ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation

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ABSTRACT

BACKGROUND

Olaparib is an oral poly(adenosine diphosphate–ribose) polymerase inhibitor that has promising antitumor activity in patients with metastatic breast cancer and a germline *BRCA* mutation.

METHODS

We conducted a randomized, open-label, phase 3 trial in which olaparib monotherapy was compared with standard therapy in patients with a germline *BRCA* mutation and human epidermal growth factor receptor type 2 (HER2)–negative metastatic breast cancer who had received no more than two previous chemotherapy regimens for metastatic disease. Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tablets (300 mg twice daily) or standard therapy with single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles). The primary end point was progression-free survival, which was assessed by blinded independent central review and was analyzed on an intention-to-treat basis.

RESULTS

Of the 302 patients who underwent randomization, 205 were assigned to receive olaparib and 97 were assigned to receive standard therapy. Median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval, 0.43 to 0.80; P<0.001). The response rate was 59.9% in the olaparib group and 28.8% in the standard-therapy group. The rate of grade 3 or higher adverse events was 36.6% in the olaparib group and 50.5% in the standard-therapy group, and the rate of treatment discontinuation due to toxic effects was 4.9% and 7.7%, respectively.

CONCLUSIONS

Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy. (Funded by AstraZeneca; OlympiAD ClinicalTrials.gov number, NCT02000622.)

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Approximately 5% of unselected patients with breast cancer carry a germline *BRCA* mutation.[1,2] Such mutations are more likely to be present in patients who have a strong family history of breast cancer, younger patients, patients who have triple-negative (i.e., human epidermal growth factor receptor type 2 [HER2]–negative, estrogen-receptor–negative, and progesterone-receptor–negative) breast cancer, and patients who are members of an ethnic group with known founder mutations in the *BRCA* genes, such as the Ashkenazi Jewish population.[1,3] Patients with a *BRCA1* mutation are predisposed to triple-negative breast cancer, whereas patients with a *BRCA2* mutation most often have tumors that express estrogen receptors.[4,5] Although patients with mutations in either *BRCA1* or *BRCA2* have an increased risk for contralateral breast cancer and metachronous ovarian cancer, whether these mutations are independent prognostic factors, particularly for metastatic breast cancer, is uncertain.[6]

BRCA1 and *BRCA2* are tumor-suppressor genes that encode proteins involved in the repair of DNA double-strand breaks by way of the homologous recombination repair pathway.[7] Members of the poly(adenosine diphosphate–ribose) polymerase (PARP) family of enzymes are central to the repair of DNA single-strand breaks.[7] In vitro, cells that lack functional *BRCA1* or *BRCA2* are sensitive to PARP inhibition; this sensitivity is most likely caused by multiple mechanisms, including the synthetic lethality that results from unresolved DNA damage and the replication arrest that results from physical obstruction of replication forks by PARP trapping.[8,9]

The oral PARP inhibitor olaparib is approved for the treatment of patients with recurrent ovarian cancer and a *BRCA* mutation, and it has been shown to provide clinically meaningful benefit among such patients.[10,11] Olaparib has also been shown to have promising activity in patients with metastatic breast cancer and a germline *BRCA* mutation.[12,13] The OlympiAD trial was designed to compare the efficacy and safety of olaparib with the efficacy and safety of standard therapy with single-agent chemotherapy of the physician's choice among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation.

Methods

Patients

Eligible patients were at least 18 years of age and had HER2-negative metastatic breast cancer that was hormone-receptor positive (i.e., estrogen-receptor positive, progesterone-receptor positive, or both) or was triple negative. Patients had a confirmed deleterious or suspected deleterious germline *BRCA* mutation; the mutation was detected by central testing with BRACAnalysis (Myriad Genetics) in 297 patients and by local testing in 167 patients (with confirmation by central testing with BRACAnalysis in all but 5 of those patients). Patients had received no more than two previous chemotherapy regimens for metastatic disease, and they had received neoadjuvant or adjuvant treatment or treatment for metastatic disease with an anthracycline (unless it was contraindicated) and a taxane. Patients with hormone-receptor–positive breast cancer had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate. Previous neoadjuvant or adjuvant treatment with platinum was allowed if at least 12 months had elapsed since the last dose. Previous treatment with platinum for metastatic disease was allowed if there was no evidence that disease progression had occurred during treatment. Patients had normal baseline organ and bone marrow function, and they had measurable disease, which was defined as the presence of at least one lesion that was suitable for baseline and subsequent assessments for disease progression according to modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Complete eligibility criteria are provided in the trial protocol, which is available with the full text of this article at NEJM.org. The protocol was approved by ethics review committees at the participating institutions. All the patients provided written informed consent.

Trial Design and Treatments

The OlympiAD trial was a randomized, controlled, open-label, multicenter, international, phase 3 trial. Randomization was stratified according to previous use of chemotherapy for metastatic dis-

ease (yes vs. no), hormone-receptor status (hormone-receptor positive vs. triple negative), and previous use of platinum-based therapy (yes vs. no); this information was obtained locally at the time of trial registration with the use of an interactive voice or Web response system. All other clinical data and disease characteristics were collected at baseline with the use of a case-report form.

Patients were randomly assigned, in a 2:1 ratio, to receive olaparib tab lets (300 mg twice daily) or standard therapy with one of the following three prespecified chemotherapy regimens: capecitabine administered orally at a dose of 2500 mg per square meter of body-surface area daily (divided into two doses) for 14 days, repeated every 21 days; eribulin mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8, repeated every 21 days; or vinorelbine administered intravenously at a dose of 30 mg per square meter on day 1 and day 8, repeated every 21 days. The assigned treatment was continued until disease progression or unacceptable toxic effects occurred. After disease progression occurred, treatment was at the discretion of the investigator. Crossover to olaparib was not permitted in this trial.

END POINTS AND ASSESSMENTS

The primary end point was progression-free survival, which was defined as the time from randomization to objective radiologic disease progression (according to modified RECIST, version 1.1) or death from any cause. The primary analysis was based on blinded independent central review, which was performed by two main reviewers, with adjudication by a third reviewer in cases in which the two main reviewers disagreed. A prespecified sensitivity analysis was based on investigator assessment. At the time of data cutoff for the primary end point (after at least 230 events had occurred), additional data were collected for the following prespecified secondary end points: safety outcomes, overall survival, time from randomization to a second progression event or death after a first progression event (based on investigator assessment), objective response rate (based on blinded independent central review, according to modified RECIST, version 1.1), and scores for health-related quality of life.

Computed tomography or magnetic resonance imaging was performed every 6 weeks until week 24 and then every 12 weeks thereafter. Overall survival and the time to a second progression event or death after a first progression event were assessed every 8 weeks after the first progression event. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Health-related quality of life was assessed with the use of the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30), which was completed by the patient at baseline and then every 6 weeks until disease progression. Scores on the QLQ-C30 range from 0 to 100, with higher scores indicating better quality of life; an increase or decrease of at least 10 points was considered to be a clinically meaningful change.[14]

TRIAL OVERSIGHT

This trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca policy on bioethics. The trial was designed in collaboration between the principal investigator and AstraZeneca. AstraZeneca was responsible for overseeing the collection, analysis, and interpretation of the data. An external independent data and safety monitoring committee performed two interim reviews of the safety data. The manuscript was written with medical-writing support, which was funded by AstraZeneca, with critical review and input from the authors. The authors had access to the data and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol.

STATISTICAL ANALYSIS

We determined that a total of 230 progression-free survival events would give the trial 90% power (at a two-sided significance level of 5%) to show a statistically significant difference in progression-free survival between the olaparib group and the standard-therapy group, with a corresponding hazard ratio for disease progression or death of 0.635. Efficacy data were analyzed on an intention-to-treat basis, and safety was assessed in all patients who received at least one dose of the assigned treatment. The primary analysis of progression-free survival was based on blinded independent central review and was performed with the use of a stratified log-rank test. The Kaplan–Meier method was used to gen-

erate time-to-event curves, from which medians were calculated. For the primary end point, a log-rank test (stratified according to hormone-receptor status and previous use of chemotherapy) was used to compare the Kaplan–Meier curves in the two treatment groups, and the P value derived from this comparison was reported. Hazard ratios and confidence intervals were estimated from the log-rank test statistics. Progression-free survival event rates at 12 months were calculated with the use of Kaplan–Meier curves.

Exploratory sensitivity analyses were conducted. The first analysis excluded patients who did not receive the assigned treatment; the second, stratifying analyses were performed with the use of values abstracted from electronic case-report forms for randomization factors. If statistical significance was shown for progression-free survival, time to a second progression event or death after a first progression event was then compared between groups with the use of a stratified log-rank test and a hierarchical multiple-testing strategy. If statistical significance was shown for time to a second progression event or death after a first progression event, overall survival was then compared between groups with the use of a stratified log-rank test. The mean change from baseline in QLQ-C30 score across all time points was analyzed with the use of a mixed model for repeated measures. Kaplan–Meier curves were used to compare time to a clinically meaningful decrease in QLQ-C30 score between the two treatment groups, and the P value derived from this comparison was reported.

RESULTS

PATIENTS

Between April 7, 2014, and November 27, 2015, a total of 302 patients underwent randomization; 205 were assigned to the olaparib group and received the assigned treatment, and 97 were assigned to the standard-therapy group, of whom 91 received the assigned treatment (Fig. 1). (For details about the 6 patients who did not receive the assigned treatment, see the Results section in the Supplementary Appendix, available at NEJM.org.) The median age was 44 years, and baseline demographic characteristics were well balanced between the two treatment groups (Table 1). On the date of data cutoff for this analysis (December 9, 2016), 36 patients were still receiving olaparib and 3 were still receiving standard therapy. The median duration of follow-up was 14.5 months (range, 2.1 to 29.5) in the olaparib group and 14.1 months (range, 0 to 28.2) in the standard-therapy group. Data on previous neoadjuvant or adjuvant treatment or treatment for metastatic disease are shown in the Results section in the Supplementary Appendix.

EFFICACY

The primary end point was assessed after 234 of the 302 patients (77.5%) had had disease progression (assessed by blinded independent central review) or had died. At the time of this analysis, median progression-free survival was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% confidence interval [CI], 0.43 to 0.80; P<0.001) (Fig. 2A). Progression-free survival results that were based on investigator assessment were consistent with results based on blinded independent central review; on the basis of investigator assessment, median progression-free survival was 7.8 months in the olaparib group and 3.8 months in the standard-therapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.36 to 0.68; P<0.001). A sensitivity analysis that excluded the 6 patients in the standard-therapy group who did not receive the assigned treatment also yielded similar results; the hazard ratio for disease progression or death was 0.58 (95% CI, 0.43 to 0.80; P<0.001).

At 12 months, 25.9% of the patients in the olaparib group and 15.0% of the patients in the standard-therapy group were free of progression or death. Subgroup analyses of progression-free survival are shown in Figure 3. At the time of this analysis, 157 of the 302 patients (52.0%) had had a second progression event or had died after a first progression event. The median time from randomization to a second progression event or death after a first progression event was 13.2 months in the olaparib group and 9.3 months in the standard-therapy group (hazard ratio, 0.57; 95% CI, 0.40 to 0.83; P=0.003).

A total of 94 patients (45.9%) in the olaparib group and 46 patients (47.4%) in the standard-therapy group had died at the time of the primary analysis. The median time to death was 19.3 months in the olaparib group and 19.6 months in the standard-therapy group. Overall survival

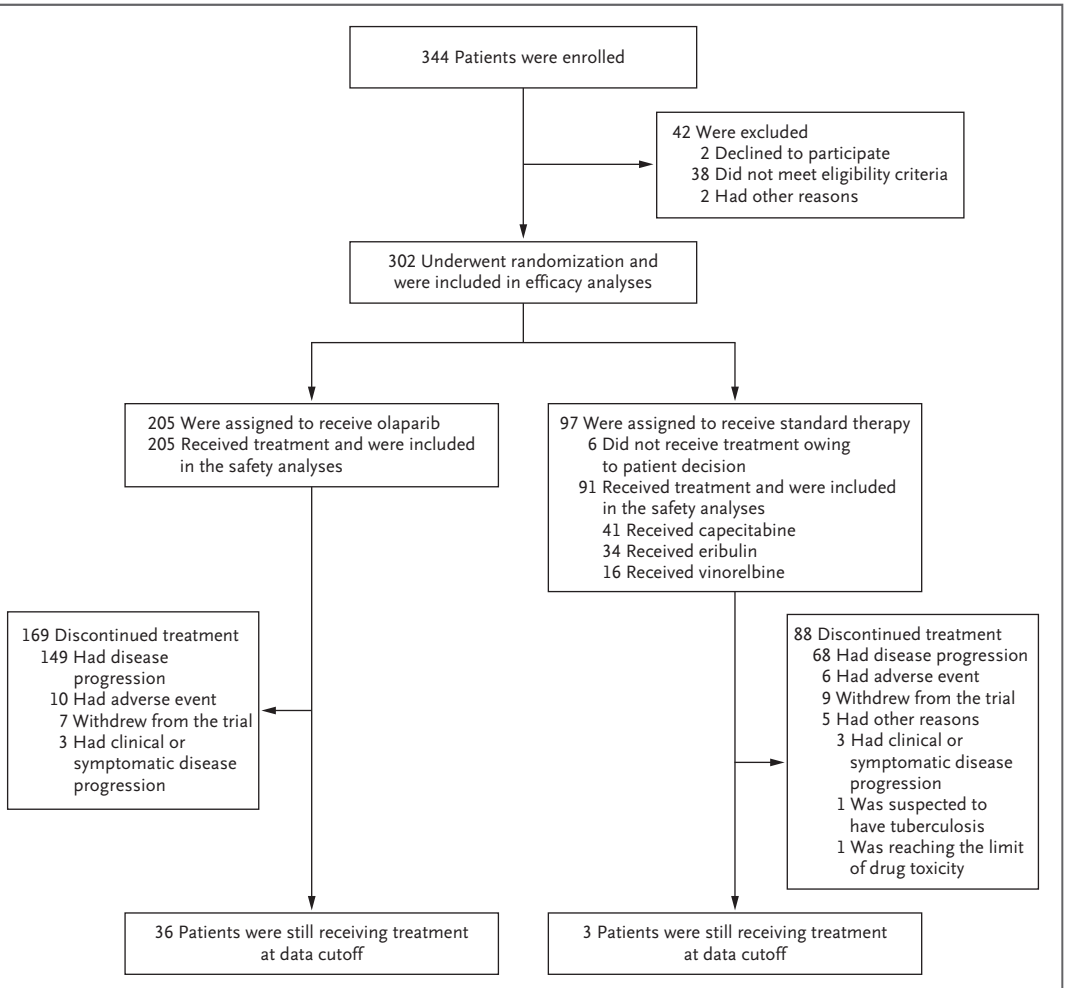

Figure 1. Enrollment, Randomization, and Treatment.
Standard therapy was a single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine).

did not differ significantly between groups (hazard ratio for death, 0.90; 95% CI, 0.63 to 1.29; P=0.57). More patients in the standard-therapy group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, or other cytotoxic chemotherapy after the first progression event (see the Results section in the Supplementary Appendix).

On the basis of blinded independent central review, a response to treatment occurred in 100 of the 167 patients who had measurable disease in the olaparib group (59.9%; 95% CI, 52.0 to 67.4) and in 19 of the 66 patients in the standard-therapy group (28.8%; 95% CI, 18.3 to 41.3). A complete response was seen in 9.0% of the patients who had measurable disease in the olaparib group and in 1.5% in the standard-therapy group. Response rates according to patient subgroup are shown in the Results section in the Supplementary Appendix. The median duration of response was 6.4 months (interquartile range, 2.8 to 9.7) in the olaparib group and 7.1 months (interquartile range, 3.2 to 12.2) in the standard-therapy group, and the median time to the onset of a response was 47 days and 45 days, respectively.

PATIENT-REPORTED OUTCOMES

The mean (±SD) score on the QLQ-C30 at baseline was 63.2±21.0 in the olaparib group and 63.3±21.2 in the standard-therapy group. The adjusted mean (±SE) change from baseline across all time points was 3.9±1.2 in the olaparib group

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Olaparib Group (N=205)	Standard-Therapy Group (N=97)
Age — yr		
Median	44	45
Range	22–76	24–68
Male sex — no. (%)	5 (2.4)	2 (2.1)
Race or ethnic group — no. (%)†		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status — no. (%)‡		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
BRCA mutation type — no. (%)§		
BRCA1	117 (57.1)	51 (52.6)
BRCA2	84 (41.0)	46 (47.4)
BRCA1 and *BRCA2*	4 (2.0)	0
Hormone-receptor status — no. (%)¶		
Hormone-receptor positive	103 (50.2)	49 (50.5)
Triple negative	102 (49.8)	48 (49.5)
New metastatic breast cancer — no. (%)	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic breast cancer — no. (%)	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer — no. (%)	60 (29.3)	26 (26.8)
≥2 Metastatic sites — no. (%)	159 (77.6)	72 (74.2)
Location of the metastasis — no. (%)		
Bone only	16 (7.8)	6 (6.2)
Other‖	189 (92.2)	91 (93.8)
Measurable disease — no. (%)	167 (81.5)	66 (68.0)

* Standard therapy was a single-agent chemotherapy of the physician's choice (capecitabine, eribulin, or vinorelbine).
† Race or ethnic group was self-reported. The other category includes black (5 patients), American Indian or Alaska Native (4), unknown (1), and declined to specify (1).
‡ Eastern Cooperative Oncology Group (ECOG) performance status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability.
§ In the majority of patients, *BRCA* mutation type was confirmed by central testing with BRACAnalysis (Myriad Genetics); in 3 patients in the olaparib group and 2 patients in the standard-therapy group, mutation type was confirmed by local testing only. Percentages may not sum to 100 because of rounding.
¶ Hormone-receptor positive disease is estrogen-receptor positive, progesterone-receptor positive, or both. Triple-negative disease is human epidermal growth factor receptor type 2 (HER2) negative, estrogen-receptor negative, and progesterone-receptor negative.
‖ Data for the other category include patients who did not have metastases in the bone, as well as patients who may have had metastases in the bone along with metastases in other locations.

(among the 191 patients who completed the questionnaire at baseline and at least once thereafter) and −3.6±2.2 in the standard-therapy group (among 73 patients), with a corresponding estimated difference of 7.5 points (95% CI, 2.5 to 12.4; P=0.004). The median time to a clinically meaningful decrease in QLQ-C30 score (≥10 points) was not reached in the olaparib group and was 15.3 months in the standard-therapy group (hazard ratio, 0.44; 95% CI, 0.25 to 0.77; P=0.004).

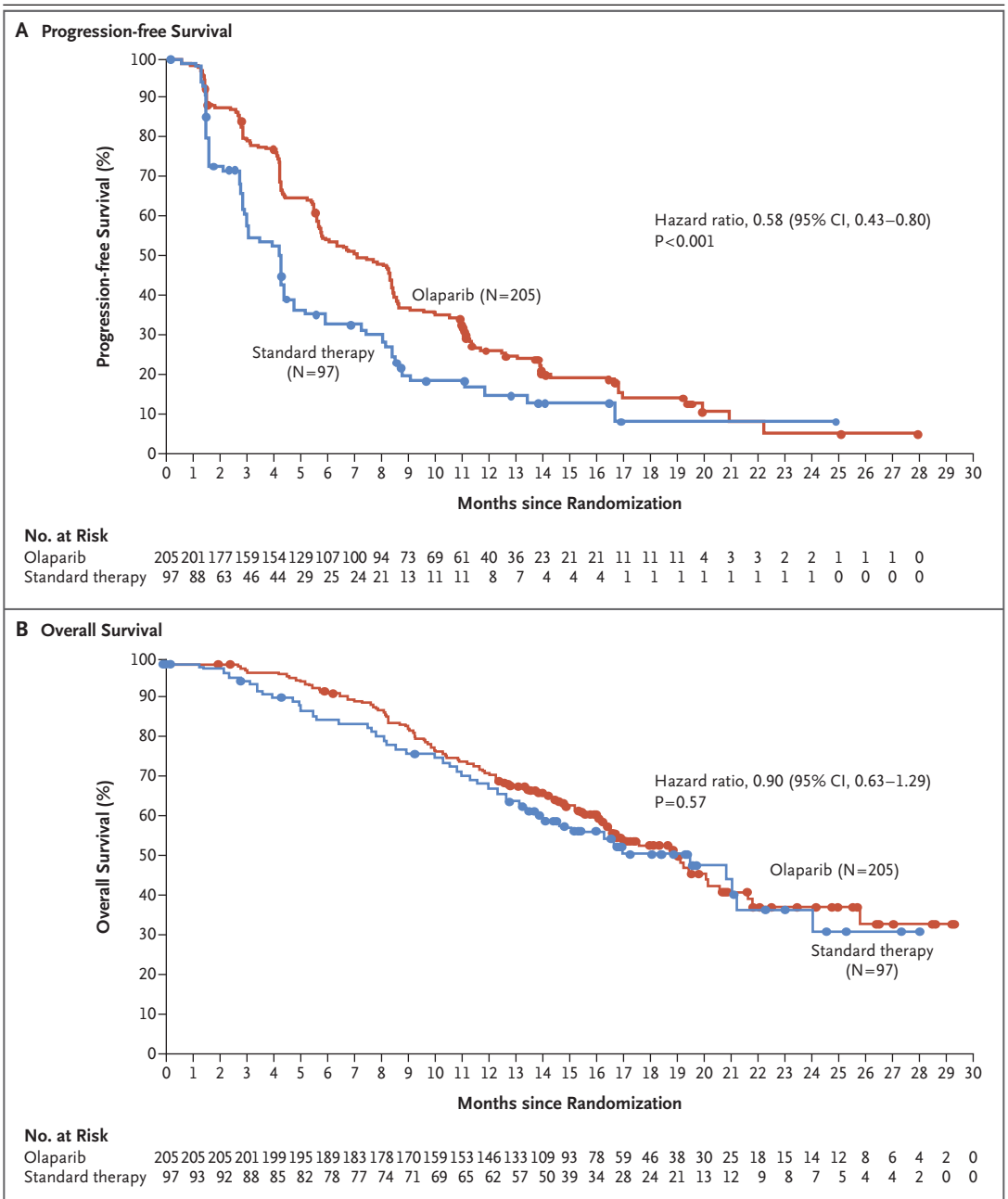

Figure 2. Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.

Panel A shows Kaplan–Meier estimates for progression-free survival (based on blinded independent central review) and Panel B shows Kaplan–Meier estimates for overall survival in the olaparib group and the standard-therapy group.

SAFETY

The median total treatment duration was 8.2 months (range, 0.5 to 28.7) in the olaparib group and 3.4 months (range, 0.7 to 23.0) in the standard-therapy group. Table 2 shows data on adverse events of any grade that occurred in at least 15% of patients in either treatment group. Anemia, nausea, vomiting, fatigue, headache, and cough occurred more frequently in the olaparib group than in the standard-therapy group; neutropenia, palmar–plantar erythrodysesthesia, and an increase in liver-function enzymes were more

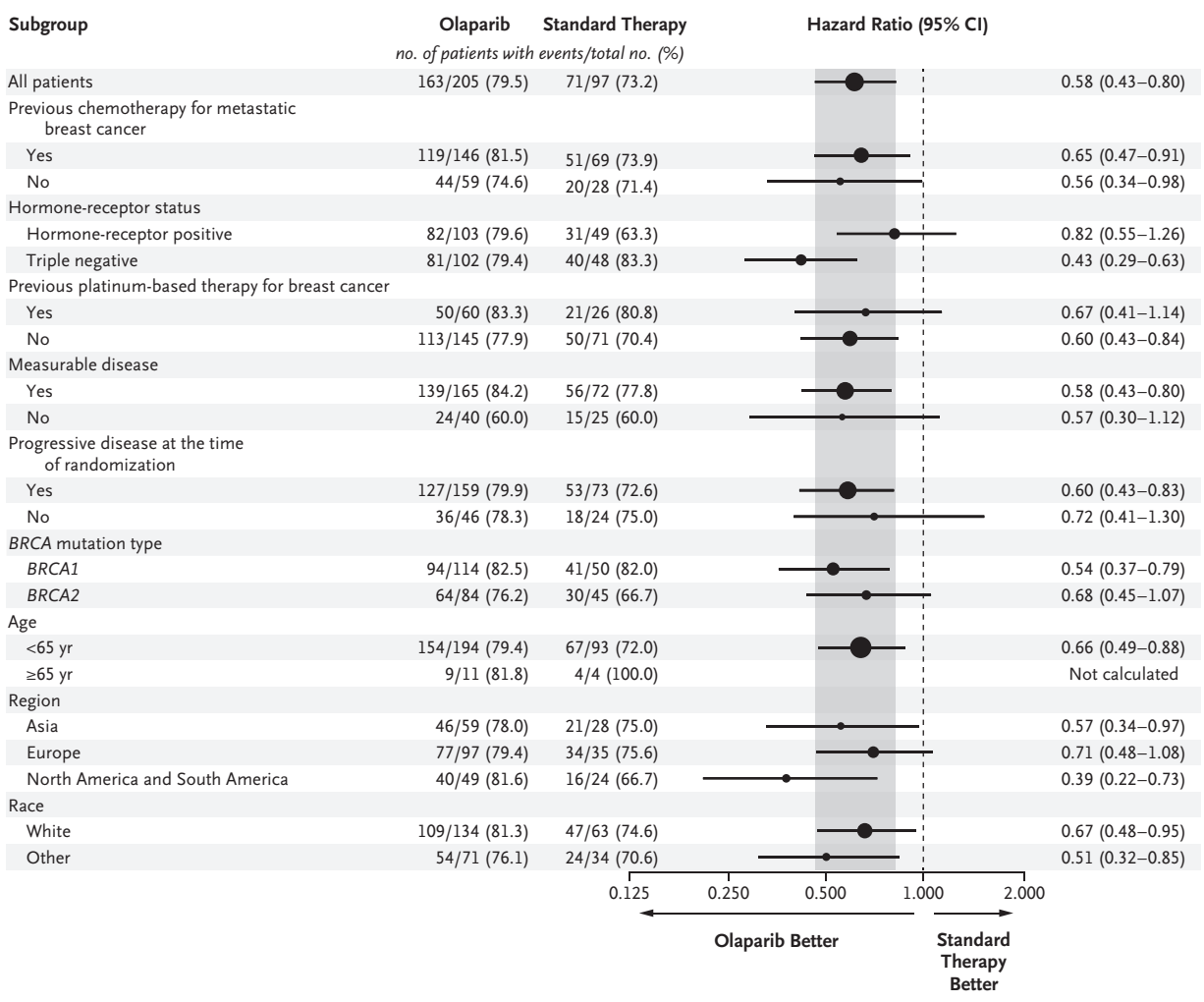

Figure 3. Subgroup Analysis of Progression-free Survival.

common in the standard-therapy group than in the olaparib group.

In the olaparib group, most adverse events were grade 1 or grade 2. The rate of grade 3 or higher adverse events was lower in the olaparib group than in the standard-therapy group (36.6% and 50.5%, respectively) (Table 2). The rates of grade 4 and grade 5 adverse events were 3.4% and 0%, respectively, in the olaparib group and 12.1% and 1.1%, respectively, in the standard-therapy group. In addition to those reported in Table 2, other grade 3 or higher adverse events that occurred in at least 2% of patients in either group were leukopenia (which occurred in 2.4% of patients in the olaparib group and 3.3% of patients in the standard-therapy group), dyspnea (1.0% and 3.3%), and a decrease in platelet count (2.4% and 1.1%).

Dose reduction was most commonly due to anemia in the olaparib group (in 13.7% of patients) and to palmar–plantar erythrodysesthesia in the standard-therapy group (7.7%). The incidence of treatment discontinuation due to anemia was similar in both groups (2.0% in the olaparib group and 2.2% in the standard-therapy group). Neutropenia led to treatment discontinuation in two patients in the standard-therapy group and in no patients in the olaparib group. Additional details on treatment exposure, dose modification, and treatment discontinuation are provided in the Results section in the Supplementary Appendix.

Table 2. Summary of Adverse Events.*

Variable	Olaparib Group (N=205)		Standard-Therapy Group (N=91)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event				
Any	199 (97.1)	75 (36.6)	88 (96.7)	46 (50.5)
Anemia†	82 (40.0)	33 (16.1)	24 (26.4)	4 (4.4)
Neutropenia‡	56 (27.3)	19 (9.3)	45 (49.5)	24 (26.4)
Decreased white-cell count	33 (16.1)	7 (3.4)	19 (20.9)	9 (9.9)
Nausea	119 (58.0)	0	32 (35.2)	1 (1.1)
Vomiting	61 (29.8)	0	14 (15.4)	1 (1.1)
Diarrhea	42 (20.5)	1 (0.5)	20 (22.0)	0
Decreased appetite	33 (16.1)	0	11 (12.1)	0
Fatigue	59 (28.8)	6 (2.9)	21 (23.1)	1 (1.1)
Headache	41 (20.0)	2 (1.0)	14 (15.4)	2 (2.2)
Pyrexia	29 (14.1)	0	16 (17.6)	0
Cough	35 (17.1)	0	6 (6.6)	0
Increased alanine aminotransferase level	23 (11.2)	3 (1.5)	16 (17.6)	1 (1.1)
Increased aspartate aminotransferase level	19 (9.3)	5 (2.4)	15 (16.5)	0
Palmar–plantar erythrodysesthesia	1 (0.5)	0	19 (20.9)	2 (2.2)
Dose reduction owing to adverse event	52 (25.4)	NA	28 (30.8)	NA
Treatment interruption or delay owing to adverse event	72 (35.1)	NA	25 (27.5)	NA
Treatment discontinuation owing to adverse event	10 (4.9)	NA	7 (7.7)	NA

* The table includes adverse events of any grade that occurred in at least 15% of patients in either treatment group and corresponding grade 3 or higher adverse events, which were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. NA denotes not applicable.
† The anemia category includes anemia, decreased hemoglobin level, decreased hematocrit, decreased red-cell count, and erythropenia.
‡ The neutropenia category includes febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count, and neutropenic infection.

Two adverse events resulted in death: one case of sepsis in the olaparib group, and one case of dyspnea in the standard-therapy group (with disease progression as a secondary cause). No cases of the myelodysplastic syndrome or acute myeloid leukemia were noted in either treatment group. In the olaparib group, one new primary cancer (melanoma in situ) occurred in a patient with a known medical history of melanoma involving the skin.

DISCUSSION

Several phase 1 and 2 studies have shown that PARP inhibitors have single-agent activity in patients with metastatic breast cancer and a germline *BRCA* mutation.[12,13,15-18] The randomized, phase 3 OlympiAD trial showed that, among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, median progression-free survival was significantly longer with oral olaparib monotherapy than with standard chemotherapy (7.0 months vs. 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80). The risk of disease progression or death was 42% lower and the median progression-free survival was 2.8 months longer with olaparib than with standard therapy. The response rate in the olaparib group was approximately double the rate in the standard-therapy group (59.9% vs. 28.8%). The median time

to the onset of a response was similar with olaparib and with standard therapy; this finding is an important consideration for symptomatic or rapidly progressing patients.

Although no significant difference in overall survival was observed between olaparib treatment and standard therapy, this trial was not powered to assess differences in overall survival between treatment groups. Analysis of overall survival is also likely to be confounded by subsequent treatment, and more patients in the standard-therapy group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy after they had disease progression while receiving the assigned treatment (see the Supplementary Appendix).

Fewer grade 3 or higher adverse events and adverse events leading to discontinuation occurred with olaparib than with standard therapy. In the olaparib group, the most common adverse event was grade 1 or 2 nausea, and the most common grade 3 or higher adverse event was anemia. The safety profile of olaparib was similar to that reported in other studies of olaparib monotherapy.[11-13] There was a small significant difference between treatment groups in the adjusted mean QLQ-C30 score across all time points,[19] and a clinically meaningful decrease in the QLQ-C30 score was delayed in the olaparib group.

This trial has some limitations. First, an open-label trial design was made necessary by the use of different treatments in the control group. Single-agent chemotherapy is widely accepted as the standard therapy for HER2-negative metastatic breast cancer after disease progression during treatment with anthracyclines, taxanes, and hormonal agents (in hormone-receptor–positive patients), but no agent is clearly preferred.[20-22] All three treatments selected for the control group constitute standard chemotherapy options for such patients.[20-22] Thus, to ensure robustness of the results of this open-label trial, the primary analysis was based on blinded independent central review for the intention-to-treat population. A second limitation of the study was the heterogeneity of the population in terms of hormonal-receptor status, previous use of chemotherapy, and previous use of platinum-based treatments. The trial was not powered to detect any differences in effect that are suggested by subgroup analyses, and thus any conclusions must be considered to be hypothesis-generating. The rationale behind the selected patient population was that a germline *BRCA* mutation would be a key determinant of the effectiveness of olaparib, despite the different clinical factors that are present in a broad patient population. Inclusion of patients with triple-negative breast cancer in this study is important, given the limited treatment options for these patients after anthracyclines and taxanes.[23]

Patients could have received platinum for metastatic disease if they had not had progression during treatment, and a small proportion of patients had received adjuvant or neoadjuvant platinum at least 12 months earlier. Although it is encouraging that efficacy was seen in patients with platinum exposure, the trial did not allow for the assessment of olaparib in truly platinum-resistant disease. Since platinum agents were not included as treatment options in the control group, the trial cannot address the relative benefits of olaparib and platinum-based chemotherapy in patients with breast cancer and a germline *BRCA* mutation. It is worth noting, however, that the response rate of 59.9% and the median progression-free survival of 7.0 months that were observed with first-, second-, or third-line olaparib in this trial are similar to the response rate of 68.0% and the median progression-free survival of 6.8 months that were observed with first-line single-agent carboplatin in a similar population.[24] In contrast, in a randomized, phase 2 study of veliparib or placebo in combination with carboplatin and paclitaxel, median progression-free survival was 12.3 to 14.1 months, and no significant improvement resulted from the addition of the PARP inhibitor.[18] Patients in that study were not required to have previously received anthracycline and taxane treatment. Substantially more grade 3 or higher toxic effects were observed in both studies of platinum-based therapy than in the OlympiAD trial.[18,24] Larger studies that investigate the differential treatment effects of olaparib among subgroups, particularly those defined according to hormone-receptor status or previous use of platinum-based therapy, would be helpful, as would a head-to-head study to determine the relative efficacy of olaparib and platinum-based chemotherapy.

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