Efficacy and Safety of Niraparib in Older Patients With Advanced Ovarian Cancer: Results From the PRIMA/ENGOT-OV26/GOG-3012 Trial

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Background

- Although studies have demonstrated that the tolerability of cytoreductive surgery and chemotherapy is comparable in older and younger patients, there is an independent effect of age on survival in older patients receiving standard-of-care treatment[1–4]
- There is no recommended difference in standard-of-care treatment of older patients; however, there is concern in this population for increased risk of severe toxicities and higher rates of treatment discontinuation
- Niraparib is an oral, highly selective poly(ADP-ribose) polymerase (PARP) inhibitor that is approved in the United States for the following indications:
  - Maintenance therapy in patients with newly diagnosed or recurrent platinum-sensitive ovarian cancer that have responded to platinum-based chemotherapy
  - Treatment for patients who have had ≥3 prior chemotherapies whose tumors have homologous recombination deficiency (HRd) and are considered platinum sensitive or have a *BRCA* mutation (regardless of platinum sensitivity status)
- The PRIMA/ENGOT-OV26/GOG-3012 (PRIMA) trial tested the efficacy and safety of niraparib maintenance therapy after a response to platinum-based chemotherapy in patients with newly diagnosed, advanced ovarian cancer at high risk for relapse
  - Niraparib demonstrated a significant improvement in PFS in the intent-to-treat population (hazard ratio, 0.62; 95% CI, 0.50–0.76)
- Here we evaluate the impact of age on the efficacy and safety of niraparib in the PRIMA trial

Conclusions

- In the PRIMA trial, efficacy, safety, and patient-reported quality of life were similar among patients receiving niraparib maintenance therapy for advanced ovarian cancer regardless of age group
- Maintenance treatment with niraparib was associated with hematologic toxicities at similar rates among age groups
- The implementation of an individualized starting dose (ISD) regimen demonstrated a reduction of grade ≥3 thrombocytopenia events in patients in all age groups
- PROs/quality of life were comparable among age groups and not different from those on placebo

Poster #819P

Dr. Valabrega has no conflicts of interest to disclose.

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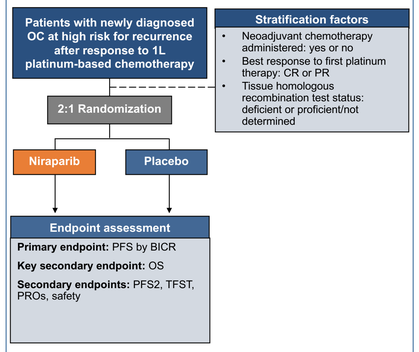
Objective

- To explore the impact of age on the efficacy and safety of niraparib maintenance therapy in patients newly diagnosed with advanced ovarian cancer after a response to platinum-based chemotherapy as a post-hoc analysis of the PRIMA trial
  - Primary objective was progression-free survival (PFS)
  - Secondary objectives included patient reported outcomes (PROs) and safety

Methods

- PRIMA is a double-blind, placebo-controlled phase 3 trial that evaluated niraparib in patients with newly diagnosed, advanced, high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer with a complete or partial response to first-line platinum-based chemotherapy
- Patients were randomized 2:1 to receive either a fixed starting dose (FSD) of 300 mg niraparib or placebo daily until disease progression (Figure 1)
  - A protocol amendment (November 2017) introduced ISD administration of niraparib: 200 mg daily in patients with body weight <77 kg or platelet count <150,000/μL; otherwise, the starting dose was 300 mg daily
- Patients were categorized by age group (<65 vs ≥65 years and <75 vs ≥75 years) to analyze efficacy and safety of niraparib vs placebo in older patients
- Assessment of progression was performed by computed tomography (CT) or magnetic resonance imaging (MRI) every 12 weeks according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1)
- PROs were assessed via administration of questionnaires at screening, throughout treatment, and 4, 8, 12, and 24 weeks after the last dose of niraparib or placebo

Figure 1. PRIMA 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.

Results

- Of 733 enrolled patients, 444 were aged <65 years (297 niraparib, 147 placebo) and 289 were aged ≥65 years (190 niraparib, 99 placebo), while 657 were aged <75 years (433 niraparib, 224 placebo) and 76 were aged ≥75 years (54 niraparib, 22 placebo) (Table 1)
  - Eastern Cooperative Oncology Group (ECOG) scores were higher in patients aged ≥65 years and ≥75 years, and there were more patients aged ≥75 years with stage IV disease
  - There was a higher proportion of patients with homologous recombination proficiency (HRp) in patients aged ≥65 years and ≥75 years
  - There was no significant difference in the rate of neoadjuvant chemotherapy between age groups

Table 1. Baseline Characteristics

	Niraparib, n (%)				Placebo, n (%)			
Parameter	<65 yr n=297	≥65 yr n=190	<75 yr n=433	≥75 yr n=54	<65 yr n=147	≥65 yr n=99	<75 yr n=224	≥75 yr n=22
ECOG PS								
0	218 (73.4)	119 (62.6)	309 (71.4)	28 (51.9)	108 (73.5)	66 (66.7)	162 (72.3)	12 (54.5)
1	79 (26.6)	71 (37.4)	124 (28.6)	26 (48.1)	39 (26.5)	33 (33.3)	62 (27.7)	10 (45.5)
Cancer stage (FIGO) at time of initial diagnosis								
III	192 (64.6)	126 (66.3)	286 (66.1)	32 (59.3)	89 (60.5)	69 (69.7)	143 (63.8)	15 (68.2)
IV	105 (35.4)	64 (33.7)	147 (33.9)	22 (40.7)	58 (39.5)	30 (30.3)	81 (36.2)	7 (31.8)
Homologous recombination test status								
HRd	173 (58.2)	74 (38.9)	222 (51.3)	25 (46.3)	88 (59.9)	38 (38.4)	120 (53.6)	6 (27.3)
HRp	88 (29.6)	81 (42.6)	148 (34.2)	21 (38.9)	41 (27.9)	39 (39.4)	71 (31.7)	9 (40.9)
HRnd	36 (12.1)	35 (18.4)	63 (14.5)	8 (14.8)	18 (12.2)	22 (22.2)	33 (14.7)	7 (31.8)
Best response to 1L platinum-based chemotherapy								
CR	187 (63.0)	135 (71.1)	281 (64.9)	41 (75.9)	93 (63.3)	74 (74.7)	150 (67.0)	17 (77.3)
PR	110 (37.0)	55 (28.9)	152 (35.1)	13 (24.1)	54 (36.7)	25 (25.3)	74 (33.0)	5 (22.7)
NACT								
Yes	206 (69.4)	131 (68.9)	304 (70.2)	33 (61.1)	102 (69.4)	70 (70.7)	161 (71.9)	11 (50.0)
No	91 (30.6)	59 (31.1)	129 (29.8)	21 (38.9)	45 (30.6)	29 (29.3)	63 (28.1)	11 (50.0)

1L, first line; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, homologous recombination not determined; NACT, neoadjuvant chemotherapy; PR, partial response; PS, performance status; yr, years.

- The efficacy of niraparib was comparable in patients <65 years and in those aged ≥65 years (Table 2), with niraparib leading to a significantly longer median PFS when compared with placebo
  - Similarly, niraparib efficacy was comparable in patients aged <75 years and in those aged ≥75 years, leading to a significantly longer median PFS when compared with placebo

Table 2. Efficacy of Niraparib vs Placebo by Age Category

	Niraparib		Placebo		PFS hazard ratio
	n	PFS, mo	n	PFS, mo	(95% CI)
Age, <65 yr	297	13.9	147	8.2	0.61 (0.47–0.81)
Age, ≥65 yr	190	13.7	99	8.1	0.53 (0.39–0.74)
Age, <75 yr	433	13.8	224	8.2	0.62 (0.50–0.77)
Age, ≥75 yr	54	13.8	22	5.6	0.37 (0.17–0.81)

mo, months; PFS, progression-free survival; yr, years.

- Treatment emergent adverse events (TEAEs) were similar in patients aged <65 years and ≥65 years, with events occurring more often in patients treated with niraparib than in those receiving placebo (Table 3)
  - TEAEs were also similar in patients aged <75 years and ≥75 years, with events occurring more frequently in patients treated with niraparib
  - A slight increase in thrombocytopenia was observed in patients aged ≥65 years and ≥75 years

Table 3. TEAEs by Age Group

	Niraparib, n (%)				Placebo, n (%)			
	<65 yr n=294	≥65 yr n=190	<75 yr n=430	≥75 yr n=54	<65 yr n=145	≥65 yr n=99	<75 yr n=222	≥75 yr n=22
Thrombocytopenia event[a]	187 (63.6)	134 (70.5)	279 (64.9)	42 (77.8)	8 (5.5)	4 (4.0)	11 (5.0)	1 (4.5)
Anemia event[b]	185 (62.9)	126 (66.3)	274 (63.7)	37 (68.5)	21 (14.5)	22 (22.2)	38 (17.1)	5 (22.7)
Leukopenia event[c]	152 (51.7)	89 (46.8)	214 (49.8)	27 (50.0)	21 (14.5)	11 (11.1)	29 (13.1)	3 (13.6)
Hypertension event[d]	50 (17.0)	37 (19.5)	76 (17.7)	11 (20.4)	7 (4.8)	10 (10.1)	14 (6.3)	3 (13.6)

[a]Includes thrombocytopenia and platelet count decreased; [b]Includes anemia, hemoglobin decreased, and anemia macrocytic; [c]Includes neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased, neutropenic sepsis, and febrile neutropenia; [d]Includes hypertension and blood pressure increased.
TEAE, treatment-emergent adverse event; yr, years.

- The rates of grade ≥3 TEAEs were also similar in patients aged <65 years and ≥65 years and similar in patients aged <75 years and ≥75 years, with a slight increase in grade ≥3 thrombocytopenia in patients aged ≥65 years and ≥75 years (Table 4)

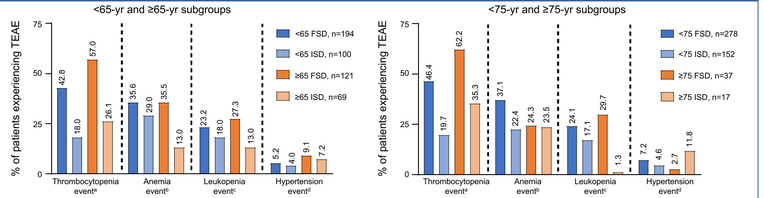
Table 4. Grade ≥3 TEAEs by Age Group

	Niraparib, n (%)				Placebo, n (%)			
	<65 yr n=294	≥65 yr n=190	<75 yr n=430	≥75 yr n=54	<65 yr n=145	≥65 yr n=99	<75 yr n=222	≥75 yr n=22
Thrombocytopenia event[a]	101 (34.4)	87 (45.8)	159 (37.0)	29 (53.7)	0	1 (1.0)	1 (0.5)	0
Anemia event[b]	98 (33.3)	52 (27.4)	137 (31.9)	13 (24.1)	1 (0.7)	3 (3.0)	3 (1.4)	1 (4.5)
Leukopenia event[c]	63 (21.4)	42 (22.1)	93 (21.6)	12 (22.2)	3 (2.1)	1 (1.0)	4 (1.8)	0
Hypertension event[d]	14 (4.8)	16 (8.4)	27 (6.3)	3 (5.6)	2 (1.4)	1 (1.0)	3 (1.4)	0

[a]Includes thrombocytopenia and platelet count decreased; [b]Includes anemia, hemoglobin decreased, and anemia macrocytic; [c]Includes neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased, neutropenic sepsis, and febrile neutropenia; [d]Includes hypertension and blood pressure increased.
TEAE, treatment-emergent adverse event; yr, years.

- A decrease in the rate of grade ≥3 thrombocytopenia events was seen in patients receiving ISD vs FSD (Figure 2)
  - With ISD implementation, rates of grade ≥3 thrombocytopenia were reduced from 42.8% to 18.0% in patients aged <65 years and from 57.0% to 26.1% in patients aged ≥65 years
  - Similarly, rates of grade ≥3 thrombocytopenia decreased from 46.4% to 19.7% in patients aged <75 years and from 62.2% to 35.3% in patients aged ≥75 years

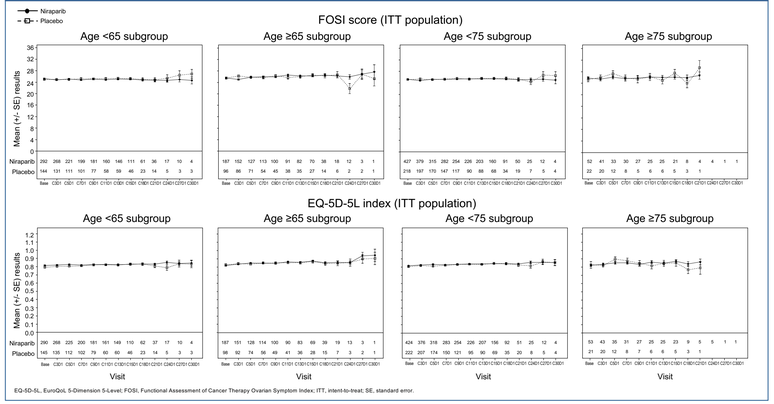
Figure 2. Grade ≥3 TEAEs by Age Group and Starting Dose Cohort in the Niraparib Arm



[a]Includes thrombocytopenia and platelet count decreased; [b]Includes anemia, hemoglobin decreased, and anemia macrocytic; [c]Includes neutropenia, neutrophil count decreased, leukopenia, white blood cell count decreased, neutropenic sepsis, and febrile neutropenia; [d]Includes hypertension and blood pressure increased.
FSD, fixed starting dose; ISD, individualized starting dose; TEAE, treatment-emergent adverse event; yr, years.

- PROs were similar between patients treated with niraparib and those treated with placebo for all age groups (Figure 3)

Figure 3. FOSI Score and EQ-5D-5L Index by Age Group



EQ-5D-5L, EuroQol 5-Dimension 5-Level; FOSI, Functional Assessment of Cancer Therapy Ovarian Symptom Index; ITT, intent-to-treat; SE, standard error.

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