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Efficacy of niraparib by time of surgery and postoperative residual disease status: A post hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 study

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HIGHLIGHTS

- Post hoc analysis of niraparib efficacy in PRIMA by surgical timing and postoperative residual disease status.
- Efficacy outcomes with niraparib treatment were similar regardless of surgical timing.
- Niraparib demonstrated efficacy in both patients with visible and nonvisible residual disease at interval cytoreduction.

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ABSTRACT

Objective. To evaluate the association between surgical timing and postoperative residual disease status on the efficacy of niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer at high risk of recurrence.

Methods. Post hoc analysis of the phase 3 PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) study of niraparib in patients with newly diagnosed primary advanced ovarian, primary peritoneal, or fallopian tube cancer with a complete/partial response to first-line platinum-based chemotherapy. Progression-free survival (PFS) was assessed by surgical status (primary debulking surgery [PDS] vs neoadjuvant chemotherapy/interval debulking surgery [NACT/IDS]) and postoperative residual disease status (no visible residual disease [NVRD] vs visible residual disease [VRD]) in the intent-to-treat population.

Results. In PRIMA ($N = 733$), 236 (32.2%) patients underwent PDS, and 481 (65.6%) received NACT/IDS before enrollment. Median PFS (niraparib vs placebo) and hazard ratios (95% CI) for progression were similar in PDS (13.7 vs 8.2 months; HR, 0.67 [0.47–0.96]) and NACT/IDS (14.2 vs 8.2 months; HR, 0.57 [0.44–0.73]) subgroups. In patients who received NACT/IDS and had NVRD ($n = 304$), the hazard ratio (95% CI) for progression was 0.65 (0.46–0.91). In patients with VRD following PDS ($n = 183$) or NACT/IDS ($n = 149$), the hazard ratios (95% CI) for progression were 0.58 (0.39–0.86) and 0.41 (0.27–0.62), respectively. PFS was not evaluable for patients with PDS and NVRD because of sample size ($n = 37$).

Conclusions. In this post hoc analysis, niraparib efficacy was similar across PDS and NACT/IDS subgroups. Patients who had NACT/IDS and VRD had the highest reduction in the risk of progression with niraparib maintenance.

1. Introduction

Worldwide, ovarian cancer is the eighth leading cause of cancer death among women and has resulted in over 200,000 deaths in 2020 alone [1]. Although most patients respond to first-line treatment, approximately 70% will experience disease progression within 3 years, and the 5-year survival rate is approximately 50% [2,3]. Patients with distant disease at diagnosis have the worst outcomes, with a 5-year survival rate of approximately 30% [2].

The current standard of care for first-line treatment of ovarian cancer is a combination of surgery and chemotherapy. Patients either undergo primary debulking surgery (PDS) followed by platinum-based chemotherapy or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and further chemotherapy; antiangiogenic therapy with bevacizumab may be added to the chemotherapy regimen followed by maintenance [4–6]. Use of NACT/IDS has been shown to be noninferior to PDS in terms of efficacy in patients with advanced ovarian cancer in clinical trials [7–10], and treatment guidelines recommend selection of the approach most likely to result in the removal of all macroscopically visible tumor [4]. Postoperative residual disease status has been shown to be an important prognostic indicator: patients with visible residual disease (VRD) experience poorer outcomes than patients with no visible residual disease (NVRD) following surgery in both clinical trials and real-world analyses [8,10,11].

Niraparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, is approved in the United States, Canada, and the European Union for use as maintenance treatment for patients with ovarian cancer following a response to platinum-based chemotherapy in the first-line setting and in recurrent ovarian cancer that is platinum sensitive [12,13]. The PRIMA/ENGOT-OV26/GOG-3012 study (NCT02655016) showed that patients who received niraparib as maintenance treatment in the first-line setting had improved progression-free survival (PFS) compared with placebo-treated patients in the overall intent-to-treat (ITT) population (hazard ratio [HR], 0.62; 95% CI, 0.50–0.76) [14]. In a subgroup analysis, patients in PRIMA who received NACT had similar efficacy outcomes compared with those who underwent PDS and had VRD or stage IV disease, HR of 0.59 (95% CI, 0.46–0.76) and HR of 0.66 (95% CI, 0.46–0.94), respectively [14].

This post hoc analysis of PRIMA evaluated the effect of surgical timing (PDS or NACT/IDS) and postoperative residual disease status (nonvisible or visible) on the efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer at a high risk for recurrence.

2. Methods

2.1. Study design

The study methods and primary results for PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) have been published previously [14]. Briefly, PRIMA was a double-blind, placebo-controlled, phase 3 clinical study that evaluated niraparib maintenance treatment in patients with newly diagnosed, histologically confirmed, primary advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III/IV), high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer. Patients were eligible if they had (1) stage III/IV disease that was inoperable or treated with NACT/IDS, (2) had stage III disease with VRD after PDS, or (3) had operable stage IV disease, regardless of the type of debulking surgery received (PDS or IDS) or postoperative residual disease status (VRD or NVRD). Patients with stage III disease who had complete cytoreduction (NVRD) after PDS and patients who had undergone more than 2 debulking surgeries were excluded from the study. Within 12 weeks of completing their last dose of platinum-based therapy, patients were randomly assigned in a 2:1 ratio to receive niraparib or placebo once daily in 28-day cycles for 36 months or until disease progression. Patients were stratified at randomization according to clinical response after first-line platinum-based chemotherapy, receipt of neoadjuvant chemotherapy, and tumor homologous recombination deficiency status (myChoice test, Myriad Genetics). The study was performed in accordance with the tenets of the Declaration of Helsinki, Good Clinical Practices, and all local laws under the auspices of an independent data and safety monitoring committee; all patients gave informed written consent [14].

2.2. Outcomes

PFS was defined as the time from randomization after completion of platinum-based chemotherapy to the earliest date of objective disease progression on imaging (according to RECIST version 1.1) or death from any cause. PFS assessed by blinded independent central review (BICR) was analyzed by hierarchical testing, first in patients with homologous recombination–deficient tumors and then in the overall

Table 1
Surgical timing and postoperative residual disease status at baseline.

Debulking surgery and residual disease status, n (%)	FIGO stage III[a]		FIGO stage IV		Overall	
	Niraparib ($n = 318$)	Placebo ($n = 158$)	Niraparib ($n = 169$)	Placebo ($n = 88$)	Niraparib ($N = 487$)	Placebo ($N = 246$)
Primary debulking surgery	114 (35.8)	56 (35.4)	44 (26.0)	22 (25.0)	158 (32.4)	78 (31.7)
No visible residual disease	1 (0.3)[b]	0	21 (12.4)	15 (17.0)	22 (4.5)	15 (6.1)
Visible residual disease	104 (32.7)	52 (32.9)	20 (11.8)	7 (8.0)	124 (25.5)	59 (24.0)
Unknown[c]	9 (2.8)	4 (2.5)	3 (1.8)	0	12 (2.5)	4 (1.6)
Interval debulking surgery	200 (62.9)	99 (62.7)	116 (68.6)	66 (75.0)	316 (64.9)	165 (67.1)
No visible residual disease	128 (40.3)	62 (39.2)	74 (43.8)	40 (45.5)	202 (41.5)	102 (41.5)
Visible residual disease	58 (18.2)	30 (19.0)	38 (22.5)	23 (26.1)	96 (19.7)	53 (21.5)
Unknown[c]	14 (4.4)	7 (4.4)	4 (2.4)	3 (3.4)	18 (3.7)	10 (4.1)
No surgery	4 (1.3)	3 (1.9)	9 (5.3)	0	13 (2.7)	3 (1.2)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics.
[a] Per protocol, patients with stage III disease at initial diagnosis with no visible residual disease after primary debulking surgery were excluded from the study.
[b] Patient enrolled in deviation of protocol.
[c] Residual disease burden information was not collected for the patients enrolled in the original protocol.

population [14]. In this post hoc analysis, PFS was assessed by surgical timing and postoperative residual disease status. For surgical timing, patients were grouped according to whether they underwent PDS or received NACT/IDS before enrollment. Residual disease status was assessed by the physician at the completion of surgery and categorized as follows: complete gross resection/NVRD or VRD.

2.3. Statistical analysis

PFS was analyzed with a stratified log-rank test using stratification factors from randomization and summarized using Kaplan-Meier methodology. Hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model with the stratification factors used in randomization. The primary data cutoff date was May 17, 2019. This analysis was not powered to determine differences among the subgroups. All analyses were performed using SAS® 9.4 (Cary, NC).

3. Results

3.1. Surgical timing and postoperative residual disease status

Primary analysis results of the PRIMA study, including full baseline demographic information and efficacy and safety findings, have been published previously. Of the 733 patients randomized in PRIMA, 476 (64.9%) and 257 (35.1%) patients had FIGO stage III or IV disease at initial diagnosis, respectively. Before study enrollment, 236 (32.2%) patients had undergone PDS, 481 (65.6%) patients received NACT/IDS, and 16 (2.2%) patients did not undergo any debulking surgery (Table 1). When surgical timing was assessed by disease stage at diagnosis, a higher percentage of patients with stage III disease underwent PDS, compared with patients with stage IV disease at diagnosis (170/476, 35.7% vs 66/257, 25.7%).

Postoperative residual disease status following PDS and NACT/IDS was assessed in the overall population and by FIGO stage at initial diagnosis (Table 1). Of the 236 patients who underwent PDS in the overall population, 37 (15.7%) patients had NVRD, 183 (77.5%) had VRD, and 16 (6.8%) had undetermined status because of missing data. As noted previously, study enrollment criteria excluded patients with stage III disease at diagnosis who had NVRD following PDS. Accordingly, most patients with NVRD after PDS had stage IV disease at diagnosis (36 of 37), and most patients with VRD after PDS had stage III disease at diagnosis (156 of 183). One patient with stage III disease who had NVRD after PDS was enrolled in error and was noted as a protocol deviation. Of the 481 patients who received NACT/IDS, 304 (63.2%) patients had NVRD, 149 (31.0%) had VRD, and 28 (5.8%) had undetermined status because of missing data. In patients who received NACT/IDS, the

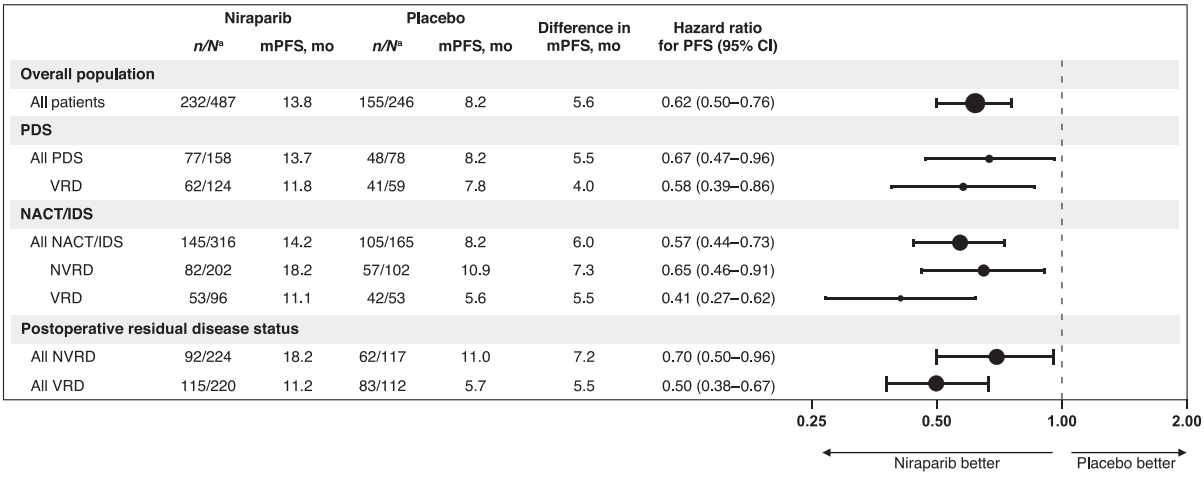

Fig. 1. Efficacy Outcomes by Surgical Timing and Postoperative Residual Disease Status.
[a]Number of patients with disease progression or death/total number of patients.
Abbreviations: IDS, interval debulking surgery; mPFS, median progression-free survival; mo, months; NACT, neoadjuvant chemotherapy; NVRD, nonvisible residual disease; PDS, primary debulking surgery; PFS, progression-free survival; VRD, visible residual disease. The size of the dot in the forest plot is proportional to *N* in subgroups.

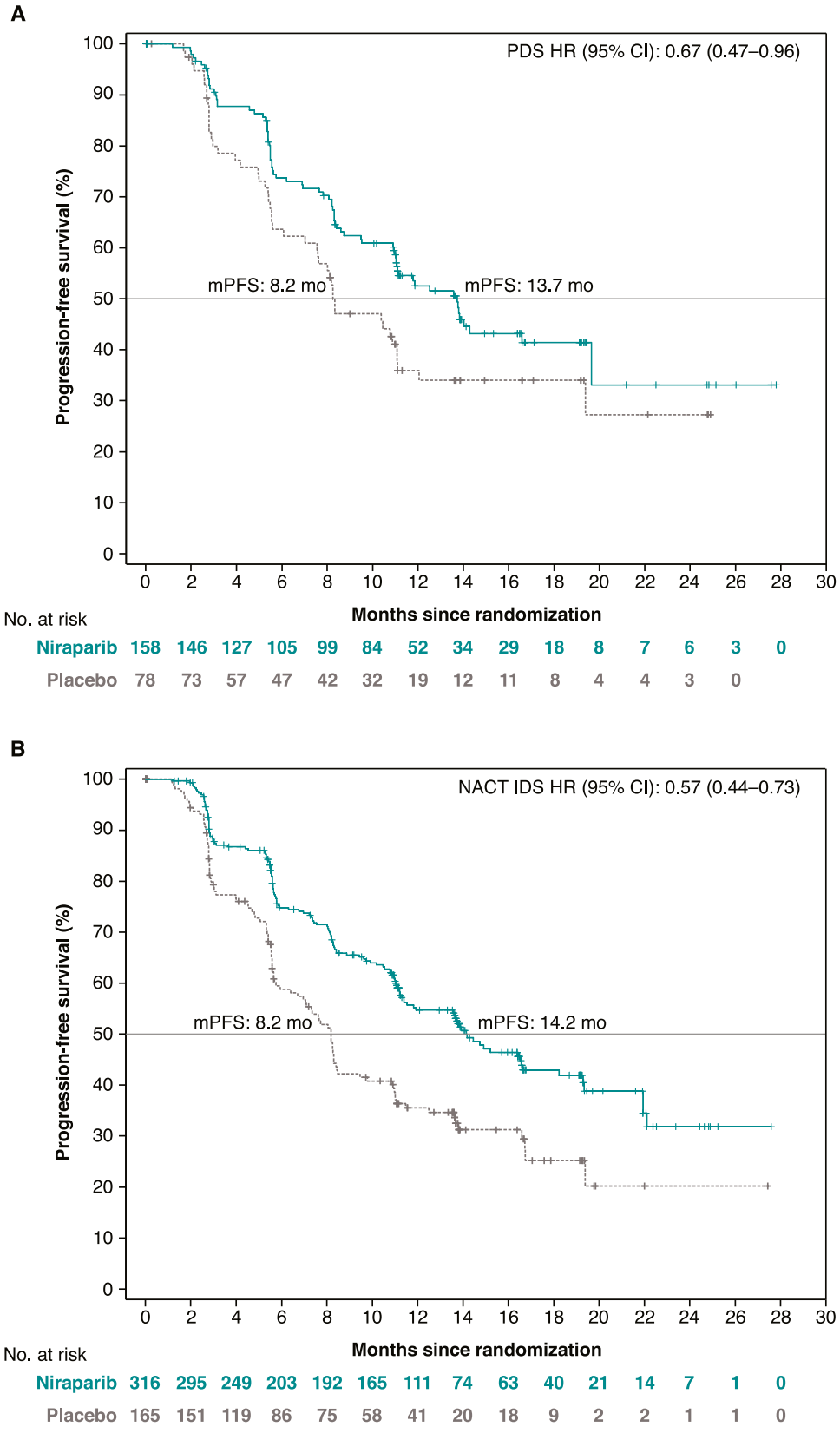

Fig. 2. PFS by Surgical Timing.
Kaplan-Meier estimates of PFS per BICR by treatment arm in (A) patients who underwent PDS and (B) patients who underwent NACT/IDS.
Abbreviations: BICR, blinded independent central review; HR, hazard ratio; IDS, interval debulking surgery; mPFS, median progression-free survival; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery.

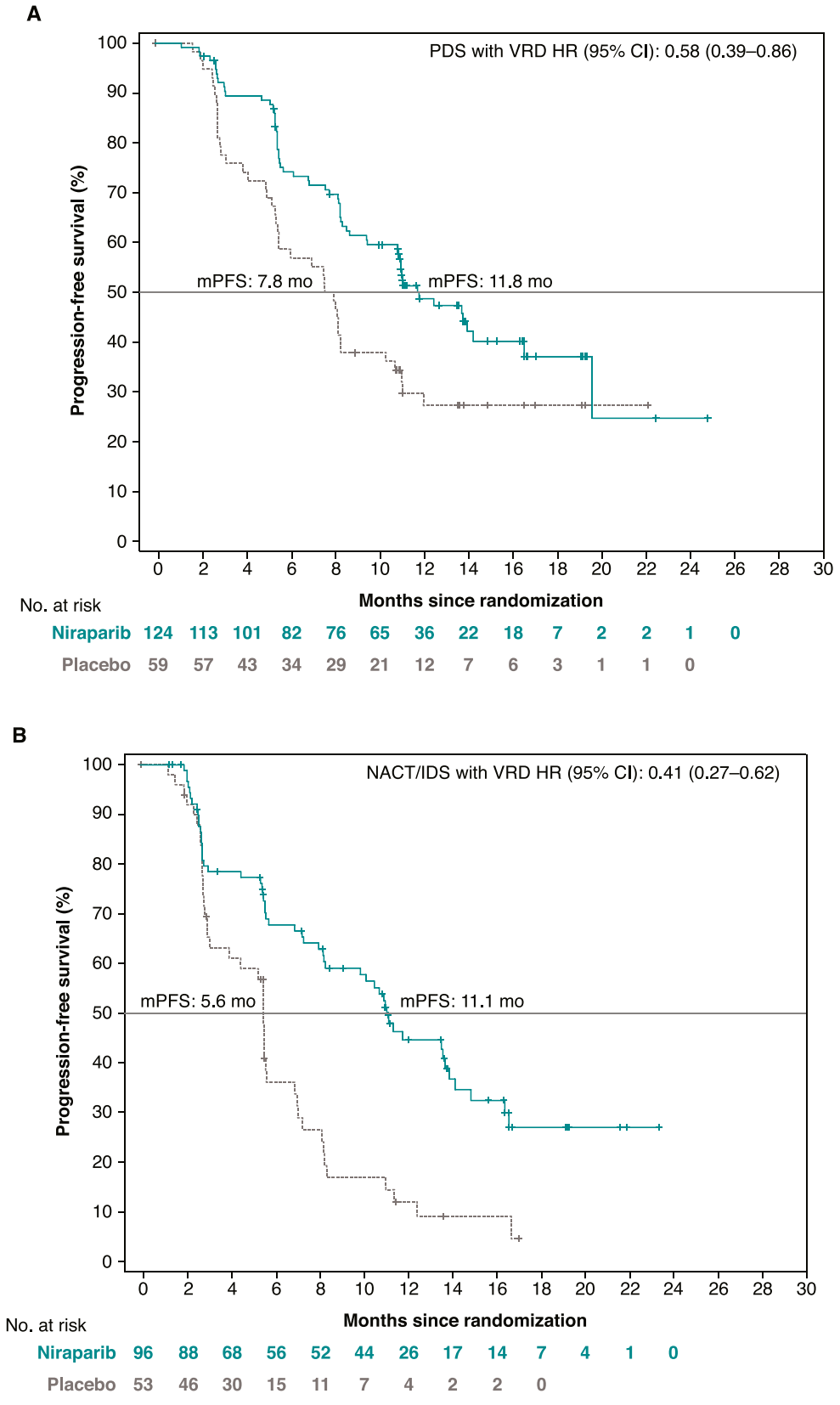

Fig. 3. PFS by Surgical Timing and Postoperative Residual Disease Status.
Kaplan-Meier estimates of PFS per BICR by treatment arm, surgical timing, and postoperative residual disease status. (A) Patients who underwent PDS with VRD. Patients who received NACT/IDS with (B) VRD and (C) NVRD.
Abbreviations: BICR, blinded independent central review; HR, hazard ratio; IDS, interval debulking surgery; mPFS, median progression-free survival; NACT, neoadjuvant chemotherapy; NVRD, nonvisible residual disease; PDS, primary debulking surgery; VRD, visible residual disease.

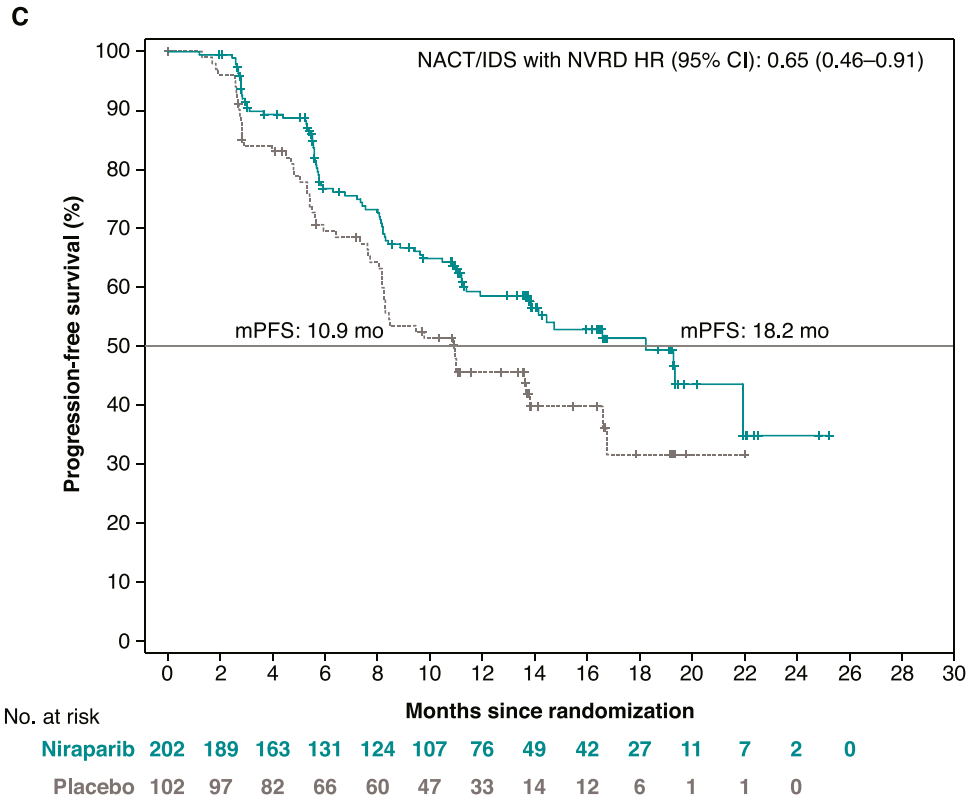

Fig. 3 (*continued*).

percentages of patients with VRD were similar in patients with stage III and patients with stage IV disease at diagnosis (88/299, 29.4% vs 61/182, 33.5%; Table 1).

3.2. Progression-free survival

Efficacy outcomes by surgical timing and postoperative residual disease status are shown in Fig. 1. PFS hazard ratios favored niraparib in all cases, with the greatest benefit seen in patients with postoperative VRD. In patients who underwent PDS, the median PFS (mPFS) was 13.7 months in the niraparib arm and 8.2 months in the placebo arm (ΔmPFS, 5.5 months; HR, 0.67; 95% CI, 0.47–0.96, Fig. 2A). In patients who received NACT/IDS, the mPFS was 14.2 months in the niraparib arm and 8.2 months in the placebo arm (ΔmPFS, 6.0 months; HR, 0.57, 95% CI, 0.44–0.73, Fig. 2B).

Within each surgical group, PFS was also assessed by postoperative residual disease status. Because patients with stage III disease with NVRD following PDS were excluded from the study, per protocol the PDS with NVRD subgroup was limited to patients with stage IV disease and was too small for analysis of PFS ($n = 37$). In patients who underwent PDS and had VRD, mPFS was 11.8 months in the niraparib arm and 7.8 months in the placebo arm (ΔmPFS, 4.0 months; HR, 0.58; 95% CI, 0.39–0.86; Fig. 3A). In patients treated with NACT/IDS, the mPFS was 18.2 months in the niraparib arm and 10.9 months in the placebo arm (ΔmPFS, 7.3 months; HR, 0.65; 95% CI, 0.46–0.91; Fig. 3C) in patients with NVRD, and 11.1 months in the niraparib arm and 5.6 months in the placebo arm (ΔmPFS, 5.5 months; HR, 0.41; 95% CI, 0.27–0.62) in patients with VRD (Fig. 3).

4. Discussion

In this post hoc analysis of the PRIMA study, we examined the effect of surgical timing and postoperative residual disease status on PFS in patients with advanced ovarian cancer treated with niraparib maintenance therapy in the first-line setting. Results for mPFS were similar across treatment arms in patients who underwent PDS compared with patients treated with NACT/IDS. Patients treated with NACT/IDS tended toward a greater reduction in the risk of disease progression with niraparib treatment, compared with patients who underwent PDS (HR, 0.57 [95% CI, 0.44–0.73] vs 0.67 [95% CI, 0.47–0.96]). One possible hypothesis to explain this observation is that a good response to platinum-based therapy could be a surrogate marker for niraparib sensitivity. Overall, these data indicate that the surgical timing had little to no effect on niraparib efficacy in PRIMA. These findings are consistent with results from a post hoc analysis of patients with *BRCA*-mutated ovarian cancer treated in the SOLO-1 trial, in which surgical timing also had limited effect on the efficacy of olaparib, with similar reductions in risk of disease progression reported regardless of the type of surgery received [15]. Maintenance niraparib extends PFS in patients with poor prognostic factors, such as receipt of NACT/IDS, because of poor candidacy for initial surgery or extensive disease at the time of diagnosis. Selection of the best surgical approach for individual patients may depend on multiple tumor-related factors [16], but according to these results, the surgical strategy will likely not affect the efficacy of maintenance niraparib.

The impact of postoperative residual disease status was also assessed, and our results from PRIMA confirm that this remains a prognostic factor. Complete gross resection of disease has previously been shown to be one of the strongest independent variables predicting overall survival in patients with advanced ovarian cancer [8,10,11]. The mPFS duration was lower in patients with VRD than with NVRD in both the niraparib (11.2 vs 18.2 months) and placebo (5.7 vs 11.0) treatment arms. When assessed by surgical timing, the same trend was observed. In patients who underwent PDS, the mPFS duration was slightly reduced in patients with VRD compared with the overall group in both study arms. Direct comparison with patients with NVRD, however, was not feasible because of the limited number of patients in the NVRD PDS group, due to PRIMA's patient selection criteria.

In patients treated with NACT/IDS, patients with NVRD had longer mPFS duration than patients with VRD in both niraparib- (18.2 vs 11.1 months) and placebo-treated (10.9 vs 5.6 months) patients. These findings are expected and consistent with literature showing that postoperative VRD is associated with poorer outcomes than NVRD [10,11]. However, niraparib-treated patients with VRD following NACT/IDS had a greater reduction in risk of progression (59%) than patients with NVRD following NACT/IDS (35%). Although this observation seems against the subgroup analysis in SOLO-1 trial [15], the limited number of patients and other uncontrolled clinical or biological factors may influence this apparent difference. No subgroup saw an increased risk of progression relative to the overall/ITT population.

This was a retrospective post hoc analysis, and its results should be interpreted accordingly. The analyses were not prespecified and were not powered to determine differences between the subgroups. A small number of patients did not receive either PDS or IDS, and postoperative residual disease status data were not available in all patients. Direct comparisons across all groups were not possible because of the small sample size of patients with NVRD after PDS. In addition, the analysis focused on results for the overall population because of sample size limitations; as such, it does not account for any potential differences based on homologous recombination deficiency or *BRCA* mutation status. In addition, the generalizability of the findings of our analysis may be limited because tumor size and postoperative residual disease were not measured quantitively.

Surgical timing had little effect on the risk of disease progression for patients receiving niraparib maintenance treatment after first-line chemotherapy in the PRIMA study. As expected, mPFS was longer in patients with NVRD than in patients with VRD. We did observe a possible benefit of niraparib treatment in the subgroup of patients who had VRD following NACT/IDS, but the study was not powered to compare subgroups. All subgroups measured showed a similar reduction in risk of progression compared to the ITT population with niraparib maintenance therapy. Taken together, these results suggest the benefit of niraparib maintenance therapy in patients with primary advanced ovarian cancer at a high risk of recurrence, regardless of the timing of surgery or postoperative residual disease status.

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Author contributions

Conception and design: All authors.

Data analysis and interpretation: YL (analysis) and all authors (interpretation).

Manuscript writing: All authors.

Final approval of manuscript: All authors.

Accountable for all aspects of the work: REO, IAM, DG, AGM.

Previous presentation

These data were originally presented at the Society of Gynecologic Oncology Annual Meeting, March 19–25, 2021 (Virtual Meeting).

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Data sharing statement

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

Declaration of Competing Interest

REO reports participating in advisory boards with Bayer, Fresenius Kabi, GlaxoSmithKline, Immunogen, Regeneron, and Seattle Genetics; personal fees from GOG Foundation; and service as a noncompensated steering committee member for the PRIMA (niraparib) and DUO-O (olaparib) studies; institutional research support grants from AstraZeneca/Merck, Atara Biotherapeutics/Bayer, Genentech, Genmab, GlaxoSmithKline, Gynecologic Oncology Group Foundation, Juno Therapeutics, Kite/Gilead, Ludwig Institute for Cancer Research, Regeneron, Sellas Life Sciences, Stem CentRx, Syndax, TapImmune Inc., and TCR2 Therapeutics. JAPF reports personal fees from Abilify Pharma, Amgen, AstraZeneca, Clinigen, Clovis, GlaxoSmithKline, and Roche; and institutional grants from GlaxoSmithKline. BJM reports consulting fees from Agenus, Akeso Bio, Amgen, Aravive, Bayer, Elevar, EMD Merck, Genmab/Seagen, GOG Foundation, Gradalis, ImmunoGen, Iovance, Karyopharm, Macrogenics, Mersana, Myriad, Novartis, Novocure, Regeneron, Sorrento, Pfizer, Puma, US Oncology Research, and VBL; speaker's bureau honoraria from AstraZeneca, Clovis, Eisai, Merck, Roche/Genentech, TESARO/GSK; and is an investigator for US Oncology Research.

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