# Phase II Trial of Veliparib and Temozolomide in Metastatic Breast Cancer Patients With and Without BRCA1/2mutations

**Jing Xu** ( lucy_xu@icloud.com )
Massachusetts General Hospital https://orcid.org/0000-0002-8046-1370

**Tanya E Keenan**
Dana-Farber Cancer Institute

**Beth Overmoyer**
Dana-Farber Cancer Institute

**Nadine Muskatel Tung**
Beth Israel Deaconess Medical Center

**Rebecca Gelman**
Dana-Farber Cancer Institute

**Karleen Habin**
Massachusetts General Hospital Cancer Center

**Judy Garber**
Dana-Farber Cancer Institute

**Leif W Ellisen**
Massachusetts General Hospital Cancer Center

**Eric P Winer**
Dana-Farber Cancer Institute

**Paul E Goss**
Massachusetts General Hospital Cancer Center

**Beow Y Yeap**
Massachusetts General Hospital Cancer Center

**Bruce Chabner**
Massachusetts General Hospital Cancer Center

**Steven J Isakoff**
Massachusetts General Hospital Cancer Center

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# Abstract

**Purpose:** We evaluated the efficacy and safety of poly-(adenosine diphosphate-ribose) polymerase (PARP) 1 and 2 inhibitor veliparib and temozolomide in metastatic breast cancer patients with and without germline *BRCA1/2* mutations.

**Methods:** In this single-arm phase II trial, patients with metastatic breast cancer received veliparib 30 to 40 mg twice daily on days 1 to 7 with concurrent temozolomide 150 mg/m$^2$ on days 1 to 5 of a 28-day cycle. The primary cohort was unselected for BRCA mutation status, and an expansion cohort enrolled only BRCA1/2 carriers. The primary endpoint was objective response rate (ORR) in each cohort. Secondary endpoints included progression free survival (PFS), clinical benefit rate (CBR), and evaluation of safety and tolerability.

**Results:** In the primary cohort of 41 unselected patients, which included 9 BRCA mutation carriers, the ORR was 10% and clinical benefit rate at 4 months (CBR) was 27%. In the expansion cohort of 21 *BRCA1/2* carriers, the ORR was 14% and CBR was 43%. Among all 30 *BRCA1/2* carriers, the ORR was 23% versus 0% among non-carriers. In the subset of *BRCA1/2* carriers, the ORR was 32% among platinum-naïve patients versus 9% among platinum-exposed patients. The median PFS was 3.3 months among *BRCA1/2* carriers compared to 1.8 months among non-carriers (HR: 0.48, p = 0.006). A longer median PFS of 6.2 months was observed among *BRCA1/2* carriers who had no prior platinum therapy. The most common grade 3 and 4 toxicities were thrombocytopenia (32%) and neutropenia (21%) that generally improved with dose modifications.

**Conclusion:** Veliparib and temozolomide demonstrated clinical activity in platinum-naïve BRCA-associated metastatic breast cancer with manageable toxicity at doses of veliparib well below the single agent active dose. Although the study did not meet its primary endpoint in unselected nor BRCA-associated breast cancer, this regimen was further evaluated in the BROCADE 2 study.

**Trial registration:** NCT01009788 (ClinicalTrials.gov), November 9, 2009


# Introduction

*BRCA 1/2* deficient breast cancers account for 5–10% of all breast cancers and about 20–25% of hereditary breast cancers [1–3]. Women with germline *BRCA1/2* mutations have a cumulative risk for developing breast cancer ranging from 49–57% by age 70 [4]. Poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitors promote synthetic lethality in BRCA-mutant cells [5, 6]. PARP enzymes are responsible for the repair of single stranded DNA breaks through base excision repair (BER). The inhibition of PARP causes single-strand DNA breaks to be converted into double-strand DNA breaks, which are repaired by the homologous recombination (HR) pathway. *BRCA1* and *BRCA2* play important roles in HR double-strand break repair, and this pathway is defective in BRCA-mutant cells [5]. Additionally, PARP inhibitors can trap PARP enzymes at damaged DNA sites by forming DNA-PARP inhibitor complexes, which can cause DNA damage and cell death [7]. In the presence of BRCA deficiency,

PARP inhibition sensitizes tumor cells to DNA-damaging chemotherapies, such as platinum compounds, topoisomerase inhibitors, and alkylating agents [5].

Clinical studies in breast cancer have demonstrated that certain single-agent PARP inhibitors have substantial antitumor activity in patients with *BRCA1/2* mutations. This has led to the approval of olaparib and talazoparib for germline BRCA-mutated, HER2-negative metastatic breast cancer [6, 8, 9]. Combination regimens of PARP inhibitors with chemotherapy agents, targeted therapies, antibody drug conjugates, checkpoint inhibitors, and other therapies are currently being explored. The optimal combination agent for PARP inhibitors in breast cancer remains unknown [10–14]. Early studies reported PARP inhibition potentiates the activity of temozolomide (TMZ), an orally administered alkylating agent, which has the advantage of crossing the blood-brain barrier (BBB) [15–19]. Veliparib, an investigational oral PARP-1 and PARP-2 inhibitor, also efficiently crosses the BBB [20]. Single-agent TMZ demonstrated no significant clinical activity in metastatic breast cancer [21, 22]. However, in preclinical studies, veliparib potentiated the activity of TMZ, demonstrating anti-tumor activity in *in vivo* models of breast cancer, including tumors resistant to TMZ monotherapy [23]. In clinical settings, this combination has demonstrated activity in relapsed small cell lung cancer, metastatic colorectal cancer, and acute myeloid leukemia and may represent a promising treatment option for metastatic breast cancer [24–26].

In this phase II trial, we evaluated the efficacy and safety of veliparib and TMZ in patients with metastatic breast cancer (MBC). The initial cohort of 41patients included all subtypes of MBC, and an expansion cohort of 21 patients included only patients with germline *BRCA1/2*-mutated MBC.

## Methods

# Patients

The initial study population included patients with all subtypes of metastatic breast cancer treated with at least one prior line of chemotherapy for metastatic disease. The expansion cohort enrolled patients with metastatic breast cancer and a known deleterious *BRCA1/2* mutation, without limitation on prior treatment. Other eligibility criteria included measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [27], normal organ and marrow function, and Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$. Both cohorts allowed for previously treated stable brain metastases. Key exclusion criteria included treatment with chemotherapy, biological therapy, targeted therapy, or radiotherapy within 2 weeks, or anti-cancer hormonal therapy within 24 hours before starting the study treatment.

All patients provided written informed consent prior to study entry.

# Study Design and Treatment

This open-label single-arm phase II study was conducted at Massachusetts General Hospital, Dana-Farber Cancer Institute, and Beth Israel Deaconess Medical Center.

The study protocol and informed consent form were reviewed and approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) institutional review board.
This study was performed according to the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

The study treatment consisted of veliparib on days 1 through 7 with concurrent TMZ on days 1 through 5 of a 28-day cycle. The study initially dosed veliparib at 40 mg oral twice daily and later reduced veliparib to 30 mg twice daily for all patients after one patient experienced grade 4 thrombocytopenia during the first cycle of treatment. The expansion cohort dosed veliparib at 30 mg twice daily for all patients. All patients in both cohorts received TMZ 150 mg/$m^2$ oral once daily, which was increased to 200 mg/$m^2$ in cycle 2 as tolerated.

Patients received study treatment until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up. Treatment could be interrupted for grade 3 or 4 treatment-related toxicities for up to 21 days, after which the study drugs were stopped if the toxicity was still not resolved. Only one dose reduction was allowed for veliparib before discontinuation of study treatment, and the TMZ dose could not be reduced below 75 mg/$m^2$ daily.

# Study Endpoints and Assessment

The primary endpoint of the study was objective response rate (ORR) based on tumor assessment every 8 weeks according to RECIST 1.1. Secondary endpoints included clinical benefit rate (CBR) at 4 months, progression free survival (PFS), and adverse event rate. CBR at 4 months was defined as the percentage of patients who had CR, PR, or SD for greater than 16 weeks of follow up. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

# Statistical Analysis

A target ORR of 20% was considered to be of clinical benefit for this combination regimen in the primary cohort based on the fact that TMZ showed no single-agent activity in breast cancer at that time. A sample size of 41 was estimated to have 93% power to detect a response rate of 20% compared to a null response rate of 5% at a one-sided significance level of 0.05. If at least 8 of 41 patients (20%) had response (CR/PR), this combination therapy would warrant further investigation. Based on the initial finding that 50% of *BRCA1/2* carriers achieved a partial response in the primary cohort, a target ORR response rate of 45% was selected for the expansion cohort, with a null response rate of 15% deemed to be of little clinical interest. The enrollment of 20 patients provided 87% power to identify the combination as worthy of further investigation if the true response rate was 45% at a one-sided significance level of 0.025. If at least 7 of 20 patients had response (CR/PR) at the end, this combination therapy would warrant further investigation.

Efficacy analyses were assessed in all patients, who received at least one cycle of study drugs. ORR and CBR at 4 months were reported as point estimates with 90% confidence intervals. PFS, defined as the time from enrollment until disease progression or death, was estimated by the Kaplan-Meier method. In

subgroup analyses stratified by *BRCA1/2* mutation status and prior platinum therapy, ORR and median PFS (mPFS) were compared by the Fisher's exact test and log rank test, respectively. Safety data were evaluated for all patients who received at least one dose of either study drug.

## Results

# Patient Characteristics

Of 63 patients with metastatic breast cancer were enrolled in this study, 62 patients received study drug and were included in the analysis. The primary cohort included 41 patients unselected for *BRCA1/2* mutations or breast cancer subtype, and the expansion cohort included 21 patients who all had *BRCA1/2* deleterious mutations.

Table 1 shows the baseline characteristics of patients in these two cohorts. Most patients had an ECOG score of less than 2 and one patient in the primary cohort was male. The primary cohort included TNBC (54%), HR+ (37 %), and HER2+ (10%) patients, while the expansion cohort included predominantly HR + patients (57%). Nine of 41 (22%) patients in the initial cohort had *BRCA1/2* mutations compared to all subjects in the expansion cohort. The most common metastatic sites were lymph nodes in the primary cohort and bone lesions in the expansion cohort. The median number of prior chemotherapeutic, hormonal, or HER2 directed regimens was 3 (range, 1–9) in the primary cohort and 2 (range, 0–9) in the expansion cohort. A total of 14 patients (34%) in the primary cohort and eight patients (38%) in the expansion cohort had received prior platinum therapy for metastatic disease.

Table 1
Baseline characteristics

| Characteristics | Primary Cohort (n = 41) | Expansion Cohort (n = 21) | Total (n = 62) |
|---|---|---|---|
| **Median age, yr (range)** | 50 (31–68) | 46 (29–81) | 48 (29–81) |
| **Female sex, no. (%)** | 40 (98) | 21 (100) | 61 (98) |
| **ECOG Performance Status, no. (%)** | | | |
| 0 | 21 (51) | 11 (52) | 32 (52) |
| 1 | 17 (42) | 9 (43) | 26 (42) |
| 2 | 3 (7) | 0 (0) | 3 (5) |
| **Subtypes, no. (%)** | | | |
| TNBC | 22 (54) | 8 (38) | 30 (48) |
| HR + HER2- | 15 (37) | 12 (57) | 27 (44) |
| HER2+ | 4 (10) | 1 (5) | 5 (8) |
| **BRCA mutation status, no. (%)** | | | |
| BRCA1 | 3 (7) | 9 (43) | 12 (19) |
| BRCA2 | 6 (15) | 12 (57) | 18 (29) |
| **Sites of disease, no. (%)** | | | |
| Bone | 26 (63) | 15 (71) | 41 (66) |
| Lung | 23 (56) | 10 (48) | 33 (53) |
| Liver | 20 (49) | 12 (57) | 32 (52) |
| CNS | 7 (17) | 6 (29) | 13 (21) |
| Lymph nodes | 29 (71) | 9 (43) | 38 (61) |
| **Prior lines therapies for metastatic diseases, median (range)** | 3 (1–9) | 2 (0–9) | 3 (0–9) |
| **Prior platinum treatment, no. (%)** | 14 (34) | 8 (38) | 22 (36) |

# Response to Treatment

Of 62 patients who received treatment, 10 patients had no follow-up imaging due to rapid clinical progression (7 in the primary cohort and 2 in the expansion cohort) or early death (one subject in the

expansion cohort). Thirty-four patients in the primary cohort and 18 patients in the expansion cohort were evaluable for response (Table 2).

Table 2

**Best objective response to treatment** [a]

| **Response, n (%)** | **Primary Cohort (n = 41)** | **Expansion Cohort (n = 21)** | **Total (n = 62)** |
|---|---|---|---|
| CR | 1 (2) | 0 | 1 (2) |
| PR | 3 (7) | 3 (14) | 6 (8) |
| SD | 13 (32) | 10 (48) | 23 (37) |
| PD | 17 (41) | 5 (24) | 22 (35) |
| NE | 7 (17)[b] | 3 (14)[c] | 10 (16) |
| *ORR* | *4 (9)* | *3 (14)* | *7 (11)* |
| *CBR at 4 mo* | *11 (27)* | *9 (43)* | *20 (32)* |

[a] *This table shows the number of patients with each response (%) in the primary cohort, the expansion cohort and the total study population; the denominators used in all calculations consisted of the total numbers of patients in each group; The subgroup analyses by status of BRCA1/2 mutation and the prior platinum treatment are presented in* Table 3;

[b] *7 patients had no follow-up imaging due to rapid clinical progression; one of these patients had a BRCA2 mutation;*

[c] *Patients had no follow-up imaging due to rapid clinical progression (n = 2) or early death (n = 1);*

*Abbreviations: CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; NE, Non-evaluable; ORR, objective response rate; CBR at 4 mo, Clinical benefit rate at 4 months*

In the combined overall population of 62 patients, the ORR (CR + PR) was 12% (7/62) and the CBR at 4 months was 32% (20/62); the primary cohort had a 10% (4/41) ORR and 27% (11/41) CBR at 4 months, while the *BRCA1/2* expansion cohort had a 14% (3/21) ORR and 43% (9/21) CBR at 4 months. The waterfall plots demonstrated the best overall response of evaluable patients in each cohort (Supplemental Fig. 1). In the primary cohort (n = 34 evaluable, Supplemental Fig. 1A), all four patients who achieved CR or PR had *BRCA1/2* mutations. Thirteen patients in this cohort, including one who had an unconfirmed partial response, demonstrated stable disease according to RECIST 1.1 criteria. Seventeen patients had PD, including eight with stable target lesions but with non-target progression or new lesions elsewhere. In the *BRCA1/2*-positive expansion cohort (n = 18 evaluable, Supplemental Fig. 1B), three patients achieved PR, an additional 10 patients had SD, and five patients had PD, including one patient who achieved SD in target lesions but had new lesions. Combining both cohorts, all seven patients who had achieved a response (CR or PR) were *BRCA1/2* carriers, including five patients with

*BRCA2* mutations and two patients with *BRCA1* mutations (Fig. 1). There were no responses in patients without *BRCA1/2* mutations (Figs. 1 and 2).

In an exploratory subgroup analysis stratified by prior platinum treatment (Table 3), the ORR was 15% (6/40) among platinum-naïve patients versus 5% (1/22) among platinum-exposed patients. The CBR at 4 months was 38% (15/40) in the platinum-naïve group compared to 23% (5/22) in the platinum-exposed group.

Table 3
Subgroup responses to treatment by *BRCA1/2* mutation status and prior platinum treatment

| **Response n (%)** | **BRCA1/2 mutation** | | **Prior platinum treatment** | | **BRCA mutation** | | **No BRCA mutation** | |
|---|---|---|---|---|---|---|---|---|
| | Yes (n = 30) | No (n = 32) | Yes (n = 22) | No (n = 40) | Prior platinum Tx (Yes, n = 11) | Prior platinum Tx (No, n = 19) | Prior platinum Tx (Yes, n = 11) | Prior platinum Tx (No, n = 21) |
| CR | 1 (3) | 0 | 0 | 1 (3) | 0 | *1 (5)* | 0 | 0 |
| PR | 6 (20) | 0 | 1(5) | 5 (13) | 1 (9) | *5 (26)* | 0 | 0 |
| SD | 12 (40) | 11 (34) | 5 (23) | 18 (45) | 3 (27) | *9 (47)* | 2 (18) | 9 (43) |
| PD | 7 (23) | 15 (47) | 11 (50) | 11 (28) | 4 (36) | *3 (16)* | 7 (64) | 8 (38) |
| NE | 4 (13) | 6 (19) | 5 (23) | 5 (13) | 3(27) | *1 (5)* | 2 (18) | 4 (19) |
| ORR | 7 (23) | 0 | 1 (5) | 6 (15) | 1 (9) | *6 (32)** | 0 | 0 |
| CBR at 4 mo | 14 (47) | 6 (19) | 5 (23) | 15 (38) | 3(27) | *11 (58)** | 2 (18) | 4 (19) |

** P < 0.01 comparing this group to all other groups by the Fisher's Exact test*

*Abbreviations: CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; NE, Non-evaluable; ORR, objective response rate; CBR at 4 mo, Clinical benefit rate at 4 months*

In the subgroup analysis based on *BRCA1/2* mutation status (Table 3 and Fig. 1), the ORR was 23% (7/30) among *BRCA1/2* carriers compared to 0% (0/32) among non-carriers. Of these seven patients, six had no previous platinum treatment (Fig. 2) and one had prior platinum exposure but did not have documented progression on platinum therapy. The CBR at 4 months was 47% (14/30) for *BRCA1/2*

carriers versus 19% (6/32) for non-carriers. Furthermore, platinum-naïve patients with *BRCA1/2* mutations had an ORR of 32% (6/19) and a 4-month CBR of 58% (11/19), while platinum-exposed patients with *BRCA1/2* mutations had an ORR of 9% (1/11) and a 4-month CBR of 27% (3/11; Table 3 and Fig. 2).

Comparing the different subtypes of metastatic breast cancer (Supplemental Table 1), the ORRs were 19% (5/27), 17% (1/6), and 3% (1/29) for HR+, HER2 + and TNBC, respectively, while the 4-month CBR rates were 41% (11/27), 50% (3/6), and 21% (6/29) for HR+, HER2 + and TNBC, respectively.

# Survival analysis

The median PFS was 2.1 months (90% CI, 1.8 to 3.0 mo) in the overall population (Fig. 3A), and 1.8 months and 3 months in the primary and expansion cohorts, respectively (Supplemental Fig. 2). The median PFS among *BRCA1/2* carriers was 3.3 months (90% CI, 2.3 to 6.2 mo) compared to 1.8 months (90% CI, 1.6 to 2.3 mo) among non-carriers (HR: 0.48, p = 0.006; Fig. 3B). Among patients who had not received prior platinum therapy, the median PFS was 2.7 months (90% CI, 1.9 to 4.0 mo) compared to 1.9 months (90% CI, 1.3 to 2.3 mo) among patients who had received prior platinum therapy (HR: 0.45, p = 0.005; Fig. 3C). Patients who were *BRCA1/2* carriers without prior platinum therapy had a significantly prolonged progression-free survival (mPFS 6.2 mo; 90% CI, 3.7 to 7.3 mo) compared to other groups (HR: 0.34, p = 0.0003; Fig. 3D). One patient, a *BRCA2* carrier who had no prior platinum therapy, had a durable complete remission for at least 5 years as of last contact. No significant difference in PFS was observed by breast cancer subtype (Supplemental Fig. 3).

# Safety

All 62 patients who received at least one dose of veliparib and TMZ were considered for safety evaluation. Patients had a median treatment duration of 9 weeks (range 0.1 to 85 weeks), with a median daily dose of 60 mg (range, 40 to 80mg) for veliparib and 200 mg (range, 75 to 480 mg) for TMZ. A total of 27 and 26 patients had a dose delay on veliparib and TMZ respectively; 29 patients (47%) had a dose modification on TMZ.

Of the 62 patients, one patient received only one dose of veliparib and TMZ and experienced no treatment-related adverse events. The most common all-grade AEs were thrombocytopenia, nausea, fatigue, anemia, and leukocytosis (Table 4), and the most frequent grade 3 or higher AEs were thrombocytopenia, neutropenia, leukocytosis, nausea, and vomiting. The most common AEs that caused dose delays or modifications were thrombocytopenia and neutropenia. One patient discontinued study treatment due to prolonged thrombocytopenia. Another patient died of sepsis after receiving 4 cycles of treatment.

Table 4
Treatment-related adverse events

| Event | All Grade | Grade3 | Grade 4 | Grade 5 |
|---|---|---|---|---|
| | n (%) (Total n = 62) | | | |
| Thrombocytopenia | 51 (82) | 20 (32) | 11 (18) | |
| Nausea | 45 (73) | 6 (10) | | |
| Fatigue | 37 (60) | 4 (6) | | |
| Anemia | 36 (58) | 4 (6) | 1 (2) | |
| Leukocytosis | 33 (53) | 10 (16) | | |
| Neutropenia | 32 (52) | 13 (21) | 4 (6) | |
| Vomiting | 21 (34) | 5 (8) | | |
| Lymphopenia | 19 (31) | 4 (6) | | |
| Anorexia | 13 (21) | 1 (2) | | |
| ALT, SGPT | 12 (19) | 0 | | |
| Alkaline phosphatase | 10 (16) | 0 | | |
| Headache | 10 (16) | 2 (3) | | |
| Constipation | 9 (15) | 0 | | |
| Diarrhea | 9 (15) | 1 (2) | | |
| Hypokalemia | 9 (15) | 1 (2) | | |
| AST, SGOT | 8 (13) | 0 | | |
| Hyperglycemia | 7 (11) | 0 | | |
| Febrile neutropenia | 3 (5) | 2 (3) | 1 (2) | |
| Dyspnea | 3 (5) | 1 (2) | 1 (2) | |
| Anxiety | 2 (3) | 1 (2) | | |
| Allergic reaction | 1 (2) | 1 (2) | | |
| Infection, lung | 1 (2) | 1 (2) | | 1 (2) |
| Hypoxia | 1 (2) | 1 (2) | 1 (2) | |

# Discussion

Although neither cohort in this study met the prespecified target ORR, the combination of veliparib and TMZ demonstrated antitumor activity among metastatic breast cancer patients with *BRCA1/2* mutations, particularly those who had not received prior platinum chemotherapy. The objective response rate was significantly greater and the median PFS was significantly longer among *BRCA1/2* carriers than non-carriers, and among patients who had not received prior platinum chemotherapy than those who had. A higher ORR (32%) and CBR at 4 mo (58%), and a longer PFS (6.2 mo) were observed in the subset of *BRCA1/2*-positive patients who had not received prior platinum therapy. Although the study was initially designed to test the hypothesis that the combination of TMZ and veliparib was active in metastatic breast cancer regardless of BRCA mutation status, there was no clinical activity observed in non-carriers despite encouraging preclinical data.

This was the first study to evaluate the efficacy of veliparib and TMZ in breast cancer. A previous trial of single-agent veliparib (400 mg BID) in platinum-naïve BRCA-mutant breast cancer showed response rates of 14% (3/22) for *BRCA1*+ patients and 36% (8/22) *BRCA2*+ patients [28]. These response rates were comparable to the ORR of 32% observed in this study among platinum-naïve BRCA+ patients (Table 3). Notably, patients in the present study received veliparib twice daily at 30–40 mg, about one tenth of the dose used in the previous trial, suggesting that the observed activity in our study was unlikely due to the single agent activity of veliparib. Rather, our data support that TMZ enhanced the efficacy of veliparib in BRCA-deficient patients. The observation that this combination led to responses only in patients with BRCA1/2 deficiency suggests that responses were dependent on the mechanism of synthetic lethality, in which inhibition of PARP in the presence of BRCA deficiency made cancer cells more vulnerable to TMZ-induced DNA damage. This may explain why the addition of TMZ to veliparib exhibited antitumor efficacy at a lower dose of veliparib, whereas single-agent veliparib required a higher dose for clinical activity in this population [28].

In this study, the combination of veliparib and TMZ had no activity in patients who had progressed on prior platinum therapy. This result is consistent with prior work showing that PARP inhibitors and platinum agents share common mechanisms of resistance [29, 30, 7], at least partly explained by secondary somatic mutations that restore the function of BRCA1/2 proteins [31, 29, 32]. Other overlapping resistance mechanisms to both PARP inhibitors and platinum therapy include microRNA-mediated restoration of HR, replication fork stabilization, PARP1 mutations, and drug efflux pumps [33, 7, 34].

Previous studies showed PARP inhibition potentiates the activity of TMZ and exacerbates TMZ hematological toxicity [15–19]. Accordingly, thrombocytopenia was the most common hematological toxicity in this study. The severity of hematologic toxicities in this study was comparable to a subsequent study with the same combination regimen [14] and was more prominent than in patients receiving veliparib monotherapy [28]. One patient in this study discontinued treatment due to thrombocytopenia, and another patient died due to severe infection possibly related to the study treatment. The observed hematological toxicity was effectively managed in most patients with dose reductions of TMZ.

This proof-of-concept phase II study had several limitations. The single-arm design and lack of a comparison group prevent drawing conclusions about the efficacy of this combination therapy compared to single-agent veliparib. Furthermore, although TMZ has no demonstrated activity in metastatic breast cancer, it has not been evaluated in breast cancer patients with BRCA1/2 mutations. Additionally, the small sample size precluded analyses with adequate power to detect enhanced efficacy in subgroups. Despite these limitations, this study suggested that veliparib with TMZ had clinical activity in platinum-naïve BRCA-deficient breast cancer patients and led to a multicenter randomized phase II BROCADE study of veliparib and TMZ compared to carboplatin and paclitaxel with or without veliparib among patients with BRCA-associated metastatic breast cancer [35, 14]. The BROCADE trial found that TMZ with veliparib yielded inferior ORR and PFS compared to carboplatin and paclitaxel with or without veliparib [14]. Thus, veliparib combined with platinum-based regimens had better efficacy than veliparib combined with TMZ. The subsequent phase III BROCADE3 trial evaluated the efficacy of carboplatin and paclitaxel with or without veliparib in BRCA1/2-deficient MBC and confirmed improved PFS with the addition of veliparib (HR 0.71) [36].

# Conclusion

In this phase II study, veliparib and TMZ showed efficacy in patients with BRCA-deficient metastatic breast cancer with no prior platinum treatment that was comparable to single-agent veliparib at a higher dose. However, the study did not meet its primary response rate endpoint in patients with MBC unselected for BRCA mutations, nor in patients with known BRCA mutation. The regimen was predominantly associated with hematologic adverse events manageable with dose modifications.

# Declarations

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### Compliance with ethical standards

## Conflicts of interest The corresponding author SJI has received institutional research funding and consulting fees from Abbvie. JX, TEK, BO, NMT, RSG, KH, JEG, LWE, EPW, PEG, BYY, and BAC report no conflicts of interest to this study.

**Ethical approval** The study protocol and informed consent form were reviewed and approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) institutional review board. This study was performed in accordance to the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

**Informed consent** Written informed consent was obtained from all patients involved in the study before any study procedure.

**Consent to participate** Not applicable

**Consent for publication** Not applicable

**Availability of data and material** Not applicable

**Code availability** Not applicable

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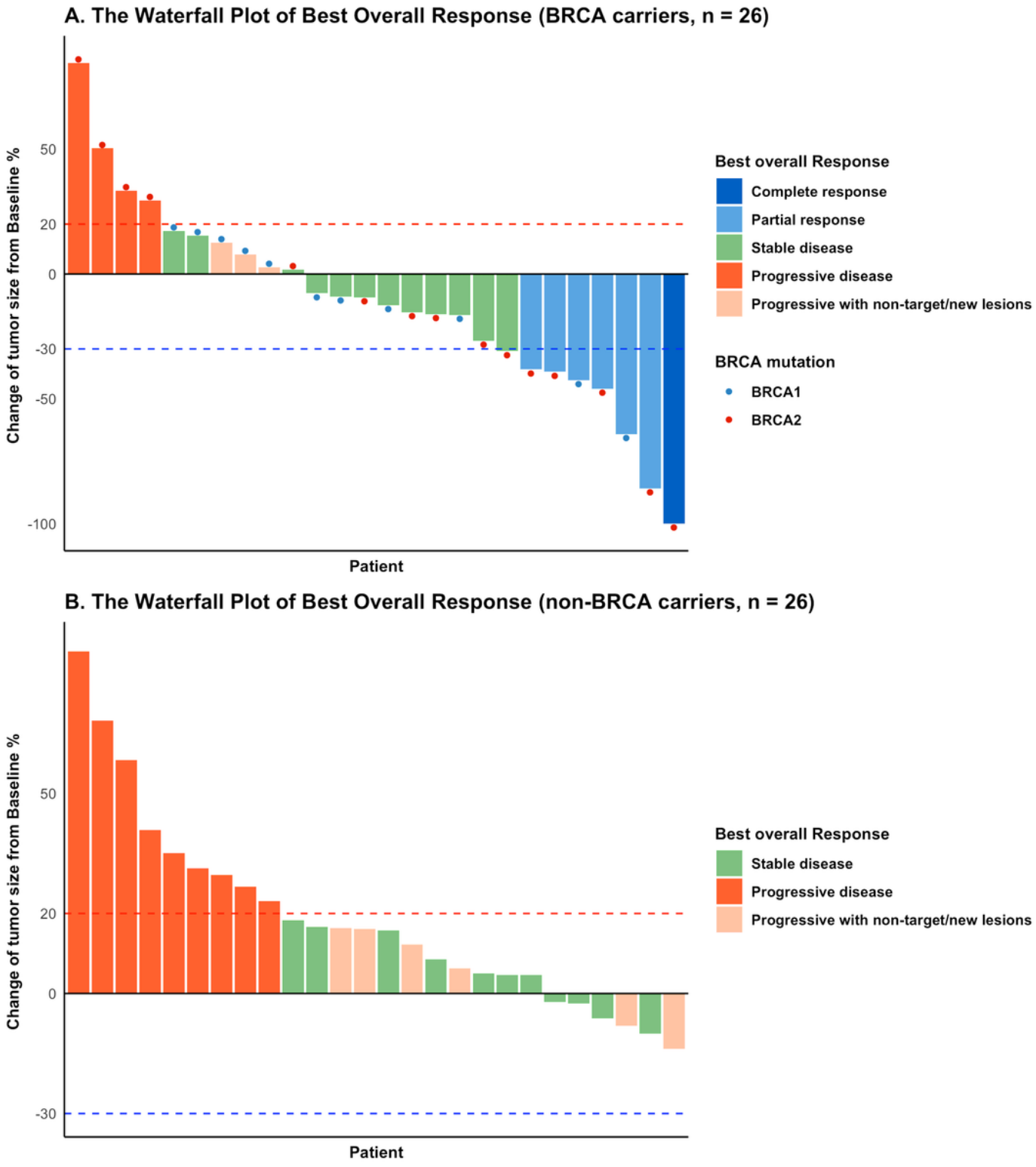
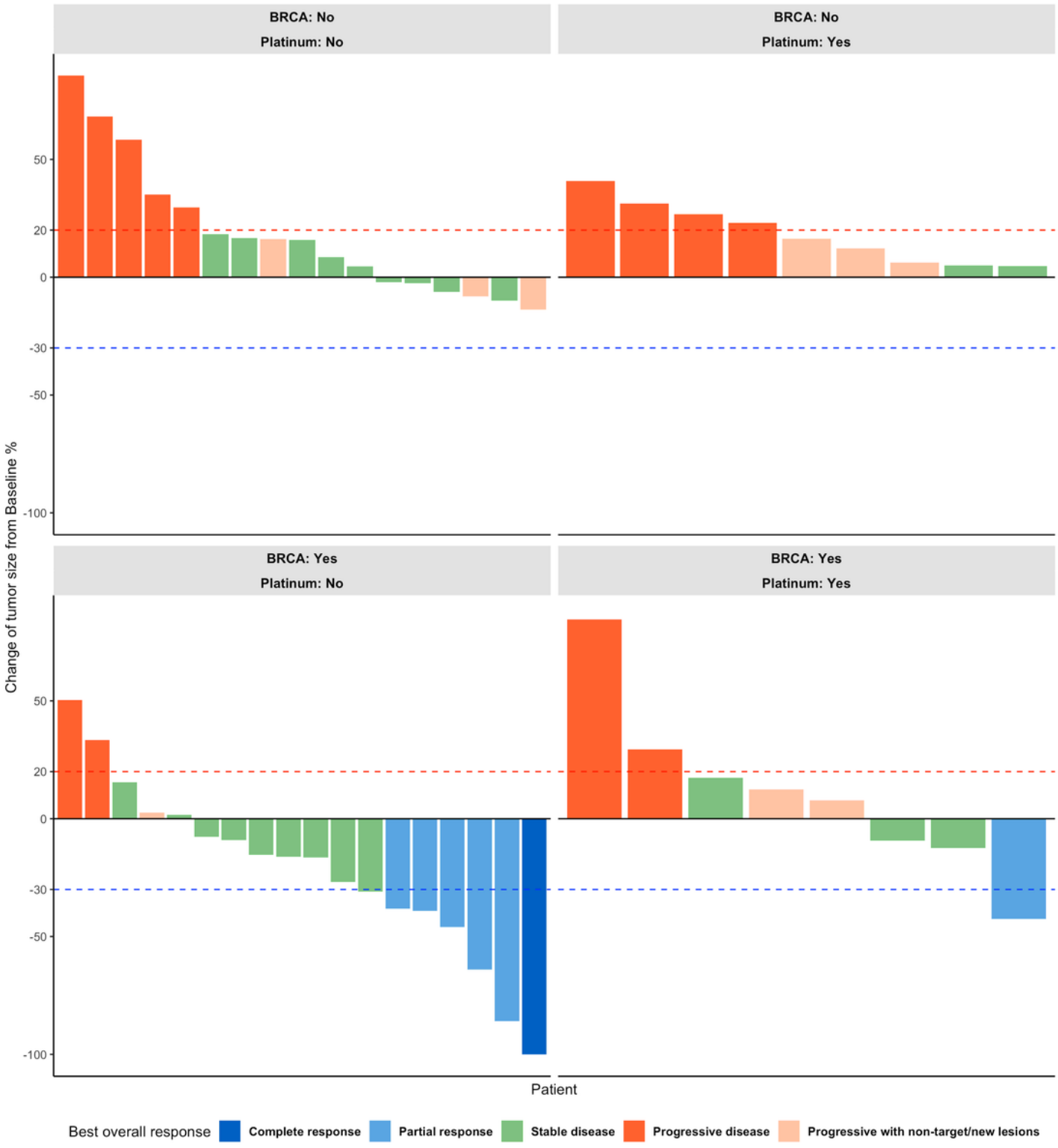
# Figures



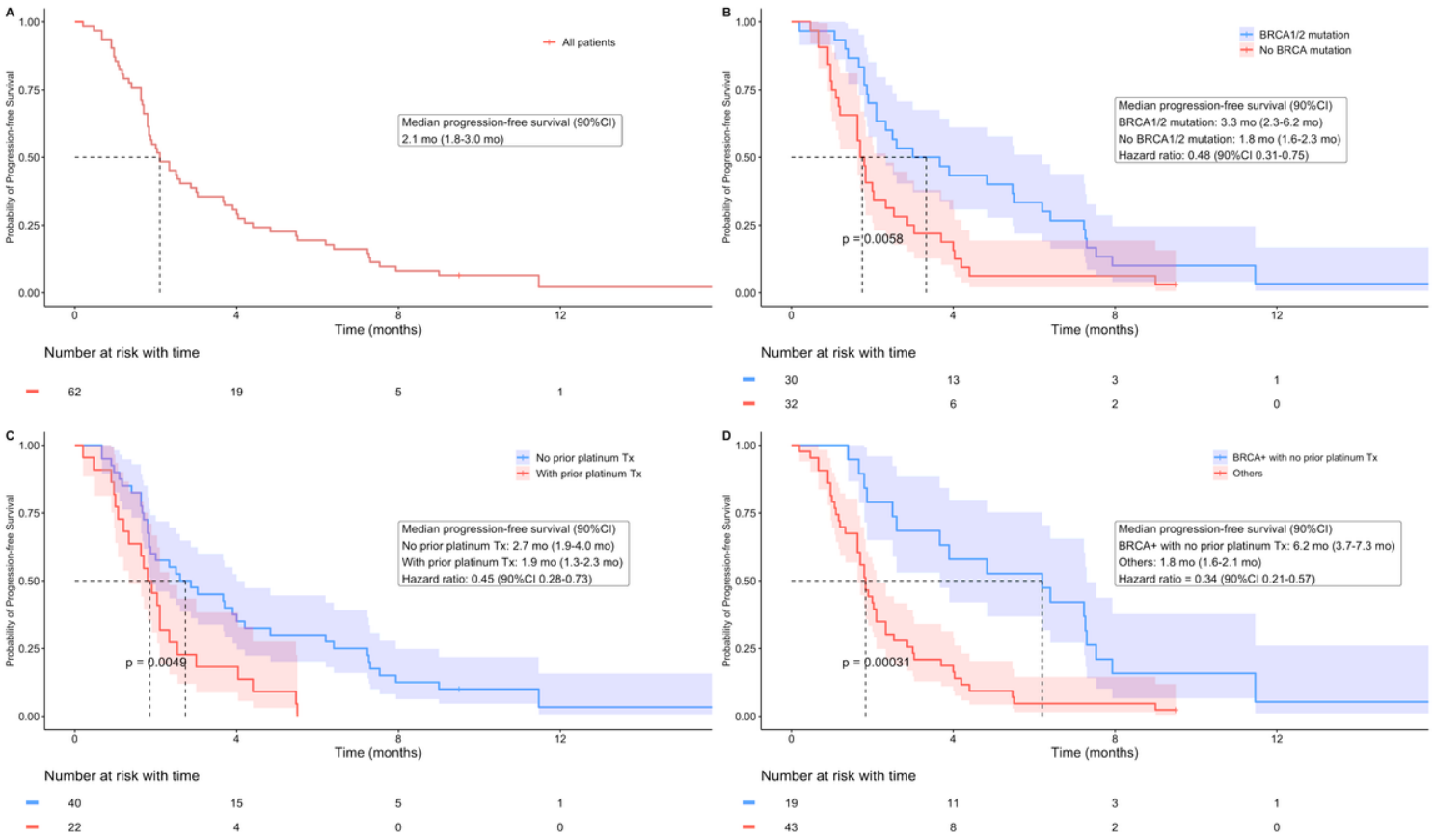

## Figure 1

Waterfall plot s of best overall response by BRCA mutation status Among BRCA carriers (A), 4 patients were non-evaluable due to clinical progression (n = 3) or early death (n = 1) before follow-up imaging. Among non-carriers (B), 6 patients were non-evaluable due to clinical progression before follow-up imaging.




## Figure 2

Waterfall plots of best overall response by prior platinum treatment and BRCA mutation status




## Figure 3

Kaplan-Meier estimates of progression-free survival (A), in overall population; (B), by BRCA mutation status; (C), by prior platinum therapy; (D), comparing patients with BRCA positive disease without prior platinum therapy to all other patients.