Cases from the Community: Investigators Discuss the Role of PARP Inhibition in the Care of Actual Patients with Ovarian Cancer

Saturday, March 20, 2021
4:00 PM – 5:00 PM ET

Faculty

Susana Banerjee, MBBS, MA, PhD
Richard T Penson, MD, MRCP
Shannon N Westin, MD, MPH

Moderator

Neil Love, MD

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Faculty

Susana Banerjee, MBBS, MA, PhD
Consultant Medical Oncologist
Research Lead, Gynecological Cancers
Reader in Women's Cancers
The Institute of Cancer Research
The Royal Marsden NHS Foundation Trust
London, United Kingdom

Shannon N Westin, MD, MPH
Associate Professor
Director, Early Drug Development
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas
MD Anderson Cancer Center
Houston, Texas

Richard T Penson, MD, MRCP
Associate Professor of Medicine
Harvard Medical School
Clinical Director, Medical Gynecologic Oncology
Massachusetts General Hospital
Boston, Massachusetts

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP and Merck.

Dr Love — Disclosures

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Dr Banerjee — Disclosures

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Dr Penson — Disclosures

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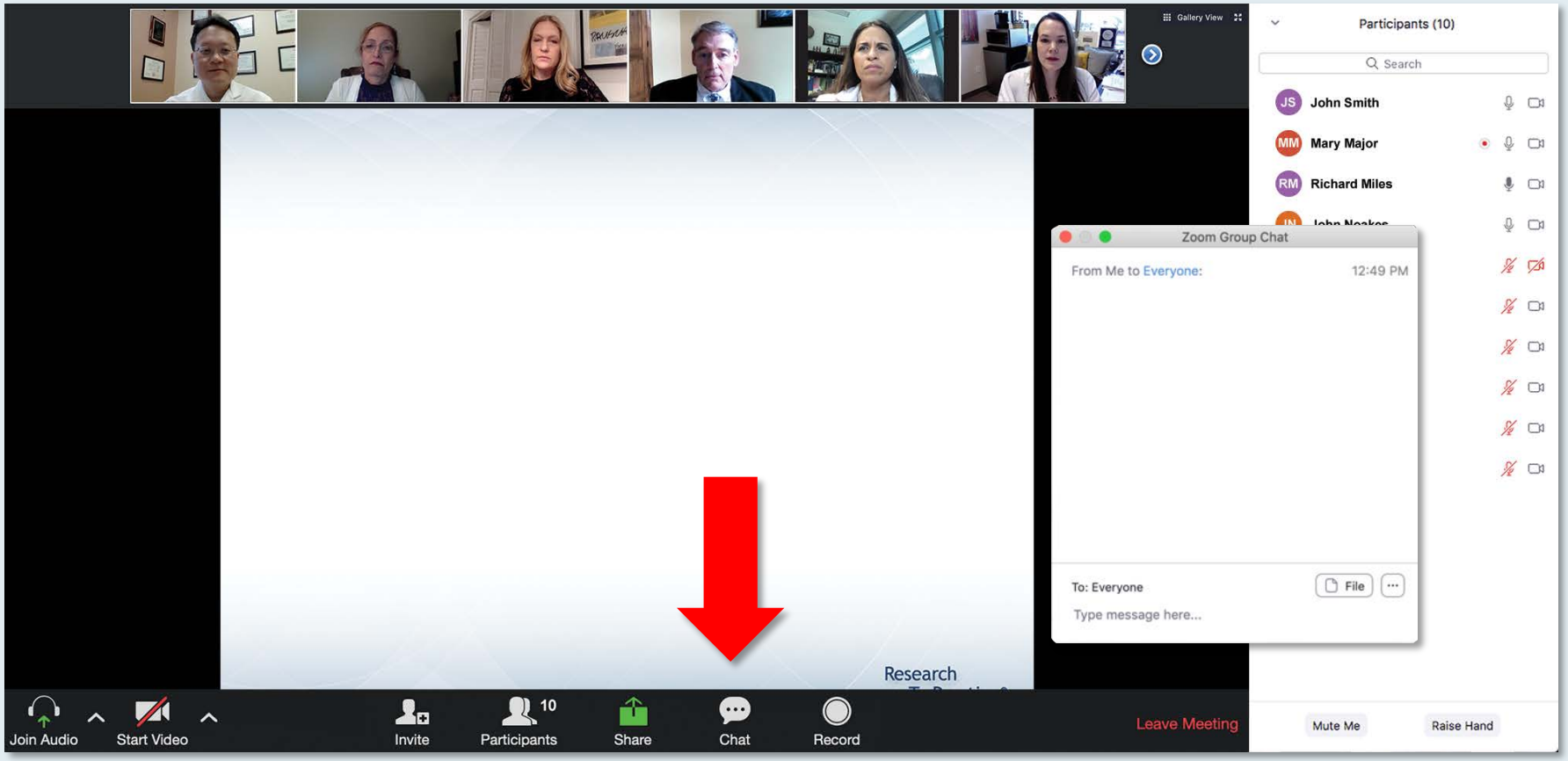
We Encourage Clinicians in Practice to Submit Questions



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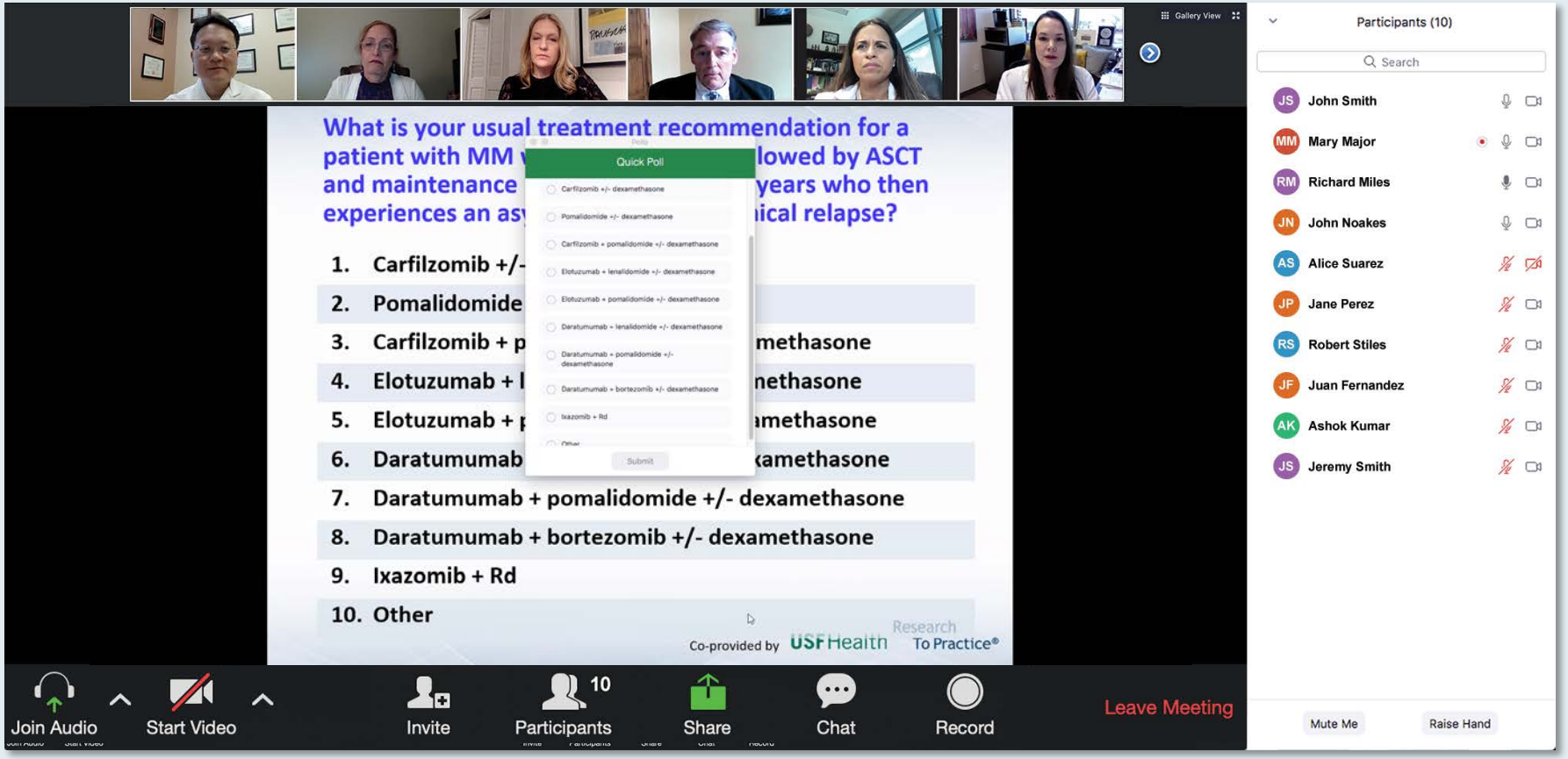
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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WITH DR NEIL LOVE

PARP Inhibitors in Ovarian Cancer

DR ANTONIO GONZÁLEZ-MARTÍN

CLÍNICA UNIVERSIDAD DE NAVARRA

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Thursday, March 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Robert J Motzer, MD

Moderator

Neil Love, MD

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Meet The Professor

Management of Chronic Lymphocytic Leukemia

Monday, March 29, 2021
5:00 PM – 6:00 PM ET

Faculty

Philip A Thompson, MB, BS

Moderator

Neil Love, MD

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Meet The Professor

Immunotherapy and Novel Agents in Gynecologic Cancers

Monday, April 5, 2021
5:00 PM – 6:00 PM ET

Faculty

Bradley J Monk, MD

Moderator

Neil Love, MD

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TO PRACTICE

Ask the Expert: Clinical Investigators Provide Perspectives on the Management of Renal Cell Carcinoma

Tuesday, April 6, 2021
12:00 PM – 1:00 PM ET

Faculty

Sumanta K Pal, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Advanced Gastrointestinal Cancers

Thursday, April 8, 2021
5:00 PM – 6:00 PM ET

Faculty

Professor Dirk Arnold, MD, PhD

Moderator

Neil Love, MD

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Ask the Investigators: Applying Emerging Clinical Research to the Care of Patients with Gastroesophageal Cancers

A Satellite Educational Symposium Held in Conjunction with the 2021 AACR Virtual Annual Meeting

Monday, April 12, 2021
6:30 PM – 7:30 PM ET

Faculty

Joseph Chao, MD
Yelena Y Janjigian, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Management of Chronic Lymphocytic Leukemia

Thursday, April 15, 2021
5:00 PM – 6:00 PM ET

Faculty

John N Allan, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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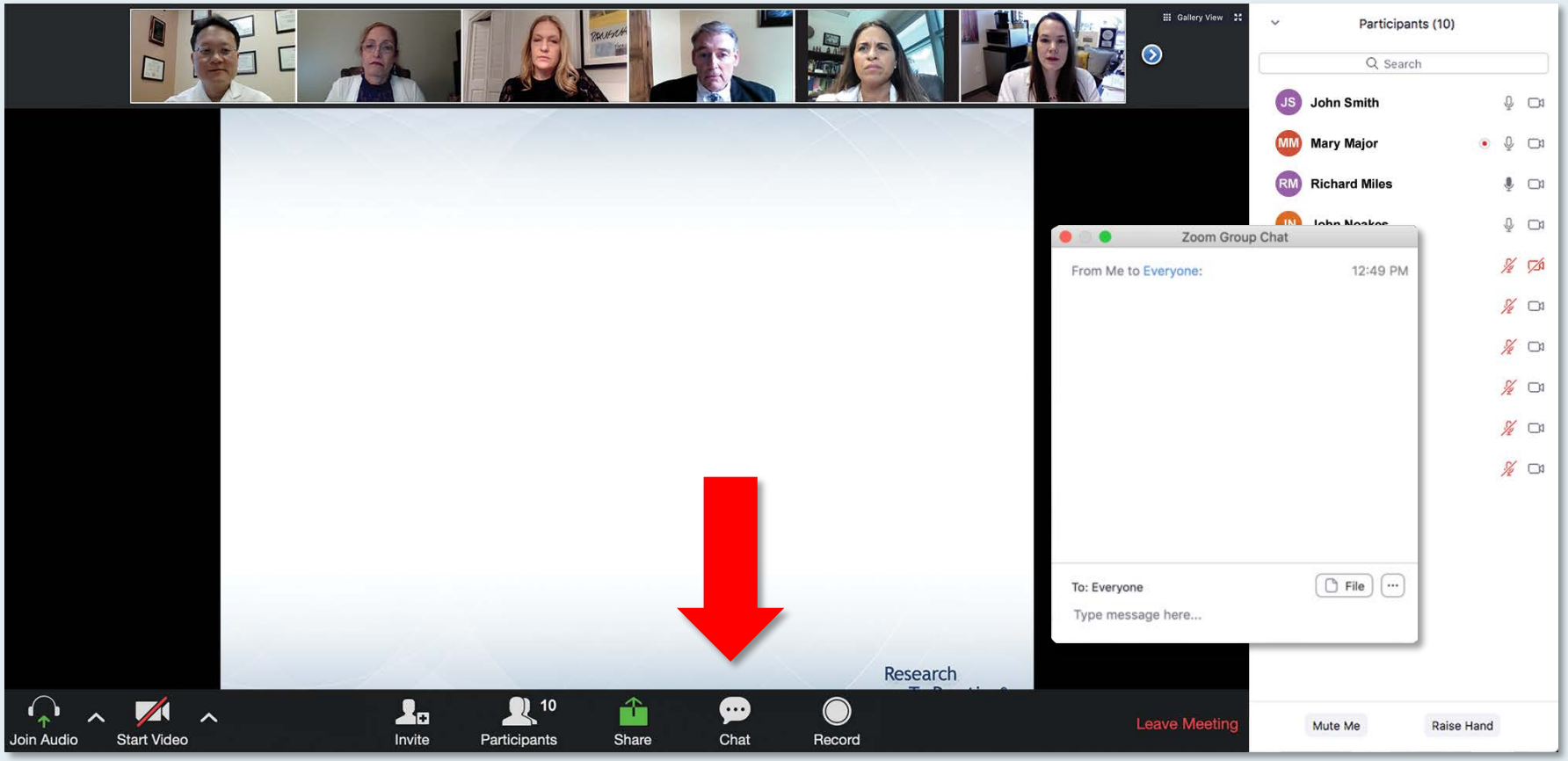

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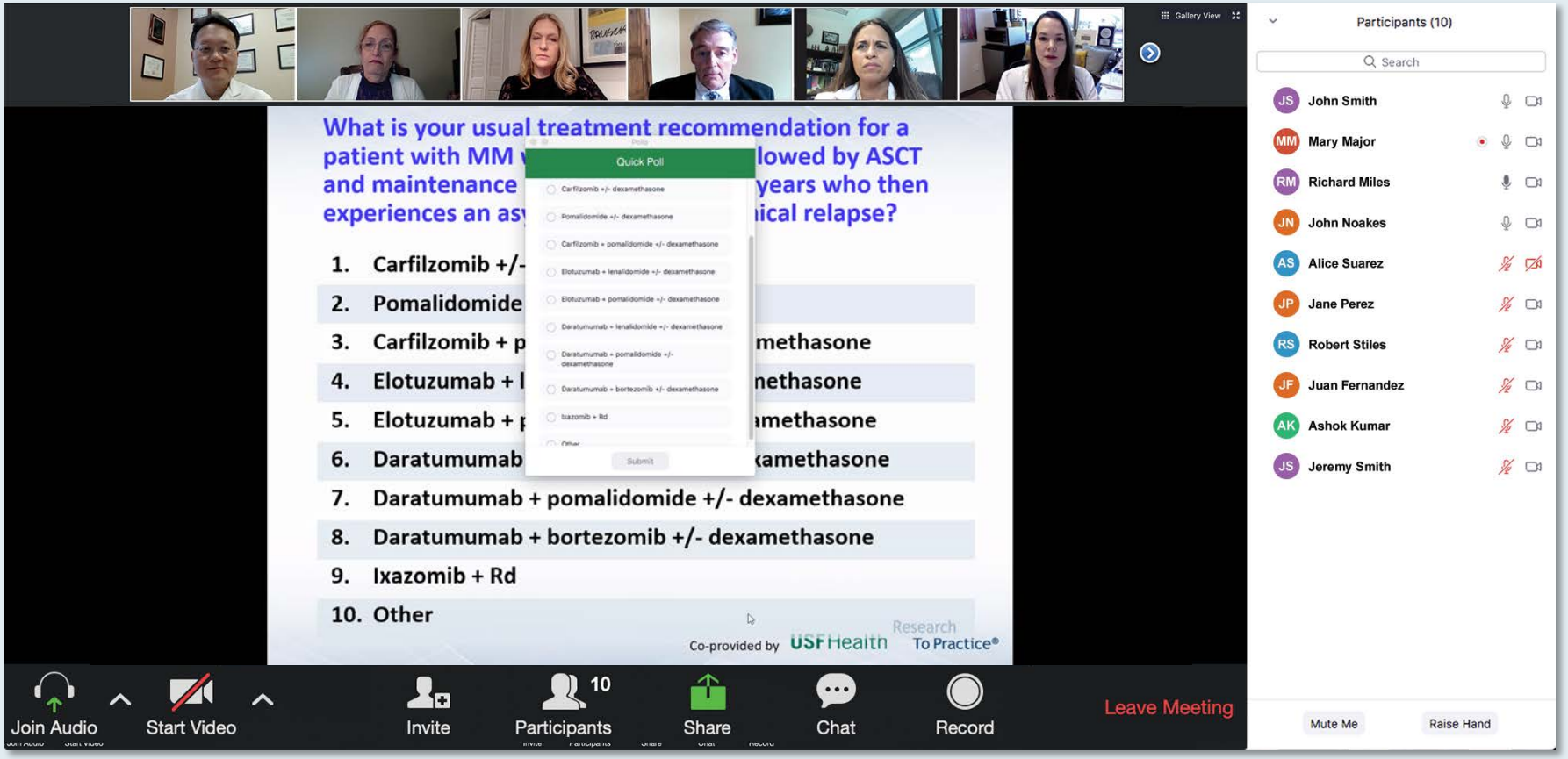

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Dana M Chase, MD
Gynecologic Oncologist
Arizona Oncology
Phoenix, Arizona

Heidi E Godoy, DO
Women's Cancer Care Associates
Albany, New York

Sulfi Ibrahim, MD
Hematology/Oncology
Reid Health
Richmond, Indiana

Yanjun Ma, MD
Tennessee Oncology
Murfreesboro, Tennessee

Laurie Matt-Amaral, MD, MPH
Attending Physician
Cleveland Clinic Akron General
Medical Center
Akron, Ohio

Shachar Peles, MD
Florida Cancer Specialists
and Research Institute
Atlantis, Florida

Lyndsay J Willmott, MD
Division of Gynecologic Oncology
Dignity Health St Joseph's Hospital
and Medical Center
Phoenix, Arizona

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Agenda

Module 1: Case Presentations

- Dr Ma: A 67-year-old woman with recurrent serous papillary adenocarcinoma of the fallopian tube – Germline BRCA1 mutation
- Dr Willmott: A 66-year-old woman with Stage IIIC fallopian tube carcinoma – No deleterious mutations
- Dr Peles: A 79-year-old woman with ovarian cancer (OC) – Germline BRCA2 mutation
- Dr Willmott: A 45-year-old woman with Stage IIIC serous OC – Germline BRCA1 mutation

Module 2: PARP Inhibitor Maintenance Therapy

Module 3: Case Presentations

- Dr Matt-Amaral: A 69-year-old woman with Stage IV OC – Germline BRCA1 mutation
- Dr Ibrahim: A 77-year-old woman with Stage IIIC OC with a germline BRCA mutation who develops anemia on olaparib
- Dr Godoy: Questions and Comments — Niraparib-associated thrombocytopenia and surgical procedures
- Dr Chase: A 76-year-old woman with recurrent OC – Germline and somatic BRCA2 mutation

Module 4: Management of Side Effects; Novel Strategies with PARP Inhibitors

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OlympiA Trial: Olaparib Crosses Superiority Boundary for Invasive Disease-Free Survival versus Placebo at Planned Interim Analysis

Press Release: February 17, 2021

“The Phase 3 OlympiA trial for olaparib will move to early primary analysis and reporting following a recommendation from the Independent Data Monitoring Committee (IDMC).
Based on the planned interim analysis, the IDMC concluded that the trial crossed the superiority boundary for its primary endpoint of invasive disease-free survival (iDFS) versus placebo in the adjuvant treatment of germline *BRCA*-mutated (g*BRCA*m), high-risk human epidermal growth factor receptor 2 (HER2)-negative early-stage breast cancer following definitive local treatment and neoadjuvant or adjuvant chemotherapy.

Andrew Tutt, global chair of the OlympiA Phase 3 trial and professor, Institute of Cancer Research and Kings College London, said, "We are delighted that our global academic and industry partnership has been able to help investigate a possible personalized treatment for women with hereditary breast cancer. The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 genes, which also may cause the disease to develop at a significantly earlier age than is usual. The OlympiA trial has allowed us to go beyond using genetic testing to identify patients who are at risk of this disease and explore the potential of olaparib to prevent disease recurrence for these patients. We look forward to analyzing and presenting the full results of the trial at a forthcoming medical meeting."

https://finance.yahoo.com/news/independent-data-monitoring-committee-concludes-115500394.html

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Case Presentation – Dr Ma: A 67-year-old woman with recurrent serous papillary adenocarcinoma of the fallopian tube – Germline BRCA1 mutation

Dr Yanjun Ma

- 2013: Stage IIIC HGSOC s/p debulking surgery and adjuvant carboplatin/paclitaxel and maintenance olaparib *off label*
- 10/2017: Local recurrence → Radioablation of hepatic dome lesion
- 5/2020: Persistently rising CA125 with radiographic change → Switched from olaparib to niraparib
- 11/2020: PD in hepatic lesion → SBRT completed 1/2021, with CA125 response

Case Presentation – Dr Willmott: A 66-year-old woman with Stage IIIC fallopian tube carcinoma – No deleterious mutations

Lyndsay J Willmott, MD

- Upfront debulking surgery (no gross residual disease) → Adjuvant carboplatin/paclitaxel x 6
- Genetic testing: Negative for deleterious mutations
- LOH assay: DDR proficiency

Case Presentation – Dr Peles: A 79-year-old woman with ovarian cancer – Germline BRCA2 mutation

Dr Schahar Peles

- 4/2018: Presented to hospital with abdominal pain/constipation
- CT consistent with bowel perforation → Emergent exploratory laparotomy, right hemicolectomy and ileostomy → Diagnosed with ovarian cancer
- Neoadjuvant carboplatin/paclitaxel x 3 → TAH/BSO, radical dissection, omentectomy
  - Testing: BRCA2 mutation
- Adjuvant carboplatin/paclitaxel x 2, discontinued due to significant fatigue affecting ADL
- Maintenance niraparib

Questions

- Are bowel perforations seen in patients with ovarian cancer at presentation? And if so, how common or uncommon is that occurrence?
- Do you agree with the use of a PARP inhibitor as maintenance therapy in a patient such as this? Which PARP inhibitor do you prefer? Is there data favoring one PARP inhibitor compared to the others in this situation? What toxicities do you typically observe with the different PARP inhibitors, and does that influence your preference?

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Case Presentation – Dr Willmott: A 45-year-old woman with Stage IIIC serous ovarian cancer – gBRCA1 mutation

Lyndsay J Willmott, MD

- Neoadjuvant carboplatin/paclitaxel x 3 → interval debulking, with no gross residual disease → adjuvant carboplatin/paclitaxel x 3 (NED)
- Genetic testing: BRCA1 germline mutation
- Olaparib maintenance
  - Required dose reduction related to fatigue and anemia
  - Plan to discontinue olaparib after 2 years

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Module 4: Management of Side Effects; Novel Strategies with PARP Inhibitors

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BRCA and beyond in advanced ovarian cancer

- Approximately 50% of patients with high grade serous EOC have HRd[1]
- *BRCA*1 and *BRCA*2 mutations are the most common alterations among HRd
  - Around 16% germline *BRCA*mut[2]
  - 4–7% somatic *BRCA*mut[3]
- *BRCA*mut testing is essential and routine clinical practice[4,5]

PARP inhibitors have clinical activity beyond *BRCA* mutated ovarian cancer

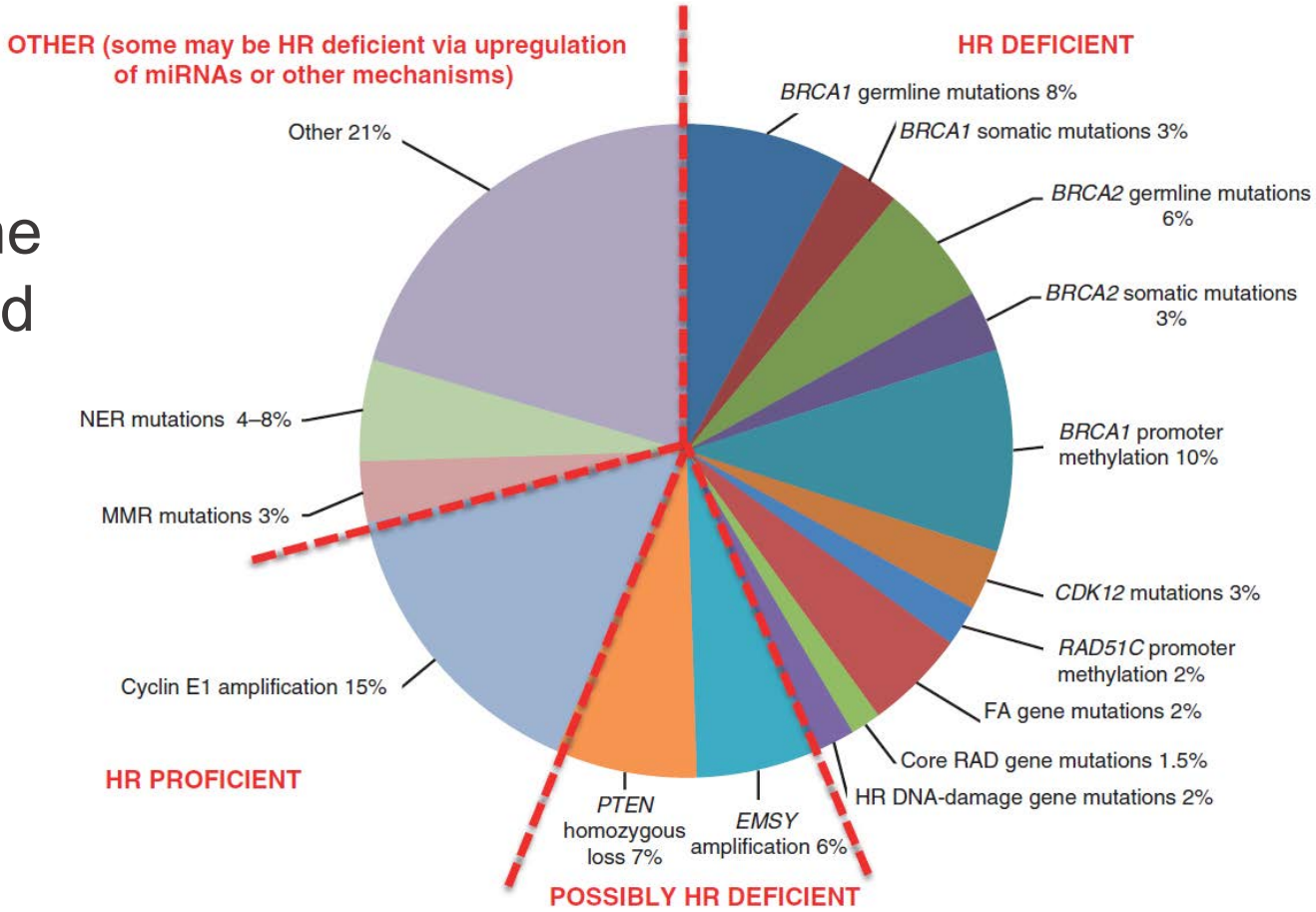


Figure reprinted from Konstantinopoulos PA, et al. *Cancer Discov* 2015;5:1137–1154 with permission from AACR.

BRCA, breast cancer susceptibility gene; *BRCA*mut, *BRCA* mutant; EOC, epithelial ovarian cancer; HR(d), homologous recombination (deficiency); miRNA, microRNA; MMR, mismatch repair; NER, nucleotide excision repair; PARP, poly(ADP-ribose) polymerase.

1. Konstantinopoulos PA, et al. *Cancer Discov* 2015;5:1137–54; 2. George A, et al. *Sci Rep* 2016;6:29506; 3. Moschetta M, et al. *Ann Oncol* 2016;27:1449–1455; 4. Percival N, et al. *Br J Nurs* 2016;25:690–694; 5. George A, et al. *Nat Rev Clin Oncol* 2017;14:284–296.

Courtesy of Susana Banerjee, MBBS, MA, PhD

How to Identify Homologous Recombination Deficiency?

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

- Panel test HRR genes (BRCA1, BRCA2, ATM, RAD51B, RAD51C, RAD54L, RAD51D, FANCJ/BRIP1, FANCL, PALB2, BARD1, CHEK1, CHEK2, CDK12, PPP2)

- Methylation *BRCA1, RAD51C*
  - Need adequate methylation assays

- HRD scarring assays

Courtesy of Susana Banerjee, MBBS, MA, PhD

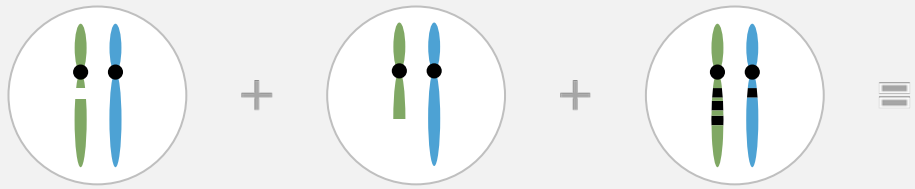
HRD ‘scarring’ assay used in PRIMA and PAOLA-1

Identifies Cancers with a history of HRD: Irrespective of cause

Next generation sequencing of DNA from tumour tissue

Provides a score based on algorithmic measurement of three tumour factors:

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



HR status is determined by the following:

- **HRd tumours:** Tissue test score ≥42 **OR** a *BRCA* mutation
- **HRp tumours:** Tissue test score <42
- HR not determined

Courtesy of Susana Banerjee, MBBS, MA, PhD

A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p optimal debulking surgery with a normal CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

1. Carboplatin/paclitaxel
2. Carboplatin/paclitaxel → olaparib
3. Carboplatin/paclitaxel → niraparib
4. Carboplatin/paclitaxel + bevacizumab → olaparib
5. Carboplatin/paclitaxel + bevacizumab → niraparib
6. Carboplatin/paclitaxel + bevacizumab → bevacizumab/olaparib
7. Carboplatin/paclitaxel + bevacizumab → bevacizumab/niraparib
8. Other

A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p suboptimal debulking surgery with an elevated CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

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A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD-positive) is s/p optimal debulking surgery with a normal CA-125 level. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?

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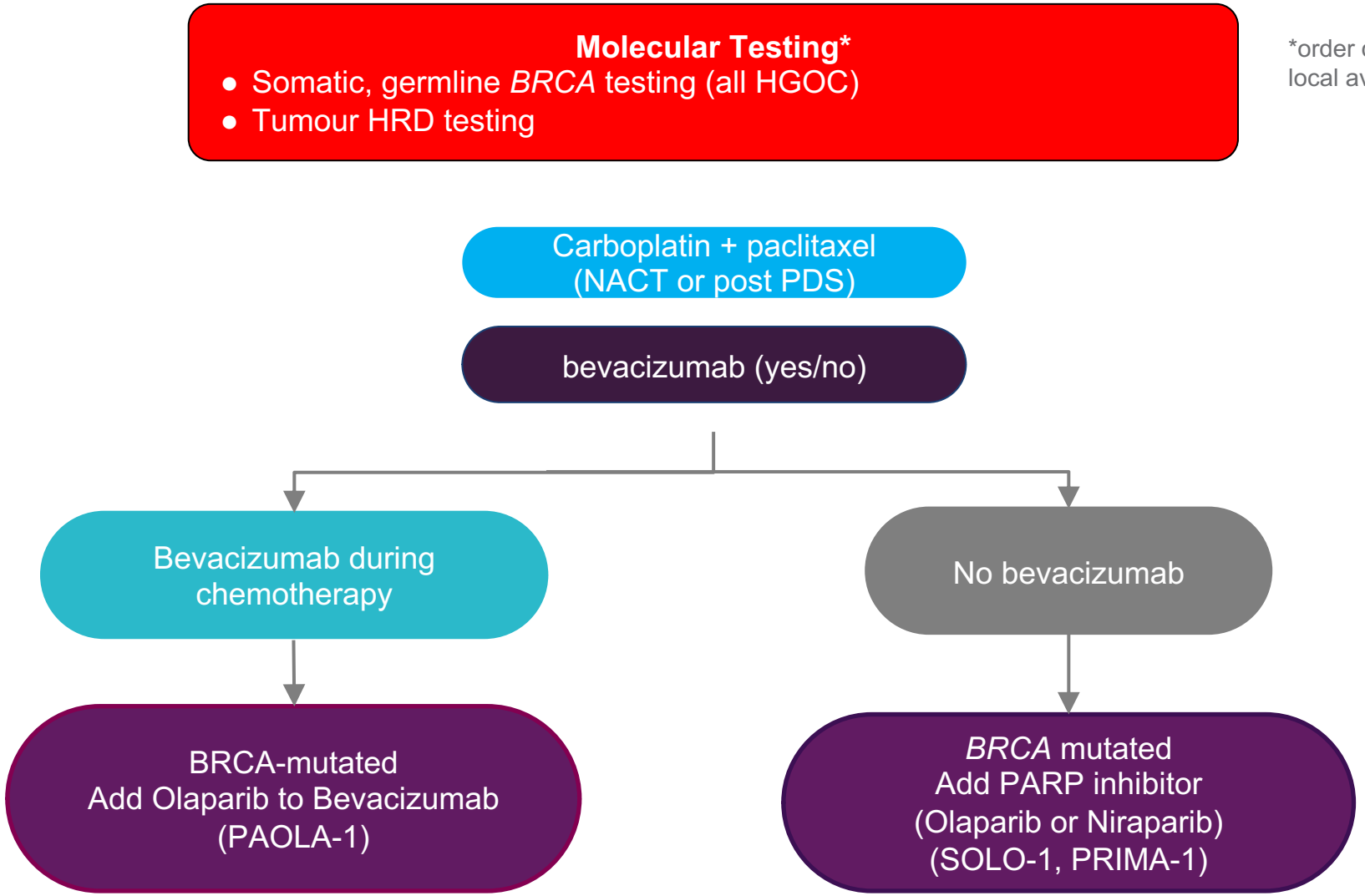
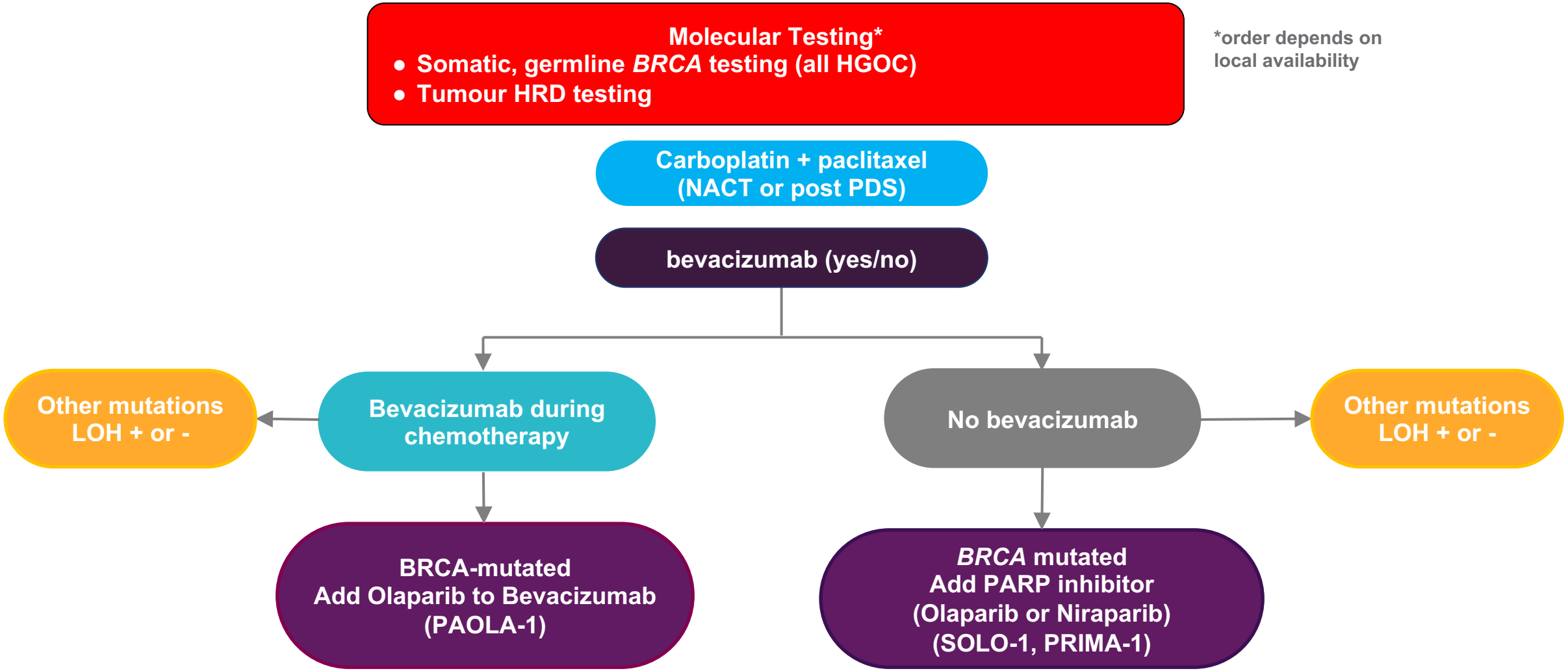
8. Other

Treatment options for newly diagnosed BRCA mutated OC



Courtesy of Susana Banerjee, MBBS, MA, PhD

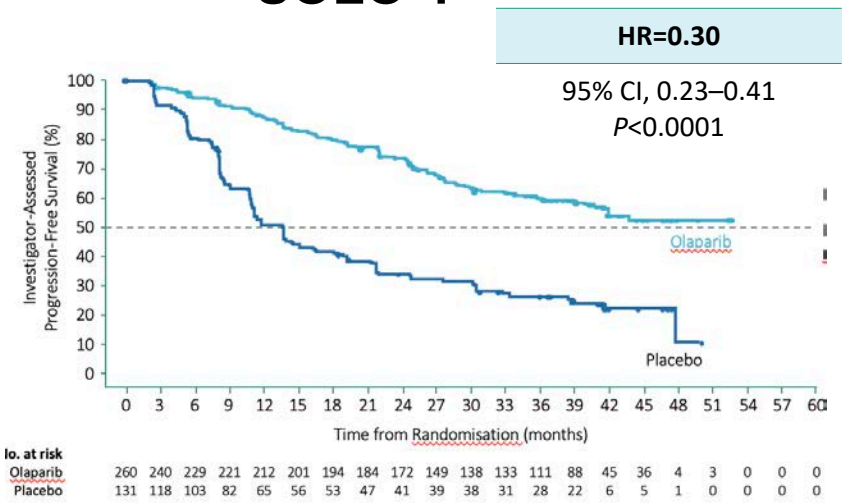
Treatment options for newly diagnosed OC



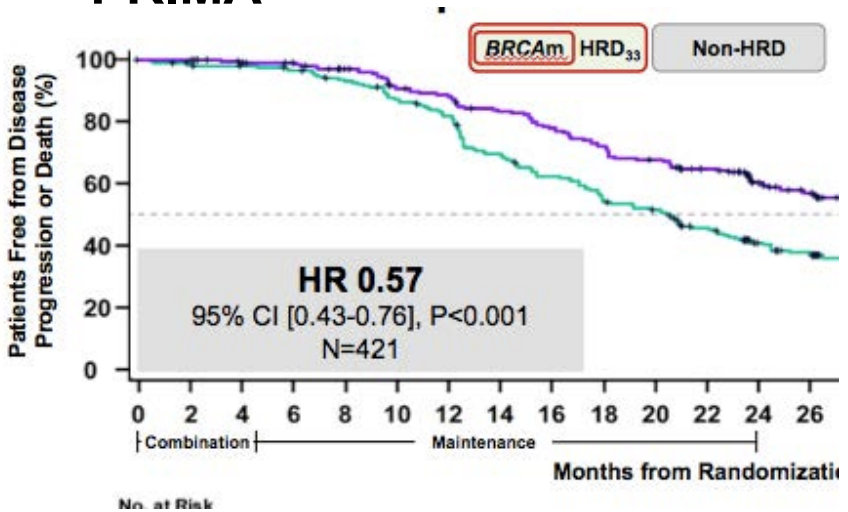
Courtesy of Susana Banerjee, MBBS, MA, PhD - *Modified*

PARP Inhibition Has Arrived in Front Line

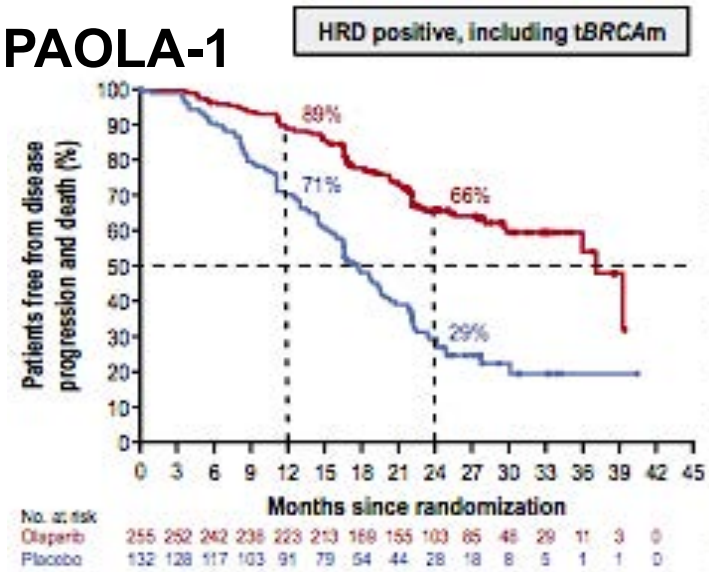
SOLO-1



PRIMA



PAOLA-1



Courtesy of Shannon N Westin, MD, MPH

Phase 3 1L Maintenance Trials

Study Design		GOG-0218 (N=1873)	SOLO-1 (N=451)	PAOLA-1 (N=612)	PRIMA (N=620)	VELIA (N=1140)
Treatment arms vs placebo		Bevacizumab (n=625)	Olaparib (n=260)	Bevacizumab ± Olaparib	Niraparib	Veliparib
Key Patient Population		All comers	*BRCA* mutation	All comers	All comers	*All comers*
Undergo tumor testing		HRR (post-hoc)	*BRCA*	*BRCA*	HRD	*BRCA*
Stage	III	73.8%	84.6%	Eligible	Eligible: Attempt upfront debulking	Eligible
	IV	26.2%	15.4%	Eligible	Eligible: Any debulking attempts	Eligible
Surgery	Residual disease after surgery	Stage III incomplete • Macroscopic: 32.8% • >1 cm: 41.0%	Macroscopic[a] • Primary: 23.0% • Interval: 19.1%	NR[b]	Required for Stage III	Primary or Interval
	Inoperable disease	0	1.5%	NR[b]	Eligible	
Treatment Duration		15 months	24 months	15 months for Bev 24 months for Olaparib	36 months or until PD	24 months

[a]Residual disease based on stage was not reported. [b]Stage III and IV eligible, but requirements for prior surgery not reported (NR) on clinicaltrials.gov

Burger RA, *N Engl J Med.* 2011; Norquist B *Clin Cancer Res* 2018*; Bevacizumab* prescribing information; Moore K, NEJM 2018; Gonzalez-Martin NEJM 2019; Ray-Coquard NEJM 2019; Coleman NEJM 2019

Courtesy of Shannon N Westin, MD, MPH

Phase 3 1L Maintenance Trials

Study	Histo	*BRCA* Status	Surgical Status	Randomization/ Start of PARPi	Experim. Arm	Control Arm	All Pts	*BRCA*-mut [HR] med PFS [months]	*BRCA*-wt HRD	HRP
SOLO-1	HGS/ HGE	mut	All comers	Maint.	Olaparib	Placebo	NT	HR 0.30 (0.23, 0.41) PFS: NYR vs 13.8	NT	NT
PRIMA	HGS/ HGE	All comers	PDS: IV or RD IDS: all	Maint.	Niraparib	Placebo	HR 0.62 (0.50, 0.76) PFS: 13.8 vs 8.2	*HR 0.43 (0.31, 0.59) PFS: 21.9 vs 10.4	HR 0.50 (0.31, 0.83) PFS: NR	HR 0.68 (0.49, 0.94) PFS: NR
VELIA	HGS/	All comers	All comers	Upfront	Veliparib	Placebo	HR 0.68 (0.56, 0.83) PFS: 23.5 vs 17.3	HR 0.44 (0.28, 0.68) PFS: 34.7 vs 22.0	HR 0.74 (0.52, 1.06) PFS: 22.9 vs 19.8	HR 0.81 (0.60, 1.09) PFS: 15.0 vs 11.5
PAOLA-1	HGS/HGE/ nonmuc. *BRCA*-positive	All comers	All comers	Maint.	Olaparib+ Bev.	Bev. + placebo	HR 0.59 (0.49, 0.72) PFS: 22.1 vs 16.6	HR 0.33 (0.25, 0.45) PFS: 37.2 vs 17.7	HR 0.43 (0.28, 0.66) PFS: 28.1 vs 16.6	HR 0.92 (0.72, 1.17) PFS: 16.6. vs 16.0

Moore K, NEJM 2018; Gonzalez-Martin NEJM 2019; Ray-Coquard NEJM 2019; Coleman NEJM 2019

Courtesy of Shannon N Westin, MD, MPH

Maintenance Olaparib for Patients with Newly Diagnosed, Advanced Ovarian Cancer and a BRCA Mutation: 5-Year Follow-Up from SOLO1

Bradley WH et al. SGO 2021;Abstract 10520.

10224 Scientific Plenary III Seminal Abstract Session: Taking a Deeper Dive into Practice Changing Trials

Saturday, 3/20/2021, 5:00 PM - 6:15 PM

RTP RESEARCH TO PRACTICE

SOLO-1: study design

Patient population

- HGSOC or HGEOC
- FIGO Stage III or IV
- Germline or somatic *BRCA* mutation
- ECOG 0–1
- Cytoreductive surgery
- CR or PR after platinum chemotherapy

Stratification

- Response to platinum chemotherapy

2:1 randomisation

Olaparib 300 mg bid (n=260)

Placebo (n=131)

Treatment until disease progression

Stop treatment if no evidence of disease at 2 years

Can continue treatment if ongoing PR at 2 years

2 years' treatment if no evidence of disease

Primary objective

- Investigator-assessed PFS*

Secondary efficacy objectives

- PFS by BICR
- PFS2
- OS
- TFST
- TSST
- HRQoL

Safety and tolerability

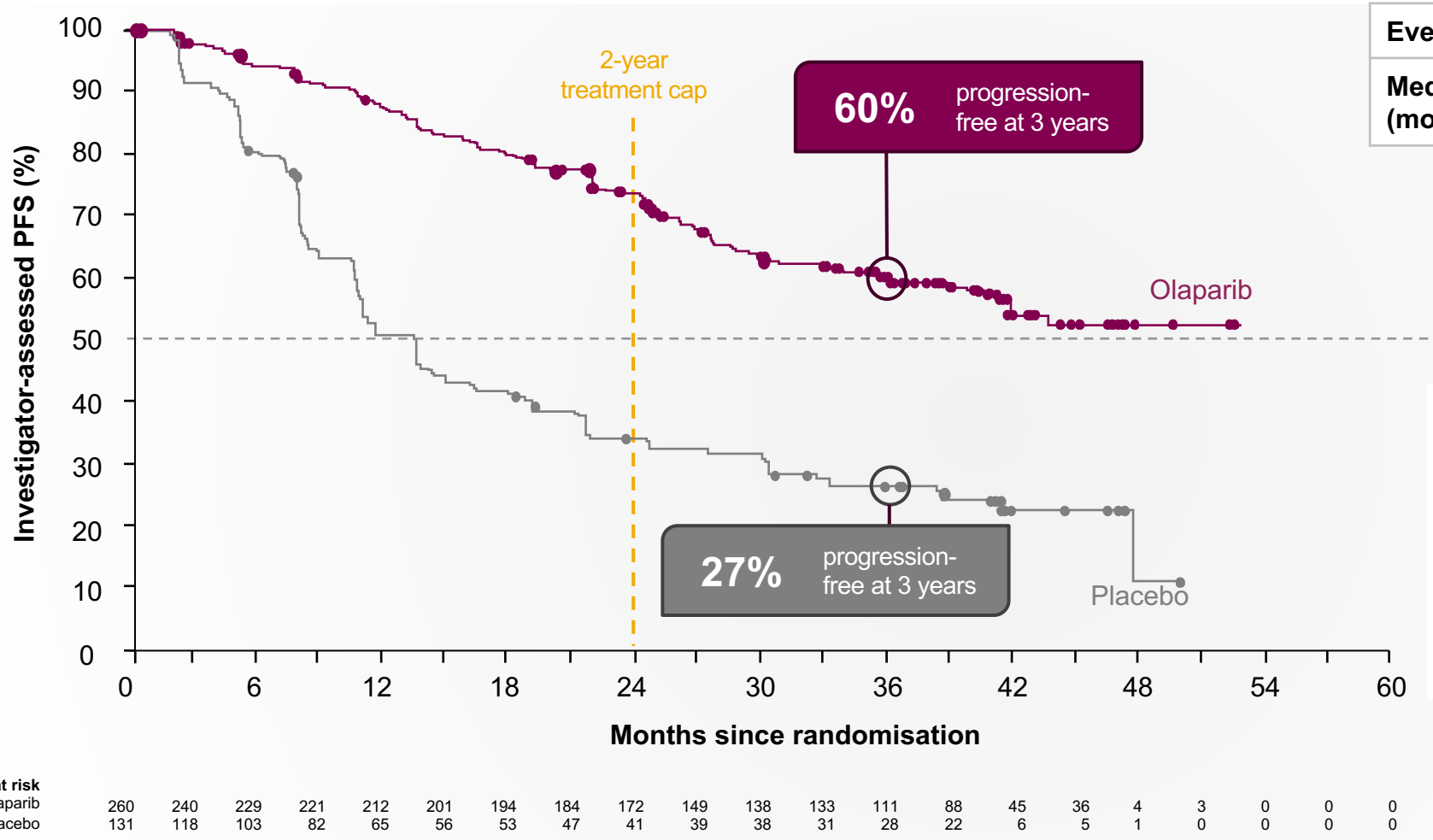
*Modified Response Evaluation Criteria in Solid Tumors version 1.1 criteria
BICR=blinded independent central review; bid=twice daily; BRCA=breast cancer gene; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FIGO=International Federation of Gynecology and Obstetrics; HGEOC=high-grade endometrioid ovarian cancer; HGSOC=high-grade serous ovarian cancer; HRQoL=health-related quality of life; OS=overall survival; PFS=progression-free survival; PFS2=time to second progression or death; PR=partial response; TFST=time from randomisation to first subsequent therapy or death; TSST=time from randomisation to second subsequent therapy or death

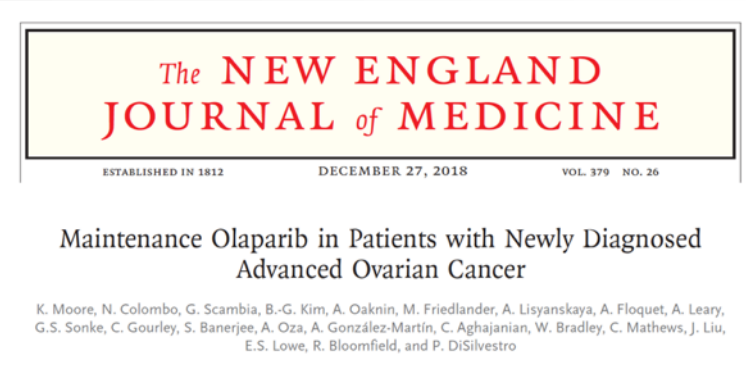
Moore K, et al. N Engl J Med 2018;379:2495–2505

Courtesy of Susana Banerjee, MBBS, MA, PhD

SOLO-1: investigator-assessed PFS (primary endpoint)

	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	102 (39)	96 (73)
Median PFS (months)	NR	13.8
	HR 0.30 95% CI 0.23–0.41 p<0.001	





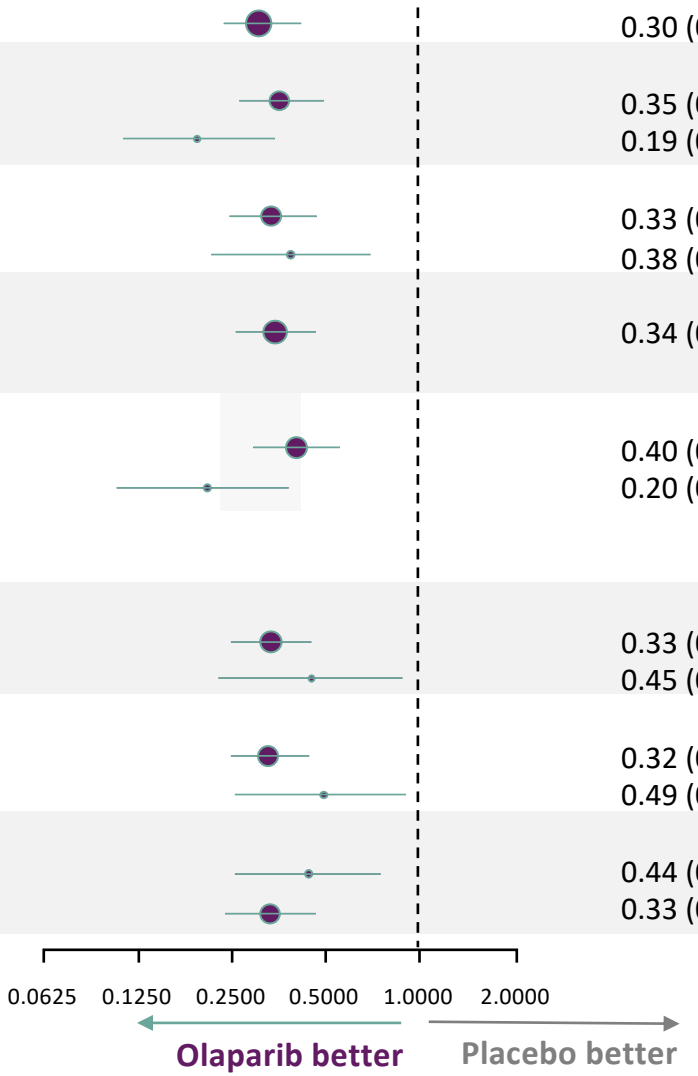
Investigator-assessed PFS
DCO: May 2018; Median follow-up: olaparib, 40.7 months; placebo, 41.2 months
Analysis was performed after 198 progression events had occurred (in 51% of patients)
BICR=blinded independent centralised review; CI=confidence interval; DCO=data cut-off; HR=hazard ratio; NR=not reached; PFS=progression-free survival.

Moore K, et al. *N Engl J Med.* 2018;379:2495–2505

Courtesy of Susana Banerjee, MBBS, MA, PhD

SOLO-1: A consistent benefit was seen across all PFS subgroups

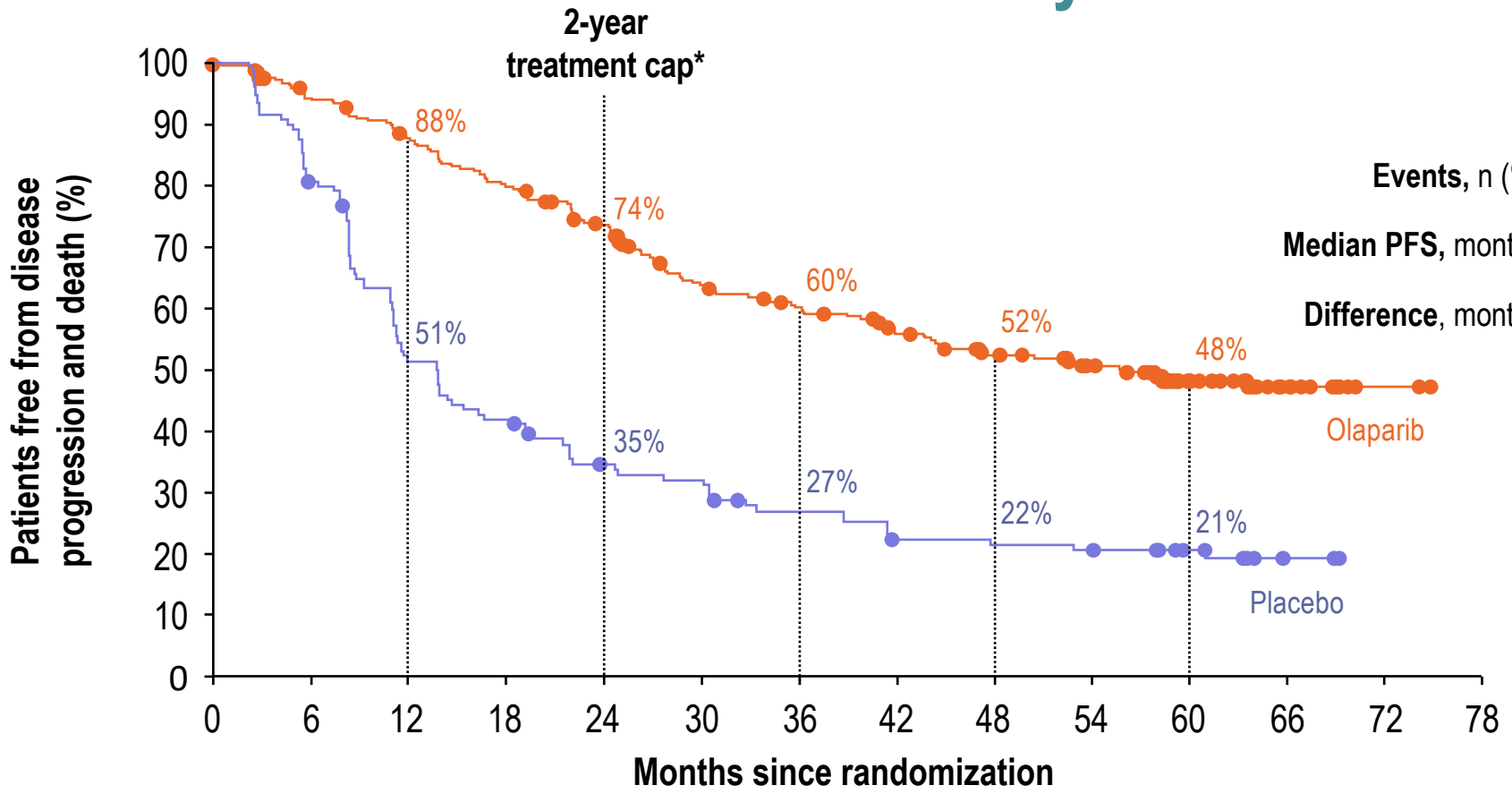
Subgroup	Olaparib	Placebo	HR (95% CI)
	Number of patients with events/total number of patients (%)		
All patients	102/260 (39)	96/131 (73)	0.30 (0.23–0.41)
Response to previous chemotherapy			
Complete response	73/213 (34)	73/107 (68)	0.35 (0.26–0.49)
Partial response	29/47 (62)	23/24 (96)	0.19 (0.11–0.34)
ECOG performance status at baseline			
Normal activity	75/200 (38)	76/105 (72)	0.33 (0.24–0.46)
Restricted activity	27/60 (45)	20/25 (80)	0.38 (0.21–0.68)
Baseline CA-125 value			
≤ULN	92/247 (37)	89/123 (72)	0.34 (0.25–0.46)
>ULN	10/13 (77)	7/7 (100)	NC
gBRCA mutation type			
BRCA1	84/188 (45)	69/91 (76)	0.40 (0.29–0.56)
BRCA2	15/62 (24)	26/39 (67)	0.20 (0.10–0.38)
BRCA1/2 (both)	0/3 (0)	0/0 (0)	NC
Negative	3/7 (43)	1/1 (100)	NC
Age			
<65 years	85/225 (38)	82/112 (73)	0.33 (0.24–0.45)
≥65 years	17/35 (49)	14/19 (74)	0.45 (0.22–0.92)
Stage of disease at initial diagnosis			
Stage III	83/220 (38)	79/105 (75)	0.32 (0.24–0.44)
Stage IV	19/40 (48)	17/26 (65)	0.49 (0.25–0.94)
Following debulking surgery prior to study entry			
Residual macroscopic disease	29/55 (53)	23/29 (79)	0.44 (0.25–0.77)
No residual macroscopic disease	70/200 (35)	69/98 (70)	0.33 (0.23–0.46)



Investigator-assessed PFS.
DCO: May 2018; Median follow-up: olaparib, 40.7 months placebo, 41.2 months.
CA-125, cancer antigen 125; ULN, upper limit of normal; NC, not calculable.
Moore K, et al. *N Engl J Med*. 2018;379:2495–2505.

Courtesy of Susana Banerjee, MBBS, MA, PhD

SOLO-1: PFS benefit of maintenance olaparib was sustained beyond the end of treatment



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
	HR 0.33 (95% CI 0.25–0.43)	

Median treatment duration:
Olaparib, 24.6 months
Placebo†, 13.9 months

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	

*13 patients, all in the olaparib arm, continued study treatment past 2 years; †n=130 (safety analysis set)
Investigator-assessed by modified RECIST v1.1. DCO: 5 March 2020

Banerjee et al ESMO Congress 2020

Courtesy of Susana Banerjee, MBBS, MA, PhD

VIRTUAL 2020 ESMO congress

Secondary efficacy outcomes* support the observed PFS benefit

	Overall		Patients in CR at baseline	
	Olaparib (n=260)	Placebo (n=131)	Olaparib (n=189)	Placebo (n=101)
PFS2				
Events, n (%)	80 (31)	61 (47)	49 (26)	45 (45)
Event free at 5 years, %	64	41	68	44
Median, months	NR	42.1	NR	52.9
	HR 0.46 (95% CI 0.33–0.65)		**HR 0.48** (95% CI 0.32–0.71)	
TSST				
Events, n (%)	95 (37)	77 (59)	64 (34)	56 (55)
Event free at 5 years, %	62	36	65	39
Median, months	NR	40.7	NR	47.7
	HR 0.46 (95% CI 0.34–0.63)		**HR 0.50** (95% CI 0.35–0.72)	

Safety profile remained consistent with the primary DCO

n (%)	Olaparib (n=260)	Placebo (n=130)
Any AE	256 (98)	120 (92)
Grade ≥3 AE	103 (40)	25 (19)
Serious AE	55 (21)	17 (13)
AE leading to dose interruption	136 (52)	22 (17)
AE leading to dose reduction	75 (29)	4 (3)
AE leading to treatment discontinuation	30 (12)	4 (3)
MDS/AML	3 (1)	0 (0)
New primary malignancy	7 (3)	5 (4)

No additional cases of MDS/AML reported; incidence remained <1.5%

Follow-up for MDS/AML continued until death due to any cause

Banerjee et al ESMO Congress 2020

*Measured from randomization. AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; MDS, myelodysplastic syndrome. DCO: 5 March 2020

Courtesy of Susana Banerjee, MBBS, MA, PhD

Differences Between PAOLA-1 & SOLO-1

Different comparator arm
PAOLA-1

- Newly diagnosed FIGO stage III–IV HGSOC or HGEOC (or peritoneal)* and in clinical complete response or partial response after **platinum-based chemotherapy including bevacizumab†**
- ECOG performance status 0–1
- Surgery (upfront or interval)
- **tBRCAm or non-tBRCAm status**

Stratification
- Tumour BRCAm status‡
- First-line treatment outcome ¶

2:1 randomisation

Olaparib (300 mg bid) plus bevacizumab† n=537

Placebo plus bevacizumab† n=269

BRCAm Only
SOLO-1

- Newly diagnosed, FIGO stage III–IV HGSOC or HGEOC (or peritoneal)* and in clinical complete response or partial response after **platinum-based chemotherapy**
- ECOG performance status 0–1
- Surgery (upfront or interval)
- **Germline or somatic BRCAm**

Stratification
- Response to first-line platinum chemotherapy

2:1 randomisation

Olaparib (300 mg bid) n=260

Placebo n=131

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation; †Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 month when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR

bid=twice daily; BRCAm=*BRCA1* and/or *BRCA2* mutation; CR=complete response; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HGEOC=hig endometrioid ovarian cancer; HGSOC=high-grade serous ovarian cancer; NED=no evidence of disease; PR=partial response; tBRCAm=tumour *BRCA1* and/or *BRCA2* mutation

1. Vergote I, et al. Presented at SGO Annual Conference 2020; 2. Moore K et al. *N Engl J Med*. 2018;379(26):2495-2505; 3. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Courtesy of Richard T Penson, MD, MRCP

Homologous Recombination Repair Mutation Gene Panels (Excluding BRCA) Are Not Predictive of Maintenance Olaparib plus Bevacizumab Efficacy in the First-Line PAOLA-1/ ENGOT-ov25 Trial

Pujade-Lauraine E et al. SGO 2021;Abstract 10543.

10224 Scientific Plenary III Seminal Abstract Session: Taking a Deeper Dive into Practice Changing Trials

Saturday, 3/20/2021, 5:00 PM - 6:15 PM

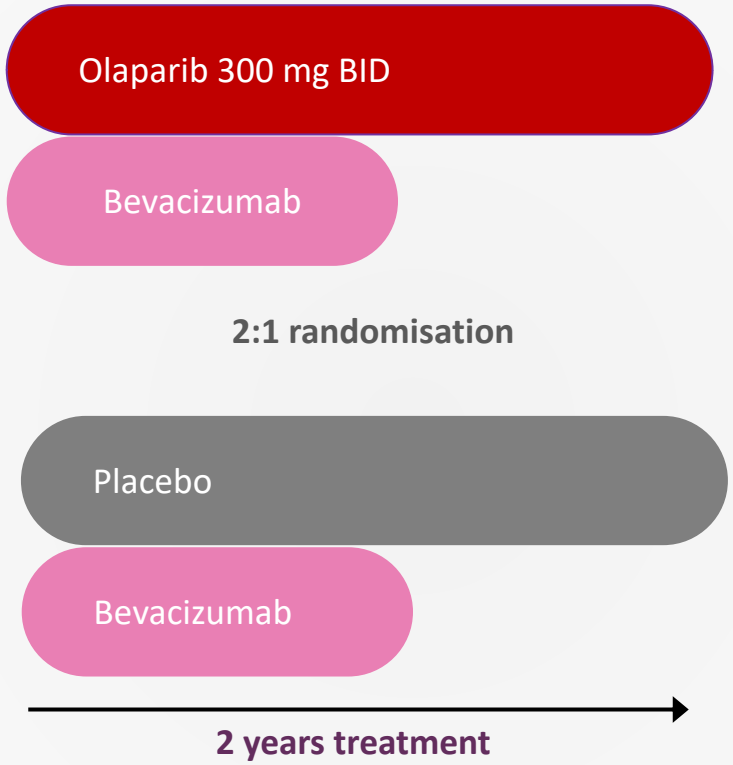
PAOLA-1: Study design

Key inclusion criteria

- Newly diagnosed, FIGO Stage III–IV HGSOC and HGEOC*
- PDS or IDS
- ≥2 cycles of bevacizumab†
- NED/CR/PR

Stratification

- Tumour *BRCA* status‡
- First-line treatment outcome §



Primary objective

- Investigator-assessed PFS*

Secondary efficacy objectives

- PFS2, OS, TFST, TSST, HRQoL

Safety and tolerability

Exploratory PFS analyses

Higher-risk patients:

- FIGO Stage III patients with PDS and residual disease or who had received NACT
- FIGO Stage IV patients

Lower-risk patients:

- FIGO Stage III patients with PDS with no residual disease

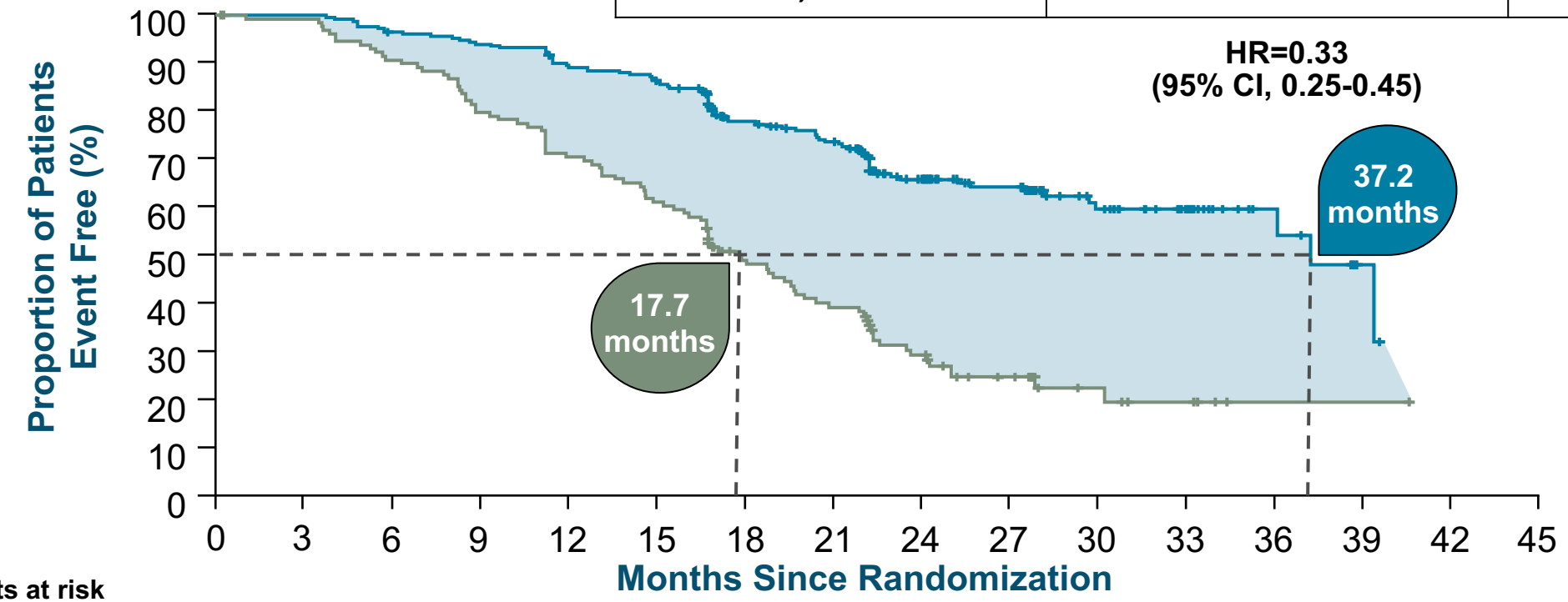
*Includes patients with primary peritoneal and/or fallopian tube cancer; patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation.
†Bevacizumab 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy.
‡By central labs.
§ According to timing of surgery and NED/CR/PR.
NED=no evidence of disease.
Ray-Coquard I, et al. *N Engl J Med.* 2019;381:2416–2428.

Courtesy of Susana Banerjee, MBBS, MA, PhD

PAOLA-1: PFS Olaparib Bevacizumab vs. Bevacizumab

Exploratory prespecified subgroup

	Olaparib + Bevacizumab (n=255)	Placebo + Bevacizumab (n=132)
Median PFS, months	37.2	17.7



No. of patients 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

Regard HRD subgroup analysis with caution:
There was some potential for imbalance bias, since patients were not stratified for HRD status.
In addition, there was some potential for selection bias (since 18% of ITT patients were HRD-unknown).
This exploratory HRD analysis was prespecified.

[a]Select patients for this indication based on an FDA-approved companion diagnostic.[2] [b]Including *BRCA*m as determined by myChoice® CDx and other causes of HRD.[3] HRD positive is defined as either a t*BRCA* mutation and/or an HRD score ≥42 by myChoice® CDx.[4] *BRCA*m=breast cancer susceptibility gene mutation; CI=confidence interval; CDx=companion diagnostic; FDA=US Food and Drug Administration; HR=hazard ratio; HRD=homologous recombination deficiency; ITT, intent to treat; t*BRCA*m=tumor breast cancer susceptibility gene mutation.

Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428.
myChoice® CDx Technical Information.

Courtesy of Richard T Penson, MD, MRCP

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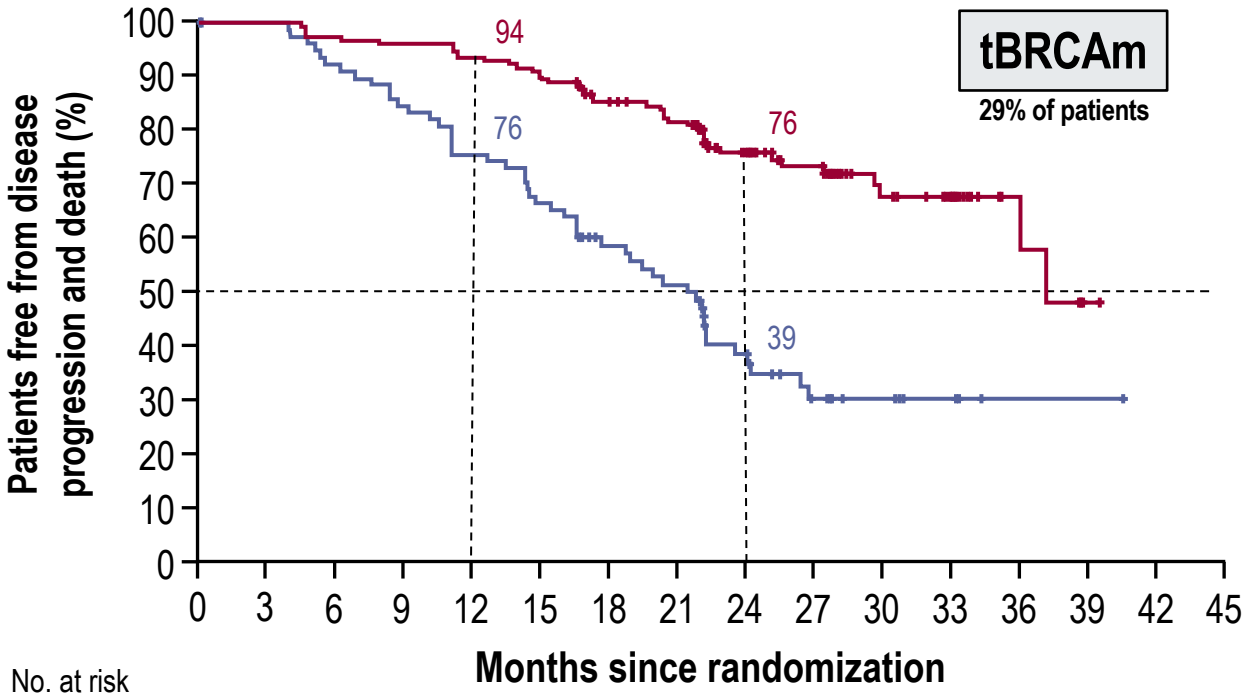
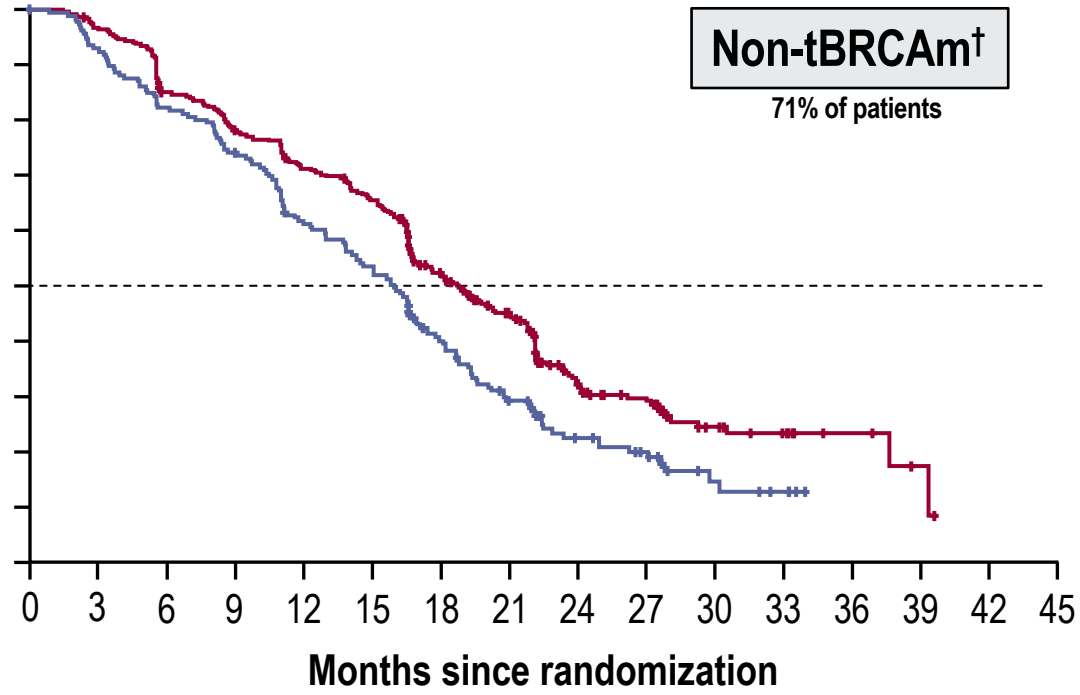
PAOLA-1: PFS by tBRCA mutation status





No. at risk

Olaparib	157	154	150	148	144	138	117	110	76	58	31	19	7	1	0
Placebo	80	78	72	66	59	52	41	36	22	13	7	4	1	1	0

Olaparib	380	359	311	285	259	236	162	130	65	54	24	18	5	2	0
Placebo	189	174	154	139	113	99	68	47	28	22	8	5	0		

	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	41 (26)	49 (61)
Median PFS, months	**37.2***	**21.7**
	HR 0.31 (95% CI 0.20–0.47)	

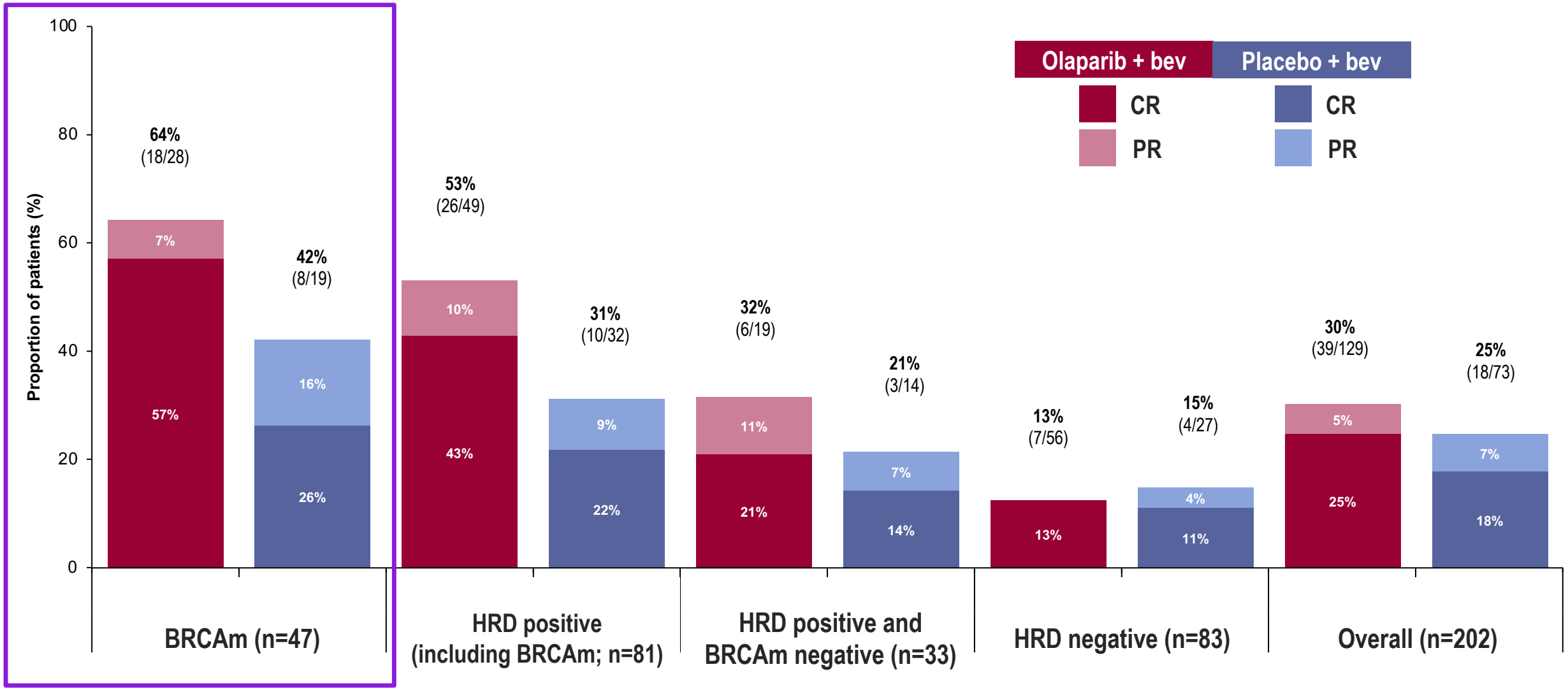
Olaparib + bevacizumab (N=380)	Placebo + bevacizumab (N=189)
239 (63)	145 (77)
18.9	**16.0**
HR 0.71 (95% CI 0.58–0.88)	

Harter et al ESGO 2019

The percentages of patients progression-free at 12 and 24 months have been calculated based on Kaplan-Meier estimates.
*This median is unstable due to a lack of events – less than 50% maturity; †Includes t*BRCA* unknown

Courtesy of Susana Banerjee, MBBS, MA, PhD

PAOLA-1: Olaparib improved RECIST response rate vs placebo when added to bevacizumab in patients with evidence of disease at baseline

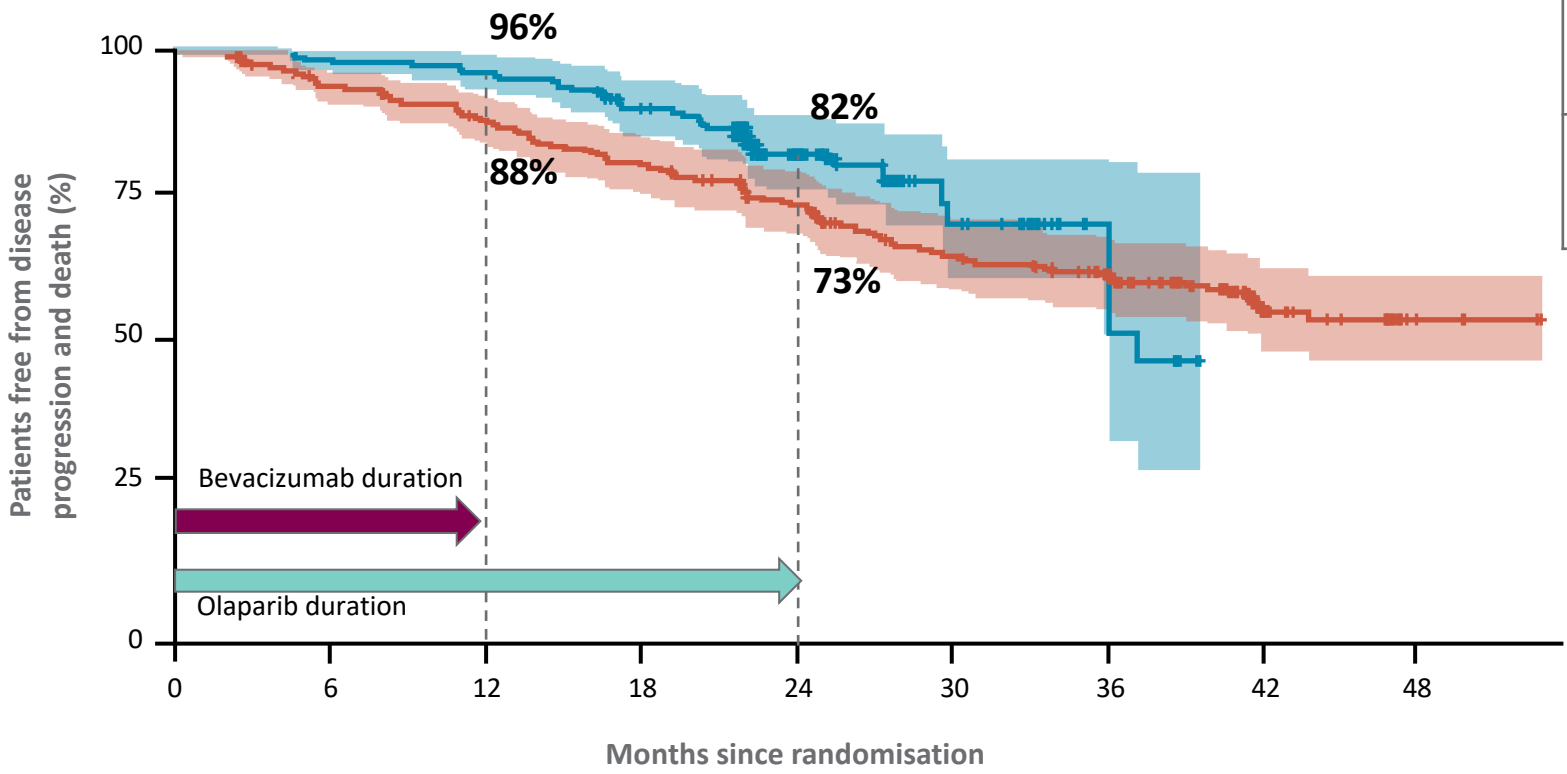


Colombo et al ESMO Congress 2020

Among patients with an HRD status of unknown, RECIST ORR was 25% (6/24) in the olaparib arm and 29% (4/14) in the placebo arm. Data are n (%) unless otherwise indicated. Patients had evidence of disease by RECIST and/or CA-125 ≥2 x ULN at baseline. Percentages may not sum to total because of rounding. *Score ≥42 by HRD test; †One patient in the olaparib arm and four patients in the placebo arm discontinued because of non-RECIST disease progression.

Courtesy of Susana Banerjee, MBBS, MA, PhD

What is the benefit of adding bevacizumab to olaparib in BRCAm patients? Not addressed in PAOLA-1 or SOLO-1 - PAIC PFS analysis[1,2]



	PAOLA-1 BRCAm subset	SOLO-1
	Olaparib + bevacizumab* n=151	Olaparib n=254
Patients progression-free at 12 months, %	96	88
Patients progression-free at 24 months, %	82	73
	HR 0.71 (95% CI 0.45–1.09)†	

- In SOLO-1 mFU was 40.7 vs 41.2 months olaparib vs placebo
- In PAOLA-1 mFU was 22.7 vs, 24.0 months vs placebo + bevacizumab

Head-to-head studies were not conducted between these products. This data is for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.
mFU, median follow-up; PAIC, population-adjusted indirect comparison. *These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval vs upfront), residual disease status after surgery, response to first-line treatment and age to SOLO-1.
†Confidence intervals generated via bootstrapping.

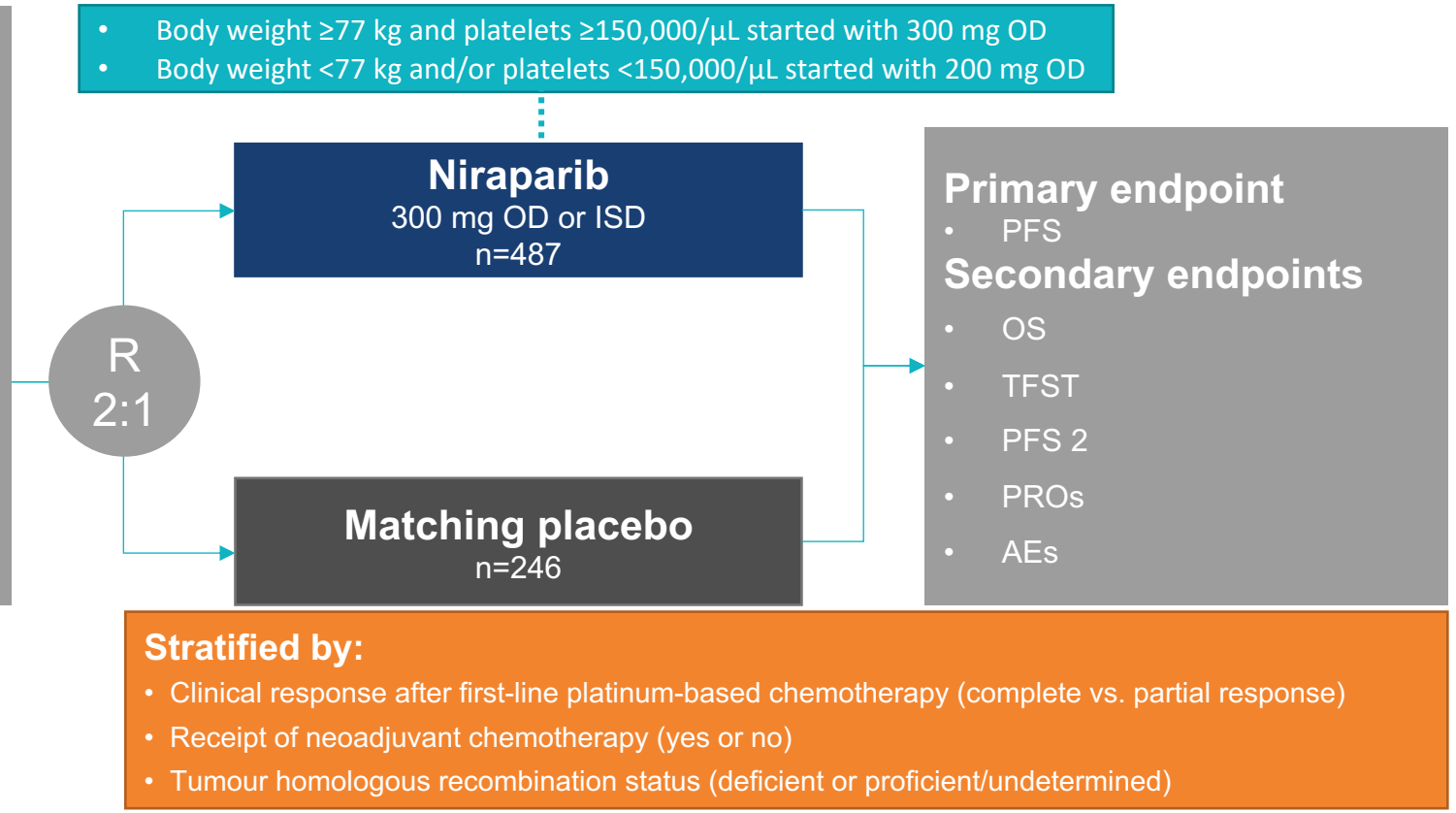
1. Vergote I, et al. Presented at the SGO Annual Meeting 2020. Abstract 35.
2. Burger RA, et al. *N Engl J Med.* 2011;365:2473–2483.

Courtesy of Susana Banerjee, MBBS, MA, PhD

PRIMA Study design: Randomised, double-blind, placebo-controlled, Phase III trial

Patient population

- N=733
- ≥18 years of age
- Newly diagnosed, histologically confirmed advanced ovarian cancer
- High-grade, predominantly serous or endometrioid histological features*
- Complete or partial response to first-line platinum-based chemotherapy
- Stage III patients with visible residual disease after primary debulking surgery
- Stage III and IV* patients with inoperable disease
- Tumour sample testing for *BRCA* mutations or HRd



Illustrative figure adapted from: González-Martín A, et al. *N Engl J Med* 2019;381:2391–402.

*According to the criteria of the International Federation of Gynaecology and Obstetrics.
AE, adverse event; *BRCA*, breast cancer susceptibility gene; HRd, homologous recombination deficient; ISD, individualised starting dose; OS, overall survival; OD, once daily; PFS, progression-free survival; PRO, patient-reported outcome; R, randomised; TFST, time to first subsequent therapy.
González-Martín A, et al. *N Engl J Med* 2019;381:2391–2402.

Courtesy of Susana Banerjee, MBBS, MA, PhD

PRIMA: PFS improved in overall and HRd groups

The NEW ENGLAND JOURNAL of MEDICINE
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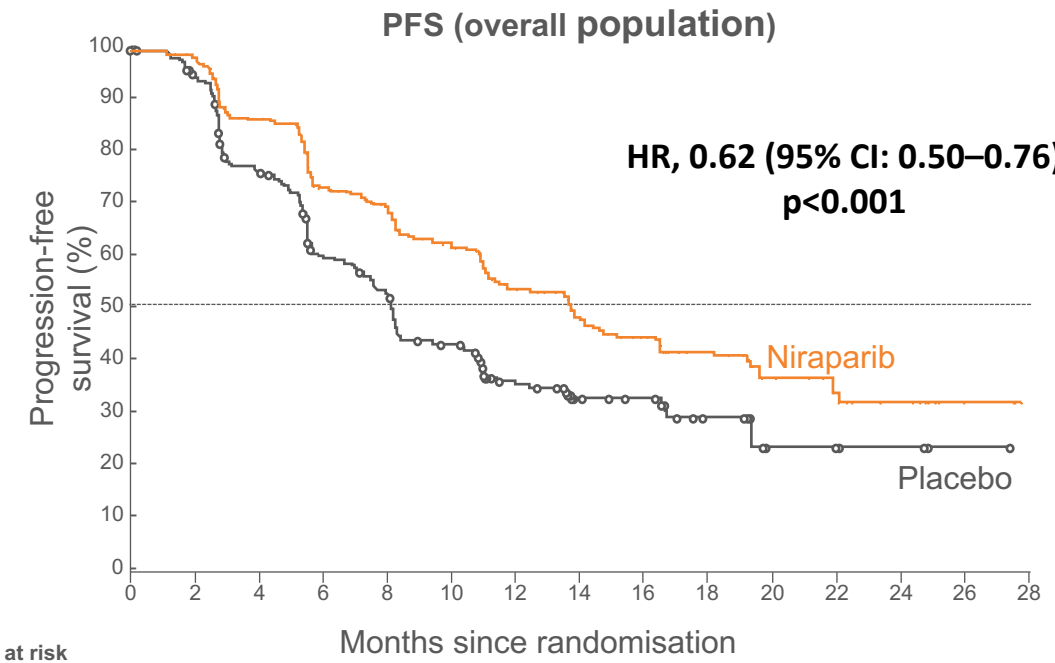
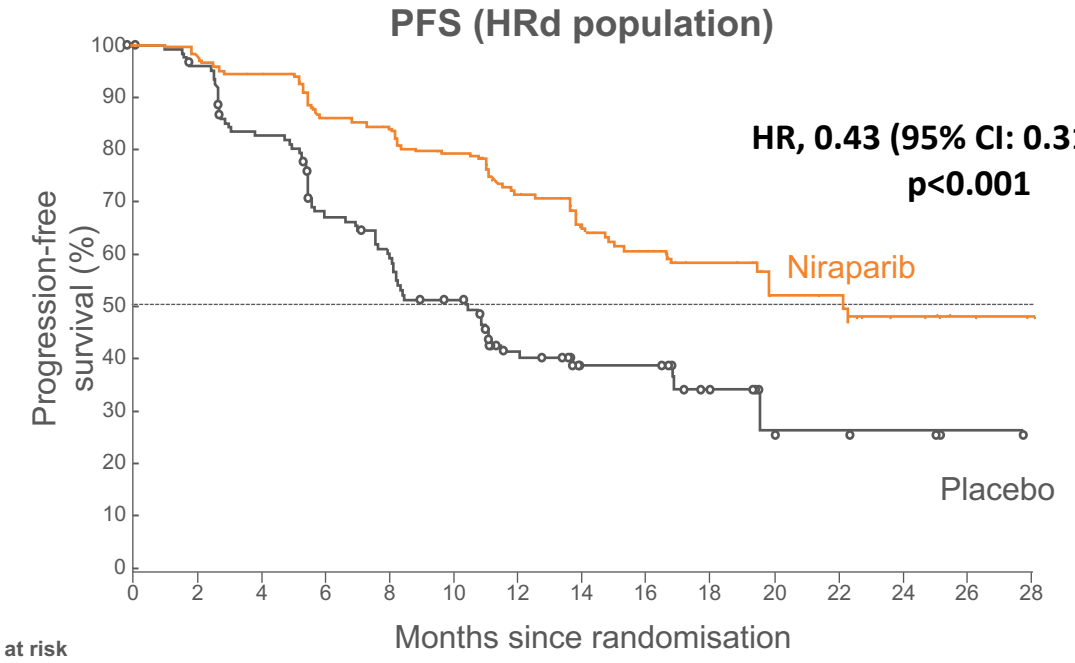
Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

A. González-Martín, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, C. McCormick, D. Lorusso, P. Hoskins, G. Freyer, K. Baumann, K. Jardon, A. Redondo, R.G. Moore, C. Vulsteke, R.E. O'Cearbhaill, B. Lund, F. Backes, P. Barretina-Ginesta, A.F. Haggerty, M.J. Rubio-Pérez, M.S. Shahin, G. Mangili, W.H. Bradley, I. Bruchim, K. Sun, I.A. Malinowska, Y. Li, D. Gupta, and B.J. Monk, for the PRIMA/ENGOT-OV26/GOG-3012 Investigators*



No. at risk

Niraparib	487	454	385	312	295	253	167	111	94	58	29	21	13	4	0
Placebo	246	226	177	133	117	90	60	32	29	17	6	6	4	1	0



No. at risk

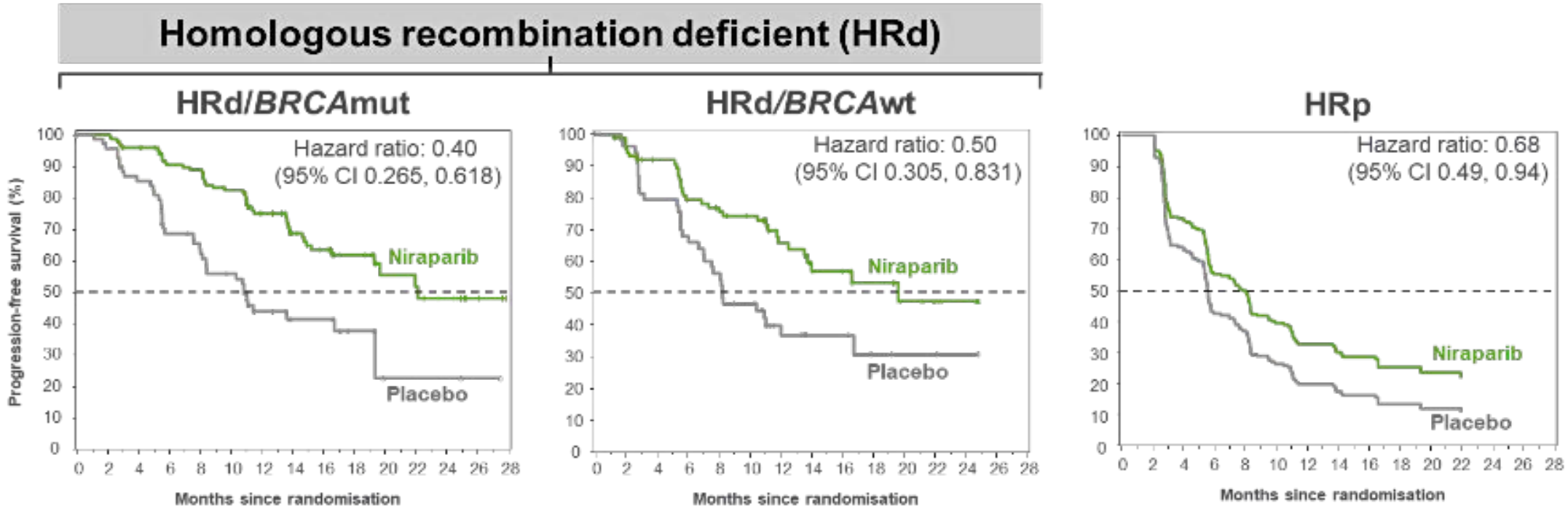
Niraparib	247	231	215	189	184	168	111	76	66	42	22	19	13	4	0
Placebo	126	117	99	79	70	57	34	21	21	11	5	5	4	1	0

Figures adapted from: González-Martín A, et al. *N Engl J Med* 2019;381:2391–402.

HR, hazard ratio; HRd, homologous-recombination deficiency; PFS, progression-free survival; mut, mutation.

Courtesy of Susana Banerjee, MBBS, MA, PhD

PRIMA – PFS Benefit in Biomarker Subgroups



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

Niraparib provided clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

BRCA, breast cancer gene; BRCAmut, BRCA mutation; BRCAwt, BRCA wildtype; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARPi, poly(ADP-ribose)polymerase inhibitor; PFS, progression-free survival.

Gonzalez-Martin A, et al. N Engl J Med 2019; DOI: 10.1056/NEJMoa1910962.

Courtesy of Shannon N Westin, MD, MPH

Phase II OVARIO Study of Niraparib + Bevacizumab Therapy in Advanced Ovarian Cancer Following Front-Line Platinum-Based Chemotherapy with Bevacizumab

Hardesty M et al. SGO 2021;Abstract 10408.

Agenda

Module 1: Case Presentations

- Dr Ma: A 67-year-old woman with recurrent serous papillary adenocarcinoma of the fallopian tube – Germline BRCA1 mutation
- Dr Willmott: A 66-year-old woman with Stage IIIC fallopian tube carcinoma – No deleterious mutations
- Dr Peles: A 79-year-old woman with ovarian cancer (OC) – Germline BRCA2 mutation
- Dr Willmott: A 45-year-old woman with Stage IIIC serous OC – Germline BRCA1 mutation

Module 2: PARP Inhibitor Maintenance Therapy

Module 3: Case Presentations

- Dr Matt-Amaral: A 69-year-old woman with Stage IV OC – Germline BRCA1 mutation
- Dr Ibrahim: A 77-year-old woman with Stage IIIC OC with a germline BRCA mutation who develops anemia on olaparib
- Dr Godoy: Questions and Comments — Niraparib-associated thrombocytopenia and surgical procedures
- Dr Chase: A 76-year-old woman with recurrent OC – Germline and somatic BRCA2 mutation

Module 4: Management of Side Effects; Novel Strategies with PARP Inhibitors

Case Presentation – Dr Matt-Amaral: A 69-year-old woman with Stage IV ovarian cancer and a germline BRCA1 mutation

Dr Laurie Matt-Amaral

- 2013: Initial diagnosis of Stage IIIC ovarian cancer and treated with carboplatin/paclitaxel
- 2014: Testing detects BRCA1 mutation
- 2017: Diagnosed with Stage IV disease at vaginal cuff
- Carboplatin/paclitaxel → neuropathy → switch to carboplatin/gemcitabine → olaparib maintenance
  - Tolerated olaparib well, but has developed joint pain
- Patient remains on olaparib maintenance; most recent CA-125 level was 4.3 U/mL

Questions

- How often have you observed joint pain in patients receiving olaparib? What do you recommend to treat this pain?
- Would you consider stopping PARP inhibitor maintenance therapy after the patient has experienced a certain disease-free interval? If so, how long is that interval?

RTP RESEARCH TO PRACTICE

Case Presentation – Dr Ibrahim: A 77-year-old woman with Stage IIIC ovarian cancer with a germline BRCA mutation who develops anemia on olaparib

Dr Sulfi Ibrahim

- Diagnosed with Stage IIIC ovarian cancer
- Neoadjuvant carboplatin/paclitaxel x 3 cycles → optimal debulking surgery → adjuvant carboplatin/paclitaxel x 3 cycles
- Olaparib maintenance therapy is initiated, however the patient develops significant anemia (Hb 5 g/dL)
- Blood transfusion accompanied by olaparib dose reduction from 300 mg BID to 300 mg in the morning and 150 mg in the evening
- Repeat CBC shows Hb at 7 g/dL → second blood transfusion

Questions

- What would be the best way to manage this patient who is extremely motivated to stay on olaparib and complete the 2 years of adjuvant therapy, but obviously does have significant anemia with the olaparib? Should I dose reduce the olaparib further or would you advocate for the use of erythropoietin-stimulating agents to manage her anemia and keep her on a higher dose of olaparib?

RTP RESEARCH TO PRACTICE

Niraparib-associated thrombocytopenia and surgical procedures

Dr Heidi Godoy

RTP
RESEARCH
TO PRACTICE

Case Presentation – Dr Chase: A 76-year-old woman with recurrent ovarian cancer – germline and somatic BRCA2 mutation

Dr Dana Chase

- 5/2016: Diagnosed with Stage IIIC ovarian cancer → Carboplatin/paclitaxel x 6
- Debulking surgery → Consolidation carboplatin/paclitaxel stopped after 2 weeks due to Grade 3 neuropathy → PD
- 9/2017: Liposomal doxorubicin/bevacizumab stopped after 1 month due to neutropenia
- Genetic testing: BRCA2 mutation
- 2/2018: Olaparib → PD
- 4/2019 – 5/2020: Gemcitabine → PD
  - 4/2020: FoundationOne®: BRCA2, MSS, TMB low

Question

- For this patient, who had a good response to olaparib previously, would you consider re-treatment with a PARP inhibitor? If so, would you use the same PARPi or a different one?

RTP RESEARCH TO PRACTICE

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Module 4: Management of Side Effects; Novel Strategies with PARP Inhibitors

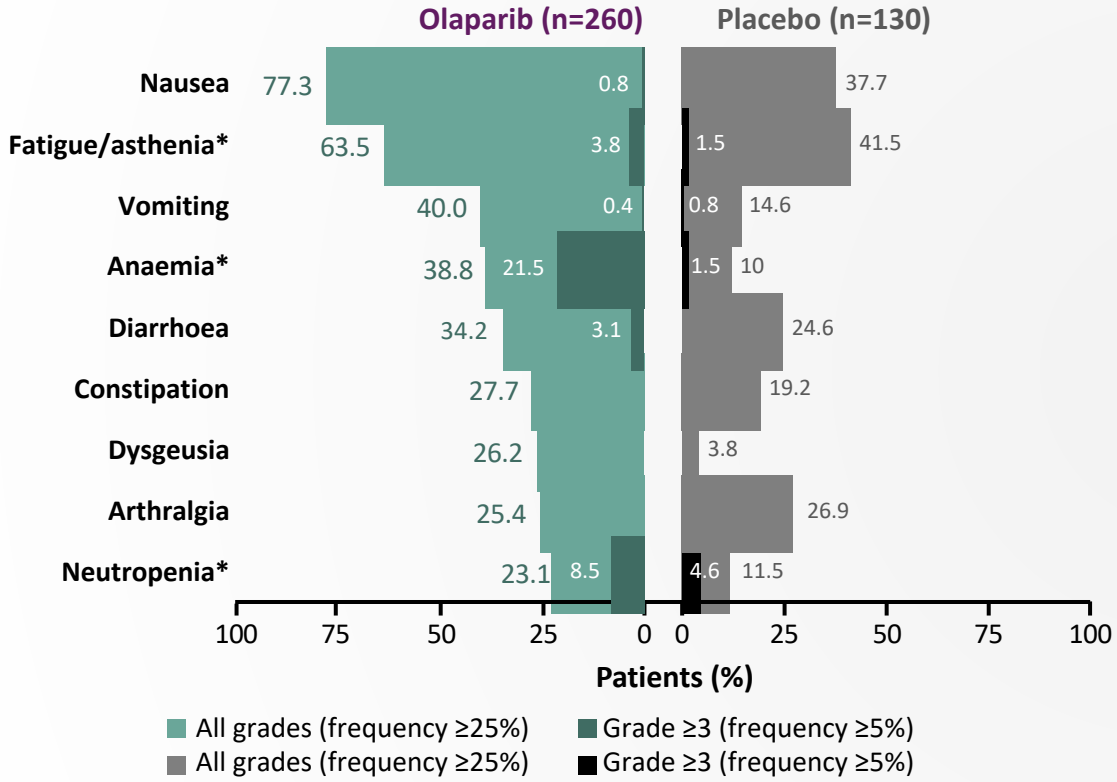
According to your clinical experience, do PARP inhibitors cause insomnia?

1. Yes
2. No
3. I don’t know

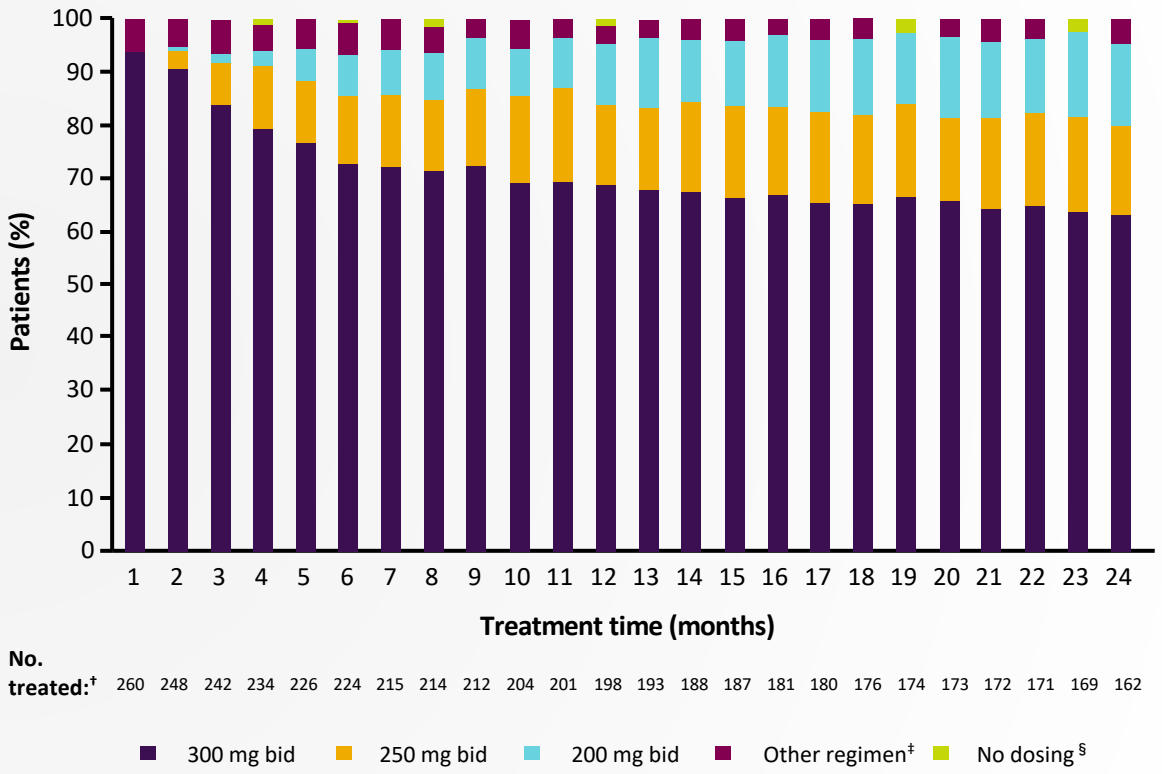
RTP
RESEARCH
TO PRACTICE

SOLO-1: Safety overview

Most common adverse events[1]



Most patients (64%) receiving olaparib could remain on the starting dose[2]

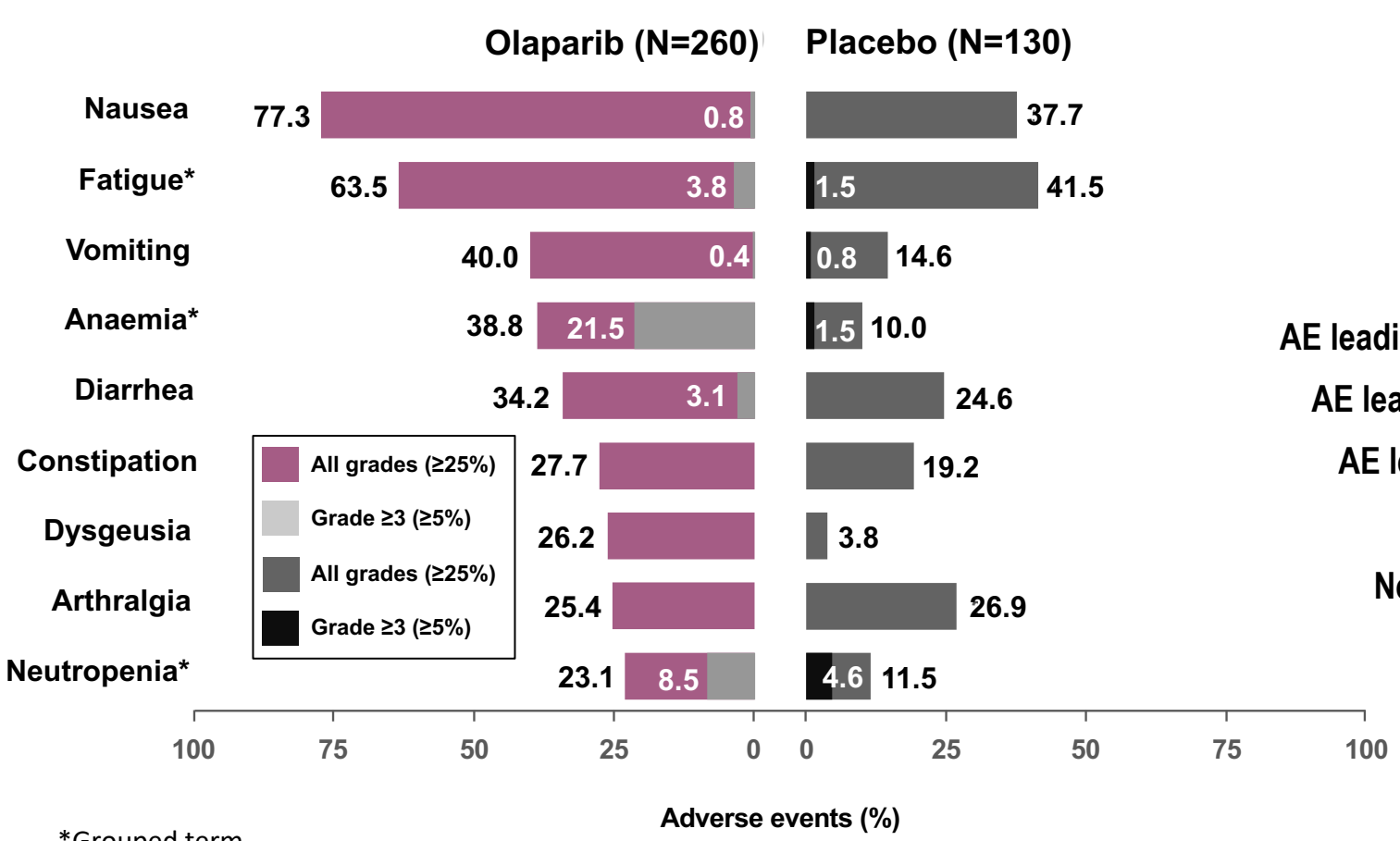


*Grouped terms. All-grade thrombocytopenia (grouped term) occurred in 11.2% of patients in the olaparib group and 3.8% of patients in the placebo group; and grade ≥3 thrombocytopenia (grouped term) occurred in 0.8% and 1.5%, respectively.
†Number of patients treated at the start of each month.
‡Other regimen' includes 150 mg qd, 150 mg bid, 200 mg qd, 250 mg qd, 300 mg od, and 450 mg bid.
§The category of 'no dosing' was assigned if the patient had dosing interrupted for the entire month window.
AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome.
1. Moore K, et al. Presented at ESMO Annual Congress 2018; 19–23 October 2018; Munich, Germany. Presentation #LBA7_PR. 2. Colombo N, et al. Presented at ASCO 2019; Chicago, IL, USA. Poster 5539.

Courtesy of Susana Banerjee, MBBS, MA, PhD

SOLO-1: Updated Toxicity

ESMO 2020: Safety still consistent with the primary DCO



n (%)	Olaparib (n=260)	Placebo (n=130)
Any AE	256 (98)	120 (92)
Grade ≥3 AE	103 (40)	25 (19)
Serious AE	55 (21)	17 (13)
AE leading to dose interruption	136 (52)	22 (17)
AE leading to dose reduction	75 (29)	4 (3)
AE leading to treatment DC	30 (12)	4 (3)
MDS/AML	3 (1)	0 (0)
New primary malignancy	7 (3)	5 (4)

No additional cases of MDS/AML; incidence remained <1.5%

*Grouped term
AE = adverse event

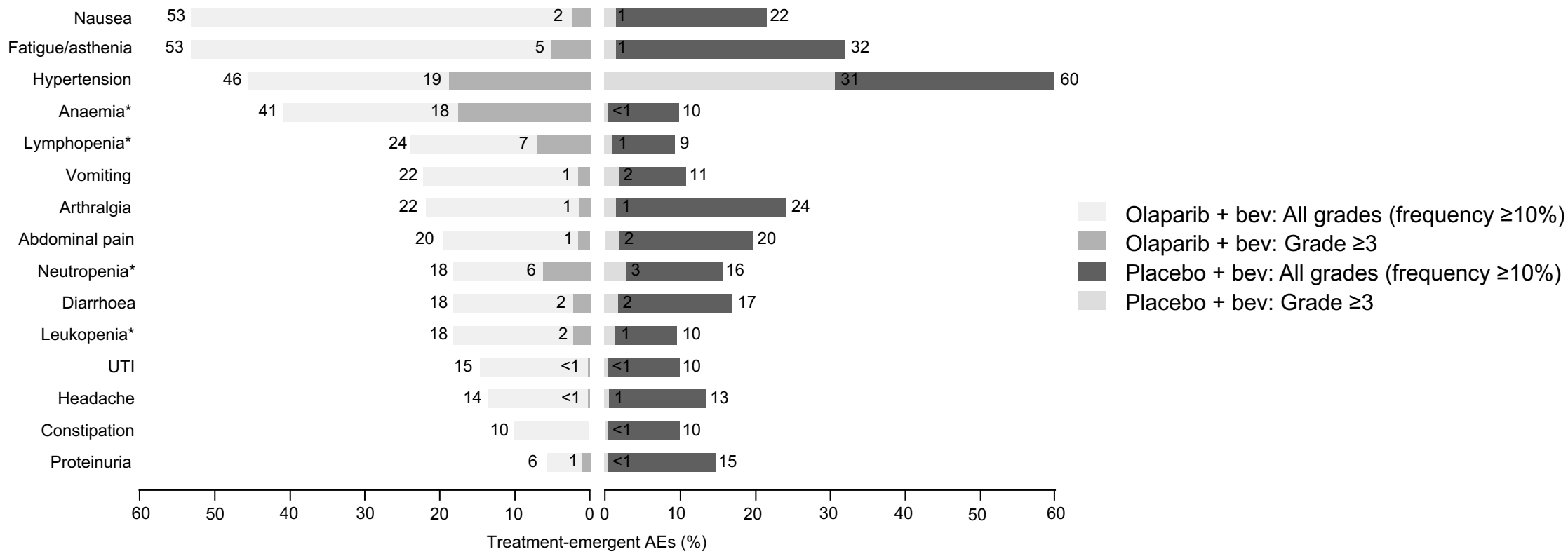
*Measured from randomization. AE, adverse event; AML, acute myeloid leukaemia; CR, complete response; MDS, myelodysplastic syndrome. DC Discontinued; DCO: 5 March 2020

Moore K et al. Oral presentation LBA7 PR ESMO 2018

Courtesy of Richard T Penson, MD, MRCP

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Adverse events reported in ≥10% of all patients in the ITT population in PAOLA-1[1]

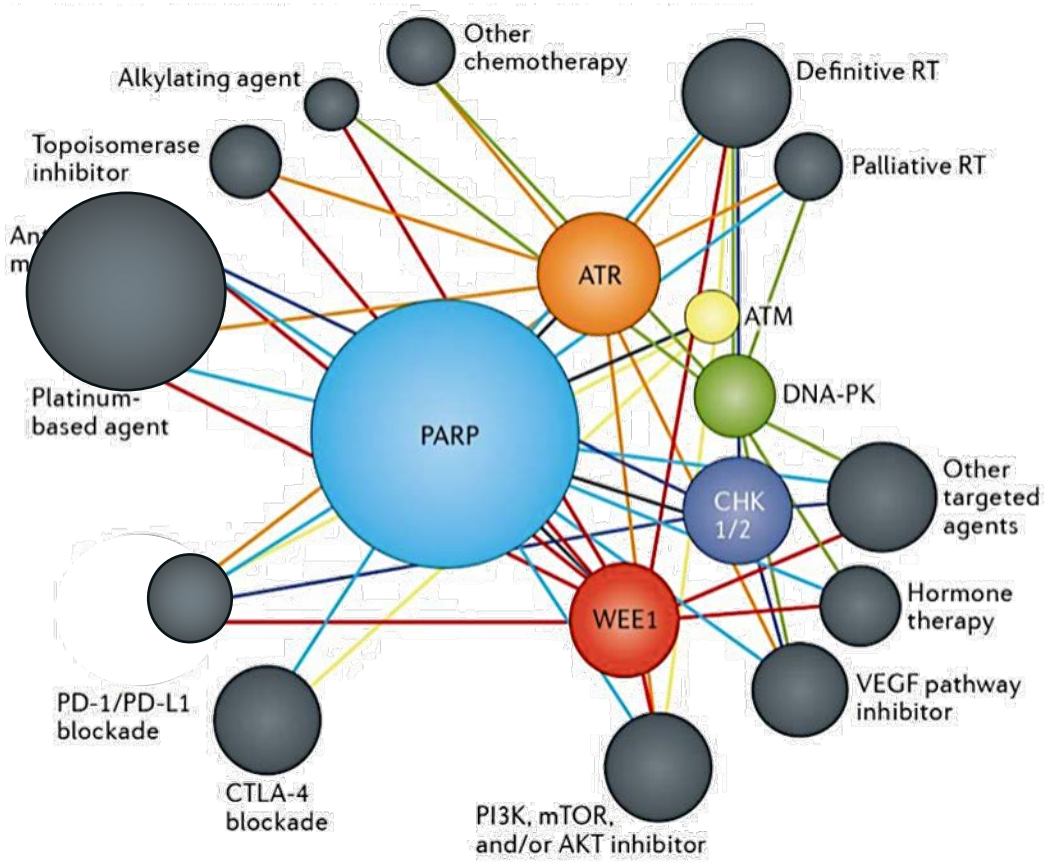


1. Ray-Coquard I, et al. *N Engl J Med*. 2019;381:2416-2428.

Secondary data cut-off: March 2020. Median duration of follow-up: Olaparib, 35.5 months; placebo, 36.5 months.
All-grade grouped-term thrombocytopenia occurred in 8% of Olaparib plus bevacizumab patients and 3% of placebo plus bevacizumab patients; grade ≥3 grouped-term thrombocytopenia occurred in 2% of olaparib plus bevacizumab patients and <1% of placebo plus bevacizumab patients.
*Grouped terms.
AE=adverse event; bev=bevacizumab; ITT=intention to treat; UTI=urinary tract infection.

Courtesy of Susana Banerjee, MBBS, MA, PhD

Resistance Mechanisms: Current Understanding



1. Restoration of *BRCA* / HRR gene function / protein expression [1-3]
2. DDR re-wiring: restoration of homologous recombination [4-7]
3. PARP mutations and red. in trapped PARP [3]
4. Replication fork protection [6-8]
5. Others: Drug Efflux, Cyclin E1 SLFN11 loss, PARG loss [3,9]

1. Norquist JCO 2011;29(22):3008 2. Lin Cancer Discov 2018;9(2):210
3. Patch Nature 2015;521(7553):489 4. Pettitt Nature Comm 2018;9(1849):1849
5. Bunting Cell 2010;141(2):243-54 6. Cruz Annals Oncol 2018;29(5):1203
7. Gupta Cell 2018; ;173(4):972 8. Taglialatela Mol Cell 2017;68(2):414
9. Yeung Clin Cancer Res 2017;23:7

AKT, protein kinase B; CTLA, cytotoxic T-lymphocyte-associated protein;
PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RT, radiation therapy.

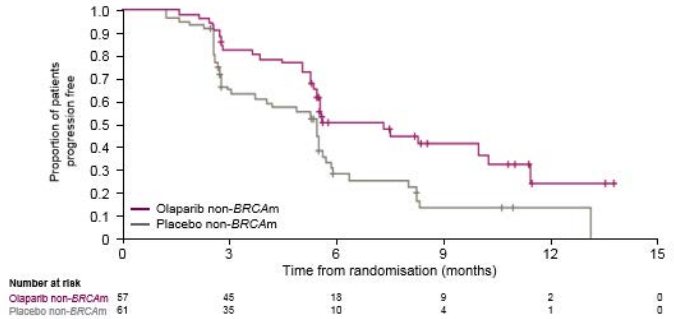
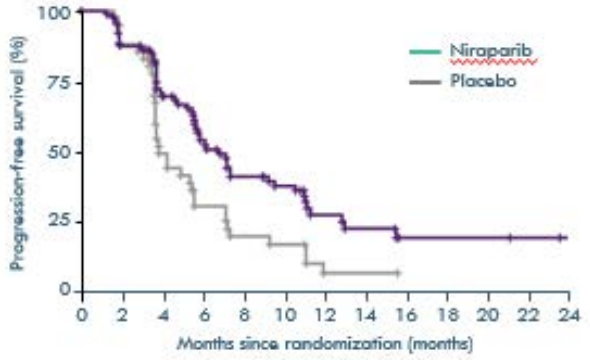
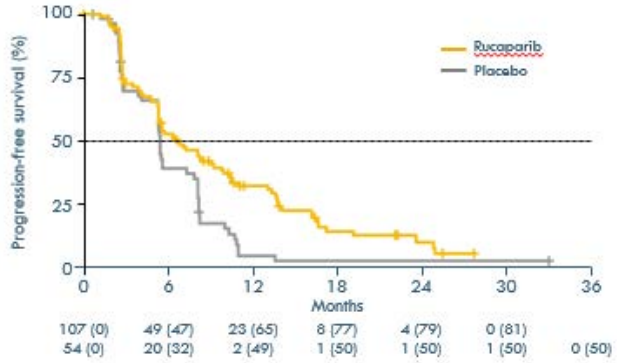
Pilie PG, et al. Nat Rev Clin Oncol. 2019;16(2):81-104.

Courtesy of Richard T Penson, MD, MRCP

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Why Combinations??

- **Improve efficacy**
- **Overcome resistance**
- **Sensitize more tumors to PARPi**

Study 19 (BRCA-)	NOVA – BRCA/HRD-[2]	ARIEL-3 – t*BRCA*/LOH-[3]	
			
7.4 vs. 5.5 months **HR 0.54 (95% CI 0.34-0.85)**		**6.7 vs. 5.4 months** **HR 0.58 (95% CI 0.40-0.85)**	**PFS by INV REVIEW**
	6.9 vs. 3.8 months **HR 0.58 (95% CI 0.361-0.922)**		**PFS by BICR REVIEW**

1. Ledermann et al. 2. Mirza et al. 3. Coleman RL et al. Lancet. 2017

Courtesy of Shannon N Westin, MD, MPH

PARPi and IO in Recurrent Ovarian Cancer

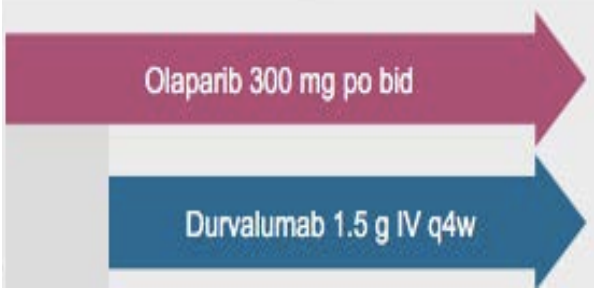
TOPACIO/KEYNOTE-162: A phase 1/2 study of niraparib + pembrolizumab in patients with advanced platinum resistant ovarian cancer NCT02657889

Niraparib 200mg/day
Pembrolizumab 200mg/21 days

Evaluable patients*	Integrated Efficacy Analysis (combined phase 1+2) PROC Cohort N=60	
	n (%)	Still on Treatment, n
Complete response (CR)	3 (5%)	1
Partial response (PR)	12 (20%)	6
Stable disease (SD)	25 (42%)	2
Progressive disease (PD)	20 (33%)	
ORR (CR+P		
Disease control rate (CR+PR+SD)	67%	

tBRCA 25% (2/8); HRD pos 25% (4/16)
HRD neg 27% (7/26)

MEDIOLA: Phase II basket study of olaparib and durvalumab: Results in germline BRCA-mutant platinum-sensitive ovarian cancer NCT02734004



	1 prior (2L)	2 prior (3L)	3+ prior (4L)	All lines
ORR	10/13=**77%**	6/9=**67%**	7/10=**70%**	23/32=**72%**
95% CI	(46%, 95%)	(30%, 93%)	(35%, 93%)	(53%, 86%)

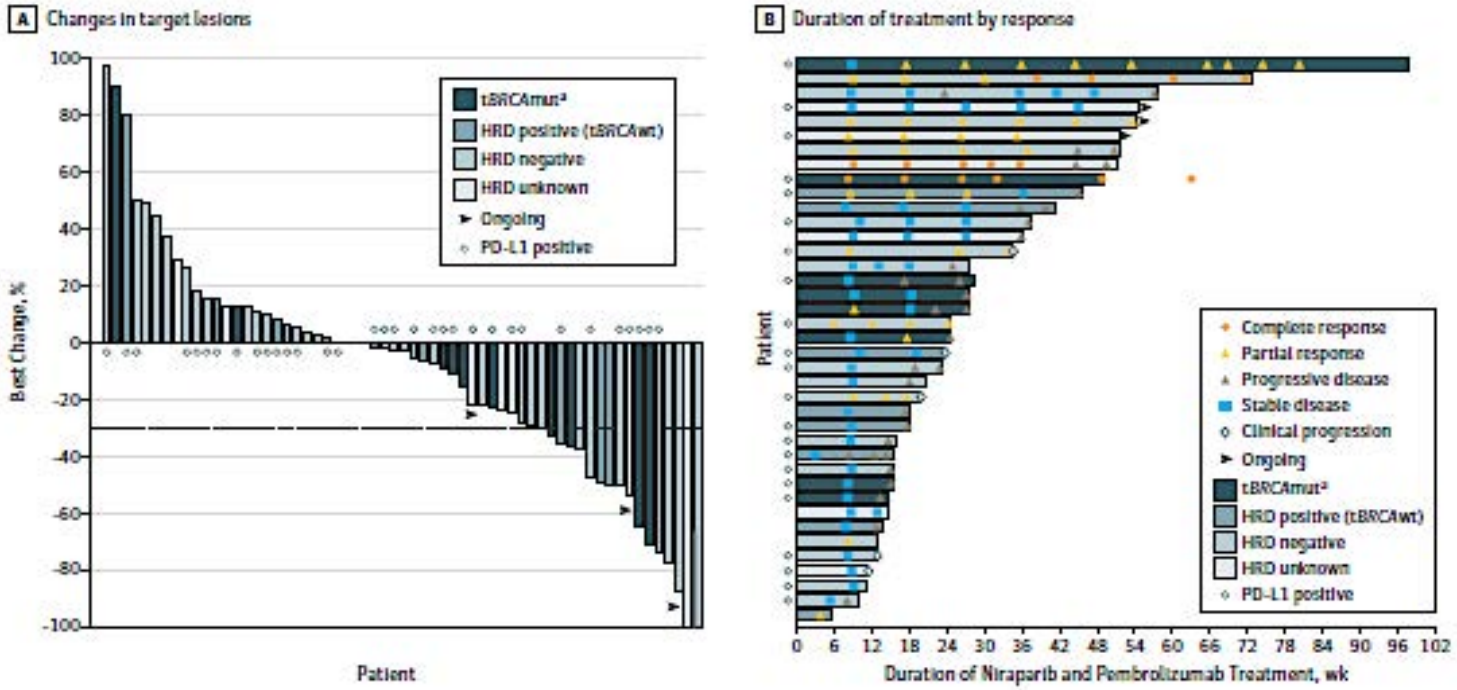
Konstantinopoulos ESMO 2017; Konstantinopoulos PA J Clin Oncol 2018 (suppl; abstr 106), Drew Y SGO 2018

Courtesy of Shannon N Westin, MD, MPH

TOPACIO: Niraparib + Pembrolizumab

Table 1. Patient Characteristics at Baseline

Characteristic	Combined Phases 1 and 2 Patients With Ovarian Carcinoma (n = 62)
Age, median (range), y	60 (46-83)
ECOG performance status, No. (%)[a]	
0	44 (71)
1	18 (29)
Prior lines of therapy, median (range)	3 (1-5)
Prior bevacizumab, No. (%)	39 (63)
Prior chemotherapy, No. (%)[b]	
Anthracycline	40 (65)
Cyclophosphamide	5 (8)
Gemcitabine hydrochloride	29 (47)
Paclitaxel	61 (98)
Platinum	62 (100)
Topotecan hydrochloride	3 (5)
Platinum status, No. (%)	
Resistant	30 (48)
Refractory	17 (27)
Not applicable[c]	15 (24)
tBRCA status, No. (%)	
BRCA1 mutation	9 (15)
BRCA2 mutation	2 (3)
BRCA wild type	49 (79)
Unknown	2 (3)
HRD status, No. (%)	
HRD positive	22 (35)
HRD negative	33 (53)
HRD unknown	7 (11)
PD-L1 status, No. (%)[d]	
Positive	35 (56)
Negative	21 (34)
Unknown	6 (10)

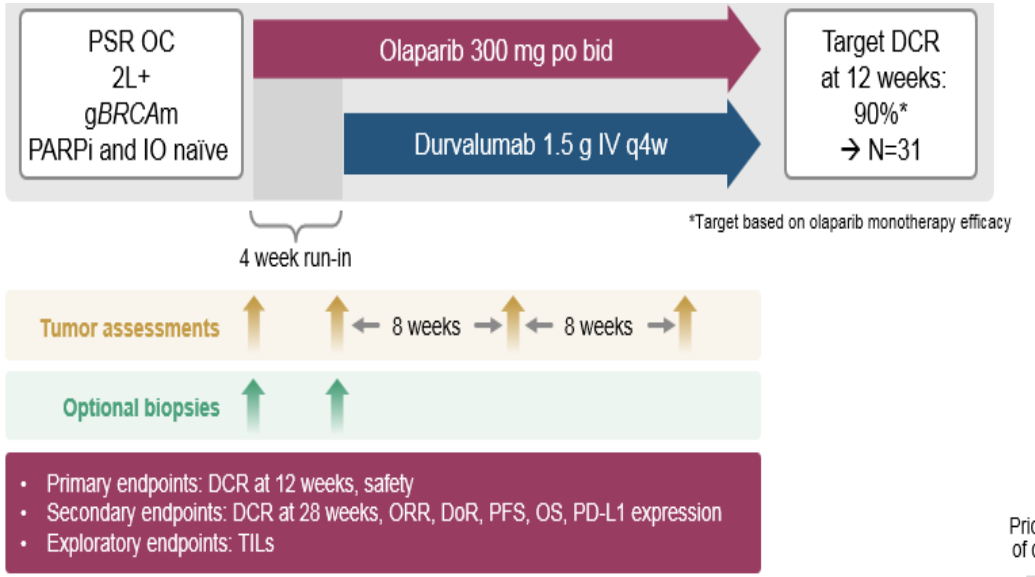


Best Overall Response	Response Data (n = 60)
Complete response, No. (%)	3 (5)
Partial response, No. (%)	8 (13)
Stable disease, No. (%)[a]	28 (47)
Progressive disease, No. (%)	20 (33)
Inconclusive, No. (%)[b]	1 (2)
ORR, % (90% CI)[c]	18 (11-29)
DCR, % (90% CI)[d]	65 (54-75)

Konstantinopoulos et al. JAMA Oncol. 2019; 5(8):1141

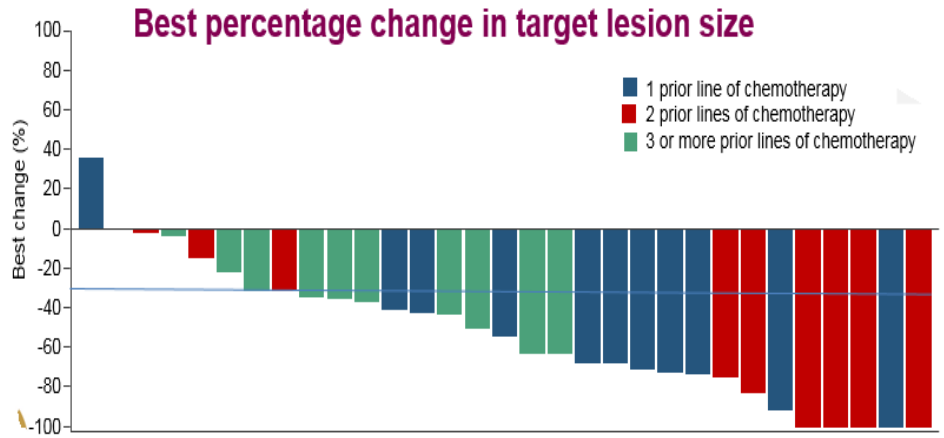
Courtesy of Shannon N Westin, MD, MPH

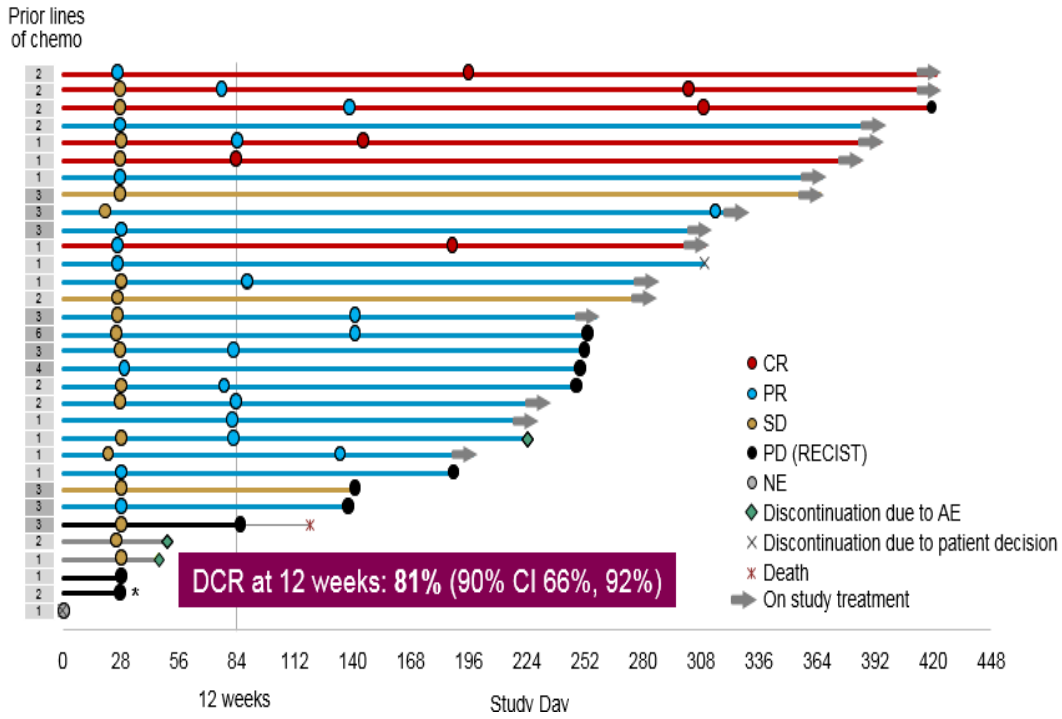
MEDIOLA: Olaparib and Durvalumab (BRCA+)/Platinum sensitive



N=32
44% with 1 prior regimen
25% with 2

ORR 72% (23/32)
CR 19%
PR 53%





Drew et al. SGO Annual Meeting,2019 Oahu, HI

Courtesy of Shannon N Westin, MD, MPH

MEDIOLA: Olaparib, Durvalumab, Bev *BRCAwt*/Platinum sensitive

Study schema

Patient population

- gBRCAwt
- PSR ovarian cancer
- ≤2 prior lines of chemotherapy
- PARP inhibitor and IO agent naïve

Triplet

- Olaparib 300 mg po bid
- Durvalumab 1.5 g IV q4w
- Bevacizumab 10 mg/kg IV q2w

Doublet

- Olaparib 300 mg po bid
- Durvalumab 1.5 g IV q4w

Treatment to disease progression

Primary endpoints

- DCR at 24 weeks (target 80%)
- Safety and tolerability

Secondary endpoints include:

- DCR at 56 weeks, ORR, DOR, PFS, OS, PK

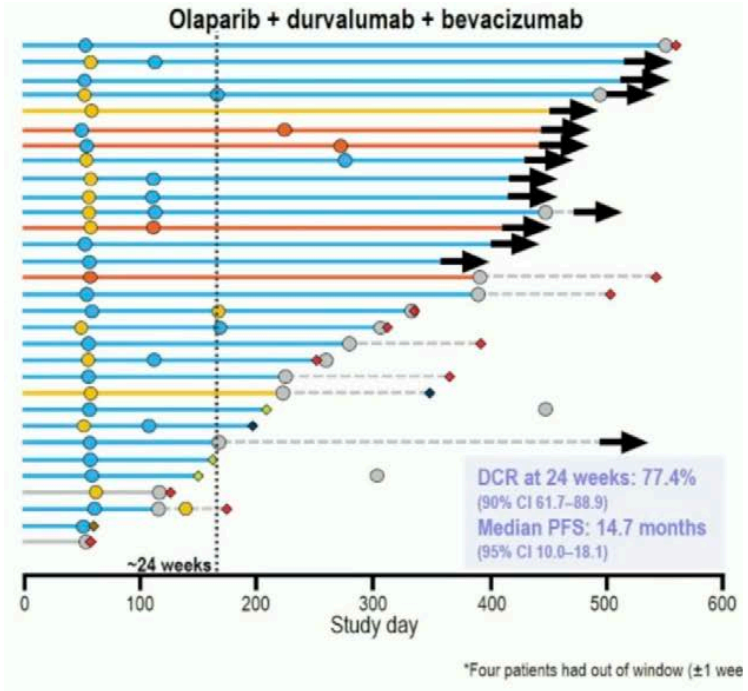
Exploratory endpoints include:

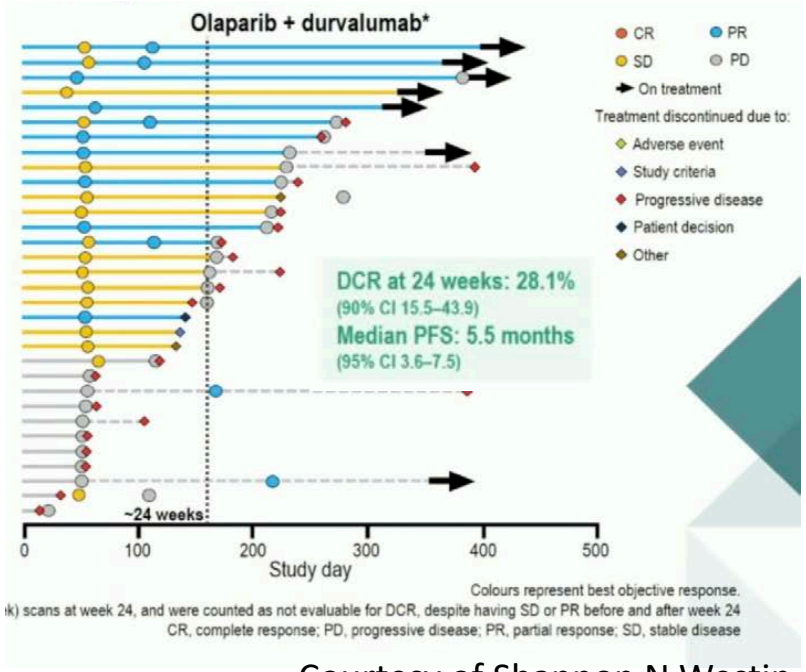
- Tumour genetics and immunology biomarkers

Sequential enrolment

Tumour assessments every 8 weeks

DCR and PFS are improved in 3 agent combination over PARP/IO alone





Drew, ESMO 2020

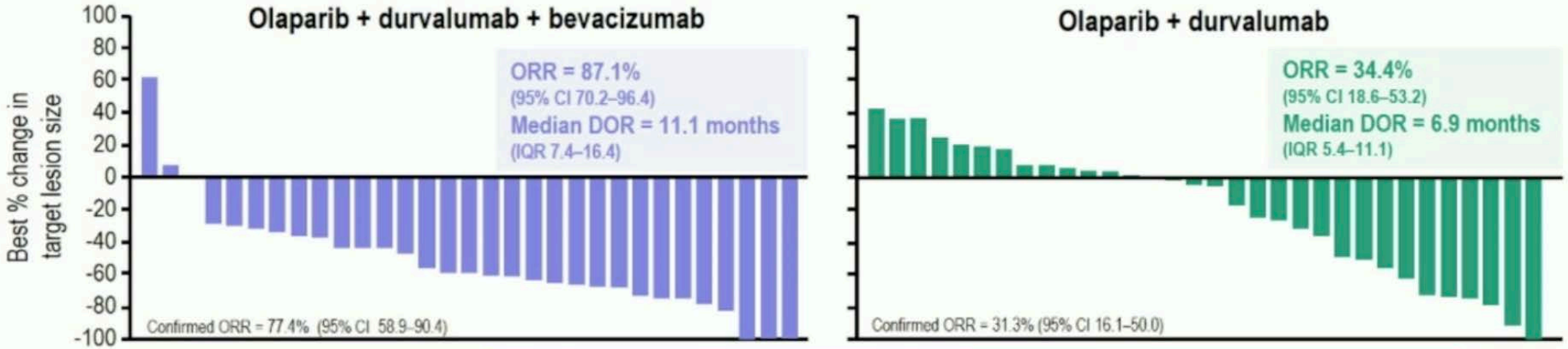
Courtesy of Shannon N Westin, MD, MPH

MEDIOLA: Olaparib, Durvalumab, Bev
BRCAwt/Platinum sensitive

VIRTUAL 2020 ESMO congress

Triplet cohort demonstrates high ORR

Exploratory analysis suggests triplet cohort ORR is not GIS-dependent



Genomic instability status* subgroup	Olaparib + durvalumab + bevacizumab		Olaparib + durvalumab	
	ORR (95% CI), %	n/N patients	ORR (95% CI), %	n/N patients
GIS-positive	100.0 (69.2–100.0)	10/10	50.0 (18.7–81.3)	5/10
GIS-negative	75.0 (34.9–96.8)	6/8	16.7 (0.4–64.1)	1/6
GIS-unknown	84.6 (54.6–98.1)	11/13	31.3 (11.0–58.7)	5/16

*GIS, as determined by Foundation Medicine tumour analysis; must have genome-wide LOH ≥14, a somatic *BRCA1* and/or *BRCA2* mutation, or a mutation in *ATM*, *BRIP1*, *PALB2*, *RAD51C*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PPP2R2A*, *RAD51B*, *RAD51D* or *RAD54L* to be considered positive. At the time of the DCO, the prespecified cut-off for genome-wide LOH of 14% was used[1]; GIS, genomic instability status; IQR, interquartile range; LOH, loss of heterozygosity. [1]Swisher *et al. Lancet Oncol* 2017;18:75–87

Drew, ESMO 2020

Courtesy of Shannon N Westin, MD, MPH

An Open-Label Phase II Study of Dostarlimab (TSR-042), Bevacizumab (bev), and Niraparib Combination in Patients (pts) with Platinum-Resistant Ovarian Cancer (PROC): Cohort A of the OPAL Trial

Liu JF et al. SGO 2021;Abstract 10415.

Ongoing Phase II MOONSTONE Trial Design

Estimated enrollment (N = 150)

- Recurrent high-grade serous, endometrioid or clear cell ovarian, fallopian tube or primary peritoneal cancer
- Platinum-resistant disease
- At least 1 but no more than 3 prior lines of therapy for advanced disease
- Must have received a platinum-based regimen, taxane agent(s) and bevacizumab
- ECOG PS 0-1
- No known BRCA1/2 mutation
- No prior anti-PD-1/PD-L1 therapy
- No prior PARP inhibitor therapy

→ **Niraparib + Dostarlimab**

Primary endpoint: Objective response rate

Secondary endpoints include PFS, OS, DoR and DCR

www.clinicaltrials.gov (NCT03955471). Accessed March 2021.

ATHENA (GOG-3020/ENGOT-ov45): phase 3 study to evaluate the safety and efficacy of rucaparib + nivolumab as maintenance treatment following front-line platinum-based chemotherapy for advanced epithelial ovarian cancer

Figure 2. ATHENA Trial Schema

Key eligibility criteria

- Newly diagnosed, stage III/IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Investigator-assessed CR or PR without disease progression or rise in CA-125 at any time during first-line platinum doublet therapy
- Completed cytoreductive surgery (R0 permitted), either prior to chemotherapy or following neoadjuvant chemotherapy, with sufficient tissue available for analysis
- ECOG PS, 0 or 1
- No prior treatment for ovarian cancer, including any maintenance treatment, other than first-line platinum regimen

Randomisation 4:4:1:1

Stratification

- Centrally assessed tumour HRD status
  - *BRCA1/2* mutation
  - *BRCA* wild type/ LOH high
  - *BRCA* wild type/ LOH low
  - *BRCA* wild type/ LOH indeterminate
- Response to first-line platinum doublet
  - No residual disease
  - Residual disease
- Timing of surgery
  - Primary
  - Interval debulking

Treatment
28-day cycles*

- Arm A: Rucaparib PO 600 mg BID + nivolumab IV 480 mg Q4W n≈400
- Arm B: Rucaparib PO 600 mg BID + placebo IV Q4W n≈400
- Arm C: Placebo PO BID + nivolumab IV 480 mg Q4W n≈100
- Arm D: Placebo PO BID + placebo IV Q4W n≈100

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

- Treatment for 24 months, or until radiographic progression, unacceptable toxicity, or other reason for discontinuation
- Disease assessment per RECIST every 12 weeks
- Safety and PRO assessment each cycle

Post-treatment

- Safety follow-up 28 days and 5 months after last dose
- Long-term follow-up
  - Tumour assessments every 12 weeks for 3 years and 24 weeks thereafter for patients who discontinue for a reason other than progression
  - All patients will be followed for survival, subsequent treatments, and secondary malignancies
- Patients receiving clinical benefit may continue treatment beyond progression for up to 24 months

*First dose of IV study drug will be administered on day 1 of cycle 2; study treatment will continue on day 1 of every 28-day cycle thereafter.

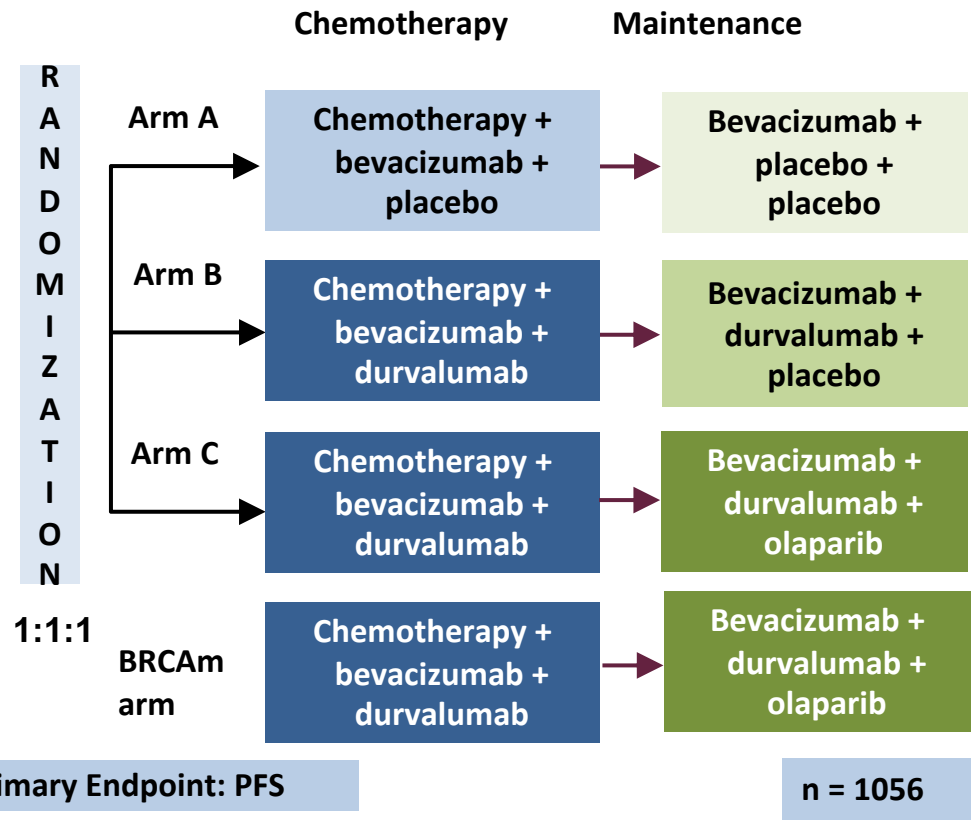
BID, twice daily; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRD, homologous recombination deficiency; IV, intravenous; LOH, loss of heterozygosity; PO, by mouth; PR, partial response; PRO, patient-reported outcomes; Q4W, every 4 weeks; R0, total cytoreduction; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1.

Courtesy of Shannon N Westin, MD, MPH

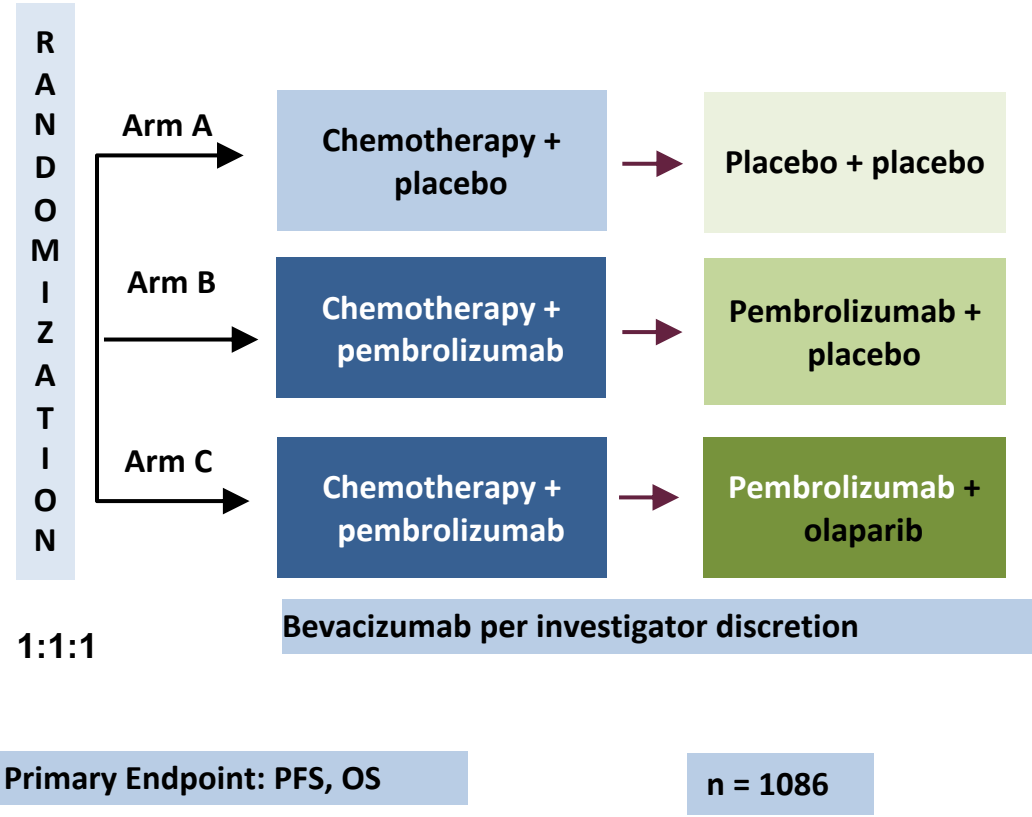
NCT03522246

Olaparib Combos in the Front Line

DUO-O/ENGOT-OV43: Phase III randomized study of durvalumab in combination with chemotherapy and bevacizumab followed by maintenance in newly diagnosed advanced ovarian cancer (NCT03737643)



KEYLYNK-001/ENGOT-OV43: Phase III randomized study of chemotherapy with pembrolizumab followed by maintenance with olaparib for the first-line treatment of BRCA non-mutated advanced epithelial ovarian cancer (NCT03740165)



Courtesy of Shannon N Westin, MD, MPH

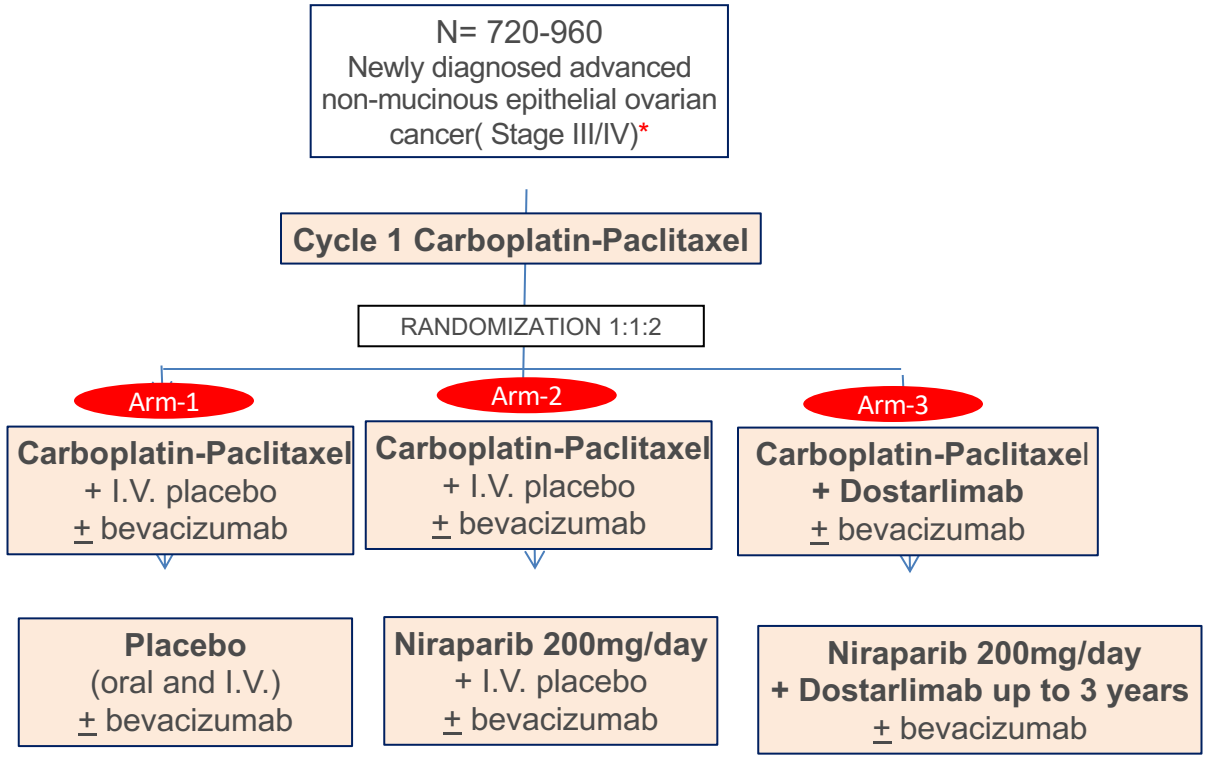
FIRST Trial: First-line ovarian cancer treatment with Niraparib plus TSR-042 (Dostarlimab)

Primary objective:
PFS by Investigator assessment per RECIST v1.1. PFS based upon blinded independent central review committee (BICR) will be a sensitivity analysis.

Secondary endpoints:
OS
ORR/DOR/DCR
Safety and tolerability of all treatments
Patient-reported outcomes (PROs)
Time to first subsequent therapy (TFST)
Time to second subsequent therapy (TSST)
PFS2

Stratification Factors

- Bevacizumab use (investigator choice).
- HRR and BRCA status based on ctDNA with tumor sample as back-up
- Stage III < 1 cm at PDS versus others



*Not eligible: complete surgical resection at primary debulking surgery **and low risk of relapse.**

Dostarlimab is an anti-PD-1 immunoglobulin G4 (IgG4) humanized monoclonal antibody (mAb) that binds with high affinity to PD-1

Courtesy of Shannon N Westin, MD, MPH

NCT03602859

Meet The Professor

Optimizing the Selection and Sequencing of Therapy for Patients with Renal Cell Carcinoma

Thursday, March 25, 2021
5:00 PM – 6:00 PM ET

Faculty

Robert J Motzer, MD

Moderator

Neil Love, MD

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Thank you for joining us!

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

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