Niraparib Efficacy and Safety in Patients with *BRCA*-Mutated (*BRCA*m) Ovarian Cancer: Results from Three Phase 3 Niraparib Trials

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Background

- Niraparib is an oral poly(ADP-ribose) polymerase (PARP) inhibitor approved for the maintenance treatment of patients with advanced ovarian, fallopian tube, or primary peritoneal cancer after first-line chemotherapy and in the recurrent setting
- *BRCA* mutations occur in approximately 20%–25% of patients with epithelial ovarian cancer and are associated with improved outcomes in comparison with patients with *BRCA* wild-type ovarian cancer[1,2]
- Niraparib has shown efficacy in tumors with and without *BRCA* mutations, and the efficacy and safety of niraparib in patients with *BRCA* mutated (*BRCA*m) was assessed in the PRIMA, NOVA, and NORA trials

Conclusions

- Patients with *BRCA*m ovarian cancer derived a significant PFS benefit from niraparib maintenance treatment across all three trials in first-line and recurrent settings after response to platinum-based chemotherapy
- No new safety signals were identified

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6. Data on file.

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- Dr. Xiaohua Wu is a new author not listed on the abstract. He contributed to the development of the poster and met ICMJE authorship criteria

Conflicts of Interest

Dr. González-Martín reports consulting or advisory role fees from Amgen, AstraZeneca, Clovis Oncology, Genmab, Mersana, MSD, ImmunoGen, Roche, Sotio, and Takeda; speakers' bureau fees from AstraZeneca, Clovis, GlaxoSmithKline, MSD, and Roche; institutional research funding from GlaxoSmithKline and Roche; travel support from AstraZeneca, GlaxoSmithKline, and Roche. **Dr. Matulonis** reports consulting/advisory fees from Merck KGaA, NextCure, and Novartis. **Dr. Korach** has nothing to disclose. **Dr. Mirza** reports personal fees and other from Karyopharm Therapeutics, Roche, and Sera Prognostics; institutional grants and personal fees from AstraZeneca, BioCad, Boehringer Ingelheim, Clovis Oncology, Geneos Therapeutics, GenMab, GlaxoSmithKline, Merck, Oncology Venture, Pfizer, Seattle Genetics, Sera Prognostics, Sotio, Takeda Pharmaceutical Company Ltd, and Zai Lab. **Dr. Moore** reports consulting fees from Aravive, AstraZeneca, Elevar, Eisai, Genentech/Roche, GSK/Tesaro, ImmunoGen, Merck, Mersana, Myriad, Sorrento, and VBL Therapeutics; and research funding from Lilly, Merck, and PTC Therapeutics. **Dr. Wu** was an investigator for the NORA trial and has no conflict of interest to declare. **Dr. Monk** reports consulting fees from Abbvie, Amgen, Aravive, AstraZeneca, Clovis, GlaxoSmithKline, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, and Roche/Genentech; speakers' bureau fees from AstraZeneca, Clovis, GlaxoSmithKline, Merck, and Roche/Genentech; and honoraria from Abbvie, Amgen, Aravive, AstraZeneca, Clovis, GlaxoSmithKline, GOG Foundation, Gradalis, ImmunoGen, Laekna Health Care, Merck, Mersana, Myriad, Nucana, Oncomed, Oncoquest, Pfizer, and Roche/Genentech. **Drs. Gupta and Lechpammer** are employees of GlaxoSmithKline.

Objectives

- To summarize the efficacy and safety of niraparib in patients with *BRCA*m ovarian cancer across three phase 3 trials:
  - PRIMA/ENGOT-OV26/GOG-3012 (PRIMA; NCT02655016)
  - ENGOT-OV16/NOVA (NOVA; NCT01847274)
  - NORA (NCT03705156)

Methods

- PRIMA was a randomized, double-blind, placebo-controlled, phase 3 trial of niraparib maintenance therapy in patients with newly diagnosed, advanced ovarian cancer that responded to first-line platinum-based chemotherapy[3]
- NOVA and NORA were randomized, double-blind, placebo-controlled phase 3 trials of niraparib maintenance therapy in patients with platinum-sensitive, recurrent ovarian cancer[4,5]
- Subgroup analysis by *BRCA*m status was prespecified in all three trials (Figure 1)

Figure 1. PRIMA, NOVA, and NORA Study Overview

	PRIMA[3] (1L maintenance)	NOVA[4] (2L maintenance)	NORA[5] (2L maintenance)
Patient population	Patients with newly diagnosed advanced ovarian cancer • Stage III or IV high-grade serous or endometrioid tumors • Complete or partial response to their first-line platinum-based chemotherapy treatment • Subgroup analysis by tumor *BRCA*m status was prespecified	Patients with platinum-sensitive recurrent ovarian cancer • Received ≥2 lines of platinum-based chemotherapy • Cohort enrollment based on g*BRCA* mutation status (g*BRCA*m vs g*BRCA*wt)	Patients with platinum-sensitive recurrent ovarian cancer • Received ≥2 lines of platinum-based chemotherapy • Subgroup analysis by tumor *BRCA*m status was prespecified
Treatment arms	2:1 Randomization → Niraparib / Placebo		
Niraparib dosing	Study start: fixed starting dose: 300 mg for all patients November 2017: individualized starting dose[a]: 200 mg for patients with baseline body weight <77 kg or baseline platelets <150,000/µL; 300 mg for patients with baseline body weight ≥77 kg and baseline platelets ≥150,000/µL	Fixed starting dose: 300 mg for all patients	Study start: fixed starting dose: 300 mg for all patients December 2017: individualized starting dose[b]: 200 mg for patients with baseline body weight <77 kg or baseline platelets <150,000/µL; 300 mg for patients with baseline body weight ≥77 kg and baseline platelets ≥150,000/µL
Primary endpoint	PFS by blinded independent central review per RECIST v1.1		

[a]In PRIMA, 475 (65%) patients were randomized prior to the November 2017 amendment and were treated with a fixed starting dose, and 258 (35%) patients were randomized after the amendment and were treated with an individualized starting dose; [b]In NORA, 16 (6%) patients were randomized prior to the December 2017 amendment and were treated with a fixed starting dose, and 249 (94%) patients were randomized after the amendment and were treated with an individualized starting dose.
1L, first-line; 2L, second-line; g, germline; m, mutated; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; wt, wild type.

Results

- Overall, 526 patients in PRIMA, NOVA, and NORA had *BRCA*m ovarian cancer (Table 1)
- Mutations in *BRCA1* were most common (60.6%–80.0%)

Table 1. *BRCA*m Patient Characteristics and Baseline Demographics[a]

Characteristic	PRIMA (1L maintenance)		NOVA (2L maintenance)		NORA (2L maintenance)	
	Niraparib (n=152)	Placebo (n=71)	Niraparib (n=138)	Placebo (n=65)	Niraparib (n=65)	Placebo (n=35)
Age, median (range), years	56.5 (32–83)	57 (33–82)	57 (36–83)	58 (38–73)	NA	NA
*BRCA*m status, n (%)[b]						
BRCA1 only	105 (69.1)	43 (60.6)	85 (61.6)	43 (66.2)	50 (76.9)	28 (80.0)
BRCA2 only	47 (30.9)	28 (39.4)	51 (37.0)	18 (27.7)	14 (21.5)	7 (20.0)
BRCA1 and *BRCA2*	0	0	9 (6.5)	4 (6.2)	1 (1.5)	0

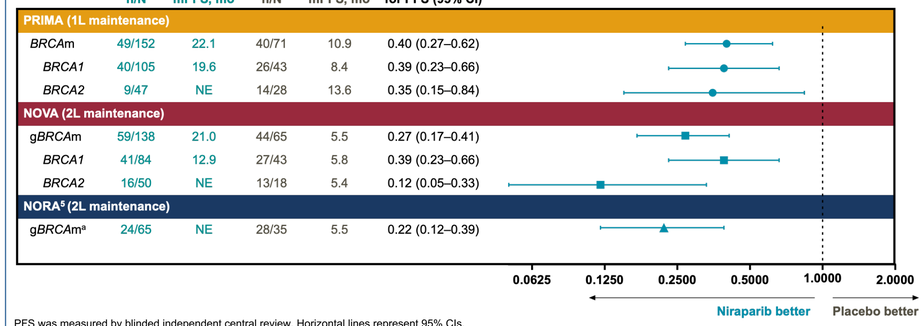
[a]Percentages may not total 100 because of rounding; [b]PRIMA, tumor mutation status; NOVA/NORA, germline mutation status.
1L, first-line; 2L, second-line; m, mutated; NA, not available.

Results (*cont'd*)

Efficacy

- In PRIMA, NOVA, and NORA, patients with *BRCA*m ovarian cancer derived a significant progression-free survival (PFS) benefit from niraparib maintenance treatment across all subgroups examined (Figure 2)

Figure 2. Progression-Free Survival in Patients with *BRCA*m Ovarian Cancer



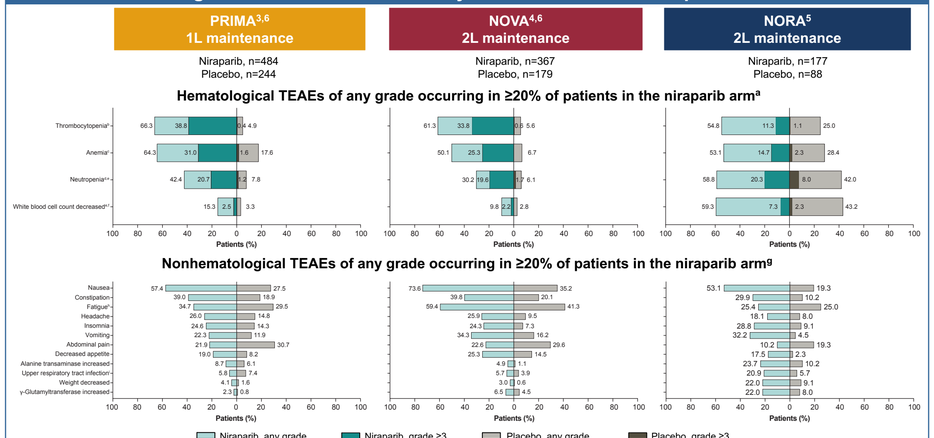
PFS was measured by blinded independent central review. Horizontal lines represent 95% CIs.
[a]*BRCA1* and *BRCA2* data are not currently available.
1L, first-line; 2L, second-line; g, germline; m, mutated; mPFS, median progression-free survival; NE, not estimable; PFS, progression-free survival.

- PRIMA
  - Hazard ratio for PFS for all patients with *BRCA*m was 0.40 (95% CI, 0.27–0.62)
  - No difference was observed in hazard ratios for PFS in patients with *BRCA1* and *BRCA2* mutations
- NOVA
  - Hazard ratio for PFS for all patients with *BRCA*m was 0.27 (95% CI, 0.17–0.41)
  - Hazard ratios for PFS in patients with *BRCA1* and *BRCA2* mutations were 0.39 (95% CI, 0.23–0.66) and 0.12 (95% CI, 0.05–0.33), respectively
- NORA
  - Hazard ratio for PFS for all patients with *BRCA*m was 0.22 (95% CI, 0.12–0.39)

Safety

- Across the three trials, the most common treatment-emergent adverse events of any grade in the overall population, regardless of *BRCA*m status, were thrombocytopenia, anemia, neutropenia, and nausea (Figure 3)

Figure 3. Adverse Events of Any Grade in the Overall Population



[a]Hematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA. Grade ≥3 TEAEs are also reported for each event; [b]Thrombocytopenia: PRIMA, NOVA, and NORA: thrombocytopenia and platelet count decreased; [c]Anemia: PRIMA, anemia; NOVA, anemia and decreased hemoglobin count; NORA, anemia; [d]Neutropenia: PRIMA, neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; NOVA, neutropenia, neutrophil count decreased, and febrile neutropenia; NORA, neutropenia and neutrophil count decreased; [e]NORA: In the niraparib group, among 105 patients who experienced white blood cell count decreased and 104 patients who experienced neutrophil count decreased, 94 patients had both events reported with overlapping duration, and among 13 patients who experienced grade 3 white blood cell count decreased, 11 patients also had grade 3 neutrophil count decreased reported with overlapping duration. In the placebo group, among the 38 patients who experienced white blood cell count decreased of any grade and 37 patients who experienced neutrophil count decreased, 32 patients reported both events with overlapping duration, and 2 patients who experienced grade 3 white blood cell count decreased also reported grade 3 neutrophil count decreased with overlapping duration; [f]White blood cell decreased: PRIMA and NOVA, white blood cell decreased; NORA, white blood cell decreased and leukopenia; [g]Nonhematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA; [h]Fatigue: PRIMA, fatigue; NOVA, fatigue, asthenia, malaise, and lethargy; NORA, asthenia; [i]Did not include viral upper respiratory tract infection for PRIMA or NOVA.
1L, first-line; 2L, second-line; TEAE, treatment-emergent adverse event.