Efficacy of Niraparib Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer by *BRCA*wt Status: PRIMA/ENGOT-OV26/GOG-3012 Study

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Dr. Braicu Disclosures

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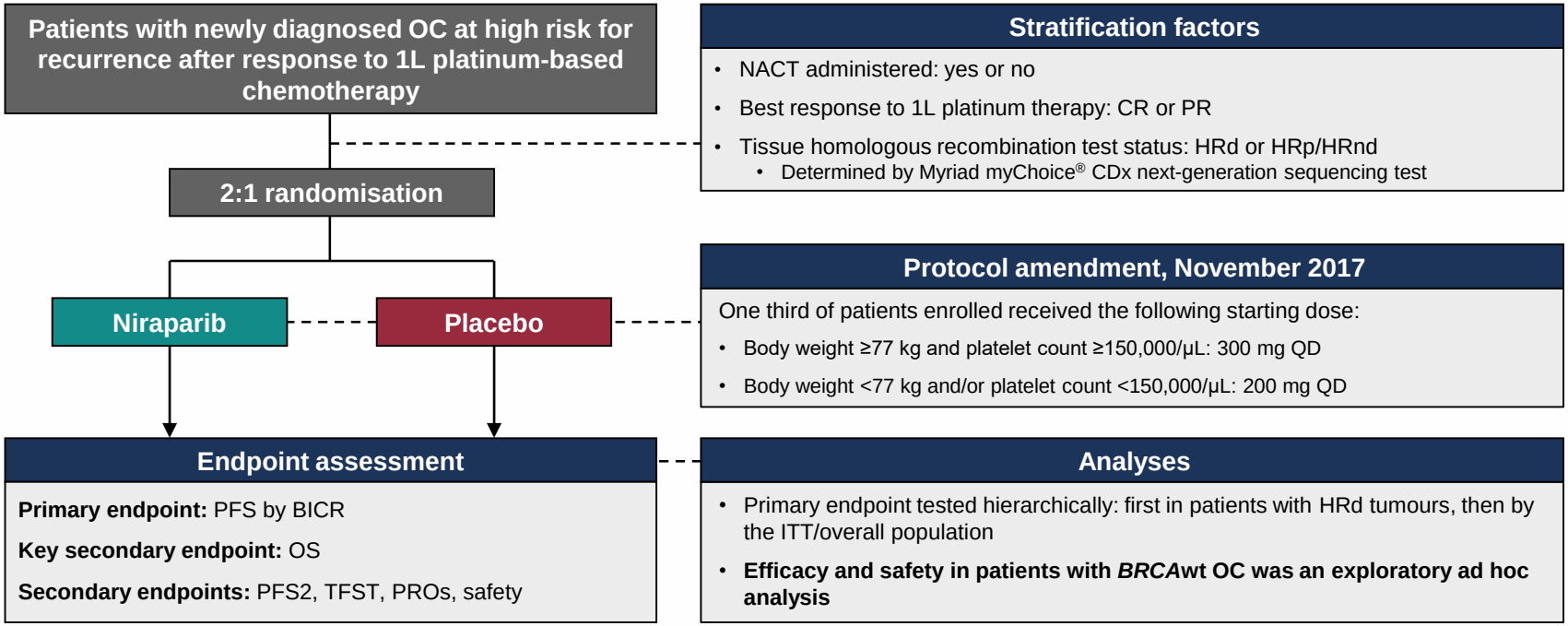
Background

- Niraparib is a PARP inhibitor approved in the US and EU for the maintenance treatment of patients with newly diagnosed advanced or recurrent ovarian cancer (OC)[1,2]
  - Niraparib is also approved in the US for the treatment of patients with advanced OC who received ≥3 lines of therapy and whose cancer is either *BRCA* mutated or homologous recombination deficient (HRd) platinum-sensitive[1]
- In the PRIMA/ENGOT-OV26/GOG-3012 trial, niraparib significantly improved progression-free survival (PFS) in patients with newly diagnosed advanced OC regardless of biomarker status[3]
  - Intention-to-treat/overall population: hazard ratio, 0.62; 95% CI, 0.50–0.76
  - HRd: hazard ratio, 0.43; 95% CI, 0.31–0.59
  - Homologous recombination proficient (HRp): hazard ratio, 0.68; 95% CI, 0.49–0.94
- *BRCA* wild-type (*BRCA*wt) OC accounts for approximately 75%–80% of patients with OC and is associated with poorer outcomes compared to patients with *BRCA*-mutated OC[4,5]
  - Treatments to improve outcomes in patients with *BRCA*wt OC represent an unmet need
- This ad hoc analysis explores efficacy and safety of niraparib in patients with *BRCA*wt advanced OC

1. GlaxoSmithKline. Zejula (niraparib) [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf. Revised April 2020. Accessed November 12, 2020; 2. GlaxoSmithKline. Zejula (niraparib) [summary of product characteristics]. https://www.ema.europa.eu/en/documents/product-information/zejula-epar-product-information_en.pdf. First authorisation November 16, 2017. Accessed November 22, 2020; 3. González-Martín A, et al. *N Engl J Med.* 2019;381:2391–2402; 4. Konstantinopoulos PA, et al. *J Clin Oncol.* 2010;28:3555–35615; 5. Huang YW. *Medicine (Baltimore).* 2018;97:e9380.

PRIMA Trial Design



1L, first line; BICR, blinded independent central review; CR, complete response; HRd, homologous recombination deficient; HRnd, homologous recombination status not determined; HRp, homologous recombination proficient; ITT, intention to treat; NACT, neoadjuvant chemotherapy; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival 2; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy; wt, wild-type.

PRIMA Patient Characteristics and Baseline Demographics

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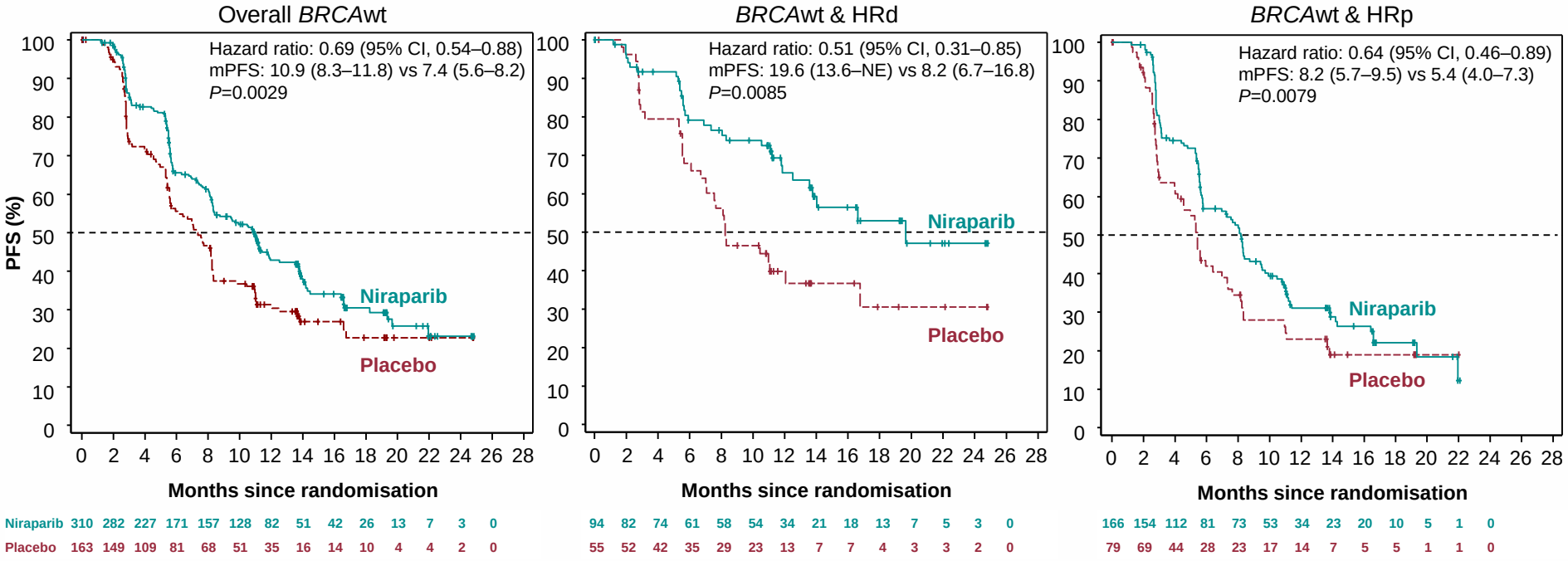
Characteristic	Overall *BRCA*wt[a]		*BRCA*wt & HRd		*BRCA*wt & HRp	
	Niraparib (n=310)	Placebo (n=163)	Niraparib (n=94)	Placebo (n=55)	Niraparib (n=166)	Placebo (n=79)
Age, median (range), years	63 (35–85)	63 (41–88)	61 (35–83)	59 (43–77)	64 (41–85)	64 (41–88)
Prior NACT, n (%)						
Yes	198 (63.9)	109 (66.9)	53 (56.4)	32 (58.2)	98 (59)	52 (65.8)
No	112 (36.1)	54 (33.1)	41 (43.6)	23 (41.8)	68 (41)	27 (34.2)
Best response to platinum-based CT, n (%)						
CR	210 (67.7)	113 (69.3)	72 (76.6)	40 (72.7)	101 (60.8)	51 (64.6)
PR	100 (32.3)	50 (30.7)	22 (23.4)	15 (27.3)	65 (39.2)	28 (35.4)
Homologous recombination test status, n (%)						
HRd	94 (30.3)	55 (33.7)	94 (100)	55 (100)	0	0
HRp	166 (53.6)	79 (48.5)	0	0	166 (100)	79 (100)
HRnd	50 (16.1)	29 (17.8)	0	0	0	0

May 2019 data cut. [a]HRD status was unknown for 79 patients; therefore, *BRCA*wt and HRd/HRp do not add up to overall *BRCA*wt.
CR, complete response; CT, chemotherapy; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; NACT, neoadjuvant chemotherapy; PR, partial response; wt, wild-type.

PFS by BICR in *BRCA*wt



May 2019 data cut. BICR, blinded independent central review; HRd, homologous recombination deficient; HRp, homologous recombination proficient; mPFS, median progression-free survival; NE, not evaluable; PFS, progression-free survival; wt, wild-type.

Ad hoc *BRCA*wt Subgroups

- Niraparib exposure time in the fixed starting dose (FSD) group was longer than in the individualised starting dose (ISD) group

	Niraparib n/N	Placebo n/N	Hazard ratio for PFS (95% CI)
Overall	170/310	108/163	0.69 (0.54–0.88)
Starting dose cohort			
FSD	105/199	73/106	0.62 (0.46–0.85)
ISD	65/111	35/57	0.84 (0.55–1.28)
Age category			
<65	91/174	56/87	0.72 (0.51–1.01)
≥65	79/136	52/76	0.62 (0.43–0.89)
ECOG performance status			
0	105/214	69/107	0.64 (0.47–0.88)
1	65/96	39/56	0.78 (0.52–1.18)
Neoadjuvant chemotherapy			
Yes	107/198	75/109	0.64 (0.48–0.87)
No	63/112	33/54	0.78 (0.51–1.19)
Best response to first platinum regimen			
CR	108/210	68/113	0.72 (0.53–0.98)
PR	62/100	40/50	0.56 (0.38–0.85)

PFS measured by blinded, independent central review. May 2019 data cut. Circle size corresponds to the number of events. Horizontal lines represent 95% CIs.
CR, complete response; ECOG, Eastern Cooperative Oncology Group; FSD, fixed starting dose; ISD, individualised starting dose; PFS, progression-free survival; PR, partial response; wt, wild-type.

PRIMA Safety Overview—*BRCA*wt

- No new safety signals were identified

Adverse Event, n (%)	Niraparib (n=307)	Placebo (n=162)
Any TEAE	304 (99)	147 (90.7)
Grade ≥3	223 (72.6)	31 (19.1)
SAE	105 (34.2)	22 (13.6)
TEAE leading to treatment discontinuation	39 (12.7)	4 (2.5)
TEAE leading to dose reduction	222 (72.3)	12 (7.4)
TEAE leading to dose interruption	249 (81.1)	30 (18.5)
TEAE leading to death	1 (0.3)	1 (0.6)

May 2019 data cut.
SAE, serious adverse event; TEAE, treatment-emergent adverse event; wt, wild-type.

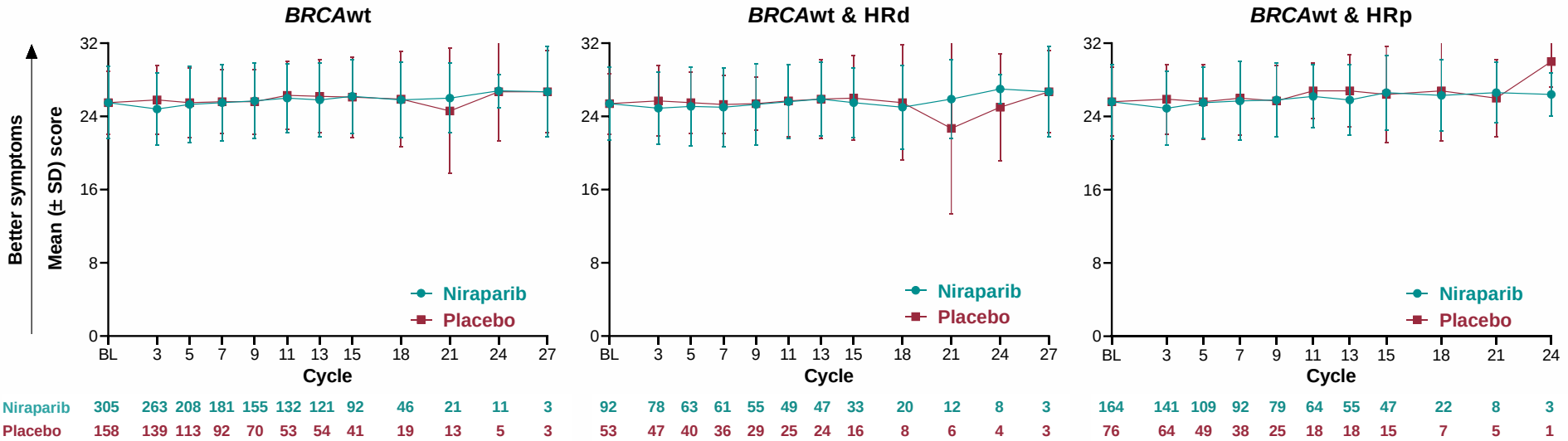
PRIMA Safety by Starting Dose—*BRCA*wt

- Implementation of ISD improved the overall safety profile and reduced grade ≥3 hematological adverse events (AEs)
  - Thrombocytopenia events were reduced by approximately 50%

	Niraparib		Placebo	
Grade ≥3 Adverse Event, n (%)	**FSD N=197**	**ISD N=110**	**FSD N=106**	**ISD N=56**
Thrombocytopenia event[a]	94 (47.7)	26 (23.6)	0	1 (1.8)
Anemia	76 (38.6)	20 (18.2)	2 (1.9)	1 (1.8)
Neutropenia event[b]	49 (24.9)	18 (16.4)	1 (0.9)	1 (1.8)
Hypertension event[c]	10 (5.1)	8 (7.3)	1 (0.9)	0

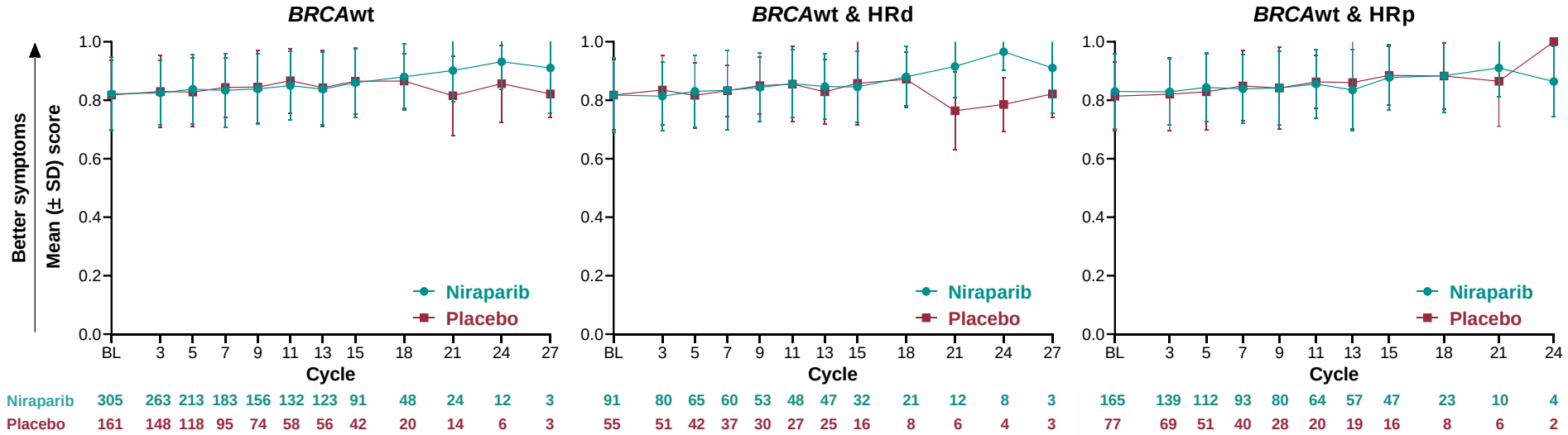
May 2019 data cut. [a]Thrombocytopenia event includes reports of thrombocytopenia and platelet count decreased; [b]Neutropenia event includes reports of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; [c]Hypertension event includes hypertension and blood pressure increased.
FSD, fixed starting dose; ISD, individualised starting dose; wt, wild-type.

PRIMA PRO—FOSI in *BRCA*wt



May 2019 data cut.
BL, baseline; FOSI, Functional Assessment of Cancer Therapy—Ovarian Symptom Index; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PRO, patient reported outcome; SD, standard deviation; wt, wild-type.

PRIMA PRO—EQ-5D-5L in *BRCA*wt



May 2019 data cut.
BL, baseline; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PRO, patient-reported outcome; SD, standard definition; wt, wild-type.

Conclusions

- Patients with newly diagnosed advanced OC with *BRCA*wt derived a clinically meaningful PFS benefit from niraparib maintenance treatment

- Patients with *BRCA*wt and HRd OC achieved a greater PFS benefit than those with *BRCA*wt and HRp OC, consistent with the overall niraparib efficacy profile observed across biomarker subgroups
  - *BRCA*wt and HRd hazard ratio: 0.51 (95% CI, 0.31–0.85)
  - *BRCA*wt and HRp hazard ratio: 0.64 (95% CI, 0.46–0.89)

- Patients who received an ISD experienced an improved overall safety profile and fewer grade ≥3 hematologic AEs than those who received an FSD
  - Thrombocytopenia events were approximately 50% lower in patients who received an ISD vs FSD

- PRO measurements showed that general quality of life was maintained for *BRCA*wt patients who received niraparib relative to placebo

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ENGOT European Network of Gynaecological Oncological Trial groups
GEICO Grupo Español de Investigación en Cáncer de Ovario
AGO Study Group
BGOG
NSGO-CTU Nordic Society of Gynaecological Oncology - Clinical Trial Unit
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