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A Phase 1 and Pharmacodynamic Study of Chronically-Dosed, Single-Agent Veliparib (ABT-888) in Patients with *BRCA1*- or *BRCA2*-Mutated Cancer; Platinum-Refractory Ovarian or Triple-Negative Breast Cancer

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CONFLICT OF INTEREST

Conflict of Interest: Jan Beumer received research support from AbbVie and has consulted as expert witness on behalf of Pfizer and Spectrum Pharmaceuticals. Shannon Puhalla has received research support from AbbVie, Pfizer, Lilly, Novartis, Incyte, Covance-Bayer, AstraZeneca, Genentech, Medivation and has been a consultant for AbbVie, MedImmune, Celldex, Puma, Pfizer, AstraZeneca, Esai, and Nanostring.

Ethical approval: All procedures performed in 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 standards. This trial was registered under ClinicalTrials.gov Identifier: NCT01154426.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Abstract

Purpose: *BRCA1* or *BRCA2* mutated cancers (*BRCA*mut) have intrinsic sensitivity to PARP inhibitors due to deficiency in homologous recombination-mediated DNA repair. There are similarities between *BRCA*mut and *BRCA*wt ovarian and basal-like breast cancers. This phase I study determined the recommended phase II dose (RP2D) and preliminary efficacy of the PARP inhibitor, veliparib (ABT-888), in these patients.

Patients and Methods: Patients (n=98) were dosed with veliparib 50–500 mg twice daily (BID). The *BRCA*mut cohort (n=70) contained predominantly ovarian (53%) and breast (23%) cancers; the *BRCA*wt cohort (n=28) consisted primarily of breast cancer (86%). The MTD, DLT, adverse events, PK, PD, and clinical response were assessed.

Results: DLTs were grade 3 nausea/vomiting at 400 mg BID in a *BRCA*mut carrier, grade 2 seizure at 400 mg BID in a patient with *BRCA*wt cancer, and grade 2 seizure at 500 mg BID in a *BRCA*mut carrier. Common toxicities included nausea (65%), fatigue (45%), and lymphopenia (38%). Grade 3/4 toxicities were rare (highest lymphopenia at 15%). Overall response rate (ORR) was 23% (95% CI 13%−35%) in *BRCA*mut overall, and 37% (95% CI 21%−55%) at 400 mg BID and above. In *BRCA*wt, ORR was 8% (95% CI 1%−26%), and clinical benefit rate was 16% (95% CI 4%−36%), reflecting prolonged stable disease in some patients. PK was linear with dose and was correlated with response and nausea.

Conclusions: Continuous veliparib is safe and tolerable. The RP2D was 400 mg BID. There is evidence of clinical activity of veliparib in patients with *BRCA*mut and *BRCA*wt cancers.

Keywords

veliparib; phase I; pharmacokinetics; pharmacodynamics; solid tumors; PARP inhibitor; DNA damage; BRCA1; BRCA2; ovarian cancer; triple-negative breast cancer

1 INTRODUCTION

The poly (ADP-ribose) polymerase (PARP) family of enzymes is important for a number of cellular processes, including several DNA repair pathways. PARP1 detects both single- and double-strand DNA breaks, while PARP2 dimerizes with PARP1 to play a role in base excision DNA repair [1]. In addition, PARP1 plays a critical role in stabilizing replication forks [2,3]. Inhibition of PARP is an important treatment strategy for cancers harboring deficiencies in BRCA1 or BRCA2 (*BRCA*) based on data showing "synthetic lethality" between BRCA deficiency and PARP inhibition [4,5].

In addition to *BRCA1* and *BRCA2* mutation carriers, there is a larger population of breast (particularly ER/PR and HER2 negative; "triple- negative") and ovarian cancer patients whose cancers have a BRCA-like phenotype with homologous recombination HR deficiency [6] due to somatic *BRCA* mutations or deletions, *BRCA1* promoter methylation, or deficiencies in other DNA repair genes. Although these mechanisms were not formally tested in this phase 1 study, a cohort of *BRCA* wild-type patients with triple-negative breast cancer (TNBC) or platinum-refractory ovarian cancer was included as we hypothesized that these patients might be similarly sensitive to single-agent PARP inhibition.

Currently, four PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) have received FDA approval for various indications. Compared to olaparib and niraparib, veliparib is a somewhat less potent PARP catalytic inhibitor and a less potent DNA-PARP trapper [7]. While there is clear demonstration of efficacy in *BRCA* mutant cancers, the optimal use of PARP inhibitors, either as monotherapy or in combination with cytotoxic chemotherapy, remains under investigation. Among the questions yet to be resolved are: (1) whether there are factors in addition to mutations in HR pathway genes such as *BRCA1* and *BRCA2* that predict response or resistance to PARP inhibitors; and (2) whether PARP inhibitors can be successfully combined with existing chemotherapy agents to enhance efficacy.

Veliparib (ABT-888) is an oral, potent, small molecule inhibitor of PARP1 and PARP2 shown to be a potentiator of DNA damaging agents in various preclinical cancer models [8,9]. A first-in-man phase 0 trial demonstrated >90% PARP 1/2 inhibition in paired tumor biopsies and companion PBMCs 3–6 hours after a 25- or 50-mg dose, and partial recovery of enzymatic activity at 24 hours [10]. This phase I trial, which was previously reported in abstract form [11], aimed to determine the dose-limiting toxicities (DLT), maximum tolerated dose (MTD), and recommended phase II dose (RP2D) of veliparib given as a single agent to patients with advanced cancers with germline *BRCA* mutation or *BRCA* wildtype ovarian cancer or TNBC. The secondary endpoints of this study were to evaluate safety

and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical response. In addition, pre- and post-treatment biopsies from an expansion cohort in patients with germline *BRCA*mut cancers were evaluated to elucidate biological determinants of response or resistance to veliparib in this patient population.

2 METHODS

2.1 Study Population

This phase I trial (NCI 8282, NCT00892736) enrolled 2 cohorts of patients. The first cohort (referred to as *BRCA*mut; n=70) included patients with a documented germline mutation in *BRCA1* or *BRCA2* (Myriad Genetic Laboratories) and a metastatic, *BRCA*-related malignancy (breast, ovarian, pancreatic, prostate, etc). The second cohort (referred to as *BRCA*wt; n=28) included patients with TNBC or platinum-refractory ovarian cancer without a known germline *BRCA* mutation. Patients with unknown *BRCA* mutation status were screened with BRCAPRO [12] and if the likelihood of mutation was ≥ 20%, were required to undergo *BRCA* gene testing for cohort allocation.

ECOG PS ≤2 was required as part of the eligibility criteria, as were adequate hepatic, renal and marrow function. Patients with stable and treated CNS metastases were allowed. Patients with history of seizure disorder were excluded, as seizures were seen at higher doses in animal studies. There was no limit to prior therapies, including prior PARP inhibitor or previous platinum-based chemotherapy.

2.2 Study Design

This was an NCI-CTEP-sponsored, multicenter trial performed at six NCI-designated cancer centers, approved by the respective institutional review boards and ethics committees. This study followed a standard 3+3 dose-escalation schema [13]. Veliparib was given orally on a continuous schedule, using a 28-day cycle. There were nine dose levels ranging from an initial dose level (DL) of 50 mg BID (DL1) to a maximum dose of 500 mg BID (DL9) (Table 1).

2.3 Safety Assessments

Dose-limiting toxicity (DLT) was defined as a significant adverse event occurring during cycle 1 considered to be at least possibly drug related, and could be any grade ≥3 non-easily correctable non-hematologic or grade 4 hematologic toxicity (neutropenia being prolonged or febrile), as defined by the Common Terminology Criteria for Adverse Events version 4.0. Toxicity resulting in holding drug for greater than 2 weeks, regardless of attribution or grade, was to be considered a DLT.

Maximum tolerated dose (MTD) was defined as the highest dose level at which ≤ 1/6 patients had a DLT in cycle 1. The recommended phase II dose (RP2D) was defined as the dose at or below the MTD where therapy was determined to be tolerable. After the first DLT, dose escalation was conducted separately in the *BRCA*mut and the *BRCA*wt cohorts because, at the time of study inception, it was not known if there would be differential

toxicity in those with germline *BRCA* mutations. A dose-expansion cohort at the RP2D enrolled *BRCA* mutation carriers and included mandatory research biopsies.

2.4 Tumor Response Assessment

Radiographic assessments were performed every 2 cycles, and the objective response rate (ORR) was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 [14]. Clinical benefit was defined as having complete response, partial response, or stable disease for ≥6 cycles. Patients were considered evaluable for response if they underwent disease re-evaluation or physical examination after receiving at least 1 cycle of therapy or had overt clinical evidence of disease progression.

2.5 Translational Correlative Science

All patients enrolled in the dose escalation had peripheral blood collected to assess PAR as pharmacodynamic (PD) endpoint using a validated assay as described [10], and in-depth PK studies were performed with a validated assay [15]. Archival tumor samples were assessed for BRCA1 protein levels by immunohistochemistry (IHC), basal markers (cytokeratin 5 and EGFR by IHC), *BRCA1* promoter methylation, and integrity of the *BRCA1*/Fanconi Anemia pathway by staining for replication-associated FANCD2 foci *in situ*. Details are described in the Supplementary File.

After the dose escalation, there was a cohort expansion (n=25) at the RP2D exclusively for patients with a known germline *BRCA* mutation, with mandatory fresh tumor tissue biopsies prior to study treatment and on Cycle 2, Day 1, 4±1 hours after veliparib administration (Supplementary File). The biopsy specimens were analyzed for PAR and γ-H2AX using validated assays, for DNA repair proteins (RAD51, 53BP1, PARP1) using IHC, and *BRCA*mut cases were evaluated for *BRCA* reversion mutations as described [16].

2.6 Statistical Analysis

Patients were considered evaluable for DLT if they received at least 75% of their scheduled doses in cycle 1 or if they experienced a DLT. Response and toxicity rates were compared using Fisher's exact tests. Statistical methods for PK data are described in the Supplementary File. The association between biomarker and response was assessed by Fisher's exact tests. Survival data was analyzed using the Kaplan-Meier method. SAS software (version 9.4) was used to analyze demographic, adverse events, efficacy, and exposure-response data.

3 RESULTS

3.1 Patients

The study activated in April 2009 and patients enrolled between April 2009 and May 2014. Of the 98 patients who received at least one dose of veliparib, the majority had a germline *BRCA* mutation (Suppl.Table 1), 86 were evaluable for DLT (59 *BRCA*mut; 27 *BRCA*wt), and 87 were evaluable for response (62 *BRCA*mut; 25 *BRCA*wt). Eleven patients (8 *BRCA*mut; 3 *BRCA*wt) were not evaluable for response because of consent withdrawal, removal from study secondary to toxicity, or inability to swallow the study drug. In the

*BRCA*mut cohort, the range of cycles administered was 1–29, with a mean of 4.8 and median of 2.5. In the *BRCA*wt cohort, the range of cycles administered was 1–59, with a mean of 5.2 and median of 2.

3.2 DLTs, MTD, and RP2D

The first DLT, grade 2 thrombocytopenia and other complications relating to disease progression, was observed at DL1 for which veliparib was held for >2 weeks. While this was considered a DLT per protocol, the event was confounded by complications of disease progression, and ultimately judged unlikely to be related to study drug. Dose escalation was continued in both cohorts. DLTs were subsequently experienced by two patients at DL8 (one *BRCA*mut carrier with grade 3 nausea and grade 3 vomiting, one patient with *BRCA*wt cancer with grade 2 seizure) and one patient at DL9 (*BRCA*mut carrier with grade 2 seizure). The MTD was 500 mg BID (DL9). Formal criteria for RP2D were not met. There was frequent nausea seen at the higher dose levels often necessitating dose reduction, although it did not formally qualify as a DLT. Seizure activity was seen in preclinical studies, so this was a side effect of particular interest. Of note, one patient had a grade 2 seizure in a dose level higher than the RP2D. Both patients with episodes of seizures had imaging of the brain performed which found no evidence of metastatic disease. After lorazepam and levetiracetam treatment, symptoms improved in both patients. Ultimately, it was determined that the RP2D was 400 mg BID (DL8) based on general toxicity and tolerability.

3.3 Adverse Event Profile

Overall, continuous single-agent veliparib was well-tolerated (Table 2 and Table 3). The incidence of grade 3/4 toxicity was 24% (95% CI 15%−36%) in the *BRCA*mut group, with the most frequent grade 3/4 toxicity being decreased lymphocyte count (14%). In the *BRCA*wt group, the incidence of grade 3/4 toxicity was 29% (95% CI 13%−49%) and the most frequent adverse event was decreased lymphocyte count in 18%. There was no significant difference in grade 3/4 toxicity rates between *BRCA*mut and *BRCA*wt groups (p=0.8). The most common all-grade adverse events were nausea (65%), fatigue (45%), and decreased lymphocyte count (38%). It is notable that there were 6 patients who came off study after experiencing non-dose limiting nausea (2 in Cycle 1 of DL7, 2 in Cycle 1 of DL8, 1 in Cycle 2 of DL8 and 1 in Cycle 1 of DL9). In general, standard anti-emetics in various dosages and regimens were not consistently effective, and the nausea responded best to dose reduction. There was no signal of secondary malignancies with only one patient with melanoma in situ of the ear, likely unrelated, and no documentation of MDS or leukemia.

3.4 Efficacy

There were 62 evaluable *BRCA*mut carriers (Table 4, Figure 1, and Suppl.Figure 1). Evidence of stable disease was observed at DL2 (100 mg every morning, 50 mg every afternoon) and beyond, with objective responses first observed at DL7 (300 mg BID). The overall ORR was 23% (95% CI 13%−35%), and the ORR at the RP2D and beyond was 37% (95% CI 21%−55%). CBR was 42% (95% CI 29%−55%) including all dose levels, and 51% (95% CI 34%−69%) at the RP2D and beyond. The median progression-free survival (PFS) in the *BRCA*mut cohort was 3.1 months (95% CI 1.8–5.9 months) (Suppl.Figure 1). All

ovarian and peritoneal cancer patients had received prior platinum-based chemotherapy, and 6 of 15 breast cancer patients had prior platinum-based chemotherapy. Three of the 4 breast cancer patients with a response (DL7–8) were platinum-naïve.

Of the 25 evaluable patients with *BRCA*wt cancer, most had breast cancer (88%) (Table 4, Figure 1, and Suppl.Figure 1). Amongst *BRCA*wt breast cancers, 14 of 22 (64%) were platinum-naïve. ORR was 8% (95% CI 1%−26%), and CBR was 16% (95% CI 4%−36%). Both rates were lower compared to the *BRCA*mut cohort (p=0.14 and 0.03 respectively). In contrast to the *BRCA*mut cohort, objective responses were observed at DL1 and DL3. The median PFS in this cohort was 1.8 months (95% CI 1.5–3.1 months) (Suppl.Figure 1). Of the patients with TNBC, 1 of 11 had stable disease for more than 6 months. This patient (1–7-51) represents an exceptional responder with stable disease on single-agent veliparib for 59 cycles (at the time of data cut-off) after 13 cycles of combined treatment with carboplatin, paclitaxel, and veliparib on NCT00535119[17]. This patient discontinued study therapy after nine years of treatment with stable, minimal disease.

3.5 Translational Correlative Science

3.5.1 Pharmacokinetics—Pharmacokinetic data were available for 67 patients (Suppl.Table 2, Suppl.Table 3, and Suppl.Figure 2). Population pharmacokinetic analysis of these data in aggregate have been previously reported [18], while here we present the first non-compartmental analysis of this dataset. Dose proportionality assessment for veliparib D1 C_{max} resulted in a coefficient of 1.066 (95% CI 0.960–1.17; 90% CI 0.978–1.15). Dose linearity assessment for D1 $AUC_{0\text{-}inf}$ resulted in a coefficient of 1.059 (95% CI 0.949–1.17; 90% CI 0.967–1.15). The accumulation indices (geometric mean and standard deviation) for C_{max} of 1.24 (1.37) and $AUC_{0–8}$ of 1.30 (1.29) were as expected based on the theoretical accumulation index of 1.34 (1.12) calculated from the D1 half-lives. Similarly, the primary, active metabolite M8 accumulation indices for C_{max} of 1.51 (1.34) and $AUC_{0–8}$ of 1.59 (1.41) were as expected based on the theoretical accumulation index of 1.51 (1.25) calculated from the D1 half-lives. The day 1 M8/ABT-888 metabolic ratio was 0.11 (1.8) and 0.21 (1.9) for C_{max} and $AUC_{0\text{-}inf}$, respectively. Exposure-response relationship assessment of day 1 veliparib C_{max} and AUC (Figure 2C,D and Suppl.Figure 3) showed increased exposure across response categories from progressive disease (PD) to stable disease (SD), partial response (PR) and complete response (CR), with statistical significance of PD vs SD/PR/CR (C_{max} p=0.049, n=58; AUC p=0.019, n=56) by Wilcoxon's non-parametric test. Within the *BRCA*mut population, the significance for Cmax was lost while for AUC it was retained (C_{max} p=0.114, n=34; AUC p=0.08, n=32). Exposure-toxicity relationship assessment of day 1 veliparib C_{max} and AUC (Figure 2A,B and Suppl.Figure 4) showed no relationship with overall toxicity, but statistical significance of grade 0–1 vs grade 2+ nausea (C_{max} p=0.003, n=67; AUC p=0.0004, n=65).

3.5.2 PAR levels—PBMC PAR levels were evaluated in 45 patients covering all dose levels (Suppl.Figure 5). In general, there was evidence of decreased PAR levels after administration of veliparib, consistent with target inhibition at the doses administered. PAR levels were decreased at 2 hours and remained decreased at 24 hours for most samples

tested, particularly at higher dose levels. At DL8, treatment reduced tumor PAR level was ≥99% in the one evaluable patient.

3.5.3 Exploratory analyses of archival tissue for *BRCA1* promoter methylation, *BRCA1*/Fanconi anemia pathway integrity, cytokeratin 5, and EGFR—

Archival tissue was available for 48 of the patients (49%; 34 *BRCA*mut; 14 *BRCA*wt). Methylation status was investigated by pyrosequencing and methylation specific PCR (MSP) (Suppl.Table 4). Tumors from 12 patients demonstrated *BRCA1* promoter methylation by pyrosequencing (12/48, 25%), while six samples demonstrated *BRCA1* promoter methylation by MSP (6/43, 14%), three of which were overlapping with the pyrosequencing methylation data (1–7-51, 3–1-09, 4–8-57), with a total concordance of 77%. None of these three patients had a germline *BRCA* mutation; BRCA1 was lost in one case (1–7-51; IHC data). With regard to response: 1–7-51 had SD, 3–1-09 had PD and 4–8-57 was non-evaluable. The small number of methylated samples precluded further correlative analysis.

Previous studies suggested that FANCD2 foci are formed during normal replication but are not seen in *BRCA*mut cancer cells because BRCA1 and BRCA2 are upstream of FANCD2 in this pathway [19]. To assess whether the *BRCA*-Fanconi Anemia (FA) repair pathway was intact and could predict sensitivity to PARP inhibition, the presence of FANCD2 foci was determined in the archival tumor specimens [19]. Among the 48 patients, information on FANCD2 foci was available for 43 (29 *BRCA*mut;14 *BRCA*wt). FANCD2 foci were absent in 37.9% of *BRCA*mut tumors versus 42.9% of *BRCA*wt cancers. This difference was not significant, and our results do not confirm that absence of FANCD2 foci is a read-out for presumed absence of BRCA1 or BRCA2. Response (CR, PR or SD; evaluable patients only) was demonstrated in 50.0% of FANCD2-negative-*BRCA*mut cases, 33.3% of FANCD2-negative-*BRCA*wt cases, 73.3% of FANCD2-positive-*BRCA*mut cases, and 66.7% of FANCD2-positive-*BRCA*wt cases. This suggests that FANCD2 status is not a good predictor of response.

Based on data supporting overlapping phenotype between basal-like breast cancer determined by IHC, microarray or genomic sequencing and *BRCA*mut breast cancer [20], we examined whether the basal breast cancer markers, cytokeratin 5 and EGFR, could be used to identify basal-like TNBC with a BRCA-like phenotype [6] in 20 breast cancer patients (8 *BRCA*mut; 12 *BRCA*wt/TNBC). Among the 12 *BRCA*wt/TNBC breast cancers evaluated, 5 (41.7%) had both, 4 (33.3%) had one, and 3 (25.0%) had no basal marker present. In contrast, among the 8 *BRCA*mut breast cancers tested, 4 (50.0%) had both and the others (50%) had no basal markers present. In the *BRCA*wt group with both basal markers present, there were 3 (60.0%) patients with PD and 2 (40%) SD, while among those with none of the basal markers present, 2 had SD as best response while the other was non-evaluable.

3.5.4 *BRCA*mut biopsy cohort—

Of the 25 biopsy cohort patients treated at the RP2D (DL8), 4 had no adequate biopsy specimens, 11 had adequate pre-treatment biopsies only and 10 had both adequate pre- and post-treatment biopsies as determined by touch prep. Of the 11 patients with only pre-treatment biopsies, 3 patients were off study prior to the post-

treatment biopsy time point and 4 patients, 3 of which were responders to therapy, did not have adequate specimens for analysis on the post-treatment biopsies. These post-treatment biopsies, although few, provided an opportunity to assess potential mechanisms that result in persistent *BRCA*mut cancer in the face of veliparib treatment.

Secondary somatic reversion mutations in BRCA have been described as a resistance mechanism to platinum-based chemotherapy and to PARP inhibitors [21]. These are secondary mutations that restore the open reading frame, leading to restoration of BRCA function. These mutations have been reported in 28% of platinum-resistant ovarian cancers in *BRCA* mutation carriers [16]. We postulated that reversion mutations may lead to PARP inhibitor resistance in the patients treated on this trial as well. In the biopsy expansion cohort, there were 30 neoplastic samples from 20 *BRCA* mutation carriers (19 pre-treatment and 11 post-treatment) analyzed for the presence of reversion mutations. All tumor samples had the germline mutation that the patient was known to have and 19 of 20 had LOH of the wild-type BRCA allele. There were no clear reversion mutations, prompting us to search for a basis of resistance that is independent of reversion mutations.

Based on preclinical studies suggesting that cells can become PARP inhibitor resistant by downregulation of PARP1 [22,7], loss of 53BP1 in *BRCA1*-mutated cancer [23], or upregulation of RAD51 [24], these proteins were assessed in biopsies from the expansion cohort using IHC (Supplementary File and Suppl.Figure 6). A wide range of PARP1 expression was observed in pretreatment samples (Suppl.Figure 6A, B). Although the results are limited by the small number of samples, there was no obvious relationship between response and pretreatment PARP1 staining, as summarized by H-score (Suppl.Figure 6A) or percentage of cells with low (0 or 1+) staining (Suppl.Figure 6B). According to the PARP trapping hypothesis [7], cancer cells that persist after PARP inhibitor treatment might be resistant because of low PARP1 expression. In the present study, comparison of paired samples failed to show consistent decreases in PARP1 in neoplastic cells after treatment (Suppl.Figure 6C). Instead, the PARP1 H-score decreased by >50 in two paired cancers and increased by >50 in three pairs and did not correlate with response.

53BP1 staining displayed a similar wide range of staining intensities (Suppl.Figure 6D). In contrast to recent results in a different PARP inhibitor trial [23], there was no obvious relationship between response and pretreatment 53BP1 expression. This lack of correlation persisted even when analysis was limited to the *BRCA1*-mutant subset of cancers. There was no relationship between response and pretreatment RAD51 expression (Fig. 6E). Although RAD51 overexpression is associated with PARP inhibitor resistance [24], we observed that RAD51 staining was highly similar in tumor cells before and after treatment ($r = 0.9$, $P = 0.011$); and there was no suggestion that tumor cells overexpressing RAD51 had been selected during treatment (Suppl.Figure 6F).

Nuclear γ-H2AX staining in tumor from 10 cases, 4 of which were pre-post biopsy pairs, revealed minimal treatment-induced changes without consistent direction.

4 DISCUSSION

Single-agent veliparib was well-tolerated and demonstrated anti-tumor activity in a *BRCA*mut population at an RP2D of 400 mg BID, while minimal activity was also seen in BRCAwt patients. The most relevant side effect was low-grade nausea, which responded best to dose reductions.

Veliparib monotherapy toxicities are consistent with those of other PARP inhibitors [25–27]. Hematological toxicities are a very common class effect of PARP inhibitors with anemia being the most common. In three phase 3 maintenance trials, grade 3 or 4 anemia was slightly higher for niraparib (25%), followed by rucaparib (19%) and olaparib (19%). In our study, while all-grade anemia was consistent with those of other PARP inhibitors, grade 3 or 4 anemia was only seen in 6% of patients. Unlike other PARP inhibitors, the most frequent hematologic AE in our study was a decrease in lymphocytes (38%).

This single agent trial was started at about the same time as several other veliparib combination trials and explored more and higher doses, and involved numerous correlative components, in part explaining its reporting after several veliparib combination trial have been published. This allows more comprehensive comparison with other trials. Veliparib demonstrated less toxicity in combination with chemotherapy than the other PARP inhibitors, which generally enhance chemotherapy induced myelosuppression limiting the dose or treatment duration of PARP inhibitors and/or chemotherapy [28–31]. One potential advantage with veliparib, therefore, is the ability to use it in combination with a number of other chemotherapeutic regimens [32–34]. The rationale for combining PARP inhibitors with platinum chemotherapy is based on the absence of intact homologous recombination DNA repair due to BRCA dysfunction, which increases sensitivity to both agents. Recent data from a phase II trial (NCT02595905) demonstrated efficacy with the addition of veliparib (300mg BID) to cisplatin which significantly improved PFS and showed a trend towards improved OS for *BRCA*-like advanced TNBC as well as tolerability with continuous daily dosing of veliparib [35]. According to new results from a phase III trial in patients with ovarian cancer (NCT02470585) in previously untreated stage III or IV high-grade serous ovarian cancer, the frontline regimen of chemotherapy plus veliparib induction therapy followed by veliparib maintenance resulted in significantly longer progression-free survival when compared with chemotherapy plus placebo with placebo maintenance [36]. The observed toxicities were consistent with the known safety profile of veliparib in both combination and maintenance phases. Recent findings from a phase III trial (NCT02163694) showed that the addition of veliparib to carboplatin plus paclitaxel with continuation of veliparib monotherapy at intensified dose and schedule if chemotherapy was withdrawn prior to disease progression led to improved PFS in *BRCA*mut patients with hormone receptor positive breast cancer and in patients with TNBC [37]. The overall toxicity profile was not substantially different between treatment arms. Veliparib can also be combined with carboplatin using continuous therapeutic daily dosing. Several phase 1 studies showed that daily continuous dosing of olaparib with carboplatin was not tolerable [38,30,31,39], and intensified hematologic toxicity resulting in significant dose reductions [38] and schedule delays [31]. However, veliparib (150 mg BID daily) in combination with weekly carboplatin and paclitaxel was well tolerated with an acceptable safety profile and demonstrated

promising anti-tumor activity in a phase 1 study in triple-negative breast cancer [40]. Additionally, in a multicenter phase 2 trial, single-agent veliparib (400 mg BID daily) followed by veliparib (150 mg BID) plus carboplatin at disease progression also showed that safety and efficacy are encouraging in *BRCA*-associated metastatic breast cancer [41].

The efficacy results seen in this phase I study, with an ORR of 37% and CBR of 51% at dose levels corresponding to the RP2D and beyond, are comparable to those reported in phase I studies with other PARP inhibitors. In particular, response rates of approximately 40% have been reported near the MTDs for cancers associated with *BRCA* mutations [42–45]. The clinical activity in our overall ovarian and breast cancer patient population is also similar to the 26% response rate in a phase II single-agent veliparib study in ovarian cancer [46].

Our study included a large proportion of patients without *BRCA* mutations allowing an evaluation of the difference between the *BRCA*mut and *BRCA*wt populations. In an early study with olaparib, it was demonstrated that 24% of patients with sporadic ovarian but not patients with sporadic breast cancer showed objective responses [43]. While the findings from our study are relatively similar, we did demonstrate stable disease in a small proportion of breast cancer (n=6) patients who did not have *BRCA* mutations on germline analysis. In this study, somatic testing was not performed, so it remains possible that some responses were associated with somatic *BRCA* mutations. One of the six responders with stable disease did not have archival tissue submitted for correlative studies. Of the remaining five responders, FANCD2 foci were absent in tumors of one patient and loss of *BRCA1* immunostaining was found in two patients. Patients with sporadic breast and ovarian cancers might derive greater benefit from combining PARP inhibitors with chemotherapy compared to PARP inhibitor alone. This study demonstrated an increase in responses seen at the higher dose levels, consistent with a steep dose response effect as has been described for other PARP inhibitors such as olaparib and niraparib [47]. We started dose escalation at 50 mg based on data from the phase 0 study, and observed response at that first dose level; however, overwhelmingly objective responses and prolonged clinical benefit were seen at doses above 300 mg BID [10].

The values for veliparib pharmacokinetic parameters calculated non-compartmentally in the current study (Cl/F 15.9 (1.40) L/h, Vss/F 123 (1.36) L, $t_{½}$ 5.9 (1.3) h) are similar to those previously reported (Cl/F 20.9 L/h, V/F 173 L, $t_{½}$ 6.1 h) in a population model [48], as well as reported (Cl/F 17.3 L/h, V/F 147 L, $t_{½}$ 4.0 h) in our previous population modeling of the current dataset [18], and veliparib pharmacokinetics reported in combination with cyclophosphamide, vinorelbine, temozolomide, bendamustine, gemcitabine, carboplatin and paclitaxel [49,34,50–52,17,53]. The notable outlier of veliparib PK is in combination with liposomal doxorubicin, where apparent clearance was much lower than in our dataset [54]. Based on both C_{max} and $AUC_{0\text{-}inf}$ of day 1, we could not reject the null hypothesis of dose proportionality of veliparib over the range of dose levels studied (95% CI of the coefficient included 1). Based on the stringent bioequivalence-derived criteria proposed by Smith et al. [55], we could also not declare dose proportionality (90% CI of the coefficient was not contained within the range of 0.903–1.097). However, these stringent criteria have been deemed impractically strict when applied over a large dose range, and our data indeed meets more lenient criteria proposed subsequently [56] (90% CI of the coefficient was

easily contained within the range of 0.699–1.301). Our data, therefore, support veliparib dose proportionality over the dose range of 50–500 mg. We did not observe any unexpected changes in veliparib PK between day 1 and day 15, suggesting there is no time-dependent effect of veliparib dosing on any of its PK parameters. We did find significant relationships between both veliparib C_{max} and AUC and response and nausea. The few patients not evaluable for response appeared to have a relatively high exposure, potentially predisposing to toxicity resulting in discontinuation of therapy and inability to derive benefit.

To identify biological features of the cancers that might predict veliparib response, we performed a number of correlative studies in this phase I trial. Decreases in PBMC and tumor PAR levels after veliparib dosing, proved target engagement, while limited tumor γ-H2AX data did not suggest DNA damage after 1 cycle of treatment. It may well be that the clinical responses observed after PARP inhibition in the absence of concomitant cytotoxic therapy is partly associated with many client proteins whose functions is modulated by PAR-ylation [9].

The mandatory biopsy cohort suffered from low biopsy yield (69%), even with onsite pathologic analysis using a touch prep of the specimen. We also learned that while 4 cores were taken, not all contained tumor or could be analyzed. This number is similar to what has been reported in the NCI literature with 60% adequate biopsy yield [57]. In a follow-up study [40] where veliparib was combined with weekly paclitaxel and carboplatin with predominantly breast cancer patients enrolled, the biopsy yield was higher (86%). In our hands, the image-guided biopsies in ovarian cancer patients with carcinomatous implants were low yield, which may be due to their deep location surrounded by large vessels and/or other organs. Iin future, caution should be taken when conducting correlative analyses in this patient population.

Potential resistance mechanisms for PARP inhibitors are under active investigation, and it is postulated that there are similar resistance mechanisms to platinum-based chemotherapy. With both platinum drugs and PARP inhibitors, there is evidence that *BRCA* reversion mutations can occur, rendering therapy ineffective. In this study, no reversion mutations were identified, likely due to the early timing of the biopsy. More recent data suggest that reversion mutations in circulating tumor DNA (ctDNA) correlate with response to the PARP inhibitor rucaparib [21], and ctDNA may identify subclonal reversion mutations that might not be present in a small needle biopsy.

Low expression of 53BP1 protein has been reported to restore homologous recombination and contribute to PARP inhibitor resistance even in the face of persistent BRCA1 deficiency [58]. Our assays performed in the context of a single-agent trial of the PARP inhibitor ABT-767 demonstrated a negative correlation between 53BP1 expression and the percentage of tumor shrinkage in recurrent BRCA1-mutant ovarian cancer [23]. In contrast, we did not observe a correlation between 53BP1 expression and response in the present trial. It is important to note, however, that the present study included both breast and ovarian cancer. In addition, the endpoint assessed in our study (response vs. no response) was different from the endpoint assayed in the previous trial (% tumor shrinkage). Further studies are required to determine whether expression of 53BP1 and/or other cellular proteins in the

same pathway [58] might provide useful information in ovarian cancer patients receiving single-agent PARP inhibitor and/or mechanistic insight into failure of tumors to respond despite the presence of HR defects.

Rigorous analysis of methylation through the use of two orthogonal approaches identified only three samples with methylated BRCA1 by both assays. Samples shown to be methylated by pyrosequencing did not show methylation by MSP and vice versa, potentially also due to false positive results with incomplete conversion of DNA in the bisulfite reaction, as previously reported [59].

5 CONCLUSION

In summary, our study shows that single agent veliparib can be used safely and tolerably at a continuous schedule of 400 mg BID, and that this treatment is associated with clinical activity both in patients with *BRCA*mut cancers and *BRCA*wt basal-like breast cancers. Target engagement was observed, and PK exposure correlated with both response and nausea, while none of the other biomarker studies yielded significant relationships. Significant advances have been made in the clinical development of PARP inhibitors for the treatment of patients with *BRCA* mutations. These agents represent personalized therapy for cancers that have underlying defects in homologous recombination-mediated DNA repair. Since the inception of this study, olaparib, rucaparib, and niraparib have been FDA-approved for ovarian cancers and olaparib and talazoparib have been FDA-approved for germline *BRCA*mut breast cancer in various settings. There are several ongoing phase 3 trials focused on breast (NCT03150576, NCT02032823) and ovarian (NCT02282020, NCT02446600, NCT02502266, NCT02855944, NCT02655016) cancer. While there is clear demonstration of efficacy in the *BRCA*mut population, the optimal use of PARP inhibitors, either as monotherapy or in combination with cytotoxic chemotherapy, as well as its potential role as maintenance therapy after chemotherapy is evolving. In addition, the exact role of these agents in the context of *BRCA*wt cancers remains unclear. With the expansion of PARP inhibitor indications and their incorporation into earlier lines of treatment, further studies are also needed to characterize the mechanisms of resistance that is emerging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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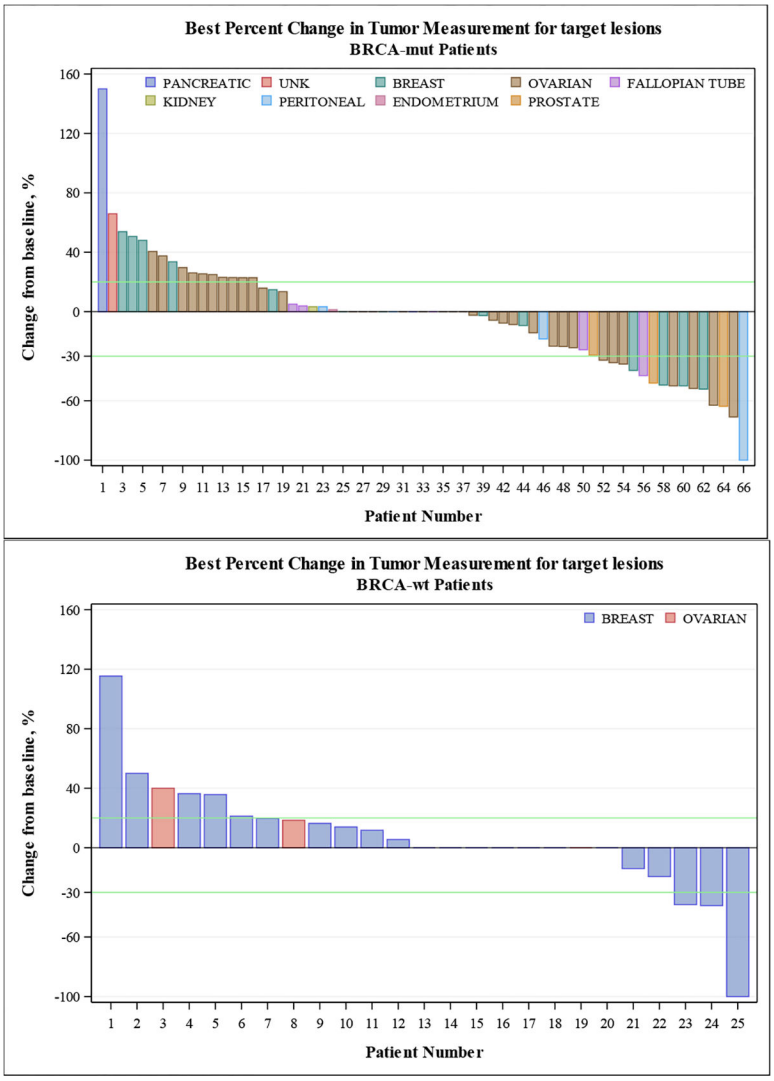

Figure 1.

Percent change in tumor measurement from baseline for target lesions for *BRCA*mut subjects).

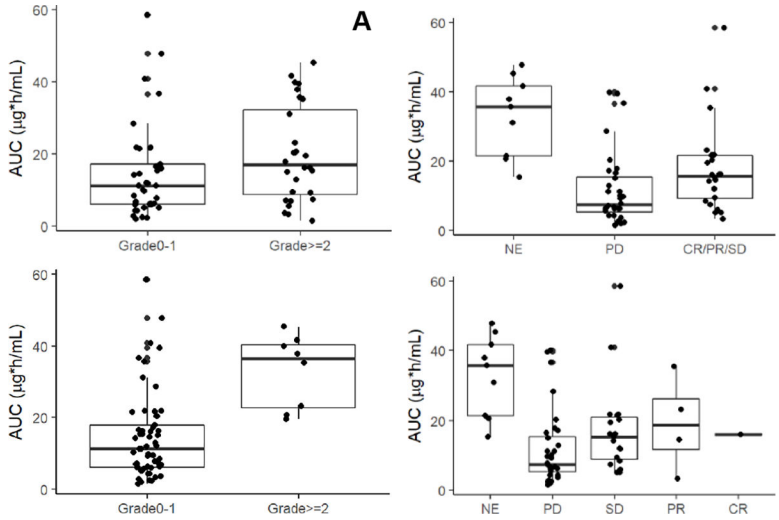

Figure 2.

Exposure-response relationship of day 1 veliparib AUC (A) by cycle 1 any toxicity grade 0–1 vs grade 2 and up (no significance); (B) by cycle 1 nausea grade 0–1 vs grade 2 and up (p=0.0004, n=65; per Wilcoxon non-parametric test); (C) by progressive disease (PD) vs stable disease (SD), partial response (PR) and complete response (CR) (p=0.019, n=56; per Wilcoxon non-parametric test); and (D) by individual response categories (patients not evaluable for response are labelled NE).

Table 1.

Dose-escalation and dose limiting toxicities (DLT).

Dose Level	Veliparib (mg AM/PM)	Enrolled mut/wt	Evaluable mut/wt	DLT mt/wt	Grade – DLT**
1	50/50	7/3	7/3	1*/0	Grade 2 thrombocytopenia, later deemed related to disease progression, necessitated hold of veliparib > 2 weeks
2	100/50	3/3	3/3		
3	100/100	3/3	3/3		
4	150/100	3/3	3/3		
5	150/150	3/3	3/3		
6	200/200	4/3	3/3		
7	300/300	6/3	4/3		
8	400/400	34/7	27/6	1/1	G3 nausea / G2 seizure
9	500/500	7/0	6/0	1/0	G2 seizure

* DLT experienced before start of parallel enrollment of *BRCA*mt and *BRCA*wt cohorts.

** Per protocol, any seizure occurring in a patient on this study was considered a DLT, unless in the setting of CNS metastases.

Table 2.

Grade 3/4 toxicities by cohort and dose level (number of patients (%)).

Toxicity (CTCAEv4.0 Term)	Total	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8	DL9
***BRCA*mut cohort**	70	7	3	3	3	3	4	6	34	7
Any Grade 3/4 toxicity	17 (24)	1 (14)	1 (33)	0	0	0	0	2 (33)	11 (32)	2 (29)
Grade 3 toxicity										
Any Grade 3 toxicity	15 (21)	1 (14)	0	0	0	0	0	2 (33)	11 (32)	1 (14)
Lymphocyte count decreased	9 (13)	0	0	0	0	0	0	1 (17)	7 (21)	1 (14)
Thromboembolic event	2 (3)	0	0	0	0	0	0	0	2 (6)	0
Nausea	2 (3)	0	0	0	0	0	0	0	2 (6)	0
Abdominal pain	2 (3)	0	0	0	0	0	0	0	2 (6)	0
Anemia	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Alkaline phosphatase increased	1 (1)	1 (14)	0	0	0	0	0	0	0	0
Aspartate aminotransferase increased	1 (1)	1 (14)	0	0	0	0	0	0	0	0
Appendicitis	1 (1)	0	0	0	0	0	0	1 (17)	0	0
Headache	1 (1)	0	0	0	0	0	0	1 (17)	0	0
Dehydration	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Urinary tract infection	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Fatigue	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Hypophosphatemia	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Grade 4 toxicity										
Any Grade 4 toxicity	3 (4)	0	1 (33)	0	0	0	0	0	1 (3)	1 (14)
Lymphocyte count decreased	1 (1)	0	0	0	0	0	0	0	1 (3)	0
Thromboembolic event	1 (1)	0	1 (33)	0	0	0	0	0	0	0
Anemia	1 (1)	0	0	0	0	0	0	0	0	1 (14)
Dyspnea	1 (1)	0	0	0	0	0	0	0	0	1 (14)
Platelet count decreased	1 (1)	0	0	0	0	0	0	0	0	1 (14)
***BRCA*wt cohort**	28	3	3	3	3	3	3	3	7	0
Grade 3 toxicity										

Toxicity (CTCAEv4.0 Term)	Total	DL1	DL2	DL3	DL4	DL5	DL6	DL7	DL8	DL9
Any Grade 3 toxicity	8 (29)	0	1 (33)	0	2 (67)	0	2 (67)	0	3 (43)	-
Lymphocyte count decreased	5 (18)	0	1 (33)	0	2 (67)	0	1 (33)	0	1 (14)	-
Basilic vein thrombosis	1 (4)	0	0	0	0	0	1 (33)	0	0	-
Dyspnea	1 (4)	0	0	0	0	0	0	0	1 (14)	-
Fatigue	1 (4)	0	0	0	0	0	0	0	1 (14)	-
Hypophosphatemia	1 (4)	0	0	0	0	0	0	0	1 (14)	-

At dose levels 3 and 5, no grade 3/4 toxicities were observed.

Table 3.

Most common all-grade toxicities attributed to veliparib, BRCAmut and BRCAwt combined (number of patients (%)).

Toxicity (CTCAEv4.0 Term)	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	92 (94)	86 (88)	54 (55)	30 (31)	3 (3)
Nausea	64 (65)	42 (43)	20 (20)	2 (2)	0 (0)
Fatigue	44 (45)	33 (34)	9 (9)	2 (2)	0 (0)
Lymphocyte count decreased	37 (38)	7 (7)	15 (15)	14 (14)	1 (1)
Vomiting	32 (33)	25 (26)	7 (7)	0 (0)	0 (0)
Anemia	31 (32)	19 (19)	10 (10)	1 (1)	1 (1)
White blood cell decreased	27 (28)	20 (20)	7 (7)	0 (0)	0 (0)
Anorexia	20 (20)	17 (17)	3 (3)	0 (0)	0 (0)
Diarrhea	19 (19)	16 (16)	3 (3)	0 (0)	0 (0)
Platelet count decreased	18 (18)	14 (14)	3 (3)	0 (0)	1 (1)
Neutrophil count decreased	17 (17)	13 (13)	4 (4)	0 (0)	0 (0)
Dysgeusia	16 (16)	16 (16)	0 (0)	0 (0)	0 (0)
Hyperglycemia	10 (10)	9 (9)	1 (1)	0 (0)	0 (0)
Aspartate aminotransferase increased	9 (9)	8 (8)	0 (0)	1 (1)	0 (0)
Constipation	9 (9)	8 (8)	1 (1)	0 (0)	0 (0)
Dizziness	9 (9)	8 (8)	1 (1)	0 (0)	0 (0)
Headache	9 (9)	7 (7)	1 (1)	1 (1)	0 (0)
Dry mouth	8 (8)	8 (8)	0 (0)	0 (0)	0 (0)
Hypophosphatemia	8 (8)	2 (2)	4 (4)	2 (2)	0 (0)
Hyponatremia	7 (7)	7 (7)	0 (0)	0 (0)	0 (0)
Insomnia	7 (7)	6 (6)	1 (1)	0 (0)	0 (0)
Abdominal pain	6 (6)	3 (3)	1 (1)	2 (2)	0 (0)
Alkaline phosphatase increased	6 (6)	3 (3)	2 (2)	1 (1)	0 (0)
Dyspepsia	6 (6)	6 (6)	0 (0)	0 (0)	0 (0)
Dyspnea	5 (5)	2 (2)	1 (1)	1 (1)	1 (1)
Myalgia	5 (5)	4 (4)	1 (1)	0 (0)	0 (0)

Table 4.

Best responses in *BRCA*mut and *BRCA*wt cohorts.

	***BRCA*mut**							***BRCA*wt**					
	#Evaluable	**CR**	**PR**	**SD**	**PD**	**ORR (%)**	**CBR (%)***	**#Evaluable**	**PR**	**SD**	**PD**	**ORR (%)**	**CBR* (%)**
All Patients	62	1	13	20	28	14/62 (23%)	26/62 (42%)	25	2	7	16	2/25 (8%)	4/25 (16%)
By Primary Tumor													
Ovarian	33	0	6	10	17	6/33 (18%)	14/33 (42%)	3	0	1	2	0/3 (0%)	0/3 (0%)
Breast	15	0	4	4	7	4/15 (27%)	5/15 (33%)	22	2	6	14	2/22 (9%)	4/22 (18%)
Fallopian Tube	4	0	1	2	1	1/4 (25%)	2/4 (50%)						
Peritoneal	3	1	0	2	0	1/3 (33%)	1/3 (33%)						
Prostate	3	0	2	1	0	2/3 (67%)	3/3 (100%)						
Pancreatic	1	0	0	0	1	0/1 (0%)	0/1 (0%)						
Endometrium	1	0	0	1	0	0/1 (0%)	1/1 (100%)						
Kidney	1	0	0	0	1	0/1 (0%)	0/1 (0%)						
Unknown	1	0	0	0	1	0/1 (0%)	0/1 (0%)						
By Dose Level													
DL1	7	0	0	0	7	0/7 (0%)	0/7 (0%)	3	1	0	2	1/3 (33%)	1/3 (33%)
DL2	3	0	0	2	1	0/3 (0%)	2/3 (67%)	3	0	1	2	0/3 (0%)	0/3 (0%)
DL3	3	0	0	1	2	0/3 (0%)	1/3 (33%)	3	1	0	2	1/3 (33%)	1/3 (33%)
DL4	3	0	0	2	1	0/3 (0%)	1/3 (33%)	3	0	0	3	0/3 (0%)	0/3 (0%)
DL5	3	0	0	1	2	0/3 (0%)	0/3 (0%)	3	0	1	2	0/3 (0%)	0/3 (0%)
DL6	4	0	0	3	1	0/4 (0%)	2/4 (50%)	3	0	2	1	0/3 (0%)	1/3 (33%)
DL7	4	0	1	1	2	1/4 (25%)	2/4 (50%)	2	0	1	1	0/2 (0%)	1/2 (50%)
DL8	30	0	12	8	10	12/30 (40%)	16/30 (53%)	5	0	2	3	0/5 (0%)	0/5 (0%)
DL9	5	1	0	2	2	1/5 (20%)	2/5 (40%)						

*CBR defined as CR, PR, or SD ≥ 6 cycles