ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*

ABSTRACT

BACKGROUND

Niraparib is an oral poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2 inhibitor that has shown clinical activity in patients with ovarian cancer. We sought to evaluate the efficacy of niraparib versus placebo as maintenance treatment for patients with platinum-sensitive, recurrent ovarian cancer.

METHODS

In this randomized, double-blind, phase 3 trial, patients were categorized according to the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort) and the type of non-g*BRCA* mutation and were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily. The primary end point was progression-free survival.

RESULTS

Of 553 enrolled patients, 203 were in the g*BRCA* cohort (with 138 assigned to niraparib and 65 to placebo), and 350 patients were in the non-g*BRCA* cohort (with 234 assigned to niraparib and 116 to placebo). Patients in the niraparib group had a significantly longer median duration of progression-free survival than did those in the placebo group, including 21.0 vs. 5.5 months in the g*BRCA* cohort (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41), as compared with 12.9 months vs. 3.8 months in the non-g*BRCA* cohort for patients who had tumors with homologous recombination deficiency (HRD) (hazard ratio, 0.38; 95% CI, 0.24 to 0.59) and 9.3 months vs. 3.9 months in the overall non-g*BRCA* cohort (hazard ratio, 0.45; 95% CI, 0.34 to 0.61; P<0.001 for all three comparisons). The most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (in 33.8%), anemia (in 25.3%), and neutropenia (in 19.6%), which were managed with dose modifications.

CONCLUSIONS

Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of progression-free survival was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of g*BRCA* mutations or HRD status, with moderate bone marrow toxicity. (Funded by Tesaro; ClinicalTrials.gov number, NCT01847274.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Mirza at the Department of Oncology, Rigshospitalet–Copenhagen University Hospital, Copenhagen DK-2100, Denmark, or at mansoor@rh.regionh.dk.

*A complete list of investigators in the ENGOT-OV16/NOVA trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 8, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1611310

Copyright © 2016 Massachusetts Medical Society.

Ovarian cancer is a leading cause of death from gynecologic cancers worldwide.[1,2] Despite a high initial response rate to platinum and taxane treatment in patients with advanced cancer, the effectiveness of the treatments diminishes over time, and most patients have a relapse.[3] Platinum retreatment is used in patients in whom there is an assumed platinum sensitivity, with diminishing effectiveness and a cumulative increase in toxicity.[3]

Niraparib is a highly selective inhibitor of poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) 1/2,[4] nuclear proteins that detect DNA damage and promote its repair. Clinical studies have evaluated PARP inhibitors in patients with recurrent ovarian cancer, including those with germline *BRCA* mutations, platinum-sensitive disease, or both.[5-9] The antitumor activity of niraparib was initially observed in a phase 1 dose-escalation study, which showed that the maximum dose of 300 mg per day resulted in an objective clinical response in patients with ovarian cancer and was associated a low frequency of high-grade toxic effects.[10]

In this randomized, placebo-controlled, phase 3 trial (ENGOT-OV16/NOVA) conducted by the European Network for Gynecological Oncological Trial groups and investigators in the United States, Canada, and Hungary, our objective was to evaluate the efficacy and safety of niraparib versus placebo as maintenance treatment in a broad population of patients with platinum-sensitive, recurrent ovarian cancer.

Methods

Patients

Eligible patients were at least 18 years of age and had histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histologic features. All the patients had shown sensitivity to platinum-based treatment and had received at least two such regimens. For the penultimate platinum-based chemotherapy before study enrollment, a patient must have had platinum-sensitive disease after this treatment, which was defined as having a complete or partial response and disease progression more than 6 months after completion of the last round of platinum therapy. (Additional eligibility criteria are provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.) All the patients provided written informed consent.

Study Oversight

The trial protocol (available at NEJM.org), amendments, and other relevant study documentation were reviewed and approved by the institutional or national review board or ethics committee at each trial site or in each country. An independent data and safety monitoring committee provided recommendations for continuation or termination of the trial on the basis of a systematic review of the safety data. An independent review committee was established to review efficacy response data for the determination of efficacy end points on the basis of radiologic and clinical data from the study.

The study was designed through a collaboration among ENGOT groups, academic researchers in the United States and Canada, the clinical trial steering committee, and the study sponsor, Tesaro. The lead group for the study was the Nordic Society of Gynecological Oncology (NSGO). The study was performed according to ENGOT model C[11] (see the Methods section in the Supplementary Appendix). Study data were collected by the clinical investigators, and trial conduct was overseen by Tesaro. The final analyses were performed and overseen by Veristat, which also prepared the statistical design. Analyses were independently reviewed and approved by a statistician from the NSGO. The first author wrote the first draft of the manuscript with the full participation of all the authors in manuscript development and with assistance from a medical writer employed by the sponsor. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

Study Design and Treatment

We enrolled two independent cohorts on the basis of the presence or absence of a germline *BRCA* mutation (g*BRCA* cohort and non-g*BRCA* cohort), as determined on BRACAnalysis testing (Myriad Genetics). Not later than 8 weeks after completing their last dose of platinum-based therapy, patients were randomly assigned in a 2:1 ratio to receive niraparib (300 mg) or placebo once daily in 28-day cycles (with no treatment breaks) until disease progression. At the time of the database lock, 109 patients (93 in the niraparib group and

16 in the placebo group) were receiving ongoing treatment. Randomization within each cohort was stratified according to the time to progression after completion of the penultimate platinum regimen (6 to <12 months vs. ≥12 months), the use of bevacizumab in conjunction with the penultimate or last platinum regimen, and the best response (complete or partial) during the last platinum regimen. Before the database lock, tumor testing of archived tissue samples was performed with the use of a central laboratory DNA-based test to define the population of patients in the non-g*BRCA* cohort in whom tumors were found to have homologous recombination deficiency (HRD), according to the myChoice HRD test (Myriad Genetics).[12] Such patients were included in the non-g*BRCA* HRD-positive subgroup. (Decreased rates of homologous recombination have been found to cause inefficient DNA repair. Additional details are provided in the Methods section in the Supplementary Appendix.)

Patients continued to receive niraparib or placebo until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up, whichever came first. Treatment could be interrupted for up to 28 days because of hematologic toxicity; after the resolution of such toxicity, treatment could be restarted at a reduced dose of 200 mg according to protocol-specified criteria to manage adverse events and minimize drug discontinuation. Dose reductions were mandated for thrombocytopenia (recurrence of grade 1 or occurrence of grade 2 or above), and additional reductions of up to 100 mg were permitted. (Details are provided in the Supplementary Appendix.) For patients in the placebo group, crossover to niraparib treatment was not allowed after disease progression.

ASSESSMENTS

We performed computed tomography or magnetic resonance imaging to assess disease progression at baseline, every 8 weeks through cycle 14, and then every 12 weeks until treatment discontinuation. The objective assessment of disease progression was determined by means of central radiologic and clinical review, according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1,[13] which was performed in a blinded fashion. Increased CA-125 levels alone were not considered to indicate disease progression. We administered the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (FOSI) and the European Quality of Life–5 Dimensions (EQ-5D-5L) questionnaires to assess health-related quality of life at the screening visit, throughout treatment, and 8 weeks after the last dose of niraparib or placebo.

END POINTS

The primary end point of the duration of progression-free survival was defined as the time from treatment randomization to the earliest date of disease progression or death from any cause. Independent radiologic review and central review by a clinician who was unaware of study-group assignments were used to define disease progression, with an identical schedule of assessments used in the two cohorts.

Secondary end points included patient-reported outcomes, chemotherapy-free interval, time to first subsequent therapy, progression-free survival 2 (the time from randomization until assessment of progression during receipt of the next anticancer therapy after the study treatment or until death), time to second subsequent therapy, and overall survival. (All end-point definitions are provided in the Supplementary Appendix.) Safety was assessed by monitoring patients for adverse events, laboratory testing, measuring vital signs, and conducting physical examinations. Additional details with respect to monitoring of adverse events are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that the enrollment of 180 patients in the g*BRCA* cohort and 310 patients in the non-g*BRCA* cohort would provide a power of more than 90% to determine statistical significance at a one-sided alpha level of 0.025. This assumption was based on an assumed median duration of progression-free survival of 9.6 months in the niraparib group versus 4.8 months in the placebo group, corresponding to a hazard ratio of 0.50 in each of the two primary efficacy populations. In these analyses, 40% of the patients in the non-g*BRCA* cohort were assumed to have an HRD-positive tumor. Primary efficacy analyses for progression-free survival were to be conducted simultaneously in the two cohorts after disease progression or death had occurred in at least 98 patients in the g*BRCA* cohort and at least 98 patients in the HRD-positive subgroup of the non-g*BRCA* cohort. For each primary efficacy pop-

ulation, we performed a two-sided log-rank test using randomization stratification factors to analyze progression-free survival, which was summarized with the use of Kaplan–Meier methods. We estimated hazard ratios with two-sided 95% confidence intervals using a stratified Cox proportional-hazards model, with the stratification factors used in randomization. Progression-free survival was assessed independently in the g*BRCA* cohort and in the non-g*BRCA* cohort. A hierarchical-testing procedure was predefined for the non-g*BRCA* cohort in which statistical analysis was first performed in patients with HRD-positive tumors, and if the results were significant, a test of the overall non-g*BRCA* cohort was performed. An exploratory analysis of progression-free survival was performed for patients in the various biomarker populations within the three subgroups without a germline *BRCA* mutation (HRD-positive plus somatic *BRCA* mutation, HRD-positive plus wild-type *BRCA*, and HRD-negative) (Fig. S1 in the Supplementary Appendix). Subgroup analyses were performed to determine the relevance of certain baseline and demographic factors that might have influenced the primary end point. Potential heterogeneity of treatment effect between subgroups was examined with statistical interaction tests and forest plots (see the Statistical Analysis section in the Supplementary Appendix).

Efficacy data were analyzed in the intention-to-treat population, which was defined as all the patients who underwent randomization in each of the two cohorts. The three predefined primary efficacy populations were the g*BRCA* cohort, the HRD-positive subgroup of the non-g*BRCA* cohort, and the overall non-g*BRCA* cohort. Safety data were analyzed in the safety population, which included all the patients who had received at least one dose of niraparib or placebo.

RESULTS

PATIENTS

The first patient was enrolled on August 26, 2013. The database for the current analysis was locked on June 20, 2016, and follow-up is ongoing. A total of 553 patients were enrolled in the study at 107 sites in the ENGOT countries, the United States, Canada, and Hungary. Of these patients, 201 received treatment in the g*BRCA* cohort and 345 in the non-g*BRCA* cohort (Fig. 1). At the time of the database lock, 51 patients in the g*BRCA* cohort and 58 in the non-g*BRCA* cohort were still receiving niraparib or placebo.

Demographic and clinical characteristics were well balanced in the two cohorts at baseline (Table 1). The median age ranged from 57 to 63 years, and the majority of the patients had stage III or IV ovarian cancer at the time of diagnosis. Approximately half the patients in the g*BRCA* cohort and one third of those in the non-g*BRCA* cohort had received three or more lines of chemotherapy (Table 1). A complete listing of demographic and clinical characteristics is provided in Table S1 in the Supplementary Appendix.

EFFICACY RESULTS

The efficacy analysis was performed after the occurrence of disease progression or death in 103 patients in the g*BRCA* cohort and in 101 in the HRD-positive subgroup of the non-g*BRCA* cohort. At that time, 213 such events had occurred in the overall non-g*BRCA* cohort. The median duration of follow-up at the time of data cutoff was 16.9 months for all the patients in the intention-to-treat population, a duration that was similar in the g*BRCA* cohort and in the non-g*BRCA* cohort (16.4 months and 17.5 months, respectively). The longest follow-up at the time of the database lock was 24 months. The median rate of compliance in the niraparib group was approximately 90% in the two cohorts; compliance in the placebo group was high (>99%).

The duration of progression-free survival in the niraparib group was significantly longer than that in the placebo group in all three primary efficacy populations (P<0.001) (Fig. 2). In the g*BRCA* cohort, the median duration of progression-free survival was 21.0 months in the niraparib group and 5.5 months in the placebo group (hazard ratio, 0.27; 95% confidence interval [CI], 0.17 to 0.41) (Fig. 2A). Niraparib treatment resulted in significantly longer progression-free survival than placebo in both the HRD-positive subgroup of the non-g*BRCA* cohort (median, 12.9 months vs. 3.8 months; hazard ratio, 0.38; 95% CI, 0.24 to 0.59) (Fig. 2B) and in the overall non-g*BRCA* cohort (median, 9.3 months vs. 3.9 months; hazard ratio, 0.45; 95% CI, 0.34 to 0.61) (Fig. 2C).

In prespecified subgroup analyses, forest plots showed the consistency of the significant superiority of niraparib with respect to progression-free survival in all three primary efficacy popu-

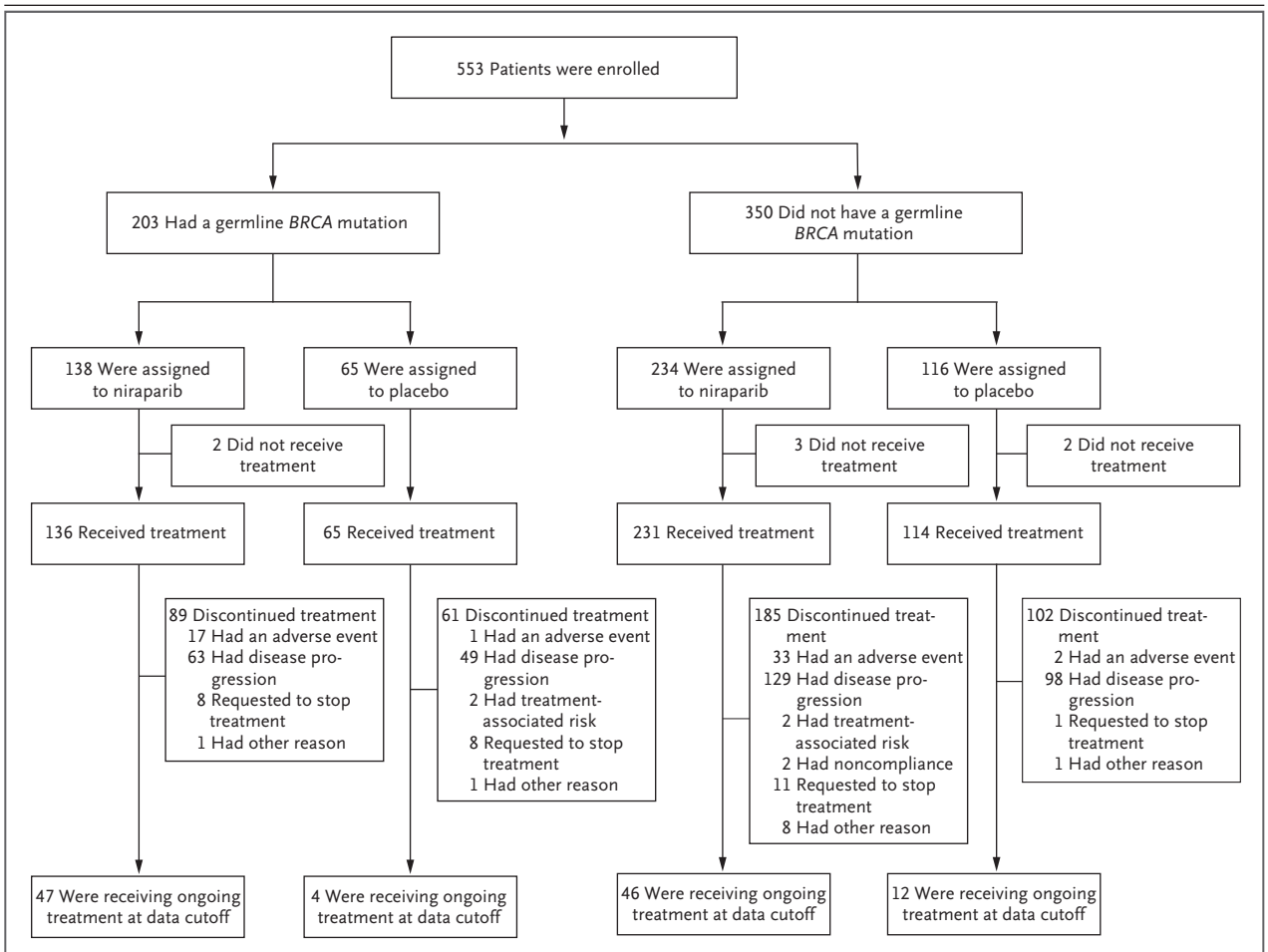

Figure 1. Enrollment and Outcomes.

lations, with upper two-sided 95% confidence limits of less than 1.00 for all subgroup hazard ratios, except for the upper limit in the category of nonwhite race, possibly due to the small sample size (Fig. 3).

Secondary end-point analyses indicated that the chemotherapy-free interval and the time until the first subsequent treatment were both significantly longer in the niraparib group than in the placebo group (Table S2 in the Supplementary Appendix). Although data regarding the time from randomization until progression during receipt of the next anticancer therapy after termination of the study treatment (progression-free survival 2) were not mature at the time of the database lock, preliminary data indicate a significantly longer duration of progression-free survival 2 for patients in the two cohorts receiving niraparib (Table S2 in the Supplementary Appendix). At the time of the database lock, the results for the time until the second subsequent therapy and overall survival were also not mature. During the study follow-up period, 60 of 372 patients (16.1%) in the niraparib group and 35 of 181 (19.3%) in the placebo group had died.

Prespecified exploratory analyses were conducted in the two populations within the HRD-positive subgroup to assess whether the observed niraparib treatment effect was driven by activity in patients with somatic *BRCA* mutations. The median duration of progression-free survival in patients with HRD-positive tumors with wild-type *BRCA* was longer in the niraparib group than in the placebo group (9.3 months vs. 3.7 months; hazard ratio, 0.38; 95% CI, 0.23 to 0.63; P<0.001) (Fig. S2A in the Supplementary Appendix). The hazard ratio was similar to that for the overall HRD-positive primary efficacy population (haz-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Germline *BRCA* Mutation		No Germline *BRCA* Mutation	
	Niraparib (N=138)	Placebo (N=65)	Niraparib (N=234)	Placebo (N=116)
Median age (range) — yr	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
Eastern Cooperative Oncology Group performance status — no. (%)				
0	91 (65.9)	48 (73.8)	160 (68.4)	78 (67.2)
1	47 (34.1)	17 (26.2)	74 (31.6)	38 (32.8)
Cancer stage — no. (%)†				
I or II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy — no. (%)				
6 to <12 mo	54 (39.1)	26 (40.0)	90 (38.5)	44 (37.9)
≥12 mo	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy — no. (%)				
Complete	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
Partial	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab use — no. (%)	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Germline *BRCA* mutation — no. (%)				
BRCA1	85 (61.6)	43 (66.2)	NA	NA
BRCA2	51 (37.0)	18 (27.7)	NA	NA
BRCA1, *BRCA2* rearrangement, or both	9 (6.5)	4 (6.2)	NA	NA
Previous lines of chemotherapy — no. (%)‡				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (53.8)	79 (33.8)	38 (32.8)

* There were no significant differences between the niraparib group and the placebo group. NA denotes not applicable.
† Staging was performed with the use of the International Federation of Gynecology and Obstetrics system. Among the patients without a germline *BRCA* mutation, data with respect to staging were not available for one patient in the placebo group, and one patient in the niraparib group had stage 0 disease at the time of diagnosis.
‡ Among the patients without a germline *BRCA* mutation, data with respect to previous lines of therapy were not available for one patient in the placebo group.

ard ratio, 0.38; 95% CI, 0.24 to 0.59). Patients with HRDpositive tumors and a *BRCA* somatic mutation had a similar reduction in the risk of disease progression as that in the g*BRCA* cohort (median, 20.9 months vs. 11.0 months; hazard ratio, 0.27; 95% CI, 0.08 to 0.90; P=0.02) (Fig. S2B in the Supplementary Appendix). Niraparib also improved progression-free survival in the HRD-negative subgroup (median, 6.9 months vs. 3.8 months; hazard ratio, 0.58; 95% CI, 0.36 to 0.92; P=0.02) (Fig. S2C in the Supplementary Appendix).

SAFETY

At least one treatment-emergent adverse event occurred in all 367 patients who received niraparib and in 171 of 179 patients (95.5%) who received placebo (Table S3 in the Supplementary Appendix). Overall, 14.7% of patients who received

niraparib discontinued treatment because of an adverse event of any grade, as compared with 2.2% in the placebo group. There were no on-treatment deaths reported during the study in either group. During the follow-up period, 3 patients (1 in the niraparib group and 2 in the placebo group) died from the myelodysplastic syndrome or acute myeloid leukemia; 2 of the deaths (1 in each group) were assessed as treatment-related by the investigator.

Treatment-emergent hematologic events of any grade that occurred in at least 10% of the patients in either group included thrombocytopenia (61.3% in the niraparib group vs. 5.6% in the placebo group), anemia (50.1% vs. 6.7%), and neutropenia (30.2% vs. 6.1%) (Table 2). The incidence of the myelodysplastic syndrome was 5 in 367 patients (1.4%) who received niraparib. There was one case each of the myelodysplastic syndrome and acute myeloid leukemia among patients who received placebo. The incidence of grade 3 or 4 treatment-emergent events was 74.1% in the niraparib group and 22.9% in the placebo group (Table S3 in the Supplementary Appendix); the majority of these events were hematologic laboratory abnormalities. Among the patients receiving niraparib, the most common thrombocytopenia-associated clinical event was grade 1 or 2 petechiae (in 5%); no patient had a grade 3 or 4 bleeding event, although 1 patient had grade 3 petechiae and hematoma concurrent with pancytopenia. Grade 3 or 4 hematologic events that were observed in at least 10% of patients receiving niraparib were thrombocytopenia (in 33.8%), anemia (in 25.3%), and neutropenia (in 19.6%). Treatment discontinuations because of these events were infrequent (Table S4 in the Supplementary Appendix). Most of the hematologic laboratory abnormalities occurred within the first three treatment cycles; after dose adjustment on the basis of an individual adverse-event profile, the incidence of grade 3 or 4 thrombocytopenia, neutropenia, or fatigue was infrequent beyond cycle 3 (Table S5 in the Supplementary Appendix). Thrombocytopenia was transient, and platelet levels stabilized beyond cycle 3 (Fig. S3 in the Supplementary Appendix).

PATIENT-REPORTED OUTCOMES

Analyses of patient-reported outcomes indicated similar outcomes for those receiving niraparib and

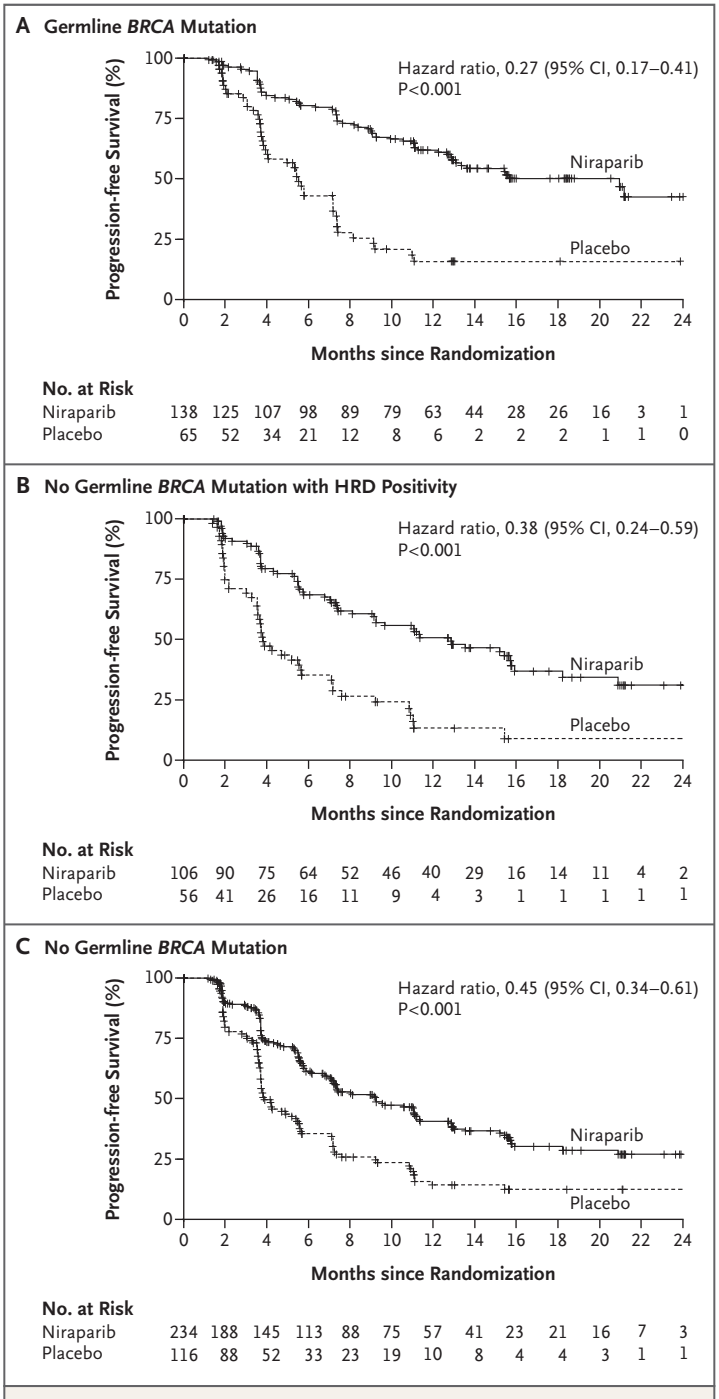

Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

Shown are the estimated rates of the primary outcome (progression-free survival) among patients with a germline *BRCA* mutation (Panel A), those without a germline *BRCA* mutation in whom tumors were found to have homologous recombination deficiency (HRD) (Panel B), and those without a germline *BRCA* mutation (Panel C). Two-sided P values were calculated with the use of the stratified log-rank test. CI denotes confidence interval.

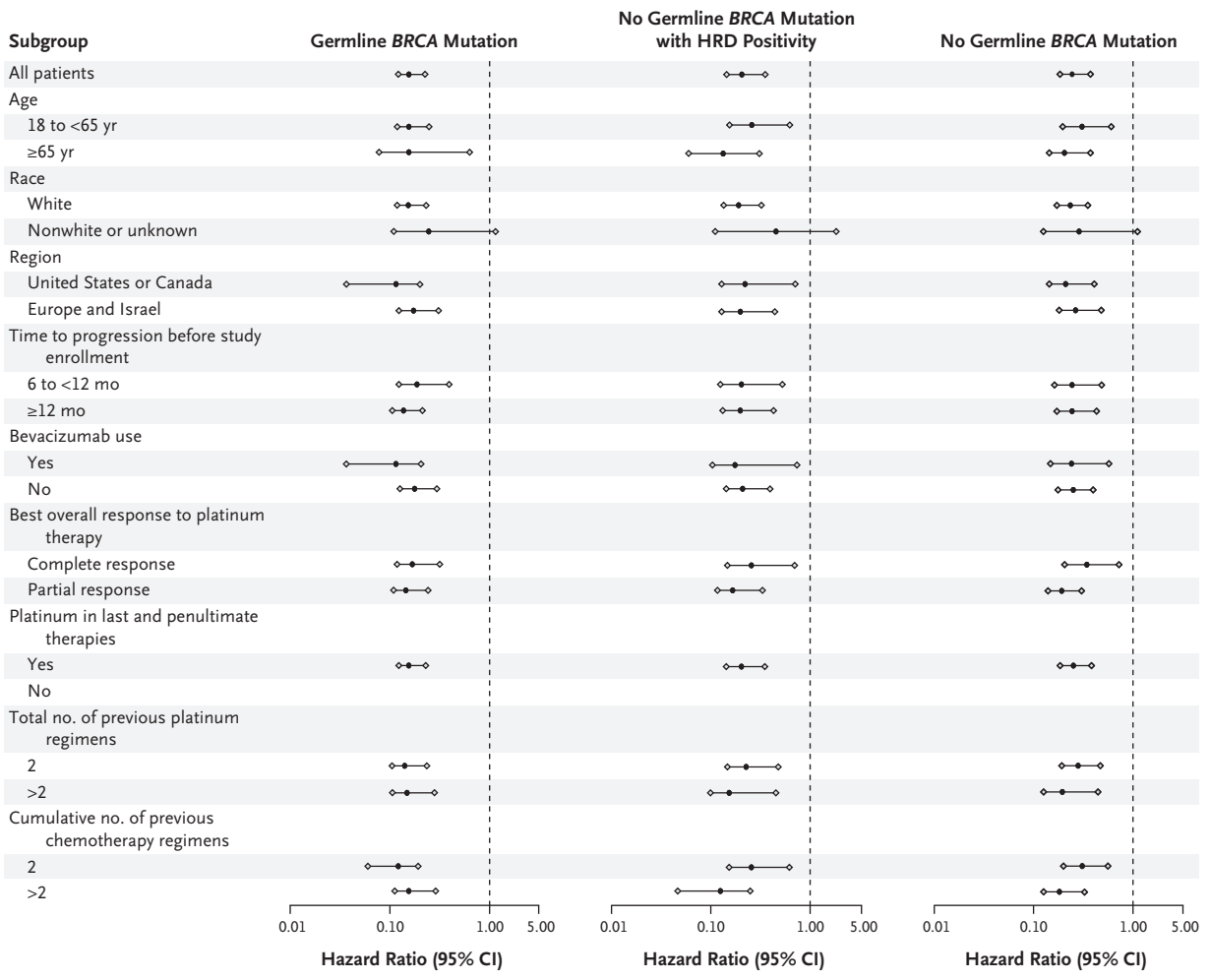

Figure 3. Subgroup Analyses of Progression-free Survival.

Shown are subgroup analyses of the primary outcome among patients with a germline *BRCA* mutation, those without a germline *BRCA* mutation in whom tumors were found to have homologous recombination deficiency (HRD), and those without a germline *BRCA* mutation. The results of statistical testing of the interaction between treatment and subgroup factors showed nearly universal consistency of the treatment effect within randomization strata, as well as within key demographic and prognostic subgroups.

those receiving placebo (Fig. S4 in the Supplementary Appendix). Patients in the niraparib group reported having a quality of life that was similar to that among patients receiving placebo. Completion rates for the FOSI and EQ-5D-5L questionnaires were high and similar in the two groups (Table S6 in the Supplementary Appendix).

DISCUSSION

In this study, we found that niraparib had a positive effect among patients with platinum-sensitive recurrent ovarian cancer. Patients receiving niraparib had a significantly longer duration of progression-free survival than did those receiving placebo in all the primary efficacy populations — along with a longer chemotherapy-free interval, a longer time until the first subsequent therapy, and better results on an extended measure of progression-free survival — in the two trial cohorts. It is too early to assess the overall survival effects associated with niraparib, and no new safety signals were identified.

A critical element of this trial was the independent evaluation of the effect of niraparib treatment regardless of the presence or absence of germ-

Table 2. Adverse Events.*

Event	Niraparib (N=367)		Placebo (N=179)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia†	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue‡	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anemia§	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia¶	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)

* Listed are the adverse events of any grade that occurred in at least 10% of the patients in either study group, along with the corresponding incidence of grade 3 or 4 events. No grade 5 events were observed in either study group.
† The category of thrombocytopenia includes reports of thrombocytopenia and decreased platelet count.
‡ The category of fatigue includes reports of fatigue, asthenia, malaise, and lethargy.
§ The category of anemia includes reports of anemia and decreased hemoglobin count.
¶ The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.

line *BRCA* mutations. The results suggest that niraparib provides significant clinical benefit regardless of *BRCA* status. The cohort of patients with non-g*BRCA* mutations included those with diverse tumor biologic features, including women in whom tumors were HRD-positive with wild-type *BRCA* as well as those with somatic *BRCA* mutations. Exploratory analyses were conducted to identify any potential biomarker drivers of the niraparib treatment effect among patients in the three populations in the non-g*BRCA* cohort (HRD-positive plus somatic *BRCA* mutations, HRD-positive plus wild-type *BRCA*, and HRD-negative). The consistency of the response in the two independent cohorts and patient populations with similar underlying tumor biologic features was shown by the same hazard ratios (0.27) observed in patients with HRD positivity plus somatic *BRCA* mutations and those with germline *BRCA* mutations. Patients with somatic *BRCA* mutations did

not entirely account for the treatment benefit associated with niraparib in the HRD-positive subgroup as a whole, since patients with HRD positivity and those with wild-type *BRCA* tumors had a lower risk of disease progression than did patients in the placebo group. Patients with HRD-negative tumors also derived a benefit from niraparib treatment (median progression-free survival, 6.9 months vs. 3.8 months), although the hazard ratio was higher (0.58) than that among patients with germline or somatic *BRCA* mutations. For all of these biomarker populations, the Kaplan–Meier curves show a consistent and sustained effect of niraparib treatment versus placebo over time (Fig. S2 in the Supplementary Appendix). Even for patients in the HRD-negative subgroup, in which the treatment effects were of a smaller magnitude, approximately 20% of the patients had a long-term (>18 months) benefit from niraparib treatment. Although *BRCA* mutation status and HRD status may provide important information regarding the magnitude of the potential treatment benefit in a given patient population, these biomarkers do not appear to be sufficiently precise to predict which individual patients who meet our definition of platinum sensitivity will and will not derive benefit from niraparib treatment.

Overall, the niraparib side-effect profile was consistent with that in previous studies, and adverse events were managed with appropriate dose modifications and delays. Although grade 3 or 4 hematologic abnormalities were common, the low incidence of discontinuation because of such events (9.3%) (Table S4 in the Supplementary Appendix) and the absence of cumulative thrombocytopenia show the effectiveness of dose modifications. Notably, patient-reported outcomes were similar in the niraparib group and the placebo group, indicating that niraparib did not adversely affect the patients' quality of life over the course of treatment.

In conclusion, the duration of progression-free survival in patients with platinum-sensitive, recurrent ovarian cancer was significantly longer in the niraparib group than in the placebo group, regardless of the presence or absence of g*BRCA* mutations or HRD status. The treatment-associated myelotoxicity required dose modifications or delays but was not associated with a long-term increase in mortality or morbidity.

Supported by Tesaro.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the patients, clinical investigators, and site personnel who participated in this study; the members of the trial-specific independent data and safety monitoring committee: Michael Quinn, M.B., Ch.B. (University of Melbourne), Larry Copeland, M.D. (Ohio State University College of Medicine), and Susan Groshen, Ph.D. (USC Norris Comprehensive Cancer Center); Julie R. Graham, Ph.D., of Tesaro, for providing medical-writing and editorial assistance; and Infusion Communications for providing assistance in the preparation of the original versions of the figures.

APPENDIX

The authors' full names and academic degrees are as follows: Mansoor R. Mirza, M.D., Bradley J. Monk, M.D., Jørn Herrstedt, M.D., D.M.Sc., Amit M. Oza, M.D., Sven Mahner, M.D., Andrés Redondo, M.D., Ph.D., Michel Fabbro, M.D., Jonathan A. Ledermann, M.D., Domenica Lorusso, M.D., Ignace Vergote, M.D., Ph.D., Noa E. Ben-Baruch, M.D., Christian Marth, M.D., Radosław Mądry, M.D., Ph.D., René D. Christensen, Ph.D., Jonathan S. Berek, M.D., Anne Dørum, M.D., Ph.D., Anna V. Tinker, M.D., Andreas du Bois, Ph.D., M.D., Antonio González-Martín, M.D., Philippe Follana, M.D., Benedict Benigno, M.D., Per Rosenberg, M.D., Ph.D., Lucy Gilbert, M.D., Bobbie J. Rimel, M.D., Joseph Buscema, M.D., John P. Balser, Ph.D., Shefali Agarwal, M.D., M.P.H., and Ursula A. Matulonis, M.D.

The authors' affiliations are as follows: the Nordic Society of Gynecological Oncology and Rigshospitalet–Copenhagen University Hospital, Copenhagen (M.R.M.), Odense University Hospital (J.H.) and European Network for Gynacological Oncological Trial and Research Unit of General Practice, Institute of Public Health, University of Southern Denmark, Odense (R.D.C.) — all in Denmark; University of Arizona and Creighton University–Phoenix, Phoenix (B.J.M.), and Arizona Oncology Associates, Tuscon (B.J.M., J.B.) — all in Arizona; Princess Margaret Consortium, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto (A.M.O.), British Columbia Cancer Agency, Vancouver (A.V.T.), and McGill University–McGill University Health Centre, Montreal (L.G.) — all in Canada; Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) and the University of Munich, Munich (S.M.), and Kliniken Essen Mitte, Essen (A.B.) — both in Germany; Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Hospital Universitario La Paz (A.R.), and GEICO and M.D. Anderson Cancer Center Madrid (A.G.-M.), Madrid; French Investigator Group for Ovarian and Breast Cancer (GINECO) and Institut du Cancer de Montpellier, Montpellier (M.F.), and GINECO and Centre Antoine Lacassagne, Nice (P.F.) — both in France; National Cancer Research Institute and UCL Cancer Institute, University College London, London (J.A.L.); Multicenter Italian Trials in Ovarian Cancer/Mario Negri Gynecologic Oncology Group, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan (D.L.); Belgium and Luxembourg Gynecological Oncology Group and University of Leuven, Leuven, Belgium (I.V.); Kaplan Medical Center, Rehovot, Israel (N.E.B.-B.); AGO–Austria and Medical University Innsbruck, Innsbruck, Austria (C.M.); Central and Eastern European Gynecologic Oncology Group and Uniwersytet Medyczny w Poznaniu, Poznan, Poland (R.M.); Stanford Comprehensive Cancer Institute, Stanford (J.S.B.), and Cedars–Sinai Medical Center, West Hollywood (B.J.R.) — both in California; Oslo University Hospital, Radiumhospitalet, Oslo (A.D.); Northside Hospital, Atlanta (B.B.); Universitetssjukhuset, Linköping, Sweden (P.R.); and Veristat, Southborough (J.P.B.), Tesaro, Waltham (S.A.), and Dana–Farber Cancer Institute, Boston (U.A.M.) — all in Massachusetts.

REFERENCES

1. SEER Cancer Statistics Review (CSR) 1975–2013. Bethesda, MD: National Cancer Institute, 2016 (http://seer.cancer.gov/csr/1975_2013/).
2. GLOBOCAN 2012 v1.0, estimated cancer incidence, mortality and prevalence worldwide: IARC CancerBase no. 11. Lyon, France: International Agency for Research on Cancer, 2013 (http://publications.iarc.fr/Databases/Iarc-Cancerbases/Globocan-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1-0-2012).
3. Hanker LC, Loibl S, Burchardi N, et al. The impact of second to sixth line therapy on survival of relapsed ovarian cancer after primary taxane/platinum-based therapy. Ann Oncol 2012;23:2605-12.
4. Jones P, Altamura S, Boueres J, et al. Discovery of 2-4-[(3S)-piperidin-3-yl]phenyl-2H-indazole-7-carboxamide (MK-4827): a novel oral poly(ADP-ribose)polymerase (PARP) inhibitor efficacious in BRCA-1 and -2 mutant tumors. J Med Chem 2009;52:7170-85.
5. Audeh MW, Carmichael J, Penson RT, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer: a proof-of-concept trial. Lancet 2010;376:245-51.
6. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. N Engl J Med 2009;361:123-34.
7. Kummar S, Ji J, Morgan R, et al. A phase I study of veliparib in combination with metronomic cyclophosphamide in adults with refractory solid tumors and lymphomas. Clin Cancer Res 2012;18:1726-34.
8. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012;366:1382-92.
9. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. Lancet Oncol 2011;12:852-61.
10. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. Lancet Oncol 2013;14:882-92.
11. du Bois A, Reuss A, Pujade-Lauraine E, et al. European Network of Gynaecological Oncological Trial Groups' requirements for trials between academic groups and industry partners — first update 2015. Int J Gynecol Cancer 2015;25:1328-30.
12. Telli ML, Timms KM, Reid J, et al. Homologous recombination deficiency (HRD) score predicts response to platinum-containing neoadjuvant chemotherapy in patients with triple-negative breast cancer. Clin Cancer Res 2016;22:3764-73.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

Copyright © 2016 Massachusetts Medical Society.