ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

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ABSTRACT

BACKGROUND

Olaparib (AZD2281) is an oral poly(adenosine diphosphate [ADP]–ribose) polymerase inhibitor that has shown antitumor activity in patients with high-grade serous ovarian cancer with or without *BRCA1* or *BRCA2* germline mutations.

METHODS

We conducted a randomized, double-blind, placebo-controlled, phase 2 study to evaluate maintenance treatment with olaparib in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had received two or more platinum-based regimens and had had a partial or complete response to their most recent platinum-based regimen. Patients were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, or placebo. The primary end point was progression-free survival according to the Response Evaluation Criteria in Solid Tumors guidelines.

RESULTS

Of 265 patients who underwent randomization, 136 were assigned to the olaparib group and 129 to the placebo group. Progression-free survival was significantly longer with olaparib than with placebo (median, 8.4 months vs. 4.8 months from randomization on completion of chemotherapy; hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.25 to 0.49; P<0.001). Subgroup analyses of progression-free survival showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression. Adverse events more commonly reported in the olaparib group than in the placebo group (by more than 10% of patients) were nausea (68% vs. 35%), fatigue (49% vs. 38%), vomiting (32% vs. 14%), and anemia (17% vs. 5%); the majority of adverse events were grade 1 or 2. An interim analysis of overall survival (38% maturity, meaning that 38% of the patients had died) showed no significant difference between groups (hazard ratio with olaparib, 0.94; 95% CI, 0.63 to 1.39; P=0.75).

CONCLUSIONS

Olaparib as maintenance treatment significantly improved progression-free survival among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer. Interim analysis showed no overall survival benefit. The toxicity profile of olaparib in this population was consistent with that in previous studies. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT00753545.)

Ovarian cancer is the leading cause of death from gynecologic tumors in the Western world.[1] Approximately 80% of patients with newly diagnosed ovarian cancer have a response to platinum-based chemotherapy. However, most patients have relapses, and responses to subsequent therapies are generally short-lived.[2-6] Maintenance chemotherapy as part of first-line treatment has been shown to prolong control of ovarian cancer,[7] and disease control has also been prolonged with the combination of bevacizumab and chemotherapy in patients receiving first-line treatment[8,9] and in those with platinum-sensitive relapsed ovarian cancer.[10] However, new treatments are needed because most patients eventually have a relapse.

Women with germline mutations in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) have an increased risk of ovarian cancer, particularly the most common type, invasive high-grade serous carcinoma.[11] About 15% of epithelial ovarian cancers are deficient in homologous recombination repair, owing to mutations in *BRCA1/2*.[12,13] In up to 50% of patients with high-grade serous tumors, the tumor cells may be deficient in homologous recombination as a result of germline or somatically acquired *BRCA1/2* mutations, epigenetic inactivation of *BRCA1*, or defects in the homologous recombination pathway that are independent of *BRCA1/2*.[14] The silencing or dysfunction of genes in *BRCA1/2*-related pathways gives rise to a "BRCAness" phenotype similar to that resulting from inherent mutations in *BRCA1/2*. Microarray studies in serous epithelial ovarian cancer have identified a BRCAness gene-expression profile that appears to correlate with responsiveness to both platinum-based chemotherapy and poly(adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors.[15,16]

PARP plays an essential part in the repair of single-stranded DNA breaks, through the base-excision-repair pathway, and it has been proposed that PARP keeps low-fidelity nonhomologous-end-joining DNA repair machinery in check.[17] Thus, PARP inhibition leads to the formation of double-stranded DNA breaks that cannot be accurately repaired in tumors with homologous recombination deficiency,[18,19] owing to aberrant activation of low-fidelity repair mediated by nonhomologous end joining,[17] a concept known as synthetic lethality.[20] Olaparib (AZD2281) is a potent oral PARP inhibitor that induces synthetic lethality in *BRCA1/2*-deficient tumor cells.[21,22] Antitumor activity at doses that were not unacceptably toxic was observed in phase 1 and phase 2 monotherapy studies involving patients with ovarian cancer who had *BRCA1/2* germline mutations.[23-25] In addition, a phase 2 study of olaparib monotherapy in patients with high-grade serous ovarian cancer with or without *BRCA1/2* mutations showed objective response rates of 41% for patients with *BRCA1/2* mutations and 24% for those without such mutations.[26]

We evaluated the efficacy of olaparib monotherapy as maintenance treatment in patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer who had had a response to their most recent platinum-based chemotherapy.

METHODS

PATIENTS

Patients were eligible if they were 18 years of age or older and had recurrent ovarian or fallopian-tube cancer or primary peritoneal cancer with high-grade (grade 2 or 3) serous features or a serous component, which was platinum-sensitive (defined by an objective response to a previous platinum-based therapy for more than 6 months). Eligible patients had completed at least two courses of platinum-based chemotherapy, and their most recent regimen induced an objective response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.0,[27] or a cancer antigen 125 (CA-125) response, according to Gynecological Cancer InterGroup criteria[28] (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The study design is shown in Figure 1. Other key inclusion criteria were CA-125 measurements before treatment that were below the upper limit of the normal range (in the case of values above this limit, any increase in a second sample, obtained more than 7 days later, had to be less than a 15% increase from the first sample). *BRCA1/2* mutation status was not required. All patients provided written informed consent.

STUDY DESIGN AND OVERSIGHT

In this randomized, double-blind, phase 2 study, eligible patients were stratified according to the interval between disease progression and completion of their penultimate platinum-based regimen (from 6 to 12 months vs. more than 12 months), objective response to their most recent regimen (complete response vs. partial response), and ancestry (Jewish vs. non-Jewish), to help balance

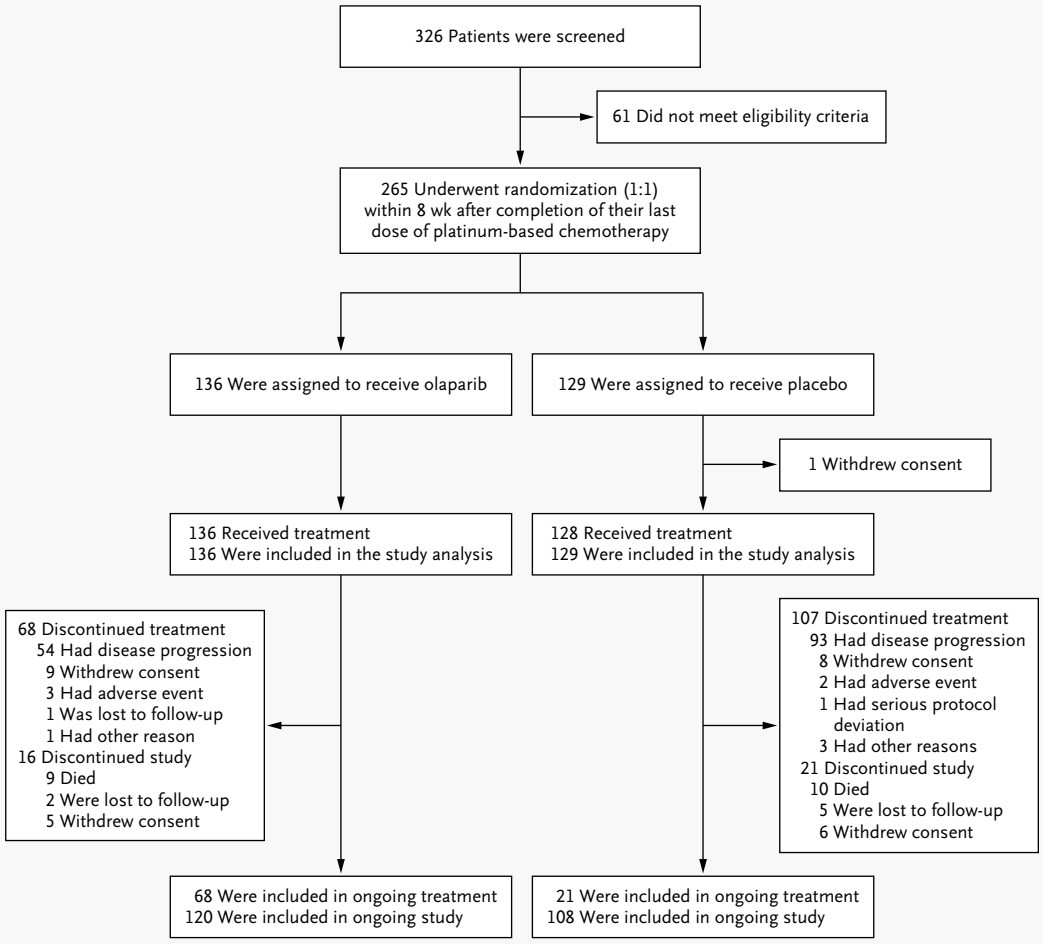

Figure 1. Enrollment, Randomization, and Treatment.

Of the 326 patients who were screened, 265 met the eligibility criteria and underwent randomization within 8 weeks after receiving their last dose of platinum-based chemotherapy. Patients could continue receiving olaparib or placebo until disease progression or as long as they were benefitting from the treatment and did not meet any criteria for discontinuation (i.e., the ongoing-treatment group). We followed patients until progression of disease, regardless of whether the treatment was discontinued or delayed or whether there were deviations from the protocol (i.e., the ongoing study group). GCIG denotes Gynecologic Cancer InterGroup.

the distribution of *BRCA1/2* germline mutations (which are found more frequently in Jewish populations). With the use of an interactive voice response system, patients were randomly assigned in a 1:1 ratio to receive olaparib capsules, at a dose of 400 mg twice daily (the monotherapy dose shown to be the maximum dose associated with acceptable adverse-event rates),[23] or matching placebo within 8 weeks after completion of the last dose of platinum-based chemotherapy (Fig. 1). Study treatment was blinded with the use of unique identifiers generated during randomization. Patients continued the assigned study treatment until objective disease progression, as defined by RECIST guidelines, provided that they did not meet any criteria for discontinuation (any grade 3 or 4 adverse event that did not resolve completely or to grade 1 within 28 days after onset, according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Treatment was interrupted for any event of CTCAE grade 3 or 4 that was considered to be related to treatment. If the toxicity resolved entirely or to a grade 1 level, treatment was restarted with a re-

duction in the dose to 200 mg or 100 mg twice daily. If the event did not resolve within 4 weeks after treatment or if two previous treatment interruptions had occurred, the patient was withdrawn from the study. Patients receiving placebo were not permitted to cross over to treatment with olaparib after disease progression.

The study protocol was approved by the institutional review board or independent ethics committee at each investigational site; the protocol and the statistical analysis plan are available at NEJM.org. The study was performed in accordance with the Declaration of Helsinki and the guidelines for Good Clinical Practice. The study was designed by the first author, in collaboration with the last author and the study sponsor, AstraZeneca. Data collection and analysis were performed by the sponsor, and all the authors had full access to the data. All the authors vouch for the completeness and accuracy of the data and analyses and the fidelity of the study to the protocol. The manuscript was written by the first author, with editorial assistance funded by the sponsor, and was reviewed by all authors and the sponsor. The decision to submit the manuscript for publication was made by all the authors and the sponsor.

STUDY END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, as assessed by the site investigator and defined as the time from randomization (on completion of chemotherapy) until objective assessment of disease progression according to RECIST guidelines[27] or death (from any cause in the absence of progression of disease). Progression-free survival was assessed with the use of computed tomographic scans obtained every 12 weeks and was calculated on the basis of measurements of target and nontarget lesions and assessment for new lesions that were recorded by the investigators. In addition, a blinded independent central review of tumor scans was performed retrospectively.

Secondary efficacy end points were time to progression, according to RECIST guidelines or CA-125 level, whichever showed earlier progression (with the CA-125 level assessed according to Gynecological Cancer InterGroup criteria; see the Supplementary Appendix)[28]; objective response rate, as determined according to RECIST guidelines or a combination of RECIST guidelines and CA-125 level; disease-control rate, according to RECIST guidelines (i.e., the percentage of patients who had confirmed complete response, partial response, stable disease, or no evidence of disease for at least 23 weeks); percentage change from baseline in the size of the target tumor lesion at weeks 12 and 24; and overall survival. Disease-related symptoms and health-related quality of life as reported by the patients were also measured (for details, see the Supplementary Appendix). Safety was assessed throughout the study by monitoring for adverse events, biochemical laboratory tests, assessment of vital signs, and physical examination.

STATISTICAL ANALYSIS

A total enrollment of 250 patients was planned for the study, and the primary analysis was to be performed when at least 137 progression-free survival events had occurred. Assuming that the true hazard ratio for progression or death with olaparib versus placebo was 0.75 (corresponding to a 33% increase in the median duration of progression-free survival, from 9 to 12 months after randomization) and that the overall type 1 error was 20% (one-sided test), we calculated that the analysis would have 80% power to show a significant difference in favor of olaparib (one-sided $P<0.20$).

Analyses of efficacy and patient-reported outcomes included all patients who were randomly assigned to a study group, and safety analyses included all patients who received at least one dose of the assigned study medication. Time-to-event variables (i.e., progression-free survival, overall survival, and time to worsening of disease-related symptoms and health-related quality of life) were analyzed with the use of a Cox proportional-hazards model that included covariates that were used as stratification factors at randomization. A supportive analysis of progression-free survival with the use of the log-rank test was performed (stratified by randomization factors). Predictive and prognostic factors for progression-free survival were explored with the use of preplanned subgroup analyses, including status with respect to *BRCA1/2* germline mutation, age, Jewish or non-Jewish ancestry, response status at baseline, and time to progression from the start of the penultimate platinum-based regimen. The heterogeneity of the treatment effect among the subgroups was assessed with the use of statistical interaction tests and forest plots. An interim analysis of overall survival was performed after 101 deaths had been recorded. The final analysis of overall survival will be performed at 60% maturity (i.e., when 60% of the patients have died).

Response rates and rates of improvement in patient-reported outcomes were analyzed with the use of logistic regression, and the percentage change in tumor size was assessed with the use of analysis of covariance; both these analyses were adjusted for the stratification factors at randomization. All reported P values and confidence intervals are two-sided.

RESULTS

PATIENTS

Between August 28, 2008, and February 9, 2010, we screened 326 patients at 82 investigational sites in 16 countries. Of the 265 patients who met the eligibility criteria, 136 were randomly assigned to receive olaparib, at a dose of 400 mg twice daily, and 129 to receive placebo (Fig. 1). At the data-cutoff point (June 30, 2010), 68 patients (50%) in the olaparib group and 21 (16%) in the placebo group were still receiving the study treatment. Demographic and baseline characteristics of the patients (Table 1) and any protocol deviations with the potential to affect the primary analysis (Table 1 in the Supplementary Appendix) were well balanced between the two study groups.

EFFICACY

An analysis performed after 153 progression events had occurred (in 57.7% of patients) showed that progression-free survival was significantly longer in the olaparib group than in the placebo group. Median progression-free survival was 8.4 months in the olaparib group versus 4.8 months in the placebo group (hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.25 to 0.49; P<0.001) (Fig. 2A). A stratified log-rank test of progression-free survival supported the primary

Table 1. Demographic and Baseline Characteristics of the Patients.

Characteristic	Olaparib (N=136)	Placebo (N=129)
Age — yr		
Median	58.0	59.0
Range	21–89	33–84
Ancestry — no. (%)*		
Non-Jewish	116 (85.3)	112 (86.8)
Jewish	20 (14.7)	17 (13.2)
Ashkenazi	16 (11.8)	12 (9.3)
Sephardi or Mizrahi	3 (2.2)	2 (1.6)
Other or unknown	1 (0.7)	3 (2.3)
ECOG performance status — no. (%)†		
0	110 (80.9)	95 (73.6)
1	23 (16.9)	30 (23.3)
2	1 (0.7)	2 (1.6)
Unknown	2 (1.5)	2 (1.6)
Primary tumor location — no. (%)		
Ovary	119 (87.5)	109 (84.5)
Fallopian tube	3 (2.2)	4 (3.1)
Peritoneum	14 (10.3)	16 (12.4)
Time to progression with penultimate platinum-based regimen — no. (%)		
>6–12 mo	53 (39.0)	54 (41.9)
>12 mo	83 (61.0)	75 (58.1)
Objective response to most recent platinum-based regimen — no. (%)		
Complete	57 (41.9)	63 (48.8)
Partial	79 (58.1)	66 (51.2)

Table 1. (Continued.)

Characteristic	Olaparib (N=136)	Placebo (N=129)
BRCA-germline-mutation status — no. (%)		
BRCA 1 or *BRCA 2* mutation	31 (22.8)	28 (21.7)
BRCA1 mutation	25 (18.4)	20 (15.5)
BRCA2 mutation	6 (4.4)	7 (5.4)
Both *BRCA1* and *BRCA2* mutations	0	1 (0.8)
Negative	18 (13.2)	20 (15.5)
Unknown	87 (64.0)	81 (62.8)
Previous chemotherapy regimens — no.		
Median	3‡	3
Range	0–11	2–8
Previous platinum-based chemotherapy regimens — no.		
Median	2‡	2
Range	0–7	2–8

* Ancestry was self-reported. Data on race or ethnic group, which was determined by the investigators, were as follows: more than 95% of the patients in each study group were white (95.6% in the olaparib group and 97.7% in the placebo group). Data for the remaining patients were as follows: black (1.5% in the olaparib group and 0.8% in the placebo group), Asian (1.5% and 1.6%, respectively), and other (1.5% and 0%, respectively).

† The Eastern Cooperative Oncology Group (ECOG) performance status is measured on a scale from 0 to 4, with 0 indicating normal activity, 1 restricted in strenuous activity but ambulatory and able to carry out light work, 2 ambulatory more than 50% of the time, 3 ambulatory 50% of the time or less and nursing care is required, and 4 bedridden and possibly requiring hospitalization.

‡ One patient received two regimens of platinum-based chemotherapy that were not recorded because the data were not entered into the database before it was locked. This patient was therefore classified as having received no chemotherapy regimens.

analysis (hazard ratio, 0.37; 95% CI, 0.26 to 0.51; P<0.001). A blinded, independent, central review of the data also showed consistent results (hazard ratio, 0.39; 95% CI, 0.27 to 0.55; P<0.001). Subgroup analyses of progression-free survival showed that, regardless of subgroup, patients in the olaparib group had a lower risk of progression than those in the placebo group (Fig. 2B). No predictive factors were identified (global treatment-by-subgroup interaction test, P=0.15). A complete response (vs. partial response) to the final platinum-based therapy before study entry was a significant prognostic factor for longer progression-free survival, regardless of study group (hazard ratio, 0.46; P<0.001).

The secondary end point of time to progression according to the RECIST guidelines or CA-125 level, whichever showed earlier progression, was also significantly longer in the olaparib group than in the placebo group (median, 8.3 months vs. 3.7 months; hazard ratio for progression, 0.35; 95% CI, 0.25 to 0.47; P<0.001). At study entry, 40% of the overall study population had measurable disease and could be assessed for an objective response according to RECIST guidelines; the response rate was 12% (7 of 57 patients with measurable disease at study entry) in the olaparib group, as compared with 4% (2 of 48) in the placebo group (odds ratio, 3.36; 95% CI, 0.75 to 23.72; P=0.12). At the time of the data-cutoff point for progression-free survival, too few deaths had occurred for a survival analysis to be performed. However, at the interim analysis of overall survival (data-cutoff point, October 31, 2011), 101 patients (38%) had died: 52 in the olaparib group and 49 in the placebo group. No significant difference in overall survival was observed (hazard ratio for death in the olaparib group, 0.94; 95% CI, 0.63 to 1.39; P=0.75). The median overall survival was similar in the two study groups (29.7 months in the olaparib group and 29.9 months in the placebo group). At the time of the interim analysis of overall survival, 29 patients were still receiving olaparib after a period of at least 21 months, and 4 patients were still receiving placebo. The secondary end points of change in tumor size, combined response rate according to RECIST guidelines and CA-125 mea-

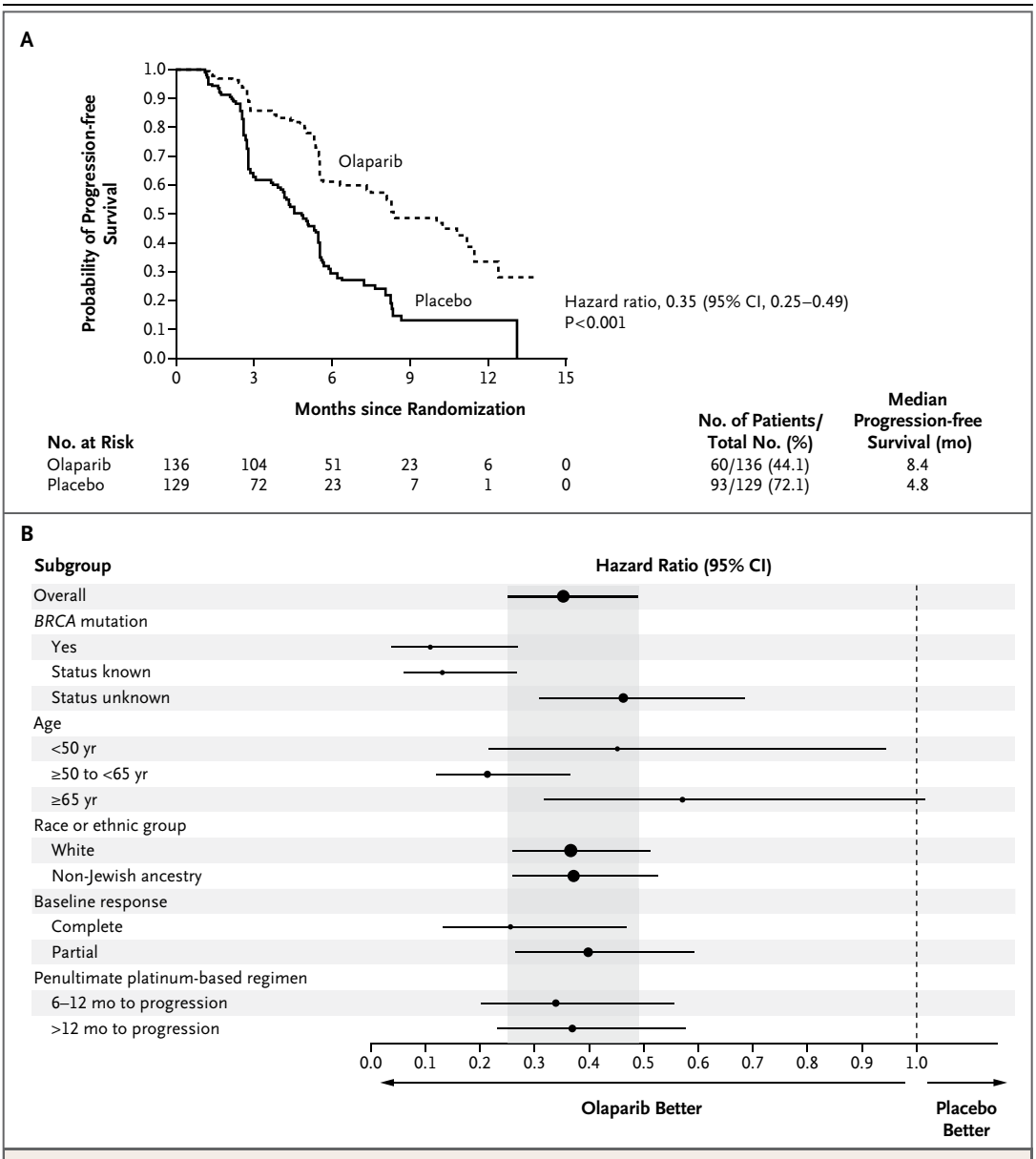

Figure 2. Kaplan–Meier Estimates and Subgroup Analysis of Progression-free Survival.

Panel A shows Kaplan–Meier curves for progression-free survival in the randomized population. Progression events were observed in 60 patients (44.1%) in the olaparib group and 93 (72.1%) in the placebo group. Panel B shows a subgroup analysis of progression-free survival in the randomized population. The size of the circles is proportional to the number of events. The gray band represents 95% confidence intervals for the overall population. The subgroups of patients who did not have the *BRCA* mutation or who were Jewish were not included in the subgroup analysis because there were fewer than 20 events in those subgroups.

surement (Table 2 in the Supplementary Appendix), and disease-control rate are reported in the Supplementary Appendix.

SAFETY

The majority of patients (246 of 264) had one or more adverse events, most of which were grade 1 or 2 (Table 2). Adverse events with an incidence that was at least 10% higher in the olaparib group than in the placebo group, were nausea, fatigue, vomiting, and anemia. In both groups, nausea, fatigue, and vomiting were intermittent and did not require discontinuation of the study treatment. The incidence of grade 3 or 4 adverse events was 35.3% in

Table 2. Adverse Events.*

Event	Olaparib (N=136)				Placebo (N=128)			
	Any Grade	Grade 1	Grade 2	Grade 3 or 4	Any Grade	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Any	130 (95.6)	NA	NA	48 (35.3)	116 (90.6)	NA	NA	26 (20.3)
Nausea	93 (68.4)	71 (52.2)	19 (14.0)	3 (2.2)	45 (35.2)	35 (27.3)	10 (7.8)	0
Fatigue	66 (48.5)	32 (23.5)	25 (18.4)	9 (6.6)	48 (37.5)	36 (28.1)	8 (6.3)	4 (3.1)†
Vomiting	43 (31.6)	27 (19.9)	13 (9.6)	3 (2.2)	18 (14.1)	12 (9.4)	5 (3.9)	1 (0.8)
Diarrhea	31 (22.8)	23 (16.9)	5 (3.7)	3 (2.2)	29 (22.7)	21 (16.4)	5 (3.9)	3 (2.3)
Headache	25 (18.4)	16 (11.8)	9 (6.6)	0	15 (11.7)	13 (10.2)	1 (0.8)	1 (0.8)
Decreased appetite	25 (18.4)	17 (12.5)	8 (5.9)	0	17 (13.3)	13 (10.2)	4 (3.1)	0
Abdominal pain	24 (17.6)	11 (8.1)	11 (8.1)	2 (1.5)	33 (25.8)	26 (20.3)	3 (2.3)	4 (3.1)
Anemia	23 (16.9)	3 (2.2)	13 (9.6)	7 (5.1)	6 (4.7)	3 (2.3)	2 (1.6)	1 (0.8)
Dyspepsia	22 (16.2)	19 (14.0)	3 (2.2)	0	11 (8.6)	9 (7.0)	2 (1.6)	0
Dysgeusia	19 (14.0)	17 (12.5)	2 (1.5)	0	8 (6.3)	8 (6.3)	0	0
Cough	18 (13.2)	14 (10.3)	4 (2.9)	0	12 (9.4)	11 (8.6)	1 (0.8)	0
Upper abdominal pain	18 (13.2)	12 (8.8)	6 (4.4)	0	10 (7.8)	6 (4.7)	3 (2.3)	1 (0.8)
Arthralgia	16 (11.8)	10 (7.4)	6 (4.4)	0	17 (13.3)	14 (10.9)	3 (2.3)	0
Nasopharyngitis	17 (12.5)	12 (8.8)	5 (3.7)	0	14 (10.9)	11 (8.6)	3 (2.3)	0
Constipation	17 (12.5)	12 (8.8)	5 (3.7)	0	13 (10.2)	11 (8.6)	2 (1.6)	0
Dizziness	17 (12.5)	14 (10.3)	3 (2.2)	0	9 (7.0)	9 (7.0)	0	0
Asthenia	16 (11.8)	10 (7.4)	5 (3.7)	1 (0.7)	12 (9.4)	11 (8.6)	1 (0.8)	0
Back pain	16 (11.8)	9 (6.6)	4 (2.9)	3 (2.2)	10 (7.8)	8 (6.3)	2 (1.6)	0
Hot flush	5 (3.7)	4 (2.9)	1 (0.7)	0	15 (11.7)	13 (10.2)	2 (1.6)	0
Abdominal distention	14 (10.3)	13 (9.6)	1 (0.7)	0	11 (8.6)	10 (7.8)	1 (0.8)	0

* Adverse events reported here occurred in at least 10% of patients in either study group. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. NA denotes not available.

† One patient in the placebo group inadvertently received olaparib at a dose of 400 mg twice daily for approximately 2 weeks between days 29 and 84. The exact dates and duration are unknown. It is not known whether the patient was receiving olaparib or placebo when the adverse event occurred on day 56. This adverse event was counted in the safety analysis for placebo, but the possibility that it was attributable to olaparib cannot be excluded.

the olaparib group and 20.3% in the placebo group (Table 2). A total of seven grade 4 events were reported in the olaparib group (in 5.1% of patients), and two were reported in the placebo group (in 1.6% of patients) (Table 3). There were no unexpected changes in biochemical laboratory measurements, vital signs, or findings on physical examination in either group.

At the time of the data-cutoff point, the median duration of exposure to the treatment was 206.5 days (range, 3 to 469) for olaparib and 141 days (range, 34 to 413) for placebo, and the mean rate of adherence to the assigned study treatment was 85% and 96%, respectively. More patients in the olaparib group had dose interruptions or reductions (27.9% and 22.8%, respectively) as a result of adverse events, as compared with the placebo group (8.6% and 4.7%). The most common adverse events that resulted in interruptions or reductions in the dose of olaparib were vomiting, nausea, and fatigue. Adverse events that led to the permanent discontinuation of treatment occurred in three patients receiving olaparib (one each with palpitations and myalgia, erythematous rash, and nausea and obstruction in the small intestine) and in one patient receiving placebo (nausea); all these adverse events were grade 2 and were considered by the investigator to be related to treatment, except for the grade 4 obstruction in the small intestine.

Table 3. Grade 4 Adverse Events.*

Event	Olaparib (N=136)		Placebo (N=128)	
	No. of Patients (%)	Action Taken	No. of Patients (%)	Action Taken
Increased blood level of creatine kinase	2 (1.5)	None (1), treatment temporarily stopped (1)	0	
Obstruction of small intestine	1 (0.7)	Treatment permanently stopped†	1 (0.8)	Treatment temporarily stopped
Anemia	1 (0.7)	None	0	
Abdominal pain	0		1 (0.8)	None
Fatigue	1 (0.7)	Reduction of dose	0	
Increased blood level of amylase	1 (0.7)	Treatment temporarily stopped	0	
Pulmonary embolism	1 (0.7)	Treatment temporarily stopped	0	

* Adverse events were graded according to the CTCAE.
† Treatment was stopped in this patient, owing to an earlier adverse event of nausea before this grade 4 adverse event.

PATIENT-REPORTED OUTCOMES

There were no significant between-group differences in disease-related symptoms or rates of improvement in health-related quality of life, as measured by scores on the Functional Assessment of Cancer Therapy (FACT)–Ovarian questionnaire, the FACT–National Comprehensive Cancer Network Ovarian Symptom Index, and the Trial Outcome Index (Table 3 in the Supplementary Appendix).[29] The time to worsening of each of these end points was shorter with olaparib than with placebo; however, the difference was not significant (Table 4 in the Supplementary Appendix).

DISCUSSION

This randomized, phase 2 clinical trial involving patients with recurrent platinum-sensitive, high-grade serous ovarian cancer targeted a histologically and phenotypically defined subgroup of patients who have tumor cells that are highly enriched for homologous-recombination deficiency. In this population, maintenance therapy with olaparib, at a dose of 400 mg twice daily, significantly improved the duration of progression-free survival, as compared with placebo. Furthermore, the lower risk of disease progression associated with olaparib treatment was consistent across all the subgroups analyzed (Fig. 2B). A significant benefit in the secondary end points of time to progression, as assessed by means of RECIST guidelines or CA-125 level, whichever showed earlier progression, and change in tumor size at 24 weeks was also observed in patients receiving olaparib. The identical hazard ratios for the primary end point of progression-free survival, according to RECIST guidelines, and for the secondary progression end point that also incorporated objective CA-125 measurements further support the validity of the significant improvement in progression-free survival. However, the observed benefit with respect to progression-free survival did not translate into an overall survival benefit at the time of the interim analysis of overall survival. Our data cannot address differences that might exist between patients with *BRCA* germline mutations and those with a BRCAness phenotype; it will be important to address these questions at the final analysis of overall survival.

There is a need to identify biomarkers to select patients for this therapy. The identification of biomarkers for homologous-recombination deficiency may provide an opportunity to target PARP inhibitors to the appropriate population. A recent study showed that the formation of Rad51 foci correlated with an in vitro response to PARP inhibition in primary epithelial ovarian-cancer cells.[30] Rad51 is involved in homologous recombination repair; it is relocalized to the nucleus in response to DNA damage to form distinct foci that are thought to be assemblages of proteins required for homologous recombination repair.

The toxicity profile of olaparib in this patient population was consistent with that reported in previous clinical studies.[24,25,31] The majority of adverse events were grade 1 or 2 and did not require interruptions of the treatment. Dose modifications were more common in the olaparib

group; however, discontinuations due to adverse events were infrequent, and adherence to therapy was high. There were no significant differences between the study groups in the end points for symptoms or health-related quality of life.

The median progression-free survival of 4.8 months from randomization in the placebo group was shorter than the expected progression-free survival specified in the protocol (9 months). At the time that the study was designed, there were no reported data from trials of maintenance treatment in patients with a relapse of platinum-responsive ovarian cancer, which would have provided a basis for estimating progression-free survival in the placebo group. However, the observed value of 4.8 months is consistent with recently published data from studies of maintenance treatment in similar patient populations (5.8 months and 2.8 months),[32,33] suggesting that progression-free survival in the placebo group in our study was in line with that expected.

Because only patients with a response to chemotherapy were enrolled in the study, just 40% had measurable disease at entry. Objective response was not an informative end point because there were limited opportunities for further responses. Response rates were low in both study groups, and some patients in the placebo group had a reduction in tumor size.

In conclusion, the results from this randomized, phase 2 study show that maintenance treatment with olaparib was associated with a significant improvement in progression-free survival among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer. However, at the interim analysis, this did not translate into an overall survival benefit. As of this writing, 21% of the patients were still receiving olaparib (and 3% were still receiving placebo), which indicates that the disease is controlled for a prolonged period in some patients.

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REFERENCES

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90. [Erratum, CA Cancer J Clin 2011;61:134.]
2. Fung-Kee-Fung M, Oliver T, Elit L, Oza A, Hirte HW, Bryson P. Optimal chemotherapy treatment for women with recurrent ovarian cancer. Curr Oncol 2007; 14:195-208.
3. Parmar MK, Ledermann JA, Colombo N, et al. Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet 2003;361:2099-106.
4. Pfisterer J, Ledermann JA. Management of platinum-sensitive recurrent ovarian cancer. Semin Oncol 2006;33:Suppl:S12-S16.
5. Pujade-Lauraine E, Wagner U, Avall-Lundqvist E, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28:3323-9.
6. Pfisterer J, Plante M, Vergote I, et al. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol 2006;24:4699-707.
7. Markman M, Liu PY, Moon J, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. Gynecol Oncol 2009;114:195-8.
8. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011;365:2473-83.
9. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011;365:2484-96. [Erratum, N Engl J Med 2012;366:284.]
10. Aghajanian C, Finkler NJ, Rutherford T, et al. OCEANS: a randomized, double-blinded, placebo-controlled phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC). J Clin Oncol 2011;29:Suppl: LBA5007. abstract.
11. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694-706.
12. Moynahan ME, Chiu JW, Koller BH, Jasin M. BRCA1 controls homology-directed DNA repair. Mol Cell 1999;4:511-8.
13. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell 2001;7:263-72.
14. Press JZ, De Luca A, Boyd N, et al. Ovarian carcinomas with genetic and epigenetic BRCA1 loss have distinct molecular abnormalities. BMC Cancer 2008;8:17.
15. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of *BRCA*ness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clin Oncol 2010;28:3555-61. [Erratum, J Clin Oncol 2010;28:4868.]
16. Weberpals JI, Clark-Knowles KV, Vanderhyden BC. Sporadic epithelial ovarian cancer: clinical relevance of BRCA1 inhibition in the DNA damage and repair pathway. J Clin Oncol 2008;26:3259-67.
17. Patel AG, Sarkaria JN, Kaufmann SH. Nonhomologous end joining drives poly(ADP-ribose) polymerase (PARP) inhibitor lethality in homologous recombination-deficient cells. Proc Natl Acad Sci U S A 2011;108:3406-11.
18. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.
19. Ashworth A. A synthetic lethal therapeutic approach: poly(ADP) ribose polymerase inhibitors for the treatment of cancers deficient in DNA double-strand break repair. J Clin Oncol 2008;26:3785-90.
20. Nijman SM. Synthetic lethality: general principles, utility and detection using genetic screens in human cells. FEBS Lett 2011;585:1-6.

21. Evers B, Drost R, Schut E, et al. Selective inhibition of BRCA2-deficient mammary tumor cell growth by AZD2281 and cisplatin. Clin Cancer Res 2008;14:3916-25.
22. Rottenberg S, Jaspers JE, Kersbergen A, et al. High sensitivity of BRCA1-deficient mammary tumors to the PARP inhibitor AZD2281 alone and in combination with platinum drugs. Proc Natl Acad Sci U S A 2008;105:17079-84.
23. 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.
24. Fong PC, Yap TA, Boss DS, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. J Clin Oncol 2010;28:2512-9.
25. 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.
26. 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.
27. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.
28. Rustin GJ, Vergote I, Eisenhauer E, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer 2011;21:419-23.
29. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 1993;11:570-9.
30. Mukhopadhyay A, Elattar A, Cerbinskaite A, et al. Development of a functional assay for homologous recombination status in primary cultures of epithelial ovarian tumor and correlation with sensitivity to poly(ADP-ribose) polymerase inhibitors. Clin Cancer Res 2010;16:2344-51.
31. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010;376:235-44.
32. Kaye SB, Fehrenbacher L, Holloway R, et al. A phase 2, randomized, placebo-controlled study of Hedgehog (Hh) pathway inhibitor GDC-0449 as maintenance therapy in patients with ovarian cancer in 2nd or 3rd complete remission (CR). Ann Oncol 2010;21:Suppl:LBA25. abstract.
33. Ledermann JA, Hackshaw A, Kaye S, et al. Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer. J Clin Oncol 2011;29:3798-804.