Evaluation of an Individualized Starting Dose of Niraparib in the PRIMA/ENGOT-OV26/GOG-3012 Study

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Background

- A post hoc decision-tree analysis identified that, in patients treated with niraparib in NOVA, baseline bodyweight and baseline platelet count were predictive factors for the development of high-grade thrombocytopenia[3]
  - Most of the thrombocytopenia events occurred by the end of month 3
  - These patients received an average dose of 207 mg during the first 3 months
  - After dose modification, 200 mg was the most commonly administered dose
  - Dose modification did not compromise efficacy in the retrospective analysis
- Based on this analysis, a new individualized starting dose paradigm was introduced in the first-line PRIMA/ENGOT-OV26/GOG-3012 study[4]

Conclusions

- The individualized starting dose regimen determined in the retrospective analysis of NOVA was prospectively validated in this analysis
- The individualized starting dose regimen of 200 mg or 300 mg based on baseline bodyweight and platelet count demonstrated comparable efficacy while improving the safety profile of niraparib
  - Clinical efficacy was similar in patients who received the 300-mg fixed starting dose or the 200- or 300-mg individualized starting dose
  - Hematologic toxicities were reduced with the individualized starting dose subgroup
- Based on these results, an individualized starting dose is recommended for first-line maintenance treatment of patients with ovarian cancer
  - 200 mg taken orally QD
  - 300 mg taken orally QD for patients weighing ≥77 kg (170 lbs) and with baseline platelet count of ≥150,000/μL

Poster #221

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Prescribing Information

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Introduction

- Niraparib is a poly(ADP-ribose) polymerase inhibitor approved for the maintenance treatment of patients with newly diagnosed or recurrent ovarian cancer following a response to platinum-based chemotherapy[1,2]
- In the pivotal phase 3 ENGOT-OV16/NOVA trial of niraparib in patients with recurrent ovarian cancer, all patients started the study with a fixed starting dose (FSD) of 300 mg once daily (QD) based on the phase 1 data
- The PRIMA/ENGOT-OV26/GOG-3012 study of niraparib in patients with newly diagnosed ovarian cancer was amended to prospectively validate an individualized starting dose (ISD; 200-mg or 300-mg niraparib QD based on baseline bodyweight and platelet count; **Table 1**)

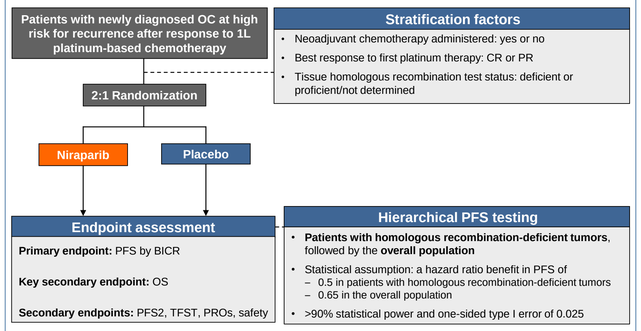
Objective

- To prospectively evaluate the safety and efficacy of an ISD based on patients' baseline bodyweight and platelet count

Methods

- PRIMA is a randomized, double-blind, placebo-controlled, phase 3 trial of niraparib maintenance therapy in patients with newly diagnosed, advanced ovarian cancer that has responded to first-line, platinum-based chemotherapy (**Figure 1**)

Figure 1. Trial Design



1L=first line; BICR=blinded independent central review; CR=complete response; OC=ovarian cancer; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival 2; PR=partial response; PRO=patient-reported outcome; TFST=time to first subsequent therapy.

- The study protocol of PRIMA/ENGOT-OV26/GOG-3012 was amended to introduce the ISD regimen on November 16, 2017 (**Table 1**)
  - After this amendment, randomized patients were assigned to receive either 200 mg or 300 mg based on their baseline bodyweight and platelet count

Table 1. ISD Criteria

Baseline Criteria	Starting Dose
Bodyweight ≥77 kg and platelets ≥150,000/μL	300 mg QD (niraparib or placebo)
Bodyweight <77 kg or platelets <150,000/μL	200 mg QD (niraparib or placebo)

ISD=individualized starting dose; QD=once daily.

- Analysis of the ISD regimen was performed on the safety population (all patients who received ≥1 dose of niraparib or placebo)

Results

- In total, 733 patients were randomized and included in the intent-to-treat (ITT) efficacy population
  - 728 patients received the study drug and comprise the safety population
- Of these, 475 started on a FSD of 300 mg QD niraparib/placebo, and 258 received the ISD of niraparib/placebo (**Table 2**)
  - 2 patients in the FSD subgroup and 3 in the ISD subgroup did not receive niraparib/placebo after randomization

Table 2. Demographics and Baseline Characteristics (ITT Population)

Parameter	Niraparib, n (%) FSD n=317	Niraparib, n (%) ISD n=170	Placebo, n (%) FSD n=158	Placebo, n (%) ISD n=88
Age at time of screening				
Median, years	61.0	63.0	62.0	60.5
Min, Max, years	32, 83	39, 85	34, 88	33, 82
ECOG PS				
0	223 (70.3)	114 (67.1)	114 (72.2)	60 (68.2)
1	94 (29.7)	56 (32.9)	44 (27.8)	28 (31.8)
Cancer stage (FIGO) at time of diagnosis				
III, NOS	5 (1.6)	5 (2.9)	4 (2.5)	0
IIIA	3 (0.9)	4 (2.4)	4 (2.5)	0
IIIB	10 (3.2)	6 (3.5)	7 (4.4)	5 (5.7)
IIIC	186 (58.7)	99 (58.2)	88 (55.7)	50 (56.8)
IV	113 (35.6)	56 (32.9)	55 (34.8)	33 (37.5)
Primary tumor site				
Ovarian	249 (78.5)	139 (81.8)	130 (82.3)	71 (80.7)
Primary peritoneal	20 (6.3)	14 (8.2)	7 (4.4)	6 (6.8)
Fallopian tube	48 (15.1)	17 (10.0)	21 (13.3)	11 (12.5)
NACT				
Yes	208 (65.6)	114 (67.1)	114 (72.2)	53 (60.2)
No	109 (34.4)	56 (32.9)	44 (27.8)	35 (39.8)
Best response to 1L platinum-based chemotherapy				
CR	233 (73.5)	104 (61.2)	117 (74.1)	55 (62.5)
PR	84 (26.5)	66 (38.8)	41 (25.9)	33 (37.5)

1L=first line; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FIGO=International Federation of Gynecology and Obstetrics; FSD=fixed starting dose; ISD=individualized starting dose; ITT=intent to treat; NACT=neoadjuvant chemotherapy; NOS=not otherwise specified; PR=partial response; PS=performance status.

Dose Exposure

- Dose-exposure analysis showed that the mean dose intensity was similar in patients in the FSD and ISD subgroups (**Table 3**)
  - Dose interruptions and reductions were lower in patients in the ISD subgroup, indicating that patients were able to tolerate niraparib better
  - Discontinuation rates due to treatment-emergent adverse events (TEAEs) were similar in the ISD and FSD subgroups

Table 3. Dose Exposure, Dose Intensity, and Dose Interruptions and Reductions (Safety Population)

Parameter	Niraparib Overall N=484	Niraparib FSD n=315	Niraparib ISD n=169
Median treatment exposure, months (range)	11.1 (0–29)	11.5 (0–29)	11 (0–16)
Median dose intensity, mg/day	181.3	181.8	178.6
Median relative dose intensity, %	62.6	60.6	66.4
Overall dose interruptions, %	79.5	84.1	71.0
Overall dose reductions, %	74.8	79.7	65.7
Discontinuations due to TEAE, %	12.0	11.1	13.6

FSD=fixed starting dose; ISD=individualized starting dose; TEAE=treatment-emergent adverse events.

Efficacy

- At the pre-specified 2-sided alpha of 0.1, a starting dose subgroup-by-treatment interaction test was not statistically significant (P=0.30), which suggests that the ISD had similar efficacy versus the FSD (**Table 4**)

Table 4. PFS Hazard Ratio and Starting-Dose Subgroup Interaction Test

	Starting-Dose Subgroup	HR (95% CI)	Interaction Test P Value
Overall	FSD	0.59 (0.46–0.76)	0.30
	ISD	0.69 (0.48–0.98)	

CI=confidence interval; FSD=fixed starting dose; HR=hazard ratio; ISD=individualized starting dose; PFS=progression-free survival.

Safety

- Incidence of grade ≥3 TEAEs, including thrombocytopenia, anemia, and neutropenia, was lower in patients in the ISD subgroup (**Table 5**)

Table 5. Grade ≥3 Hematologic TEAEs Reported in ≥5% of Patients in Either Dosing Subgroup

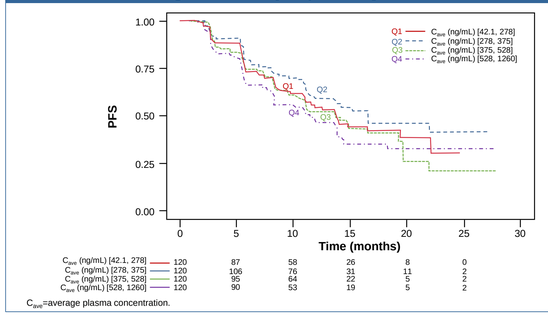
TEAE	Niraparib Overall, n (%) N=484	Niraparib FSD, n (%) n=315	Niraparib ISD, n (%) n=169	Placebo All, n (%) N=244
Any grade ≥3 TEAE	**341 (70.5)**	239 (75.9)	102 (60.4)	46 (18.9)
Thrombocytopenia event[a]	**188 (38.8)**	152 (48.3)	36 (21.3)	1 (0.4)
Anemia event[b]	**150 (31.0)**	112 (35.6)	38 (22.5)	4 (1.6)
Neutropenia event[c]	**100 (20.7)**	75 (23.8)	25 (14.8)	3 (1.2)
Hypertension	**29 (6.0)**	20 (6.7)	9 (5.3)	3 (1.2)

[a]Includes thrombocytopenia and platelet count decreased; [b]Includes anemia and hemoglobin decreased; [c]Includes neutropenia and neutrophil count decreased.
FSD=fixed starting dose; ISD=individualized starting dose; TEAE=treatment-emergent adverse events.

Exposure-Response Analysis

- The ISD and FSD subgroups were comparably represented across all 4 exposure quartiles
  - Dose exposure is increased from Q1 to Q4
- Progression-free survival (PFS) over time for patients by exposure quartile is shown in **Figure 2**
  - The overlapping curves indicate that there is no observed relationship between improved response and increased drug exposure
- However, the rate of high-grade thrombocytopenia increased with higher exposure

Figure 2. PFS by Exposure Quartile



C_{ave}=average plasma concentration.

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