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Cisplatin with veliparib or placebo in metastatic triple-negative breast cancer and/or *BRCA* mutation-associated breast cancer (S1416): a randomised, phase 2 trial

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Abstract

BACKGROUND: Poly[ADP-ribose] polymerase inhibitors (PARPi) are effective in germline *BRCA1 or BRCA2* (g*BRCA*) mutation-associated metastatic breast cancer (MBC). However, studies evaluating PARPi plus platinum chemotherapy in g*BRCA*-wildtype triple-negative breast cancer (TNBC) are lacking. A large proportion of g*BRCA*-wildtype TNBC demonstrates homologous recombination deficiency (HRD) resulting in BRCA-like phenotype which might render sensitivity to PARPi. S1416 compared the efficacy of cisplatin plus the PARPi veliparib or placebo in three predefined groups of MBC: g*BRCA*-mutated; BRCA-like; and non-BRCA-like.

METHODS: S1416 was a randomised, placebo-controlled, phase II trial. Eligible patients (aged ≥18 years) had metastatic TNBC or g*BRCA*-associated MBC, an Eastern Cooperative Oncology Group performance status 0–2, and had received ≤1 line of chemotherapy for metastatic disease. Patients were randomized (1:1) using the NCTN Open interactive system with dynamic balancing on the stratification factor (0 vs 1 prior cytotoxic regimens for metastatic disease) to cisplatin ($75mg/m^2$) on day 1 plus veliparib or matching placebo (300 mg orally twice daily, days 1–14) on a 21-day cycle. Central g*BRCA* testing classified patients as g*BRCA*-mutated or wildtype. *A priori* established biomarker panel classified g*BRCA*-wildtype patients into BRCA-like and non-BRCA-like groups, and included genomic instability (GI) score, somatic *BRCA* mutations, *BRCA1* promoter methylation, and non-*BRCA* homologous recombination repair germline mutations. The primary endpoint was investigator-assessed progression-free survival (PFS). Efficacy analyses were done by intention to treat, which included all eligible patients, and safety analyses included all patients who received at least one dose of veliparib or placebo. PFS analyses were conducted separately for each biomarker group with a prespecified α for each analysis. The study is ongoing and is registered with ClinicalTrials.gov NCT02595905.

FINDINGS: Between July 7, 2016 and June 15, 2019, 335 patients (334 female; 1 male) were enrolled. 320/335 randomized patients were eligible for efficacy evaluation; 31% had received 1 prior chemotherapy for MBC. 247 patients were classified into the three groups: (1) 37 g*BRCA*-mutated; (2) 101 BRCA-like; (3) 109 non-BRCA-like. The remaining 73 could not be classified due to missing biomarker information. Median follow-up was 11.1 months (interquartile range 5.6–20.8 months). In the g*BRCA*-mutated group, PFS was similar with veliparib compared to placebo (HR=0.79; 95% CI 0.38–1.67; p=0.54). In the BRCA-like group, improved PFS was noted with veliparib vs placebo (median PFS 5.9 vs 4.2 months, HR=0.57; 95% CI 0.37–0.88; p=0.010). The non-BRCA-like group did not show PFS benefit from veliparib (HR=0.89; 95% CI 0.60–1.33, p=0.57). The most common grade 3–4 adverse events were neutropenia (71/155 [46%] patients in the veliparib arm vs 29/147 [20%] patients in the placebo arm], anaemia (35/155 [23%] in the veliparib arm vs 12/147 [8%] in the placebo arm), and thrombocytopenia (29/155 [19%] in the veliparib arm vs 4/147 [3%] in the placebo arm). Serious adverse events occurred in 48/155 (31%) patients in the veliparib arm and 53/147 (36%) patients in the placebo arm. Treatment-related adverse events led to death in one patient in the veliparib-cisplatin arm and one patient in the placebo-cisplatin arm.

INTERPRETATION: Addition of veliparib to cisplatin significantly improved PFS for BRCA-like metastatic TNBC. We identified a subgroup of g*BRCA*-wildtype TNBC patients who benefited from addition of PARPi to cisplatin; PARPi plus platinum combination should be explored further in BRCA-like TNBC.

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analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

INTRODUCTION

Triple-negative breast cancer (TNBC), which is defined by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR) and absence of HER2 overexpression and/or gene amplification, accounts for approximately 15% of all breast cancers. Compared to other breast cancer subtypes, TNBC is associated with higher risk of recurrence and shorter survival following recurrence.[1,2] Thus, evaluation of more effective treatments is an area of highly unmet need for TNBC.

TNBC is enriched for homologous recombination DNA repair deficiency (HRD). Germline *BRCA* (g*BRCA)* mutations are noted in 10% to 20% of patients with TNBC.[3,4] However, HRD can be mediated by mechanisms other than g*BRCA* mutation, such as somatic *BRCA* mutation, somatic or germline mutations in other homologous recombination repair (HRR) genes, *BRCA1* promoter methylation, or attenuated mRNA expression of HRR genes. In addition to testing for causative molecular alterations, HRD can also be identified by typical genomic mutational patterns.[5,6] Published studies show that 40% to 60% of TNBC demonstrate HRD, making this a rational therapeutic target for this subtype.[5,7] g*BRCA* mutations confer sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors in breast and other cancers.[8–12] Clinical trials have demonstrated superior progression-free survival (PFS) with PARP inhibitor monotherapy compared to chemotherapy for g*BRCA* mutation-associated, HER2-negative metastatic breast cancer, leading to approval of two PARP inhibitors for this patient population.[8,9]

Efficacy of PARP inhibitor monotherapy beyond g*BRCA* mutation has been noted in ovarian and prostate cancers.[12,13] However, there has been limited PARP inhibitor efficacy beyond g*BRCA* mutation in breast cancer. Patient selection based on presence of HRD and combinatorial approaches of PARP inhibitor with DNA-damaging chemotherapy may be needed to demonstrate activity of PARP inhibitors in g*BRCA* wildtype TNBC. Combination of DNA-damaging chemotherapy and PARP inhibitors at adequate dosing of both has been challenging due to myelosuppression.[14,15] Preclinical studies show that the potency of PARP trapping and cytotoxic specificity vary among various PARP inhibitors and these differences may impact clinical efficacy and safety profiles of these agents.[16,17] PARP trapping potency may also contribute to bone marrow toxicity, as PARP inhibitors with higher trapping potency are noted to have more pronounced bone marrow toxicity compared to those with lower trapping potency. Veliparib is an oral small molecule inhibitor of PARP1 and PARP2 and has shown antitumor activity both as a single agent and in combination with platinum-based chemotherapy in g*BRCA* mutation-associated metastatic breast and ovarian cancer.[18–21] Veliparib has less hematologic toxicity, likely secondary to reduced PARP trapping activity, making it more suitable than other available PARP inhibitors to be combined with platinum-based chemotherapy. A phase I study demonstrated that standard doses of cisplatin could be delivered safely in combination with a near-maximal single-agent dose (300mg BID days 1–14 in a 21 day cycle) of veliparib in patients with metastatic TNBC.[22] The purpose of S1416 was to determine if the addition of veliparib to platinum

therapy can improve outcomes for patients with g*BRCA*-wildtype metastatic TNBC with HRD/BRCA-like phenotype.

METHODS

Study Design and Participants

SWOG trial S1416 was a randomized phase II trial comparing cisplatin with veliparib versus cisplatin with placebo. Eligible patients were ≥18 years of age and had histologically confirmed metastatic TNBC (ER and PR immunohistochemical staining ≤1% and HER2 negativity per 2013 ASCO/CAP guidelines[23]) or metastatic ER or PR positive, HER2-negative breast cancer with known deleterious/suspected deleterious germline *BRCA1* or *BRCA2* mutation. Patients could have received no more than one prior cytotoxic treatment regimen for metastatic disease, had to have adequate hematologic, hepatic, and renal function and Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with measurable or non-measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) were eligible. Patients with treated brain metastases and clinically controlled neurological symptoms were eligible if >14 days from surgical excision and/or radiation. Prior neo/adjuvant carboplatin was permitted if completed >12 months prior to study entry. There was no minimal time requirement from end of neo/adjuvant chemotherapy and study entry. Patients were excluded if they had ongoing grade ≥1 peripheral neuropathy, had grade ≥2 hearing impairment, or had received prior cisplatin or PARP inhibitor therapy. The study was approved by the Central Independent Review Board (CIRB) or local institutional review board at each participating site, and all patients provided written informed consent. An independent Data and Safety Committee reviewed the trial every six months and assessed the interim and final analyses.

Randomisation and Masking

Eligible patients were randomly assigned (1:1) to either cisplatin plus veliparib or cisplatin plus placebo with stratification by number of prior cytotoxic regimens for metastatic disease (0 vs. 1). Central randomization was performed using the NCTN Open interactive system with dynamic balancing on the stratification factor. Clinics directly enrolled patients with treatment randomization immediately performed by the computer. Placebo tablets were identical in shape and color to veliparib tablets. Investigators, patients, and the sponsor were masked to treatment assignment, but the study statistician is unmasked. Success of masking was not assessed. Treatment assignment was unblinded at time of progression if requested by the treating physician. Patients were randomized, and then classified post-randomization into specified efficacy analysis biomarker groups. Central germline testing and tissue BRCA-like biomarker testing were done post-randomization to allocate patients into the three pre-specified groups (g*BRCA*-mutated, BRCA-like, and non-BRCA-like) for statistical analysis.

Procedures

Patients received intravenous cisplatin at 75 mg/m^2 on day 1 of each 21-day cycle in combination with either oral veliparib or placebo 300 mg twice per day (BID) on days 1–14 of a 21-day cycle. Toxicity was assessed after each 21-day cycle. Treatment was

continued until disease progression, intolerable toxicity, or withdrawal from the study. In case of adverse events (AEs), veliparib or placebo dose could be reduced to 200 BID and subsequently to 100 mg BID. Veliparib or placebo could be interrupted for up to 3 consecutive weeks for toxicity. After 4 cycles of combination therapy, cisplatin could be discontinued (at the discretion of the treating physician) and patients could continue veliparib/placebo monotherapy at dose of 400 mg orally BID on days 1–21 of a 21-day cycle. Myeloid growth factor support was permitted per treating physician discretion after completion of treatment cycle 1.

Tumor response was assessed radiographically (computerized tomography or magnetic resonance imaging) by investigators according to RECIST v1.1 every 9 weeks for the first 54 weeks, then every 18 weeks. Patients were to be followed for survival up to a minimum of five years after registration. Safety was assessed and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Post-randomization centralized testing for g*BRCA* mutations and BRCA-like biomarkers was performed in CLIA labs to allocate patients in the three groups (g*BRCA*-mutated or BRCA-like or non-BRCA-like).

Germline testing was the first step for group allocation and was performed by a targeted capture and massively parallel sequencing test (BROCA-HR: 40 genes with known involvement in hereditary breast/ovarian cancer or homologous recombination, including *BRCA1/2*).[24] Deleterious mutations were defined in the standard fashion, and both “BIC” and “HGVS” nomenclatures were used to report the deleterious mutations. Variants of uncertain significance were not reported. Details of the technique and processing are included onpage 9 of the Appendix.

The following four pre-defined markers were utilized (listed in rank order priority) to allocate BRCA-like group for g*BRCA*-wildtype patients: i) Genomic instability (GI) score ≥42, ii) Somatic *BRCA1/2* mutation, iii) *BRCA1* promoter methylation (PM), and iv) Germline mutation in HRR genes (excluding *BRCA1/2*). A positive result on any of one of the four markers placed the patient in the BRCA-like group. Availability of all four makers was not required to assign to the BRCA-like group. One or more of the BRCA-like biomarkers was anticipated to be positive in approximately 50% of enrolled patients.

GI score and somatic *BRCA* mutations were assessed on genomic DNA isolated from formalin-fixed paraffin-embedded (FFPE) primary tumor tissue via the myChoice Plus CDx assay. This assay, combines genomic patterns of loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions scores to generate a GI score and provides tumor *BRCA* sequencing using a custom IDT xGen capture followed by sequencing on Illumina HiSeq250 as previously published.[6] A pre-specified GI score cut point of ≥42 was used to designate GI-positive status.[6,7,25] Deleterious or suspected deleterious sequencing mutation or large rearrangement in *BRCA1/2* in g*BRCA*-wildtype patients was designated as somatic *BRCA* mutation.

To assess *BRCA1* promoter methylation, genomic DNA was isolated from FFPE primary tumor tissue using commercially available kits (EpiTect Plus FFPE Bisulfite Kit, Qiagen),

followed by subjecting the purified DNA to methylation-specific PCR using the EpiTect® MSP Kit (Qiagen), as previously described.[7]

Outcomes

The primary efficacy outcome was investigator-assessed PFS (defined as time from registration (randomization) to progression or death due to any cause) in the three pre-specified groups: g*BRCA*-mutated, BRCA-like, and non-BRCA-like, with each having a pre-specified α. Secondary outcomes included OS (time from registration to death due to any cause), toxicity due to treatment (including serious adverse events), ORR (complete response or partial response per RECIST 1.1), and clinical benefit (complete or partial response or stable disease per RECIST 1.1).

Statistical Analysis

Outcomes are evaluated using intent-to-treat analysis of eligible patients. The benefit of veliparib for the primary outcome of PFS (measured by the hazard ratio, HR) was anticipated to be similar for the g*BRCA*-mutated and BRCA-like groups, with no/minimal benefit for the non-BRCA-like group. A log-rank test stratified by line of cytotoxic therapy was used to compare PFS for cisplatin + veliparib versus cisplatin + placebo for each biomarker group, with additional analyses using stratified Cox regression in an intent-to-treat analysis. The proportional hazards assumption of the Cox model was tested using the interaction of Schoenfeld residuals with the time axis. ORR and clinical benefit rate were tested in a 2×2 table using Fisher's exact test. Pvalues and 95% confidence intervals are reported for prespecified analyses including: separate analyses of PFS and OS for the three biomarker groups and testing of ORR and clinical benefit rate. Testing of a treatment effect in a subset of the BRCA-like group with GI score ≥ 42 was a planned prespecified secondary translational aim of the study. Post hoc sensitivity analyses include the forest plot of the PFS treatment hazard ratio by each factor for the BRCA-like group.

Post hoc analyses have only 95% confidence intervals and also include analysis of the unclassified group and analysis of the BRCA-like group patients who received trial treatment as first line of cytotoxic therapy. There was a single interim analysis for futility only and for assessment of enrollment numbers in each biomarker group.

For the g*BRCA*-mutated group, assuming a PFS of 4 months for cisplatin plus placebo and HR=0.57, the study had 80% power (1-sided α=0.10) to detect if cisplatin plus veliparib was superior to cisplatin plus placebo with an expected total sample size of 63 patients. The smaller sample size and higher α was set for the g*BRCA*-mutated group since PARP inhibitor efficacy in g*BRCA* mutation-associated metastatic breast cancer was already being addressed in several ongoing phase III trials at the time of S1416 study design. For the BRCA-like group, assuming a PFS of 4 months for cisplatin plus placebo arm and HR=0.57, the study had 80% power (1-sided α=0.05) to detect if cisplatin plus veliparib was superior to cisplatin plus placebo with an expected total sample size of 86. For the non-BRCA-like group (expected sample size 86), even though little or no effect was expected, a test of efficacy was conducted at 1-sided α=0.10. Patients who could not be classified into the three pre-specified groups due to missing biomarkers were included in a separate analysis.

There was no a priori hypothesis for the unclassified group and no expected sample size. All analyses were performed in Stata/MP 15.1 and SAS Version 9.4. The trial also enrolled a cohort of patients (n=9) with progressive brain metastases who underwent the same randomization, but without BRCA-like biomarker analysis. Per protocol this cohort is to be reported separately.

The initial overall trial sample size was 235 (excluding patients with progressive brain metastasis) assuming all randomized patients could be assigned to the specific biomarker groups: (1) g*BRCA*-mutated (n=63); (2) BRCA-like (n=86) and (3) non-BRCA-like (n=86). Since the biomarker groups were not known at randomization, only the total accrual was fixed and the individual group sample sizes were estimates.

However, some randomized patients could not be assigned to specific groups due to sample (blood and/or tissue) submission non-adherence and assay failure. Thus, accrual was temporarily suspended from 4/15/2018 to 7/18/2018 to assess numbers enrolled in each biomarker group and to re-evaluate the overall trial sample size. Outcome data were not used for these assessments. The total trial sample size was adjusted via protocol amendment to 324 in June 2018 and the trial reopened to enrollment. It was recognized at that time that the gBRCA group would not reach 63 patients in this placebo-controlled study since PARPi had become available for patients with known gBRCA mutation.

This study is registered with ClinicalTrials.gov, number NCT02595905.

Role of funding source

This study was primarily supported by the National Cancer Institute (NCI). Abbvie, Inc. provided veliparib and Myriad Genetics conducted the myChoice Plus CDx assay. The trial was administered by SWOG on behalf of the National Clinical Trials Network. The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing the report, or the decision to submit for publication. The study statistician (WEB) had full access to all of the raw data in the study. All authors were involved in writing the report and approving the final version for submission. The joint first authors had final responsibility for the decision to submit for publication.

RESULTS

Three hundred thirty-five patients were enrolled between July 7, 2016 and June 15, 2019 at 154 community and academic clinical sites. Figure 1 (CONSORT) provides patient disposition of enrolled patients. 15 patients (4.5%) were ineligible (5 due to treatment just before enrollment; 3 due to disallowed prior treatment; 3 had two prior metastatic regimens; 1 had HER2-positive disease; 1 had ER-positive disease; 1 was not within disease assessment time limits; 1 declined specimen submission) and are excluded from the analyses. Of the 320 eligible patients, 162 were randomized to cisplatin plus veliparib and 158 to cisplatin plus placebo.

Demographic and clinical characteristics are depicted in Table 1. Sixty-nine percent of patients had not received any prior chemotherapy for metastatic disease, 10% had neo/adjuvant carboplatin exposure, and <5% had received prior checkpoint inhibitor therapy.

Patient distribution in the three pre-defined groups is described in Figure 2. Blood for germline testing was not submitted for 26 (8.1%) of the 320 patients. Out of 294 patients for whom germline testing was done, 37 (12.6%) had deleterious *BRCA* mutations. BRCA-like biomarker assessment was performed for 210/257 (81.8%) patients with negative germline *BRCA* testing. Among these 210 patients, 101 (48.1%) had BRCA-like phenotype and 109 (51.9%) were non-BRCA-like. Distribution of qualifying markers among the 101 patients in the BRCA-like group (per rank order priority) was as follows: GI score ≥42 = 76.2% (n=77/101), *BRCA1* PM = 16.8% (n=17/101), germline HRR mutations (excluding *BRCA*) = 6.9% (n=7/101). While 8% (8/101) had somatic *BRCA* mutations, all were already classified as BRCA-like with an GI score ≥42. Details of distribution and overlap of the BRCA-like marker results are provided on page 6 of the Appendix. Distribution of GI score is provided on page 1 of the Appendix. Twenty-three percent (73/320) of patients remained unclassified due to either lack of blood submission precluding central g*BRCA* testing (8% [26/320]), lack of tissue submission (7% [22/320]), or tissue assay failure (8% [25/320]). Demographic and clinical characteristics of patients in the three pre-defined groups are provided on page 7 of the Appendix.

Patients were followed until at least 5 years or death, whichever was sooner. Median follow-up was 11.1 months (interquartile range 5.6–20.8 months). At data cutoff, progression-free survival events had been recorded in 141/162 (87%) patients in the veliparib-cisplatin arm and 150/158 (95%) patients in the placebo-cisplatin arm; 135/162 (83%) patients in the veliparib-cisplatin arm and 133/158 (84%) patients in the placebo-cisplatin arm had died. Analysis of PFS and OS by each biomarker group is shown on page 8 of the Appendix, including demonstration that the proportional hazards assumption was not violated. In the g*BRCA*-mutated group, median PFS was 6.2 (95% confidence interval (CI) 2.3–9.2) months in the veliparib-cisplatin arm and 6.4 (95% CI 4.3–8.2) months in the placebo-cisplatin arm (HR=0.79; 95% CI 0.38–1.67; log-rank p=0.54) (Figure 3A). With 37 randomized patients, the g*BRCA*-mutated group reached only 59% of the initially expected accrual of 63.

In the BRCA-like group, PFS was significantly prolonged with veliparib-cisplatin compared to placebo-cisplatin; median PFS was 5.9 (95% CI 4.3–7.8) months in the veliparib-cisplatin arm compared to 4.2 (95% CI 2.3–5.0) months in the placebo-cisplatin arm (HR=0.57; 95% CI 0.37–0.88; log-rank p=0.010) (Figure 3B). One-year PFS was 18.3% (95% CI 9.0%−30.1%) in the veliparib-cisplatin arm and 4.7% (95% CI 0.9%−14.0%) in the placebo-cisplatin arm.

In the non-BRCA-like group, there was no benefit of veliparib for PFS; median PFS was 4.0 (95% CI 2.5–4.7) months in the veliparib-cisplatin arm and 3.0 (95% CI 2.2–4.4) months in the placebo-cisplatin arm (HR=0.89; 95% CI 0.60–1.33; log-rank p=0.57) (Figure 3C).

In the unclassified group (unplanned analysis), median PFS was 2.4 (95% CI 2.2–5.6) months in the veliparib-cisplatin arm and 2.2 (95% CI 1.5–4.1) months in the placebo-cisplatin arm (HR=0.87; 95% CI 0.52–1.45) (page 2 of the Appendix).

In the g*BRCA*-mutated group, there was no OS benefit of veliparib; median OS was 14.2 (95% CI 8.1–21.0) months in the veliparib-cisplatin arm and 15.6 (95% CI 12.6–21.4) months in the placebo-cisplatin arm (HR=1.20; 95% CI 0.56–2.55; log-rank p=0.64) (Figure 3D).

In the BRCA-like group, OS was not significantly longer with veliparib-cisplatin compared to placebo-cisplatin; median OS was 14.0 (95% CI 10.3–20.2) months in the veliparib-cisplatin arm compared to 12.1 (95% CI 9.0–15.0) months in the placebo-cisplatin arm (HR=0.75; 95% CI 0.48–1.17; log-rank p=0.21) (Figure 3E).

In the non-BRCA-like group, there was no OS benefit of veliparib; median OS was 10.9 (95% CI 8.5–13.1) months in the veliparib-cisplatin arm and 11.1 (95% CI 8.2–16.1) months in the placebo-cisplatin arm (HR=1.14; 95% CI 0.76–1.71; log-rank p=0.53) (Figure 3F).

In the unclassified group, there was no OS benefit of veliparib. Median OS was 11.7 (95% CI 5.7–19.2) months in the veliparib-cisplatin arm and 8.4 (95% CI 6.0–12.6) months in the placebo-cisplatin arm (HR=1.01; 95% CI 0.59–1.73) (page 2 of the Appendix).

In the BRCA-like group, among 83 patients with measurable disease, ORR was numerically higher in the veliparib-cisplatin arm compared to the placebo-cisplatin arm (ORR=45% (21/47) vs. 33% (12/36); p=0.37); in the BRCA-like group clinical benefit rate was 55% (26/47) in the veliparib-cisplatin arm and 56% (20/36) placebo-cisplatin arm (p=1.00). In the non-BRCA-like group, among 91 patients with measurable disease, ORR was 17% (8/47) in the veliparib arm compared to 19% (8/43) in the placebo arm; in the non-BRCA-like group clinical benefit rate was 49% (23/47) in the veliparib-cisplatin arm and 49% (21/43) in the placebo-cisplatin arm (p=1.00). ORR and CBR are not reported for the g*BRCA*-mutated group given small numbers of patients in this group.

Forest-plot analyses of PFS in the BRCA-like group are shown on page 3 of the Appendix. The benefits of veliparib-cisplatin on PFS were generally consistent across subgroups.

Exploratory efficacy analysis of PFS and OS within the BRCA-like group among patients receiving first-line therapy is shown on page 4 of the Appendix. PFS was prolonged among patients receiving first-line therapy in the veliparib-cisplatin arm compared to the placebo-cisplatin arm. Median PFS in the veliparib-cisplatin and placebo-cisplatin arms was 6.1 (95% CI 3.7–10.2) and 3.8 (95% CI 2.2–5.5) months, respectively (HR=0.53, 95% CI 0.32–0.88). One-year PFS was 21.4% (95% CI 10.1%−35.5%) and 3.1% (95% CI 0.2% −13.4%) in the veliparib-cisplatin and placebo-cisplatin arms, respectively. Median OS in the veliparib-cisplatin and placebo-cisplatin arms was 16.1 (95% CI 11.3–23.9) months and 11.9 (95% CI 9.0–19.7) months, respectively (HR=0.69, 95% CI 0.41–1.15).

One of the prespecified translational secondary aims of the study was to evaluate the impact of GI score independent of other three BRCA-like markers on efficacy of veliparib.

This analysis includes the 77 of 101 patients who were assigned to the BRCA-like group based solely on GI score of ≥42. PFS was significantly higher in veliparib arm compared to placebo (page 5 of the Appendix). Median PFS in the veliparib-cisplatin and placebo-cisplatin arms was 6.1 (95% CI 4.4–10.2) and 4.2 (95% CI 2.2–6.1) months, respectively (HR=0.57, 95% CI 0.35–0.95). The HR for PFS using GI score as the sole BRCA-like criterion was similar to the HR in the overall BRCA-like group.

Eighteen randomized patients did not receive protocol therapy and are not included in toxicity assessment. Three hundred and two patients were evaluable for treatment exposure and AEs (veliparib-cisplatin n=155; placebo-cisplatin n=147). Serious adverse events occurred in 48/155 (31%) patients in the veliparib arm and 53/147 (36%) patients in the placebo arm. The most common grade 3 or worse adverse events were neutropenia (71/155 [46%] patients in the veliparib group vs 29/147 [20%] patients in the placebo group)], anaemia (35/155 [23%] in the veliparib group vs 12/147 [8%] in the placebo group), and thrombocytopenia (29/155 [19%] in the veliparib group vs 4/147[3%] in the placebo group). (Table 2). (Table 2). Compared to placebo-cisplatin, veliparib-cisplatin treatment was associated with higher rates of grade ≥3 anemia, neutropenia, leukopenia, and thrombocytopenia. Treatment-related AEs led to death in one patient in the veliparib-cisplatin arm (sepsis) and one patient in the placebo-cisplatin arm (acute kidney injury due to cisplatin plus heart failure from previous doxorubicin exposure). 30% (49/162) of patients in the veliparib-cisplatin arm and 17% (27/158) in the placebo-cisplatin arm discontinued study treatment due to toxicity. There were no reported cases of treatment-related acute myeloid leukemia. There was one report of grade 4 myelodysplastic syndrome in the placebo-cisplatin arm and none in the veliparib-cisplatin arm. In the veliparib-cisplatin arm, among patients completing 4 cycles of treatment (n=76), 33% (25) and 29% (22) of patients required dose reductions in veliparib and cisplatin, respectively. In comparison, in the veliparibplacebo arm, among patients completing 4 cycles of treatment (n=77), 5% (4) and 19% (15) required dose reductions in placebo and cisplatin, respectively.

At the discretion of the treating physician, cisplatin could be discontinued per protocol after 4 cycles of combination therapy, and patients could continue veliparib/placebo monotherapy. Among 125 patients receiving a fifth cycle of study treatment, only 8% (n=10/125) of patients had discontinued cisplatin and were on veliparib/placebo monotherapy. Monotherapy use increased over time for patients who stayed longer on study treatment. Among 73 patients receiving a seventh cycle of study treatment, 32.9% (n=24/73) were on veliparib/placebo monotherapy, and among 38 patients receiving a tenth cycle of study treatment, 71.1% (n=27/38) were on veliparib/placebo monotherapy.

DISCUSSION

The S1416 randomized phase II trial shows that in patients with g*BRCA*-wildtype metastatic TNBC with BRCA-like phenotype, veliparib when added to cisplatin decreased the PFS event rate by 43%. Furthermore, this combination of cisplatin plus veliparib demonstrated durability of efficacy in the BRCA-like group, with 18.3% of patients remaining progression-free at 12 months. The median PFS of 4.2 months for the placebo-controlled arm in the BRCA-like phenotype group of our study is in line with observations

from previous first/second-line metastatic platinum monotherapy studies.[5,26] Similarly, the median OS of 12 months in the cisplatin-placebo control arm of our study is consistent with results from other similar studies (median OS was 11 months in TBCRC009 and 12.8 months in the carboplatin arm of TNT).[5,26] Addition of veliparib to cisplatin in our study was not beneficial in the non-BRCA-like group, an observation that is in line with our a-priori study hypothesis.

In S1416 addition of veliparib to cisplatin did not improve PFS in patients with g*BRCA* mutation. However, with 37 randomized patients, the g*BRCA*-mutated group reached only 59% of projected accrual and was underpowered. U.S. Food and Drug Administration (FDA) approval of two PARP inhibitors (olaparib and talazoparib) for treatment of g*BRCA* mutation-associated metastatic breast cancer during the course of this trial impacted accrual to this group. Efficacy of veliparib when added to platinum-based chemotherapy in g*BRCA* mutation-associated metastatic breast cancer has already been addressed by the randomized phase III BROCADE3 trial, which enrolled 513 patients and demonstrated that addition of veliparib to platinum-taxane doublet chemotherapy (with continuation as monotherapy if the doublet chemotherapy was discontinued) resulted in significant improvement in PFS (HR=0.71) in patients with g*BRCA* mutation-associated advanced breast cancer.[20] PFS of 6.4 months in the cisplatin-placebo arm of the g*BRCA*-mutated cohort of our study is in line with what was noted with platinum monotherapy in g*BRCA* mutation carriers in the TNT trial.[5]

PARP inhibitor maintenance post platinum-based chemotherapy is a commonly employed approach in ovarian cancer treatment. S1416 also allowed veliparib maintenance; however, patients were required to complete a minimum of four cycles of cisplatin plus veliparib/placebo combination before moving to veliparib/placebo monotherapy maintenance. S1416 was not designed to address the “maintenance-only” question in absence of upfront combination of platinum plus PARP inhibitor. Only a small proportion of patients in S1416 went on maintenance monotherapy, thus limiting specific analysis related to monotherapy use.

The question of relative contribution of combination versus maintenance PARP inhibitor towards efficacy in the BRCA-like group of our study is relevant given the findings from ovarian cancer trials. In the BRCA-like group we observed very early separation of PFS curves while patients were still on combination therapy. This observation, along with the low percentage of patients utilizing monotherapy maintenance, suggests that the efficacy in S1416 was likely driven by the combination of cisplatin plus veliparib, rather than by maintenance veliparib. The role of maintenance PARP inhibitor post platinum-based chemotherapy has not been evaluated in g*BRCA* mutation-associated advanced breast cancer or in TNBC with HRD and should be studied in future trials.

S1416 utilized four different biomarkers to designate BRCA-like phenotype; using these markers almost 50% of g*BRCA*-wildtype TNBC demonstrated BRCA-like phenotype. The approach of performing BRCA-like markers for assignment of three efficacy cohorts post randomization was deemed justifiable for this design given the turnaround time for assay results and urgency for patients with metastatic disease to start timely treatment.

Imbalance in baseline characteristics between arms could result with this study design approach. Despite this limitation, comparison of treatments remains unbiased in this placebo-controlled trial, and baseline patient characteristics were balanced within biomarker groups.

Among the 4 markers used in our study, GI score ≥42 identified three-fourths of BRCA-like patients, thus contributing the most to this group selection. *BRCA1/2* somatic mutation was noted in 8%, but all of these also had GI score ≥42. Seven percent and 17% of patients, respectively, had germline non-*BRCA* HRR gene mutation and *BRCA1* methylation as the only BRCA-like qualifying biomarker. We did not observe any overlap between non-*BRCA* germline HRR mutations and *BRCA1* methylation. An exploratory efficacy analysis performed to evaluate impact of GI score independent of other three BRCA-like markers demonstrated that PFS was significantly higher in the veliparib arm compared to placebo, with a HR that was similar to the overall BRCA-like group HR ratio. This finding suggests that future confirmatory trials evaluating the combinatorial approach of platinum chemotherapy plus PARP inhibitor in g*BRCA*-wildtype disease could use a single BRCA-like biomarker (i.e., GI score) as a selection criterion. In future we also plan to also explore an alternate GI score of 33 (which has been assessed in recent studies) in S1416.

Toxicity of veliparib plus cisplatin was as expected, and no new toxicity signals were noted with the combination. Compared to placebo, the veliparib arm was associated with higher grade 3 and 4 hematologic toxicities, including anemia, neutropenia, leukopenia, and thrombocytopenia. In this study, a near-maximal single-agent dose of veliparib was able to be combined with a standard dose of cisplatin while maintaining a manageable toxicity profile. Treatment discontinuation rates were not insignificant but similar to other chemotherapy plus veliparib combination trials. Perhaps future studies can explore more intermittent PARPi scheduling when used in combination with chemotherapy to mitigate toxicity related discontinuation. No cases of acute myeloid leukemia or myelodysplastic syndromes were reported in the veliparib arm of our study.

A limitation of our study was the inability to classify patients due to missing specimens or assay failure. This required a midtrial increase in the accrual goal to restore power to expected levels. However, this accrual goal adjustment was done without using/assessing any outcome data. Overall, 23% of enrolled patients could not be assigned to pre-specified groups. Lack of blood submission or inadequate tumor sample submission accounted for 15%, with tissue assay failure accounting for the remainder of 8%.

For metastatic TNBC patients whose tumors express programmed death ligand 1 (PD-L1), standard first-line treatment now includes chemotherapy in combination with PD-1/PD-L1 antibody.[27,28] One limitation of our study is that fewer than 5% of patients had received prior checkpoint inhibitor therapy, as enrollment was completed prior to availability of anti-PD-1/PD-L1 antibody for first-line treatment of metastatic TNBC. Thus, we cannot speculate on whether the veliparib treatment effect seen in the BRCA-like group would be impacted by prior exposure to checkpoint inhibitor therapy or tumor PD-L1 status. The degree of overlap between PD-L1 positivity and BRCA-like phenotype in our study is also

not yet known, although central PD-L1 analysis for S1416 is currently ongoing to address these and other questions.

To our knowledge, S1416 is the first trial to report efficacy of the addition of a PARP inhibitor to platinum chemotherapy in metastatic g*BRCA*-wildtype TNBC with a BRCA-like phenotype. With demonstration of efficacy in BRCA-like phenotype TNBC, S1416 results lay a foundation for expanding the role of PARP inhibitors beyond g*BRCA* mutation in breast cancer. Another PARPi, olaparib can also be safely combined with platinum chemotherapy, thus in addition to veliparib other PARPi could be considered for future chemotherapy combination studies in BRCA-like phenotype TNBC.[29,30] Combination of PARPi plus platinum chemotherapy warrants further evaluation in larger randomized trials for patients with BRCA-like phenotype TNBC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of interests

PS reports S1416 sub-award from SWOG (payments made to the institution) as support for the present work; other relationships include grants (payments made to the institution) from Novartis, Bristol-Myers Squibb, Merck, and Gilead; royalties from UpToDate; and advisory board participation for Pfizer, Merck, Gilead, Genzyme Corporation, Novartis, AstraZeneca, GSK, and Seattle Genetics.

WEB reports a grant from the National Cancer Institute (payments made to the institution) as support for the present work; other relationships include grants (payments made to the institution) from Merck and AstraZeneca; and data safety monitoring board participation for Frontier Science and National Eye Institute.

JRG reports steering committee membership for Roche/Genentech; advisory board participation for AstraZeneca and Puma Biosciences; consulting for SeaGen; data safety monitoring board or advisory board participation (no compensation) for Roche/Genentech, AstraZeneca, Novartis, and Immunomedics; and role as Chief Medical Officer for the American Society of Clinical Oncology.

SLP reports grants (payments made to the institution) from Pfizer, AstraZeneca, Puma Biosciences, Medivation, Genentech, Eli Lilly, and Bayer HealthCarePharm; faculty/speaker payment or honoraria from Pfizer; and steering committee membership (no compensation) for Roche/Genentech and Abbvie.

CKA reports grants from Puma Biosciences, Lilly, Merck, Seattle Genetics, Nektar, Tesaro, G1-Therapeutics, ZION, Novartis, Pfizer, AstraZeneca, and Elucida; royalties or licenses from UpToDate and Jones and Bartlett Publishing Company; consulting fees from Genentech, Eisai, Seattle Genetics, AstraZeneca, Novartis, Immunomedics, Elucida, and Athenex; and data safety monitoring board or advisory board participation for Genentech.

LG reports grants (payments made to the institution) from Genentech and Merck; advisory board participation for Genentech, Merck, AstraZeneca, Novartis, Syndax, Biovica, GE Health, Pfizer, Nanostring, Immunomedics, Aduro,

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KMT reports HRD patents, employment, and stock or stock options from Myriad Genetics.

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Data sharing statement

Individual deidentified data will be available from the NCTN data archive https://nctn-dataarchive.nci.nih.gov/ along with a data dictionary approximately 6 months after publication.

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Research in context

Evidence before the study:

We searched PubMed for articles published up to November 3, 2022, using the search terms “triple negative breast cancer” and “poly(ADP-ribose) polymerase (PARP) inhibitors.” Our search identified phase I and dose expansion single-arm studies where PARP inhibitor, either alone or in combination with another agent, was assessed in cohorts that included a small number of patients with advanced triple-negative breast cancer (TNBC) without germline *BRCA* mutation. Some of these studies suggested activity of PARP inhibitor in patients without a germline *BRCA* mutation, although no specific patient selection biomarker/s were prospectively tested in these studies. Optimal methods to identify germline *BRCA*-wildtype TNBC patients who are most likely to respond to PARP inhibitor, and the most effective means to employ PARP inhibitor in this patient population are lacking. Patient selection based on presence of homologous recombination DNA repair deficiency and combinatorial approaches of PARP inhibitor with DNA-damaging chemotherapy may be needed to demonstrate activity of PARP inhibitors in germline *BRCA*-wildtype breast cancer.

Added value of this study:

To our knowledge, S1416 is the first trial to report efficacy of the addition of a PARP inhibitor to platinum chemotherapy in metastatic germline *BRCA*-wildtype TNBC with a BRCA-like phenotype. This phase II randomized trial examined the treatment effect of a PARP inhibitor added to platinum chemotherapy in a priori-defined biomarker-selected subpopulations of TNBC and showed that the addition of veliparib to cisplatin improves progression-free survival for patients with advanced TNBC with a BRCA-like phenotype.

Implications for all available evidence:

With demonstration of efficacy in biomarker-selected BRCA-like phenotype TNBC, S1416 results provide a basis for expanding the therapeutic role of PARP inhibitors (e.g., veliparib) beyond germline *BRCA* mutation in breast cancer. Combination of veliparib plus cisplatin warrants further evaluation in larger randomized trials for patients with BRCA-like TNBC.

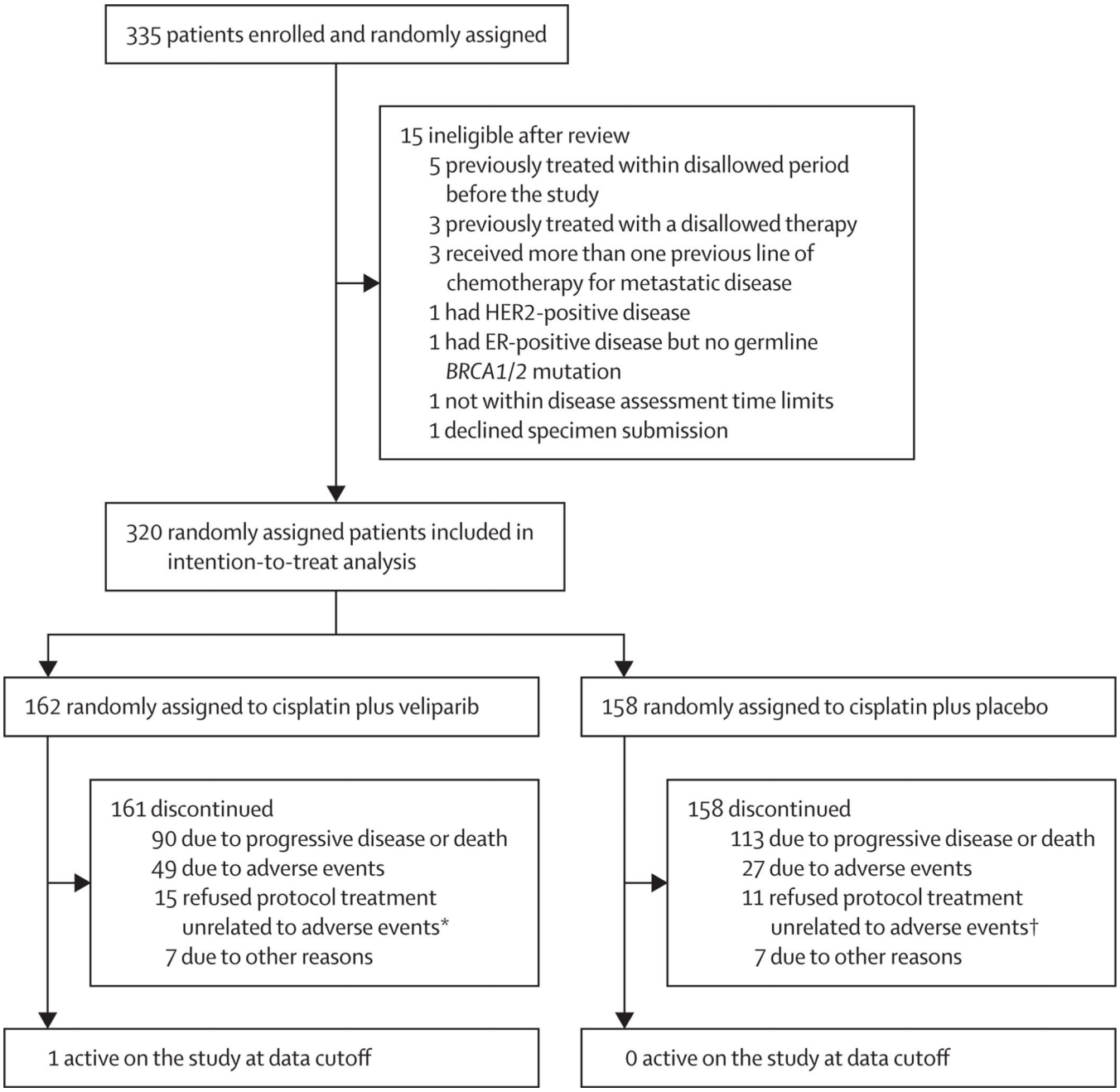

Figure 1:
CONSORT profile and patient disposition

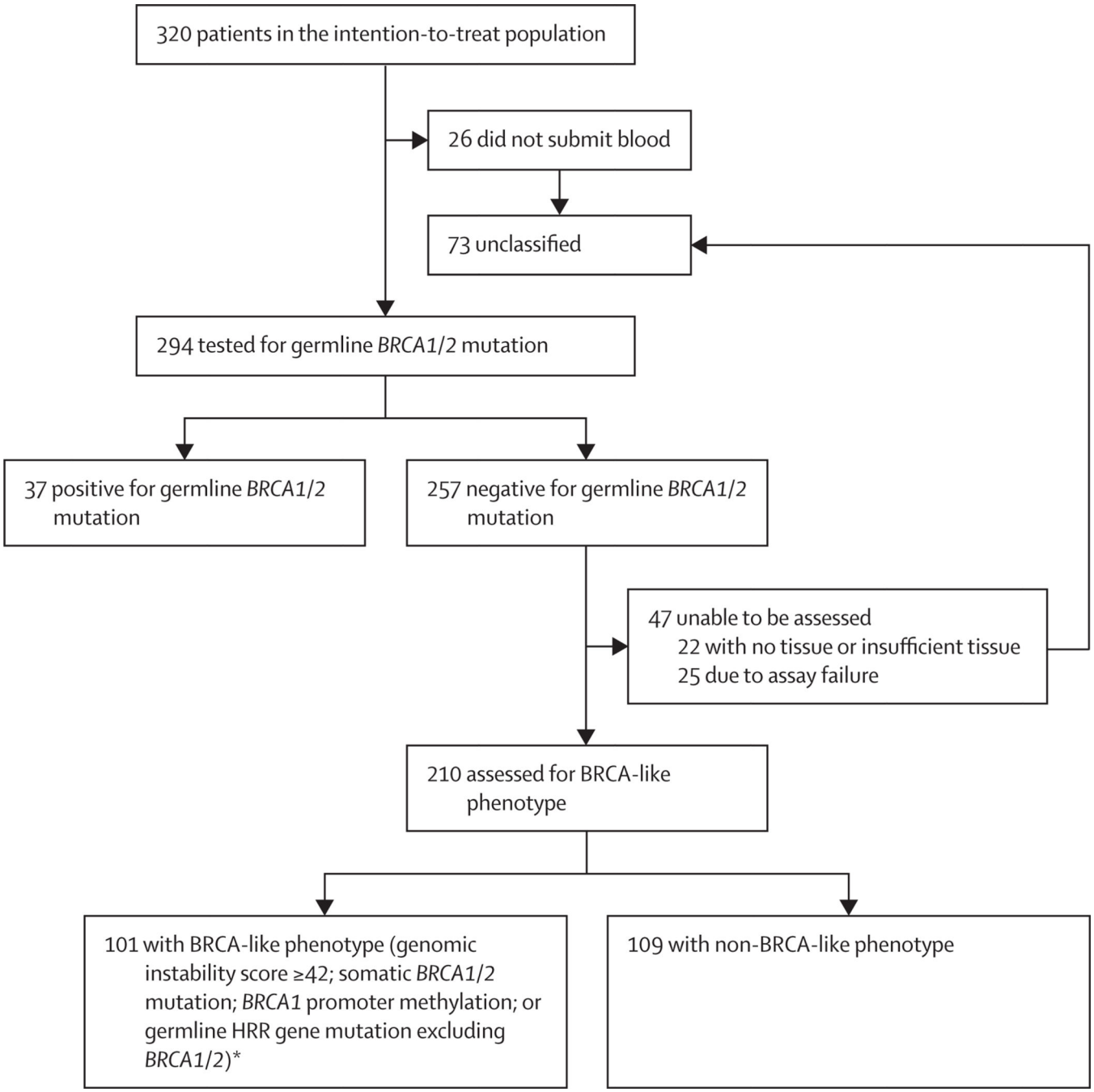

Figure 2.
Distribution of patients in the predefined biomarker groups

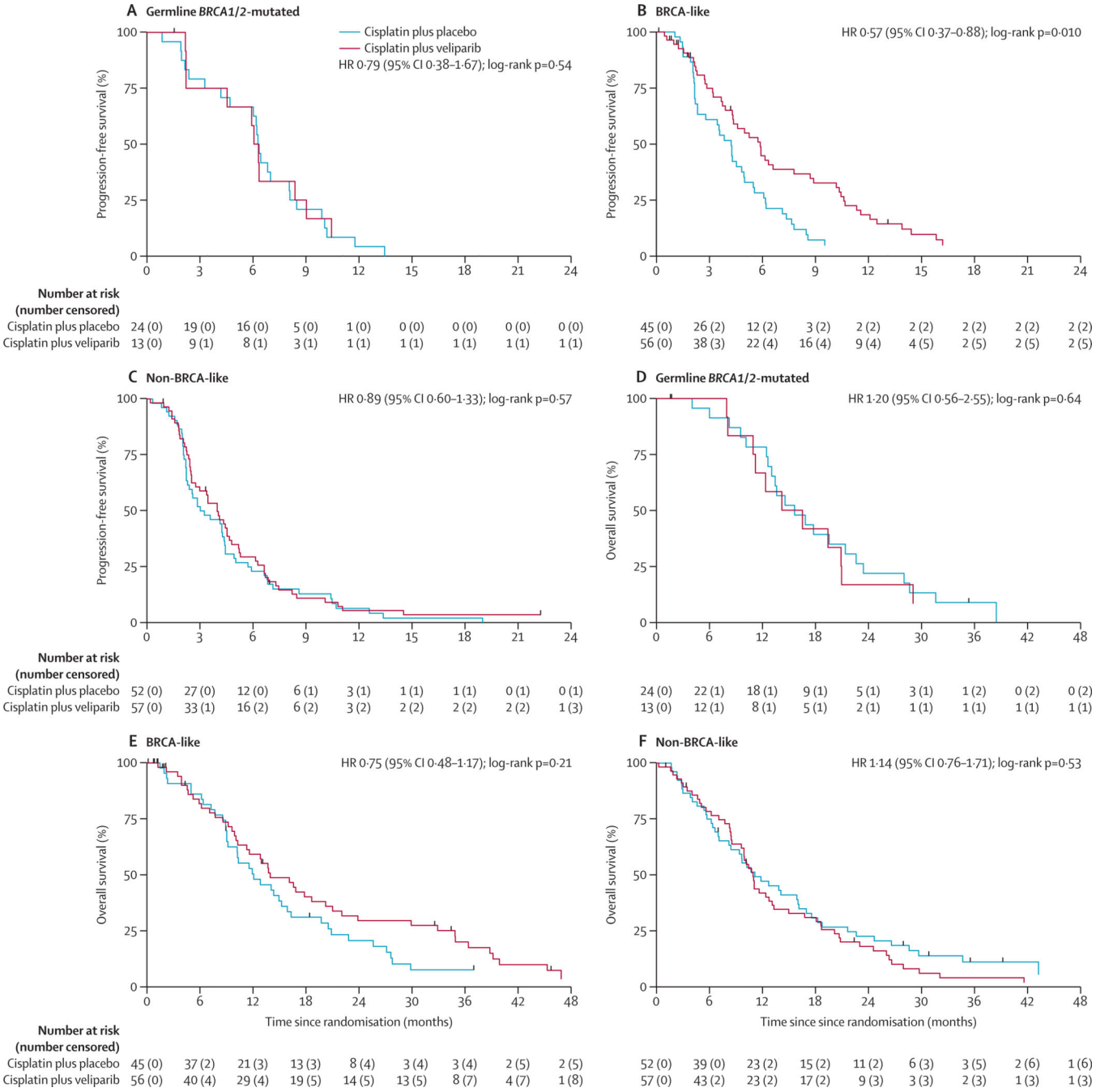

Figure 3:

Kaplan-Meier estimates of progression-free survival (A-C) and overall survival (D-F) in the predefined biomarker groups

Table 1:

Baseline characteristics

Characteristic, N (%)	Cisplatin + Veliparib (N=162)	Cisplatin + Placebo (N=158)
Age, years – median (range)	55.5 (27–80)	56 (26–80)
Sex		
Female	162 (100%)	157 (99.4%)
Race		
White	129 (80%)	116 (73%)
Black	23 (14%)	28 (18%)
Asian	6 (4%)	5 (3%)
Other/unknown	4 (2%)	9 (6%)
Ethnicity		
Hispanic	15 (9%)	7 (4%)
ECOG performance score		
0	96 (59%)	89 (56%)
1–2	66 (41%)	69 (44%)
Subtype[a]		
TNBC	158 (98%)	147 (93%)
ER/PR-positive	4 (2%)	11 (7%)
Prior lines of chemotherapy for metastatic disease		
0	111 (69%)	111 (70%)
1	51 (31%)	47 (30%)
Prior (neo)adjuvant chemotherapy	120 (74%)	116 (73%)
Prior carboplatin	14 (9%)	17 (11%)
Measurable disease	134 (83%)	134 (85%)
Visceral disease	106 (65%)	107 (68%)
Prior biologic or immune checkpoint inhibitor therapy	6 (4%)	6 (4%)

[a]Eligible patients had histologically confirmed metastatic TNBC (ER and PR immunohistochemical nuclear staining of ≤1% and HER2 negativity per 2013 ASCO/CAP guidelines) or metastatic HER2-negative breast cancer with known deleterious or suspected deleterious *BRCA1* or *BRCA2* germline mutation.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor; TNBC, triple-negative breast cancer.

Table 2:

Treatment-related adverse events

Adverse event, N (%)	Cisplatin + Veliparib (N=155[a])				Cisplatin + Placebo (N=147[a])			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	37 (24%)	85 (55%)	29 (19%)	1 (1%)[b]	63 (43%)	67 (46%)	8 (5%)	1 (1%)[c]
Abdominal pain	12 (8%)	0 (0%)	0 (0%)	0 (0%)	11 (7%)	2 (1%)	0 (0%)	0 (0%)
Acute kidney injury	0 (0%)	2 (1%)	0 (0%)	0 (0%)	8 (5%)	2 (1%)	0 (0%)	0 (0%)
Alkaline phosphatase increased	12 (8%)	1 (1%)	0 (0%)	0 (0%)	16 (11%)	0 (0%)	0 (0%)	0 (0%)
Anemia	61 (39%)	35 (23%)	0 (0%)	0 (0%)	71 (48%)	12 (8%)	0 (0%)	0 (0%)
Anorexia	44 (28%)	0 (0%)	0 (0%)	0 (0%)	31 (21%)	3 (2%)	0 (0%)	0 (0%)
AST increased	6 (4%)	0 (0%)	0 (0%)	0 (0%)	16 (11%)	1 (1%)	0 (0%)	0 (0%)
Back pain	5 (3%)	0 (0%)	0 (0%)	0 (0%)	3 (2%)	3 (2%)	0 (0%)	0 (0%)
Constipation	35 (23%)	1 (1%)	0 (0%)	0 (0%)	43 (29%)	0 (0%)	0 (0%)	0 (0%)
Creatinine increased	18 (12%)	3 (2%)	0 (0%)	0 (0%)	21 (14%)	4 (3%)	1 (1%)	0 (0%)
Diarrhea	30 (19%)	1 (1%)	0 (0%)	0 (0%)	21 (14%)	1 (1%)	0 (0%)	0 (0%)
Dizziness	22 (14%)	2 (1%)	0 (0%)	0 (0%)	18 (12%)	1 (1%)	0 (0%)	0 (0%)
Dyspnea	17 (11%)	1 (1%)	0 (0%)	0 (0%)	7 (5%)	0 (0%)	0 (0%)	0 (0%)
Fatigue	89 (57%)	8 (5%)	0 (0%)	0 (0%)	74 (50%)	9 (6%)	0 (0%)	0 (0%)
Febrile neutropenia	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Dehydration	7 (5%)	8 (5%)	0 (0%)	0 (0%)	14 (10%)	4 (3%)	0 (0%)	0 (0%)
Headache	21 (14%)	2 (1%)	0 (0%)	0 (0%)	22 (15%)	3 (2%)	0 (0%)	0 (0%)
Hearing impaired	5 (3%)	1 (1%)	0 (0%)	0 (0%)	9 (6%)	2 (1%)	0 (0%)	0 (0%)
Hyperglycemia	7 (5%)	1 (1%)	0 (0%)	0 (0%)	6 (4%)	2 (1%)	0 (0%)	0 (0%)
Hypertension	8 (5%)	4 (3%)	0 (0%)	0 (0%)	13 (9%)	0 (0%)	0 (0%)	0 (0%)
Hypokalemia	21 (14%)	5 (3%)	1 (1%)	0 (0%)	15 (10%)	7 (5%)	0 (0%)	0 (0%)
Hypomagnesemia	29 (19%)	2 (1%)	0 (0%)	0 (0%)	32 (22%)	0 (0%)	0 (0%)	0 (0%)
Hyponatremia	8 (5%)	3 (2%)	1 (1%)	0 (0%)	13 (9%)	2 (1%)	0 (0%)	0 (0%)
Infections/infestations-Other	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Lung infection	0 (0%)	2 (1%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)

Adverse event, N (%)	Cisplatin + Veliparib (N=155[a])				Cisplatin + Placebo (N=147[a])			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Lymphocyte count decreased	26 (17%)	10 (6%)	1 (1%)	0 (0%)	31 (21%)	7 (5%)	1 (1%)	0 (0%)
Nausea	97 (63%)	19 (12%)	0 (0%)	0 (0%)	83 (56%)	11 (7%)	0 (0%)	0 (0%)
Neutrophil count decreased	21 (14%)	48 (31%)	23 (15%)	0 (0%)	35 (24%)	29 (20%)	0 (0%)	0 (0%)
Peripheral sensory neuropathy	38 (25%)	2 (1%)	0 (0%)	0 (0%)	35 (24%)	2 (1%)	0 (0%)	0 (0%)
Platelet count decreased	50 (32%)	23 (15%)	6 (4%)	0 (0%)	32 (22%)	2 (1%)	2 (1%)	0 (0%)
Syncope	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	4 (3%)	0 (0%)	0 (0%)
Thromboembolic event	2 (1%)	2 (1%)	0 (0%)	0 (0%)	2 (1%)	4 (3%)	0 (0%)	0 (0%)
Vomiting	60 (39%)	9 (6%)	0 (0%)	0 (0%)	47 (32%)	5 (3%)	0 (0%)	0 (0%)
Weight loss	19 (12%)	0 (0%)	0 (0%)	0 (0%)	15 (10%)	1 (1%)	0 (0%)	0 (0%)
White blood cell decreased	41 (26%)	38 (25%)	4 (3%)	0 (0%)	58 (39%)	11 (7%)	0 (0%)	0 (0%)

Listed are adverse events that occurred during randomly allocated study treatment. The as-treated population included all patients who underwent randomization and received ≥1 dose of study treatment. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Treatment-related adverse events that occurred in at least 10% of patients (grade 1–2) in at least 1% of patients (grade 3–4) are reported; all treatment-related grade 5 events are reported. Patients might have had more than one event.

[a] N=18 randomized patients did not receive protocol therapy and are not included in toxicity assessment

[b] Sepsis

[c] Acute kidney injury due to cisplatin plus heart failure from previous doxorubicin exposure