Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer (PRIMA/ENGOT-OV26/GOG-3012)

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Disclosures

Advisory/Consultancy

AstraZeneca, Clovis Oncology, Genmab, ImmunoGen, Merck Sharp & Dohme, Oncoinvent, Pfizer/Merck, PharmaMar, Roche, TESARO: A GSK Company

Speaker Bureau/Expert Testimony

AstraZeneca, PharmaMar, Roche, TESARO: A GSK Company

Research Grant/Funding

Roche, TESARO: A GSK Company

Travel/Accommodation/Expenses

AstraZeneca, Roche, TESARO: A GSK Company

Niraparib is Effective in Recurrent OC (*BRCA*mut and *BRCA*wt)

- 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]
- Despite current options for maintenance treatment, there is still a high unmet need for many patients
  - **Olaparib**: limited to patients with *BRCA* mutations; ≈20% of OC patients[2]
  - **Bevacizumab**: limited use due to safety concerns and limited data in the growing number of patients receiving NACT
  - **Active surveillance**: many patients undergo watchful waiting following chemotherapy
- Niraparib was the first oral PARP inhibitor approved as maintenance for all patients with recurrent OC (*BRCA*mut and *BRCA*wt)
  - NOVA study demonstrated efficacy of niraparib maintenance after platinum CT in all biomarker populations: g*BRCA*mut: hazard ratio 0.27 (95% CI 0.17–0.41, P<0.0001); homologous recombination deficient: hazard ratio 0.38 (95% CI 0.24–0.59, P<0.0001) and non-g*BRCA*mut: hazard ratio 0.45 (95% CI 0.34–0.61, P<0.0001)[3]
  - QUADRA study showed niraparib treatment benefit in patients with at least 3 prior therapies: *BRCA*mut 39% ORR, homologous recombination deficient 26% ORR, duration of response 9.4 months[4]

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.

1. GLOBOCAN, 2018; 2. Moore, NEJM 2018; 3. Mirza, NEJM 2016; 4. Moore, Lancet Oncol 2019.

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

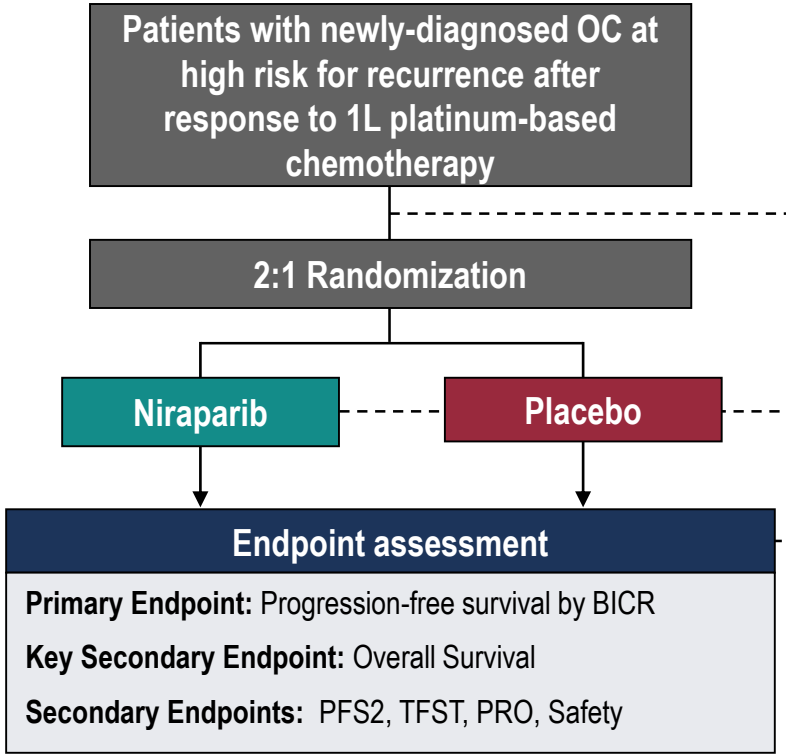
- High grade serous or endometroid pathology
- Stage III: PDS with visible residual disease post surgery, NACT, or inoperable
- Stage IV: PDS regardless of residual disease, NACT, or inoperable
- CR or PR following platinum first-line treatment
- Tissue for homologous recombination testing was required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

CR, complete response, HRD, homologous recombination deficiency; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; PDS, primary debulking surgery, PR partial response.

PRIMA Trial Design



Stratification Factors

- Neoadjuvant chemotherapy administered: Yes or no
- Best response to first platinum therapy: CR or PR
- Tissue homologous recombination test status: deficient or proficient/not-determined

- Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD
- Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

Hierarchical PFS Testing

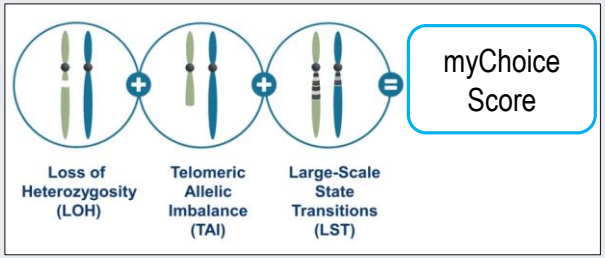
- **Patients with homologous recombination deficient tumors**, followed by the **overall population**.
- Statistical assumption: a hazard ratio benefit in PFS of
  - 0.5 in homologous recombination deficient patients
  - 0.65 in the overall population
- >90% statistical power and one-sided type I error of 0.025

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

PRIMA Tissue Test for Homologous Recombination

Testing for Homologous Recombination Deficiency (HRd) and Proficiency (HRp)

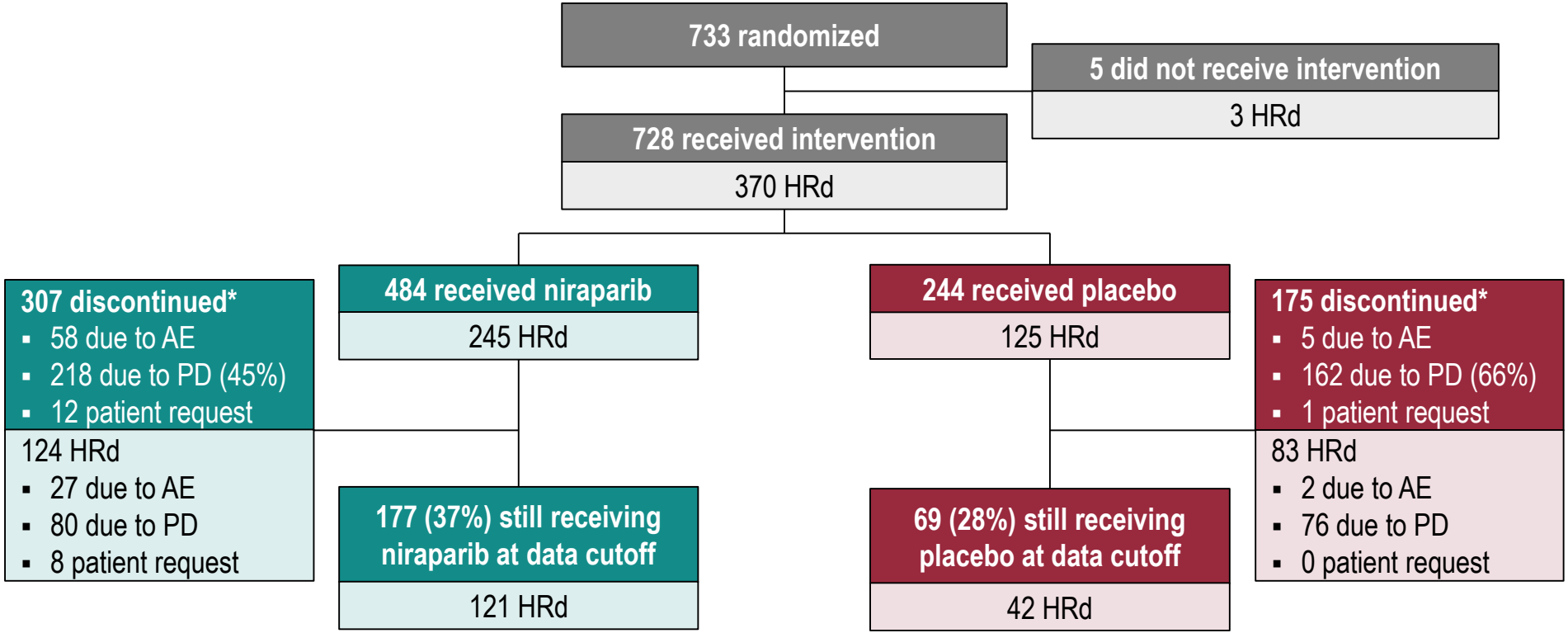
- Next generation sequencing of DNA from tumor tissue (Myriad Genetics myChoice® Test)
  - Provides a score based on algorithmic measurement of 3 tumor factors:
    - Loss of heterozygosity (LOH)
    - Telomeric allelic imbalance (TAI)
    - Large-scale state transitions (LST)
- Homologous recombination status is determined by the following:
  - HR-deficient tumors: Tissue test score ≥42 **OR** a *BRCA* mutation
  - HR-proficient tumors: Tissue test score <42
  - HR-not-determined



HRD, homologous recombination deficient

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

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

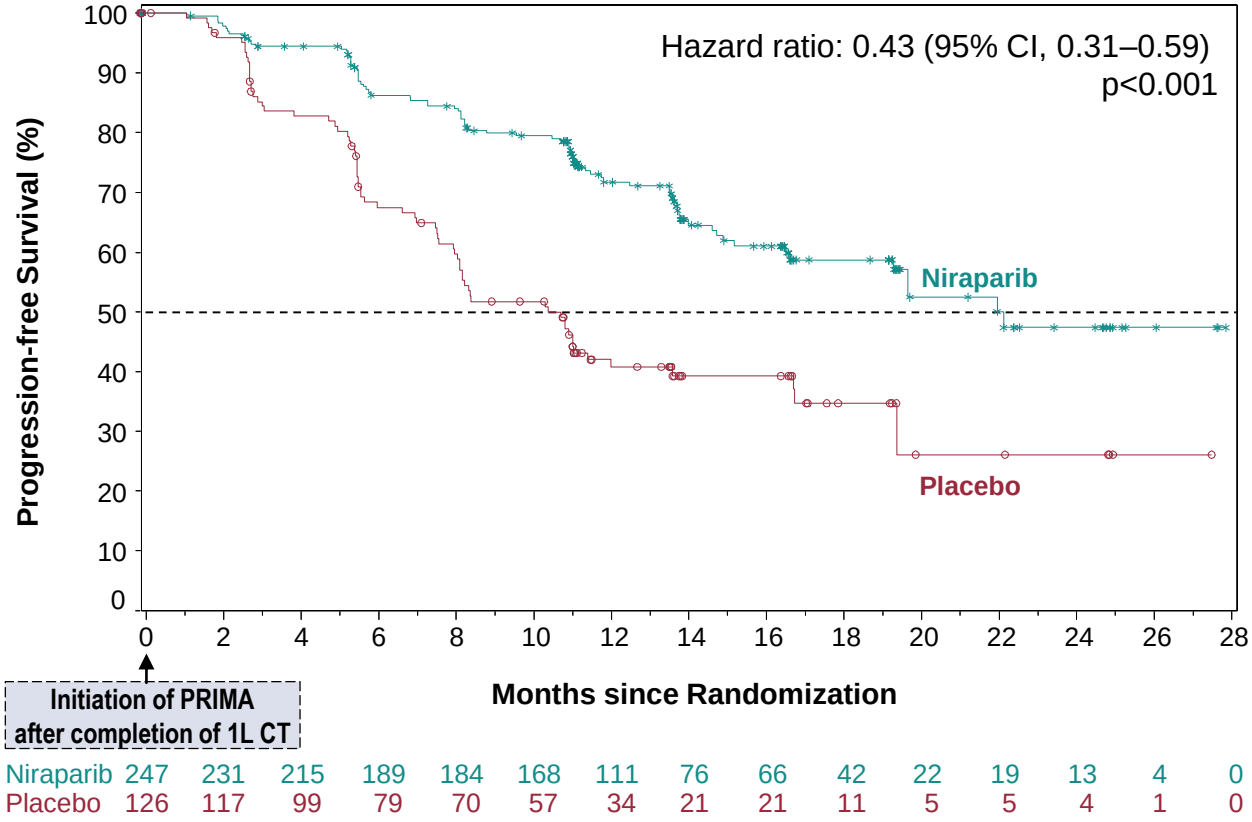
Characteristic	Niraparib (n=487)	Placebo (n=246)	Overall (N=733)
Age, median (range), years	62 (32, 85)	62 (33,88)	62 (32, 88)
Weight, median, kg	66	66	66
Stage at initial diagnosis, n (%)			
III	318 (65)	158 (64)	476 (65)
IV	169 (35)	88 (36)	257 (35)
Prior NACT, n (%)			
Yes	322 (66)	167 (68)	489 (67)
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)
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

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

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

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



57% reduction in risk 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%

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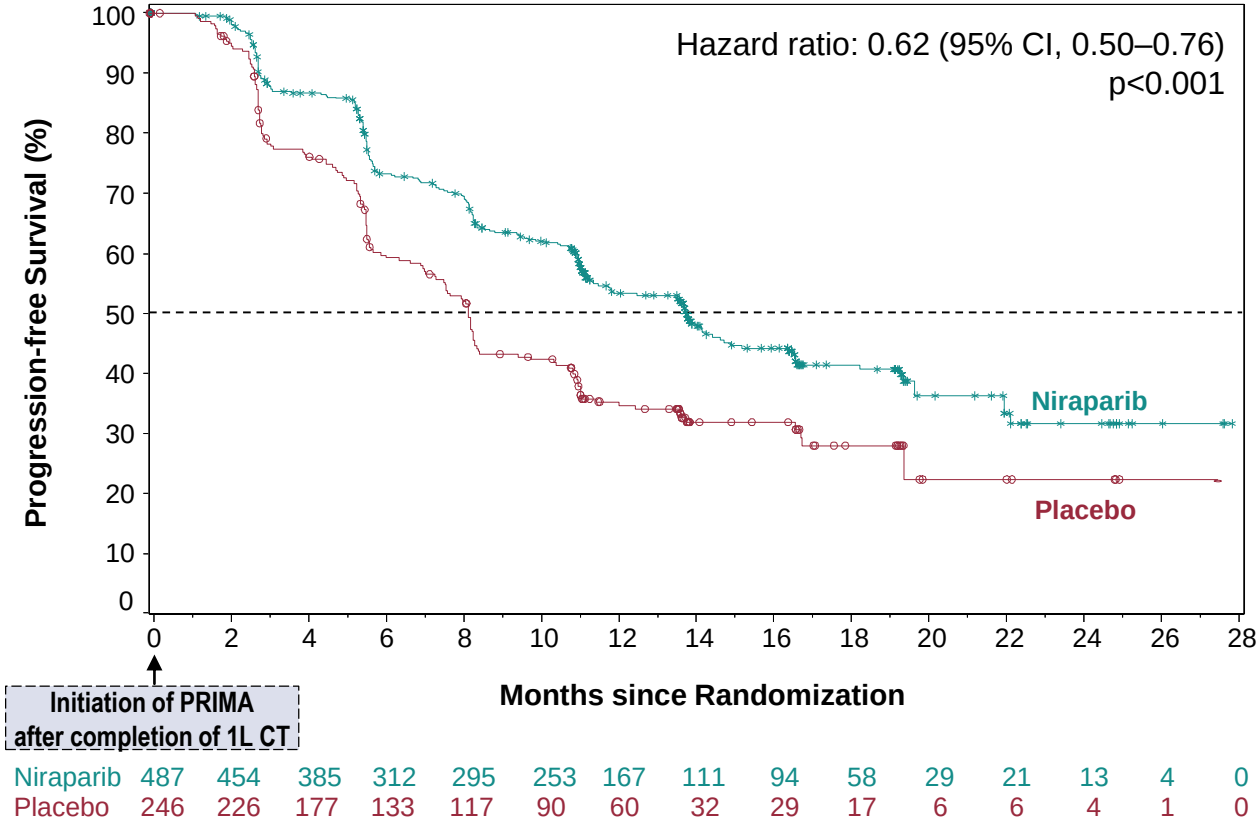
CI, confidence interval; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Sensitivity analysis of PFS by the investigator was similar to and supported the BICR analysis.

PRIMA Primary Endpoint, PFS Benefit in the Overall Population



38% reduction in risk 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%

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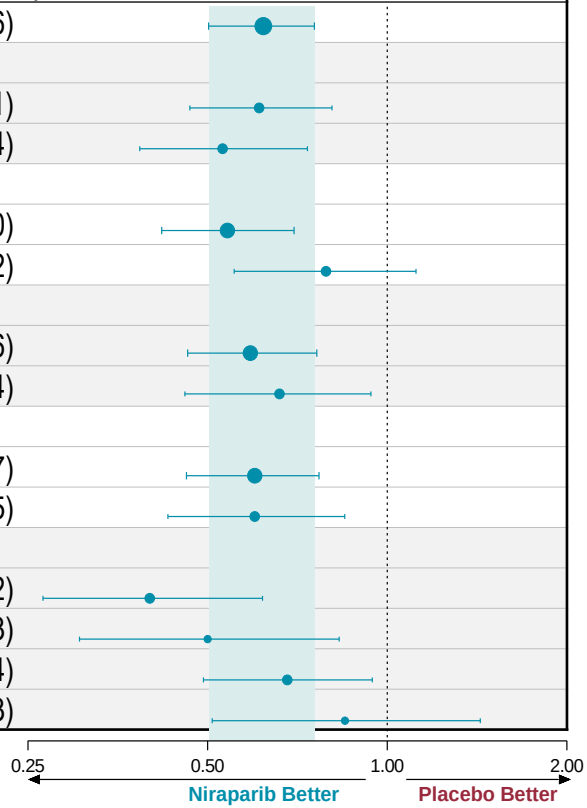
CI, confidence interval; NE, not estimable; PD, progressive disease; PFS, progression-free survival.
Discordance in PFS event between investigator assessment vs BICR ≈12%.

PRIMA Exploratory Analysis, PFS Benefit in Pre-specified Groups

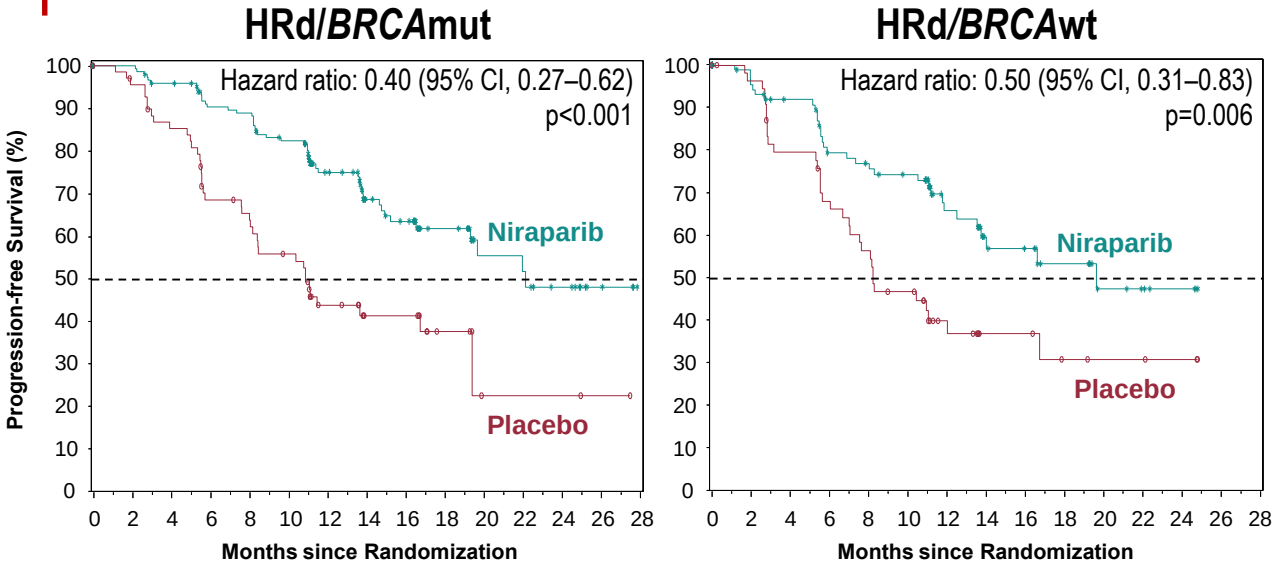
	HR for PFS (95% CI)
Overall	0.62 (0.50–0.76)
Age group	
<65 years	0.61 (0.47–0.81)
≥65 years	0.53 (0.38–0.74)
Stage of disease at initial diagnosis	
III	0.54 (0.42–0.70)
IV	0.79 (0.55–1.12)
Neoadjuvant chemotherapy	
Yes	0.59 (0.46–0.76)
No	0.66 (0.46–0.94)
Best response to platinum therapy	
CR	0.60 (0.46–0.77)
PR	0.60 (0.43–0.85)
Homologus 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)



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 PFS Benefit in Biomarker Subgroups

Homologous Recombination Deficient (HRd)

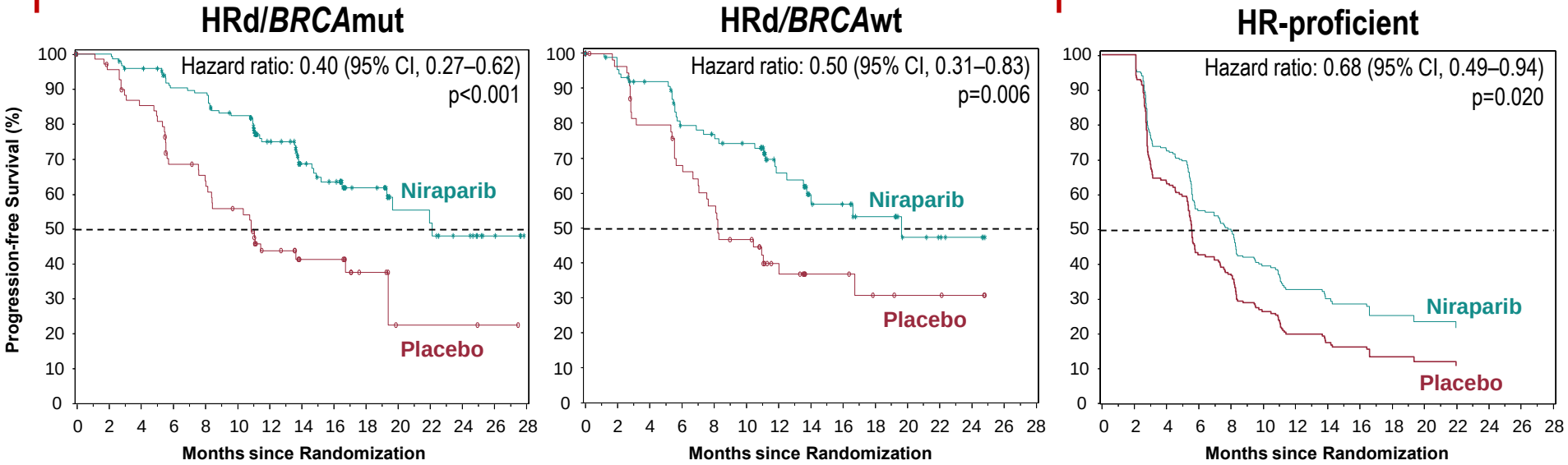


- Niraparib provided similar clinical benefit in the HRd subgroups (*BRCA*mut and *BRCA*wt)

CI, confidence interval; HRd, homologous recombination deficient; mut, mutation; PFS, progression-free survival wt, wild-type.

PRIMA PFS Benefit in Biomarker Subgroups

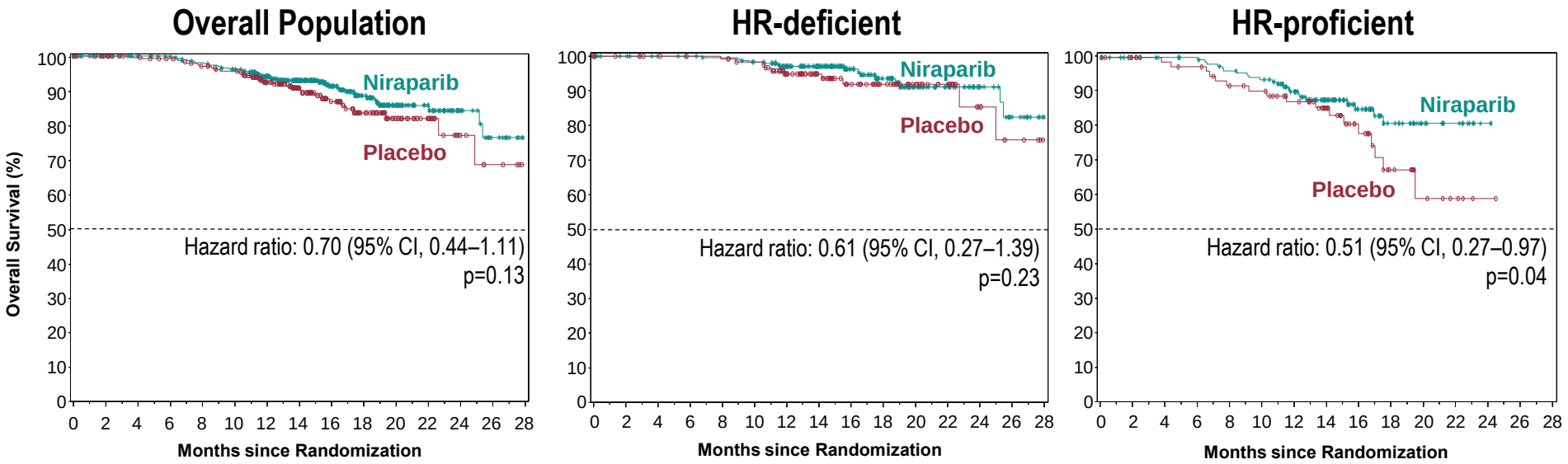
Homologous Recombination Deficient (HRd)



- 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; HRd, homologous recombination deficient; mut, mutation; PFS, progression-free survival wt, wild-type.

PRIMA Key Secondary Endpoint, Overall Survival (11% data maturity)



- **Pre-planned** interim analysis of overall survival numerically favors niraparib over placebo
  - Overall population 84% vs 77% alive at 2 years
  - HR-deficient 91% vs 85% alive at 2 years
  - HR-proficient 81% vs 59% alive at 2 years

CI, confidence interval; HR, homologous recombination.

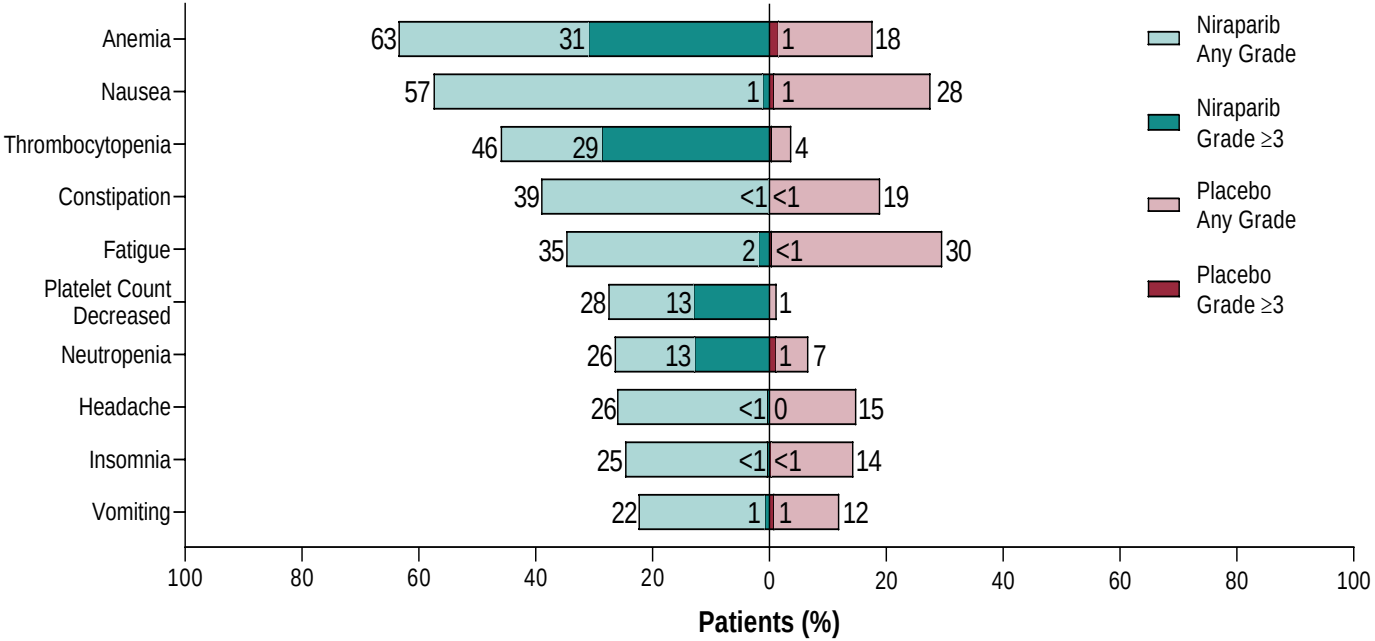
PRIMA Safety Overview

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.

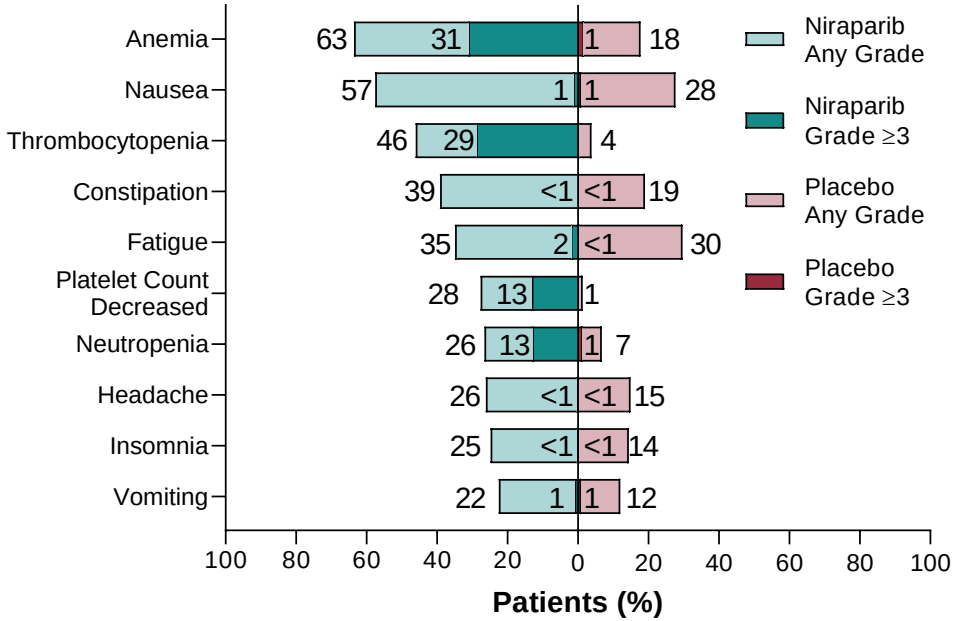
PRIMA Safety

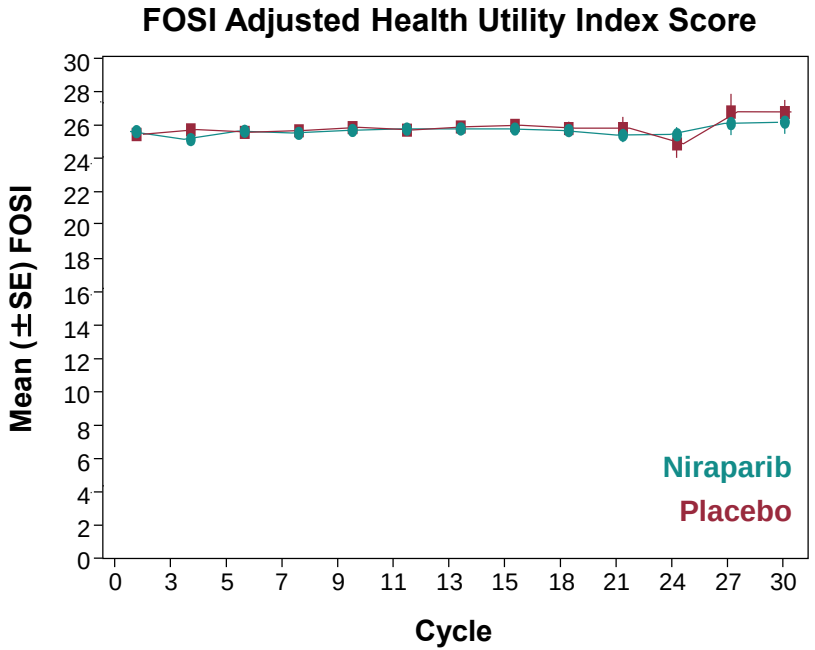


- No new safety signals were identified for niraparib
- Most common TEAE was reversible myelosuppression
- One patient was diagnosed with MDS after 9 months of niraparib treatment

TEAEs ≥20% incidence in niraparib arm. Note: Hematologic TEAEs are not combined with laboratory results
MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

PRIMA Safety and Patient-Reported Outcomes





- 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

- No impact in quality of life with niraparib treatment

TEAEs ≥20% incidence in niraparib arm. Note: Hematologic TEAEs are not combined with laboratory results
FOSI, FACIT ovarian cancer symptom index; MDS, myelodysplastic syndrome; 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 homologous recombination proficient: hazard ratio, 0.68; p=0.020

- Niraparib is **the first** PARP-inhibitor to demonstrate benefit in patients across biomarkers 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

Acknowledgements

We sincerely thank patients and their families for participating in this trial

ENGOT

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Belgium	**Spain**		**Germany**	**France**	**Israel**	**Finland**	**Denmark**	**Sweden**	**Italy**	**Ireland**	**UK**	**Poland**	**Czechia**	**Switzerland**	**Hungary**
J-F. Baurain	A. Oaknin	M. Gil Martin	I. Braicu	M. Fabbro	J. Korach	J. Maenpaa	U. Peen	K. Hellman	G. Artioli	P. Calvert	J. Krell	R. Madry	D. Cibula	P. Imesch	R. Poka
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D. O'Malley	E. Ratner	B. Slomovitz	V. Shirinkin	I. Lytvyn	A. Santillan-Gomez	A. Kumar	
L. Rojas	S. Ghamande	J. Press	A. Buiniakova	S. Shevnia	C. Bailey	D. Mirchandani	
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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

NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit

BGOG Belgian Gynaecological Oncology Group

MITO Multicentre Italian Trials in Ovarian cancer

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AGO Study Group

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ORIGINAL ARTICLE

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