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Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

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ABSTRACT

BACKGROUND

Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate–ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

METHODS

We conducted an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) who had a complete or partial clinical response after platinum-based chemotherapy. The patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival.

RESULTS

Of the 391 patients who underwent randomization, 260 were assigned to receive olaparib and 131 to receive placebo. A total of 388 patients had a centrally confirmed germline *BRCA1/2* mutation, and 2 patients had a centrally confirmed somatic *BRCA1/2* mutation. After a median follow-up of 41 months, the risk of disease progression or death was 70% lower with olaparib than with placebo (Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years, 60% vs. 27%; hazard ratio for disease progression or death, 0.30; 95% confidence interval, 0.23 to 0.41; P<0.001). Adverse events were consistent with the known toxic effects of olaparib.

CONCLUSIONS

The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. (Funded by AstraZeneca and Merck; SOLO1 ClinicalTrials.gov number, NCT01844986.)

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A Quick Take is available at NEJM.org

Standard therapy for patients with newly diagnosed advanced ovarian cancer consists of cytoreductive surgery and platinum-based chemotherapy.[1,2] Although the majority of such patients have no evidence of disease after treatment, approximately 70% have a relapse within the subsequent 3 years.[2] Recurrent ovarian cancer is typically incurable, with most patients receiving multiple additional lines of treatment before ultimately dying from the disease.

In primary analyses of phase 3 trials, the addition of intravenous bevacizumab to carboplatin plus paclitaxel (followed by bevacizumab alone) led to prolonged progression-free survival among patients with newly diagnosed advanced ovarian cancer, with hazard ratios for disease progression or death of 0.72 (Burger et al.[3]) and 0.81 (Perren et al.[4]). However, there was no improvement in overall survival.[5]

Poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors, such as olaparib, trap PARP on DNA at sites of single-strand breaks, thereby preventing the repair of the single-strand breaks and generating double-strand breaks that cannot be repaired accurately in tumors that have defects in homologous recombination repair, such as tumors with a mutation in *BRCA1* or *BRCA2*. The use of PARP inhibitors leads to an accumulation of DNA damage and tumor-cell death.[6]

Olaparib has been approved in the United States and Europe as maintenance treatment for women with platinum-sensitive relapsed ovarian cancer who have a response to their most recent platinum-based regimen, regardless of *BRCA* mutation status.[7,8] It has also been approved in the United States for the treatment of women with advanced ovarian cancer and a deleterious or suspected deleterious germline *BRCA* mutation who have been treated with three or more lines of chemotherapy, regardless of sensitivity to platinum-based therapy.[7] National Comprehensive Cancer Network guidelines state that maintenance therapy with a PARP inhibitor should be considered in patients with relapsed ovarian cancer with sensitivity to platinum-based therapy, regardless of *BRCA* mutation status.[1] We conducted the phase 3 SOLO1 trial to evaluate the efficacy of maintenance therapy with a PARP inhibitor (olaparib) in patients with newly diagnosed advanced ovarian cancer with a germline or somatic mutation in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) who had a complete or partial clinical response after platinum-based chemotherapy.

Methods

Patients

Patients were eligible if they were 18 years of age or older and had newly diagnosed, histologically confirmed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof). Those with stage III disease had undergone an attempt at cytoreductive surgery before the start chemotherapy (up front) or after the start but before the end of chemotherapy (interval). Those with stage IV disease had undergone either biopsy or up-front or interval cytoreductive surgery. Eligible patients had a deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation, as determined by local or central testing, with the use of the BRACAnalysis test (Myriad) or, in China, with the use of a *BRCA1/2* genetic testing assay (BGI). Germline *BRCA1/2* mutation status that was determined locally was confirmed centrally at Myriad or BGI, and tumor *BRCA1/2* mutation status was assessed retrospectively at Foundation Medicine. Eligible patients also had received platinum-based chemotherapy without bevacizumab and were having a complete clinical response (no evidence of disease on imaging after chemotherapy and a normal CA-125 level) or a partial clinical response (a ≥30% decrease in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range). Further details and a complete list of 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.

Trial Design and Interventions

This randomized, double-blind, placebo-controlled, phase 3 trial was conducted in 15 countries. Randomization was performed centrally with a block design, with stratification according to clinical response after platinum-based chemotherapy (complete or partial). Patients were assigned to a trial group through an interactive Web-based or voice-response system.

After completion of platinum-based chemotherapy, patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg

twice daily) or placebo. The trial intervention was continued until investigator-assessed objective disease progression on imaging (according to modified Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1), provided that the patient was having a benefit and did not meet any discontinuation criteria. Patients who had no evidence of disease at 2 years stopped receiving the trial intervention, but patients who had a partial response at 2 years were permitted to continue receiving the trial intervention in a blinded manner. Crossover between trial groups was not specified in the protocol. After discontinuation of the trial intervention, patients could receive treatments at the investigators' discretion.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival as assessed by investigators. Progression-free survival was defined as the time from randomization to objective disease progression on imaging (according to modified RECIST, version 1.1) or death from any cause. Computed tomography or magnetic resonance imaging was performed at baseline and every 12 weeks for up to 3 years and then every 24 weeks, until objective disease progression. A sensitivity analysis of progression-free survival as assessed by blinded independent central review was performed. Other sensitivity analyses of progression-free survival were also performed (see the Methods section in the Supplementary Appendix).

Secondary end points were second progression–free survival (the time from randomization to second disease progression or death), overall survival, the time from randomization to the first subsequent therapy or death, the time from randomization to the second subsequent therapy or death, and health-related quality of life, which was assessed with the use of the Trial Outcome Index score on the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) questionnaire (see the Methods section in the Supplementary Appendix). Trial Outcome Index scores range from 0 to 100, with higher scores indicating better health-related quality of life and a difference of 10 points indicating a clinically meaningful difference. FACT-O questionnaires were completed at baseline, on day 29, and every 12 weeks for 3 years and then every 24 weeks, until the time of data cutoff for the primary efficacy analysis. The analysis of health-related quality of life evaluated the change from baseline in the Trial Outcome Index score for the first 2 years. Adverse events were graded with the use of National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

TRIAL OVERSIGHT

This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy of bioethics,[8] under the auspices of an independent data and safety monitoring committee. The trial was designed by the first and last authors in collaboration with AstraZeneca and the Gynecologic Oncology Group. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. All the authors had full access to the data. The manuscript was written by the authors, with medical writing assistance funded by AstraZeneca and Merck. Olaparib is being codeveloped by AstraZeneca and Merck, and Merck provided input regarding the interpretation of the data. The authors attest to the accuracy and completeness of the data and the fidelity of the trial to the protocol (available at NEJM.org).

STATISTICAL ANALYSIS

We determined that 206 primary end-point events (disease progression or death) would provide the trial with 90% power, at a two-sided significance level of 0.05, to show a significant difference in progression-free survival between the olaparib group and the placebo group, with a corresponding hazard ratio for disease progression or death of 0.62 (assuming a median progression-free survival of 13 months in the placebo group). Because the rate of primary end-point events was lower than projected, the protocol was amended such that the primary analysis of progression-free survival was to be performed when approximately 196 events had occurred (data maturity, approximately 50%) or when the last patient to undergo randomization had done so at least 3 years earlier, whichever came first.

Data on efficacy and health-related quality of life were summarized and analyzed in the intention-to-treat population (all patients who underwent randomization, regardless of the intervention that they actually received). Data on safety were summarized in the safety population (all patients who received ≥1 dose of the trial intervention).

A multiple-testing procedure was used to con-

trol the type I error rate, with a test for progression-free survival to be performed first, a test for second progression–free survival to be performed if the null hypothesis for progression-free survival were rejected, and a test for overall survival to be performed if the results for progression-free survival and second progression–free survival were significant. The analyses of time to the first subsequent therapy and time to the second subsequent therapy were not adjusted for multiple comparisons. To describe the potential benefit of olaparib, tests for time to the first subsequent therapy, time to the second subsequent therapy, and change from baseline in the Trial Outcome Index score were performed at a two-sided significance level of 0.05.

The analysis of progression-free survival was performed with a stratified log-rank test, with calculation of a hazard ratio, an accompanying 95% confidence interval, and a P value (see the Methods section in the Supplementary Appendix). Analyses of second progression–free survival, overall survival, time to the first subsequent therapy, and time to the second subsequent therapy were performed with a method similar to that used for the analysis of progression-free survival. The analysis of change from baseline in the Trial Outcome Index score was performed with a mixed-effects model for repeated measures. The statistical analysis plan is available with the protocol at NEJM.org.

RESULTS

PATIENTS

From September 3, 2013, to March 6, 2015, a total of 391 patients underwent randomization. All 260 patients who were assigned to the olaparib group and 130 of the 131 patients who were assigned to the placebo group received the trial intervention; 1 patient in the placebo group decided to withdraw before receiving the intervention (Fig. 1).

The baseline characteristics were well balanced between the trial groups (Table 1). At baseline, the majority of patients had no evidence of disease, a good performance status, and a CA-125 level within the normal range.

With regard to *BRCA* mutation status, 210 patients underwent randomization on the basis of results of local testing and 181 on the basis of results of central testing (at Myriad or BGI). Central germline testing confirmed that 388 of the 391 patients had a *BRCA1/2* mutation, 1 had a *BRCA* variant of uncertain significance, and 2 had wild-type *BRCA*. Testing at Foundation Medicine showed that the 2 patients with wild-type *BRCA* on central germline testing had somatic *BRCA* mutations (see the Results section in the Supplementary Appendix). Overall, of the 210 locally determined *BRCA* mutations, 207 (99%) were confirmed by central germline testing.

The median duration of follow-up was 40.7 months (interquartile range, 34.9 to 42.9) in the olaparib group and 41.2 months (interquartile range, 32.2 to 41.6) in the placebo group. A total of 123 patients (47%) in the olaparib group and 35 (27%) in the placebo group completed the trial intervention at 2 years, in accordance with the protocol, and 26 (10%) and 3 (2%), respectively, continued to receive the trial intervention beyond 2 years. Of the patients who received the trial intervention beyond 2 years, 13 were still receiving olaparib and 1 was still receiving placebo at the time of data cutoff for the primary analysis (May 17, 2018).

EFFICACY

The analysis of the primary end point was performed after 198 of the 391 patients had had investigator-assessed disease progression or had died (data maturity, 51%). In the primary analysis, the Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years was 60% in the olaparib group, as compared with 27% in the placebo group (hazard ratio for disease progression or death, 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001) (Fig. 2A). The median progression-free survival from the end of chemotherapy was 13.8 months in the placebo group.

In the analysis of progression-free survival as assessed by blinded independent central review (data maturity, 38%), the Kaplan–Meier estimate of the rate of freedom from disease progression and from death at 3 years was 69% in the olaparib group, as compared with 35% in the placebo group (hazard ratio for disease progression or death, 0.28; 95% CI, 0.20 to 0.39; P<0.001) (Fig. 2B); these results are consistent with the benefit of olaparib with regard to progression-free survival as assessed by investigators. In a sensitivity analysis of investigator-assessed progression-free survival that was performed to

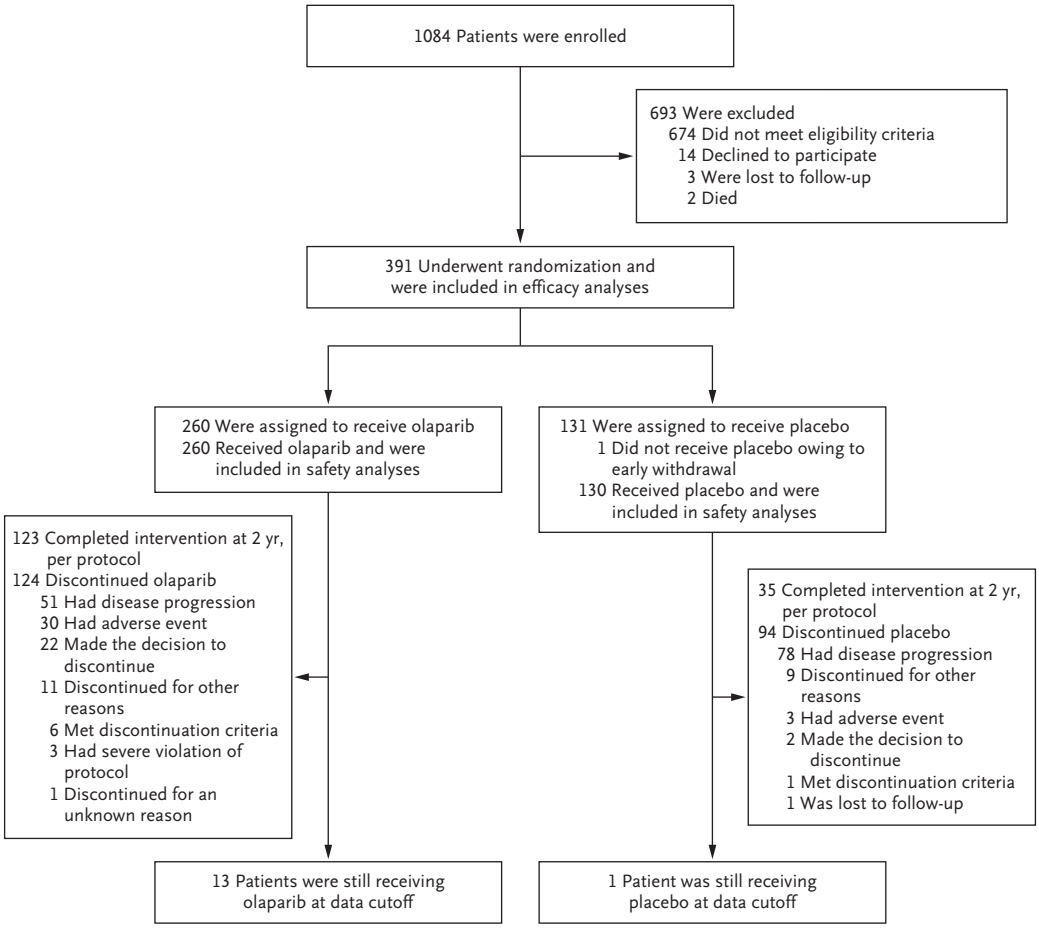

Figure 1. Enrollment, Randomization, and Intervention.

evaluate for possible attrition bias, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group (see the Results section and Table S3 of the Supplementary Appendix).

The Kaplan–Meier estimate of the rate of freedom from investigator-assessed disease progression and from death was 88% in the olaparib group and 51% in the placebo group at 1 year; 74% and 35%, respectively, at 2 years; 60% and 27% at 3 years; and 53% and 11% at 4 years (Fig. S1 of the Supplementary Appendix). Subgroup analyses of progression-free survival are shown in Figure 3.

In the analysis of second progression–free survival (data maturity, 31%), the Kaplan–Meier estimate of the rate of freedom from second disease progression and from death at 3 years was 75% in the olaparib group, as compared with 60% in the placebo group (hazard ratio for second disease progression or death, 0.50; 95% CI, 0.35 to 0.72; P<0.001). The median second progression–free survival was 41.9 months in the placebo group (Fig. S2 of the Supplementary Appendix).

In an interim analysis of overall survival (data maturity, 21%), the Kaplan–Meier estimate of the rate of freedom from death at 3 years was 84% in the olaparib group and 80% in the placebo group (hazard ratio for death, 0.95; 95% CI, 0.60 to 1.53). The median time to the first subsequent therapy or death was 51.8 months in the olaparib group and 15.1 months in the placebo group (hazard ratio, 0.30; 95% CI, 0.22 to 0.40). The Kaplan–Meier estimate of the rate of freedom from the use of a second subsequent therapy and

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Olaparib Group (N=260)	Placebo Group (N=131)
	no. of patients (%)	
Clinical response after platinum-based chemotherapy†		
Complete response	213 (82)	107 (82)
Partial response	47 (18)	24 (18)
No. of cycles of platinum-based chemotherapy		
4	2 (1)	0
5	2 (1)	1 (1)
6	198 (76)	106 (81)
7	17 (7)	10 (8)
8	18 (7)	7 (5)
9	23 (9)	7 (5)
ECOG performance status		
Normal activity	200 (77)	105 (80)
Restricted activity	60 (23)	25 (19)
Missing data	0	1 (1)
Primary tumor location		
Ovary	220 (85)	113 (86)
Fallopian tube	22 (8)	11 (8)
Peritoneum	15 (6)	7 (5)
Other‡	3 (1)	0
International FIGO stage§		
Stage III	220 (85)	105 (80)
Stage IV	40 (15)	26 (20)
CA-125 level		
≤ULN	247 (95)	123 (94)
>ULN	13 (5)	7 (5)
Missing data	0	1 (1)
Histologic type		
Serous	246 (95)	130 (99)
Endometrioid	9 (3)	0
Mixed serous and endometrioid	5 (2)	1 (1)
BRCA mutation¶		
BRCA1	191 (73)	91 (69)
BRCA2	66 (25)	40 (31)
BRCA1 and *BRCA2*	3 (1)	0

* Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group.
† Complete response was defined as no evidence of disease on imaging (according to modified Response Evaluation Criteria in Solid Tumors, version 1.1) after chemotherapy and a normal CA-125 level. Partial response was defined as a decrease of at least 30% in tumor volume from the start to the end of chemotherapy or no evidence of disease on imaging after chemotherapy but a CA-125 level above the upper limit of the normal range (ULN).
‡ Other tumor locations included a combination of the ovary, fallopian tube, peritoneum, and omentum (in one patient), a combination of the ovary and peritoneum (one patient), and a combination of the ovary and fallopian tube (one patient).
§ International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal metastasis.
¶ *BRCA* mutation status was determined centrally (at Myriad or BGI) or locally. For the five patients from China, germline *BRCA* mutation status was determined in China with the use of the BGI test.

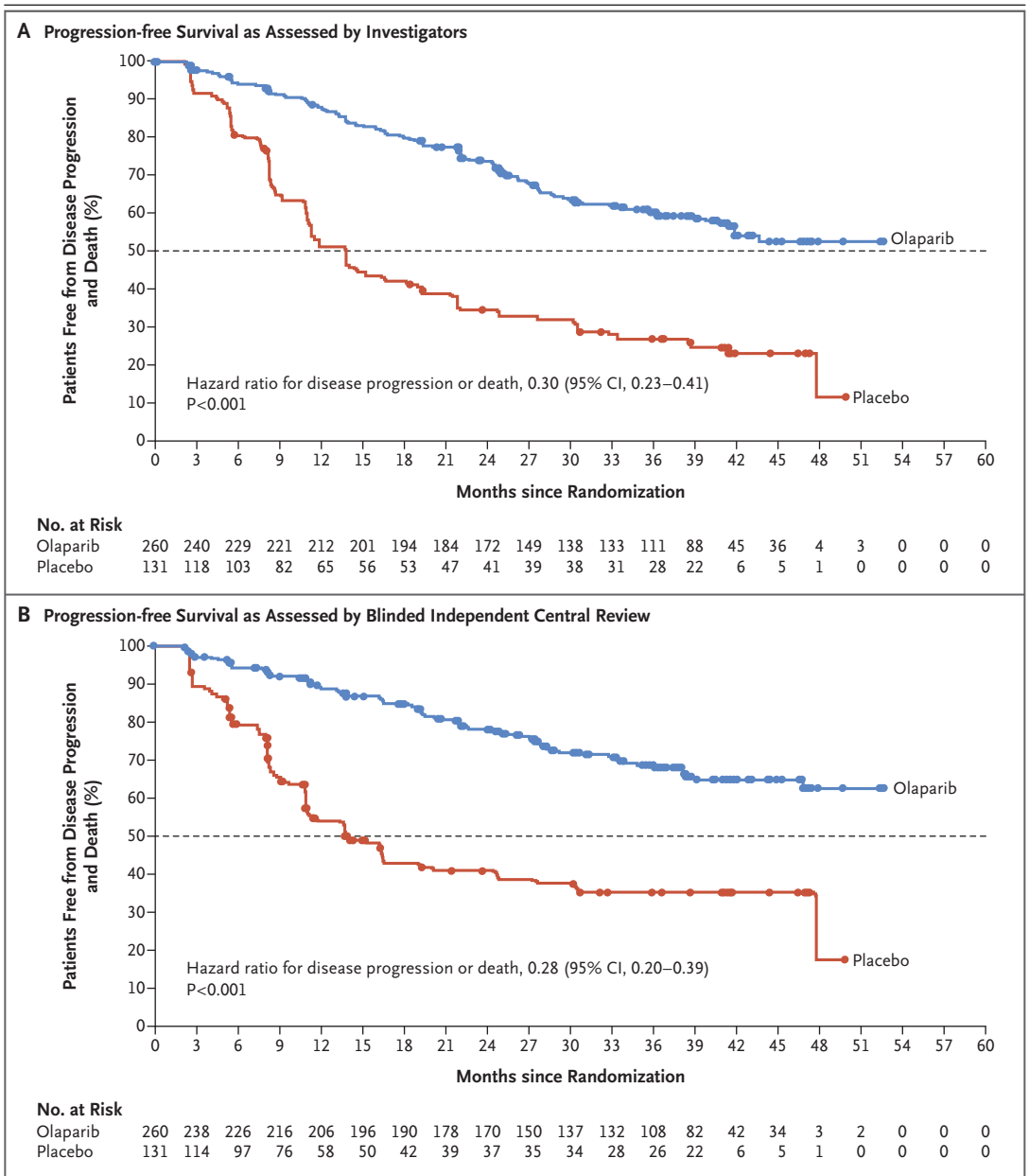

Figure 2. Kaplan–Meier Estimates of Progression-free Survival.

Panel A shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by investigators, and from death in the olaparib group and the placebo group. There was no evidence of a change in the shape of the Kaplan–Meier curve for olaparib after 24 months, when patients with no evidence of disease stopped the intervention, in accordance with the protocol; this finding indicates a sustained benefit of olaparib beyond the completion of treatment. In a sensitivity analysis of investigator-assessed progression-free survival that was performed to evaluate for possible attrition bias, the median progression-free survival was approximately 36 months longer in the olaparib group than in the placebo group (see the Supplementary Appendix). Panel B shows Kaplan–Meier estimates of the rate of freedom from disease progression, as assessed by blinded independent central review, and from death. The dashed line indicates the median.

from death at 3 years was 74% in the olaparib group and 56% in the placebo group (hazard ratio for the use of a second subsequent therapy or death, 0.45; 95% CI, 0.32 to 0.63), with a median time to the second subsequent therapy or death of 40.7 months in the placebo group.

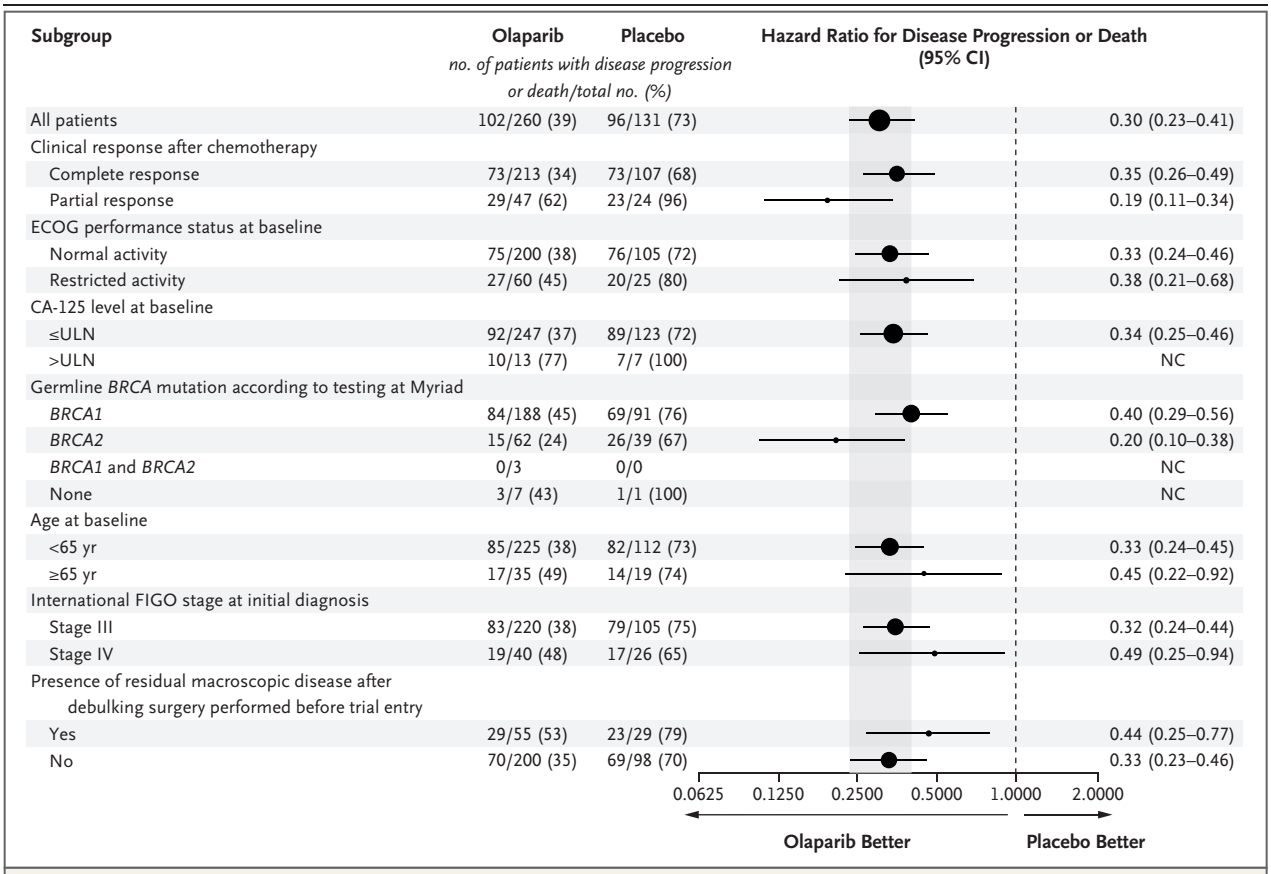

Figure 3. Subgroup Analysis of Progression-free Survival.

For the hazard ratios, the size of the circle is proportional to the number of events. The gray band represents the 95% confidence interval for all patients, and the dashed line indicates the point of no effect. International Federation of Gynecology and Obstetrics (FIGO) stage III indicates involvement of one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis or metastasis to the retroperitoneal lymph nodes (or both), and stage IV indicates distant metastasis excluding peritoneal metastasis. NC denotes not calculated, ECOG Eastern Cooperative Oncology Group, and ULN upper limit of the normal range.

SAFETY

The median duration of the trial intervention in the olaparib group was 24.6 months (range, 0.0 to 52.0), a finding consistent with the 2-year treatment cap. The median duration in the placebo group was 13.9 months (range, 0.2 to 45.6), a finding consistent with the median progression-free survival in that group (see the Results section and Table S4 of the Supplementary Appendix).

The most common adverse events that occurred during the trial intervention or up to 30 days after discontinuation of the intervention are shown in Table 2; most were grade 1 or 2 events. Serious adverse events occurred in 21% of the patients in the olaparib group and 12% of the patients in the placebo group (Table S5 of the Supplementary Appendix). Anemia was the most common serious adverse event (in 7% of the patients in the olaparib group and in no patients in the placebo group). No adverse events that occurred during the trial intervention or up to 30 days after discontinuation of the intervention resulted in death.

Adverse events were usually managed by dose interruption or dose reduction, rather than discontinuation (Table 2). The most common adverse events that led to discontinuation were nausea and anemia (Table S6 of the Supplementary Appendix).

Acute myeloid leukemia occurred in 3 of 260 patients (1%) in the olaparib group and in none of 130 patients in the placebo group, new primary cancers occurred in 5 (2%) and 3 (2%), respectively, and pneumonitis or interstitial lung disease occurred in 5 (2%) and none (see the Results section in the Supplementary Appendix). All three cases of acute myeloid leukemia oc-

Table 2. Summary of Adverse Events.*

Adverse Event	Olaparib (N=260)		Placebo (N=130)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any	256 (98)	102 (39)	120 (92)	24 (18)
Nausea	201 (77)	2 (1)	49 (38)	0
Fatigue or asthenia	165 (63)	10 (4)	54 (42)	2 (2)
Vomiting	104 (40)	1 (<1)	19 (15)	1 (1)
Anemia†	101 (39)	56 (22)	13 (10)	2 (2)
Diarrhea	89 (34)	8 (3)	32 (25)	0
Constipation	72 (28)	0	25 (19)	0
Dysgeusia	68 (26)	0	5 (4)	0
Arthralgia	66 (25)	0	35 (27)	0
Abdominal pain	64 (25)	4 (2)	25 (19)	1 (1)
Neutropenia‡	60 (23)	22 (9)	15 (12)	6 (5)
Headache	59 (23)	1 (<1)	31 (24)	3 (2)
Dizziness	51 (20)	0	20 (15)	1 (<1)
Decreased appetite	51 (20)	0	13 (10)	0
Upper abdominal pain	46 (18)	0	17 (13)	0
Dyspepsia	43 (17)	0	16 (12)	0
Cough	42 (16)	0	28 (22)	0
Back pain	40 (15)	0	16 (12)	0
Dyspnea	39 (15)	0	7 (5)	0
Thrombocytopenia§	29 (11)	2 (1)	5 (4)	2 (2)
Led to discontinuation of intervention	30 (12)	NA	3 (2)	NA
Led to dose reduction	74 (28)	NA	4 (3)	NA
Led to dose interruption	135 (52)	NA	22 (17)	NA

* Shown are data on adverse events that occurred in at least 15% of the patients in either trial group (except where noted) during the trial intervention or up to 30 days after discontinuation of the intervention. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA denotes not available.

† The data include patients with anemia, a decreased hemoglobin level, a decreased hematocrit, a decreased red-cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.

‡ The data include patients with neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, a decreased neutrophil count, idiopathic neutropenia, granulocytopenia, a decreased granulocyte count, or agranulocytosis.

§ Thrombocytopenia occurred in less than 15% of the patients in each trial group, but the data are provided to complete the profile of hematologic toxic effects. The data include patients with thrombocytopenia, decreased platelet production, decreased platelet count, or decreased plateletcrit.

curred more than 30 days after the end of treatment with olaparib.

HEALTH-RELATED QUALITY OF LIFE

The mean Trial Outcome Index score at baseline was 73.6 in the olaparib group and 75.0 in the placebo group. The score remained stable in the olaparib group (237 patients), with an adjusted mean change from baseline to 2 years of 0.30 points (95% CI, −0.72 to 1.32), as compared with a change of 3.30 points (95% CI, 1.84 to 4.76) in the placebo group (125 patients) (Fig. S3 of the Supplementary Appendix). The estimated between-group difference in change was −3.00 points (95% CI, −4.78 to −1.22); the difference was not considered to be clinically meaningful.

DISCUSSION

In the phase 3 SOLO1 trial, the use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free

survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo. Results of a sensitivity analysis and the time to first subsequent therapy or death support an estimated difference in median progression-free survival between the olaparib group and the placebo group of approximately 3 years. The median progression-free survival of 13.8 months in the placebo group, which was measured from the end of chemotherapy rather than from the start of chemotherapy, is consistent with results reported in studies of carboplatin plus paclitaxel in patients with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation.[9,10] The results of sensitivity analyses and subgroup analyses of progression-free survival were consistent with the results of the primary analysis. The absolute longer progression-free survival with olaparib than with placebo that was seen in a sensitivity analysis in this trial was substantially greater than the increases in progression-free survival that were seen with PARP inhibitors in relapsed disease,[11-13] and some patients (e.g., those who have platinum resistance) are not eligible to receive olaparib as a second-line therapy. Some patients in this trial were able to stop receiving the trial intervention at 2 years and to live progression-free for months without treatment. Patients with newly diagnosed advanced ovarian cancer are the only patients with ovarian cancer in whom treatment has curative potential. Ongoing follow-up of patients in this trial would be necessary to evaluate whether a subgroup has a durable long-term benefit with olaparib (which has been seen in relapsed disease with sensitivity to platinum-based therapy[14]) or even a cure.

A significant increase in time to second disease progression was also noted with olaparib, a finding that suggests that olaparib did not diminish patients' ability to benefit from subsequent therapy. This finding was observed despite the use of PARP inhibitors in 33 of 94 patients (35%) in the placebo group who received subsequent therapy, which may potentially explain the median second progression–free survival of 42 months in the placebo group. Data on overall survival are currently immature but show no evidence that olaparib had a detrimental effect on survival.

Most patients in this trial had a germline *BRCA1/2* mutation. However, the results of other studies[11,12] suggest that the findings could be applicable to patients with a somatic *BRCA1/2* mutation.

The safety profile of olaparib in the SOLO1 trial was consistent with that seen in patients with relapsed disease (i.e., in patients in the SOLO2 trial[13]), despite the longer duration of treatment. Rates of adverse events that led to dose reduction or discontinuation were relatively low. The safety profile of olaparib appeared to be generally acceptable in patients receiving maintenance treatment for newly diagnosed advanced ovarian cancer.

The incidence of acute myeloid leukemia that was reported in the SOLO1 trial (1%) is consistent with the incidence of the myelodysplastic syndrome or acute myeloid leukemia that was reported in the SOLO2 trial (2%)[13] and other trials of PARP inhibitors.[11,12,15] Comparative data regarding the incidence of the myelodysplastic syndrome or acute myeloid leukemia after the use of platinum-based chemotherapy alone in patients with newly diagnosed ovarian cancer are limited.

In this trial, neither trial group had a clinically significant change in health-related quality of life. Although there was a between-group difference in the change in the Trial Outcome Index score, the difference was less than 10 points and thus was not considered to be clinically meaningful.[16]

In conclusion, the SOLO1 trial showed that the use of maintenance therapy with olaparib, as compared with placebo, after platinum-based chemotherapy provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation.

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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