The Clinical Implications of Key Recent Data Sets in Oncology: A Daylong Multitumor Educational Symposium in Partnership with Florida Cancer Specialists

A CME/MOC- and NCPD-Accredited Event

Saturday, October 22, 2022
7:30 AM – 5:30 PM ET

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RESEARCH
TO PRACTICE

Agenda

Module 1 — Lung Cancer: *Drs Langer and Lovly*

Module 2 — Chronic Lymphocytic Leukemia and Lymphomas: *Drs LaCasce and Smith*

Module 3 — Prostate and Bladder Cancers: *Drs Morgans and Yu*

Module 4 — Renal Cell Carcinoma: *Prof Powles*

Module 5 — Multiple Myeloma: *Dr Usmani*

Module 6 — Hepatobiliary Cancers: *Dr Abou-Alfa*

Agenda

Module 7 — Breast Cancer: *Drs Goetz and Krop*

Module 8 — Endometrial Cancer: *Dr Westin*

Module 9 — Ovarian Cancer and PARP Inhibitors: *Dr O'Malley*

Module 10 — Gastrointestinal Cancers: *Drs Messersmith and Strickler*

Module 11 — Melanoma: *Prof Long*

Ovarian Cancer and PARP Inhibitors Faculty

David M O'Malley, MD
Professor
Division Director, Gynecologic Oncology
The Ohio State University and The James Cancer Center
Columbus, Ohio

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Ovarian Cancer and PARP Inhibitors Agenda

MODULE 1: Primary Maintenance Therapy

MODULE 2: Current Management of Relapsed Disease

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Ovarian Cancer and PARP Inhibitors Agenda

MODULE 1: Primary Maintenance Therapy

MODULE 2: Current Management of Relapsed Disease

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Discussion Questions

- What is the optimal approach to genomic evaluation in patients presenting with ovarian cancer?

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Primary maintenance therapy in **OVARIAN CANCER**

David O'Malley, MD
Professor
Division Director, Gynecologic Oncology
Co-Director, Gyn Oncology Phase I Program

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

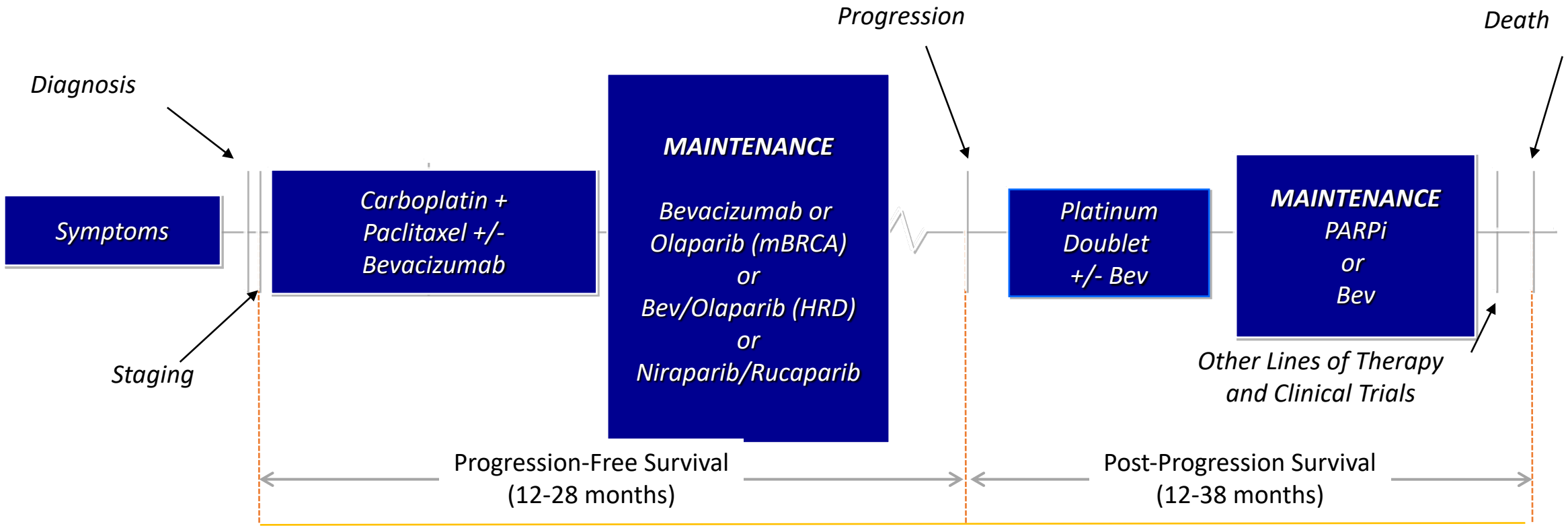
Creating a cancer-free world. One person, one discovery at a time.



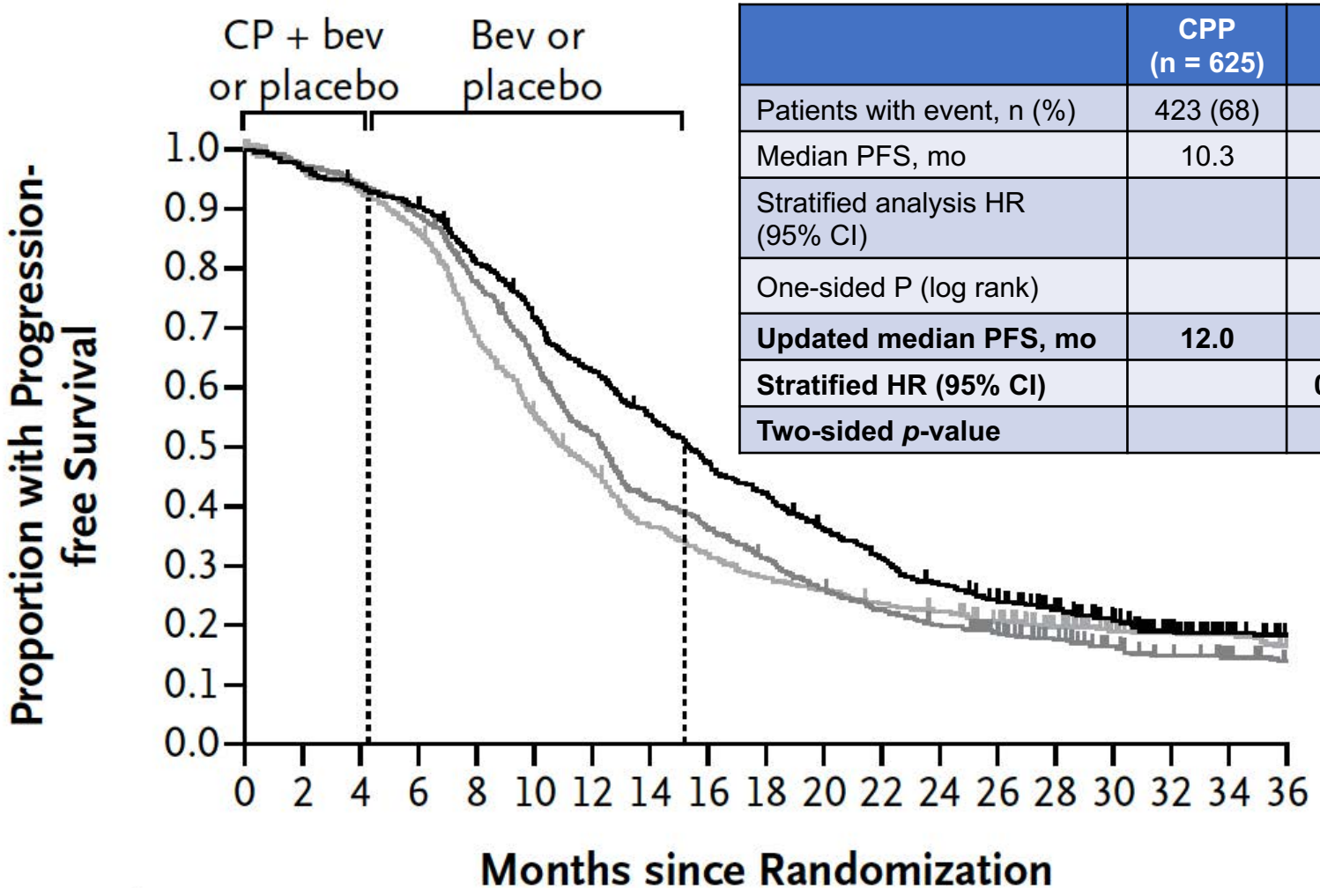

Agenda

- Background
- Upfront/First Line
  - Bevacizumab
  - PARPi
  - Bev/PARPi

Integrated Treatment Paradigm for Use of Maintenance Therapy in Ovarian Cancer



GOG-0218: Primary Endpoint
Primary PFS Analysis (Censored for CA125 progression)



	CPP (n = 625)	CP + Bev (n = 625)	CP + Bev → Bev (n = 623)
Patients with event, n (%)	423 (68)	418 (69)	360 (58)
Median PFS, mo	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.795-1.040)	0.717 (0.625-0.824)
One-sided P (log rank)		.16	<.001
Updated median PFS, mo	**12.0**	**12.8**	**18.2**
Stratified HR (95% CI)		**0.83 (0.70, 0.98)**	**0.62 (0.52, 0.75)**
Two-sided *p*-value		**Not significant**	**<0.0001**

Burger et al. *N Engl J Med.* 2011;365:2473-2483.

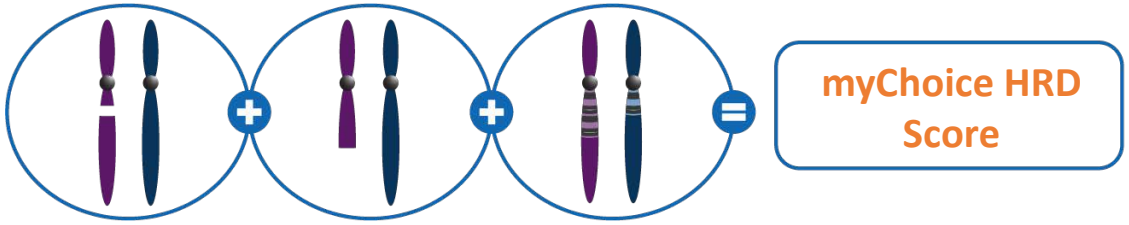
PARPi for 1LM: Study Design

Study design	PRIMA[1] (N=733)	PRIME[2] (N=384) (study performed only in China)	SOLO-1[3] (N=391)	ATHENA-MONO[4] (N=538)	PAOLA-1[5] (N=806)	OVARIO[6] (N=105)
Study treatment	Niraparib (n=487) Placebo (n=246)	Niraparib (n=255) Placebo (n=129)	Olaparib (n=260) Placebo (n=131)	Rucaparib (n=427) Placebo (n=111)	Olaparib + bevacizumab (n=537) Placebo + bevacizumab (n=269)	Niraparib + bevacizumab
Patient population	• Newly diagnosed stage III with residual or inoperable disease, stage IV, and those who received NACT • CR or PR to 1L CT	• Newly diagnosed stage III-IV regardless of residual disease at PDS or IDS • CR or PR to 1L CT	• Newly diagnosed • g/s*BRCA*m • Cytoreductive surgery (PDS and IDS) • NED, CR, or PR to 1L CT	• Newly diagnosed stage III-IV • CR or PR to 1L CT • Cytoreductive surgery (PDS and IDS)	• Newly diagnosed ovarian cancer or *BRCA*m nonmucinous EOC • Regardless of surgical outcome (PDS or IDS) • NED, CR, or PR to 1L CT + bevacizumab	• Newly diagnosed stage IIIB-IV • NED, CR, or PR to 1L CT + bevacizumab
***BRCA* status** *BRCA*m, %	Niraparib: 31.2 Placebo: 28.9	Niraparib: 33.3 Placebo: 31.0	Olaparib: 100 Placebo: 100	NA	Olaparib + bevacizumab: 30 Placebo + bevacizumab: 30	28
Randomization	2:1	2:1	2:1	4:1	2:1	-
Stratification factors	NACT, response to CT, and HRD status	*BRCA* status, HRD status, NACT, response to CT	Response to CT	BRCA status, HRD status, response to CT, timing of surgery	*BRCA* status, response to CT	-
Treatment duration	Until PD or 36 months	Until PD or 36 months	Until PD or 24 months[a]	Until PD or 24 months	Olaparib: until PD or 24 months Bevacizumab: 15 months	Niraparib: until PD or 36 months Bevacizumab: 15 months
Primary endpoint	PFS by BICR	PFS (ITT) by BICR	PFS by INV	PFS by INV	PFS by INV	PFS at 18 months
Key secondary endpoints	OS, PFS2, PROs, safety	OS and TFST (ITT), PFS and OS (HRD), safety	PFS2, OS, HRQoL, safety	PFS by BICR, OS, ORR, DOR, safety	PFS2, OS, safety, HRQoL	PFS, OS, TFST, TSST, safety, tolerability, PROs

[a]Patients with a PR at 2 years were permitted to continue receiving the trial intervention in a blinded manner. 1L, first line; 1LM, first-line maintenance; BICR, blinded independent central review; *BRCA*m, *BRCA* mutant; CR, complete response; CT, chemotherapy; DOR, duration of response; EOC, epithelial ovarian cancer; g/s*BRCA*m, germline or somatic *BRCA* mutant; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; IDS, interval debulking surgery; INV, investigator; ITT, intention-to-treat; NA, not available; NACT, neoadjuvant chemotherapy; NED, no evidence of disease; ORR, objective response rate; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PD, progressive disease; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, second progression-free survival; PR, partial response; PRO, patient-reported outcome; TFST, time to first subsequent anticancer therapy; TSST, time to second subsequent therapy or death. 1. Gonzalez-Martin A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 2. Li N, et al. Presented at SGO 2022. Abstract 244. 3. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505. 4. Monk BJ, et al. *Int J Gynecol Cancer* 2021;31:1589–1594. 5. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 6. Hardesty M, et al. Presented at SGO 2022. Abstract 170B.

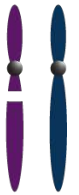
How to Identify Homologous Recombination Deficiency[1,a]

myChoice
(CDx olaparib, niraparib)



Loss of heterozygosity (LOH) | Telomeric allelic imbalance (TAI) | Large-scale state transitions (LST)

FoundationOne LOH
(CDx rucaparib, olaparib)



LOH

HR status is determined by genomic instability score (GIS)

- **HR-deficient tumors:** tissue GIS ≥42 **OR** a *BRCA*m
- **HR-proficient tumors:** tissue GIS <42
- HR not determined

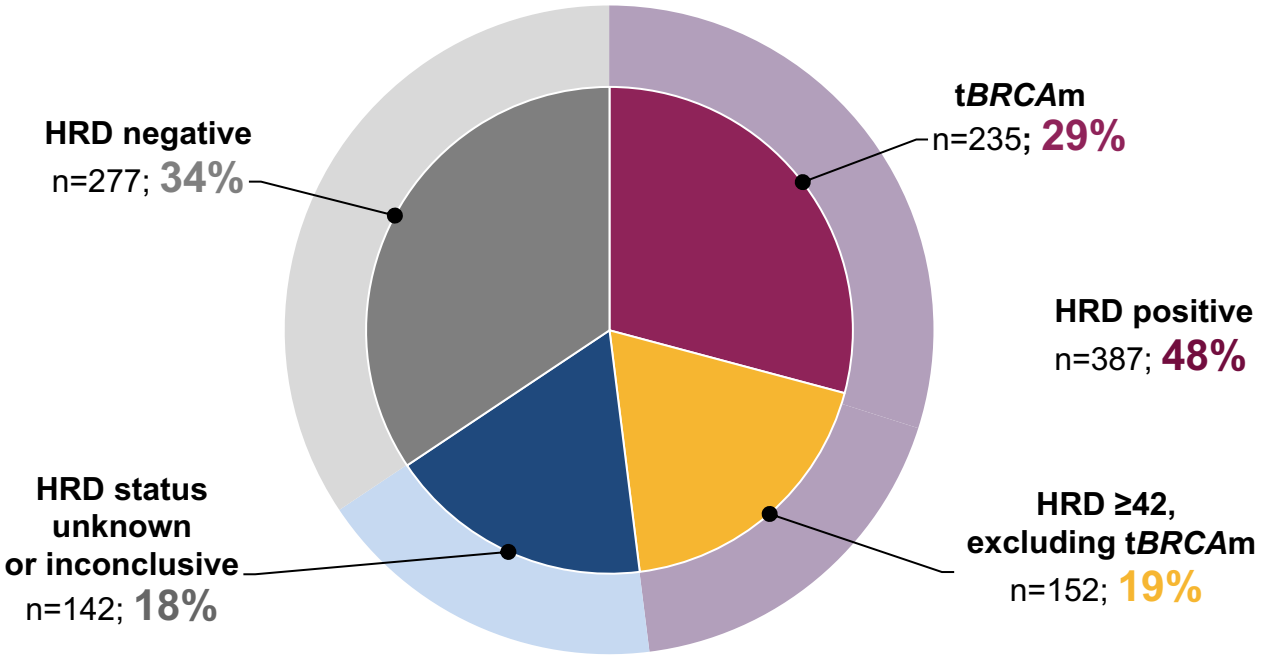
- **HRR pathway–related genes**
  BRCA (germline, somatic)
- **Non-*BRCA* HRR gene mutations**
  (eg, *RAD51C, RAD51D, BRIP1, ATM, CDK12, CHEK1, CHEK2*)

[a] Tests have not been compared head to head. Paired with development of respective drugs.

1. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

PAOLA-1 as an example - Myriad myChoice

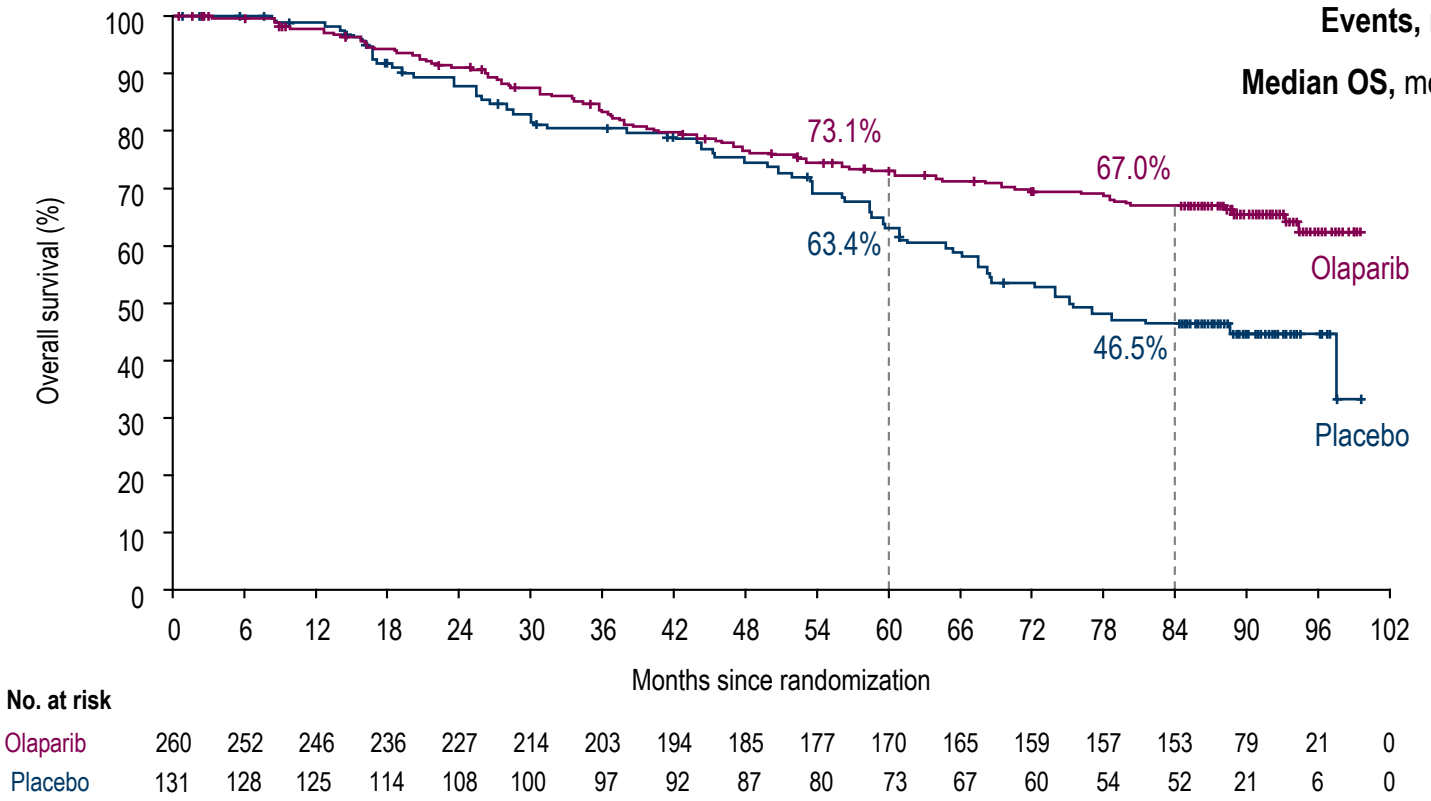
Around half of HRD test–positive patients were tBRCAm



Reasons for HRD status unknown: 4.2% missing; 2.1% fail; 11.3% inconclusive.
HRD, homologous recombination deficiency; t*BRCA*m, tumor breast cancer susceptibility gene mutation-positive.
Ray-Coquard I, et al. Presented at: ESMO Congress; September 27-October 1, 2019; Barcelona, Spain. LBA2 N Engl J Med. 2019; 381(25):2416-2428.

2022 Updates

SOLO-1 Maintenance olaparib provided a clinically meaningful OS benefit



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**

HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*

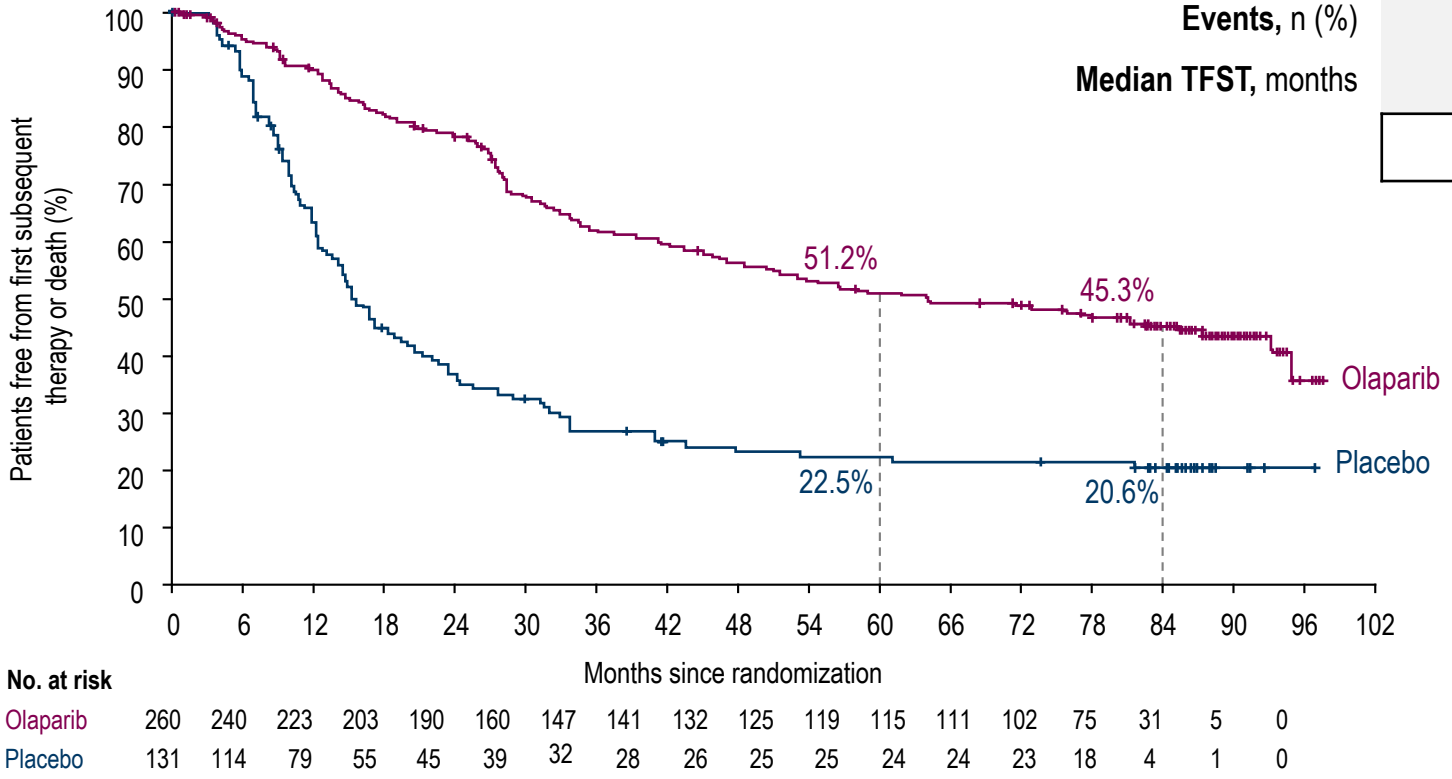
44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

**P*<0.0001 required to declare statistical significance

Paul DiSilvestro, et al ESMO 2022

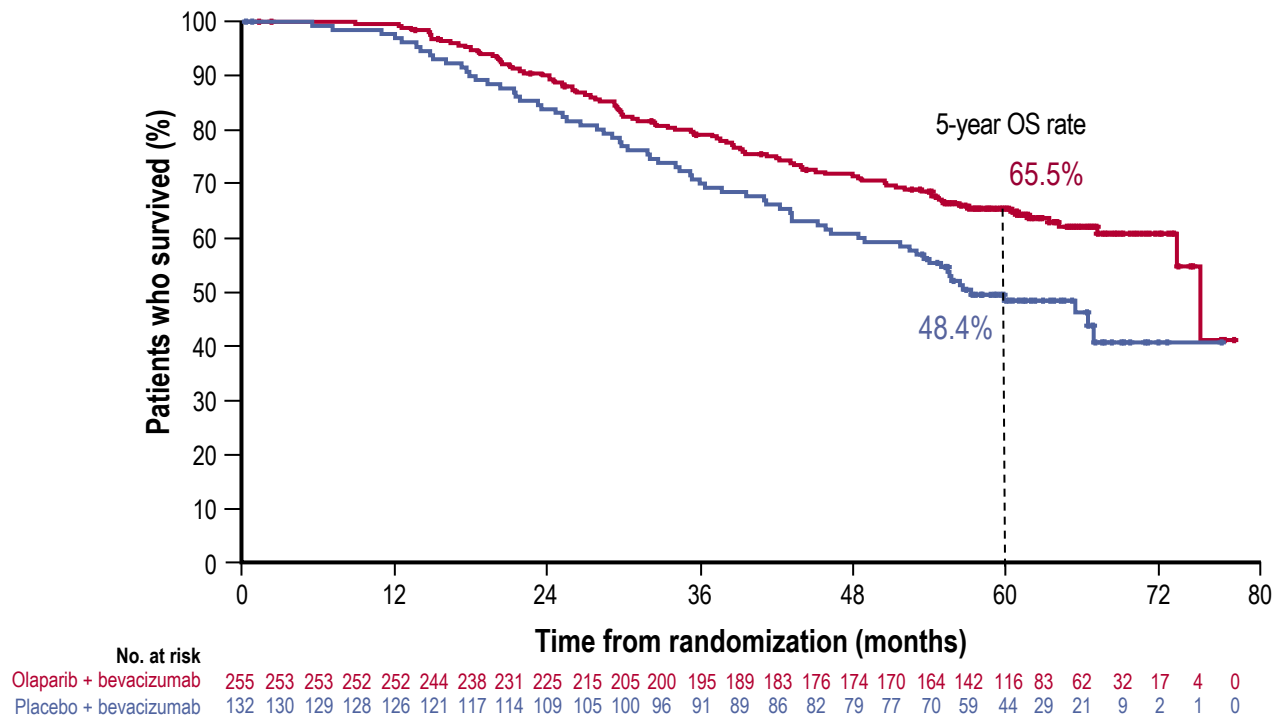
SOLO-1 TFST substantially delayed by maintenance olaparib

	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
HR 0.37 (95% CI 0.28–0.48)		



Paul DiSilvestro, et al ESMO 2022

PAOLA-1 OS was prolonged in the HRD-positive subgroup



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**

HR 0.62 (95% CI 0.45–0.85)

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

Patients receiving a PARP inhibitor during any subsequent treatment

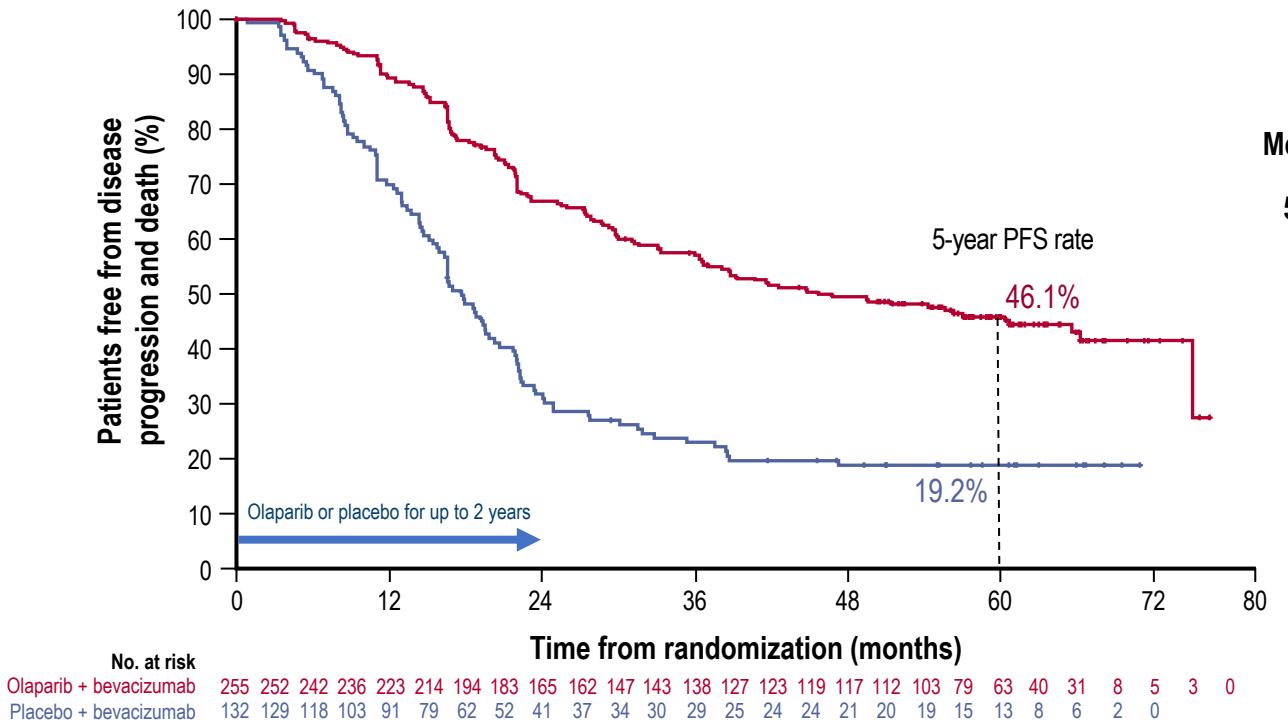
Olaparib + bevacizumab: **17.3%** (44/255)

Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.

HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

PAOLA-1 Updated PFS: HRD-positive population*



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	136 (53.3)	104 (78.8)
Median PFS, months	**46.8**	**17.6**
5-year PFS rate, %	**46.1**	**19.2**

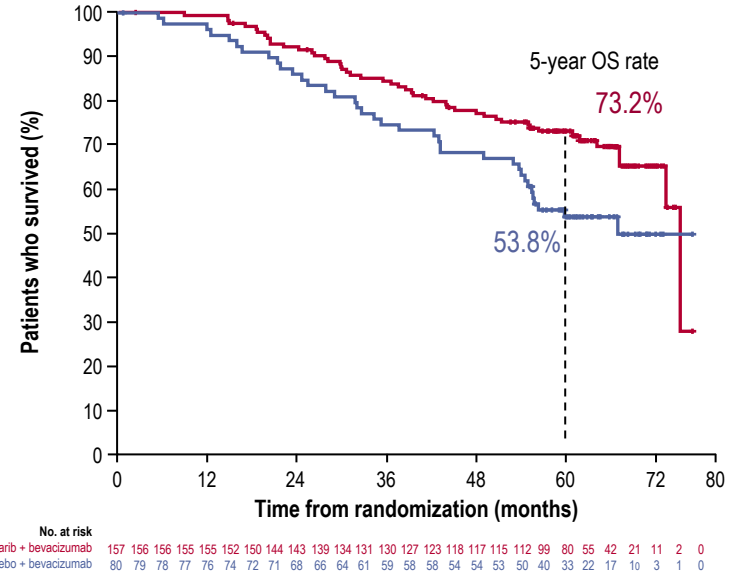
HR 0.41 (95% CI 0.32–0.54)

59% reduction in risk of disease progression or death for olaparib + bevacizumab vs bevacizumab alone

*Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).

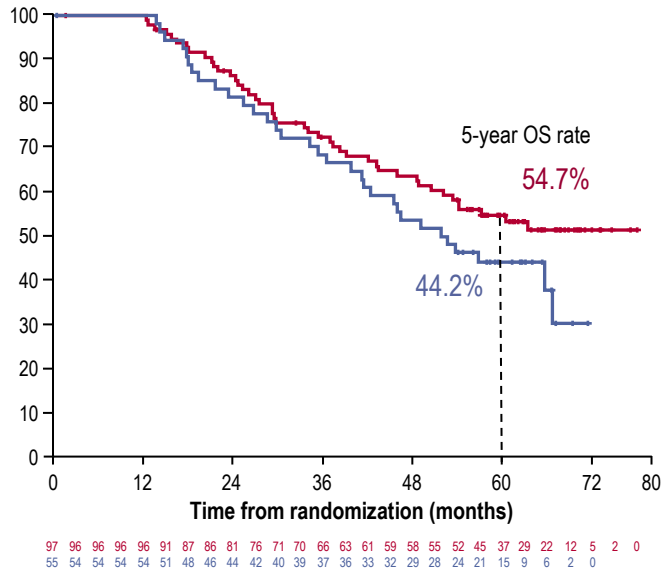
PAOLA-1 OS subgroup analysis by BRCAm and HRD status

BRCAm*



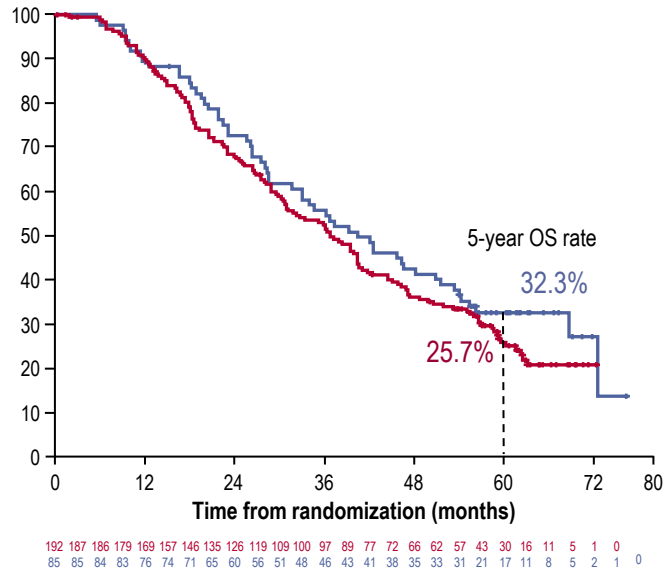
	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

HRD positive‡ excluding BRCAm



	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	44 (45.4)	32 (58.2)
	NR	52.0
	54.7	**44.2**
	9 (9.3)	23 (41.8)
	HR 0.71 (95% CI 0.45–1.13)	

HRD negative†



	Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
	140 (72.9)	58 (68.2)
	36.8	40.4
	25.7	**32.3**
	46 (24.0)	34 (40.0)
	HR 1.19 (95% CI 0.88–1.63)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

ATHENA–MONO Study Schema

Athena
RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 STUDY OF NIVOLUMAB AND RUCAPARIB

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than frontline platinum regimen

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Treatment for 24 months*, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Randomization Stratification Factors

- Tumor HRD test status†
- Disease status post-chemotherapy
- Timing of surgery

Study Analyses

ATHENA–MONO

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

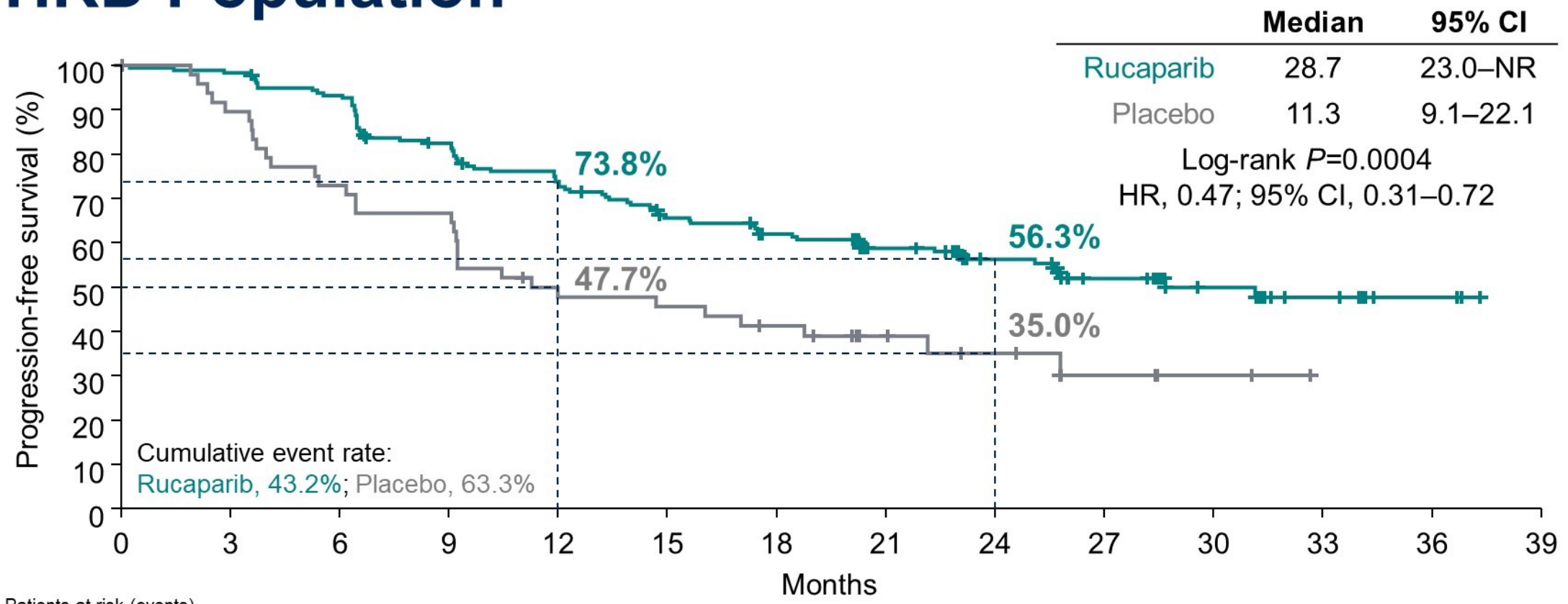
Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

*After initiation of oral/IV combination study treatment (IV drug was initiated cycle 2 day 1; 28-day cycles). †Centrally assessed, determined by FoundationOne CDx (BRCA^{mut}, BRCA^{wt}/LOH^{high} [LOH ≥16%], BRCA^{wt}/LOH^{low} [LOH <16%], BRCA^{wt}/LOH^{indeterminate}). BID, twice daily; BRCA, *BRCA1* or *BRCA2*; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; mut, mutant; PO, by mouth; PR, partial response; wt, wild type.

PRESENTED BY:
Bradley J. Monk, MD, FACS, FACOG (LBA5500)

Monk et al, ASCO 2022

Primary Endpoint – Investigator-Assessed PFS: HRD Population



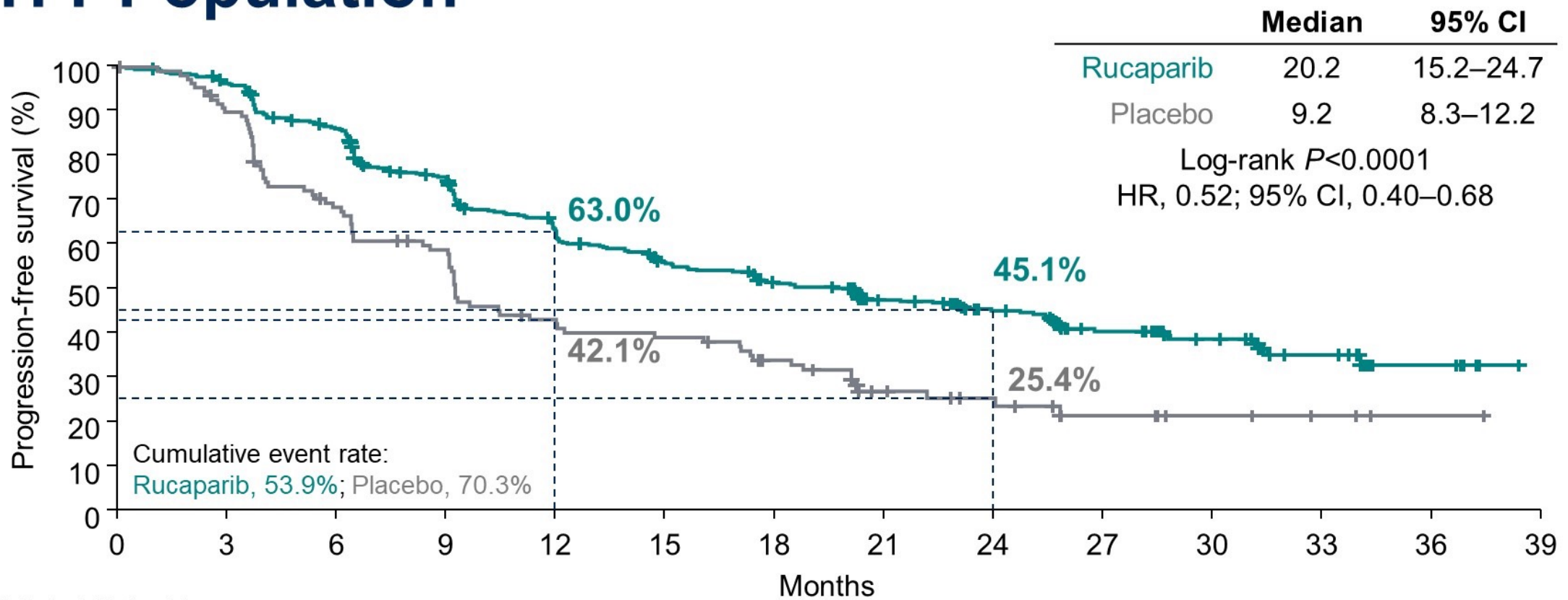
Patients at risk (events)

Rucaparib	185(0)	175(3)	165(12)	143(31)	127(46)	110(60)	100(66)	82(71)	59(74)	36(78)	22(79)	12(80)	3(80)	0(80)
Placebo	49(0)	43(5)	35(13)	32(16)	22(25)	21(26)	18(28)	11(29)	8(30)	4(31)	2(31)	0(31)		

Data cutoff date: March 23, 2022.
HR, hazard ratio; HRD, homologous recombination deficiency; NR, not reached; PFS, progression-free survival.

Monk et al, ASCO 2022

Primary Endpoint – Investigator-Assessed PFS: ITT Population



Patients at risk (events)

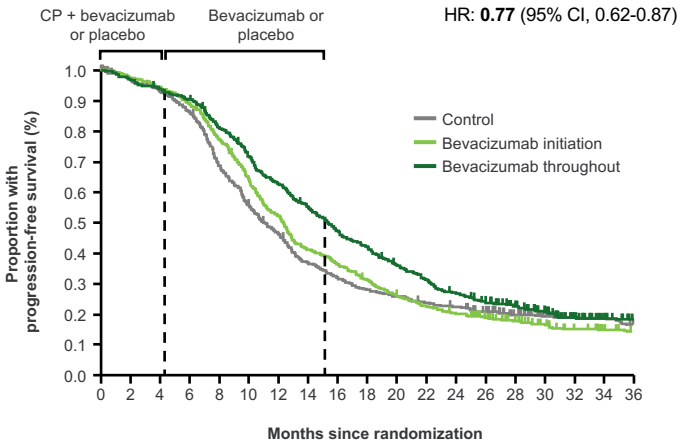
Rucaparib	427 (0)	398 (15)	351 (57)	298 (101)	245 (149)	213 (176)	190 (193)	151 (207)	114 (214)	67 (224)	42 (226)	23 (229)	7 (230)	0 (230)
Placebo	111 (0)	97 (11)	72 (34)	60 (44)	42 (61)	39 (64)	31 (69)	18 (75)	14 (76)	8 (78)	5 (78)	3 (78)	1 (78)	0 (78)

Data cutoff date: March 23, 2022.
HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

Monk et al, ASCO 2022

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer: *BRCA*

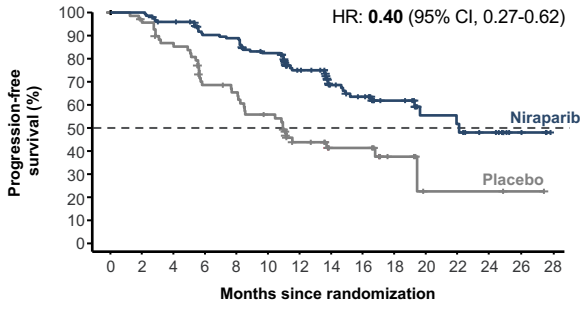
GOG-0218[1]



No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

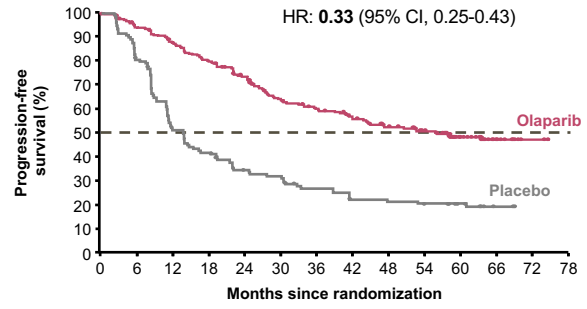
PARP inhibitors

PRIMA: HRd *BRCA*m[2]



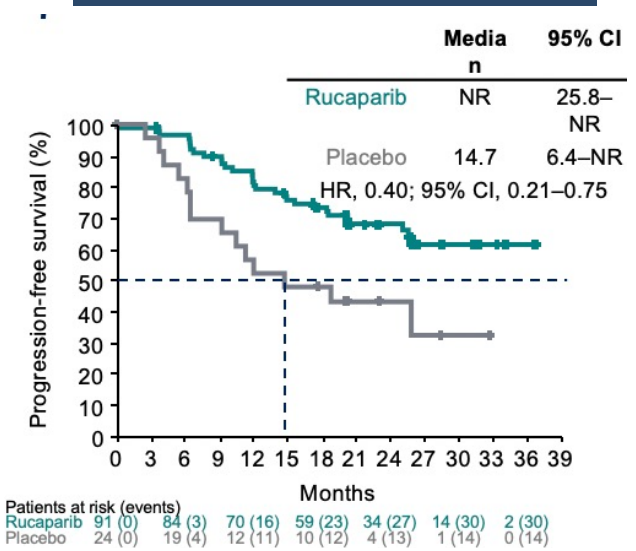
No. at risk														
Niraparib	152	148	140	127	125	113	77	55	48	29	15	14	10	4
Placebo	71	65	57	44	41	34	21	14	14	7	2	2	2	1

SOLO1: *BRCA*m[4]

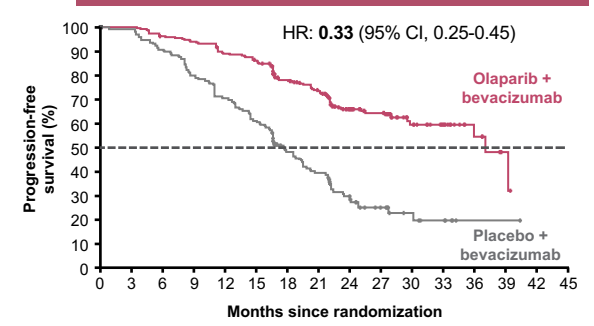


No. at risk														
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	0

ATHENA: HRd BRCAm[3]



PAOLA-1: BRCA[5]



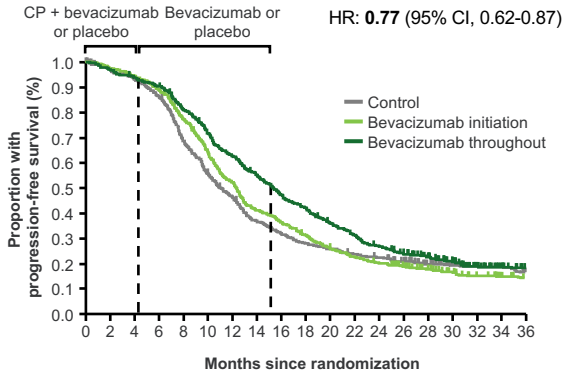
No. at risk														
Olaparib + bevacizumab	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo + bevacizumab	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.**Monk et al. ASCO/JCO 2022. **4.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer: *BRCAwt*/HRD

PARP inhibitors

GOG-0218[1]



No. at risk							
Control	625	535	283	169	133	78	49
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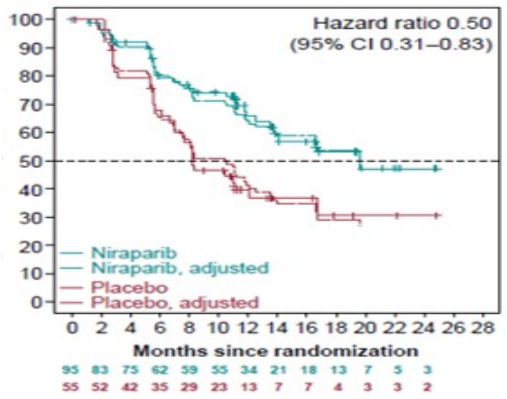
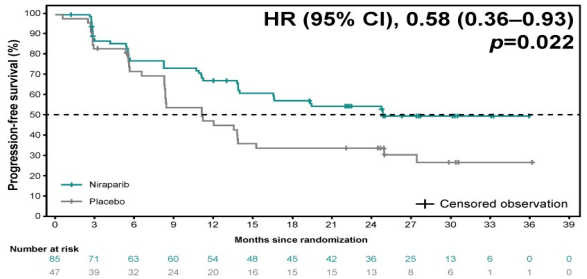
PRIMA: HRd *BRCAwt*[2]

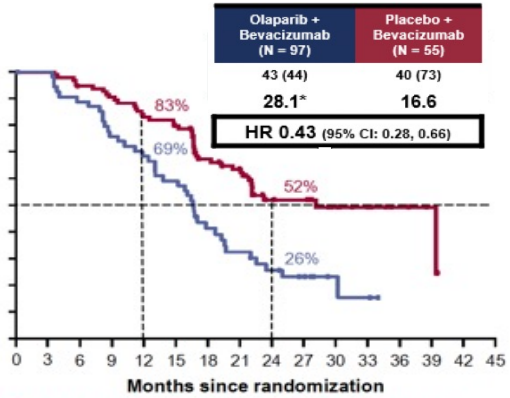


PRIME:: HRd *BRCAwt*[3]

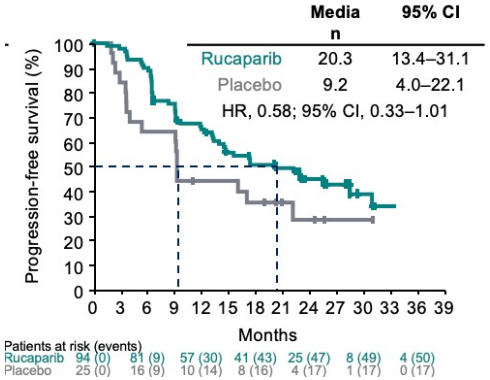


	Niraparib (N=85)	Placebo (N=47)
mPFS (95% CI), months	24.8 (14.0–NE)	11.1 (8.3–13.8)

PAOLA-1: HRd *BRCAwt*[5]



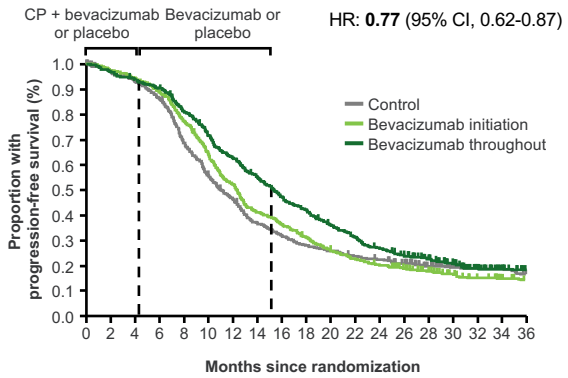
ATHENA MONO: *HRd BRCAwt*[4]



1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. **2.** Monk BJ et al. Presented at: SGO Annual Meeting; March 29, 2020. Presentation 31. **3.** Li et al. SGO 2022 Phoenix. **4.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. **5.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARP inhibitors are changing the course of disease progression in patients with advanced ovarian cancer : HRp

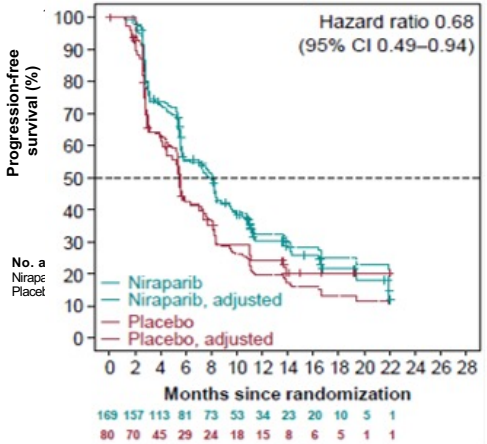
GOG-0218[1]



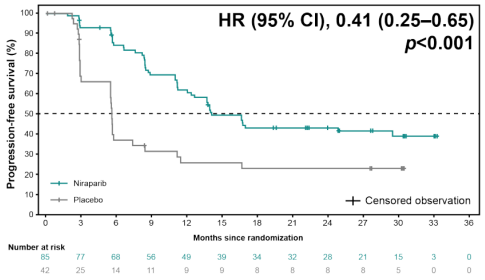
No. at risk							
Control	625	535	283	169	133	78	49
Bevacizumab initiation	625	552	319	190	121	67	40
Bevacizumab throughout	623	559	386	256	162	97	56

PARP inhibitors

PRIMA: HRp [2]

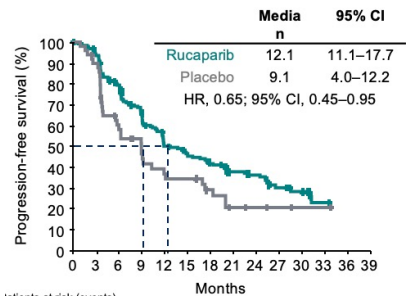


PRIME: HRp [2]

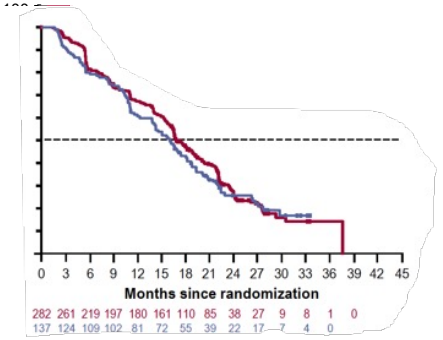


	Niraparib (N=85)	Placebo (N=42)
mPFS (95% CI), months	14.0 (11.9–NE)	5.5 (2.9–7.3)

ATHENA MONO: *HRp*[4]



PAOLA-1: HRp[5]



1. Burger RA et al. *N Engl J Med.* 2011;365(26):2473-2483. **2. Liu et al. SGO 2022**
31. **3.** González Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **4.** Monk ASCO/JCO 2022
5. Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428.

PARPi for 1LM: Key Efficacy Data

Efficacy	PRIMA[1] (N=733)	PRIME[2] (N=384) (study performed only in China)	SOLO-1[3] (N=391) (5-year follow-up)	ATHENA-MONO[4] (N=538)	PAOLA-1[5] (N=806)	OVARIO[6] (N=105) (updated analysis)
Median PFS, months HR[a] (95% CI)						
ITT	N=733 13.8 vs 8.2 0.62 (0.50-0.76)	N=384 24.8 vs 8.3 0.45 (0.34-0.60)	-	N=538 20.2 vs 9.2 0.52 (0.40-0.68)	N=806 22.1 vs 16.6 0.59 (0.49-0.72)	N=105 19.6
*BRCA*wt/HRp	n=249 8.1 vs 5.4 0.68 (0.49-0.94)	n=127[b] 14.0 vs 5.5 0.41 (0.25-0.65)	-	n=238 12.1 vs 9.1 0.65 (0.45-0.95)	n=211 16.9 vs 16.0 1.00 (0.75-1.35)[b]	n=38 14.2
*BRCA*wt/HRd	n=150 19.6 vs 8.2 0.50 (0.31-0.83)	n=132[c] 24.8 vs 11.1 0.58 (0.36-0.93)	-	n=119 20.3 vs 9.2 0.58 (0.33-1.01)	n=152 28.1 vs 16.6 0.43 (0.28-0.66)[b]	n=16 28.3
*BRCA*m	n=223 22.1 vs 10.9 0.40 (0.27-0.62)	n=125[d] NR vs 10.8 0.40 (0.23-0.68)	n=391 56.0 vs 13.8 0.33 (0.25-0.43)	n=115 NR vs 14.7 0.40 (0.21-0.75)	n=90 37.2 vs 21.7 0.31 (0.20-0.47)[b]	n=29 NR
Median duration of follow-up, months	13.8	27.5	59	26.1	22.9	28.7

[a] HR for disease progression or death. [b] Non-*gBRCA*m/HRp. [c] Non-*gBRCA*m/HRd. [d] g*BRCA*m population. 1LM, first-line maintenance; *BRCA*wt, *BRCA* wild type; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention-to-treat; NA, not available; NR, not reached; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

1. Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 2. Li N, et al. Presented at SGO 2022. Abstract 244. 3. Banerjee S, et al. *Lancet Oncol*. 2021;22(12):1721-1731. 4. B Monk, JCO , 6/2022 on line..
5. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 6. Hardesty M, et al. Presented at SGO 2022. Abstract 170B.

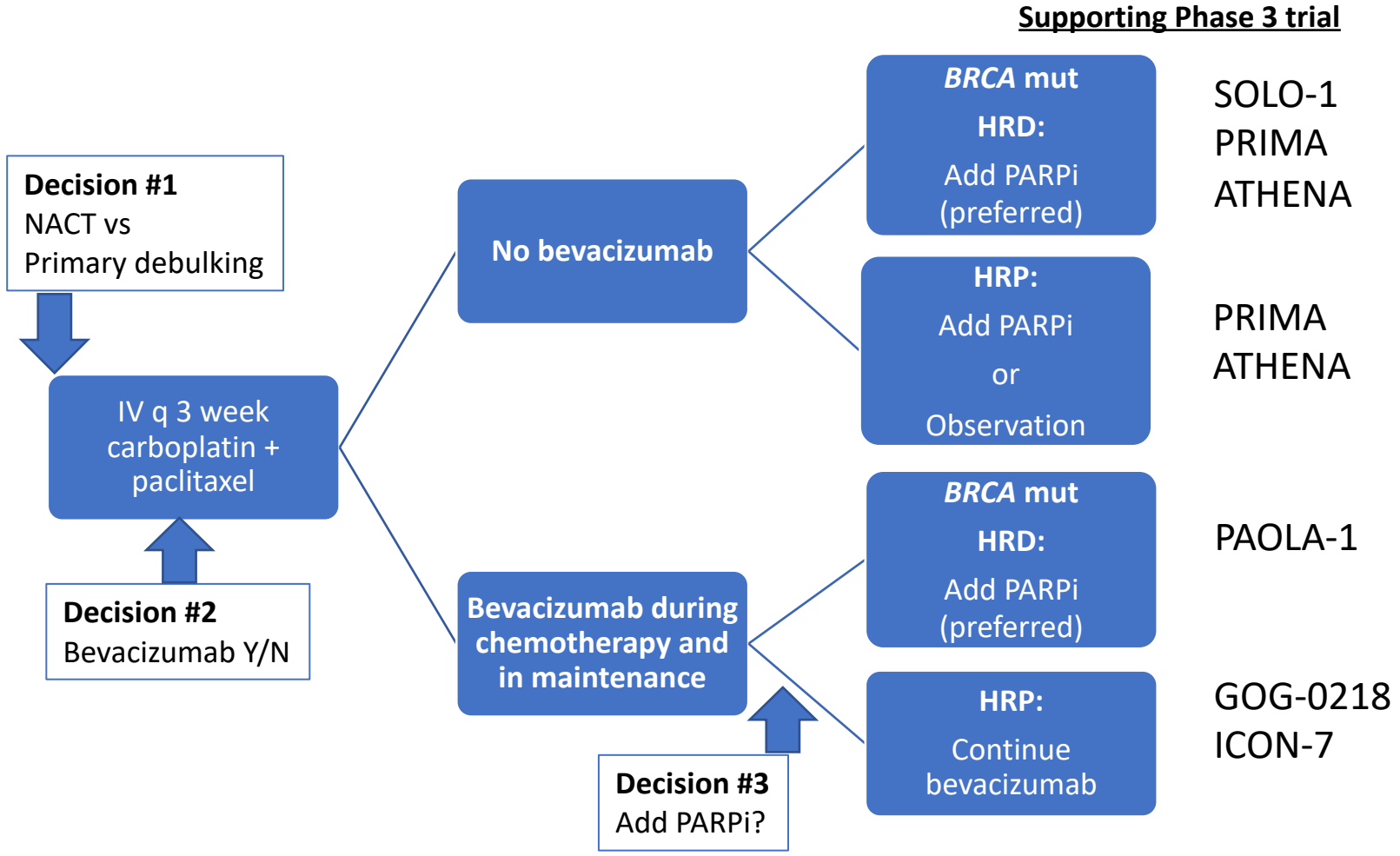
PARPi for 1LM: Key Safety Data

Safety	PRIMA[1] (N=733)	PRIME[2] (N=384) No new safety signal identified	SOLO-1[3,4] (N=391) (5-year follow-up)	ATHENA-MONO[5] (N=538) No new safety signal identified	PAOLA-1[g,6] (N=806)	OVARIO[7] (N=105) (updated analysis) No new safety signal identified
Most common grade ≥3 AE, %						
Anemia	31.0	18.0	22.0[e]	28.7	17[e]	34[i]
Thrombocytopenia	28.7	-	<1.0	7.1	-	39[j]
Neutropenia	12.8	-	8.0[f]	14.6	6[f]	12[k]
Neutrophil count decrease	-	17.3[a]	-	-	-	-
White blood cell count decrease	-	6.7[b]	-	-	-	-
Platelet count decrease	13.0	14.1[c]	-	-	-	-
Lymphopenia	-	-	-	-	7[h]	-
GGT increase	-	5.1	-	-	-	-
ALT/AST increase	-	0.4/1.2	-	10.6	-	-
Fatigue/asthenia	1.9	0.8	4.0	4.9	5	9
Hypertension	-	-	-	-	19	27
Treatment discontinuation, %	Niraparib: 12.0 Placebo: 2.5	Niraparib: 6.7 Placebo: 5.4	Olaparib: 11.5 Placebo: 3,1	Rucaparib: 11.8 Placebo: 5.5	Olaparib + bevacizumab: 20.0 Placebo + bevacizumab: 6.0	Niraparib: 30 Bevacizumab: 22
Dose interruption, %	Niraparib: 79.5 Placebo: 18.0	Niraparib: 62.7 Placebo: 19.4	Olaparib: 52.3 Placebo: 16.7	Rucaparib: 60.7 Placebo: 20.0	Olaparib + bevacizumab: 54 Placebo + bevacizumab: 24	Niraparib: 86 Bevacizumab: 55
Dose reduction, %	Niraparib: 70.9 Placebo: 8.2	Niraparib: 40.4[d] Placebo: 6.2	Olaparib: 28.8 Placebo: 3.1	Rucaparib: 49.4 Placebo: 8.2	Olaparib + bevacizumab: 41 Placebo + bevacizumab: 7	Niraparib: 73 Bevacizumab: 26
MDS/AML, %	Niraparib: 0.2 Placebo: 0	Niraparib: AML (fatal), 0.4; MDS, 0.4 Placebo: 0	No new cases of MDS/AML since primary data cut off (Olaparib: AML, 1 Placebo: 0)	Rucaparib: 0.4 Placebo: 0	Olaparib + bevacizumab: 1.1 Placebo + bevacizumab: <1	-

1LM. first line maintenance; AE, adverse event; ALT, alanine transaminase; AML, acute myeloid leukemia; AST, aspartate transaminase; GGT, gamma-glutamyltransferase ; MDS, myelodysplastic syndrome; NA, not available; PARPi, poly(ADP-ribose) polymerase inhibitor.

[a]Includes neutrophil count decrease, neutropenia, febrile neutropenia. [b]Includes white blood cell count decrease, leukopenia. [c]Includes platelet count decrease and thrombocytopenia. [d] Dose reduction includes both direct dose reduction and dose reduction following treatment interruption; dose reduction in all patients was lower than in previous niraparib trials. [e]Includes anemia, decreased hemoglobin level, decreased hematocrit, decreased red-cell count, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, or normocytic anemia. [f]Includes neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count, or agranulocytosis. [g]Adverse events with olaparib or placebo in patients also receiving bevacizumab. [h]Includes decreased lymphocyte count, lymphopenia, decreased B-lymphocyte count, or decreased T-lymphocyte count. [i]Includes hemoglobin decreased. [j]Includes decreased platelet count. [k]Includes decreased neutrophil count. 1. Gonzalez-Martin A, et al. *N Engl J Med.* 2019;381(25):2391-2402. 2. Li, et al. Presented at SGO 2022. Abstract 244. 3. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505. 4. Moore K, et al. *N Engl J Med.* 2018;379(26):2495-2505. 5. Clovis Oncology. News Release. March 31, 2022. 6. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 7. Hardesty M, et al. Presented at SGO 2022. Abstract 170B.

Integrated Maintenance Treatment Paradigm for Use in 1-L Ovarian Cancer (2022)



Future Directions in the Front Line: What is Potentially Exciting?

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O[b] ENGOT OV-46	~1254	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43[d] KEYLYNK-001	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

- a. ClinicalTrials.gov. NCT03602859; b. ClinicalTrials.gov. NCT03737643; c. ClinicalTrials.gov. NCT03522246; d. NCT03740165.

Upfront Ovarian Cancer Maintenance Treatment

- PARPi versus Bev versus Both
- Curative intent is the goal
- Biomarker derived therapy is now the standard
- Management of Toxicity is essential

Discussion Questions

- What is the optimal duration of primary PARP inhibitor maintenance, and does it vary based on type of PARP inhibitor and clinical and genomic setting?
- What is the optimal approach to prevention and amelioration of side effects/toxicity with PARP inhibitors?
- What is the risk of AML/MDS with PARP inhibitors?

Ovarian Cancer and PARP Inhibitors Agenda

MODULE 1: Primary Maintenance Therapy

MODULE 2: Current Management of Relapsed Disease

RTP RESEARCH TO PRACTICE

Discussion Questions

- In which situations, if any, would you use a PARP inhibitor in a patient who previously received that therapy?
- Other than the use of PARP inhibitor monotherapy for patients with BRCA wild-type, HRD-negative disease, do you have concerns about possible adverse consequences on survival with PARP inhibition?

Voluntary Withdrawals of Late-Line Indications for PARP Inhibitors

Niraparib – September 14, 2022

The indication for niraparib has been voluntarily withdrawn for the treatment of advanced ovarian, fallopian tube or primary peritoneal cancer in adult patients who have received 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency status. The decision was made in consultation with the US FDA and based on a totality of information from PARP inhibitors for ovarian cancer in the late-line treatment setting.

Olaparib – August 26, 2022

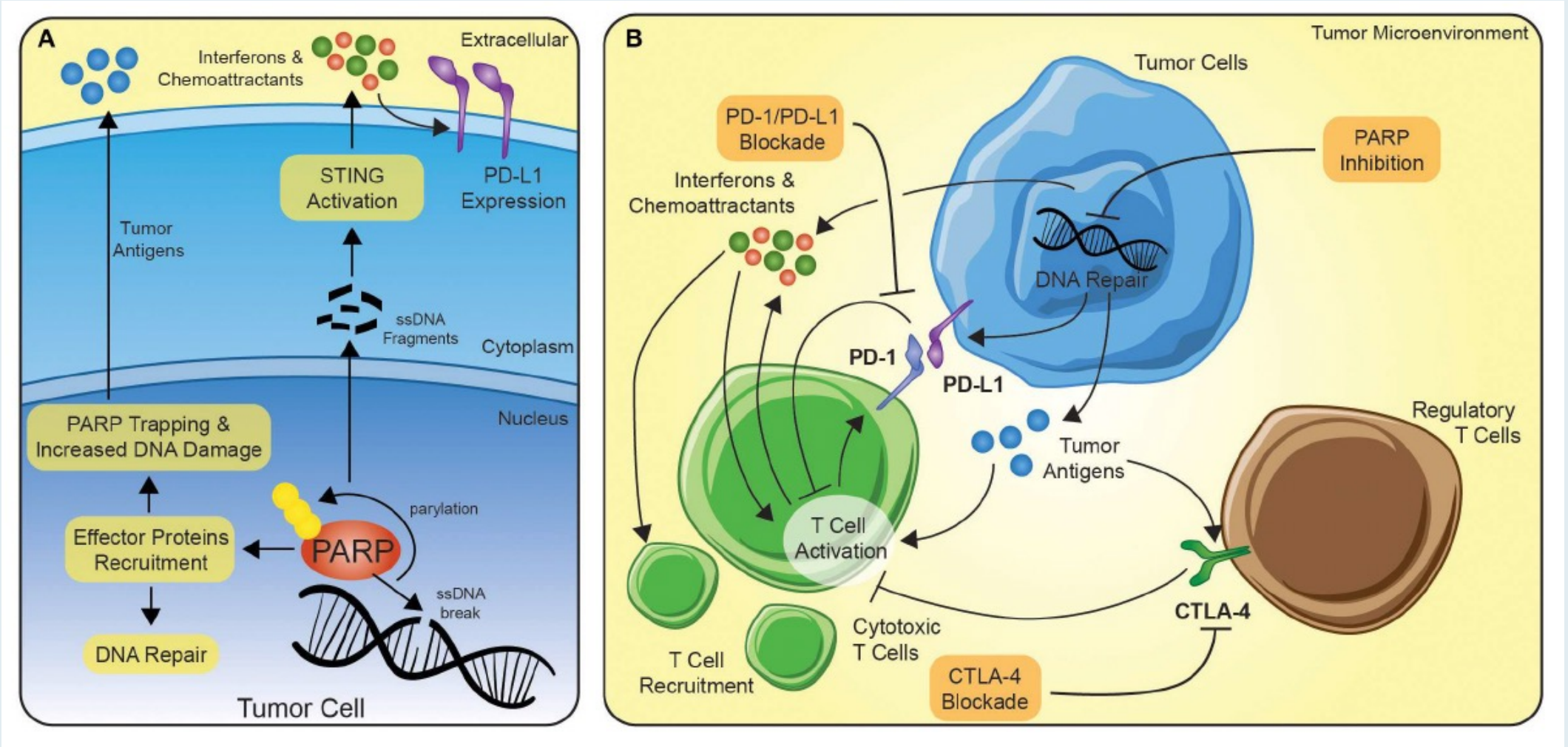
The indication for olaparib has been voluntarily withdrawn for the treatment of deleterious or suspected deleterious gBRCAm advanced ovarian cancer in adult patients who have received 3 or more prior lines of chemotherapy. The decision was made in consultation with the US FDA after a recent subgroup analysis indicated a potential detrimental effect on overall survival with olaparib compared to the chemotherapy control arm in the subgroup of patients who had received 3 or more prior lines of chemotherapy in the randomized Phase III study **SOLO-3**.

Rucaparib – June 10, 2022

The indication for rucaparib has been voluntarily withdrawn for the treatment of BRCA-mutated ovarian cancer after 2 or more chemotherapies. The withdrawal is based on discussions with the US FDA after submission of overall survival data from the ***ARIEL4 trial***, which demonstrated an increased risk of death for participants with BRCA-mutated ovarian cancer treated with rucaparib after 2 or more therapies.

https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/57e2a3fa-7b9b-432f-a220-5976a509b534/57e2a3fa-7b9b-432f-a220-5976a509b534_viewable_rendition__v.pdf?medcommid=REF--ALL-004447; https://www.lynparzahcp.com/content/dam/physician-services/us/590-lynparza-hcp-branded/hcp-global/pdf/solo3-dhcp-final-signed.pdf; https://www.hayesinc.com/news/market-withdrawal-rubraca-for-third-line-ovarian-cancer-indication/

Potential Synergy Between PARP Inhibition and Immune Checkpoint Blockade



Vikas P et al. *Front Oncol* 2020;10:570.

Phase II Study of Olaparib + Durvalumab (MEDIOLA): Updated Results in Germline BRCA-Mutated Platinum-Sensitive Relapsed (PSR) Ovarian Cancer (OC)

Drew Y et al.

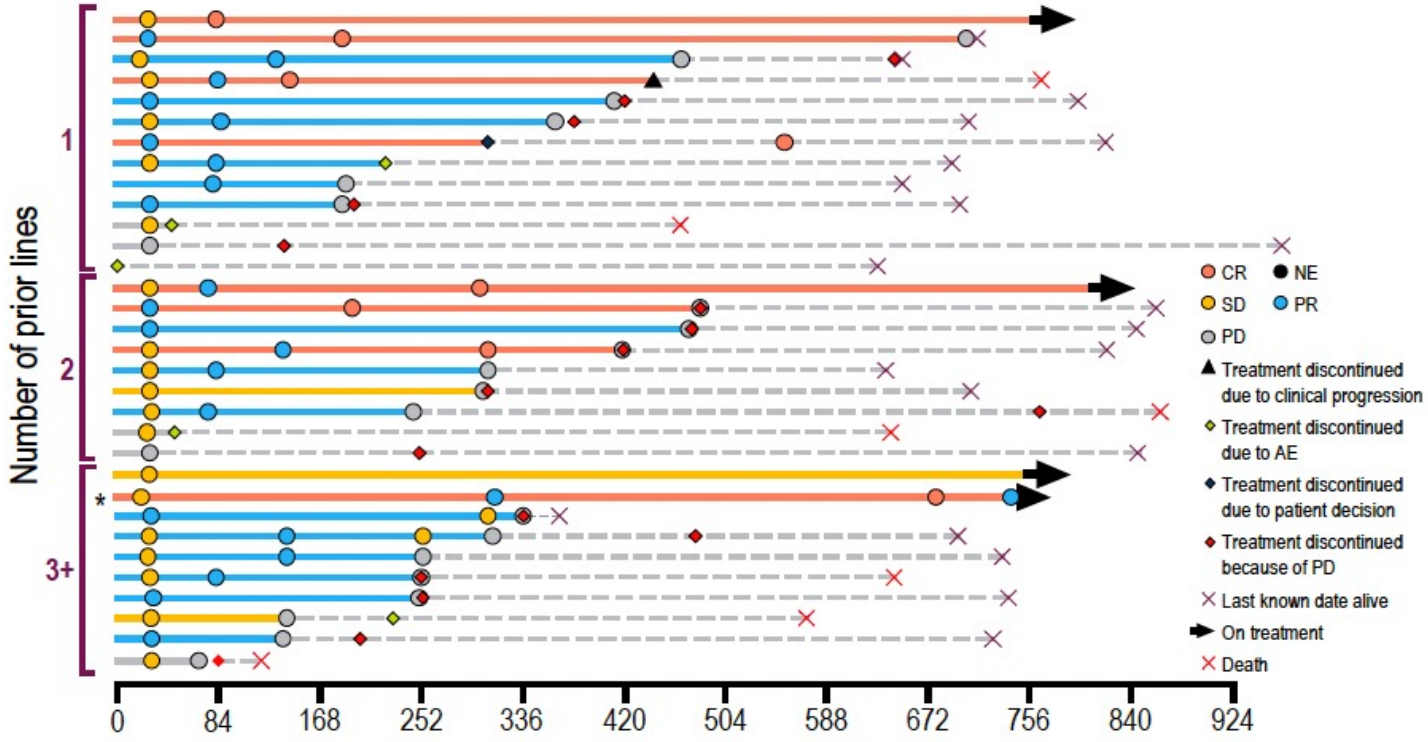
ESMO 2019;Abstract 1190PD.

MEDIOLA BRCA-Mutation Cohort: Efficacy

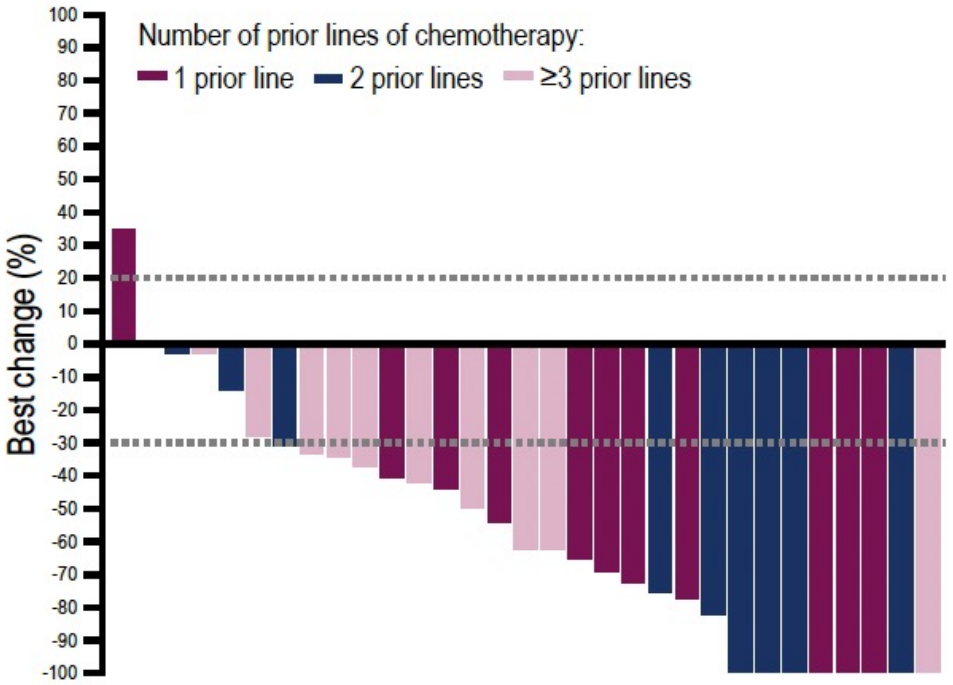
- DCR at 12 weeks: 81.3% (90% CI 66.3, 91.5)
- DCR at 28 weeks: 65.6% (90% CI 49.6, 79.4)
- Unconfirmed ORR: 71.9% (95% CI 53.3, 86.3)
- mPFS: 11.1 months (95% CI 8.2, 15.6)

Greater clinical activity was seen in earlier- versus later-line patients

Time to progression or treatment discontinuation



Best percentage change in target lesion size†



DCR = disease control rate; ORR = objective response rate; mPFS = median progression-free survival

Drew Y et al. ESMO 2019;Abstract 1190PD.

RTP RESEARCH TO PRACTICE

PARIS 2022 ESMO congress

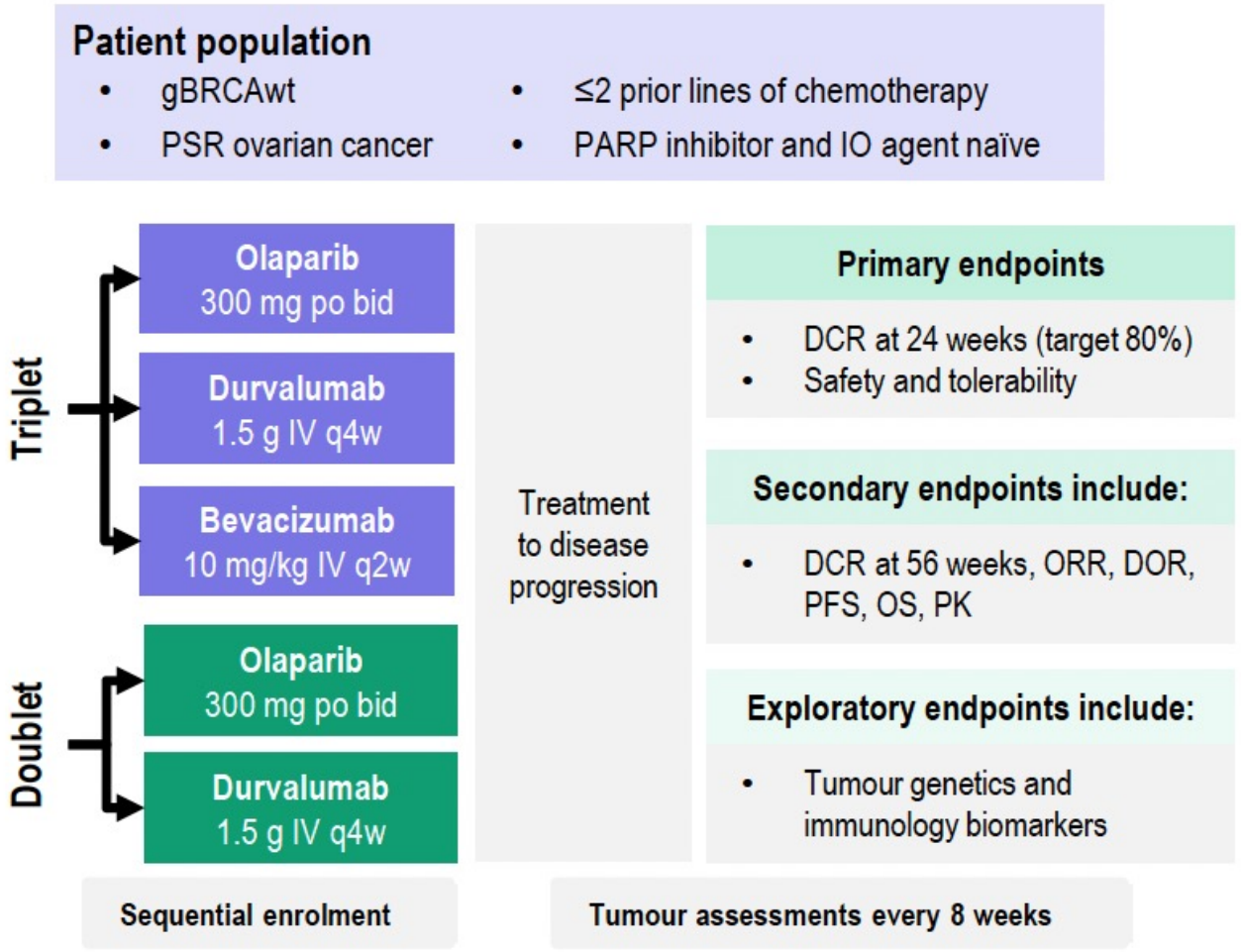
Abstract 529MO.

Phase II study of olaparib plus durvalumab with or without bevacizumab (MEDIOLA): final analysis of overall survival in patients with non-germline BRCA-mutated platinum-sensitive relapsed ovarian cancer

Susana Banerjee,[1] Martina Imbimbo,[2] Patricia Roxburgh,[3] Jae-Weon Kim,[4] Min Hwan Kim,[5] Ruth Plummer,[6] Salomon M. Stemmer,[7] Benoit You,[8] Michelle Ferguson,[9] Richard T. Penson,[10] David M. O'Malley,[11] Kassondra Meyer,[12] Haiyan Gao,[13] Helen K. Angell,[14] Ana T. Nunes,[15] Susan Domchek,[16] Yvette Drew[6*]

RTP RESEARCH TO PRACTICE

MEDIOLA: Germline BRCA Wild Type Study Schema



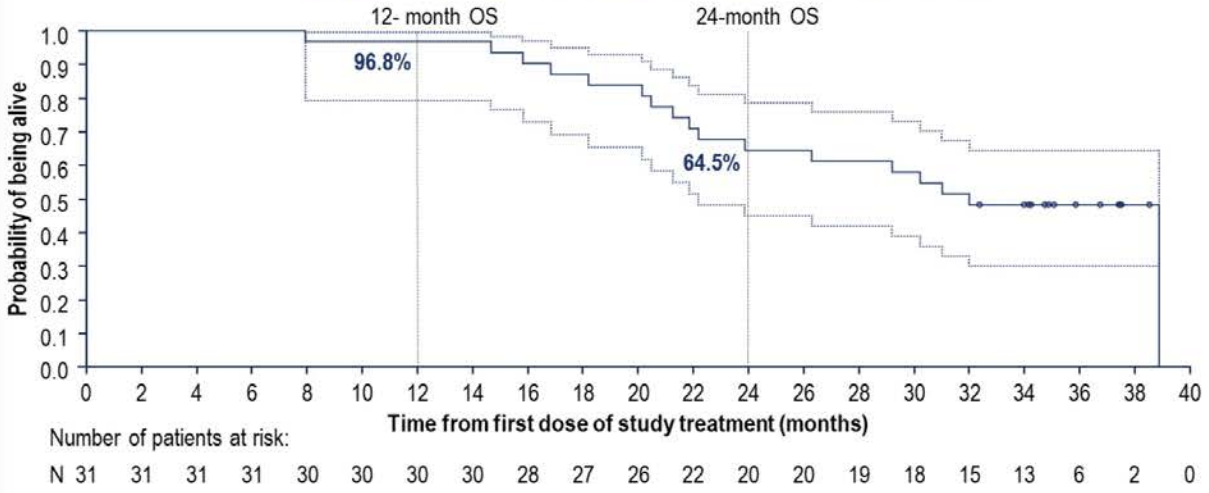
	Olap + durva + bev (N=31)	Olap + durva (N=32)
Median age, years	64.0	68.5
Age group (years), n (%)		
<50	3 (9.7)	4 (12.5)
≥50–<65	14 (45.2)	8 (25.0)
≥65	14 (45.2)	20 (62.5)
Race, n (%)		
White	20 (64.5)	24 (75.0)
Asian	10 (32.3)	3 (9.4)
Other	1 (3.2)	5 (15.6)
Platinum sensitivity, n (%)		
>6–12 months	18 (58.1)	14 (43.8)
>12 months	13 (41.9)	18 (56.3)
Number of prior lines of chemotherapy, n (%)		
1 prior line	20 (64.5)	23 (71.9)
2 prior lines	11 (35.5)	9 (28.1)
Enrolment completed	January 2019	February 2019
Patients on study treatment at DCO, n (%) (13 February 2020)		
Olap; durva; bev	13 (41.9); 13 (41.9); 12 (38.7)	7 (21.9); 6 (18.8); NA

PSR = platinum-sensitive relapsed; IO = immuno-oncology therapy

Drew Y et al. ESMO 2020;Abstract 814MO.

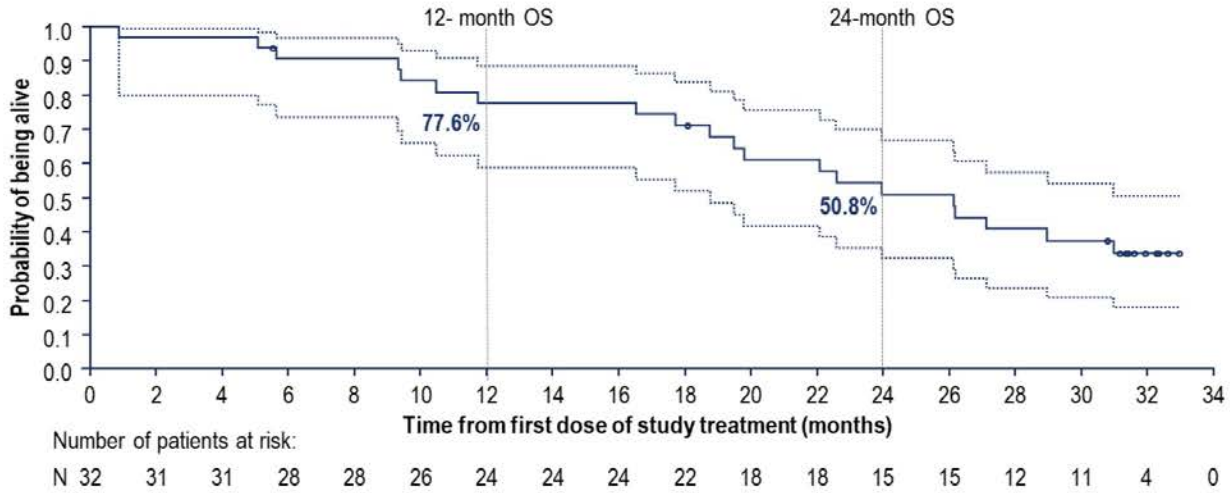
MEDIOLA Non-gBRCA Cohorts: OS and 56-Week DCR

Olaparib plus durvalumab and bevacizumab



	Olaparib plus durvalumab and bevacizumab
Median follow-up for OS, months	31.9
Events, n	17
Median OS (95% CI), months	**31.9 (22.1–NC)**
56-week DCR (90% CI), %	38.7 (24.1–55.0)

Olaparib plus durvalumab



	Olaparib plus durvalumab
Median follow-up for OS, months	23.2
Events, n	20
Median OS (95% CI), months	**26.1 (18.7–NC)**
56-week DCR (90% CI), %	9.4 (2.6–22.5)

Circles represent censored events. Dashed lines represent 95% CI.
Comparisons are not randomized; doublet cohort enrolment commenced once triplet cohort enrolment was complete.

OS = overall survival; DCR = disease control rate

Banerjee S et al. ESMO 2022;Abstract 529MO.

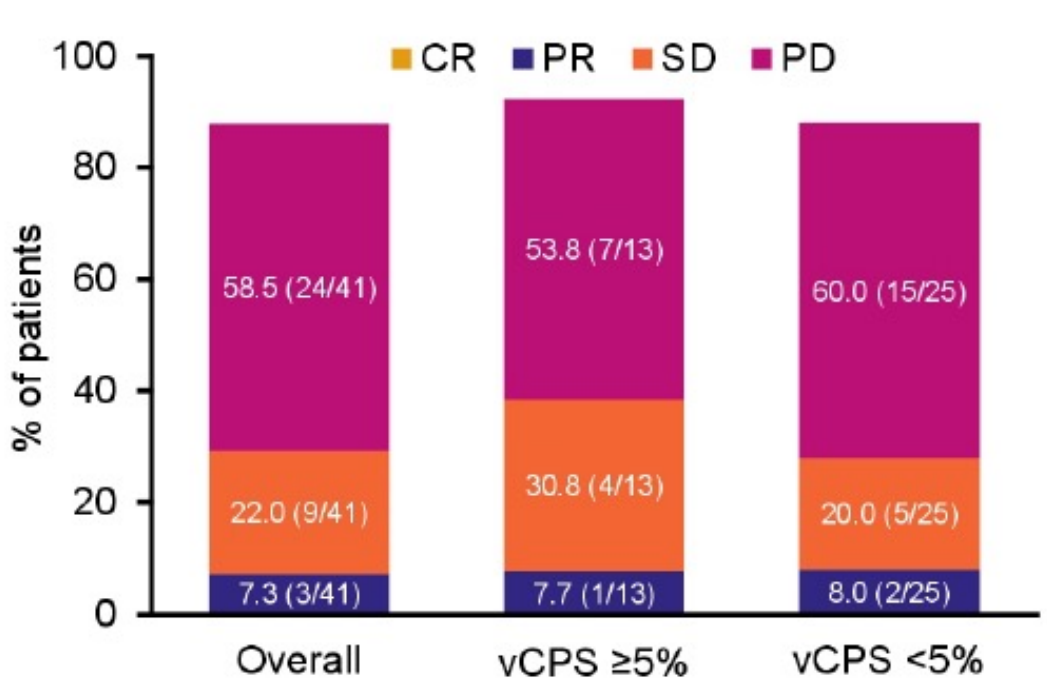
RTP RESEARCH TO PRACTICE

MOONSTONE/GOG-3032: Interim Analysis of a Phase 2 Study of Niraparib + Dostarlimab in Patients (pts) with Platinum-Resistant Ovarian Cancer (PROC)

Randall LM et al.

ASCO 2022;Abstract 5573.

MOONSTONE: Efficacy Summary of Niraparib with Dostarlimab for Platinum-Resistant Ovarian Cancer



Efficacy, n (%) [95% CI]*	Overall N=41	PD-L1 status	
		vCPS ≥5% n=13	vCPS <5% n=25
ORR (CR + PR)	3 (7.3) [1.5–19.9]	1 (7.7) [0.2–36.0]	2 (8.0) [1.0–26.0]
DCR (CR + PR + SD)	12 (29.3) [16.1–45.5]	5 (38.5) [13.9–68.4]	7 (28.0) [12.1–49.4]
Median PFS, months (95% CI)	2.1 (2.0–2.2)	2.2 (1.6–not evaluable)	2.1 (1.8–2.2)

vCPS = visually estimated combined positive score (PD-L1); ORR = objective response rate

Randall LM et al. ASCO 2022;Abstract 5573.

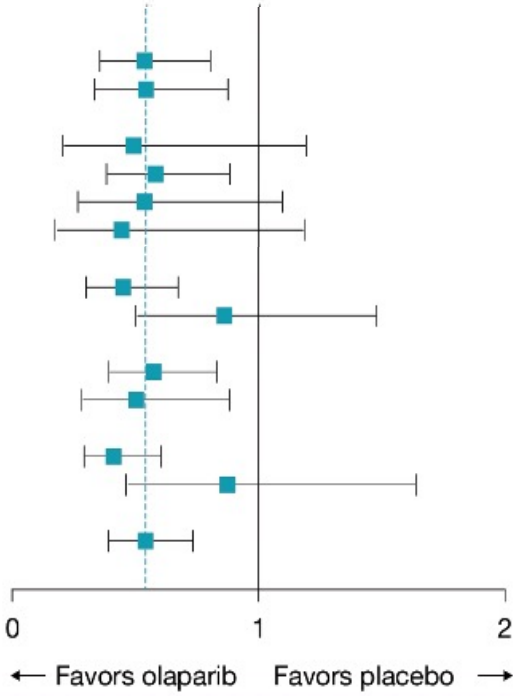
OReO/ENGOT Ov-38 Trial: Impact of Maintenance Olaparib Rechallenge According to Ovarian Cancer Patient Prognosis — An Exploratory Joint Analysis of the BRCA and Non-BRCA Cohorts

Selle F et al.

ASCO 2022;Abstract 5558.

OReO: Post-hoc Analysis of Progression-Free Survival According to Patient Characteristics and Prognostic Factors

Subgroup	Events/N olaparib	Events/N placebo	Hazard ratio (95% CI)	Interaction
Age				0.89
<65	66/84	40/43	0.53 (0.35–0.80)	
≥65	47/62	28/31	0.54 (0.33–0.87)	
Genomic BRCAm and HRD status				0.93
BRCAwt HRD negative	18/31	8/11	0.49 (0.20–1.19)	
BRCAm	65/74	38/38	0.58 (0.38–0.88)	
BRCAwt HRD positive	21/28	13/16	0.53 (0.26–1.09)	
BRCAwt HRD unknown	9/13	9/9	0.44 (0.17–1.18)	
CA-125				0.19
<35	79/104	43/48	0.45 (0.30–0.67)	
≥35	31/39	24/25	0.86 (0.50–1.48)	
ECOG performance status				0.59
0	84/108	44/47	0.57 (0.39–0.83)	
1	29/38	24/27	0.50 (0.28–0.88)	
Visceral site of metastatic disease				0.07
N	71/99	55/60	0.41 (0.29–0.60)	
Y	42/47	13/14	0.87 (0.46–1.64)	
All patients	113/146	68/74	0.54 (0.39–0.73)	



- Olaparib rechallenge was effective regardless of prognostic subgroup
- CA-125 levels and the presence of visceral disease at baseline were the best predictors of patient outcome

Selle F et al. ASCO 2022;Abstract 5558.

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Thank you for joining us!

CME/MOC and NCPD credit information will be emailed to each participant within 5 business days.

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