scores will be prorated as long as more than 50% of the items were answered (ie, at least 5 of 8 items). The proration is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered.

FOSI score = [Sum of item scores] x 8 / [N of items answered]

The EQ-5D-5L measures the patient's perceived health state in the following five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[5] Each domain has five possible levels: no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4), and extreme problems (level 5). Each domain is assigned a level, and all levels are combined to create a five-digit number describing the patient's health state (eg, 11111, 12345). For each patient, an index value is determined from the health states using the US value set.[6,7] An index value of 1 indicates full health; the closer to 1 the better the health of the patient. A higher index value indicates a better QOL. The EQ-5D index value is regarded as missing when responses are missing for 1 or more of the 5 dimensions.

The EORTC-QLQ-C30 is a validated, 30-item, health-related quality-of-life instrument developed to assess health outcomes from a wide variety of interventions on a common scale.[8] The instrument comprises three domains. The first domain asks patients to rate their need for assistance with or difficulty completing certain activities

(such as walking or lifting) and daily self-care tasks on a Likert-type scale, where 0 corresponds to “not at all” (ie, no difficulty or assistance needed) and 4 corresponds to “very much” (ie, very much difficulty or assistance required). The second domain, using the same Likert scale, asks the patient to rate—specific to the previous week—their limitations on work/hobbies, family life, social activities, and finances; shortness of breath; need for rest/tiredness; pain and its interference with activity; ability to sleep; weakness; appetite; symptoms of nausea, vomiting, constipation, and diarrhea; ability to concentrate/remember; and emotions (irritability and depression). The third domain asks patients to rate their overall health and overall quality of life on a seven-point Likert scale, where 1 corresponds to “very poor” and 7 corresponds to “excellent.”

The EORTC-QLQ-C30 is often used as a companion to other disease-specific instruments such as the ovarian-specific EORTC-QLQ-OV28, which assesses ovarian cancer patients’ abdominal/gastrointestinal symptoms, other chemotherapy side effects, hormonal/menopausal symptoms, body image, attitude to disease/treatment, and sexual functioning.[9]

Scale scores are calculated by averaging items within scales and transforming average scores linearly. All of the scales range in score from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning whereas a high score for a symptom scale or item represents a high level of symptomatology or problems.

If there are missing items in a scale, the scale score will be calculated on the completed items if at least 50% of the component items have been completed; otherwise the scale score is regarded as missing.

PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) were collected every 8 weeks (±7 days) for 56 weeks beginning on cycle 1/day 1, then every 12 weeks (±7 days) thereafter while the patient received study treatment. Once a patient discontinued treatment, PRO evaluations were performed at the time of treatment discontinuation and then at 4, 8, 12, and 24 weeks (±1 week for each timepoint) after the end of treatment, regardless of the status of subsequent treatment.

PROs could only be completed by the study patient in their native language and could have been done remotely. It is estimated that PRO evaluations take less than 20 minutes at each time point. Since these are questionnaires, their completion does not interfere with, or prevent, future treatment or clinical studies. PRO evaluations should be administered before conducting any other procedures at each assessment.

For PROs, compliance was summarized by visit. Compliance by visit is calculated as the number of patients with an evaluable form at that visit, divided by the number of patients expected to complete the form at that visit.

A mixed effects model for repeated measures (MMRM) was performed to compare between-treatment difference adjusting for correlations across multiple time points within a patient and controlling for the baseline value. Adjusted mean difference and 95% CIs were presented to illustrate the effect of treatment. Adjusted means and standard error bars were plotted over time.

SUPPLEMENTAL TABLES AND FIGURES

Table S5. Secondary Endpoints.

	Homologous Recombination Deficient		Homologous Recombination Proficient		Overall Population	
Endpoint	**Niraparib (n=247)**	**Placebo (n=126)**	**Niraparib (n=169)**	**Placebo (n=80)**	**Niraparib (n=487)**	**Placebo (n=246)**
Overall survival*						
24-month survival	91%	85%	81%	59%	84%	77%
HR (95% CI)	0.61 (0.27–1.39)		0.51 (0.27–0.97)		0.70 (0.44–1.11)	
Time to first subsequent therapy†						
Median	NE	13.7	11.6	7.9	18.6	12.0
(95% CI) — mo	(24.7–NE)	(11.6–19.3)	(9.7–14.2)	(6.6–10.4)	(15.8–24.7)	(10.3–13.9)
HR (95% CI)	0.46 (0.33–0.64)		0.64 (0.46–0.90)		0.65 (0.52–0.80)	
Progression-free survival 2‡						
HR (95% CI)	0.84 (0.49–1.45)		0.56 (0.34–0.91)		0.81 (0.58–1.14)	

*Overall Survival data maturity: 10.8% data maturity in overall population. Median estimates were not shown due to low event rate and insufficient follow-up time.

†Time to first subsequent therapy data maturity: 47% in the overall population

‡Progression-free survival 2 data maturity: 20% in the overall population. Median estimates were not shown due to low event rate and insufficient follow-up time.

CI, confidence interval; HR, hazard ratio; NE, not estimable.

Table S6. Key Subgroup Analyses.

	Homologous recombination deficient, *BRCA*mut		**Homologous recombination deficient, *BRCA*wt**		**Homologous recombination proficient**	
PFS	**Niraparib (n=152)**	**Placebo (n=71)**	**Niraparib (n=95)**	**Placebo (n=55)**	**Niraparib (n=169)**	**Placebo (n=80)**
Median (95% CI) — mo	22.1 (19.3–NE)	10.9 (8.0–19.4)	19.6 (13.6–NE)	8.2 (6.7–16.8)	8.1 (5.7–9.4)	5.4 (4.0–7.3)
HR (95% CI)	0.40 (0.27–0.62)		0.50 (0.31–0.83)		0.68 (0.49–0.94)	
P value	<0.001		0.006		0.020	

CI, confidence interval; HR, hazard ratio; mut, mutated; NE, not estimable; PFS, progression-free survival; wt, wild type.

Table S7. PFS Sensitivity Analyses for Investigator vs BICR.

	PFS by Investigator (overall population)		PFS by BICR (per-protocol population)	
PFS	**Niraparib (n=487)**	**Placebo (n=246)**	**Niraparib (n=487)**	**Placebo (n=246)**
Median (95% CI) — mo	13.8 (11.3–14.2)	8.2 (7.6–9.8)	13.8 (11.4–14.9)	8.2 (7.1–8.4)
HR (95% CI)	0.63 (0.51–0.76)		0.60 (0.49–0.73)	
P value	<0.001		<0.001	

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table S8. Treatment Discontinuations Due to Myelosuppressive Adverse Events (Safety Population, N=728).

Adverse Event — no. (%)	Niraparib (n=484)	Placebo (n=244)
Thrombocytopenia*	21 (4.3)	0
Neutropenia*	9 (1.9)	0
Leukopenia*	10 (2.1)	0
Anemia	9 (1.9)	0
Pancytopenia	0	0

*Grouped terms

Table S9. Treatment-emergent Adverse Events Occurring in ≥10% of Patients (Safety Population, N=728).

	Niraparib (n=484)		Placebo (n=244)	
MedDRA Preferred Term — no. (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Anemia	307 (63.4)	150 (31.0)	43 (17.6)	4 (1.6)
Nausea	278 (57.4)	6 (1.2)	67 (27.5)	2 (0.8)
Thrombocytopenia	222 (45.9)	139 (28.7)	9 (3.7)	1 (0.4)
Constipation	189 (39.0)	1 (0.2)	46 (18.9)	0
Fatigue	168 (34.7)	9 (1.9)	72 (29.5)	1 (0.4)
Platelet count decreased	133 (27.5)	63 (13.0)	3 (1.2)	0
Neutropenia	128 (26.4)	62 (12.8)	16 (6.6)	3 (1.2)
Headache	126 (26.0)	2 (0.4)	36 (14.8)	0
Insomnia	119 (24.6)	4 (0.8)	35 (14.3)	1 (0.4)
Vomiting	108 (22.3)	4 (0.8)	29 (11.9)	2 (0.8)
Abdominal pain	106 (21.9)	7 (1.4)	75 (30.7)	1 (0.4)
Decreased appetite	92 (19.0)	3 (0.6)	20 (8.2)	0
Diarrhea	91 (18.8)	3 (0.6)	55 (22.5)	1 (0.4)
Dyspnea	88 (18.2)	2 (0.4)	30 (12.3)	2 (0.8)
Arthralgia	85 (17.6)	2 (0.4)	47 (19.3)	0
Neutrophil count decreased	82 (16.9)	37 (7.6)	5 (2.0)	0
Hypertension	82 (16.9)	29 (6.0)	17 (7.0)	3 (1.2)
Asthenia	78 (16.1)	4 (0.8)	31 (12.7)	2 (0.8)
White blood cell count decreased	74 (15.3)	12 (2.5)	8 (3.3)	0
Cough	74 (15.3)	0	35 (14.3)	1 (0.4)

	Niraparib (n=484)		Placebo (n=244)	
MedDRA Preferred Term — no. (%)	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Dizziness	71 (14.7)	0	26 (10.7)	1 (0.4)
Back pain	64 (13.2)	0	24 (9.8)	0
Leukopenia	57 (11.8)	10 (2.1)	13 (5.3)	0
Blood creatinine increased	55 (11.4)	1 (0.2)	10 (4.1)	0
Hot flush	54 (11.2)	1 (0.2)	20 (8.2)	0
Viral upper respiratory tract infection	49 (10.1)	0	25 (10.2)	0
Abdominal distension	32 (6.6)	0	30 (12.3)	0

MedDRA, Medical Dictionary for Regulatory Activities.

Table S10. Any Grade Hematologic TEAEs in Patients Receiving a Fixed Versus Individualized Dose of Niraparib (Safety Population, N=728).

	Niraparib		Placebo	
MedDRA preferred term — no. (%)	**Fixed Dose (n=315)**	**Individualized Dose (n=169)**	**Fixed Dose (n=158)**	**Individualized Dose (n=86)**
Anemia	223 (70.8)	84 (49.7)	19 (12.0)	24 (27.9)
Thrombocytopenia	165 (52.4)	57 (33.7)	6 (3.8)	3 (3.5)
Platelet count decreased	95 (30.2)	38 (22.5)	2 (1.3)	1 (1.2)
Neutropenia	87 (27.6)	41 (24.3)	10 (6.3)	6 (7.0)
Neutrophil count decreased	61 (19.4)	21 (12.4)	3 (1.9)	2 (2.3)
Hemoglobin decreased	4 (1.3)	1 (0.6)	0	0
Febrile neutropenia	3 (1.0)	1 (0.6)	0	0
Myelodysplastic syndrome	1 (0.3)	0	0	0
Pancytopenia	1 (0.3)	0	0	0
Neutropenic sepsis	0	1 (0.6)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table S11. Grade ≥3 Hematologic TEAEs in Patients Receiving a Fixed Versus Individualized Dose of Niraparib (Safety Population, N=728).

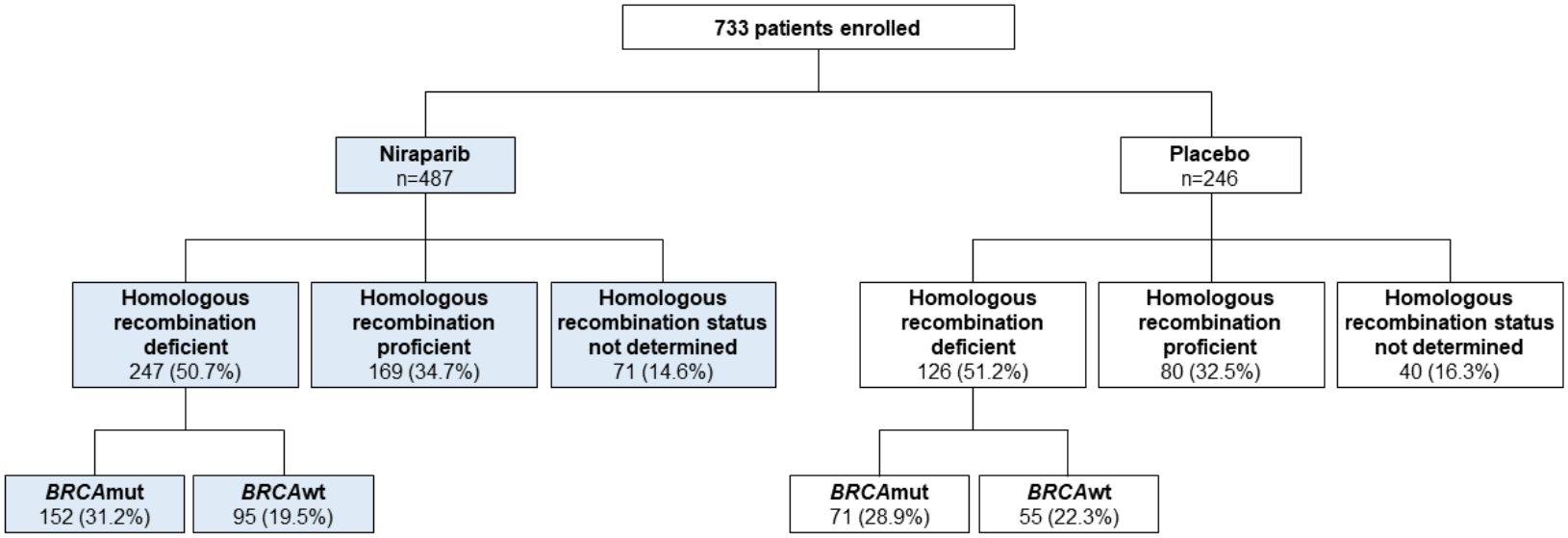
	Niraparib		Placebo	
MedDRA preferred term — no. (%)	Fixed Dose (n=315)	Individualized Dose (n=169)	Fixed Dose (n=158)	Individualized Dose (n=86)
Thrombocytopenia	114 (36.2)	25 (14.8)	0	1 (1.2)
Anemia	112 (35.6)	38 (22.5)	3 (1.9)	1 (1.2)
Platelet count decreased	51 (16.2)	12 (7.1)	0	0
Neutropenia	46 (14.6)	16 (9.5)	2 (1.3)	1 (1.2)
Neutrophil count decreased	28 (8.9)	9 (5.3)	0	0
Febrile neutropenia	3 (1.0)	1 (0.6)	0	0
Myelodysplastic syndrome	1 (0.3)	0	0	0
Pancytopenia	1 (0.3)	0	0	0
Neutropenic sepsis	0	1 (0.6)	0	0

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table S12. Functional Assessment of Cancer Therapy-Ovarian Symptom Index (FOSI) Completion Status by Visit.

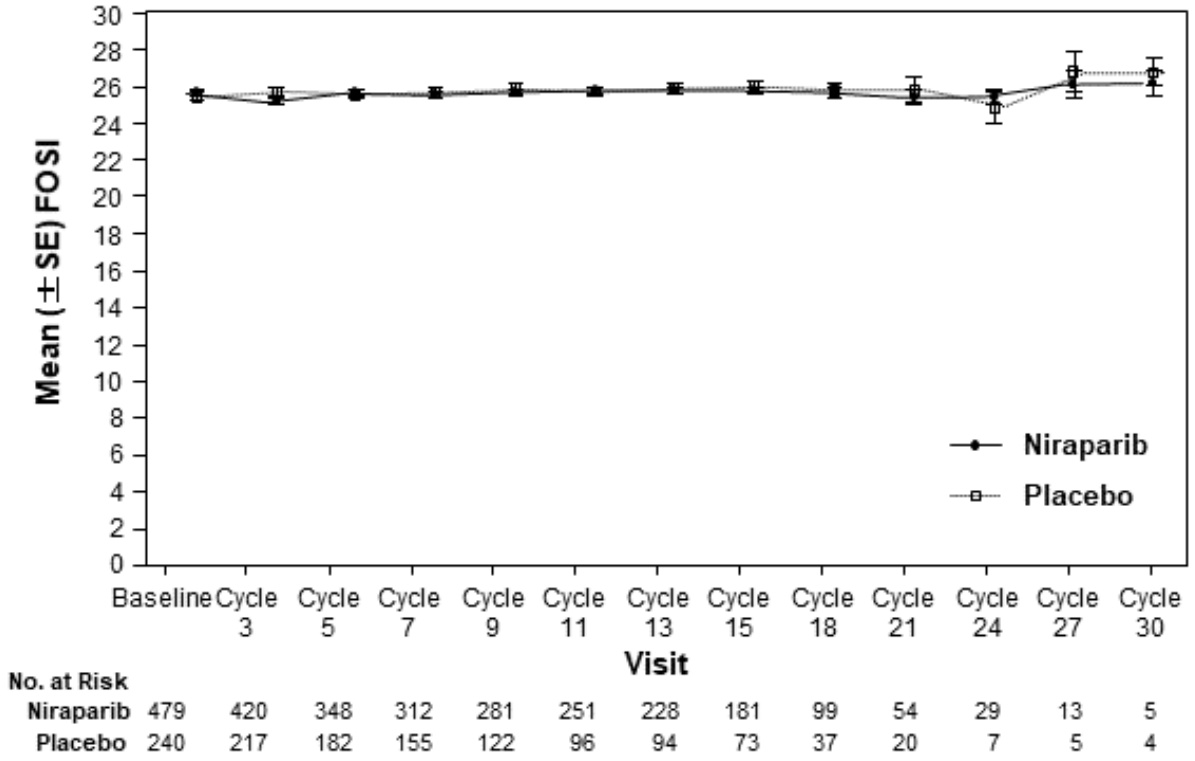
Number of Completed FOSI — no (%)	Niraparib (n=487)	Placebo (n=246)
Screening	483/487 (99.2)	242/246 (98.4)
Cycle 3	424/441 (96.1)	221/232 (95.3)
Cycle 5	352/375 (93.9)	185/196 (94.4)
Cycle 7	316/344 (91.9)	158/177 (89.3)
Cycle 9	285/299 (95.3)	125/138 (90.6)
Cycle 11	254/266 (95.5)	99/109 (90.8)
Cycle 13	231/249 (92.8)	97/98 (99.0)
Cycle 15	185/198 (93.4)	74/83 (89.2)
Cycle 18	100/109 (91.7)	38/39 (97.4)
Cycle 21	56/61 (91.8)	21/22 (95.5)
Cycle 24	30/33 (90.9)	8/8 (100)
Cycle 27	13/16 (81.3)	5/5 (100)
Cycle 30	5/6 (83.3)	4/4 (100)

Figure S1. Patient Enrollment by Biomarker Status.



mut, mutated; wt, wild type.

Figure S2. Health-related Quality of Life/Patient-reported Outcomes.



FOSI, Functional Assessment of Cancer Therapy-Ovarian Symptoms Index; SE, standard error.

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