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Phase I Study of Veliparib (ABT-888) Combined with Cisplatin and Vinorelbine in Advanced Triple-Negative Breast Cancer and/or *BRCA* Mutation-Associated Breast Cancer

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Abstract

PURPOSE—Cisplatin is synergistic with vinorelbine and the poly(ADP-ribose) polymerase (PARP) inhibitor veliparib, and has anti-neoplastic activity in TNBC and *BRCA* mutation-associated breast cancer. This phase I study assessed veliparib with cisplatin and vinorelbine.

PATIENTS AND METHODS—A 3+3 dose escalation design evaluated veliparib administered BID for 14 days with cisplatin (75 mg/m^2 day 1) and vinorelbine (25 mg/m^2 days 1,8) every 21 days, for six to ten cycles, followed by veliparib monotherapy. Pharmacokinetics, measurement of poly(ADP-ribose) in peripheral blood mononuclear cells, and preliminary efficacy were assessed. Immunohistochemistry and gene expression profiling were evaluated as potential predictors of response.

RESULTS—Forty-five patients enrolled in nine dose cohorts plus five in an expansion cohort at the highest dose level and recommended phase II dose, 300 mg BID. Maximum tolerated dose of veliparib was not reached. Neutropenia (36%), anemia (30%), and thrombocytopenia (12%) were the most common grade 3/4 adverse events. Best overall response for 48 patients was radiologic response with 9-week confirmation for 17 (35%; 2 complete, 15 partial), and stable disease for 21 (44%). Germline *BRCA* mutation presence versus absence was associated with 6-month progression-free survival (10 of 14 (71%) vs 8 of 27 (30%), mid-p=0.01). Median progression-free survival for all 50 patients was 5.5 months (95% confidence interval 4.1–6.7).

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CONCLUSION—Veliparib at 300 mg BID combined with cisplatin and vinorelbine is well tolerated with encouraging response rates. A phase II randomized trial is planned to assess veliparib's contribution to cisplatin chemotherapy in metastatic TNBC and *BRCA* mutation-associated breast cancer.

Translational Relevance—We hypothesize that TNBC tumors have defects in homologous recombination DNA repair similar to *BRCA* mutation associated tumors, which will render them sensitive to platinum therapy and PARP inhibition. This report describes a phase I study that explored the safety and efficacy of cisplatin, vinorelbine and veliparib. This combination was tolerable and reached the highest dose of veliparib in combination with chemotherapy used in breast cancer to date. Antineoplastic activity was observed both in *BRCA* mutation associated breast cancer and in *BRCA* wild-type TNBC. We measured changes in PARP activity and performed gene expression profiling and immunohistochemistry studies. Based on promising results from this study, a randomized phase II study has been developed to evaluate the addition of veliparib to cisplatin chemotherapy for patients with advanced TNBC. This study will incorporate a multi-pronged biomarker approach to identify a homologous recombination repair deficiency (HRD) phenotype that derives benefit from PARP inhibition.

Keywords

triple-negative; *BRCA* mutation; veliparib; ABT-888

Introduction

The triple-negative breast cancer (TNBC) phenotype (negative for estrogen receptor, progesterone receptor, and overexpression of human epidermal growth factor receptor (HER)2), found in 10–17% of breast cancers, is associated with early relapse (1) and short survival following recurrence (2). The need for more effective treatments has led to the investigation of DNA-damaging chemotherapy agents and targeted therapies.

TNBCs and *BRCA1* germline mutation-associated breast cancers share histologic and molecular features, including a basal-like molecular phenotype (3, 4). Approximately 10–20% of patients with TNBC carry germline *BRCA1* or *BRCA2* mutations and have an underlying defect in DNA repair (5, 6). However, DNA repair may be altered through other mechanisms, such as somatic or germline mutations in other genes, DNA methylation, or attenuated mRNA expression. It is speculated that 50–60% of TNBC will demonstrate "BRCAness", homologous recombination repair deficiency (HRD) phenotype (7, 8).

Poly(ADP-ribose) polymerase (PARP) enzymes recognize DNA damage and facilitate DNA repair. PARP inhibitors have shown preclinical and clinical activity in cancers with DNA repair defects, in particular *BRCA1* and *BRCA2* mutated carcinomas (9, 10). Veliparib (ABT-888) is an oral small molecule inhibitor of PARP-1 and PARP-2 that inhibits PARP activity in xenograft models and in human cancers (11, 12). Veliparib monotherapy has clinical activity in patients with *BRCA* mutation-associated breast, ovarian and prostate cancers (13–15).

Cisplatin causes the formation of DNA-platinum adducts and intra- and inter-strand DNA crosslinks. This blocks replication and transcription, resulting in single and double-strand DNA breaks leading to cytotoxicity. Cisplatin has single agent anti-tumor activity in TNBC and *BRCA* mutation-associated breast cancer breast cancer (16, 17), and synergy with veliparib in breast cancer xenograft models (11). Platinum agents and taxanes are generally synergistic for breast cancer, however, *in vitro* studies suggest that BRCA1-deficient cells are resistant to taxanes (18–20). Although vinorelbine is also an anti-microtubule agent, BRCA1-deficient cells were noted to be sensitive to vinorelbine, with differential apoptotic potential and impact on the ERK pathway as possible mechanisms (20). Cisplatin and vinorelbine have also shown synergy in breast cancer animal models (21).

Clinically, cisplatin combined with vinorelbine has shown safety and efficacy in patients with pretreated metastatic breast cancer with response rates of 41% to 61% in several small Phase II studies (22), compared to a response rate of less than 10% to single agent cisplatin. The vinorelbine/cisplatin combination is generally well tolerated due to non-overlapping toxicities, and appears not to alter pharmacokinetics of either vinorelbine or ultrafilterable platinum (23,24). Thus vinorelbine, while not a DNA damaging agent, is a non-cross resistant drug with potential synergistic activity to cisplatin.

We hypothesized that veliparib combined with cisplatin and vinorelbine would prove safe and effective in patients with advanced TNBC. We performed a veliparib dose-finding phase I design, incorporating pharmacokinetic correlatives of cisplatin and veliparib because of the common renal elimination of these agents.

Patients and Methods

Trial Design

The primary objective was to determine the maximum tolerated dose (MTD) of veliparib administered daily for 14 days of a 21-day cycle in combination with cisplatin and vinorelbine. Secondary objectives were to assess the safety, tolerability, pharmacokinetic (PK) profile, and preliminary efficacy of the combination, and to quantify PARP inhibition at various dose levels. An exploratory objective was to identify potential biomarkers of response to this PARP inhibition/platinum-based chemotherapy regimen.

This trial [ClinicalTrials.gov: NCT0110429] was conducted at the University of Washington under an investigator initiated IND with Institutional Review Board approval. Veliparib was supplied by Abbott Laboratories (AbbVie).

Cisplatin was administered at 75 mg/m^2 intravenously over 1 hour on day 1 of each cycle with hydration and mannitol for renal protection. Vinorelbine was given at 25 mg/m^2 intravenously over 10–20 minutes on day 1 (prior to cisplatin) and on day 8. Peg-filgrastim was administered on day 8 of each cycle. Cycles of chemotherapy were repeated every 3 weeks. Veliparib, at the pre-specified cohort dose level, was self-administered twice daily days 1 through 14, except cycle 1 when administration was days 0 through 13 for PK evaluation of veliparib alone on day 0.

The starting dose of veliparib was 20 mg orally twice daily (BID). Following a standard 3 + 3 design, cohorts of 3 to 6 patients were recruited at each dose level. To be evaluable for cohort dose escalation decisions, a patient must either have experienced a dose limiting toxicity (DLT), or have completed cycle 1 of treatment (at least 75% of the cohort dose for each agent) and been observed for 21 days for adverse events. Patients who were not evaluable for dose escalation were replaced for that purpose, but could remain enrolled. Dose limiting toxicity (DLT) was defined as an adverse event (AE) that occurred in the first cycle, was felt to be related to study therapy, and fulfilled one of the following criteria: grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L) for > 5 days or ANC $< 0.1 \times 10^9$/L for > 3 days; grade 3 neutropenia with fever; grade 4 thrombocytopenia; grade 3 or greater non-hematologic toxicity that represented at least a 2 grade increase from baseline (except grade 3 nausea/vomiting and diarrhea without adequate symptomatic treatment, grade 3 creatinine that corrected to grade 1 or baseline within 24 hours and grade 3 metabolic toxicities that corrected to at least grade 2 within 24 hours); or a delay of more than 2 weeks in starting the next cycle due to toxicity. (Further details on dose escalation found in Supplement.) An expansion cohort of 5 patients was enrolled for evaluation at the recommended phase II dose, to further evaluate safety and to aid in planning for a Phase II study.

The planned duration of combination treatment was 6 cycles, to avoid neuropathy associated with cumulative cisplatin of 500–600 mg/m^2. Patients without progressive disease or significant toxicity could continue the combination regimen for up to 10 cycles. Patients without progressive disease after 6–10 cycles could continue on veliparib monotherapy. The monotherapy dose was initially the same dose that the patient received on enrollment, increased to 400 mg BID during the trial based on external safety data. (Additional details in Supplement.)

Eligibility Criteria

Patients eligible for the trial were adults with recurrent and/or metastatic breast cancer meeting one of two criteria: 1) histologically confirmed primary or metastatic site ER-negative (less than 10%), PR-negative (less than 10%), and HER2 non-over expressing by IHC (0, 1) or non-amplified by fluorescence in situ hybridization (FISH); 2) confirmed *BRCA1* or *BRCA2* germline mutation associated breast cancer.

Patients were required to have: measurable disease by RECIST or clinical exam; Eastern Cooperative Oncologic Group performance status < 2; and adequate organ and marrow function (defined in Supplement). Any number of prior anti-cancer therapies was permitted, including prior platinum therapy. Patients with brain metastases were eligible if they had surgical excision and/or radiation therapy followed by 14 days of stable neurologic function prior to the first dose of study drug. (Additional details in Supplement.)

Safety evaluation

Toxicities were defined by NCI common toxicity criteria (CTCAE v4.0). Clinical evaluations were conducted at baseline and repeated on day 1, 8, and 15 of the first 3 cycles, and then on day 1 and 8 of each cycle of combined therapy thereafter. An audiogram was

performed before the first dose of cisplatin and repeated after cycle 4 of treatment, or earlier if symptoms of ototoxicity developed.

Pharmacokinetic (PK) evaluations

Drug-drug interactions may be important, primarily due to the common renal elimination pathway for cisplatin and veliparib (25,26). Metabolism plays a secondary role in veliparib clearance, with cytochrome P450 enzyme (CYP) 2D6 and additional liver metabolism accounting for ~18% and 10% of veliparib oral clearance, respectively (27). CYP2D6 is the major enzyme metabolizing veliparib with minor contribution from CYP1A2, and negligible contribution from 2C9, 2C19, and 3A4 (26,27). Vinorelbine is predominantly eliminated via CYP3A metabolism and biliary excretion, and renal excretion represents approximately 10% of the administered dose (28). Although vinorelbine is a substrate for drug efflux transporters, such as P-glycoprotein (P-gp), veliparib does not appear to inhibit or induce the activity of major CYP enzymes, is a weak P-glycoprotein (P-gp) substrate, and does not appear to inhibit or induce P-gp (26,29). Thus, veliparib appears to have a low potential for clinically significant P-gp or CYP-mediated drug-drug interactions. Therefore, vinorelbine concentrations were not measured.

PK sampling was performed in all patients receiving treatment during the 9 cohorts of dose-escalation. For PK analyses, plasma (for veliparib and cisplatin) and urine (for veliparib) were collected on days 0 and 1 of cycle 1 (C1D0, C1D1) and day 1 of cycle 4 (C4D1). (Detailed schedule in Table S1.)

PK sampling was performed during cycle 1 and cycle 4 to evaluate initial effects as well as changes in veliparib PK due to cumulative cisplatin nephrotoxicity (25). Plasma concentrations of veliparib were quantitated using a validated LC-MS method (30). Urine concentrations of veliparib were quantitated after 500-fold dilution with control human plasma. Concentrations of total platinum and ultrafilterable platinum (platinum not bound to macromolecules) were quantitated by atomic absorption spectrophotometry (AAS), as previously described (31).

Pharmacodynamic evaluation

Poly(ADP-ribose) (PAR) in peripheral blood mononuclear cells (PBMC) was quantitated with the PARP in-vivo Pharmacodynamic Assay® (Trevigen, Inc., Gaithersburg, MD). This assay is any immunoassay with purified monoclonal antibody to PAR as the capture reagent and rabbit anti-PAR antiserum as the detecting agent, described previously (32). PAR levels in PBMCs were evaluated 2, 4, 6 and 24 hours post administration of the first oral dose of veliparib for cycles 1 and 4. Timing of post-therapy PBMC sampling was adapted from the NIH Phase 0 study of veliparib (12) to coincide with PK evaluations.

Pharmacogenetic evaluation

Primary tumor specimens (formalin fixed paraffin embedded (FFPE) and/or fresh/frozen) were obtained from 37 patients, and metastatic tumor tissue was obtained from seven patients according to IRB-approved protocols. The following protein markers were assessed by standard immunohistochemistry protocols and used to evaluate triple negative and basal-

like status: ER, PR, HER2, EGFR, BRCA1, p53, CK5/6, survivin, and vimentin. Tumors were defined as basal-like by IHC if negative for ER/PR expression and HER2 amplification and if positive for EGFR and/or CK5/6. For gene expression profiling, transcripts (probes) were assessed using the WG-DASL® (*HumanHT-12 v4*) Assay (Illumina, Inc., San Diego CA). (Additional details in Supplement.) MIAME-compliant microarray data were deposited into the Gene Expression Omnibus (GEO) of NCBI under the accession number GSE72795.

Efficacy and statistical analyses

Patients who took at least one dose of veliparib were included in the safety analysis. Adverse events and serious adverse events were summarized in order of prevalence, with the highest grade experienced by each patient reported for each adverse event.

PK parameters of veliparib and platinum were determined using non-compartmental methods (WinNonlin version 5.2, Pharsight Corporation, Mountain View, CA, USA). Proportionality of exposure (C_{max} and $AUC_{0–6}$) with dose was evaluated by a power model (33), with linear mixed effects models fitted with random patient intercept and categorical time (C1D1, C4D1). Change in individual PK parameters between cycles was evaluated using the Wilcoxon signed rank test.

Response analysis excluded patients who withdrew before the first radiographic assessment due to reasons other than disease or toxicity. Patients who withdrew due to disease or toxicity were categorized as non-responders. The proportion of subjects with a complete (CR) or partial response (PR) based on RECIST 1.1 was estimated, with a corresponding 95% Wilson (score) confidence interval. Confirmation (a second radiographic assessment 4 or more weeks after CR or PR) was required for best overall response. Radiographic assessments occurred at 9-week intervals. Progression-free survival (PFS) was defined as the time from starting study therapy to radiographically confirmed disease progression or death. If a patient stopped study therapy and radiographic assessment prior to progression, death was a PFS event if it occurred within 12 weeks. Otherwise, PFS was censored at the time of stopping study therapy. Overall survival (OS) was defined as the time from starting study therapy until death, with censoring at the time of last contact or date of data lock (12/15/2014). Median PFS and OS and the corresponding 95% confidence intervals were estimated using the Kaplan-Meier method. Median PFS and OS and the corresponding 95% confidence intervals were estimated using the Kaplan-Meier method. Comparisons of rates (response and 6-month PFS [PFS6]) were performed using the mid-p correction to Fisher’s exact test (34).

Study data were managed using REDCap electronic data capture tools hosted at the University of Washington (35). Statistical tests were two-sided. Statistical analyses were conducted using SAS/STAT software, version 9.4 (SAS Institute, Inc., Cary, NC) and R version 3.0.3 and 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Demographics

Between July 2010 and February 2014, 50 patients were treated; 45 in nine dose levels and five in a safety expansion cohort. Although there were few DLTs, most cohorts enrolled more than three patients for dose escalation decisions (Table S2). Patient and disease characteristics are summarized in Table 1. Fourteen patients (28%) were confirmed germline *BRCA1* or *BRCA2* mutation carriers. Most patients (68%) had three or more disease sites. Seven patients had treated brain metastases. The majority of patients had received prior chemotherapy for metastatic disease, as well as (neo)adjuvant chemotherapy. Seventeen patients (34%) had received prior platinum.

Toxicity

The regimen was well tolerated. Patients received a median of six cycles of combined chemotherapy plus veliparib (range 0–9 cycles). Within the first 6 cycles, median drug delivery was 90% for cisplatin, 73% for vinorelbine, and 93% for veliparib. Thirty patients (60%) completed at least six cycles of combined chemotherapy and veliparib; one patient declined further study participation, 8 patients had progressive disease before starting monotherapy, and 23 patients proceeded to veliparib monotherapy (Figure 1, including two who started monotherapy after 5 cycles of combination therapy).

The most common treatment related adverse events (AEs) of all grades were nausea, fatigue, thrombocytopenia, anemia, and neutropenia (Table 2), mainly grade 1/2. Grade 3/4 AEs included neutropenia (36%, 3/18 with fever), anemia (30%), and thrombocytopenia (12%) (Table S3). No grade 3/4 AEs of neuropathy, creatinine elevation or hearing loss were observed. Six of 23 patients reported AEs while on monotherapy, including one with grade 3 anemia. The most common AEs of any grade on monotherapy were dyspepsia, nausea, and vomiting (each 17%).

The MTD of veliparib was not reached. Single DLT events in 3 dose cohorts are listed in Table S2. A patient with grade 4 thrombocytopenia (40 mg dose level) was found to have bone marrow involvement of breast cancer. Another patient (60 mg dose level), with 10 prior lines of therapy in the metastatic setting, had grade 4 neutropenic fever. She died of disease progression 3 weeks after C1D0. The final DLT (200 mg dose level) was grade 3 neutropenic fever in the setting of a breast abscess. The patient recovered from her infection and remained on study for 14 cycles.

Five patients (2 at 20 mg, 1 at 40 mg, 1 at 60 mg, and 1 at 120 mg veliparib) died within 30 days of stopping study therapy. These deaths were attributed to rapid disease progression soon after enrollment (within the first cycle in 3 patients).

Pharmacokinetics

Figure S1 shows dose proportionality of veliparib C_{max} and $AUC_{0–6}$ for C1D1 and C4D1. For the combination regimen with cisplatin and vinorelbine, veliparib PK appears to be linear with dose, with an apparent downward fluctuation at 200 mg. For recommended

proportionality limits Θ_L=0.8, Θ_H=1.25 (21) and dose ratio 300/20 = 15, the reference interval for a dose proportionality slope is (0.918, 1.082). The 90% confidence interval (CI) for the slope parameter was (0.719, 0.897) for C_{max} and (0.753, 0.928) for $AUC_{0–6}$. These intervals do not include a slope of 1.0, and only the $AUC_{0–6}$ slope CI overlaps with the reference interval.

Figure S2 shows veliparib PK parameters for C1D0 and C4D1, by dose cohort. Relative to cycle 1, the cycle 4 veliparib PK is in the presence of the cisplatin-vinorelbine backbone and after 3 cycles of this regimen. The median C4/C1 ratio (N=32) was 0.82 for $AUC_{0–6}$ (range 0.44–1.64, Wilcoxon signed-rank test p=0.002). For C_{max}, the median ratio was 0.85 (range 0.36–2.00, p=0.09). In contrast, ultrafilterable platinum PK parameters (dividing by dose to accommodate 7/31 patients analyzed with reduced cisplatin dose at cycle 4) did not appear to differ between cycle 1 and cycle 4 (Figure S3). The median C4/C1 ratio for ultrafilterable platinum C_{max} was 0.99 (range 0.34–2.41, Wilcoxon signed-rank p=0.58); the median C4/C1 ratio for ultrafilterable platinum $AUC_{0–24}$ was 0.98 (range 0.33–2.30, p=0.53). Overall, a similar proportion of the first veliparib dose was excreted in the urine over 12 hours for cycles 1 and 4 (median 61.7% and 66.7%, respectively; p=0.70, Wilcoxon signed-rank test with N=20). Additional PK results are shown in the Supplement.

Efficacy

Of 50 patients evaluable for safety, two were not evaluated for response due to early withdrawal for reasons other than disease or toxicity; one of these two died within 6 months and is assessable for 6-month PFS (Table 3). Best overall response was a complete response for 2/48 patients (4%) and partial response for 15 patients (31%), for an overall response rate of 35% (95% CI 23%–50%). Twenty-one patients (44%) had stable disease, and 10 (21%) had progressive disease as best response or were not assessed due to disease or toxicity. Table 3 displays tumor response by genetic phenotype. (Also see Figure S4.) *BRCA* mutation presence versus absence appears to be associated with both response (CR+PR, 57% vs 31%, mid-p=0.14) and PFS6 (71% vs 30%, mid-p=0.01).

A waterfall plot (Figure 2) and Table 3 suggest that germline *BRCA* mutation carriers are most likely to benefit from study therapy, regardless of veliparib dose, but responses occurred in patients of all genotypes.

The median PFS was 5.5 months (95% CI 4.1 −6.7), and the median OS was 9.6 months (95% CI 8.1 – 20.7). PFS and OS were greater for patients with a germline *BRCA* mutation (median 9.2 months PFS, 22.6 months OS) than for germline *BRCA* wild-type (4.2 months, 8.7 months) or unknown mutational status (4.0 months, 6.2 months) (log-rank test, p<0.001 for PFS, p=0.003 for OS) (Figure 3). Age, number of metastatic sites, and presence of individual metastatic sites did not predict PFS or OS. Veliparib dose did not predict PFS or OS in univariate or multivariable (with mutational status) Cox regression models.

The two patients with confirmed radiographic complete response are long-term responders and remain on veliparib (Figure 1). A patient in the 60 mg dose cohort with a *BRCA1* mutation (exon 13 insert 6kb rearrangement) received 6 cycles of combination therapy. Complete radiographic response of liver and distant lymph node lesions was observed at 36

weeks, and has been sustained through 57 cycles of monotherapy. The second long-term responder with radiographic CR (120 mg dose cohort) tested negative for a germline *BRCA1/2* mutation. She received 6 cycles of combination therapy, achieved radiographic CR at 54 weeks in supraclavicular and mediastinal lymph node sites of disease, and remains on veliparib monotherapy after 37 cycles. This patient had tumor tissue sampled at the time of stage IV diagnosis and had a basal-like phenotype by IHC. A DNA sequencing test, (BROCA, University of Washington, Division of Medical Genetics, Laboratory) was performed on DNA isolated from blood and showed no deleterious mutations in 40 genes in the Fanconi anemia/DNA repair pathway. However, gene expression analysis of BRCA1 and BRCA2 demonstrated reduced levels of both genes in her tumor compared to the other patient tumors tested in this study. (Further details on long term responders are in the Supplement.) A third patient from the expansion cohort also remains on study after 15 cycles.

Pharmacodynamics & Pharmacogenetics

Poly(ADP-ribose) (PAR) in peripheral blood mononuclear cells (PBMC) was assessed for 14 patients in dose cohorts 6–8 (120–200 mg). Figure S5 shows the PAR assay results (pg/mL) for each measurement (including duplicate measurements on the same sample), with one panel per patient. The PAR assay results were limited by low baseline PAR values and high inter-patient and intra-patient variability. Linear mixed effects models predicting log(concentration) with random intercept and linear contrasts did not find statistically significant differences between baseline and either cycle 1 or cycle 4 measurements ($p>0.15$), between cycle 1 and cycle 4 ($p>0.35$), or between the two earlier and two later post-dose measures for either cycle ($p>0.15$). There was also not evidence that PAR concentration (pg/mL) was associated with clinical benefit (PFS6) (Wilcoxon rank sum tests for selected time points, $p>0.15$).

Pre-therapy biopsies were assessed by immunohistochemistry for 28 patients. Twenty-five (89%) showed a basal-like phenotype by IHC (Table S6), which was not associated with PFS or OS ($p > 0.4$, log-rank test) or PFS6 (mid-p=0.16). Sixteen of 28 (57%) pre-therapy carcinomas showed high p53 protein expression; 22 (79%) were positive for vimentin protein expression. All carcinomas assessed showed expression of survivin and PARP. None of these markers were associated with PFS or OS.

Pre-treatment tissue from 24 patients had sufficient neoplastic tissue for gene expression profiling of over 29,000 transcripts by the WG-DASL® Assay; 23 tumor samples passed quality standards. Using intrinsic subtyping determined by the single sample prediction approach (36), cancer subtypes were 39% Basal-like, 9% Luminal A, 4% Luminal B, 0% HER2-enriched, 26% Normal Breast-like, 22% Unclassified. For 22 patients, 63% with Basal-like tumors had CR/PR, compared to 43% with non-basal-like tumors (mid-p=0.30). Using an alternative gene expression classification specific for TNBC (37), subtypes were: Basal-like1/Basal-like2 (26%); Immune modulatory (39%); Mesenchymal/Mesenchymal Stem-like (13%); Luminal AR (4%); Unstable (17%). There was no association between any of the TNBC subtypes and response. We observed no enrichment of differentially expressed genes with p-value <0.05 when comparing patients with response to no response. In gene

pathway analyses, the lowest false discovery rate for a positive or negative relationship between the response groups was 0.57 and 0.19, respectively.

Discussion

This phase I trial demonstrates that the novel combination of cisplatin, vinorelbine and veliparib is well tolerated and active in patients with advanced TNBC and/or *BRCA* mutation associated breast cancer. The recommended phase II dose (RP2D) of veliparib, 300 mg BID, is close to the maximal monotherapy dose and is a clinically active single agent dose. Anti-neoplastic activity was observed in patients both with and without germline *BRCA* mutations.

The maximum tolerated dose (MTD) of veliparib was not reached. As monotherapy, the current RP2D for veliparib is 400 mg BID throughout a 28-day cycle. At this dose, the most notable toxicities have been gastrointestinal. In a single arm study in *BRCA* mutation carriers with recurrent ovarian cancer, nausea was a common reason for dose delay and dose reduction (38). To avoid potential compromise of the back-bone regimen, veliparib dosing did not exceed 300 mg BID in combination with cisplatin and vinorelbine. Unlike other PARP inhibitor platinum combination chemotherapy regimens, in which myelotoxicity has significantly limited dose delivery of the agents (39,40), this regimen offered high dose intensity of both cisplatin and veliparib, though more frequent dose reductions and delays occurred with vinorelbine. Dose delivery of vinorelbine was limited by hematologic toxicity, including anemia and neutropenia, the latter in spite of the use of pegfilgrastim.

Nephrotoxicity was not notable, despite the common renal elimination of veliparib and cisplatin. No patients experienced grade 3 or 4 platinum-related toxicities (elevated creatinine, peripheral sensory or motor neuropathy, or ototoxicity) which is in line with prior cisplatin/vinorelbine use in metastatic breast cancer (41). Data from animal models suggest that PARP inhibitors can protect against nephrotoxicity (42,43) and peripheral neuropathy (44,45) of cisplatin. PARP inhibition reduced cisplatin induced increase in BUN and creatinine levels, prevented structural degeneration of the kidney, decreased tubular necrosis, normalized cisplatin induced increase in poly-ADP ribosylation, and preserved ATP level in the kidney (42,43). It is postulated (42) that inhibition of PARP in the well oxygenated kidney tissue prevented excess activation of PARP enzyme when faced with the oxidative damage from cisplatin and prevented death of normal cells. In addition preclinical work using behavioral assays showed that PARP inhibition can reduce pain in cisplatin induced cold hyperalgesia and mechanical allodynia (44) and vincristine induced mechanical allodynia (45). Activation of PARP by platinum compounds may cause activation of primary afferent nociceptors through a TRPA1 dependent mechanism, and inhibition of PARP might explain in part a reduction of neuropathic pain (44). A larger randomized trial is required to evaluate these hypotheses of PARP inhibition protection from cisplatin induced nephrotoxicity and neurotoxicity.

PK analysis at C1 and C4 suggest that three cycles of the combination regimen did not affect exposure to ultrafilterable platinum, nor did it change veliparib renal excretion. This is consistent with existing data. Previous reports (46) showed that even at median cisplatin

doses of 603 mg/m^2, much more than 3 × 75= 225 mg/m^2 in our study, loss of glomerular filtration rate was modest (110 to 92 mL/min). Veliparib C_{max} and $AUC_{0–6}$ appeared to increase less than proportional with dose, although this effect was small over the dose range evaluated and exposure did continue to increase with dose. Slightly lower values of veliparib exposure at C4 could in part be due to increased renal activity from hydration (2 Liters normal saline over 2 hours before cisplatin and afterward) and mannitol during cisplatin infusion in cycle 4, which was not present at C1D0 when veliparib was administered alone.

Our RP2D of veliparib in combination with cisplatin and vinorelbine, 300 mg BID, is the highest veliparib dose reached to date in combination chemotherapy trials for breast cancer. This is significant because there is evidence for a dose response relationship with veliparib, and single agent activity is observed beginning at 300 mg BID (13). In germline *BRCA* mutation-associated cancer, a recently completed phase I study evaluated 9 dose levels of veliparib monotherapy and demonstrated a 29% overall response rate (at all dose levels combined) and a higher response rate of 60% at the RP2D (47). The finding of higher clinical response rates with higher doses of veliparib, despite achieving 90% PARP inhibition at lower doses by PAR assay (12, 13) suggests that combinations which allow for higher PARP inhibitor dosing may be preferred in order to achieve the best therapeutic response. In this study, conversion from partial to complete responses were observed on veliparib monotherapy (300 mg BID), providing evidence of the antineoplastic activity of single agent veliparib at a high dose, and suggesting that veliparib contributed to anti-neoplastic responses.

Although we emphasize that efficacy was not a primary endpoint, our results suggest a superior response rate and median PFS to trials of platinum monotherapy (48,49). Similar to other studies, we saw a higher response rate and median PFS in germline *BRCA* mutation positive patients compared to germline *BRCA* wild-type TNBC patients (48,49).

Many germline BRCA wild-type patients in our study responded to treatment, including a long-term responder, supporting the existence of a HRD phenotype that may predict response to PARP inhibition. These results are consistent with other veliparib studies in which patients with BRCA wild-type TNBC experienced objective tumor response (13, 47). Patients whose carcinomas had a basal phenotype by IHC did not have better responses than patients with non-basal-like TNBCs. This is consistent with results from the phase III TNT trial in which subtyping by the gene expression assay, PAM50, did not identify a subpopulation of germline *BRCA* mutation negative TNBC patients with better response to carboplatin than to docetaxel (49). In this small study, we found no gene expression subtype or profile associated with response. Since many putative mechanisms may result in a HR deficiency, a single biomarker is unlikely to detect all patients with the HRD phenotype. Thus, a multipronged approach should be explored. It remains to be demonstrated clinically which patients without a deleterious germline BRCA mutation may have other defects in the HR pathway which would render their tumors sensitive to PARP inhibition.

The high relative dose intensity achieved in this trial suggests that cisplatin may be a better platinum partner than carboplatin for veliparib in TNBC and germline *BRCA* mutation positive breast cancer. In contrast to the high dose of veliparib attained with cisplatin based

therapy in this phase I study, myelosuppression has limited the dose of veliparib that can be combined with carboplatin as a single agent (50) or with carboplatin and paclitaxel doublet (51). Data from ovarian cancer literature demonstrate that patients with a *BRCA1/2* mutation have increased susceptibility and shortened time to carboplatin hypersensitivity reactions, independent of other risk factors for hypersensitivity reactions (52). Therefore, cisplatin compared to carboplatin may improve the tolerability and durability of the platinum based combination regimens in *BRCA* mutation carriers in the metastatic setting where patients receive multiple cycles of chemotherapy.

A randomized, placebo-controlled trial is planned within the Southwest Oncology Group to determine the relative contribution of the PARP inhibitor to cisplatin chemotherapy. Vinorelbine will not be included in the phase II trial; doublets are being used less frequently in metastatic breast cancer in the era of molecularly targeted therapies, with a goal of advancing regimens balancing efficacy and toxicity. The veliparib dose in combination with cisplatin (75 mg/m^2 every three weeks) will be 300mg orally BID, with the option to continue monotherapy at 400mg orally BID after a minimum of 4 cycles of cisplatin and veliparib/placebo. Pharmacodynamics of PARP inhibition will not be evaluated; however, this trial will utilize a multipronged biomarker approach to define a HRD phenotype. It will test the hypothesis that the combination of platinum therapy and veliparib will be most active in breast cancers associated with germline *BRCA* mutations and in those harboring the HRD phenotype. Future investigation of PARP inhibitors in TNBC should incorporate robust correlative studies to define those subsets of TNBC most likely to respond to platinum based therapy and PARP inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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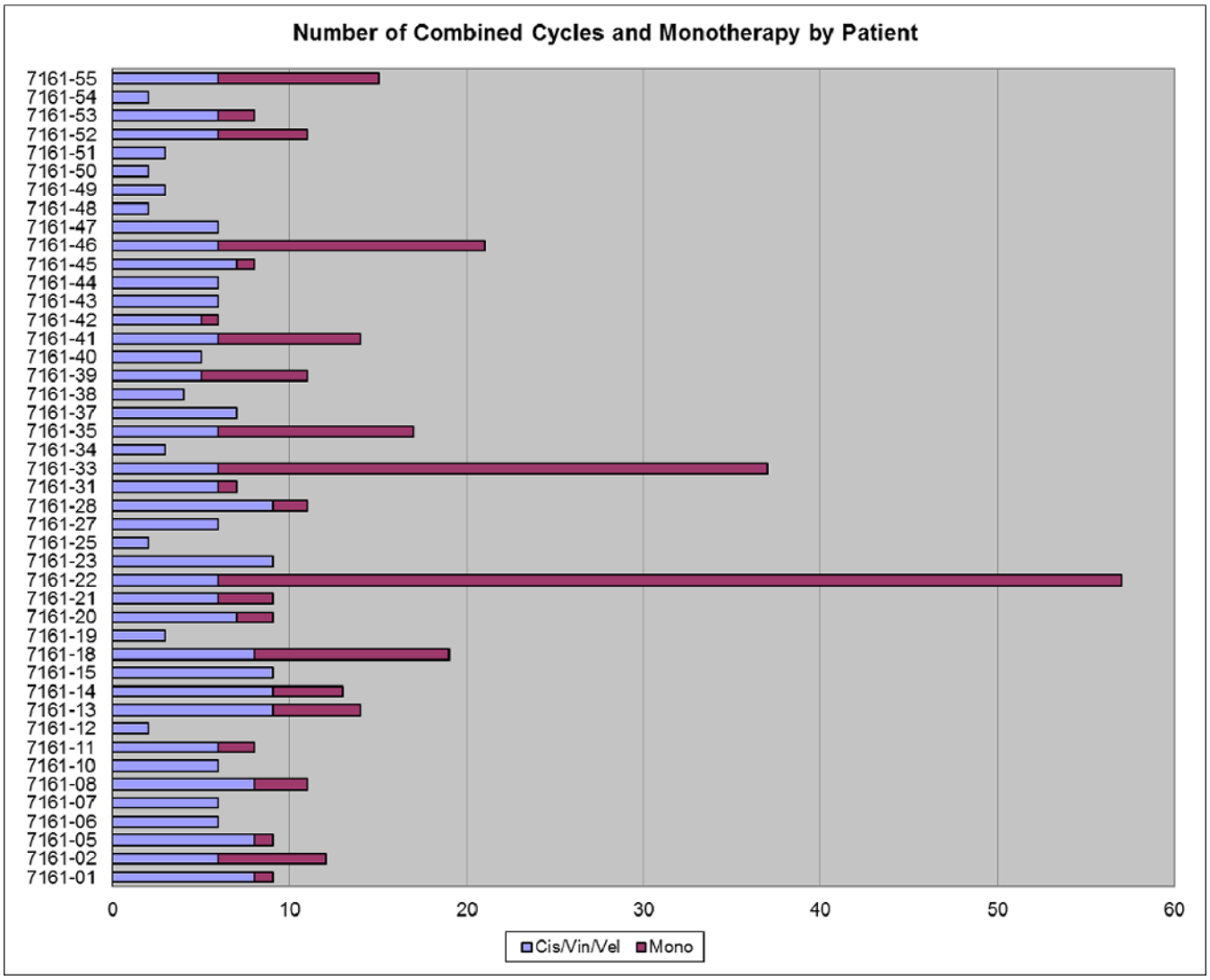

Figure 1.

Cycles (x-axis) received per patient (y-axis); combined cisplatin/vinorelbine/veliparib shown in blue; monotherapy with veliparib shown in red; three patients remain on study therapy (7161-22, 7161-33, 7161-55).

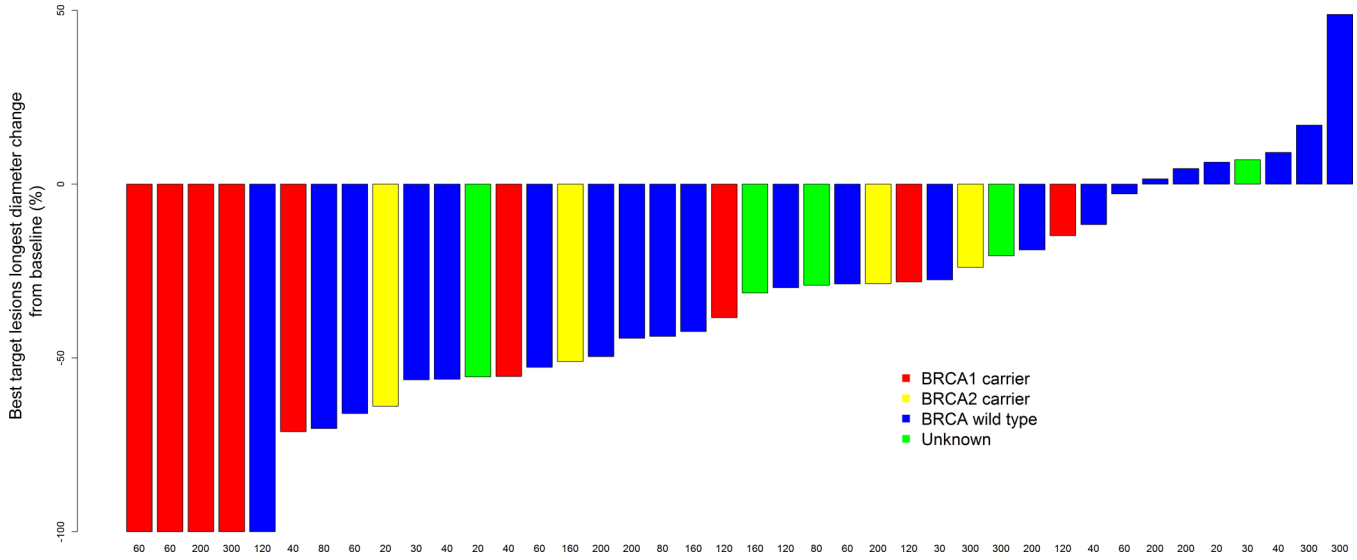

Figure 2.

Waterfall plot for best overall response (percentage change in sum of longest diameter of target lesions). Genetic phenotype is shown by color coding, and veliparib dose cohort is displayed on the X axis

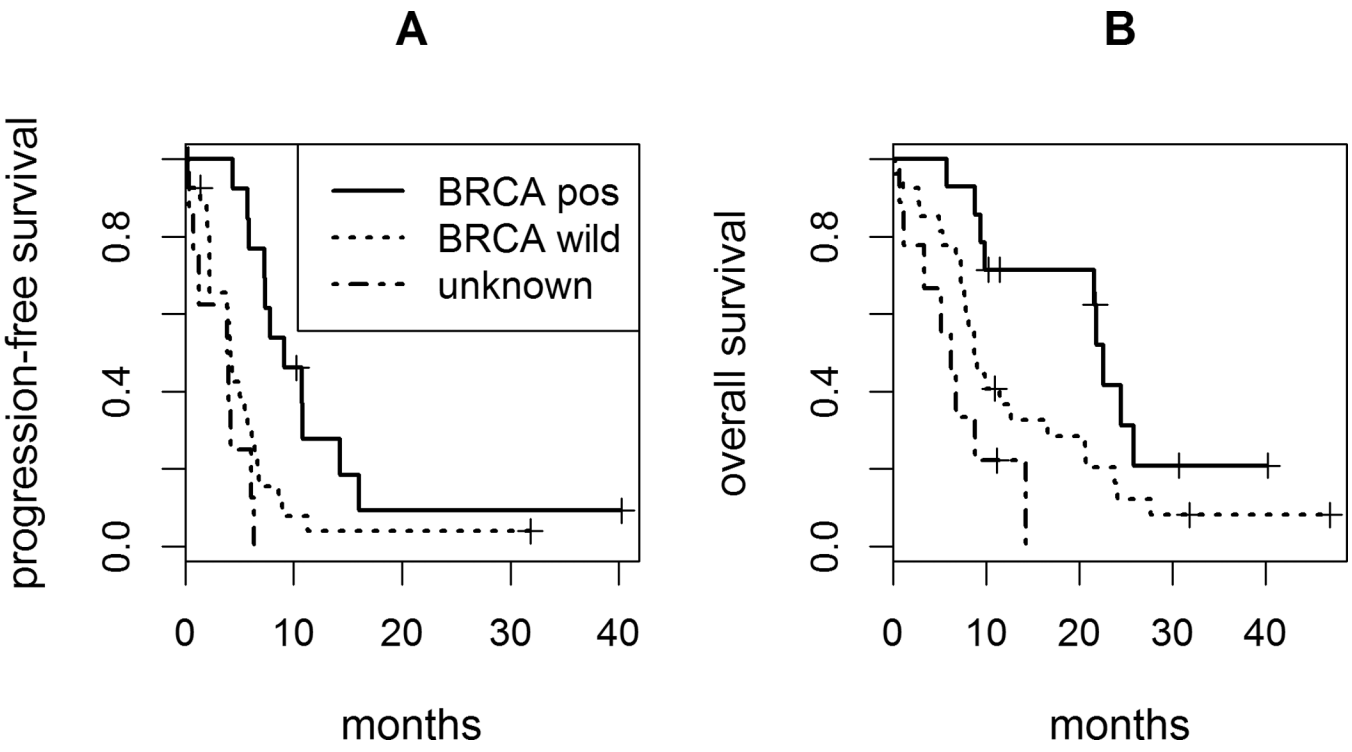

Figure 3.
Kaplan-Meier estimates of (A) progression-free survival and (B) overall survival by mutational status (pos=positive; wild=wild-type) (N=50)

Table 1

Patient and Disease Characteristics (N=50)

	N (%)
Age at registration (median, range)	50 (30–78)
Ethnicity	
Caucasian	41 (82)
African American	5 (10)
Hispanic	3 (6)
Asian	1 (2)
ECOG status at registration or cycle 1	
0	35 (70)
1	10 (20)
2	5 (10)
Hormone receptor status (metastatic site and/or primary site)	
Estrogen receptor negative	41 (82)
Progesterone receptor negative	43 (86)
HER2/neu negative	49 (98)
Germline BRCA mutation status	
BRCA1+	10 (20)
BRCA2+	4 (8)
wild-type	27 (54)
unknown	9 (18)
# Metastatic organ sites	
1–2	16 (32)
3–4	30 (60)
5+	4 (8)
Metastatic site involvement	
Lung/Pleura	26 (52)
Liver	23 (46)
CNS/Brain	7 (14)
Bone	18 (36)
Skin/Soft Tissue	10 (20)
Locoregional Lymph Node	27 (54)
Distant Lymph Node	29 (58)
Breast	5 (10)
Other viscera	4 (6)
De novo metastatic or relapse within 12 mo.	18 (36)
Prior neoadjuvant or adjuvant chemotherapy	41 (82)
Prior metastatic regimens	

	N (%)
0	12 (24)
1	17 (34)
2	11 (22)
3	4 (8)
4+	6 (12)
Prior anthracycline	36 (72)
Prior taxane	48 (96)
Prior platinum	17 (34)
carboplatin	6
cisplatin	3
both	4
unknown	4
Prior vinorelbine	10 (20)

Table 2

Most common adverse events (any grade) reported in > 20% of patients reported at any time during the study

	CTCAE grade				
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**All grades N (%)**
Nausea	16	26	1	0	43 (86%)
Fatigue	13	26	1	0	40 (80%)
Platelet count decreased	19	8	5	1	33 (66%)
Anemia	3	14	15	0	32 (64%)
Neutrophil count decreased	5	8	9	9	31 (62%)
Tinnitus	25	1	0	0	26 (52%)
Vomiting	18	2	1	0	21 (42%)
Peripheral sensory neuropathy	13	8	0	0	21 (42%)
Anorexia	13	4	0	0	17 (34%)
Dehydration	5	11	1	0	17 (34%)
Hypokalemia	12	1	0	0	13 (26%)
Dyspepsia	6	5	0	0	11 (22%)

Table 3

Tumor response (confirmed best overall response) and clinical benefit by genetic phenotype (n=48) *

Response	Germline *BRCA1* or *BRCA2* mutation positive, n=14	Germline *BRCA1* and *BRCA2* wild-type n=26	Unknown mutation status n=8	Total, n=48*
Best overall response, n(%)				
Complete response (CR)	1 (7%)	1 (4%)	--	2 (4%)
Partial response (PR)	7 (50%)	7 (27%)	1(12%)	15 (31%)
Stable disease (SD)	5 (36%)	12 (46%)	4 (50%)	21 (44%)
Progressive disease (PD) **	1 (7%)	6 (23%)	3 (38%)	10 (21%)
Clinical benefit (PFS6) rate, n(%)	10 (71%)	8/27 * (30%)	2 (25%)	20/49 (41%)

* excludes one patient who withdrew after C1D1 for insurance reasons (unknown mutation status) and one (from response but not PFS6) who withdrew after 2 cycles to avoid study travel and died within 6 months of enrollment (*BRCA 1/2* wild-type).

** includes as PD 2 patients who withdrew consent due to anxiety about disease (*BRCA1* mutation positive, unknown mutation status); 2 patients who withdrew early in C1 for worsening disease (*BRCA 1/2* wild type), and 2 patients with dose-limiting toxicities (unknown mutation status)

PFS6 = disease progression >6 months after starting study therapy