Niraparib in Patients With Newly Diagnosed Advanced Ovarian *BRCA*m Cancer: A Post Hoc Analysis of the PRIMA/ENGOT-OV26/GOG-3012 Trial

Jacob Korach,[1] Whitney Graybill,[2] Andrés Redondo,[3] David M. O'Malley,[4] Sileny Han,[5] Noelle Cloven,[6] Anja Ør Knudsen,[7] Stanislav Lechpammer,[8] Antonio Gonzalez-Martin,[9] Bradley J. Monk[10]

[1]Gynecology Oncology Department, Sheba Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [2]Gynecologic Oncology Group (GOG) and Gynecologic Oncology, Medical University of South Carolina, Charleston, SC, USA; [3]Hospital La Paz Institute for Health Research, Hospital Universitario La Paz, Madrid, Spain; [4]Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital, Columbus, OH, USA; [5]Department of Gynaecology and Obstetrics, University Hospital Leuven, Leuven, Belgium; [6]Texas Oncology, Fort Worth, TX, USA; [7]Department of Oncology, Odense University Hospital, Odense, Denmark; [8]GlaxoSmithKline, Waltham, MA, USA; [9]El Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain; [10]Arizona Oncology (US Oncology Network), College of Medicine, University of Arizona, and School of Medicine, Creighton University, Phoenix, AZ, USA

Dr. Korach Disclosures

- Dr. Korach has nothing to disclose

Background

- The PRIMA/ENGOT-OV26/GOG-3012 trial showed that niraparib significantly improves progression-free survival (PFS) in patients with newly diagnosed advanced ovarian cancer (OC) that responded to first-line platinum-based chemotherapy (hazard ratio, 0.62; 95% CI, 0.50–0.76)[1]

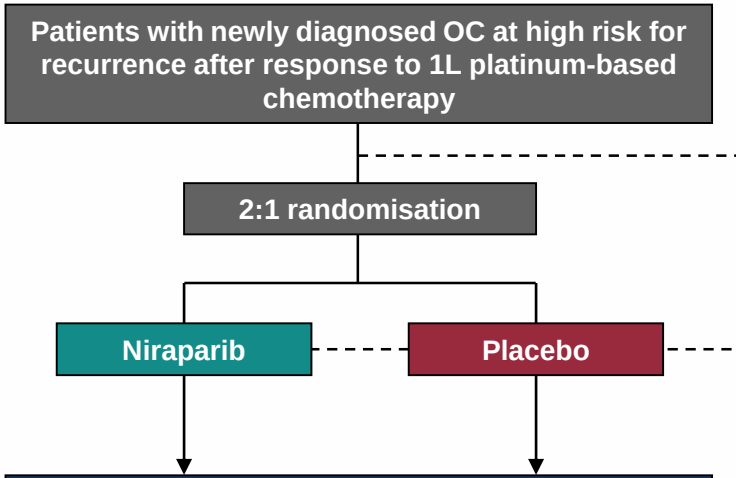
- On the basis of these results, niraparib has been approved in the US, EU, Canada, and Israel for maintenance treatment of patients with newly diagnosed advanced OC[2,3]

- *BRCA* mutations occur in approximately 20%–25% of patients with epithelial OC and are associated with improved outcomes in comparison with patients with *BRCA* wild-type OC[4,5]

- In this exploratory ad hoc analysis we report the efficacy of niraparib in the subgroup of patients with *BRCA* mutation (*BRCA*m) as determined from tumour samples

1. González-Martín A, et al. *N Engl J Med.* 2019;381:2391–2402; 2. GlaxoSmithKline. Zejula (niraparib) [prescribing information]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf. Revised April 2020. Accessed September 29, 2020; 3. 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 12, 2020; 4. Konstantinopoulos PA, et al. *J Clin Oncol.* 2010;28:3555–3561; 5. Huang YW. *Medicine (Baltimore)* 2018;97:e9380.

PRIMA Trial Design



Stratification factors

- NACT administered: yes or no
- Best response to 1L platinum therapy: CR or PR
- Tissue homologous recombination test status: HRd or HRp/HRnd
  - Determined by Myriad myChoice® CDx next-generation sequencing test

Protocol amendment, November 2017

One third of patients enrolled received the following individualized starting dose:

- Body weight ≥77 kg and platelet count ≥150,000/μL: 300 mg QD
- Body weight <77 kg and/or platelet count <150,000/μL: 200 mg QD

Endpoint assessment

Primary endpoint: PFS by BICR

Key secondary endpoint: OS

Secondary endpoints: PFS2, TFST, PROs, safety

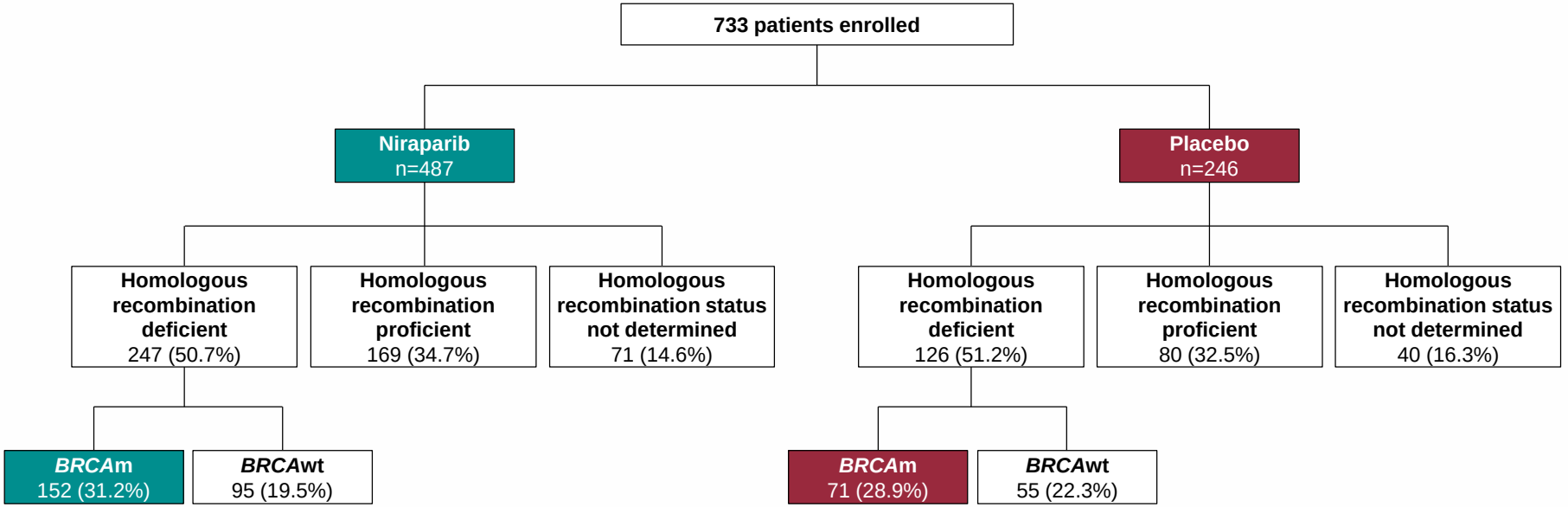
Analyses

- Primary endpoint tested hierarchically: first in patients with HRd tumours, then in the ITT/overall population
- **Efficacy and safety in patients with *BRCA*m OC and by starting dose cohort were exploratory ad hoc analyses**

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; m, mutant; 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.

PRIMA Enrollment by Biomarker

- Approximately 30% of enrolled patients had *BRCA*m OC



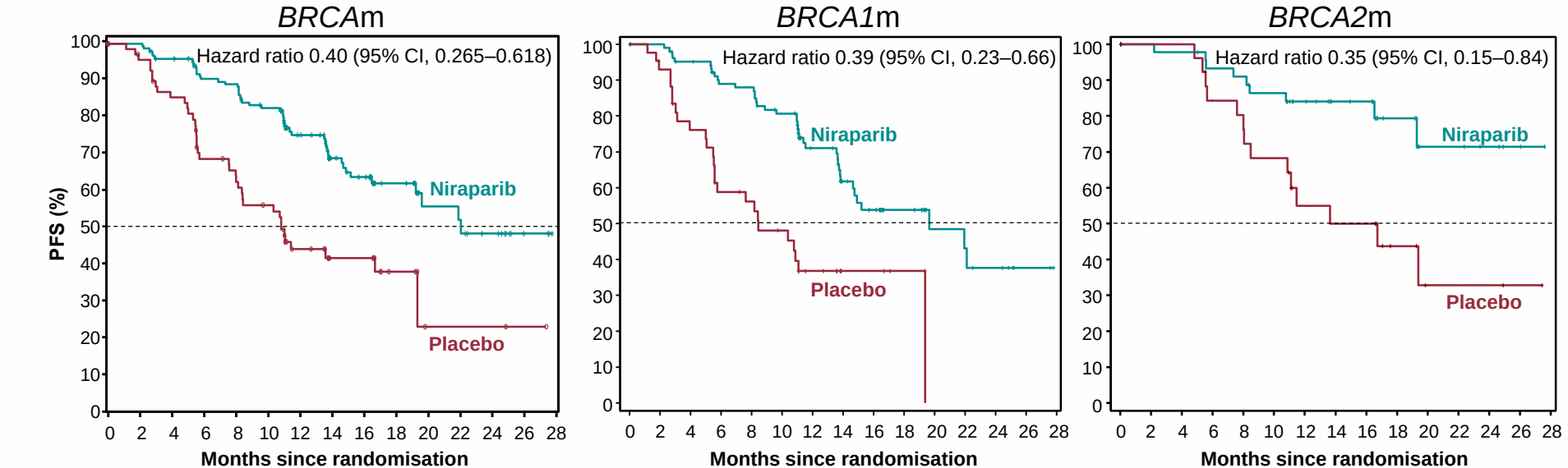
m, mutation; wt, wild-type.

PRIMA Patient Characteristics and Baseline Demographics

Characteristic	*BRCA*m	
	Niraparib (n=152)	Placebo (n=71)
Age, median (range), years	56.5 (32–83)	57 (33–82)
Weight, median, kg	65.7	65.2
Prior NACT, n (%)		
Yes	102 (67.1)	48 (67.6)
No	50 (32.9)	23 (32.4)
Best response to platinum-based CT, n (%)		
CR	113 (74.3)	53 (74.6)
PR	39 (25.7)	18 (25.4)
*BRCA*m status		
BRCA1 only	105 (69.1)	43 (60.6)
BRCA2 only	47 (30.9)	28 (39.4)
BRCA1 and *BRCA2*	0	0

CR, complete response; CT, chemotherapy; m, mutation; NACT, neoadjuvant chemotherapy; PR, partial response.

Background: Progression-Free Survival[1]



Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4	0
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1	0

Niraparib	105	103	96	86	85	76	48	32	26	17	9	8	6	2	0
Placebo	43	39	31	23	21	17	10	4	4	2	0				

Niraparib	47	45	44	41	40	37	29	23	22	12	6	6	4	2	0
Placebo	28	26	26	21	20	17	11	10	10	5	2	2	2	1	0

m, mutation; PFS, progression-free survival.

1. Monk, BJ, et al. *Gynecol Oncol.* 2020;159(suppl 1):18.

PRIMA Individualised Starting Dose (ISD) Cohorts

- Enrolled patients initially received a fixed starting dose (FSD) of 300 mg niraparib once daily
- In November 2017 a protocol amendment allowed for an ISD according to the criteria below

200-mg starting dose for patients with

Baseline body weight **<77 kg**

or

Baseline platelets **<150,000/μL**

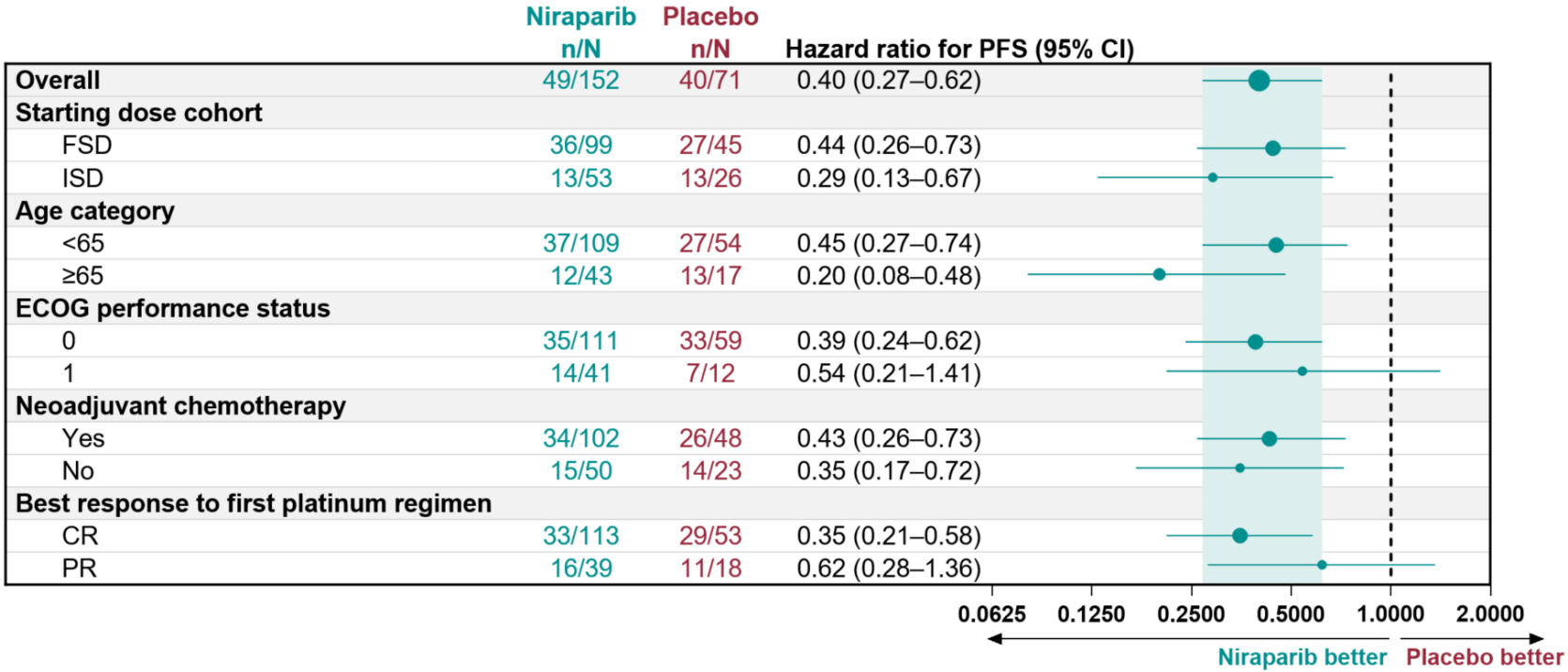
300-mg starting dose for patients with

Baseline body weight **≥77 kg**

and

Baseline platelets **≥150,000/μL**

Ad hoc *BRCA*m Subgroups



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; m, mutant; PFS, progression-free survival; PR, partial response.

PFS in *BRCA*m by Dose Cohorts

- PFS was comparable between the FSD and ISD dose cohorts

		FSD		ISD	
		Niraparib	Placebo	Niraparib	Placebo
PFS by blinded, independent central review (May 2019)	Median PFS (95% CI)	22.1 (19.3–NE)	11.1 (7.6–19.4)	14.8 (14.8–NE)	10.9 (5.6–NE)
	Hazard ratio (95% CI)	0.44 (0.26–0.73)		0.29 (0.13–0.67)	
	P value	0.0011		0.0021	
	Interaction *P* value	0.7406			
PFS by investigator assessment (November 2019)	Median PFS (95% CI)	24.8 (18.7–NE)	13.7 (7.9–19.2)	NE (16.5–NE)	11.2 (7.9–14.3)
	Hazard ratio (95% CI)	0.45 (0.29–0.71)		0.38 (0.19–0.74)	
	P value	0.0004		0.0029	
	Interaction *P* value	0.7050			

FSD, fixed starting dose; ISD, individualised starting dose; m, mutant; NE, not evaluable; PFS, progression-free survival.

PRIMA Safety Overview: *BRCA*m

- No new safety signals were identified

AE, n (%)	Niraparib (n=152)	Placebo (n=70)
Any TEAE	150 (98.7)	66 (94.3)
Grade ≥3	99 (65.1)	15 (21.4)
SAE	42 (27.6)	10 (14.3)
TEAE leading to treatment discontinuation	14 (9.2)	1 (1.4)
TEAE leading to dose reduction	103 (67.8)	7 (10.0)
TEAE leading to dose interruption	114 (75.0)	12 (17.1)
TEAE leading to death	1 (0.7)	0

AE, adverse event; m, mutant; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

PRIMA Any-Grade TEAEs: *BRCA*m

Any-grade AE affecting ≥25% of patients in the niraparib arm, n (%)	Niraparib		Placebo	
	FSD (n=99)	ISD (n=53)	FSD (n=45)	ISD (n=25)
Haematological AEs				
Thrombocytopenia event[a]	71 (71.1)	21 (39.6)	2 (4.4)	0
Anaemia	69 (69.7)	26 (49.1)	6 (13.3)	8 (32.0)
Neutropaenia event[b]	45 (45.5)	20 (37.7)	4 (8.9)	3 (12.0)
Non-haematological AEs				
Nausea	68 (68.7)	26 (49.1)	20 (44.4)	6 (24.0)
Constipation	47 (47.5)	8 (15.1)	14 (31.1)	7 (28.0)
Fatigue	39 (39.4)	13 (24.5)	18 (40.0)	11 (44.0)
Insomnia	31 (31.3)	10 (18.9)	10 (22.2)	5 (20.0)
Diarrhoea	28 (28.3)	6 (11.3)	9 (20.0)	7 (28.0)
Abdominal pain	27 (27.3)	9 (17.0)	15 (33.3)	10 (40.0)
Hypertension event[c]	25 (25.3)	7 (13.2)	4 (8.9)	5 (20.0)
Vomiting	25 (25.3)	8 (15.0)	6 (13.3)	4 (16.0)

[a]Thrombocytopenia event includes reports of thrombocytopenia and platelet count decreased; [b]Neutropaenia event includes reports of neutropaenia, neutrophil count decreased, febrile neutropaenia, and neutropaenic sepsis; [c]Hypertension event includes hypertension and blood pressure increased.
AE, adverse event; FSD, fixed starting dose; ISD, individualized starting dose; m, mutant; TEAE, treatment-emergent adverse event.

PRIMA Safety by Starting Dose: *BRCA*m

- Incorporation of an ISD improved the overall safety profile and reduced grade ≥3 thrombocytopenia approximately 60% in comparison with FSD

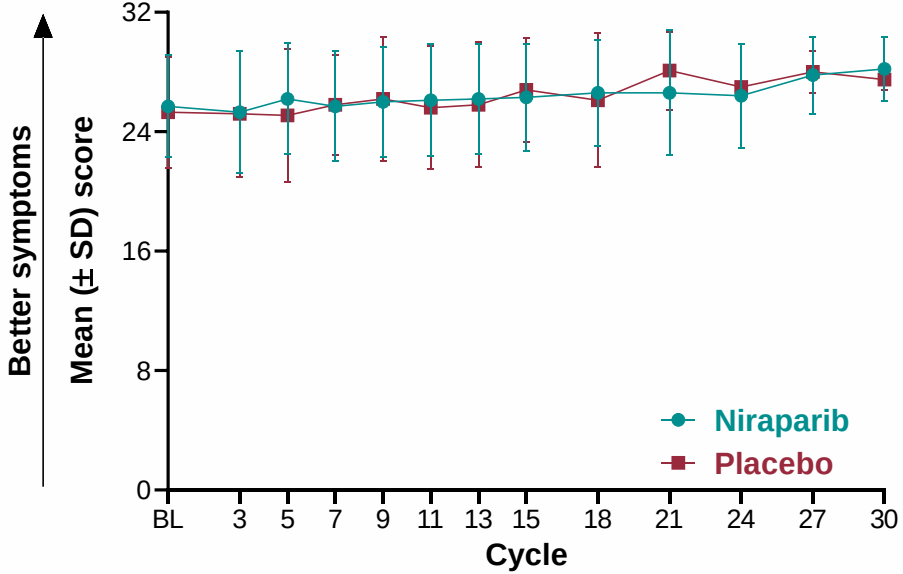
	Niraparib		Placebo	
Grade ≥3 AEs, n (%)	**FSD (n=99)**	**ISD (n=53)**	**FSD (N=45)**	**ISD (N=25)**
Thrombocytopenia event[a]	49 (49.5)	10 (18.9)	0	0
Anaemia	32 (32.3)	16 (30.2)	1 (2.2)	0
Neutropaenia event[b]	18 (18.2)	7 (13.2)	1 (2.2)	0
Hypertension event[c]	9 (9.1)	1 (1.9)	0	2 (8.0)

[a]Thrombocytopenia includes reports of thrombocytopenia and platelet count decreased; [b]Neutropaenia includes reports of neutropaenia, neutrophil count decreased, febrile neutropaenia, and neutropaenic sepsis; [c]Hypertension includes hypertension and blood pressure increased.
AE, adverse event; FSD, fixed starting dose; ISD, individualized starting dose; m, mutant.

PRIMA PRO in *BRCA*m Subgroup

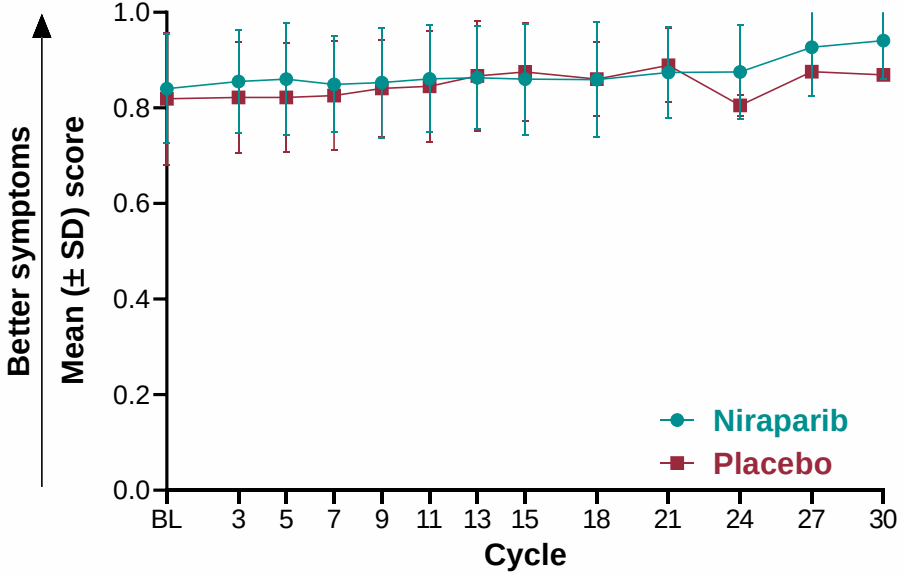
ESGO
European Society of Gynaecological Oncology

FOSI *BRCA*m



Niraparib	149	135	124	118	114	110	99	83	48	31	18	10	5
Placebo	70	67	59	55	45	38	36	28	16	7	2	2	2

EQ-5D-5L *BRCA*m



Niraparib	147	134	123	118	113	110	101	82	48	30	18	10	5
Placebo	70	67	59	55	47	38	36	28	16	7	2	2	2

BL, baseline; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FOSI, Functional Assessment of Cancer Therapy—Ovarian Symptom Index; m, mutation; PRO, patient-reported outcome; SD, standard deviation.

Conclusions

- Patients with advanced OC carrying *BRCA* mutations derived a significant PFS benefit from niraparib maintenance treatment after front-line platinum-based chemotherapy
- The discontinuation rate in the *BRCA*m subgroup was lower than in the overall PRIMA population (9.2% vs 12.0%)
- ISD regimen in the *BRCA*m subgroup improved the overall safety profile without impacting efficacy
  - Patients who received an ISD had approximately 60% fewer grade ≥3 thrombocytopenia events than did patients who received an FSD
- No relevant difference was seen in mean FOSI and EQ-5D-5L scores between niraparib and placebo in patients with *BRCA*m OC
- ISD should be considered the standard clinical practice for the maintenance treatment of patients with OC with low body weight or decreased platelet count

Acknowledgements

ESGO
European Society of Gynaecological Oncology

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

ENGOT

GEICO
Spain
A. Oaknin
E. Guerra
C. Churruca
R. Bratos
J. Perez
I. Romero
I. Tusquets
L. Gaba Garcia
M. Gil Martin
E. Calvo-Garcia
L. Sanchez
J. Pradera
A. Sanchez-Heras
A. Yubero
M. Romeo-Marin

ICORG
Ireland
P. Calvert

NSGO-CTU
Finland
J. Maenpaa
S. Hietanen
M. Anttila
Sweden
K. Hellman
B. Tholander
Denmark
U. Peen
A. Knudsen
Norway
A. Dorum

ISGO
Israel
J. Korach
T. Levy
A. Amit
T. Safra
M. Meirovitz

BGOG
Belgium
J-F. Baurain
S. Han
F. Forget
H. Denys
P. Vulsteke
C. Lamot
B. Honhon
E. Joosens
C. Martinez-Mena
H. Van Den Bulck

GINECO
France
G. Freyer
M. Fabbro
P. Follana
F. Selle
F. Joly-Lobbedez
T. De La Motte Rouge
D. Berton-Rigaud
S. Abadie Lacourtoisie

AGO
Germany
I. Braicu
V. Hanf
F. Heitz
F. Marme
A. Scheeweiss
A. Burges
B. Schmalfeldt
G. Emons

MITO
Italy
G. Artioli

United Kingdom
J. Krell
J. Mcgrane
D. Badea
R. Bhana
C. Chau
R. Bowen
C. Gourley
J. Forrest
R. Glasspool

Poland
R. Madry
M. Sikorska
J. Podlodowska

Czechia
D. Cibula
L. Rob
D. Berezovskiy

Switzerland
P. Imesch
V. Heinzelmann
M. Rabaglio

Hungary
R. Poka
T. Pinter

Germany
M. Karthaus

Ireland
P. Donnellan

GOG

United States
L. Holman
M. Gold
S. Yap
M. Callahan
T. Myers
D. O'Malley
L. Rojas
E. Chalas
C. Zarwan
L. Perry
K. ElSahwi
A. Brown
S. Memarzadeh
D. Bender
J. Barter
L-M. Chen
P. Disilvestro
E. Ratner
J. Lesnock
K. Yost
S. Lewin
P. Rose
M. Bergman
B. Slomovitz
J. Press
D. Moore
K. Wade
J. Burke
T. Werner
J. Chan
Y. Zhuo
W. Gajewski
L. Van Le
S. Ghamande
S. Chambers

United States
P. Braly
S. Keck
G. Colon-Otero
A. Lee
S. Sharma

Ukraine
A. Kryzhanivska
H. Adamchuk
I. Bondarenko
O. Kolesnik
I. Lytvyn
S. Shevnia
I. Sokur

USOR
N. Cloven
J. Buscema
D. Chase
C. Anderson
C. Lee
A. Santillan-Gomez
C. Bailey

Canada
D. Provencher
A. Oza
J. Weberpals
S. Lau
S. Welch
A. Kumar
D. Mirchandani
A. Covens

Russian Federation
V. Vladimirov
E. Gotovkin
V. Moiseenko
S. Safina
D. Yukalchuk
V. Shirinkin
A. Buiniakova
O. Gladkov
O. Mikheeva
N. Musaeva
M. Nechaeva
T. Semiglazov

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
GINECO
ISGO
MITO
GOG FOUNDATION

Writing and editorial support, funded by GlaxoSmithKline (Waltham, MA, USA) and provided by Eric Scocchera, PhD, and Anne Cooper, MA, of Ashfield Healthcare Communications (Middletown, CT, USA). This study (NCT02655016) was funded by GlaxoSmithKline.