Niraparib therapy in patients with newly diagnosed advanced ovarian cancer after chemotherapy: PRIMA/ENGOT-OV26/GOG-3012 Study

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ENGOT European Network of Gynaecological Oncological Trial groups

GEICO Grupo Español de Investigación en Cáncer de Ovario

GOG Gynecologic Oncology Group

Disclosures

Company Name	Honoria/ Expenses	Consultancy/ Advisory Board	Research Funding	Royalties/ Patents	Ownership/ Equity Position	Employee	Speaker Bureau/ Expert Testimony
AstraZeneca	X	X					X
Clovis Oncology		X					
Genmab		X					
Immunogen		X					
Merck Sharp & Dohme		X					
Oncoinvent		X					
Pfizer/Merck		X					
PharmaMar		X					X
Roche	X	X	X				X
TESARO: A GSK Company	X	X	X				X

PARPi: From Recurrent OC to 1L Setting

- Advanced ovarian cancer is a leading cause of cancer deaths in women with up to 85% recurrence after completion of standard first-line platinum-based chemotherapy[1]

- Niraparib was the first oral PARP inhibitor approved as maintenance for all patients with recurrent OC (*BRCA*mut and *BRCA*wt)
  - NOVA: g*BRCA*mut: hazard ratio 0.27 (95% CI 0.17–0.41, P<0.0001); non-g*BRCA*mut: hazard ratio 0.45 (95% CI 0.34–0.61, P<0.0001)[2]

- Recently, PARPi have shown efficacy in the 1L setting:
  - SOLO1: olaparib following response to 1L platinum in *BRCA*mut patients[3]
  - PRIMA: niraparib following response to 1L platinum in patients at high-risk of recurrence[4]
  - PAOLA: olaparib + bevacizumab (vs bevacizumab alone) following response to 1L platinum[5]
  - VELIA: veliparib + chemotherapy then veliparib maintenance (vs chemotherapy alone)[6]

1. GLOBOCAN, 2018; 2. Mirza, *NEJM* 2016; 3. Moore, *NEJM* 2018; 4. González-Martín, *NEJM* 2019; 5. Ray-Coquard, ESMO 2019; 6. Coleman, *NEJM* 2019.
1L, first line; CI, confidence interval; CT, chemotherapy; NACT, neoadjuvant chemotherapy; mut, mutant; OC, ovarian cancer; ORR, objective response rate; PARP, poly (ADP-ribose) polymerase; wt, wild-type.

PRIMA Was Designed to Address the Unmet Need in 1L Advanced OC

Hypothesis: PRIMA/ENGOT-OV26/GOG-3012 was designed to test the efficacy and safety of niraparib therapy after response to platinum-based chemotherapy in patients with newly diagnosed advanced ovarian cancer, including those at high risk of relapse (ClinicalTrials.gov: NCT02655016)

Key Inclusion Criteria

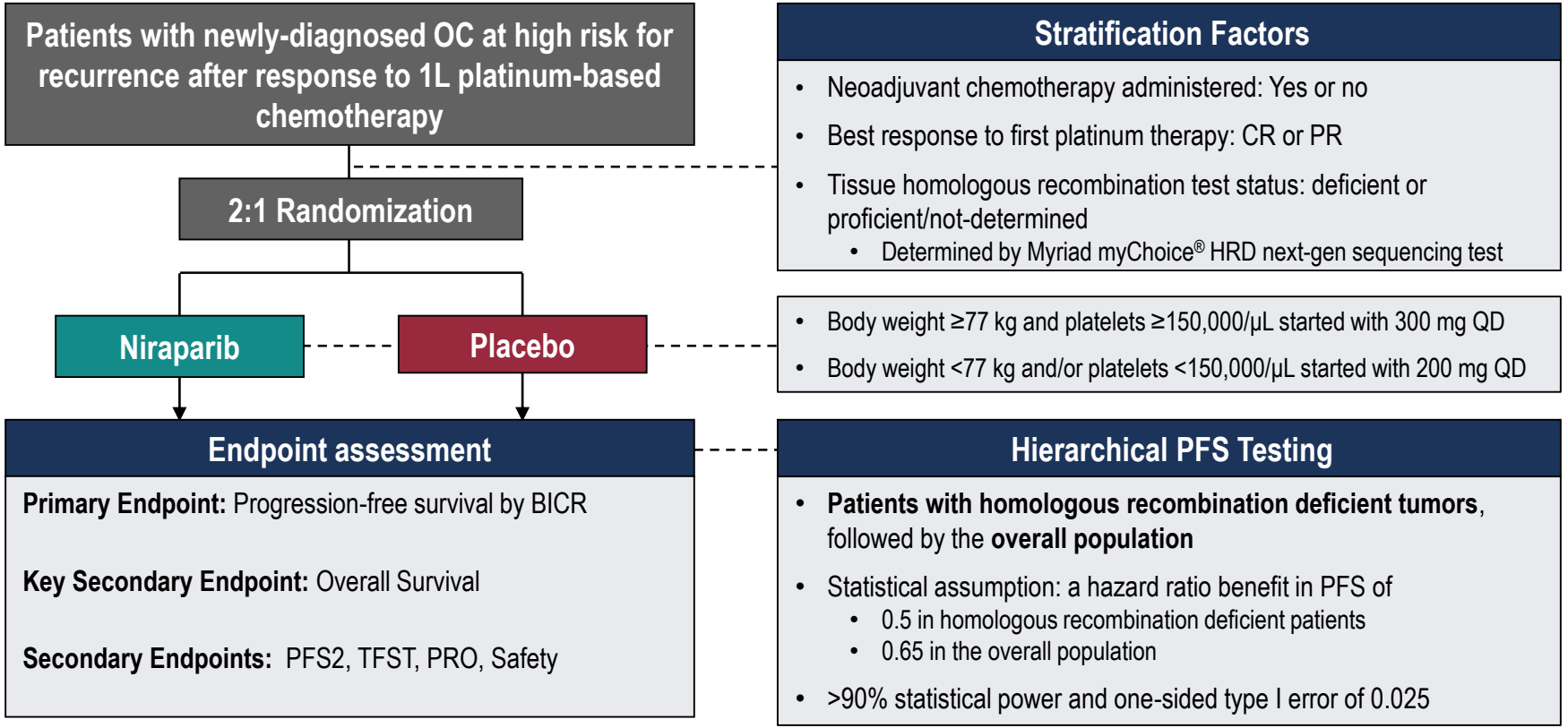
- High grade serous or endometroid pathology
- Stage III: PDS with visible residual disease post surgery, NACT, or inoperable
- Stage IV: PDS regardless of residual disease, NACT, or inoperable
- CR or PR following platinum first-line treatment
- Tissue for homologous recombination testing was required at screening (Myriad myChoice®)

Key Exclusion Criteria

- Patients with Stage III disease who have had complete cytoreduction (i.e., no visible residual disease) after PDS

1L, first-line; CR, complete response, NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PDS, primary debulking surgery, PR partial response.

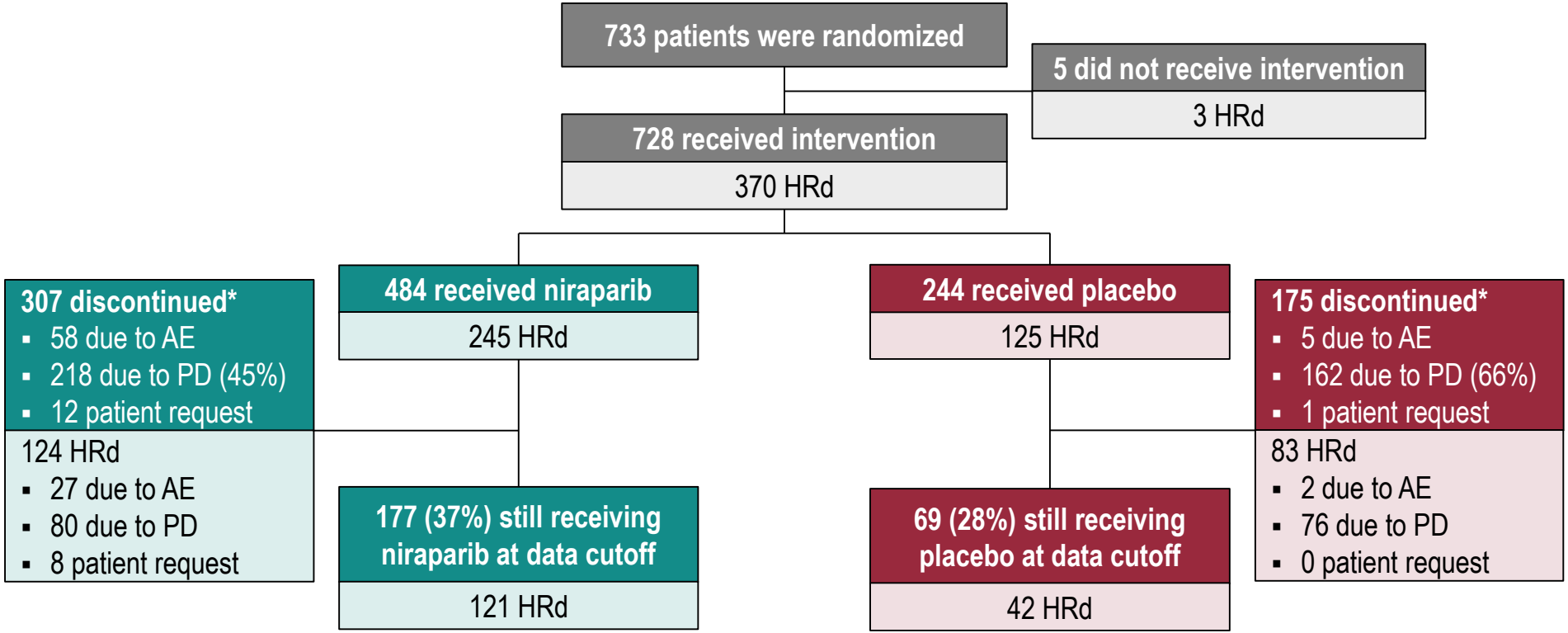
PRIMA Trial Design



https://myriadmychoice.com/portfolio/ovarian-cancer/mychoice-hrd-ovarian-cancer/#result

1L, first-line; BICR, blinded independent central review; CR, complete response; OC, ovarian cancer; PFS2, progression-free survival 2; PR partial response; PRO, patient-reported outcomes; QD, once daily; TFST, time to first subsequent therapy.

PRIMA Enrollment and Outcomes



Median follow up of 13.8 months

*19 patients (8 HRd) and 7 patients (5 HRd) discontinued due to other reasons in the niraparib and placebo arms, respectively.
AE, adverse event, HRd, homologous recombination deficient, PD, progression of disease

PRIMA Patient Characteristics and Baseline Demographics

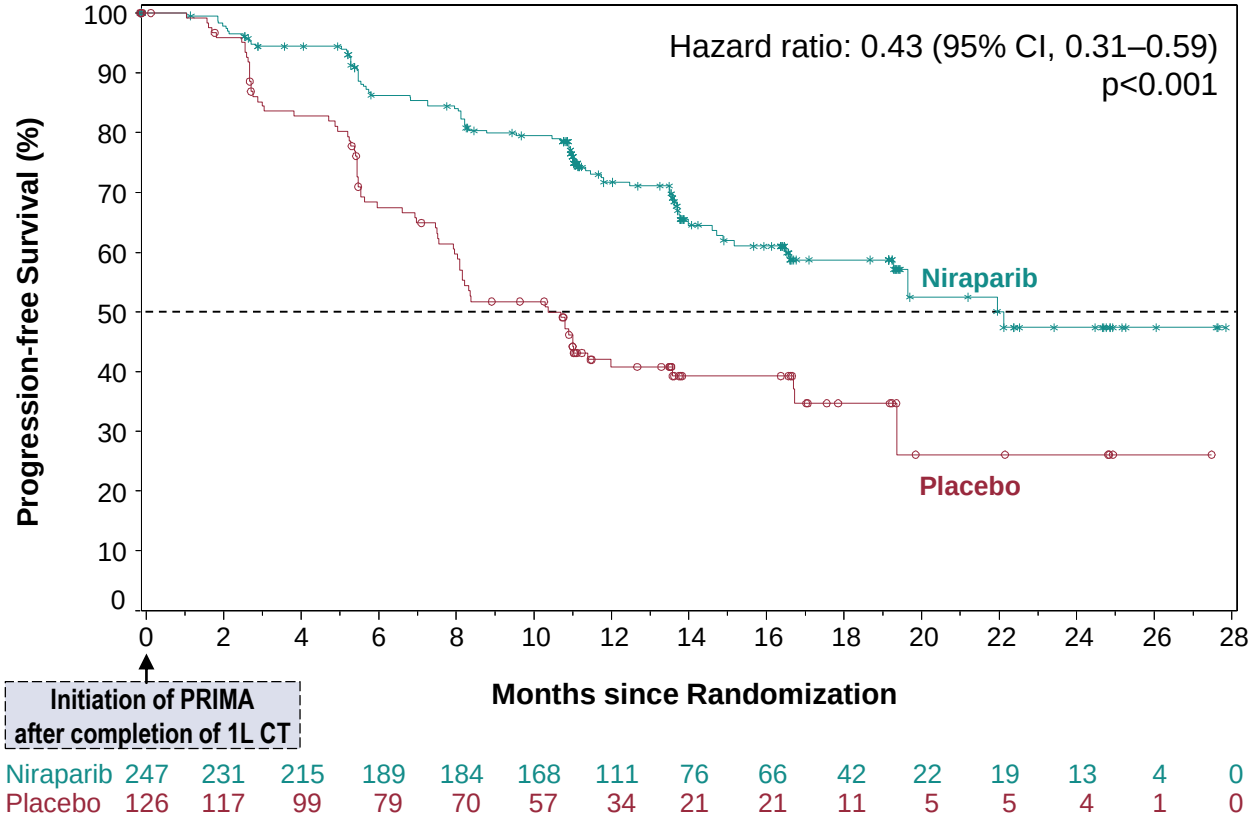
Characteristic	Niraparib (n=487)	Placebo (n=246)	Overall (N=733)
Age, median (range), years	62 (32, 85)	62 (33,88)	62 (32, 88)
Weight, median, kg	66	66	66
Stage at initial diagnosis, n (%)			
III	318 (65)	158 (64)	476 (65)
IV	169 (35)	88 (36)	257 (35)
Prior NACT, n (%)			
Yes	322 (66)	167 (68)	489 (67)
No	165 (34)	79 (32)	244 (33)
Best response to platinum-based CT, n (%)			
CR	337 (69)	172 (70)	509 (69)
PR	150 (31)	74 (30)	224 (31)
Residual disease after PDS or IDS*, n (%)			
No visible disease	224 (46)	117 (48)	341 (47)
Visible disease	220 (45)	112 (46)	332 (45)
No surgery	13 (3)	3 (1)	16 (2)
Homologous recombination test status, n (%)			
HRd	247 (51)	126 (51)	373 (51)
*BRCA*mut	152 (31)	71 (29)	223 (30)
*BRCA*wt	95 (20)	55 (22)	150 (20)
HRp	169 (35)	80 (33)	249 (34)
HRnd	71 (15)	40 (16)	111 (15)

- 35% of patients were Stage IV
- 99.6% with Stage III had residual disease post PDS
- 67% received NACT
- 31% achieved a PR to 1L CT
- 51% had HRd tumors
- 30% had *BRCA*mut tumors
- 34% had HRp tumors

*44 patients had missing data (30 niraparib, 14 placebo)

1L, first-line; CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, homologous recombination not determined; IDS, interval debulking surgery; mut, mutation; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; PR, partial response; wt, wild-type.

PRIMA Primary Endpoint, PFS Benefit in the HR-deficient Population

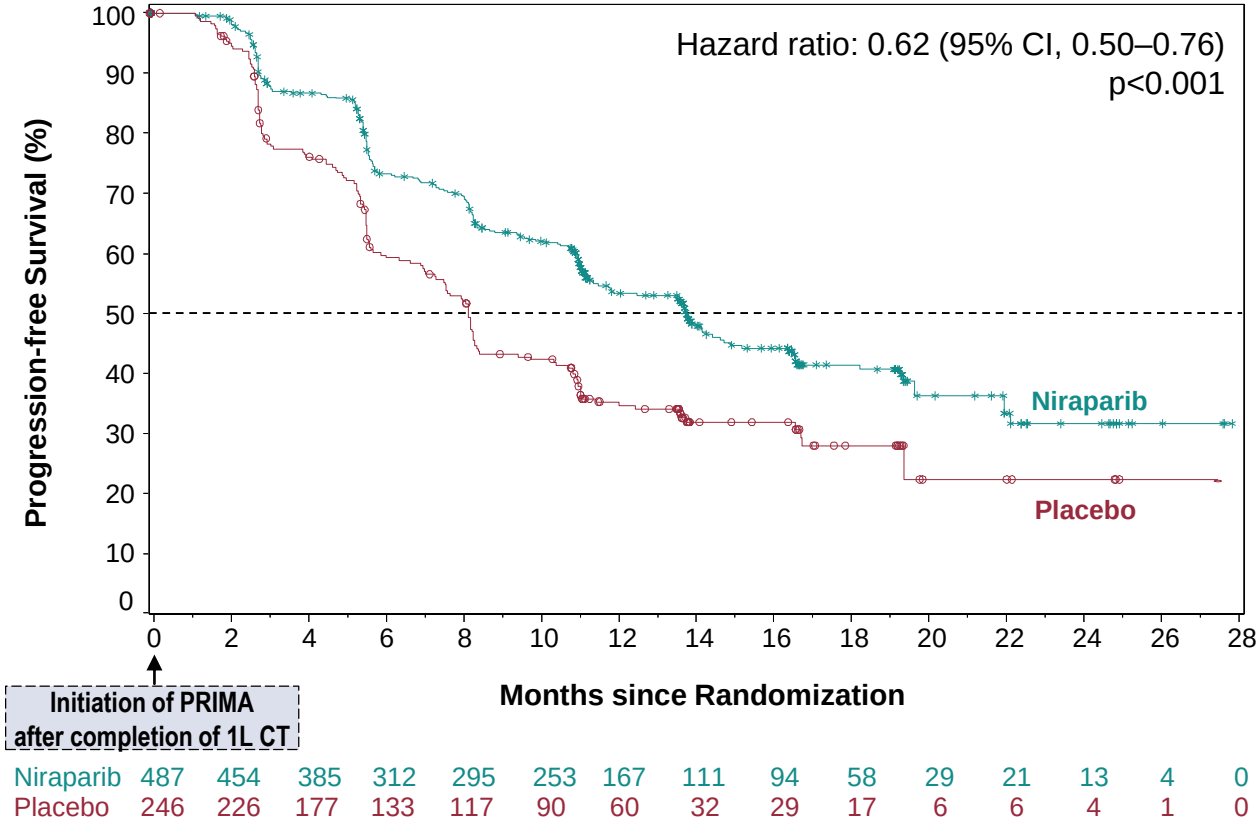


57% reduction in hazard of relapse or death with niraparib

	Niraparib (n=247)	Placebo (n=126)
Median PFS		
months (95% CI)	21.9 (19.3–NE)	10.4 (8.1–12.1)
Patients without PD or death (%)		
6 months	86%	68%
12 months	72%	42%
18 months	59%	35%

1L, first-line; CI, confidence interval; CT, chemotherapy; HR, homologous recombination; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population

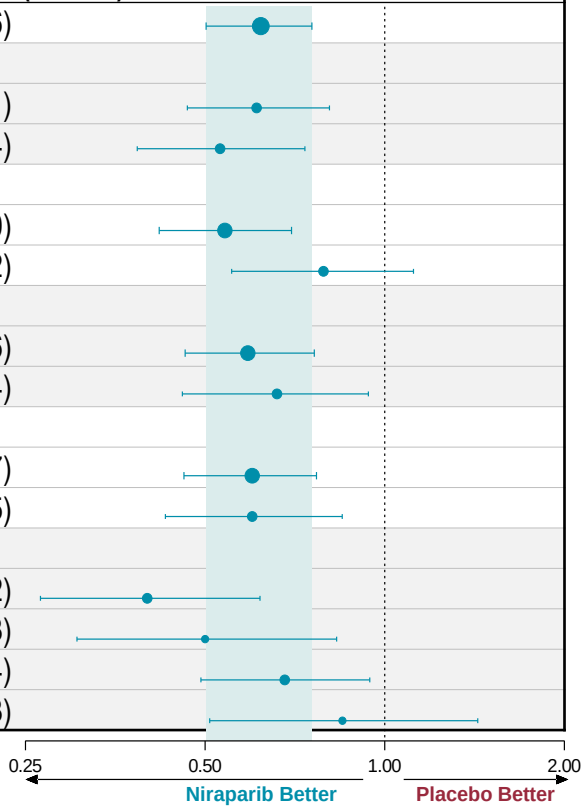


38% reduction in hazard of relapse or death with niraparib	Niraparib (n=487)	Placebo (n=246)
Median PFS		
months (95% CI)	13.8 (11.5–14.9)	8.2 (7.3–8.5)
Patients without PD or death (%)		
6 months	73%	60%
12 months	53%	35%
18 months	42%	28%

1L, first-line; CI, confidence interval; CT, chemotherapy; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

PRIMA Exploratory Analysis, PFS Benefit in Pre-specified Groups

	Hazard ratio for PFS (95% CI)
	0.62 (0.50–0.76)
Age group	
<65 years	0.61 (0.47–0.81)
≥65 years	0.53 (0.38–0.74)
Stage of disease at initial diagnosis	
III	0.54 (0.42–0.70)
IV	0.79 (0.55–1.12)
Neoadjuvant chemotherapy	
Yes	0.59 (0.46–0.76)
No	0.66 (0.46–0.94)
Best response to platinum therapy	
CR	0.60 (0.46–0.77)
PR	0.60 (0.43–0.85)
Homologous recombination status	
HRd–*BRCA*mut	0.40 (0.27–0.62)
HRd–*BRCA*wt	0.50 (0.31–0.83)
HRp	0.68 (0.49–0.94)
HRnd	0.85 (0.51–1.43)



- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provide clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

CI, confidence interval; CR, complete response; HRd, homologous recombination deficient; HRp, homologous recombination proficient; HRnd, homologous recombination not determined; mut, mutation; PFS, progression-free survival; PR, partial response; wt, wild-type.

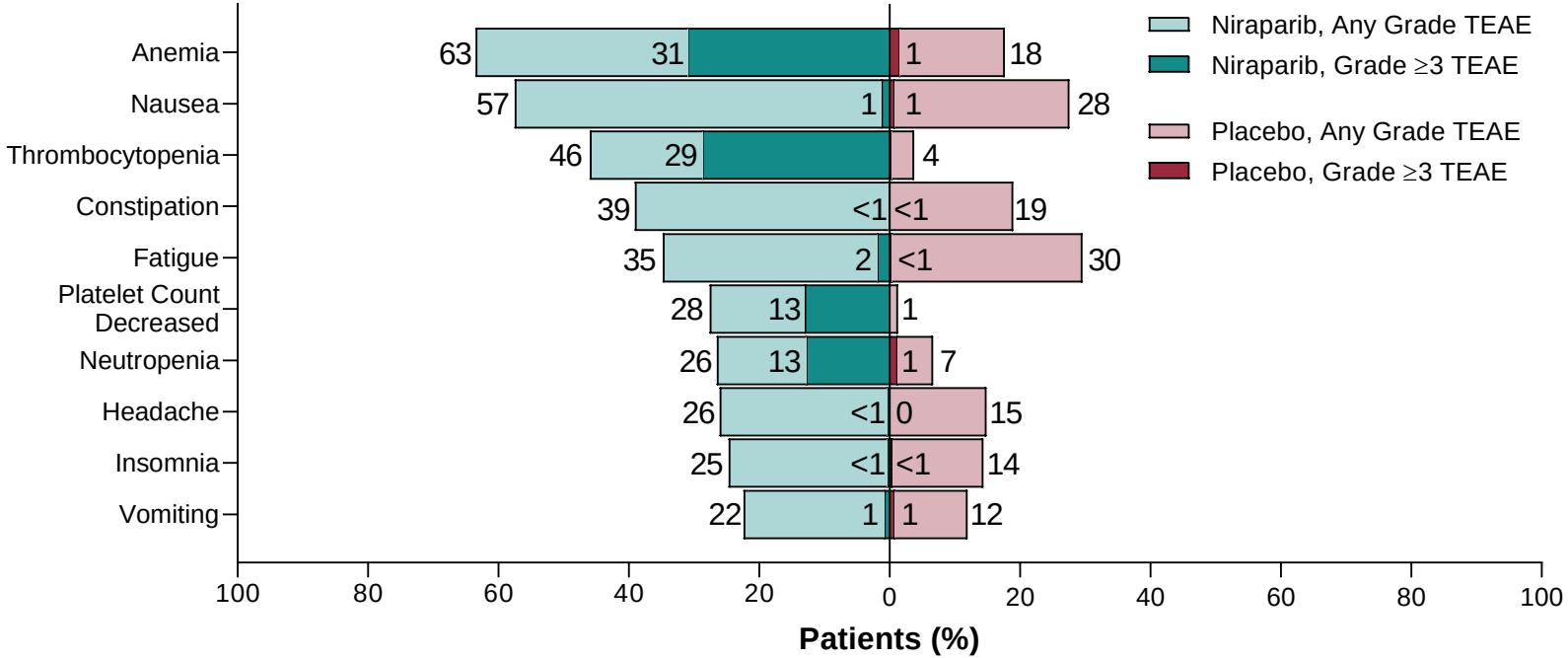
PRIMA Safety Overview

Adverse Event, no. (%)	Niraparib (n=484)	Placebo (n=244)
Any TEAE	478 (98.8)	224 (91.8)
Grade ≥3	341 (70.5)	46 (18.9)
Led to treatment discontinuation	58 (12.0)	6 (2.5)
Led to dose reduction	343 (70.9)	20 (8.2)
Led to dose interruption	385 (79.5)	44 (18.0)
TEAEs leading to death	2 (0.4)	1 (0.4)

- TEAEs were manageable and consistent with the PARP inhibitor class
- Dose interruptions were similar to those in the previous niraparib trials
- Treatment discontinuation due to thrombocytopenia was 4.3%
- TEAEs leading to death were determined to be not treatment-related

PARP, poly(ADP-ribose) polymerase; TEAE, treatment-emergent adverse event.

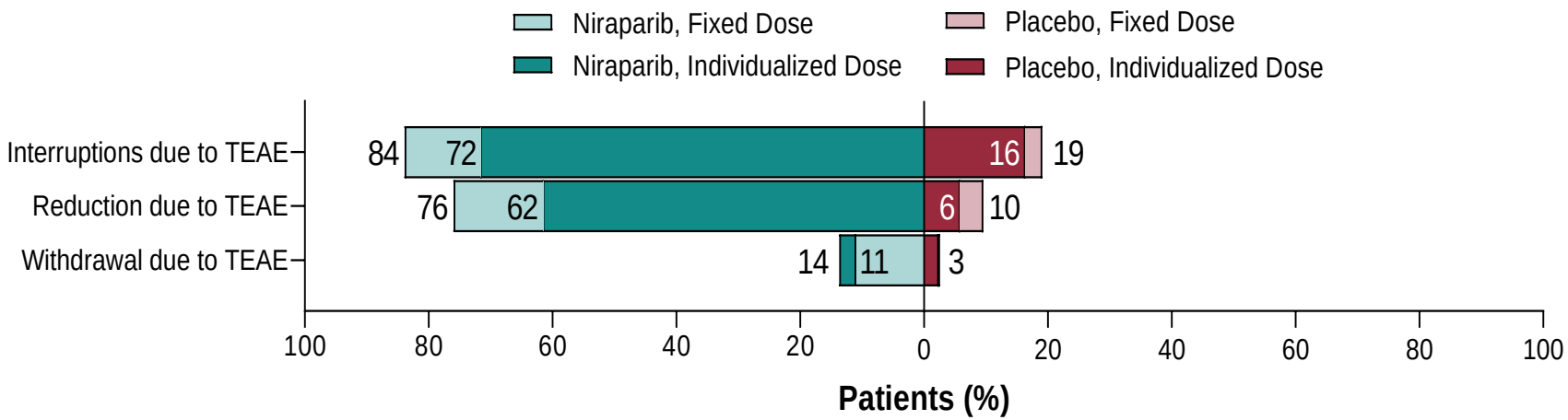
PRIMA TEAE Incidence



- No new safety signals were identified for niraparib
- Most common TEAE was reversible myelosuppression
- One patient was diagnosed with MDS after 9 months of niraparib treatment

TEAEs >20% incidence in niraparib arm. MedDRA preferred terms.
MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

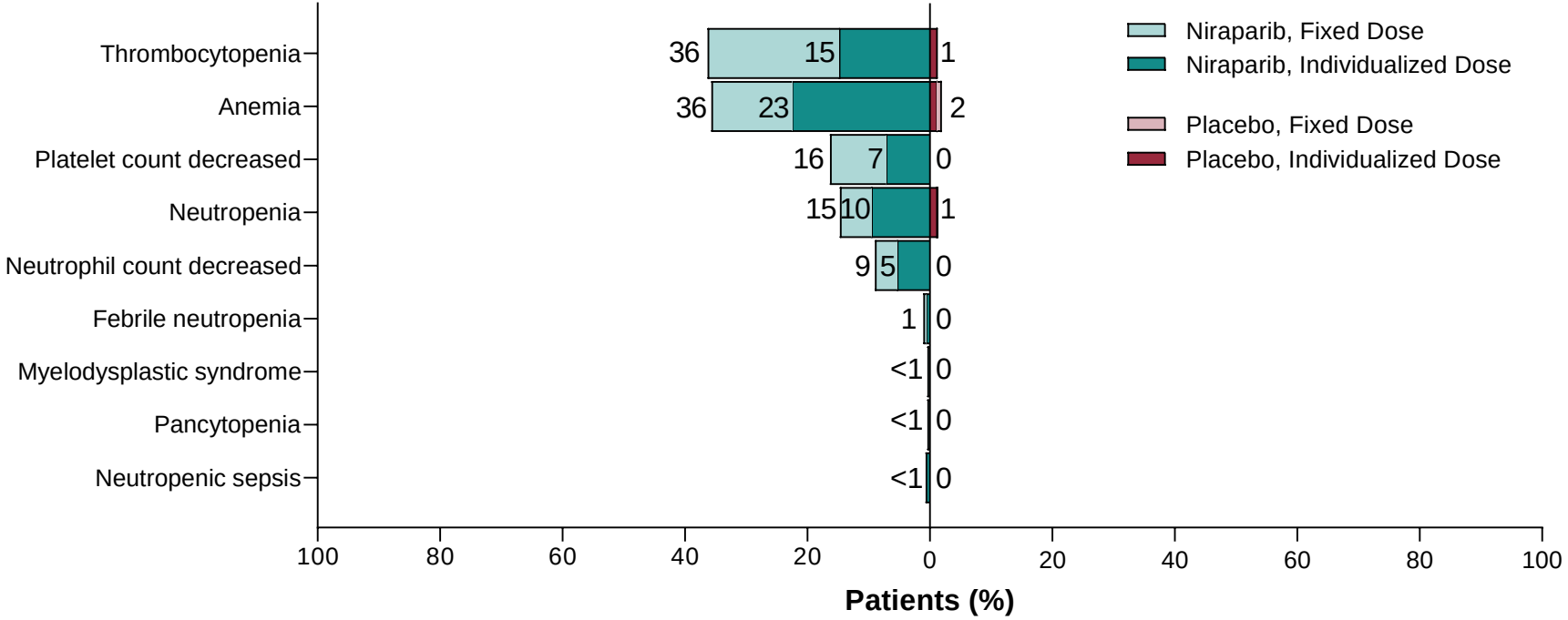
PRIMA TEAE, Fixed vs. Individualized Dosing



- Dose interruptions and reductions due to TEAEs were lower in patients who received an individualized dose of niraparib

TEAE, treatment-emergent adverse event.

PRIMA Grade ≥3 Hematologic TEAEs, Fixed vs. Individualized Dosing



- Incidence of grade ≥3 hematologic TEAEs were lower in patients who received an individualized dose of niraparib

MedDRA preferred terms.
TEAE, treatment-emergent adverse event.

PRIMA Conclusions

- Available therapies and active surveillance do not address the high unmet need for many patients with newly diagnosed advanced ovarian cancer after platinum-based chemotherapy

- Niraparib therapy in patients with advanced ovarian cancer provided a clinically significantly improvement in PFS after response to 1L platinum-based chemotherapy in **ALL** patients
    - PFS overall population: hazard ratio, 0.62; p<0.001
    - PFS homologous recombination deficient: hazard ratio, 0.43; p<0.001
    - PFS *BRCA*mut: hazard ratio, 0.40

- Niraparib demonstrates benefit in patients across biomarker subgroups after platinum-based chemotherapy in frontline, consistent with prior clinical studies of niraparib in recurrent ovarian cancer (NOVA and QUADRA)

- Patients with ovarian cancer at the highest risk of early disease progression (NACT, partial responders to 1L platinum chemotherapy) had significant benefit with niraparib therapy

- No new safety signals were observed, and quality of life was maintained on niraparib

- Niraparib monotherapy after first-line platinum-based chemotherapy should be considered a new standard of care

1L, first-line; NACT, neoadjuvant chemotherapy; PFS, progression-free survival

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ESGO European Society of Gynaecological Oncology
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