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A. González-Martín, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, C. McCormick, D. Lorusso, P. Hoskins, G. Freyer, K. Baumann, K. Jardon, A. Redondo, R.G. Moore, C. Vulsteke, R.E. O'Cearbhaill, B. Lund, F. Backes, P. Barretina-Ginesta, A.F. Haggerty, M.J. Rubio-Pérez, M.S. Shahin, G. Mangili, W.H. Bradley, I. Bruchim, K. Sun, I.A. Malinowska, Y. Li, D. Gupta, and B.J. Monk, for the PRIMA/ENGOT-OV26/GOG-3012 Investigators*

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.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. González-Martín at the Medical Oncology Department, Clínica Universidad de Navarra, Calle Marquesado de Santa Marta 1, Madrid 28027, Spain, or at agonzalezma@unav.es.

*A complete list of investigators in the PRIMA/ENGOT-OV26/GOG-3012 trial is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

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 vs. 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 independent 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 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 are provided in Figure 3 and Table S6. Within

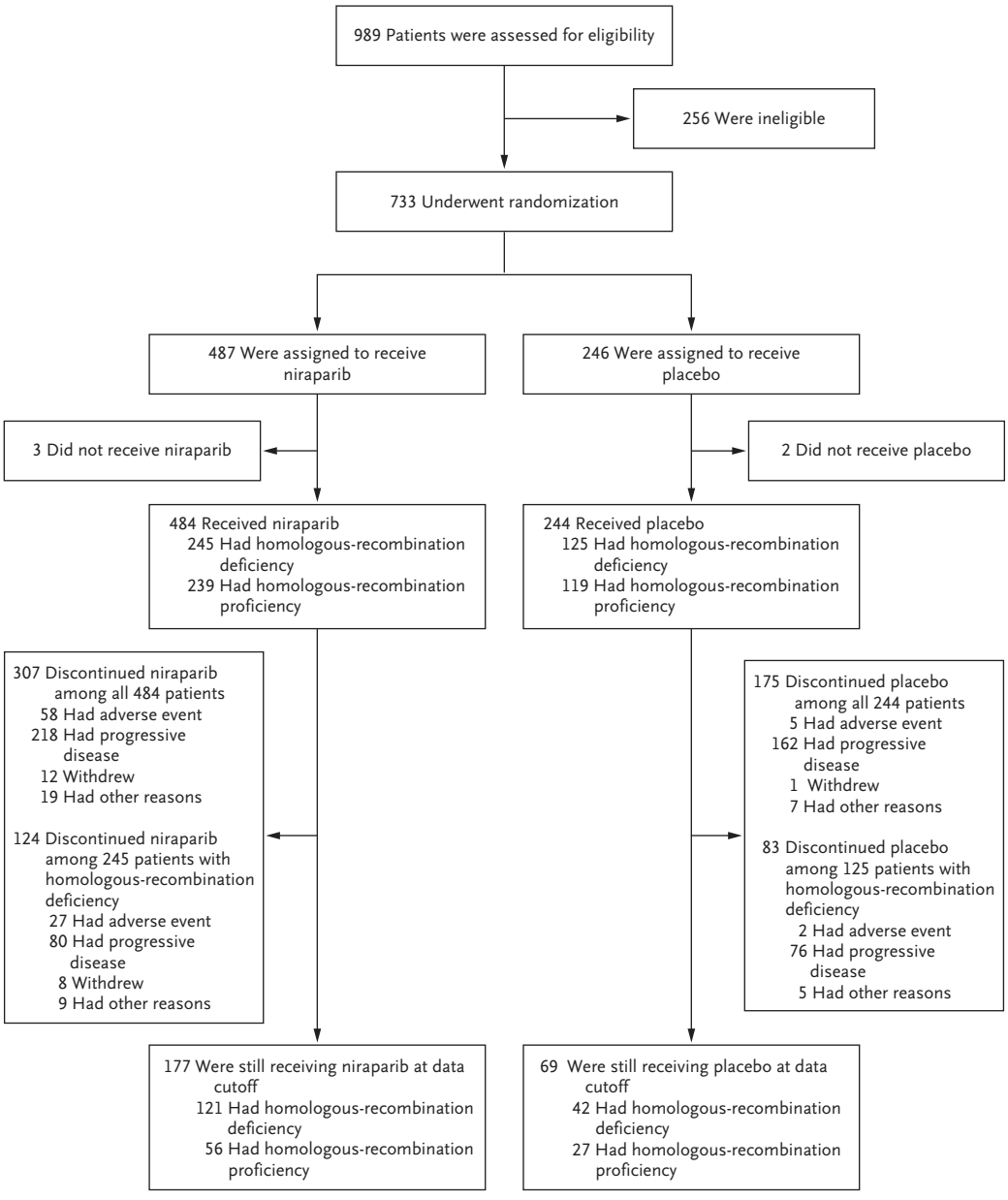

Figure 1. Enrollment and Outcomes in the Two Primary Populations.

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.

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 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

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.

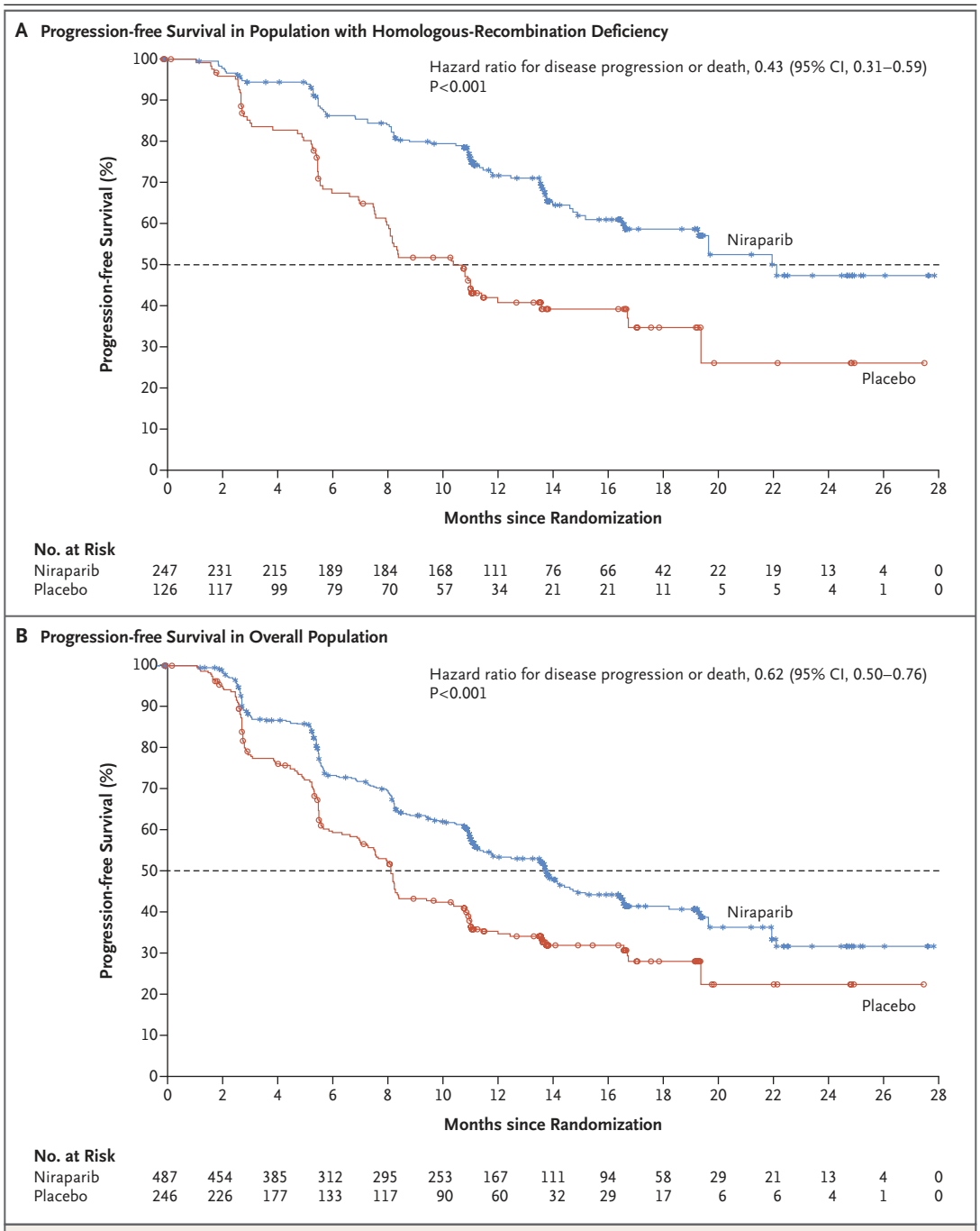

Figure 2. Progression-free Survival in the Two Primary Populations.

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.

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

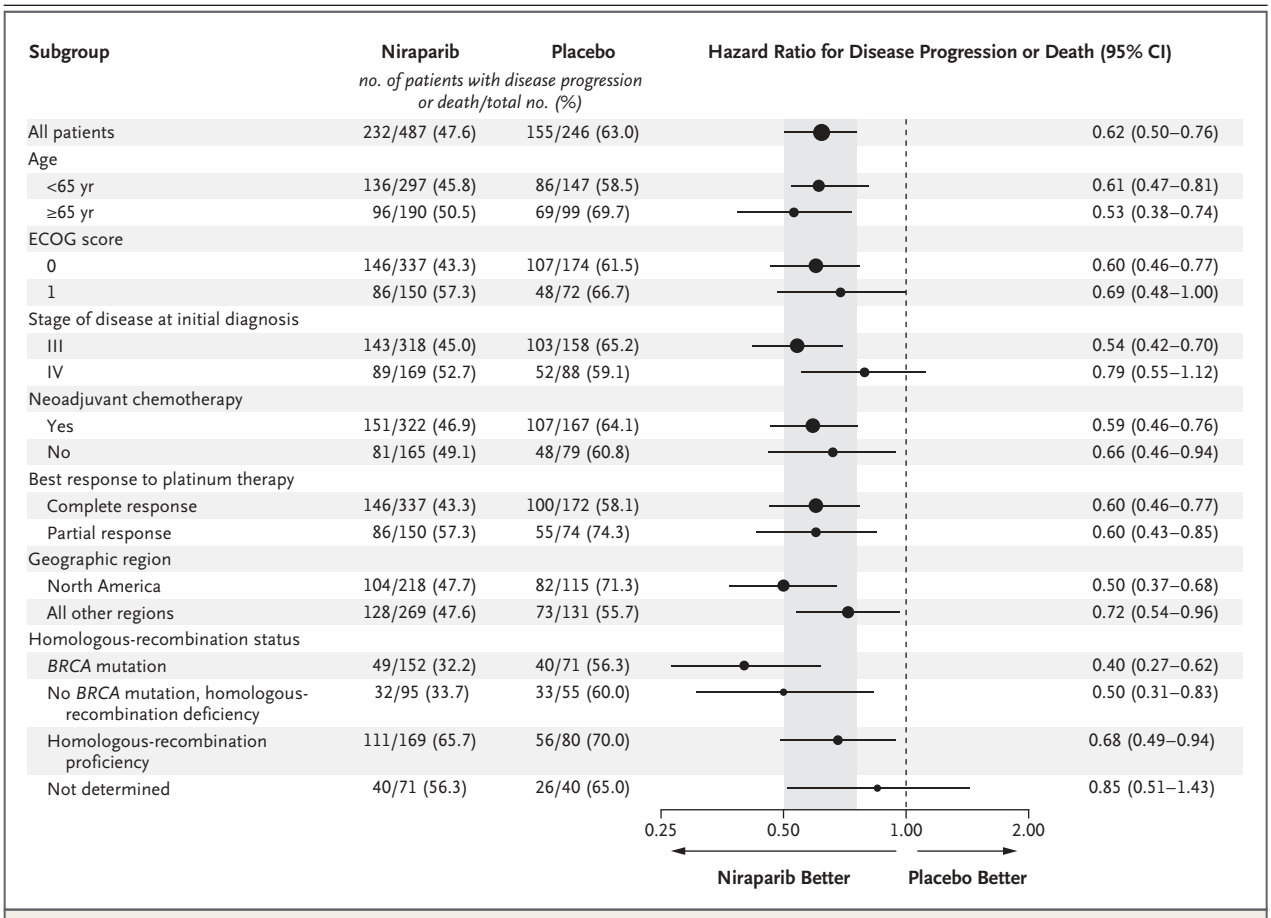

Figure 3. Disease Progression or Death, According to Prespecified Subgroups.

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. The vertical shading indicates the 95% confidence interval for the overall population.

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 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 gener-

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.

ally 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 28% 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.

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APPENDIX

The authors' full names and academic degrees are as follows: Antonio González-Martín, M.D., Ph.D., Bhavana Pothuri, M.D., Ignace Vergote, M.D., Ph.D., René DePont Christensen, Ph.D., Whitney Graybill, M.D., Mansoor R. Mirza, M.D., Colleen McCormick, M.D., M.P.H., Domenica Lorusso, M.D., Ph.D., Paul Hoskins, M.D., Gilles Freyer, M.D., Klaus Baumann, M.D., Kris Jardon, M.D., Andrés Redondo, M.D., Ph.D., Richard G. Moore, M.D., Christof Vulsteke, M.D., Ph.D., Roisin E. O'Cearbhaill, M.D., Bente Lund, M.D., Floor Backes, M.D., Pilar Barretina-Ginesta, M.D., Ashley F. Haggerty, M.D., Maria J. Rubio-Pérez, M.D., Mark S. Shahin, M.D., Giorgia Mangili, M.D., William H. Bradley, M.D., Ilan Bruchim, M.D., Kaiming Sun, Ph.D., Izabela A. Malinowska, M.D., Ph.D., Yong Li, Ph.D., Divya Gupta, M.D., and Bradley J. Monk, M.D.

The authors' affiliations are as follows: Grupo Español de Investigación en Cáncer de Ovario (GEICO) and the Medical Oncology Department, Clínica Universidad de Navarra (A.G.-M.) and GEICO and Hospital Universitario La Paz-IdiPAZ (A.R.), Madrid, GEICO and Medical Oncology, Catalan Institute of Oncology, Girona Biomedical Research Institute, and the Department of Medical Sciences, Medical School University of Girona, Girona (P.B.-G.), and GEICO and Hospital Universitario Reina Sofía, Cordoba (M.J.R.-P.) — all in Spain; the Gynecologic Oncology Group (GOG) and the Department of Obstetrics/Gynecology, Perlmutter Cancer Center, NYU Langone Health (B.P.), and GOG and the Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College (R.E.O.), New York, and US Oncology Research (USOR) and the Division of Gynecologic Oncology, Wilmot Cancer Institute, Department of Obstetrics and Gynecology, University of Rochester, Rochester (R.G.M.) — all in New York; Belgium and Luxembourg Gyne-

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