A Phase II Study of Talazoparib After Platinum or Cytotoxic Nonplatinum Regimens in Patients With Advanced Breast Cancer and Germline *BRCA1/2* Mutations (ABRAZO)

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Translational Relevance

In this study we report that talazoparib demonstrates encouraging efficacy in *BRCA*-mutated advanced breast cancer, both in patients whose cancer responded to prior platinum therapy (cohort 1) and patients who had received at least three prior nonplatinum cytotoxic chemotherapy regimens for advanced disease (cohort 2). Adverse events were primarily mild to moderate in severity. In cohort 1, a longer platinum-free interval was associated with increased efficacy (defined by objective response rate and progression-free survival) with talazoparib.

The findings presented in this manuscript are important as they show that a heavily pretreated population (who had not received prior platinum) could be highly responsive to talazoparib. Additionally, given the increased use of platinum chemotherapy in patients with *BRCA*-mutated advanced breast cancer, this study emphasizes the need to robustly assess the activity of PARP inhibitors in patients with prior platinum exposure and the predictive potential of a platinum-free interval.

Abstract

Purpose: To assess talazoparib activity in germline *BRCA1/2* mutation carriers with advanced breast cancer (aBC).

Experimental Design: ABRAZO (NCT02034916) was a two-cohort, two-stage, phase II study of talazoparib (1 mg/day) in germline *BRCA* mutation carriers with a response to prior platinum with no progression on or within 8 weeks of the last platinum dose (cohort 1) or ≥3 platinum-free cytotoxic regimens (cohort 2) for aBC. Primary endpoint was confirmed objective response rate (ORR) by independent radiological assessment.

Results: We enrolled 84 patients (cohort 1, *n* = 49; cohort 2, *n* = 35) from May 2014 to February 2016. Median age was 50 (range, 31–75) years. Triple-negative breast cancer incidence was 59% (cohort 1) and 17% (cohort 2). Median number of prior cytotoxic regimens for aBC was two and four, respectively. Confirmed ORR was 21% (95% CI, 10 to 35) (cohort 1) and 37% (95% CI, 22 to 55) (cohort 2). Median duration of response was 5.8 and 3.8 months, respectively. Confirmed ORR was 23% (*BRCA1*), 33% (*BRCA2*), 26% (TNBC) and 29% (hormone receptor positive). The most common all-grade adverse events (AEs) included anemia (52%), fatigue (45%), and nausea (42%). Talazoparib-related AEs led to drug discontinuation in three (4%) patients. In an exploratory analysis, longer platinum-free interval was associated with higher response rate in cohort 1 (0% ORR with interval <8 weeks; 47% ORR with interval >6 months).

Conclusions: Talazoparib exhibited promising antitumor activity in patients with aBC and germline *BRCA* mutation.

Introduction

Breast cancer susceptibility (*BRCA*) genes 1 and 2 (*BRCA1* and *BRCA2* [*BRCA1/2*]) are key components in the repair pathway for DNA double-strand breaks. Mutations in these genes account for 20% to 25% of hereditary breast cancers and approximately 5% of all breast cancers (1).

With improved understanding of the functions of *BRCA1/2* in DNA repair, the focus of developmental therapeutics has shifted in recent years from cytotoxic chemotherapy to molecularly targeted agents. Cancer cells with a *BRCA1/2* mutation are deficient in homologous recombination DNA repair, and poly(ADP-ribose) polymerase (PARP) inhibition causes synthetic lethality in these cells. This is at least in part because PARP inhibition traps PARP on sites of DNA damage, creating DNA damage that cannot be repaired in cancer cells with defective homologous recombination DNA repair mechanisms (2–4). This vulnerability in *BRCA*-mutant tumors has led to the clinical development of PARP inhibitors for a variety of cancers (2–9). Talazoparib is an oral PARP inhibitor that has recently emerged as a promising anticancer therapy (5). In nonclinical models, talazoparib has been shown to be the most potent PARP inhibitor in development, with the lowest concentrations required for inhibition of PARP enzymatic activity and PARP trapping at DNA breaks (9–11).

In the first-in-human phase I study, the maximum tolerated dose of talazoparib was defined as 1 mg once daily; the dose-limiting toxicity was reversible thrombocytopenia. Talazoparib treatment resulted in a 50% response rate and an 86% clinical benefit rate at 24 weeks in 18 patients with a germline *BRCA1/2* mutation and advanced breast

cancer (5). Treatment-emergent adverse events (AEs) in the phase I trial were hematologic and gastrointestinal toxicity.

The purpose of this phase II study (ABRAZO, NCT02034916) was to evaluate the efficacy and safety of talazoparib as a single agent in patients with advanced breast cancer with a germline *BRCA1/2* mutation. Cohort 1 included patients with platinum-sensitive disease to explore the impact of previous platinum therapy on the effectiveness of subsequent treatment with a PARP inhibitor, as it had been previously demonstrated that patients with ovarian cancer treated with other PARP inhibitors who had platinum-resistant disease (progression within 6 months after the last dose of platinum) or platinum-refractory disease (progression on or within 2 months following last dose of platinum) showed a lower observed response rate than patients with longer platinum-free intervals (6, 7). Cohort 2 was designed to investigate the response rate in a heavily pretreated population who had not received previous platinum therapy.

Methods

Study design and participants

This open-label, two-cohort, phase II study evaluated talazoparib in patients with metastatic breast cancer with a deleterious or a suspected deleterious germline *BRCA1/2* mutation using the BRACAnalysis CDx assay (Myriad Genetics, Salt Lake City, UT, USA). We enrolled patients from 33 locations throughout France, Germany, Spain, the United Kingdom, and the United States. Initially, a total of 35 patients were enrolled in stage 1 into each of two cohorts. If five or more patients had objective

responses as determined by the local investigator in either cohort, an additional 35 patients were to be enrolled in stage 2 into that cohort, for a total of up to 140 patients in the study. Final assessment of ORR (all patients) was performed by an independent central review.

Cohort 1 included patients with a complete response or partial response to a previous platinum-containing regimen for metastatic disease, with no disease progression within 8 weeks of the last dose of platinum therapy. For patients treated with more than one previous platinum-containing regimen, platinum response and stability of disease from the last dose had to occur with the most recent regimen. Seven patients in cohort 1 were enrolled in violation of the eligibility criteria because of disease progression within 8 weeks of the last dose of platinum. These patients are included in all analyses.

Cohort 2 included patients who had received three or more previous cytotoxic chemotherapy regimens for metastatic disease and no previous platinum therapy for metastatic disease. Previous adjuvant or neoadjuvant therapy with platinum was allowed if the first disease recurrence was more than 6 months after the last dose of adjuvant or neoadjuvant platinum therapy. Patients with human epidermal growth factor receptor 2 (HER2)-positive disease were eligible for either cohort, provided they were considered to be refractory to HER2-targeted therapy. Patients with HER2-positive breast cancer had to have discontinued HER2-directed therapies prior to day 1, although there might have been some overlap due to washout. Furthermore, HER2-directed combination therapy was not permitted on study.

In addition to the key eligibility standards described for cohorts 1 and 2 above, additional criteria included measurable disease as defined by Response Evaluation

Criteria In Solid Tumors version 1.1 (RECIST v 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate organ and bone marrow function. A full list of exclusion criteria is provided in the Supplementary data (Supplementary Methods). The study was conducted in accordance with the protocol, good clinical practice standards, the Declaration of Helsinki, and the International Conference on Harmonisation. The appropriate institutional review board or ethics committee at each participating institution approved the protocol. All enrolled patients provided written informed consent before undergoing study-specific procedures.

Study treatments and procedures

Patients received talazoparib 1 mg once daily by mouth as continuous therapy; patients were evaluated in repeated 21-day cycles. Talazoparib dosing could be interrupted for recovery from toxicity for up to 28 days. For interruptions longer than 28 days, treatment could be resumed at the same or a reduced dose at the discretion of the sponsor and investigator if clinical benefit was evident. Patients had study visits on days 1, 8, and 15 for the first two cycles; the day 8 and 15 visits were optional for subsequent cycles in the absence of significant toxicities. Treatment with talazoparib continued until radiographic disease progression, unacceptable toxicity, withdrawal of consent, or the investigator's decision to discontinue treatment. End-of-treatment assessments were performed 30 days after the last dose of the study drug or before initiation of a new antineoplastic therapy, whichever occurred first.

An independent radiology facility evaluated imaging data and prior and on-study radiation therapy. Tumor assessments were performed by computed tomography, magnetic resonance imaging, or radiography. Tumor assessments were performed at screening or baseline, every 6 weeks for the first 24 weeks, and every 12 weeks thereafter until radiographic disease progression was confirmed by the independent radiology facility or until initiation of a new antineoplastic therapy. Tumor response could also be assessed as clinically indicated, at the time of clinical suspicion of disease progression, and to confirm complete or partial response at least 4 weeks after an initial response was observed.

All patients were monitored for survival and subsequent anticancer therapy every 60 days after the last dose of study drug for the first year, every 90 days thereafter, and at the sponsor's request. Survival follow-up continued until death or withdrawal of consent.

Safety and tolerability were evaluated by assessment of AEs; physical examinations; vital signs; laboratory evaluations; electrocardiograms; and use of concomitant medications during the treatment period through 30 days after the last dose of study drug or before initiation of a new antineoplastic therapy or investigational therapy, whichever occurred first.

Sparse pharmacokinetic sampling was performed on day 1 of cycles 1 through 4, consisting of a predose sample collected no more than 60 minutes prior to dosing and two postdose samples collected at least 30 minutes after dosing. The collection times of the two postdose samples were separated by at least 2 hours. Blood and tumor tissue

samples were collected for pharmacodynamic and genomic research. These analyses will be reported separately.

Outcomes

The intention-to-treat analysis population was defined as all patients with an enrollment date (*n* = 84). The tumor-evaluable population was defined as all patients who had received at least one dose of talazoparib, had a baseline tumor assessment, and had at least one postbaseline tumor assessment (*n* = 83). This population was used for the efficacy analysis, with the exception of progression-free survival and overall survival, which used the intention-to-treat population.

The primary efficacy endpoint was objective response rate (ORR), defined as the proportion of patients in the tumor-evaluable population who had a confirmed objective response (best overall response of complete or partial response) confirmed by the independent radiology facility using Response Evaluation Criteria In Solid Tumors version 1.1 at the time of data cutoff. Secondary efficacy endpoints were clinical benefit rate at 24 weeks and duration of response confirmed by the independent radiology facility, progression-free survival confirmed by the investigator, and overall survival. Exploratory endpoints were ORR, clinical benefit rate at 24 weeks, and duration of response assessed by the investigator.

Statistical analysis

This study was designed to provide adequate power for the primary efficacy endpoint of ORR. We initially planned for a total enrollment of up to 140 patients, depending on the number of patients with an objective response in the first stage of each cohort using the two-stage design. If five or more responses were observed for 35 patients in the first stage of each cohort, enrollment of an additional 35 patients into each cohort was to occur in the second stage, for a total of 70 treated patients per cohort. Talazoparib would be considered effective as a single agent if at least 16 patients in a cohort had an objective response. This design provided 0.90 power to distinguish between an active drug with a 30% true response rate and a drug with a response rate of 15% or less with an alpha level of 0.05.

After the trial met the criteria for continuation to the second stage for each of the two cohorts, the sponsor stopped enrollment in this study, after an amendment to the phase III EMBRACA trial (NCT01945775) of talazoparib versus physician's choice of chemotherapy in patients with advanced breast cancer and a germline *BRCA1/2* mutation resulted in overlapping enrollment criteria with this phase II study.

Results

Patient characteristics

Between May 2014 and February 2016, we enrolled 84 patients in the intention-to-treat population. Patient disposition for the intention-to-treat population is shown in Fig. 1.

One patient in cohort 1 did not receive any study drug because of rapidly worsening liver function tests and was excluded, for a total of 83 patients in the tumor-evaluable population, including 48 patients in cohort 1 and 35 patients in cohort 2. All 83 patients were included in the safety population.

Baseline characteristics of patients are given in Table 1. *BRCA1/2* status was assessed by a central laboratory for 79 patients; patients had to carry at least one risk factor for hereditary breast cancer in order to be screened by the central laboratory for this trial. *BRCA1/2* status was determined by local assessment for four of the remaining five patients whose samples were not available for central assessment, and *BRCA1/2* status was unknown for one patient (the local *BRCA1/2* mutation report was not entered into the database prior to database lock. There was an insufficient amount of material to obtain a result so the patient was listed as unknown. However, the sample was then retested by a central laboratory and appeared to be a *BRCA* mutant). No patient carried mutations in both *BRCA1* and *BRCA2 genes*.

Treatment efficacy

The cutoff date for all efficacy analyses was September 1, 2016 (nine patients continued on treatment at this time), with the exception of overall survival for which the data cutoff was April 7, 2017. Talazoparib demonstrated efficacy in patients with a *BRCA1/2* mutation and a response to previous platinum therapy (cohort 1), and in patients who had at least three previous chemotherapy regimens and no previous platinum therapy (cohort 2; Table 2). In an examination of subgroups in this study, the

ORR (95% CI) in patients carrying a *BRCA1* or *BRCA2* mutation was 23% (11–39) and 33% (20–50; Fig. 2A, B), and the ORR (95% CI) in patients with triple-negative breast cancer (TNBC) and hormone receptor–positive breast cancer was 26% (13–43) and 29% (17–44; Fig. 2C, D). The study recruited six patients with HER2-positive breast cancer, who were considered refractory to previous HER2-targeting therapies. All HER2-positive breast cancers were also hormone receptor positive. In these patients, an objective response was confirmed in two of the six patients by the independent radiology facility.

Investigator-assessed median progression-free survival was 4.0 months (95% CI, 2.8–5.4) in cohort 1 and 5.6 months (95% CI, 5.5–7.8) in cohort 2 (Supplementary Fig. S1). Based on reverse Kaplan–Meier estimates, the median follow-up time was 13.7 months for each cohort. The median overall survival was 12.7 months (95% CI, 9.6–15.8) in cohort 1 and 14.7 months (95% CI, 11.0–24.4) in cohort 2 (Supplementary Fig. S1), with 36 events (74%) in cohort 1 and 22 events (62.9%) in cohort 2.

The median time from the last platinum dose to progression in cohort 1 was 4.0 months (range, 0.03–49.15). Exploratory subgroup analyses of the effect of platinum-free interval on ORR and the median progression-free survival suggested that a longer platinum-free interval following the last dose of platinum was associated with greater clinical activity (Fig. 3). Of the seven patients who entered cohort 1 with disease progression within 8 weeks of the last dose of platinum, none responded to talazoparib.

Treatment safety

Drug-related AEs that led to study drug discontinuation occurred in three patients overall, two patients in cohort 1 and one patient in cohort 2, and included anemia (one patient) and liver function test abnormalities (two patients). The most common reason for dose reduction was myelosuppression (anemia); 23 patients (28%) received at least one transfusion of red blood cells. The transfusion rate was higher in cohort 2 (37%), the group who had received more prior cytotoxic chemotherapy; 21% of patients in cohort 1 received at least one red blood cell transfusion. Few patients received an erythropoietin-stimulating agent (8% and 3% for cohorts 1 and 2, respectively). Time to first dose reduction was 10.9 weeks in cohort 1 and 13.3 weeks in cohort 2.

Hematologic treatment-emergent AEs and grade 3 or higher hematologic treatment-emergent AEs occurring in 15% or more and in 5% or more of patients, respectively, are shown in Table 3. In both cohorts, anemia was the most common hematologic AE (50% and 57% of patients in cohorts 1 and 2, respectively). Neutropenic sepsis occurred in one patient. No acute myeloid leukemia or myelodysplastic syndrome was observed. Nonhematologic treatment-emergent AEs and grade 3 or higher nonhematologic treatment-emergent AEs occurring in 20% or more and 5% or more of patients, respectively, are shown in Table 3. No grade 5 treatment-emergent AEs were observed. No clinically significant cardiovascular toxicity was observed.

Pharmacokinetics

The plasma concentration of talazoparib at approximately 2 hours following the first dose was 3650 pg/mL (coefficient of variation [CV%] 93.6). On cycle 2 day 1 (approximately 21 days later), the plasma concentration was 10,700 pg/mL (CV% 46.2) in patients without a dose modification. Talazoparib plasma trough concentrations were similar for cycles 2, 3, and 4 for patients without any dose modification (between 3300 and 3900 pg/mL), suggesting that talazoparib reached steady state by cycle 2. In general, trough concentrations had high interpatient variability, between 46% and 60% for patients without dose modification, which was consistent with previous observations (5). Talazoparib showed accumulation at steady state where postdose concentrations (two postdose samples, >2 hours between) in cycles 2 to 4 were 2.7- to 3-fold higher than observed in cycle 1, consistent with historical data.

Discussion

In this open-label, phase II study of patients with metastatic breast cancer carrying a germline *BRCA1/2* mutation, talazoparib had clinical activity both in patients who had a previous response to platinum chemotherapy and in those who received at least three previous cytotoxic regimens for advanced breast cancer without prior platinum exposure. In the group who previously received platinum, an exploratory analysis demonstrated an association between higher ORR and longer median progression-free survival with a longer platinum-free interval.

Platinum chemotherapy and PARP inhibitors target defective HR DNA repair in *BRCA1/2*-mutant breast cancer. Although the mechanisms of resistance to platinum

chemotherapy in this setting are incompletely understood, reversion mutations that restore HR repair proficiency appear to play a role in at least some patients. Such mutations have been identified in preclinical models and in the circulating tumor DNA of heavily pretreated breast cancers (12, 13). In an exploratory analysis, response to talazoparib was less likely in patients progressing with a short platinum-free interval than in patients with a long platinum-free interval (Fig. 3), suggesting that patients who progress on platinum chemotherapy or shortly after stopping may show reduced sensitivity to PARP inhibitors. Previous studies of PARP inhibitors in breast cancer have included relatively few patients with prior platinum chemotherapy. In a phase II study with olaparib, the ORR was 9.5% in 42 patients who had received platinum and was 20% in 20 patients without prior platinum exposure (14). In the OlympiAD phase III study of olaparib, prior platinum chemotherapy as a whole did not affect the relative benefit of olaparib (hazard ratio for PFS was 0.67 and 0.60 for patients with and without prior platinum), although olaparib efficacy in relation to the timing of platinum chemotherapy was not reported (15). Our results emphasize the importance of robustly assessing platinum-free interval in future studies.

The safety profile of PARP inhibitors is generally consistent across the different agents, with the primary toxicity being clinically manageable myelosuppression. Additional toxicities include mild-to-moderate gastrointestinal toxicity (ie, nausea, vomiting, diarrhea, and abdominal pain) and fatigue (16). Three of the 83 evaluable patients from our study discontinued therapy for a drug-related toxicity, suggesting that most toxicity could be managed with supportive care. Although myelosuppression was common, the clinical sequelae (ie, hemorrhage and infection) were rare and included one patient with

a severe but transient episode of epistaxis and one with neutropenic sepsis successfully treated for infection and later had a confirmed partial response. Grade 3/4 thrombocytopenia occurred in 29% (14/48) of patients in cohort 1 and 23% (8/35) of patients in cohort 2. Hemorrhage was rare, occurring in only one patient, suggesting that thrombocytopenia only rarely had clinical sequelae. No acute myeloid leukemia or myelodysplastic syndrome was noted during the median follow up time of 13.7 months. Acute myeloid leukemia or myelodysplastic syndrome has been noted to occur at an incidence of 1% to 3% among patients following a few months up to several years of treatment with PARP inhibitors (3, 17–19), although this has been exclusively reported in patients with ovarian cancer.

There are several limitations to our study. The open-label design may have led to investigator bias in assessment of response and progression; therefore, the primary endpoint was ORR by independent imaging facility assessment. Additionally, the termination of enrollment prior to completion of the targeted 70 patients per cohort limits the conclusions that may be drawn from this study. We recruited few patients with HER2-positive breast cancer. Although antitumor activity was observed in these patients, the data are preliminary and further studies would be required to assess the activity of talazoparib in patients with HER2-positive disease. In addition, the two cohorts differed in tumor subtype, which may have had an influence on PFS and overall survival (Table 1), with triple-negative cancers in general having adverse PFS and overall survival compared with estrogen receptor–positive cancers. Of note, a phase III clinical trial (EMBRACA, NCT01945775) recently reported improved PFS for talazoparib

compared to treatment of physician's choice, with a doubling of ORR and prolonged duration of response (20).

In conclusion, talazoparib is a novel and highly potent PARP inhibitor with a manageable safety profile, pharmacokinetics that support once-daily dosing, and encouraging single-agent efficacy in germline *BRCA1/2* mutation carriers with advanced breast cancer previously treated with platinum and in patients treated with multiple lines of prior nonplatinum-based chemotherapy. The impact of prior platinum exposure and platinum-free interval on sensitivity to PARP inhibitors should be further investigated.

Authors' Contributions

Concept and design: N.C.Turner, S.A. Hurvitz, A.L. Hannah, and M.E. Robson

Development of methodology: N.C.Turner, S.A. Hurvitz, A.L. Hannah, and M.E. Robson

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Site investigators

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Chappey

Writing, review, and/or revision of the manuscript: N.C.Turner, A.L. Hannah, and M.E. Robson guided the initial drafting of the manuscript, with input from all other authors.

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Chappey

Study supervision: Site investigators

Other: All authors had full access to the study data, contributed to the revision and approval of the manuscript, and participated in the decision to submit the manuscript for publication.

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20. Litton J, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH. et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. *N Engl J Med.* 2018; 379:753-763.

Table 1. Select baseline characteristics (intention-to-treat population)

Characteristic	**Cohort 1 prior platinum therapy (*n* = 49)**	**Cohort 2 third-line treatment, No. prior platinum therapy (n = 35)**	**Total (*N* = 84)**
Age, median (range), years	50 (31 to 74)	52 (33 to 75)	50 (31 to 75)
ECOG performance status = 0, No. (%)	34 (69)	15 (43)	49 (58)
History of central nervous system metastasis, No. (%)	8 (16)	1 (3)	9 (11)
Visceral disease, No. (%)	38 (78)	23 (66)	61 (73)
Hormone receptor status, No. (%)			
HER2 positive	1 (2)	5 (14)	6 (7)
Triple negative	29 (59)	6 (17)	35 (42)
ER positive or PgR positive	20 (41)	29 (83)	49 (58)
BRCA mutation status, No. (%)			
BRCA1 positive	26 (53)	15 (43)	41 (49)
BRCA2 positive	22 (45)	20 (57)	42 (50)
Unknown	1 (2)	0	1 (1)
Number of prior cytotoxic regimens for advanced disease			
1 to 2, No. (%)	26 (53)	1 (3)*	27 (32)
3 to 4, No. (%)	17 (35)	22 (63)	39 (46)
≥5, No. (%)	6 (12)	12 (34)	18 (21)
Median	2	4	3
Min, max	1, 10	1, 9	1, 10

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor. *Protocol deviation: eligibility criteria not met (≥3 prior cytotoxic regimens).

Table 2. Primary, secondary, and exploratory efficacy endpoints

Endpoint	**Cohort 1 prior platinum therapy (*n* = 48)**	**Cohort 2 Third-line treatment, No. prior platinum therapy (*n* = 35)**	**Total (*N* = 83)**
Primary efficacy endpoint, objective response rate assessed by independent radiology facility			
Objective response rate, % (95% CI)	21 (10 to 35)	37 (22 to 55)	28 (18 to 39)
Best overall response, No. (%)			
Complete response	2 (4)	0	2 (2)
Partial response	8 (17)	13 (37)	21 (25)
Stable disease	18 (38)	18 (51)	36 (43)
Progressive disease	18 (38)	4 (11)	22 (27)
Not evaluable	2 (4)	0	2 (2)
Secondary efficacy endpoints (intention-to-treat population)			
Duration of response assessed by independent radiology facility			
No.	10	13	23
Events, No. (%)	5 (50)	10 (77)	15 (65)
Median (95% CI), months	5.8 (2.8–NE)	3.8 (2.8–10.1)	4.9 (2.9–9.7)
Clinical benefit rate assessed by independent radiology facility (complete response, partial response, or stable disease ≥ 24 weeks), No. (%)	13 (27)	16 (46)	29 (35)
95% CI	15–42	29–63	25–46
Exploratory endpoint, investigator assessments of efficacy (tumor-evaluable population)	**Cohort 1 prior platinum therapy (*n* = 48)**	**Cohort 2 third-line treatment, No. prior platinum therapy (*n* = 35)**	**Total (*N* = 83)**
Objective response rate, % (95% CI)	23 (12–37)	51 (34–69)	35 (25–46)
Duration of response			
No.	11	18	29
Events, No. (%)	8 (73)	15 (83)	23 (79)
Median (95% CI), months	4.9 (2.8–NE)	4.2 (3.2–5.5)	4.4 (3.2–5.6)
Clinical benefit rate assessed by investigator	18 (38)	23 (66)	41 (49)

(complete response, partial response, or stable disease ≥ 24 weeks), No. (%)			
95% CI	24–53	48–81	38–61

Abbreviations: CI, confidence interval; NE, not evaluable. Confirmation of complete response and partial response required; data cutoff for primary endpoint was September 1, 2016.

Table 3. Treatment-emergent adverse events in descending order of all grades in cohort 1 (safety population)

	Cohort 1 prior platinum therapy (*n* = 48), No. (%)			**Cohort 2 third-line treatment, No. prior platinum therapy (*n* = 35), No. (%)**		
	All Grades	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
Hematologic*						
Patients with treatment-emergent adverse event(s)	33 (69)	25 (52)	3 (6)	26 (74)	17 (49)	4 (11)
Anemia	24 (50)	16 (33)	0	20 (57)	14 (40)	0
Thrombocytopenia	23 (48)	11 (23)	3 (6)	12 (34)	4 (11)	4 (11)
Neutropenia	15 (31)	6 (13)	0	16 (46)	8 (23)	0
Leukopenia	10 (21)	1 (2)	0	10 (29)	3 (9)	0
Nonhematologic†						
Patients with treatment-emergent adverse event(s)	47 (98)	11 (23)	2 (4)	34 (97)	10 (29)	1 (3)
Fatigue	29 (60)	3 (6)	0	8 (23)	0	0
Nausea	20 (42)	2 (4)	0	15 (43)	0	0
Diarrhea	17 (35)	1 (2)	0	10 (29)	0	0
Decreased appetite	11 (23)	1 (2)	0	9 (26)	0	0
Dyspnea	11 (23)	1 (2)	1 (2)	9 (26)	2 (6)	0
Alopecia (grade 1)	11 (23)	0	0	7 (20)	0	0
Back pain	11 (23)	0	0	7 (20)	0	0
Vomiting	10 (21)	0	0	7 (20)	0	0
Pleural effusion	4 (8)	3 (6)	0	4 (11)	2 (6)	0

The category of thrombocytopenia incudes reports of thrombocytopenia and platelet count decreased. The category of neutropenia includes reports of neutropenia, decreased neutrophil count, and neutropenic sepsis. The category of anemia includes reports of anemia and hemoglobin decreased. *All treatment-emergent adverse events in ≥ 15% of patients and grade 3 and 4 treatment-emergent adverse events in ≥ 5% of patients. Transfusions: one patient with platelet transfusion and 23 patients (28%) with packed red blood cells (10 and 13 patients in cohorts 1 and 2, respectively). Hemorrhage: one patient had grade 3 hemorrhage (transient epistaxis). No patients had acute myeloid leukemia or

myelodysplastic syndrome. †All treatment-emergent adverse events in ≥ 20% of patients and grade ≥ 3 treatment-emergent adverse events in ≥ 5% of patients. No grade 5 treatment-emergent adverse events and no clinically significant cardiovascular toxicities were observed.

Figure 1. Patient disposition. [a]Intention-to-treat (ITT) population.

Figure 2. Change in tumor size on talazoparib by *BRCA* mutation status and breast cancer subtype. Percentage change by *BRCA* mutation status in (A) cohort 1 and (B) cohort 2 and by breast cancer subtype in (C) cohort 1 and (D) cohort 2. [a]Ongoing patients as of data cutoff of September 1, 2016. Line at -30% indicates a partial response as determined by RESIST version 1.1. Triple-negative defined as ER-negative, PgR-negative, and HER2-negative. Hormone receptor–positive, defined as ER-positive or PgR-positive, includes 6 patients who were hormone receptor-positive and HER2-positive. *BRCA,* breast cancer susceptibility gene; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; RESIST, Response Evaluation Criteria In Solid Tumors.

Figure 3. Impact of platinum-free interval on efficacy of talazoparib. Exploratory assessment of the platinum-free interval (time from last dose of platinum chemotherapy to disease progression) and confirmed objective response rate by (A) independent review and (B) PFS in cohort 1. ORR, objective response rate; PFS, progression-free survival.

Figure 1.

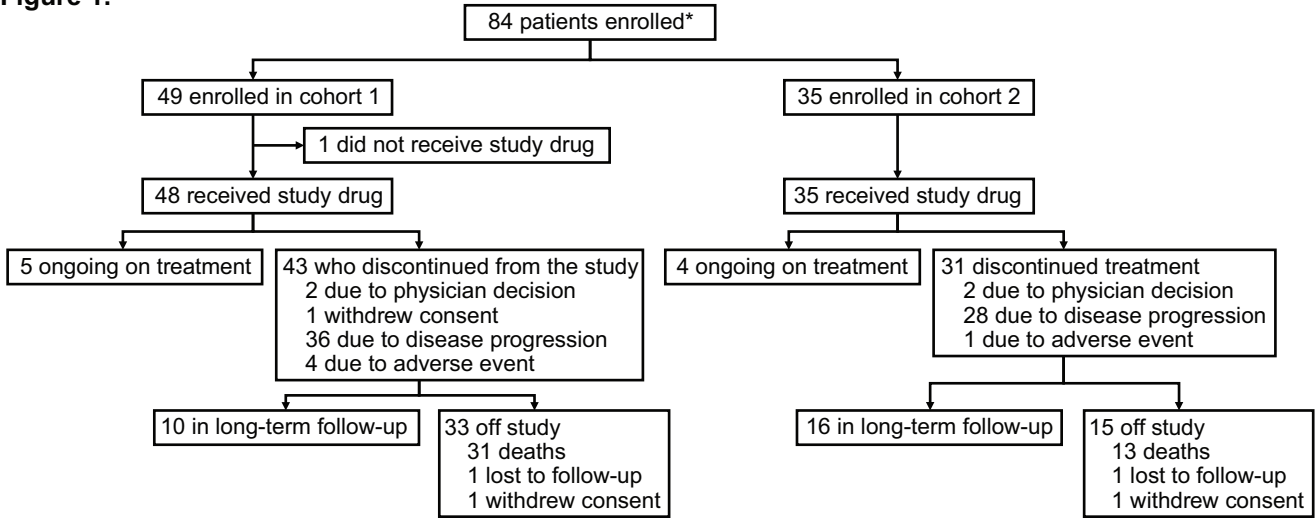

84 patients enrolled*
49 enrolled in cohort 1
1 did not receive study drug
48 received study drug
5 ongoing on treatment
43 who discontinued from the study
2 due to physician decision
1 withdrew consent
36 due to disease progression
4 due to adverse event
10 in long-term follow-up
33 off study
31 deaths
1 lost to follow-up
1 withdrew consent
35 enrolled in cohort 2
35 received study drug
4 ongoing on treatment
31 discontinued treatment
2 due to physician decision
28 due to disease progression
1 due to adverse event
16 in long-term follow-up
15 off study
13 deaths
1 lost to follow-up
1 withdrew consent

Figure 2.

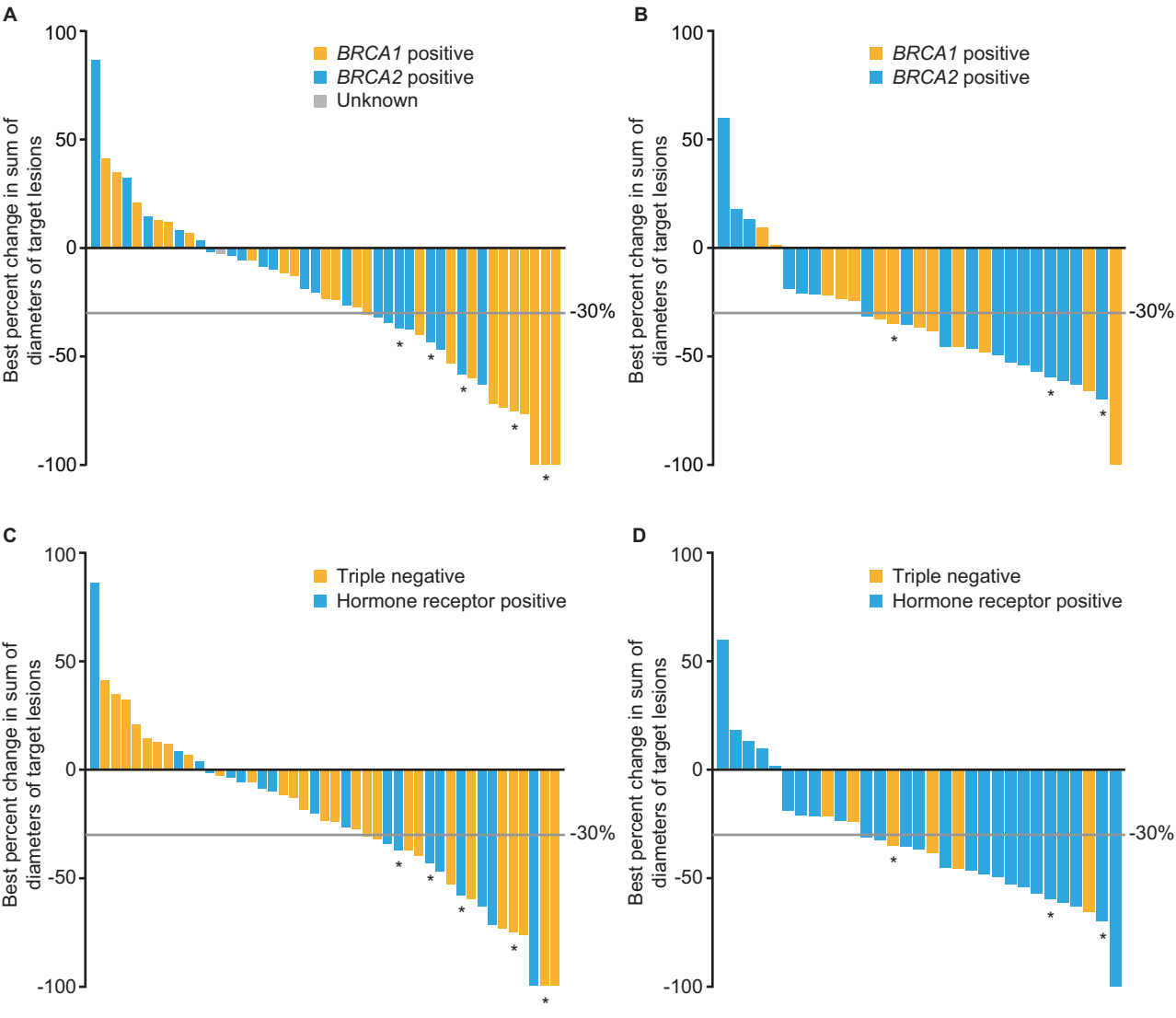
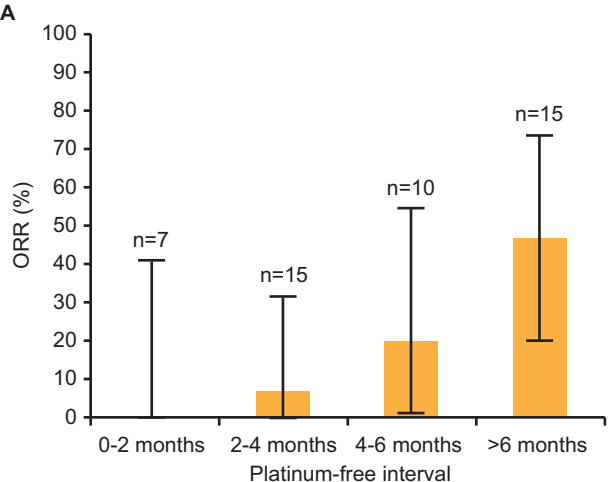
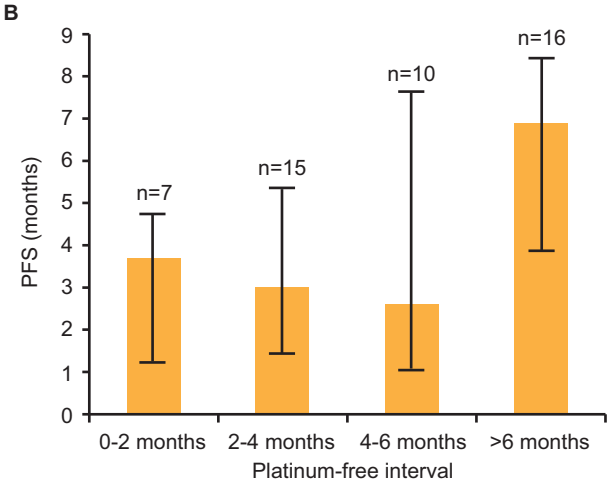

A
100
50
0
-50
-100
Best percent change in sum of diameters of target lesions
BRCA1 positive
BRCA2 positive
Unknown
-30%
*
B
BRCA1 positive
BRCA2 positive
C
Triple negative
Hormone receptor positive
D

Figure 3.





ORR (%)	0	7	20	47
PFS (months)	3·7	3·0	2·6	6·9