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

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

9

10 Institut Curie, Paris, and Centre Eugène Marquis, Rennes, France (V Diéras MD);

11 Moffitt Cancer Center, Tampa, FL, USA (H S Han MD);

12 Sheba Medical Center, Tel Hashomer, and Tel-Aviv University, Tel-Aviv, Israel (B Kaufman
13 MD);

14 Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium (Prof
15 H Wildiers MD);

16 Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia (Prof M
17 Friedlander MBChB);

18 Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada (J P Ayoub MD);

19 UPMC Cancer Centers, Pittsburgh, PA, USA (S L Puhalla MD);

20 Dnipropetrovsk Medical Academy, City Clinical Hospital No.4, Dnipro, Ukraine (Prof I
21 Bondarenko MD);

22 Institut de Cancérologie de l'Ouest -Pays de la Loire, France (Prof M Campone MD);

23 Vejle Hospital/Lillebaelt Hospital, Vejle, Denmark (E H Jakobsen MD);

24 University Medical Center Groningen, University of Groningen, Groningen, The Netherlands (M
25 Jalving MD);

26 University of Medicine and Pharmacy Timisoara; Oncomed SRL, Timisoara, Romania (C
27 Oprean MD);

28 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

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46

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

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52 **SUMMARY**

53 **Background**

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

60 **Methods**

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

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

80 **Findings**

81 Between July 30, 2014 and January 17, 2018, 513 patients were randomised. In the
82 intention-to-treat population, 337 patients were assigned to receive veliparib plus
83 carboplatin/paclitaxel (investigational arm) and 172 to placebo plus
84 carboplatin/paclitaxel (control arm). Median follow-up at data cutoff (April 5, 2019) was
85 35.7 months (IQR 24.9–43.6) in the investigational arm and 35.5 months (IQR 23.1–
86 45.9) in the control arm. The hazard ratio for PFS was 0.71 (95% confidence interval
87 [CI], 0.57–0.88; $p=0.0016$), with median PFS of 14.5 months (95% CI 12.5–17.7) for
88 the investigational arm versus 12.6 months (10.6–14.4) for the control arm. The most
89 common grade 3 or higher adverse events were neutropenia (272 [81%] of 336 patients
90 in the investigational group vs. 143 [84%] of 171 patients in the control group), anemia
91 (142 [42%] vs. 68 [40%]), and thrombocytopenia (134 [40%] vs. 48 [28%]). Serious
92 adverse events occurred in 115 (34%) patients in the investigational arm vs. 49 (29%)
93 patients in the control arm. There were no study drug-related deaths.

94 **Interpretation**

95 Addition of veliparib to a highly active platinum doublet, with continuation as
96 monotherapy if the doublet was discontinued, resulted in significant and durable
97 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

102 **RESEARCH IN CONTEXT**

103 **Evidence before this study**

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

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

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

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

125 with advanced g*BRCA*-associated breast cancer, without substantial additional toxicity
126 or dose intensity reduction in the platinum doublet. These results warranted further
127 study in a larger phase 3 trial.

128

129 **Added value of this study**

130 To our knowledge, BROCADE3 is the first phase 3 study to evaluate a PARP inhibitor
131 with platinum doublet chemotherapy for *BRCA*-associated breast cancer, demonstrating
132 significant improvement in PFS upon the addition of veliparib to carboplatin and
133 paclitaxel, a highly active comparator with a median PFS of over one year. When added
134 to carboplatin and paclitaxel, veliparib more than doubled the proportion of patients alive
135 and progression free at three years. The PFS benefit was similar in patients with TNBC
136 and patients with hormone receptor-positive breast cancer. The addition of veliparib to
137 carboplatin and paclitaxel also resulted in improvement in PFS2 and duration of
138 response. There was no statistically significant difference in overall survival at the
139 planned interim analysis.

140

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

147

148 **Implications of all the available evidence**

149 Deleterious mutations in *BRCA1* or *BRCA2* impair the ability of cancer cells to repair
150 DNA damage via homologous recombination, thereby conferring additional sensitivity to
151 platinum salts and PARP inhibitors. Clinical evidence to date has demonstrated that this
152 vulnerability can be exploited for the treatment of advanced, HER2-negative breast
153 cancer, and has led to the inclusion of both classes of agents in current treatment
154 guidelines. However, reports of the emergence of reversion mutations that restore
155 *BRCA* function in patients treated with either platinum chemotherapy or PARP inhibitors
156 have led to concerns about cross resistance, and for this reason patients who are
157 resistant or refractory to platinum chemotherapy are often excluded from PARP inhibitor
158 clinical trials. Given this concern, combination and maintenance strategies are rational
159 approaches to maximize the therapeutic benefit derived from exploiting pathogenic
160 *BRCA* mutations. BROCADE3 demonstrated for the first time that the combination of a
161 PARP inhibitor, veliparib, with platinum chemotherapy significantly improves PFS with
162 limited additional toxicity in patients with advanced HER2-negative breast cancer and a
163 *BRCA* mutation. The PFS benefit was durable, with a quarter of patients in the veliparib-
164 containing arm alive and progression free at three years. These data suggest that
165 veliparib, in combination with carboplatin and paclitaxel, should be considered as a new
166 treatment option for patients with *BRCA*-associated advanced breast cancer who are
167 candidates for chemotherapy.

168 **INTRODUCTION**

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

176
177 *BRCA1/2* mutated breast cancers have a deficiency in homologous recombination
178 repair of DNA damage, and are known to be sensitive to both PARP inhibitors and
179 platinum agents.⁵⁻⁸ There is a strong scientific rationale to combine PARP inhibitors with
180 platinum chemotherapy based on common mechanisms of sensitivity and acquired
181 resistance,⁹ and observed potentiation of platinum activity by PARP inhibitors
182 preclinically.¹⁰ However clinical application of these combinations has been
183 challenging,^{11,12} largely due to hematologic toxicity.¹³⁻¹⁴

184
185 Veliparib (ABT-888) is a potent, orally bioavailable, selective PARP1/2 inhibitor¹⁰ that
186 has shown antitumour activity and acceptable toxicity as a single-agent and in
187 combination with carboplatin and paclitaxel.^{15,16} Veliparib selectively inhibits the
188 polymerase activity of PARP without substantial trapping of PARP protein onto DNA
189 damage repair intermediates.^{17,18} This makes veliparib more suitable than other PARP
190 inhibitors to be administered in combination with platinum-based chemotherapy, as

191 PARP trapping has been shown to be associated with myelosuppression.¹⁹ In a
192 randomised, placebo-controlled phase 2 study (BROCADE), numerical (though not
193 statistically significant) increases in median PFS and OS were observed with the
194 addition of veliparib to carboplatin and paclitaxel versus carboplatin and paclitaxel alone
195 in patients with *BRCA*-mutated advanced breast cancer. The safety profile was
196 comparable between arms, with common adverse events generally hematologic and
197 gastrointestinal.²⁰ Here, we report results from BROCADE3, a phase 3 trial comparing
198 veliparib versus placebo in combination with carboplatin and paclitaxel, and continued
199 as monotherapy if carboplatin and paclitaxel are discontinued prior to progression, in
200 patients with HER2-negative inoperable locally advanced or metastatic breast cancer
201 with *BRCA1* or *BRCA2* germline mutation.

202

203 **METHODS**

204 ***Study design and participants***

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

207

208 Patients (≥ 18 years of age) with metastatic or locally advanced unresectable HER2-
209 negative breast cancer and suspected deleterious or deleterious *gBRCA1/2* mutations
210 and an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled.
211 Patients had adequate hematologic, renal, and hepatic function (absolute neutrophil
212 count ≥ 1500 cells per mm^3 , platelet count $\geq 100,000$ cells per mm^3 , haemoglobin ≥ 95
213 g/L, serum creatine ≤ 1.5 times the upper limit of normal (ULN) or creatine clearance ≥ 50

214 mL/min/1.73 m², bilirubin ≤1.5 times the ULN, aspartate aminotransferase and alanine
215 transaminase concentrations ≤2.5 times the ULN, activated partial thromboplastin time
216 ≤1.5 times the ULN, and international normalized ratio <1.5). All patients were tested for
217 g*BRCA1/2* mutations by the core lab. Patients with g*BRCA1/2* mutations based on local
218 testing were eligible but retesting by the core laboratory was required. Patients had
219 received ≤2 prior lines of cytotoxic chemotherapy for metastatic breast cancer, and ≤1
220 prior line of platinum therapy without progression within 12 months of completing
221 treatment. Patients could have prior taxane for neo-adjuvant/adjuvant therapy or to treat
222 locally advanced disease, if given >6 months before study start. Prior taxane for
223 metastatic breast cancer was not allowed unless it was administered without
224 progression >12 months before study start. Prior treatment with targeted agents was
225 allowed except for prior PARP inhibitor therapy. Hormone receptor-positive patients and
226 patients with bone-only metastases were to be considered appropriate candidates for
227 combination chemotherapy. Patients with active brain metastases, leptomeningeal
228 disease, history of uncontrolled seizure disorder, pre-existing neuropathy exceeding
229 grade 1, or previous or concurrent cancer distinct from breast cancer were not included
230 in this study. Also any patients with clinically significant uncontrolled active infection,
231 symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia,
232 myocardial infarction within 6 months before randomisation, hepatitis B or C,
233 uncontrolled hypertension, or major surgery within 3 weeks of randomisation were
234 excluded. Additional eligibility criteria are in the protocol (p.3-6).

235

236 The study was conducted according to the protocol approved by institutional review
237 boards at investigational sites, International Conference on Harmonization Good Clinical
238 Practice guidelines, regulations governing clinical study conduct, and ethical principles
239 with their origin in the Declaration of Helsinki. All patients provided written informed
240 consent. An independent data monitoring committee reviewed safety data.

241

242 ***Randomisation and masking***

243 Patients were prospectively randomised in a 2:1 ratio to carboplatin and paclitaxel with
244 veliparib (investigational arm) or carboplatin and paclitaxel with placebo (control arm) by
245 an interactive response technology (IRT) system using permuted blocks within strata.
246 Variable block sizes of 3 and 6 were used. Randomisation in a 2:1 ratio was intended to
247 facilitate recruitment of this patient population with a rare biomarker. Randomisation was
248 stratified according to estrogen and/or progesterone receptor expression (positive or
249 negative), prior platinum therapy (yes or no), and history of CNS metastases (yes or no).
250 The randomisation schedule was created by the AbbVie statistics department and
251 forwarded to a third-party vendor to be implemented via the IRT system.

252

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

258

259 ***Procedures***

260 Patients received veliparib (120 mg p.o. BID) or placebo (capsules matching
261 veliparib capsules BID) on Days –2 to 5, carboplatin (C; AUC 6 mg/mL/min IV) on Day
262 1, and paclitaxel (P; 80 mg/m² IV) on Days 1, 8, and 15 (21-day cycles) until disease
263 progression or unacceptable toxicity. Any of the three agents could be dose reduced or
264 discontinued individually at the discretion of the investigator to manage toxicity (protocol
265 p.91-94). The dose of blinded study drug could be reduced to 80 or 40 mg. The dose of
266 C could be reduced to AUC 5 or 4, and the dose of P could be reduced to 70 or 60
267 mg/m². Treatment interruptions were required if hematologic parameters were below
268 protocol-specified thresholds (absolute neutrophil count of ≥ 1500 cells per mm³, platelet
269 count of $\geq 100,000$ cells per mm³ on cycle day 1) or in the event of grade 3 or higher
270 toxicity. Patients discontinuing both carboplatin and paclitaxel for reasons other than
271 disease progression received continuous single-agent veliparib or placebo at 300 mg
272 BID, increasing to 400 mg BID if tolerated. Patients in the control arm could receive
273 crossover open-label veliparib monotherapy after disease progression.

274

275 CT or MRI of the full chest, abdomen, and pelvis, and brain MRI or contrast CT,
276 occurred at screening (within 28 days of randomization) and every 9 weeks thereafter
277 until disease progression. Post-baseline brain MRI or contrast CT was required only for
278 patients with CNS lesions at baseline. Evaluation of tumour response was done by both
279 the local investigator and by blinded independent central review (BICR). Subsequent
280 treatment and survival information was collected every 2 months until death or loss to
281 follow-up. Laboratory evaluations included haematology and blood chemistry, and were

282 done at day -2 of cycle 1, days 1, 8, and 15 of each treatment cycle, the final visit, and
283 the 30-day follow-up visit. Patients were assessed for adverse events on the same
284 schedule. Adverse events were graded according to the National Cancer Institute
285 Common Terminology Criteria for Adverse Events, version 4.03. Patient-reported
286 outcomes (PROs) questionnaires were administered pre-dose at day -2 and day 1 of
287 cycle 1, day 1 of every other cycle thereafter beginning with cycle 2, final visit, and at
288 follow-up visit (appendix p.60). Eastern Cooperative Oncology Group (ECOG)
289 performance status was evaluated at day 1 of each cycle, final visit, and follow-up visit.

290

291 ***Outcomes***

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

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

306

307 ***Statistical analysis***

308 The trial sought to enroll 500 patients to accrue 344 PFS events to provide $\geq 90\%$ power
309 at a 2-sided alpha level of 0.05 (assuming a hazard ratio of 0.69) to detect a statistically
310 significant treatment effect. The sample size was increased to 500 patients on June 17,
311 2016 due to a pre-planned blinded sample size re-estimation based on the hazard ratio
312 observed in the phase 2 BROCADE study²⁰ for which data became available during the
313 course of the current study. Efficacy analyses were performed on the intent-to-treat
314 population, which included all randomised patients with a suspected deleterious or
315 deleterious *BRCA* mutation per the core laboratory (Myriad BRACAnalysis CDx assay).
316 Safety analyses included all patients who received at least one dose of
317 veliparib/placebo. Data-cutoff for the primary analysis was April 5, 2019.

318

319 For the primary analysis, between-group differences were determined with a two-sided
320 log-rank test, stratified by prior platinum therapy (yes, no) and hormone receptor status
321 (ER and/or PgR positive, ER/PgR negative). History of CNS metastases was not
322 included as stratification factor in the analysis as few patients were anticipated to have a
323 history of CNS metastases. Statistical significance was measured using a two-sided α of
324 0.05. Hazard ratios and 95% confidence intervals were estimated using a stratified Cox
325 proportional hazard model. The Kaplan-Meier method was used to generate time-to-

326 event curves and calculate landmark values including medians and the proportion of
327 patients alive and progression free at 24 and 36 months. If statistical significance was
328 shown for the primary endpoint analysis of PFS per investigator, secondary end points
329 were to be tested using a fixed-sequence testing procedure in the following order: OS,
330 CBR, ORR, and PFS2. Duration of overall response was changed from a secondary
331 endpoint to a tertiary endpoint on May 30, 2019 prior to database lock for the primary
332 analysis. Interim OS was analyzed at the time of primary PFS analysis as part of a pre-
333 planned analysis. The final OS analysis is planned when 357 events have been
334 observed. Hazard ratios (HR) were estimated using stratified Cox regression model.
335 PFS per BICR was exploratory. Results of investigator-assessed PFS for pre-specified
336 sub-groups are also presented. PROs are reported as mean change from baseline to
337 each scheduled post-baseline visit for the EORTC QLQ-C30 (overall and domain-
338 specific scores), EORTC QLQ-BR23 (domain-specific scores), Brief Pain Inventory
339 (pain interference and overall severity) and EQ-5D-5L (visual analog scale and health
340 index score) questionnaires.

341

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

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

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

356 **Role of the funding source**

357 AbbVie Inc. provided financial support for this study and participated in the design,
358 study conduct, analysis and interpretation of the data, as well as the writing, review, and
359 approval of this manuscript. All authors had access to full data and vouch for its integrity
360 and completeness and were responsible for writing the manuscript, with editorial
361 assistance funded by AbbVie. All authors reviewed draft and final versions of the
362 manuscript prior to submission and have approved the final manuscript. The
363 corresponding author had the final responsibility to submit for publication.

364

365 **RESULTS**

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

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

377

378 Patients in the investigational arm remained on blinded study drug longer than those in
379 the control arm, with means (SD) of 237 (272) and 181 (209) treatment days,
380 respectively (excludes non-treatment days during intermittent study drug dosing in
381 combination with carboplatin and paclitaxel). A subset of patients discontinued
382 carboplatin and paclitaxel prior to disease progression and received blinded study drug
383 monotherapy. This included 40.5% (136/336) of patients in the investigational arm and
384 33.9% (58/171) of patients in the control arm. Mean (SD) overall duration of blinded
385 monotherapy in these patients was 350 (318) vs 252 (263) days, in the investigational
386 and control arms, respectively (**Table S2**). Chemotherapy exposure prior to transitioning
387 to blinded monotherapy was highly variable (**Fig.S2**), with the most frequent point of
388 transition being after six cycles of combination therapy. Among patients receiving
389 monotherapy, 31% (42/136) in the investigational arm and 55% in the control arm
390 (32/58) escalated the dose of blinded study drug from 300 mg BID to 400 mg BID. At
391 the time of data-cutoff, 192 (57%) of 337 patients in the investigational arm and 121
392 (70%) of 171 in the control arm had discontinued study drug due to disease
393 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)

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

432

433 In a pre-planned interim analysis, median overall survival was 33.5 months (95% CI
434 27.6–37.9) for the investigational arm and 28.2 months (95% CI 24.7–35.2) for the
435 control arm (HR 0.95, 95% CI 0.73–1.23; $p=0.667$; 167 [50%] events in 337 patients vs.
436 87 [51%] events in 172 patients) **(Fig.1B)**. At the time of analysis, 44% of patients
437 randomised to the control arm had received open label veliparib (crossover) as first
438 subsequent therapy. Per investigator assessment, clinical benefit rate (95% CI) was
439 estimated as 90.7% (87.9–92.9) for the investigational arm and 93.2% (89.5–95.7) for

440 the control arm. ORR (95% CI) was 75.8% (70.4–80.6) versus 74.1% (66.1–81.1)
441 (**Table 3**). Among patients with a confirmed complete or partial response, duration of
442 response was 14.7 months (95% CI 12.1–18.7) vs 11.0 months (95% CI 10.2–12.3)
443 (**Fig.S4**). Median PFS2 was 21.3 (19.8–25.1) months for the investigational arm and
444 17.4 (16.0–20.0) months for the control arm (HR 0.76, 95% CI 0.60–0.96; nominal
445 $p=0.020$; 196 [58%] events in 337 patients vs. 114 [66%] events in 172 patients)
446 (**Fig.S5**). **Table S5** summarizes subsequent therapies. Changes from baseline in ECOG
447 performance status at each cycle were generally comparable between treatment arms
448 (**Fig.S6**).

449

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

461

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

468

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

475

476 Adverse events were evaluated for the entire veliparib/placebo treatment period
477 including both combination therapy and monotherapy if applicable, and separately
478 during the blinded monotherapy period only in the applicable subset of patients.

479

480 Common adverse events occurring more frequently (absolute difference of $\geq 5\%$) in the
481 investigational arm vs control arm during the entire blinded treatment period were
482 thrombocytopenia, anemia, nausea, and diarrhea; peripheral sensory neuropathy
483 occurred less frequently in the investigational arm (**Table 2**). Serious adverse events
484 (**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

531 veliparib vs placebo was seizure (3 [2.2%] of 136 patients vs 0 of 58) (**Table S6**). One
532 patient experiencing a seizure event had a history of CNS metastases. The seizure
533 events (all grade 2) occurred after approximately 1 year of veliparib 400 mg BID in 2
534 patients (1 of whom inadvertently took a second dose of 400 mg later the same morning
535 on the day of the event) and after the initial dose of 300 mg in another patient. Two
536 patients resumed veliparib monotherapy at a reduced dose (300 mg BID) after
537 treatment with levetiracetam and continued until disease progression (6-9 months later)
538 without another seizure event. During blinded single agent veliparib/placebo exposure,
539 grade 5 AEs occurred in 2 patients (1.5%; 1 malignant neoplasm progression, 1 sepsis)
540 receiving veliparib and none receiving placebo. No grade 5 AEs were considered
541 related to study drug by the investigator.

542

543 **DISCUSSION**

544 BROCADE3 is the first phase 3 clinical trial to evaluate a PARP inhibitor in combination
545 with platinum-based chemotherapy in patients with metastatic breast cancer. When
546 added to carboplatin and paclitaxel, and continued as monotherapy if carboplatin and
547 paclitaxel are discontinued before disease progression, veliparib resulted in durable
548 improvement in PFS, with benefit evident at the 2-year and 3-year landmarks, in
549 patients with advanced HER2-negative breast cancer and a germline *BRCA1/2*
550 mutation. These results are noteworthy given the high activity of the
551 carboplatin/paclitaxel control arm, for which median PFS was greater than 1 year.
552 Overall survival was not yet mature at the time of the primary analysis, and the results
553 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

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

585

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

594

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

600 the transition indeed contributes to nonproportionality. It is noteworthy that the
601 estimated HR for combination therapy is nearly identical to that observed in the phase 2
602 BROCADE study, which compared C/P with veliparib to C/P with placebo in a similar
603 patient population and did not allow treatment with veliparib/placebo monotherapy.²⁰
604 Collectively, these results suggest that the overall PFS benefit observed in BROCADE3
605 is derived both from the inclusion of veliparib with C/P and from the continuation of
606 veliparib monotherapy when chemotherapy is discontinued prior to disease progression.
607 However, these HR estimates cannot be interpreted as isolating the treatment effect for
608 each treatment phase because all patients receiving veliparib monotherapy did so after
609 first receiving veliparib in combination with C/P. Moreover, the subset of patients
610 receiving monotherapy does not represent a randomized sample, and the decision to
611 transition (and the variable timing thereof) may be influenced in part by depth and
612 duration of response to combination therapy. The inability to isolate the treatment effect
613 during combination therapy and monotherapy is a limitation of the study design.

614

615 Another limitation of the trial is that it does not allow for the identification of the optimal
616 duration of combination therapy with veliparib and cytotoxic chemotherapy before
617 transitioning to single agent veliparib. The potential for veliparib to maintain responses
618 after a fixed duration of veliparib, carboplatin, and paclitaxel warrants further
619 investigation, as this strategy would represent a paradigm shift in the treatment of
620 metastatic breast cancer, akin to recently validated strategies in ovarian cancer.²²

621

622 The potential for crossover to confound interpretation of the PFS2 analysis is another
623 limitation, particularly if treatment with platinum chemotherapy during the blinded portion
624 of the trial led to resistance to subsequent PARP inhibitor therapy in some patients. The
625 sequencing of PARP inhibitors and platinum chemotherapy requires further
626 investigation.

627

628 The results of this trial indicate that veliparib, in combination with C/P and continued as
629 monotherapy after discontinuation of chemotherapy, is a compelling treatment option for
630 patients with advanced HER2-negative breast cancer and a germline *BRCA* mutation
631 who are candidates for cytotoxic chemotherapy. This population includes patients with
632 TNBC and those with hormone-receptor positive metastatic breast cancer. Although the
633 role of cytotoxic chemotherapy differs between these two patient subgroups, treatment
634 guidelines converge in cases where hormone-receptor positive patients are no longer
635 candidates for endocrine therapy. Treatment guidelines generally recommend
636 sequential single-agent chemotherapy, however the durable PFS and OS observed with
637 the control regimen in this trial and the phase 2 BROCADE trial suggest that the
638 carboplatin/paclitaxel combination may provide unique benefit to this particular group of
639 patients.²⁰

640

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

645 carboplatin and *nab*-paclitaxel experienced a median PFS of 8.3 months and a median
646 OS of 16.8 months. In addition, a growing body of evidence supports the use of
647 platinum chemotherapy in patients with advanced TNBC and a germline *BRCA1/2*
648 mutation.^{7,8,20,23} Studies of single-agent platinum chemotherapy reported median PFS of
649 3.3–6.8 months,^{7,8} and OS of 13.7 months.⁸ The median PFS of 16.6 months and
650 median OS of 35 months observed in the TNBC subgroup of BROCADE3 suggest that
651 combination therapy with veliparib, carboplatin and paclitaxel may improve long-term
652 outcomes relative to sequential single-agent therapy for this patient population with
653 more limited treatment options and poorer prognosis compared to other breast cancer
654 subtypes.

655

656 In hormone receptor-positive breast cancer, established guidelines^{21,24} indicate that
657 chemotherapy is most appropriate in patients who are not candidates for endocrine
658 therapy, and combination chemotherapy should generally be reserved for those with
659 visceral metastases or rapidly progressive disease. Real world evidence indicates that
660 the usage of chemotherapy, including combination regimens, is more common in early
661 lines than might be expected according to these guidelines.²⁵ This is consistent with the
662 observation in this study that only 65% of hormone-receptor positive patients enrolled
663 had prior endocrine therapy. Of note, CDK4/6 inhibitors were largely unavailable in most
664 participating countries during enrollment of this trial and in some participating countries
665 endocrine therapy options are limited in premenopausal women. Treatment utilization
666 patterns should continue to evolve, given recent evidence demonstrating an OS benefit
667 with the addition of CDK4/6 inhibitors to endocrine therapy, along with the previously

668 reported PFS benefit and manageable safety profile.²⁶ However, limited information
669 exists regarding the benefits of these therapies in patients with hormone receptor-
670 positive breast cancer associated with a germline *BRCA* mutation. Although more
671 research is required to further define the appropriate role of chemotherapy in these
672 patients, endocrine therapy with or without a CDK4/6 inhibitor remains the standard of
673 care for eligible patients. For patients who are no longer candidates for endocrine
674 therapy with or without CDK4/6 inhibitors, those with *BRCA*-associated hormone
675 receptor-positive metastatic breast cancer may be suitable for combination
676 chemotherapy, because they are more likely to have tumours with aggressive luminal B
677 features²⁷ and are often younger with fewer comorbidities. The veliparib and
678 carboplatin/paclitaxel regimen may be a beneficial option for this group of patients, in
679 whom a median PFS and OS of 13.0 months and 32.4 months was observed. Further
680 characterization of this subgroup, including those with no prior endocrine therapy, would
681 be of interest.

682

683 Two recent phase 3 trials have supported regulatory approvals of the PARP inhibitors
684 olaparib and talazoparib as monotherapy for treatment of patients with HER2-negative
685 advanced breast cancer and g*BRCA1/2* mutations, based on improved PFS when
686 compared to physicians' choice of single-agent chemotherapy.^{5,6} Notably, these trials
687 did not include platinum amongst the comparator therapies, and the objective response
688 rates (60–63%) and median PFS (7.0–8.6 months) reported for PARP inhibitor
689 monotherapy were comparable to previously reported data for carboplatin monotherapy
690 in g*BRCA1/2* mutation positive patients with TNBC.⁷ As such, it remains an unanswered

691 question whether PARP inhibitor monotherapy is superior to single-agent platinum
692 chemotherapy. Also unknown is the optimal sequence of PARP inhibitors and platinum-
693 based chemotherapy in patients with g*BRCA1/2* mutations. In cells with *BRCA*
694 mutations, treatment with platinum agents or PARP inhibitors has been shown to
695 produce *BRCA*-reversion mutations, which can restore function and mediate treatment
696 resistance.²⁸ As such, combining platinum and PARP inhibitors may be a rational
697 strategy to allow patients to benefit from both agents before developing cross-
698 resistance. Accordingly, while median overall survival reported for a subgroup of
699 patients receiving single-agent olaparib for first-line treatment of *BRCA*-associated
700 advanced breast cancer was 14.7 months,²⁹ the median overall survival observed in the
701 interim analysis for veliparib plus carboplatin/paclitaxel in the BROCADE3 study was
702 33.5 months, suggesting the treatment strategy under investigation in this study may
703 provide a promising alternative to conventional sequential single-agent therapy with
704 PARP inhibitors and chemotherapy.

705

706 In the phase 3 BrightNess trial,³⁰ the addition of veliparib to neoadjuvant chemotherapy
707 with C/P, followed by doxorubicin and cyclophosphamide, did not improve the frequency
708 of pathological complete response in patients with early stage TNBC, with similar results
709 in the subgroup of patients with g*BRCA1/2* mutations. These results are consistent with
710 the observation that the addition of veliparib did not improve the high objective response
711 rate observed with C/P in BROCADE3. Follow up for event-free survival in BrightNess
712 is ongoing and it remains to be determined if the long-term benefit observed in
713 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
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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
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756 **MP:** Received fees as the speaker from Pfizer, Roche, Eisai.

757 **YHP:** Consultancy or advisory board member for AstraZeneca, Pfizer, Eisai and Novartis
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759 **YS:** Advisory Board: Pfizer; Speaker: Roche, AstraZeneca, Pfizer; Research /Clinical studies:
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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

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776

777 **AVAILABILITY OF DATA AND MATERIAL**

778 AbbVie is committed to responsible data sharing regarding the clinical trials we
779 sponsor. This includes access to anonymized, individual and trial-level data (analysis
780 data sets), as well as other information (e.g., protocols and Clinical Study Reports), as
781 long as the trials are not part of an ongoing or planned regulatory submission. This
782 includes requests for clinical trial data for unlicensed products and indications.
783 This clinical trial data can be requested by any qualified researchers who engage in
784 rigorous, independent scientific research, and will be provided following review and
785 approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a
786 Data Sharing Agreement (DSA). Data requests can be submitted at any time and the
787 data will be accessible for 12 months, with possible extensions considered. For more
788 information on the process, or to submit a request, visit the following link:
789 [https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-](https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html)
790 [sharing/data-and-information-sharing-with-qualified-researchers.html](https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html).

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880 **Figure Legends**

881

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

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

888

889

890 **Figure 2. Subgroup Analysis of Progression-free Survival.**

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

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

897

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

900 Mean change from baseline (with standard error bars) is shown for each treatment arm.
901 Score was determined on Day 1 of Cycles shown on X-axis. Number of observations for
902 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.

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		
<i>BRCA1</i> mutation positive	177 (52.5)	89 (51.7)
<i>BRCA2</i> 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

911

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

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

927 **Table 3. Additional Efficacy Analyses**

928

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)

929

930 CR, complete response; ORR, objective response rate; PFS2, time from randomization

931 until disease progression on subsequent therapy or death; PR, partial response.

932 Data are per investigator assessment.

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

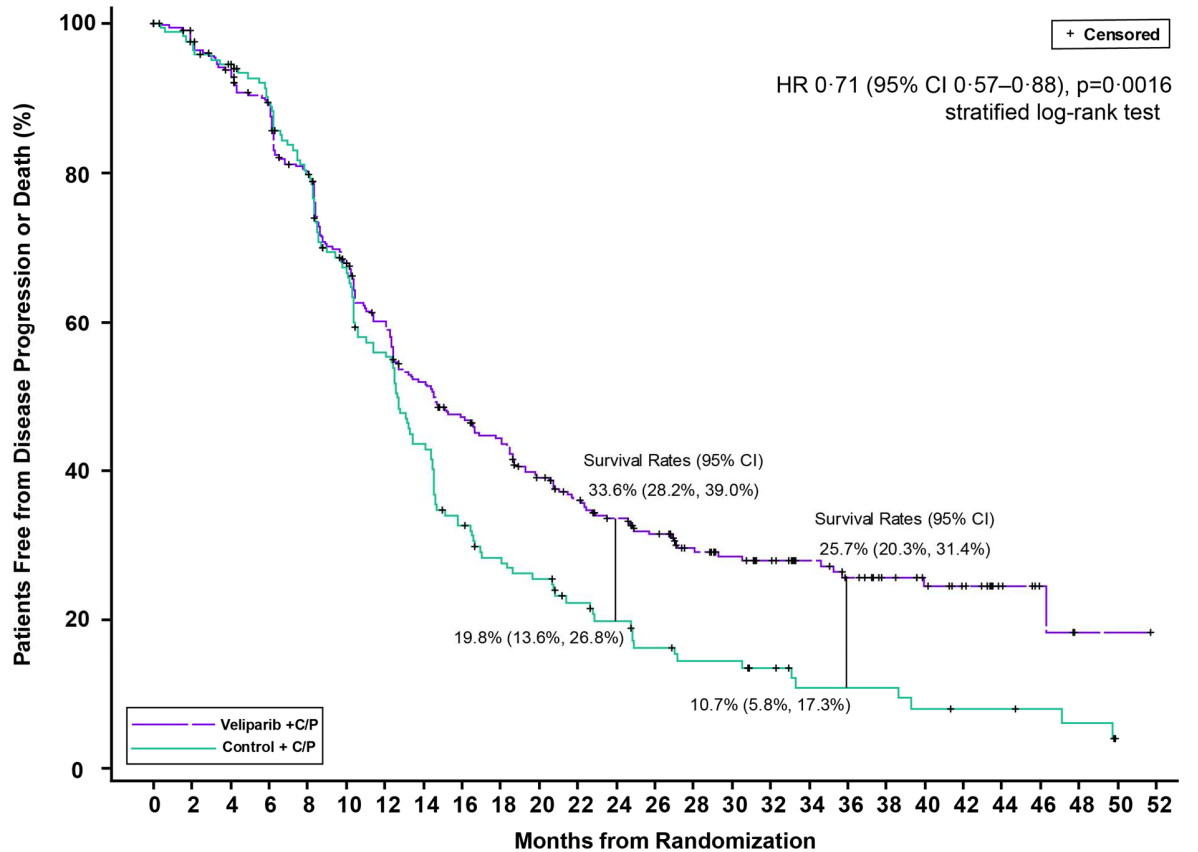
934 †Includes patients with at least one measurable disease at baseline. Patients who never

935 experienced a confirmed PR or CR are not included in the analysis.

936

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

938 **A. PFS by Investigator Assessment**



No. at Risk (censored)

Veliparib+C/P	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0
	(0)	(13)	(16)	(21)	(24)	(29)	(32)	(34)	(37)	(40)	(44)	(51)	(56)	(60)	(68)	(75)	(80)	(87)	(90)	(97)	(101)	(105)	(113)	(117)	(119)	(119)	(120)
Control+C/P	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0	
	(0)	(8)	(10)	(15)	(17)	(21)	(22)	(22)	(23)	(25)	(25)	(29)	(30)	(31)	(32)	(32)	(34)	(36)	(36)	(36)	(36)	(36)	(37)	(37)	(38)	(38)	(40)

939

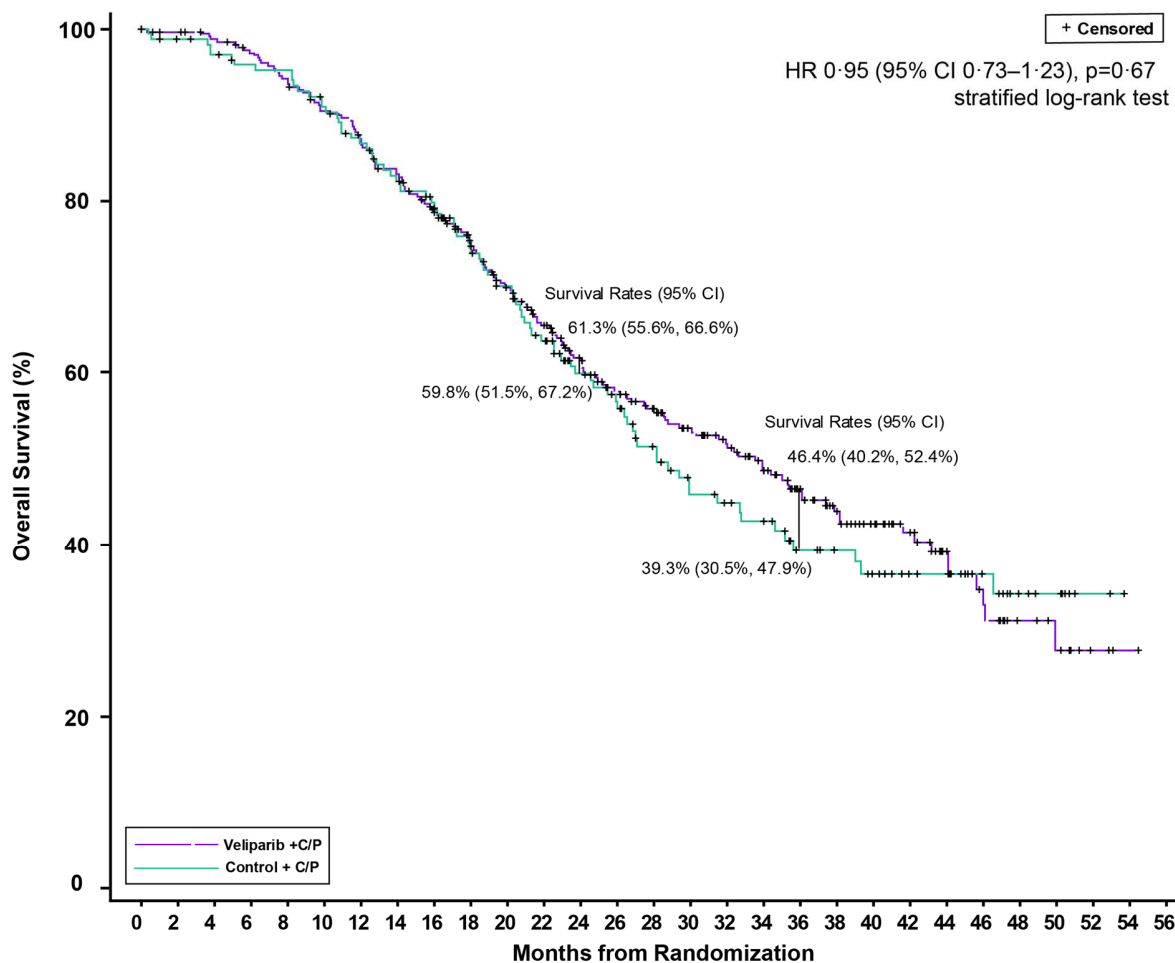
	No. of events/ No. of patients (%)	Median PFS, months (95% CI)	24-month rate of PFS, % (95% CI)	36-month rate of PFS, % (95% CI)
Veliparib + C/P	217 / 337 (64.4)	14.5 (12.5, 17.7)	34 (28, 39)	26 (20, 31)
Control + C/P	132 / 172 (76.7)	12.6 (10.6, 14.4)	20 (14, 27)	11 (6, 17)

940

941

942

943 **B. Overall Survival**



No. at Risk (censored)

Time (Months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	54	56
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
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	

944

945

	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)

946

Figure 2. Subgroup Analysis of Progression-free Survival

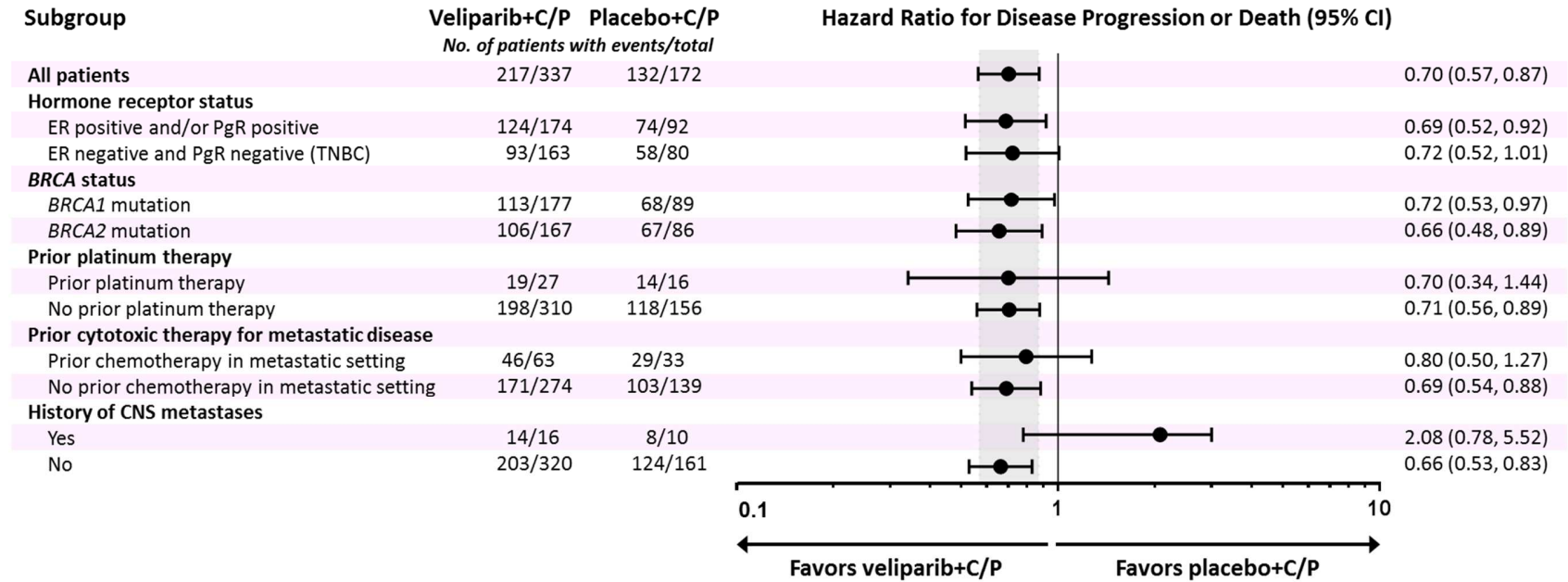


Figure 3.

