



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, et al.

► To cite this version:

Véronique Diéras, Hyo S Han, Bella Kaufman, Hans Wildiers, Michael Friedlander, et al.. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology*, 2020, 21, pp.1269 - 1282. <10.1016/S1470-2045(20)30447-2>. <hal-03492139>

HAL Id: hal-03492139

<https://hal.science/hal-03492139v1>

Submitted on 17 Oct 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

Veliparib with carboplatin and paclitaxel in *BRCA* mutated advanced breast cancer: a randomised, placebo-controlled, phase 3 trial

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

Institut Curie, Paris, and Centre Eugène Marquis, Rennes, France (V Diéras MD);
Moffitt Cancer Center, Tampa, FL, USA (H S Han MD);
Sheba Medical Center, Tel Hashomer, and Tel-Aviv University, Tel-Aviv, Israel (B Kaufman MD);
Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium (Prof H Wildiers MD);
Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia (Prof M Friedlander MBChB);
Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada (J P Ayoub MD);
UPMC Cancer Centers, Pittsburgh, PA, USA (S L Puhalla MD);
Dnipropetrovsk Medical Academy, City Clinical Hospital No.4, Dnipro, Ukraine (Prof I Bondarenko MD);
Institut de Cancérologie de l'Ouest -Pays de la Loire, France (Prof M Campone MD);
Vejle Hospital/Lillebaelt Hospital, Vejle, Denmark (E H Jakobsen MD);
University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (M Jalving MD);
University of Medicine and Pharmacy Timisoara; Oncomed SRL, Timisoara, Romania (C Oprean MD);
Masaryk Memorial Cancer Institute, Brno, Czech Republic (M Palácová MD);

29 Samsung Medical Center, Seoul, Korea (Y H Park MD);
30 Lviv State Regional Treatment and Diagnostic Oncology Center, Lviv, Ukraine (Y Shparyk MD);
31 Universidad de la Frontera, Temuco, Chile (E Yañez MD);
32 AbbVie Inc., North Chicago, IL, USA (N Khandelwal PhD, M G Kundu PhD, M Dudley PhD, CK
33 Ratajczak PhD, D Maag PhD);
34 The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA (Prof B K Arun MD)

35 *Co-first authors

36

37 **Correspondence to:**

38 Véronique Diéras, M.D.
39 Oncologie sénologique /Breast Oncology
40 Centre Eugène Marquis
41 Avenue de la bataille Flandres-Dunkerque
42 CS 44229, 35042 Rennes Cedex, France
43 Email: v.dieras@rennes.unicancer.fr
44 Phone: +332 99 25 29 66

45

46

47 **Keywords:** PARP inhibitor, chemotherapy, breast cancer, BRCA

48

49

50

51

SUMMARY

Background

BRCA1/2 mutated breast cancers are sensitive to PARP inhibitors and platinum agents due to deficiency in homologous recombination repair of DNA damage. This study compared veliparib versus placebo in combination with carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel were discontinued prior to progression, in patients with HER2-negative advanced breast cancer and a *BRCA1* or *BRCA2* germline mutation.

Methods

This was a double-blind, randomised, placebo-controlled phase 3 trial conducted at 147 centres in 36 countries. Eligible patients (aged ≥ 18 years) had deleterious germline (g) *BRCA1/2* mutation-associated, advanced HER2-negative breast cancer, ≤ 2 prior lines of chemotherapy for metastatic disease, and an Eastern Cooperative Oncology Group performance status of 0–2. Patients were randomised (2:1) by interactive response technology using permuted blocks within strata (block size of 3 or 6) to carboplatin (area under the concentration curve [AUC] 6 mg/mL/min intravenously, day 1) every 3 weeks and paclitaxel (80 mg/m² intravenously, day 1, 8, and 15) weekly combined with either veliparib (120 mg p.o. BID, day -2 through 5) or placebo. If patients discontinued carboplatin and paclitaxel prior to progression, they could continue veliparib or placebo at an intensified dose (300 mg BID continuous, escalating to 400 mg BID if tolerated) until progression. Randomisation was stratified by prior platinum use, history of CNS metastases, and estrogen/progesterone receptor status. The primary end point was investigator-assessed progression-free survival (PFS) per Response Evaluation Criteria

in Solid Tumors version 1.1. Efficacy analyses were done by intention-to-treat, which included all randomised patients with *BRCA* mutation confirmed by the core lab, and safety analyses included all patients who received at least one dose of study drug. These are results of the primary analysis of this ongoing trial. This study is registered with ClinicalTrials.gov, number NCT02163694.

Findings

Between July 30, 2014 and January 17, 2018, 513 patients were randomised. In the intention-to-treat population, 337 patients were assigned to receive veliparib plus carboplatin/paclitaxel (investigational arm) and 172 to placebo plus carboplatin/paclitaxel (control arm). Median follow-up at data cutoff (April 5, 2019) was 35.7 months (IQR 24.9–43.6) in the investigational arm and 35.5 months (IQR 23.1–45.9) in the control arm. The hazard ratio for PFS was 0.71 (95% confidence interval [CI], 0.57–0.88; $p=0.0016$), with median PFS of 14.5 months (95% CI 12.5–17.7) for the investigational arm versus 12.6 months (10.6–14.4) for the control arm. The most common grade 3 or higher adverse events were neutropenia (272 [81%] of 336 patients in the investigational group vs. 143 [84%] of 171 patients in the control group), anemia (142 [42%] vs. 68 [40%]), and thrombocytopenia (134 [40%] vs. 48 [28%]). Serious adverse events occurred in 115 (34%) patients in the investigational arm vs. 49 (29%) patients in the control arm. There were no study drug-related deaths.

Interpretation

Addition of veliparib to a highly active platinum doublet, with continuation as monotherapy if the doublet was discontinued, resulted in significant and durable improvement in PFS in patients with *gBRCA* mutation-associated advanced breast

98 cancer. These data indicate the utility of combining platinum and PARP inhibitors in this
99 patient population.

100 **Funding** AbbVie

101

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 2015 and November 2019. We selected phase 2 or phase 3 studies of platinum chemotherapy, poly(adenosine diphosphate–ribose) polymerase (PARP) inhibitors, or both, in patients with advanced breast cancer and germline (g) *BRCA* mutations.

The phase 3 TNT trial demonstrated a higher proportion of objective responses and improved progression-free survival (PFS) when advanced triple-negative breast cancer (TNBC) patients carrying g*BRCA1/2* mutations were treated with carboplatin compared to docetaxel. The phase II trial TBCRC009 evaluated cisplatin or carboplatin in patients with metastatic TNBC, demonstrating a higher proportion of objective responses in the subgroup of patients with g*BRCA* mutations. These trials indicate that platinum chemotherapy may be particularly effective in treating patients with g*BRCA* mutation-associated advanced TNBC, and this has led to recent updates to both National Comprehensive Cancer Network and ESO-ESMO breast cancer guidelines where platinum chemotherapy is now included as a preferred regimen for these patients.

The phase 3 OlympiAD and EMBRACA trials demonstrated improved PFS with olaparib (median 7.0 months) and talazoparib (median 8.6 months) monotherapy, respectively, when compared to physicians’ choice of non-platinum chemotherapy in patients with advanced, HER2-negative breast cancer and a g*BRCA* mutation.

The phase 2 BROCADE trial demonstrated numerical trends towards improved PFS and overall survival upon addition of veliparib to carboplatin and paclitaxel in patients

with advanced g*BRCA*-associated breast cancer, without substantial additional toxicity or dose intensity reduction in the platinum doublet. 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 study to evaluate a PARP inhibitor with platinum doublet chemotherapy for *BRCA*-associated breast cancer, demonstrating significant improvement in PFS upon the addition of veliparib to carboplatin and paclitaxel, a highly active comparator with a median PFS of over one year. When added to carboplatin and paclitaxel, veliparib more than doubled the proportion of patients alive and progression free at three years. The PFS benefit was similar in patients with TNBC and patients with hormone receptor-positive breast cancer. The addition of veliparib to carboplatin and paclitaxel also resulted in improvement in PFS2 and duration of response. There was no statistically significant difference in overall survival at the planned interim analysis.

The most common adverse events were hematologic toxicities, with the most notable differences between treatment arms being a 10% absolute increase in the incidence of anemia (any grade) and a 12% absolute increase in the incidence of grade 3/4 thrombocytopenia in the veliparib arm. Importantly, patient-reported outcomes revealed no clinically meaningful increase in symptom burden with the addition of veliparib to the platinum doublet.

Implications of all the available evidence

Deleterious mutations in *BRCA1* or *BRCA2* impair the ability of cancer cells to repair DNA damage via homologous recombination, thereby conferring additional sensitivity to platinum salts and PARP inhibitors. Clinical evidence to date has demonstrated 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 current 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, combination and maintenance strategies are rational approaches to maximize the therapeutic benefit derived from exploiting pathogenic *BRCA* mutations. BROCADE3 demonstrated for the first time that the combination of a PARP inhibitor, veliparib, with platinum chemotherapy significantly improves PFS with limited additional toxicity in patients with advanced HER2-negative breast cancer and a *BRCA* mutation. The PFS benefit was durable, with a quarter of patients in the veliparib-containing arm alive and progression free at three years. 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.

INTRODUCTION

Approximately 5% of all breast cancers are associated with germline mutations in *BRCA1/2*, and these patients are more likely to be diagnosed at a young age and to have triple-negative breast cancer (TNBC), for which treatment options are limited in the metastatic setting.¹⁻³ The reported 5-year survival rate for patients with metastatic breast cancer is 27%, and is only 11% for patients with metastatic TNBC.⁴ Thus, new treatments that provide durable benefit for patients with g*BRCA*-associated advanced breast cancer are needed.

BRCA1/2 mutated breast cancers have a deficiency in homologous recombination repair of DNA damage, and are known to be sensitive to both PARP inhibitors and platinum agents.⁵⁻⁸ There is a strong scientific rationale to combine PARP inhibitors with platinum chemotherapy based on common mechanisms of sensitivity and acquired resistance,⁹ and observed potentiation of platinum activity by PARP inhibitors preclinically.¹⁰ However clinical application of these combinations has been challenging,^{11,12} largely due to hematologic toxicity.¹³⁻¹⁴

Veliparib (ABT-888) is a potent, orally bioavailable, selective PARP1/2 inhibitor¹⁰ that has shown antitumour activity and acceptable toxicity as a single-agent and in combination with carboplatin and paclitaxel.^{15,16} Veliparib selectively inhibits the polymerase activity of PARP without substantial trapping of PARP protein onto DNA damage repair intermediates.^{17,18} This makes veliparib more suitable than other PARP inhibitors to be administered in combination with platinum-based chemotherapy, as

PARP trapping has been shown to be associated with myelosuppression.¹⁹ In a randomised, placebo-controlled phase 2 study (BROCADE), numerical (though not statistically significant) increases in median PFS and OS 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 comparable between arms, with common adverse events generally hematologic and gastrointestinal.²⁰ Here, we report results from BROCADE3, a phase 3 trial comparing veliparib versus placebo in combination with carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel are discontinued prior to progression, in patients with HER2-negative inoperable locally advanced or metastatic breast cancer with *BRCA1* or *BRCA2* germline mutation.

METHODS

Study design and participants

BROCADE3 is a phase 3, double-blinded, randomized, placebo-controlled study, fully funded by AbbVie, conducted at 147 centres in 36 countries (appendix p.1).

Patients (≥18 years of age) with metastatic or locally advanced unresectable HER2-negative breast cancer and suspected deleterious or deleterious *gBRCA1/2* mutations and an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled. Patients had adequate hematologic, renal, and hepatic function (absolute neutrophil count ≥1500 cells per mm³, platelet count ≥100,000 cells per mm³, haemoglobin ≥95 g/L, serum creatine ≤1.5 times the upper limit of normal (ULN) or creatine clearance ≥50

mL/min/1.73 m², bilirubin ≤1.5 times the ULN, aspartate aminotransferase and alanine transaminase concentrations ≤2.5 times the ULN, activated partial thromboplastin time ≤1.5 times the ULN, and international normalized ratio <1.5). All patients were tested for g*BRCA1/2* mutations by the core lab. Patients with g*BRCA1/2* mutations based on local testing were eligible but retesting by the core laboratory was required. Patients had received ≤2 prior lines of cytotoxic chemotherapy for metastatic breast cancer, and ≤1 prior line of platinum therapy without progression within 12 months of completing treatment. Patients could have prior taxane for neo-adjuvant/adjuvant therapy or to treat locally advanced disease, if given >6 months before study start. Prior taxane for metastatic breast cancer was not allowed unless it was administered without progression >12 months before study start. Prior treatment with targeted agents was allowed except for prior PARP inhibitor therapy. Hormone receptor-positive patients and patients with bone-only metastases were to be considered 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. Also 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, uncontrolled hypertension, or major surgery within 3 weeks of randomisation were excluded. Additional eligibility criteria are in the protocol (p.3-6).

The study was conducted 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. An independent data monitoring committee reviewed safety data.

Randomisation and masking

Patients were prospectively randomised in a 2:1 ratio to carboplatin and paclitaxel with veliparib (investigational arm) or carboplatin and paclitaxel with placebo (control arm) by an interactive response technology (IRT) system using 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 estrogen and/or progesterone receptor expression (positive or negative), prior 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 IRT system.

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

Procedures

Patients received veliparib (120 mg p.o. BID) or placebo (capsules matching veliparib capsules BID) on Days –2 to 5, carboplatin (C; AUC 6 mg/mL/min IV) on Day 1, and paclitaxel (P; 80 mg/m² IV) on Days 1, 8, and 15 (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 (protocol p.91-94). The dose of blinded study drug could be reduced to 80 or 40 mg. The dose of C could be reduced to AUC 5 or 4, and the dose of P could be reduced to 70 or 60 mg/m². Treatment interruptions were required if hematologic parameters were below protocol-specified thresholds (absolute neutrophil count of ≥ 1500 cells per mm³, platelet count of $\geq 100,000$ cells per mm³ on cycle day 1) or in the event of grade 3 or higher toxicity. Patients discontinuing both carboplatin and paclitaxel for reasons other than disease progression received continuous single-agent veliparib or placebo at 300 mg BID, increasing to 400 mg BID if tolerated. Patients in the control arm could receive crossover open-label veliparib monotherapy after disease progression.

CT or MRI of the full chest, abdomen, and pelvis, and brain MRI or contrast CT, occurred at screening (within 28 days of randomization) 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 (BICR). 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, the final visit, and 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. Patient-reported outcomes (PROs) questionnaires were administered pre-dose at day -2 and day 1 of cycle 1, day 1 of every other cycle thereafter beginning with cycle 2, final visit, and at follow-up visit (appendix p.60). Eastern Cooperative Oncology Group (ECOG) performance status was evaluated at day 1 of each cycle, final visit, and follow-up visit.

Outcomes

The primary end point was progression-free survival (PFS) (time from randomisation to disease progression or death from any cause within 63 days of last tumor assessment) according to Response Evaluation Criteria in Solid Tumors, version 1.1, as assessed by the local investigator. Secondary end points were overall survival (OS) (time from randomisation to death from any cause), clinical benefit rate (CBR, progression-free rate at 24 weeks), objective response rate (ORR) (proportion of confirmed responders), and PFS2 (time from randomisation to disease progression on first subsequent therapy or death from any cause). Tertiary endpoints included duration of overall response (time from response to disease progression) and PROs assessed using European Organization for Research and Treatment of Cancer (EORTC) questionnaire for patients with cancer (EORTC-QLQ-C30) and the breast cancer-specific EORTC questionnaire for patients with breast cancer (QLQ-BR23), the EuroQoL 5Dimension 5-

Level (EQ-5D-5L), and the Brief Pain Inventory – Short Form (BPI-SF). PFS as assessed by BICR was evaluated as a sensitivity analysis.

Statistical analysis

The trial sought to enroll 500 patients to accrue 344 PFS events to provide $\geq 90\%$ power at a 2-sided alpha level of 0.05 (assuming a hazard ratio of 0.69) to detect a statistically significant treatment effect. The sample size was increased to 500 patients on June 17, 2016 due to a pre-planned blinded sample size re-estimation based on the hazard ratio observed in the phase 2 BROCADE study²⁰ for which data became available during the course of the current study. Efficacy analyses were performed on the intent-to-treat population, which included all randomised patients with a suspected deleterious or deleterious *BRCA* mutation per the core laboratory (Myriad BRACAnalysis CDx assay). Safety analyses included all patients who received at least one dose of veliparib/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 prior platinum therapy (yes, no) and hormone receptor status (ER and/or PgR positive, ER/PgR negative). History of CNS metastases was not included as stratification factor in the analysis as few patients were anticipated to have a history of CNS metastases. Statistical significance was measured using a two-sided α of 0.05. Hazard ratios and 95% confidence intervals were estimated using a stratified Cox proportional hazard 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 statistical significance was shown for the primary endpoint analysis of PFS per investigator, secondary end points were to be tested using a fixed-sequence testing procedure in the following order: OS, CBR, ORR, and PFS2. Duration of overall response was changed from a secondary endpoint to a tertiary endpoint on May 30, 2019 prior to database lock for the primary analysis. Interim OS was analyzed at the time of primary PFS analysis as part of a pre-planned analysis. The final OS analysis is planned when 357 events have been observed. Hazard ratios (HR) were estimated using stratified Cox regression model. PFS per BICR was exploratory. Results of investigator-assessed PFS for pre-specified sub-groups are also presented. PROs are reported as mean change from baseline to each scheduled post-baseline visit for the EORTC QLQ-C30 (overall and domain-specific scores), EORTC QLQ-BR23 (domain-specific scores), Brief Pain Inventory (pain interference and overall severity) and EQ-5D-5L (visual analog scale and health index score) questionnaires.

Visual inspection of the Kaplan-Meier curves for PFS suggested nonproportionality of hazards between treatment arms, where treatment effect increases as time from randomization increases. Due to the observed delayed separation of the curves, we sought to evaluate the influence of the transition of a subset of patients to blinded monotherapy (at an intensified dose and schedule) on the primary analysis of PFS. Therefore, a post-hoc analysis of PFS (Cox model) with a time-varying covariate, indicating the transition from veliparib/placebo in combination with chemotherapy to

veliparib/placebo as monotherapy, was developed to model the main effect of treatment (i.e., placebo vs. treatment), treatment phase (i.e., the combination phase vs the subsequent monotherapy phase) and their interaction. The Cox model was stratified by prior platinum therapy (yes vs no) and receptor status (ER and/or PgR positive vs ER/PgR negative).

Analyses were done with SAS version 9.4 or later under the UNIX operating system. This study is ongoing and is registered with ClinicalTrials.gov (NCT02163694).

Role of the funding source

AbbVie Inc. provided financial support for this study and participated in the design, study conduct, analysis and interpretation of the data, as well as the writing, review, and approval of this manuscript. All authors had access to full 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 prior to submission and have approved the final manuscript. The corresponding author had the final responsibility to submit for publication.

RESULTS

Between July 30, 2014 and January 17, 2018, 513 patients were randomised (**Fig.S1**). A total of 509 patients (n=337, investigational arm; n=172, control arm) had a g*BRCA1/2* mutation confirmed by the core laboratory; these patients comprised the ITT population. Among all randomised patients, 507 received ≥ 1 dose of veliparib or placebo and were included in safety analyses. Baseline characteristics were balanced

between arms (**Table 1**). Approximately half the patients had triple-negative breast cancer (i.e. were ER and PgR negative). Most patients had received prior chemotherapy in the neo-adjuvant or adjuvant setting; however, the majority had not received prior cytotoxic chemotherapy in the metastatic setting. Among 266 total patients with hormone receptor positive breast cancer, 174 (65%) had received prior endocrine therapy in any setting (**Table S1**).

Patients in the investigational arm remained on blinded study drug longer than those in the control arm, with means (SD) of 237 (272) and 181 (209) treatment days, respectively (excludes non-treatment days during intermittent study drug dosing in combination with carboplatin and paclitaxel). A subset of patients discontinued carboplatin and paclitaxel prior to disease progression and received blinded study drug monotherapy. This included 40.5% (136/336) of patients in the investigational arm and 33.9% (58/171) of patients in the control arm. Mean (SD) overall duration of blinded monotherapy in these patients was 350 (318) vs 252 (263) days, in the investigational and control arms, respectively (**Table S2**). Chemotherapy exposure prior to transitioning to blinded monotherapy was highly variable (**Fig.S2**), with the most frequent point of transition being after six cycles of combination therapy. Among patients receiving monotherapy, 31% (42/136) in the investigational arm and 55% in the control arm (32/58) escalated the dose of blinded study drug from 300 mg BID to 400 mg BID. At the time of data-cutoff, 192 (57%) of 337 patients in the investigational arm and 121 (70%) of 171 in the control arm had discontinued study drug due to disease progression.

394

395 Patients in both arms received a similar duration of chemotherapy. In the investigational
396 and control arms, mean (SD) durations of carboplatin and paclitaxel were 10·7 (8·5)
397 cycles vs. 11·0 (8·2) cycles and 11·5 (10) cycles vs 10·6 (8·6) cycles, respectively
398 (**Table S2**). The mean [SD] duration of cycle delays was similar between treatment
399 arms (5·9 [4·3] vs 5·1 [3·7] days for carboplatin and 5·2 [3·9] vs 4·6 [3·6] days for
400 paclitaxel). Rates of dose reductions of carboplatin and paclitaxel were similar between
401 treatment arms (carboplatin: 88% [293/335] vs 86% [145/169]; paclitaxel: 74% [248/335]
402 vs 70% [119/169]). Each chemotherapy agent could be discontinued individually to
403 manage toxicity. Carboplatin was administered with blinded study drug in 23% (77/336)
404 of patients in the investigational arm and 29% (50/171) of patients in the control arm
405 after paclitaxel discontinuation, for a mean (SD) duration of 6·1 (7·4) and 7·2 (8·4)
406 cycles, respectively. Paclitaxel was administered with blinded study drug after
407 carboplatin discontinuation in 21% (69/336) of patients in the investigational arm and
408 19% (33/171) of patients in the control arm for a mean (SD) duration of 10·4 (10·4) and
409 9·1 (9·2) cycles, respectively.

410

411 At the time of data-cutoff, median follow-up time was 35·7 months (IQR 24·9–43·6) in
412 the investigational arm and 35·5 months (IQR 23·1–45·9) in the control arm. At data cut-
413 off, progression-free survival events had been recorded in 217 (64%) of 337 patients in
414 the investigational arm and 132 (77%) of 172 patients in the control arm. Median PFS
415 (95% CI) was 14·5 (12·5–17·7) months in the investigational arm vs 12·6 (10·6–14·4)
416 months in the control arm (HR 0·71, 95% CI 0·57–0·88; 2-sided log-rank p=0·0016)

(**Fig.1A**). More patients were alive and progression-free in the investigational vs control arm at 2 years (34% vs 20%) and at 3 years (26% vs 11%). Blinded independent central review demonstrated a similar PFS HR (HR 0.70, 95% CI 0.54–0.90; median PFS [95% CI] 19.3 [16.5–23.3] vs 13.5 [12.5–16.3] months; 159 [47%] events in 337 patients vs. 94 (55%) events in 172 patients) (**Fig.S3**), although difference in median PFS was greater by central than by investigator review due to an earlier separation of the curves. Concordance between investigator and central review was high and comparable between arms (>75%), and the lack of systemic evaluation bias is supported by the nearly identical HRs. Analyses of PFS in pre-specified subgroups, including patients with ER/PgR-positive breast cancer (HR 0.69, 95% CI 0.52–0.92) and with TNBC (ER and PgR-negative) (0.72, 95% CI 0.52–1.01], were conducted (**Fig.2, Table S3**). Due to limited sample sizes, point estimates in smaller subgroups such as patients with prior platinum therapy, patients with prior cytotoxic therapy for metastatic disease and patients with a history of CNS metastases should be interpreted with caution.

In a pre-planned interim analysis, median overall survival was 33.5 months (95% CI 27.6–37.9) for the investigational arm and 28.2 months (95% CI 24.7–35.2) for the control arm (HR 0.95, 95% CI 0.73–1.23; $p=0.667$; 167 [50%] events in 337 patients vs. 87 [51%] events in 172 patients) (**Fig.1B**). At the time of analysis, 44% of patients randomised to the control arm had received open label veliparib (crossover) as first subsequent therapy. Per investigator assessment, clinical benefit rate (95% CI) was estimated as 90.7% (87.9–92.9) for the investigational arm and 93.2% (89.5–95.7) for

the control arm. ORR (95% CI) was 75.8% (70.4–80.6) versus 74.1% (66.1–81.1) (**Table 3**). Among patients with a confirmed complete or partial response, duration of response was 14.7 months (95% CI 12.1–18.7) vs 11.0 months (95% CI 10.2–12.3) (**Fig.S4**). Median PFS2 was 21.3 (19.8–25.1) months for the investigational arm and 17.4 (16.0–20.0) months for the control arm (HR 0.76, 95% CI 0.60–0.96; nominal $p=0.020$; 196 [58%] events in 337 patients vs. 114 [66%] events in 172 patients) (**Fig.S5**). **Table S5** summarizes subsequent therapies. Changes from baseline in ECOG performance status at each cycle were generally comparable between treatment arms (**Fig.S6**).

The delayed separation noted in the Kaplan-Meier curves for PFS suggested the presence of non-proportional hazards, which may have been influenced by the transition of a subset of patients (38% of the ITT) to monotherapy prior to disease progression. To further characterize the impact of this transition on the PFS treatment effect, a Cox model for PFS with a time-varying covariate indicating the transition from veliparib/placebo in combination with chemotherapy to veliparib/placebo as monotherapy was fitted in a post-hoc analysis. The nominal P value for the interaction effect was 0.0384. The interaction term was therefore retained in the fitted model together with the indicator variables for combination therapy and monotherapy. The PFS HR estimates were < 1 during both combination therapy and monotherapy (**Table S4**).

Mean changes from baseline to each subsequent cycle in global health status/quality of life score based on the EORTC QLQ-C30 questionnaire v.3.0 (©1995, EORTC Quality of Life Group) are shown in **Fig.3**. No clinically meaningful difference between treatment arms was apparent. Mean changes from baseline for all functional and symptom scales of the EORTC QLQ-C30 v.3.0 are shown in **Fig.S7**. No clinically meaningful difference between treatment arms was evident in any of the 14 scores.

Systemic therapy side effects as assessed by QLQ-BR23 generally worsened in both treatment arms and were consistently reported for each group through Cycle 36 (**Fig.S8**). No clinically meaningful differences between treatment arms were apparent in any of the domains for QLQ-BR23. Similarly, outcomes reported via the EQ-5D-5L (visual analog scale and health index score) and BPI (pain interference and overall pain severity) questionnaires were comparable between treatment arms (**Fig.S9**).

Adverse events were evaluated for the entire veliparib/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.

Common adverse events occurring more frequently (absolute difference of $\geq 5\%$) in the investigational arm vs control arm during the entire blinded treatment period were thrombocytopenia, anemia, nausea, and diarrhea; peripheral sensory neuropathy occurred less frequently in the investigational arm (**Table 2**). Serious adverse events (**Table S6**) were more frequent in the investigational arm, occurring in 115 (34%) of 336

485 patients compared to 49 (29%) of 171 patients in the control arm. Serious adverse
486 events that occurred more frequently (absolute difference between arms of $\geq 2\%$) in the
487 investigational arm vs control arm were neutropenia (8 patients [2.4%] vs 0) and
488 pneumonia (7 patients [2.1%] vs 0). Study-drug related serious adverse events occurred
489 in 41 patients (12.2%) in the investigational arm and 7 patients (4.1%) in the control
490 arm; the most common study drug-related serious adverse events in the investigational
491 arm were anemia in 12 patients (3.6%) and thrombocytopenia in 11 patients (3.3%).
492 The most common grade 3 or higher adverse events were neutropenia (272 [81%] vs.
493 143 [84%]), anemia (142 [42%] vs. 68 [40%]), and thrombocytopenia (134 [40%] vs. 48
494 [28%]). Grade 3 or higher adverse events occurring more frequently (absolute
495 difference of $\geq 3\%$) in the investigational arm vs control arm were thrombocytopenia and
496 fatigue. Grade 3 or higher infections within 14 days of neutropenia occurred in 18
497 patients (5.4%) vs 3 patients (1.8%), and grade 3 or higher hemorrhage within 14 days
498 of thrombocytopenia occurred in 1 patient (0.3%) vs 0 patients in the investigational and
499 control arms, respectively (**Table S7**). Adverse events leading to study drug dose
500 reductions occurred in 58 patients (17%) and 13 patients (7.6%) in the investigational
501 and control arms. In the investigational arm, the adverse events most commonly leading
502 to study drug dose reductions were neutropenia (18 patients [5.4%]), thrombocytopenia
503 (16 patients [4.8%]), and nausea (14 patients [4.2%]). During all blinded
504 veliparib/placebo exposure, grade 5 AEs occurred in 6 patients (1.8%) in the
505 investigational arm (4 malignant neoplasm progression, 1 pulmonary embolism, 1
506 sepsis), and in 3 patients (1.8%) in the control arm (2 malignant neoplasm progression,
507 1 pulmonary artery thrombosis). No grade 5 event was considered study-drug related.

508

509 The majority of patients in each arm experienced an adverse event leading to study
510 drug interruption at some time during the entire treatment period (301 [90%] of 336
511 patients in the investigational arm and 147 [86%] of 171 patients in the control arm),
512 most commonly due to neutropenia (231 patients [69%] and 125 patients [73%]) and
513 thrombocytopenia (213 patients [63%] and 89 patients [52%]). Adverse events led to
514 study drug discontinuation in 53 patients (16%) and 18 patients (11%), respectively
515 (**Table S8**). These events were considered related to study drug in 19 patients (5.7%)
516 and 5 patients (2.9%); the most common of these related events in the investigational
517 arm was fatigue (3 patients). Adverse events led to carboplatin discontinuation in 168
518 patients (50%) in the investigational arm and 70 patients (41%) in the control arm, most
519 commonly owing to thrombocytopenia (60 patients [18%] vs. 16 patients [9.4%]) and
520 neutropenia (32 patients [9.5%] vs. 19 patients [11.1%]). Adverse events led to
521 paclitaxel discontinuation in 156 patients and 78 patients (46% in both arms), most
522 commonly owing to neutropenia (38 patients [11%] vs. 25 patients [15%]) and
523 peripheral sensory neuropathy (42 patients [13%] vs. 31 patients [18%]).

524

525 In the subgroup of patients who received blinded study drug monotherapy, the most
526 common adverse events that occurred more frequently (absolute difference of $\geq 5\%$)
527 with veliparib vs placebo were nausea, fatigue, and diarrhea. The only grade 3 or higher
528 adverse event that occurred more frequently (absolute difference of $\geq 3\%$) in patients
529 receiving veliparib vs placebo was nausea (**Table S10**). The only serious adverse event
530 occurring more frequently (absolute difference between arms $\geq 2\%$) in patients receiving

veliparib vs placebo was seizure (3 [2.2%] of 136 patients vs 0 of 58) (**Table S6**). One patient experiencing a seizure event had a history of CNS metastases. The seizure events (all grade 2) occurred after approximately 1 year of veliparib 400 mg BID in 2 patients (1 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 BID) after treatment with levetiracetam and continued until disease progression (6-9 months later) without another seizure event. During blinded single agent veliparib/placebo exposure, grade 5 AEs occurred in 2 patients (1.5%; 1 malignant neoplasm progression, 1 sepsis) receiving veliparib and none receiving placebo. No grade 5 AEs were considered related to study drug by the investigator.

DISCUSSION

BROCADE3 is the first phase 3 clinical trial to evaluate a PARP inhibitor in combination with platinum-based chemotherapy in patients with metastatic breast cancer. When added to carboplatin and paclitaxel, and continued as monotherapy if carboplatin and paclitaxel are discontinued before disease progression, veliparib resulted in durable improvement in PFS, with benefit evident at the 2-year and 3-year landmarks, in patients with advanced HER2-negative breast cancer and a germline *BRCA1/2* mutation. These results are noteworthy given the high activity of the carboplatin/paclitaxel control arm, for which median PFS was greater than 1 year. Overall survival was not yet mature at the time of the primary analysis, and the results of the pre-planned interim analysis were not statistically significant.

554

555 Overall, the addition of veliparib to carboplatin and paclitaxel was well-tolerated, with
556 toxicity leading to discontinuation in fewer than 10% of patients. Dose reductions of
557 veliparib were relatively infrequent, however dose reductions were very frequent in both
558 arms for carboplatin and paclitaxel. The starting dose of carboplatin (AUC6) is
559 recommended by the NCCN,²¹ however the recommended dose of paclitaxel is 175-200
560 mg/m² (every 3 weeks) when combined with carboplatin. The paclitaxel dose and
561 schedule chosen for this study (80 mg/m², weekly) reflects a general trend towards
562 more frequent use of dose dense paclitaxel and is consistent with standard practice in
563 other solid tumors where C/P is the standard of care. However, in such cases, treatment
564 is often limited to six cycles. Further research is required to determine if alternate doses
565 or schedules of C/P or a limited treatment duration would improve outcomes in patients
566 with advanced breast cancer, for whom treatment until disease progression is standard.

567

568 Although hematologic toxicities were generally frequent in both treatment arms, the
569 incidences of clinically important sequelae, including grade 3 or higher infections
570 associated with neutropenia and grade 3 or higher hemorrhages associated with
571 thrombocytopenia, were relatively infrequent. For the subgroup of patients who
572 transitioned to blinded monotherapy at a more intensive dose and schedule, the only
573 grade 3 or higher adverse event that occurred more frequently with veliparib vs placebo
574 was nausea, and the only serious adverse event that occurred more frequently was
575 seizure. The clinical significance of the difference in seizure frequency between
576 treatment arms is unclear. Seizures were observed to be exposure dependent in

nonclinical studies primarily involving dogs, however the seizure rate observed in this study is consistent with background rates based on a comparable patient population identified in a real-world database (data on file). Patient-reported outcomes revealed no clinically meaningful differences between treatment arms, indicating that the addition of veliparib to C/P does not increase treatment-related symptom burden. Moreover, these analyses revealed no systematic, clinically meaningful deterioration in global health status/quality of life scores with time, suggesting that the regimen was generally well-tolerated.

The Kaplan-Meier curves for PFS (**Fig.1**) exhibited a delayed separation between treatment arms and persistent “tail” in the investigational arm. The delayed separation suggests nonproportionality of hazards between treatment arms, where the treatment effect increases as time from randomization increases. One possibility is that a well-represented clinically or biologically defined subgroup of patients do not experience benefit with the addition of veliparib. However, subgroup analyses of PFS did not identify such a subgroup defined by clinical characteristics. Further research is warranted to identify biomarkers that can select patients likely to benefit.

As the proportion of patients receiving blinded monotherapy also increased with time from randomization, it is plausible to hypothesize that the transition to monotherapy by a subset of patients contributed to the delayed separation of curves observed. A post-hoc exploratory analysis using a Cox model for PFS with a time-varying covariate (**Table S4**) indicating the transition from combination therapy to monotherapy suggested that

the transition indeed contributes to nonproportionality. It is noteworthy that the estimated HR for combination therapy is nearly identical to that observed in the phase 2 BROCADE study, which compared C/P with veliparib to C/P with placebo in a similar patient population and did not allow treatment with veliparib/placebo monotherapy.²⁰ Collectively, these results suggest that the overall PFS benefit observed in BROCADE3 is derived both from the inclusion of veliparib with C/P and from the continuation of veliparib monotherapy when chemotherapy is discontinued prior to 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 C/P. Moreover, the subset of patients receiving monotherapy does not represent a randomized sample, and the decision to transition (and the variable timing thereof) may be influenced in part by depth and duration of response to combination therapy. The inability to isolate the treatment effect during combination therapy and monotherapy is a limitation of the study design.

Another 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, as this strategy would represent a paradigm shift in the treatment of metastatic breast cancer, akin to recently validated strategies in ovarian cancer.²²

The potential for crossover to confound interpretation of the PFS2 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 C/P 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 TNBC 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 PFS and OS observed with the control regimen in this trial and the phase 2 BROCADE trial suggest that the carboplatin/paclitaxel combination may provide unique benefit to this particular group of patients.²⁰

The utility of a carboplatin/taxane doublet for the first-line treatment of metastatic TNBC was recently demonstrated by the phase 2 tnAcity trial, which demonstrated superior PFS with carboplatin and *nab*-paclitaxel compared to doublets of carboplatin with gemcitabine or *nab*-paclitaxel with gemcitabine.²³ In this trial, patients treated with

carboplatin and *nab*-paclitaxel experienced a median PFS of 8.3 months and a median OS of 16.8 months. In addition, a growing body of evidence supports the use of platinum chemotherapy in patients with advanced TNBC and a germline *BRCA1/2* mutation.^{7,8,20,23} Studies of single-agent platinum chemotherapy reported median PFS of 3.3–6.8 months,^{7,8} and OS of 13.7 months.⁸ The median PFS of 16.6 months and median OS of 35 months observed in the TNBC subgroup of BROCADE3 suggest that combination therapy with veliparib, carboplatin and paclitaxel may improve long-term outcomes relative to sequential single-agent therapy for this patient population with more limited treatment options and poorer prognosis compared to 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 usage of chemotherapy, including combination regimens, is more common in early lines than might be expected according to these guidelines.²⁵ This is consistent with the observation in this study that only 65% of hormone-receptor positive patients enrolled had prior endocrine therapy. Of note, CDK4/6 inhibitors were largely unavailable in most participating countries during enrollment of this trial and in some participating countries endocrine therapy options are limited in premenopausal women. Treatment utilization patterns should continue to evolve, given recent evidence demonstrating an OS benefit with the addition of CDK4/6 inhibitors to endocrine therapy, along with the previously

reported PFS benefit and manageable safety profile.²⁶ However, limited 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 may 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 may be a beneficial option for this group of patients, in whom a median PFS and OS of 13·0 months and 32·4 months was observed. Further characterization of this subgroup, including those with no prior endocrine therapy, would be of interest.

Two recent 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 g*BRCA1/2* mutations, based on improved PFS when compared to physicians' choice of single-agent chemotherapy.^{5,6} Notably, these trials did not include platinum amongst the comparator therapies, and the objective response rates (60–63%) and median PFS (7·0–8·6 months) reported for PARP inhibitor monotherapy were comparable to previously reported data for carboplatin monotherapy in g*BRCA1/2* mutation positive patients with TNBC.⁷ As such, it remains an unanswered

question whether PARP inhibitor monotherapy is superior to single-agent platinum chemotherapy. Also unknown is the optimal sequence of PARP inhibitors and platinum-based chemotherapy in patients with g*BRCA1/2* 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 may be a rational strategy to allow patients to benefit from both agents before developing cross-resistance. Accordingly, while median overall survival reported for a subgroup of patients receiving single-agent olaparib for first-line treatment of *BRCA*-associated advanced breast cancer was 14.7 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 the treatment strategy under investigation in this study may 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 C/P, followed by doxorubicin and cyclophosphamide, did not improve the frequency of pathological complete response in patients with early stage TNBC, with similar results in the subgroup of patients with g*BRCA1/2* mutations. These results are consistent with the observation that the addition of veliparib did not improve the high objective response rate observed with C/P in BROCADE3. Follow up for event-free survival in BrighTNess is ongoing and it remains to be determined if the long-term benefit observed in BROCADE3 will also be seen in patients with early stage TNBC; however a direct

714 comparison of the two trials will be confounded by differences in dose and schedule of
715 veliparib and differences in patient population.

716

717

718 **CONTRIBUTORS**

719 Conception, design, and recruitment: all authors;

720 Provision of patients and patient care: VD, HSH, BK, HW, MF, J-PA, SLP, IB, MC, EHJ, MJ,
721 CO, MP, YHP, YS, EY, BA;

722 Data analysis, collection, and interpretation: all authors;

723 All authors were responsible for writing the manuscript and have approved the final manuscript.

724

725 **DECLARATION OF INTERESTS**

726 **VD:** Consulting/advisory role Roche/Genentech, Novartis, Lilly, Pfizer, AbbVie, MSD, Daiichi
727 Sankyo, Seattle Genetics, Astra Zeneca. Speakers fees: Roche/Genentech, Novartis, Lilly,
728 Pfizer, Astra Zeneca, Daiichi Sankyo.

729 **HSH:** Research funding to institution: AbbVie, Prescient, Horizon, Karyopharm, BMS, Novartis,
730 Pfizer, Tesaro, TapImmune, Seattle Genetics. Grant: Department of Defense. Speakers'
731 bureau: Lilly.

732 **BK:** No Conflicts of Interest.

733 **HW:** His institution received consulting fees and honoraria from Roche, Astra Zeneca, Amgen,
734 Lilly, Novartis, AbbVie, Vifor Pharma, Pfizer, Celldex Therapeutics, Janssen-CILAG, TRM
735 Oncology, PUMA Biotechnology, ORION Corporation and an unrestricted research grant from
736 Roche. He received travel support from Roche and Pfizer.

737 **MF:** Consulting/advisory role: AstraZeneca, MSD, AbbVie, Lilly, Takeda, Novartis. Speakers'
738 bureau: Astra Zeneca. Honoraria: AstraZeneca, MSD, Lilly, Takeda. Research funding:
739 BeiGene, Novartis, Astra Zeneca

740 **JPA:** Research funding to institution: AbbVie, Boston Biomedical. Consultancy: AstraZeneca,
741 Eisai, Eli Lilly, Novartis, Pfizer, Puma, Roche.

742 **SLP:** Consultant: AbbVie, MedImmune, Celldex, Puma, Pfizer, AstraZeneca, Eisai, Nanostring.
743 Research funding to institution: AbbVie, Pfizer, Lilly, Novartis, Incyte, Covance-Bayer,
744 AstraZeneca, Genentech, Medivation.

745 **IB and E Y:** No Conflicts of Interest.

746 **MC:** Consulting/advisory role: AstraZeneca, Sanofi, Servier, AbbVie, Lilly, Accord. Speakers'
747 bureau: Novartis. Honoraria: Lilly.

748 **EJ:** Consulting/advisory role: Pfizer, Roche, Novartis, Eli Lilly.

749 **MJ:** Advisory Board, honoraria to institution: Merck, BMS, Novartis, Pierre Fabre, Tesaro,
 750 AstraZeneca. Speakers fees: Sanofi. Clinical studies: BMS, AbbVie, Merck, Cristal
 751 Therapeutics.

752 **CO:** Advisory Board: Eli Lilly, Sandoz, Merck, Pfizer; Speaker: Eli Lilly, Roche, Teva, BMS,
 753 Sanofi, Boehringer Ingelheim, Novartis, AstraZeneca, Astellas, Janssen, Sandoz; Research
 754 /Clinical studies: BMS, AbbVie, Roche, Genentech, Novartis, Boehringer Ingelheim, BeiGene,
 755 Trio Oncology.

756 **MP:** Received fees as the speaker from Pfizer, Roche, Eisai.

757 **YHP:** Consultancy or advisory board member for AstraZeneca, Pfizer, Eisai and Novartis
 758 Pharmaceuticals. Research fund from AstraZeneca, Eisai, Merck, Pfizer, Novartis and Roche.

759 **YS:** Advisory Board: Pfizer; Speaker: Roche, AstraZeneca, Pfizer; Research /Clinical studies:
 760 AbbVie, Roche, MSD, Boehringer Ingelheim.

761 **BKA:** Research support to the Institution: AbbVie, PharmaMar, Astra Zeneca, Invitae. Steering
 762 committee (non-paid): AbbVie.

763 **NKI, MGK, CKR, and DM:** AbbVie employees and own stock.

764 **MD:** Former AbbVie employee and may own stock.

765

766 **ACKNOWLEDGMENTS**

767 AbbVie Inc. provided financial support for this study (NCT02163694) and participated in the
 768 design, study conduct, analysis and interpretation of the data, as well as the writing, review, and
 769 approval of this manuscript. No honoraria or payments were made for authorship. AbbVie and
 770 the authors thank all the trial investigators and the patients who participated in this clinical trial,
 771 the study coordinators, support staff, and all study investigators for their contributions. We thank
 772 Bruce A. Bach, M.D., Ph.D., Stacie Peacock Shepherd, M.D., Ph.D., Marlene Schumansky, and
 773 Melissa Shah for clinical trial oversight, and George Somlo, M.D. for his participation as a
 774 member of the steering committee. Medical writing assistance was provided by Ana Mrejeru,
 775 Ph.D., an employee of AbbVie.

776

AVAILABILITY OF DATA AND MATERIAL

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual and trial-level data (analysis data sets), as well as other information (e.g., 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 unlicensed 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 (SAP) and execution of a Data Sharing Agreement (DSA). 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 following link:
<https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

REFERENCES

1. 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.
2. 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.
3. Atchley DP, Albarracin CT, Lopez A, et al. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. *J Clin Oncol* 2008; **26**:4282-8.
4. National Cancer Institute. SEER Cancer Stat Facts: Female Breast Cancer Subtypes. Website: <https://seer.cancer.gov/statfacts/html/breast-subtypes.html>. Accessed Jan 13, 2020.
5. 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**: 753-763.
6. 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**: 523-533.
7. Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nature Medicine* 2018; **24**: 628-637.
8. 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**: 1902-9.
9. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science* 2017; **355**:1152-1158.

- 817 10. Donawho CK, Luo Y, Luo Y, et al. ABT-888, an orally active poly(ADP-ribose)
818 polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models.
819 *Clin Cancer Res* 2007; **13**: 2728-2737.
- 820 11. Dhawan MS, Bartelink IH, Aggarwal RR, et al. Differential toxicity in patients with and
821 without DNA repair mutations: phase I study of carboplatin and talazoparib in advanced
822 solid tumors. *Clin Cancer Res* 2017; **23**: 6400–6410.
- 823 12. Lee JM, Hays JL, Chiou VL, et al. Phase I/Ib study of olaparib and carboplatin in women
824 with triple negative breast cancer. *Oncotarget* 2017; **8**: 79175-87.
- 825 13. Faraoni I, Graziani G. Role of BRCA Mutations in Cancer Treatment with Poly(ADP-
826 ribose) Polymerase (PARP) Inhibitors. *Cancers (Basel)* 2018;**10**: pii E487.
- 827 14. McCann KE, Hurvitz SA. Advances in the use of PARP inhibitor therapy for breast
828 cancer. *Drugs Context* 2018; **7**: 212540.
- 829 15. Somlo G, Frankel PH, Arun BK, et al. Efficacy of the PARP Inhibitor Veliparib with
830 Carboplatin or as a Single Agent in Patients with Germline BRCA1- or BRCA2-
831 Associated Metastatic Breast Cancer: California Cancer Consortium Trial
832 NCT01149083. *Clin Cancer Res* 2017; **23**: 4066-76.
- 833 16. Puhalla S, Beumer JH, Pahuja S, et al. Final results of a phase 1 study of single-agent
834 veliparib (V) in patients (pts) with either BRCA1/2-mutated cancer (BRCA+), platinum-
835 refractory ovarian, or basal-like breast cancer (BRCA-wt). *J Clin Oncol* 2014; **32** (Suppl
836 15): abst 2570.
- 837 17. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP
838 Inhibitors. *Cancer Res* 2012; **72**: 5588-99.
- 839 18. Pommier Y, O'Connor MJ, de Bono J. Laying a trap to kill cancer cells: PARP inhibitors
840 and their mechanisms of action. *Sci Transl Med* 2016; **8** (362): 362ps17.

- 841 19. Hopkins TA, Ainsworth WB, Ellis PA, et al. PARP1 Trapping by PARP Inhibitors Drives
842 Cytotoxicity in Both Cancer Cells and Healthy Bone Marrow. *Mol Cancer Res* 2019; **17**:
843 409-19.
- 844 20. Han HS, Dieras V, Robson M, et al. Veliparib with temozolomide or carboplatin/paclitaxel
845 versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/
846 metastatic breast cancer: randomized phase II study. *Ann Oncol* 2018; **29**: 154-161.
- 847 21. National Comprehensive Cancer Network. NCCN clinical practice guidelines in
848 oncology: breast cancer, version 4.2020. 2020 ([https://www .nccn .org/
849 professionals/physician_gls/ pdf/ breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf)).
- 850 22. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly
851 Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2018; **379**: 2495-2505.
- 852 23. Yardley DA, Coleman R, Conte P, et al. nab-Paclitaxel plus carboplatin or gemcitabine
853 versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative
854 metastatic breast cancer: results from the tnAcity trial. *Ann Oncol* 2018; **29**: 1763-70.
- 855 24. Cardoso F, Senkus E, Costa A, et al. 4th ESO-ESMO International Consensus
856 Guidelines for Advanced Breast Cancer (ABC 4)†. *Ann Oncol* 2018; **29**:1634-57.
- 857 25. Dalal AA, Gauthier G, Gagnon-Sanschagrin P, et al. Treatment and Monitoring Patterns
858 Among Premenopausal Women with HR+/HER2- Advanced Breast Cancer. *Adv Ther*
859 2018; **35**: 1356-67.
- 860 26. Han Y, Wang J, Wang Z, Xu B. Comparative efficacy and safety of CDK4/6 and
861 PI3K/AKT/mTOR inhibitors in women with hormone receptor-positive, HER2-negative
862 metastatic breast cancer: a systematic review and network meta-analysis. *Curr Probl*
863 *Cancer* 2020; 100606 [ePub May 12]. doi:10.1016/j.crrproblcancer.2020.100606.
- 864 27. Larsen MJ, Kruse TA, Tan Q, et al. Classifications within molecular subtypes enables
865 identification of BRCA1/BRCA2 mutation carriers by RNA tumor profiling. *PLoS One*
866 2013; **8**: e64268.

- 867 28. Waks AG, Cohen O, Kochupurakkal B, et al. Reversion and non-reversion mechanisms
868 of resistance (MoR) to PARP inhibitor (PARPi) or platinum chemotherapy (chemotx) in
869 patients (pts) with BRCA1/2-mutant metastatic breast cancer (MBC). *J Clin Oncol* 2019;
870 **37** (15_suppl): 1085-1085. doi: 10.1200/JCO.2019.37.15_suppl.1085.
- 871 29. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability
872 results: Olaparib versus chemotherapy treatment of physician's choice in patients with a
873 germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol* 2019;
874 **30**: 558-566.
- 875 30. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus
876 carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative
877 breast cancer (BrighTNess): a randomised, phase 3 trial. *Lancet Oncol* 2018; **19**: 497-
878 509.
- 879

Figure Legends

Figure 1. Kaplan Meier Analysis of Progression-free Survival and Overall Survival

Distributions were estimated using Kaplan-Meier method for (A) progression-free survival (PFS) by investigator assessment, and (B) overall survival. PFS was compared by stratified log-rank test. Hazard ratios estimated by Cox model stratified by same factors as log-rank test. Kaplan-Meier estimates of the proportion progression-free at 24 months and 36 months are shown.

Figure 2. Subgroup Analysis of Progression-free Survival.

CNS, central nervous system; ER, estrogen receptor; PgR, progesterone receptor; TNBC, triple-negative breast cancer.

Hazard ratio compares progression-free survival for the veliparib plus carboplatin and paclitaxel arm to the control arm. Hazard ratios presented for subgroups other than ER/PgR are from a Cox model stratified by ER/PgR status. The ER/PgR subgroup hazard ratios are from an unstratified model.

Figure 3. Mean Change from Baseline in EORTC QLQ-C30 Global Health Status/Quality of Life for ITT Patients.

Mean change from baseline (with standard error bars) is shown for each treatment arm. Score was determined on Day 1 of Cycles shown on X-axis. Number of observations for each treatment arm is shown below graphs. Asterisk denotes a statistically significant

903 (P<0.05) difference between treatment groups. Increases in the Global Health Status
904 Quality of Life score represent improvements in functioning.
905 C/P, carboplatin and paclitaxel; Pbo, placebo; Vel, veliparib.

906 **Table 1. Patient Demographic and Clinical Characteristics**

Characteristic, no. (%)	Veliparib + Carboplatin/Paclitaxel (N = 337)	Placebo + Carboplatin/Paclitaxel (N = 172)
Sex		
Female	333 (98.8)	169 (98.3)
Male	4 (1.2)	3 (1.7)
Age, years, median (range)	47 (24–82)	45 (28–75)
Race		
White	294 (87.2)	153 (89.0)
Asian	24 (7.1)	12 (7.0)
Black	14 (4.2)	6 (3.5)
Other	5 (1.5)	1 (0.6)
Geographic region		
United States	46 (13.6)	27 (15.7)
Non-United States	291 (86.4)	145 (84.3)
ECOG performance status		
0	208 (61.7)	102 (59.3)
1	121 (35.9)	63 (36.6)
2	8 (2.4)	7 (4.1)
Measurable disease	285 (84.6)	143 (83.6)
Liver or Lung Metastases	219 (65.0)	104 (60.8)
Bone-only disease	11 (3.3)	9 (5.3)
Prior platinum therapy use	27 (8.0)	16 (9.3)
Prior chemotherapy in neo- adjuvant/adjuvant setting	236 (70.0)	113 (65.7)
Prior taxane in neo- adjuvant/adjuvant setting	175 (51.9)	86 (50.0)

Prior chemotherapy in metastatic setting	63 (18.7)	33 (19.2)
Prior taxane in the metastatic setting	20 (5.9)	9 (5.2)
History of CNS metastases	16 (4.7)	10 (5.8)
Hormone receptor expression		
ER or PgR positive	174 (51.6)	92 (53.5)
ER and PgR negative	163 (48.4)	80 (46.5)
BRCA1/2 mutation status by core lab		
BRCA1 mutation positive	177 (52.5)	89 (51.7)
BRCA2 mutation positive	167 (49.6)	86 (50)
Stage at diagnosis		
0	3 (0.9)	1 (0.6)
1	43 (13.0)	22 (13.0)
II	128 (38.6)	69 (40.8)
III	84 (25.3)	39 (23.1)
IV	74 (22.3)	38 (22.5)

907

908 C/P, carboplatin/paclitaxel; CNS, central nervous system; ER, estrogen receptor; PgR, progesterone

909 receptor. Percentages are calculated on non-missing values.

910 **Table 2. Summary of Adverse Events**

n (%)	Veliparib + Carboplatin/Paclitaxel				Placebo + Carboplatin/Paclitaxel			
All blinded veliparib/placebo exposure								
	N = 336				N = 171			
	G1/2	G3	G4	G5*	G1/2	G3	G4	G5*
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
Anemia	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
Diarrhea	136 (41%)	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
Hypomagnesemia	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
Dyspnea	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 edema	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/placebo exposure								
	N=136				N=58			
	G1/2	G3	G4	G5*	G1/2	G3	G4	G5*
Any adverse event	78 (57%)	40 (29%)	5 (4%)	2 (2%)	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
Diarrhea	27 (20%)	1 (<1%)	0	0	5 (9%)	0	0	0

Adverse events (AEs) occurring in at least 20% of patients at any grade during all blinded veliparib/placebo exposure or during blinded single-agent veliparib/placebo exposure are shown. The “all blinded veliparib/placebo exposure” AE rates include all AEs during the treatment-emergent period, which includes veliparib/placebo in combination with carboplatin/paclitaxel and veliparib/placebo single-agent, if applicable. The “blinded single-agent veliparib/placebo exposure” AE rates include all treatment-emergent AEs during blinded single-agent veliparib/placebo dosing. **Tables S9** and **S10** include a complete listing of all AEs by maximum grade.

*During all blinded veliparib/placebo exposure, grade 5 AEs occurred in 6 patients (1.8%) on veliparib+carboplatin/paclitaxel (4 malignant neoplasm progression, 1 pulmonary embolism, 1 sepsis), and in 3 patients (1.8%) on placebo+carboplatin/paclitaxel (2 malignant neoplasm progression, 1 pulmonary artery thrombosis). During blinded single agent veliparib/placebo exposure, grade 5 AEs occurred in 2 patients (1.5%; 1 malignant neoplasm progression, 1 sepsis) on veliparib and none on placebo+carboplatin/paclitaxel. No grade 5 AEs were considered related to study drug by the investigator.

Table 3. Additional Efficacy Analyses

Variable	Veliparib + Carboplatin/Paclitaxel (N = 337)	Placebo + Carboplatin/Paclitaxel (N = 172)
Clinical benefit rate (week 24 progression free rate, % (95%CI)	90.7 (87.9, 92.9)	93.2 (89.5, 95.7)
ORR (CR+PR), n/N (%) (95% CI)*	216 / 285 (75.8) (70.4, 80.6)	106 / 143 (74.1) (66.1, 81.1)
PFS2		
Events, n (%)	196 (58.2)	114 (66.3)
Median PFS2 (95% CI), months	21.3 (19.8, 25.1)	17.4 (16.0, 20.0)
Hazard Ratio (95% CI)	0.76 (0.60, 0.96)	
Duration of response		
Events, n/N (%)†	128 / 216 (59.3)	87 / 106 (82.1)
Median duration of response (95% CI), months	14.7 (12.1, 18.7)	11.0 (10.2, 12.3)

CR, complete response; ORR, objective response rate; PFS2, time from randomization until disease progression on subsequent therapy or death; PR, partial response.

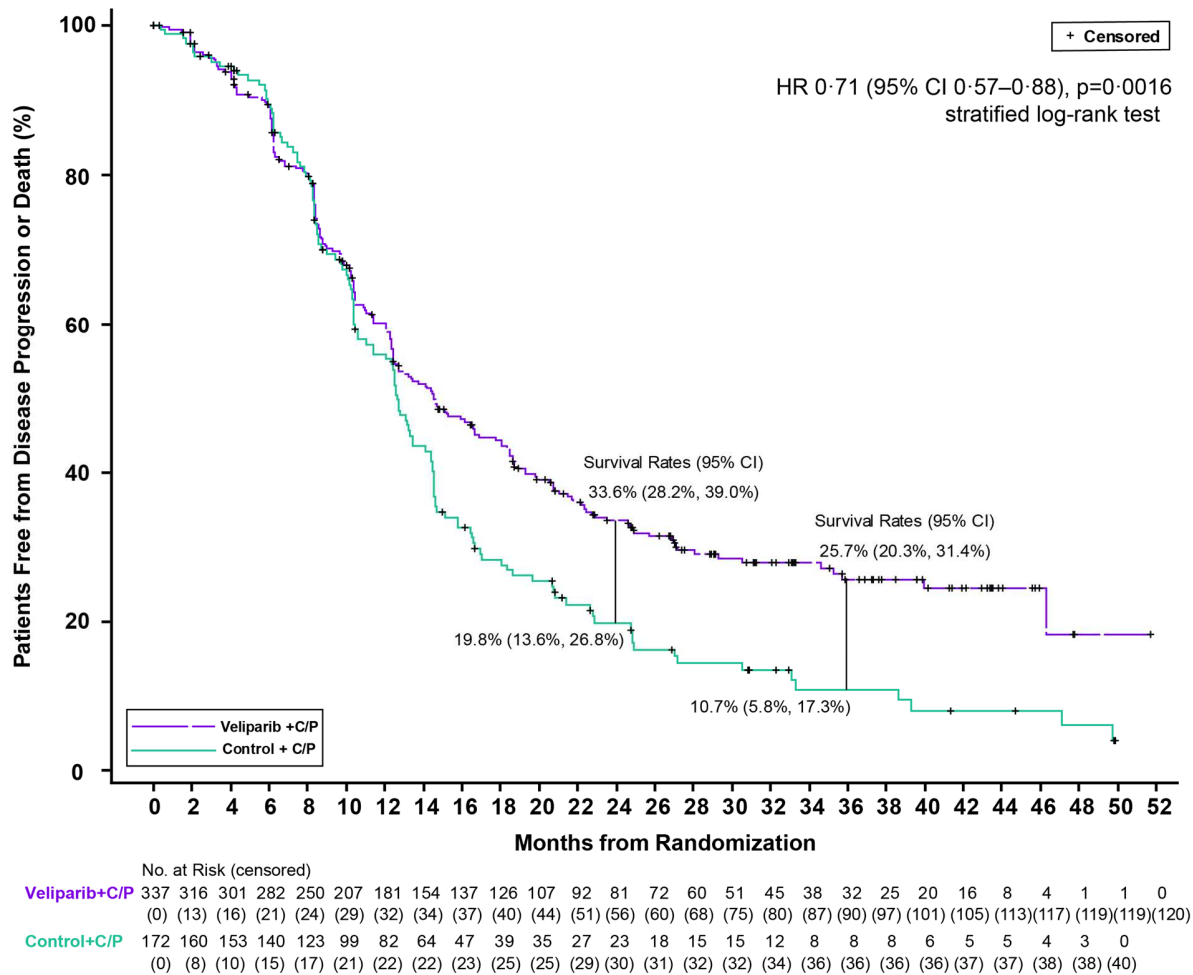
Data are per investigator assessment.

*Includes patients with at least one measurable disease per investigator.

†Includes patients with at least one measurable disease at baseline. Patients who never experienced a confirmed PR or CR are not included in the analysis.

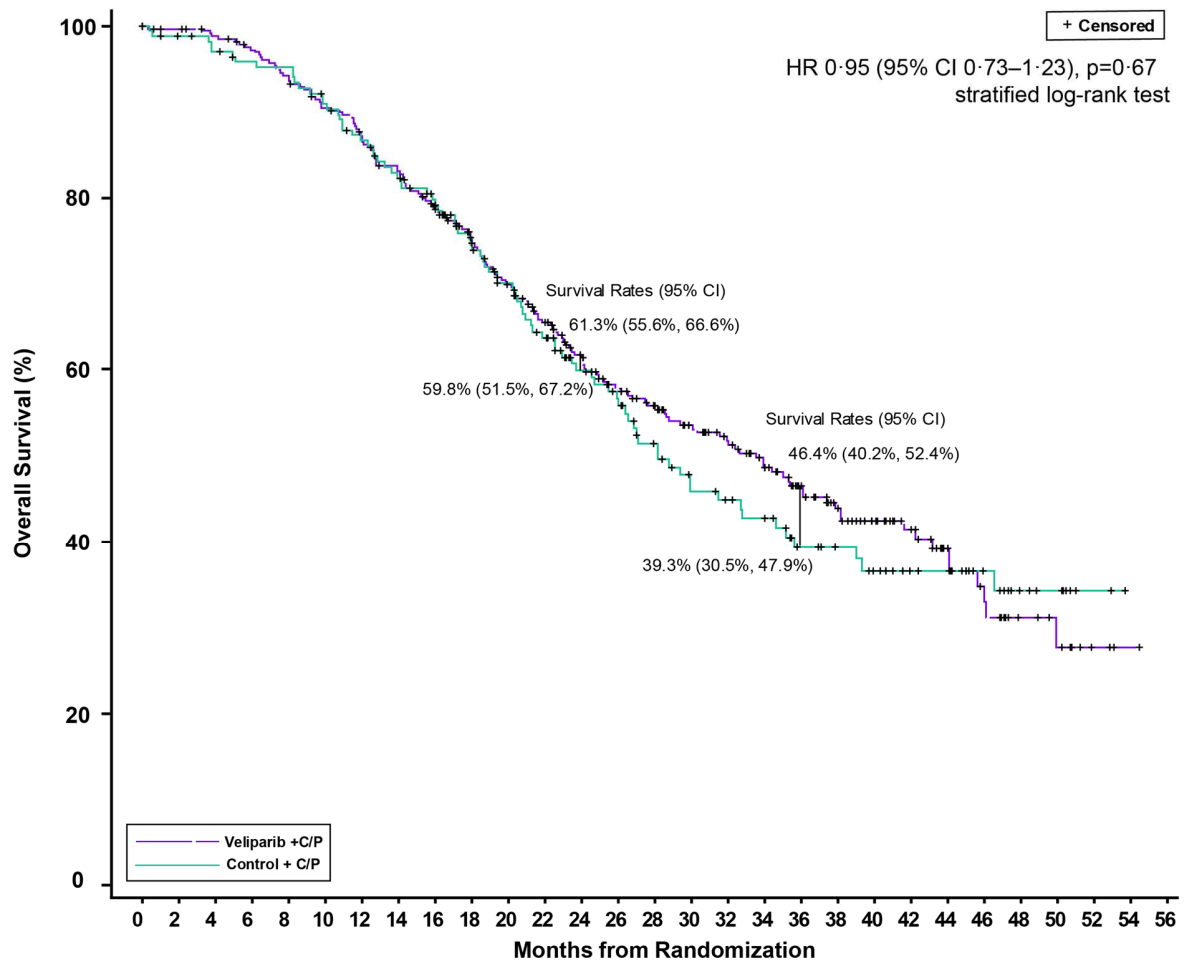
Figure 1. Kaplan Meier Analysis of Progression-free Survival and Overall Survival

A. PFS by Investigator Assessment



	No. of events/ No. of patients (%)	Median PFS, months (95% CI)	24-month rate of PFS, % (95% CI)	36-month rate of PFS, % (95% CI)
Veliparib + C/P	217 / 337 (64.4)	14.5 (12.5, 17.7)	34 (28, 39)	26 (20, 31)
Control + C/P	132 / 172 (76.7)	12.6 (10.6, 14.4)	20 (14, 27)	11 (6, 17)

B. Overall Survival



No. at Risk (censored)	
Veliparib+C/P	337 332 326 318 307 294 281 265 247 223 203 185 161 145 132 117 106 90 76 62 50 41 30 18 11 8 3 1 0 (0) (4) (7) (10) (10) (12) (14) (17) (22) (34) (39) (44) (57) (64) (72) (82) (89) (99) (109) (119) (129) (137) (146) (154) (160) (162) (167) (169) (170)
Control+C/P	172 166 162 158 157 149 141 134 125 111 102 90 75 68 57 47 44 40 32 29 25 19 18 15 9 7 2 0 (0) (4) (5) (7) (7) (8) (9) (9) (14) (19) (22) (25) (35) (38) (43) (47) (49) (51) (56) (59) (61) (67) (68) (71) (76) (78) (83) (85)

	No. of events/ No. of patients (%)	Median OS, months (95% CI)
Veliparib + C/P	167 / 337 (49.6)	33.5 (27.6, 37.9)
Control + C/P	87 / 172 (50.6)	28.2 (24.7, 35.2)

Figure 2. Subgroup Analysis of Progression-free Survival

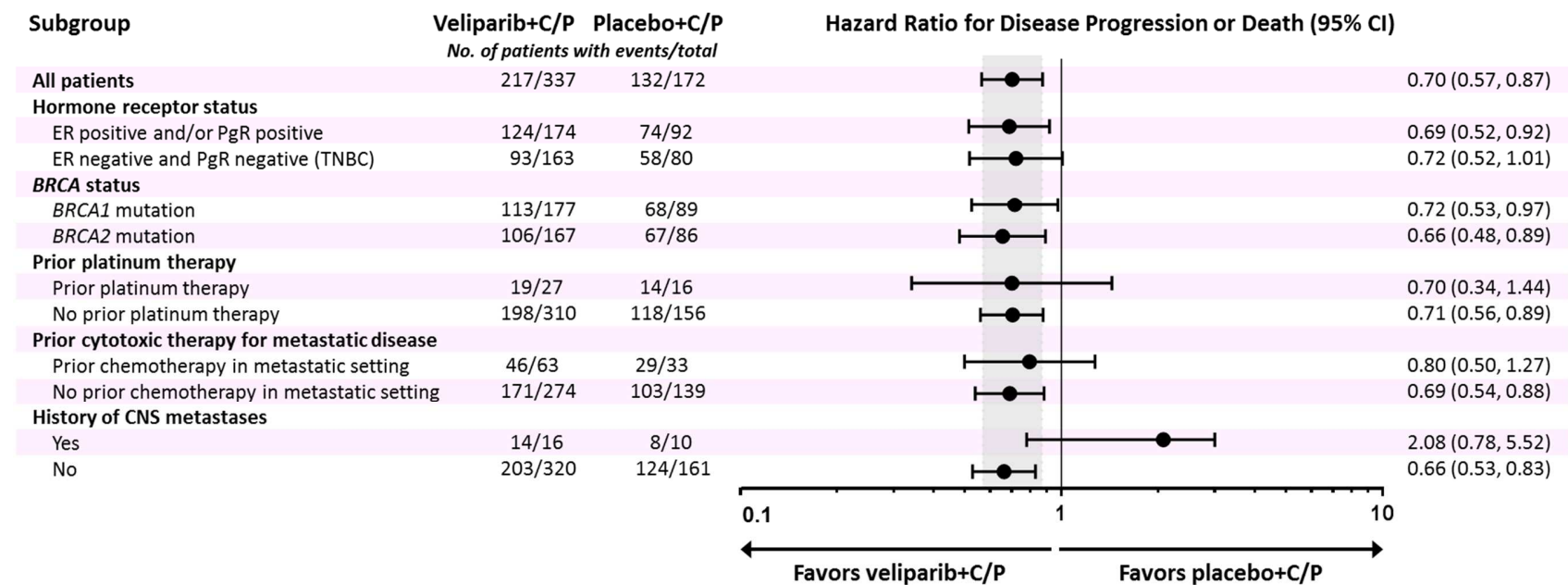


Figure 3.

