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Impact of homologous recombination status and responses with veliparib combined with first-line chemotherapy in ovarian cancer in the Phase 3 VELIA/GOG-3005 study

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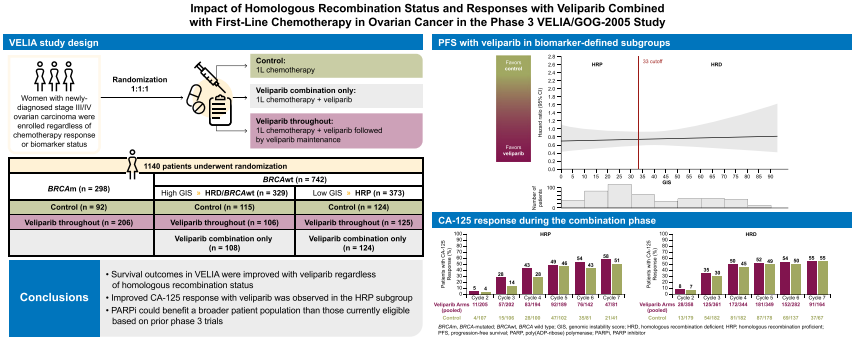
HIGHLIGHTS

- The VELIA trial assessed the PARPi veliparib, combined with frontline chemotherapy and continued as maintenance monotherapy.
- Within the *BRCA* wild type population, survival outcomes were improved regardless of homologous recombination status.
- During chemotherapy, radiographic and CA-125 responses were numerically higher with veliparib vs control in all subgroups.
- PARPi could benefit a broader patient population than those currently eligible based on prior Phase 3 trials.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. In the Phase 3 VELIA trial (NCT02470585), PARP inhibitor (PARPi) veliparib was combined with first-line chemotherapy and continued as maintenance for patients with ovarian carcinoma enrolled regardless of chemotherapy response or biomarker status. Here, we report exploratory analyses of the impact of homologous recombination deficient (HRD) or proficient (HRP) status on progression-free survival (PFS) and objective response rates during chemotherapy.

Methods. Women with Stage III-IV ovarian carcinoma were randomized to veliparib-throughout, veliparib-combination-only, or placebo. Stratification factors included timing of surgery and germline *BRCA* mutation status. HRD status was dichotomized at genomic instability score 33. During combination therapy, CA-125 levels were measured at baseline and each cycle; radiographic responses were assessed every 9 weeks.

Results. Of 1140 patients randomized, 742 had *BRCA* wild type (*BRCA*wt) tumors (HRP, $n = 373$; HRD/*BRCA*wt, $n = 329$). PFS hazard ratios between veliparib-throughout versus control were similar in both *BRCA*wt populations (HRD/*BRCA*wt: 22.9 vs 19.8 months; hazard ratio 0.76; 95% confidence interval [CI] 0.53–1.09; HRP: 15.0 vs 11.5 months; hazard ratio 0.765; 95% CI 0.56–1.04). By Cycle 3, the proportion with ≥90% CA-125 reduction from baseline was higher in those receiving veliparib (pooled arms) versus control (34% vs 23%; $P = 0.0004$); particularly in *BRCA*wt and HRP subgroups. Complete response rates among patients with measurable disease after surgery were 24% with veliparib (pooled arms) and 18% with control.

Conclusions. These results potentially broaden opportunities for PARPi utilization among patients who would not qualify for frontline PARPi maintenance based on other trials.

1. Introduction

Poly (ADP-ribose) polymerase (PARP) enzymes facilitate the repair of deoxyribonucleic acid (DNA) damage [1,2]. Cancers with defects in genes involved in homologous recombination repair, such as the breast cancer susceptibility genes *BRCA*1 and *BRCA*2 (*BRCA*), are particularly sensitive to PARP inhibition [3,4] reflecting reliance of these cancer cells on PARP-mediated replication fork stabilization and alternative end-joining in the absence of homologous recombination. Defining these and other categories of homologous recombination deficiency (HRD) or proficiency (HRP) beyond loss of *BRCA* function could expand utilization of PARP inhibitors (PARPi) to cancers with related molecular defects. Beyond *BRCA* mutations, only a few HRD biomarkers have been prospectively tested in PARPi trials and their correlation with PARPi sensitivity has varied across trial design and cancer type [5–7].

Veliparib is an oral PARP-1/PARP-2 inhibitor that has demonstrated activity as a monotherapy in patients with ovarian carcinoma associated with germline *BRCA* mutations [8,9]. Preclinical studies have shown that PARP inhibition enhances sensitivity of neoplastic cells to DNA-damaging agents [10–14]. Combining chemotherapy with a PARPi might, therefore, provide therapeutic benefit and enhance antitumor activity beyond cancers with HRD. The VELIA study (NCT02470585) was an international, placebo-controlled, three-arm Phase 3 study that assessed the efficacy of veliparib when added to first-line chemotherapy with or without continued veliparib maintenance (veliparib-throughout and veliparib-combination only) in patients with previously untreated Stage III or IV high-grade serous ovarian, peritoneal, or fallopian tube carcinoma (HGSC) [15]. The veliparib-throughout regimen led to significantly longer progression-free survival (PFS) compared with chemotherapy alone, but no improvement in PFS was observed with chemotherapy plus veliparib followed by placebo maintenance [15]. The PFS benefit with veliparib-throughout was seen in each of the primary analytical cohorts: 1) patients with germline or somatic *BRCA* mutations; 2) patients with HRD, including *BRCA* mutated (*BRCA*m) cases; and 3) intention-to-treat (ITT) population [15]. Exploratory analyses in the HRP population showed effects on PFS that were smaller, but directionally consistent with those of the primary analysis (hazard ratio 0.81, 95% CI 0.60 to 1.09) [15].

Prior studies with other PARPi, as frontline maintenance post chemotherapy selectively enrolled patients with a clinical response to platinum-based chemotherapy, *BRCA* mutations, or both [5,16,17]. In contrast, VELIA enrolled patients at diagnosis and did not select for patients with platinum-sensitive disease or specific biomarkers [15]. VELIA, therefore, provides a unique opportunity to investigate PARP-inhibition effects on a broader patient population and the opportunity to assess the impact of combining PARP inhibition with chemotherapy.

To better understand how to utilize this unique regimen to treat newly diagnosed ovarian cancer, we performed an exploratory analysis with two goals: first, to evaluate the contribution of veliparib to first-line chemotherapy (and maintenance) in *BRCA* wild type (*BRCA*wt) cancers with various levels of genomic instability as assessed using the Myriad myChoice® CDx assay (Myriad Genetics, Inc., Salt Lake City, UT); and second, to explore whether the addition of veliparib to the chemotherapy phase impacted treatment response. As the number of early (during chemotherapy) PFS events was small in VELIA, analyses of PFS precluded a meaningful comparison between those who only received veliparib with chemotherapy (and not as maintenance) versus chemotherapy alone. Therefore, we conducted analyses exploring the added benefit of veliparib using potentially more sensitive measures (cancer antigen 125 [CA-125] and radiographic responses) during the first six cycles of treatment.

2. Materials and methods

2.1. Study design

Full details of the study design, inclusion and exclusion criteria, treatment, and endpoints have been previously published [15]. Women aged ≥18 years with a diagnosis of HGSC were randomized 1:1:1 to receive either carboplatin/paclitaxel (C/P) plus placebo, followed by placebo maintenance (control arm); C/P plus veliparib, followed by placebo maintenance (veliparib-combination–only arm); or C/P plus veliparib, followed by veliparib maintenance (veliparib-throughout arm). Stratification factors for randomization have been described previously, and included timing of surgery received and residual disease status after primary surgery [15]. HRD status (independent of *BRCA* status) was not a prospective stratification factor.

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

2.2. HRD assessment

Homologous recombination status was assessed using the Myriad myChoice CDx assay, which combines *BRCA* tumor mutation sequencing and assessment of three measures of genomic instability: loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions [7,18]. These three measures are combined into a genomic instability score (GIS). HRD was defined as GIS ≥33 or the presence of deleterious germline or somatic *BRCA* mutation. HRP was defined as GIS <33 and the absence of a detectable *BRCA* mutation, consistent with previous analyses [19].

BRCA mutation status was evaluated using the Myriad BRACAnalysis CDx® or myChoice CDx assay for blood (germline) and tissue (somatic and germline) mutations, respectively.

2.3. PFS assessment

The data cutoff for this analysis was May 3, 2019. PFS was investigator-assessed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The current exploratory analysis evaluated PFS in the veliparib-throughout arm and the control arm, in patients with confirmed *BRCA*wt (wild type) with and without HRD (HRD/*BRCA*wt and HRP, respectively), for whom a GIS could be obtained (**Supplementary Fig. S1**).

PFS was also analyzed in the veliparib-throughout, veliparib-combination only, and control arms, in patients with stable disease (SD) following combination treatment, regardless of *BRCA* status (**Supplementary Fig. S1**). The analysis of progression-free survival (PFS) in patients with SD at the end of the combination phase included *BRCA*m (mutation) and *BRCA*wt patients with measurable disease assessed by RECIST v1.1 as well as patients with nonmeasurable disease. In patients with nonmeasurable disease, overall response was categorized as complete response (CR), progressive disease (PD), non-CR/non-PD, or not evaluable. Patients undergoing interval surgery had a tumor baseline reassessment after surgery; therefore, response was considered for 3 cycles. PFS since randomization was compared between all 3 treatment arms.

2.4. CA-125 response endpoints and assessments

CA-125 levels were measured as a marker of response to therapy [20] at baseline and Day 1 of each treatment cycle during the combination phase (Cycles 1–6) using standard methodology at local laboratories. CA-125 response was defined as ≥90% reduction from baseline, in line with previously published studies [21–23]. A confirmatory value was not required. CA-125 response was calculated in both *BRCA*m and *BRCA*wt subgroups using the change in CA-125 levels from baseline to each analysis timepoint. This includes patients with interval cytoreductive surgery (**Supplementary Fig. S1**).

2.5. Radiographic response endpoints and assessments

Radiographic response during treatment Cycles 1–6 was assessed at baseline and then every 9 weeks in all patients. Imaging scans were reviewed by the investigator. Objective response rate (ORR; CR + partial response [PR]) at the end of the combination phase was calculated per RECIST v1.1 only for patients who had measurable residual disease following primary cytoreductive surgery, within the whole population and in subgroups according to *BRCA* mutation and HRD status. Patients who underwent interval debulking surgery were not included because they were re-baselined at the start of Cycle 4 and generally did not have residual disease after surgery (**Supplementary Fig. S1**). The end of the combination phase was defined as 30 days after the last dose of carboplatin or paclitaxel, and the last postbaseline tumor assessment within this window was used to determine response.

2.6. Statistical analysis

CIs for response rates were calculated using the normal approximation to the binomial distribution. PFS was estimated using the Kaplan−Meier method. Stratified Cox proportional-hazards models were used to estimate hazard ratios and 95% CIs, and treatment arms were compared via stratified log-rank tests. For analysis of PFS by HRD status, stratification factors were International Federation of Gynecology and Obstetrics stage and residual disease status (no visible residual disease vs any [>1 cm] residual disease). Hazard ratios and 95% CIs for the veliparib-throughout versus control arms were calculated for all GIS using generalized additive model with Cox proportional hazards. The analysis of PFS in patients with SD following combination treatment was stratified by residual disease, stage of disease, choice of paclitaxel dosing regimen, and *BRCA* status. This was a post-hoc subgroup analysis and is potentially biased. Formal hypothesis testing was not performed.

CA-125 response and radiographic responses were analyzed for the combination phase. During this time, treatment in the veliparib-containing arms was identical; therefore, these arms were pooled for response analysis. The number and percentage of patients having each type of response were summarized for the control arm and for both veliparib arms combined. A proportion test was used to compute the one-sided *P*-value comparing the ratio of patients with a CA-125 response in the treatment arm with respect to the control arm. No formal comparisons were made for ORR. All analyses were exploratory in nature; statistics are therefore descriptive only.

3. Results

3.1. Patients

A total of 1140 patients were randomized in the VELIA study; baseline demographics and clinical characteristics were broadly balanced between treatment arms and have been previously published, together with PFS in *BRCA*m and HRD cohorts, as well as the whole (entire) population [15]. The primary study endpoints evaluated PFS between the veliparib-throughout and control arms.

3.2. Correlation of PFS and GIS in biomarker-defined subgroups within the *BRCA*wt population

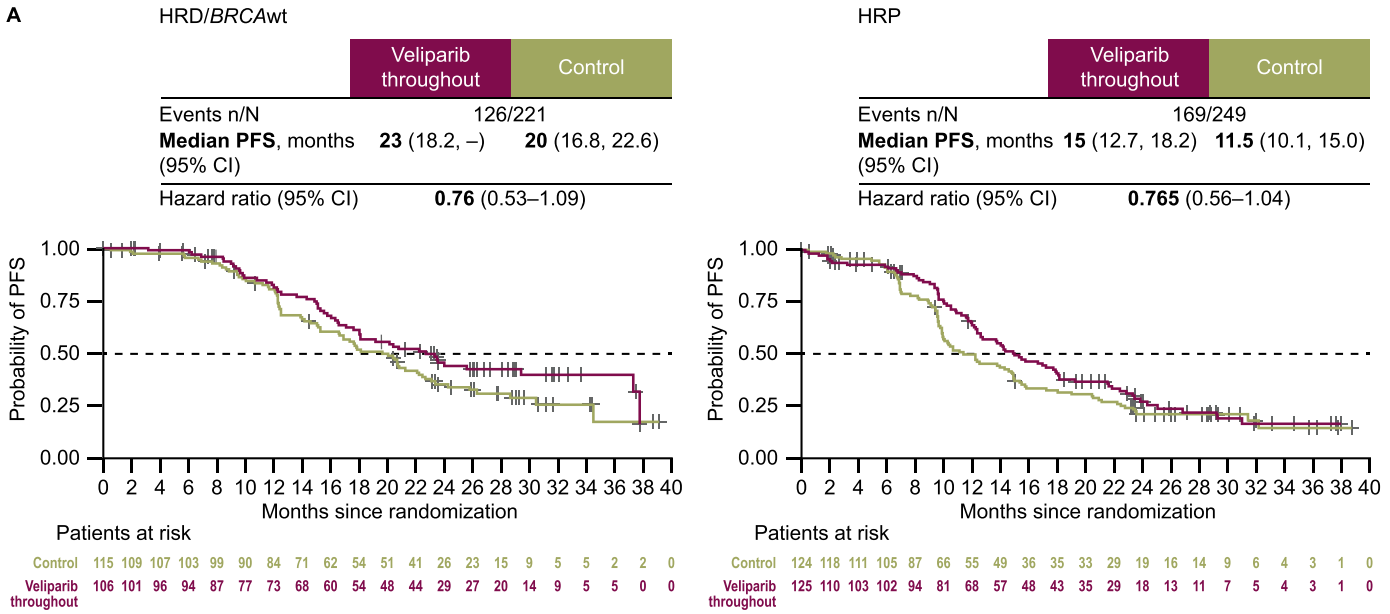
*BRCA*wt patients ($N = 742$) were grouped according to tumor HRD status: 373 patients had HRP (low GIS, <33) tumors and 329 patients had HRD/*BRCA*wt (high GIS, ≥33) tumors; there were 40 patients with unknown GIS (**Supplementary Fig. S1**). Baseline demographic and clinical characteristics for the HRP and HRD/*BRCA*wt subgroups are listed in **Table S1**.

Median PFS was compared between the veliparib-throughout arm and the control arm (as per the primary endpoint analysis) in both HRD/*BRCA*wt and HRP subgroups (Fig. 1). Overall, median PFS was longer in the HRD/*BRCA*wt group compared with the HRP subgroup, but HRs between the veliparib-throughout and control arms were similar for both groups (HRD/*BRCA*wt: 22.9 vs 19.8 months; hazard ratio 0.76; HRP: 15.0 vs 11.5 months; hazard ratio 0.765, with veliparib-throughout vs control, respectively; Fig. 1A, **Supplementary Fig. S2**), suggesting benefits of veliparib treatment were similar in both subgroups.

Evaluation of mPFS HRs between the primary study arms across a continuum of GIS in the *BRCA*wt population revealed similar veliparib treatment effect across all GIS, including HGSC with high GIS as well as those with very low GIS (Fig. 1B). Moving the GIS cutoff from 33 to 42, a GIS cutoff used in other PARPi trials, did not change this observation.

3.3. Veliparib in combination with chemotherapy: CA-125 response analysis

The main CA-125 response analysis included all patients (*BRCA*m and *BRCA*wt) with evaluable CA-125 measurements and pooled data



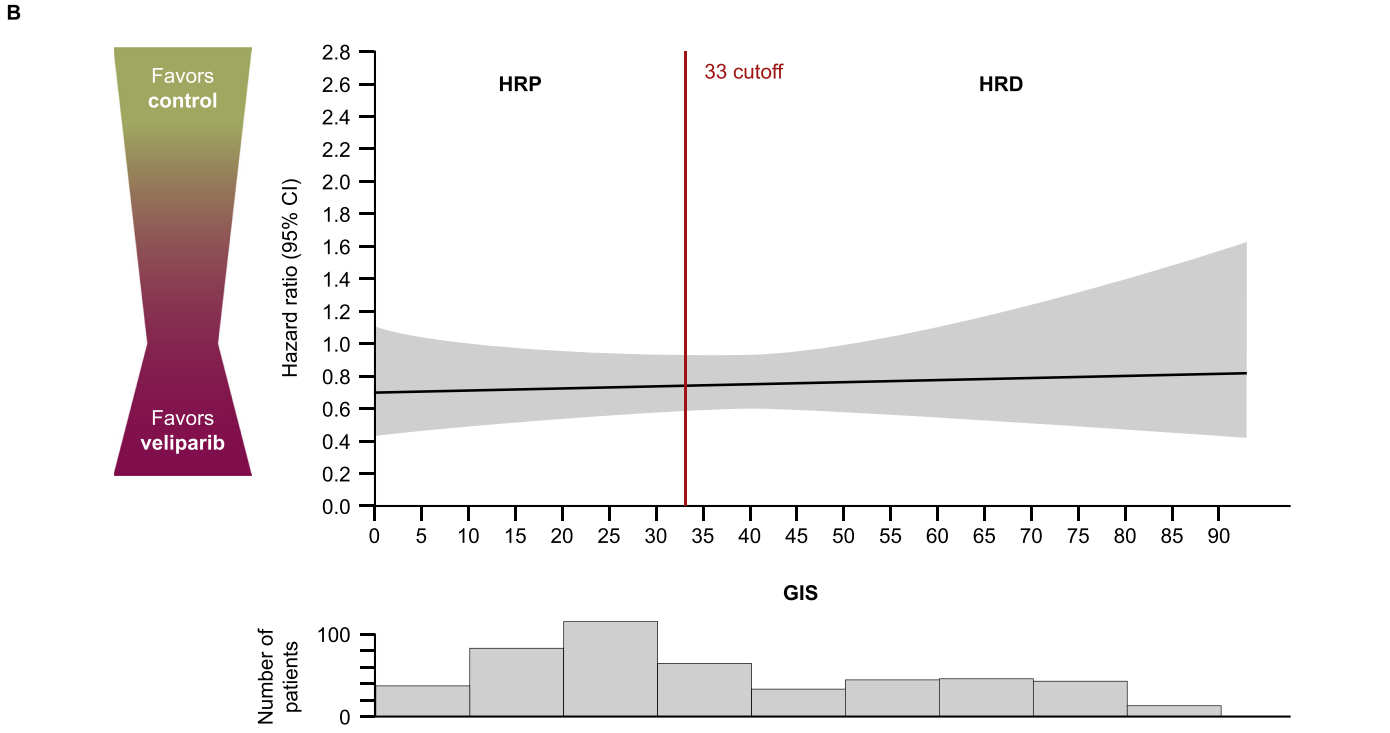


Fig. 1. (A) Kaplan–Meier curves of PFS in HRP and HRD/*BRCA*wt and patient subgroups. (B) PFS benefit in HRP and HRD/*BRCA*wt patient subgroups.
The black line represents hazard ratio and grey shading indicates 95% CI. Abbreviations: *BRCA*wt, *BRCA* wild type; CI; confidence interval; GIS, genomic instability score; HRD, homologous recombinant deficient; HR, homologous recombination; HRP, homologous recombinant proficient; PFS, progression-free survival.

from patients in the veliparib-containing arms because they received the same treatment for the first 6 cycles. Table 1 shows the baseline characteristics for the pooled veliparib-containing ($N = 765$) and control arms ($N = 375$), including 213 and 107 patients in each arm, respectively, who received interval surgery; molecular characteristics were balanced, and CA-125 was elevated (according to local laboratory definitions) at baseline in the majority of patients.

By Day 1 of Cycle 3 in the combination phase, the proportion of patients with a CA-125 response defined as ≥90% reduction (regardless of surgery type) was higher in the pooled veliparib arm relative to the control arm (34% vs 23% of patients, respectively; $P = 0.0004$; **Supplementary Fig. S3A**). CA-125 response rates were similar between the pooled veliparib and control arms for the remainder of the combination phase (56% vs 51% on Day 1 of Cycle 7; $P = 0.179$). For the subgroup of patients undergoing neoadjuvant chemotherapy, CA-125 responses up to interval surgery (Day 1 of Cycle 3) were 51% (95/187) and 37% (37/100) in the pooled veliparib and control arms, respectively ($P = 0.017$) (Fig. 2A).

CA-125 responses in biomarker-defined subgroups according to *BRCA* mutation status and HRD status are shown in Fig. 2 **and Supplementary Fig. S3**. The proportion of patients achieving CA-125 responses was generally higher in the pooled veliparib arms compared with the control arm. Of note, this difference was most evident at Cycle 3 in the *BRCA*wt and HRP subgroups (pooled veliparib vs control arm: 31% vs

Table 1
Key patient characteristics in the veliparib-containing pooled arms and control arm of the VELIA study (CA-125 and radiographic response analysis).

Characteristic	Veliparib-containing arms (pooled) ($n = 765$)	Control arm ($n = 375$)
Age, median (range), years	62 (22–88)	62 (33–86)
Age distribution, *n* (%)		
<65 years	454 (59.3)	233 (62.1)
≥65 years	311 (40.7)	142 (37.9)
Geographic region, *n* (%)		
North America	528 (69.0)	266 (70.9)
Japan	55 (7.2)	23 (6.1)
Rest of world	182 (23.8)	86 (22.9)
ECOG status, *n* (%)		
0	434 (57.6)	226 (60.9)
≥1	319 (42.4)	145 (39.1)
Unknown	12	4
Stage of disease, *n* (%)[a]		
Stage III	583 (76.3)	292 (78.1)
Stage IV	181 (23.7)	82 (21.9)
Surgery received,[b,c] *n* (%)		
Primary	514 (67.2)	250 (66.7)
Interval	213 (27.8)	107 (28.5)
None	38 (5.0)	18 (4.8)
Residual disease after primary surgery, n/N (%)		
No residual disease	242/514 (47.1)	116/250 (46.4)
Microscopic residual disease only	100/514 (19.5)	58/250 (23.2)
Any macroscopic residual disease	172/514 (33.5)	76/250 (30.4)
Residual disease after interval surgery, n/N (%)		
No residual disease	91/206 (44.2)	50/103 (48.5)
Microscopic residual disease only	54/206 (26.2)	22/103 (21.4)
Any macroscopic residual disease	61/206 (29.6)	31/103 (30.1)
Unknown	7	4
Biomarker status,[d,e] *n* (%)		
*BRCA*m	206 (29.7)	92 (26.6)
*BRCA*wt (includes HRD and HRP)	488 (70.3)	254 (73.4)
HRD (includes *BRCA*m and *BRCA*wt)	420 (62.9)	207 (62.5)
HRD/*BRCA*wt	214 (32.0)	115 (34.7)
HRP	248 (37.1)	124 (37.5)
CA-125 status, *n* (%)		
Baseline CA-125 > ULN[f]	642 (85.3)	316 (85.6)

Abbreviations: CA-125, cancer antigen 125; *BRCA*m, *BRCA* mutation; *BRCA*wt, *BRCA* wild type; ECOG, Eastern Cooperative Oncology Group; HRD, homologous recombination deficient; HRP, homologous recombination proficient; ULN, upper limit of normal.
All percentages are calculated on nonmissing values.
[a] Status unknown for 1 patient in each arm.
[b] 68% of all primary surgeries were gross resection.
[c] 70% of all interval surgeries were gross resection.
[d] *BRCA* status unknown for 71 patients (veliparib pooled) and 29 patients (control).
[e] HRD status unknown for 97 patients (veliparib pooled) and 44 patients (control).
[f] All evaluable, status unknown for 12 patients (veliparib pooled) and 6 patients (control).

22% and 28% vs 14%, respectively; Figs. 2C **and S3D**) as compared with more similar proportions in the biomarker-selected subgroups, i.e., those with HRD and *BRCA*m tumors (pooled veliparib vs control arm: 35% vs 30% and 36% vs 27%, respectively; **Figs. S3B and 2B**).

3.4. Veliparib in combination with chemotherapy: Radiographic response analysis

Baseline characteristics for patients with measurable disease after primary surgery ($n = 290$) were generally similar to the overall population and between treatment arms (**Table S2**; Table 1). At the end of the combination phase, CRs were seen in 24% (95% CI 18.4 to 30.4) of patients in the pooled veliparib arms and 18% (95% CI 10.4 to 26.1) of patients in the control arm in the overall population. Response rates per RECIST v1.1 for each of the biomarker-selected and -unselected subgroups are shown in Fig. 3; ORR in the HRP subgroup was generally lower than in biomarker-positive subgroups and the whole population.

3.5. PFS in patients with stable disease following combination treatment

At the end of the combination phase, 28% ($n = 104$) of patients in the control arm, 23% ($n = 89$) in the veliparib-combination–only arm, and 21% ($n = 82$) in the veliparib-throughout arm had SD for those with measurable disease, or non-CR/non-PD for those with only nonmeasurable disease (**Fig. S4**). These patients are typically not eligible for PARPi maintenance therapy, but were allowed to continue maintenance in this study. Baseline characteristics for these patients are shown in **Table S3**. Notably, fewer patients in the veliparib combination-only arm have Stage IV disease than in the control and veliparib-throughout arms, and fewer patients in the control arm had a *BRCA* mutation than in the veliparib arms. A waterfall plot illustrating the change in tumor size from baseline in each arm is shown in **Fig. S4A**. Median PFS in patients with SD following combination treatment was 13 months for the control arm, 14 months for the veliparib-combination–only arm (hazard ratio 1.03; 95% CI 0.72 to 1.47 vs control), and 16 months for the veliparib-throughout arm (hazard ratio 0.79; 95% CI 0.54 to 1.16 vs control; **Fig. S4B**). At Month 10, the PFS rate was 83% for the veliparib-throughout arm, 78% in the veliparib-combination–only arm, and 73% in the control arm.

4. Discussion

VELIA is the first Phase 3 trial to evaluate PARP inhibition in newly diagnosed patients with advanced HGSC regardless of *BRCA* status, surgical management, or response to platinum therapy. This distinguishes VELIA from other reported primary maintenance trials in HGSC in that it enrolled a broader patient population. The results of these exploratory analyses of PFS within the *BRCA*wt population suggest that veliparib provided a similar improvement in PFS compared with placebo regardless of tumor HRD status. Median PFS was also generally longer for patients with *BRCA*wt/HRD cancers relative to those with HRP cancers, regardless of study arm. Taken together, these data indicate that the GIS may be a prognostic marker of PFS regardless of treatment arm; however, GIS is not a predictive marker of response to veliparib. That GIS is not a predictive marker represents an important finding because patients with HRP cancers may still derive benefit from the veliparib-throughout regimen. A PFS benefit with the veliparib-throughout regimen versus control was observed across a range of GIS, including patients whose cancers had a GIS as low as 0–10. The lack of a difference between the hazard ratios across treatment arms for HRD/*BRCA*wt and HRP cancers is unique to VELIA, differing from other PARPi maintenance trials of HGSC both in the recurrent and frontline settings [5,24]. In previous studies of PARPi as maintenance therapy [5,6], a GIS cutoff of 42 was used. The rationale for using a cutoff of 33 in VELIA was based on findings reported by Hodgson et al., [19] wherein the threshold of 33 aimed to exclude patients who were least likely to benefit from PARPi. Because we found no GIS cutoff that separated those in whom a veliparib treatment benefit was not seen (i.e., to define HRD and HRP subgroups), we conclude that using a cutoff of 33 was not responsible for the lack of predictive ability for the test within VELIA.

To explore whether the addition of veliparib to chemotherapy contributed to eliminating the difference in hazard ratios between HRD and HRP cancers, we used CA-125 as a sensitive measure of tumor regression in *BRCA*m and *BRCA*wt cases. CA-125 responses occurred earlier in the veliparib-containing treatment arms compared with the control arm. Likewise, in the neoadjuvant setting a higher proportion of patients in the veliparib arms than in the control arm had CA-125 responses after the first two cycles of chemotherapy (prior to interval debulking surgery). CA-125 responses have been previously associated with improved surgical and response outcomes [21]; however, in our analysis the placebo arm caught up in CA-125 response by the end of chemotherapy and the clinical significance of this CA-125 decrease is uncertain.

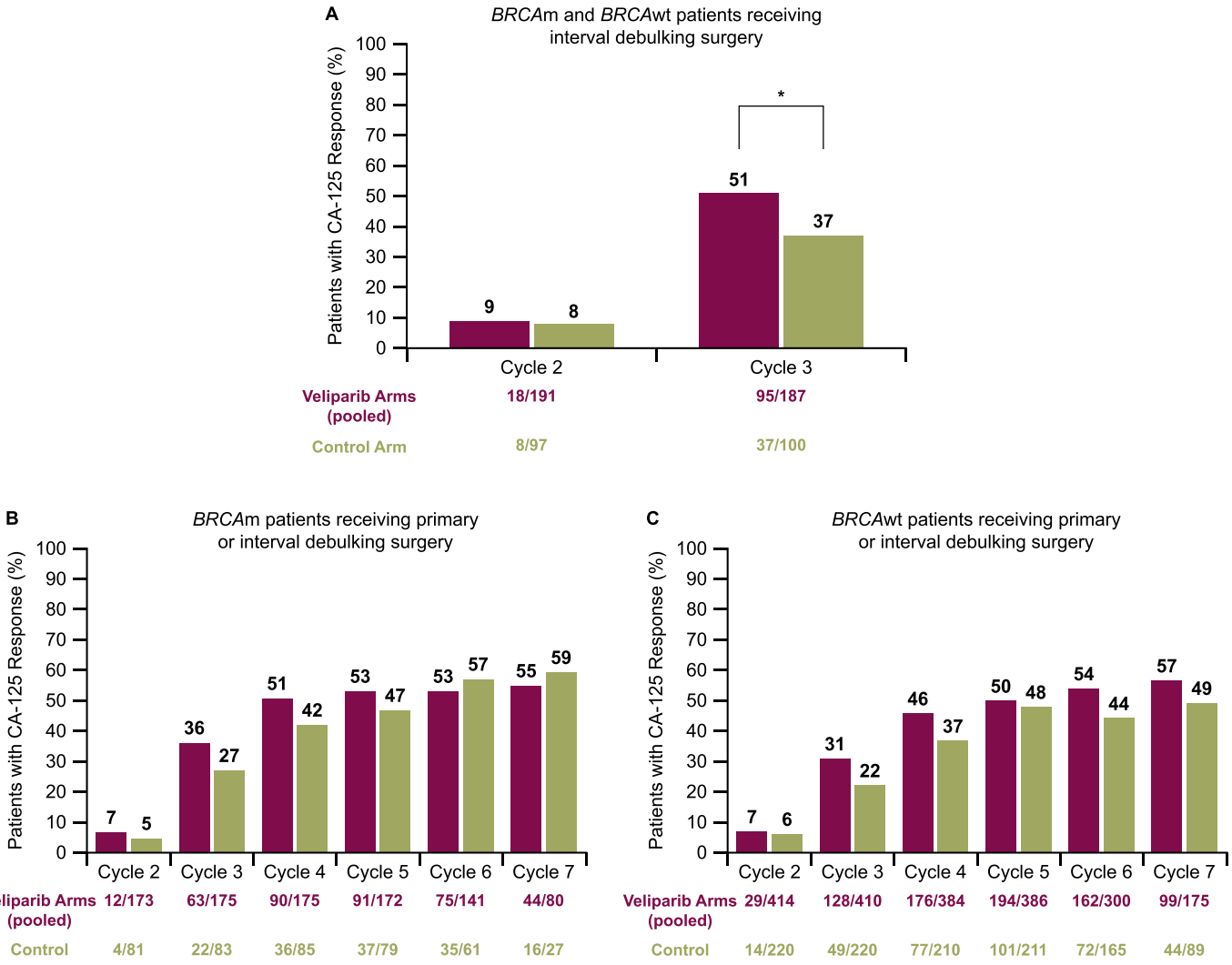


Fig. 2. CA-125 response during the combination phase in (A) *BRCA*m and *BRCA*wt patients receiving interval debulking surgery, and in (B) *BRCA*m and (C) *BRCA*wt subgroups regardless of surgery type. Abbreviations: *BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type; CA-125, cancer antigen 125.
*$P < 0.05$. CA-125 was measured on Day 1 of each cycle, thereby reflecting the previous cycle.

Notably, the CA-125 analyses showed a trend toward a higher response rate with the addition of veliparib primarily in HRP cancers, with a smaller benefit seen in the HRD/*BRCA*wt subgroup. One hypothesis is that HRD cancers are already highly sensitive to platinum-based chemotherapy [25], and their response is not further augmented by adding veliparib, whereas the addition of veliparib produces a more prominent effect in HRP cancers. While higher CA-125 responses have been reported in HRD/*BRCA*wt HGSC treated with PARPi or chemotherapy [26], VELIA uniquely combined chemotherapy with a PARPi inhibitor. These results provide rationale for further exploration of veliparib in combination with chemotherapy in patients with HRP cancers.

To corroborate the CA-125 response findings, we assessed radiographic ORR after the chemotherapy combination phase in *BRCA*m and *BRCA*wt patients, acknowledging the limitations associated with volumetric analysis and the application only to patients with measurable disease after primary surgery. We demonstrate that during the combination phase, addition of veliparib to chemotherapy led to numerically higher radiographic response rates relative to chemotherapy alone. The higher rates of CR observed across the ITT population support a potential benefit of veliparib added to chemotherapy in higher risk patients with measurable disease after primary cytoreductive surgery. In addition, patients without disease progression at the end of the combined therapy phase were eligible to receive veliparib (or placebo, according to randomization) in the maintenance setting in VELIA; this resulted in an extra 21%–28% of patients in each arm being eligible for maintenance treatment, in contrast to other PARPi maintenance trials.

It should be noted that these analyses were exploratory in nature and hypothesis-generating; sample sizes also preclude a conclusive interpretation of the data. Furthermore, a lack of PFS difference for the veliparib arm without maintenance calls into question the clinical significance of these findings. However, these findings may explain the similar PFS hazard ratios in VELIA for HRD/*BRCA*wt and HRP HGSC. The veliparib combination phase may have improved the overall outcomes specifically for the HRP patients, including those who would not have qualified for other PARPi maintenance trials because of inadequate platinum response. Alternative explanations for the different behavior of the HRD biomarker in VELIA relative to other studies include differences in selection criteria between trials, differences in the design of the control arms in the maintenance phase (eg, the PAOLA study used bevacizumab in combination with chemotherapy) [5,6], the very low event rate during chemotherapy in general, or variation in the mode of action of different PARPi [27].

Overall, HRD has some utility in terms of relative risk and prognostic expectations, but its use to inform who to treat or not treat with veliparib is limited.

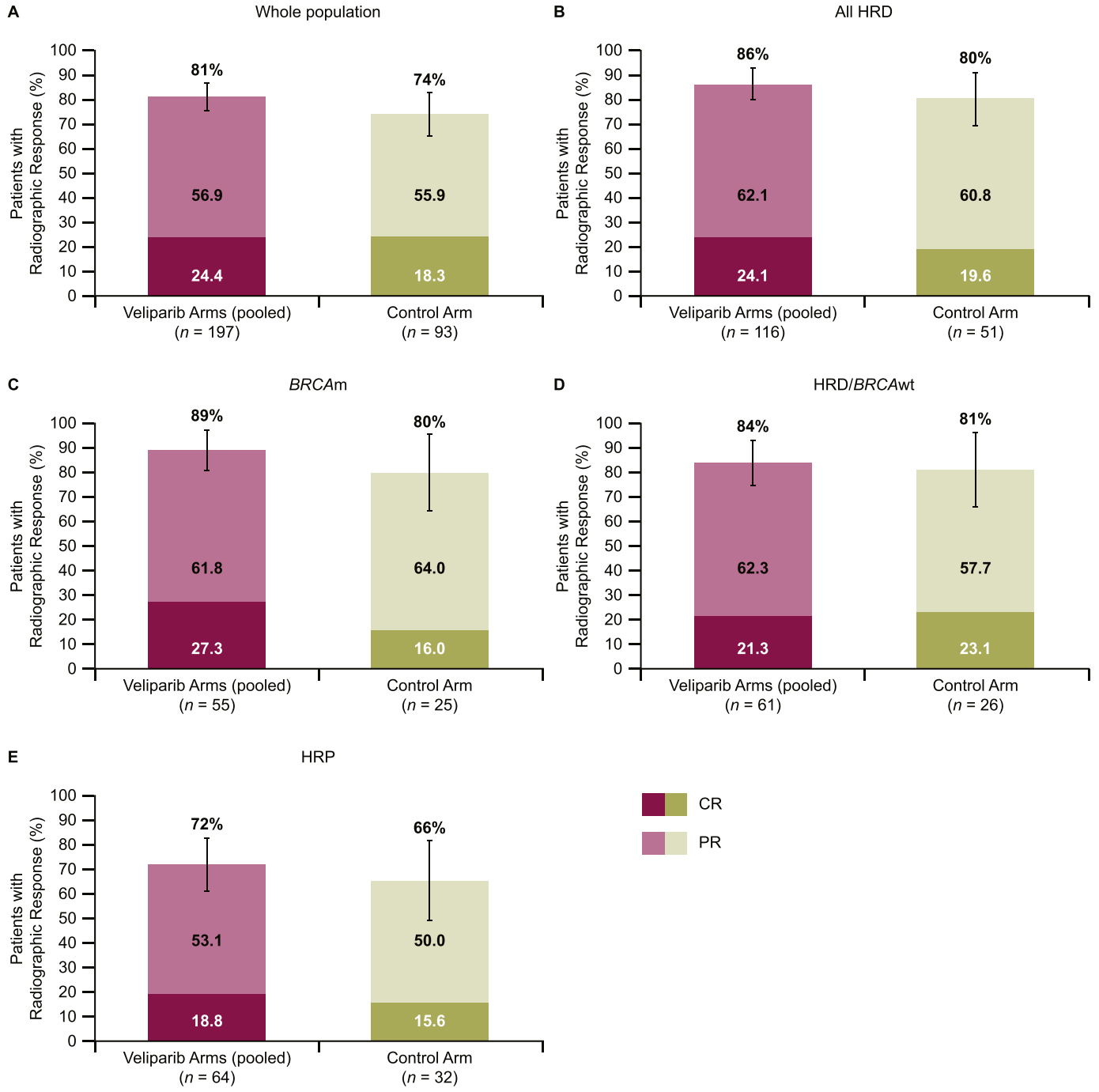


Fig. 3. ORR at the end of the combination phase in (A) all patients with primary surgery and measurable disease and in the (B) all HRD, (C) *BRCA*m, (D) HRD/*BRCA*wt, and (E) HRP subgroups.
Abbreviations: *BRCA*m, *BRCA* mutated; *BRCA*wt, *BRCA* wild type; CR, complete response; HRD, homologous recombination deficient; HRP, homologous recombinant proficient; ORR, objective response rate; PR, partial response

5. Conclusion

Our data demonstrate that the VELIA regimen is effective in various subgroups of HGSC, obviating the question of when and whether to use HRD testing before PARPi maintenance, and potentially broadening the application of PARPi therapy in HGSC that would not have been sufficiently chemo-responsive to qualify for maintenance in other frontline PARPi trials.

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 (eg, 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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Disclosures

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Appendix A. Supplementary data

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