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Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial

Véronique Diéras*, Hyo S Han*, Bella Kaufman, Hans Wildiers, Michael Friedlander, Jean-Pierre Ayoub, Shannon L Puhalla, Igor Bondarenko, Mario Campone, Erik H Jakobsen, Mathilde Jalving, Cristina Oprean, Marketa Palácová, Yeon Hee Park, Yaroslav Shparyk, Eduardo Yañez, Nikhil Khandelwal, Madan G Kundu, Matthew Dudley, Christine K Ratajczak, David Maag, Banu K Arun

Summary

Background *BRCA1* or *BRCA2*-mutated breast cancers are sensitive to poly(ADP-ribose) polymerase (PARP) inhibitors and platinum agents owing to deficiency in homologous recombination repair of DNA damage. In this trial, we compared veliparib versus placebo in combination with carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel were discontinued before progression, in patients with HER2-negative advanced breast cancer and a germline *BRCA1* or *BRCA2* mutation.

Methods BROCADE3 was a randomised, double-blind, placebo-controlled, phase 3 trial done at 147 hospitals in 36 countries. Eligible patients (aged ≥ 18 years) had deleterious germline *BRCA1* or *BRCA2* mutation-associated, histologically or cytologically confirmed advanced HER2-negative breast cancer, an Eastern Cooperative Oncology Group performance status of 0–2, and had received up to two previous lines of chemotherapy for metastatic disease. Patients were randomly assigned (2:1) by interactive response technology by means of permuted blocks within strata (block size of 3 or 6) to carboplatin (area under the concentration curve 6 mg/mL per min intravenously) on day 1 and paclitaxel (80 mg/m² intravenously) on days 1, 8, and 15 of 21-day cycles combined with either veliparib (120 mg orally twice daily, on days –2 to 5) or matching placebo. If patients discontinued carboplatin and paclitaxel before progression, they could continue veliparib or placebo at an intensified dose (300 mg twice daily continuously, escalating to 400 mg twice daily if tolerated) until disease progression. Patients in the control group could receive open-label veliparib monotherapy after disease progression. Randomisation was stratified by previous platinum use, history of CNS metastases, and oestrogen and progesterone receptor status. The primary endpoint was investigator-assessed progression-free survival per Response Evaluation Criteria in Solid Tumors version 1.1. Efficacy analyses were done by intention to treat, which included all randomly assigned patients with a centrally confirmed *BRCA* mutation, and safety analyses included all patients who received at least one dose of veliparib or placebo. This study is ongoing and is registered with ClinicalTrials.gov, NCT02163694.

Findings Between July 30, 2014, and Jan 17, 2018, 2202 patients were screened, of whom 513 eligible patients were enrolled and randomly assigned. In the intention-to-treat population (n=509), 337 patients were assigned to receive veliparib plus carboplatin–paclitaxel (veliparib group) and 172 were assigned to receive placebo plus carboplatin–paclitaxel (control group). Median follow-up at data cutoff (April 5, 2019) was 35·7 months (IQR 24·9–43·6) in the veliparib group and 35·5 months (23·1–45·9) in the control group. Median progression-free survival was 14·5 months (95% CI 12·5–17·7) in the veliparib group versus 12·6 months (10·6–14·4) in the control group (hazard ratio 0·71 [95% CI 0·57–0·88], p=0·0016). The most common grade 3 or worse adverse events were neutropenia (272 [81%] of 336 patients in the veliparib group vs 143 [84%] of 171 patients in the control group), anaemia (142 [42%] vs 68 [40%]), and thrombocytopenia (134 [40%] vs 48 [28%]). Serious adverse events occurred in 115 (34%) patients in the veliparib group versus 49 (29%) patients in the control group. There were no study drug-related deaths.

Interpretation The addition of veliparib to a highly active platinum doublet, with continuation as monotherapy if the doublet were discontinued, resulted in significant and durable improvement in progression-free survival in patients with germline *BRCA* mutation-associated advanced breast cancer. These data indicate the utility of combining platinum and PARP inhibitors in this patient population.

Funding AbbVie.

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Introduction

Approximately 5% of all breast cancers are associated with germline mutations in *BRCA1* or *BRCA2*, and these

patients are more likely to be diagnosed at a young age and to have triple-negative breast cancer, for which few treatment options are available in the metastatic setting.^{1–3}

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Research in context

Evidence before this study

We searched PubMed in November, 2019, using the search terms “BRCA1”, “BRCA2”, and “breast cancer” for primary publications published between June 1, 2015, and November, 2019. We selected phase 2 or phase 3 studies of platinum chemotherapy, poly(ADP-ribose) polymerase (PARP) inhibitors, or both, in patients with advanced breast cancer and germline *BRCA* mutations.

The phase 3 TNT trial showed a higher proportion of objective responses and improved progression-free survival when patients with advanced *BRCA1* or *BRCA2* mutation-positive triple-negative breast cancer were treated with carboplatin compared with docetaxel. The phase 2 TBCRC009 trial evaluated cisplatin or carboplatin in patients with metastatic triple-negative breast cancer, showing more objective responses in the subgroup of patients with germline *BRCA* mutations. These trials indicate that platinum chemotherapy might be particularly effective in treating patients with *BRCA* mutation-positive advanced triple-negative breast cancer, which has led to updates to both National Comprehensive Cancer Network and European School of Oncology–European Society of Medical Oncology breast cancer guidelines where platinum chemotherapy is now included as a preferred regimen for these patients.

The phase 3 OlympiAD and EMBRACA trials showed improved progression-free survival with olaparib or talazoparib monotherapy, respectively, when compared with physicians’

choice of non-platinum chemotherapy in patients with advanced, HER2-negative breast cancer and a germline *BRCA* mutation. The phase 2 BROCADE trial showed numerically longer (although not significant) progression-free survival and overall survival with the addition of veliparib to carboplatin and paclitaxel in patients with advanced germline *BRCA* mutation-positive breast cancer, without substantial additional toxicity. These results warranted further study in a larger phase 3 trial.

Added value of this study

To our knowledge, BROCADE3 is the first phase 3 trial to evaluate a PARP inhibitor with platinum doublet chemotherapy for *BRCA* mutation-associated breast cancer, showing a significant improvement in progression-free survival with the addition of veliparib to carboplatin and paclitaxel. In subgroup analyses, the progression-free survival benefit was similar in patients with triple-negative breast cancer and those with hormone receptor-positive breast cancer.

Implications of all the available evidence

BROCADE3 has shown, we believe for the first time, that the combination of a PARP inhibitor, veliparib, with platinum chemotherapy significantly improves progression-free survival with little additional toxicity in patients with advanced HER2-negative breast cancer and a *BRCA* mutation. These data suggest that veliparib, in combination with carboplatin and paclitaxel, should be considered as a new treatment option for patients with *BRCA*-associated advanced breast cancer who are candidates for chemotherapy.

The reported 5-year survival for patients with metastatic breast cancer is 27%, and is only 11% for patients with metastatic triple-negative breast cancer.⁴ Thus, new treatments that provide durable benefit for patients with germline *BRCA* mutation-associated advanced breast cancer are needed.

BRCA1 and *BRCA2*-mutated breast cancers have a deficiency in homologous recombination repair, impairing the ability of cancer cells to repair DNA damage, and are known to be sensitive to both poly(ADP-ribose) polymerase (PARP) inhibitors and platinum agents.^{5–8} Clinical evidence has shown that this vulnerability can be exploited for the treatment of advanced, HER2-negative breast cancer, and has led to the inclusion of both classes of agents in treatment guidelines. However, reports of the emergence of reversion mutations that restore *BRCA* function in patients treated with either platinum chemotherapy or PARP inhibitors have led to concerns about cross-resistance and, for this reason, patients who are resistant or refractory to platinum chemotherapy are often excluded from PARP inhibitor clinical trials. Given this concern, a strong scientific rationale exists to combine PARP inhibitors with platinum chemotherapy on the basis of common mechanisms of sensitivity and acquired resistance,⁹ and observed potentiation of platinum activity

by PARP inhibitors preclinically, to maximise the therapeutic benefit derived from exploiting pathogenic *BRCA* mutations.¹⁰ However clinical application of these combinations has been challenging,^{11,12} largely owing to haematological toxicity.^{13,14}

Veliparib (ABT-888) is a potent, orally bioavailable, selective PARP1 and PARP2 inhibitor¹⁰ that has shown antitumour activity and acceptable toxicity as a single agent and in combination with carboplatin and paclitaxel in patients with *BRCA* mutation-associated breast cancer.^{15,16} Veliparib selectively inhibits the polymerase activity of PARP without substantial trapping of PARP protein onto DNA damage repair intermediates.^{17,18} This mechanism of action makes veliparib more suitable than other PARP inhibitors to be administered in combination with platinum-based chemotherapy, since PARP trapping has been shown to be associated with myelosuppression.¹⁹ In a randomised, placebo-controlled, phase 2 study (BROCADE),²⁰ numerical (although not significant) increases in median progression-free survival and overall survival were observed with the addition of veliparib to carboplatin and paclitaxel versus carboplatin and paclitaxel alone in patients with *BRCA*-mutated advanced breast cancer. The safety profile was similar between the two treatment groups, with common adverse events

generally being haematological and gastrointestinal.²⁰ Haematological events were generally manageable with dose reductions and standard supportive measures and gastrointestinal events were typically low grade. Here, we report results from BROCADE3, a randomised, controlled, phase 3 trial comparing veliparib with placebo in combination with carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel are discontinued before progression, in patients with HER2-negative, inoperable, locally advanced or metastatic breast cancer with germline *BRCA1* or *BRCA2* mutations.

Methods

Study design and participants

BROCADE3 is a phase 3, double-blind, randomised, placebo-controlled study done at 147 centres (eg, hospitals) in 36 countries worldwide (appendix pp 1–6).

Patients (aged ≥ 18 years) with histologically or cytologically confirmed metastatic or locally advanced, unresectable, HER2-negative breast cancer and suspected deleterious or deleterious germline *BRCA1* or *BRCA2* mutations and an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled. Patients could have measurable or non-measurable disease (but radiologically evaluable) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Patients had adequate haematological, renal, and hepatic function (absolute neutrophil count ≥ 1500 cells per μL , platelet count $\geq 100\,000$ per μL , haemoglobin concentration ≥ 95 g/L, serum creatine $\leq 1.5 \times$ the upper limit of normal [ULN] or creatine clearance ≥ 50 mL/min per 1.73 m², bilirubin $\leq 1.5 \times$ ULN, aspartate aminotransferase and alanine aminotransferase concentrations $\leq 2.5 \times$ ULN, activated partial thromboplastin time $\leq 1.5 \times$ ULN, and international normalised ratio < 1.5). All patients were tested for germline *BRCA1* or 2 mutations by means of the BRACAnalysis CDx assay (Myriad Genetics, Salt Lake City, UT, USA). Patients with germline *BRCA1* or *BRCA2* mutations based on local testing were eligible but retesting by Myriad was required to confirm their *BRCA* mutational status. Patients had received up to two previous lines of cytotoxic chemotherapy for metastatic breast cancer, and up to one previous line of platinum therapy without progression within 12 months of completing treatment. Patients could have received a previous taxane as neoadjuvant or adjuvant therapy or to treat locally advanced disease, if given more than 6 months before study start. Previous taxane for metastatic breast cancer was not allowed unless it was administered without progression more than 12 months before study start. Previous treatment with targeted agents was allowed except for previous PARP inhibitor therapy. Hormone receptor-positive patients and patients with bone-only metastases were eligible provided the investigator considered them appropriate candidates for combination chemotherapy. Patients with active brain metastases,

leptomeningeal disease, history of uncontrolled seizure disorder, pre-existing neuropathy exceeding grade 1, or previous or concurrent cancer distinct from breast cancer were not included in this study. Furthermore, any patients with clinically significant uncontrolled active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, myocardial infarction within 6 months before randomisation, hepatitis B or C virus infection, uncontrolled hypertension, or major surgery within 3 weeks of randomisation were excluded. Additional eligibility criteria are in the protocol (appendix pp 260–63).

The study was done according to the protocol approved by institutional review boards at investigational sites, International Conference on Harmonization Good Clinical Practice guidelines, regulations governing clinical study conduct, and ethical principles with their origin in the Declaration of Helsinki. All patients provided written informed consent.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (2:1) to carboplatin and paclitaxel with veliparib (veliparib group) or carboplatin and paclitaxel with placebo (control group) by an interactive response technology system with use of permuted blocks within strata. Variable block sizes of 3 and 6 were used. Randomisation in a 2:1 ratio was intended to facilitate recruitment of this patient population with a rare biomarker. Randomisation was stratified according to oestrogen and progesterone receptor expression (positive or negative), previous platinum therapy (yes or no), and history of CNS metastases (yes or no). The randomisation schedule was created by the AbbVie statistics department and forwarded to a third-party vendor to be implemented via the interactive response technology system.

All parties were masked to treatment assignment until investigator-assessed disease progression, after which the physician and patient could be unmasked to establish eligibility for crossover therapy. The primary analysis was done by statistics personnel employed by AbbVie, who remained masked throughout the course of the study, and were unmasked at the time of the primary analysis.

Procedures

Patients received veliparib (120 mg orally twice daily) or placebo (capsules matching veliparib capsules twice daily) on days –2 to 5, carboplatin (area under the concentration curve [AUC] 6 mg/mL per min intravenously) on day 1, and weekly paclitaxel (80 mg/m² intravenously) on days 1, 8, and 15 (of 21-day cycles) until disease progression or unacceptable toxicity. Any of the three agents could be dose reduced or discontinued individually at the discretion of the investigator to manage toxicity (appendix pp 346–58). The dose of veliparib or placebo could be reduced to 80 or 40 mg. The dose of carboplatin could be reduced to AUC 5 or 4, and the dose of

paclitaxel could be reduced to 70 or 60 mg/m². Treatment interruptions were required if haematological parameters were below protocol-specified thresholds (absolute neutrophil count of ≥ 1500 cells per μL , platelet count of $\geq 100\,000$ per μL on cycle day 1) or in the event of grade 3 or worse toxicity. Patients discontinuing both carboplatin and paclitaxel for reasons other than disease progression received continuous single-agent veliparib or placebo at 300 mg twice daily, increasing to 400 mg twice daily if tolerated. Patients in the control group could receive crossover open-label veliparib monotherapy after disease progression.

CT or MRI scans of the full chest, abdomen, and pelvis, and brain MRI or contrast CT, were done at screening (within 28 days of randomisation) and every 9 weeks thereafter until disease progression. Post-baseline brain MRI or contrast CT was required only for patients with CNS lesions at baseline. Evaluation of tumour response was done by both the local investigator and by blinded independent central review. Subsequent treatment and survival information was collected every 2 months until death or loss to follow-up. Laboratory evaluations included haematology and blood chemistry, and were done at day -2 of cycle 1; days 1, 8, and 15 of each treatment cycle; at the final visit; and at the 30-day follow-up visit. Patients were assessed for adverse events on the same schedule. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Adverse events were evaluated for the entire veliparib or placebo treatment period including both combination therapy and monotherapy if applicable, and separately during the blinded monotherapy period only in the applicable subset of patients.

Patient-reported outcome questionnaires (European Organization for Research and Treatment of Cancer [EORTC] questionnaire for patients with cancer [EORTC-QLQ-C30] version 3.0, the breast cancer-specific EORTC questionnaire [QLQ-BR23], the EuroQoL 5 Dimension 5-Level [EQ-5D-5L], and the Brief Pain Inventory—Short Form) were administered predose at day -2 and day 1 of cycle 1, day 1 of every other cycle thereafter beginning with cycle 2, at the final visit, and at the follow-up visit (appendix pp 400–05). Eastern Cooperative Oncology Group (ECOG) performance status was evaluated at day 1 of each cycle, at the final visit, and at the follow-up visit.

Outcomes

The primary endpoint was progression-free survival (defined as the time from randomisation to disease progression or death from any cause within 63 days of the last tumour assessment) according to RECIST, version 1.1, as assessed by the local investigator. Secondary endpoints were overall survival (time from randomisation to death from any cause), clinical benefit rate (progression-free rate at 24 weeks), objective response rate (proportion of patients with confirmed

partial or complete response per RECIST 1.1), and progression-free survival 2 (time from randomisation to disease progression on first subsequent therapy or death from any cause). Tertiary endpoints were duration of overall response (time from first response to disease progression), change in ECOG performance status, and patient-reported outcomes.

Statistical analysis

We aimed to enrol 500 patients to accrue 344 progression-free survival events to provide at least 90% power at a two-sided α level of 0.05 (assuming a hazard ratio [HR] of 0.69) to detect a significant treatment effect. In a protocol amendment, the sample size was increased to 500 patients from 270 on June 17, 2016, owing to a preplanned masked sample size re-estimation on the basis of the HR observed in the phase 2 BROCADE study²⁰ for which data became available during the course of the current study. Efficacy analyses were done on the intention-to-treat population, which included all randomly assigned patients with a suspected deleterious or deleterious *BRCA* mutation confirmed by the core laboratory. Safety analyses included all patients who received at least one dose of veliparib or placebo. Data cutoff for the primary analysis was April 5, 2019.

For the primary analysis, between-group differences were determined with a two-sided log-rank test, stratified by previous platinum therapy (yes vs no) and hormone receptor status (positive for oestrogen receptor or progesterone receptor or both vs negative for both oestrogen receptor and progesterone receptor). History of CNS metastases was not included as a stratification factor because enrolment in this stratum was low. Significance was measured by means of a two-sided α of 0.05. HRs and 95% CIs for the primary endpoint were estimated by means of a stratified Cox proportional hazards model. The Kaplan-Meier method was used to generate time-to-event curves and calculate landmark values including medians and the proportion of patients alive and progression free at 24 and 36 months. If significance was shown for the primary endpoint analysis of progression-free survival per investigator assessment, secondary endpoints were to be tested by means of a fixed-sequence testing procedure in the following order: overall survival, clinical benefit rate, objective response rate, and progression-free survival 2. Duration of overall response was changed from a secondary endpoint to a tertiary endpoint on May 30, 2019, before database lock for the primary analysis because of expected lack of statistical power. Interim overall survival was analysed at the time of primary progression-free survival analysis as part of a preplanned analysis. The final overall survival analysis is planned when 357 events (deaths) have been observed. HRs for overall survival were estimated by means of a stratified Cox regression model. Progression-free survival per blinded independent central review was a prespecified sensitivity analysis. Concordance rate was defined as the

proportion of patients with progressive disease (regardless of date of event) by both investigator and central review or non-progressive disease by both investigator and central review.

We also evaluated investigator-assessed progression-free survival for prespecified subgroups (previous platinum use, history of CNS metastases, oestrogen and progesterone receptor status, *BRCA* status, and previous cytotoxic therapy for metastatic disease). Mean (SD) change from baseline for each patient-reported outcome tool were summarised descriptively for each scheduled post-baseline visit for the EORTC QLQ-C30 (overall and domain-specific scores), EORTC QLQ-BR23 (domain-specific scores), Brief Pain Inventory—Short Form (pain interference and overall severity), and EQ-5D-5L (visual analogue scale and health index score) questionnaires.

Visual inspection of the Kaplan-Meier curves for progression-free survival suggested non-proportionality of hazards between treatment groups, whereby treatment effect increases as time from randomisation increases. Owing to the observed delayed separation of the curves, we sought to evaluate the effect of the transition of a subset of patients to blinded monotherapy (at an intensified dose and schedule) on the primary analysis of progression-free survival. Therefore, a post-hoc analysis of progression-free survival (Cox model) with a time-varying covariate, indicating the transition from veliparib or placebo in combination with chemotherapy to veliparib or placebo as monotherapy, was developed to model the main effect of treatment (ie, placebo vs treatment), treatment phase (ie, the combination phase vs the subsequent monotherapy phase), and their interaction. The Cox model was stratified by previous platinum therapy (yes vs no) and hormone receptor status (positive for oestrogen receptor or progesterone receptor or both vs negative for both hormone receptors). Proportions of patients alive and progression free at 2 and 3 years and proportions of patients alive at 2 and 3 years were evaluated as post-hoc analyses.

Analyses were done with SAS version 9.4 or later under the UNIX operating system. An independent data monitoring committee reviewed safety data. This study is registered with ClinicalTrials.gov, NCT02163694.

Role of the funding source

The funder of the study provided financial support and participated in study design, study conduct, data collection, data analysis, and data interpretation, and the writing, review, and approval of the manuscript. All authors had full access to all of the data and vouch for its integrity and completeness and were responsible for writing the manuscript, with editorial assistance funded by AbbVie. All authors reviewed draft and final versions of the manuscript before submission and approved the final version. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Figure 1: Trial profile

Six patients (three in each group) did not receive a dose of study drug and were excluded from the safety analyses. Four patients (two in each group) did not have a suspected deleterious or deleterious *BRCA1* or *BRCA2* mutation confirmed by the core laboratory and were excluded from the efficacy analyses. ITT=intention-to-treat. *Some patients discontinued treatment for more than one reason. †On any component of study treatment (carboplatin, paclitaxel, veliparib, or placebo).

Results

Between July 30, 2014, and Jan 17, 2018, 2202 patients were screened, of whom 513 eligible patients were randomly assigned (figure 1). A total of 509 patients ($n=337$ in the veliparib group; $n=172$ in the control group) had a germline *BRCA1* or *BRCA2* mutation confirmed by the core laboratory; these patients comprised the intention-to-treat population. Among all randomly assigned patients, 507 received at least one dose of veliparib or placebo and were included in the safety analyses (336 in the veliparib group and 171 in

	Veliparib plus carboplatin-paclitaxel (n=337)	Placebo plus carboplatin-paclitaxel (n=172)
Sex		
Female	333 (99%)	169 (98)
Male	4 (1%)	3 (2%)
Age, years	47 (39–54)	45 (39–54)
Race		
White	294 (87%)	153 (89%)
Asian	24 (7%)	12 (7%)
Black	14 (4%)	6 (3%)
Other	5 (1%)	1 (1%)
Geographical region		
USA	46 (14%)	27 (16%)
Other	291 (86%)	145 (84%)
ECOG performance status		
0	208 (62%)	102 (59%)
1	121 (36%)	63 (37%)
2	8 (2%)	7 (4%)
Measurable disease	285 (85%)	143/171 (84%)
Liver or lung metastases	219 (65%)	104/171 (61%)
Bone-only disease	11 (3%)	9/171 (5%)
Previous platinum therapy use	27 (8%)	16 (9%)
Previous chemotherapy in neoadjuvant or adjuvant setting	236 (70%)	113 (66%)
Previous taxane in neo-adjuvant or adjuvant setting	175 (52%)	86 (50%)
Previous chemotherapy in metastatic setting	63 (19%)	33 (19%)
Previous taxane in the metastatic setting	20 (6%)	9 (5%)
History of CNS metastases	16/336 (5%)	10/171 (6%)
Hormone receptor expression		
Oestrogen receptor or progesterone receptor positive	174 (52%)	92 (53%)
Oestrogen receptor and progesterone receptor negative	163 (48%)	80 (47%)
BRCA1 or BRCA2 mutation status by core laboratory		
BRCA1 mutation positive	177 (53%)	89 (52%)
BRCA2 mutation positive	167 (50%)	86 (50%)
Stage at diagnosis		
0	3/332 (1%)	1/169 (1%)
I	43/332 (13%)	22/169 (13%)
II	128/332 (39%)	69/169 (41%)
III	84/332 (25%)	39/169 (23%)
IV	74/332 (22%)	38/169 (22%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: Baseline characteristics in the intention-to-treat population

the control group). Baseline characteristics are shown in table 1. Approximately half the patients had triple-negative breast cancer (ie, they were oestrogen receptor and progesterone receptor negative). Most patients had received previous chemotherapy in the neoadjuvant or

adjuvant setting; however, the majority had not received previous cytotoxic chemotherapy in the metastatic setting. Of the 266 patients with hormone receptor-positive breast cancer, 174 (65%) had received previous endocrine therapy in any setting (appendix pp 22–24).

Patients in the veliparib group remained on masked study drug longer (mean 237 treatment days [SD 272]) than did those in the control group (181 treatment days [209]); the number of treatment days excludes non-treatment days during intermittent study drug dosing in combination with carboplatin and paclitaxel. A subset of patients (136 [41%] of 336 patients in the veliparib group and 58 [34%] of 171 in the control group) discontinued carboplatin and paclitaxel before disease progression and received blinded study drug monotherapy. The mean overall duration of blinded monotherapy in these patients was 350 days (SD 318) in the veliparib group versus 252 days (263) in the control group (appendix p 24). Chemotherapy exposure before transitioning to blinded monotherapy was highly variable (appendix p 8), with the most frequent point of transition being after six cycles of combination therapy. Among patients receiving monotherapy, 42 (31%) of 136 in the veliparib group and 32 (55%) of 58 in the control group escalated the dose of blinded study drug from 300 mg twice daily to 400 mg twice daily. At data cutoff (April 5, 2019), 192 (57%) of 337 patients in the veliparib group and 121 (70%) of 172 in the control group had discontinued study drug owing to disease progression.

Patients in both groups received a similar duration of chemotherapy. In the veliparib group, patients received a mean of 10·7 cycles (SD 8·5) of carboplatin and 11·5 cycles (10) of paclitaxel; patients in the control group received a mean of 11·0 cycles (8·2) of carboplatin and 10·6 cycles (8·6) of paclitaxel (appendix p 24). The mean duration of cycle delays was similar between treatment groups (5·9 days [SD 4·3] vs 5·1 days [3·7] for carboplatin and 5·2 days [3·9] vs 4·6 days [3·6] for paclitaxel). The proportion of patients receiving dose reductions of carboplatin and paclitaxel were similar between treatment groups (carboplatin: 293 [87%] of 335 patients in the veliparib group who received at least one dose of carboplatin vs 145 [86%] of 169 patients in the control group who received at least one dose of carboplatin; paclitaxel: 248 [74%] of 335 vs 119 [70%] of 169). Each chemotherapy agent could be discontinued individually to manage toxicity. Carboplatin was administered with blinded study drug after paclitaxel discontinuation in 77 (23%) of 336 patients in the veliparib group, for a mean of 6·1 cycles (7·4), and in 50 (29%) of 171 patients in the control group, for a mean of 7·2 cycles (8·4). Paclitaxel was administered with blinded study drug after carboplatin discontinuation in 69 (21%) of 336 patients in the veliparib group, for a mean of 10·4 cycles (10·4) and in 33 (19%) of 171 patients in the control group, for a mean of 9·1 cycles (9·2).

At data cutoff, median follow-up was 35·7 months (IQR 24·9–43·6) in the veliparib group and 35·5 months

Figure 2: Survival outcomes

Distributions were estimated by means of the Kaplan-Meier method for progression-free survival by investigator assessment (A) and overall survival (B). Kaplan-Meier estimates of the proportion of patients alive and progression-free at 24 months and 36 months are shown. HR=hazard ratio.

Figure 3: Subgroup analysis of progression-free survival

Hazard ratios presented for subgroups other than hormone receptor status are from a Cox model stratified by hormone receptor status only. The hormone receptor status subgroup hazard ratios are from an unstratified model. ER=oestrogen receptor. PgR=progesterone receptor. TNBC=triple-negative breast cancer.

	Veliparib plus carboplatin-paclitaxel (n=337)	Placebo plus carboplatin-paclitaxel (n=172)
Clinical benefit rate (week 24 progression-free survival rate)	90·7% (87·9–92·9)	93·2% (89·5–95·7)
Objective response rate (complete response or partial response)*	216/285 (75·8%; 70·4–80·6)	106/143 (74·1%; 66·1–81·1)
Progression-free survival 2		
Events	196 (58%)	114 (66%)
Median progression-free survival 2, months	21·3 (19·8–25·1)	17·4 (16·0–20·0)
Hazard ratio	0·76 (0·60–0·96)	..
Duration of response		
Events†	128/216 (59%)	87/106 (82%)
Median duration of response, months	14·7 (12·1–18·7)	11·0 (10·2–12·3)

Data are % (95% CI), n/N (%; 95% CI), n (%), or median (95% CI). Data are per investigator assessment. *Includes patients with at least one measurable lesion per investigator assessment. †Includes patients with at least one measurable lesion at baseline. Patients who never had a confirmed partial response or complete response are not included in the analysis of duration of response.

Table 2: Additional efficacy analyses

(23·1–45·9) in the control group. At data cutoff, progression-free survival events had been recorded in 217 (64%) of 337 patients in the veliparib group and 132 (77%) of 172 patients in the control group. Median progression-free survival was 14·5 months (95% CI

12·5–17·7) in the veliparib group versus 12·6 months (10·6–14·4) in the control group (HR 0·71, 95% CI 0·57–0·88; two-sided log-rank $p=0·0016$; figure 2A). More patients were alive and progression free in the veliparib group than in the control group at 2 years and 3 years (figure 2A).

The sensitivity analysis of progression-free survival by blinded independent central review showed similar results to the primary analysis: median progression-free survival was 19·3 months (95% CI 16·5–23·3) in the veliparib group (with 159 [47%] events in 337 patients) versus 13·5 months (12·5–16·3) in the control group (with 94 [55%] events in 172 patients; HR 0·70 [95% CI 0·54–0·90]; log-rank $p=0·0054$; appendix p 10). Concordance between investigator and central review was high and similar between groups (258 [77%] of 337 patients in the veliparib group and 130 [76%] of 172 patients in the control group). Analyses of progression-free survival in prespecified subgroups are shown in figure 3; analyses of progression-free survival (by investigator and central review) and overall survival by hormone receptor status are presented in the appendix (p 24).

In our preplanned interim analysis of overall survival at data cutoff, 167 (50%) of 337 patients in the veliparib group and 87 (51%) of 172 patients in the control group had died. Median overall survival was 33·5 months (95% CI 27·6–37·9) in the veliparib group and 28·2 months (24·7–35·2) in the control group (HR 0·95, 95% CI 0·73–1·23; $p=0·67$; figure 2B). At the time of analysis, 75 (44%) of 172 patients randomly assigned to

Figure 4: Mean change from baseline in EORTC QLQ-C30 Global Health Status Quality of Life score

Mean change in score from baseline (with SD bars) in the intention-to-treat population is shown for each treatment group. Score was determined on day 1 of cycles shown on x-axis. Increases in the Global Health Status Quality of Life score represent improvements in functioning. EORTC QLQ-C30=European Organization for Research and Treatment of Cancer questionnaire for patients with cancer.

the control group had received open-label veliparib (crossover) as first subsequent therapy.

Investigator-assessed clinical benefit rate and objective response rate were similar between the treatment groups (table 2). Median duration of response in patients with a confirmed complete or partial response and median progression-free survival 2 are shown in table 2 and in the appendix (pp 11–12). Changes from baseline in ECOG performance status at each cycle were generally similar between the treatment groups (appendix p 13). Subsequent therapies are summarised in the appendix (p 27).

The delayed separation noted in the Kaplan-Meier curves for progression-free survival suggested the presence of non-proportional hazards, which might have been influenced by the transition of a subset of patients (194 [38%] of 509 patients in the intention-to-treat population) to monotherapy before disease progression. Therefore, we did a post-hoc analysis for progression-free survival with a time-varying covariate indicating the transition from veliparib or control in combination with chemotherapy to veliparib or control as monotherapy (appendix pp 7, 25). The nominal *p* value for the interaction effect was 0.038. The interaction term was therefore retained in the fitted model together with the indicator variables for combination therapy and monotherapy. The progression-free survival HR estimates were less than one during both combination therapy and monotherapy (appendix p 25).

Mean changes from baseline to each subsequent cycle in global health status quality of life score based on the EORTC QLQ-C30 questionnaire are shown in figure 4. No clinically meaningful difference between treatment

groups was apparent. Mean changes from baseline for all functional and symptom scales of the EORTC QLQ-C30 are shown in the appendix (pp 14–16). No clinically meaningful difference between treatment groups was evident in any of the 14 scores.

No clinically meaningful differences between treatment groups were apparent in any of the domains for the breast cancer-specific QLQ-BR23 questionnaire (appendix pp 17–19). Similarly, outcomes reported via the EQ-5D-5L (visual analog scale and health index score) and Brief Pain Inventory (pain interference and overall pain severity) questionnaires were similar between treatment groups (appendix pp 20–21).

Common treatment-emergent adverse events of any grade by treatment group are shown in table 3. Serious adverse events were more frequent in the veliparib group, occurring in 115 (34%) of 336 patients compared with 49 (29%) of 171 patients in the control group (appendix p 28). Study drug-related serious adverse events occurred in 41 (12%) patients in the veliparib group and seven (4%) patients in the control group. The most common study drug-related serious adverse events in either group were anaemia (12 [4%] patients in the veliparib group and two [1%] patients in the control group) and thrombocytopenia (11 [3%] patients in the veliparib group and two [1%] patients in the control group). The most common grade 3 or worse adverse events were neutropenia (272 [81%] of 336 patients in the veliparib group vs 143 [84%] of 171 patients in the control group), anaemia (142 [42%] vs 68 [40%]), and thrombocytopenia (134 [40%] vs 48 [28%]). Grade 3 or worse adverse events of special interest are listed in the appendix (p 29).

	Veliparib plus carboplatin–paclitaxel				Placebo plus carboplatin–paclitaxel			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
All blinded veliparib or placebo exposure (n=336 in the veliparib group; n=171 in the placebo group)								
Any adverse event	10 (3%)	174 (52%)	144 (43%)	6 (2%)	8 (5%)	94 (55%)	66 (39%)	3 (2%)
Neutropenia	28 (8%)	161 (48%)	111 (33%)	0	13 (8%)	94 (55%)	49 (29%)	0
Thrombocytopenia	137 (41%)	97 (29%)	37 (11%)	0	74 (43%)	40 (23%)	8 (5%)	0
Anaemia	128 (38%)	139 (41%)	3 (1%)	0	51 (30%)	67 (39%)	1 (1%)	0
Nausea	224 (67%)	20 (6%)	0	0	102 (60%)	7 (4%)	0	0
Alopecia	181 (54%)	0	0	0	87 (51%)	0	0	0
Fatigue	145 (43%)	24 (7%)	0	0	79 (46%)	7 (4%)	0	0
Peripheral sensory neuropathy	141 (42%)	14 (4%)	1 (<1%)	0	80 (47%)	8 (5%)	0	0
Diarrhoea	136 (40%)	16 (5%)	0	0	57 (33%)	5 (3%)	0	0
Leukopenia	37 (11%)	86 (26%)	12 (4%)	0	18 (11%)	44 (26%)	3 (2%)	0
Headache	116 (35%)	4 (1%)	0	0	57 (33%)	3 (2%)	0	0
Vomiting	107 (32%)	13 (4%)	0	0	58 (34%)	3 (2%)	0	0
Constipation	113 (34%)	1 (<1%)	0	0	54 (32%)	1 (1%)	0	0
Asthenia	76 (23%)	8 (2%)	0	0	40 (23%)	3 (2%)	0	0
Hypomagnesaemia	74 (22%)	6 (2%)	2 (1%)	0	28 (16%)	4 (2%)	4 (2%)	0
Decreased appetite	76 (23%)	3 (1%)	0	0	46 (27%)	0	0	0
Cough	70 (21%)	0	0	0	28 (16%)	0	0	0
Dyspnoea	67 (20%)	3 (<1%)	0	0	32 (19%)	2 (1%)	0	0
Dizziness	65 (19%)	1 (<1%)	0	0	29 (17%)	1 (1%)	0	0
Dysgeusia	65 (19%)	1 (<1%)	0	0	28 (16%)	0	0	0
Pain in extremity	65 (19%)	1 (<1%)	0	0	27 (16%)	0	1 (1%)	0
Back pain	57 (17%)	8 (2%)	0	0	38 (22%)	1 (1%)	1 (1%)	0
Peripheral oedema	64 (19%)	0	0	0	17 (10%)	1 (1%)	0	0
Epistaxis	63 (19%)	0	0	0	29 (17%)	0	0	0
Arthralgia	62 (18%)	0	0	0	37 (22%)	2 (1%)	0	0
Pyrexia	59 (18%)	3 (<1%)	0	0	36 (21%)	1 (1%)	0	0
Blinded monotherapy veliparib or placebo exposure (n=136 in the veliparib group; n=58 in the placebo group)								
Any adverse event	78 (57%)	40 (29%)	5 (4%)	2 (1%)	36 (62%)	11 (19%)	1 (2%)	0
Nausea	64 (47%)	7 (5%)	0	0	5 (9%)	1 (2%)	0	0
Fatigue	25 (18%)	6 (4%)	0	0	6 (10%)	1 (2%)	0	0
Headache	26 (19%)	3 (2%)	0	0	9 (16%)	1 (2%)	0	0
Diarrhoea	27 (20%)	1 (1%)	0	0	5 (9%)	0	0	0

Data are n (%). The table shows adverse events occurring in at least 20% of patients at any grade during all blinded veliparib or placebo exposure or during blinded single-agent veliparib or placebo exposure. The all blinded veliparib or placebo exposure adverse event rates include all adverse events during the treatment-emergent period, which includes veliparib or placebo in combination with carboplatin–paclitaxel and veliparib or placebo single agent, if applicable. The blinded single-agent veliparib or placebo exposure adverse event rates include all treatment-emergent adverse events during blinded single-agent veliparib or placebo dosing. A complete listing of all treatment-emergent adverse events by maximum grade is shown in the appendix (pp 31–98).

Table 3: Adverse events

During all blinded veliparib or placebo exposure, deaths due to adverse events occurred in six patients (2%) in the veliparib group (four malignant neoplasm progression, one pulmonary embolism, and one sepsis), and in three patients (2%) in the control group (two malignant neoplasm progression, one pulmonary artery thrombosis). None of these events were considered study drug related.

Adverse events leading to study drug dose reductions occurred in 58 (17%) patients in the veliparib group and 13 (8%) patients in the control group. Most patients in each group had an adverse event leading to study drug

interruption at some time during the treatment period (301 [90%] of 336 patients in the veliparib group vs 147 [86%] of 171 patients in the control group). Adverse events led to study drug discontinuation in 53 (16%) patients in the veliparib group versus 18 (11%) patients in the control group (appendix p 30). These events were considered related to study drug in 19 (6%) patients and five (3%) patients, respectively; the most common of these related events was fatigue in the veliparib group (three patients) and thrombocytopenia in the control group (two patients). Adverse events led to carboplatin discontinuation in 168 (50%) of 336 patients in the

veliparib group and 70 (41%) of 171 in the control group, most commonly owing to thrombocytopenia (60 [18%] vs 16 [9%]) and neutropenia (32 [10%] vs 19 [11%]). Adverse events led to paclitaxel discontinuation in 156 patients in the veliparib group and 78 patients in the control group (46% in both groups), most commonly owing to neutropenia (38 [11%] vs 25 [15%]) and peripheral sensory neuropathy (42 [13%] vs 31 [18%]).

Adverse events in the subgroup of patients who received blinded study drug monotherapy are shown in table 3. The most frequent grade 3 or worse adverse event in this subgroup was nausea (seven [5%] of 136 patients in the veliparib group vs one [2%] of 58 patients in the control group; table 3; appendix p 81). The most common serious adverse event aside from progression was seizure (three [2%] vs none; appendix p 28). One patient having a seizure event had a history of CNS metastases. The seizure events (all grade 2) occurred after approximately 1 year of veliparib 400 mg twice daily in two patients (one of whom inadvertently took a second dose of 400 mg later the same morning on the day of the event) and after the initial dose of 300 mg in another patient. Two patients resumed veliparib monotherapy at a reduced dose (300 mg twice daily) after treatment with levetiracetam and continued until disease progression (6–9 months later) without another seizure event. During blinded single-agent veliparib or placebo exposure, deaths from adverse events occurred in two patients receiving veliparib (1%; one malignant neoplasm progression, one sepsis) and none receiving placebo. No deaths due to adverse events were considered related to study drug by the investigator.

Discussion

The results of this phase 3 trial show that when added to carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel were discontinued before disease progression, veliparib resulted in a durable improvement in progression-free survival, with benefit evident at 2 years and 3 years after randomisation, in patients with advanced HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation. These results are noteworthy given the high activity of the carboplatin and paclitaxel control group, in which median progression-free survival was longer than 1 year. The high concordance between the investigator-assessed and centrally reviewed progression-free survival results and the nearly identical HRs lend further support to these findings, and indicate a lack of systematic evaluation bias. Overall survival was not yet mature at the time of the primary analysis, and the results of the preplanned interim analysis were not significant.

Overall, the addition of veliparib to carboplatin and paclitaxel was well tolerated, with toxicity (adverse events unrelated to disease progression) leading to discontinuation in fewer than 10% of patients. Dose reductions of veliparib were relatively infrequent; however, dose reductions of carboplatin and paclitaxel were frequent in

both groups. The starting dose of carboplatin (AUC6) is recommended by the National Comprehensive Cancer Network;²¹ however, the recommended dose of paclitaxel is 175–200 mg/m² (every 3 weeks) when combined with carboplatin. The paclitaxel dose and schedule chosen for this study (80 mg/m² weekly) reflects a general trend towards more frequent use of dose-dense paclitaxel and is consistent with standard practice in other solid tumours, such as ovarian cancer and non-small-cell lung cancer, in which carboplatin–paclitaxel is the standard of care. However, in such cases, treatment is often limited to six cycles. Further research is required to establish whether alternative doses or schedules of carboplatin–paclitaxel or a shorter treatment duration would improve outcomes in patients with advanced breast cancer, for whom treatment until disease progression is standard.

Although haematological toxicities were frequent in both treatment groups, the incidences of clinically important sequelae, including grade 3 or worse infections associated with neutropenia and grade 3 or worse haemorrhages associated with thrombocytopenia, were relatively infrequent. For the subgroup of patients who transitioned to blinded monotherapy at a more intensive dose and schedule, the only grade 3 or worse adverse event that occurred more frequently with veliparib versus placebo was nausea, and the only serious adverse event that occurred more frequently was seizure. The clinical significance of the difference in seizure frequency between treatment groups is unclear. Seizures have been observed to be exposure dependent in non-clinical studies primarily involving dogs (unpublished preclinical toxicity studies by AbbVie); however, the seizure rate observed in this study is consistent with background rates based on a similar patient population identified in a real-world database (data on file with AbbVie). Patient-reported outcomes showed no clinically meaningful differences between treatment groups, indicating that the addition of veliparib to carboplatin–paclitaxel does not increase treatment-related symptom burden. Moreover, these analyses revealed no systematic, clinically meaningful deterioration in global health status or quality of life scores with time, suggesting that the regimen was generally well tolerated.

The Kaplan-Meier curves for progression-free survival exhibited a delayed separation between treatment groups and a persistent tail in the veliparib group. The delayed separation suggests non-proportionality of hazards between treatment groups, where the treatment effect increases as time from randomisation increases. One possibility is that a well-represented clinically or biologically defined subgroup of patients does not benefit from the addition of veliparib. However, subgroup analyses of progression-free survival did not identify such a subgroup defined by clinical characteristics. Owing to small sample sizes, point estimates in smaller subgroups, such as patients with previous platinum therapy, patients with previous cytotoxic therapy for metastatic disease, and patients with a history of CNS

metastases should be interpreted with caution. Further research is warranted to identify biomarkers that can identify patients who are likely to benefit.

As the proportion of patients receiving blinded monotherapy also increased with time from randomisation, it is plausible to hypothesise that the transition to monotherapy by a subset of patients contributed to the delayed separation of the survival curves observed. A post-hoc exploratory analysis by means of a Cox model for progression-free survival with a time-varying covariate suggested that the transition from combination therapy to monotherapy indeed contributes to non-proportionality. It is noteworthy that the estimated HR for combination therapy is nearly identical to that observed in the phase 2 BROCADE study,²⁰ which compared carboplatin–paclitaxel with veliparib to carboplatin–paclitaxel with placebo in a similar patient population and did not allow treatment with veliparib or placebo monotherapy. Collectively, these results suggest that the overall progression-free survival benefit observed in BROCADE3 is derived both from the inclusion of veliparib with carboplatin–paclitaxel and from the continuation of veliparib monotherapy when chemotherapy is discontinued before disease progression. However, these HR estimates cannot be interpreted as isolating the treatment effect for each treatment phase because all patients receiving veliparib monotherapy did so after first receiving veliparib in combination with carboplatin–paclitaxel, which is a limitation of the study design. Moreover, the subset of patients receiving monotherapy does not represent a randomised sample, and the decision to transition (and the variable timing thereof) might be partly affected by depth and duration of response to combination therapy.

A limitation of the trial is that it does not allow for the identification of the optimal duration of combination therapy with veliparib and cytotoxic chemotherapy before transitioning to single-agent veliparib. The potential for veliparib to maintain responses after a fixed duration of veliparib, carboplatin, and paclitaxel warrants further investigation, because this strategy would represent a major shift in the treatment of metastatic breast cancer, akin to validated strategies in ovarian cancer.²²

The potential for crossover to confound interpretation of the progression-free survival 2 analysis is another limitation, particularly if treatment with platinum chemotherapy during the blinded portion of the trial led to resistance to subsequent PARP inhibitor therapy in some patients. The sequencing of PARP inhibitors and platinum chemotherapy requires further investigation.

The results of this trial indicate that veliparib, in combination with carboplatin–paclitaxel and continued as monotherapy after discontinuation of chemotherapy, is a compelling treatment option for patients with advanced HER2-negative breast cancer and a germline *BRCA* mutation who are candidates for cytotoxic chemotherapy. This population includes patients with triple-negative breast cancer and those with hormone receptor-positive

metastatic breast cancer. Although the role of cytotoxic chemotherapy differs between these two patient subgroups, treatment guidelines converge in cases where hormone-receptor-positive patients are no longer candidates for endocrine therapy. Treatment guidelines generally recommend sequential single-agent chemotherapy; however, the durable progression-free survival and overall survival observed with the control regimen in this trial and the phase 2 BROCADE trial suggest that the carboplatin–paclitaxel combination might provide unique benefit to this particular group of patients.²⁰

The utility of a carboplatin–taxane doublet for the first-line treatment of metastatic triple-negative breast cancer has been shown by the phase 2 tnAcity trial,²³ which showed superior progression-free survival with carboplatin and nab-paclitaxel compared with doublets of carboplatin with gemcitabine or nab-paclitaxel with gemcitabine. In this trial, patients treated with carboplatin and nab-paclitaxel had a median progression-free survival of 8·3 months and a median overall survival of 16·8 months. In addition, a growing body of evidence supports the use of platinum chemotherapy in patients with advanced triple-negative breast cancer and a germline *BRCA1* or 2 mutation.^{7,8,20,23} Studies of single-agent platinum chemotherapy reported median progression-free survival of 3·3–6·8 months,^{7,8} and overall survival of 13·7 months.⁸ The median progression-free survival of 16·6 months and median overall survival of 35 months observed in the triple-negative breast cancer subgroup of BROCADE3 suggest that combination therapy with veliparib, carboplatin, and paclitaxel might improve long-term outcomes relative to sequential single-agent therapy for this patient population with fewer treatment options and a worse prognosis compared with other breast cancer subtypes.

In hormone receptor-positive breast cancer, established guidelines^{21,24} indicate that chemotherapy is most appropriate in patients who are not candidates for endocrine therapy, and combination chemotherapy should generally be reserved for those with visceral metastases or rapidly progressive disease. Real-world evidence indicates that the use of chemotherapy, including combination regimens, is more common in early lines than might be expected according to these guidelines.²⁵ This concept is consistent with the observation in this study that only 65% of hormone receptor-positive patients enrolled had received previous endocrine therapy. Notably, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors were largely unavailable in most participating countries during enrolment of this trial, and in some participating countries, such as South Korea, fewer endocrine therapy options are available for premenopausal women. Treatment use patterns should continue to evolve, in view of published evidence showing an overall survival benefit with the addition of CDK4/6 inhibitors to endocrine therapy, along with the previously reported progression-free survival benefit and manageable safety profile.²⁶ However, little information exists regarding the

benefits of these therapies in patients with hormone receptor-positive breast cancer associated with a germline *BRCA* mutation. Although more research is required to further define the appropriate role of chemotherapy in these patients, endocrine therapy with or without a CDK4/6 inhibitor remains the standard of care for eligible patients. For patients who are no longer candidates for endocrine therapy with or without CDK4/6 inhibitors, those with *BRCA*-associated hormone receptor-positive metastatic breast cancer might be suitable for combination chemotherapy, because they are more likely to have tumours with aggressive luminal B features²⁷ and are often younger with fewer comorbidities. The veliparib and carboplatin–paclitaxel regimen might be a beneficial option for this group of patients, in whom a median progression-free survival and overall survival of 13·0 months and 32·4 months was observed in the veliparib group. Further characterisation of this subgroup, including those with no previous endocrine therapy, would be of interest.

Two phase 3 trials have supported regulatory approvals of the PARP inhibitors olaparib and talazoparib as monotherapy for treatment of patients with HER2-negative advanced breast cancer and germline *BRCA1* or *2* mutations, on the basis of improved progression-free survival when compared with physicians' choice of single-agent chemotherapy.^{5,6} Notably, these trials did not include platinum among the comparator therapies, and the objective response rates (60–63%) and median progression-free survival (7·0–8·6 months) reported for PARP inhibitor monotherapy were similar to previously reported data for carboplatin monotherapy in germline *BRCA1* or *BRCA2* mutation-positive patients with triple-negative breast cancer.⁷ As such, whether or not PARP inhibitor monotherapy is superior to single-agent platinum chemotherapy remains an unanswered question. Also unknown is the optimal sequence of PARP inhibitors and platinum-based chemotherapy in patients with germline *BRCA1* or *BRCA2* mutations. In cells with *BRCA* mutations, treatment with platinum agents or PARP inhibitors has been shown to produce *BRCA*-reversion mutations, which can restore function and mediate treatment resistance.²⁸ As such, combining platinum and PARP inhibitors might be a rational strategy to allow patients to benefit from both agents before developing cross-resistance. Accordingly, although median overall survival reported for a subgroup of patients receiving single-agent olaparib for first-line treatment of *BRCA*-associated advanced breast cancer was 22·6 months,²⁹ the median overall survival observed in the interim analysis for veliparib plus carboplatin–paclitaxel in the BROCADE3 study was 33·5 months, suggesting that the treatment strategy under investigation in this study might provide a promising alternative to conventional sequential single-agent therapy with PARP inhibitors and chemotherapy.

In the phase 3 BrighTNess trial,³⁰ the addition of veliparib to neoadjuvant chemotherapy with carboplatin–paclitaxel,

followed by doxorubicin and cyclophosphamide, did not improve the frequency of pathological complete response in patients with early-stage triple-negative breast cancer, with similar results in the subgroup of patients with germline *BRCA1* or *BRCA2* mutations. These results are consistent with the observation that the addition of veliparib did not improve the high objective response rate observed with carboplatin–paclitaxel in BROCADE3. Follow-up for event-free survival in BrighTNess is ongoing and it remains to be established whether the long-term benefit observed in BROCADE3 will also be seen in patients with early stage triple-negative breast cancer; however a direct comparison of the two trials will be confounded by differences in dose and schedule of veliparib and differences in patient populations.

Contributors

All authors contributed to study conception, design, and recruitment. VD, HSH, BK, HW, MF, J-PA, SLP, IB, MC, EHJ, MJ, CO, MP, YHP, YS, EY, and BKA contributed to provision of patients and patient care. All authors contributed to data analysis, collection, and interpretation, and were responsible for writing the manuscript and approval of the final version.

Declaration of interests

VD has consulting or advisory roles at Roche–Genentech, Novartis, Lilly, Pfizer, AbbVie, Merck Sharpe & Dohme, Daiichi Sankyo, Seattle Genetics, and AstraZeneca, and has received speakers' fees from Roche–Genentech, Novartis, Lilly, Pfizer, AstraZeneca, and Daiichi Sankyo. HSH has received institutional research funding from AbbVie, Prescient, Horizon, Karyopharm, Bristol Myers-Squibb, Novartis, Pfizer, Tesaro, TapImmune, and Seattle Genetics; a grant from the Department of Defense; and has served on the speakers' bureau for Lilly. HW received consulting fees to his institution and honoraria from Roche, AstraZeneca, Amgen, Lilly, Novartis, AbbVie, Vifor Pharma, Pfizer, Celldex Therapeutics, Janssen-Cilag, TRM Oncology, PUMA Biotechnology, and ORION Corporation; an unrestricted research grant from Roche; and travel support from Roche and Pfizer. MF has consulting or advisory roles at AstraZeneca, Merck Sharp & Dohme, AbbVie, Lilly, Takeda, and Novartis; has served on the speakers' bureau for AstraZeneca; and has received honoraria from AstraZeneca, Merck Sharp & Dohme, Lilly, and Takeda; and research funding from BeiGene, Novartis, and AstraZeneca. J-PA has received institutional research funding from AbbVie and Boston Biomedical; and has undertaken consultancy roles for AstraZeneca, Eisai, Eli Lilly, Novartis, Pfizer, Puma, and Roche. SLP is a consultant for AbbVie, MedImmune, Celldex, Puma, Pfizer, AstraZeneca, Eisai, and Nanostring, and has received research funding to her institution from AbbVie, Pfizer, Lilly, Novartis, Incyte, Covance-Bayer, AstraZeneca, Genentech, and Medivation. MC has consulting or advisory roles at AstraZeneca, Sanofi, Servier, AbbVie, Lilly, and Accord; speakers' bureau fees from Novartis; and honoraria from Eli Lilly. EHJ has consulting or advisory roles at Pfizer, Roche, Novartis, and Eli Lilly. MJ is on the advisory board or receives institutional honoraria from Merck, Bristol-Myers Squibb, Novartis, Pierre Fabre, Tesaro, and AstraZeneca; and has been involved in clinical studies sponsored by Bristol-Myers Squibb, AbbVie, Merck, and Celldex Therapeutics. CO is on the advisory board at Eli Lilly, Sandoz, Merck, and Pfizer; is a speaker at Eli Lilly, Roche, Teva, Bristol-Myers Squibb, Sanofi, Boehringer Ingelheim, Novartis, AstraZeneca, Astellas, Janssen, and Sandoz; and has been involved in research or clinical studies at Bristol-Myers Squibb, AbbVie, Roche, Genentech, Novartis, Boehringer Ingelheim, BeiGene, and Trio Oncology. MP has received fees as the speaker from Pfizer, Roche, and Eisai. YHP has a consultancy role or is an advisory board member for AstraZeneca, Pfizer, Eisai, and Novartis Pharmaceuticals; and has received research funding from AstraZeneca, Eisai, Merck, Pfizer, Novartis, and Roche. YS is on the advisory board of Pfizer; is a speaker at Roche, AstraZeneca, and Pfizer; and has been involved in research or clinical studies at AbbVie, Roche, Merck Sharpe & Dohme, and Boehringer Ingelheim. BKA has received institutional research support from AbbVie, PharmaMar, AstraZeneca,

and Invitae; and is on the steering committee (non-paid) at AbbVie. NK, MGK, CKR, and DM are AbbVie employees and own stock. MD is a former AbbVie employee and owns stock. BK, IB, and EY declare no competing interests.

Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised individual and trial-level data (analysis datasets), as well as other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlabeled products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the website.

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References

- Malone KE, Daling JR, Doody DR, et al. Prevalence and predictors of *BRCA1* and *BRCA2* mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res* 2006; 66: 8297–308.
- Peto J, Collins N, Barfoot R, et al. Prevalence of *BRCA1* and *BRCA2* gene mutations in patients with early-onset breast cancer. *J Natl Cancer Inst* 1999; 91: 943–49.
- Atchley DP, Albarracín CT, Lopez A, et al. Clinical and pathologic characteristics of patients with *BRCA*-positive and *BRCA*-negative breast cancer. *J Clin Oncol* 2008; 26: 4282–88.
- National Cancer Institute. SEER cancer stat facts: female breast cancer subtypes. <https://seer.cancer.gov/statfacts/html/breast-subtypes.html> (accessed Jan 13, 2020).
- Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline *BRCA* mutation. *N Engl J Med* 2018; 379: 753–63.
- Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline *BRCA* mutation. *N Engl J Med* 2017; 377: 523–33.
- Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in *BRCA1/2*-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018; 24: 628–37.
- Isakoff SJ, Mayer EL, He L, et al. TBCRC009: a multicenter phase II clinical trial of platinum monotherapy with biomarker assessment in metastatic triple-negative breast cancer. *J Clin Oncol* 2015; 33: 1902–09.
- Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. *Science* 2017; 355: 1152–58.
- Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res* 2007; 13: 2728–37.
- Dhawan MS, Bartelink IH, Aggarwal RR, et al. Differential toxicity in patients with and without DNA repair mutations: phase I study of carboplatin and talazoparib in advanced solid tumors. *Clin Cancer Res* 2017; 23: 6400–10.
- Lee JM, Hays JL, Chiou VL, et al. Phase I/II study of olaparib and carboplatin in women with triple negative breast cancer. *Oncotarget* 2017; 8: 79175–87.
- Faraoni I, Graziani G. Role of *BRCA* mutations in cancer treatment with poly(ADP-ribose) polymerase (PARP) inhibitors. *Cancers* 2018; 10: e487.
- McCann KE, Hurvitz SA. Advances in the use of PARP inhibitor therapy for breast cancer. *Drugs Context* 2018; 7: 212540.
- Somlo G, Frankel PH, Arun BK, et al. Efficacy of the PARP inhibitor veliparib with carboplatin or as a single agent in patients with germline *BRCA1*- or *BRCA2*-associated metastatic breast cancer: California Cancer Consortium Trial NCT01149083. *Clin Cancer Res* 2017; 23: 4066–76.
- Puhalla S, Beumer JH, Pahuja S, et al. Final results of a phase 1 study of single-agent veliparib (V) in patients (pts) with either *BRCA1/2*-mutated cancer (BRCA+), platinum-refractory ovarian, or basal-like breast cancer (BRCA-wt). *Proc Am Soc Clin Oncol* 2014; 32 (suppl 15): abstr 2570.
- Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res* 2012; 72: 5588–99.
- Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors and their mechanisms of action. *Sci Transl Med* 2016; 8: 362ps17.
- Hopkins TA, Ainsworth WB, Ellis PA, et al. PARP1 trapping by PARP inhibitors drives cytotoxicity in both cancer cells and healthy bone marrow. *Mol Cancer Res* 2019; 17: 409–19.
- Han HS, Diéras V, Robson M, et al. Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with *BRCA1/2* locally recurrent/metastatic breast cancer: randomized phase II study. *Ann Oncol* 2018; 29: 154–61.
- National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer, version 4. 2020. 2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (accessed May 8, 2020).
- Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018; 379: 2495–505.
- Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. *Ann Oncol* 2018; 29: 1763–70.
- Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol* 2018; 29: 1634–57.
- Dalal AA, Gauthier G, Gagnon-Sanschagrin P, et al. Treatment and monitoring patterns among premenopausal women with HR-/HER2- advanced breast cancer. *Adv Ther* 2018; 35: 1356–67.
- Han Y, Wang J, Wang Z, Xu B. Comparative efficacy and safety of CDK4/6 and PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative metastatic breast cancer: a systematic review and network meta-analysis. *Curr Probl Cancer* 2020; published online May 12. <https://doi.org/10.1016/j.cuprob.cancer.2020.100606>.
- Larsen MJ, Kruse TA, Tan Q, et al. Classifications within molecular subtypes enables identification of *BRCA1/BRCA2* mutation carriers by RNA tumor profiling. *PLoS One* 2013; 8: e64268.
- Waks AG, Cohen O, Kochupurakkal B, et al. Reversion and non-reversion mechanisms of resistance (MoR) to PARP inhibitor (PARPi) or platinum chemotherapy (chemotx) in patients (pts) with *BRCA1/2*-mutant metastatic breast cancer (MBC). *Proc Am Soc Clin Oncol* 2019; 37 (suppl 15): abstr 1085.
- Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline *BRCA* mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019; 30: 558–66.
- Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; 19: 497–509.

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