ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

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ABSTRACT

BACKGROUND

The poly(adenosine diphosphate–ribose) inhibitor talazoparib has shown antitumor activity in patients with advanced breast cancer and germline mutations in *BRCA1* and *BRCA2* (*BRCA1/2*).

METHODS

We conducted a randomized, open-label, phase 3 trial in which patients with advanced breast cancer and a germline *BRCA1/2* mutation were assigned, in a 2:1 ratio, to receive talazoparib (1 mg once daily) or standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine in continuous 21-day cycles). The primary end point was progression-free survival, which was assessed by blinded independent central review.

RESULTS

Of the 431 patients who underwent randomization, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy. Median progression-free survival was significantly longer in the talazoparib group than in the standard-therapy group (8.6 months vs. 5.6 months; hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.41 to 0.71; P<0.001). The interim median hazard ratio for death was 0.76 (95% CI, 0.55 to 1.06; P=0.11 [57% of projected events]). The objective response rate was higher in the talazoparib group than in the standard-therapy group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; P<0.001). Hematologic grade 3–4 adverse events (primarily anemia) occurred in 55% of the patients who received talazoparib and in 38% of the patients who received standard therapy; nonhematologic grade 3 adverse events occurred in 32% and 38% of the patients, respectively. Patient-reported outcomes favored talazoparib; significant overall improvements and significant delays in the time to clinically meaningful deterioration according to both the global health status–quality-of-life and breast symptoms scales were observed.

CONCLUSIONS

Among patients with advanced breast cancer and a germline *BRCA1/2* mutation, single-agent talazoparib provided a significant benefit over standard chemotherapy with respect to progression-free survival. Patient-reported outcomes were superior with talazoparib. (Funded by Medivation [Pfizer]; EMBRACA ClinicalTrials.gov number, NCT01945775.)

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Cancer cells with deleterious mutations in breast cancer susceptibility genes 1 or 2 (*BRCA1/2*) are deficient in the repair mechanism for DNA double-strand breaks, leaving these tumors highly dependent on the repair pathway for single-strand breaks. This pathway is regulated by the enzyme poly(adenosine diphosphate–ribose) polymerase (PARP).[1-3] In cells with a *BRCA1/2* mutation, inhibition of PARP causes cell death due to accumulation of irreparable DNA damage.[1-3] In addition to catalytic inhibition, PARP inhibitors induce PARP trapping at sites of DNA damage. The capacity to trap PARP–DNA complexes varies among PARP inhibitors and is not correlated with PARP catalytic inhibition.[4-7] Preclinical models have indicated that trapping PARP on DNA may be more effective in inducing cancer-cell death than enzymatic inhibition alone.[4-7] Preclinically, talazoparib has been shown to be a potent PARP inhibitor, with both strong catalytic inhibition (half-maximal inhibitory concentration, 4 nM) and a PARP-trapping potential that is approximately 100 times greater than that of other PARP inhibitors currently under investigation.[5]

In a phase 1 trial, talazoparib monotherapy (at a dose of 1 mg once daily) resulted in a 50% response rate and an 86% clinical benefit rate at 24 weeks among 18 patients with advanced breast cancer and a germline *BRCA1/2* mutation.[8] The most common adverse events related to talazoparib were anemia, thrombocytopenia, and mild-to-moderate fatigue.[8]

In the phase 2 ABRAZO study (ClinicalTrials.gov number, NCT02034916), talazoparib also had single-agent activity in two cohorts of patients with metastatic breast cancer and a germline *BRCA1/2* mutation. The response rate was 21% among patients who had previously had a response to platinum chemotherapy and 37% among patients who had previously received three or more cytotoxic regimens for advanced breast cancer without previous exposure to platinum agents.[9]

Our phase 3 trial (EMBRACA) compared the efficacy and safety of talazoparib with standard chemotherapy of the physician's choice for the treatment of locally advanced or metastatic breast cancer in patients with a germline *BRCA1/2* mutation.

Methods

Patients

Eligible patients were at least 18 years of age and had either locally advanced breast cancer that had not been amenable to curative therapy or metastatic breast cancer. Patients had a deleterious or suspected deleterious germline *BRCA1/2* mutation detected by central testing with BRACAnalysis (Myriad Genetics). Patients had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane, an anthracycline, or both, unless this treatment was contraindicated. Previous neoadjuvant or adjuvant platinum-based therapy was permitted, provided the patient had had a disease-free interval of at least 6 months after the last dose; patients were excluded if they had objective disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., the patient could not have had progressive disease according to Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, within approximately 8 weeks after the last dose).

There was no limit on the number of previous hormone therapies received by patients with hormone-receptor–positive breast cancer. Patients with central nervous system (CNS) metastases were eligible provided they had completed definitive local therapy, had stable CNS lesions on repeat brain imaging, and were receiving low-dose or no glucocorticoids.

Additional eligibility criteria are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial protocol (available at NEJM.org) was approved by an independent ethics committee at each site before initiation of the trial, and all enrolled patients provided written informed consent.

Trial Design and Oversight

The EMBRACA trial was an open-label, randomized, international, phase 3 trial comparing the efficacy and safety of talazoparib with a protocol-specified single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine). Patients with advanced breast cancer underwent randomization in a 2:1 ratio (Fig. S1 in the Supplementary Appendix). Patients under-

went central randomization with stratification according to the number of previous cytotoxic chemotherapy regimens for advanced disease received (0 vs. 1 to 3), hormone-receptor status (triple negative vs. hormone-receptor positive), and a history of CNS metastases (yes or no). Patients with human epidermal growth factor receptor type 2–positive breast cancer were not eligible for this trial.

Patients who received talazoparib received a dose of 1 mg orally once daily continuously, with or without food. Laboratory values were monitored every 3 weeks, and decisions to withhold doses and dose reductions were made as outlined in the Methods section of the Supplementary Appendix.

The standard-therapy group received protocol-specified chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) in continuous 21-day cycles, in accordance with the institution's dose and regimen guidelines. The choice of standard-therapy drug for each patient was determined before randomization.

Treatment continued until disease progression, unacceptable toxic effects, or withdrawal of consent occurred, or unless the physician decided to end treatment. Crossover from the standard-therapy group to the talazoparib group was not permitted.

Four academic authors and one employee of the sponsor designed this phase 3 trial in collaboration with the trial sponsor (Pfizer). Local site investigators recruited patients, contributed to patient care, and collected patient data, which were analyzed by the sponsor. Three of the authors, one of whom was an employee of the sponsor, guided the initial drafting of the manuscript with medical-writing support that was funded by the sponsor and with input from all other authors. Three authors who were employees of the sponsor contributed to the data analysis and the reporting and review of the data and the manuscript. All authors had full access to the trial data after the primary analysis was conducted, contributed to the revision and approval of the manuscript, and participated in the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and analyses and for adherence of the trial conduct to the trial protocol.

END POINTS AND TRIAL ASSESSMENTS

The primary end point was radiologic progression–free survival, as determined by blinded independent central review (according to RECIST, version 1.1). Progression-free survival was defined as the time from randomization to the date of first documented radiologic progression according to RECIST or the date of death from any cause, whichever occurred first. Patients underwent imaging (computed tomography, magnetic resonance imaging, and nuclear-medicine bone imaging) at baseline, every 6 weeks until week 30, and then every 9 weeks, with head imaging repeated during the trial as clinically indicated and bone imaging every 12 weeks after week 30. All tumor imaging was centrally reviewed by two radiologists, with an adjudication assessment in case of disagreement regarding progression, according to the central imaging charter.

Secondary efficacy end points included overall survival, the objective response rate, the clinical benefit rate at 24 weeks (defined as the rate of complete response, partial response, or stable disease at 24 weeks or more), and the duration of response. After discontinuation of the trial treatment, patients were followed every 12 weeks for survival and use of anticancer therapy after the trial.

Safety was assessed according to adverse events, use of concomitant medications, and clinically relevant changes in laboratory values. Adverse events were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Patient-reported outcomes were measured with the use of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and the breast cancer–specific QLQ-BR23 at baseline, the beginning of each treatment cycle, and the end of treatment as supportive prespecified exploratory end points (additional details are provided in the statistical analysis plan, version 4.0, in the Supplementary Appendix). The EORTC QLQ-C30 is a 30-item questionnaire composed of five multiple-item functional subscales, three multiple-item symptom scales, a global health status–quality-of-life subscale, and six single-item symptom scales assessing other cancer-related symptoms.

The questionnaire includes 4-point Likert scales with responses from "not at all" (reflecting a good outcome) to "very much" (reflecting a poor outcome) to assess functioning and symptoms and two 7-point Likert scales for the global health status–quality-of-life scale (with higher scores indicating a better outcome). The EORTC QLQ-BR23 is a 23-item breast cancer–specific companion module to the EORTC QLQ-C30 that consists of four functional scales and four symptom scales. On all scales, responses to all items are converted to a 0-to-100 scale with a standard scoring algorithm. For functional and global health status–quality-of-life scales, higher scores indicate a better level of functioning and quality of life. For symptom scales, a higher score indicates greater symptom severity. Hence, a negative change from baseline in symptom scales reflects an improvement, and a positive change reflects a deterioration. Conversely, a negative change from baseline in functional and global health status–quality-of-life scales reflects a deterioration, and a positive change reflects an improvement. Blood and tumor samples were collected at baseline and blood samples were collected on disease progression in order to identify additional biologic markers that might indicate potential sensitivity or resistance to talazoparib.

STATISTICAL ANALYSIS

We determined that a total of 288 events of disease progression or death following the enrollment of 429 patients would give the trial 90% power (at a two-sided alpha level of 5%) to show a significant difference in progression-free survival between the talazoparib group and the standard-therapy group, with a targeted hazard ratio for disease progression or death of 0.67. To maintain the overall two-sided type I error rate of 5%, the analyses for the primary end point (progression-free survival) and the key secondary end point (overall survival) were protected under a multiplicity-adjustment schema with the use of a gatekeeping method. Additional details of the multiplicity-adjustment method are described in the statistical analysis plan, version 4.0, in the Supplementary Appendix.

Efficacy analyses were performed in the intention-to-treat population. Progression-free survival was analyzed with the use of a stratified log-rank test (with the use of randomization factors) and summarized with the use of Kaplan–Meier methods. We estimated stratified hazard ratios with two-sided 95% confidence intervals using a stratified Cox proportional-hazards model, with randomization factors. Subgroup analyses were performed and are detailed in the Methods section in the Supplementary Appendix.[10,11] Prespecified patient-reported outcome analyses included the overall mean change from baseline (estimated with the use of the longitudinal mixed-effects model) and the time to clinically meaningful deterioration (analyzed with the use of a stratified log-rank test, summarized with the use of Kaplan–Meier methods). The time to clinically meaningful deterioration according to the global health status–quality-of-life scale was defined as the time from randomization to the first observation with a decrease of 10 points or more and no subsequent observations with a decrease of less than 10 points from baseline; the time to deterioration according to the breast symptoms scale on the breast cancer–specific QLQ-BR23 was defined as the time from randomization to the first observation with an increase of 10 points or more and no subsequent observations with an increase of less than 10 points from baseline.[12]

RESULTS

PATIENTS

Between October 2013 and April 2017, patients underwent randomization at 145 sites in 16 countries. A total of 431 patients were included in the intention-to-treat population. Of these patients, 287 were assigned to receive talazoparib and 144 were assigned to receive standard therapy (capecitabine [44%], eribulin [40%], gemcitabine [10%], and vinorelbine [7%]; percentages total >100% because of rounding). Eighteen patients who were randomly assigned to standard therapy and 1 patient in the talazoparib group withdrew consent without receiving treatment (Fig. S2 in the Supplementary Appendix). Baseline characteristics of the patients are shown in Table 1. The data cutoff date was September 15, 2017.

EFFICACY

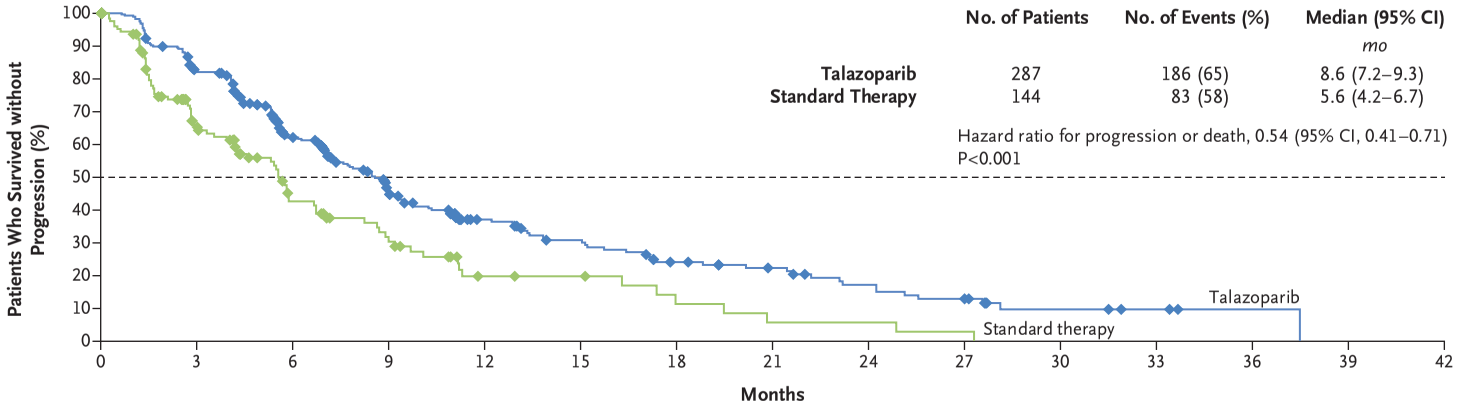
We calculated that the median duration of follow-up for progression-free survival was 11.2 months on the basis of the reverse Kaplan–Meier estimator of progression-free survival. The primary end

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Talazoparib Group (N = 287)	Standard-Therapy Group (N = 144)
Age — yr		
Median	45	50
Range	27.0–84.0	24.0–88.0
Age <50 yr — no. (%)	182 (63.4)	67 (46.5)
Female sex — %	98.6	97.9
ECOG performance status score — %†		
0	53.3	58.3
1	44.3	39.6
2	2.1	1.4
Breast cancer stage — no. (%)‡		
Locally advanced	15 (5.2)	9 (6.2)
Metastatic	271 (94.4)	135 (93.8)
Measurable disease assessed by investigator — no. (%)	219 (76.3)	114 (79.2)
History of CNS metastases — no. (%)	43 (15.0)	20 (13.9)
Visceral disease — no. (%)	200 (69.7)	103 (71.5)
Hormone-receptor status — no. (%)		
Triple-negative	130 (45.3)	60 (41.7)
Hormone-receptor–positive	157 (54.7)	84 (58.3)
BRCA status — no. (%)§		
BRCA1-positive	133 (46.3)	63 (43.8)
BRCA2-positive	154 (53.7)	81 (56.2)
<12-mo disease-free interval from initial diagnosis to advanced breast cancer — no. (%)	108 (37.6)	42 (29.2)
Previous adjuvant or neoadjuvant therapy — no. (%)	238 (82.9)	121 (84.0)
No. of previous hormone-therapy–based regimens for hormone-receptor–positive breast cancer in the talazoparib group (157 patients) and the standard-therapy group (84 patients)		
Median	2.0	2.0
Range	0–6	0–6
Previous platinum therapy — no. (%)	46 (16.0)	30 (20.8)
Previous cytotoxic regimens for advanced breast cancer — no. (%)		
0	111 (38.7)	54 (37.5)
1	107 (37.3)	54 (37.5)
2	57 (19.9)	28 (19.4)
3	12 (4.2)	8 (5.6)

* Standard therapy was a single-agent chemotherapy of the physician's choice. Percentages may not total 100 because of rounding. *BRCA* denotes breast cancer susceptibility gene, and CNS central nervous system.
† 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.
‡ Data were missing for one patient in the talazoparib group.
§ Only 10 patients (6 patients in the talazoparib group and 4 patients in the standard-therapy group) were identified as having a suspected deleterious mutation. The remainder who underwent central testing with BRACAnalysis had a known pathogenic variation.

A Progression-free Survival



	No. of Patients	No. of Events (%)	Median (95% CI)
			mo
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard Therapy	144	83 (58)	5.6 (4.2–6.7)

Hazard ratio for progression or death, 0.54 (95% CI, 0.41–0.71)
P<0.001

No. at Risk (events/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
Standard therapy	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

B Progression-free Survival, According to Subgroup

Subgroup	No. of Patients (%)	Hazard Ratio for Disease Progression or Death (95% CI)
All patients	431 (100)	0.54 (0.41–0.71)
BRCA1 mutation type, according to central testing		
BRCA1	183 (42.5)	0.59 (0.39–0.90)
BRCA2	225 (52.2)	0.47 (0.32–0.70)
Hormone-receptor status according to most recent biopsy		
Triple-negative breast cancer	190 (44.1)	0.60 (0.41–0.87)
Hormone-receptor positive	241 (55.9)	0.47 (0.32–0.71)
History of CNS metastasis		
Yes	63 (14.6)	0.32 (0.15–0.68)
No	368 (85.4)	0.58 (0.43–0.78)
Visceral disease assessed by investigator		
Yes	303 (70.3)	0.51 (0.37–0.70)
No	128 (29.7)	0.59 (0.34–1.02)
Previous platinum treatment		
Yes	76 (17.6)	0.76 (0.40–1.45)
No	355 (82.4)	0.52 (0.39–0.71)
Previous regimens of cytotoxic chemotherapy for advanced breast cancer		
0	165 (38.3)	0.57 (0.34–0.95)
1	161 (37.4)	0.51 (0.33–0.80)
≥2	105 (24.4)	0.56 (0.34–0.95)

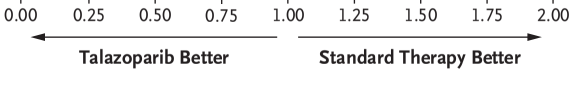


Figure 1 (facing page). Progression-free Survival among All Patients and According to Subgroup.
Panel A shows progression-free survival among patients in the talazoparib and standard-therapy groups, as assessed by blinded independent central review. Panel B shows the subgroup analysis of progression-free survival. The dashed vertical line represents the overall treatment effect in all patients. Percentages may not total 100 because of rounding. *BRCA1* denotes breast cancer susceptibility gene 1, *BRCA2* breast cancer susceptibility gene 2, and CI confidence interval.

point (radiologic progression-free survival) was assessed after 269 progression events or deaths were confirmed by blinded independent central review. The median progression-free survival among patients in the talazoparib group was longer than that among patients in the standard-therapy group (8.6 months [95% confidence interval {CI}, 7.2 to 9.3] vs. 5.6 months [95% CI, 4.2 to 6.7]; hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; P<0.001) (Fig. 1A). A total of 37% of the patients in the talazoparib group and 20% of the patients in the standard-therapy group did not have disease progression or death at 1 year, as determined by independent review. The hazard ratio for disease progression or death that was determined by investigator assessment was identical to the hazard ratio that was determined by independent review (0.54 [95% CI, 0.42 to 0.69]).

A subgroup analysis of progression-free survival in the talazoparib group and the standard-therapy group is provided in Figure 1B. In all clinically relevant subgroups, the risk of disease progression was lower in the talazoparib group than in the standard-therapy group, with previous use of platinum agents resulting in the only 95% confidence interval with an upper bound exceeding 1.0.

At the time of the primary analysis, 163 patients had died (108 in the talazoparib group and 55 in the standard-therapy group). The median overall survival at the interim analysis was 22.3 months (95% CI, 18.1 to 26.2) in the talazoparib group and 19.5 months (95% CI, 16.3 to 22.4) in the standard-therapy group (hazard ratio for death, 0.76; 95% CI, 0.55 to 1.06, P=0.11) (Fig. 2). Anticancer therapy after the trial was received by 62% of the patients in the talazoparib group and 68% of the patients in the standard-therapy group. The use of platinum therapy was similar in the two groups (approximately one third of the patients received either carboplatin or cisplatin after the trial); however, the percentage of patients who received a PARP inhibitor after the trial was higher in the standard-therapy group (18% vs. <1%).

The response rate determined by the investigators was 62.6% (95% CI, 55.8 to 69.0) among patients who received talazoparib and 27.2% (95% CI, 19.3 to 36.3) among those who received standard therapy. A total of 5.5% of patients in the talazoparib group had a complete response, as compared with no patients in the standard-therapy group (Table 2). The median time to response was 2.6 months in the talazoparib group and 1.7 months in the standard-therapy group (Fig. S6 in the Supplementary Appendix). The response rate according to subgroup is provided in Table S2 in the Supplementary Appendix.

The clinical benefit rate at 24 weeks was 68.6% (95% CI, 62.9 to 74.0) in the talazoparib group, as compared with 36.1% (95% CI, 28.3 to 44.5) in the standard-therapy group (Table 2). The median duration of response was 5.4 months among patients who received talazoparib, as compared with 3.1 months among those who received standard therapy (Table 2, and Fig. S3 in the Supplementary Appendix).

SAFETY

A summary of adverse events is shown in Table 3. Common adverse events included anemia, fatigue, and nausea in the talazoparib group and nausea, fatigue, and neutropenia in the standard-therapy group (Table S3 in the Supplementary Appendix). Grade 3 or 4 hematologic adverse events occurred in 55% of the patients in the talazoparib group and in 38% of the patients in the standard-therapy group, whereas grade 3 nonhematologic adverse events occurred in 32% of patients in the talazoparib group and in 38% of patients in the standard-therapy group. The majority of nonhematologic adverse events in the talazoparib group were grade 1 in severity.

Adverse events resulting in discontinuation of the drug occurred in 5.9% of patients who received talazoparib and in 8.7% of patients who received chemotherapy. Adverse events resulting in dose modification (reduction or interruption) occurred in 66% of patients who received talazoparib and 60% of patients who received chemotherapy. The most common adverse events leading

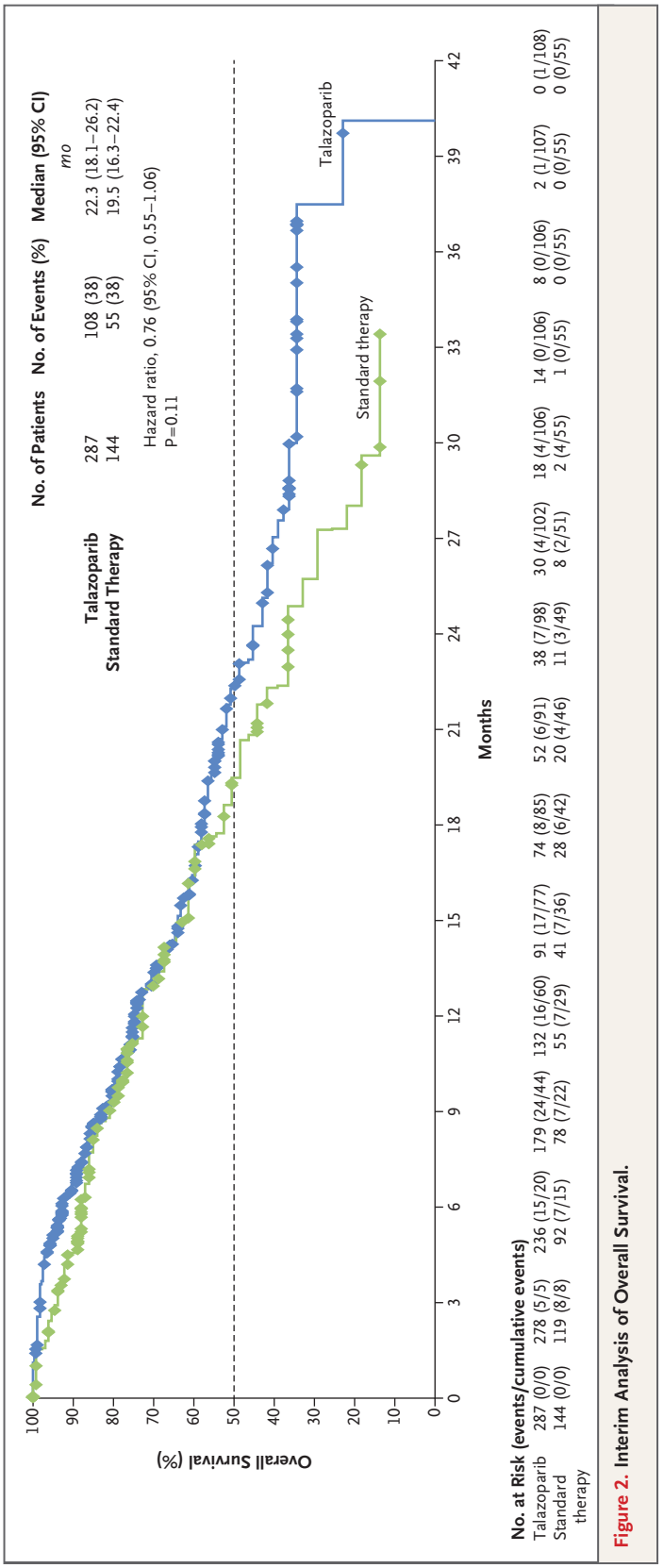


Figure 2. Interim Analysis of Overall Survival.

to dose modification were anemia, neutropenia, and thrombocytopenia in the talazoparib group and neutropenia, palmar–plantar erythrodysesthesia, nausea, and diarrhea in the standard-therapy group. An analysis of dose modification over time involving patients who had at least one hematologic adverse event was performed; this analysis reviewed dose modifications at months 1, 2, 3, 4 to 6, and 7 to 12, and at more than 12 months. By months 4 to 6 after the first dose of talazoparib, approximately half the patients had had at least one dose interruption or dose reduction (Table S4 in the Supplementary Appendix).

Serious adverse events related to the trial drug were reported in 9% of patients in both the talazoparib and standard-therapy groups, with anemia being the most common in the talazoparib group and neutropenia the most common in the standard-therapy group. One case of acute myeloid leukemia occurred in a 59-year-old female patient in the standard-therapy group who received capecitabine. She underwent randomization on August 26, 2014, and received a diagnosis of acute promyelocytic leukemia on March 12, 2015. She had received a diagnosis of breast cancer in 1993, had relapses in 2007, 2010, and 2014, and had received multiple courses of radiation therapy and chemotherapy. One drug-related death was observed in each group: one patient in the talazoparib group had veno-occlusive disease that was diagnosed by the trial site investigator and noted on imaging without biopsy evidence or classic signs, and one patient in the standard-therapy group had sepsis. No clinically significant cardiovascular toxicity was observed. Hepatic toxicity was more common in the standard-therapy group than in the talazoparib group (20% vs. 9%).

PATIENT-REPORTED OUTCOMES

A significant improvement in the estimated overall mean change from baseline in the global health status–quality-of-life scale on the EORTC QLQ-C30 was documented in the talazoparib group, as compared with a significant deterioration in the standard-therapy group (3.0 [95% CI, 1.2 to 4.8] vs. −5.4 [95% CI, −8.8 to −2.0]; P<0.001). As compared with standard therapy, treatment with talazoparib resulted in a significant delay in the onset of clinically meaningful deterioration according to the global health status–quality-of-life scale (Fig. S4 in the Supplementary Appendix). In addition, there was a significant improve-

Table 2. Secondary and Exploratory Efficacy End Points.

Variable	Talazoparib Group (N=219)	Standard-Therapy Group (N=114)	Odds Ratio (95% CI)	P Value*
	number (percent)			
Best overall response among patients with measurable disease — no. (%)†				
Complete response	12 (5.5)	0	—	—
Partial response	125 (57.1)	31 (27.2)	—	—
Stable disease	46 (21.0)	36 (31.6)	—	—
Could not be evaluated	4 (1.8)	19 (16.7)	—	—
Investigator-assessed overall objective response among patients with measurable disease — % of patients (95% CI)†	62.6 (55.8–69.0)	27.2 (19.3–36.3)	5.0 (2.9–8.8)	<0.001
Clinical benefit rate at 24 wk in intention-to-treat population				
Patients with clinical benefit — no./total no.	197/287	52/144	—	—
Percent of patients (95% CI)	68.6 (62.9–74.0)	36.1 (28.3–44.5)	4.3 (2.7–6.8)	<0.001
Investigator-assessed response in subgroup of patients with objective response				
No. with response	137	31	—	—
Median duration of response — mo	5.4	3.1	—	—
Interquartile range	2.8–11.2	2.4–6.7	—	—

* The P value was calculated with the use of the stratified Cochran–Mantel–Haenszel method. Stratification factors were the number of previous cytotoxic chemotherapy regimens, triple-negative status, and history of central nervous system metastases.
† According to Response Evaluation Criteria in Solid Tumors, version 1.1, confirmation of complete response or partial response was not required.

ment in the estimated overall mean change from baseline in the scale for breast symptoms (EORTC QLQ-BR23) in the talazoparib group, as compared with a nonsignificant change in the standard-therapy group (–5.1 [95% CI, –6.7 to –3.5] vs. –0.1 [95% CI, –2.9 to 2.6]; P=0.002). As compared with standard therapy, treatment with talazoparib resulted in a significant delay in the onset of clinically meaningful deterioration according to the breast symptoms scale (Fig. S5 in the Supplementary Appendix).

DISCUSSION

The EMBRACA trial was a controlled, phase 3 clinical trial involving patients with advanced breast cancer that expresses a germline *BRCA1/2* mutation. This trial compared a PARP inhibitor, talazoparib, with chemotherapy. The risk of disease progression or death, as assessed by blinded central review, was 46% lower in the talazoparib group than in the standard-therapy group (hazard

Table 3. Summary of Adverse Events.*

Adverse Event	Talazoparib Group (N=286)	Standard-Therapy Group (N=126)
	number of patients (percent)	
Any adverse event	282 (98.6)	123 (97.6)
Serious adverse event†	91 (31.8)	37 (29.4)
Serious and drug-related adverse event	26 (9.1)	11 (8.7)
Grade 3 or 4 serious adverse event	73 (25.5)	32 (25.4)
Adverse event resulting in permanent drug discontinuation	17 (5.9)	11 (8.7)

* Adverse-event grades were evaluated with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Patients with multiple adverse events were counted once for each preferred term, system organ class, and overall. Data on adverse events leading to permanent discontinuation of a trial drug were obtained from the adverse-event electronic case report form.
† A serious adverse event was defined as any adverse event that resulted in death, was considered to be life-threatening or medically important, resulted in hospitalization or prolongation of existing hospitalization, or resulted in persistent or clinically significant disability or incapacity or a congenital anomaly or birth defect.

ratio, 0.54; 95% CI, 0.41 to 0.71), with a doubling of the response rate (62.6% in the talazoparib group vs. 27.2% in the standard-therapy group). All clinically relevant subgroups in the analysis of progression-free survival favored talazoparib.

All secondary efficacy end points favored talazoparib over standard therapy, including the response rate and duration of response. Time-to-event end points (progression-free and overall survival, duration of response, and time to clinically meaningful deterioration according to the global health status–quality-of-life and breast symptoms scales) were all superior with talazoparib. A subgroup of patients had long-lasting responses to talazoparib that were not seen with standard therapy. Correlative studies of archival tumor and blood specimens are under way to assess whether a biologic signature can predict these exceptional responses. This trial was prospectively designed to detect an improvement in overall survival; interim survival data are promising, although survival data are immature. These data are encouraging given that approximately one third of the patients received subsequent platinum therapy (in both groups), and 18% of the patients received a subsequent PARP inhibitor (in the standard-therapy group).

In the OlympiAD trial, olaparib was also associated with longer progression-free survival than standard therapy (hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80).[13] Baseline characteristics differed in the trial populations: the EMBRACA trial included patients with locally advanced breast cancer and had a lower proportion of patients with an Eastern Cooperative Oncology Group performance status of 0 (53.3% of the patients in the EMBRACA trial vs. 72.2% of the patients in the OlympiAD trial).

It is important to note both the qualitative and quantitative differences in safety between talazoparib and standard chemotherapy for the treatment of patients with breast cancer. Most grade 3–4 toxic effects associated with the use of talazoparib were hematologic laboratory abnormalities, were not associated with substantial clinical sequelae, and did not result in drug discontinuation. In both the patient-reported global health status–quality-of-life and the breast symptoms scales, significant overall improvements and significant delays in the times to clinically meaningful deterioration were noted. We are highlighting an improvement in progression-free survival of only 3 months. Much more progress is needed.

One limitation of this phase 3 trial is the open-label design, necessitated by the mix of oral and intravenous treatment options in the standard-therapy group. Eighteen patients in the standard-therapy group (as compared with one patient in the talazoparib group) withdrew consent before receiving the first dose of trial drug; this led to censoring of data for the primary efficacy end point. Of note, many of these patients consented to be followed for overall survival; all received further anticancer therapy (including agents that were received by patients in the standard-therapy group). To ensure the robustness of the results of this open-label trial, the primary analysis was based on blinded independent central review of data in the intention-to-treat population.

Several studies have evaluated the use of platinum agents in patients with germline *BRCA* mutations.[14,15] Byrski et al. reported a response rate of 80% among 20 patients with a *BRCA1* mutation who received cisplatin.[14] The results of the Triple Negative Breast Cancer Trial, reported during the course of the EMBRACA trial, showed an objective response rate of 68% with carboplatin versus 33% with docetaxel among 43 patients with metastatic triple-negative breast cancer and a known *BRCA* mutation.[15] The EMBRACA trial permitted the use of platinum-based agents before the trial (which occurred in approximately 20% of the patients) as long as patients had no objective disease progression while receiving platinum therapy for advanced disease or relapse within 6 months while receiving neoadjuvant or adjuvant platinum therapy. Approximately one third of the patients received platinum-based agents after the trial. The failure to include platinum-based agents as an option in the standard-therapy group is a limitation of this trial, and data from a head-to-head comparison of a PARP inhibitor with platinum therapy to understand the relative efficacy, toxicity, and effects on patient-reported outcomes are lacking. In addition, the EMBRACA trial did not evaluate the sequencing of PARP and platinum-based drugs after disease progression with the use of either agent. Studies to compare platinum-based agents with PARP inhibitors and to compare the response rates after progression among classes of inhibitors are lacking.

In conclusion, talazoparib resulted in a significantly longer progression-free survival than standard-of-care chemotherapy. Treatment-associated myelotoxicity was managed by dose modifications or delays. Improvements in patient-reported outcomes indicated that talazoparib had a good side-effect profile.

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