TARGETED THERAPIES FOR THE TREATMENT OF METASTATIC BREAST CANCER

By

Jing Xu, MD PhD MSc

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Area of Concentration: Clinical Drug Development, Oncology
Thesis Mentors:
Dr. Bruce A. Chabner (Primary mentor)
Dr. Steven J. Isakoff (Co-mentor)

I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

Primary Mentor: Revised Date:

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OVERVIEW OF THE THESIS STUDIES

In the United States, 13% of women are diagnosed with invasive breast cancer in their lifetime and 6% of breast cancer patients have metastatic disease at initial diagnosis [1]. Moreover, nearly 30% of women with early stage breast cancer will develop metastatic disease [2]. About 42,000 deaths from breast cancer occur annually, largely due to metastatic breast cancer (MBC). The prognosis of MBC is poor and the five-year survival rate is about 27% [1].

Metastatic breast cancer is characterized with high heterogeneity [3]. It consists of many different molecular subtypes, which include hormone receptor positive (HR+), epidermal growth factor receptor type 2 positive (HER2+) and triple negative breast cancer (TNBC) [4]. In addition to molecular heterogeneity, individuals often reveal various inherited genetic alterations, such as germline mutations in BRCA 1 or 2, PALB2, CHEK2, and others which may influence the outcome of therapies [5-7]. Tumor molecular features may also change as drug resistance emerges during the course of disease. All of these make the treatment of MBC and the evaluation of new therapies a complex process. However, in recent years, a better understanding of molecular features and genetic heterogeneity have contributed to the development of new targeted therapies such as HER2 inhibitors, CDK4/6 inhibitors, PI3K inhibitors and PARP inhibitors, as well as combined strategies including hormone therapy with CDK4/6 inhibitors for HR+ disease and HER2 inhibitors with chemotherapy for HER+ [3]. Despite the efficacy of these new therapies, drug resistance remains a major issue in the management of MBC. Therefore, development of new targeted strategies will always be necessary for treating MBC.

The purpose of my work was to investigate how new therapeutic drugs or combinations, advance the knowledge and guide clinical practice in treating MBC. I have advanced my understanding

of the process of clinical research through analysis and interpretation of two Phase II clinical trials of targeted therapies in breast cancer.

Overexpression of MET, RET and VEGFR are prominent in subsets of metastatic breast cancer, which implicate tumor proliferation, angiogenesis, progression and survival [8-10]. Cabozantinib targeting these receptor tyrosine kinases (RTKs) poses a promising therapeutic strategy for improving breast cancer treatment [11, 12]. However, clinical experience with Cabozantinib is very limited in metastatic breast cancer. In addition, bone lesions are a prominent challenge for treatment of MBC. Nearly 75% of patients with HR+ MBC develop bone metastasis and many have bone-only disease, which has been difficult to evaluate for response [13]. Cabozantinib has been noted to contribute to an improved bone scan response in metastatic prostate cancer patients, but this observation has not been translated into a survival benefit in a randomized clinical trial [14]. Therefore, my first study was to assess the efficacy of cabozantinib in patients of HR+ breast cancer with bone metastases using bone scan response as a primary endpoint and evaluating whether bone scan response was correlated with other important clinical endpoints, such as overall survival and progression free survival.

PARP inhibitors, which block an important initial step in the repair of DNA, offer a very promising therapeutic strategy for metastatic breast cancer, particularly for BRCA1/2 deficient tumors. These inhibitors are known to potentiate the cytotoxic effects of DNA-damaging chemotherapies, such as temozolomide, an alkylating agent [15]. Veliparib (ABT888) as a novel oral PARP inhibitor, has modest activity as a monotherapy in breast cancer because of low trapping efficiency [16]; however, it demonstrated potential in the combination setting due to less toxicity profile, compared to other PARP inhibitors [17]. Combination of veliparib (a PARP inhibitor) and temozolomide has demonstrated substantial activity against breast cancer in

preclinical models and in patients with other solid tumors [18-20]. Thus, my second study evaluated this novel, oral combination therapy in breast cancer patients with or without germline BRCA mutations.

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A phase II trial of cabozantinib in hormone-receptor positive breast cancer with bone metastases

Jing Xu, MD, PhD[1,2], Michaela J. Higgins, MD[3*], Sara M. Tolaney, MD[4,2], Steven E. Come, MD[5,2], Matthew R. Smith MD, PhD[1,2], Monica Fornier, MD[6], Umar Mahmood, MD, PhD[7,2], Jose Baselga, MD, PhD[6,8], Beow Y. Yeap, ScD[1,2], Bruce A. Chabner, MD[1,2], Steven J. Isakoff, MD, PhD[1,2]*

1 Massachusetts General Hospital Cancer Center, Boston, MA 02114

2 Harvard Medical School, Boston, MA 02115

3 Department of Medical Oncology, Mater Misericordiae University Hospital

4 Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA 02115

5 Department of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA 02215

6 Memorial Sloan Kettering Cancer Center, New York, NY 10065

7 Department of Radiology, Massachusetts General Hospital, Boston, MA 02114

8 Research & Development Oncology, AstraZeneca Pharmaceuticals, Gaithersburg, MD 20878, USA

* These authors contributed equally to this work

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Corresponding Author:
Steven J. Isakoff, MD PhD
Massachusetts General Hospital Cancer Center
55 Fruit Street
Boston, MA 02114
Tel: 617-726-4920
Fax: 617-643-0589
Email: sisakoff@mgh.harvard.edu

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Implication for practice

Most patients with metastatic hormone receptor positive (HR+) breast cancer have bone involvement, and many have bone-only disease which is difficult to evaluate for response. In this phase II single arm study, we evaluated the clinical activity of the small molecule MET/RET/VEGR2 inhibitor cabozantinib in patients with metastatic HR+ breast cancer with bone metastases. This study met its primary endpoint and cabozantinib treatment resulted in a significant bone scan response rate correlating with improved survival. This is the first study to use bone scan response as a primary endpoint in breast cancer. Our results support further study of cabozantinib in HR+ breast cancer.

Abstract

Background

We assessed the antitumor activity of cabozantinib, a potent multi-receptor oral tyrosine kinase inhibitor, in patients with hormone-receptor positive breast cancer with bone metastases.

Patients and Methods

In this single-arm multicenter phase II study, patients received an initial starting dose of 100 mg, later reduced to 60 mg per day. The primary endpoint was the bone scan response rate. Secondary endpoints included objective response rate (ORR) by RECIST, progression free (PFS) and overall survival (OS).

Results

Of 52 women enrolled, 20 (38%) experienced a partial response on bone scan and 6 (12%) had stable disease. Prior to the first repeat bone scan at 12 weeks, 19 (35%) patients discontinued study treatment because of early clinical progression or unacceptable toxicity. RECIST evaluation based on best overall response by CT revealed stable disease in extraosseous tissues in 26 patients (50%), but no complete or partial responses. In 25 patients with disease control on bone scan at 12 weeks, only 3 (12%) patients developed extraosseous progression. The median PFS was 4.3 months and median OS was 19.6 months. The most common grade 3 or 4 toxicities were hypertension (10%), anorexia (6%), diarrhea (6%), fatigue (4%) and hypophosphatemia (4%).

Conclusion

Bone scans improved in 38% of patients with metastatic hormone receptor positive breast cancer and remained stable in an additional 12% for a minimum duration of 12 weeks on cabozantinib. Further investigations should assess the activity of cabozantinib in combination with other hormonal and other breast cancer therapies and determine whether bone scan responses correlate with meaningful antitumor effects.

Introduction

Cabozantinib (Cometriq, XL184) inhibits multiple receptor tyrosine kinases including MET, RET, vascular endothelial growth factor receptor 2 (VEGFR2) and AXL [1-3]. These kinases play an important role in tumor angiogenesis, invasion and metastasis [1-3]. Cabozantinib is approved for the treatment of metastatic medullary thyroid cancer, advanced renal cell carcinoma and hepatocellular carcinoma [4-6].

Overexpression of MET has been observed in all pathological subtypes of breast cancers [1]. Both MET and its ligand hepatocyte growth factor (HGF) promote tumor proliferation, angiogenesis, progression and survival [7, 8]. RET overexpression in hormone-receptor-positive (HR+) breast cancer is also associated with endocrine resistance to tamoxifen and aromatase inhibitors [9-11]. A recent study of metastatic breast cancer discovered RET alterations including amplification, missense mutations, and fusions which activate RET kinase and downstream signaling pathways through MAPK and PI3K [2]. Furthermore, cabozantinib showed anti-tumor activity in a patient with RET fusion positive tumor in the same study. High expression of VEGFR2 in breast cancer may promote tumor progression and metastasis [3, 12]. Based on these considerations, cabozantinib offers a promising therapeutic strategy for breast cancer.

Currently, clinical experience with cabozantinib in breast cancer is limited. In vitro and in vivo studies have shown cabozantinib inhibits MET, VEGFR2 and RET, resulting in anti-tumor activity in many tumor models, including breast cancer [13-17]. In a phase II clinical study, 45 patients with metastatic estrogen receptor positive (ER+) or triple-negative breast cancer (TNBC) received cabozantinib and 21 (47%) achieved partial response or stable disease [18].

Although overexpression of MET is associated with poor clinical outcomes in TNBC, cabozantinib showed a clinical benefit rate of 34% in this subset of patients after 15-weeks of cabozantinib treatment [19]. Further investigations are required to establish the activity of cabozantinib in breast cancer subgroups and identify biomarkers of response.

Up to 75% of patients with metastatic breast cancer develop bone metastases during the course of their disease with even higher rates in hormone-receptor positive disease [20-22]. For many patients with ER+ metastatic breast cancer, bone may be their only metastatic site [23]. Metastatic bone lesions from cancer as imaged on a bone scan, FDG-PET scan or plain films are not considered 'measurable' by the widely accepted RECIST v1.1 [24]. This excludes many patients with bone only disease from the many clinical trials that require response measurements as a primary endpoint. Therefore, there remains a need to optimize a clinical trial endpoint in this population with bone metastases and to evaluate novel agents that may effectively treat their metastatic disease burden in bone as well as soft tissue sites.

In a previous phase III trial of cabozantinib in metastatic prostate cancer, bone scan response (BSR) at week 12 was used as a key secondary end point [25]. Interestingly, in this study cabozantinib produced a 42% BSR at week 12. However, the benefit in bone scan response did not translate to a significant improvement in OS [25]. The lack of correlation of bone scan improvement with improved overall survival led to speculation that the drug, perhaps through its antiangiogenic activity, is limiting bone scan nuclide uptake.

This trial sought to evaluate the BSR to cabozantinib in metastatic breast cancer patients and whether BSR may be a reliable surrogate primary endpoint for determining clinical benefit. We report an open-label, single arm, multi-site phase II trial of cabozantinib in women with metastatic hormone-receptor-positive (HR+) breast cancer with bone metastases. The primary endpoint of this study was bone scan response rate and we also evaluated whether bone scan response correlated with improved survival.

Methods

Patients

Eligible patients were ≥ 18 years of age and had histologically confirmed ER+ and/or PR+, HER2 negative metastatic breast cancer with clear evidence of metastases to bone on isotope bone scan at screening, with or without extraosseous metastases. At baseline, subjects with bone-only disease were required to have at least two bone lesions that were not within a previously irradiated field. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status < 2, an estimated life-expectancy > 3 months, at least one prior line of hormonal or chemotherapy for treatment of their metastatic disease, and adequate liver, kidney and marrow function. Patients were excluded if they had received chemotherapy, bone modulating agents, small-molecular kinase inhibitors or any investigational agent within 4 weeks, or hormonal anticancer therapy, immunotherapy, or radiotherapy to bone and brain metastasis within 2 weeks, or biological agents within 6 weeks before the first dose of cabozantinib.

The study protocol and informed consent documents were reviewed and approved by the institutional review boards at Dana Farber Cancer Institute (DFCI) and Memorial Sloan-Kettering Cancer Center (MSKCC), and all patients provided written informed consent. This study was performed according to the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

Study design and treatment

This open-label, multi-center single arm study was conducted at Massachusetts General Hospital (MGH), DFCI, Beth Israel Deaconess Medical Center (BIDMC), and MSKCC. The primary endpoint was bone scan response rate. Secondary endpoints included objective response rate of extraosseous sites by RECIST, overall and progression free survival.

Patients received cabozantinib orally at 100 or 60 mg (freebase weight) once per day. The initial dose was reduced from 100 to 60 mg after enrollment of the first 7 patients because of excessive toxicity at the higher dose. All patients were instructed to take cabozantinib each morning in a fasting state either 2 hours after or 1 hour before a meal and continued to take cabozantinib until disease progression or unacceptable adverse events.

Dose reductions or interruptions were allowed for unacceptable adverse events (AEs). Cabozantinib dose was sequentially reduced from 100 to 60 mg, and in the presence of grade 3/4 toxicity, further reductions to 40 mg and 20 mg were allowed. Patients recovering from AEs

within 6 weeks after dose interruptions or reductions were allowed to continue the study treatment.

Study outcomes and assessment

Tumor response was assessed by isotope bone scan and whole body FDG-PET/CT. Patients had screening bone scan and PET/CT scan within 28 days prior to the initial dose of cabozantinib and every 12 weeks thereafter until discontinuation of treatment or death. All bone and PET/CT images collected at the above prespecified times underwent independent radiologic assessment (MedQIA, Los Angeles, CA). Only patients who had at least six weeks of treatment and had follow-up bone scans or PET/CT scans were evaluable for response. Bone scan response (BSR) was determined by the percentage change of bone scan area from baseline (% BSA). Responses were categorized as complete (complete resolution), partial (>= 30% reduction), stable disease (between < 30% reduction and < 20% increase), or progressive disease (>= 20% increase). Bone scan response rate was defined as the percentage of patients experiencing a complete or partial response in bone scan lesions. Overall response rate (ORR) was defined as the proportion of treated patients experiencing a complete response (CR) or a partial response (PR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Those who had less than 6 weeks of treatment, or had developed progressive disease or died before the re-evaluation date, or had not undergone re-evaluation were considered non-responders. The best overall response was defined as the best response from the time of enrollment until termination of study treatment.

Adverse events (AEs) were assessed from the start of treatment according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

The primary endpoint was bone scan response rate. A total sample size of 50 was estimated using Simon's two-stage design with 92% power to detect a bone response rate of 30%, compared to a null response rate of 10%, at a significance level of 0.1 (type I error). In the first stage, 17 patients were recruited and if two or fewer bone responses were observed the study would be stopped. Otherwise, 33 additional patients would be accrued for a total of 50. If 8 or more responses were observed in 50 patients, the null hypothesis would be rejected and cabozantinib was considered promising for further investigation.

Descriptive statistics were used to summarize baseline characteristics. Bone scan response rate and ORR were reported as point estimates with 90% confidence intervals. Median OS and PFS were estimated for the overall study population, along with 90% confidence intervals, using the Kaplan-Meier approach. Stratified OS and PFS analyses were performed to compare subjects with bone lesions only to those with bone plus other site lesions to provide point estimates with 90% confidence intervals. The log-rank test was used to compare these two subgroups. Exploratory landmark analysis of OS or PFS was performed based on the 12-week bone scan responses [26]. Patients who achieved PR or SD on bone scans at 12 weeks were classified as the disease control (DC) group. Those who progressed on bone scans (PD) or were non-evaluable at 12 weeks (due to treatment discontinuation or early disease progression) were classified as the

non-DC group. In this analysis, only patients alive or progression-free at the landmark time (12 weeks from baseline) were included in the analysis of overall survival or progression-free survival. Kaplan Meier estimates of survival probability were conditional on the status of bone scan response at the landmark time of 12 weeks for patients who survived up to this time. Treatment-related grade 3 or 4 were summarized by descriptive statistics.

Results

Patients and treatment

From November 2011 through January 2013, a total of 55 patients were enrolled at four study centers. Three patients withdrew from this study before receiving any treatment. In total, 52 patients received cabozantinib treatment and were evaluable for data analysis. The flowchart (Figure 1) shows the status of patient enrollment, treatment, and follow-up for the primary endpoint. In the first stage, 4 of 17 patients showed significant improvement (PR) after the 12-week bone scan and the study continued to stage 2.

Baseline demographics and clinical characteristics of the 52 treated patients are listed in Table 1 (and Supplemental Table 1). All patients were ER+, as assessed in either metastatic lesions (45 patients) or primary tissues (7 patients), and 40 patients (77%) were PR +. All patients had evidence of bone metastases on bone scan at baseline and 18 (35%) had bone-only disease. The majority of patients were heavily pre-treated for metastatic disease with 45 (87%) and 37 patients (71%) having previously received endocrine therapy or chemotherapy, respectively. 28 (54%)

and 22 patients (42%) had at least 2 lines of endocrine therapy or chemotherapy, respectively, for metastatic disease and 45 patients (87%) had received bisphosphonate bone modifying agents.

The first 7 patients (13%) had an initial cabozantinib daily dose of 100 mg (freebase weight), but due to toxicity the remaining patients started at a daily dose of 60 mg. Treatment durations of patients ranged from 1 to 204 weeks; 30 patients were treated for at least 12 weeks and 22 were treated for less than 12 weeks, of whom 9 had less than six weeks of treatment.

Bone scan response

All 52 patients who received cabozantinib treatment were included in the data analysis for bone scan responses. According to the prespecified criteria, 19 patients (36.5%) were considered non-evaluable for bone scan response because they either had no follow-up images (n = 16, early treatment discontinuation before re-evaluation date), or follow-up images were not available for central review (n =3). The remaining 33 patients (63.5%) who received at least 6 weeks of cabozantinib and had at least one follow-up bone scan at week 12 or at the last study point were considered evaluable for bone scan responses.

Table 2 shows the bone scan responses to cabozantinib treatment. The bone scan response rate was 38.5% (90% CI 27.1% to 51.0%), including 20 patients who achieved a partial response (PR) and none with a complete response (CR) of bone lesions. The disease control rate (DCR) was 50% (26/52), defined as the percentage of patients with PR or SD (6 patients), based on the best overall response by bone scan. Progressive disease was the best response in 7 patients

(13.5%). Among 18 patients with bone-only disease, the bone scan response rate was 61% and in 34 patents with extra-osseous disease, the bone scan response rate was 26.5% (Table 2).

Figure 2A shows the waterfall plot of best overall bone scan response for the patients having a 12-week follow-up bone scan (n = 33). Of these patients, 60.6% (20/33) demonstrated at least 30% reduction in bone scan lesion area and 78.8% (26/33) achieved disease control (PR + SD). 30.3% (10/33) had treatment duration for over 6 months and their bone scans demonstrated either PR or SD. Two patients received treatment for over 12 months and achieved significant improvement (PR) in bone lesions. Figure 2B shows the treatment duration with bone scan response for the 33 protocol-defined evaluable patients who had baseline and repeated bone scans. Among the 24 patients who had cabozantinib treatment of 12 weeks duration or longer, 96% achieved disease control (PR or SD) as assessed by bone lesions and one patient received cabozantinib treatment for 46 months. Patients discontinued treatment due to progression (n = 28), unacceptable toxicity (n = 3) and other reasons including impending pathological fracture (n = 1) and physician discretion (n =1).

Overall response rate (ORR) by RECIST

The ORR was evaluated based on the results of CT scans by conventional RECIST criteria. As shown in Table 2, 33 of 52 patients had at least one follow-up evaluation for ORR per RECIST. Those without subsequent evaluation were treated as non-responders (n = 19). No patients achieved a CR or PR per RECIST, 26 (50%) achieved SD, and 7 (13.5%) had PD at extraosseous sites.

The correlation between bone scan response and RECIST response at 12 weeks was further explored (Table 3 and Supplemental Figure 1). 31 of 33 patients who were evaluable for bone scan response at 12 weeks also had their RECIST response evaluated by central review at the same time. Among 25 patients who had disease control (PR + SD) on bone scan at 12 weeks, 20 patients (80%) had stable disease, three patients (12%) had progressive disease, and the other two patients (8%) were unevaluable for RECIST. Of eight patients who had PD on bone scan at 12 weeks, three patients (37.5%) had PD and five patients (62.5%) had SD in extraosseous lesions.

Overall survival/ progression-free survival

52 patients were followed up for over five years (Figure 3A and 3B). The median follow-up time was 28.5 months (1.5 – 86.3 months). The median overall survival (OS) was 19.6 months (90% CI, 18.0 – 26.8 months) and median progression-free survival (PFS) was 4.3 months (90% CI, 2.8 – 5.5 months).

Both OS and PFS analyses were stratified based on metastatic sites (bone only vs. bone plus other sites) at baseline. The stratified median OS was 26.8 months (90% CI, 21.1 – 33.0 months) for patients with bone only lesions and 18.7 months (90% CI, 14.3 – 20.0 months) for those with bone and other lesions (HR = 0.64, 90% CI, 0.37 – 1.1; p = 0.17; Figure 3C). The median PFS was 4.9 months (90% CI, 2.8 – 7.8 months) for patients with bone only lesions and 3.4 months (90% CI, 2.7 – 5.8 months) for those with bone plus other lesions (HR = 0.91, 90% CI, 0.56 –

1.5; p = 0.77; Supplemental Figure 2). No significant difference in OS and PFS was observed among patients with bone only versus bone plus other sites.

In a post hoc analysis, the landmark method was utilized to determine whether the bone scan responses correlated with improved survival. The landmark estimates were based on the bone scan status at 12 weeks. The 48 patients known to be alive at 12 weeks were included for OS analysis (Figure 3D) and the 31 patients alive without death or progression at 12 weeks were included in the PFS analysis (Supplemental Figure 3). A significant difference was observed between patients with and without disease control by bone scan response (Figure 3D). The group with disease control at 12 weeks had a significantly longer survival (median OS: 24.2 months, 90% CI of 16.4 – 31.7 months), compared to that without disease control (median OS: 13.3 months, 90% CI: 9.5 – 18.2 months) with a hazard ratio of 0.37 (90% CI: 0.21-0.65). No PFS benefit was observed for the disease control group (Supplemental Figure 3), but the number of patients at risk in each subset was small (9 in non-disease control group vs. 22 in disease control group).

Adverse events

All 52 patients who received cabozantinib treatment are included in the safety analysis. The median treatment duration was 12 weeks (range, 1 to 204 weeks). Patients received a median average daily dose of 51.5 mg (range, 21.4 – 100 mg). 42 patients (80.8%) had dose modifications (dose reduction or dose held) and 7 patients (13.5%) discontinued their treatments due to unacceptable toxicity.

Of the 52 patients, three had received treatments for less than 3 weeks (one cycle) and no related adverse events were reported for these patients. In total, 123 types of related adverse events (AE) were reported for 49 patients (94.2%). The most common all-grade AEs were fatigue (63%), elevation in either alanine aminotransferase (52%) or aspartate aminotransferase (48%), diarrhea (48%), nausea (46%), palmar-plantar erythrodysesthesia syndrome (44%), oral mucositis (37%) and anorexia (35%). A total of 19 Grade-3 AEs was observed in 26 patients. The most frequent Grade 3 AEs were hypertension (10%), anorexia (6%), diarrhea (6%), fatigue (4%), hypophosphatemia (4%), lymphocyte count decrease (4%), febrile neutropenia (4%), hyponatremia (4%) (Table 4). Three Grade 4 AEs were seen in three patients including dehydration, hypercalcemia and neutropenia. No deaths occurred during the treatment period of this study. The common AEs leading to treatment discontinuation included fatigue, dyspnea, anorexia, diarrhea, hypertension and musculoskeletal and connective tissue disorder.

Discussion

In this single arm phase II study in patients with hormone-receptor positive breast cancer with bone metastases, cabozantinib treatment resulted in a high rate of bone scan response and disease control rate. Patients who achieved a bone scan response to cabozantinib had improved overall survival compared to patients without bone scan response. Responses assessed by traditional RECIST were not observed, but prolonged disease control using traditional response evaluation by CT imaging was observed in a significant percentage of patients. Together, our findings suggest that cabozantinib is active in advanced hormone receptor positive breast cancer with bone metastases.

To our knowledge, this is the first study to use prespecified bone scan response in breast cancer as the primary endpoint. Our primary finding is in agreement with a previous study in metastatic prostate cancer where cabozantinib improved bone scans with a BSR of 42% and a DCR of 62%. The lack of correlation of bone scan findings with survival improvement in prostate cancer patients treated with cabozantinib leaves unanswered whether the bone scan changes reflect true disease control, and potential clinical benefit, or simply interference with radionuclide uptake in bone lesions [25]. In the current study, bone scan response correlated with overall survival and disease control in extraosseous sites. Interestingly, 80% of patients who achieved disease control with bone scans at 12 weeks maintained the same status in extraosseous lesions. This suggests that the bone scan responses may reflect antitumor activity in HR+ metastatic breast cancer. Furthermore, in a landmark analysis, patients with disease control (PR + SD) based on the bone scan response at 12 weeks had a longer survival compared with those in the non-disease control group (PD + non-evaluable). These findings support the notion that disease control status based on 12-week bone scans may predict patient survival and may guide continuation of cabozantinib treatment. Definitive proof of clinical benefit would require a randomized trial.

A challenge with cabozantinib use has been intolerance to treatment. The most common toxicities leading to discontinuation are fatigue, abnormal liver function, diarrhea and nausea, as well as hypertension and proteinuria which are associated with its anti-angiogenic action [4-6]. In our study, cabozantinib was not tolerable at the 100 mg/day starting dose in all patients, but at the currently approved dose of 60 mg/day it was better tolerated through dose modification and other supportive care. The rate of treatment discontinuation (13.5%) due to unacceptable

AEs was similar to the rate (16%) observed in phase III trials of hepatocellular carcinoma and thyroid cancer [4, 6]. Our results are similar with the 88% rate of dose reduction reported in the phase III study of metastatic castration-resistant prostate cancer in which the starting dose of 100 mg used [25].

The results of our study in hormone-receptor positive breast cancer together with prior results showing a clinical benefit rate of 34% in triple negative breast cancer raise the possibility of testing cabozantinib in combination with other therapies. However, studies evaluating cabozantinib and nivolumab in TNBC and cabozantinib and trastuzumab in patients with breast cancer brain metastases showed insufficient activity to support further development of the combinations [27, 28]. In our study, a separate cohort combining cabozantinib with fulvestrant was initiated but closed early for slow accrual. An ongoing trial is evaluating the efficacy of cabozantinib in combination with atezolizumab for metastatic breast cancer (clinicaltrials.gov: NCT03170960).

A limitation of this study was the single-arm study design which did not permit comparison to a standard therapy. Therefore, it was not possible to assess the clinical benefit for cabozantinib as compared to other available therapies. The missing data and small sample size precluded more detailed subgroup analysis for clinical endpoints. In our study, the landmark analysis allowed for an unbiased way to estimate the survival probabilities conditional on the disease control status of bone lesions at a landmark time of 12 weeks. However, the correlation of survival and response may be confounded by the baseline difference between the DC and Non-DC group. We did not observe any significant difference in terms of baseline disease status and prior lines of hormone

or chemotherapy (Supplemental Table 2). This only provided more confidence about the association but could not eliminate any unmeasured confounders. For causal inference, an RCT is still needed. Furthermore, our use of bone scan response as a novel primary endpoint in this proof of concept study would not be appropriate as a single measure of efficacy in a larger study because it neglects assessment of extraosseous lesions. In addition, the identification of biomarkers that may correlate with bone scan response or extraosseous response are needed.

Conclusion

In this phase II study we showed that cabozantinib monotherapy led to improvement in bone lesions in pretreated patients with HR+ breast cancer with bone metastases. Patients who achieved disease control by bone scan response at 12 weeks had improved overall survival. These results support further studies to evaluate the clinical activity of cabozantinib in HR+ metastatic breast cancer and to confirm the utility of bone scan response as a meaningful tool to assess responses to treatment with this drug.

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Disclosure of Potential Conflicts of Interest

Michaela J. Higgins: Roche (Other); **Sara M. Tolaney:** Merck (RF, C/A), Bristol-Myers Squibb (RF, C/A), Exelixis (RF), Eli Lilly (RF, C/A), Pfizer (RF, C/A), Novartis (RF, C/A), AstraZeneca (RF, C/A), Eisai (RF, C/A), Nektar (RF, C/A), Odenate (RF), Sanofi (RF, C/A), Immunomedics (RF, C/A), Cyclacel (RF), Genentech (RF, C/A), Celldex (C/A), Paxman (C/A), Seattle Genetics (C/A), Nanostring (C/A), Daiichi-Sankyo (C/A), Sanofi (C/A), Abbvie (C/A), Athenex (C/A), Puma (C/A); **Matthew R. Smith**: Bayer (RF, C/A, Other), Janssen Oncology (RF, C/A, Other), Amgen (C/A, Other), Pfizer (C/A), Lilly (RF, C/A, Other), Novartis (C/A), Astellas Pharma (C/A), Gilead Sciences (RF); **Monica Fornier:** Eisai (C/A), Genentech (C/A); **Umar Mahmood:** CytoSite Biopharma (C/A, RF, OI, IP); **Jose Baselga:** AstraZeneca (E). Grail (C/A, OI), PMV Pharma (C/A), ApoGen (C/A, OI), Juno (C/A, OI), Lilly (C/A, H, other), Seragon (C/A), Novartis (C/A, H, other), Northern Biologics (C/A). PMV Pharma (OI), Varian (OI), Foghorn Therapeutics (OI), Aura (OI), Infinity Pharmaceuticals (OI), Tango (OI), Venthera (OI), Roche (H, other). Board of directors: Foghorn Therapeutics, Varian Medical Systems, Bristol-Myers Squibb, Grail, Aura Biosciences and Infinity Pharmaceuticals; **Bruce A. Chabner:** EMD Serono (C/A), Eli Lilly (C/A), Chugai Pharmaceuticals (C/A), Cyteir (C/A), Takeda (C/A), PharmaMar (OI), Bluebird (OI), Alnylam (OI), Biomarin (OI), Seattle genetics (OI), Springworks (OI), Forty Seven (OI), Constellation (OI), Glaxo Smith Klein (OI); **Steven J. Isakoff:** Genentech (RF, C/A), Abbvie (RF), OncoPep (RF, C/A), AstraZeneca (RF), Mylan (C/A), Myriad Genetics (C/A); **Jing Xu, Steven E. Come and Beow Y. Yeap** have no relationship to disclose.

C/A (Consulting/advisory relationship), **RF** (Research Funding), **E** (Employment), **ET** (Expert Testimony), **H** (Honoraria), **OI** (Ownership Interests), **IP** (Intellectual Property Rights/inventor/patent holder), **SAB** (Scientific Advisory Board), **Other** (e.g. support for accommodation and travel to conferences).

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Figure Legends

Figure 1. Flowchart of patient enrollment, treatment and follow-up for bone scan response

Figure 2. Waterfall plot of best overall bone scan response (A) and treatment duration with best overall bone scan response (B) among 33 patients with follow-up bone scan

▲ Patient 16 and 22 discontinued treatment due to physician discretion and impending pathological fracture, respectively.

Figure 3. Kaplan-Meier estimates of overall survival, progression-free Survival and overall Survival according to subgroups

Kaplan-Meier estimates of overall survival (A), progression-free survival (B), overall survival by different disease site at baseline (C) and landmark analysis of overall survival by disease control status based on bone scan response at 12 weeks (D); in panel D, time zero started after 12 weeks of treatment and three patients died and one censored before 12 weeks, thus 48 patients were included in Landmark OS analysis

Supplemental Figure 1. Bone scan response and RECIST response at 12 weeks

UE (unable to evaluate): two patients had bone scan evaluation at 12 weeks but had no RECIST response evaluable by central review. However, the patient with PR on bone scan showed stable disease (SD) per RECIST at 18 weeks and the other patient with SD on bone scan revealed stable disease in extraosseous sites at 12 weeks, both by institutional CT scans.

Supplemental Figure 2. Kaplan-Meier estimates of progression-free survival by disease site

Supplemental Figure 3. Landmark analysis of progression-free survival by disease control status based on bone scan response at 12 weeks

Tables

Table 1 Baseline characteristics of patients

Characteristics	Summary statistics (N=52)
Female sex, no. (%)	52 (100)
Median age, yr (range)	55 (33 – 79)
Race white, no. (%)	42 (81)
ECOG Performance Status, no. (%)	
0	37 (71)
1	15 (29)
Estrogen[a] /Progestogen receptors, no. (%)	
ER+/PR+	40 (77)
ER+/PR-	12 (23)
Sites of disease, no. (%)	
Bone only	18 (35)
Bone + others	34 (65)
Liver	5 (10)
Lung/pleura	7 (13)
Brain	0
One other site	8 (15)
≥ 2 Other sites	14 (27)
Prior Lines of endocrine therapy for metastatic disease, no. (%)	
0	7 (13)
1	17 (33)
2 – 4	28 (54)
Prior lines of chemotherapy for metastatic disease, no. (%)	
0	15 (29)
1	15 (29)
2 – 9	22 (42)
Prior therapy of bone modifying agents, no. (%)	35 (67)
Bisphosphonates	34 (65)
Denosumab	5 (10)

[a] *ER+ in either metastatic lesions (45 patients) or primary tissues (7 patients)*

Abbreviation: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, Progestogen

Table 2 Response to treatment (n = 52)

Bone Scan Response and RECIST Response[a]		
Responses	**Method of Response Assessment**	
	Bone Scan	***RECIST***
	No. (%)	
Complete Response (CR)	0	0
Partial Response (PR)	20 (38.5)	0
Stable Disease (SD)	6 (11.5)	26 (50.0)
Progression Disease (PD)	7 (13.5)	7 (13.5)
Bone Scan Response Rate (90% CI) / Overall Response Rate	38.5% (27.1 – 51.0%)	0
No. patients evaluable[b]	33 (63.5)	33 (63.5)
Non-evaluable[c]	19 (36.5)	19 (36.5)
Bone Scan Response by Disease Site		
Responses	***Disease Site at Baseline***	
	Bone Only (n=18)	**Bone + other (n=34)**
	No. (%)	
Complete Response (CR)	0 (0)	0 (0)
Partial Response (PR)	11 (61.1)	9 (26.5)
Stable Disease (SD)	0 (0)	6 (17.6)
Progression Disease (PD)	2 (11.1)	5 (14.7)
Non-evaluable[c]	5 (27.8)	14 (41.2)

[a] *All responses are based on best overall response during the study period. The percentage calculations are based on intention-to-treat analysis using a denominator of **52** patients who received cabozantinib treatment in this trial.*

[b] *Patients evaluable for bone scan response are defined as patients who received ≥ 6 weeks of cabozantinib and had at least one follow-up bone scan evaluable for central review. Patients evaluable for RECIST response are defined as patients who received ≥ 6 weeks of cabozantinib and had at least one follow-up CT scan evaluable for central review.*

[c] *The 19 patients non-evaluable for bone scan response include 16 patients who discontinued treatment prior to re-evaluation date due to toxicity (4), disease progression (9), or patient withdrawal from trial including too ill to continue (1), difficulty traveling (1) and unrelated illness (1). An additional three patients did not have their bone scans sent for central review.*

Abbreviation: CR, complete response; PR, partial response; SD, stable disease; PD, progression disease.

Table 3 Correlation of bone scan and RECIST response at 12 weeks (n = 33)[a]

		By RECIST		
		SD	**PD**	**UE**
		No. (%)		
By bone scan	**PR**	12 (85.7)	1 (7.1)	1 (7.1)[b]
	SD	8 (72.7)	2 (18.2)	1 (9.1)[b]
	PD	5 (62.5)	3 (37.5)	0 (0)

[a] *33 patients were evaluable for bone scan response by central review at 12 weeks*
31 of them had their RECIST response evaluated by central review at 12 weeks

[b] *two patients had their RECIST response un-evaluable by central review at 12 weeks but institutional CT scans showed stable disease at extraosseous sites for these two patients at 12 and 18 weeks, respectively*

Abbreviation: PR, partial response; SD, stable disease; PD, progression disease; UE, unable to evaluate.

Table 4 Treatment-related Grade 3 or 4 adverse events

Adverse Event	Grade3	Grade4
	No. (%)	
Hypertension	5(10)	0
Anorexia	3(6)	0
Diarrhea	3(6)	0
Fatigue	2(4)	0
Febrile neutropenia	2(4)	0
Hyponatremia	2(4)	0
Hypophosphatemia	2(4)	0
Lymphocyte count decreased	2(4)	0
Alanine aminotransferase increased	1(2)	0
Alkaline phosphatase increased	1(2)	0
Cardiac disorders	1(2)	0
Erythema multiforme	1(2)	0
Fracture	1(2)	0
Hypokalemia	1(2)	0
Neutropenia	1(2)	1(2)
Lung infection	1(2)	0
Mucositis oral	1(2)	0
Palmar-plantar erythrodysesthesia syndrome	1(2)	0
Pulmonary embolus	1(2)	0
Dehydration	0	1(2)
Hypercalcemia	0	1(2)

Figures

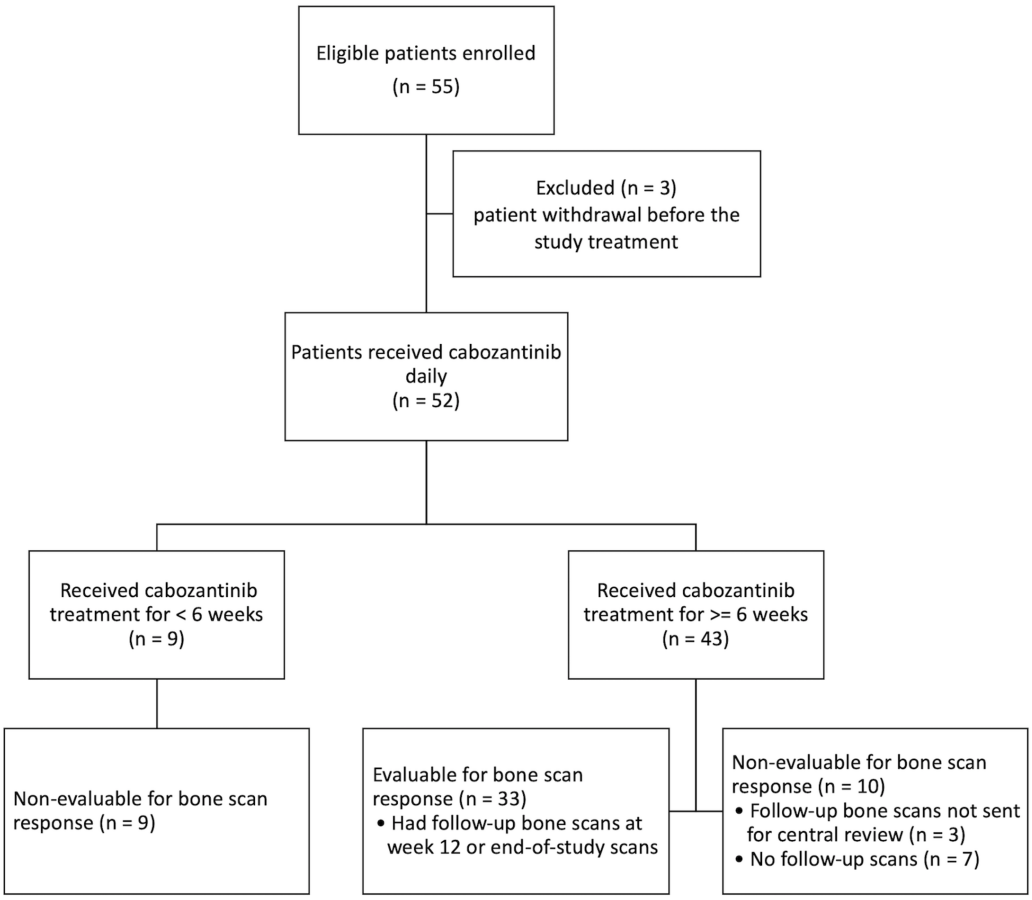


Figure 1 Flowchart of patient enrollment, treatment and follow-up for bone scan response

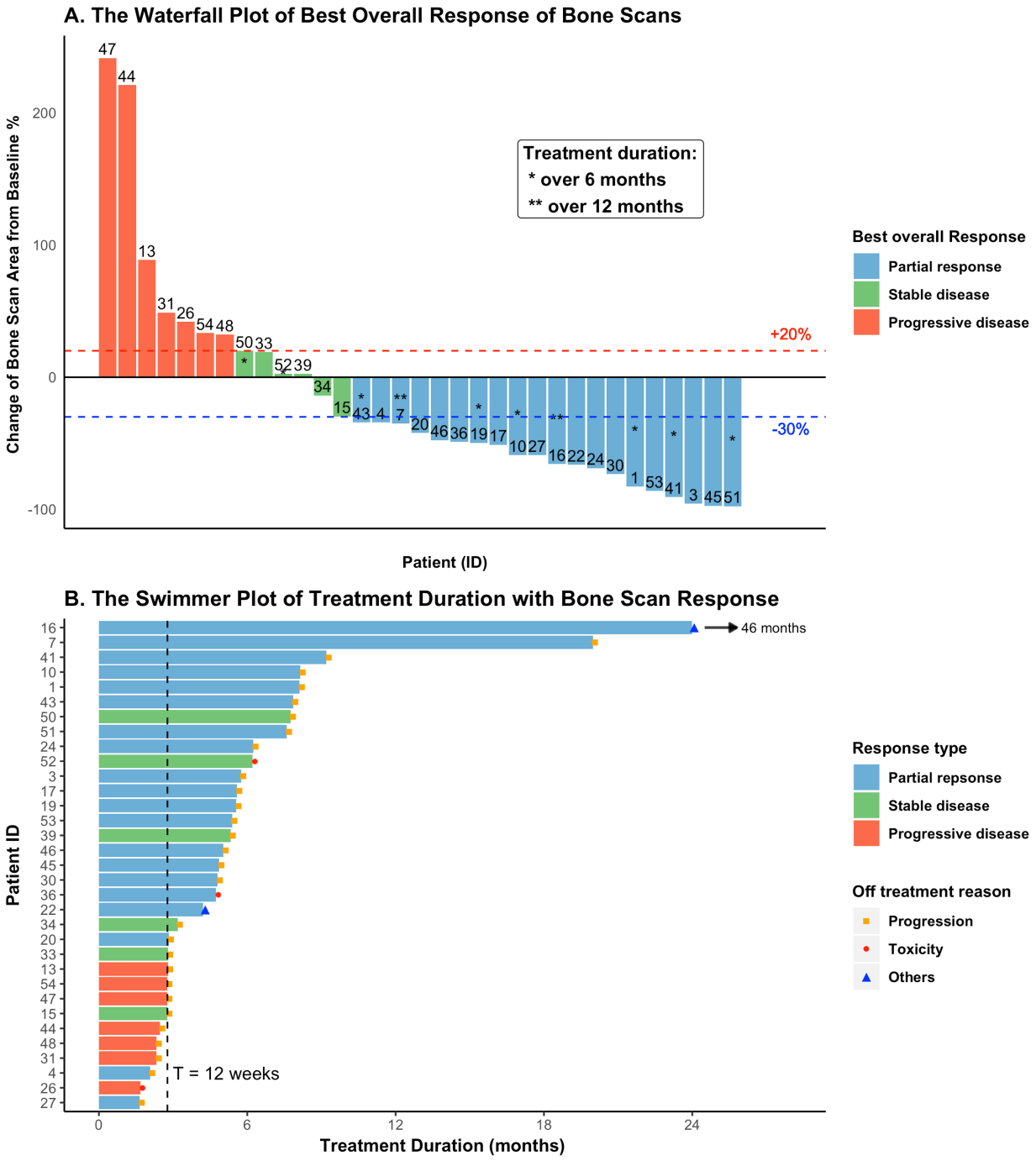


Figure 2 Waterfall plot of best overall bone scan response (A) and treatment duration with best overall bone scan response (B) among 33 patients with follow-up bone scan

▲ *Patient 16 and 22 discontinued treatment due to physician discretion and impending pathological fracture, respectively.*

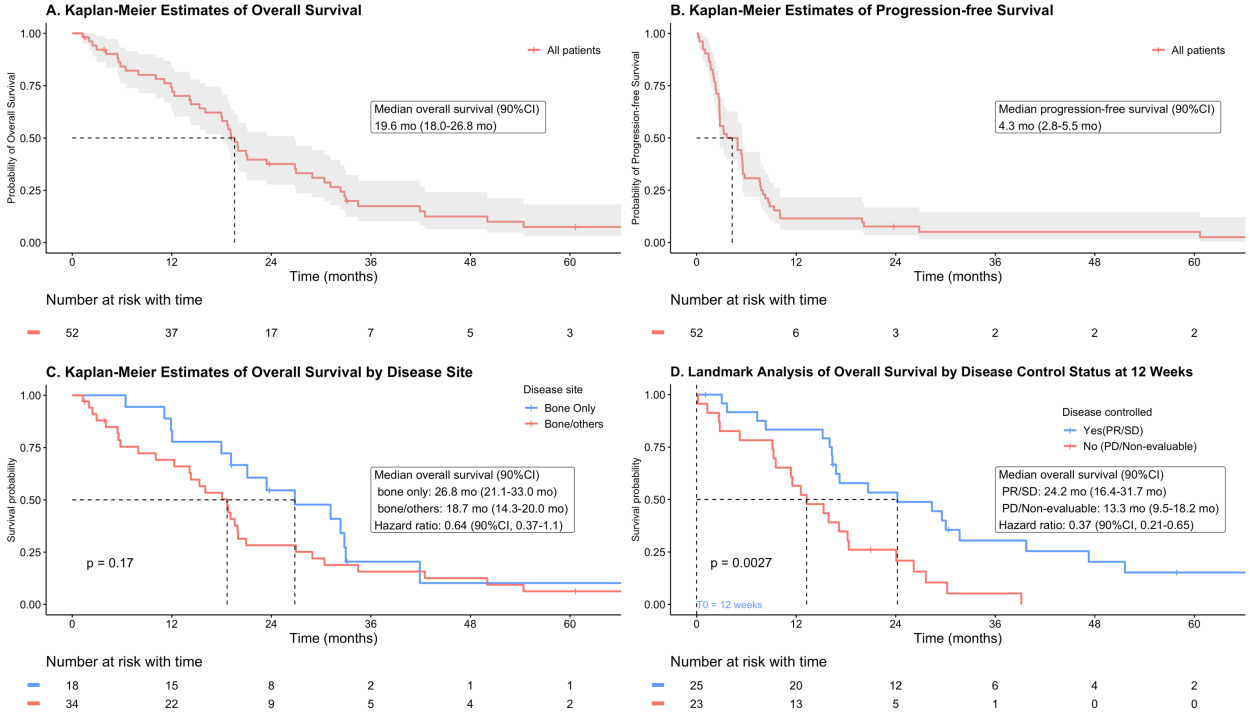


Figure 3 Kaplan-Meier estimates of overall survival, progression-free Survival and overall Survival according to subgroups

Kaplan-Meier estimates of overall survival (A), progression-free survival (B), overall survival by different disease site at baseline (C) and landmark analysis of overall survival by disease control status based on bone scan response at 12 weeks (D); in panel D, time zero started after 12 weeks of treatment and three patients died and one censored before 12 weeks, thus 48 patients were included in Landmark OS analysis

Supplemental Data

Supplemental Table 1: Baseline characteristics of patients based on disease site

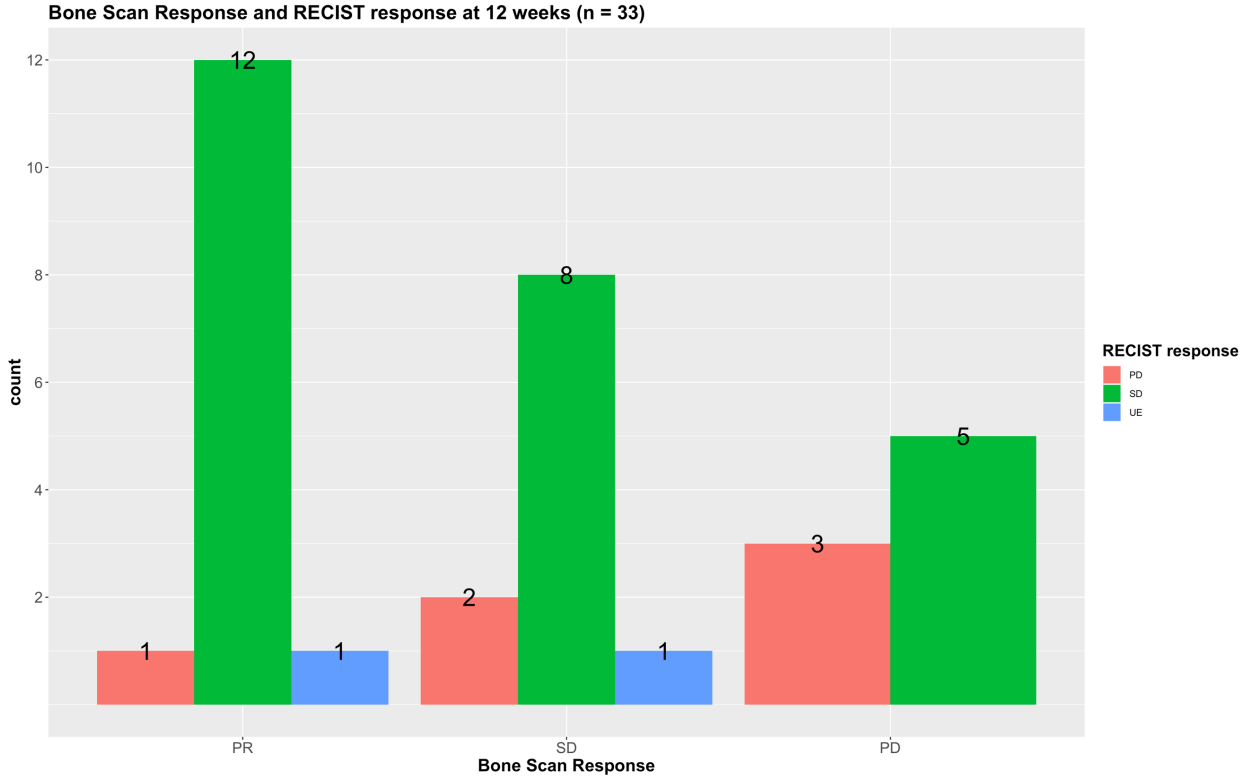
	Bone Only	Bone plus other
	n=18	n=34
Age-yr (range)	55 (40 -72)	56 (33-79)
Race (white) – no.(%)	13 (72.2%)	29 (85.3%)
ECOG 0	13 (72.2%)	24 (70.6%)
ECOG 1	5 (27.8%)	10 (29.4%)
Surgery – no.(%)	4 (22.2%)	5 (14.7%)
Endocrine therapy – no.(%)	16 (88.9%)	29 (85.3%)
Line of endocrine therapy		
0	2 (11.1%)	5 (14.7%)
1	7 (38.9%)	10 (29.4%)
2	5 (27.8%)	10 (29.4%)
3	3 (16.7%)	8 (23.5%)
4	1 (5.6%)	1 (2.9%)
Anthracycline – no.(%)	2 (11.1%)	9 (26.5%)
Taxane – no.(%)	4 (22.2%)	10 (29.4%)
Chemo – no.(%)	13 (72.2%)	24 (70.6%)
Line of chemotherapy		
1	7 (53.8%)	8 (33.3%)
2	3 (23.1%)	3 (12.5%)
3	2 (15.4%)	5 (20.8%)
5	1 (7.7%)	3 (12.5%)
6	0 (0.0%)	1 (4.2%)
8	0 (0.0%)	2 (8.3%)
9	0 (0.0%)	2 (8.3%)
Bone Modulating agents – no.(%)	14 (77.8%)	23 (67.6%)
Pain medication – no.(%)	6 (33.3%)	12 (35.3%)
Opioid use– no.(%)	1 (5.6%)	7 (20.6%)

Supplemental Table 2: Baseline Characteristics by the Disease Control Status based on 12-week Bone Scans

	Disease Control Status at 12 Weeks		
	Non-DC group	**DC group**	**P***
N	23	25	
Age (median [IQR])	55 [49, 62]	56 [49, 61]	0.543
Race white, no. (%)	20 (87)	18 (72)	0.575
ECOG, no. (%)			1
0	16 (70)	18 (72)	
1	7 (30)	7 (28)	
PR +, no. (%)	16 (70)	21 (84)	0.311
Bone only disease, no. (%)	7 (30)	11 (44)	0.383
surgery = Yes, no. (%)	2 (9)	7 (28)	0.14
Hormone Tx = Yes, no. (%)	19 (83)	22 (88)	0.696
No. lines of prior Hormone Tx (median [IQR])	2 [1, 3]	1 [1, 2]	0.514
Chemotherapy = Yes, no. (%)	16 (70)	17 (68)	1
No. lines of prior Chemo (median [IQR])	1 [0, 4]	1 [0, 2]	0.212
Bone modulating agent = Yes, no. (%)	16 (70)	20 (80)	0.511

** P values were provided by Fisher exact test or non-parametric test*

Supplemental Figure 1: Bone scan response and RECIST response at 12 weeks



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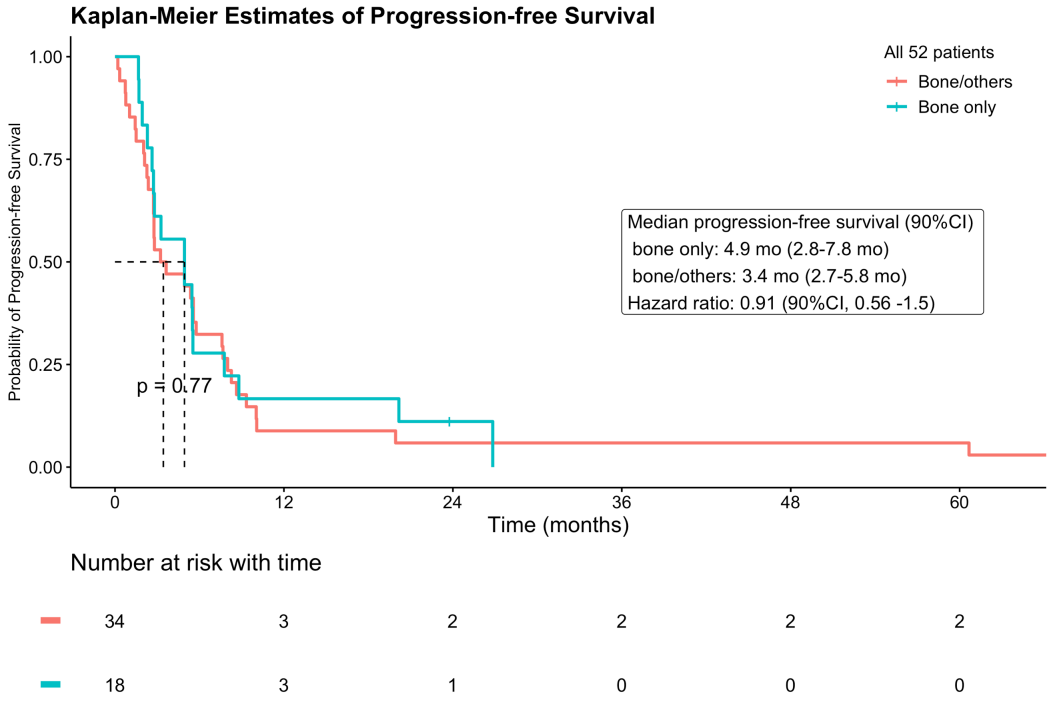
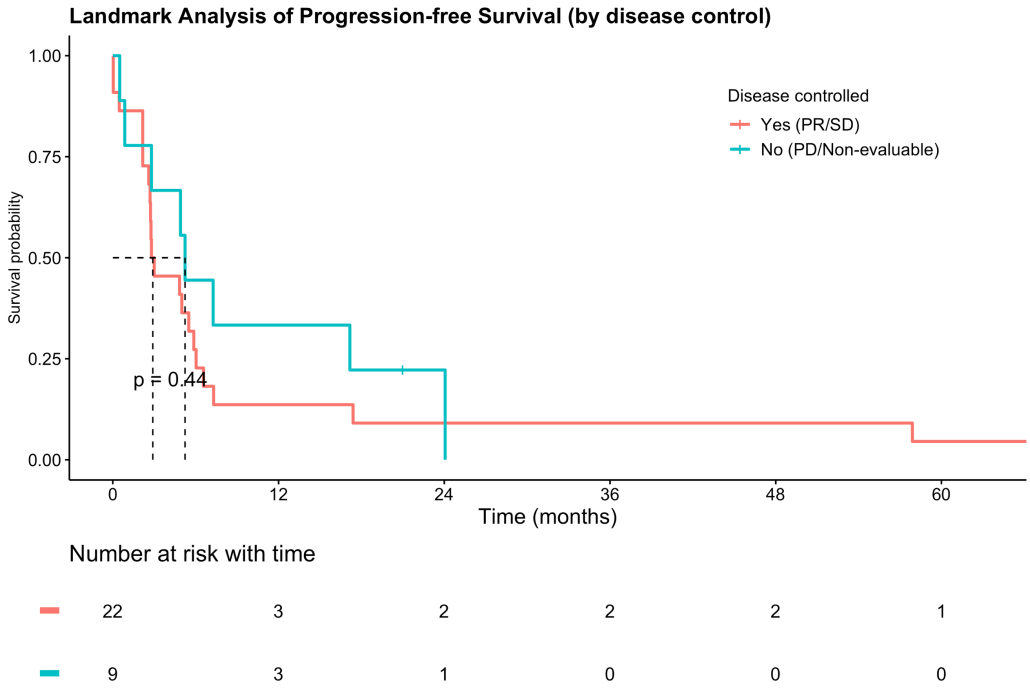
Supplemental Figure 2: Kaplan-Meier estimates of progression-free survival by disease site



Supplemental Figure 3: Landmark analysis of progression-free survival by disease control status based on bone scan response at 12 weeks



Phase II trial of veliparib and temozolomide in metastatic breast cancer patients with and without *BRCA1/2* mutations

Jing Xu[1,5*], Tanya E Keenan[1,2,5*], Beth Overmoyer[2,5], Nadine M Tung[3,5], Rebecca S Gelman[2,5], Karleen Habin[1], Jane Qian[4], Vincent Giranda[4], Stacie Shepherd[4], Judy E Garber[2,5], Leif W Ellisen[1,5], Eric P Winer[2,5], Paul E Goss[1,5], Beow Y. Yeap[1,5], Bruce A. Chabner[1,5], Steven J Isakoff[1,5]

[1]Massachusetts General Hospital Cancer Center, Boston
[2]Dana-Farber Cancer Institute, Boston
[3]Beth Israel Deaconess Medical Center, Boston
[4]Abbott Laboratories, Abbott Park, IL
[5]Harvard Medical School, Boston, MA

* These authors contributed equally to this work

Correspondence:
Steven J Isakoff, MD PhD
Cancer Center
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02141
Tel: 617-726-6500
Fax: 617-643-0589
Email: SISAKOFF@mgh.harvard.edu

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Translational Relevance

Breast cancer is the most common cancer in woman worldwide. About 5% of all breast cancers are associated with *BRCA1* or *BRCA2* (*BRCA1/2*) mutations, and women with these mutations have around a 50% or greater lifetime risk of developing breast cancer. Poly-(adenosine diphosphate-ribose) polymerase (PARP) inhibitors represent a promising therapeutic class for *BRCA*-associated cancers. These agents as a monotherapy are approved for use in advanced *BRCA*-mutated ovarian cancer and metastatic BRCA-mutated HER2 negative breast cancer. PARP inhibition potentiates the cytotoxic effects of DNA-damaging chemotherapies, including temozolomide, particularly in tumors that carry defects in double strand break repair. In this phase II trial, veliparib and temozolomide were assessed as a novel oral regimen for metastatic breast cancer with and without germline *BRCA1/2* mutations. The combination of veliparib and temozolomide demonstrated clinical activity in *BRCA*-associated metastatic breast cancer with a manageable side-effect profile, meriting further investigations.

Word Count: 141

Abstract

Background: The poly-(adenosine diphosphate-ribose) polymerase (PARP) 1 and 2 inhibitor veliparib and the alkylating agent temozolomide are a novel oral combination for the treatment of breast cancer. We evaluated the efficacy and safety of veliparib and temozolomide in metastatic breast cancer patients with and without germline BRCA1/2 mutations.

Patients and Methods: In this single-arm phase II trial, patients 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. An expansion study enrolled only BRCA1/2 carriers. The primary end point was objective response rate.

Results: The study enrolled 62 patients with an objective response rate (ORR) of 11% and a clinical benefit rate at 4 months of 32% (CBR at 4 mo) in the overall population. In the primary cohort we found a 9% ORR and 27% CBR at 4 months, and in the expansion cohort of BRCA1/2 carriers, a 14% ORR and 43% CBR at 4 months. Among 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 prolonged median PFS of 6.2 months was observed among 19 BRCA1/2 carriers who had no prior platinum therapy. The most common grade 3 and 4 toxicities were thrombocytopenia (32%) and neutropenia (21%).

Conclusion: Veliparib and temozolomide have clinical activity in BRCA-associated metastatic breast cancer with manageable toxicity, meriting further investigations.

Word Count: 250

Introduction

BRCA 1/2 deficient breast cancers comprise of about 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% to 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 a process known as Base Excision Repair (BER). The inhibition of PARP causes single stranded DNA breaks to be converted into double stranded DNA breaks, which are repaired by the homologous recombination (HR) pathway. BRCA 1 and BRCA 2 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 towards DNA-damaging chemotherapies, such as platinum, topoisomerase inhibitors, and alkylating agents [5].

Clinical studies in breast cancer have shown some PARP inhibitors as a monotherapy has demonstrated great antitumor potential 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]. Combinations of PARP inhibitors with chemotherapy agents, targeted therapies, and others are currently being explored. The optimal combination for breast cancer is still unknown [10-14]. Early studies have reported PARP inhibition potentiates temozolomide, an orally administered alkylating agent, which has the advantage of crossing the blood-brain barrier (BBB) [15-19]. Veliparib, an investigational oral inhibitor of PARP-1 and PARP-2 also

possesses the property of efficiently crossing the BBB [20]. Temozolomide as a monotherapy demonstrates no significant clinical activity in metastatic breast cancer [21, 22]. However, in preclinical studies, veliparib potentiated the activity of DNA damaging agents such as temozolomide (TMZ) and platinum agents; the combination of veliparib /TMZ exhibited anti-tumor activity in multiple *in vivo* models including breast cancer and even against 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 offer a promise for the treatment of metastatic breast cancer [24-26].

In this phase II trial, we evaluated the efficacy and safety of veliparib and temozolomide as a treatment for patients with metastatic breast cancer (MBC). The primary cohort included all subtypes of MBC whereas the expansion cohort only consisted of germline *BRCA1/2* mutated MBC.

Methods

Patients

The initial study population consisted of patients with all subtypes of metastatic breast cancer, who had received at least one prior metastatic chemotherapy regimen. The expansion cohort had patients with metastatic breast cancer and a known deleterious BRCA1/2 mutation, without limitation on prior treatment. Other eligibility criteria included Response Evaluation Criteria in Solid Tumors (RECIST) measurable disease [27], normal organ and marrow function, and Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. Both cohorts of the study allowed for previously treated stable brain metastases. BRCA status was determined using

archived primary or metastatic tumor samples. Patients were excluded if they had received 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.

Study Design and Treatment

This open-label, multi-center single arm Phase II study was conducted at Massachusetts General Hospital (MGH), Dana-Farber Cancer Institute (DFCI), Beth Israel Deaconess Medical Center (BIDMC), and Brigham and Women's Hospital. 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 treatment plan consisted of veliparib on days 1 through 7 with concurrent temozolomide on days 1 through 5 on a 28-day cycle. The primary 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 study dosed veliparib at 30 mg twice daily for all patients. All patients in both cohorts received temozolomide 150 mg/m^2 orally once daily, which was increased to 200 mg/m^2 as tolerated.

Patients continued to receive the study drugs 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 still had not been resolved. For grade 3 or 4 toxicities attributable to temozolomide, pre-specified dose reduction and delay guidelines were followed. For all grade 3 or 4 toxicities not attributable to temozolomide or the underlying disease, the dose of veliparib was delayed until the toxicity resolved to Grade 2 or less and later reduced to 20 mg every 12 hours and the dose of temozolomide was reduced by one dose level. Only one dose reduction was allowed for veliparib before discontinuation of study treatment and, the temozolomide dose could not be lower than 75 mg/m^2 daily.

Study Endpoints and Assessment

The primary end point of the study was objective response rate (ORR) based on computed tomography (CT) scans assessed every 8 weeks. The ORR was defined as the percentage of patients who had either partial or complete response according to RECIST 1.1. Responses were defined as follows. Complete response (CR) required the disappearance of all target lesions and the reduction of all pathological lymph nodes to <10 mm in short axis, as well as the disappearance of all non-target lesions and the normalization of tumor marker level. Partial response (PR) required at least a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) required at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or the appearance of one or more new lesions. Stable disease (SD) was defined as neither a sufficient decrease for PR nor increase for PD. Both CR and PR were required for confirmation at least 4 weeks from the initial observation.

Secondary endpoints included clinical benefit rate (CBR) at 4 months, progression free survival (PFS) and safety. CBR at 4 months was defined as the percentage of patients who had CR/PR/SD at greater than 16 weeks of follow up. Patients were monitored for adverse events with regular vital sign measurements, physical examinations, and laboratory testing. This study used the adverse event descriptions and grading scales according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The DF/HCC Data and Safety Monitoring Committee regularly reviewed and monitored toxicity and accrual data from this trial.

Statistical Analysis

A response rate of 20% was considered to be of clinical benefit for this combination therapy in the study population of the primary cohort based on the fact that TMZ claimed no activity in breast cancer at that time. A sample size of 41 was estimated with 93% power to detect the response rate of 20%, compared to a null response rate of 5%, at a significance level of 0.05 (one sided). If at least 8 of 41 patients had response (CR/PR), this combination therapy warranted further investigation. For the expansion study, based on the finding in the primary cohort that 50% of BRCA1/2 carriers achieved a partial response in the primary study, a response rate of 45% would be of considerable clinical benefit, while a null response rate of 15% would be of little clinical interest. A Simon 2-stage design was employed for estimating the sample size in this cohort [28]. The enrollment of 20 patients would provide a power of 87% (beta = 0.13) to deem the combination worthy of further research if the true response rate was 45% at a significance level of 0.025 (one-sided). If at least 7 of 20 patients had response to treatment, this combination therapy was worthy of further investigations.

Data was analyzed, combining both cohorts. Efficacy and PFS analyses were assessed in all patients, who received at least one cycle of the study drugs. Patients who had their disease re-evaluated were considered evaluable for response per RECIST 1.1. ORR and CBR at 4 months were reported as points estimates with 90% confidence intervals. PFS was defined as the time from enrollment until disease progression or death, and patients alive and free from disease progression at the date of last contact were censored. Median PFS (mPFS) was estimated by the Kaplan-Meier method. Subgroup analyses (un-prespecified) of ORR and mPFS based on the BRCA status and status of prior platinum therapy were compared by Fisher'exact test and the log rank test, respectively. Safety data were evaluated for all patients, who had received at least one dose of either study drug.

Results

Patient Characteristics

A total of 63 subjects with metastatic breast cancer were enrolled in this study, of which one patient did not receive any treatment. 41 patients in the primary cohort, which contained both BRCA1/2+ and BRCA1/2– subjects, and a second cohort containing 21 subjects, all of whom were BRCA 1/2+, was subsequently entered into the study. All 62 patients in both cohorts received both ABT-888 and temozolomide and were evaluable for data analysis.

Table 1 shows the baseline characteristics of patients in these two cohorts. Most patients had an ECOG score of less than 2 and only one patient, in the primary cohort, was male. The primary cohort included TNBC (54%), HR+ (37 %), and HER+ (10%) patients, while the expansion cohort contained a predominance of 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 site was the lymph node involvement in the primary cohort and bone lesions in the second cohort. The median number of prior chemotherapeutic, hormonal, or HER directed regimens was 3 (range, 1 – 9) in the primary cohort and 2 (range, 0 – 9) in the expansion cohort. 14 patients (34%) in the primary cohort and eight patients (38%) had received prior platinum treatment for metastatic disease.

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 to the study treatment (Table 2).

The ORR (CR + PR) was 11% (7/62) and the CBR at 4 months was 32% (20/62) in the overall population; the primary cohort has a 9% (4/41) ORR and 27% (11/41) CBR at 4 months, while, in the second cohort of exclusively BRCA mutant patients, we found a 14% (3/21) ORR and 43% (9/21) CBR at 4 months in the expansion cohort. The waterfall plots demonstrated the best overall response of evaluable patients in each cohort (Figure 1). In the primary cohort (n = 34, Figure 1A), all four patients who achieved CR or PR had BRCA1/2 mutations.
Thirteen patients in this cohort, including one who had an un-confirmed partial response, demonstrated stable disease without progression 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 expansion cohort (n = 18 evaluable, Figure 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 progressive new lesions. Combining both cohorts, seven patients who had achieved response (CR or PR) were all BRCA carriers including five BRCA2 and two BRCA1 carriers (Figure 1 and 2). Of these seven patients, six had no previous platinum treatment (Figure 3). No patient achieved response among BRCA non-carriers (Figure 2 and 3).

In an exploratory subgroup analysis based on the status of prior platinum treatment (Supplemental Table 2), the objective response rate was 15% (6/40) among platinum-naïve patients versus 5% (1/22) among platinum-exposed patients. 38% (15/40) of platinum-naïve patients achieved clinical benefit at 4 months of treatment, compared to 23% (5/22) among the platinum-exposed group.

In the subgroup analysis based on BRCA status (Supplemental Table 2 and Figure 2), the objective response rate was 23% (7/30) among BRCA carriers, compared to 0% (0/32) among those without BRCA non-carriers. The clinical benefit rate at 4 months was 47% (14/30) for BRCA carriers versus 19% (6/32) for non-carriers. Furthermore, among all BRCA carriers (Supplemental Table 3 and Figure 3), we found an objective response rate of 32% (6/19) and clinical benefit rate of 58% (11/19) at 4 months among platinum-naïve patients, compared to 9% (1/11) and 27% (3/11) among patients who had received prior platinum.

Comparing the different types of metastatic breast cancers (Supplemental Table 4), the objective response rates were 19% (5/27), 17% (1/6) and 3% (1/29) respectively for HR+, HER2+ and

TNBC., and the 4 month CBR rates were 41% (11/27), 50% (3/6) or 21% (6/29) for patients with HR+, HER2+ or TNBC.

Survival analysis

The median PFS was 2.1 months (90% CI, 1.8 to 3.0 mo) in the overall population (Figure 4A), 1.8 months and 3 months in the primary and expansion cohort. However, the median PFS was significantly greater at 3.3 months (90% CI, 2.3 to 6.2 mo) among BRCA1/2 carriers compared to 1.8 months (90% CI, 1.6 to 2.3 mo) among non-carriers (HR: 0.48, p = 0.006; Figure 4B). 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 the patients who had received prior platinum therapy with a hazard ratio of 0.45 (p = 0.005; Figure 4C). The greatest benefit of treatment was observed for patients who were BRCA 1/2 carriers and had no prior platinum therapy (Figure 4D). They had a significantly prolonged progression-free survival (mPFS 6.2 mo; 90% CI, 3.7 to 7.3 mo) as compared to other groups (HR: 0.34, p = 0.0003). One patient, a BRCA2 carrier who had no prior platinum therapy, had a durable complete remission, now ongoing for 5 years.

Safety

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

Of the 62 patients, one patient had only received one dose of veliparib and TMZ and had no related adverse events (AEs). 68 types of AEs occurred to the other 61 patients during study period. The most common all-grade AEs (Table 3) were thrombocytopenia, nausea, fatigue, anemia and leukocytosis. The most frequent AEs of Grade 3 or higher were thrombocytopenia, neutropenia, leukocytosis, nausea and vomiting. The most common AEs to cause dose delay or modification were thrombocytopenia and neutropenia. One patient discontinued the treatment due to prolonged thrombocytopenia. Another patient died of Grade 5 infection after receiving 4 cycles of treatment.

Discussion

In this study ORR in the overall population did not meet the pre-specified criteria. However, the combination of veliparib and temozolomide demonstrated efficacy among metastatic breast cancer with patients *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. Indeed, there was no clinical activity in non-carriers despite encouraging preclinical data. The objective response rate was greater and the median PFS longer among patients who had not received prior platinum chemotherapy than among those who had. A high ORR (32%) and CBR at 4 mo (58%) were observed in the subset of patients with BRCA1/2 carriers and without prior platinum therapy, together with a prolonged progression-free survival of 6.2 months. Overall, these results have led to a multicenter three-arm, randomized, phase II study of veliparib and temozolomide compared to carboplatin/paclitaxel with or without veliparib among patients with *BRCA*-associated metastatic breast cancer [14, 29].

This was the first study to evaluate the efficacy of veliparib and temozolomide in breast cancer. This combination only showed response among patients with the BRCA1/2 deficiency. This was based on the mechanism of *synthetic lethality* whereas inhibition of a single pathway was not efficient. Inhibition of PARP in the presence of BRCA deficiency would make cancer cells highly vulnerable to DNA damaging agents such as TMZ. This may explain why the addition of veliparib to TMZ exhibited efficacy, where as a single-agent TMZ showed no activity in this population [21]. In a previous study, BRCA-mutant breast cancer patients who had received no prior platinum treatment after the monotherapy of veliparib (400mg BID) showed response rates of 14% (3/22 for BRCA1+) and 36% (8/22 for BRCA2+) [30]. These response rates were comparable to the ORR (32%) obtained in this study within a similar population (Supplemental Table 3). However, patients in this study only received veliparib twice daily at 30-40mg, about one tenth of the dose used in the previous trial. Further studies are needed to understand the mechanism of this combination therapy better.

BRCA deficient tumors demonstrate sensitivity to both PARP inhibitors and platinum. These two classes of drugs also may share a common mechanism of resistance [7, 31, 32]. However, this is not completely understood. Secondary somatic mutations restoring the function of BRCA1/2 proteins may explain half of the drug resistance [31, 33, 34]. Other mechanisms may include microRNA-mediated resistance through HR rescue, replication fork stabilization, PARP1 mutations and drug efflux pumps [7, 35, 36]. In this study that the combination of veliparib and temozolomide was ineffective in patients who have received prior platinum therapy. Because patients who had progressed with prior platinum therapy also displayed resistance to PARP inhibitors.

Previous studies showed PARP inhibition potentiates the activity of TMZ and exacerbated TMZ hematological toxicity [15-19]. Accordingly, in the study the combination of veliparib and temozolomide led commonly to hematologic adverse effects, specifically thrombocytopenia. The severity of hematologic toxicities was comparable to our later study with a same treatment regimen [14]. Those toxicities were more frequent in patients receiving the TMZ/veliparib compared to veliparib monotherapy as reported previously [30]. One patient in this study discontinued treatment due to thrombocytopenia and another patient died due to severe infection that may be possibly related to the study treatment. The observed hematological toxicity was effectively managed in most patients with dose reductions mainly by TMZ.

This Phase II study was for proof of concept and limited by the single-arm design, which included no comparison group. This made it impossible to make a conclusion on the causal effect of this combination therapy. The small sample size especially in subgroups limited the power to conclude the subgroup of interest. However, this study has generated the hypothesis for testing in a RCT setting.

Veliparib/TMZ may provide a potential oral regimen for the treatment of BRCA1/2 deficient metastatic breast cancer. A phase II randomized trial found the addition of veliparib to carboplatin/paclitaxel improved ORR and mPFS, compared to veliparib/TMZ [14], which implicated PARP inhibitors combined with platinum-based regimens may have a better efficacy than its combination with TMZ. Despite this result, veliparib/TMZ may be further tested in breast cancer with brain metastasis and BRCA mutations, as both of them have great potential to cross the blood-brain barrier and an early phase I study demonstrated encouraging activity of

veliparib combined with the standard radiation therapy in brain metastases from breast cancer [37]. Moreover, future studies should continue exploring the potential application of veliparib or other PARP inhibitors in combination with platinum or other alkylating agents. A phase III trial to further evaluate the efficacy of veliparib with carboplatin and weekly paclitaxel in BRCA mutant MBC is ongoing (NCT02163694). Another ongoing trial will examine the safety and efficacy of another PARP inhibitor (Olaparib) added to carboplatin/paclitaxel in a neoadjuvant setting in TNBC and or germline BRCA positive breast cancer (NCT03150576). In addition, the combination of PARP inhibitors with other agents that may modulate the HR pathway is another promising strategy, e.g. CDK1 inhibitors, HSP90 inhibitors, PI3K or AKT inhibitors. There are ongoing trials investigating the safety of two PI3K inhibitors with a PARP inhibitor (Olaparib) in advanced TNBC and ovarian cancer (NCT01623349), and the safety of AKT inhibitor with Olaparib in advanced solid tumors (NCT02338622).

Conclusion

In this phase II study, veliparib and temozolomide showed efficacy, but only in patients with BRCA-deficient metastatic breast cancer who had no prior platinum treatment. Such combination therapy was mainly associated with hematologic adverse events manageable with dose modifications. The optimal application of veliparib in a combination setting is still under exploration.

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Conflicts of Interest

The corresponding author SJI has no potential financial conflicts of interest to declare. JQ, VG, and SS are or have been employed by Abbott Laboratories. SJI, TEK, BO, NMT, RSG, KH, JEG, LWE, EPW, and PEG report no conflicts of interest.

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Figure Legends

Figure 1. The Waterfall Plots of Best Overall Response Rate.

In the primary cohort (A), seven patients were non-evaluable because of no follow-up imaging due to rapid clinical progression; In the expansion cohort (B), patients had no follow-up imaging due to rapid clinical progression (n = 2) or early death (n = 1).

Figure 2. The Waterfall Plots of Best Overall Response by BRCA status.

Among BRCA carriers (A): 4 patients were non-evaluable because of clinical progression (n = 3) or early death (n = 1) before re-evaluation date; Among non-carriers (B): 6 patients were non-evaluable because of clinical progression before re-evaluation date.

Figure 3. The Waterfall Plots of Best Overall Response by Status of Prior Platinum Treatment and BRCA Mutations

Figure 4. Kaplan-Meier Estimates of Progression-free Survival.

(A), in overall population; (B), by BRCA Mutation Status; (C), by the Status of Prior Platinum Therapy;(D), Comparing patients with BRCA positive without Prior Platinum Therapy to others

Supplemental Figure 1. Kaplan-Meier Estimates of Progression-free Survival in Each Cohort

Supplemental Figure 2. Kaplan-Meier Estimates of Progression-free Survival by Receptor Status

Tables

Table 5 Baseline characteristics

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

Table 6 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 refer to the online supplemental tables;*

[b] *7 patients had no follow-up imaging due to rapid clinical progression; one of these patients had 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, table disease; PD, Progressive disease; NE, Non-evaluable; ORR, objective response rate; CBR at 4 mo, Clinical benefit rate at 4 months

Table 7 Treatment-related Adverse Events of all Grade and Grade ≥ 3

Event	All Grade	Grade3	Grade 4	Grade 5
	N (%)			
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)	

Figures

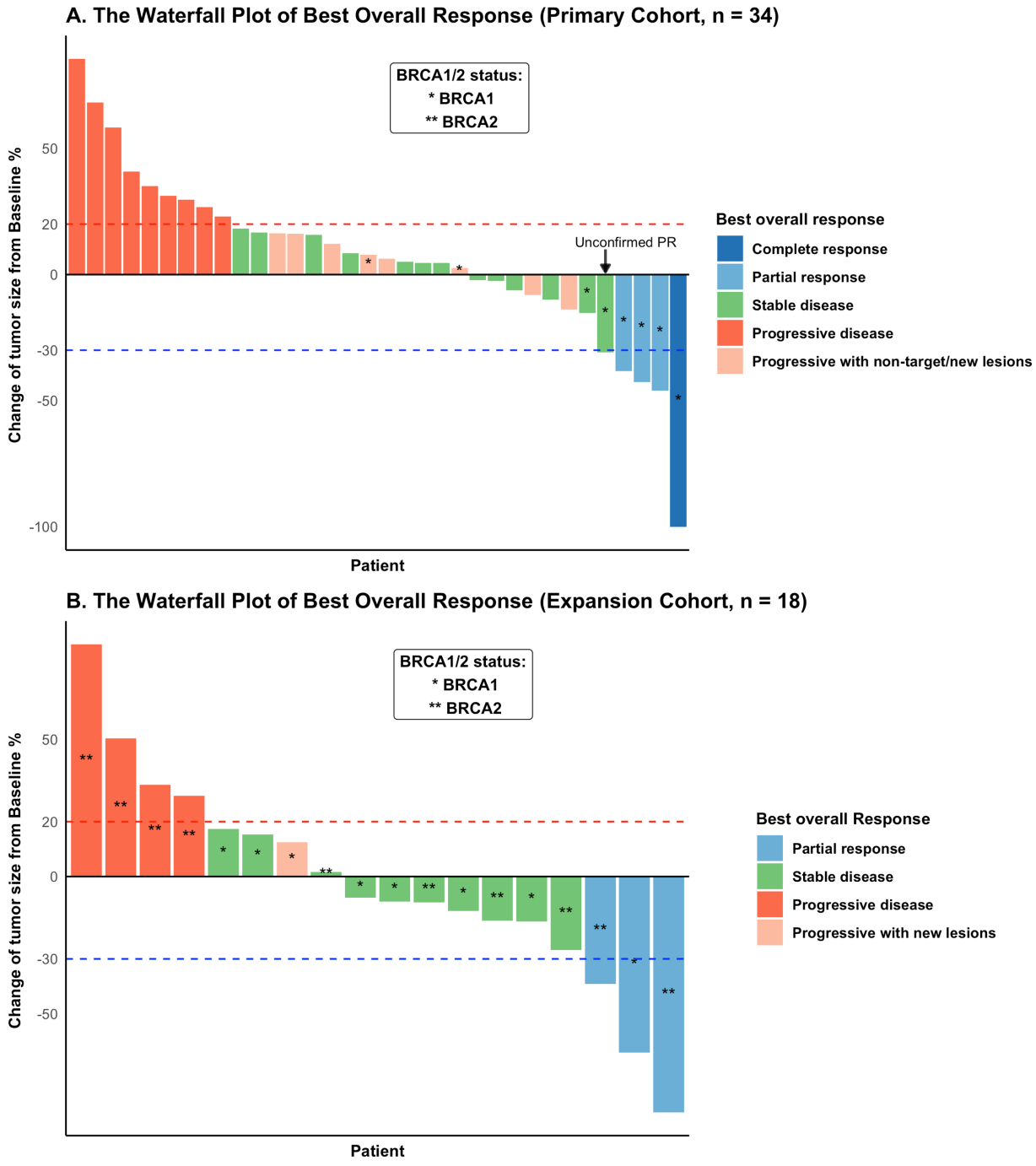


Figure 1 The Waterfall Plots of Best Overall Response Rate

In the primary cohort (A), seven patients were non-evaluable because of no follow-up imaging due to rapid clinical progression; In the expansion cohort (B), patients had no follow-up imaging due to rapid clinical progression (n = 2) or early death (n = 1).

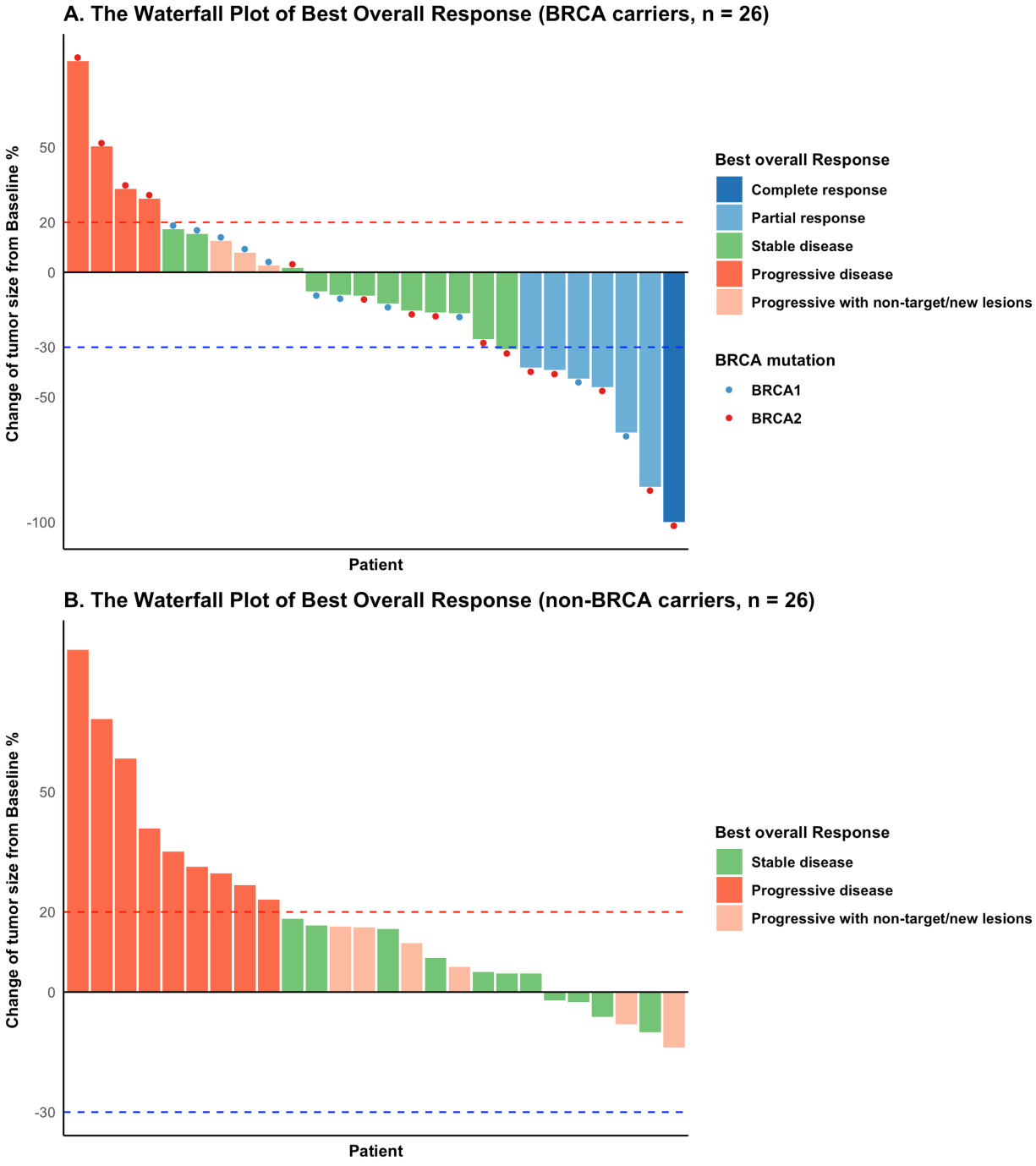


Figure 2 The Waterfall Plots of Best Overall Response by BRCA status

Among BRCA carriers (A): 4 patients were non-evaluable because of clinical progression (n = 3) or early death (n = 1) before re-evaluation date; Among non-carriers (B): 6 patients were non-evaluable because of clinical progression before re-evaluation date.

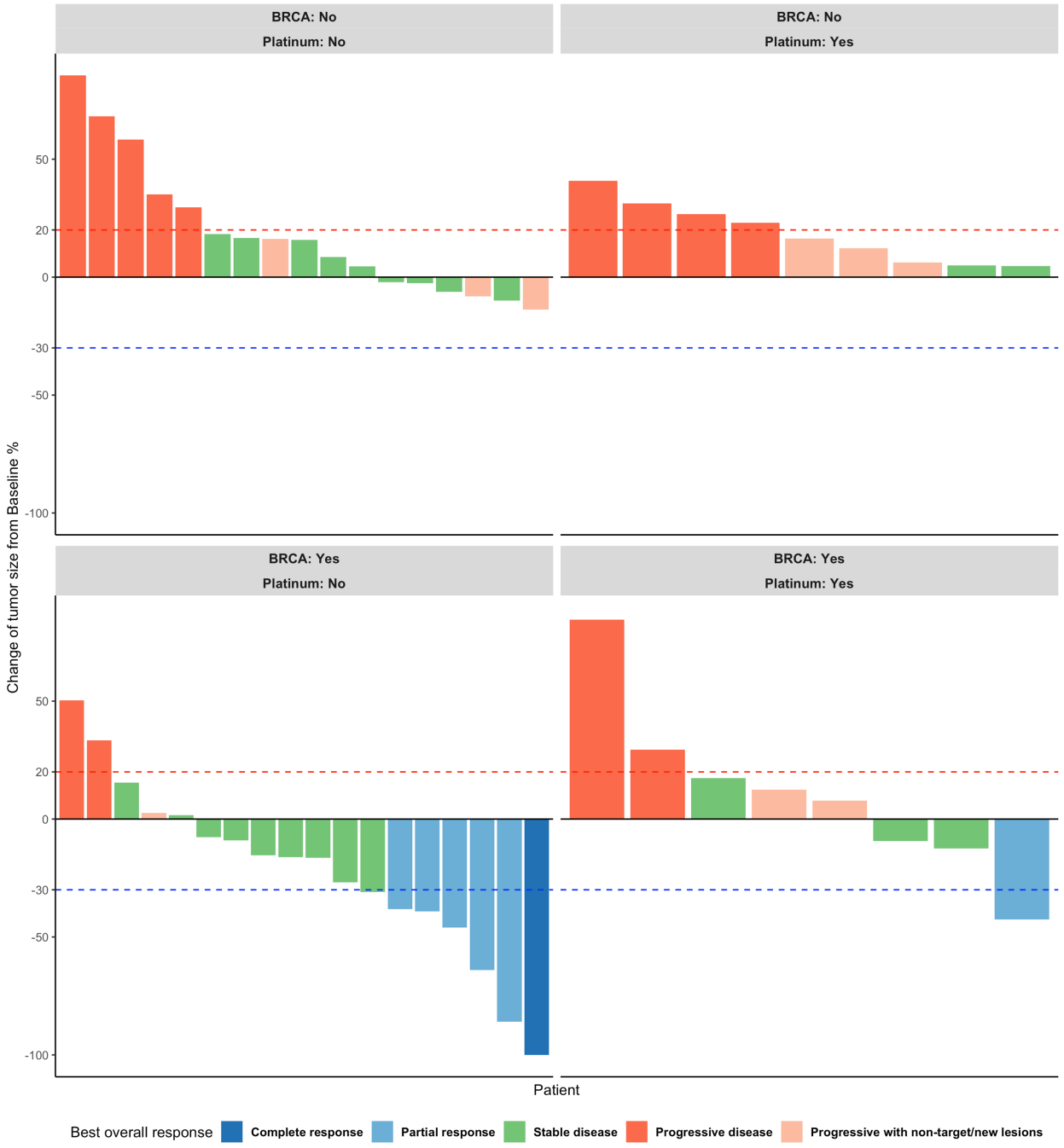


Figure 3 The Waterfall Plots of Best Overall Response by Status of Prior Platinum Treatment and BRCA Mutations

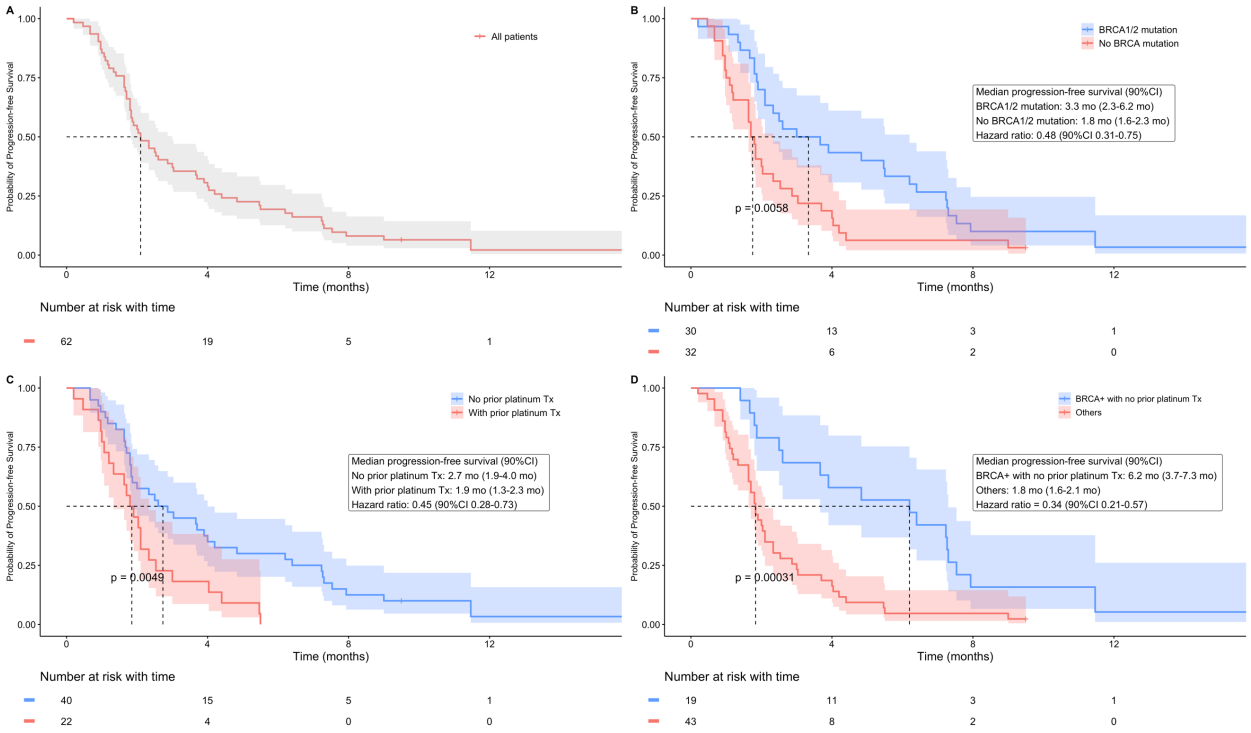


Figure 4 Kaplan-Meier Estimates of Progression-free Survival

***(A)**, in overall population; **(B)**, by BRCA mutation status; **(C)**, by the status of prior platinum therapy;**(D)**, comparing patients with BRCA positive without prior platinum therapy to others.*

Supplemental Data

Supplemental Tables

Supplemental Table 1. Response to treatment by BRCA status in each cohort

Response n (%)	Primary cohort		Expansion cohort	
	No BRCA (n = 32)	BRCA1/2 (n =9)	BRCA1 (n = 9)	BRCA2 (n = 12)
CR	0	1 (11)	0	0
PR	0	3 (33)	1 (11)	2 (17)
SD	11 (34)	2 (22)	6 (67)	4 (33)
PD	15 (47)	2 (22)	1 (11)	4 (33)
NE	6 (19)	1 (11)	1 (11)	2 (17)
ORR	0	4 (44)	1 (11)	2 (17)
CBR at 4 mo	6 (19)	5 (56)	5 (56)	9 (75)

Supplemental Table 2. Response to treatment by status of BRCA1/2 mutation and prior platinum treatment

Response n (%)	BRCA1/2 status		Prior platinum treatment	
	Positive (n = 30)	Negative (n = 32)	Yes (n = 22)	No (n = 40)
CR	1 (3)	0	0	1 (3)
PR	6 (20)	0	1(5)	5 (13)
SD	12 (40)	11 (34)	5 (23)	18 (45)
PD	7 (23)	15 (47)	11 (50)	11 (28)
NE	4 (13)	6 (19)	5 (23)	5 (13)
ORR	7 (23)	0	1 (5)	6 (15)
CBR at 4 mo	14 (47)	6 (19)	5 (23)	15 (38)

Supplemental Table 3. Response to treatment by prior platinum treatment among patients with/without BRCA mutations

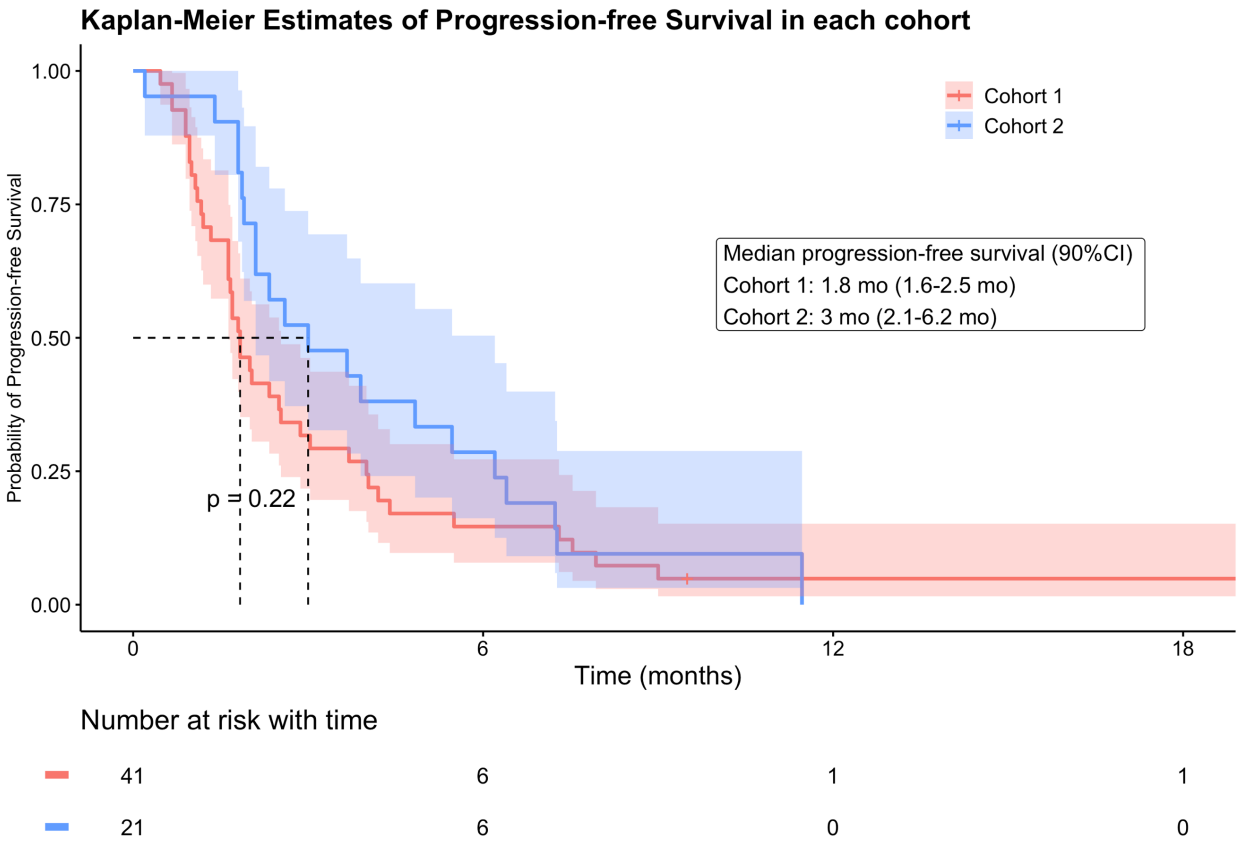
Response n (%)	BRCA mutation		No BRCA mutation	
	Prior platinum Tx		Prior platinum Tx	
	Yes (n = 11)	No (n = 19)	Yes (n = 11)	No (n = 21)
CR	0	*1 (5)*	0	0
PR	1 (9)	*5 (26)*	0	0
SD	3 (27)	*9 (47)*	2 (18)	9 (43)
PD	4 (36)	*3 (16)*	7 (64)	8 (38)
NE	3(27)	*1 (5)*	2 (18)	4 (19)
ORR	1 (9)	*6 (32)**	0	0
CBR at 4 mo	3(27)	*11 (58)**	2 (18)	4 (19)

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

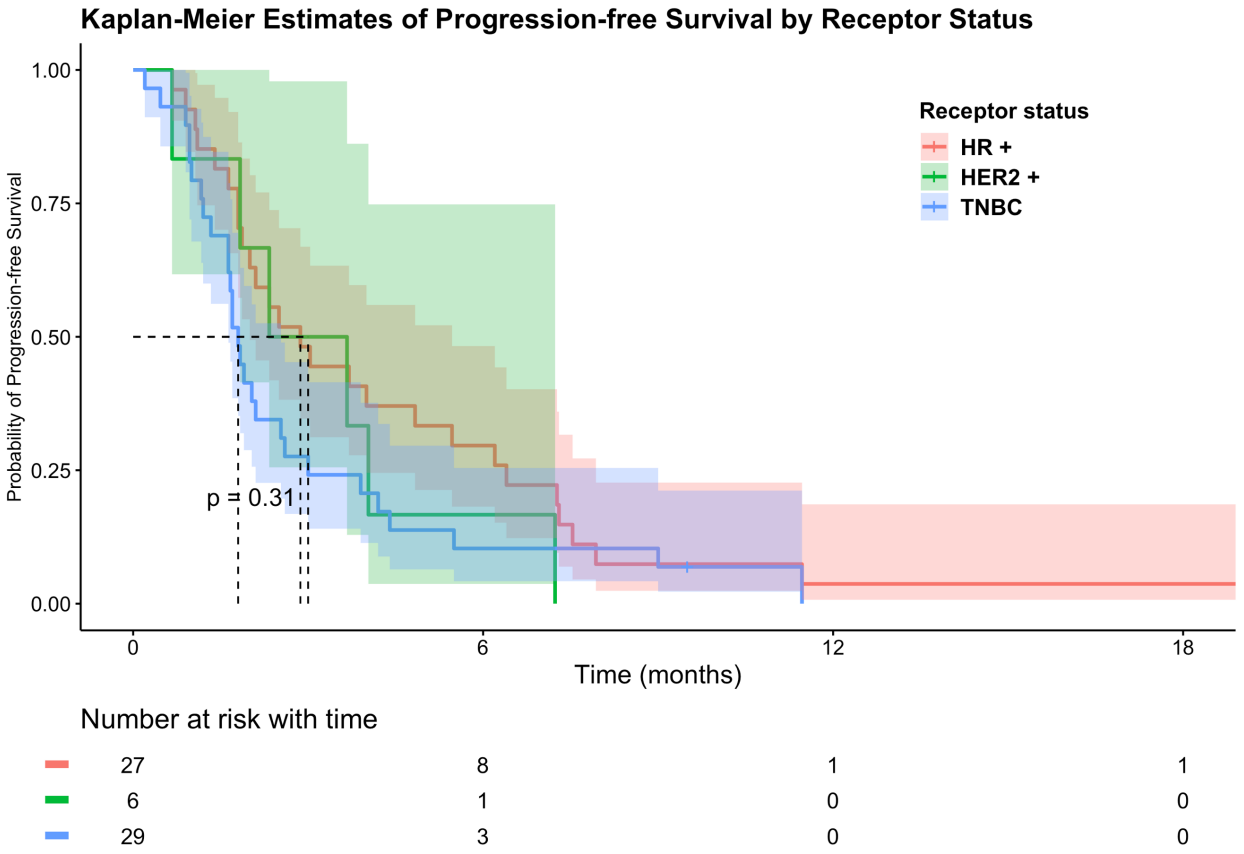
Supplemental Table 4. Response to treatment by types of metastatic breast cancer

Response, n (%)	HR+ (n = 27)	HER2+ (n = 6)	TNBC (n = 29)
CR	1 (4)	0	0
PR	4 (15)	1 (17)	1 (3)
SD	10 (37)	2 (33)	11 (38)
PD	7 (26)	3 (50)	12 (41)
NE	5 (19)	0	5 (17)
ORR	5 (19)	1 (17)	1 (3)
CBR at 4 mo	11 (41)	3 (50)	6 (21)

Supplemental Figures



Supplemental Figure 1. Kaplan-Meier Estimates of Progression-free Survival in Each Cohort



Supplemental Figure 2. Kaplan-Meier Estimates of Progression-free Survival by Receptor Status

SUMMARY OF THESIS STUDIES

Study one examines the clinical activity of cabozantinib monotherapy in HR+ breast cancer with bone metastases, and utilizes a novel primary endpoint, bone scan response rate, in this study population. The study met its primary endpoint, achieving a high bone scan response rate (39%) and disease control rate (50%). Disease control status based on response on 12-week bone scans correlated with the disease control in extraosseous sites. In addition, patients who maintained disease control on bone scans at 12 weeks had an improved overall survival, as compared to patients who experienced disease progression. In summary, cabozantinib monotherapy demonstrated promising clinical activity in bone lesions for patients with metastatic HR+ breast cancer. Our data supports further investigation of cabozantinib in HR+ metastatic breast cancer and further supports the novel endpoint of bone scan response to provide a valuable tool for assessing responses to treatment in patients with bone only or bone-predominant disease.

My second study assessed the efficacy and safety of a novel drug combination, veliparib and temozolomide, an oral regimen in 62 patients with metastatic breast cancer. The trial evaluated this therapy in subjects with (30 subjects) or without (32 subjects) germline BRCA1/2 mutations. This combination was only effective among BRCA carriers particularly in the trial participants who had not receiving prior treatment with a platinum agent. Among the BRCA carriers, 23% (7/30) of patients achieved response and 47% (14/ 30) of them had obtained clinical benefit for at least 4 months. Compared with all other subgroups, BRCA carriers without exposure to platinum therapy had a high objective response rate (32%), clinical benefit rate (58%) at 4 months and longer median progression-free survival of 6.2 months. These findings have led to our multicenter randomized phase II trial of veliparib and temozolomide compared to

carboplatin/paclitaxel/veliparib and carboplatin/paclitaxel in BRCA deficient metastatic breast cancer patients reported elsewhere [1].

DISCUSSION AND FUTURE PERSPECTIVES

In my first study, we observed a higher bone scan response in patients with bone lesions as compared to the RESIST-derived response rate in extraosseous disease. This finding suggests that this drug may have better activity in managing bone lesions, a common problem in ER+ breast cancer. In addition, bone scan response correlated with overall survival as well as disease control (response or stable disease) in extraosseous sites. This suggested that bone scan responses may reflect true antitumor activity of cabozantinib in HR+ breast cancer and the disease control status based on 12-week bone scans may predict patient survival. However, this study was limited by the single-arm design and small sample size, which made it impossible to draw a firm conclusion and limited the impact of detailed information from subgroup analyses. Considering the mechanism of action of this molecularly multi-targeted agent, the lack of a biomarker information in this trial, especially for drug targets including MET, RET and VEGFR2, detracts from understanding of its mechanism in breast cancer.

Regarding further studies, combined use of cabozantinib with other categories of breast cancer therapy, such as hormonal therapy or CDK4/6 inhibitors, would be the next logical step in evaluating this drug, and these studies are in progress. For example, in order to confirm and extend the findings of this study, a future double-blinded randomized trial may be conducted to compare cabozantinib combined with a standard therapy such as hormonal therapy to the standard therapy plus placebo in HR+ breast cancer with bone metastasis. In this study, both bone scan response rate and objective response rate are suggested to be used as primary endpoints and the expression of patient biomarkers would be considered as an exploratory endpoint to look for any evidence for personalized medicine.

PARP inhibitors are a new class of targeted therapies, which show great potential in tumors with BRCA deficiency. Veliparib, compared with other PARP inhibitors, is a less potent inhibitor due to its poor PARP trapping activity [2, 3]. However, it has promising potential for combination therapies due to its lower toxicity profile [2]. Veliparib has been tested widely in the combination setting in multiple types of human cancer. In our trial, veliparib/temozolomide demonstrated efficacy in patients with BRCA deficient metastatic breast cancers, especially those without exposure to prior platinum treatment. However, temozolomide has modest activity as a single agent in breast cancer and is likely not the optimal partner of veliparib for BRCA mutant breast cancer. The finding of this study has contributed to our later randomized trial, whereby veliparib with carboplatin/paclitaxel achieved higher efficacy than the combination of veliparib and temozolomide in a comparable population [1]. This oral regimen of veliparib/temozolomide, as both drugs show excellent drug delivery into the brain by passing through the blood brain barrier (BBB).

Targeted therapy is very attractive for individualized treatment. However, patients often develop drug resistance during the course of treatment due to genetic alterations. Moreover, the lack of novel genetic drivers in MBC and optimization of patient selection limit the clinical development of new targeted therapies [4]. Genetic testing may not be feasible in patients with bone-only metastatic disease. Analysis of circulating tumor DNA, or "liquid biopsies" would add valuable information regarding mechanisms of drug action and drug resistance in the patient population in which direct tumor biopsy is unfeasible [5].

REFERENCES FOR SUMMARY AND DISCUSSION

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