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ORIGINAL ARTICLE

Exposure–response analysis to inform the optimal dose of veliparib in combination with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer patients

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Abstract

Purpose Veliparib, a poly(ADP-ribose)-polymerase (PARP) 1 and 2 enzyme inhibitor, was administered at 120 mg twice daily (BID) for 7 days in a 21-day cycle with carboplatin/paclitaxel in the Phase 2 BROCADE study in patients with BRCA-deficient recurrent or metastatic breast cancer, a dose based on Phase 1 results. Population pharmacokinetic (PK) and exposure–response analyses were undertaken to retrospectively evaluate whether an optimal dose was used in BROCADE.
Methods A population PK analysis was performed using data from 168 patients in BROCADE along with data from 288 subjects in another 5 studies. The relationship between veliparib exposure and efficacy variables (including progression-free survival [PFS] and objective response rate [ORR]) and safety variables (selected grade 3 or greater hematological adverse events) were analyzed.
Results Veliparib PK parameters in BROCADE were comparable to the previous studies. Creatinine clearance on veliparib apparent clearance and lean body weight on veliparib apparent volume of distribution were identified as covariates. A trend of better efficacy (PFS and ORR) in the veliparib arm compared to placebo was observed. However, veliparib exposure-efficacy response was relatively flat with higher veliparib exposures not showing better efficacy. No exposure–response relationship was observed in grade 3 or greater hematological toxicities (anemia, neutropenia, leukopenia, and thrombocytopenia).
Conclusions The exposure–response analysis suggested that intermittent 7-day veliparib 120 mg BID dosing in a 21-day cycle provided additional efficacy without meaningfully impacting the safety and tolerability when co-administered with carboplatin and paclitaxel in patients with BRCA-deficient breast cancer. A higher dose of veliparib is unlikely to provide greater benefit in this combination in patients with BRCA-deficient recurrent or metastatic breast cancer.

Keywords Veliparib · Exposure–response · Breast cancer · Carboplatin · Paclitaxel

Introduction

Poly(ADP-ribose)-polymerase (PARP) is a nuclear enzyme that facilitates deoxyribonucleic acid (DNA) repair by recognizing DNA damage, and also plays a role in cell proliferation, differentiation, and transformation [1–3]. Veliparib (ABT-888) is an orally bioavailable, potent, small molecule inhibitor of the PARP1 and PARP2 enzymes.

Preclinical evidence has revealed synergistic anticancer activity of PARP inhibitors with DNA alkylating and platinum agents [4]. A number of clinical studies have been conducted to evaluate the ability of veliparib to potentiate the efficacy of DNA-damaging chemotherapy in indications with underlying defects in DNA-damage repair, including BRCA-mutated breast cancer and ovarian cancer, and broader indications including colorectal, triple negative breast,

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and lung cancers (e.g., NCT02163694, NCT02470585, NCT01051596, NCT02921256, NCT02106546) [5, 6].

The BROCADE study (NCT01506609) was a randomized, partially blinded Phase 2 study to evaluate the efficacy and tolerability of veliparib in combination with temozolomide (TMZ) or in combination with carboplatin/paclitaxel compared with placebo plus carboplatin/paclitaxel in patients with *BRCA*1 or *BRCA*2 deleterious mutation and locally recurrent or metastatic breast cancer [6]. The dose regimen of veliparib with carboplatin/paclitaxel, 120 mg twice daily (BID) on days 1–7 in every 21-day cycle, was selected based on the tolerability and preliminary evidence of efficacy of veliparib in combination with carboplatin/paclitaxel from several Phase 1 studies [7]. While the highest tolerable veliparib dose in this combination was 150 mg BID at the start of the BROCADE study, a more recent Phase 1 study in patients with non-small cell lung cancer suggested that a veliparib dose as high as 240 mg BID was tolerable in combination with carboplatin (AUC 6)/paclitaxel (200 mg/m^2) [8]. The maximum tolerated dose of veliparib maintenance monotherapy was 400 mg BID in patients with ovarian cancer [9]. To evaluate whether an optimal veliparib dose was selected for the BROCADE study, an exposure–response analysis was conducted following the completion of the study.

Materials and methods

Study design and patient population

The BROCADE study was a Phase 2 randomized, partially blinded study to evaluate the efficacy and tolerability of veliparib in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in subjects with *BRCA1* or *BRCA2* mutation and locally recurrent breast cancer or metastatic breast cancer who have received not more than two prior lines of cytotoxic therapy for metastatic disease. Details on the study design and patient population were previously described [6]. At each clinical trial site, an independent ethics committee/independent review board approved the study. The trial followed the principles of Declaration of Helsinki and all patients provided written informed consent.

The current analyses utilized data from two of the three arms—veliparib plus carboplatin/paclitaxel and placebo plus carboplatin/paclitaxel. Briefly, patients received 120 mg veliparib or placebo BID on days 1–7 of each 21-day cycle starting 2 days prior to receiving chemotherapy. Paclitaxel was administered at 175 mg/m^2 intravenously over approximately 3 h and carboplatin was administered at an area under the concentration–time curve (AUC) of 6 mg min/mL intravenously over approximately 15–30 min immediately following paclitaxel infusion on day 3 of each 21-day cycle. Treatment was continued until disease progression or unmanageable toxicity. Veliparib plasma pharmacokinetic samples were collected pre-dose and at 1, 2, and 3 h after dosing on cycle 1 day 3 and pre-dose on cycle 2 day 3.

The endpoints of interest for the current exposure–response analyses were progression-free survival (PFS), the primary endpoint of the study, and objective response rate (ORR), a secondary study objective. Tumor response was assessed by computed tomography scan as per the Response Evaluation Criteria in Solid Tumors v1.1 at screening, thereafter at 9-week intervals, and at the final visit. Safety was monitored throughout the study and adverse events were graded with the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0.

Population pharmacokinetic analysis

The population pharmacokinetic (PK) analysis included sparse veliparib plasma concentration data from 168 patients in the current study (Study 1) along with the data from 288 patients in 5 other veliparib Phase 1/2 studies conducted in patients with non-hematological malignancies (Supplementary Table 1).

The population PK model was developed using a non-linear mixed effects modeling approach with NONMEM (version 7.3, ICON development solutions, Ellicott City, MD, USA). The first-order conditional estimation (FOCE) with eta (η)—epsilon (ε) interaction was employed in the analysis. Graphical exploration of the data and processing of NONMEM output were performed with R (version 3.4.0). In the development of base model, one- and two-compartment models with first-order absorption and elimination were evaluated. Individual PK parameters were assumed to be log-normally distributed. Proportional and proportional plus additive (combined error model) residual error models were assessed.

Following identification of the structural model, a covariate model was built to assess the impact of patient demographics and baseline characteristics on veliparib pharmacokinetics. The following covariates were screened: body weight, body mass index (BMI), body surface area (BSA), lean body weight (LBW), age, sex, race, creatinine clearance, liver function markers (AST, ALT, and bilirubin), and albumin.

The functional relationship between continuous covariates and PK parameters was characterized using the following equation:

$$\mathrm{TVP} = \theta \times \left(\frac{\mathrm{COV}}{\mathrm{medianCOV}}\right)^{\theta_{\mathrm{cont}}}$$

where TVP is the typical value of the population PK parameter, θ is the PK parameter estimate at the median value of

the covariate (COV), and θ_{cont} is the power exponent for the covariate effect.

The relationship between categorical covariates and PK parameters was modeled using the following equation

$$TVP = \theta \times \theta_{cat}^{I_{cat}}$$

where TVP is the typical value of the population PK parameter when I_{cat} is 0 (binary categorical covariate) and θ_{cat} is the proportional change in TVP when I_{cat} is 1.

Covariate modeling was carried out by forward inclusion (0.01 significance level) and backward elimination (0.001 significance level) using the likelihood ratio test. The final model was chosen based on reduction in the objective function value (OFV), goodness-of-fit plots, visual predictive checks, precision of parameter estimates, and reduction in the inter-individual and residual variability.

Exposure–response analysis

Exposure–response analyses were conducted using data from the BROCADE study. All subjects with or without measurable disease per RECIST (ver 1.1) criteria were utilized for PFS analysis using the Kaplan–Meier method while only subjects with measurable disease were considered for PFS analysis using the Cox proportional hazards model and ORR analysis. Because overall adherence was high without any pronounced differences across exposure quartiles, for these analyses, steady-state area under the plasma concentration–time curve over the 12 h dosing interval (AUC_{12}) was used as the measure of veliparib exposure. The AUC_{12} was calculated from a posteriori Bayesian estimates of individual PK parameters obtained from the population PK model.

To evaluate the exposure–response relationship compared with the placebo group, patients in the veliparib exposure populations were stratified into high and low exposure groups by splitting the steady-state AUC_{12} at the median. Kaplan–Meier curves were used to visualize PFS for each of the individual exposure groups vs. the placebo arm.

Cox regression analysis was used to quantify the effect of treatment and exposures of veliparib on PFS. The following baseline characteristics were included to balance potential confounders: baseline tumor size (sum of the longest diameters of the target lesions), prior cytotoxic therapy, hormone receptor status (progesterone receptor [PgR] and/or estrogen receptor [ER]), age, Eastern Cooperative Oncology Group (ECOG) performance status, and baseline albumin level. Hormone receptor status, prior cytotoxic therapy, and ECOG status were the stratification factors used during randomization of the study. Baseline serum albumin, tumor size, and age were reported to be important prognostic factors influencing survival in breast cancer [10–13]. Binary coding was used for categorical covariates while continuous covariates were standardized. Treatment effect was tested in the presence of potential confounders in all subjects. Effect of veliparib exposure (steady-state AUC_{12}) was tested in the presence of potential confounders within the veliparib arm.

Logistic regression analysis was used to evaluate the relationship between the occurrence of complete response (CR) and partial response (PR) constituting overall response rate (ORR) and veliparib daily exposure (steady-state AUC_{12}). Both linear and non-linear (E_{max} model) relationships were explored. A range of fixed EC_{50} values was compared to a model that is linear in exposure and a model that only considers treatment as a binary variable. The Akaike Information Criterion (AIC) was used to choose among those models. Covariates baseline tumor size, prior cytotoxic therapy, hormone receptor status (PgR and/or ER), age, ECOG performance status, and baseline albumin level were tested for their influence on the intercept.

For Cox and logistic regression analyses, only complete cases where all predictors were known were considered. The analyses were conducted using R (version 3.5.1).

The safety endpoints selected for the exposure-safety analyses were neutropenia, thrombocytopenia, leukopenia, and anemia. For exposure-safety analyses, veliparib exposure populations were divided into the exposure groups defined by steady-state AUC_{12} quartiles. The maximum decrease from baseline for all the safety variables was compared between the placebo and veliparib exposure quartiles.

Dose intensity of veliparib and carboplatin and paclitaxel

Dose intensity of veliparib, carboplatin, and paclitaxel was calculated by dividing the cumulative dose of each of the drugs over the treatment period by treatment duration. Median dose intensity of each of the drugs was compared between placebo and veliparib exposure quartiles (as defined above in the exposure-safety analyses).

Results

Veliparib population pharmacokinetics

A total of 4048 plasma concentrations from 456 patients with solid tumors were analyzed. Of these, approximately 3% were reported as below the limit of quantitation. Given the low incidence of observations below the limit of quantification, the M5 method was used wherein all the observations below the limit of quantification were replaced with half of the lowest limit of quantification values (LLOQ/2) [14]. A summary of patient demographics and baseline characteristics in the BROCADE study and the whole population PK dataset are presented in Table 1 and Supplementary Table 2,

respectively. The median age of the whole population PK dataset was 55 years with a median body weight of 70 kg. The majority of the whole population was White (87%) and female (71%).

A one-compartment model with first-order absorption best described the pharmacokinetics of veliparib. The model was parameterized in terms of absorption rate constant (k_a), apparent oral clearance (CL/F), and apparent volume of distribution (V/F). Inter-subject variability was estimated on CL/F and V/F in the final model and correlation between the intersubject variability terms was estimated to be 0.457 in the final model. A combined (proportional plus additive) error model was used to account for residual variability. Covariate analysis identified creatinine clearance on clearance (CL/F) and lean body weight (LBW) on apparent volume of distribution (V/F) as significant covariates affecting veliparib pharmacokinetics. Covariates explained 24% and 34% of the variability in CL/F and V/F, respectively, in the final model relative to the base model. Supplementary Table 3 shows the parameter estimates of the final model and the precision associated with them. All parameters were estimated with high precision (relative standard error (RSE) ≤ 14%) and low shrinkage was associated with random effects (≤ 27%). The final equations for the typical values of CL/F and V/F are as follows:

Table 1 Patient demographics and baseline factors in Phase 2 BROCADE study

	Veliparib plus carboplatin/paclitaxel ($N=95$)	Placebo plus carboplatin/paclitaxel ($N=98$)
Age (year), median (range)	44 (25–65)	46 (24–66)
Prior cytotoxic therapy		
No, *N* (%)	14 (14.7)	20 (20.4)
Yes, *N* (%)	81 (85.3)	78 (79.6)
ECOG status		
0–1, *N* (%)	91 (95.8)	92 (93.9)
2, *N* (%)	4 (4.2)	6 (6.1)
Baseline tumor size (mm), median (range)	54 (11–207)	51 (11–209)
ER and/or PgR		
Any positive, *N* (%)	57 (60.0)	55 (57.9)
Both negative, *N* (%)	38 (40.0)	40 (42.1)
BRCA1		
Positive, *N* (%)	51 (53.7)	53 (54.1)
Negative, *N* (%)	44 (46.3)	45 (45.9)
BRCA2		
Positive, *N* (%)	44 (46.3)	46 (46.9)
Negative, *N* (%)	51 (53.7)	52 (53.1)
TNBC		
Yes	38 (40.0)	40 (42.1)
No	57 (60.0)	55 (57.9)

$$CL/F = 454\left(\frac{CRCL}{102\ mL/min}\right)^{0.457}\exp\left(\eta_1\right)$$

$$V/F = 172\left(\frac{LBW}{45\ kg}\right)^{0.846}\exp\left(\eta_2\right)$$

Goodness-of-fit plots for the final model in Supplementary Fig. 1 showed adequate agreement between observed and model-predicted veliparib plasma concentrations (Supplementary Fig. 1A and 1B) and the conditional weighted residuals vs. population predicted concentrations (Supplementary Fig. 1C) or time (Supplementary Fig. 1D) plots suggest lack of significant bias in the model fit.

Post hoc parameters from the BROCADE study were compared with those from the rest of the studies used in the population PK analyses. Veliparib CL/F in the BROCADE study is consistent with other studies (480 L/day in BROCADE vs. 489 L/day in other studies) while *V/F* estimate was less compared to other studies (151 L in BROCADE vs. 179 L in other studies). This apparent difference in *V/F* can be explained by the lower LBW in the current study which included mostly female subjects who tend to have lower LBW compared to male subjects [mean LBW of 43.0 kg in BROCADE (98.2% female subjects) vs. 49.7 kg in other studies (53.8% female subjects)].

Exposure–response relationship

A total of 193 subjects (95 in the veliparib plus carboplatin/paclitaxel arm and 98 in the placebo plus carboplatin/paclitaxel arm) with or without measurable disease at baseline were used in the PFS analysis using the Kaplan–Meier method. Kaplan–Meier plots of PFS stratified by veliparib steady-state AUC_{12} demonstrated that the veliparib plus carboplatin/paclitaxel arm showed a trend of improvement in PFS over placebo plus carboplatin/paclitaxel arm, but there was no significant relationship between the level of veliparib exposure and PFS (Fig. 1). Baseline variables were compared between placebo plus carboplatin/paclitaxel and low and high veliparib exposure groups and they were generally balanced between all three groups.

A total of 156 subjects (77 in the veliparib plus carboplatin/paclitaxel arm and 79 in the placebo plus carboplatin/paclitaxel arm) with measurable disease at baseline and no missing covariate values were used in the Cox proportional hazards model. In the Cox regression analysis, there was a trend of improvement in PFS in veliparib arm compared to placebo, although not statistically significant. Baseline tumor size, albumin, and age were identified as significant covariates for PFS (Table 2). For every unit increase in continuous covariate (increase corresponding to one standard deviation

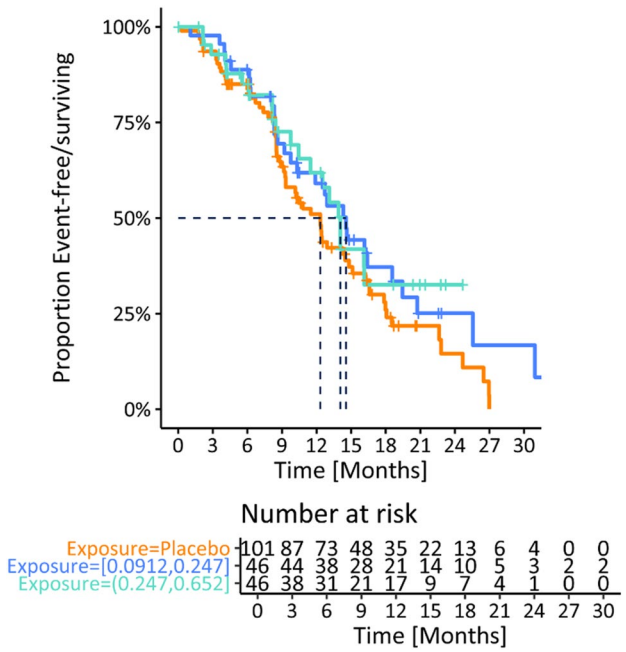

Fig. 1 Comparison of PFS between placebo, low and high veliparib exposure groups in combination with carboplatin/paclitaxel. Exposure represents model estimated post hoc steady-state AUC_{12}, in mg * day/L

in the observed population), the hazard would change by the estimated ratio. However, within the veliparib arm, when veliparib steady-state exposure (AUC_{12}) was incorporated in the model along with potential confounding variables, no trend was observed between veliparib exposure and PFS.

For the ORR model, a total of 139 subjects (67 in the veliparib plus carboplatin/paclitaxel arm and 72 in the placebo plus carboplatin/paclitaxel arm) with valid response assessment and no missing covariates were included in the model. As previously published, the ORR in the veliparib plus carboplatin/paclitaxel arm was 78%, which was a significant improvement ($P < 0.05$) compared to 61% in the placebo plus carboplatin/paclitaxel arm [6]. The density plot of tumor best response to characterize antitumor activity shows that patients in the veliparib plus carboplatin/paclitaxel arm had deeper tumor best response compared to those in the placebo plus carboplatin/paclitaxel arm (Fig. 2). Comparing linear, non-linear E_{max}, and binary predictors for the impact of treatment on ORR, the model with binary treatment effect was selected by AIC (Fig. 3). This is consistent with decreasing AIC with decreasing EC_{50} indicating that other than the treatment effect, there is a flat exposure–response relationship among subjects treated with veliparib at 120 mg BID. No significant covariates were identified.

For hematological toxicities (anemia, neutropenia, leukopenia, and thrombocytopenia), no exposure–response relationship in the maximum decrease from baseline was observed (Fig. 4).

Table 2 Cox proportional hazards survival analysis on PFS with covariates

Parameter	Variable type	Progression-free survival Hazard ratio (95% CI)
All subjects (active + placebo)		
Treatment	Yes vs. no	0.785 (0.519–1.19)
Prior cytotoxic therapy	Yes vs. no	0.63 (0.381–1.04)
Albumin	Continuous	0.548 (0.352–0.851)**
ECOG	2 vs. 0 or 1	1.58 (0.725–3.44)
Age	Continuous	0.759 (0.614–0.937)*
Baseline tumor size	Continuous	1.32 (1.07–1.63)*
Estrogen receptor and/or progesterone receptor	Any positive vs. both negative	0.703 (0.471–1.05)
Veliparib arm only		
Exposure ($AUC_{SS,12\,h}$)	Continuous	1.02 (0.716–1.47)
Prior cytotoxic therapy	Yes vs. no	0.235 (0.108–0.512)***
Albumin	Continuous	0.677 (0.337–1.36)
ECOG	2 vs. 0 or 1	1.65 (0.350–7.80)
Age	Continuous	0.897 (0.647–1.24)
Baseline tumor size	Continuous	1.66 (1.14–2.42)**
Estrogen receptor and/or progesterone receptor	Any positive vs. both negative	0.515 (0.277–0.959)*

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

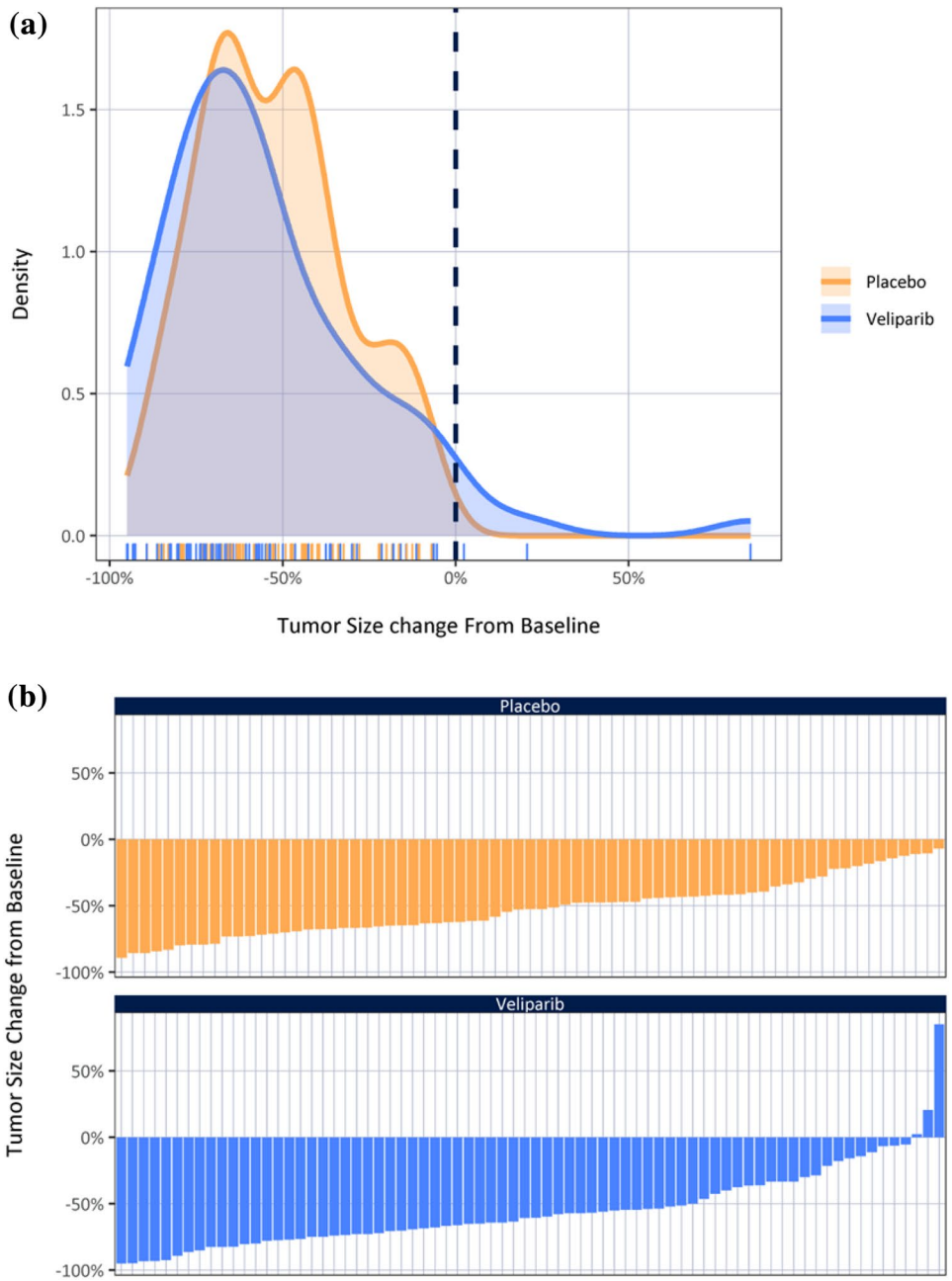

Fig. 2 Density (**a**) and waterfall (**b**) plots of best tumor response in placebo and veliparib arms in combination with carboplatin/paclitaxel

Comparison of dose intensity of chemotherapy agents and veliparib across veliparib exposure quartiles and placebo group

Median dose intensity of carboplatin, paclitaxel, placebo, and veliparib was comparable between placebo and veliparib exposure quartiles (Supplementary Fig. 2) suggesting that there was no apparent difference in the dose interruptions and dose reductions of chemotherapy agents in the veliparib exposure quartiles and the placebo arm, and no apparent difference in the dose interruptions and dose reductions of veliparib in the veliparib exposure quartiles.

Discussion

Randomized, placebo-controlled dose ranging studies are rarely conducted for anti-cancer drugs [15], which casts the uncertainty on whether the optimal dose of an investigational drug is studied in the pivotal study. An exposure–response analysis that takes the advantage of inter-subject variability in PK exposure following the same dose of veliparib was performed to evaluate whether 120 mg BID was an optimal dose of veliparib in combination with carboplatin and paclitaxel in patients with BRCA-deficient advanced breast cancer.

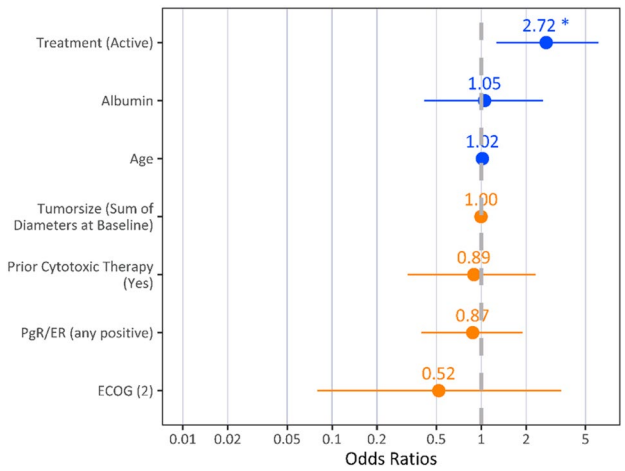

Fig. 3 Logistic regression analysis of overall response rate

In the BROCADE study, a veliparib dose of 120 mg BID was selected based on the data available from an ongoing Phase 1 dose escalation study of veliparib in combination with carboplatin/paclitaxel or cisplatin/paclitaxel in newly diagnosed patients with previously untreated ovarian/fallopian or primary peritoneal cancer (NCT00989651). For BROCADE study, 120 mg BID was determined to be the recommended Phase 2 dose based on in vitro data and immature data from the Phase I study at the time. Doses greater than 120 mg BID were eventually tested in this study and more recent studies in patients with lung cancers tested doses as high as 240 mg BID [16, 17].

A deeper tumor best response was observed in the veliparib plus carboplatin/paclitaxel arm compared to the placebo plus carboplatin/paclitaxel arm, consistent with a significantly higher ORR in the veliparib arm (78%) vs. the placebo arm (61%) [6]. There was a trend of improvement in PFS in the veliparib plus carboplatin/paclitaxel arm compared to the placebo plus carboplatin/paclitaxel arm although it did not reach statistical significance [6]. Although the BROCADE study evaluated veliparib at only one dose level, a difference of about two-fold between the medians of the highest and lowest exposure quartiles (i.e., 12.5th and 87.5th percentiles) was observed in the study population.

Exposure-efficacy response analysis revealed that within the veliparib arm, the relationship between the efficacy variable (PFS or ORR) and steady-state AUC_{12} of veliparib was relatively flat and reached a plateau. In addition to the stratification factors (that includes prior cytotoxic therapy and receptor status), baseline tumor size and albumin level were included as covariates in the PFS and ORR analysis because tumor size has been reported to be an independent prognostic factor influencing survival in breast cancer patients [12] and albumin is an indicator of patient's nutritional status, and lower serum albumin levels significantly

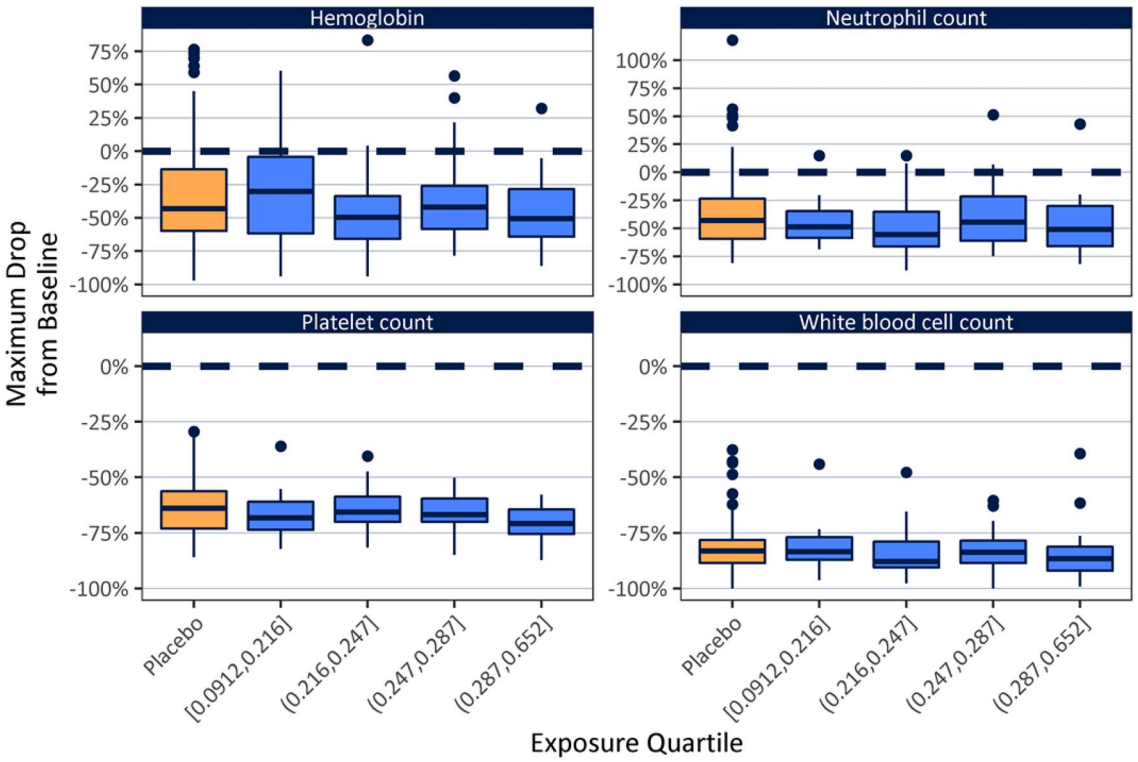

Fig. 4 Maximum drop from baseline of anemia, neutropenia, leukopenia, and thrombocytopenia, by veliparib AUC_{12} (mg*day/L) quartiles

affected the survival in all stages of breast cancer and also other cancer types [10, 18]. With regard to safety, the class effects of PARP inhibitors include hematological toxicities such as anemia, thrombocytopenia, and neutropenia and gastrointestinal effects such as nausea and vomiting. Hematological effects are dose-limiting toxicities both as a single agent and in combination with chemotherapy [19, 20], while nausea and vomiting are more commonly dose limiting for the monotherapy regimens which entail continuous dosing with higher exposures. Hence, an exposure-safety response analysis was conducted on selective hematological toxicities (anemia, leucopenia, neutropenia, and thrombocytopenia). There was no significant exposure–response with regard to maximum decrease from baseline of anemia, leucopenia, neutropenia, and thrombocytopenia in the study and is consistent with no significant difference in the grade 3/4 hematological toxicities between the veliparib and placebo groups [6]. This suggested that veliparib did not add to the toxicity of the chemotherapy backbone and 120 mg BID veliparib dosed intermittently for 7 days in a 21-day cycle is well tolerated in this combination. A similar favorable trend in PFS vs. chemotherapy alone was observed in a randomized, placebo-controlled, Phase II study of veliparib in combination with carboplatin and paclitaxel in non-small cell lung cancer [5]; however, ORR was similar between veliparib plus carboplatin/paclitaxel arm compared to the placebo plus carboplatin/paclitaxel arm. In that study, grade 3/4 anemia, thrombocytopenia, and neutropenia were similar between the treatment groups.

In contrast to cytotoxic drugs which are dosed at the maximum tolerated dose, targeted therapy may achieve maximum efficacy at a dose lower than the maximum tolerated dose. Veliparib showed greater than 50% PARP inhibitory activity up to 24 h after a single dose at 25 and 50 mg in PBMC from healthy volunteers and tumor tissues from patients [21]. This is consistent with other PARP inhibitors such as olaparib, niraparib, and rucaparib, where PARP inhibition plateaued at doses significantly lower than their respective maximum tolerated/recommended Phase 2 monotherapy doses [22–24]. Therefore, significant inhibition of PARP activity is believed to occur at 120 mg BID, well below veliparib monotherapy maximum tolerated dose of 400 mg BID [25]. Based on the current analysis, doses higher than 120 mg BID given for 7 days in a 21-day cycle in combination with carboplatin and paclitaxel may not significantly enhance the efficacy of veliparib in *BRCA*-mutated breast cancer patients.

Population PK analysis inclusive of the BROCADE study contains the largest dataset available yet for veliparib. Consistent with the previous reports [26–28], renal clearance and LBW were found to be significant covariates of systemic clearance (CL/F) and *V*/*F*, respectively. It is also consistent with the renal clearance being the primary elimination pathway for veliparib [29]. The *V*/*F* was lower in the BROCADE study in BRCA-mutated breast cancer patients when compared to previous studies and this can be explained by difference in body weight in the BROCADE study. The current study consisted of primarily female subjects who tend to have lower LBW compared to the other studies in various solid tumors that contained both male and female subjects, and hence lower apparent volume of distribution.

In summary, moderate increases in both PFS and ORR had been reported in patients with BRCA1/2-mutated recurrent/metastatic breast cancer receiving veliparib in combination with carboplatin and paclitaxel compared with placebo combined with carboplatin and paclitaxel in the BROCADE study. The current exposure–response analyses showed a flat relationship between veliparib exposure and PFS as well as ORR in the exposure range observed at 120 mg BID dose. Exposure–response analyses also supported that the combination regimen did not add toxicity to the chemotherapy backbone. These findings suggest that a higher veliparib dose given intermittently in combination with carboplatin and paclitaxel is unlikely to provide additional efficacy benefit in this population. In an ongoing Phase 3 study of veliparib in combination with carboplatin and paclitaxel in HER2-negative metastatic or locally advanced unresectable BRCA-associated breast cancer, veliparib is dosed at 120 mg BID for 7 days in a 21-day cycle until progression or unacceptable toxicity and patients can continue on veliparib maintenance therapy dosed at higher doses of 300–400 mg BID if they discontinue carboplatin and paclitaxel and have not progressed (NCT02163694).

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Data sharing 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

Compliance with ethical standards

Conflict of interest Silpa Nuthalapati, Sven Stodtmann, Christine K Ratajczak, Sven Mensing, Rajeev Menon, and Hao Xiong are employees of AbbVie. Stacie Peacock Shepherd is a former employee of AbbVie. All authors may hold AbbVie stock or stock options.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard.

Statement of human and animal rights The article does not contain any studies with animals performed by any of the authors.

Statement of informed consent Informed consent was obtained from all individual participants included in the study.

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