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Impact of veliparib, paclitaxel dosing regimen, and germline *BRCA* status on the primary treatment of serous ovarian cancer – an ancillary data analysis of the VELIA trial

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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Abstract

Objective.—In the Phase 3 VELIA trial (NCT02470585), veliparib added to carboplatin plus paclitaxel concomitantly and as maintenance for women with newly-diagnosed advanced ovarian cancer significantly improved progression-free survival (PFS) versus chemotherapy alone. Here we present exploratory analyses by paclitaxel dosing schedule and germline *BRCA* (g*BRCA*) status.

Methods.—Women with untreated ovarian carcinoma were randomized (1:1:1) to: veliparib during chemotherapy and maintenance (veliparib-throughout), veliparib during chemotherapy followed by placebo maintenance (veliparib-combination only), or placebo during chemotherapy and maintenance (control). Chemotherapy included carboplatin plus dose-dense (DD; weekly) or every-3-week (Q3W) paclitaxel (a stratification factor at randomization), selected at the investigator's discretion pre-randomization. PFS was assessed by paclitaxel dosing schedule using a Cox proportional hazard model adjusted by treatment arm and stratification factors; safety was analyzed based on paclitaxel dosing schedule and g*BRCA* status.

Results.—1132 patients were analyzed by paclitaxel schedule. Pooled treatment arms demonstrated longer median PFS with DD (n = 586) versus Q3W (n = 546) paclitaxel (ITT: 20.5 vs 15.7 months, hazard ratio [HR] 0.77; homologous recombination proficient cancer: 15.1 vs 11.8 months, HR 0.64; *BRCA*wt: 18.0 vs 12.9 months, HR 0.70). Comparison between arms favored

veliparib-throughout versus control in both DD (PFS, 24.2 vs 18.3 months, hazard ratio 0.67) and Q3W (19.3 vs 14.6, hazard ratio 0.69) subgroups. DD paclitaxel was associated with higher incidence of Grade 3/4 neutropenia, fatigue, and anemia versus Q3W. There were no differences in toxicity between *gBRCA*m ($n = 211$) and *gBRCA*wt ($n = 902$) subgroups.

Conclusions.—DD paclitaxel was tolerable and associated with longer PFS in the HR proficient and *gBRCA*wt groups, versus Q3W. *gBRCA* status did not impact safety.

Keywords

Veliparib; Ovarian cancer; PARP inhibitor; Dose-dense paclitaxel; g*BRCA*; Homologous recombination deficiency

1. Introduction

Ovarian cancer is the leading cause of gynecological cancer–related death worldwide, and the majority of patients diagnosed with ovarian cancer present with advanced disease [1,2]. Despite treatment advances, including the optimization of surgery and chemotherapy protocols, as well as incorporation of targeted therapy, there remains unmet need in terms of improving clinical outcomes [1,3].

Chemotherapy with carboplatin and paclitaxel, with or without the use of the vascular endothelial growth factor (VEGF)–inhibitor bevacizumab, is the current standard of care for the first-line (1L) treatment of ovarian cancer [4–6]. In the front-line setting, the JGOG 3016 trial (NCT00226915; without bevacizumab) found that a dose-dense (DD) schedule of paclitaxel improved both progression-free survival (PFS) and overall survival (OS) compared with an every-3-week (Q3W) schedule [7]. In contrast, the GOG-0262 (NCT01167712, bevacizumab permitted) and ICON8 (NCT01654146; without bevacizumab) trials found no difference in PFS or OS between DD and Q3W paclitaxel regimens among the overall population with untreated ovarian cancer [8,9]. However, in an exploratory analysis of patients who did not receive bevacizumab in GOG-0262, PFS was improved with DD compared with Q3W paclitaxel [8]. These data suggest that DD paclitaxel may be the preferable dosing schedule for patients who do not receive concomitant bevacizumab. With these variations in clinical outcomes from prospective randomized trials, both regimens are used in the treatment of ovarian cancer. However, it is unclear which regimen should be applied to which patient population.

In recent years, poly(ADP-ribose) polymerase (PARP) inhibitors have also been added to the treatment guidelines for 1L ovarian carcinoma (OC) as maintenance therapy for those who respond to platinum-based chemotherapy [10,11]. Efficacy and safety of 1L PARP inhibitors in this setting has now been demonstrated in those with pathogenic germline *BRCA* (g*BRCA*) variants, homologous recombination deficiency (HRD), and biomarker unrestricted OC [12,13]. The presence of HRD increases responsiveness to PARP inhibitors and platinating agents in OC [12], but it has been hypothesized that hemizygous g*BRCA* mutations may also make patients more susceptible to treatment-related toxicities [14–16]. There are conflicting data on whether *BRCA* mutation (*BRCA*m) carriers with breast or ovarian cancer experience more hematologic toxicity from chemotherapy; however, none

of the evidence stems from large randomized controlled trials [14–19]. One phase 1 study in patients with solid tumors, including breast cancer, suggested *BRCA* mutation carriers experience differential toxicity from PARP inhibitors; however, no reliable conclusions can be drawn from this study due to its small patient population [20].

Veliparib is a PARP inhibitor that has demonstrated activity and tolerability both as a single agent and in combination with carboplatin and paclitaxel [21–24]. The phase 3 VELIA trial assessed the efficacy and safety of veliparib when added upfront with carboplatin and paclitaxel, and then, in the absence of progression, continued as maintenance monotherapy, in patients with newly diagnosed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma (HGSOC) [25]. In contrast to prior studies of PARP inhibitors [12,13,26], VELIA enrolled patients at diagnosis and did not select for patients with prior response to platinum-based chemotherapy or *BRCA* mutations [25]. In that study, PFS was significantly improved in patients treated with veliparib plus carboplatin and paclitaxel followed by veliparib maintenance (veliparib-throughout arm) compared with the carboplatin and paclitaxel control arm. This result was demonstrated in the *BRCA*m (germline or somatic), HRD (including *BRCA*m cohort), and intention-to-treat (ITT) populations [25].

In the VELIA trial, investigators chose (prior to patient randomization) between intravenous (IV) paclitaxel at 175 mg/m^2 Q3W or 80 mg/m^2 DD weekly as part of the carboplatin and paclitaxel chemotherapy (plus veliparib or placebo, without bevacizumab), allowing for the analysis of efficacy and safety by paclitaxel schedule. Paclitaxel regimen, DD or Q3W, was included as a stratification factor at randomization. Inclusion of patients regardless of g*BRCA* mutation status allowed for additional safety analyses to be performed to determine the contribution of increased PARP-inhibitor sensitivity associated with g*BRCA* mutations and observed toxicities in the VELIA trial. These exploratory analyses are presented here.

2. Methods

2.1. Trial design

Full details of the trial design, inclusion and exclusion criteria, treatment, and endpoints have been published previously [25]. In summary, women aged ≥18 years with previously untreated HGSOC were randomized 1:1:1 to receive either carboplatin and paclitaxel plus placebo, followed by placebo maintenance (control arm); carboplatin and paclitaxel plus veliparib, followed by placebo maintenance (veliparib-combination–only arm); or carboplatin and paclitaxel plus veliparib, followed by veliparib maintenance (veliparib-throughout arm). Combination therapy was administered in six 21-day cycles. In the absence of disease progression, patients then received up to 30 cycles of maintenance therapy, either veliparib or placebo, according to assigned trial arm. Dose of veliparib/placebo was 150 mg twice daily (BID), continuously administered during combination therapy, and 300 mg BID, increasing to 400 mg BID if tolerated, during the maintenance period. Carboplatin was dosed at area under curve 6. Patients received 1 of 2 dosing schedules of IV paclitaxel; either 175 mg/m^2 delivered Q3W, or 80 mg/m^2 delivered weekly in a DD schedule, at the discretion of the Investigator. Stratification factors for randomization included geographic region (Japan vs Rest of World), disease stage (International Federation of Gynecology and

Obstetrics [FIGO] Stage III or IV disease), timing of debulking surgery received (primary or interval), residual disease status after primary surgery, paclitaxel dosing regimen, and g*BRCA* status.

2.2. PFS assessment

The data cutoff for this analysis was May 3, 2019. Investigator-assessed PFS was determined according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and radiologic tumor assessments were performed at baseline; every 9 weeks during the combination phase; then every 12 weeks for 2 years, then every 6 months for 3 years, and then annually, until the occurrence of imaging-based progression.

2.3. Biomarker assessments

*BRCA*m status was evaluated using the BRACAnalysis CDx® or myChoice® CDx assay (Myriad Genetic Laboratories, Inc., Salt Lake City, UT) for blood (germline) and tissue (somatic and germline) mutations, respectively. *BRCA*m is defined as mutated *BRCA*1 or *BRCA*2 detected in either blood or neoplastic tissue. HRD status was assessed using the Myriad myChoice CDx assay, which combines *BRCA* tumor mutation sequencing and assessment of 3 measures of genomic instability, which are combined into a genomic instability score (GIS). HRD was defined as GIS ≥33 or the presence of deleterious germline or somatic *BRCA* mutation. Homologous recombination proficient (HRP) was defined as GIS <33 and the absence of a detectable *BRCA*m, consistent with previous analyses.

2.4. Safety

Treatment emergent adverse events (TEAEs) were assessed according to Common Terminology Criteria for Adverse Events (CTCAE version 4.03) and laboratory evaluations were monitored throughout the trial. Data were analyzed separately for combination phase, maintenance phase, and whole trial period, and were also analyzed according to paclitaxel dosing schedule. A separate safety analysis was conducted according to g*BRCA* status (g*BRCA*m vs g*BRCA* wildtype [wt]).

2.5. Statistical analysis

Efficacy analyses included all randomized patients with a confirmed investigator choice of paclitaxel schedule available. PFS was estimated using the Kaplan–Meier method. Cox proportional hazard models were used to compare PFS between DD and Q3W paclitaxel dosing groups, with covariates adjusted. Hazard ratios and 95% confidence intervals (CIs) were provided. Covariates included treatment arm (control vs veliparib-combination only vs veliparib-throughout), residual disease (no residual disease after primary surgery vs interval surgery or any residual disease after primary surgery), stage of disease (Stage III vs Stage IV), and *BRCA* status (germline or somatic; *BRCA*m vs *BRCA*wt or unknown/missing). *BRCA* status was not included as a covariate when conducting analyses in subgroups defined by that status, as all patients in a given group were either *BRCA*wt or *BRCA*m. Analyses were conducted in the whole population and in subgroups according to region of enrollment (Japan vs non-Japan), *BRCA* status (*BRCA*wt and *BRCA*m) and HRD status (HRD including *BRCA*m, HRD excluding *BRCA*m and HRP). Safety data are presented

descriptively. Safety analyses included all patients who received at least 1 dose of veliparib/placebo and had either a documented investigator choice of paclitaxel dosing schedule prior to randomization, or for whom g*BRCA* mutation status was available for the purposes of the subanalyses presented (g*BRCA*m vs g*BRCAwt*).

2.6. Clinical trial conduct

The trial protocol was approved by all relevant institutional review boards prior to trial initiation, and the trial was conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines, regulations governing clinical trial conduct, and the Declaration of Helsinki. All participants provided written informed consent.

3. Results

3.1. DD versus Q3W paclitaxel

3.1.1. Patients—A total of 1140 patients were enrolled in VELIA across the 3 treatment arms with confirmation of investigator's choice of paclitaxel scheduling in 1132 patients, of whom 586 (51.8%) received DD paclitaxel and 546 (48.2%) received Q3W paclitaxel (Supplemental Fig. 1). Demographic and baseline characteristics were generally balanced between groups; proportions of patients with interval and primary surgery were similar between dosing groups (Table 1). Of the 77 patients enrolled in Japan, 53 patients received Q3W and 24 received DD paclitaxel, respectively. Median paclitaxel dose intensity across treatment arms ranged from 84.2–94.1% in the DD paclitaxel group, and from 94.7–99.2% in the Q3W group.

3.1.2. Efficacy—In a pooled analysis combining patients from each of the 3 treatment arms, PFS was longer with DD paclitaxel than with Q3W: median 20.5 versus 15.7 months; hazard ratio 0.77 (95% CI 0.66–0.89), respectively (Fig. 1). In subgroups defined by biomarker status, improved PFS with DD versus Q3W paclitaxel was seen in patients with *BRCA*wt (median 18.0 vs 12.9 months; hazard ratio 0.70 [95% CI 0.59, 0.84]) or HRP cancers (median 15.1 vs 11.8 months; hazard ratio 0.64 [95% CI 0.50–0.81]). A trend of improved PFS with DD versus Q3W paclitaxel was observed in patients with HRD excluding *BRCA*m (median 20.9 vs 17.2 months; hazard ratio 0.77 [95% CI 0.58–1.02]) and patients with HRD including *BRCA*m (median 24.2 vs 20.7 months; hazard ratio 0.87 [95% CI 0.70, 1.08]). PFS was similar with DD versus Q3W paclitaxel in the *BRCA*m subgroup (median 28.2 vs 26.0 months; hazard ratio 1.05 [95% CI 0.75–1.46]).

PFS with DD versus Q3W paclitaxel was examined in subgroups defined by region of enrollment. In patients enrolled outside Japan, longer PFS was with DD paclitaxel compared to Q3W subgroup (median 20.4 vs 15.4 months; hazard ratio 0.76 [95% CI 0.65–0.89]) (Figs. 1 & 2). Patients enrolled in Japan had a similar hazard ratio for PFS with DD (n = 24) versus Q3W (n = 53) (hazard ratio, 0.69; 95% CI 0.33–1.42; median 23.4 vs 20.6 months).

In an analysis comparing the veliparib-throughout versus control regimens in subgroups defined by paclitaxel dosing schedule, PFS favored veliparib-throughout in both the DD (median 24.2 vs 18.3 months; hazard ratio 0.67 [95% CI 0.51–0.88]) and Q3W (median

19.3 vs 14.6 months; hazard ratio 0.69 [95% CI 0.52–0.91]) paclitaxel subgroups (Fig. 1). To further evaluate observations made in the HR proficient population, PFS with DD versus Q3W paclitaxel in veliparib-throughout and control arms is shown in Supplementary Fig. 2.

3.1.3. Safety—All patients experienced at least 1 TEAE, regardless of treatment arm or paclitaxel schedule (Supplementary Table 2). The most common TEAEs of any grade were nausea, neutropenia, peripheral sensory neuropathy, fatigue, and anemia. Within treatment arms, the frequency of these common TEAEs was consistently higher for DD paclitaxel versus Q3W paclitaxel, with the exception of peripheral sensory neuropathy, which had similar rates regardless of paclitaxel dosing in the veliparib-containing arms. Grade 3/4 TEAEs were more frequent in the DD paclitaxel group than the Q3W group overall (control arm: 89.6% [*n* = 172] vs 63.1% [*n* = 113]; veliparib-combination–only arm: 94.0% [*n* = 188] vs 80.1% [*n* = 141]; veliparib-throughout arm: 94.2% [*n* = 178] vs 81.9% [*n* = 154], respectively). The most common Grade 3/4 TEAEs, neutropenia and anemia were also more frequent in the DD, compared to the Q3W group, in each arm (Supplementary Table 2). In the control arm, serious TEAEs were more frequent in the DD paclitaxel group than the Q3W group (44.8% [*n* = 86] 30.7% [*n* = 55], respectively). In the veliparib-combination–only and veliparib-throughout arms, frequency of serious TEAE were similar with DD and Q3W dosing (30.5% [*n* = 61] vs 38.6% [*n* = 68], and 34.9% [*n* = 66] vs 39.9% [*n* = 75], respectively).

The rates of TEAEs leading to discontinuation of veliparib/placebo were similar between the DD paclitaxel group and the Q3W group in all trial arms in the overall population (DD vs Q3W regimens, respectively): control arm 11.5% (*n* = 22) versus 11.7% (*n* = 21); veliparib-combination–only arm 10.5% (*n* = 21) versus 15.9% (*n* = 28); veliparib-throughout arm 24.3% (*n* = 46) versus 27.1% (*n* = 51) (Supplementary Table 2).

3.2. Germline BRCA mutation status

3.2.1. Safety—A total of 1113 patients were included in an additional safety analysis by g*BRCA* status (g*BRCA*m, *n* = 211; g*BRCA*wt, *n* = 902). Patients with g*BRCA*m received a higher median number of veliparib cycles (30.0, range 1.0–36.0) than patients with g*BRCA*wt (14.0, range 1.0–36.0) (Supplementary Table 3). There were no consistent differences in rates of common Grade 2–4 TEAEs in the g*BRCA*m versus g*BRCA*wt across treatment arms (Table 2, Fig. 3, Supplemental Figs. 3 & 4). The frequency of any Grade 3/4 TEAEs was similar for the g*BRCA*m and g*BRCA*wt populations within treatment arms (control, 74.6% [*n* = 47] vs 77.0% [*n* = 235]; veliparib-combination only, 91.4% [*n* = 64] vs 86.4% [*n* = 260]; veliparib-throughout, 85.9% [*n* = 67] vs 89.2% [*n* = 264]). The incidences of most frequent Grade 3/4 hematologic TEAEs (ie, neutropenia, anemia, thrombocytopenia, and leukopenia) were similar between g*BRCA*m and g*BRCA*wt groups for all treatment arms (Fig. 3, Supplemental Figs. 3 & 4). Overall, the frequency of Grade 3/4 hematologic TEAEs decreased at the end of Cycle 6, regardless of g*BRCA* status, as patients transitioned from combination to maintenance therapy in each treatment arm. Prevalence of common nonhematologic TEAEs also decreased during the maintenance compared to the combination phase within each treatment arm, regardless of *BRCA* status. A notable exception was the increase in nausea during the maintenance phase in the

veliparib-throughout arm in both g*BRCA*m and g*BRCA*wt patients (Fig. 3, Supplementary Figs. 3 and 4).

Frequency of serious adverse events was similar between the 2 populations in the control and veliparib-combination–only arms, but there was a lower frequency in the g*BRCA*m versus g*BRCA*wt population in the veliparib-throughout arm (control, 36.5% [*n* = 23] vs 38.0% [*n* = 116]; veliparib-combination only, 32.9% [*n* = 23] vs 33.6% [*n* = 101]; veliparib-throughout, 28.2% [*n* = 22] vs 39.9% [*n* = 118], respectively). Frequency of TEAEs leading to veliparib/placebo discontinuation was similar for the g*BRCA*m and g*BRCA*wt populations within each treatment arm (control, 7.9% [*n* = 5] vs 12.5% [*n* = 38]; veliparib-combination only, 11.4% [*n* = 8] vs 13.3% [*n* = 40]; veliparib-throughout, 24.4% [*n* = 19] vs 26.4% [*n* = 78]).

In the g*BRCA*m subgroup, Q3W paclitaxel was associated with higher rates of TEAEs leading to discontinuation of veliparib/placebo in all trial arms compared with DD paclitaxel (Supplementary Table 2). In the g*BRCA*wt subgroup, the rate of TEAEs leading to discontinuation of veliparib/placebo was relatively higher with Q3W paclitaxel versus DD in veliparib-combination–only arm, while the rates were similar between Q3W and DD in the control and veliparib-throughout arms.

4. Discussion

In the VELIA trial, investigator assignment to a DD paclitaxel schedule, which was incorporated into randomization stratification, was associated with longer PFS than a Q3W schedule (median PFS: 20.5 vs 15.7 months; hazard ratio 0.77 [95% CI 0.66–0.89]). This effect was most pronounced in the *BRCA*wt and HRP cancer subgroups, and not significantly different in patients with a *BRCA* mutation or HRD tumors. The DD regimen was accompanied by an increase in toxicity, though the toxicity was manageable. Grade 3/4 AEs, and specifically hematologic toxicities, were consistently more frequent with the DD versus Q3W paclitaxel. It is important to note that the investigator's choice of paclitaxel schedule may have reflected subtle differences in the populations that influenced the better outcomes for DD paclitaxel, despite the apparent similarities between the groups (Table 1).

These data may offer an additional perspective regarding published findings from the GOG-0262 trial (carboplatin and paclitaxel with and without bevacizumab) [8]. In this context, the findings from VELIA are not without precedent, though the prospective data are conflicting. In contrast to the findings in the present study, in GOG-0262, there was no significant improvement in PFS with DD versus Q3W paclitaxel (median PFS 14.7 vs 14.0 months; hazard ratio 0.89 [95% CI 0.74–1.06]; *P* = 0.18) [8]. However, in the exploratory subgroup of those patients who did not receive bevacizumab, DD paclitaxel was associated with improved PFS compared with Q3W paclitaxel (median PFS 14.2 vs 10.3 months; hazard ratio 0.62 [95% CI 0.40–0.95]; *P* = 0.03) [8]. It should be noted that this subgroup comprised only a small number of patients (*n* = 112) and the authors suggested the possibility that the use of maintenance bevacizumab (84% of patients) may have masked the true treatment effect in the overall population [8]. Paclitaxel has demonstrated an antiangiogenic effect in in vitro studies; this could potentially result in those receiving

bevacizumab having a saturated antiangiogenic effect, and explain the lack of observed difference between DD and Q3W paclitaxel [27]. The effect of bevacizumab was not investigated in the VELIA trial, and its effect on efficacy and toxicity in the context of veliparib is yet to be investigated in a randomized trial.

Consistent with the above interpretation of the GOG-0262 study, our present findings can also add new insight into the ICON8 and JGOG 3016 trials (carboplatin and paclitaxel without bevacizumab), which both compared DD (80 mg/m^2 weekly) paclitaxel to standard Q3W dosing [7,9]. The JGOG 3016 study of 631 Japanese patients with advanced epithelial ovarian cancer found that the DD paclitaxel regimen improved PFS and OS compared with the conventional Q3W regimen [7]. The ICON8 trial was conceived following the JGOG 3016 trial, and although it did not show any survival benefit of DD versus Q3W paclitaxel dosing, both regimens were better tolerated in the predominantly European population than in JGOG 3016 [9]. Multiple factors could potentially contribute to the observed variance in efficacy: the current study included high-grade (FIGO Stage III/IV) serous patients, whereas the ICON8 trial enrolled patients including both serous and other types of ovarian cancer (FIGO Stage Ic-IV) [9]; furthermore, pharmacogenomic variations between Asians versus non-Asians with respect to treatment response and toxic effects may partially explain these differences in trial results [28]. In this study, patients enrolled in Japan had a similar hazard ratio, for PFS with DD versus Q3W paclitaxel, to the non-Japanese patient group (0.69 and 0.76, respectively). However, as the patient group in Japan was small, whether there were differential responses by region, was inconclusive.

Prior retrospective study of patients with *BRCA* mutated ovarian cancer has demonstrated that paclitaxel, as a monotherapy, produced high response rates regardless of DD or Q3W dosing; those data also suggested increased activity in platinum-sensitive disease [29]. In patients with platinum resistant disease, however, it has been shown that DD paclitaxel resulted in better survival benefit and quality of life [30]. Here, our study showed that DD paclitaxel was associated with longer median PFS versus Q3W dosing in HRP and *BRCA*wt subgroups, but this effect was observed to a lesser extent in patients with a deleterious *BRCA*m or HRD. Because previous clinical trials of DD versus Q3W paclitaxel dosing for ovarian cancer did not report outcomes according to biomarker status [7–9], further studies are warranted to understand if specific subgroups of patients will benefit from DD paclitaxel dosing, particularly those with platinum-resistant and/or HRP ovarian cancer. JGOG2016A1, which was a survey study of JGOG3016, explored the efficacy of DD paclitaxel by histological subtype of high-grade serous carcinoma, and identified subgroups that were sensitive to DD regimen and subgroups that were less sensitive [31]. The correlation between these histological subtypes and *BRCA*/HRD status has not yet been investigated. Based on these findings reported in a Japanese patient population, further analysis of histological subtype in regard to *BRCA*/HRD status from the GOG-0262 [8] and ICON8 [9] trials may further help to identify appropriate patient subgroups for the DD paclitaxel regimen.

Cancers in patients with *BRCA* mutations are particularly responsive to platinum-based chemotherapy and PARP inhibitors due to defects in homologous recombination repair [32–34]. Presence of a germline mutation could lead to increased drug-related toxicity

in addition to enhanced activity of these agents, as patients with germline mutations harbor hemizygous mutations in all tissues [16]. Whether there is a functional impact of *BRCA* haploinsufficiency in normal cells, however, is uncertain. In VELIA, additional analyses were performed to evaluate the differential toxicity of veliparib according to g*BRCA* status. Small subgroup sample sizes precluded the evaluation of g*BRCA* within paclitaxel regimen subgroups. Overall, the frequency and severity of common adverse events were similar between patients with and without g*BRCA*m, suggesting that presence of a g*BRCA*m does not increase toxicity of either platinum or of PARP inhibitor. In addition, as patients with g*BRCA*m were equally distributed across the arms and regimens, there did not appear to be any impact of paclitaxel dosing on the lack of differences observed in terms of toxicities between the g*BRCA*m and g*BRCA*wt cohorts (data not shown). These findings are consistent with several smaller studies that found no significant differences in acute chemotherapy-induced hematologic toxicity between g*BRCA*m carriers and noncarriers [14,16–18], yet contrast with others that found an increased hematologic toxicity in g*BRCA*m carriers [15,19,20]. While data on whether *BRCA*m carriers experience differential toxicity to PARP inhibitors are limited, our findings provide support that toxicity with a PARP inhibitor is equivalent for g*BRCA*m carriers and noncarriers. Follow-up study of rates of second acute myeloid leukemia and myelodysplastic syndrome in VELIA are ongoing and will be reported separately.

VELIA was a randomized trial with large numbers of patients and showed the survival benefit with DD paclitaxel, consistent with several studies of ovarian cancer and breast cancer [7,8,35]. General limitations of the VELIA trial have been discussed previously [25]. For example, the selection of paclitaxel dosing scheduling was at investigator's discretion in VELIA, as opposed to JGOG and ICON8 [7,9]. Nevertheless, this is one of the only studies to have evaluated the efficacy and safety of DD paclitaxel based on biomarker status, and included the largest group of Asian versus non-Asian patients in one trial, and furthermore, is the largest study to examine the combination of DD paclitaxel in combination with a PARP inhibitor. In terms of the current analysis, it should be noted that it was ad hoc in nature, and the results should therefore be interpreted with caution. Further study might be conducted to determine the optimum paclitaxel dosing regimen for patients receiving veliparib in combination for newly diagnosed HGSOC.

5. Conclusions

In the VELIA trial, DD paclitaxel was associated with longer PFS than Q3W paclitaxel, particularly in the HRP and g*BRCA*wt groups, without altering the hazard ratios associated with veliparib versus placebo, but also with increased toxicity. Overall, DD paclitaxel may be a promising option for patients with HGSOC and *BRCA*wt and HRP tumors, a patient population with a substantial unmet need. Furthermore, the evaluated regimens were not associated with increased toxicity in *BRCA*m carriers compared with those without, suggesting that the activity of paclitaxel, platinum agents and PARP inhibitors in this population is not countered with lower tolerability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing statement

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

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HIGHLIGHTS

- Weekly (compared to every 3 weeks) paclitaxel was associated with longer PFS in HRP and *BRCA*wt cohorts
- PFS was improved with veliparib compared with control regardless of paclitaxel dosing schedule
- In general, grade 3/4 adverse events were more common in dose-dense paclitaxel groups compared with every-3-week paclitaxel
- Germline *BRCA* status showed no impact on incidences of adverse events across arms

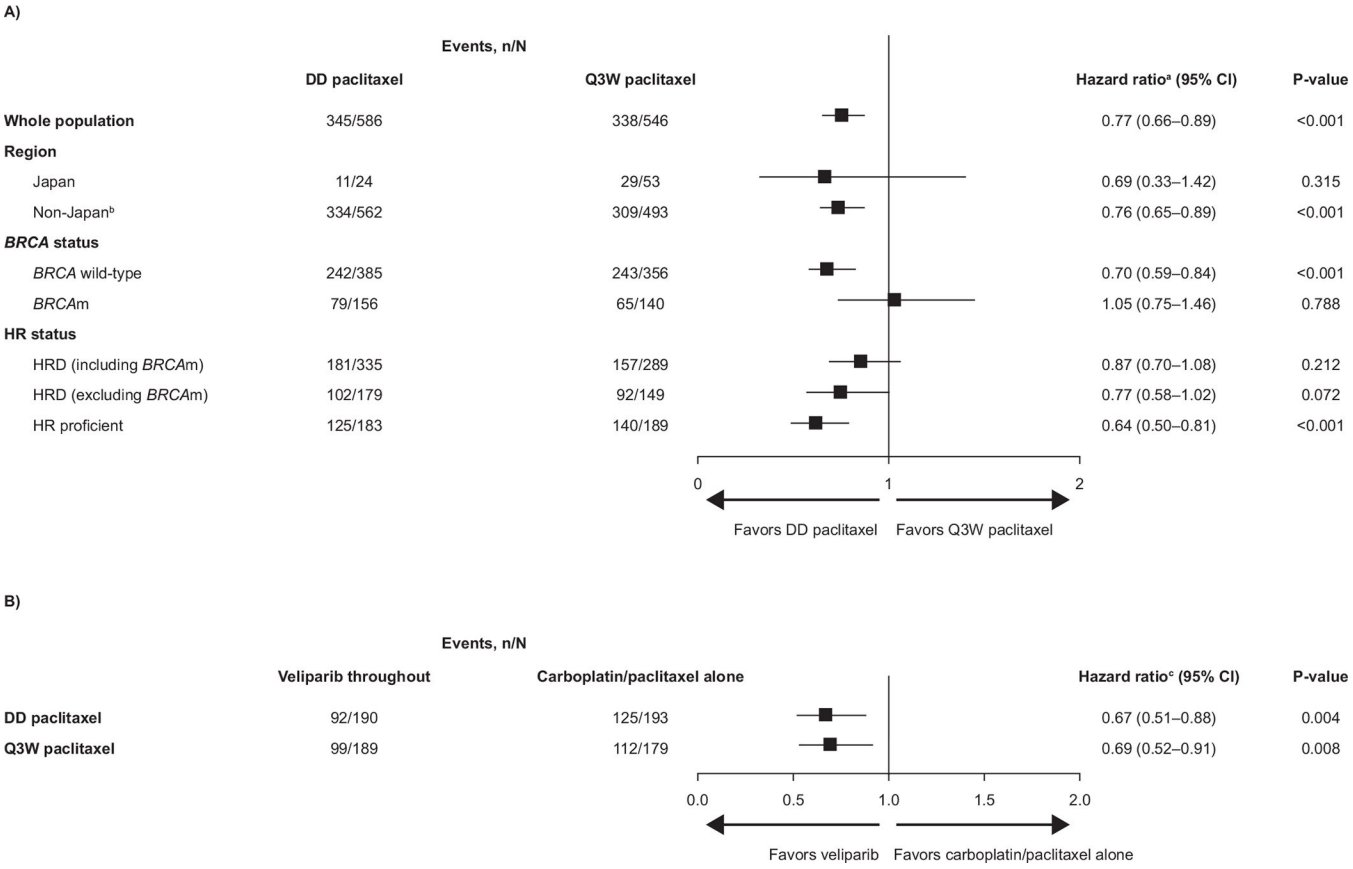

Fig. 1.

A) PFS in the DD and Q3W Paclitaxel Groups According to Baseline Characteristics and B) PFS in the Carboplatin and Paclitaxel Alone and Veliparib-Throughout Arms, According to Paclitaxel Dosing Schedule (ITT Population).

[a]Adjusted for treatment arm and stratification factors. *BRCA* status was not included as a covariate when conducting analyses in subgroups defined by *BRCA* status.

[b]Includes North America and Rest of World.

[c]Adjusted for stratification factors.

CI, confidence interval; DD, dose-dense [weekly]; HR, homologous recombination; HRD, homologous recombination deficient; ITT, intention-to-treat; PFS, progression-free survival; VEL, veliparib; Q3W, every 3 weeks.

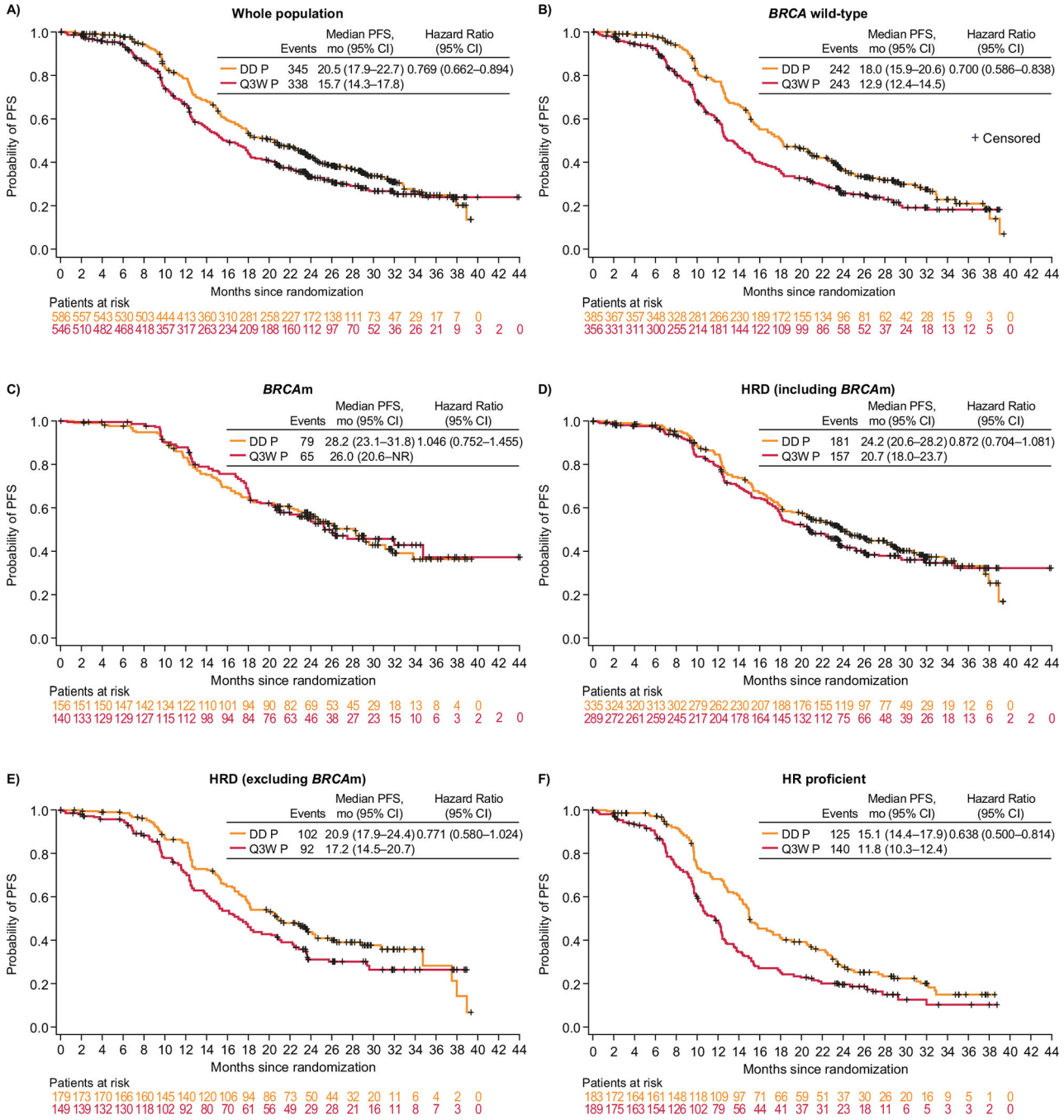

Fig. 2.

PFS in the DD and Q3W Paclitaxel Groups According to *BRCA* and HRD Status (ITT Population).

Adjusted for treatment arm and stratification factors. *BRCA* status was not included as a covariate when conducting analyses in subgroups defined by *BRCA* status.

*BRCA*m, *BRCA* mutation; CI, confidence interval; DD, dose-dense [weekly]; HR, homologous recombination; HRD, homologous recombination deficient; ITT, intention-to-treat; NR, not reached; P, paclitaxel; PFS, progression-free survival; Q3W, every 3 weeks.

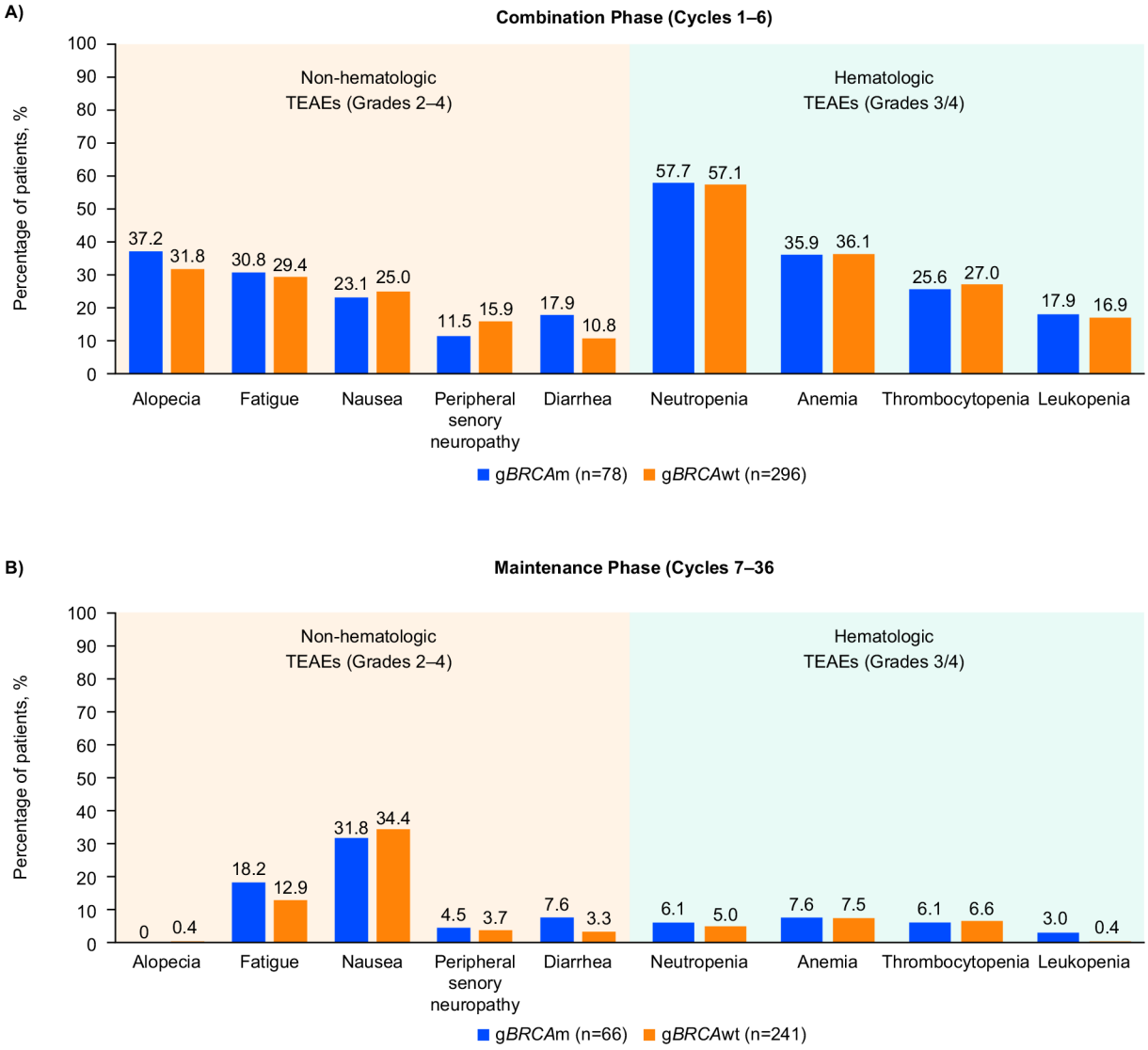

Fig. 3.

Nonhematologic Grade 2–4 TEAEs Experienced by ≥20% of Patients Over the Whole Trial Period and Corresponding Grade 3/4 Hematologic TEAEs in Veliparib-Throughout Arm by g*BRCA* Status in A) the Combination Phase, and B) the Maintenance Phase (As-Treated Population).

g*BRCA*m, germline *BRCA* mutation; g*BRCA*wt. Germline *BRCA* wildtype; TEAE, treatment-emergent adverse event.

Table 1

Baseline characteristics by paclitaxel dosing schedule (Pooled Study Arms).

Characteristic	DD (*n* = 586)	Q3W (*n* = 546)	Total (*N* = 1132)[a]
Age, median (range), years	62.0 (22.0–86.0)	63.0 (35.0–88.0)	62.0 (22.0–88.0)
ECOG PS			
0	362 (62.3)	298 (54.9)	660 (58.7)
1	204 (35.1)	232 (42.7)	436 (38.8)
2	15 (2.6)	13 (2.4)	28 (2.5)
Missing	5	3	8
FIGO stage of disease			
III	443 (75.7)	427 (78.2)	870 (76.9)
IV	142 (24.3)	119 (21.8)	261 (23.1)
Missing	1	0	1
Timing of surgery			
Primary	402 (68.6)	357 (65.4)	759 (67.0)
Interval	161 (27.5)	159 (29.1)	320 (28.3)
None	23 (3.9)	30 (5.5)	53 (4.7)
Race			
White	503 (86.6)	386 (71.1)	889 (79.1)
Black	21 (3.6)	22 (4.1)	43 (3.8)
Asian	52 (9.0)	131 (24.1)	183 (16.3)
Other	5 (0.9)	4 (7)	9 (8.0)
Missing	5	3	8
Region			
Japan	24 (4.1)	53 (9.7)	77 (6.8)
Non-Japan[b]	562 (95.9)	493 (90.3)	1055 (93.2)
No macroscopic disease after primary surgery[c], n/N (%)	283/402 (70.4)	230/357 (64.4)	513/759 (67.6)
Missing	3	8	11
BRCA status			
Any *BRCA*m	156 (28.8)	140 (28.2)	296 (28.5)
g*BRCA*m	108 (20.0)	104 (21.0)	212 (20.4)
*BRCA*wt	385 (71.2)	356 (71.8)	741 (71.5)
Missing	45	50	95
Homologous recombination status			
HRD (including *BRCA*m)	335 (64.7)	289 (60.5)	624 (62.7)
HRD (excluding *BRCA*m)	179 (34.6)	149 (31.2)	328 (32.9)
HRP	183 (35.3)	189 (39.5)	372 (37.3)
Missing	68	68	136

Values reported are n (%) unless otherwise stated. Percentages were calculated on nonmissing values.

*BRCA*m, *BRCA1/2* mutation; DD, dose-dense [weekly]; ECOG PS, Eastern Cooperative Oncology Group Performance Status; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*m, germline *BRCA* mutation; g*BRCA*wt, germline *BRCA* wildtype; HR, homologous recombination; HRD, homologous recombination deficient; HRP, homologous recombination proficient; Q3W, every 3 weeks.

[a] Includes all patients with confirmed investigator's choice of paclitaxel schedule.

[b] Includes North America and Rest of World.

[c] Percentages were calculated in patients who had primary surgery.

Table 2

Grade 2–4 TEAEs experienced by ≥20% of patients and corresponding grade 3/4 TEAEs throughout the whole trial period according to g*BRCA* status.

Event, n (%)	Control				Veliparib-combination only				Veliparib-throughout			
	g*BRCA*m (*n* = 63)		g*BRCA*wt (*n* = 305)		g*BRCA*m (*n* = 70)		g*BRCA*wt (*n* = 301)		g*BRCA*m (*n* = 78)		g*BRCA*wt (*n* = 296)	
	Grade 2–4	Grade 3/4	Grade 2–4	Grade 3/4	Grade 2–4	Grade 3/4	Grade 2–4	Grade 3/4	Grade 2–4	Grade 3/4	Grade 2–4	Grade 3/4
Any event	62 (98.4)	47 (74.6)	300 (98.4)	235 (77.0)	69 (98.6)	64 (91.4)	298 (99.0)	260 (86.4)	77 (98.7)	67 (85.9)	292 (98.6)	264 (89.2)
Neutropenia	44 (69.8)	34 (54.0)	194 (63.6)	149 (48.9)	56 (80.0)	50 (71.4)	213 (70.8)	179 (59.5)	53 (67.9)	47 (60.3)	220 (74.3)	170 (57.4)
Anemia	35 (55.6)	15 (23.8)	138 (45.2)	81 (26.6)	42 (60.0)	26 (37.1)	189 (62.8)	125 (41.5)	43 (55.1)	28 (35.9)	179 (60.5)	116 (39.2)
Thrombocytopenia	15 (23.8)	9 (14.3)	49 (16.1)	21 (6.9)	41 (58.6)	29 (41.4)	132 (43.9)	85 (28.2)	36 (46.2)	20 (25.6)	133 (44.9)	85 (28.7)
Alopecia	27 (42.9)	0	134 (43.9)	2 (0.7)	31 (44.3)	0	120 (39.9)	0	29 (37.2)	0	95 (32.1)	0
Nausea	13 (20.6)	2 (3.2)	74 (24.3)	8 (2.6)	25 (35.7)	5 (7.1)	73 (24.3)	8 (2.7)	33 (42.3)	7 (9.0)	134 (45.3)	24 (8.1)
Fatigue	14 (22.2)	2 (3.2)	80 (26.2)	10 (3.3)	21 (30.0)	3 (4.3)	100 (33.2)	15 (5.0)	33 (42.3)	10 (12.8)	104 (35.1)	21 (7.1)
Leukopenia	16 (25.4)	9 (14.3)	50 (16.4)	25 (8.2)	17 (24.3)	10 (14.3)	55 (18.3)	34 (11.3)	20 (25.6)	15 (19.2)	75 (25.3)	51 (17.2)
Peripheral sensory neuropathy	14 (22.2)	2 (3.2)	72 (23.6)	7 (2.3)	9 (12.9)	3 (4.3)	51 (16.9)	3 (1.0)	11 (14.1)	2 (2.6)	52 (17.6)	7 (2.4)
Diarrhea	7 (11.1)	2 (3.2)	40 (13.1)	7 (2.3)	11 (15.7)	2 (2.9)	45 (15.0)	8 (2.7)	19 (24.2)	1 (1.3)	39 (13.2)	7 (2.4)

g*BRCA*, germline *BRCA*; g*BRCA*m, germline *BRCA* mutation; g*BRCA*wt, germline *BRCA* wildtype; TEAE, treatment-emergent adverse event