A Conversation with the Investigators: Ovarian Cancer

Wednesday, July 7, 2021
5:00 PM – 6:00 PM ET

Faculty

Michael J Birrer, MD, PhD
Kathleen Moore, MD
Richard T Penson, MD, MRCP

Moderator

Neil Love, MD

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Faculty

Michael J Birrer, MD, PhD
Vice Chancellor, UAMS
Director, Winthrop P Rockefeller Cancer Institute
Director, Cancer Service Line
University of Arkansas for Medical Sciences
Little Rock, Arkansas

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

Kathleen Moore, MD
The Virginia Kerley Cade Endowed Chair in Cancer Development
Associate Director, Clinical Research
Director, Oklahoma TSET Phase I Program
Stephenson Cancer Center
Associate Professor, Section of Gynecologic Oncology
Director, Gynecologic Oncology Fellowship
Department of Obstetrics and Gynecology
University of Oklahoma Health Sciences Center
Oklahoma City, Oklahoma

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Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GlaxoSmithKline, ImmunoGen Inc and Merck.

Dr Love — Disclosures

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, Epizyme Inc, Exact Sciences Inc, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, Genentech, a member of the Roche Group, Gilead Sciences Inc, GlaxoSmithKline, Grail Inc, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc and Verastem Inc.

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Research To Practice CME Planning Committee Members, Staff and Reviewers

Planners, scientific staff and independent reviewers for Research To Practice have no relevant conflicts of interest to disclose.

Dr Birrer — Disclosures

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Dr Moore — Disclosures

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Contracted Research	PTC Therapeutics, US Department of Defense

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Dr Penson — Disclosures

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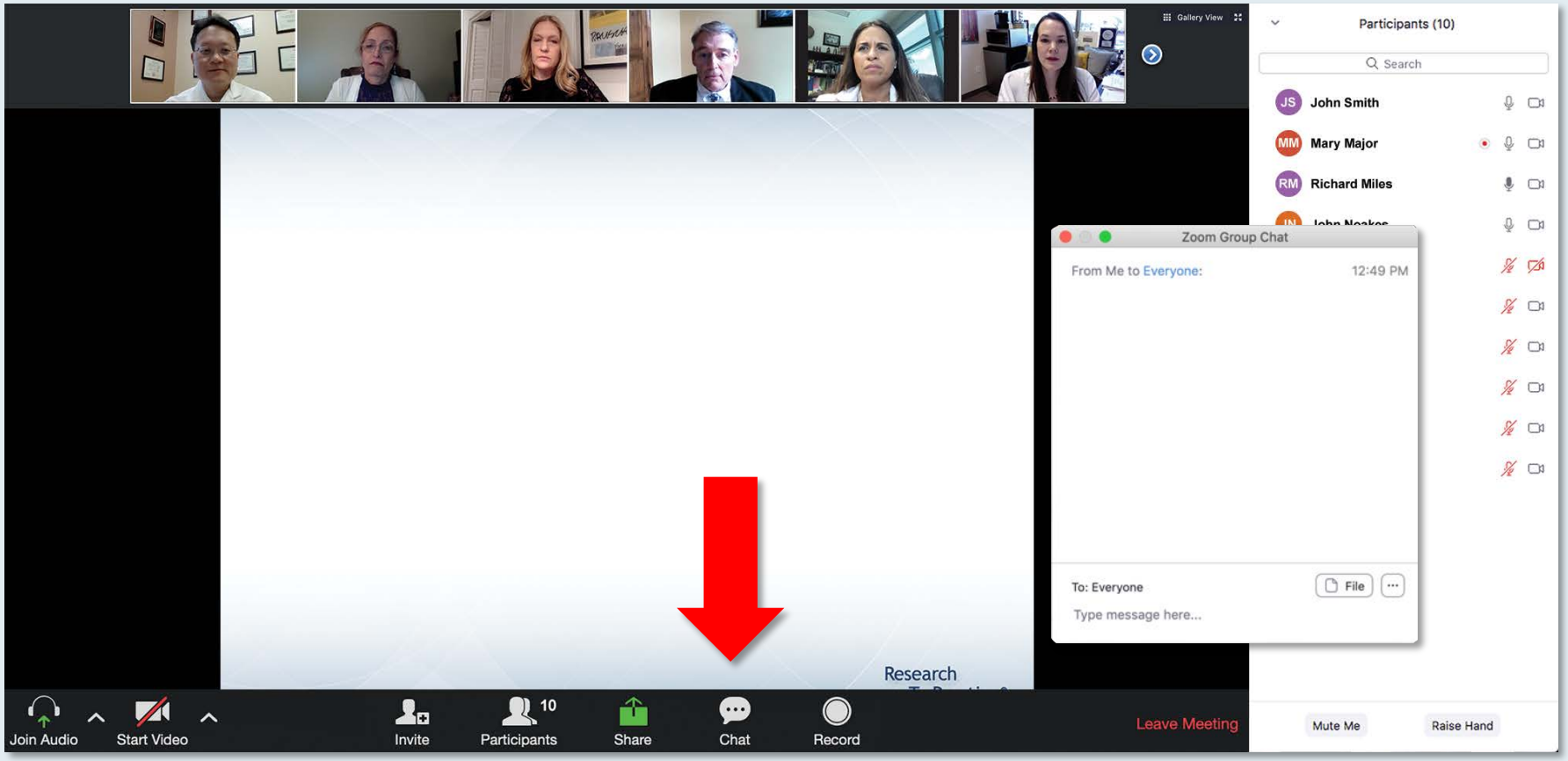
We Encourage Clinicians in Practice to Submit Questions



Feel free to submit questions now before the program begins and throughout the program.

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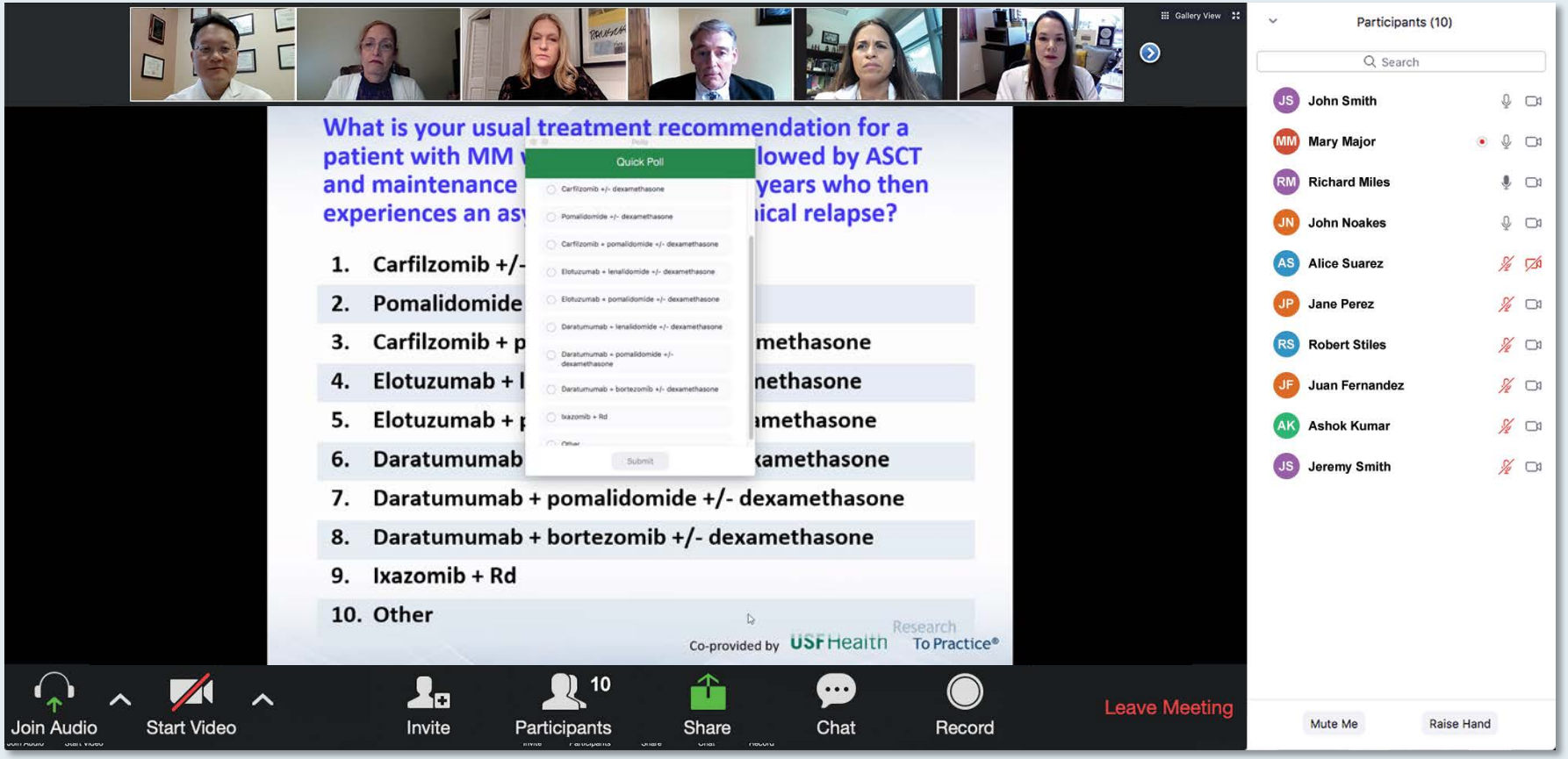
Familiarizing Yourself with the Zoom Interface

How to answer poll questions



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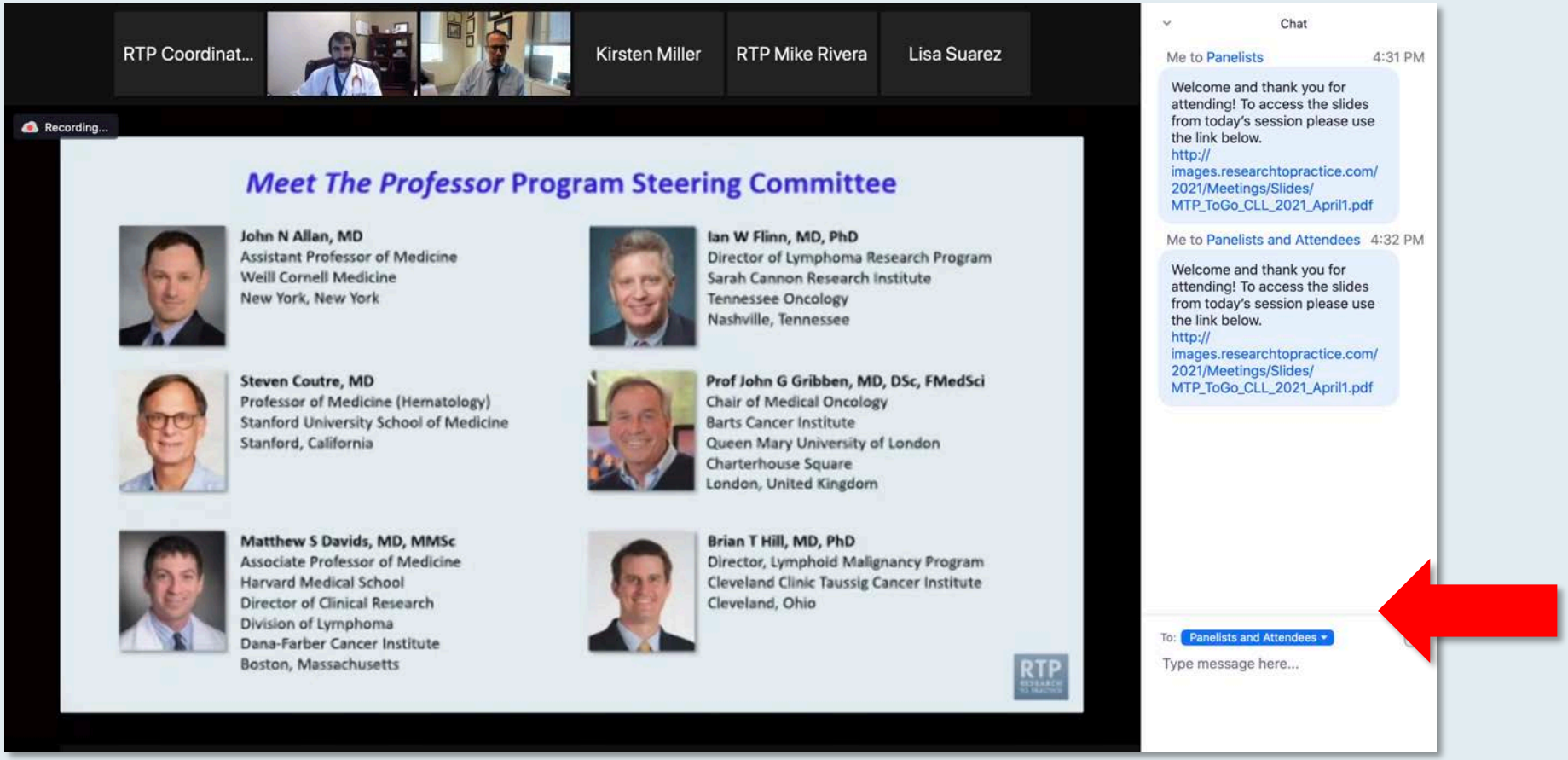
Familiarizing Yourself with the Zoom Interface

Expand chat submission box



Drag the white line above the submission box up to create more space for your message.

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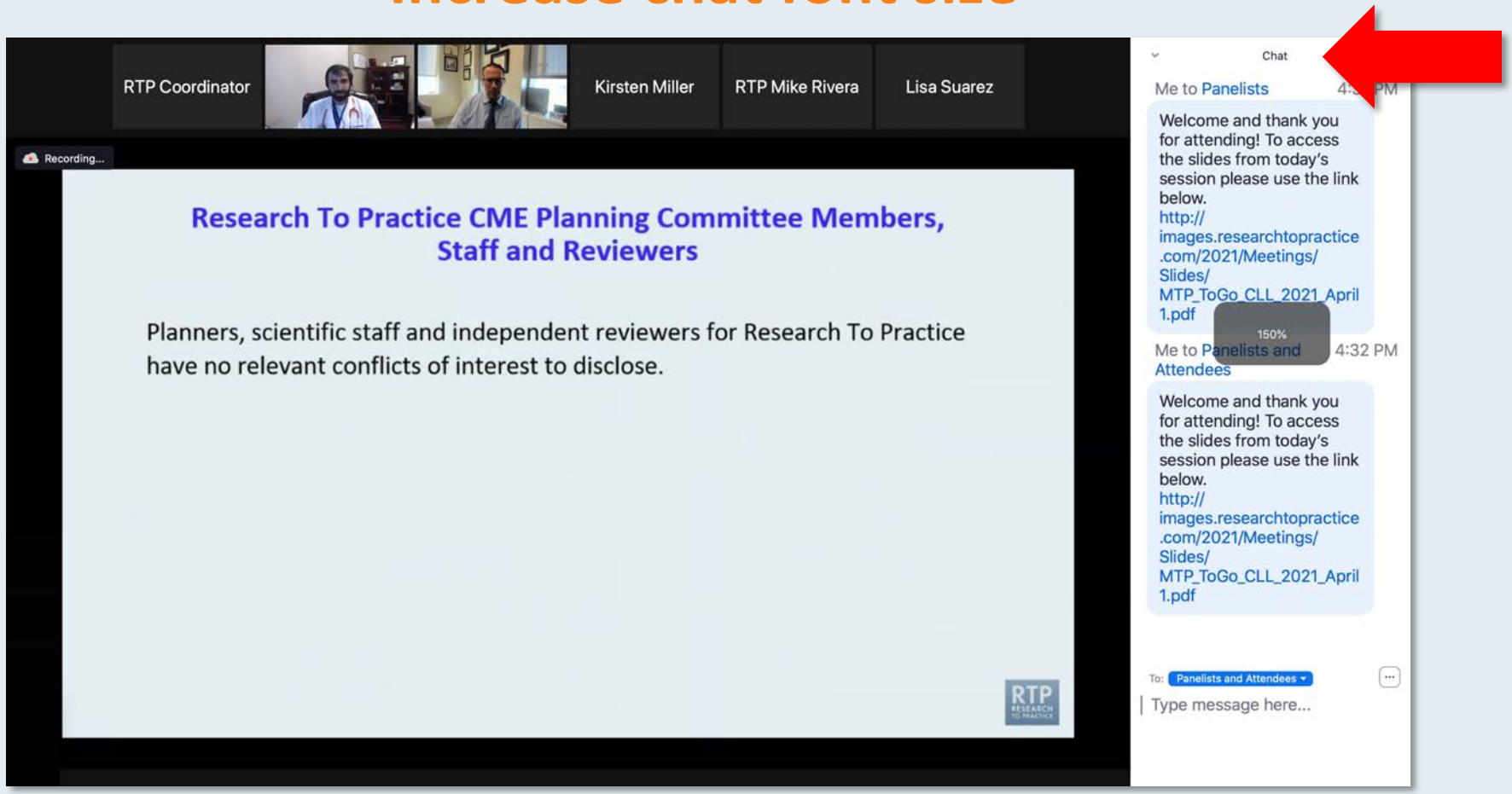
Familiarizing Yourself with the Zoom Interface

Increase chat font size



Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

ONCOLOGY TODAY

WITH DR NEIL LOVE

PARP Inhibitors in Ovarian Cancer

DR ANTONIO GONZÁLEZ-MARTÍN

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13 Exciting CME/MOC Events You Do Not Want to Miss

A Live Webinar Series Held in Conjunction with the 2021 ASCO Annual Meeting

Ovarian Cancer
Wednesday, July 7
5:00 PM – 6:00 PM ET

Bladder Cancer
Wednesday, July 21
5:00 PM – 6:00 PM ET

Colorectal and Gastroesophageal Cancers
Tuesday, August 3
5:00 PM – 6:30 PM ET

Hormonal Therapy for Prostate Cancer
Monday, July 12
5:00 PM – 6:00 PM ET

Endometrial and Cervical Cancers
Monday, July 26
5:00 PM – 6:00 PM ET

Hepatocellular Carcinoma and Pancreatic Cancer
Wednesday, August 4
5:00 PM – 6:30 PM ET

Chimeric Antigen Receptor T-Cell Therapy
Tuesday, July 13
5:00 PM – 6:00 PM ET

Targeted Therapy for Non-Small Cell Lung Cancer
Tuesday, July 27
5:00 PM – 6:00 PM ET

Head and Neck Cancer
Wednesday, August 11
5:00 PM – 6:00 PM ET

Acute Myeloid Leukemia and Myelodysplastic Syndromes
Wednesday, July 14
5:00 PM – 6:00 PM ET

Immunotherapy and Other Nontargeted Approaches for Lung Cancer
Wednesday, July 28
5:00 PM – 6:00 PM ET

Metastatic Castration-Resistant Prostate Cancer
Tuesday, July 20
5:00 PM – 6:00 PM ET

Mantle Cell, Diffuse Large B-Cell and Hodgkin Lymphoma
Monday, August 2
5:00 PM – 6:00 PM ET

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A Conversation with the Investigators: Hormonal Therapy for Prostate Cancer

Monday, July 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Chimeric Antigen Receptor T-Cell Therapy in Hematologic Cancers

Tuesday, July 13, 2021
5:00 PM – 6:00 PM ET

Faculty

Caron Jacobson, MD
David G Maloney, MD, PhD
Nikhil C Munshi, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Acute Myeloid Leukemia and Myelodysplastic Syndromes

Wednesday, July 14, 2021
5:00 PM – 6:00 PM ET

Faculty

Courtney D DiNardo, MD, MSCE
Gail J Roboz, MD
Eytan M Stein, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Metastatic Castration-Resistant Prostate Cancer

Tuesday, July 20, 2021
5:00 PM – 6:00 PM ET

Faculty

Emmanuel S Antonarakis, MD
Johann de Bono, MBChB, MSc, PhD
Julie N Graff, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

A Conversation with the Investigators: Bladder Cancer

Wednesday, July 21, 2021
5:00 PM – 6:00 PM ET

Faculty

Petros Grivas, MD, PhD
Daniel P Petrylak, MD
Arlene Siefker-Radtke, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

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

Thursday, July 22, 2021
5:00 PM – 6:00 PM ET

Faculty

David F McDermott, MD

Moderator

Neil Love, MD

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A Conversation with the Investigators: Endometrial and Cervical Cancers

Monday, July 26, 2021
5:00 PM – 6:00 PM ET

Faculty

Mansoor Raza Mirza, MD
David M O'Malley, MD
Angeles Alvarez Secord, MD, MHSc

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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University of Oklahoma Health Sciences Center
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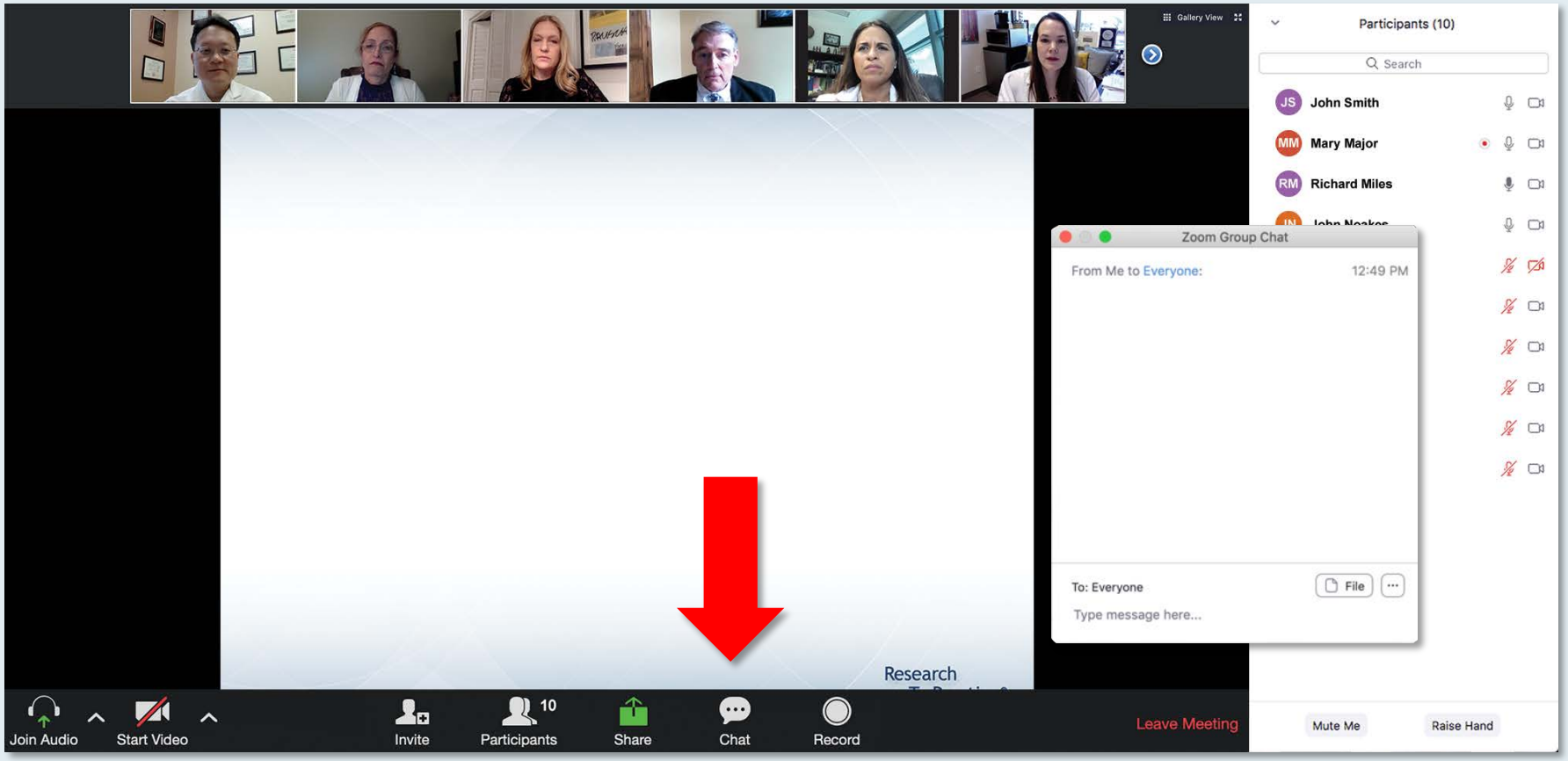
We Encourage Clinicians in Practice to Submit Questions



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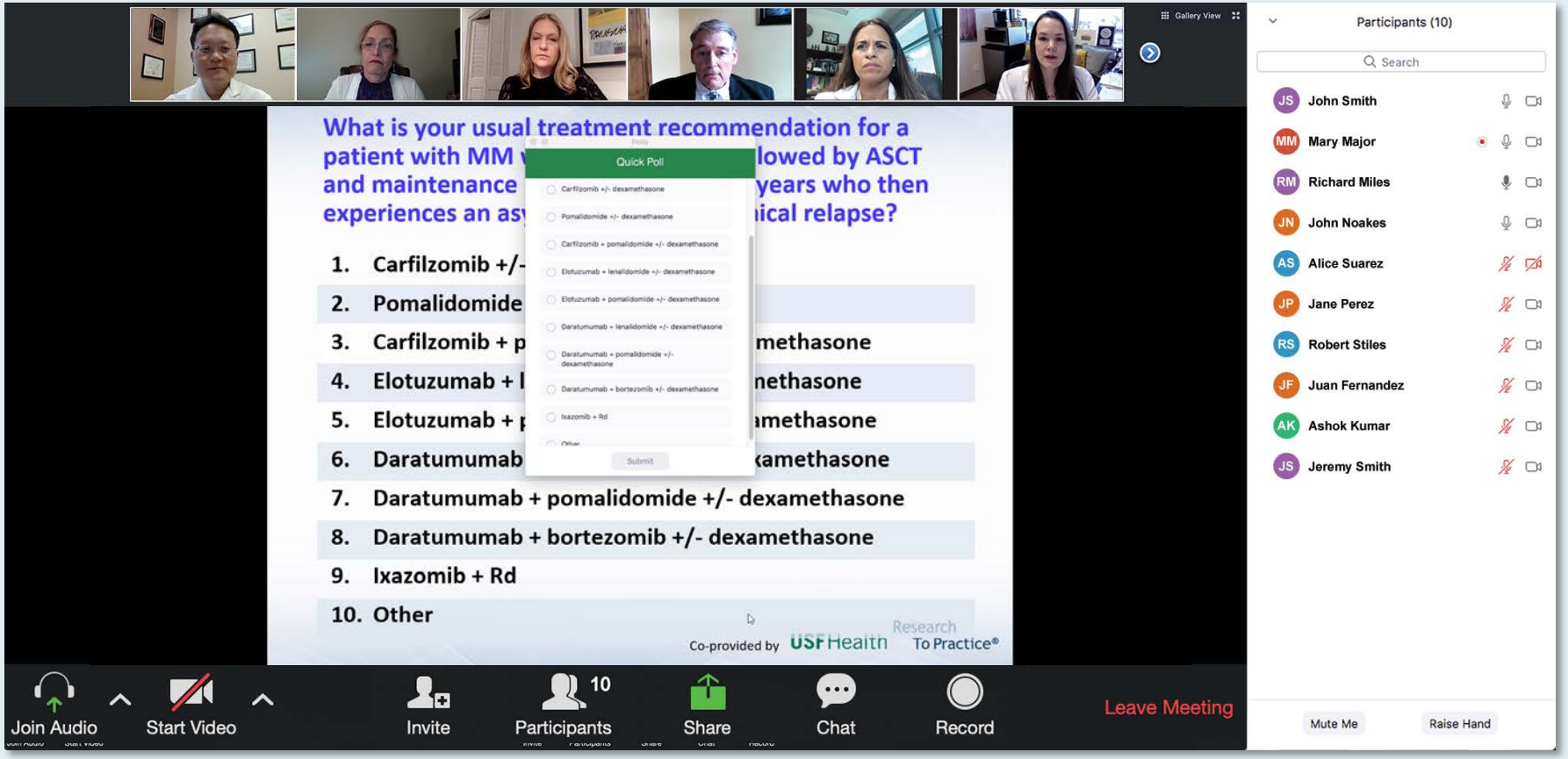

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Agenda

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- Treatment strategies based on germline and somatic genomic assays
- ASCO 2021 updates for the SOLO-1, PRIMA and PAOLA-1 trials
- Findings from the OVARIO trial: Niraparib/bevacizumab maintenance therapy

Module 2: Recurrence, Toxicity and Resistance to PARP Inhibitors

- Selection of PARP inhibitor for patients with recurrent OC
- ARIEL4: Rucaparib versus chemotherapy for relapsed, BRCA-mutated OC
- Mechanisms of resistance to PARP inhibitor therapy

Module 3: Mirvetuximab Soravtansine

- Scientific rationale for targeting folate receptor alpha in OC
- Mirvetuximab soravtansine with or without bevacizumab for platinum-resistant OC
- Ongoing trials evaluating mirvetuximab soravtansine for platinum-resistant OC: MIRASOL, SORAYA

Module 4: Immune Checkpoint Inhibitors in OC

- Biologic rationale for combining PARP inhibitors with anti-PD-1/PD-L1 antibodies
- Ongoing Phase III trials evaluating immune checkpoint inhibitors with PARP inhibitors for advanced OC

BIG Breast International Group

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A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

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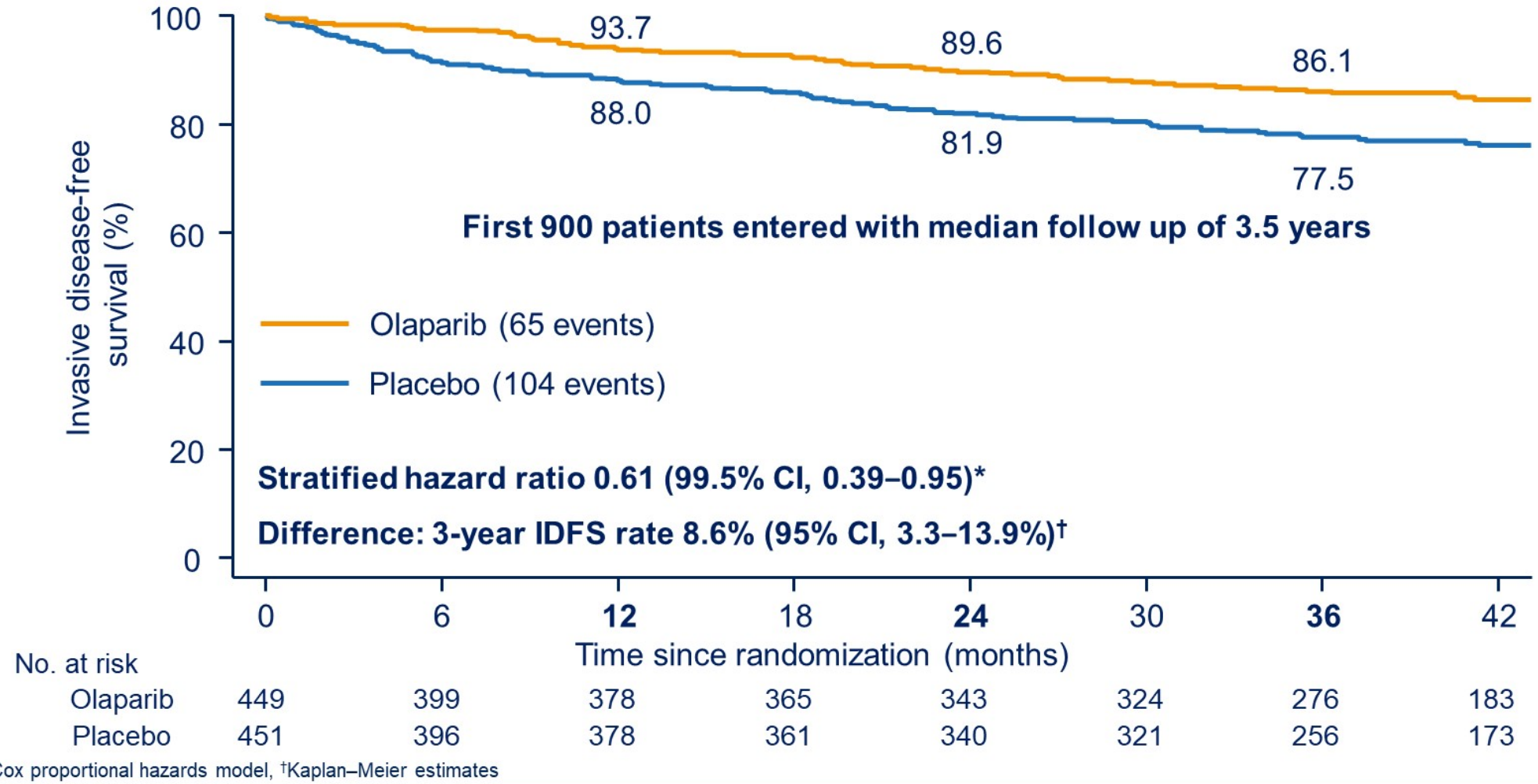
OlympiA: Invasive disease-free survival (mature cohort)

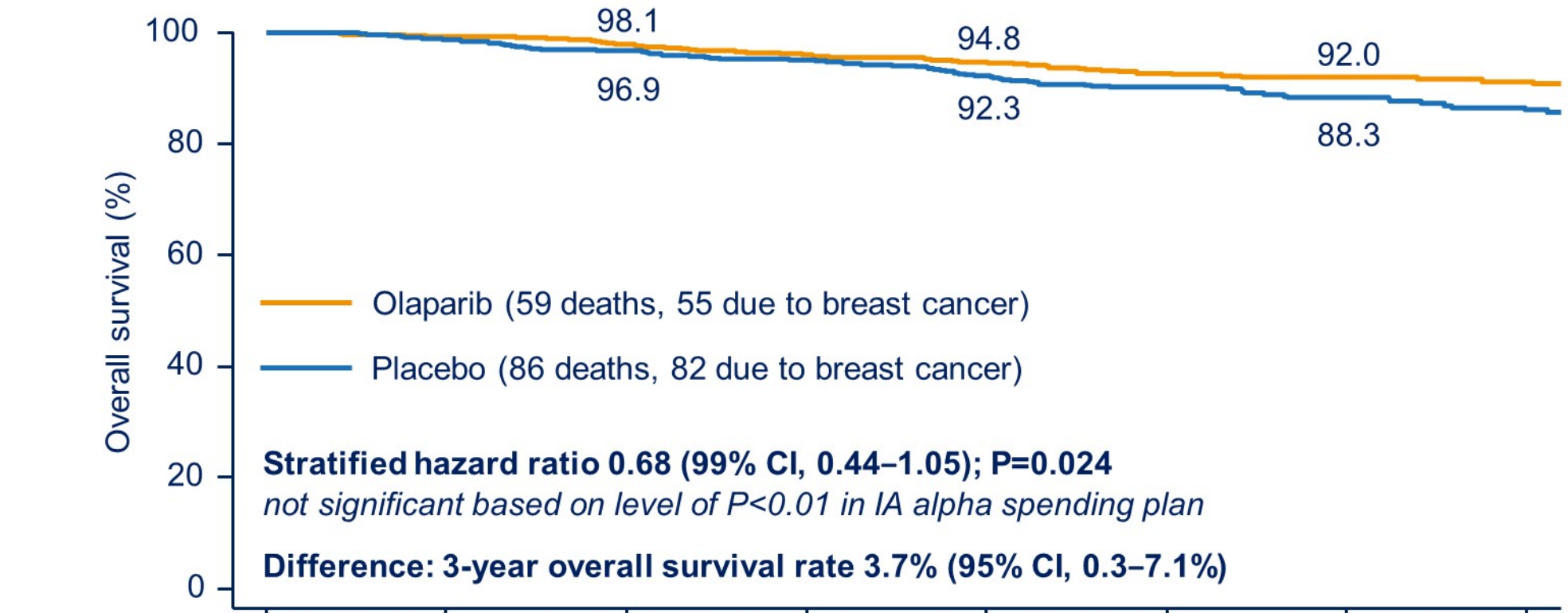


*Stratified Cox proportional hazards model, †Kaplan–Meier estimates

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

OlympiA: Overall survival



No. at risk							
Olaparib	921	856	801	659	531	400	310	205
Placebo	915	865	801	659	516	397	292	199

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

Courtesy of Matthew P Goetz, MD

2021 ASCO ANNUAL MEETING

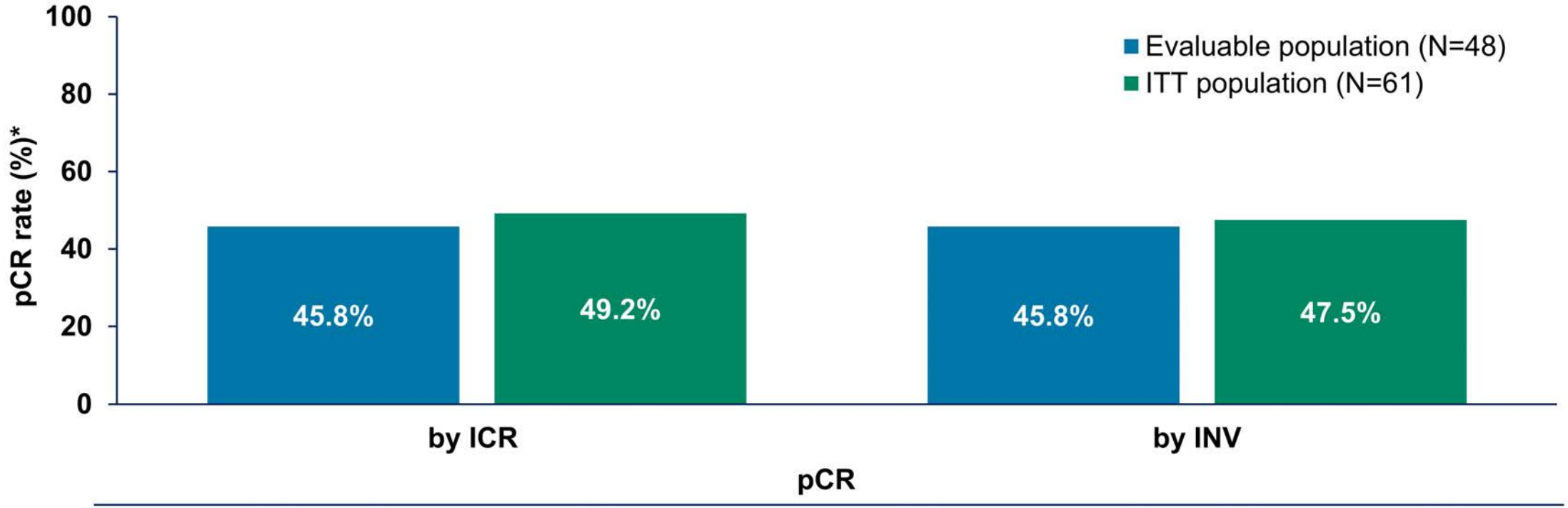
NEOADJUVANT TALAZOPARIB IN PATIENTS WITH GERMLINE *BRCA1/2* MUTATION-POSITIVE, EARLY HER2-NEGATIVE BREAST CANCER: RESULTS OF A PHASE 2 STUDY

Jennifer K. Litton,[1] J. Thaddeus Beck,[2] Jason M. Jones,[3] Jay Andersen,[4] Joanne L. Blum,[5] Lida A. Mina,[6] Raymond Brig,[7] Michael Danso,[8] Yuan Yuan,[9] Antonello Abbattista,[10] Kay Noonan,[11] Jayeta Chakrabarti,[12] Akos Czibere,[13] William F. Symmans,[1] Melinda L. Telli[14]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Highlands Oncology Group, Fayetteville, AR, USA; [3]Avera Cancer Institute, Sioux Falls, SD, USA; [4]Compass Oncology, West Cancer Center, Tigard, OR, USA; [5]Texas Oncology-Baylor Charles A. Sammons Cancer Center, US Oncology Network, Dallas, TX, USA; [6]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [7]Brig Center for Cancer Care and Survivorship, Knoxville, TN, USA; [8]Virginia Oncology Associates, Norfolk, VA, USA; [9]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [10]Pfizer Oncology, Milan, Italy; [11]Pfizer Inc., Groton, CT, USA; [12]Pfizer, Walton Oaks, Surrey, UK; [13]Pfizer Inc., Cambridge, MA, USA; [14]Stanford University School of Medicine, Stanford, CA, USA

June 6, 2021

Pathologic Complete Response



95% CI†	(32.0–60.6)	(36.7–61.6)	(32.0–60.6)	(35.0–60.1)
80% CI†	(36.4–55.2)	(41.0–57.4)		
Posterior probability that true pCR rate exceeds 45%	0.55	0.75		

*The denominator is N, the number of patients in the evaluable/ITT analysis set as per ICR/INV.
†The exact CI was calculated using the Blaker's method.

Agenda

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- Findings from the OVARIO trial: Niraparib/bevacizumab maintenance therapy

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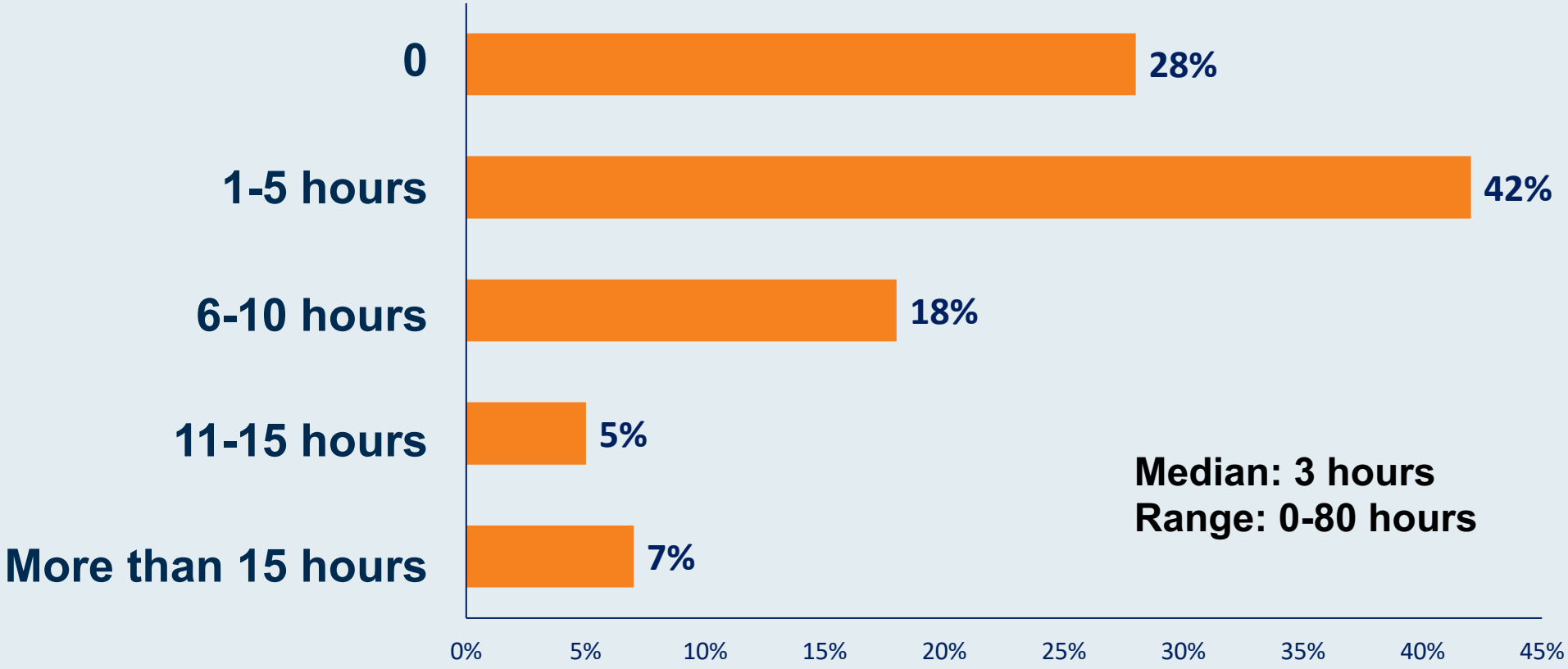
- Biologic rationale for combining PARP inhibitors with anti-PD-1/PD-L1 antibodies
- Ongoing Phase III trials evaluating immune checkpoint inhibitors with PARP inhibitors for advanced OC

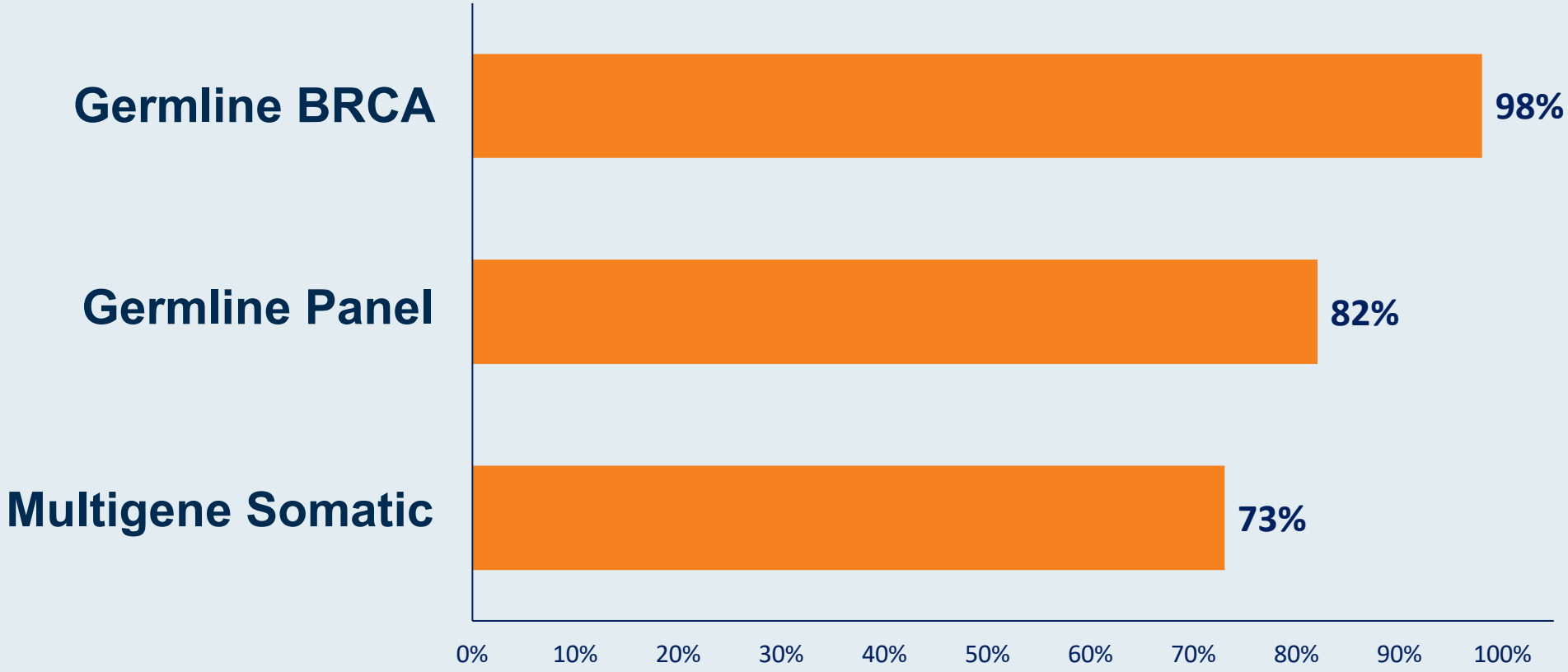
In the past month, approximately how many hours did you spend conducting telemedicine visits with patients?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

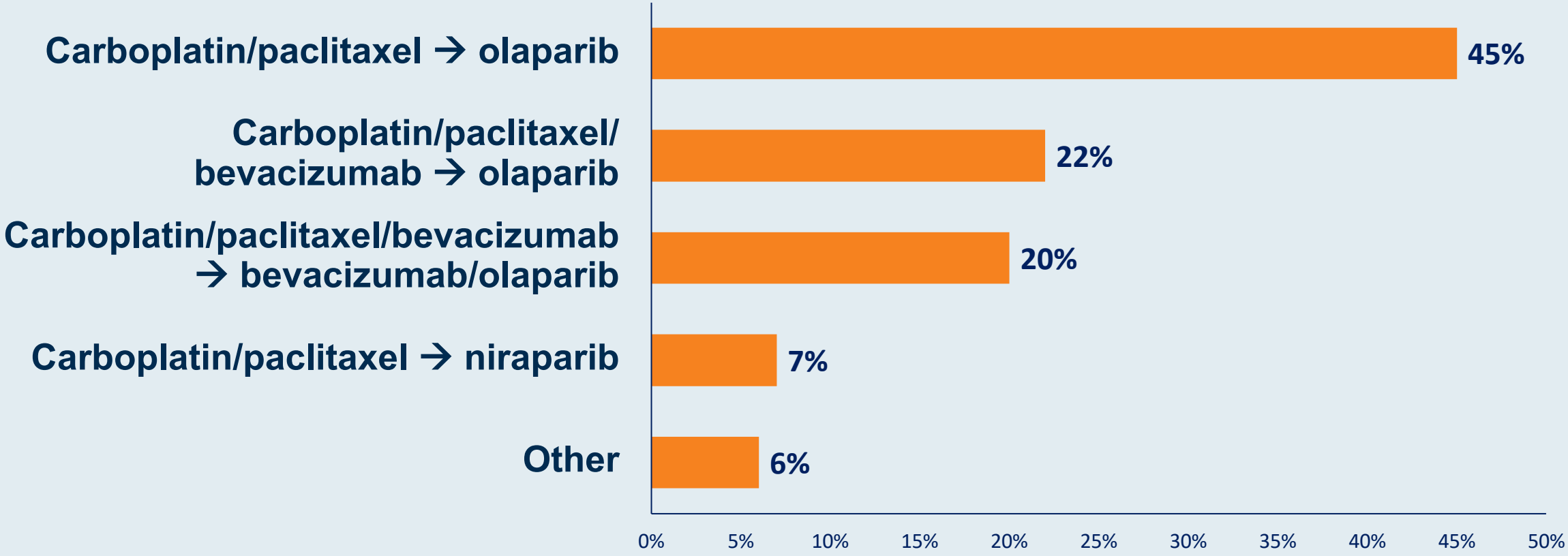
Would you order any of the following assays for a 65-year-old woman diagnosed with ovarian cancer whose family history is negative? (Percent responding “Yes”)



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

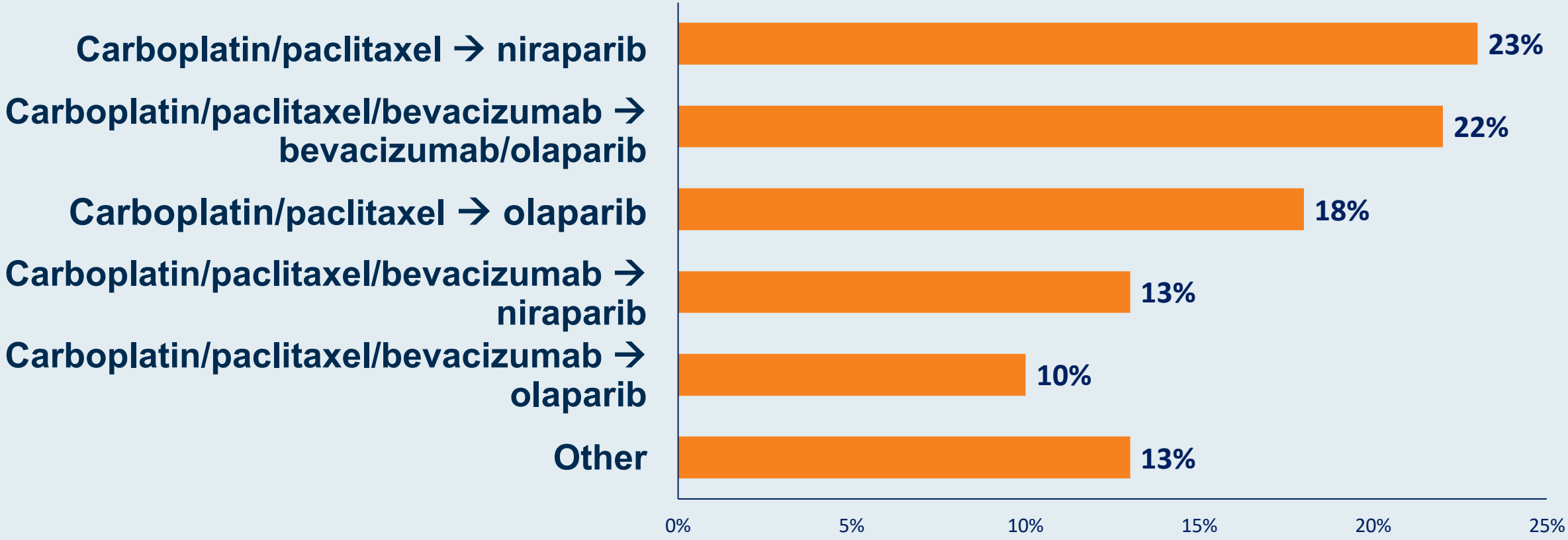
A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation is s/p optimal debulking surgery. Regulatory and reimbursement issues aside, what would you recommend as postoperative systemic therapy?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

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



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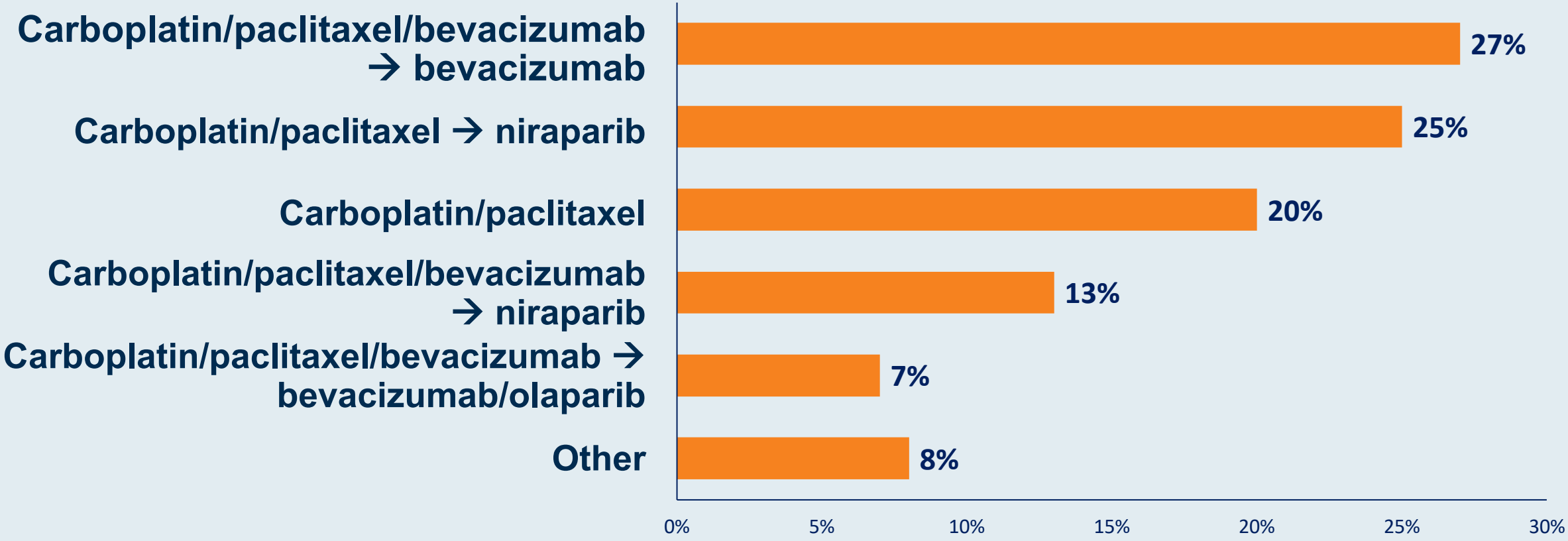
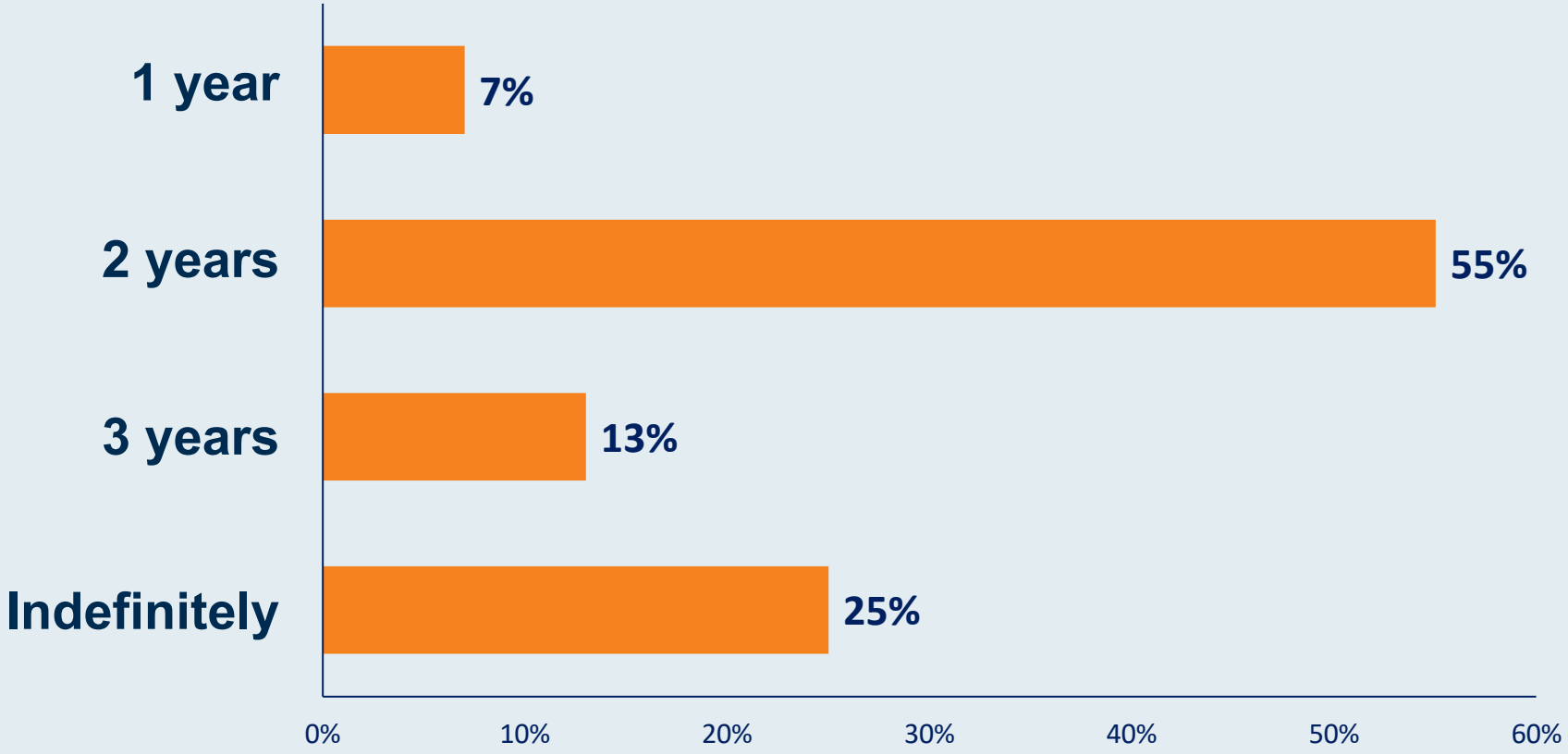


Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

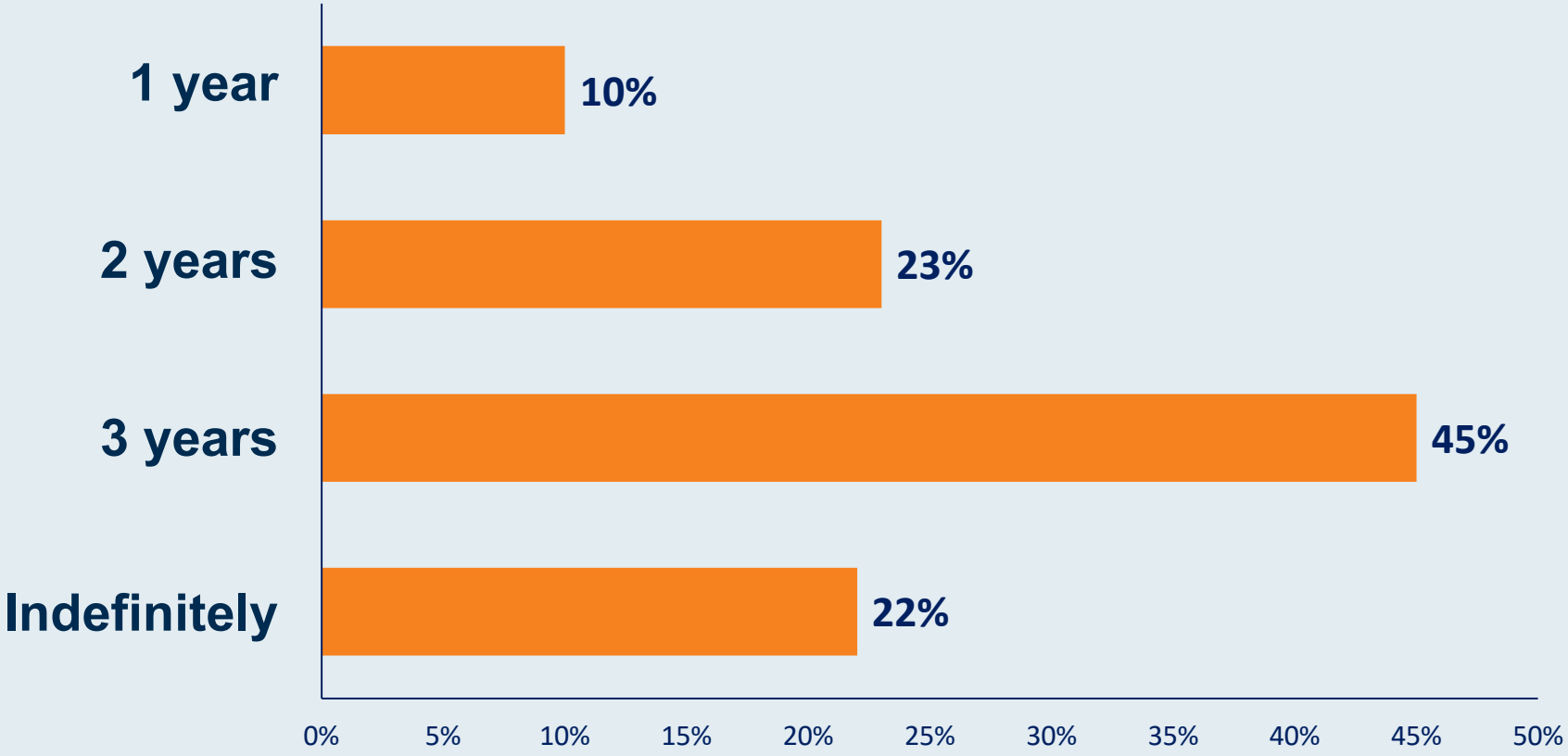
A 60-year-old woman with Stage IIIC ovarian cancer and a germline BRCA mutation undergoes debulking surgery and receives carboplatin/paclitaxel followed by olaparib. For how long would you typically continue the olaparib if the patient is tolerating it well?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

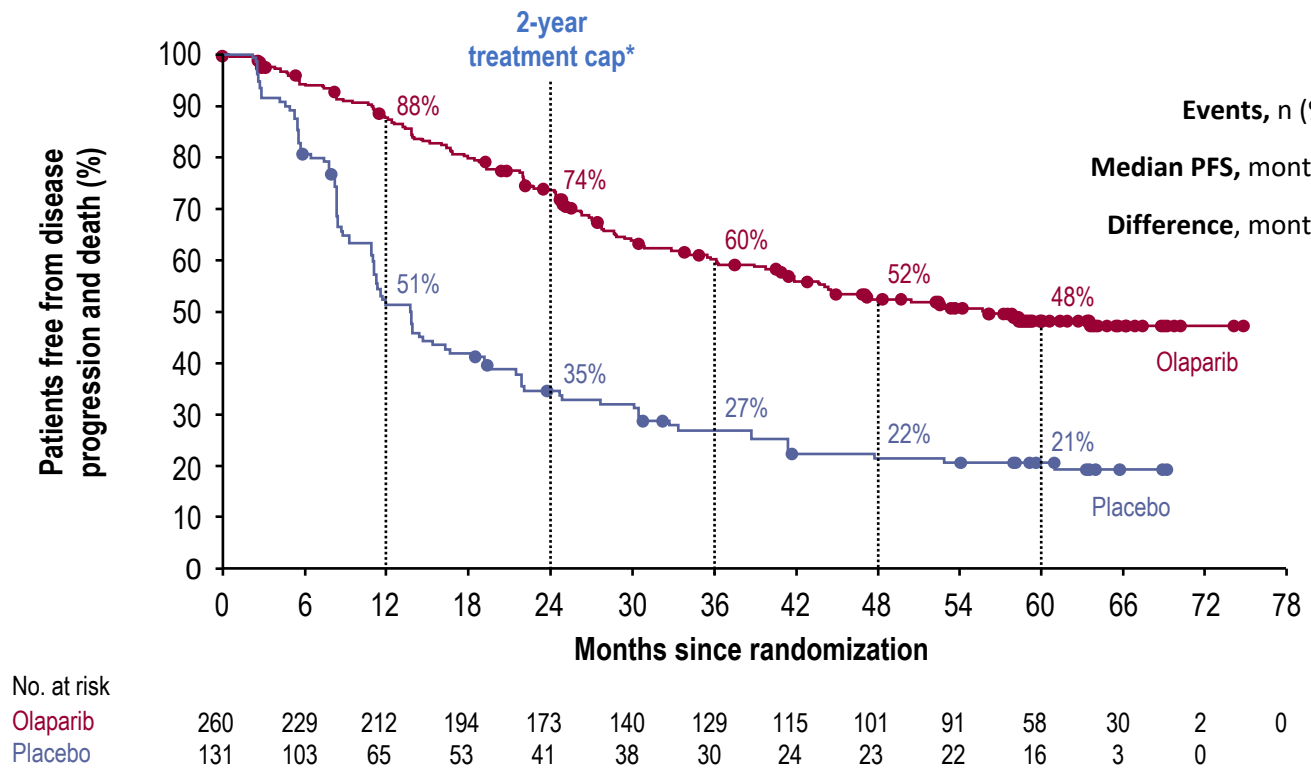
A 60-year-old woman with Stage IIIC ovarian cancer (BRCA wild type, HRD-negative) undergoes debulking surgery and receives carboplatin/paclitaxel followed by niraparib. For how long would you typically continue the niraparib if the patient is tolerating it well?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

Phase 3 SOLO1: PFS at 5 Years of Follow-Up



	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

*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

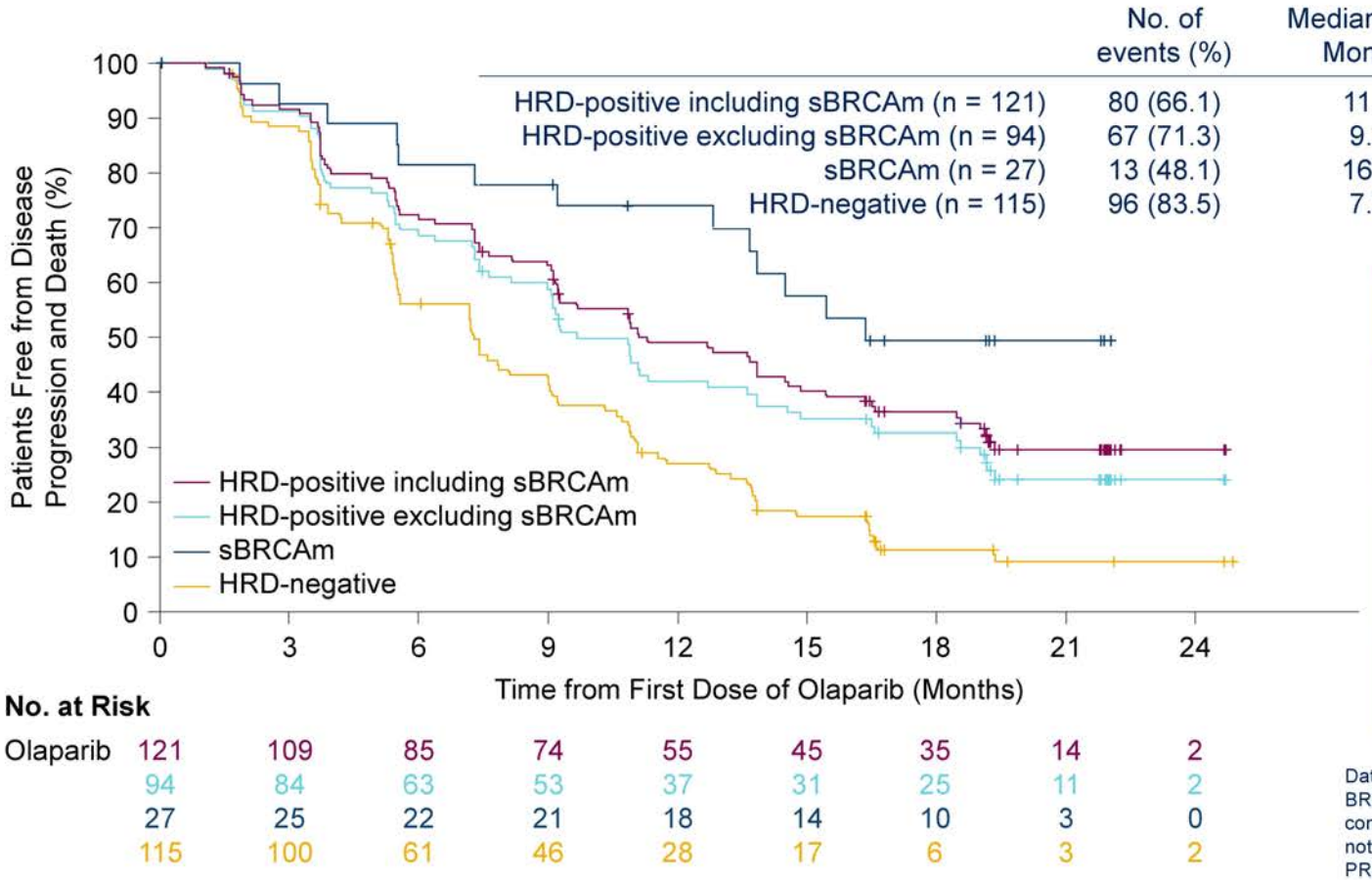
Median follow-up for PFS: olaparib, 4.8 y; placebo, 5.0 years.

Banerjee S, et al. ESMO 2020.

Courtesy of Michael J Birrer, MD, PhD

Primary Analysis of the Phase IIIb OPINION Study – ASCO 2021 "SOLO-1 Update"

Median PFS was prolonged across Myriad HRD/sBRCAm status and other baseline demographic/disease characteristics subgroups



	No. of events (%)	Median PFS, Months	95% CI, Months
HRD-positive including sBRCAm (n = 121)	80 (66.1)	11.1	9.2 to 14.6
HRD-positive excluding sBRCAm (n = 94)	67 (71.3)	9.7	8.1 to 13.6
sBRCAm (n = 27)	13 (48.1)	16.4	12.8 to NE
HRD-negative (n = 115)	96 (83.5)	7.3	5.5 to 9.0

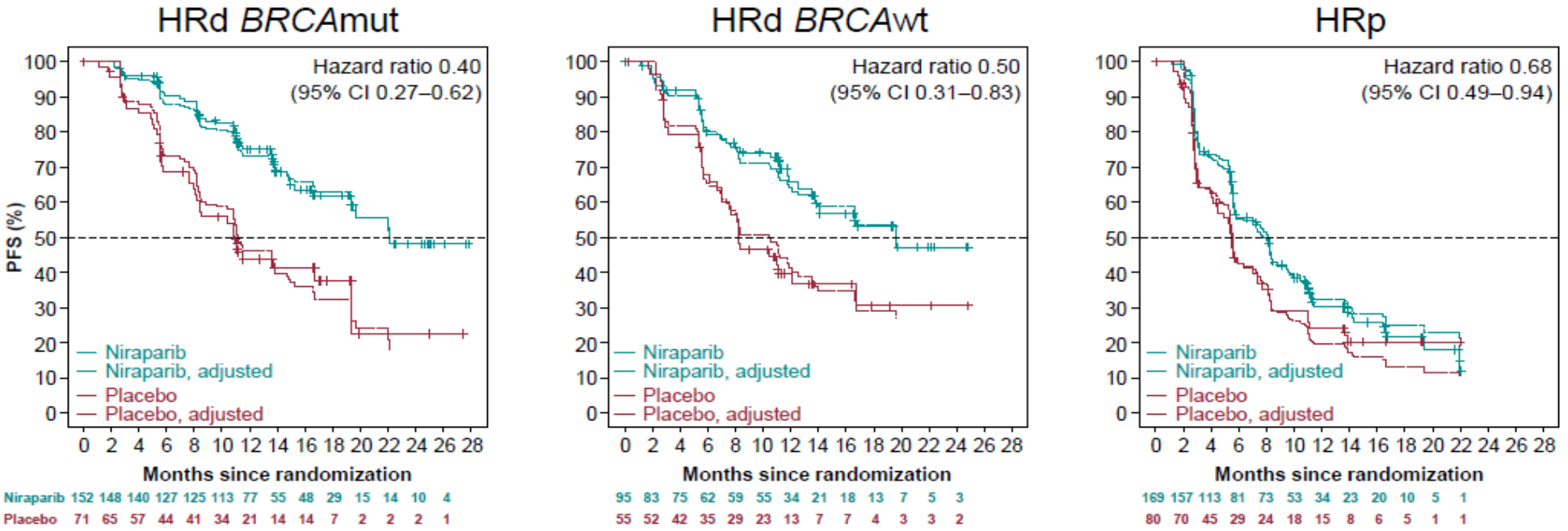
	No. of events (%)	Median PFS, Months	95% CI, Months
Prior platinum-based chemotherapy regimens			
2 (n = 165)	127 (77.0)	9.2	7.4–11.1
>2 (n = 114)	83 (72.8)	9.0	7.2–10.9
Response to most recent platinum-based chemotherapy			
CR/NED (n = 92)	60 (65.2)	13.7	9.3–16.4
PR (n = 184)	147 (79.9)	7.4	5.6–9.1
Age at enrolment			
<65 (n = 132)	100 (75.8)	9.2	7.8–12.8
≥65 (n = 147)	110 (74.8)	9.0	7.2–10.8

Data cut-off: 2 October 2020. Tickmarck indicates a censored observation. BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; CR, complete response; HRD, homologous recombination repair deficiency; NE, not evaluable; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; sBRCAm, somatic BRCA mutation

Courtesy of Michael J Birrer, MD, PhD

Phase 3 PRIMA PFS Benefit in HRd and HRp Subgroups by BICR

- Niraparib provided clinical benefit in the HRd (*BRCA*mut and *BRCA* wt) and HRp subgroups
- All subgroups were analyzed using the adjusted Cox regression method to account for stratification imbalances



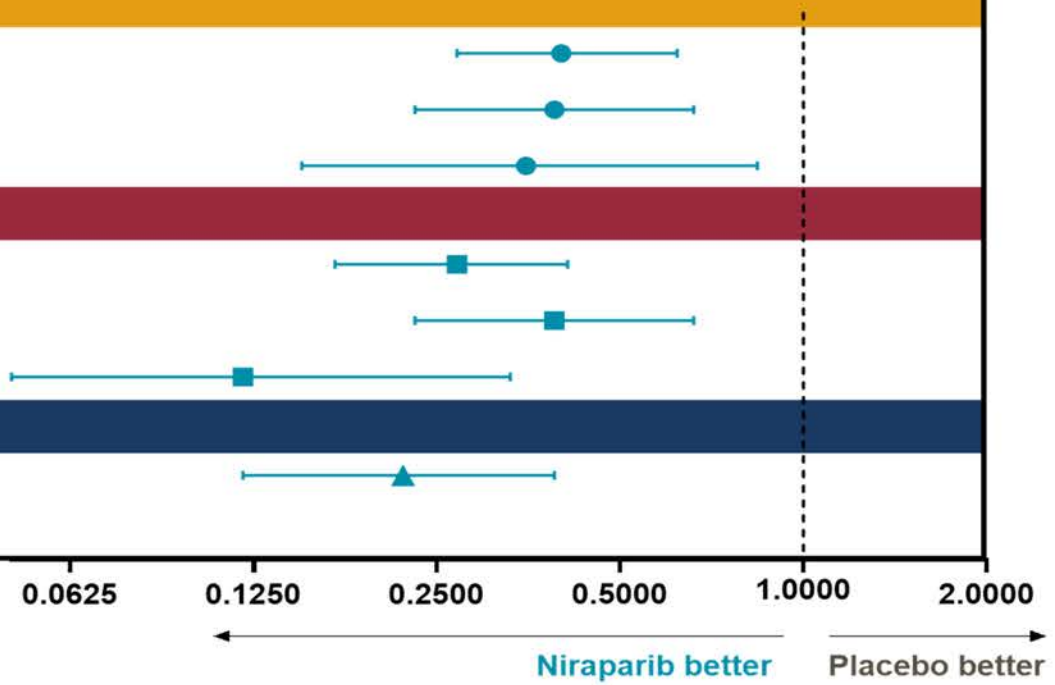
González-Martín A, et al. ESMO 2019. Abstract LBA1. González-Martín A, et al. *N Engl J Med.* 2019;381:2391-2402.

Courtesy of Michael J Birrer, MD, PhD

ASCO 2021 UPDATE- PRIMA

Progression-Free Survival in Patients with *BRCA*m Ovarian Cancer

	Niraparib		Placebo		Hazard ratio for PFS (95% CI)
	n/N	mPFS, mo	n/N	mPFS, mo	
PRIMA (1L maintenance)					
*BRCA*m	49/152	22.1	40/71	10.9	0.40 (0.27–0.62)
BRCA1	40/105	19.6	26/43	8.4	0.39 (0.23–0.66)
BRCA2	9/47	NE	14/28	13.6	0.35 (0.15–0.84)
NOVA (2L maintenance)					
g*BRCA*m	59/138	21.0	44/65	5.5	0.27 (0.17–0.41)
BRCA1	41/84	12.9	27/43	5.8	0.39 (0.23–0.66)
BRCA2	16/50	NE	13/18	5.4	0.12 (0.05–0.33)
NORA[1] (2L maintenance)					
g*BRCA*m[a]	24/65	NE	28/35	5.5	0.22 (0.12–0.39)



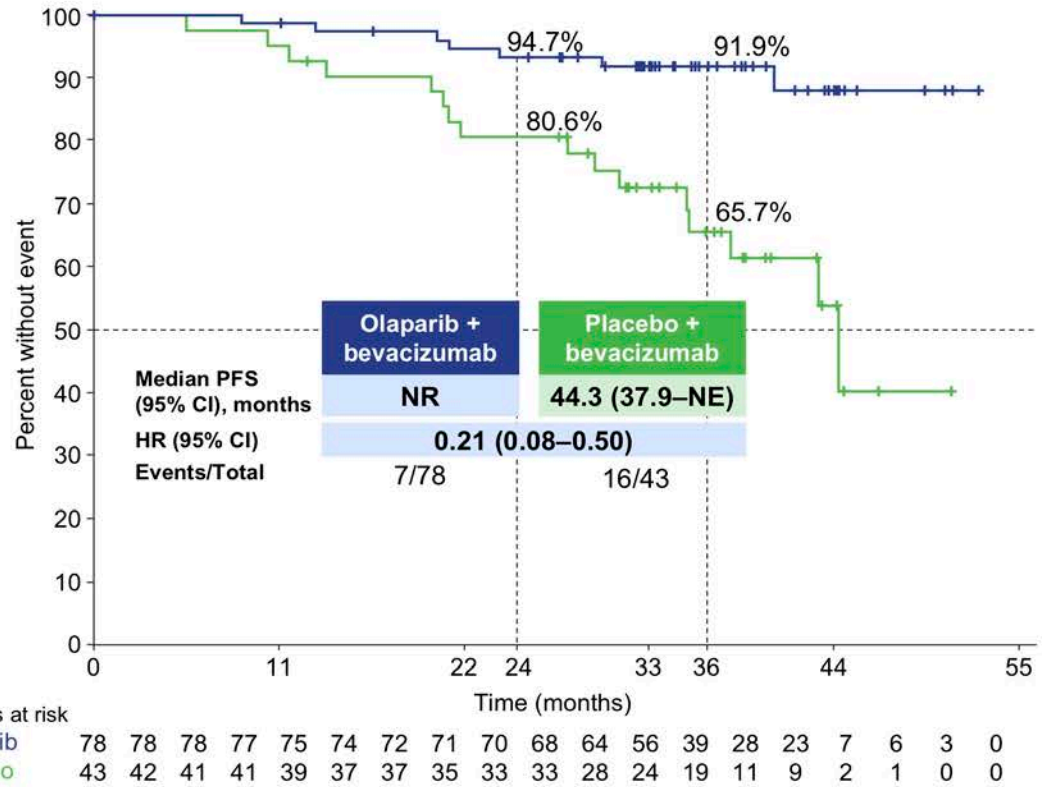
PFS was measured by blinded independent central review. Horizontal lines represent 95% CIs.
[a]*BRCA1* and *BRCA2* data are not currently available.
1L, first-line; 2L, second-line; g, germline; m, mutated; mPFS, median progression-free survival; NE, not estimable; PFS, progression-free survival.
[1]Wu XH, et al. *Ann Oncol* 2021;32(4):512–521.

Courtesy of Michael J Birrer, MD, PhD

ASCO 2021 UPDATE – PAOLA-1

PFS2 by FIGO stage and surgical outcome in patients with HRD-positive tumors

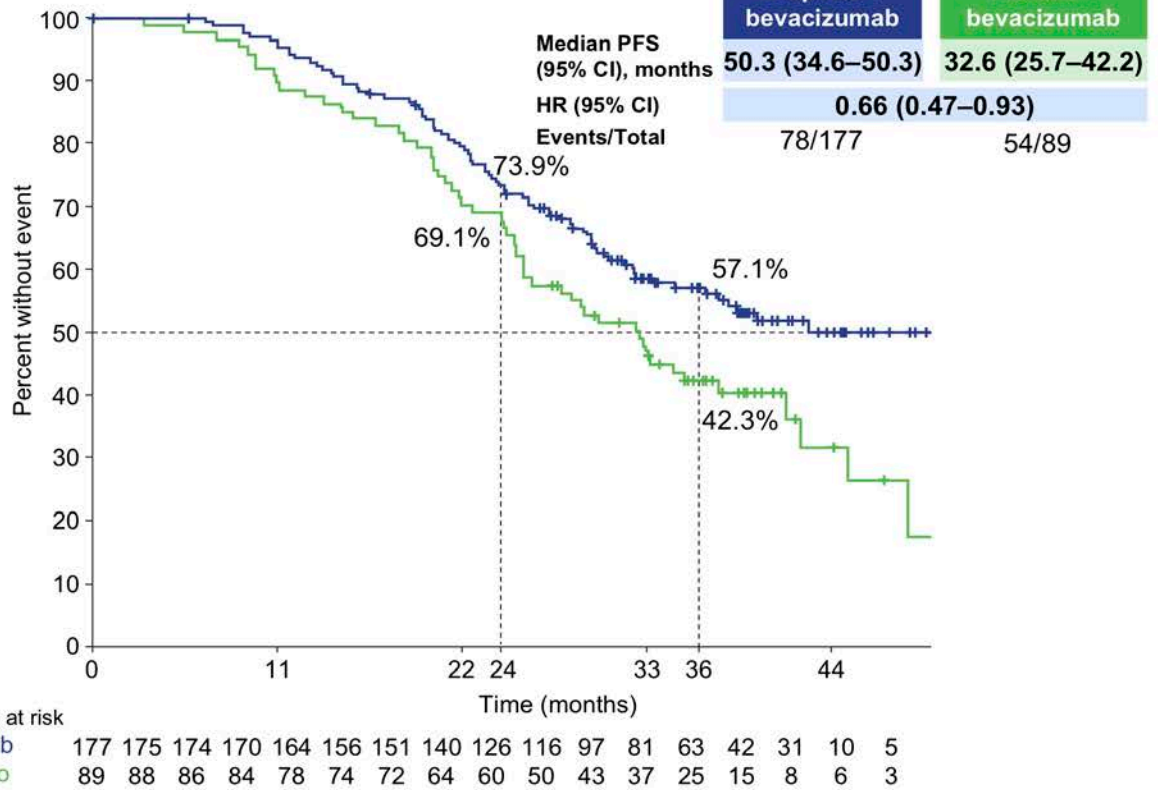
Lower risk*



Patients at risk

Olaparib	78	78	78	77	75	74	72	71	70	68	64	56	39	28	23	7	6	3	0
Placebo	43	42	41	41	39	37	37	35	33	33	28	24	19	11	9	2	1	0	0

Higher risk†



Patients at risk

Olaparib	177	175	174	170	164	156	151	140	126	116	97	81	63	42	31	10	5		
Placebo	89	88	86	84	78	74	72	64	60	50	43	37	25	15	8	6	3		

The median time from the first cycle of chemotherapy to randomization was 7 months. *Patients with HRD-positive tumors who had stage III disease and complete resection following upfront surgery (median follow-up overall: 37.0 months); †Stage III patients with residual disease after upfront surgery or who received neoadjuvant chemotherapy, or HRD-positive stage IV patients (median follow-up overall: 37.5 months).
NR, not reached; PFS2, second progression-free survival.

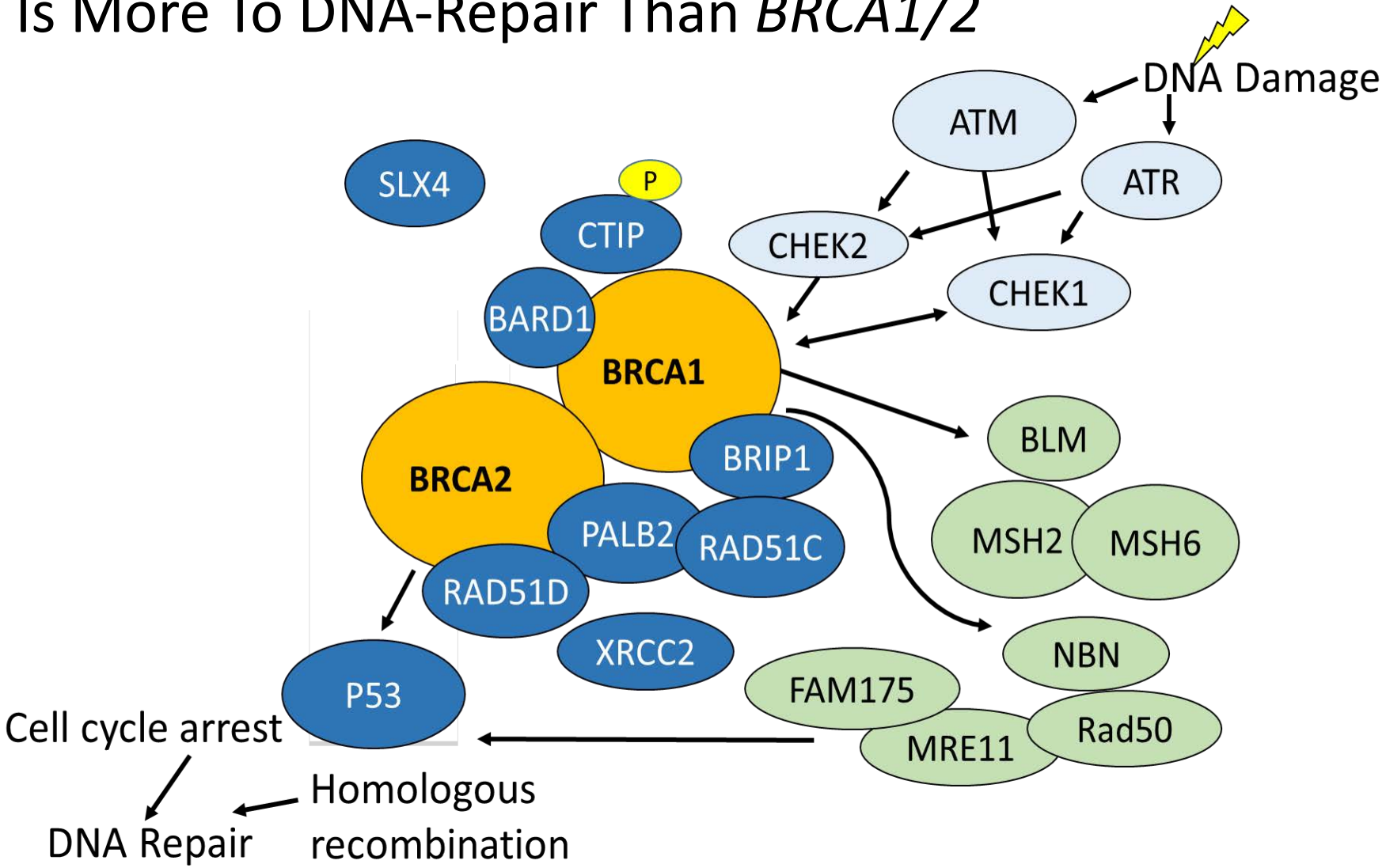
Courtesy of Michael J Birrer, MD, PhD

OVARIO Clinical Trial – SGO 2021
Bevacizumab plus niraparib in upfront maintenance

- Newly diagnosed high grade ovarian cancer responding to chemotherapy
- Single ARM Phase II
- Safe combination – no new toxicities found
- PFS at 6, 12, and 18 months revealed 90%, 75% and 62% respectively
- 27% discontinued treatment
- These results are consistent in efficacy and safety with PAOLA-1

Courtesy of Michael J Birrer, MD, PhD

There Is More To DNA-Repair Than *BRCA1/2*



Meindl et al, Nat Genetics 2010
Loveday et al, Nat Genetics 2011
Rafnar et al, Nat Genetics 2011
Casadei et al, Cancer Res 2011

Courtesy of Michael J Birrer, MD, PhD

Guidelines Recommend Screening for Hereditary Mutations for Risk Assessment and Genetic Counseling

National Comprehensive Cancer Network® (NCCN®)[1]

- All patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancers should be referred for genetic risk evaluation[a]

Society for Gynecologic Oncology[2]

- All patients with epithelial ovarian cancer should receive genetic counseling and be offered genetic testing, regardless of age or family history

American Society of Clinical Oncology[3]

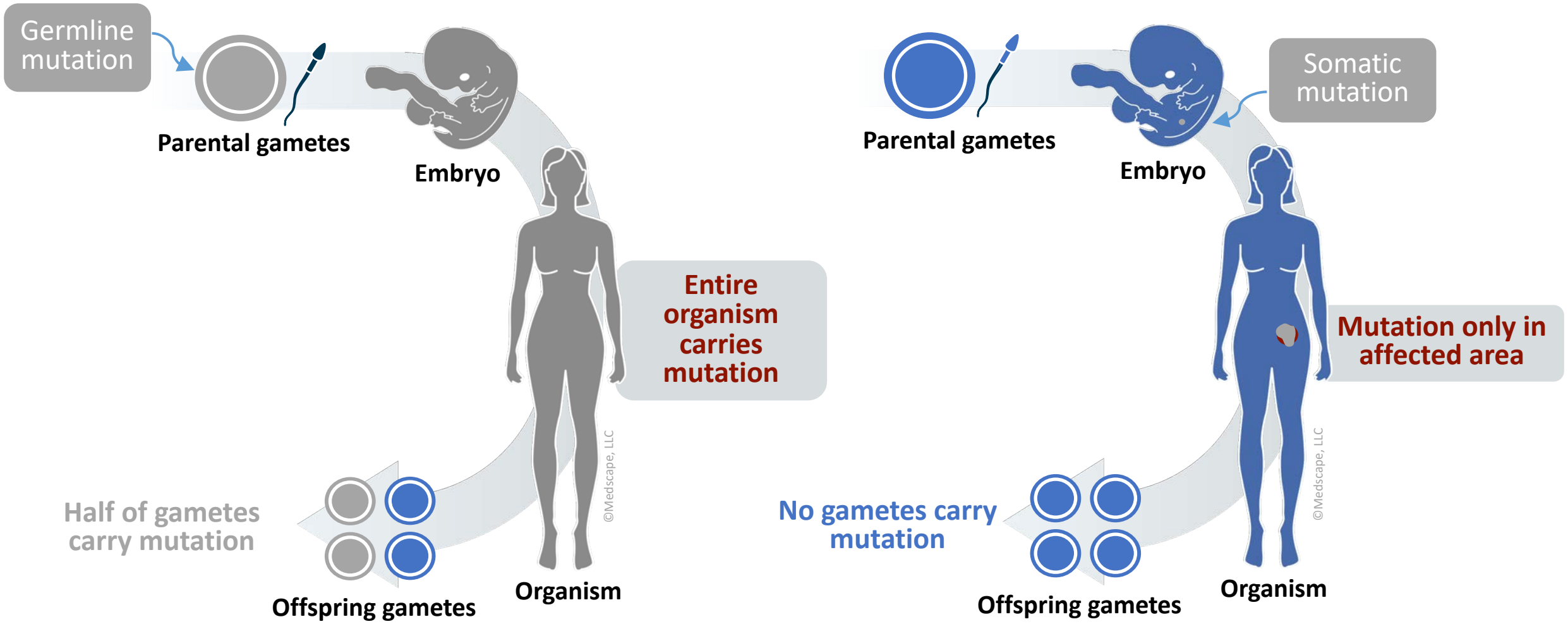
- Individuals with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should be considered for genetic testing to identify germline susceptibility genes, regardless of family history
- Prevention interventions are available that affect cancer risk in the patient and her relatives

[a] Primary treatment should not be delayed for a genetic counseling referral.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer V.2.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed February 1, 2019. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Lancaster JM, et al. *Gynecol Oncol.* 2015;136(1):3-7. **3.** American Society of Clinical Oncology. Assessing Your Patient's Hereditary Cancer Risk. https://www.asco.org/practice-guidelines/cancer-care-initiatives/genetics-toolkit/assessing-your-patient's-hereditary. Updated December 2018. Accessed January 17, 2019.

Courtesy of Michael J Birrer, MD, PhD

Germline vs Somatic Mutations

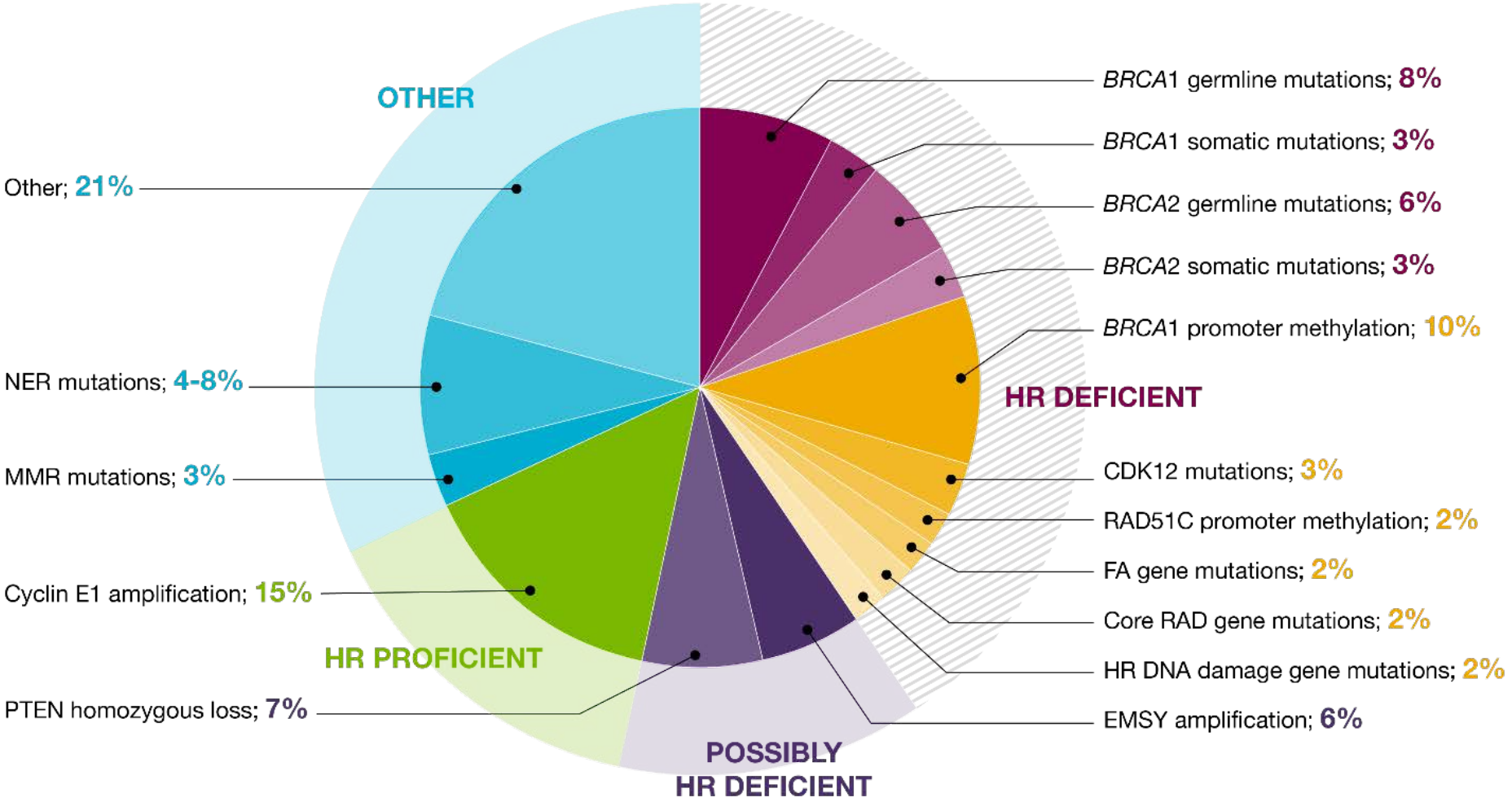


Germline mutations are inherited and found in all cells;
somatic mutations are not inherited and are found within the tumor

Courtesy of Michael J Birrer, MD, PhD

Approximately Half of High Grade Epithelial Ovarian Cancers Harbor Defects in Homologous Recombination

These defects can be identified using different clinical and molecular biomarkers



Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137-1154.

Courtesy of Michael J Birrer, MD, PhD

Agenda

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- Treatment strategies based on germline and somatic genomic assays
- ASCO 2021 updates for the SOLO-1, PRIMA and PAOLA-1 trials
- Findings from the OVARIO trial: Niraparib/bevacizumab maintenance therapy

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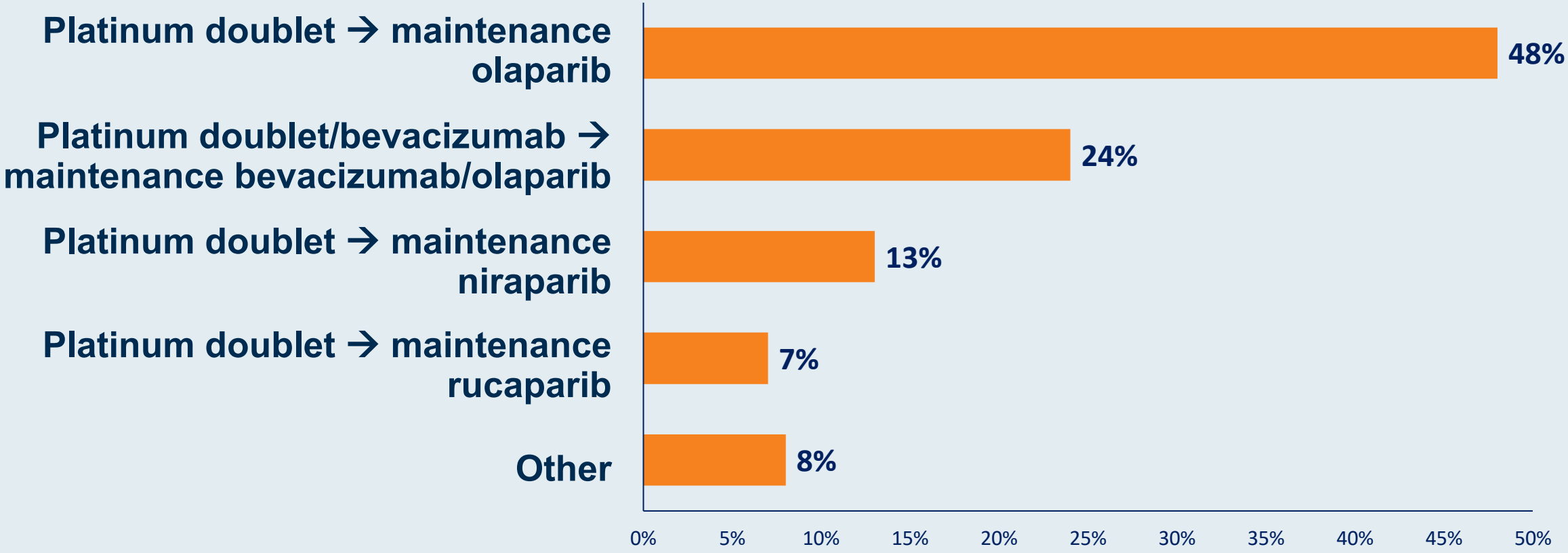
Module 4: Immune Checkpoint Inhibitors in OC

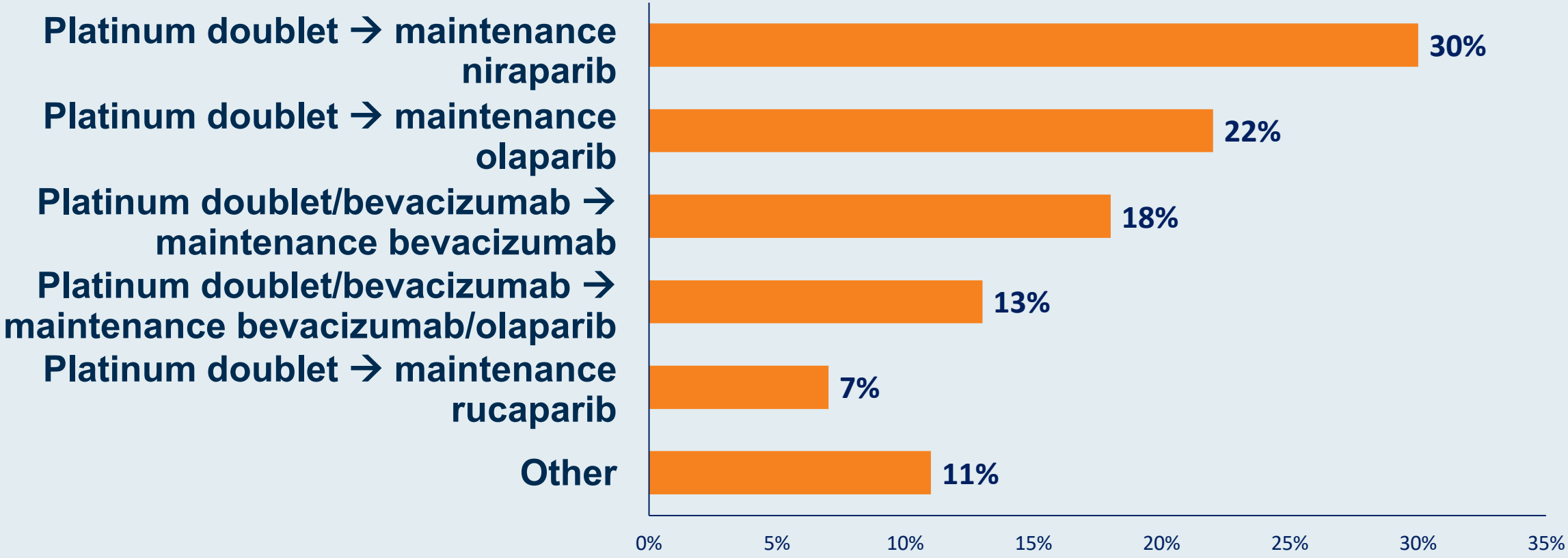
- Biologic rationale for combining PARP inhibitors with anti-PD-1/PD-L1 antibodies
- Ongoing Phase III trials evaluating immune checkpoint inhibitors with PARP inhibitors for advanced OC

A 70-year-old woman with advanced ovarian cancer and a germline BRCA mutation undergoes debulking surgery followed by chemotherapy with carboplatin/paclitaxel and experiences disease relapse 1 year later. Which treatment would you likely recommend?



Premeeting survey: July 2021

A 70-year-old woman with advanced ovarian cancer (BRCA wild type, HRD-positive) undergoes debulking surgery followed by chemotherapy with carboplatin/paclitaxel and experiences disease relapse 1 year later. Which treatment would you likely recommend?



Premeeting survey: July 2021

RTP RESEARCH TO PRACTICE

FDA-Approved PARP Inhibitors as Maintenance Therapy for Recurrent, Platinum-Sensitive Disease

Niraparib

Indications:
- Maintenance following response to platinum-based therapy
- Irrespective of BRCA status

Pivotal study: ENGOT-OV16/NOVA

Approved: 3/2017

Rucaparib

Indications:
- Maintenance following response to platinum-based therapy
- Irrespective of BRCA status

Pivotal study: ARIEL3

Approved: 4/2018

Olaparib

Indications:
- Maintenance following response to platinum-based therapy
- Irrespective of BRCA status

Pivotal studies: SOLO-2, Study 19

Approved: 8/2017

Niraparib FDA insert, revised 3/2017; Rucaparib FDA insert, revised 4/2018; Olaparib FDA insert, revised 1/2018; Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64; Coleman RL et al. *Lancet* 2017;390(10106):1949-61; Ledermann J et al. *N Engl J Med* 2012;366:1382-92.

Efficacy Summary of PARP Inhibitors for Recurrent, Platinum-Sensitive OC

	PARPi	Control	HR
NOVA[1] — Niraparib			
gBRCA mutation	21.0 mo	5.5 mo	0.27
No gBRCA mutation, HRD+	12.9 mo	3.8 mo	0.38
No gBRCA mutation	9.3 mo	3.9 mo	0.45
SOLO-2[2] — Olaparib			
gBRCA mutation	19.1 mo	5.5 mo	0.30
ARIEL3[3-4] — Rucaparib			
ITT (All comers)	10.8 mo	5.4 mo	0.36
g or sBRCA mutation	16.6 mo	5.4 mo	0.23
HRD+	13.6 mo	5.4 mo	0.32
$BRCA^{WT}$/High LOH	13.6 mo	5.4 mo	0.32
$BRCA^{WT}$/Low LOH	6.7 mo	5.4 mo	0.58

[1] Mirza MR et al. *N Engl J Med* 2016;375(22):2154-64; [2] Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; [3] Coleman RL et al. *Lancet* 2017;390(10106):1949-61; [4] Ledermann JA et al. *Lancet Oncol* 2020;21(5):710-722.

FDA-Approved PARP Inhibitors as Monotherapy for Multiply Relapsed Disease

Olaparib	Rucaparib	Niraparib
Indications: • 4th-line therapy and beyond • Germline BRCA mutation **Dosing:** • 300 mg BID **Approved: 12/2014**	**Indications:** • 3rd-line therapy and beyond • Germline and/or somatic BRCA mutation **Dosing:** • 600 mg BID **Approved: 12/2016**	**Indications:** • 4th-line therapy and beyond • HRD-positive **Dosing:** • Weight- and platelet count-dependent: 200 or 300 mg QD **Approved: 102/2019**

Olaparib prescribing information, revised 12/2018; Rucaparib prescribing information, revised 4/2018; Niraparib prescribing information, revised 04/2020

Rucaparib vs Chemotherapy in Patients With Advanced, Relapsed Ovarian Cancer and a Deleterious BRCA Mutation: Efficacy and Safety From ARIEL4, a Randomized Phase 3 Study

Rebecca Kristeleit,[1] Alla Lisyanskaya,[2] Alexander Fedenko,[3] Mikhail Dvorkin,[4] Andreia Cristina de Melo,[5] Yaroslav Shparyk,[6] Irina Rakhmatullina,[7] Igor Bondarenko,[8] Nicoletta Colombo,[9] Valentyn Svintsitskiy,[10] Luciano Biela,[11] Marina Nechaeva,[12] Francesco Raspagliesi,[13] Giovanni Scambia,[14] David Cibula,[15] Róbert Póka,[16] Ana Oaknin,[17] Tamar Safra,[18] Beata Mackowiak-Matejczyk,[19] Ling Ma,[20] Daleen Thomas,[21] Kevin K. Lin,[21] Karen McLachlan,[21] Sandra Goble,[21] Amit M. Oza[22]

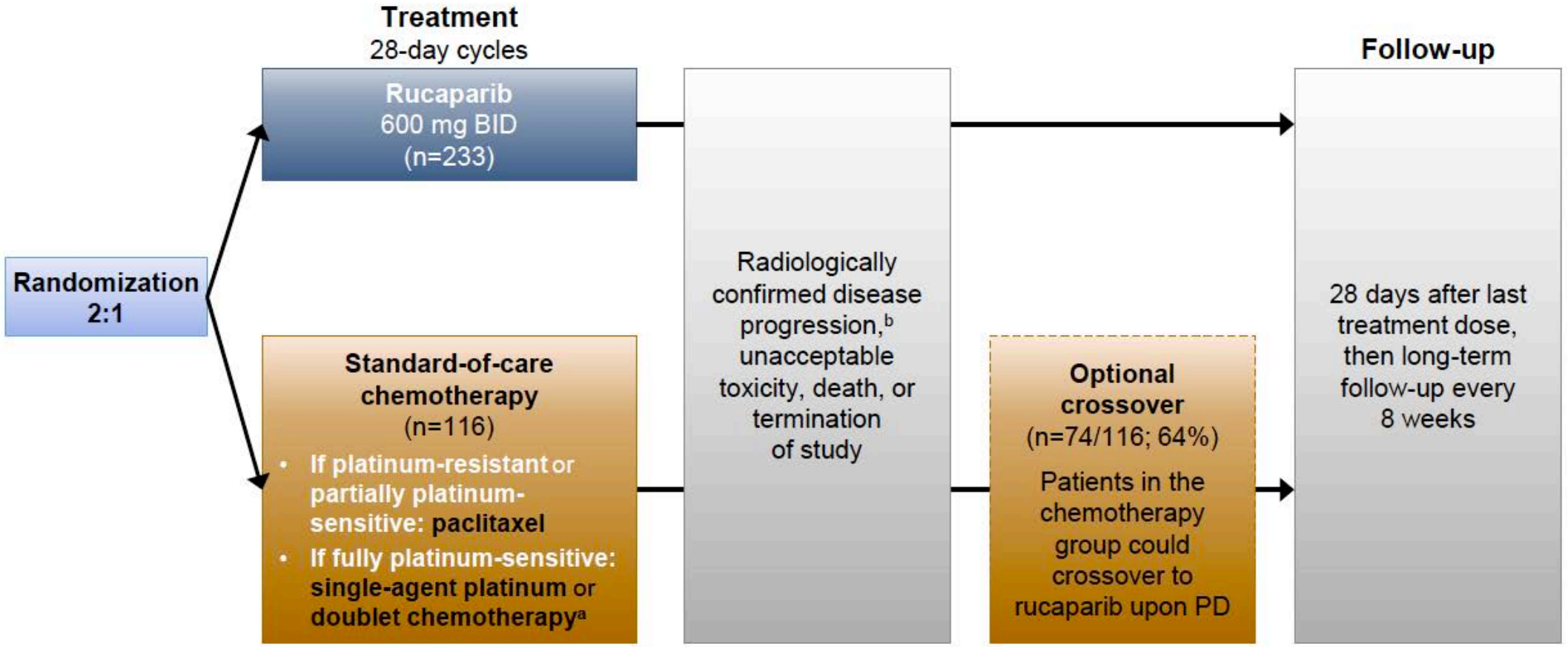
[1]Guy's and St. Thomas' NHS Foundation Trust, London, UK; [2]Saint Petersburg City Oncological Dispensary, Russia; [3]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [4]Omsk Region Clinical Oncologic Dispensary, Russia; [5]Instituto Nacional de Câncer - Hospital do Câncer II, Rio de Janeiro, Brazil; [6]Lviv Regional Oncology Dispensary, Ukraine; [7]Republic Clinical Oncology Dispensary of the Ministry of Healthcare of Republic of Bashkortostan, Ufa, Russia; [8]Dnipropetrovsk Medical Academy, Dnipro, Ukraine; [9]University of Milan-Bicocca and European Institute of Oncology (IEO) IRCCS, Italy; [10]National Cancer Institute of the Ministry of Health of Ukraine, Kyiv, Ukraine; [11]Instituto de Oncologia do Parana (IOP), Curitiba, Brazil; [12]Arkhangelsk Clinical Oncological Dispensary, Russia; [13]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [14]Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy; [15]Charles University and General University Hospital in Prague, Czech Republic; [16]University of Debrecen, Hungary; [17]Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Spain; [18]Sourasky Medical Center, Tel Aviv, Israel; [19]Bialostockie Centrum Onkologii im. Marii Sklodowskiej-Curie, Poland; [20]Rocky Mountain Cancer Centers, Lakewood, USA; [21]Clovis Oncology, Inc., Boulder, USA; [22]Princess Margaret Cancer Centre, University Health Network, Toronto, Canada

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Courtesy of Richard T Penson, MD, MRCP

Society of Gynecologic Oncology

ARIEL4: Study Schema

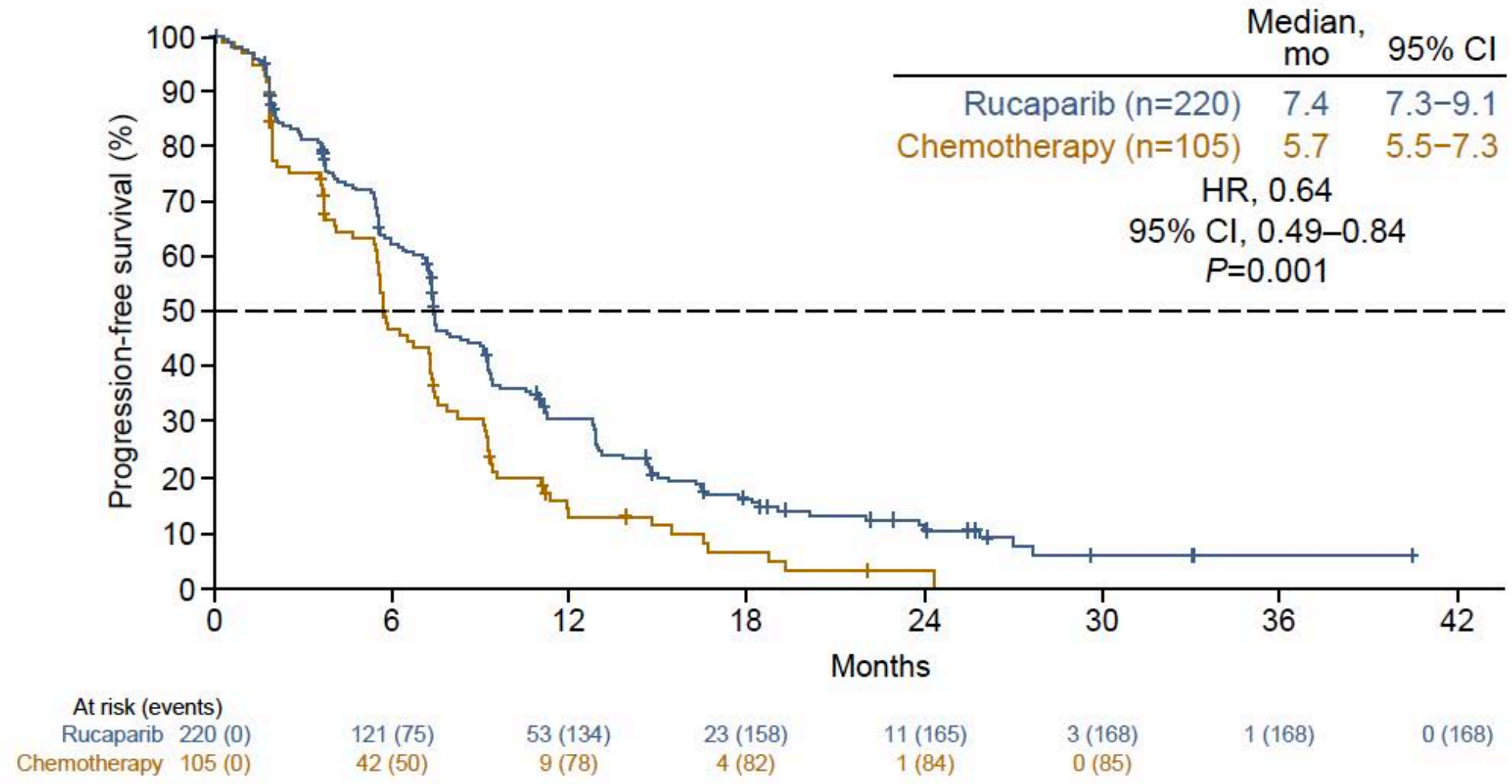


Randomization stratification factor: Platinum status (platinum-resistant, partially platinum-sensitive, fully platinum sensitive)[c]

[a]At investigator's discretion. [b]Per RECIST. [c]Platinum resistant: PFI ≥1–<6 months, partially platinum sensitive: PFI ≥6–<12 months, fully platinum sensitive: PFI ≥12 months.
BID, twice daily; BRCA, *BRCA1* or *BRCA2;* PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFI, progression-free interval; RECIST, Response Evaluation Criteria In Solid Tumors, version 1.1.

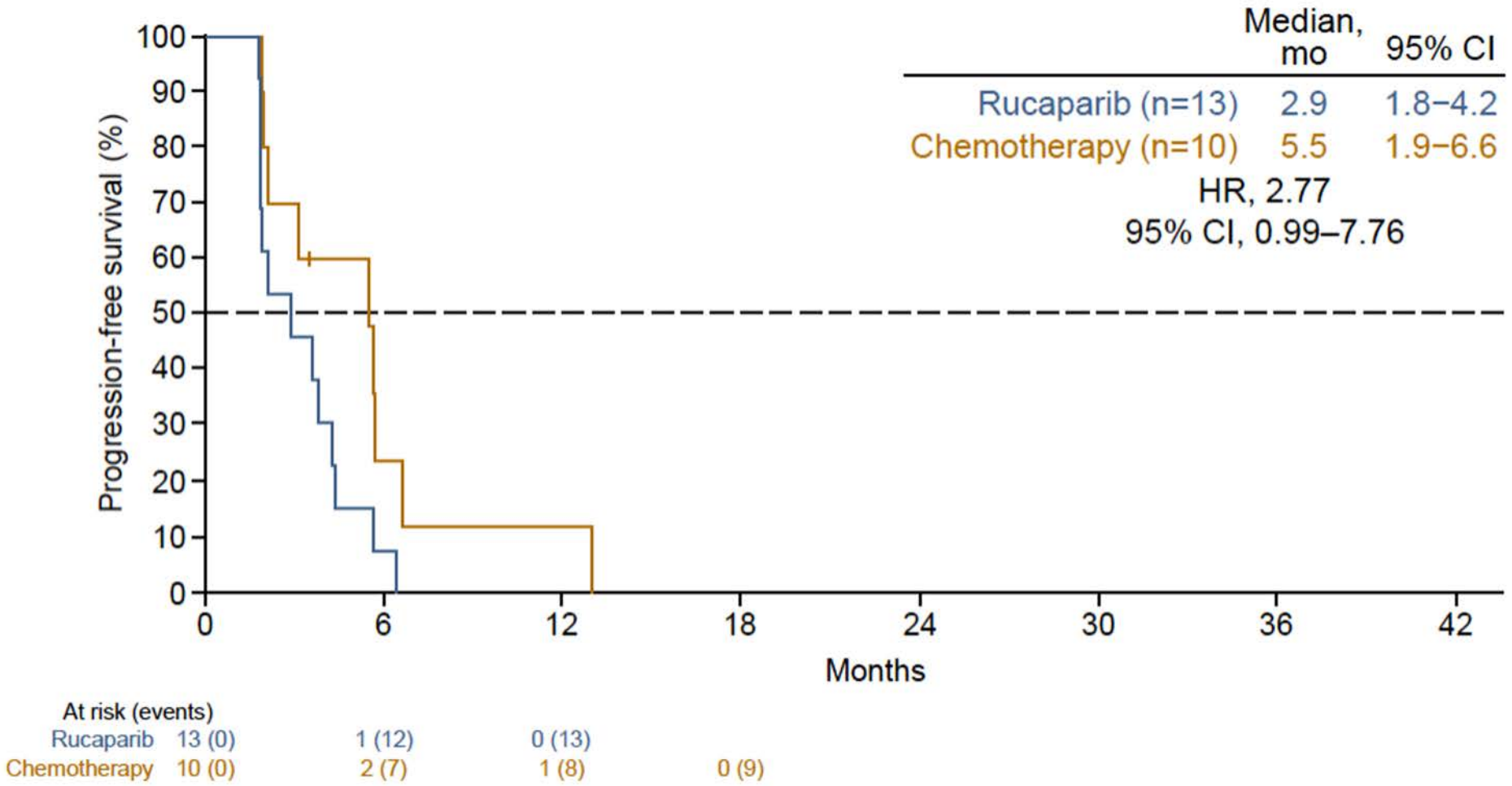
Courtesy of Richard T Penson, MD, MRCP

ARIEL4: Investigator-Assessed PFS



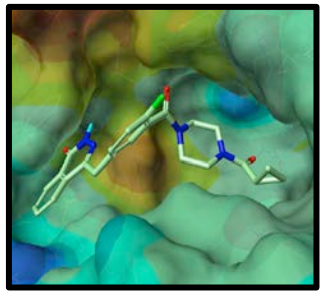
Courtesy of Richard T Penson, MD, MRCP

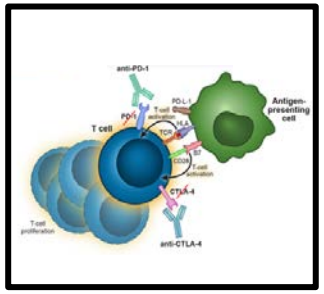
ARIEL4: Investigator-Assessed PFS BRCA^{mut} Reversion

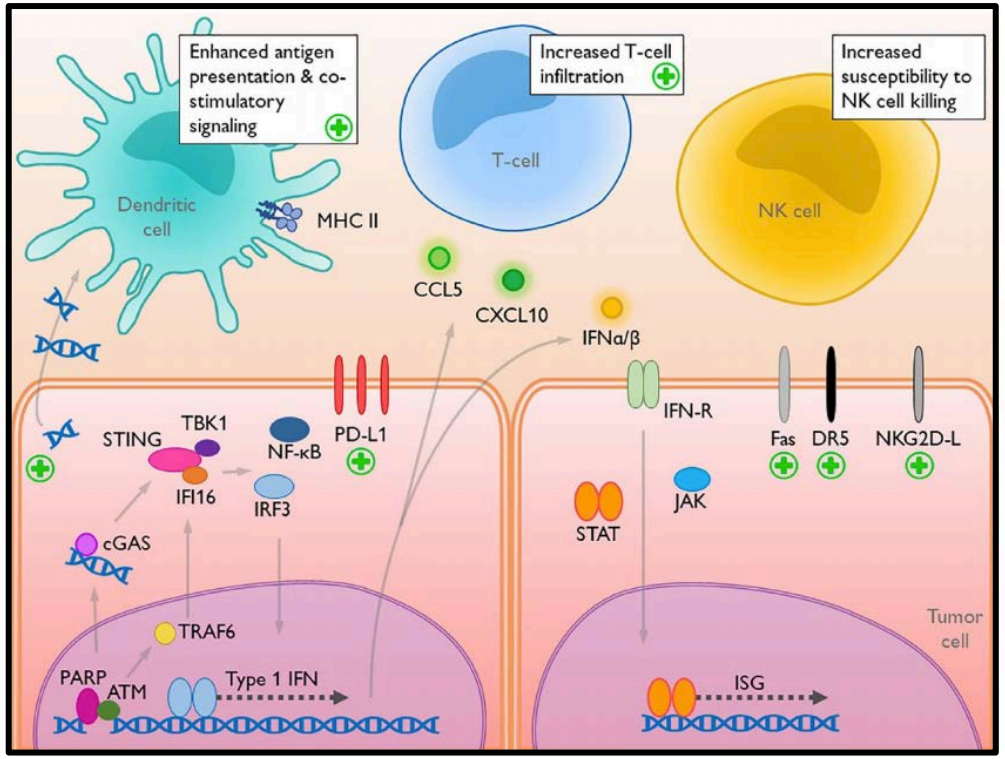


Courtesy of Richard T Penson, MD, MRCP

Resistance Mechanisms: Issue 1







Error Prone Repair → Neoantigens

CD80 & 86, MHC II → Ag presentation

PD-L1 upregulation → 'Warmer' Tumors

NKG2D Ligands → 'Warmer' Tumors

STING Pathway → Type I IFN response

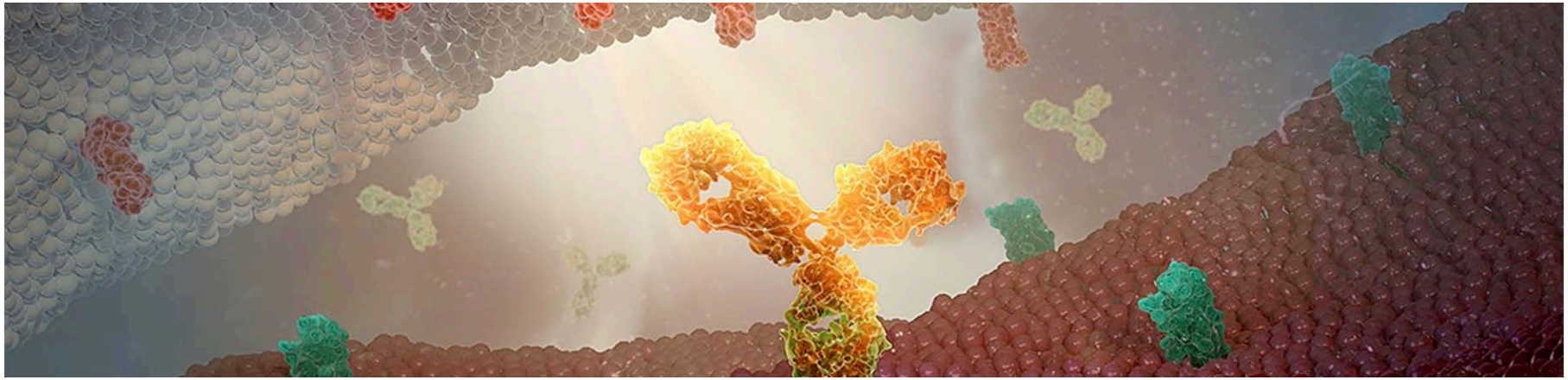
Courtesy of Richard T Penson, MD, MRCP

Lee LK & Konstantinopoulos PA. Trends Cancer. 2019;5(9):524-8

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Resistance Mechanisms: Issue 2

OReO



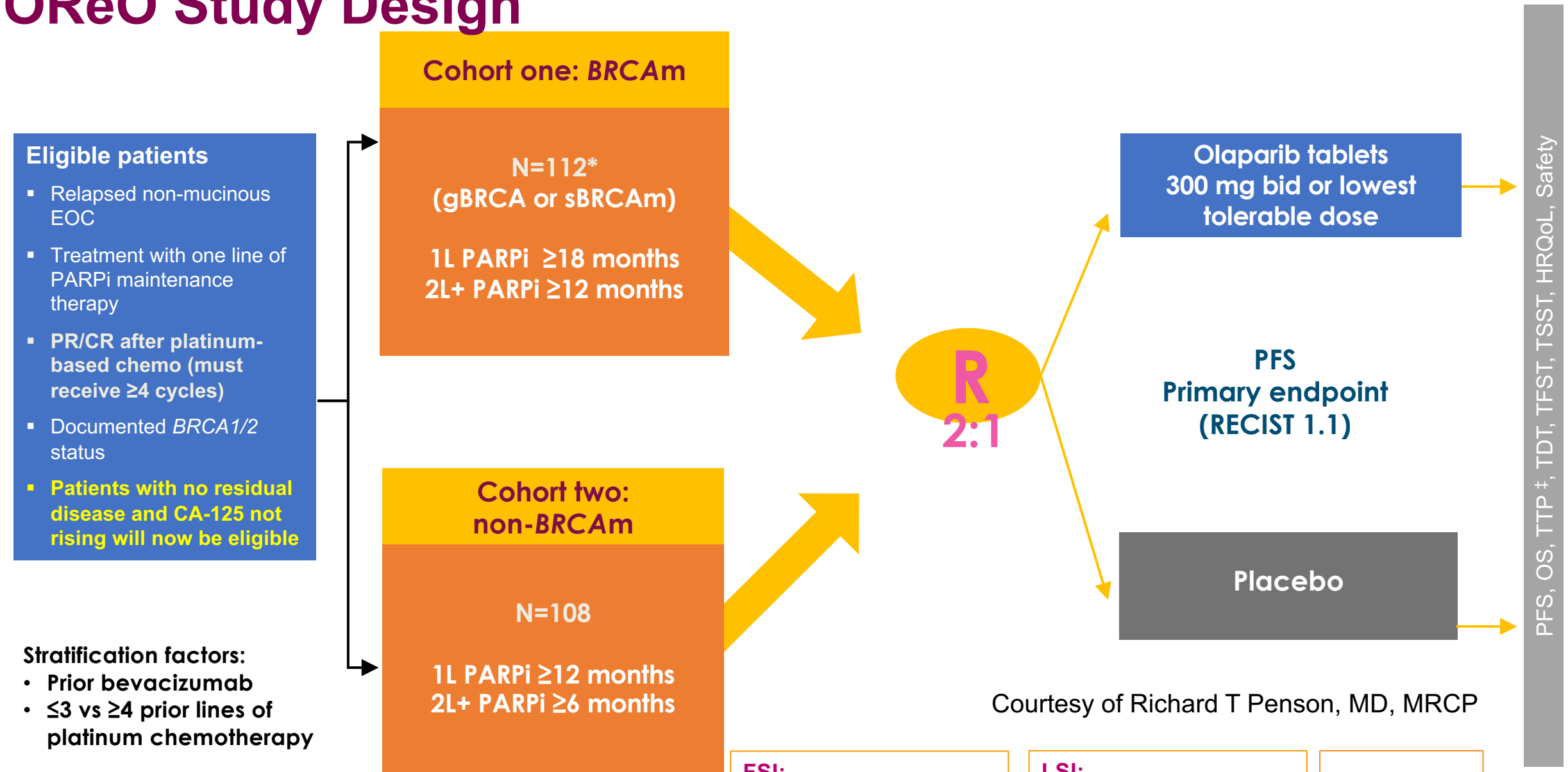
A Phase IIIb, Randomised, Double-blind, Placebo-controlled, multi-centre Study of Olaparib Maintenance Re-treatment in Patients with Epithelial Ovarian Cancer Previously treated with a PARPi and Responding to Repeat Platinum Chemotherapy (D0816C00014 ENGOT ov38)

Courtesy: Eric Pujade-Lauraine MD

Courtesy of Richard T Penson, MD, MRCP

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

OReO Study Design



Courtesy of Richard T Penson, MD, MRCP

FSI:		
BRCAm	July 2017	
non BRCAm	Oct 2017	
LSI:		
BRCAm	Apr 2020	
non BRCAm	Feb 2021	
DCO Feb 15th 2021		

*BRCAm cohort: N=120 planned but 112 randomised, due to required number of events being reached.

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Platinum Resistant Ovarian Cancer: Improving on AURELIA

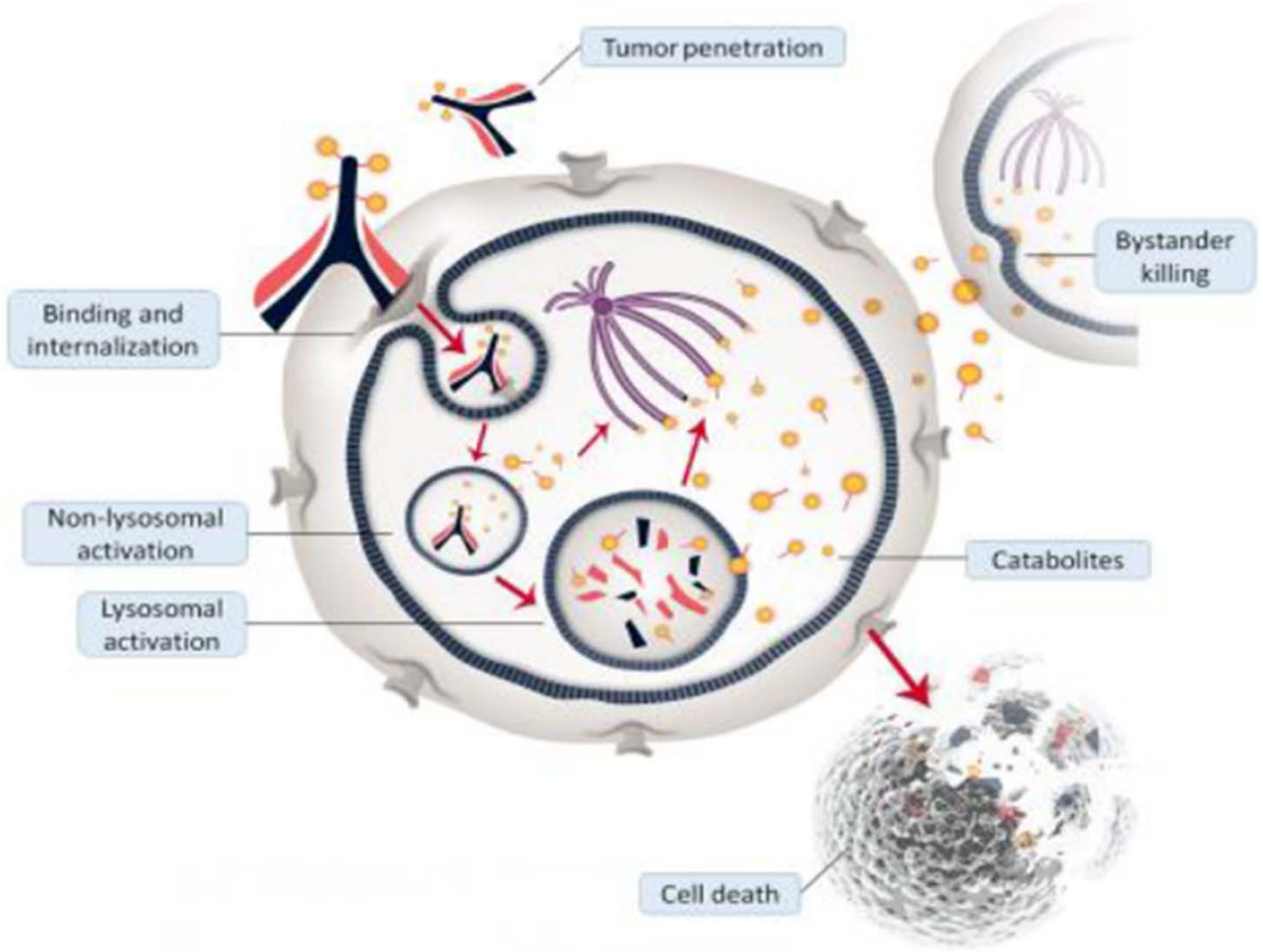
	AURELIA	Mirvetuximab	AVB500	Navicixizumab
Regimen	Chemo/Bev	**Mirv/Bev**	**AVB500/PAC**	**Navi/PAC**
Median age	61	**64**	**64**	**63**
Patient population	Platinum resist 1-2 priors **60% - 1 prior** **40% - 2 prior**	**40% 1-2 priors**	**≥2 priors in 66%**	**Median # priors 4**
Prior bevacizumab	7%	**40%**	**47%**	**68%**
ORR	27%	**59%**	**34.8%**	**43%**
mPFS	6.7 (95% 5.7, 7.9)	**9.7 (95% CI 5.6-11)**	**mDOR 7.0 months**	**NR**

O'Malley et al ASCO 2021, Fuh et al SGO Annual Meeting 2021; Moore et al. SGO Annual Meeting 2020

Courtesy of Kathleen Moore, MD

Mirvetuximab + Bevacizumab in Recurrent Ovarian Cancer: Abstract 5504

Mirvetuximab soravtansine is an antibody-drug conjugate targeting the folate receptor alpha



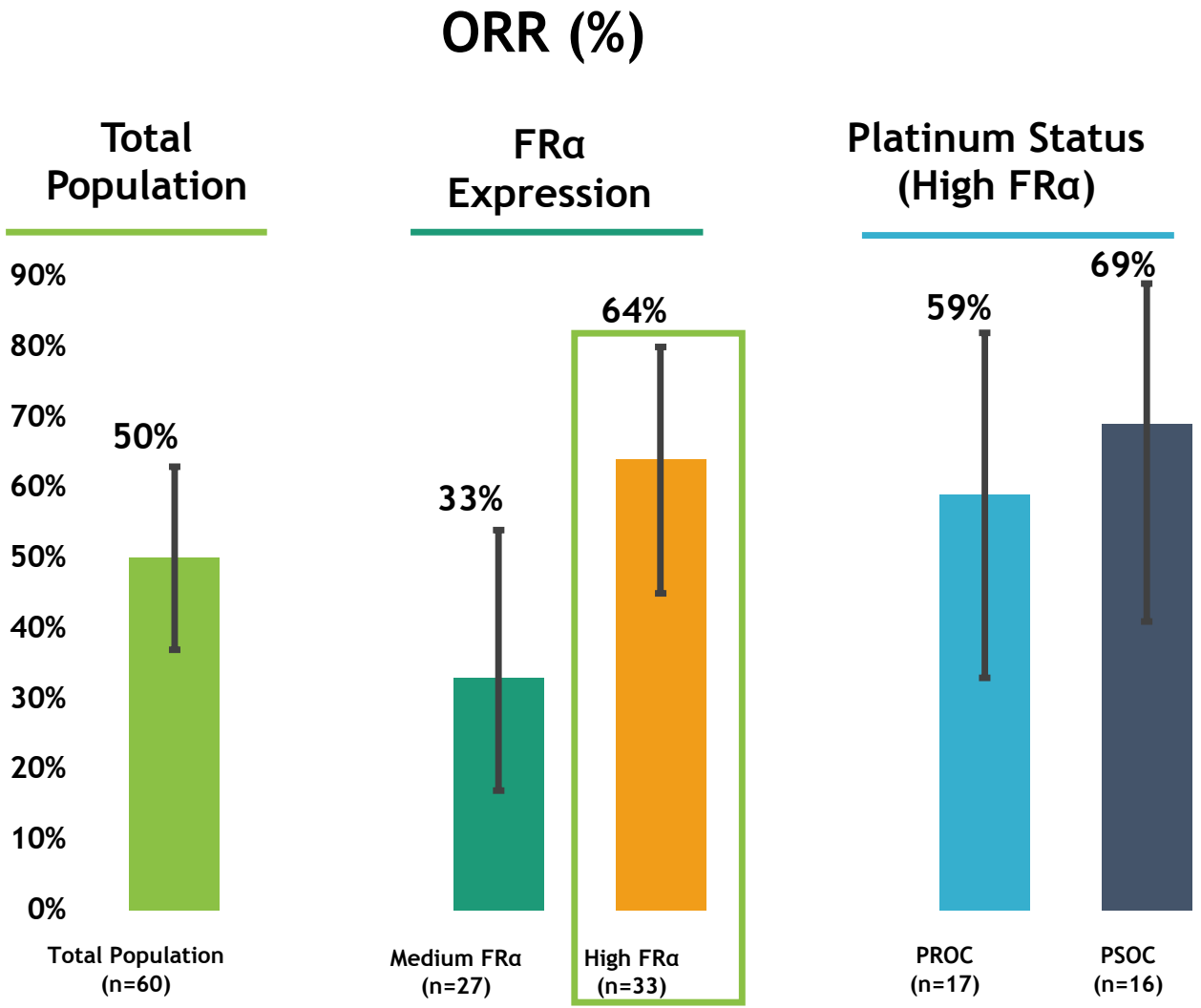
Mirvetuximab 6 mg/kg + bevacizumab 15 mg/kg

- PFI
  - < 6 months 53%
  - 6-12 months 33%
  - >12 months 13%
- Prior Treatments
  - Bevacizumab 40%
  - PARPi 35%
- Prior Therapies
  - 1-2 priors 68%
  - ≥3 32%

O'Malley et al. J Clin Oncol 39, 2021 (suppl 15; abstr 5504)

Courtesy of Kathleen Moore, MD

Confirmed ORR by FRα Expression and Platinum Status

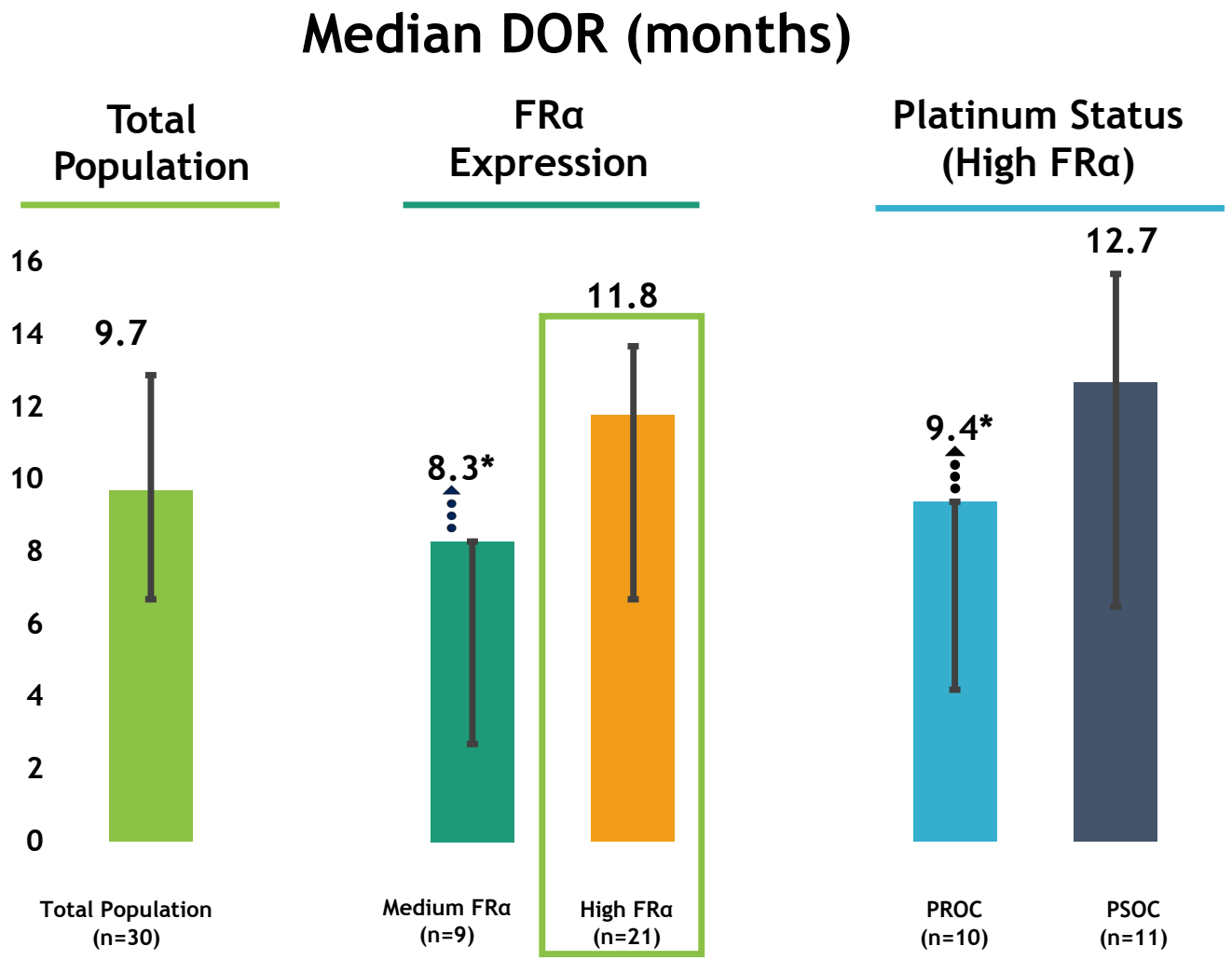


- **50% ORR** (30/60) for overall cohort
- **64% ORR** (21/33) in high FRα tumors
  - **59% ORR** (10/17) in PROC subset
  - **69% ORR** (11/16) in PSOC subset

David O'Malley, Ohio State University

Courtesy of Kathleen Moore, MD

Median Duration of Response (mDOR) by FRα Expression and Platinum Status



- **9.7 mo mDOR** for overall cohort
- **11.8 mo mDOR** in high FRα tumors
  - **9.4 mo mDOR** in PROC subset
  - **12.7 mo mDOR** in PSOC subset

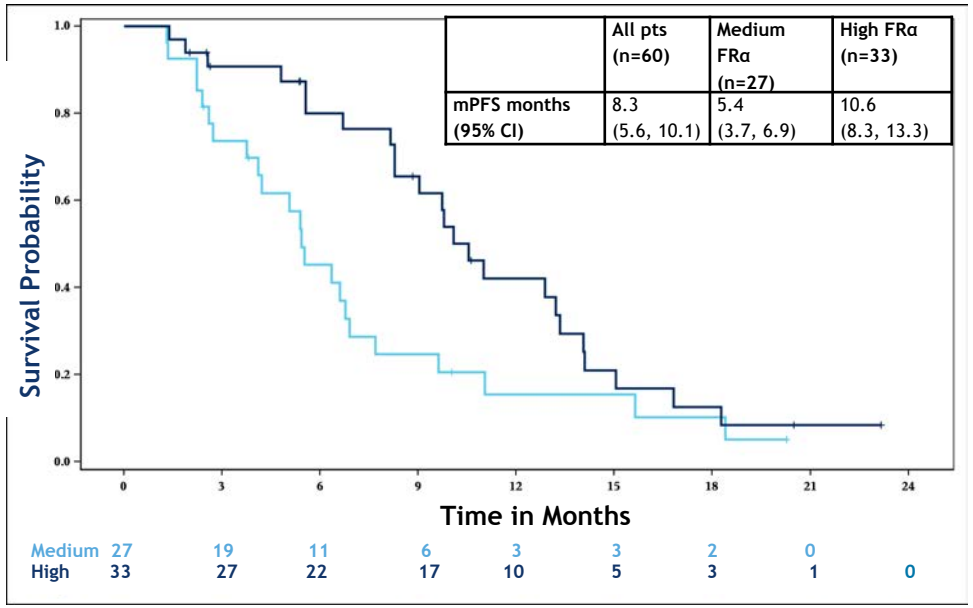
*Upper limit of 95% confidence interval not reached

David O'Malley, Ohio State University

Courtesy of Kathleen Moore, MD

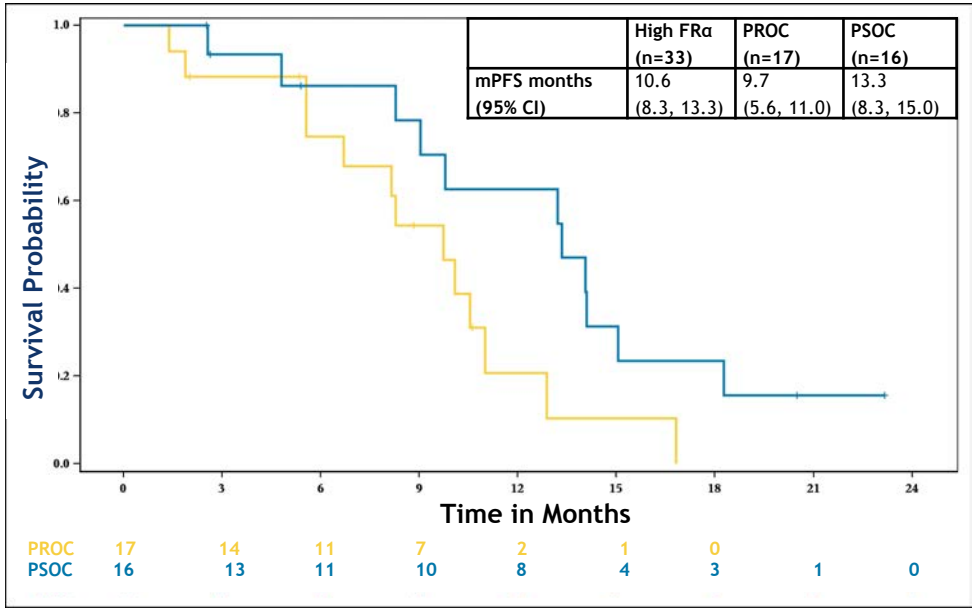
Longer PFS in High FRα Tumors Regardless of Platinum Status

Medium and High FRα Tumors



- mPFS 10.6 months in high FRα tumors
- mPFS 5.4 months in medium FRα tumors
- High FRα 6-month and 12-month PFS rate of 80% and 42%, respectively

High FRα Tumors (PROC and PSOC)



- mPFS 9.7 months in high FRα PROC tumors
- mPFS 13.3 months in high FRα PSOC tumors

mPFS = median progression free survival

Courtesy of Kathleen Moore, MD

Efficacy Comparison of Mirvetuximab + Bev Combo: PSOC

	OCEANS	GOG-0213	FORWARD II
Regimen	Carbo/Gem	Carbo/Pac	**Bev/Mirv**
Median age	61	60	**66**
Patient population	plat sensitive, 1 prior	plat sensitive, 1 prior	**1-2 priors 65%**
Prior bevacizumab	0	10%	**40%**
ORR	79%	78%	**69%**
mPFS	12.3(95% 10.7-14.6)	13.8 (95% 13.0-14.7)	**13.3 (95% 8.3, 15.0)**

Encouraging clinical benefit in patients with platinum-sensitive disease who had received multiple prior lines of therapies

USPI, Aghajanian C et al. JCO. 2012;30: 2039-2045,
Coleman R et al. Lancet Onc 2017

O'Malley et al ASCO 2017 **Data cutoff 28 APR 2017**

Pujade-Lauraine E et al J Clin Oncol. 2014 May 1;32(13):1302-8

Courtesy of Kathleen Moore, MD

Efficacy Comparison of Mirvetuximab + Bevacizumab Combo: PROC

	AURELIA	FORWARD II
Regimen	Chemo/Bev	**Mirv/Bev**
Median age	61	**64**
Patient population	Platinum resist 1-2 priors **60% - 1 prior** **40% - 2 priors**	**40% 1-2 priors**
Prior bevacizumab	7%	**40%**
ORR	27%	**59%**
mPFS	6.7 (95% 5.7, 7.9)	**9.7 (95% CI 5.6-11)**

Aghajanian C et al. JCO. 2012;30: 2039-2045,

O'Malley et al ASCO 2017

Data cutoff 28 APR 2017

Courtesy of Kathleen Moore, MD

Mirvetuximab/Bev: Treatment-Related Emergent Adverse Events >20%

N=60	All Grades	Grade 3/4
Adverse Event	N (%)	N (%)
Diarrhea^	37 (62)	1 (2)
Blurred vision	36 (60)	0 (0)
Fatigue^	36 (60)	2 (3)
Nausea	34 (57)	0 (0)
Keratopathy†	26 (43)	0 (0)
Peripheral neuropathy*	24 (40)	1 (2)
Dry eye	20 (33)	3 (5)
Decreased appetite	20 (33)	0 (0)
Hypertension^	19 (32)	10 (17)
Headache	17 (28)	0 (0)
AST increased	17 (28)	2 (3)
Vomiting	17 (28)	0 (0)
Abdominal pain	16 (27)	0 (0)
Visual acuity reduced	14 (23)	0 (0)
Thrombocytopenia	14 (23)	2 (3)
Neutropenia	13 (22)	8 (13)
ALT increased	13 (22)	3 (5)
Dysphonia^	13 (22)	0 (0)
Asthenia	13 (22)	0 (0)
Weight decrease^	13 (22)	1 (2)

AST, aspartate aminotransferase; ALT, alanine aminotransferase;
*Includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia
† Includes keratopathy, keratitis, corneal deposits, and corneal epithelial microcysts

- **Most AEs were low grade**
  - GI and Ocular were most frequent
  - Ocular AE class effect of ADC manageable with eye drops
- **Grade 3+ events were infrequent**
  - 17% hypertension
  - 13% neutropenia
- **Eighteen patients (30%) discontinued BEV and/or MIRV** due to treatment-related AEs
  - Discontinuations occurred after a median of 13 cycles of treatment
  - Discontinuations by agent
    - MIRV: 23%
    - BEV: 18%

AE rates are similar for MIRV/BEV compared with MIRV alone (n=243 from FORWARD I), when adjusted for exposure
^Exceptions (p <0.05, not adjusted for multiplicity testing) include Diarrhea, Fatigue, Hypertension, Dysphonia, and Weight Decrease

David O'Malley, Ohio State University

Courtesy of Kathleen Moore, MD

GOG-3045

MIRASOL

PHASE 3 RANDOMIZED TRIAL FOR MIRVETUXIMAB USING PS2+ SCORING IN FRα-HIGH, PLATINUM-RESISTANT OVARIAN CANCER

ENROLLMENT AND KEY ELIGIBILITY

- 430 patients/330 events for PFS by Investigator
- Platinum-resistant disease (primary PFI >3 mos)
- Prior bevacizumab allowed*
- Prior PARPi allowed
- Patients with BRCA mutations allowed

*Eligibility criterion different than SORAYA
IC: investigator's choice; PRO: patient reported outcomes

FPI Q1 2020

TOPLINE DATA 1H 2022

1:1 RANDOMIZATION

Mirvetuximab

STRATIFICATION FACTORS
IC Chemotherapy (Paclitaxel, PLD, Topotecan)
Prior Therapies (1 vs 2 vs 3)

Investigator's Choice Chemotherapy Paclitaxel, PLD, or Topotecan

PRIMARY ENDPOINT
PFS by Investigator
BICR for Sensitivity Analysis

SECONDARY ENDPOINTS
ORR by Investigator, OS, and PRO

Courtesy of Kathleen Moore, MD

SORAYA

SINGLE-ARM PIVOTAL TRIAL FOR MIRVETUXIMAB USING PS2+ SCORING IN FRα-HIGH, PLATINUM-RESISTANT OVARIAN CANCER

TARGET TIMELINES

- **FPI** Q1 2020
- **TOPLINE DATA** MID 2021
- **BLA** H2 2021

FPI: first patient in; DOR: duration of response; PFI: platinum-free interval

PRIMARY ENDPOINT

ORR by Investigator

SECONDARY ENDPOINT

DOR by Investigator

ENROLLMENT AND KEY ELIGIBILITY

~100 patients

Platinum-resistant disease (primary PFI >3 mos)

Prior bevacizumab required

Prior PARPi allowed

Patients with BRCA mutations allowed

Courtesy of Kathleen Moore, MD

Agenda

Module 1: Up-Front Management of Ovarian Cancer (OC), Including Maintenance

- Treatment strategies based on germline and somatic genomic assays
- ASCO 2021 updates for the SOLO-1, PRIMA and PAOLA-1 trials
- Findings from the OVARIO trial: Niraparib/bevacizumab maintenance therapy

Module 2: Recurrence, Toxicity and Resistance to PARP Inhibitors

- Selection of PARP inhibitor for patients with recurrent OC
- ARIEL4: Rucaparib versus chemotherapy for relapsed, BRCA-mutated OC
- Mechanisms of resistance to PARP inhibitor therapy

Module 3: Mirvetuximab Soravtansine

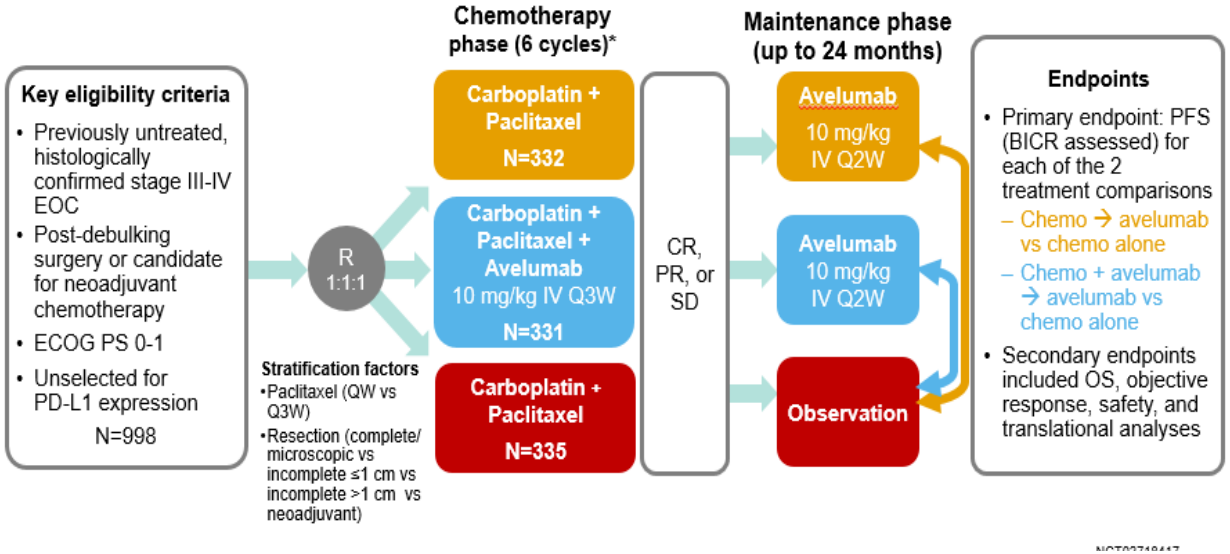
- Scientific rationale for targeting folate receptor alpha in OC
- Mirvetuximab soravtansine with or without bevacizumab for platinum-resistant OC
- Ongoing trials evaluating mirvetuximab soravtansine for platinum-resistant OC: MIRASOL, SORAYA

Module 4: Immune Checkpoint Inhibitors in OC

- Biologic rationale for combining PARP inhibitors with anti-PD-1/PD-L1 antibodies
- Ongoing Phase III trials evaluating immune checkpoint inhibitors with PARP inhibitors for advanced OC

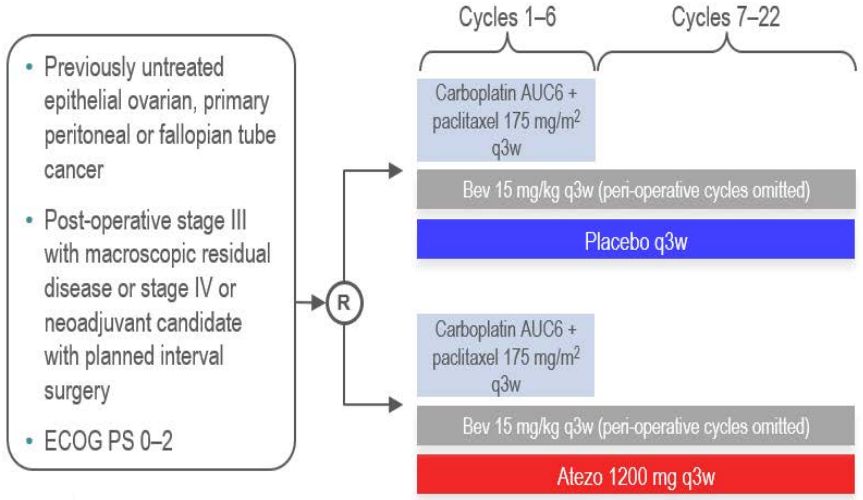
Randomized Phase 3 Trials of Immune Checkpoint Inhibitors in Front Line Ovarian Cancer: A Tale of Two Trials

JAVELIN OVARIAN 100



PFS	Chemo → Avel (N=332)	Chemo + Avel → Avel (N=331)	Chemo → Obs (N=335)
Events, n (%)	99 (29.8)	88 (26.6)	70 (20.9)
Median (95% CI), months	16.8 (13.5, NE)	18.1 (14.8, NE)	NE (18.2, NE)
Stratified HR vs control (95% CI)	1.43 (1.051, 1.946)	1.14 (0.832, 1.565)	–
p value vs control*	0.9890	0.7935	–

IMagyn050

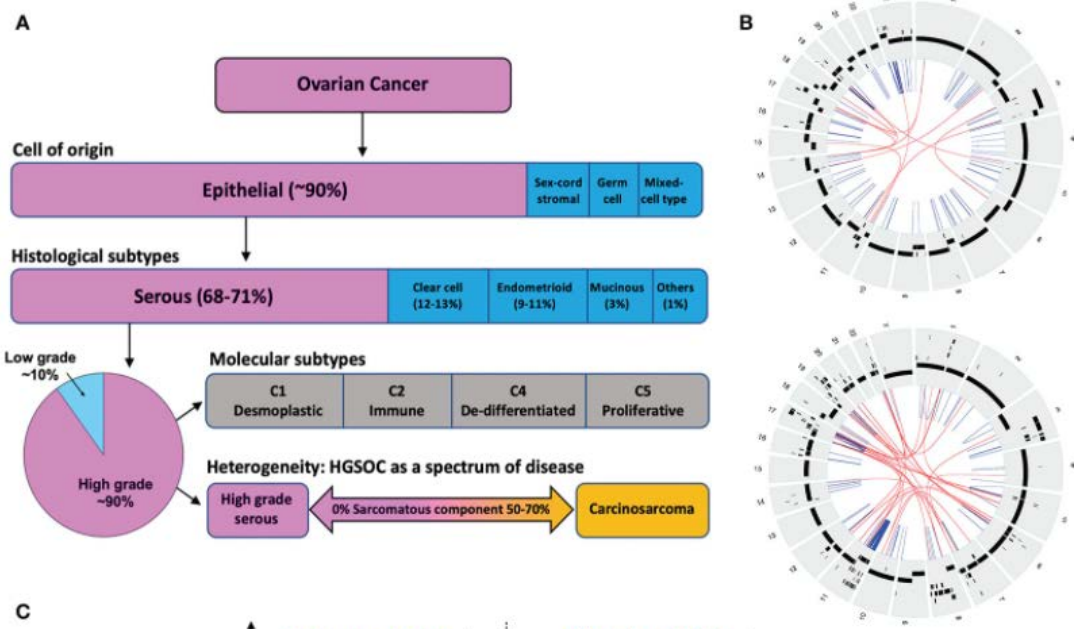


PFS	ITT population: Placebo + CP + bev (n=650)	ITT population: Atezo + CP + bev (n=651)
Patients with events, n (%)	341 (52.5)	323 (49.6)
Median PFS, months (95% CI)	18.4 (17.2–19.8)	19.5 (18.1–20.8)
Stratified HR (95% CI)	0.92 (0.79–1.07)	
Stratified log-rank p-value	0.2785	
2-year event-free rate (95% CI)	29.1 (23.9–34.3)	35.1 (30.0–40.3)

Ledermann et al. SGO Annual Meeting (virtual) 2020); Moore et al. J Clin Oncol 2021

Courtesy of Kathleen Moore, MD

Randomized Phase 3 Trials of Immune Checkpoint Inhibitors in Front Line Ovarian Cancer: A Tale of Two Trials



What Happened?

- At baseline, the majority of epithelial ovarian cancer has a lower probability of responding to immunotherapy
- Over expression of FAK and VEGF may impair T-cell trafficking, although if this were major obstacle, IMagyn050 should have worked
- No biomarkers for patient selection
- **How about Combinations?**

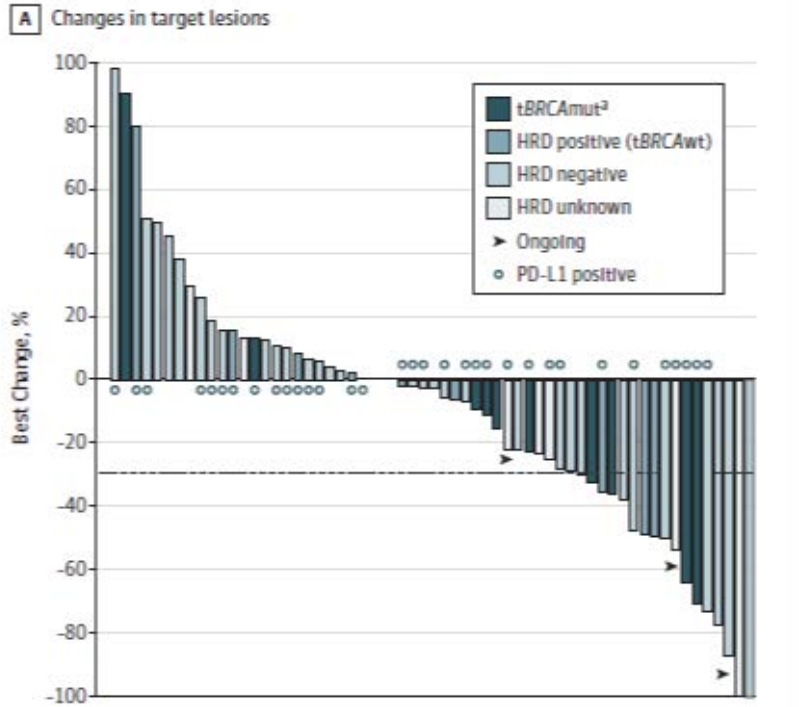
Wu et al. Frontiers in Immunology 2021

Courtesy of Kathleen Moore, MD

Early Reports of Combination of PARPi and Immune Checkpoint Inhibitors Have Demonstrated Modest Efficacy in platinum-resistant ovarian cancer

TOPACIO

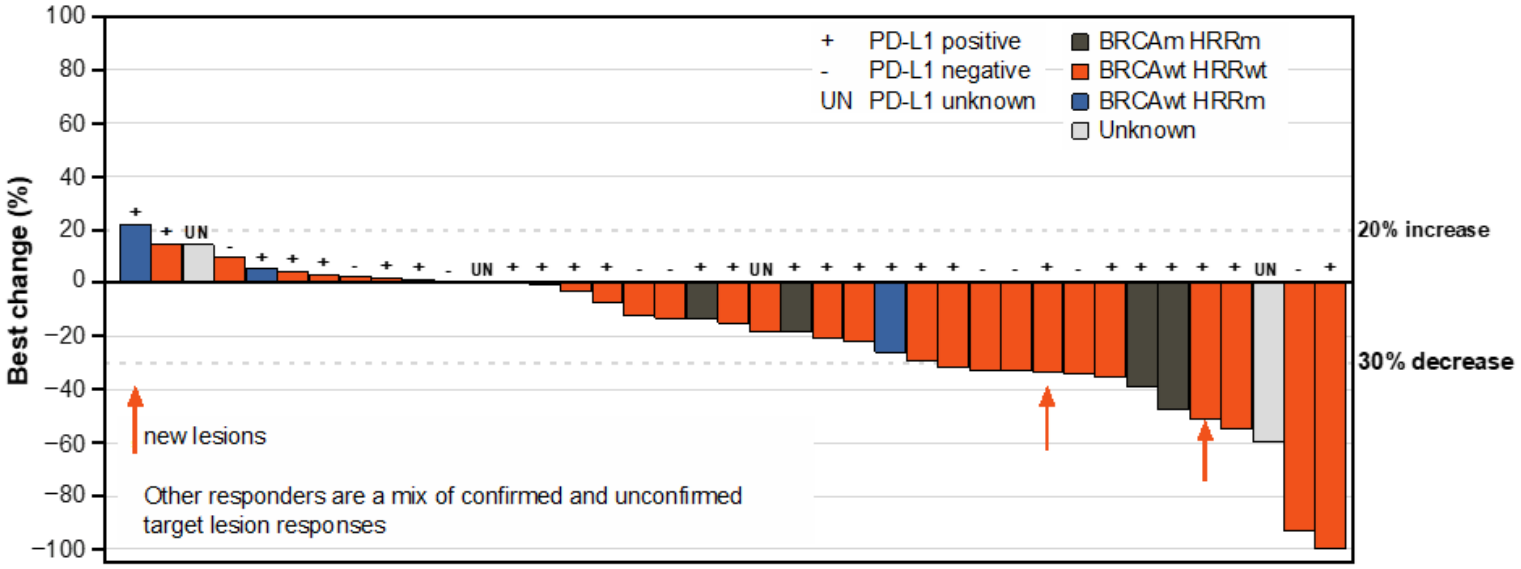
Niraparib + Pembrolizumab



ORR 18% (11-29%)
DOR NR

OPAL

Niraparib + Dostarlimab + Bevacizumab

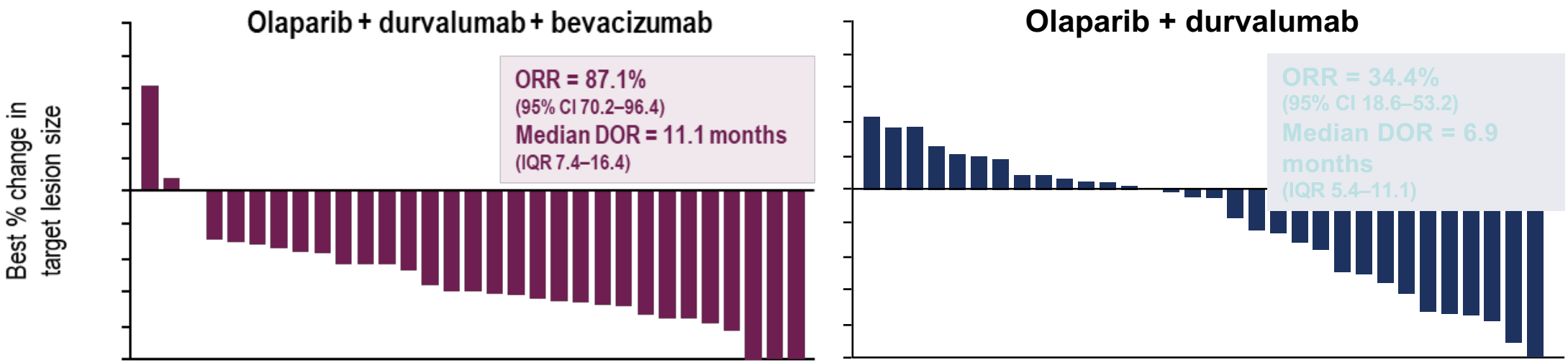


ORR 17.9% (8.7-31.3)

Konstantinopoulos et al. *JAMA Oncol*. 2019;5(8):1141-1149; Liu et al. Society of Gynecologic Oncology Annual Meeting 2021

Courtesy of Kathleen Moore, MD

Is this more a platinum sensitive strategy? MEDIOLA



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

Drew et al. ESMO Virtual 2020 Congress

Courtesy of Kathleen Moore, MD

Future Directions in the Front Line

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.

Courtesy of Kathleen Moore, MD

A Conversation with the Investigators: Hormonal Therapy for Prostate Cancer

Monday, July 12, 2021
5:00 PM – 6:00 PM ET

Faculty

Simon Chowdhury, MD, PhD
Tanya B Dorff, MD
Matthew R Smith, MD, PhD

Moderator

Neil Love, MD

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 24 hours.

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