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ORIGINAL ARTICLE

Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial

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Abstract

Background: The PRIMA/ENGOT-OV26/GOG-3012 (NCT02655016) trial was amended to prospectively evaluate the safety and efficacy of an individualized starting dose (ISD) regimen of niraparib for first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer.

Methods: In the phase 3 PRIMA trial, patients with newly diagnosed advanced ovarian cancer with a complete/partial response to first-line platinum-based chemotherapy (N = 733) were initially treated with a fixed starting dose (FSD) regimen of 300 mg once daily. Subsequently, the protocol was amended so newly enrolled patients received an ISD: 200 mg once daily in patients with baseline body weight < 77 kg or baseline platelet count < 150,000/μL, and 300 mg once daily in all other patients. Efficacy and safety outcomes were assessed by starting dose.

Results: Overall, 475 (64.8%) patients were assigned to an FSD (niraparib, n = 317; placebo, n = 158) and 258 (35.2%) were assigned to an ISD (niraparib, n = 170; placebo, n = 88). Efficacy in patients who received FSD or ISD was similar for the overall (FSD hazard ratio [HR], 0.59 [95% CI, 0.46–0.76] vs. ISD HR, 0.69 [95% CI, 0.48–0.98]) and the homologous recombination–deficient (FSD HR, 0.44 [95% CI, 0.30–0.64] vs. ISD HR, 0.39 [95% CI, 0.22–0.72]) populations. In patients with low body weight/platelet count, rates of grades ≥3 and 4 hematologic treatment-emergent adverse events, dose interruptions, and dose reductions were lower for those who received ISD than for those who received FSD.

Conclusions: In PRIMA, similar dose intensity, similar efficacy, and improved safety were observed with the ISD compared with the FSD regimen.

KEYWORDS
individualized starting dose, niraparib, ovarian cancer, poly(ADP-ribose) polymerase inhibitors/adverse effects, poly(ADP-ribose) polymerase inhibitors/therapeutic use

INTRODUCTION

Niraparib is a poly(ADP-ribose) polymerase inhibitor approved for the maintenance treatment of patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively called ovarian cancer [OC]).[1,2]

Based on the results of the phase 1 PN001 study, a starting dose of niraparib 300 mg once daily was used in the pivotal ENGOT-OV16/NOVA (NOVA) trial (NCT01847274) for patients with recurrent OC.[3] The most common grade ≥3 treatment-emergent adverse events (TEAEs) among patients receiving niraparib in NOVA were hematologic (thrombocytopenia, anemia, and neutropenia), and dose reductions were implemented in 66.5% of niraparib-treated patients.[4] To evaluate whether a lower dose would decrease hematologic TEAEs, a retrospective decision-tree analysis of NOVA was conducted, which identified that niraparib-treated patients with low baseline body weight (BW < 77 kg) or low platelet count (PC < 150,000/μL)—the low weight or platelet (low W/P) subgroup—had a higher incidence of grade ≥3 thrombocytopenia.[5] The retrospective decision-tree analysis included bodyweight and body mass index as variables, but of these two, bodyweight was found to be a predictor of thrombocytopenia and dose reductions, whereas body mass index was not.[5] Because of early dose reductions, patients in the low W/P population received a 207-mg average niraparib dose during the first 2 months of treatment, suggesting that this population could benefit from starting dose optimization.[5] Moreover, efficacy was similar in patients who received niraparib 100 mg or 200 mg once daily following dose modification compared with patients who remained on niraparib 300 mg once daily.[5]

In response to the posology findings from NOVA retrospective analysis,[5] the PRIMA/ENGOT-OV26/GOG-3012 (PRIMA) trial of niraparib for first-line advanced OC maintenance was amended to prospectively evaluate an individualized starting dose (ISD) of niraparib: 200 mg once daily for patients with baseline BW < 77 kg or baseline PC < 150,000/μL (low W/P), and 300 mg in patients with baseline BW ≥ 77 kg and baseline PC ≥ 150,000/μL.

Here, we report the results of the safety and efficacy evaluations of the ISD regimen analysis from the PRIMA trial.

METHODS

Patients and treatment

A detailed methodology of PRIMA (NCT02655016) has been published previously.[6] Briefly, eligible patients were aged ≥18 years and had newly diagnosed, histologically confirmed, high-grade serous or endometrioid OC. Tumor samples underwent central tumor homologous recombination testing (myChoice HRD test; Myriad Genetics, Inc, Salt Lake City, UT). Within 12 weeks of completion of their last dose of platinum-based therapy, patients were randomized 2:1 to receive niraparib or placebo orally once daily in 28-day cycles until progressive disease or intolerable toxicity. Patients were stratified by clinical response after first-line, platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and status regarding tumor homologous recombination (deficient vs. proficient or not determined). Initially, all patients received the fixed starting dose (FSD) of 300 mg once daily. The trial 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.[6]

Individualized starting dose

The trial protocol was amended on November 16, 2017, to incorporate an ISD based on baseline BW and PC. Patients with a baseline BW ≥ 77 kg and PC ≥ 150,000/μL were assigned to a starting dose of 300 mg once daily. Patients with a baseline BW < 77 kg or baseline PC < 150,000/μL (low W/P) were assigned to a starting dose of 200 mg once daily. For patients whose initial starting dosage was 200 mg/day, escalation to 300 mg/day was permitted if no treatment interruption or discontinuation was required during the first two cycles of therapy.

Outcomes

Progression-free survival (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 the primary efficacy end point analyzed by hierarchical testing, first in patients who were homologous recombination deficient (HRd) and then in the overall population. PFS per investigator assessment (IA), safety outcomes, and patient-reported outcomes were secondary end points. BICR-assessed PFS analyses in the overall and HRd populations by starting dose were prespecified at the time of protocol amendment. No adjustments were made for baseline covariates.

Additional post hoc analyses were planned to characterize the efficacy and safety for each starting dose subgroup by baseline BW and PC: subgroup A (FSD subgroup [300-mg starting dose] with BW ≥ 77 kg and PC ≥ 150,000/μL); subgroup B (ISD subgroup [300-mg starting dose] with BW ≥ 77 kg and PC ≥ 150,000/μL); subgroup C (FSD subgroup [300-mg starting dose] with BW < 77 kg or PC < 150,000/μL); and subgroup D (ISD subgroup [200-mg starting dose] with BW < 77 kg or PC < 150,000/μL). Patients with low W/P were included in subgroups C and D. For the primary analysis,[6] the intention to treat included all patients regardless of dose level; for this analysis, only patients who received the protocol-specified starting dose according to their baseline BW and PC at their time of enrollment were included.

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 stratification factors used in randomization. A prespecified subgroup analysis was performed on the starting dose subgroup (FSD or ISD) to assess the consistency of the treatment effect, including a statistical test of treatment–subgroup interaction. The primary data cutoff date was May 17, 2019. PFS by both BICR and IA was analyzed. Because of limited follow-up time by primary data cutoff date among patients who received the ISD regimen, an updated data cut was taken on November 17, 2019 (6 months after the primary data cut), to perform an ad hoc analysis of PFS by IA with increased follow-up time and event maturity. See Appendix S1 for further details concerning the statistical analysis.

RESULTS

Primary analysis results from PRIMA have been published previously.[6] In PRIMA, 728 of the 733 randomized patients received at least one dose of the study drug (safety population).

Patient characteristics

Of the 733 patients, 475 (64.8%) were randomized before the November 2017 amendment and were assigned to receive an FSD of 300 mg once daily, and 258 (35.2%) patients were randomized after the amendment and were assigned to receive an ISD of 200 or 300 mg once daily (Figure 1). Baseline characteristics by starting dose subgroup and treatment arm were generally well matched across the subgroups. However, more patients in the ISD subgroup than in the FSD subgroup had a partial response to first-line chemotherapy: niraparib/placebo FSD 26.5%/25.9% versus ISD 38.8%/37.5% (Table S1).

Of the 122 patients with low W/P who received the niraparib 200-mg starting dose, 120 (98.4%) had BW < 77 kg and two (1.6%)

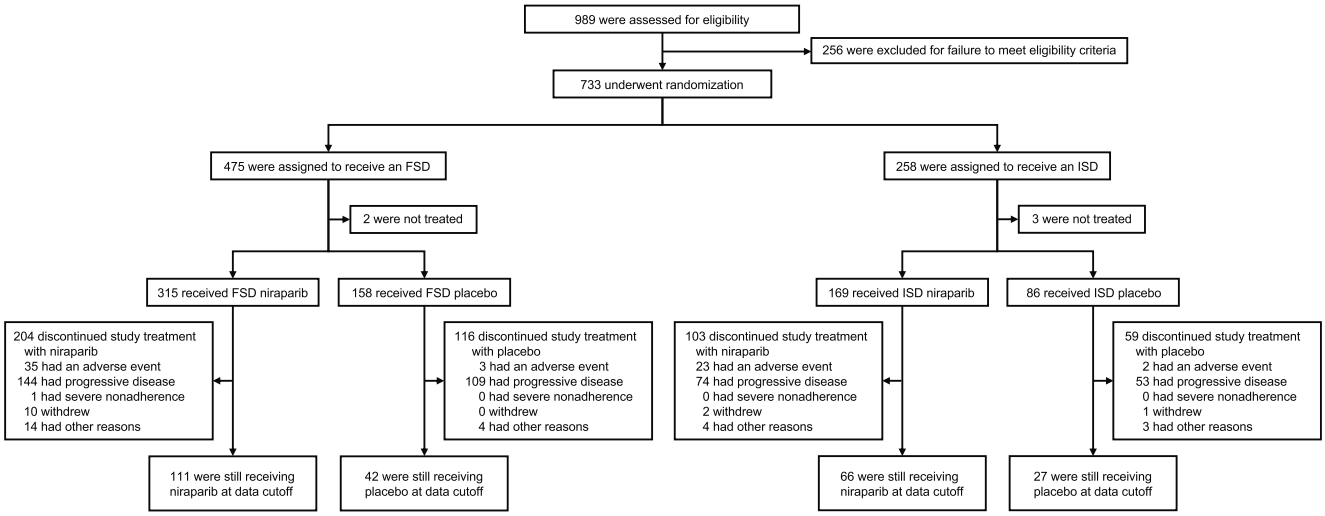


FIGURE 1 Study enrollment and outcomes as of the data cutoff date May 17, 2019. FSD indicates fixed starting dose; ISD, individualized starting dose.

patients had PC < 150,000/μL. Thirteen patients receiving an ISD escalated from 200 mg once daily to 300 mg once daily (seven niraparib, six placebo). Of 258 patients who received an ISD, 17 (6.6%) received the incorrect starting dose: 14 patients with low W/P received 300 mg of niraparib and three with high W/P received 200 mg. Incorrectly dosed patients were excluded from safety and efficacy analysis and from the analysis of subgroups A through D. See Figure S1 for a complete dosing breakdown.

Dose exposure, modification, and safety

Overall exposure during the treatment period is listed in Table 1. The median niraparib dose intensities were similar between FSD and ISD subgroups (181.8 vs. 178.6 mg/day), although the median relative dose intensity was slightly higher in the ISD subgroup than in the FSD subgroup (66.4% vs. 60.6%). The median niraparib treatment exposure time was similar between both subgroups (FSD, 11.5 months; ISD, 11.0 months). Rates of niraparib dose interruptions because of TEAEs were lower in the ISD subgroup than in the FSD subgroup (71.6% vs. 83.8%), as were rates of dose reductions because of TEAEs (61.5% vs. 75.9%). In niraparib-treated patients, incidence of treatment discontinuations because of TEAEs was similar in both subgroups (FSD, 11.1%; ISD, 13.6%).

Most patients in PRIMA required early dose modification, with the majority reaching a tolerable dose by month 4 or 5 (Figure S2). Most patients with a high BW and PC remained at 200 mg or 300 mg of niraparib at month 12, whereas those patients with the low W/P had been reduced to 100 mg of niraparib by month 12. In niraparib-treated patients, rates of grade ≥3 hematological TEAEs were lower in the ISD than in the FSD subgroup. Grade ≥3 thrombocytopenia events were reduced from 48.3% in FSD to 21.3% in ISD (Figure 2A). Similarly, grade ≥3 anemia and neutropenia events were reduced from 35.6% and 23.8%, respectively, in the FSD subgroup to 22.5% and 14.8% in the ISD subgroup. No difference was observed in grade ≥3 hypertension between FSD (6.3%) and ISD (5.3%) subgroups. For nonhematological TEAEs of any grade, incidence was generally lower in the ISD subgroup than in the FSD subgroup (Table S2).

Dose modifications and safety among patients with low W/P

At trial start, patients who met the low W/P criteria received the 300-mg FSD (subgroup C), and dose interruptions and dose reductions because of adverse events occurred in 85.2% and 79.8% of niraparib-treated patients, respectively. Following implementation of the ISD, patients who met the low W/P criteria received the 200-mg ISD (subgroup D), and dose interruptions and dose reductions because of adverse events occurred in 64.8% and 56.6% of niraparib-treated patients, respectively (Table S3). In the low W/P subgroup, hematologic toxicities were reduced with a 200-mg ISD versus a 300-mg FSD. Notably, the incidence of grade ≥3 thrombocytopenia reduced from 51.9% to 17.2% and grade 4 thrombocytopenia reduced from 38.7% to 6.6% (Figure 2B,C). Grade ≥3 anemia rates were reduced from 35.0% to 20.5%, whereas incidence of grade 4 anemia was low in both subgroups (<1%). Grade ≥3 neutropenia was reduced from 27.2% to 14.8%, and grade 4 neutropenia was reduced from 10.7% to 0.8%. In niraparib-treated patients, rates of transfusion were lower in the ISD subgroup than in the FSD subgroup: red blood cells, 23.7% versus 36.5%; platelet transfusion, 7.1% versus 27.9%.

Efficacy

Niraparib efficacy in patients who received ISD versus FSD was similar for the overall population (ISD hazard ratio [HR], 0.69 [95%

TABLE 1 Dose exposure, safety, and dose modifications by starting dose regimen in the overall population.

	Niraparib			
	Overall (*n* = 484)	**FSD (*n* = 315)**	**ISD (*n* = 169)**	**Placebo (*n* = 244)**
Median treatment exposure (range), months	11.1 (0-29)	11.5 (0–29)	11.0 (0–16)	8.3 (0–28)
Median dose intensity, mg/day	181.3	181.8	178.6	290.6
Median relative dose intensity, %	62.6	60.6	66.4	98.9
Overall dose interruptions because of TEAE, *n* (%)	385 (79.5)	264 (83.8)	121 (71.6)	44 (18.0)
Because of hematologic TEAE	337 (69.6)	238 (75.6)	99 (58.6)	5 (2.0)
Because of nonhematologic TEAE	157 (32.4)	108 (34.3)	49 (29.0)	40 (16.4)
Overall dose reductions because of TEAE, *n* (%)	343 (70.9)	239 (75.9)	104 (61.5)	20 (8.2)
Because of hematologic TEAE	317 (65.5)	226 (71.7)	91 (53.8)	5 (2.0)
Because of nonhematologic TEAE	66 (13.6)	48 (15.2)	18 (10.7)	16 (6.6)
Discontinuations because of TEAE, *n* (%)	58 (12.0)	35 (11.1)	23 (13.6)	6 (2.5)

Data cutoff date: May 17, 2019.

Abbreviations: FSD, fixed starting dose; ISD, individualized starting dose; TEAE, treatment-emergent adverse event.

CI, 0.48–0.98] vs. FSD HR, 0.59 [95% CI, 0.46–0.76]) and the HRd population (ISD HR, 0.39 [95% CI, 0.22–0.72] vs. FSD HR, 0.44 [95% CI, 0.30–0.64]; Table 2). At the prespecified two-sided alpha of 0.1, the treatment interaction test for starting dose subgroups was not statistically significant in the overall or HRd populations. Based on the post hoc analysis, PFS HRs were similar among patients with BW of 77 kg and PC of 150,000/μL who received a starting dose of 300 mg before or after amendment (subgroups A vs. B; Figure 3A). Hazard ratios were also similar among patients with low W/P receiving an FSD of 300 mg before amendment and those receiving an ISD of 200 mg once daily after amendment (subgroups C vs. D; Figure 3A).

Because the patients who received an ISD entered the trial more than a year after initiation, the median follow-up time at the time of the primary data analysis (May 17, 2019) was only 11.2 months compared with 17.1 months in the FSD subgroup. Another data cut was conducted to add 6 months to the efficacy analysis (November 17, 2019), which increased the median follow-up time to 17.0 months and 22.4 months in the ISD and FSD subgroups, respectively. In addition, event maturity per IA increased from 57% (59% FSD and 54% ISD) to 65% (66% FSD and 62% ISD).

The PFS by IA hazard ratios for patients who received ISD versus FSD in the HRd and homologous recombination proficient (HRp) subgroups were similar across the primary and updated data cuts (Figures 3B and 4B,C). For the overall population, median PFS with ISD increased from 8.2 months with placebo to 12.5 months with niraparib treatment (HR, 0.68 [95% CI, 0.49–0.94]). Similarly, in the HRd population receiving an ISD, median PFS increased from 12.9 months with placebo to 19.4 months with niraparib (HR, 0.54 [95% CI, 0.33–0.91]). When comparing low W/P patients in dosing subgroups C and D, efficacy was maintained in the overall, HRd, and HRp populations, with consistent HRs from the primary and updated data cuts (Table S4).

Patient-reported outcomes

No differences were seen in mean Functional Assessment of Cancer Therapy–Ovarian Symptom Index or EQ-5D-5L health utility index scores between patients receiving niraparib and placebo in the ISD and FSD subgroups (Figure S3).

DISCUSSION

In the phase 3 PRIMA trial of niraparib first-line maintenance treatment in patients with advanced OC, use of an ISD regimen for niraparib, determined based on a patient's baseline BW and PC, was associated with improved tolerability with no apparent decrement to PFS, compared with the FSD regimen of niraparib 300 mg. Thrombocytopenia, anemia, and neutropenia events were less common in the ISD subgroup than in the FSD subgroup. Implementation of the ISD also affected hematological adverse event severity, with fewer grade ≥3 anemia and neutropenia events reported in the ISD subgroup than in the FSD subgroup. Patients who received an ISD also underwent fewer red blood cell or platelet transfusions. Rates of grade ≥3 anemia and neutropenia events in patients in the ISD subgroup were similar to those seen for olaparib from the SOLO-1 trial (anemia, 22%; neutropenia, 9%).[7] In the low W/P patients, the rate of clinically significant grade 4 thrombocytopenia events decreased from 38.7% in the 300-mg FSD subgroup to 6.6% in the 200-mg ISD subgroup, a reduction of more than 80%. Available patient-reported outcome data indicated no notable differences in the overall health-related quality of life between FSD and ISD groups; however, additional investigation may be warranted to better understand ISD impact on gastrointestinal tolerability and the overall disease and treatment experience.

In comparison to the FSD subgroup, rates of dose modifications and dose interruptions were decreased in the ISD subgroup, especially

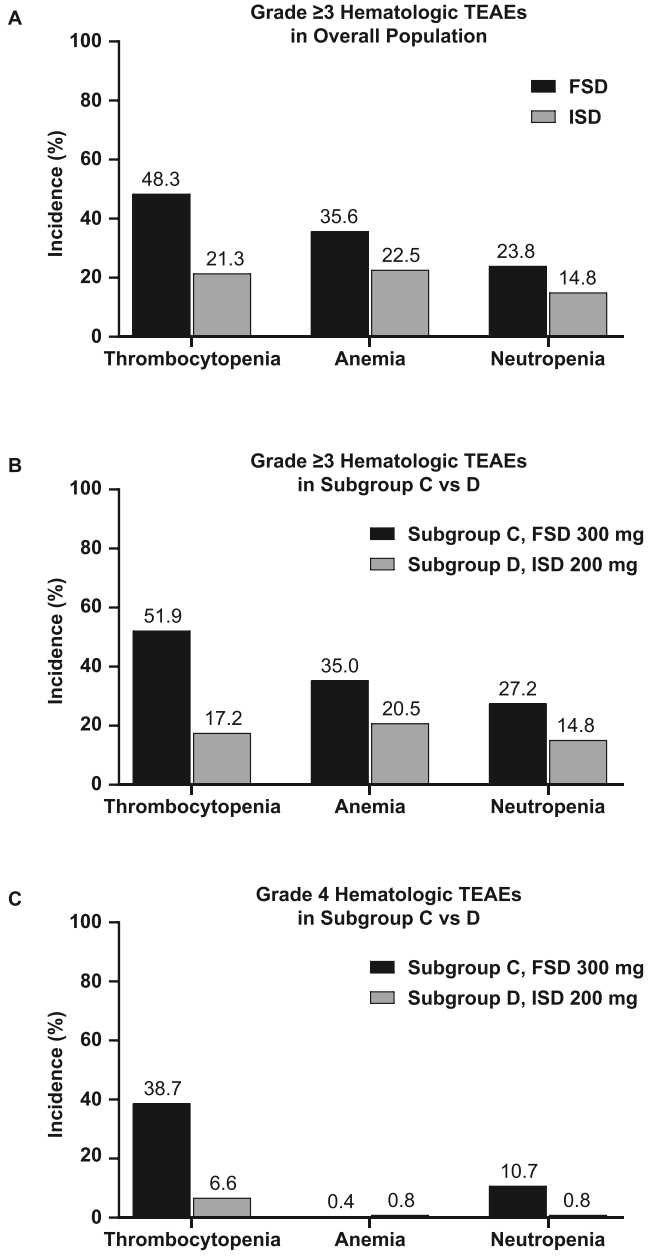


FIGURE 2 Grade 3 and 4 hematologic TEAEs in niraparib-treated patients. (A) Grade 3 or higher hematologic TEAE by starting dose regimen in the overall population (FSD, $n = 315$; ISD, $n = 169$). (B) Grade 3 or higher hematologic TEAEs in subgroups C (FSD 300 mg, baseline bodyweight < 77 kg or platelet count < 150,000/μL, $n = 243$) and D (ISD 200 mg, baseline bodyweight < 77 kg or platelet count < 150,000/μL, $n = 122$). (C) Grade 4 hematologic TEAEs in subgroups C and D. Data cutoff date: May 17, 2019. Thrombocytopenia events include thrombocytopenia and platelet count decrease; anemia events include anemia, hematocrit decrease, and red blood cell count decrease; neutropenia events include neutropenia, neutrophil count decrease, febrile neutropenia, and neutropenic sepsis. FSD indicates fixed starting dose; ISD, individualized starting dose; TEAE, treatment-emergent adverse event.

TABLE 2 PFS per BICR hazard ratio and starting dose regimen subgroup interaction test.

	Starting dose subgroup	Hazard ratio (95% CI)	Interaction test *p* value
Overall	FSD	0.59 (0.46–0.76)	.30
	ISD	0.69 (0.48–0.98)	
HRd	FSD	0.44 (0.30–0.64)	.75
	ISD	0.39 (0.22–0.72)	

Data cutoff date: May 17, 2019. Efficacy in ISD versus FSD subgroups was also maintained in the HRp population: ISD hazard ratio, 0.70 (95% CI, 0.40–1.23) versus FSD hazard ratio, 0.64 (95% CI, 0.42–0.97); per the statistical analysis plan, treatment interaction testing was not performed in the HRp population.

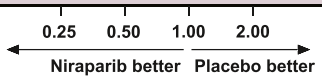
Abbreviations: BICR, blinded independent central review; FSD, fixed starting dose; HRd, homologous recombination deficient; ISD, individualized starting dose; PFS, progression-free survival.

in patients who met the low W/P criteria. Although patients in the FSD subgroup received a higher dose initially, the median dose intensity was similar in patients in the ISD subgroup because of dose modifications. Subgroup analysis by baseline W/P category showed a similar median relative niraparib dose intensity in subgroups A (67.7%) and B (66.8%), indicating that, as expected, patients in the subgroup with baseline BW ≥ 77 kg or baseline PC ≥ 150,000/μL were treated similarly with FSD and ISD regimens. In patients who met the low W/P criteria, the median relative dose intensity was greater in subgroup D patients who received a starting dose of niraparib 200 mg (65.2%) than in patients in subgroup C who received a 300-mg starting dose (52.5%), possibly indicating earlier discontinuation of niraparib treatment in the FSD-treated patients. In addition, quality of life outcomes were similar across the FSD and ISD subgroups.

Efficacy outcomes were similar across the ISD and FSD regimens, and interaction testing in the overall and HRd populations demonstrated that the differences in the PFS HRs in the ISD and FSD subgroups were not statistically significant. Because the ISD protocol amendment was implemented more than 1 year after the trial began enrolling, the follow-up time for patients receiving an ISD was 6 months less than those receiving an FSD. To address the discrepancy in follow-up time and increase overall data maturity, an additional data cut was taken 6 months after the primary analysis clinical cutoff date, and PFS by IA was evaluated in the FSD and ISD subgroups. Importantly, the updated data demonstrated that the PFS HRs in patients with low W/P who received a 200-mg ISD (subgroup D), the subgroup most affected by ISD implementation date, were nearly identical at both time points for the overall (0.67, 0.67), HRd (0.48, 0.53), and HRp populations (0.46, 0.43). Because of the strong concordance between PFS results based on BICR and IA in the primary analysis, the IA results from the additional data cut support the clinical efficacy of the ISD.

A

	Niraparib n/N	Placebo n/N	Hazard Ratio for PFS (95% CI)
Overall Population			
All patients	232/487	155/246	0.62 (0.50-0.76)
FSD	150/317	104/158	0.59 (0.46-0.76)
ISD	82/170	51/88	0.69 (0.48-0.98)
Regular W/P Population: BW ≥77 kg and PC ≥150,000/μL			
Subgroup A: FSD 300 mg	29/72	28/42	0.47 (0.27-0.82)
Subgroup B: ISD 300 mg	18/34	14/21	0.42 (0.19-0.95)
Low W/P Population: BW <77 kg or PC <150,000/μL			
Subgroup C: FSD 300 mg	121/243	76/116	0.62 (0.47-0.83)
Subgroup D: ISD 200 mg	58/122	35/61	0.68 (0.44-1.06)



B

	Median PFS (Months)		
	Niraparib	Placebo	Hazard Ratio for PFS (95% CI)
Overall			
Overall, original[a]	13.8	8.2	0.63 (0.51-0.76)
Overall, updated[b]	13.8	8.2	0.64 (0.53-0.77)
FSD, original	13.8	8.2	0.60 (0.47-0.77)
FSD, updated	13.9	8.2	0.62 (0.49-0.78)
ISD, original	11.4	8.2	0.68 (0.48-0.96)
ISD, updated	12.5	8.2	0.68 (0.49-0.94)
HRd			
Overall, original	21.9	11.2	0.46 (0.34-0.63)
Overall, updated	24.2	11.2	0.48 (0.36-0.63)
FSD, original	24.2	10.8	0.46 (0.33-0.66)
FSD, updated	24.8	10.8	0.46 (0.32-0.64)
ISD, original	13.9	11.2	0.45 (0.25-0.80)
ISD, updated	19.4	12.9	0.54 (0.33-0.91)
HRp			
Overall, original	8.3	5.4	0.62 (0.45-0.85)
Overall, updated	8.3	5.4	0.62 (0.46-0.84)
FSD, original	10.8	5.4	0.62 (0.41-0.93)
FSD, updated	10.8	5.4	0.64 (0.44-0.95)
ISD, original	5.9	5.5	0.59 (0.35-1.01)
ISD, updated	6.6	5.5	0.56 (0.34-0.93)

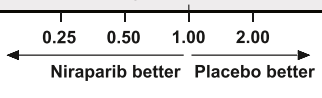


FIGURE 3 Efficacy outcomes by starting dose regimen and baseline W/P group. (A) PFS by blinded independent central review committee assessment by starting dose regimen and baseline W/P group with data cutoff date of May 17, 2019. (B) PFS by IA by starting dose regimen and homologous recombination deficiency status. [a]The original data cutoff date was May 17, 2019. [b]The updated data cutoff date was November 17, 2019. BW indicates body weight; FSD, fixed starting dose; HRd, homologous recombination deficiency; HRp, homologous recombination proficiency; IA, investigator assessment; ISD, individualized starting dose; PFS, progression-free survival; W/P, weight or platelet count.

The niraparib ISD was also prospectively evaluated in two phase 3 placebo-controlled trials in Chinese patients with platinum-sensitive recurrent OC (NORA) and newly diagnosed advanced OC (PRIME). In NORA, 94% of patients were enrolled to receive an ISD of niraparib.[8] The rates of grade ≥3 hematologic TEAEs were similarly lowered by ISD implementation: thrombocytopenia events were

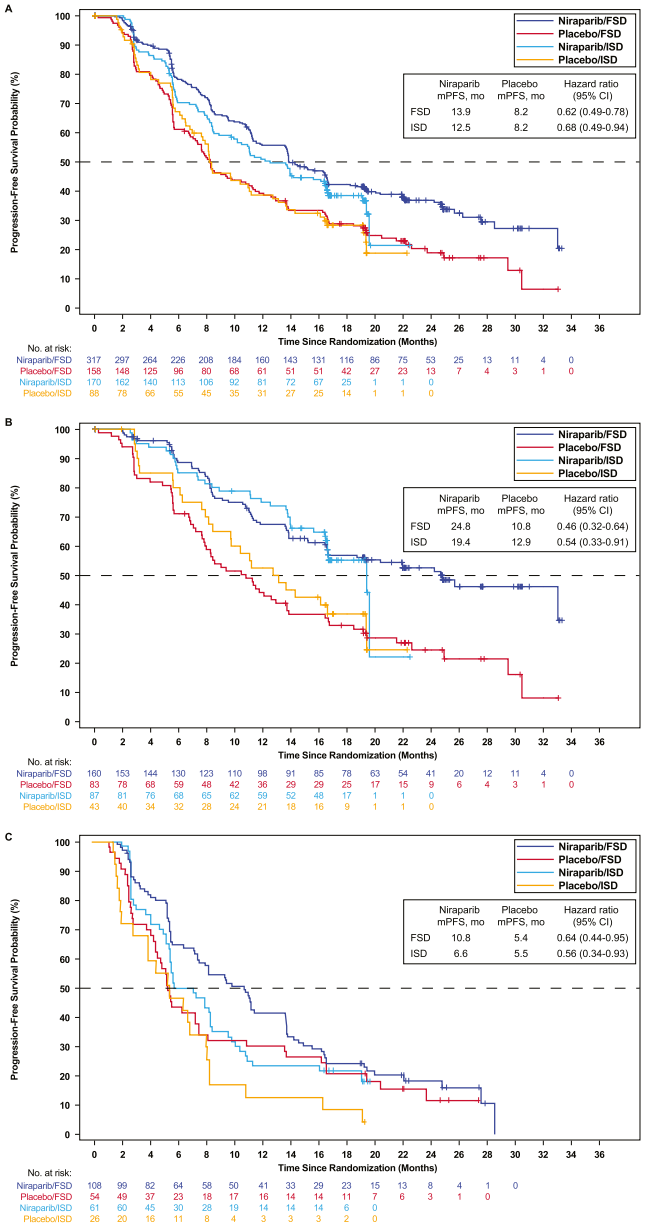


FIGURE 4 Kaplan–Meier estimates of PFS per IA by treatment arm and starting dose regimen in the (A) overall population, (B) HRd population, and (C) HRp population. Data cutoff date: May 17, 2019. FSD indicates fixed starting dose; HRd, homologous recombination deficient; HRp, homologous recombination proficient; IA, investigator assessment; ISD, individualized starting dose; mPFS, median progression-free survival; PFS, progression-free survival.

reported in 11.3%, neutropenia events in 20.3%, and anemia events in 14.7% of patients. TEAEs leading to dose reductions occurred in 59.9% of patients. Risk of disease progression or death was similarly reduced for patients receiving niraparib versus those receiving placebo between the NORA and NOVA trials,[4,8] showing that ISD implementation had no apparent effect on niraparib efficacy. In the PRIME study in Chinese patients with newly diagnosed advanced OC, the niraparib ISD demonstrated substantial PFS benefit in the intent-to-treat population compared with placebo (24.8 vs. 8.3 months; HR, 0.45; $p < .001$).[9] In the niraparib arm of the PRIME study, the incidences of grade ≥3 TEAEs and dose modifications or discontinuations because of TEAEs were numerically lower than in the previous niraparib trials using an FSD.[9] Although the studies were conducted in different populations, the NORA and PRIME safety findings are consistent with the PRIMA ISD results and support the use of a niraparib ISD overall.

A key limitation of this analysis is that an ISD was added as an amendment to an ongoing trial. PRIMA was not powered to detect a difference in efficacy between an FSD and an ISD. Although the interaction testing in the overall and HRd populations was prespecified in the primary statistical analysis plan, other analyses presented here were conducted on a post hoc basis. In addition, the small ISD sample size for some of the subgroups (e.g., HRp, homologous recombination status not determined) should be taken into consideration because it potentially limits the interpretation and generalizability of the findings. Also, per protocol, patients were enrolled within 12 weeks of completing chemotherapy. No analysis was prespecified or performed to determine if the duration of this interval impacted rates or severity of hematologic adverse events.

In PRIMA, the ISD regimen resulted in similar dose intensity, similar efficacy, and improved safety compared with the FSD regimen. Taken together, these data validate the findings from retrospective analysis of the NOVA trial, which identified the importance of adjusting the starting dose of niraparib based on a patient's baseline BW and PC. Based on these results, patients with advanced OC after response to first-line platinum-based chemotherapy should start niraparib at 200 mg once daily if baseline BW is < 77 kg (170 lb) or baseline PC is < 150,000/μL or at 300 mg once daily if baseline BW is ≥ 77 kg (170 lb) and baseline PC is ≥ 150,000/μL, as indicated by regulatory approvals.

PRIOR PRESENTATION

Portions of these data were previously presented at the American Society of Clinical Oncology 56th Annual Meeting, May 29–31, 2020 (virtual meeting); the Heartland Association for Gynecologic Oncology First Annual Meeting, July 1, 2020; the International Gynecologic Cancer Society Second Global Meeting, September 10–14, 2020 (virtual meeting); the Chinese Society of Clinical Oncology 23rd Annual Meeting, September 16–20, 2020; the European Society for Medical Oncology (ESMO) Asia Congress 2020, September 19–21, 2020; the Deutsche Gesellschaft fur Gynakologie und Geburtshilfe – 63rd Kongress, October 7–9, 2020; the European Society of Gynaecological Oncology Fourth State of the Art Conference, December 14–16, 2020; and the Japan Society of Obstetrics and Gynecology 73rd Annual Congress, April 22–25, 2021.

AUTHOR CONTRIBUTIONS

Mansoor R. Mirza: Conceptualization, investigation, resources, data curation, visualization, writing—review and editing, and validation. **Antonio González-Martín:** Conceptualization, investigation,

resources, data curation, visualization, and writing—review and editing. **Whitney S. Graybill:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **David M. O'Malley:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Lydia Gaba:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Oi Wah Stephanie Yap:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Eva M. Guerra:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Peter G. Rose:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Jean-François Baurain:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Sharad A. Ghamande:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Hannelore Denys:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Emily Prendergast:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Carmela Pisano:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Philippe Follana:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Klaus Baumann:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Paula M. Calvert:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Jacob Korach:** Conceptualization, investigation, resources, data curation, visualization, and writing—review and editing. **Yong Li:** Conceptualization, investigation, resources, data curation, visualization, writing—original draft, writing—review and editing, and validation. **Izabela A. Malinowska:** Conceptualization, project administration, investigation, resources, data curation, visualization, writing—original draft, and writing—review and editing. **Divya Gupta:** Conceptualization, project administration, investigation, resources, data curation, visualization, writing—original draft, writing—review and editing, and validation. **Bradley J. Monk:** Conceptualization, investigation, resources, data curation, visualization, writing—review and editing, and validation.

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CONFLICT OF INTEREST STATEMENT

Mansoor R. Mirza reports a consulting or advisory role at AstraZeneca, Biocad, GSK, Karyopharm, Merck, Roche, Zailab; speakers' bureau fees from AstraZeneca and GSK; research funding (to institution) from Apexigen, AstraZeneca, Deciphera (trial chair), GSK, and Ultimovacs; and personal financial interest in Karyopharm (stocks/shares, member of Board of Directors). Antonio González-Martín reports consulting or advisory role at Amgen, AstraZeneca, Clovis Oncology, Genmab, GSK, Immunogen, MSD, Mersana, Novartis, Oncoinvent, PharmaMar, Roche/Genentech, Sotio, Sutro, and Takeda; research funding from GSK and Roche; and speakers' bureau fees from AstraZeneca, Clovis Oncology, GSK, MSD, and Roche. Whitney S. Graybill reports honoraria from GSK. David M. O'Malley reports honoraria from AbbVie, Agenus, Ambry, Amgen, AstraZeneca, Clovis, Eisai, Elevar, Genentech/Roche, GOG Foundation, Immunogen, Iovance Biotherapeutics, Janssen/J&J, Merck, Mersana, Myriad Genetics, Novartis, Novocure, Regeneron, Rubis, SeaGen, Tarveda, and Tesaro/GSK; research funding (to institution) from AbbVie, Agenus, Ajinomoto Inc, Amgen, Array Biopharma, AstraZeneca, BBI, Bristol-Myers Squibb Co, Cerulean Pharma, Clovis, Eisai, EMD Serono, Ergomed, Genentech/Roche, GenMab, GOG Foundation, Immunogen, INC Research, inVentiv Health Clinical, Iovance Biotherapeutics, Janssen/J&J, Ludwig Cancer Research, Merck, Mersana, NCI, New Mexico Cancer Care Alliance, Novocure, PRA Intl, Regeneron, SeaGen, Serono Inc, Stemcentrx, Tesaro/GSK, TRACON Pharmaceuticals, VentiRx, and Yale University. Lydia Gaba reports honoraria from AstraZeneca, Clovis Oncology, GSK, Merck Sharp & Dohme Corp, and PharmaMar; and travel support from AstraZeneca, GSK, and Merck Sharp & Dohme Corp. Hannelore Denys reports consulting or advisory role (to institution) from Amgen, AstraZeneca, Eli Lilly, GSK, Novartis, Pfizer, PharmaMar, Roche, and Tesaro; research funding (to institution) from Roche; travel, accommodations, expenses (to institution) from AstraZeneca, Pfizer, PharmaMar, Roche, and Teva. Bradley J. Monk reports honoraria from AbbVie, Amgen, Aravive, AstraZeneca, Clovis, GSK, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, and Roche/Genentech; consulting or advisory role at AbbVie, Amgen, Aravive, AstraZeneca, Clovis, GSK, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, and Roche/Genentech; speakers' bureau fees from AstraZeneca, Clovis, GSK, Merck, and Roche/Genentech. Divya Gupta reports employment at GSK. The other authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

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

CLINICAL TRIAL INFORMATION

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REFERENCES

1. US Food and Drug Administration. ZEJULA (niraparib). Accessed October 14, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf

2. European Medicines Agency. ZEJULA (niraparib). Accessed October 14, 2020. https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf
3. Sandhu SK, Schelman WR, Wilding G, et al. The poly(ADP-ribose) polymerase inhibitor niraparib (MK4827) in BRCA mutation carriers and patients with sporadic cancer: a phase 1 dose-escalation trial. *Lancet Oncol*. 2013;14(9):882-892. doi:10.1016/s1470-2045(13)70240-7
4. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375(22):2154-2164. doi:10.1056/nejmoa1611310
5. Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. *Ann Oncol*. 2018;29(8):1784-1792. doi:10.1093/annonc/mdy181
6. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402. doi:10.1056/nejmoa1910962
7. Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505.
8. Wu XH, Zhu JQ, Yin RT, et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. *Ann Oncol*. 2021;32(4):512-521. doi:10.1016/j.annonc.2020.12.018
9. Li N, Zhu J, Yin R, et al. Efficacy and safety of niraparib as maintenance treatment in Chinese patients with newly diagnosed advanced ovarian cancer (PRIME Study): a randomized, double-blind, placebo-controlled, phase 3 trial. *Gynecol Oncol*. 2022;(Suppl1):S50-S51.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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