Meet The Professor
Optimizing the Management of Ovarian Cancer

Prof Jonathan A Ledermann
Professor of Medical Oncology
UCL Cancer Institute
London, United Kingdom

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Merck, and Mersana Therapeutics Inc.

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, ADC Therapeutics, 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, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI BioPharma Corp, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab, 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, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sanofi Genzyme, Seagen Inc, Servier Pharmaceuticals LLC, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc and Zymeworks Inc.

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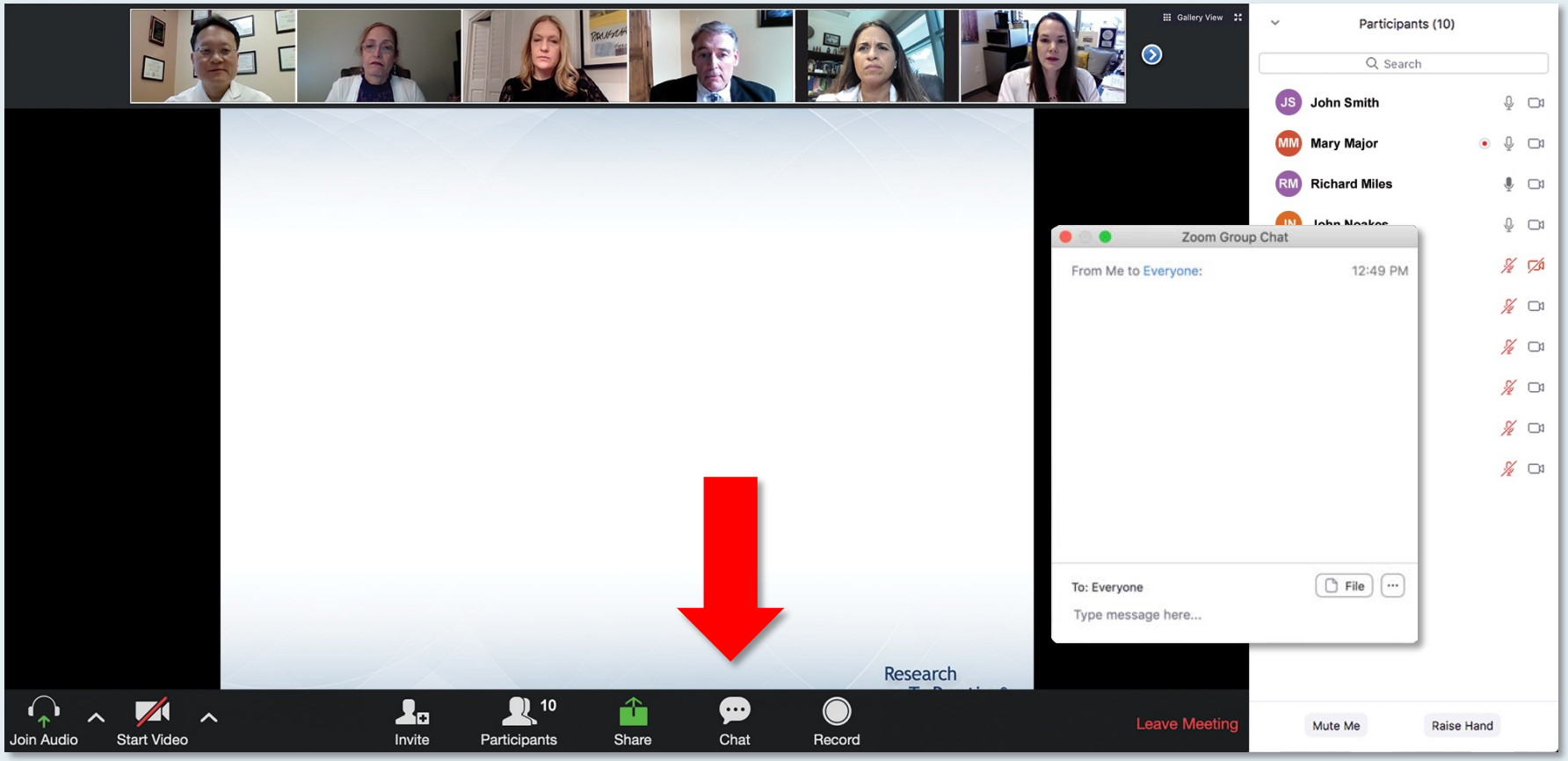
We Encourage Clinicians in Practice to Submit Questions



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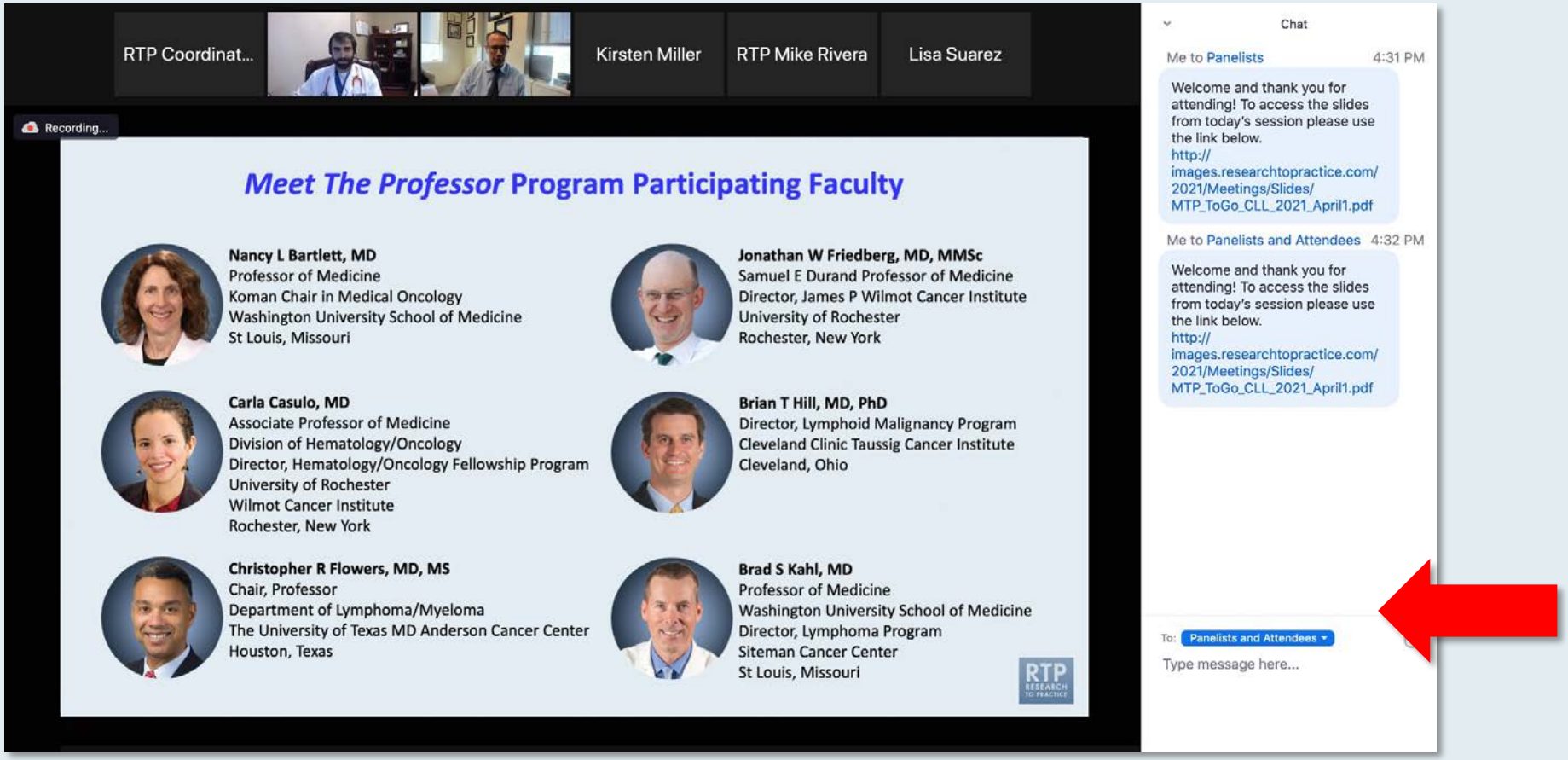

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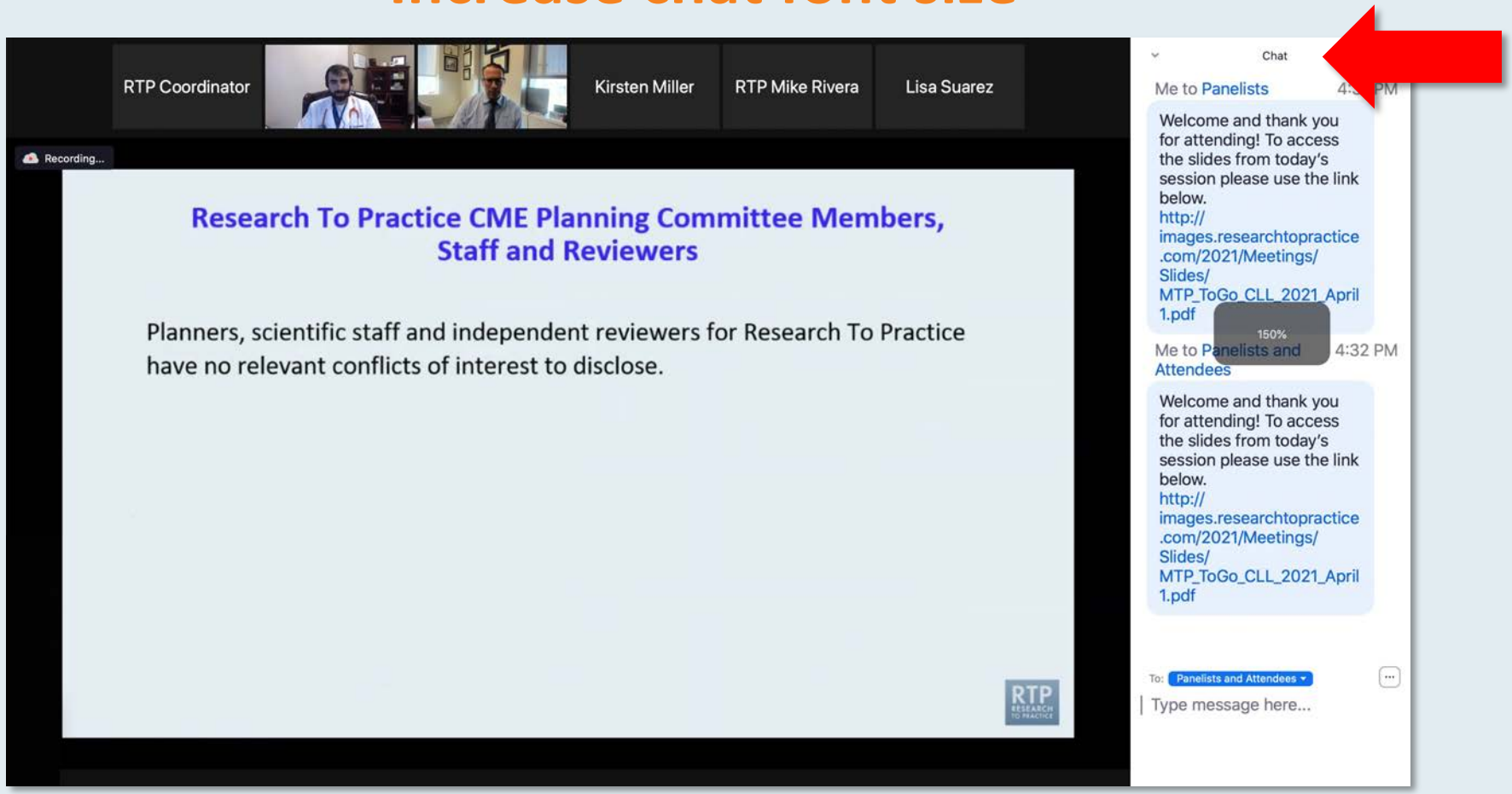

Press Command (for Mac) or Control (for PC) and the + symbol.
You may do this as many times as you need for readability.

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WITH DR NEIL LOVE

Updates on Ovarian Cancer from SGO 2022

DR DAVID O'MALLEY

THE OHIO STATE UNIVERSITY AND
THE JAMES CANCER CENTER

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Recent Advances in Medical Oncology:
A daylong CME hybrid (live/online) event

Saturday, August 6, 2022

9:00 AM – 4:30 PM PT (12:00 PM – 7:30 PM ET)

Bellagio Las Vegas | Las Vegas, Nevada

Faculty

Neeraj Agarwal, MD
Harold J Burstein, MD, PhD
Ibiayi Dagogo-Jack, MD
Rafael Fonseca, MD
Brad S Kahl, MD
Rutika Mehta, MD, MPH
Craig Moskowitz, MD
Joyce O'Shaughnessy, MD
Krina Patel, MD, MSc
Philip A Philip, MD, PhD, FRCP
Suresh S Ramalingam, MD
Sandy Srinivas, MD

Moderator

Neil Love, MD

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Data + Perspectives — Investigators Discuss the Current and Future Roles of Chimeric Antigen Receptor T-Cell Therapy and Bispecific Antibodies in the Care of Patients with Hematologic Cancers

Tuesday, August 9, 2022

5:00 PM – 6:30 PM ET

Faculty

Ajai Chari, MD
Ian W Flinn, MD, PhD
Nikhil C Munshi, MD
Laurie H Sehn, MD, MPH

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

Meet The Professor

Optimizing the Management of Small Cell Lung Cancer

Thursday, August 11, 2022
5:00 PM – 6:00 PM ET

Faculty

Jacob Sands, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Gastroesophageal Cancers

Wednesday, August 17, 2022
5:00 PM – 6:00 PM ET

Faculty

John Strickler, MD

Moderator

Neil Love, MD

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Meet The Professor

Optimizing the Management of Ovarian Cancer

Thursday, August 25, 2022
5:00 PM – 6:00 PM ET

Faculty

Richard T Penson, MD, MRCP

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 5 business days.

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Meet The Professor
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Prof Jonathan A Ledermann
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Meet The Professor Program Participating Faculty

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Professor of Medicine
Harvard Medical School
Boston, Massachusetts

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Associate Professor of Medicine
Harvard Medical School
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Boston, Massachusetts

MODERATOR
Neil Love, MD
Research To Practice

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Reproductive Medicine
The University of Texas
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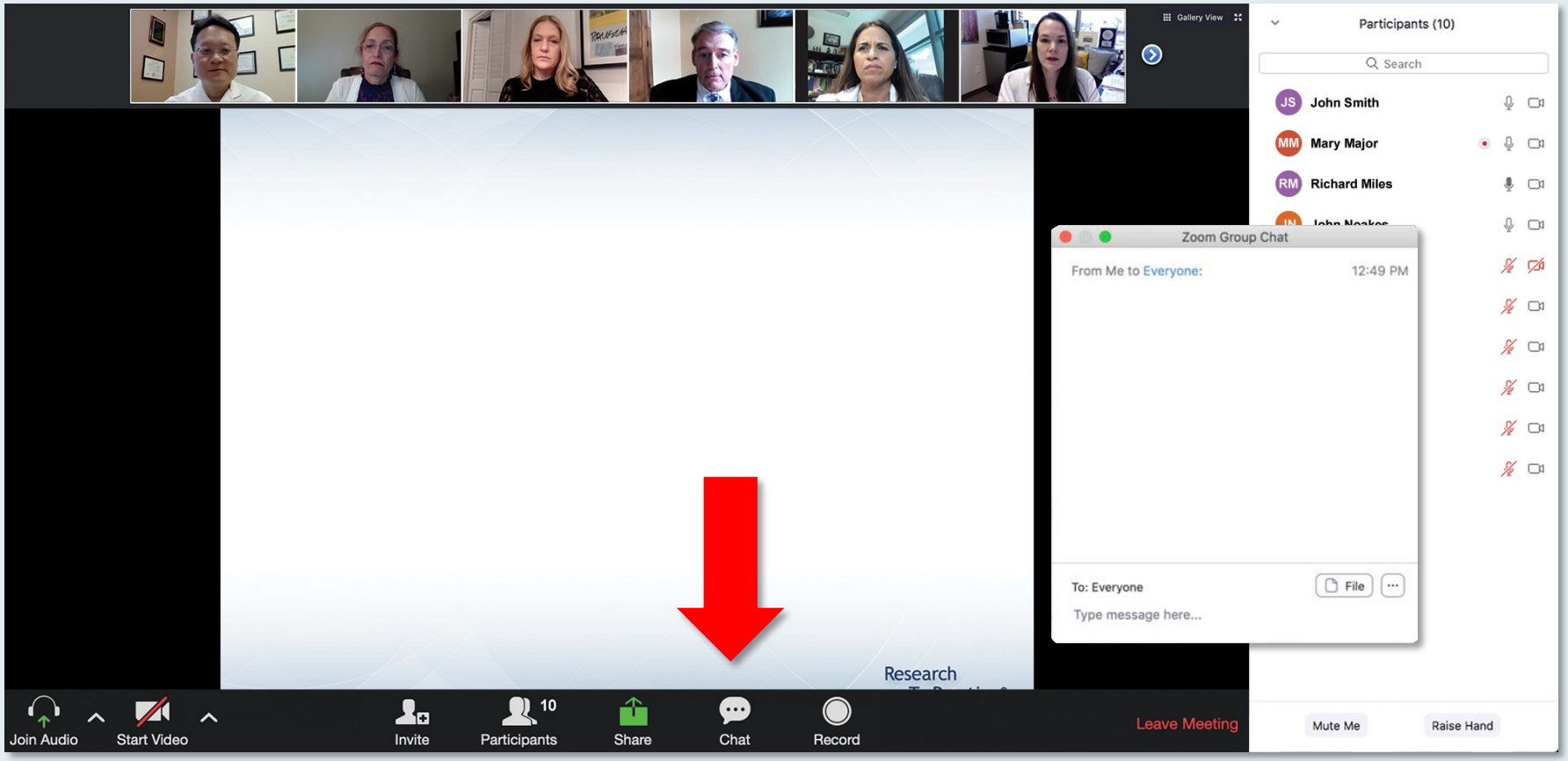

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Join Us Online

Recent Advances and Real-World Implications in Medical Oncology

A Daylong Multitumor Educational Symposium in Partnership with the American Oncology Network

Saturday, August 6, 2022

Breast Cancer

9:00 AM – 10:05 AM PT

Faculty

Harold J Burstein, MD, PhD

Joyce O'Shaughnessy, MD

Genitourinary Cancers

10:05 AM – 11:05 AM PT

Faculty

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Saturday, August 6, 2022

Multiple Myeloma

11:25 AM – 12:25 PM PT

Faculty

Rafael Fonseca, MD

Krina Patel, MD, MSc

CLL and Lymphomas

1:05 PM – 2:05 PM PT

Faculty

Brad S Kahl, MD

Craig Moskowitz, MD

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Recent Advances and Real-World Implications in Medical Oncology

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Saturday, August 6, 2022

Gastrointestinal Cancers

2:05 PM – 3:05 PM PT

Faculty

Rutika Mehta, MD, MPH

Philip A Philip, MD, PhD, FRCP

Lung Cancer

3:25 PM – 4:25 PM PT

Faculty

Ibiayi Dagogo-Jack, MD

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Northside Hospital Cancer Institute
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Syed F Zafar, MD
Lee Health
Fort Myers, Florida

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Meet The Professor with Prof Ledermann

Introduction: Journal Club with Prof Ledermann – Part 1

MODULE 1: Case Presentations

MODULE 2: Faculty Survey

MODULE 3: Journal Club with Prof Ledermann – Part 2

MODULE 4: Appendix of Key Publications

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Clinical Trial in Progress: Pivotal Study of VB-111 Combined with Paclitaxel vs. Paclitaxel for Treatment of Platinum-Resistant Ovarian Cancer (OVAL, VB-111-701/GOG-3018)

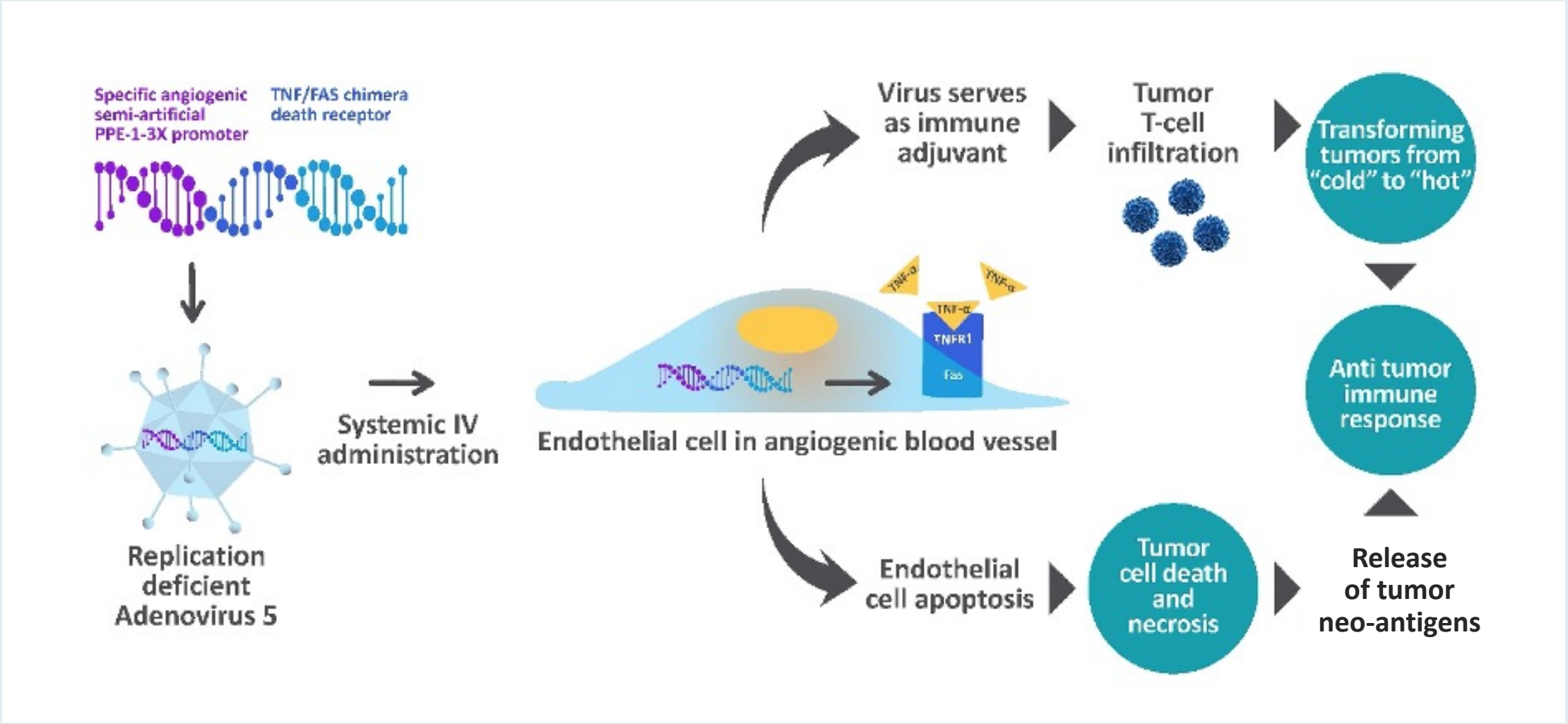
Primary Endpoint Changed to either PFS or OS, PFS Readout Expected in 2022

Authors: Arend RC[1], Monk BJ[2], Herzog TJ[3], Ledermann JA[4], Moore KN[5], Alvarez Secord A[6], Shapira-Frommer R[7], Tewari KS[8], Rachmilewitz Minei T[9], Harats D[9], Penson RT[10].

ASCO 2021;Abstract TPS5599.

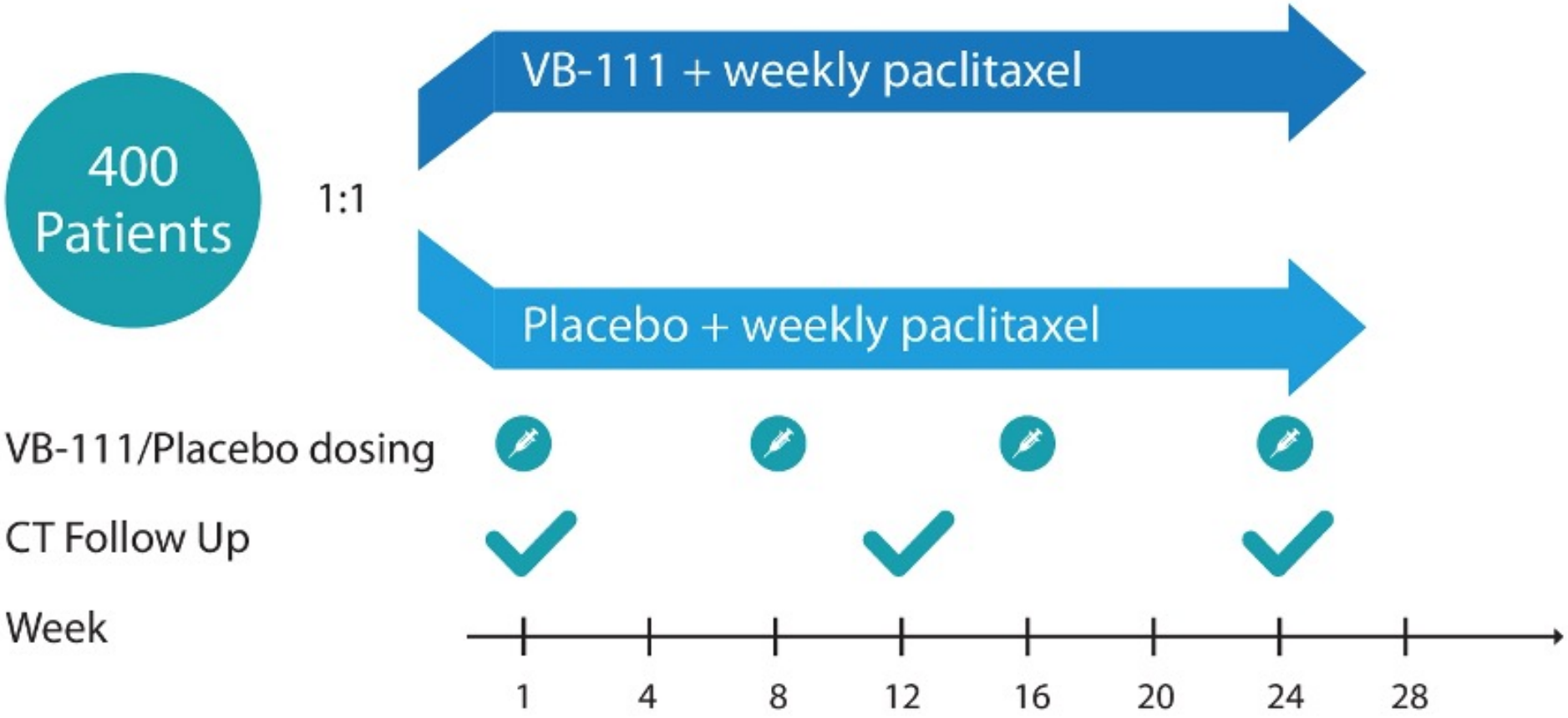
JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

OVAL Background



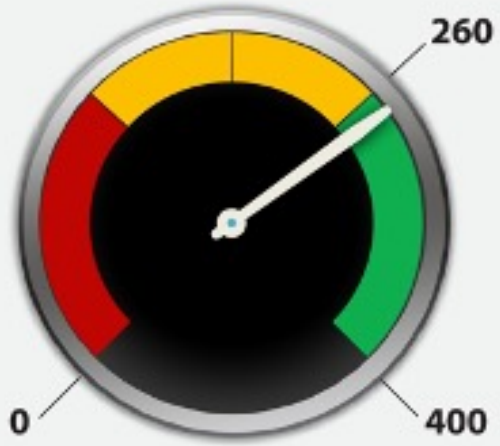
Arend RC et al. ASCO 2021;Abstract TPS5599.

OVAL Study Design



Arend RC et al. ASCO 2021;Abstract TPS5599.

OVAL Current Status



Over 65% randomized to date

New Primary Efficacy Endpoints:

- **Either Progression-free Survival (PFS) or Overall Survival (OS)**
- **A positive outcome in either PFS or OS will enable submission for registration**
- **Protocol amended following agreement with FDA**

Expected Event Timeline

- **Next DSMC Review in 3Q 2021**
- **PFS: Prespecified number of events to unblind study anticipated in 2022**
- **OS: Prespecified number of events to unblind study anticipated in 2023**

Arend RC et al. ASCO 2021;Abstract TPS5599

Phase III OVAL Trial of Ofra-vec (Ofranergene Obadenovec; VB-111) for Platinum-Resistant Ovarian Cancer Fails to Meet Its Primary Endpoints

Press Release: July 19, 2022

Top-line data from the Phase 3 OVAL clinical trial of ofra-vec (ofranergene obadenovec; VB-111) in platinum-resistant ovarian cancer demonstrated that the trial did not meet the primary endpoints of achieving a statistically significant improvement in progression-free survival (PFS) or overall survival (OS).

The OVAL trial demonstrated that patients randomized to the combination of ofra-vec and paclitaxel had a median PFS of 5.29 months, versus 5.36 months for the paclitaxel control arm (HR = 1.03). The interim overall survival analysis was also not significantly different between the two study arms (median OS 13.37 months in the treatment arm versus 13.14 months in the control arm; HR = 0.97) and did not support study continuation.

https://ir.vblrx.com/news-releases/news-release-details/vbl-therapeutics-announces-top-line-data-phase-3-oval-trial-ofra

Meet The Professor with Prof Ledermann

MODULE 1: Case Presentations

- Dr Mushtaq: An 80-year-old Asian woman with ovarian cancer and a gBRCA mutation, s/p surgery and adjuvant chemotherapy, now on maintenance olaparib
- Dr Rudolph: An 86-year-old woman with gBRCA wild-type HGSOC who develops recurrent disease after declining maintenance niraparib
- Dr ElSahwi: A 73-year-old woman with HGSOC and gBRCA1 and 2 mutations who responds to olaparib for 5 years but then develops PD after stopping
- Dr Chen: A 69-year-old woman with gBRCA wild-type Stage IIIC ovarian cancer who receives IV/IP adjuvant chemotherapy
- Dr Zafar: A 46-year-old woman with MSI-high BRCA wild-type clear cell ovarian cancer with SD on pembrolizumab and niraparib
- Dr Chase: A 59-year-old woman with recurrent BRCA wild-type (HRp) low-grade ovarian cancer with rising CA-125, pleural effusion and a new lung nodule on salvage chemotherapy
- Dr DiSilvestro: A 57-year-old woman with Stage IIIA ovarian cancer and a gBRCA1 mutation, s/p neoadjuvant chemotherapy and surgery, doing well on maintenance olaparib
- Dr McKenna: A 92-year-old woman with PMH of untreated CLL, with Stage III/IV ovarian cancer
- Dr Chen: A 53-year-old woman with recurrent BRCA wild-type low-grade ovarian cancer who has a CR to niraparib/bevacizumab but develops lymphedema

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Case Presentation: An 80-year-old Asian woman with ovarian cancer and a gBRCA mutation, s/p surgery and adjuvant chemotherapy, now on maintenance olaparib

Dr Rao Mushtaq (Thornton, Colorado)

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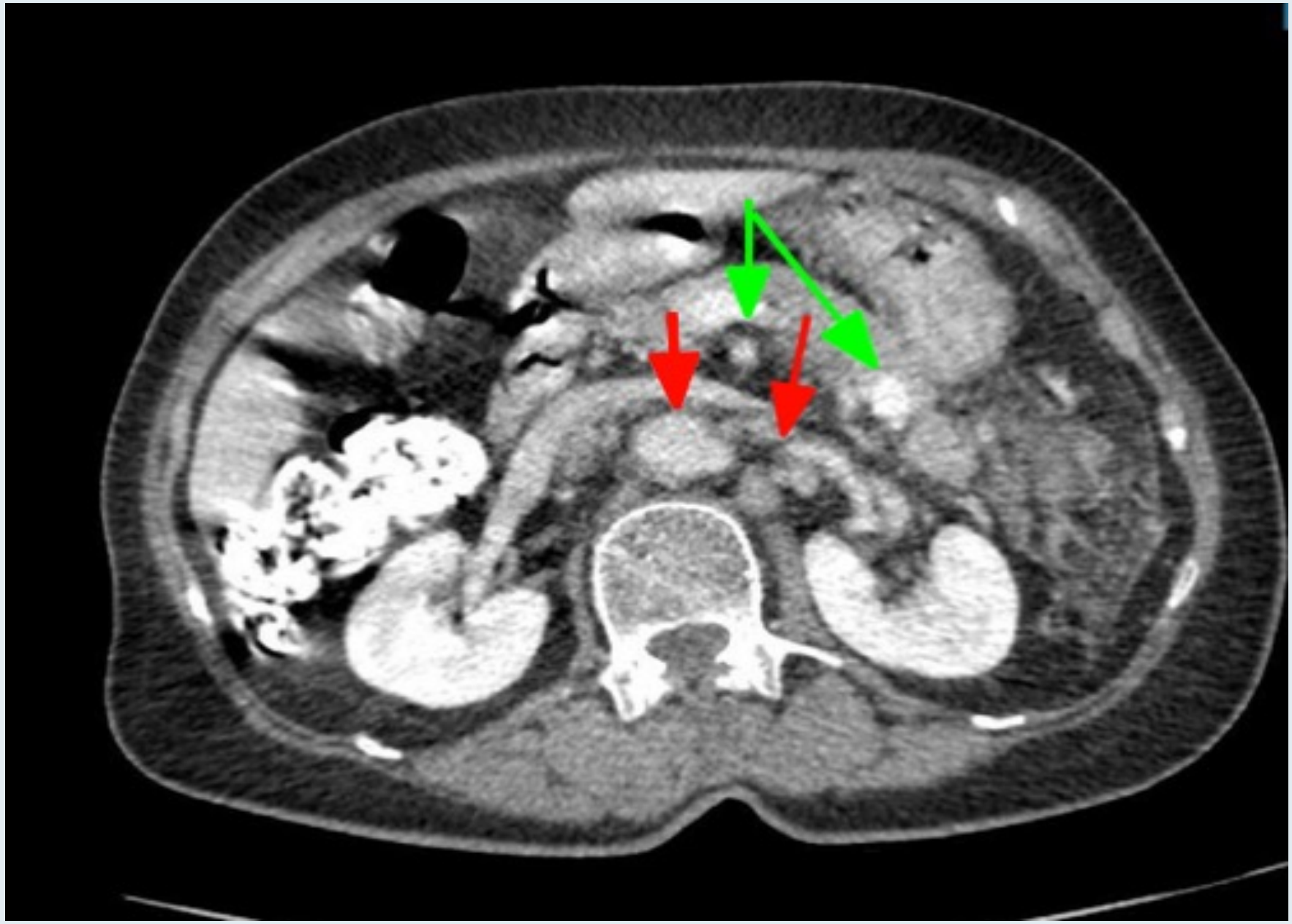
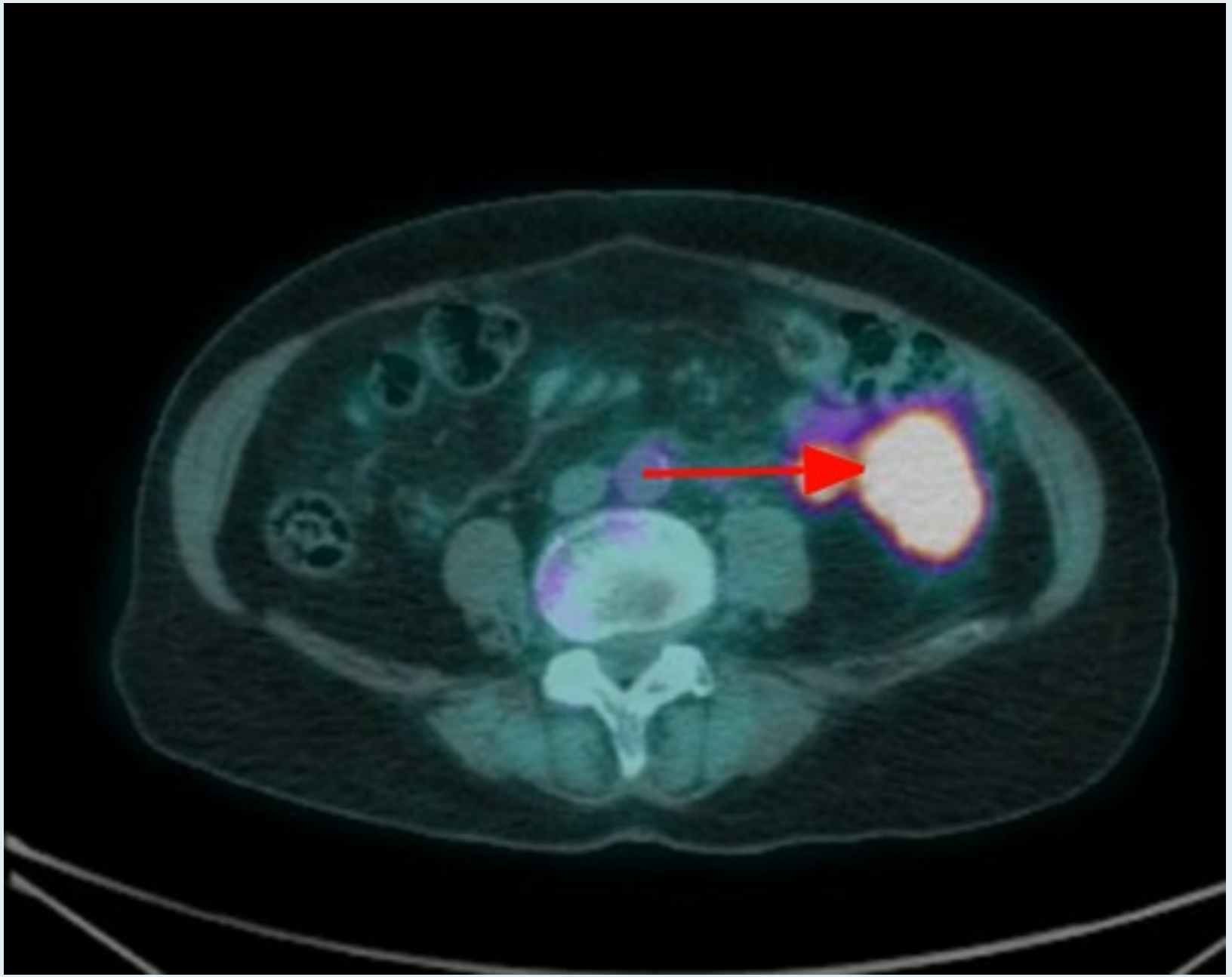




Current Oncology Reports (2021) 23: 97
https://doi.org/10.1007/s11912-021-01088-w

GYNECOLOGIC CANCERS (J BROWN AND RW NAUMANN, SECTION EDITORS)

Frontline Maintenance Treatment for Ovarian Cancer

Osnat Elyashiv [1,2] · Yien Ning Sophia Wong [1,2] · Jonathan A. Ledermann [1,2]

Best Practice & Research Clinical Obstetrics and Gynaecology 78 (2022) 64–73

Contents lists available at ScienceDirect

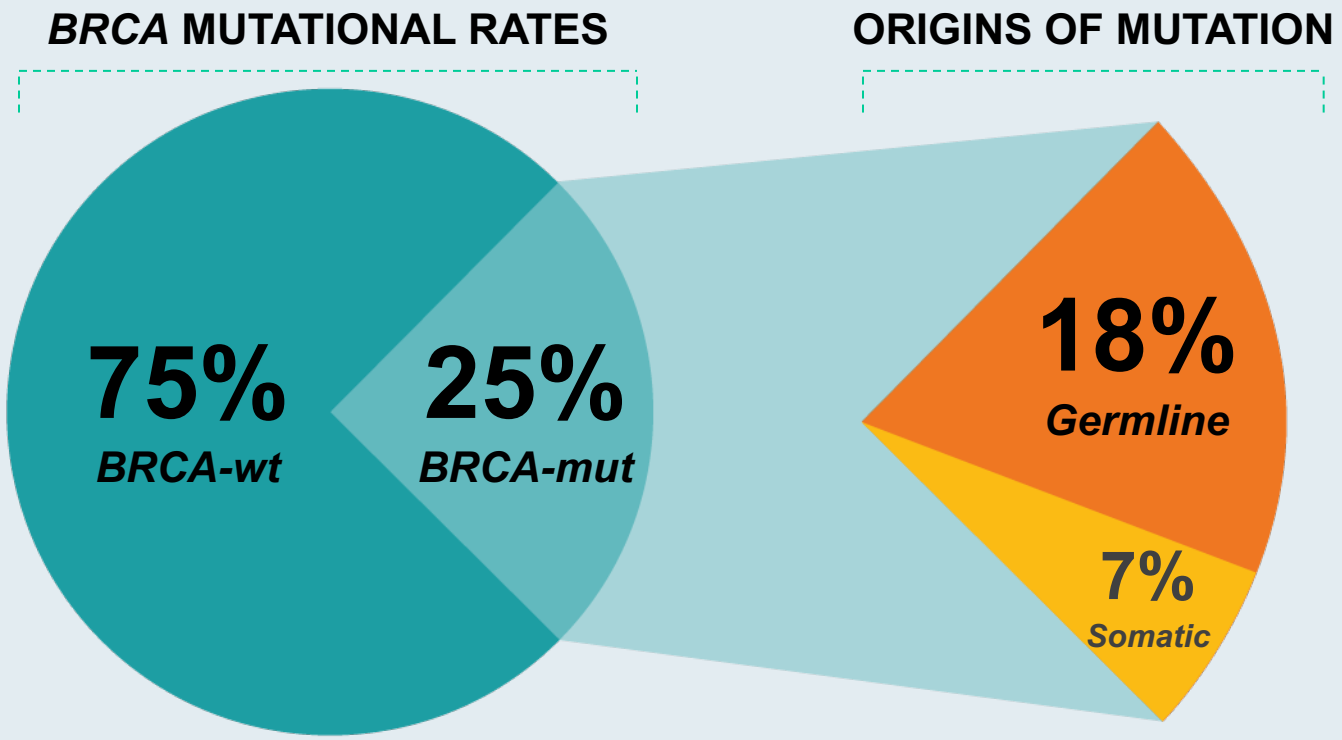
Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

Adjuvant and post-surgical treatment in high-grade epithelial ovarian cancer

Georgina E. Wood [a], Jonathan A. Ledermann [a, b, *]

An Estimated 25% of Newly Diagnosed Ovarian Cancers Harbor BRCA1/2 Mutations



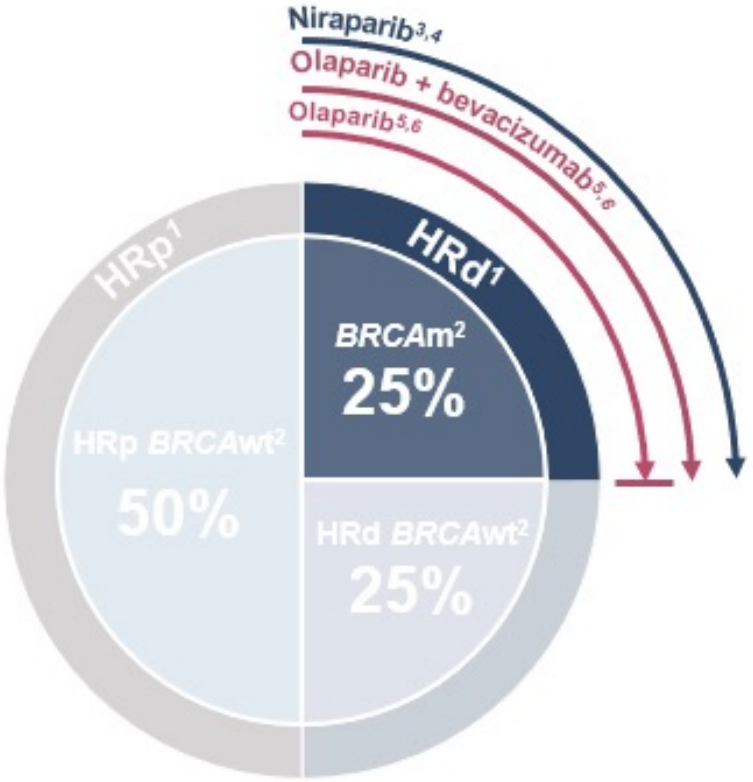
An estimated 1 in 4 women with EOC will have a *BRCA*-positive tumor result
Tumor testing detects more patients with *BRCA* mutations than blood/saliva tests that do not look at tumor DNA

EOC = epithelial ovarian cancer; mut = mutation; wt = wild type

Pennington et al. *Clin Cancer Res* 2014;20(3):764-75.

Courtesy of Kathleen Moore, MD

PARP Inhibitors Are Available for First-Line Maintenance Therapy Across Biomarkers



BRCAm/HRd

Niraparib (PRIMA)[3,4,7]

HR: 0.40 (95% CI, 0.27-0.62)

Niraparib (PRIME)[3,4,7,10]

HR: 0.40 (95% CI, 0.23-0.68)

Olaparib + bevacizumab (PAOLA-1)[5,6,8]

HR: 0.31 (95% CI, 0.20-0.47)

Olaparib (SOLO1)[5,6,9]

HR: 0.33 (95% CI, 0.25-0.43)

Percentages denote proportion of patients with genomic mutations in ovarian cancer.[2]

1L, first line; *BRCA*m, breast cancer gene mutant; *BRCA*wt, breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; PARP, poly (ADP-ribose) polymerase.

1. The Cancer Genome Atlas Research Network. *Nature*. 2011;474(7353):609-615. **2.** Pennington KP et al. *Clin Cancer Res*. 2014;20(3):764-775. **3.** ZEJULA. Summary of Product Characteristics. GlaxoSmithKline (Ireland) Ltd; 2021. **4.** ZEJULA. Prescribing Information. GlaxoSmithKline; 2021. **5.** Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **6.** Lynparza. Summary of Product Characteristics. AstraZeneca AB; 2021. **7.** González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. **8.** Ray-Coquard I et al. *N Engl J Med*. 2019;381(5):2416-2428. **9.** Banerjee S et al. Presented at: ESMO Virtual Congress; September 19-21, 2020. Presentation 811MO. 10. Li et al. PRIME SGO 2022 Phoenix

Courtesy of Brian M Slomovitz MD

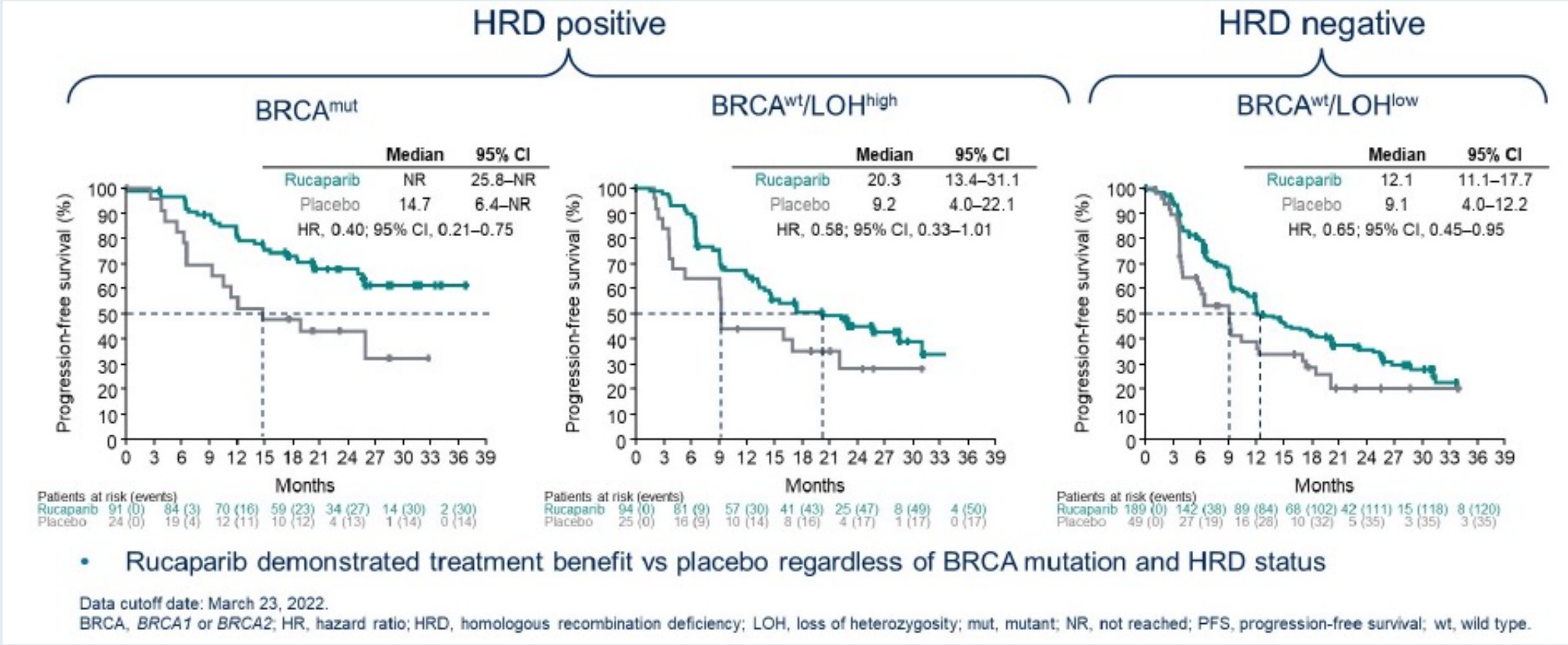
Ovarian cancer 1L PARPi maintenance trials: design and populations

Trial	PARP inhibitor	Duration	BRCA status	R0 at PDS allowed	% PDS	CR/PR to platinum
SOLO1[1,2]	Olaparib	2 years	*BRCA*mt only	Yes	62.9	Yes
PRIMA[3]	Niraparib	3 years	All comers	No if Stage III	33	Yes
PRIME[4]	Niraparib	3 years	All comers	Yes	53.1	Yes
PAOLA1[5]	Olaparib (w/bevacizumab)	2 years	All comers	Yes	50.7	Yes
VELIA[6]	Veliparib (w/chemo)	36 total cycles	All comers	Yes	67.5	No (tx starts with chemo)
ATHENA-MONO[7]	Rucaparib	2 years	All comers	Yes	48.9	Yes

[1]Moore et al., *N Engl J Med* 2018; [2]Banerjee et al., 2020 ESMO Congress; [3]Gonzalez-Martin et al., *N Engl J Med* 2019; [4]Li et al., 2022 SGO Annual Meeting; [5]Ray-Coquard et al., *N Engl J Med* 2019; [6]Coleman et al., *N Engl J Med* 2019; [7]Monk et al., 2022 ASCO Annual Meeting

Liu N. ASCO 2022;Highlights of the Day: Gynecologic Cancers.

ATHENA-MONO: Investigator-Assessed PFS – Exploratory Subgroups



- Rucaparib demonstrated treatment benefit vs placebo regardless of BRCA mutation and HRD status

Data cutoff date: March 23, 2022.

BRCA, *BRCA1* or *BRCA2*; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; mut, mutant; NR, not reached; PFS, progression-free survival; wt, wild type.

Monk BJ et al. ASCO 2022;Abstract LBA5500; Liu N. ASCO 2022;Highlights of the Day: Gynecologic Cancers.

Trials of 1L PARPi maintenance in ovarian cancer

Trial	PARP inhibitor	Duration	All comers	BRCAmt	BRCAwt overall	BRCAwt – HRD	BRCAwt – HRP	HRD assay
ATHENA-MONO[1]	Rucaparib	2 years	**HR 0.52** 20.2 vs 9.2 mos	**HR 0.40** NR vs 14.7 mos	--	**HR 0.58** 95%CI 0.33-1.01 20.3 vs 9.2 mos	**HR 0.65** 95%CI 0.45-0.95 12.1 vs 9.1 mos	Foundation One CDx
SOLO1[2,3]	Olaparib	2 years	--	**HR 0.33** 56.0 vs 13.8 mos	--	--	--	--
PRIMA[4]	Niraparib	3 years	**HR 0.62** 13.8 vs 8.2 mos	**HR 0.40** 22.1 vs 10.9 mos	--	**HR 0.50** 19.6 vs 8.2 mos	**HR 0.68** 8.1 vs 5.4 mos	Myriad MyChoice
PRIME[5]	Niraparib	3 years	**HR 0.45** 24.8 vs 8.3 mos	**HR 0.40** NR vs 10.8 mos	**HR 0.48*** 19.3 vs 8.3 mos	**HR 0.58** 24.8 vs 11.1 mos	**HR 0.41** 14.0 vs 5.5 mos	Not published
PAOLA1[6]	Olaparib (w/bevacizumab)	2 years	**HR 0.59** 22.1 vs 16.6 mos	**HR 0.31** 37.2 vs 21.7 mos	**HR 0.71** 18.9 vs 16.0 mos	**HR 0.43** 28.1 vs 16.6 mos	**HR 0.92 (NS)** 18.9 vs 16.0 mos	Myriad MyChoice
VELIA[7]	Veliparib (w/chemo)	36 total cycles	**HR 0.68** 23.5 vs 17.3 mos	**HR 0.44** 34.7 vs 22.0 mos	**HR 0.80** 18.2 vs 15.1 mos	**HR 0.74 (NS)** 15.0 vs 11.5 mos	**HR 0.81 (NS)** 18.2 vs 15.1 mos	Myriad MyChoice

*does not exclude pts with sBRCAmt tumors

[1]Monk et al., 2022 ASCO Annual Meeting; [2]Moore et al., *N Engl J Med* 2018; [3]Banerjee et al., 2020 ESMO Congress; [4]Gonzalez-Martin et al., *N Engl J Med* 2019; [5]Li et al., 2022 SGO Annual Meeting; [6]Ray-Coquard et al., *N Engl J Med* 2019; [7]Coleman et al., *N Engl J Med* 2019

Liu N. ASCO 2022;Highlights of the Day: Gynecologic Cancers.

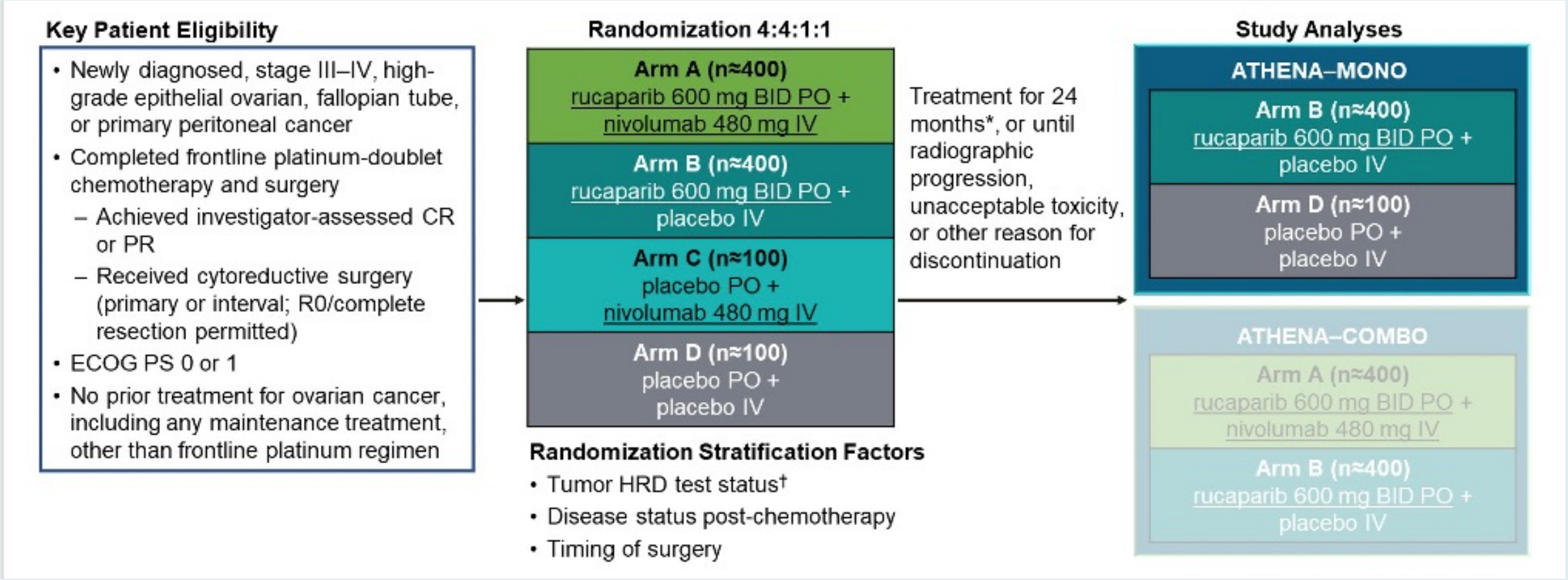
original reports

A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

Bradley J. Monk, MD[1]; Christine Parkinson, MD[2]; Myong Cheol Lim, MD, PhD[3]; David M. O'Malley, MD[4]; Ana Oaknin, MD, PhD[5]; Michelle K. Wilson, MD[6]; Robert L. Coleman, MD[7]; Domenica Lorusso, MD, PhD[8]; Paul Bessette, MD[9]; Sharad Ghamande, MD[10]; Athina Christopoulou, MD, PhD[11]; Diane Provencher, MD[12]; Emily Prendergast, MD[13]; Fuat Demirkiran, MD[14]; Olga Mikheeva, MD[15]; Oladapo Yeku, MD, PhD[16]; Anita Chudecka-Glaz, MD, PhD[17]; Michael Schenker, MD, PhD[18]; Ramey D. Littell, MD[19]; Tamar Safra, MD[20]; Hung-Hsueh Chou, MD[21,22]; Mark A. Morgan, MD[23]; Vít Drochýtek, MD[24]; Joyce N. Barlin, MD[25]; Toon Van Gorp, MD[26]; Fred Ueland, MD[27]; Gabriel Lindahl, MD[28,29]; Charles Anderson, MD[30]; Dearbhaile C. Collins, MBBCh, MA, PhD[31]; Kathleen Moore, MD[32]; Frederik Marme, MD, PhD[33]; Shannon N. Westin, MD, MPH[34]; Iain A. McNeish, MD, PhD[35]; Danny Shih, BA[36]; Kevin K. Lin, PhD[37]; Sandra Goble, MS[38]; Stephanie Hume, PhD[39]; Keiichi Fujiwara, MD, PhD[40]; and Rebecca S. Kristeleit, MD, PhD[41]

J Clin Oncol 2022;[Online ahead of print].

ATHENA-MONO Study Schema



Monk BJ et al. ASCO 2022;Abstract LBA5500.

Lancet Oncol 2022;23(4):465-78.

Articles

Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious *BRCA1* or *BRCA2* mutation (ARIEL4): an international, open-label, randomised, phase 3 trial

Rebecca Kristeleit, Alla Lisyanskaya, Alexander Fedenko, Mikhail Dvorkin, Andreia Cristina de Melo, Yaroslav Shparyk, Irina Rakhmatullina, Igor Bondarenko, Nicoletta Colombo, Valentyn Svintsitskiy, Luciano Biela, Marina Nechaeva, Domenica Lorusso, Giovanni Scambia, David Cibula, Róbert Póka, Ana Oaknin, Tamar Safra, Beata Mackowiak-Matejczyk, Ling Ma, Daleen Thomas, Kevin K Lin, Karen McLachlan, Sandra Goble, Amit M Oza

FDA Advises Manufacturer Not to Submit First-Line Maintenance sNDA for Rucaparib Until OS Survival Data from the ATHENA-MONO Trial Are More Mature

June 17, 2022

"In consultation with the FDA, [the manufacturer of rucaparib] recently was advised not to file a supplemental new drug application based on data from a cohort of the Phase III ATHENA study until the study's overall survival data mature.

In the 8-K, [the manufacturer] said the FDA has accepted a request for a pre-NDA meeting and noted that the ATHENA-MONO portion of the Phase III study has met its primary endpoint of progression-free survival compared to placebo. OS is a secondary endpoint for ATHENA-MONO and the data are approximately 25% mature at present. [The manufacturer] said the FDA urged it to hold off filing for supplemental approval until the OS data reach 50% maturity, and indicated an advisory committee review would likely be necessary if the data were filed earlier than that point.

In a statement to *Scrip*, the firm said that although it cannot anticipate the outcome of the pre-NDA meeting, 'we are encouraged that the FDA is willing to have a dialogue.' [They] estimate the ATHENA-MONO OS data will reach 50% maturity in approximately two years."

https://scrip.pharmaintelligence.informa.com/SC146575/Clovis-Withdraws-Rubraca-Ovarian-Cancer-Indication-Due-To-Survival-Imbalance?vid=Pharma

RTP RESEARCH TO PRACTICE

Dear Health Care Provider Letter (Niraparib)

May 2022

IMPORTANT DRUG WARNING

Subject: Zejula (Niraparib) Important Drug Warning For The Maintenance Treatment In Recurrent Ovarian Cancer (2L+)

Dear Health Care Provider:

The purpose of this letter is to inform you of important information for Zejula® (niraparib) a poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy received in the 2nd line or higher settings. GlaxoSmithKline (GSK) would like to inform you of updated overall survival (OS) data from the ENGOT- OV16/NOVA study.

Updated OS Data from the ENGOT-OV16/NOVA study, a Phase III trial which evaluated the efficacy and safety of niraparib as maintenance treatment for patients with platinum-sensitive recurrent ovarian cancer

Updated OS from ENGOT-OV16/NOVA Indicates Possible Detriment for Patients in the Overall Non-gBRCAmut and the Non-gBRCA-Mut/HRD Populations

Figure 1: OS Kaplan Meier curve for the non-g*BRCA*mut cohort

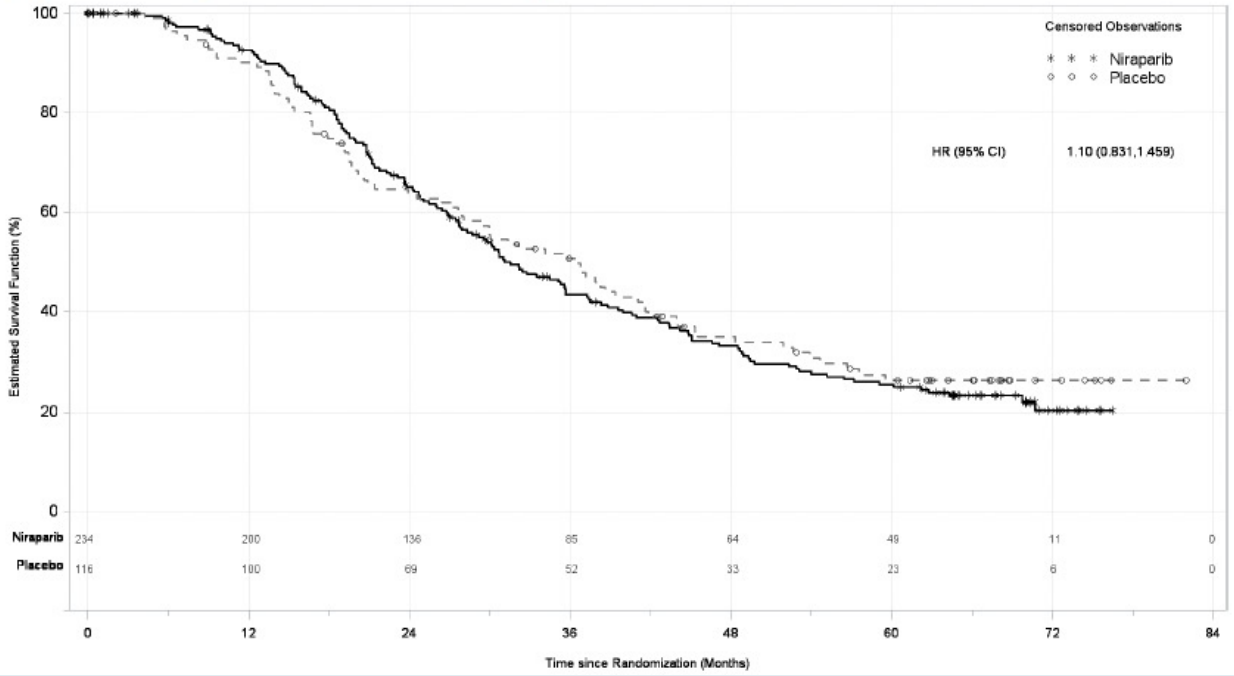
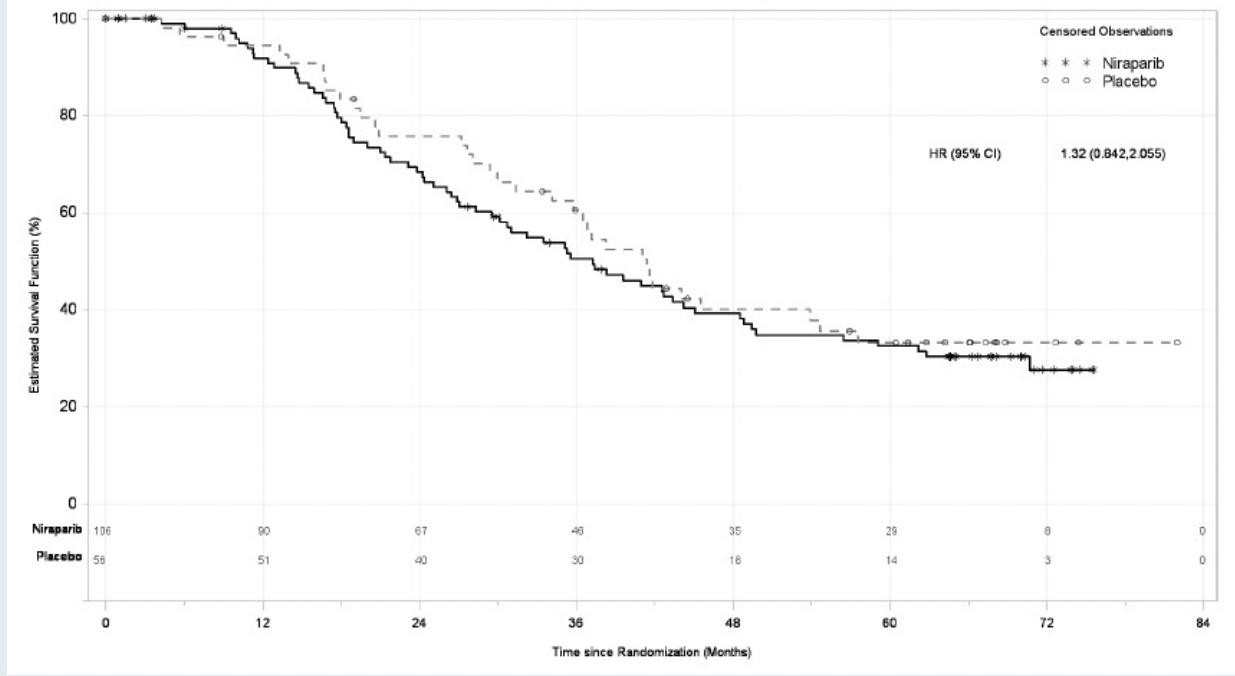


Figure 2: OS Kaplan Meier curve for the non-g*BRCA*mut HRD positive subgroup



Dear Health Care Provider Letter (Niraparib); May 2022.

RTP RESEARCH TO PRACTICE

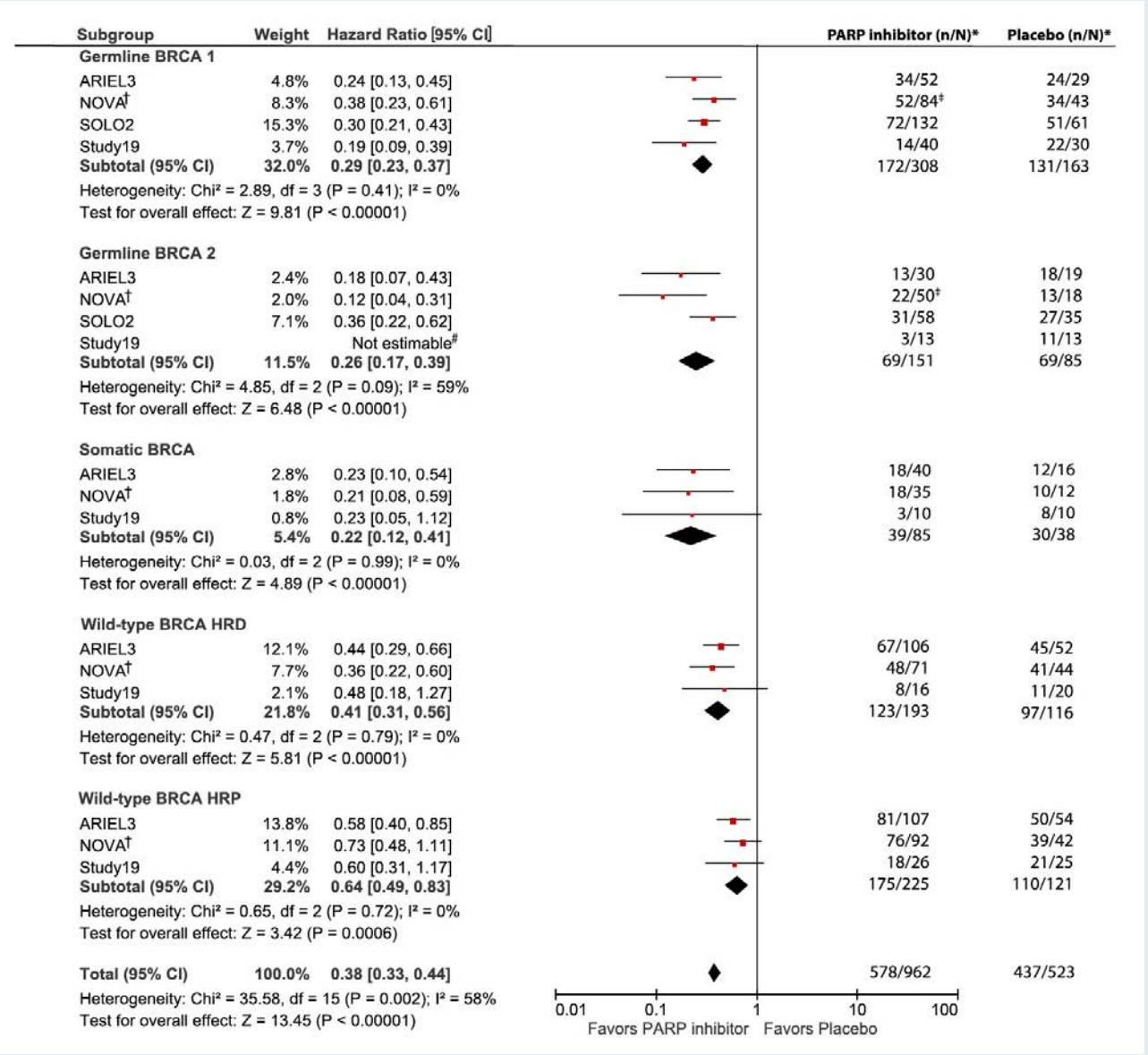
Cancer 2021 July 15;127(14):2432-41.

Original Article

Molecular and Clinical Predictors of Improvement in Progression-Free Survival With Maintenance PARP Inhibitor Therapy in Women With Platinum-Sensitive, Recurrent Ovarian Cancer: A Meta-Analysis

Chee Khoon Lee, PhD [1,2]; Michael L. Friedlander, PhD[2,3]; Angelina Tjokrowidjaja, MPH[1,2]; Jonathan A. Ledermann, MD[4]; Robert L. Coleman, MD[5]; Mansoor R. Mirza, MD[6,7]; Ursula A. Matulonis, MD[8]; Eric Pujade-Lauraine, PhD[9,10]; Ralph Bloomfield, MSc[11]; Sandra Goble, MS[12]; Ping Wang, PhD[13]; Rosalind M. Glasspool, PhD[14,15]; Clare L. Scott, PhD[2,16]; and the Gynecologic Cancer Intergroup Meta-Analysis Committee

Forest Plot of Hazard Ratios for Investigator-Assessed PFS



Lee CK et al. *Cancer* 2021 July 15;127(14):2432-41.

Case Presentation: An 86-year-old woman with gBRCA wild-type HGSOC who develops recurrent disease after declining maintenance niraparib

Dr Priya Rudolph (Athens, Georgia)

RTP
RESEARCH
TO PRACTICE

2022 ASCO ANNUAL MEETING

DESTINY-Breast04

Abstract LBA3

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, NY, USA

June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2022;387(1):9-20.

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron, for the DESTINY-Breast04 Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2022;387(1):75-6.

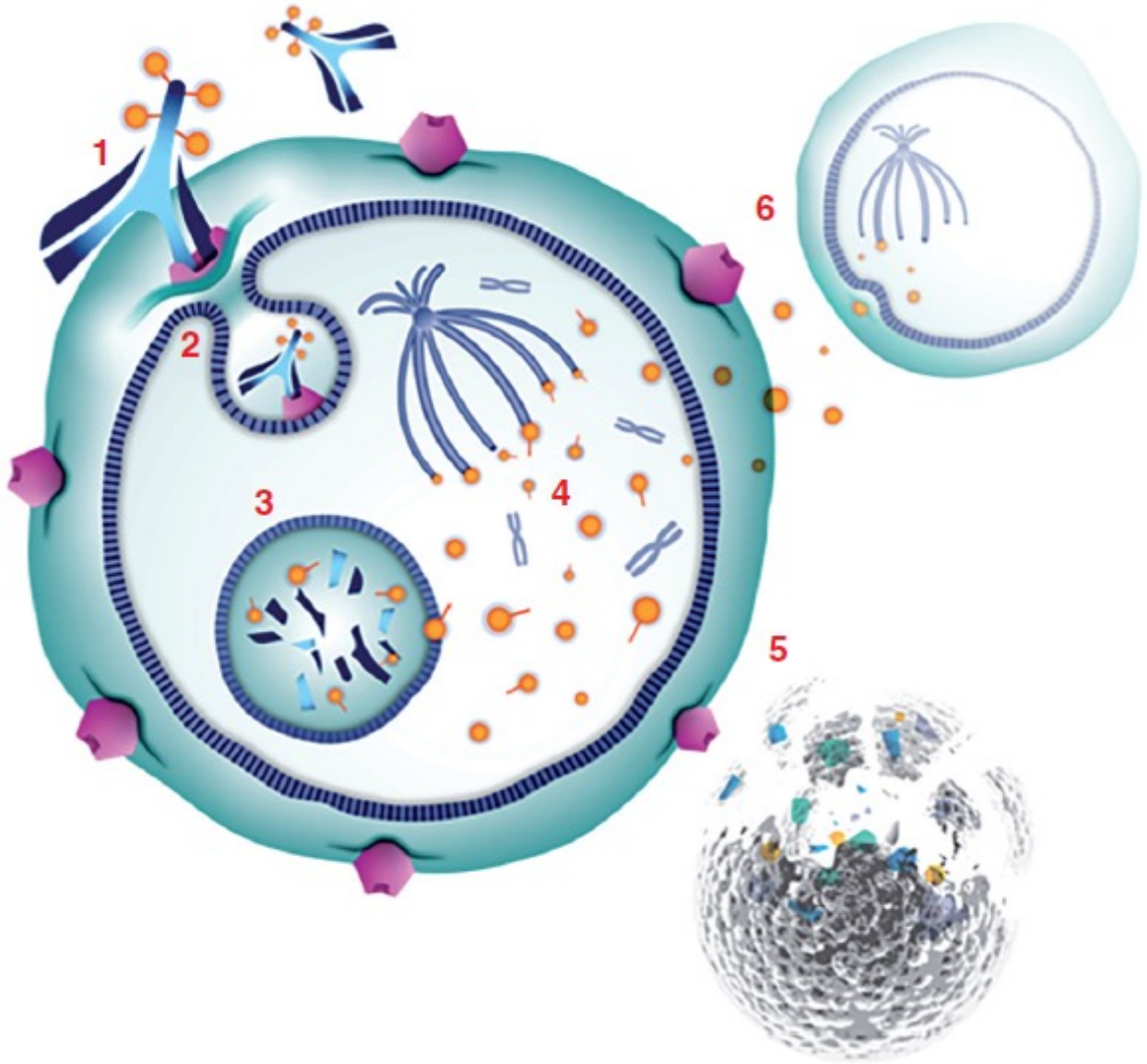
EDITORIALS

DESTINY-Changing Results for Advanced Breast Cancer

Sara A. Hurvitz, M.D.

RTP RESEARCH TO PRACTICE

Mirvetuximab Soravtansine: Mechanism of Action



(1) Mirvetuximab soravtansine binds with high affinity to FRα expressed on the tumor cell surface

(2) The antibody-drug conjugate (ADC)/receptor complex becomes internalized via antigen-mediated endocytosis

(3) Lysosomal processing releases active DM4 catabolites from the ADC molecule

(4) These maytansinoid derivatives inhibit tubulin polymerization and microtubule assembly

(5) The potent antimitotic effects result in cell-cycle arrest and apoptosis

(6) Active metabolites can also diffuse into neighboring cells and induce further cell death — in other words, bystander killing

Moore K et al. *Future Oncol* 2018:14(2);123-36.

RTP RESEARCH TO PRACTICE

Mirvetuximab Soravtansine (MIRV) in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha (FRα) Expression: Characterization of Antitumor Activity in the SORAYA Study

Matulonis UA et al.

ASCO 2022;Abstract 5512.

MIRASOL Phase III Study Schema

MIRASOL

Enrollment and Key Eligibility

- Platinum-resistant disease (PFI ≤ 6 mo)
  - 1° platinum refractory disease excluded (primary PFI < 3 mo)
- Prior bevacizumab and PARPi allowed
- 1-3 prior lines of therapy
- Patients with BRCA mutations allowed
- FRα-high by PS2+ scoring (≥75% PS2+)

Statistical Assumptions

- 430 patients/ 330 events for PFS by INV
- α=0.05 (two-sided)
- Power=90%; HR=0.7; control arm mPFS 3.5 mo

Mirvetuximab Soravtansine
6 mg/kg AIBW (calculated using adjusted ideal body weight) intravenously once every 3 weeks

1:1 Randomization
STRATIFICATION FACTORS
Investigator's Choice (IC) Chemotherapy
(Paclitaxel, PLD, Topotecan)
Prior Therapies
(1 vs 2 vs 3)

Investigator's Choice (IC) Chemotherapy
Paclitaxel, PLD,† or Topotecan
Paclitaxel: 80 mg/m2 weekly; PLD: 40 mg/m² every 4 weeks;
Topotecan: 4 mg/m² on days 1, 8, and 15 every four weeks;
or 1.25 mg/m² on days 1-5 every 3 weeks

Moore KN et al. SGO 2022;Abstract 297.

PICCOLO Phase II Trial Schema

PICCOLO

Enrollment and Key Eligibility

- Platinum-sensitive disease (PFI >6 mo)
- At least 2 prior lines of platinum-based therapy
  - Patients with documented platinum allergy require only 1 prior line of platinum
- FRα-high by IHC scoring (≥75% PS2+)
- Appropriate for single agent therapy as next line of therapy as determined by investigator

Statistical Assumptions

- N=75
- Null hypothesis: ORR is ≤ 28% tested using an optimal Simon's two-stage design w/o pause in enrollment

→

Mirvetuximab Soravtansine

6 mg/kg AIBW (calculated using adjusted ideal body weight) intravenously once every 3 weeks

Alvarez Secord A et al. SGO 2022;Abstract 300.

Updated Results From the Phase 1b Expansion Study of Upifitamab Rilsodotin (UpRi; XMT-1536), a NaPi2b-directed Dolaflexin Antibody Drug Conjugate (ADC) in Ovarian Cancer

Richardson, Debra L[1]; Hamilton, Erika P[2]; Barve, Minal[3]; Anderson, Charles K[4]; Taylor, Sara K[5]; Lakhani, Nehal[6]; Buscema, Joseph[7]; Tolcher, Anthony W[8]; Zarwan, Corrine[9]; Werner, Theresa L[10]; Hays, John L[11]; Richards, Paul[12]; Arend, Rebecca[13]; Edenfield, Jeffery[14]; Putiri, Emily[15]; Bernardo, Patricia[15]; Burger, Robert A[15]; Matulonis, Ursula A[16]

[1]Stephenson Cancer Center, University of Oklahoma Health Sciences Center and the Sarah Cannon Research Institute, Oklahoma City, OK; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [3]Mary Crowley Cancer Research, Dallas, TX; [4]Willamette Valley Cancer Institute and Research Center, Eugene, OR; [5]BC Cancer - Kelowna, Kelowna BC, Canada; [6]START Midwest, Grand Rapids, MI; [7]Arizona Oncology, Tucson, AZ; [8]NEXT Oncology, San Antonio, TX; [9]Lahey Clinic, Burlington, MA; [10]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [11]Arthur James Cancer Hospital, Ohio State University, Columbus, OH; [12]US Oncology, Oncology and Hematology Assoc. of Southwest VA, Salem, VA; [13]University of Alabama at Birmingham, Birmingham, AL; [14]Prisma Health Cancer Institute, Greenville, SC; [15]Mersana Therapeutics, Inc, Cambridge, MA; [16]Dana-Farber Cancer Institute, Boston, MA

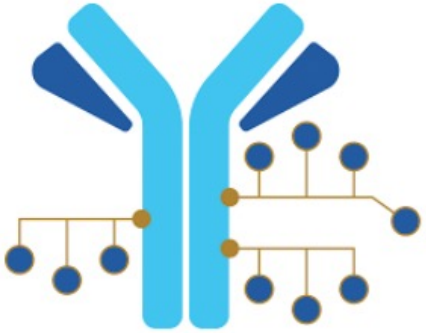
Abstract 76

ANNUAL MEETING ON WOMENS' CANCER®
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 18 - 21, 2022

SGO 2022;Abstract 76.

Society of Gynecologic Oncology

Upifitamab Rilsodotin (UpRi): First-in-Class ADC Targeting NaPi2b



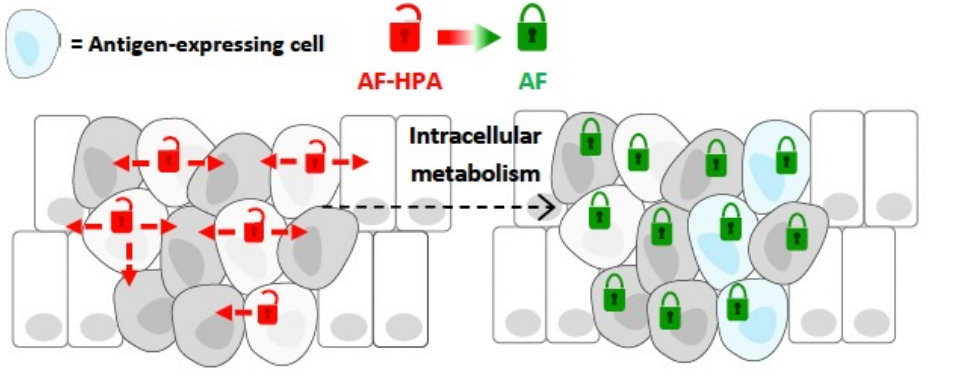
UpRi

Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

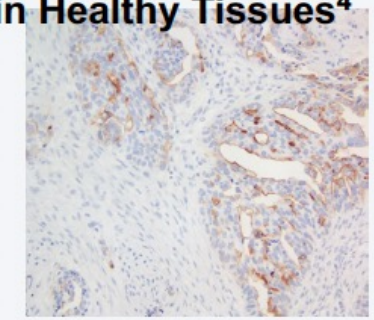
Drug-to-Antibody Ratio: ~10



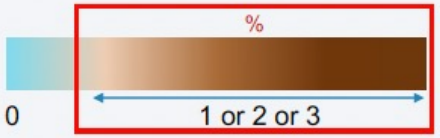
Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy cells[2,3]

NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[4]

- NaPi2b expressed by tumor cells in two-thirds of patients with high-grade serous ovarian cancer[2]
- NaPi2b is a lineage antigen (not an oncogene)[1]



NaPi2b IHC assay in development *– an optimal diagnostic assay would be robust, predictive, reproducible, easily able to distinguish a wide range of expression using* ***TPS scoring method***[2]

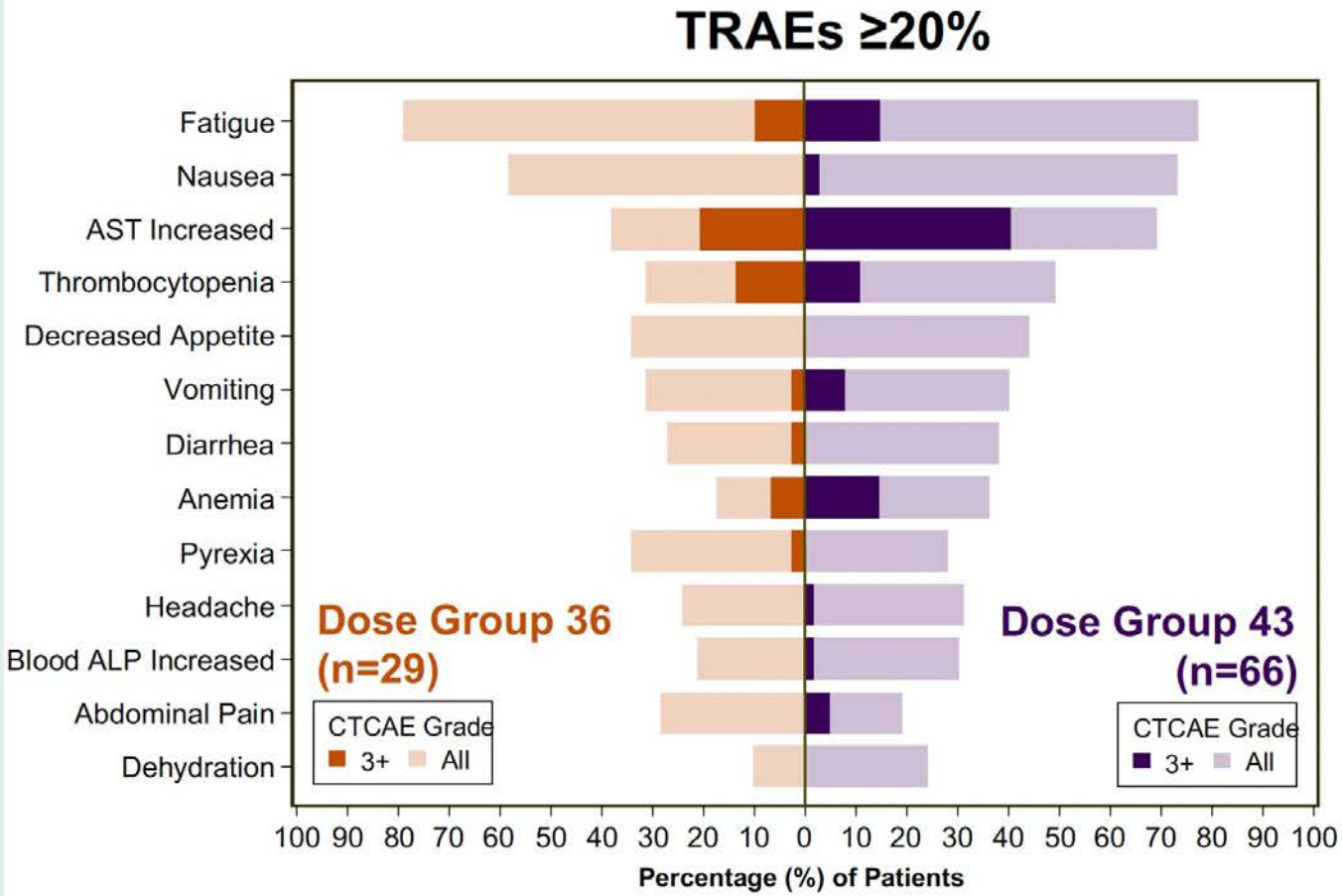


Richardson DL et al. SGO 2022;Abstract 76.

RTP RESEARCH TO PRACTICE

TRAEs by UpRi Dose Group

Dose Group 36 Had a More Favorable Safety Profile Compared to Dose Group 43



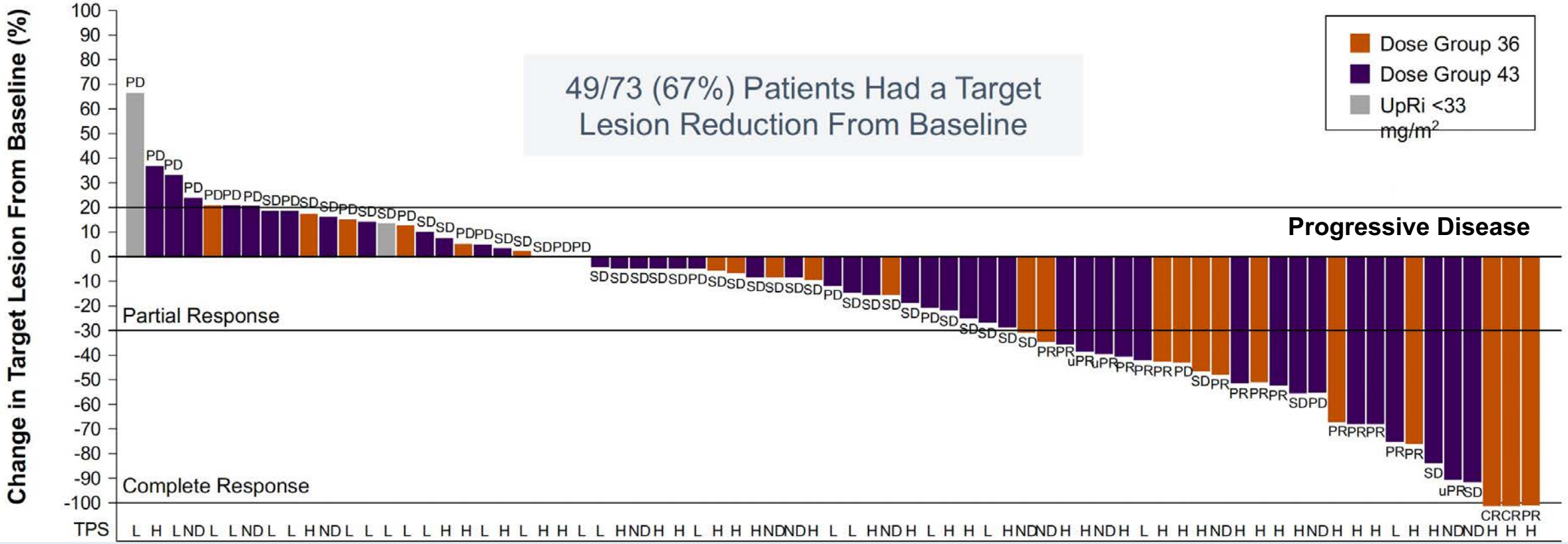
- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43[a]

Richardson DL et al. SGO 2022;Abstract 76.

RTP RESEARCH TO PRACTICE

Best Response by UpRi Dose Group

Similar Tumor Reduction in Both Dose Groups: Two-thirds of Patients Had Reductions in Target Tumor Lesions by RECIST 1.1



Richardson DL et al. SGO 2022;Abstract 76.

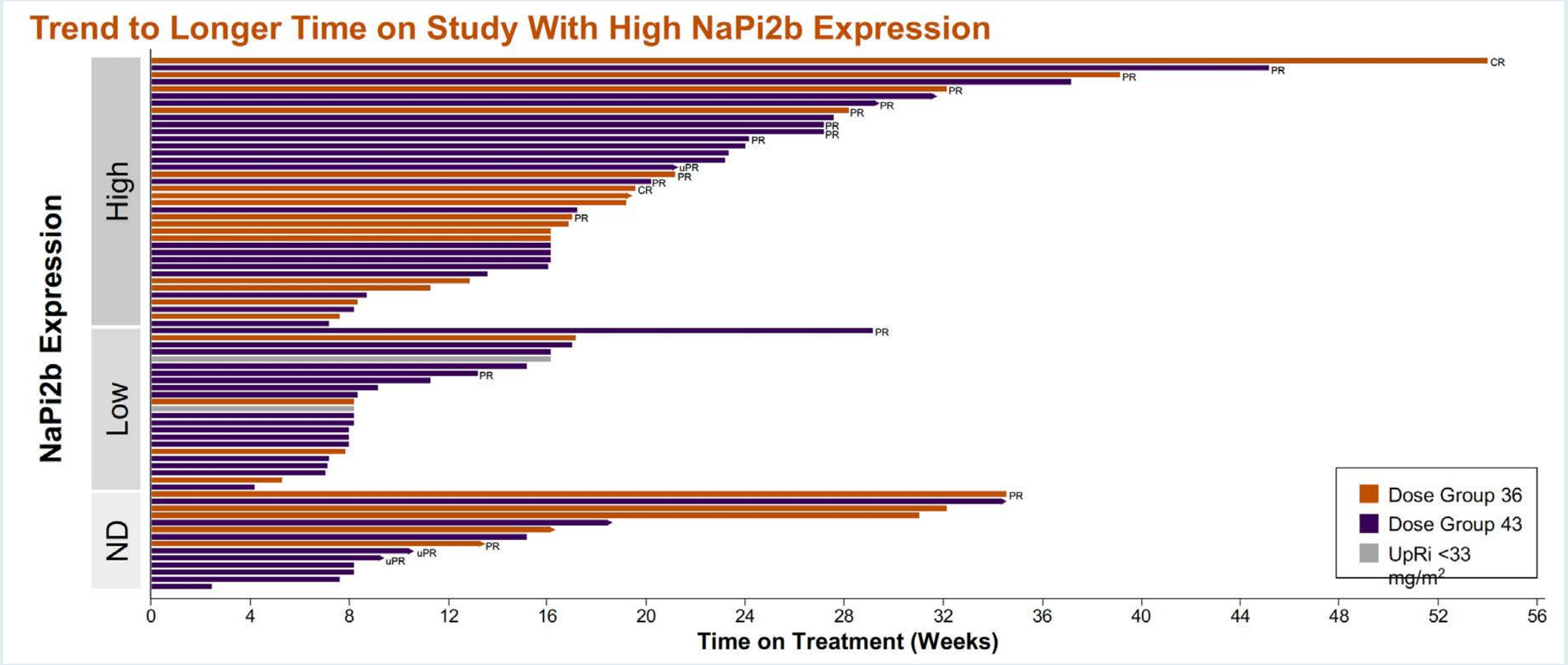
Confirmed ORR by UpRiDose Group and NaPi2b Level and Duration of Response (DoR)

		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

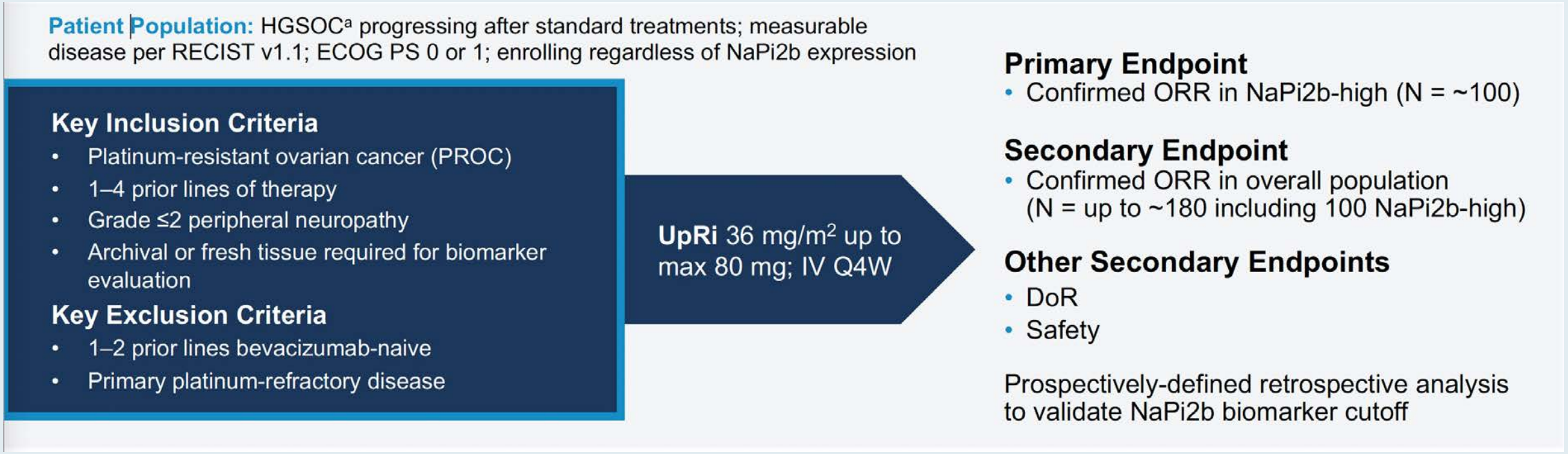
Richardson DL et al. SGO 2022;Abstract 76.

Time on UpRi Study in Evaluable Patients



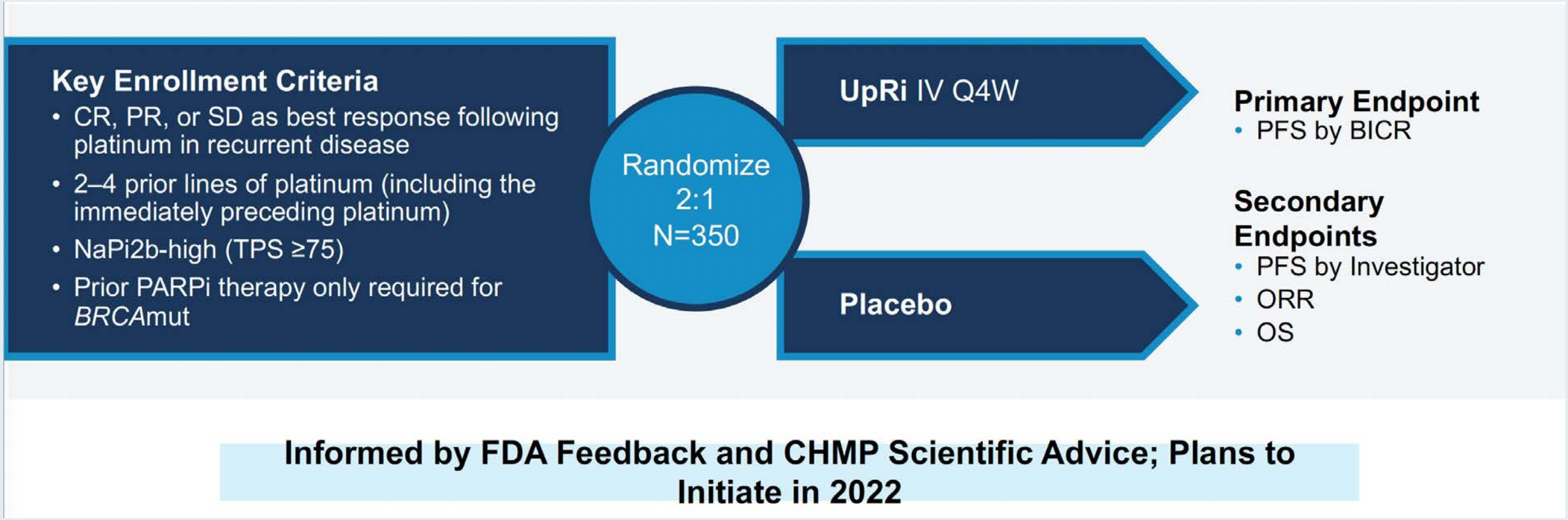
Richardson DL et al. SGO 2022;Abstract 76.

Ongoing UPLIFT (ENGOT-OV67/GOG-3048) Study Schema



Richardson DL et al. SGO 2022;Abstract 76.

Ongoing UP-NEXT Phase III (ENGOT-OV71-NSGO-CTU/GOG-3049) Study Schema

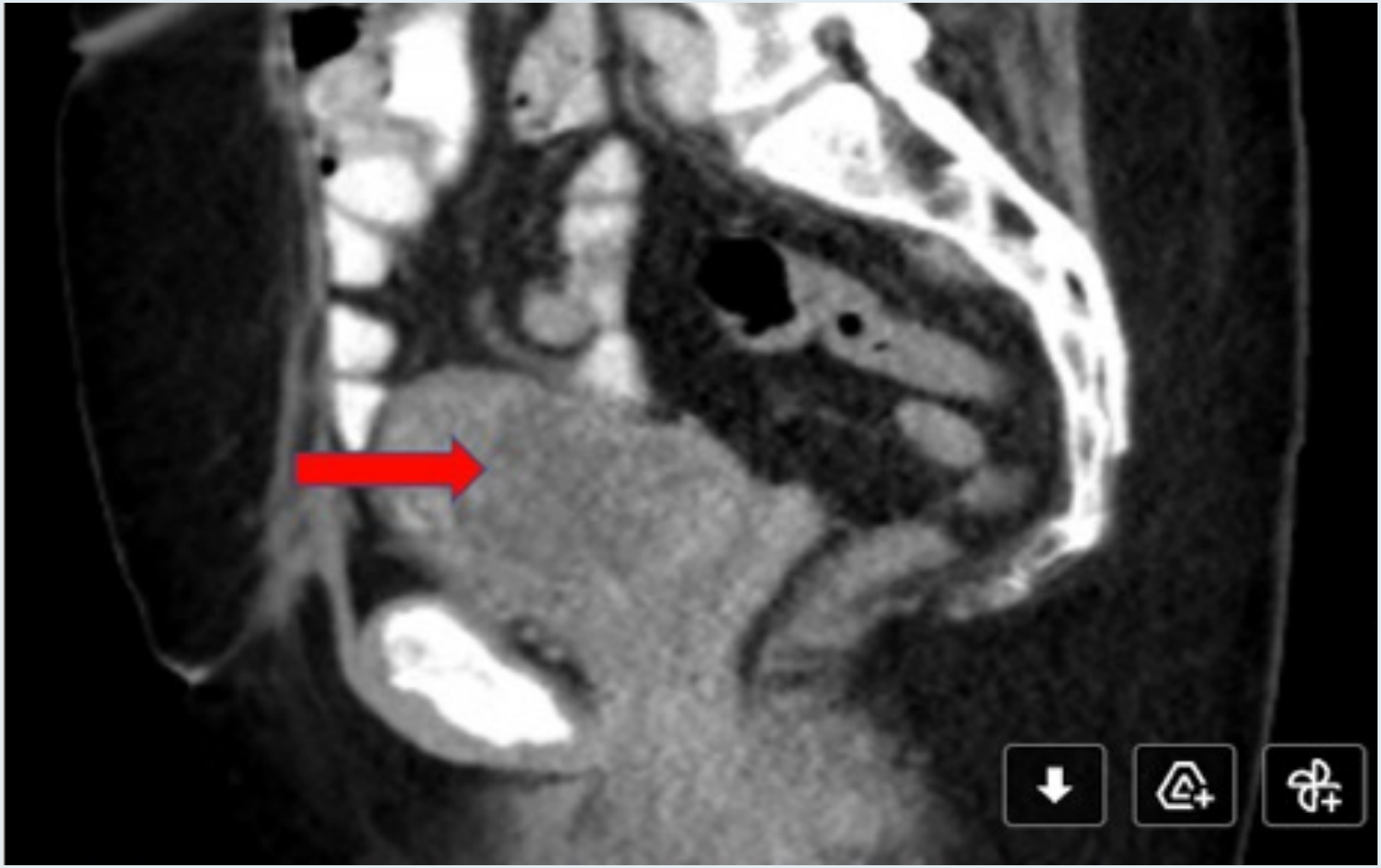


Richardson DL et al. SGO 2022;Abstract 76.

Case Presentation: A 73-year-old woman with HGSOC and gBRCA1 and 2 mutations who responds to olaparib for 5 years but then develops PD after stopping

Dr Karim ElSahwi (Neptune City, New Jersey)

RTP
RESEARCH
TO PRACTICE



Research

JAMA Oncol 2021 December 1;7(12):1772-81.

JAMA Oncology | Original Investigation

Preexisting *TP53*-Variant Clonal Hematopoiesis and Risk of Secondary Myeloid Neoplasms in Patients With High-grade Ovarian Cancer Treated With Rucaparib

Tanya T. Kwan, PhD; Amit M. Oza, MD; Anna V. Tinker, MD; Isabelle Ray-Coquard, MD, PhD; Ana Oaknin, MD, PhD; Carol Aghajanian, MD, PhD; Domenica Lorusso, MD, PhD; Nicoletta Colombo, MD, PhD; Andrew Dean, MD; Johanne Weberpals, MD; Eric Severson, MD, PhD; Lan-Thanh Vo, BS; Sandra Goble, MS; Lara Maloney, BA; Thomas Harding, PhD; Scott H. Kaufmann, MD, PhD; Jonathan A. Ledermann, MD; Robert L. Coleman, MD; Iain A. McNeish, MD, PhD; Kevin K. Lin, PhD; Elizabeth M. Swisher, MD

Case Presentation: A 69-year-old woman with gBRCA wild-type Stage IIIC ovarian cancer who receives IV/IP adjuvant chemotherapy

Dr Gigi Chen (Pleasant Hill, California)

Case Presentation: A 46-year-old woman with MSI-high BRCA wild-type clear cell ovarian cancer with SD on pembrolizumab and niraparib

Dr Syed Zafar (Fort Myers, Florida)

RTP
RESEARCH
TO PRACTICE

PATIENT RESULTS

15 genomic findings

14 therapies associated with potential clinical benefit

0 therapies associated with lack of response

37 clinical trials

TUMOR TYPE: OVARY CLEAR CELL CARCINOMA

Genomic Alterations Identified†

ERBB2 R678Q
PIK3CA Y1021C
PTEN N323fs*2, splice site 1027-1G>T
ARID1A A1522fs*5, R2158*
ERRFI1 R286fs*7
ARID1B Q1797*
HNF1A P291fs*51
MSH6 T1219I, Y397C
SMAD2 splice site 730+2T>C
STAG2 splice site 3468-1G>A

Additional Findings†

Microsatellite status MSI-High

Tumor Mutational Burden TMB-High; 43 Muts/Mb

† For a complete list of the genes assayed and performance specifications, please refer to the Appendix

Immunotherapy in Gynecological Cancers

Special Collection

Therapeutic Advances in Medical Oncology

Review

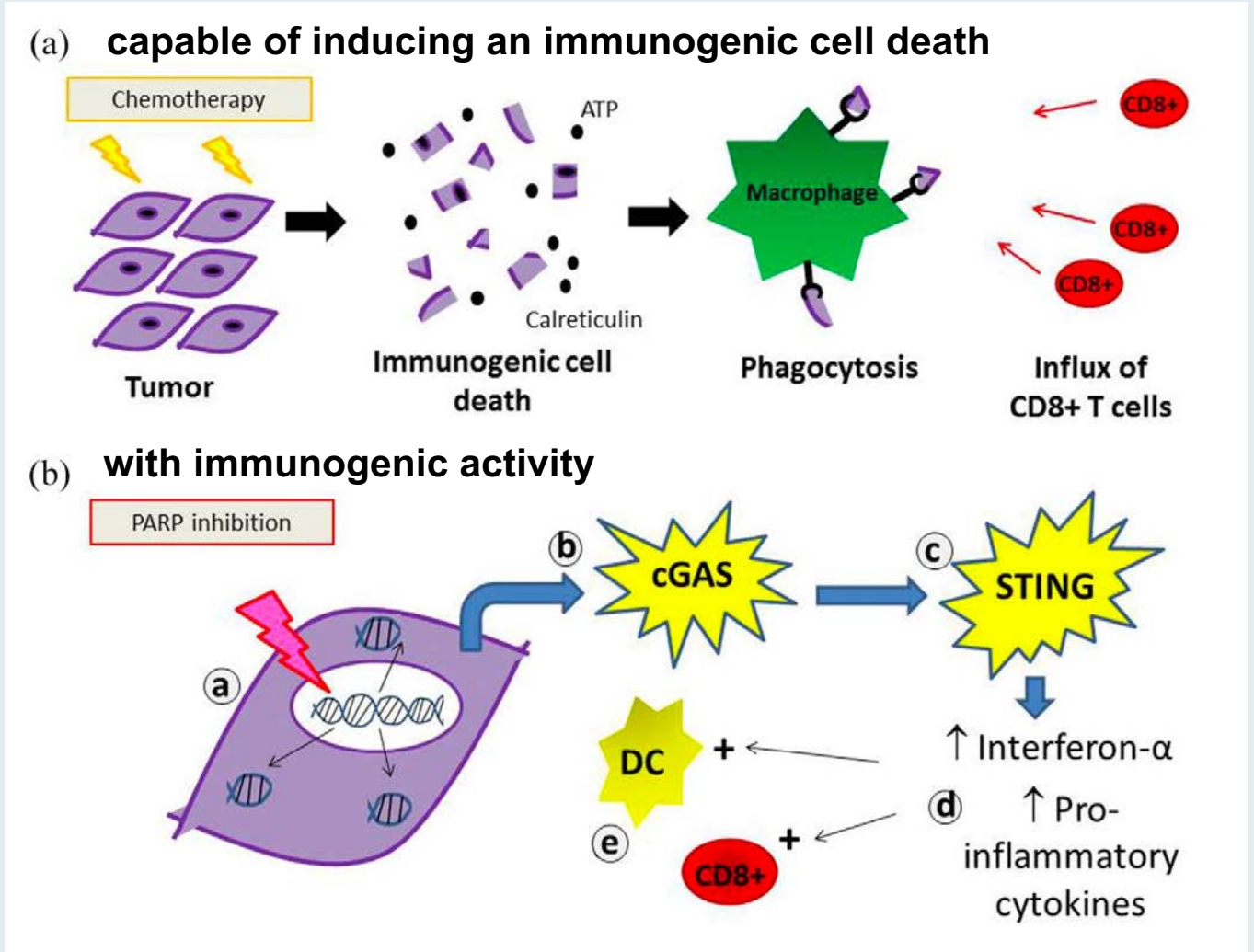
Immune checkpoint inhibitors in ovarian cancer: where do we stand?

Ther Adv Med Oncol

2021, Vol. 13: 1–13

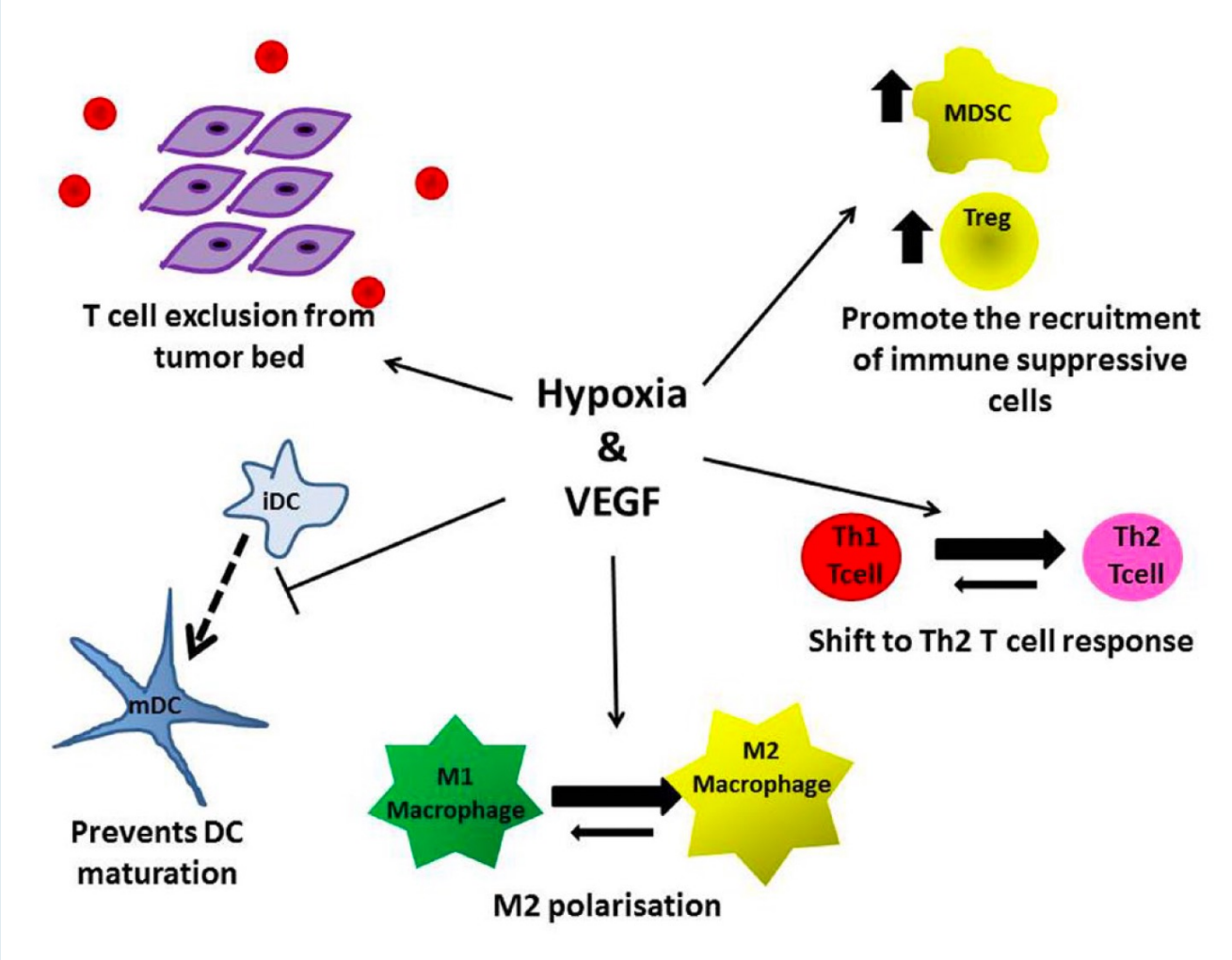
Alexandra Leary, David Tan and Jonathan Ledermann

Proposed Immune-Stimulatory Properties of Certain Cytotoxic Agents



Leary A et al. *Ther Adv Mol Oncol* 20021;13:1-13.

Both Hypoxia and Vascular Endothelial Growth Factor (VEGF) Promote Immune Tolerance via a Number of Mechanisms



Leary A et al. *Ther Adv Mol Oncol* 20021;13:1-13.

Case Presentation: A 59-year-old woman with recurrent BRCA wild-type (HRp) low-grade ovarian cancer with rising CA-125, pleural effusion and a new lung nodule on salvage chemotherapy

Dr Dana Chase (Phoenix, Arizona)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 57-year-old woman with Stage IIIA ovarian cancer and a gBRCA1 mutation, s/p neoadjuvant chemotherapy and surgery, doing well on maintenance olaparib

Dr Paul DiSilvestro (Providence, Rhode Island)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 92-year-old woman with PMH of untreated CLL, with Stage III/IV ovarian cancer

Dr Rajalaxmi McKenna (Willowbrook, Illinois)

RTP
RESEARCH
TO PRACTICE

Case Presentation: A 53-year-old woman with recurrent BRCA wild-type low-grade ovarian cancer who has a CR to niraparib/bevacizumab but develops lymphedema

Dr Gigi Chen (Pleasant Hill, California)

RTP
RESEARCH
TO PRACTICE

Meet The Professor with Prof Ledermann

Introduction: Journal Club with Prof Ledermann – Part 1

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RTP
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A patient presenting with ovarian cancer with extensive intra-abdominal disease (clinical Stage IIIC) receives neoadjuvant carboplatin/paclitaxel/ bevacizumab with good response and proceeds to surgery with R0 resection. Regulatory and reimbursement issues aside, what would be your preferred approach to maintenance therapy if genetic testing revealed a germline BRCA mutation?

 Dr Eskander	Olaparib/bevacizumab	 Dr Matulonis	Olaparib/bevacizumab
 Prof Ledermann	Olaparib/bevacizumab	 Dr Penson	Olaparib
 Dr Lheureux	Olaparib/bevacizumab	 Dr Westin	Olaparib/bevacizumab

A patient presenting with ovarian cancer with extensive intra-abdominal disease (clinical Stage IIIC) receives neoadjuvant carboplatin/paclitaxel/ bevacizumab with good response and proceeds to surgery with R0 resection. Genetic testing revealed a germline BRCA mutation. Beyond your preferred approach, which other approaches to maintenance therapy do you believe are acceptable in this situation?

 Dr Eskander	Niraparib Olaparib Rucaparib	 Dr Matulonis	Niraparib
 Prof Ledermann	Niraparib Olaparib Rucaparib	 Dr Penson	Niraparib Olaparib Rucaparib
 Dr Lheureux	Niraparib Olaparib Rucaparib	 Dr Westin	Niraparib Olaparib Rucaparib

RTP RESEARCH TO PRACTICE

A patient presenting with Stage IIIC ovarian cancer undergoes R0 resection and receives adjuvant carboplatin/paclitaxel with good response. Regulatory and reimbursement issues aside, what would you most likely recommend as maintenance therapy if genetic testing revealed BRCA wild type, HR proficient (eg, LOH low)?

 Dr Eskander	Niraparib	 Dr Matulonis	None Bevacizumab
 Prof Ledermann	Bevacizumab	 Dr Penson	Niraparib
 Dr Lheureux	Niraparib	 Dr Westin	Niraparib

RTP
RESEARCH
TO PRACTICE

A patient presenting with Stage IIIC ovarian cancer undergoes R0 resection and receives adjuvant carboplatin/paclitaxel with good response. Regulatory and reimbursement issues aside, what would you most likely recommend as maintenance therapy if genetic testing revealed a germline PALB2 mutation?

 Dr Eskander	Olaparib	 Dr Matulonis	Niraparib
 Prof Ledermann	None	 Dr Penson	Olaparib
 Dr Lheureux	Niraparib	 Dr Westin	Olaparib

RTP RESEARCH TO PRACTICE

A patient presenting with Stage IIIC ovarian cancer undergoes R0 resection and receives adjuvant carboplatin/paclitaxel with good response. Regulatory and reimbursement issues aside, what would you most likely recommend as maintenance therapy if genetic testing revealed a somatic BRCA mutation?

 Dr Eskander	Olaparib	 Dr Matulonis	Olaparib
 Prof Ledermann	Olaparib	 Dr Penson	Olaparib
 Dr Lheureux	Olaparib	 Dr Westin	Olaparib

RTP RESEARCH TO PRACTICE

A patient presenting with Stage IIIC ovarian cancer undergoes R0 resection and receives adjuvant carboplatin/paclitaxel with good response. Regulatory and reimbursement issues aside, what would you most likely recommend as maintenance therapy if genetic testing revealed BRCA wild type, HR deficient (eg, LOH high)?

 Dr Eskander	Niraparib	 Dr Matulonis	Niraparib
 Prof Ledermann	Olaparib/bevacizumab	 Dr Penson	Niraparib
 Dr Lheureux	Niraparib	 Dr Westin	Niraparib

RTP RESEARCH TO PRACTICE

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RTP
RESEARCH
TO PRACTICE

Lancet Oncol 2022;23:919-30.

Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal cancer treatment (ICON8): overall survival results from an open-label, randomised, controlled, phase 3 trial

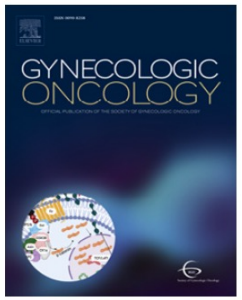
Andrew R Clamp, Elizabeth C James, Iain A McNeish, Andrew Dean, Jae-Won Kim, Dearbhaile M O'Donnell, Dolores Gallardo-Rincon, Sarah Blagden, James Brenton, Tim J Perren, Sudha Sundar, Rosemary Lord, Graham Dark, Marcia Hall, Susana Banerjee, Rosalind M Glasspool, C Louise Hanna, Sarah Williams, Kate M Scatchard, Helena Nam, Sharadah Essapen, Christine Parkinson, Lucy McAvan, Ann Marie Swart, Babasola Popoola, Francesca Schiavone, Jonathan Badrock, Fuad Fananapazir, Adrian D Cook, Mahesh Parmar, Richard Kaplan, Jonathan A Ledermann

Gynecologic Oncology 166 (2022) 254–262

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno



Measure of Ovarian Symptoms and Treatment concerns (MOST) indexes and their associations with health-related quality of life in recurrent ovarian cancer

Rachel Campbell [a,*], Daniel S.J. Costa [a], Martin R. Stockler [b], Yeh Chen Lee [b,c,d], Jonathan A. Ledermann [e], Dominique Berton [f,g], Jalid Sehouli [h,i], Felicia T. Roncolato [b,c,d,j], Rachel O. Connell [b], Aikou Okamoto [k,l], Jane Bryce [m,n], Amit M. Oza [o,p], Elisabeth Avall-Lundqvist [q,r,s], Jonathan S. Berek [t,u], Anne Lanceley [v], Florence Joly [f,w], Felix Hilpert [h,x], Amanda Feeney [e], Marie C. Kaminsky [f,y], Katrina Diamante [b], Michael L. Friedlander [c,d,1], Madeleine T. King [a,1], GCIG Symptom Benefit Group

Flynn *et al. Cancer Drug Resist* 2022;5:424-35
DOI: 10.20517/cdr.2022.13

Cancer
Drug Resistance

Review

Open Access

Ovarian cancer recurrence: is the definition of platinum resistance modified by PARPi and other intervening treatments? The evolving landscape in the management of platinum-resistant ovarian cancer

Michael J. Flynn[1], Jonathan A. Ledermann[1,2]

Gynecologic Oncology 164 (2022) 243–244

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Testing for homologous recombination deficiency – does it provide new insights for the use of veliparib?

Ledermann JA

Gynecologic Oncology 164 (2022) 245–253

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Impact of homologous recombination status and responses with veliparib combined with first-line chemotherapy in ovarian cancer in the Phase 3 VELIA/GOG-3005 study

Elizabeth M. Swisher [a,*], Carol Aghajanian [b], David M. O'Malley [c], Gini F. Fleming [d], Scott H. Kaufmann [e], Douglas A. Levine [f], Michael J. Birrer [g], Kathleen N. Moore [h], Nick M. Spirtos [i], Mark S. Shahin [j], Thomas J. Reid [k], Michael Friedlander [l], Karina Dahl Steffensen [m], Aikou Okamoto [n], Vasudha Sehgal [o], Peter J. Ansell [o], Minh H. Dinh [o], Michael A. Bookman [p], Robert L. Coleman [q]

Homologous Recombination Status and Responses to Veliparib Combined with First-Line Chemotherapy in Ovarian Cancer for the Phase III VELIA/GOG-2005 Study

VELIA study design

Women with newly-diagnosed stage III/IV ovarian carcinoma were enrolled regardless of chemotherapy response or biomarker status

Randomization 1:1:1

- **Control:** 1L chemotherapy
- **Veliparib combination only:** 1L chemotherapy + veliparib
- **Veliparib throughout:** 1L chemotherapy + veliparib followed by veliparib maintenance

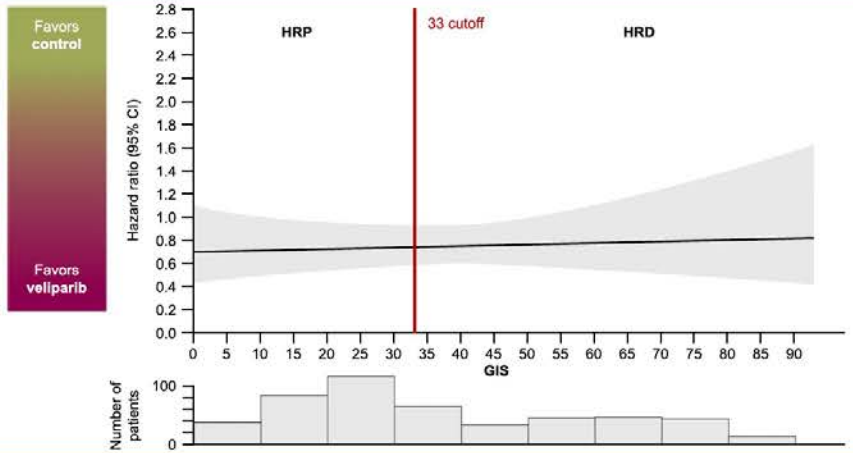
1140 patients underwent randomization

*BRCA*m (n = 298)	*BRCA*wt (n = 742)	
	High GIS » HRD/*BRCA*wt (n = 329)	Low GIS » HRP (n = 373)
Control (n = 92)	Control (n = 115)	Control (n = 124)
Veliparib throughout (n = 206)	Veliparib throughout (n = 106)	Veliparib throughout (n = 125)
	Veliparib combination only (n = 108)	Veliparib combination only (n = 124)

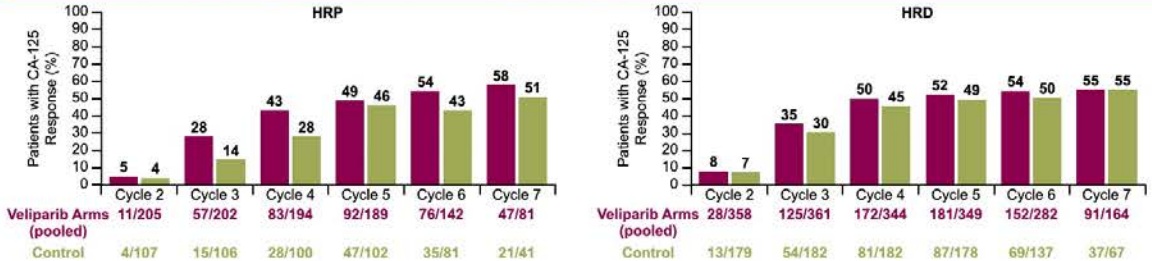
Conclusions

- Survival outcomes in VELIA were improved with veliparib regardless of homologous recombination status
- Improved CA-125 response with veliparib was observed in the HRP subgroup
- PARPi could benefit a broader patient population than those currently eligible based on prior phase 3 trials

PFS with veliparib in biomarker-defined subgroups



CA-125 response during the combination phase



*BRCA*m, *BRCA*-mutated; *BRCA*wt, *BRCA* wild type; GIS, genomic instability score; HRD, homologous recombination deficient; HRP, homologous recombination proficient; PFS, progression-free survival; PARP, poly(ADP-ribose) polymerase; PARPi, PARP inhibitor

Swisher EM et al. *Gynecol Oncol* 2022;164(2):245-53.

Original research

Symptom burden and quality of life with chemotherapy for recurrent ovarian cancer: the Gynecologic Cancer InterGroup-Symptom Benefit Study

OPEN ACCESS

Yeh Chen Lee ,[1,2,3] Madeleine T King,[4] Rachel L O'Connell,[2] Anne Lanceley,[5] Florence Joly,[6,7] Felix Hilpert,[8,9] Alison Davis,[1,10] Felicia T Roncolato,[1,2] Aikou Okamoto,[11,12] Jane Bryce,[13,14,15] Paul Donnellan,[16] Amit M Oza,[17,18] Elisabeth Avall-Lundqvist,[19,20,21] Jonathan S Berek,[22,23] Jonathan A Ledermann ,[24] Dominique Berton,[6,25] Jalid Sehouli,[26,27] Amanda Feeney,[24] Marie-Christine Kaminsky,[6,28] Katrina Diamante,[2] Martin R Stockler,[2] Michael L Friedlander ,[1,3] for the GCIG Symptom Benefit Group

Int J Gynecol Cancer 2022 June 6;32(6):761-8.

JC JOURNAL CLUB RTP RESEARCH TO PRACTICE

2021 ASCO ANNUAL MEETING

Abstract 5545

Olaparib maintenance monotherapy for non-germline BRCA1/2-mutated platinum-sensitive relapsed ovarian cancer patients: Phase IIIb OPINION primary analysis

Andrés Poveda, MD

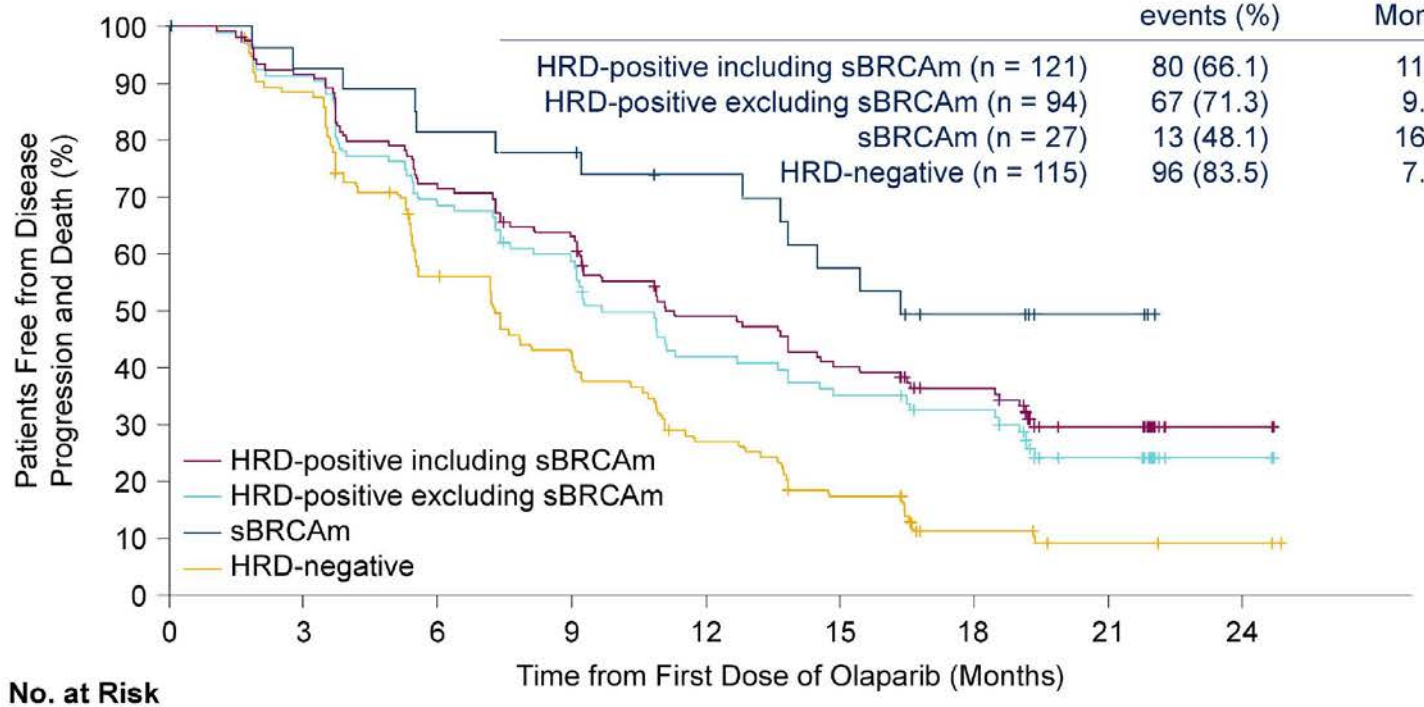
Oncogynecologic Department, Initia Oncology, Hospital Quironsalud, Valencia, Spain

June 2021

Download poster

ClinicalTrials.gov identifier NCT03402841. This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Median PFS Was Prolonged Across Many HRD/Somatic BRCA Mutation-Status and Other Demographic and Disease-Characteristic 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

Poveda A et al. ASCO 2021;Abstract 5545.

European Journal of Cancer 154 (2021) 190–200

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Prognostic nomogram for progression-free survival in patients with BRCA mutations and platinum-sensitive recurrent ovarian cancer on maintenance olaparib therapy following response to chemotherapy

Angelina Tjokrowidjaja [a,b,c,*], Michael Friedlander [c,d], Sarah J. Lord [a,e], Rebecca Asher [a], Manuel Rodrigues [f,g], Jonathan A. Ledermann [h], Ursula A. Matulonis [i], Amit M. Oza [j], Ilan Bruchim [k], Tomasz Huzarski [l], Charlie Gourley [m], Philipp Harter [n], Ignace Vergote [o,p], Clare L. Scott [q], Werner Meier [r,s], Ronnie Shapira-Frommer [t], Tsveta Milenkova [u], Eric Pujade-Lauraine [v,w], Val Gebski [a], Chee K. Lee [a,b,c]

Meet The Professor with Prof Ledermann

Introduction: Journal Club with Prof Ledermann – Part 1

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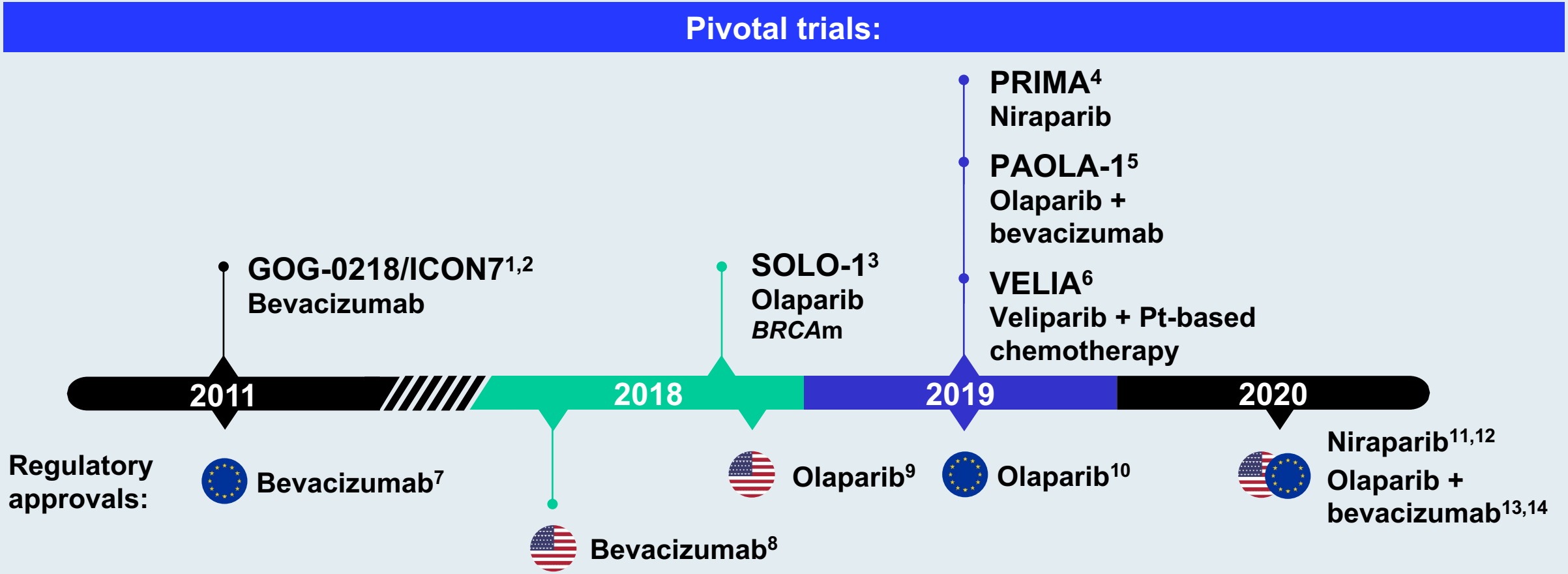
MODULE 4: Appendix of Key Publications

RTP
RESEARCH
TO PRACTICE

Optimal Biomarker Evaluation and Front-Line Management

Pivotal Trials and Regulatory Milestones in First-Line Maintenance Therapy for Advanced Ovarian Cancer



Dates shown indicate the year of the publication of the pivotal studies and regulatory approvals for these compounds.

*BRCA*m, breast cancer gene mutant; GOG, Gynecologic Oncology Group; Pt, platinum.

1. Burger RA et al. *N Engl J Med*. 2011;365(26):2473-2483. 2. Perren TJ et al. *N Engl J Med*. 2011;365(26):2484-2496. 3. Moore K et al. *N Engl J Med*. 2018;379(26):2495-2505. 4. González-Martín A et al. *N Engl J Med*. 2019;381(25):2391-2402. . Ray-Coquard I et al. *N Engl J Med*. 2019;381(25):2416-2428. 6. Coleman RL et al. *N Engl J Med*. 2019;381(25):2403-2415. 7. European Medicines Agency. Published September 22, 2011. Accessed June 7, 2021. 8. F. Hoffmann-La Roche Ltd. Published June 13, 2018. Accessed June 7, 2021. 9. US Food and Drug Administration. Published December 26, 2018. Accessed June 7, 2021. 10. European Medicines Agency. Published April 26, 2019. Accessed June 7, 2021. 11. GlaxoSmithKline. Published April 29, 2020. Accessed June 7, 2021. 12. GlaxoSmithKline. Published October 29, 2020. Accessed June 7, 2021. 13. US Food and Drug Administration. Published May 11, 2020. Accessed June 7, 2021. 14. European Medicines Agency. Published September 17, 2020. Accessed June 7, 2021.

Courtesy of Kathleen Moore, MD

RTP RESEARCH TO PRACTICE

Phase III First-Line PARP Inhibitor Maintenance Trials

Study design	SOLO-1[1] (N = 391)	PAOLA-1[2] (N = 612)	PRIMA[3] (N = 620)	VELIA[4] (N = 1,140)
Treatment arms vs placebo	**Olaparib (n=260)**	**Bevacizumab ± olaparib**	**Niraparib**	**Veliparib**
Patient population	*BRCA* mutation	All comers	All comers	All comers
Treatment duration	24 mo	15 mo for bev 24 mo for olaparib	36 mo or until PD	24 mo
Median PFS	56 mo vs 14 mo HR: 0.33	22.1 mo vs 16.6 mo HR: 0.59	22.1 mo vs 10.9 mo HR 0.40	23.5 mo vs 17.3 mo HR: 0.68

bev = bevacizumab; PD = disease progression

[1] Banerjee et al. *Lancet Oncol* 2021;22(12):1721-31; [2] Ray-Coquard et al. SGO 2020;Abstract 33; [3] González-Martín A et al. ASCO 2021;Abstract 5518; [4] Aghajanian C et al. *Gyn Oncol* 2021;162(2):375-81.

Phase 2 OVARIO Study of Niraparib + Bevacizumab Therapy in Advanced Ovarian Cancer Following Frontline Platinum-Based Chemotherapy with Bevacizumab

Melissa M. Hardesty,[1] Thomas Krivak,[2] Gail S. Wright,[3] Erika Hamilton,[4] Evelyn L. Fleming,[5] Jimmy Belotte,[6] Erika Keeton,[6] Ping Wang,[6] Aine Clements,[7] Heidi J. Gray,[8] Gottfried E. Konecny,[9] Richard G. Moore,[10] Debra L. Richardson[11]

[1]Alaska Women's Cancer Care, Anchorage, AK, USA; [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, The Western Pennsylvania Hospital, Pittsburgh, PA, USA; [3]Florida Cancer Specialists and Research Institute, New Port Richey, FL, USA; [4]Sarah Cannon Research Institute; Tennessee Oncology, Nashville, TN, USA; [5]Division of Gynecologic Oncology, Norris Cotton Cancer Center, Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [6]GlaxoSmithKline, Waltham, MA, USA; [7]Department of Gynecologic Oncology, Riverside Methodist Hospital, Columbus, OH, USA; [8]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Washington, Seattle, WA, USA; [9]University of California Los Angeles, Los Angeles, CA, USA; [10]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [11]Division of Gynecologic Oncology, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA

ANNUAL MEETING ON WOMENS' CANCER
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 19 - 21, 2022

Society of Gynecologic Oncology

SGO 2022;Abstract 40.

RTP RESEARCH TO PRACTICE

Patients with newly diagnosed high-grade serous or endometrioid stage IIIB to IV epithelial ovarian, fallopian tube, or peritoneal cancer who achieved a CR, PR, or NED result after front-line platinum-based chemotherapy + bevacizumab

All patients underwent tissue testing for HRd at enrollment

Niraparib (200 or 300 mg QD) + bevacizumab (15 mg/kg Q3W)

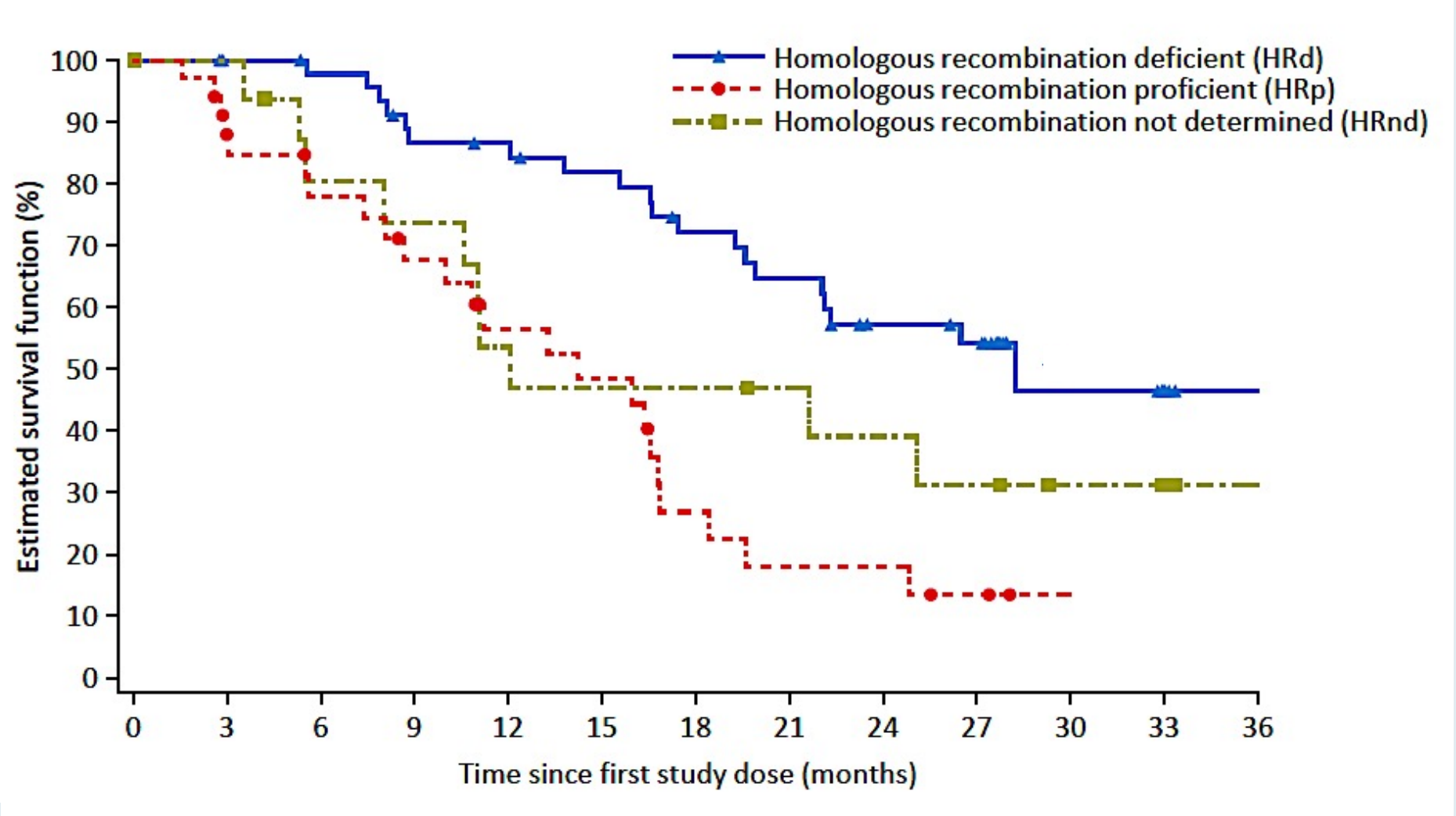
Starting niraparib dose, n (%)	N=105
200 mg (<77 kg and/or platelet count <150,000/µL)	82 (78)
300 mg (all others)	23 (22)

Endpoint assessment

Primary endpoint	• PFS rate at 18 months (PFS18)
Secondary endpoints	• PFS • Overall survival • RECIST or CA-125 PFS • Time to first subsequent therapy • Time to second subsequent therapy • Safety and tolerability • Patient-reported outcome
Exploratory endpoints	• PFS rate at 6 months (PFS6) and 12 months (PFS12)
Statistical analysis plan	• Efficacy: PFS18 and PFS24 will be estimated by frequency analysis, with corresponding 95% exact CI will be reported • The time to event endpoints (PFS, TFST, TSST) will be analyzed using Kaplan-Meier methodology • Progression will be assessed by RECIST v1.1 per investigator

Hardesty et al. SGO 2022;Abstract 40.

OVARIO: PFS by Homologous Recombination Deficiency Status



Overall (n = 105)	
18-mo PFS rate	62
24-mo PFS rate	53

HRd (n = 49)	
18-mo PFS rate	76
24-mo PFS rate	63

HRp (n = 38)	
18-mo PFS rate	47
24-mo PFS rate	42

HRnd (n = 18)	
18-mo PFS rate	56
24-mo PFS rate	50

Hardesty et al. SGO 2022;Abstract 40.

OVARIO: Treatment-Related Adverse Events (TRAEs)

Parameter, n (%)	N=105		
	Related to nira or bev	Related to nira	Related to bev
Any TRAE	105 (100)	104 (99)	96 (91)
Any Grade ≥3 TRAE	84 (80)	81 (77)	54 (51)
Any serious TRAE	21 (20)	19 (18)	7 (7)
TRAE leading to treatment discontinuation	42 (40)	32 (30)	23 (22)
TRAE leading to dose reduction	78 (74)	77 (73)	27 (26)
TRAE leading to treatment interruption	93 (88)	90 (86)	58 (55)

TRAEs in ≥20% of patients (N=105) Related to niraparib or bevacizumab		
Preferred term, n (%)	Any Grade	Grade ≥3
Thrombocytopenia[a]	74 (70)	41 (39)
Fatigue	60 (57)	9 (9)
Anemia[b]	55 (52)	36 (34)
Nausea	55 (52)	1 (1)
Hypertension[c]	53 (50)	28 (27)
Proteinuria	41 (39)	5 (5)
Headache	32 (30)	6 (6)
Neutropenia[d]	28 (27)	13 (12)
Leukopenia[e]	24 (23)	0

Hardesty et al. SGO 2022;Abstract 40.

Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial

Ning Li*, Jianqing Zhu, Rutie Yin, Jing Wang, Lingya Pan, Beihua Kong, Hong Zheng, Jihong Liu, Xiaohua Wu, Li Wang, Yi Huang, Ke Wang, Dongling Zou, Hongqin Zhao, Chunyan Wang, Weiguo Lu, An Lin, Ge Lou, Guiling Li, Pengpeng Qu, Hongying Yang, Xiaoa Zhen, Wenzhao Hang, Jianmei Hou, Lingying Wu*

* National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

SGO 2022;Abstract LBA5.

PRIME: Study Design

PRIME is a randomized, double-blind, placebo-controlled phase III trial (NCT03709316).

Schema

Eligible Patients

- Age ≥18 years
- FIGO stage III/IV ovarian cancer
- High-grade serous or endometroid tumor[a]
- Receipt of primary or interval cytoreductive surgery, irrespective of postoperative residual disease status
- CR/PR to 1L Pt-based chemotherapy

Stratified randomization

- Status of g*BRCA* mutations (g*BRCA*mut/non-g*BRCA*mut)
- Tumor HRD status[b] (positive/negative)
- Receipt of neoadjuvant chemotherapy (Y/N)
- Response to 1L Pt-based chemotherapy (CR/PR)

2:1 Randomization

- **Niraparib***
- **Placebo***

36 months or until disease progression or unacceptable toxicity

*Individualised starting dose (ISD) was adopted in **ALL** patients: *starting dose of 200 mg administered orally, once daily, but 300 mg for patients with body weight ≥77 kg AND platelet count ≥150,000/μL*

Primary Endpoint

- **PFS by BICR in the ITT population**

Secondary Endpoints

- OS and TFST in the ITT population
- PFS and OS in the HRD subgroup[c]
- Safety

Li et al. SGO 2022;Abstract LBA5.

PRIME: Demographics and Baseline Characteristics

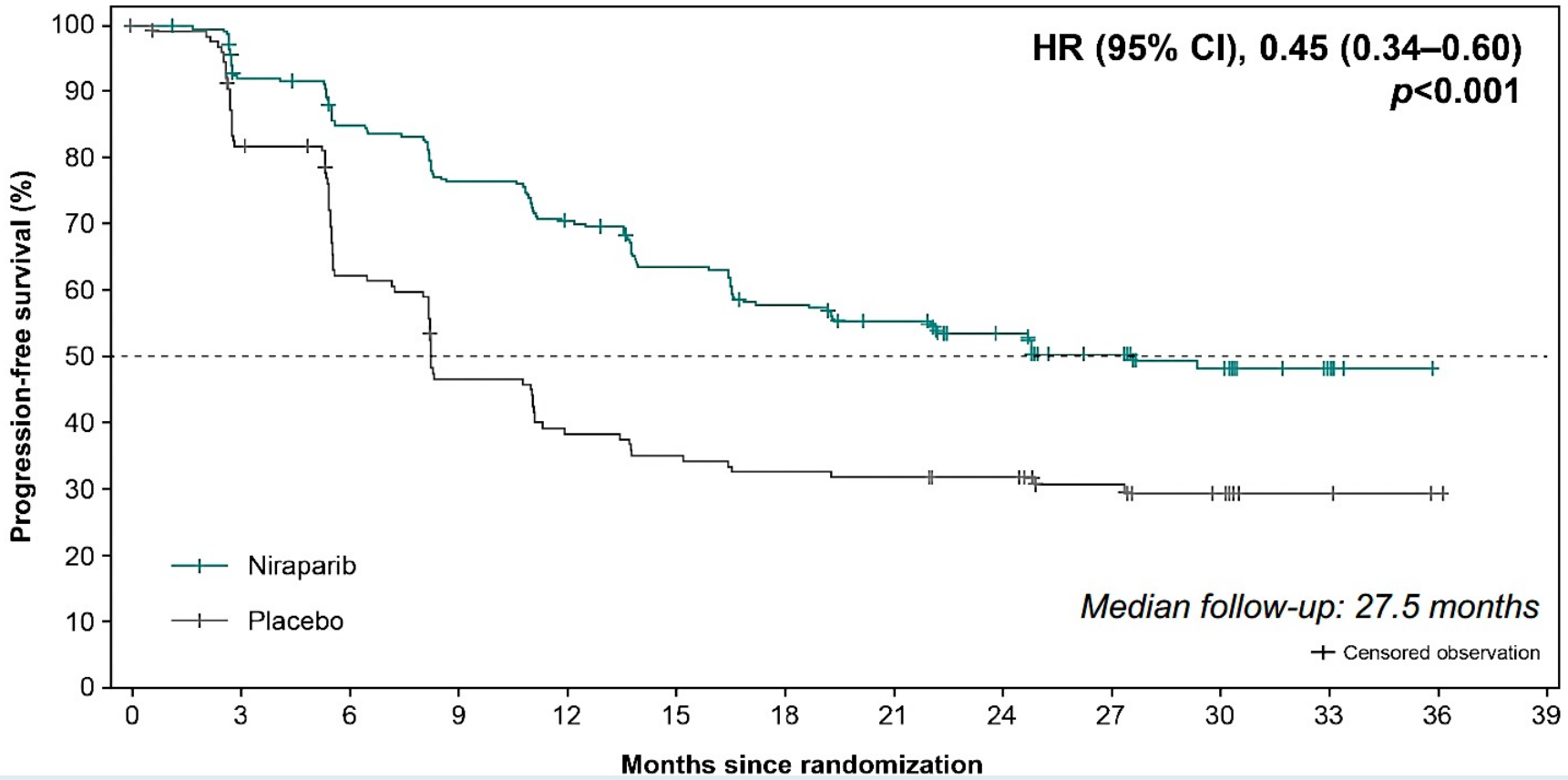
Characteristic	Niraparib (N=255)	Placebo (N=129)
Median age (range), years	53.0 (32–77)	54.0 (33–77)
Median weight (range), kg	59.0 (39.5–100.0)	57.0 (37.0–97.0)
ECOG performance status, n (%)		
0	98 (38.4)	52 (40.3)
1	157 (61.6)	77 (59.7)
FIGO stage, n (%)		
III	182 (71.4)	94 (72.9)
IV	73 (28.6)	35 (27.1)
Primary tumor location, n (%)		
Ovary	229 (89.8)	117 (90.7)
Fallopian tube	19 (7.5)	9 (7.0)
Peritoneum	7 (2.7)	3 (2.3)
Histologic subtype, n (%)		
Serous ovarian cancer	253 (99.2)	128 (99.2)
Endometrioid carcinoma	2 (0.8)	0
Other	0	1 (0.8)

Characteristic	Niraparib (N=255)	Placebo (N=129)
Neoadjuvant chemotherapy, n (%)		
Yes	121 (47.5)	59 (45.7)
No	134 (52.5)	70 (54.3)
Response to Pt-based CT, n (%)		
CR	212 (83.1)	103 (79.8)
PR	43 (16.9)	26 (20.2)
g*BRCA* mutation status, n (%)		
g*BRCA*mut	85 (33.3)	40 (31.0)
Non-g*BRCA*mut	170 (66.7)	89 (69.0)
Homologous recombination[a], n (%)		
Deficient	170 (66.7)	87 (67.4)
Proficient	85 (33.3)	42 (32.6)
Postoperative residual disease status, n (%)		
Optimal (R0/R1)	193 (75.7)	105 (81.4)
Suboptimal (R2) or missing	52 (24.3)	24 (18.6)

- The niraparib and placebo groups were well-balanced.

Li et al. SGO 2022;Abstract LBA5.

PRIME: PFS (by Blinded Independent Central Review) in the ITT Population



16.5 months longer median PFS with niraparib versus placebo

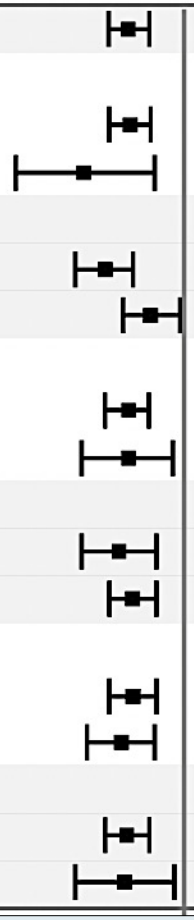
	Niraparib (N=255)	Placebo (N=129)
PFS (54.4% data maturity)		
Events, n (%)	123 (48.2)	86 (66.7)
mPFS (95% CI), months	24.8 (19.2–NE)	8.3 (7.3–11.1)
Patients without PD or death (%)		
24 months	52.6	30.4

Li et al. SGO 2022;Abstract LBA5.

RTP RESEARCH TO PRACTICE

PRIME: PFS Benefit in Prespecified Subgroups

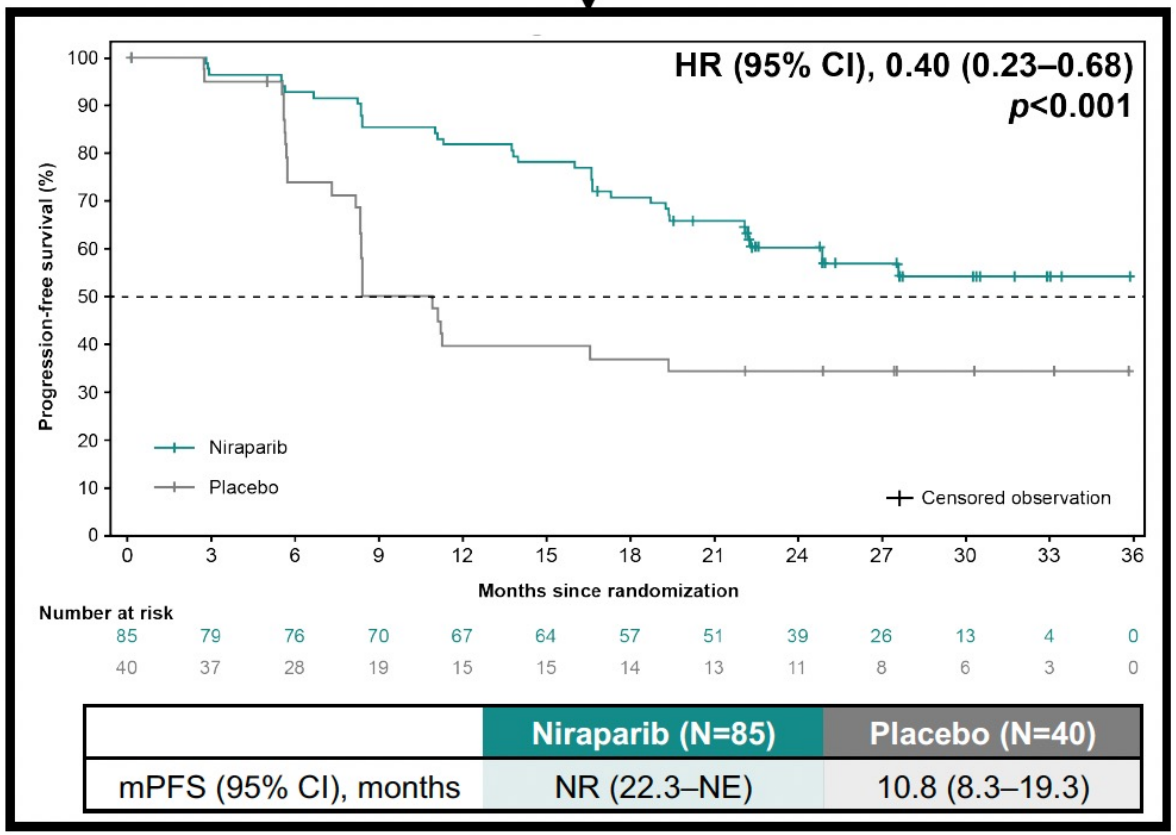
Subgroup	Events/patients (%)		Hazard ratio for PFS (95% CI)
	Niraparib	Placebo	
Overall	123/255 (48.2)	86/129 (66.7)	0.45 (0.34–0.60)
Age			
<65 years	108/229 (47.2)	73/114 (64.0)	0.47 (0.34–0.63)
≥65 years	15/26 (57.7)	13/15 (86.7)	0.24 (0.09–0.66)
Neoadjuvant chemotherapy			
Yes	62/121 (51.2)	46/59 (78.0)	0.32 (0.21–0.48)
No	61/134 (45.5)	40/70 (57.1)	0.63 (0.42–0.94)
Response to Pt-based chemotherapy			
Complete response	98/212 (46.2)	66/103 (64.1)	0.45 (0.32–0.61)
Partial response	25/43 (58.1)	20/26 (76.9)	0.45 (0.23–0.86)
***gBRCA* mutation status**			
*gBRCA*mut	35/85 (41.2)	25/40 (62.5)	0.40 (0.23–0.68)
Non-g*BRCA*mut	88/170 (51.8)	61/89 (68.5)	0.48 (0.34–0.67)
Homologous recombination			
Deficient	75/170 (44.1)	57/87 (65.5)	0.48 (0.34–0.68)
Proficient	48/85 (56.5)	29/42 (69.0)	0.41 (0.25–0.65)
Postoperative residual disease status			
Optimal	94/193 (48.7)	71/105 (67.6)	0.44 (0.32–0.61)
Suboptimal or missing	29/62 (46.8)	15/24 (62.5)	0.43 (0.21–0.87)



Li et al. SGO 2022;Abstract LBA5.

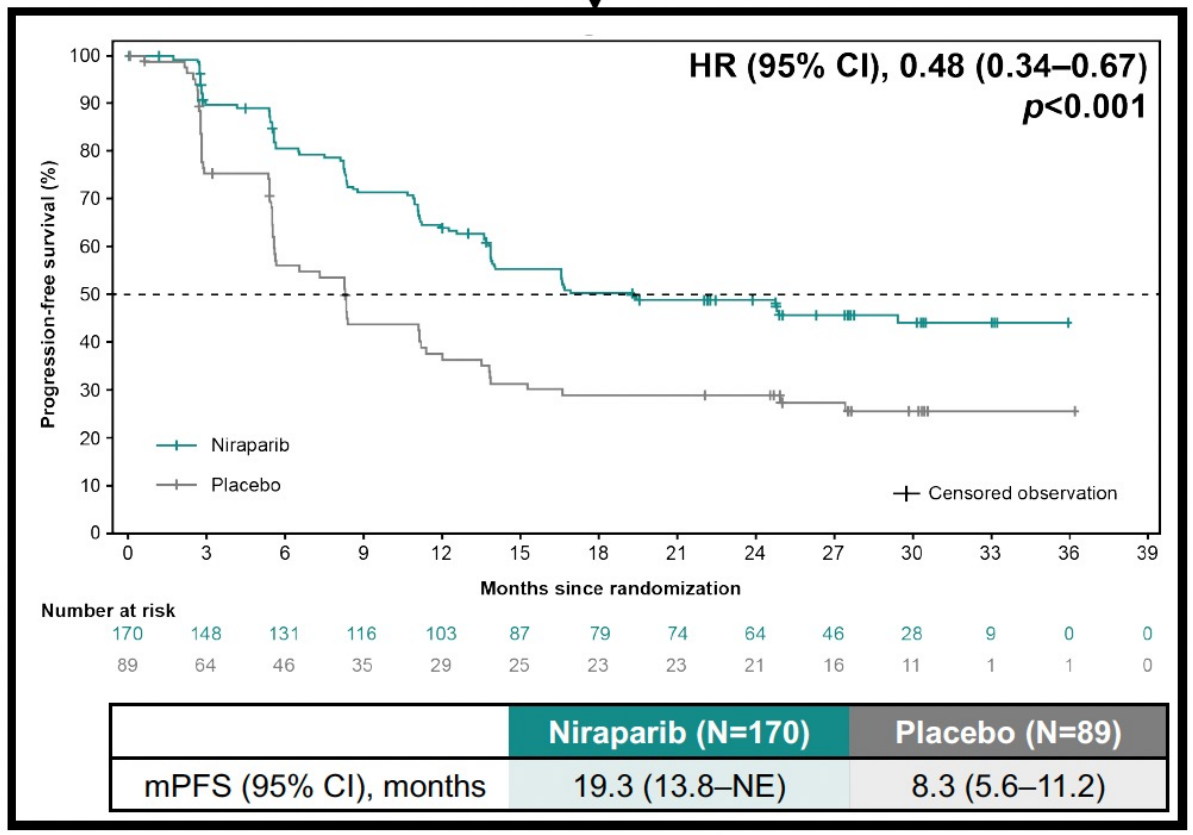
PRIME: PFS Benefit by Germline BRCA Mutation Status

g*BRCA*mut



	Niraparib (N=85)	Placebo (N=40)
mPFS (95% CI), months	NR (22.3–NE)	10.8 (8.3–19.3)

Non-g*BRCA*mut



	Niraparib (N=170)	Placebo (N=89)
mPFS (95% CI), months	19.3 (13.8–NE)	8.3 (5.6–11.2)

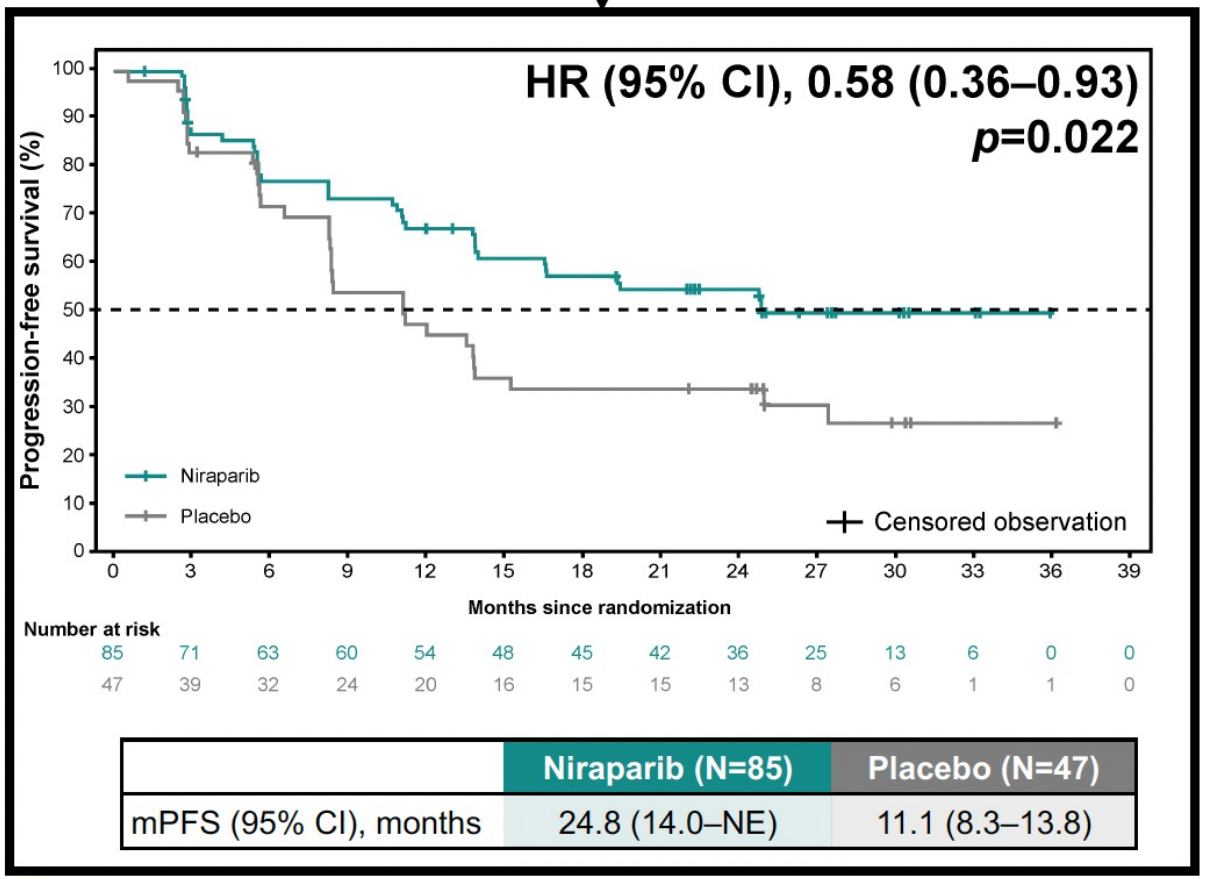
- Median PFS has not been yet reached for the g*BRCA*mut population.
- The benefit of niraparib in the non-g*BRCA*mut population is confirmed.

Li et al. SGO 2022;Abstract LBA5.

RTP RESEARCH TO PRACTICE

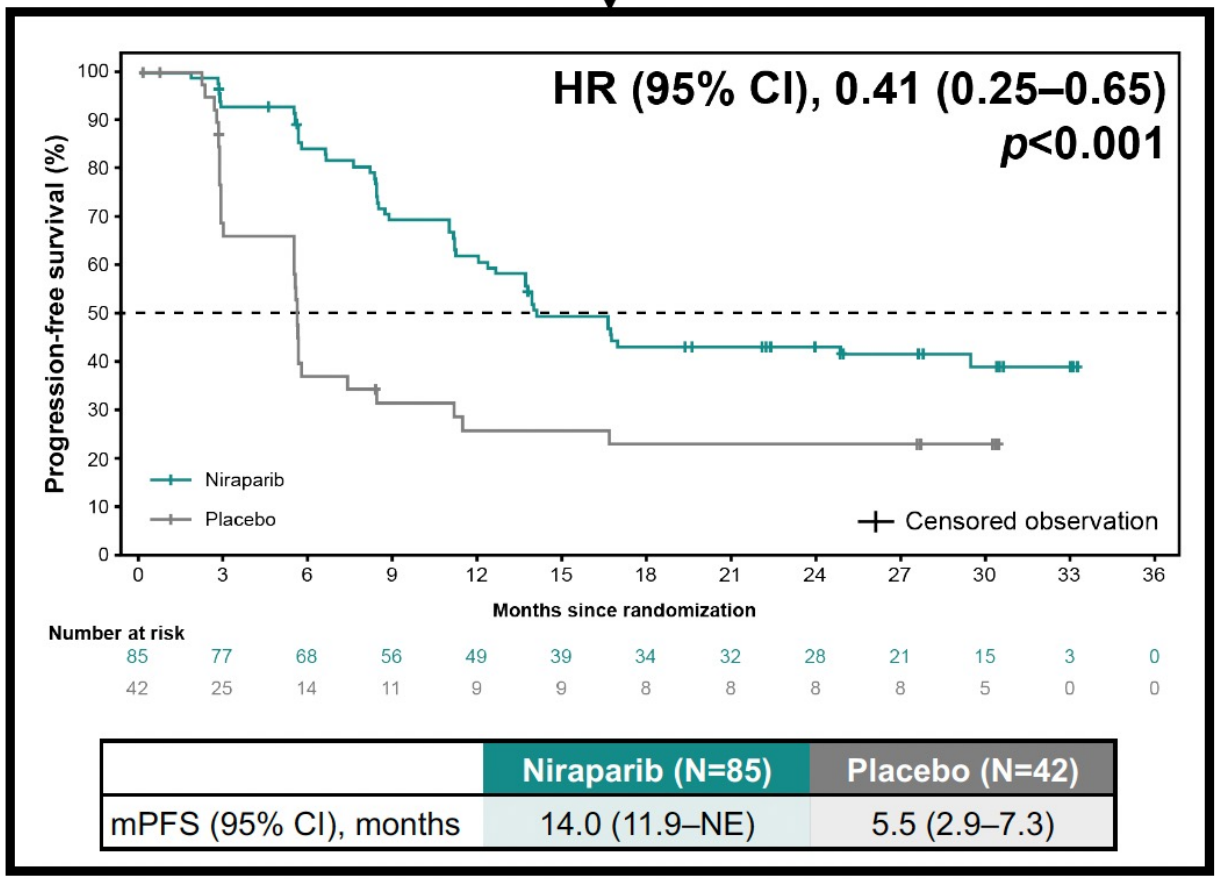
PRIME: PFS Benefit in Non-gBRCAmut Subgroups

Non-g*BRCA*mut/HRd



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

Non-g*BRCA*mut/HRp



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

Li et al. SGO 2022;Abstract LBA5.

RTP RESEARCH TO PRACTICE

PRIME and PRIMA Trials: Safety Overview

TEAEs, n (%)	PRIME		PRIMA[1]	
	Niraparib (N=255)	Placebo (N=129)	Niraparib (N=484)	Placebo (N=244)
Any TEAEs	253 (99.2)	121 (93.8)	478 (98.8)	224 (91.8)
Treatment-related	249 (97.6)	111 (86.0)	466 (96.3)	168 (68.9)
Grade≥3 TEAEs	139 (54.5)	23 (17.8)	341 (70.5)	46 (18.9)
Treatment-related	125 (49.0)	9 (7.0)	316 (65.3)	16 (6.6)
Serious TEAEs	48 (18.8)	11 (8.5)	156 (32.2)	32 (13.1)
Treatment-related	38 (14.9)	5 (3.9)	118 (24.4)	6 (2.5)
TEAEs leading to treatment interruption	160 (62.7)	25 (19.4)	385 (79.5)	44 (18.0)
TEAEs leading to dose reduction[b]	103 (40.4)	8 (6.2)	343 (70.9)	20 (8.2)
TEAEs leading to discontinuation	17 (6.7)	7 (5.4)	58 (12.0)	6 (2.5)
TEAEs leading to death	1 (0.4)	0	2 (0.4)	1 (0.4)

Li et al. SGO 2022;Abstract LBA5.

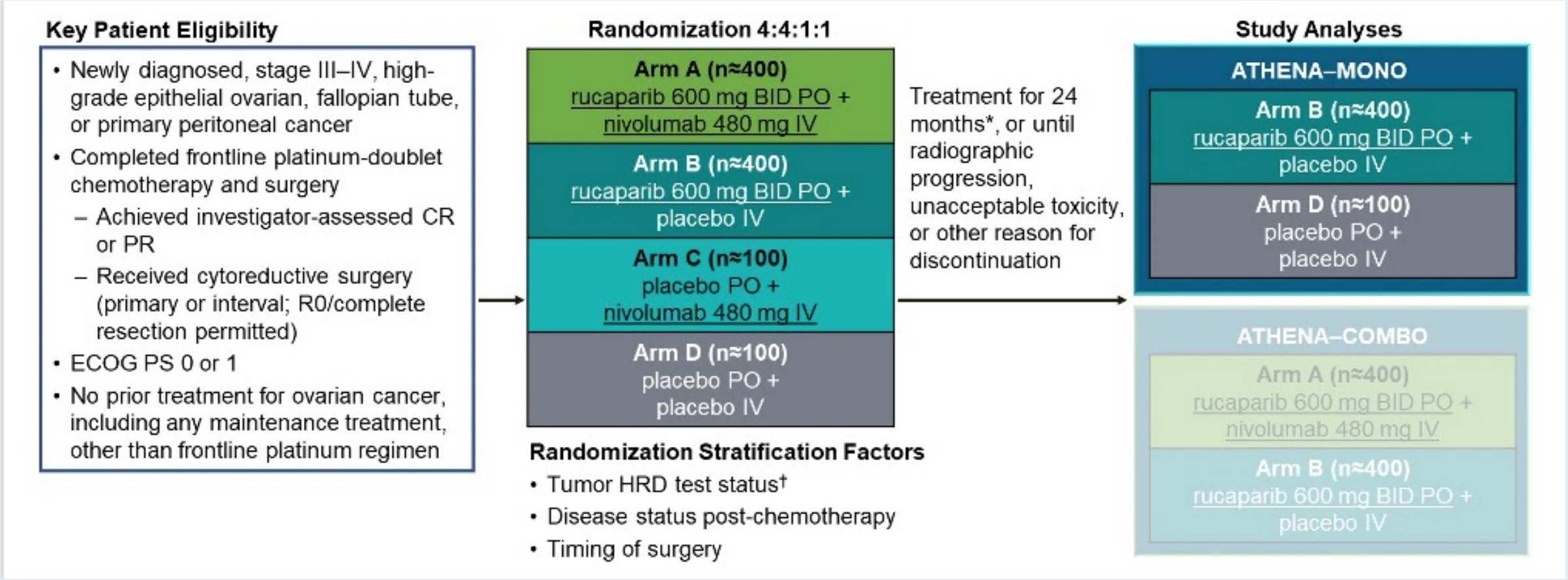
original reports

A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45)

Bradley J. Monk, MD[1]; Christine Parkinson, MD[2]; Myong Cheol Lim, MD, PhD[3]; David M. O'Malley, MD[4]; Ana Oaknin, MD, PhD[5]; Michelle K. Wilson, MD[6]; Robert L. Coleman, MD[7]; Domenica Lorusso, MD, PhD[8]; Paul Bessette, MD[9]; Sharad Ghamande, MD[10]; Athina Christopoulou, MD, PhD[11]; Diane Provencher, MD[12]; Emily Prendergast, MD[13]; Fuat Demirkiran, MD[14]; Olga Mikheeva, MD[15]; Oladapo Yeku, MD, PhD[16]; Anita Chudecka-Glaz, MD, PhD[17]; Michael Schenker, MD, PhD[18]; Ramey D. Littell, MD[19]; Tamar Safra, MD[20]; Hung-Hsueh Chou, MD[21,22]; Mark A. Morgan, MD[23]; Vít Drochýtek, MD[24]; Joyce N. Barlin, MD[25]; Toon Van Gorp, MD[26]; Fred Ueland, MD[27]; Gabriel Lindahl, MD[28,29]; Charles Anderson, MD[30]; Dearbhaile C. Collins, MBBCh, MA, PhD[31]; Kathleen Moore, MD[32]; Frederik Marme, MD, PhD[33]; Shannon N. Westin, MD, MPH[34]; Iain A. McNeish, MD, PhD[35]; Danny Shih, BA[36]; Kevin K. Lin, PhD[37]; Sandra Goble, MS[38]; Stephanie Hume, PhD[39]; Keiichi Fujiwara, MD, PhD[40]; and Rebecca S. Kristeleit, MD, PhD[41]

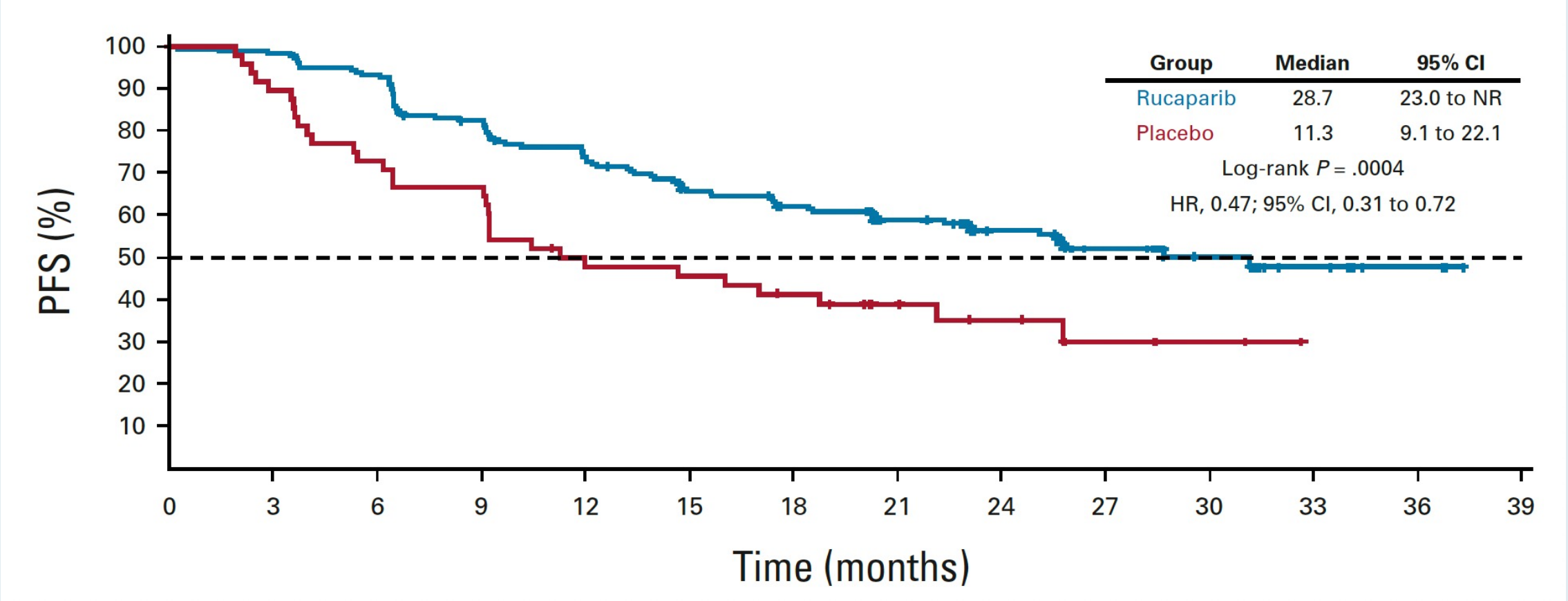
J Clin Oncol 2022;[Online ahead of print].

ATHENA-MONO Study Schema



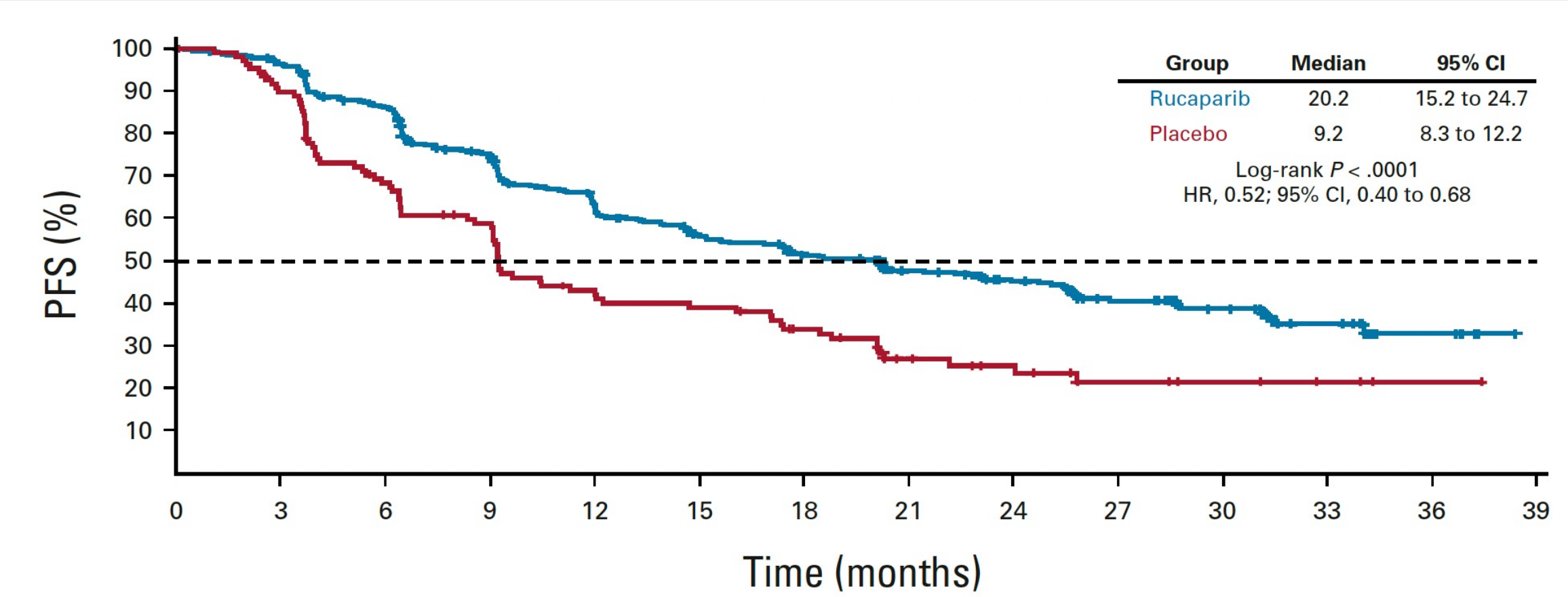
Monk BJ et al. ASCO 2022;Abstract LBA5500.

ATHENA-MONO: Investigator-Assessed PFS in the HRD Population (N = 234)



Monk BJ et al. *J Clin Oncol* 2022;[Online ahead of print].

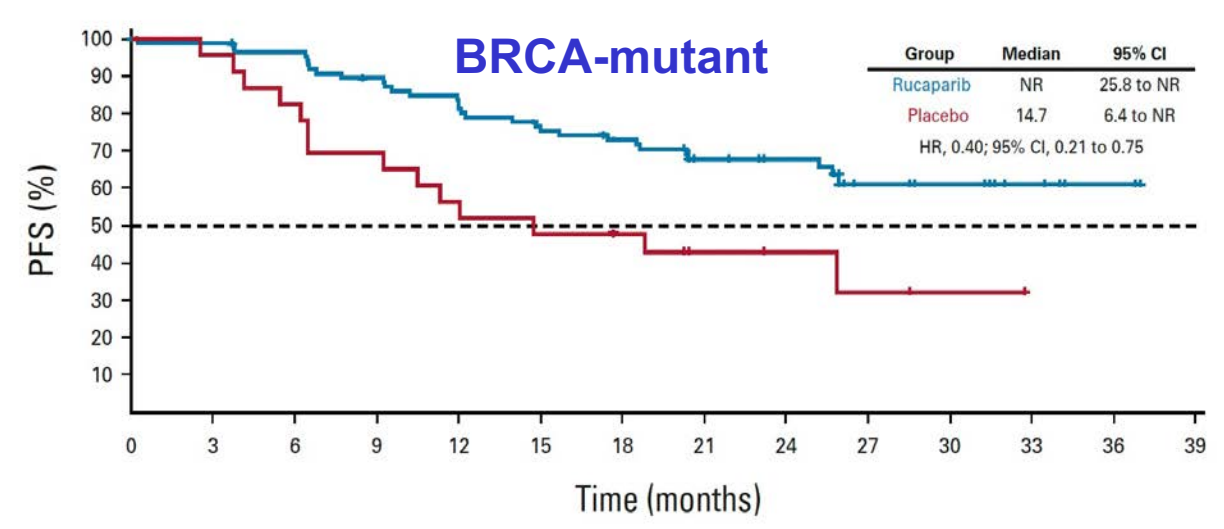
ATHENA-MONO: Investigator-Assessed PFS in the ITT Population (N = 538)

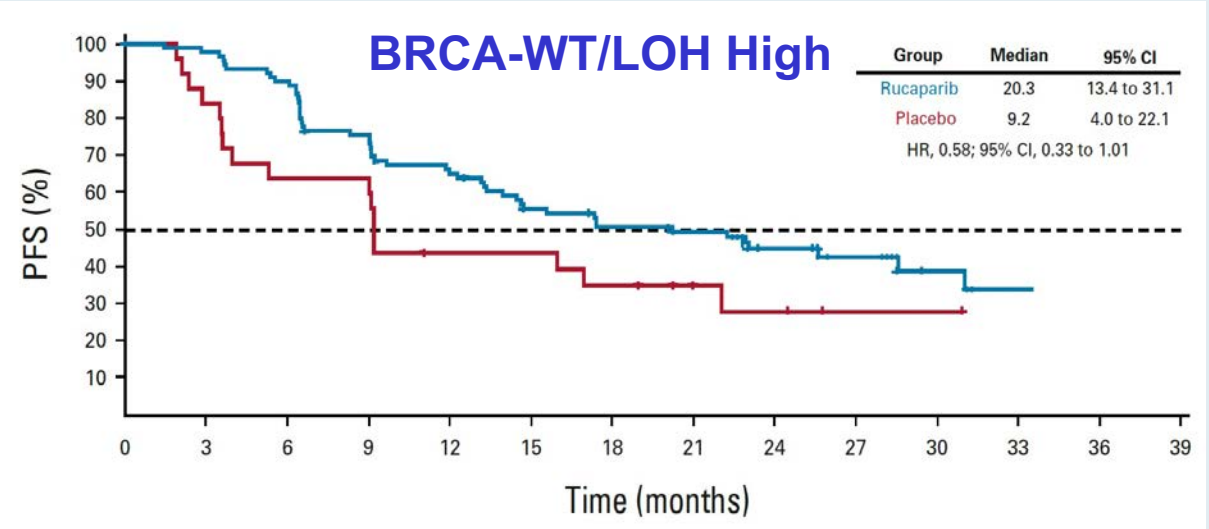


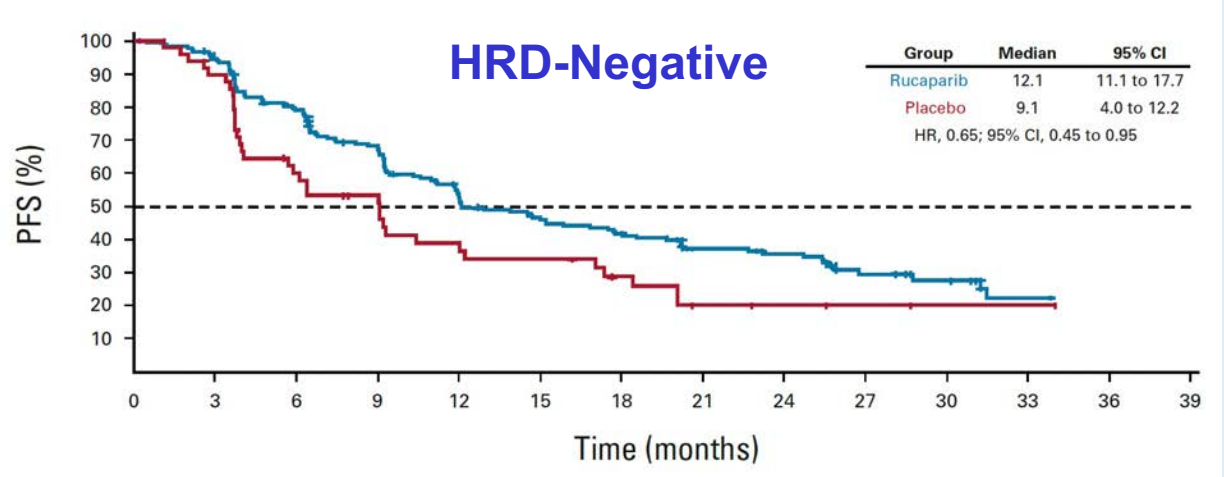
Monk BJ et al. *J Clin Oncol* 2022;[Online ahead of print].

RTP RESEARCH TO PRACTICE

ATHENA-MONO: Investigator-Assessed PFS







Monk BJ et al. *J Clin Oncol* 2022;[Online ahead of print].

ATHENA-MONO: Investigator-Confirmed ORR

	HRD Population		ITT Population	
Response	**Rucaparib (n = 17)**	**Placebo (n = 5)**	**Rucaparib (n = 41)**	**Placebo (n = 11)**
Confirmed ORR per RECIST				
No.	10	1	20	1
% (95% CI)	58.8 (32.9 to 81.6)	20.0 (0.5 to 71.6)	48.8 (32.9 to 64.9)	9.1 (0.2 to 41.3)
CR, No. (%)	0	0	1 (2.4)	0
PR, No. (%)	10 (58.8)	1 (20.0)	19 (46.3)	1 (9.1)
Stable disease, No. (%)	6 (35.3)	2 (40.0)	10 (24.4)	4 (36.4)
Progressive disease, No. (%)	1 (5.9)	2 (40.0)	10 (24.4)	6 (54.5)
Not evaluable, No. (%)	0	0	1 (2.4)	0

ORR = objective response rate

Monk BJ et al. *J Clin Oncol* 2022;[Online ahead of print].

ATHENA-MONO: Common Treatment-Emergent Adverse Events

	Rucaparib (n = 425)		Placebo (n = 110)	
TEAE	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
At least one TEAE, No. (%)	411 (96.7)	257 (60.5)	102 (92.7)	25 (22.7)
Nausea	239 (56.2)	8 (1.9)	33 (30.0)	0
Asthenia/fatigue	237 (55.8)	21 (4.9)	41 (37.3)	1 (0.9)
Anemia/decreased hemoglobin	198 (46.6)	122 (28.7)	10 (9.1)	0
Increased ALT/AST	181 (42.6)	45 (10.6)	9 (8.2)	1 (0.9)
Neutropenia/neutrophil count decreased	118 (27.8)	62 (14.6)	8 (7.3)	1 (0.9)
Abdominal pain	106 (24.9)	2 (0.5)	31 (28.2)	2 (1.8)
Diarrhea	102 (24.0)	6 (1.4)	23 (20.9)	1 (0.9)
Thrombocytopenia/platelet count decreased	101 (23.8)	30 (7.1)	1 (0.9)	0
Vomiting	100 (23.5)	6 (1.4)	13 (11.8)	0
Dysgeusia	90 (21.2)	1 (0.2)	6 (5.5)	0
Arthralgia	86 (20.2)	1 (0.2)	25 (22.7)	0
Headache	85 (20.0)	2 (0.5)	16 (14.5)	0

Monk BJ et al. *J Clin Oncol* 2022;[Online ahead of print].

FDA Advises Manufacturer Not to Submit First-Line Maintenance sNDA for Rucaparib Until OS Survival Data from the ATHENA-MONO Trial Are More Mature

June 17, 2022

"In consultation with the FDA, [the manufacturer of rucaparib] recently was advised not to file a supplemental new drug application based on data from a cohort of the Phase III ATHENA study until the study's overall survival data mature.

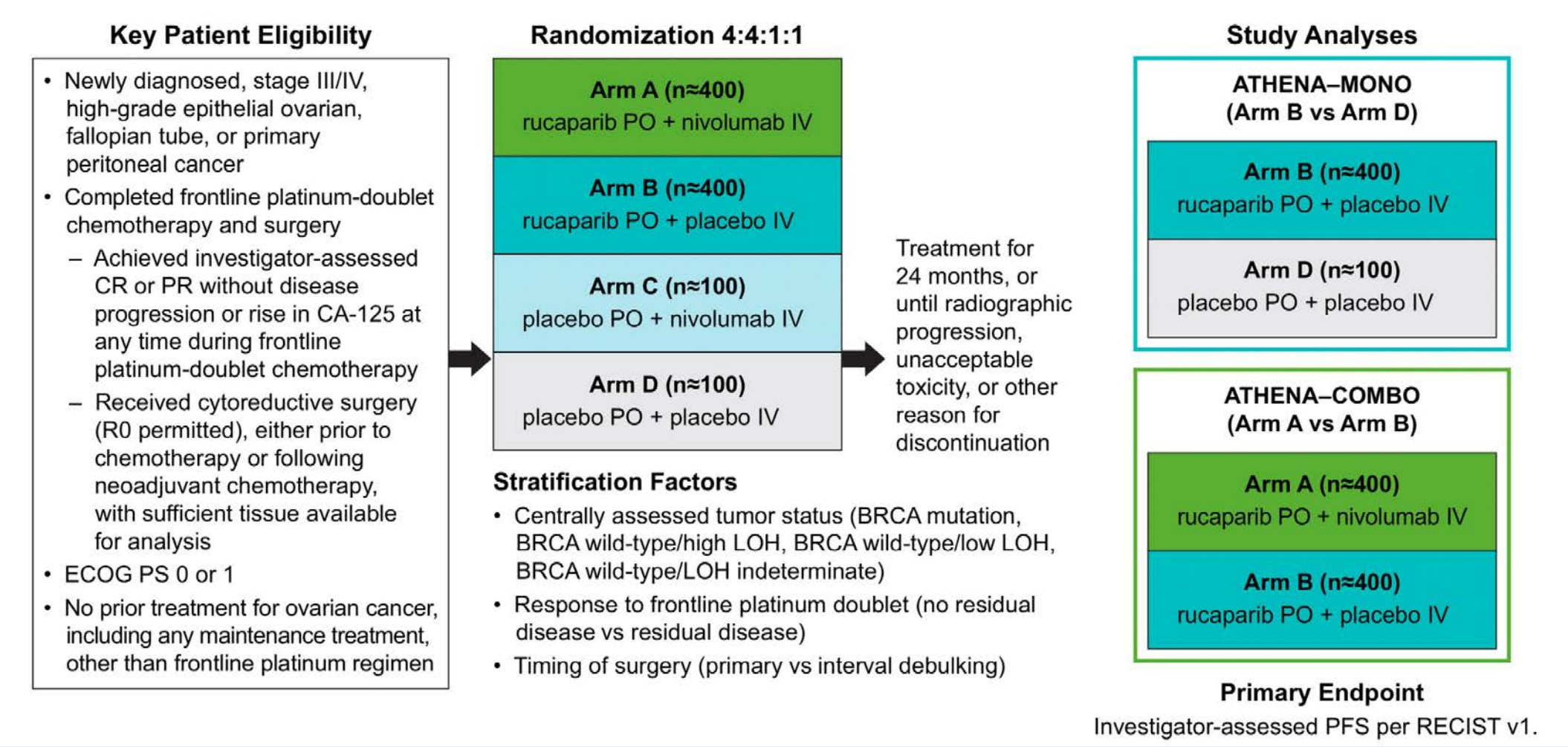
In the 8-K, [the manufacturer] said the FDA has accepted a request for a pre-NDA meeting and noted that the ATHENA-MONO portion of the Phase III study has met its primary endpoint of progression-free survival compared to placebo. OS is a secondary endpoint for ATHENA-MONO and the data are approximately 25% mature at present. [The manufacturer] said the FDA urged it to hold off filing for supplemental approval until the OS data reach 50% maturity, and indicated an advisory committee review would likely be necessary if the data were filed earlier than that point.

In a statement to *Scrip*, the firm said that although it cannot anticipate the outcome of the pre-NDA meeting, 'we are encouraged that the FDA is willing to have a dialogue.' [They] estimate the ATHENA-MONO OS data will reach 50% maturity in approximately two years."

https://scrip.pharmaintelligence.informa.com/SC146575/Clovis-Withdraws-Rubraca-Ovarian-Cancer-Indication-Due-To-Survival-Imbalance?vid=Pharma

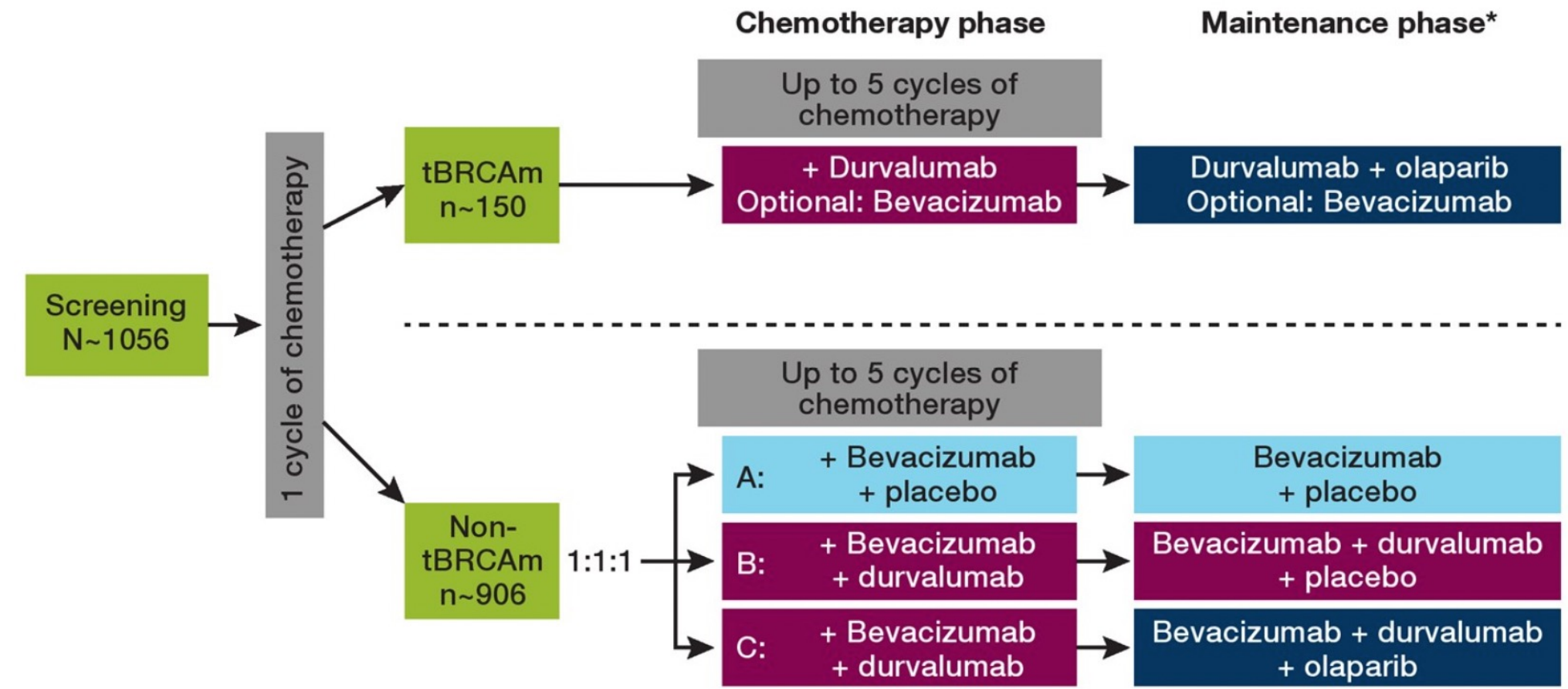
RTP RESEARCH TO PRACTICE

ATHENA-MONO and ATHENA-COMBO Study Design



Monk BJ et al. *Int J Gynecol Cancer* 2021;31(12):1589-94.

DUO-O Study Design in Newly Diagnosed Advanced Ovarian Cancer



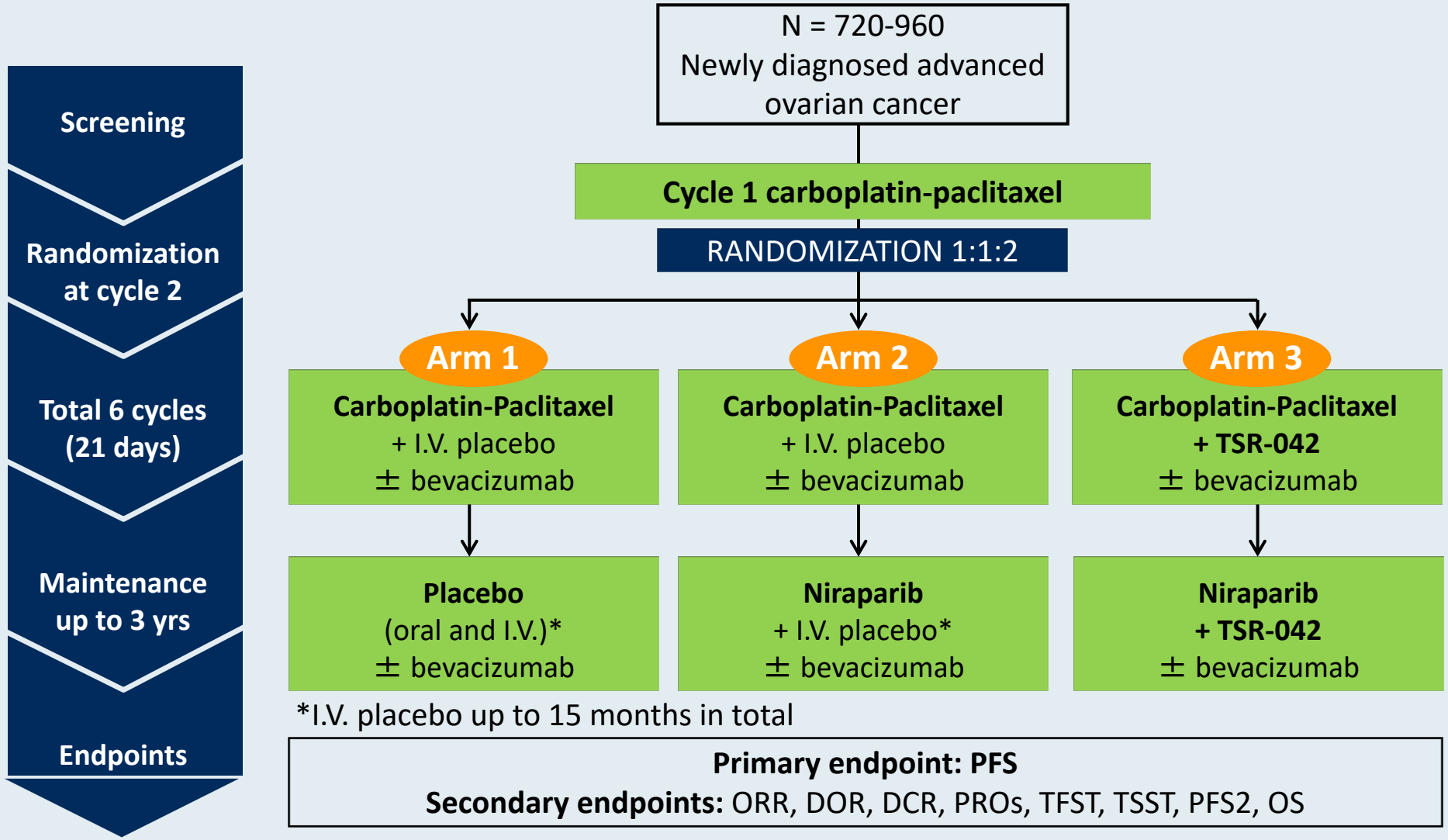
*Olaparib administered for a maximum of 24 months after chemotherapy. Durvalumab and bevacizumab administered for a maximum of 15 months

Estimated completion date: July 2023

Harter P et al. ASCO 2019;Abstract TPS5598; www.clinicaltrials.gov (NCT03737643) Accessed July 2022.

RTP RESEARCH TO PRACTICE

FIRST Phase III Trial of Dostarlimab (TSR-042) for Newly Diagnosed Ovarian Cancer



www.clinicaltrials.gov/ct2/show/NCT03602859

Courtesy of Ursula Matulonis, MD

Current Treatment Paradigm for Recurrent Disease

Ongoing Research with PARP Inhibitors for Newly Diagnosed and Relapsed Disease

Eligibility and Dosing in Pivotal Studies of PARP Inhibitors for Recurrent, Platinum-Sensitive Ovarian Cancer

	NOVA[1] (niraparib)	SOLO-2[2] (olaparib)	ARIEL3[3] (rucaparib)
BRCA status	With or without gBRCA mutation	gBRCA mutation (Study 19: +/- gBRCA mutation)	With or without gBRCA mutation
HRD testing	Yes	No	Yes
Tumor assessment schedule	Every 8 wk to C14 → every 12 wk	Every 12 wk until wk 72 → every 24 wk	Every 8 wk to C14 → every 12 wk
Dosing/formulation	300 mg qd	300 mg BID	600 mg BID
No. of prior lines of chemo	2 or more	2 or more	2 or more

[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.

Progression-Free Survival with PARP Inhibitors for Recurrent, Platinum-Sensitive Ovarian Cancer

	PARPi	Control	HR
NOVA[1-2] — 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[3-4] — olaparib			
gBRCA mutation	19.1 mo	5.5 mo	0.30
Overall survival	51.7 mo	38.8 mo	0.74
ARIEL3[5-6] — 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]Del Campo JM et al. *J Clin Oncol* 2019;37(32):2968-73. [3]Poveda A et al. *Lancet Oncol* 2021;22(5):620-31. [4]Pujade-Lauraine E et al. *Lancet* 2017;18(9):1274-84; [5] Coleman RL et al. *Lancet* 2017;390(10106):1949-61; [6]Ledermann JA et al. *Lancet Oncol* 2020;21(5):710-722.

Lancet Oncol 2022;23(4):465-78.

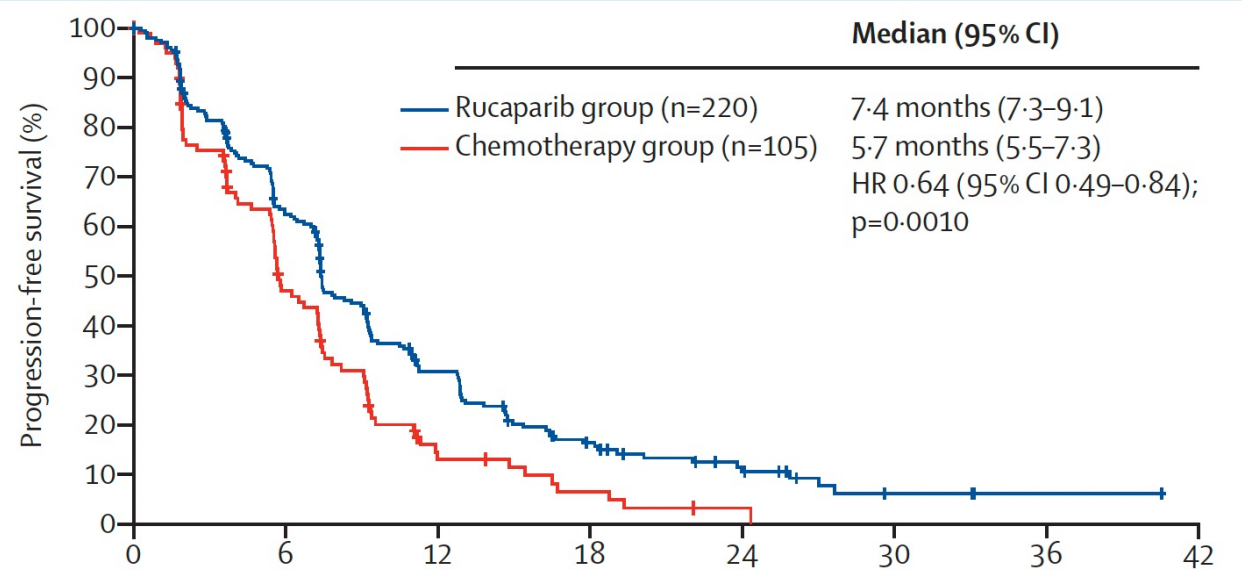
Articles

Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious *BRCA1* or *BRCA2* mutation (ARIEL4): an international, open-label, randomised, phase 3 trial

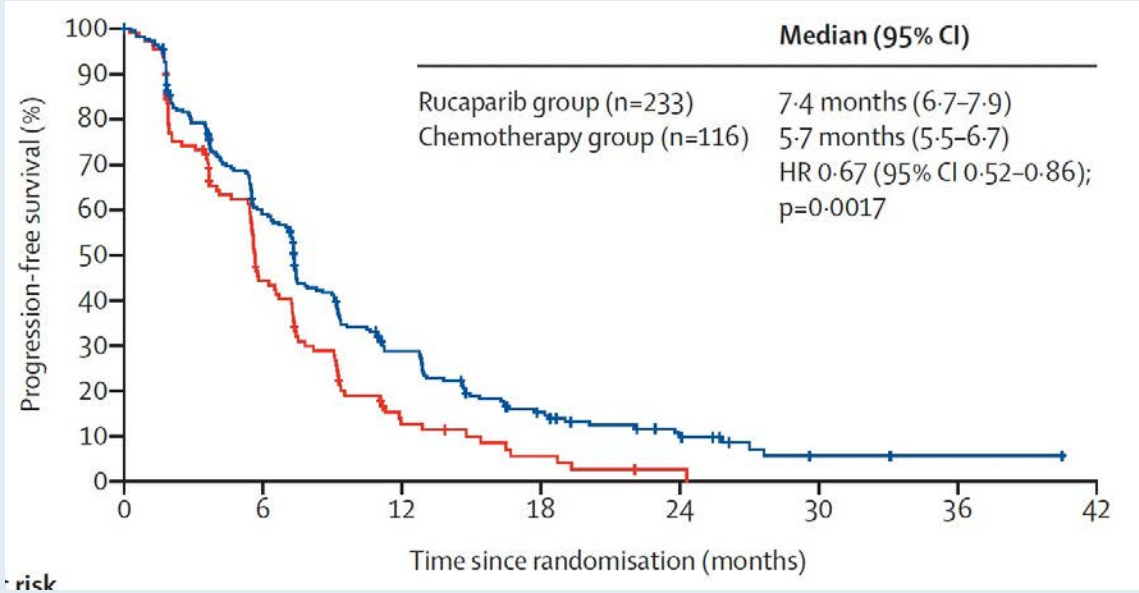
Rebecca Kristeleit, Alla Lisyanskaya, Alexander Fedenko, Mikhail Dvorkin, Andreia Cristina de Melo, Yaroslav Shparyk, Irina Rakhmatullina, Igor Bondarenko, Nicoletta Colombo, Valentyn Svintsitskiy, Luciano Biela, Marina Nechaeva, Domenica Lorusso, Giovanni Scambia, David Cibula, Róbert Póka, Ana Oaknin, Tamar Safra, Beata Mackowiak-Matejczyk, Ling Ma, Daleen Thomas, Kevin K Lin, Karen McLachlan, Sandra Goble, Amit M Oza

ARIEL4: Progression-Free Survival in the Efficacy and ITT Populations

Efficacy population (BRCA1 or BRCA2 mutations with reversion mutations)



Intent to treat population



Kristeleit et al. *Lancet Oncol* 2022;23(4):465-78.

RTP RESEARCH TO PRACTICE

ARIEL4: Overall Response Rate and Duration of Response

Endpoint	Efficacy population			ITT population		
	Rucaparib (n = 220)	Chemotherapy (n = 105)	*p*-value	Rucaparib (n = 233)	Chemotherapy (n = 116)	*p*-value
ORR	40%	32%	0.13	38%	30%	0.13
DoR, median	9.4 mo	7.2 mo	—	9.4 mo	7.2 mo	—

ORR = overall response rate; DoR = duration of response

Kristeleit et al. *Lancet Oncol* 2022;23(4):465-78.

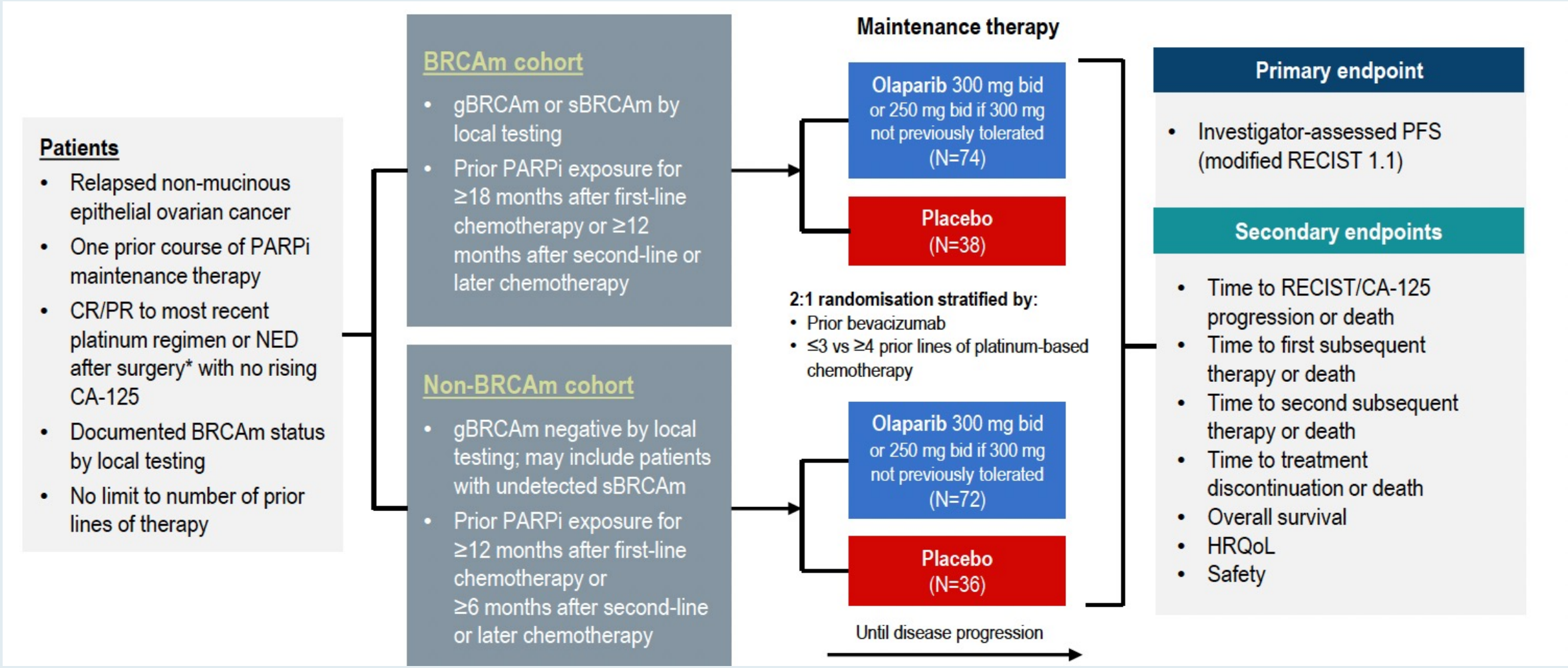
2021 ESMO congress

Abstract LBA33

Maintenance olaparib rechallenge in patients with ovarian carcinoma previously treated with a PARP inhibitor: Phase IIIb OReO/ENGOT Ov-38 trial

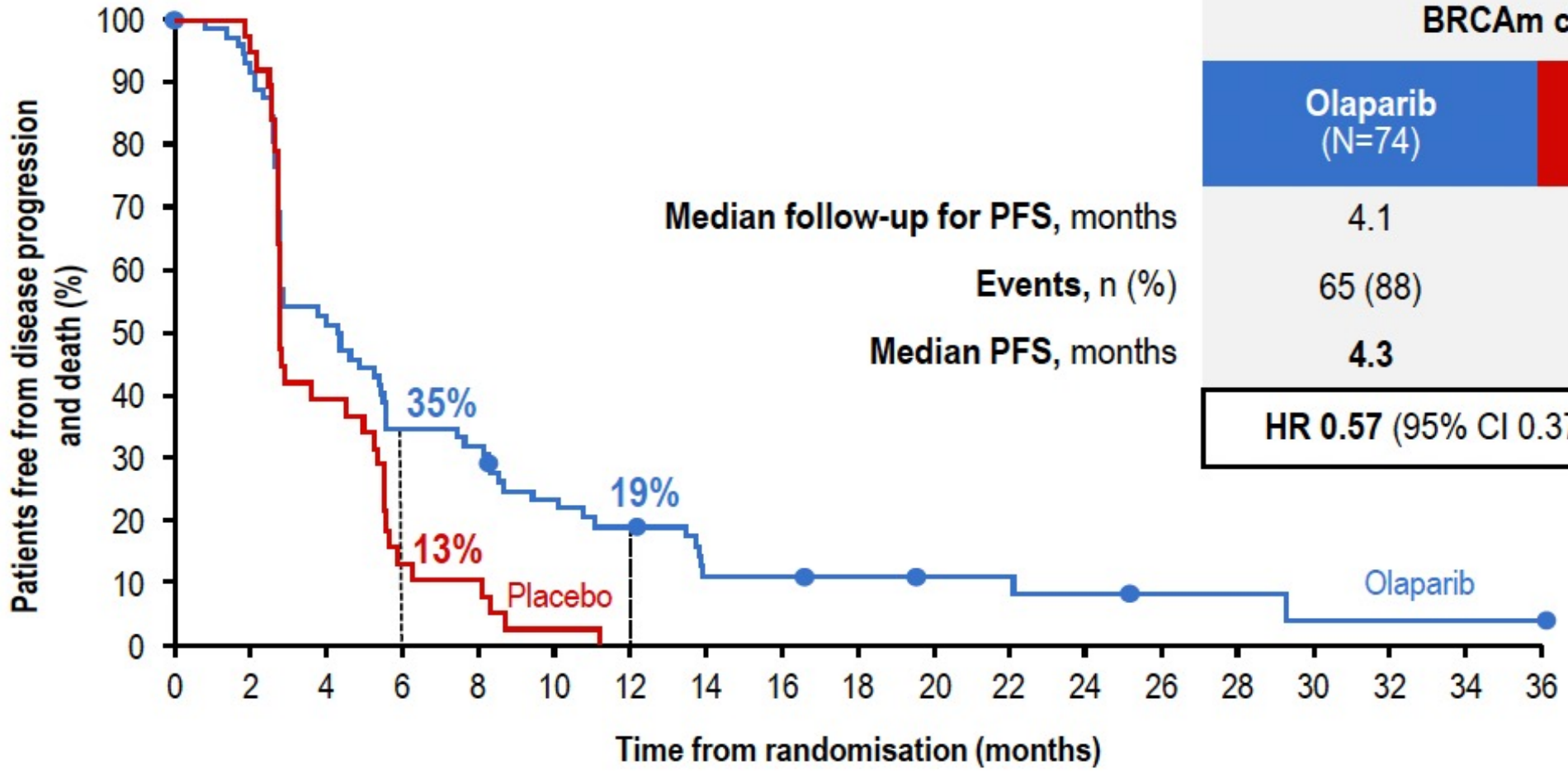
Eric Pujade-Lauraine,[1] Frédéric Selle,[2] Giovanni Scambia,[3] Bernard Asselain,[4] Frederik Marmé,[5] Kristina Lindemann,[6] Nicoletta Colombo,[7] Radoslaw Madry,[8] Rosalind Glasspool,[9] Coraline Dubot,[10] Ana Oaknin,[11] Claudio Zamagni,[12] Florian Heitz,[13] Laurence Gladieff,[14] Maria Jesús Rubio-Pérez,[15] Paolo Scollo,[16] Christopher Blakeley,[17] Bob Shaw,[17] Isabelle Ray-Coquard,[18] Andrés Redondo[19]

OReO Phase IIIB Study Schema



Pujade-Lauraine E et al. ESMO 2021;Abstract LBA33.

OReO: Progression-Free Survival in the BRCAm Cohort

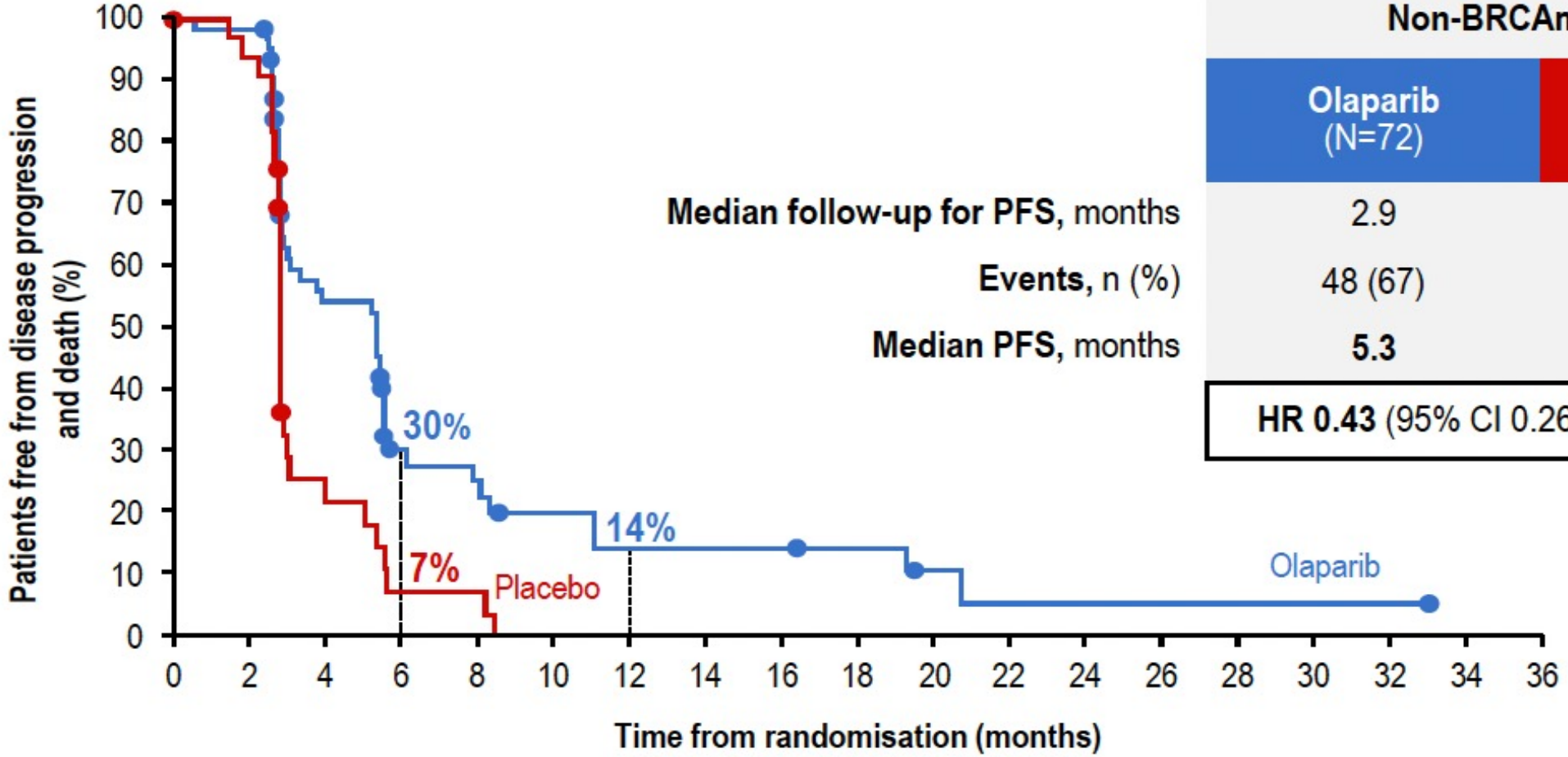


BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**

HR 0.57 (95% CI 0.37–0.87); *P*=0.022

Pujade-Lauraine E et al. ESMO 2021;Abstract LBA33.

OReO: Progression-Free Survival in the Non-BRCAm Cohort

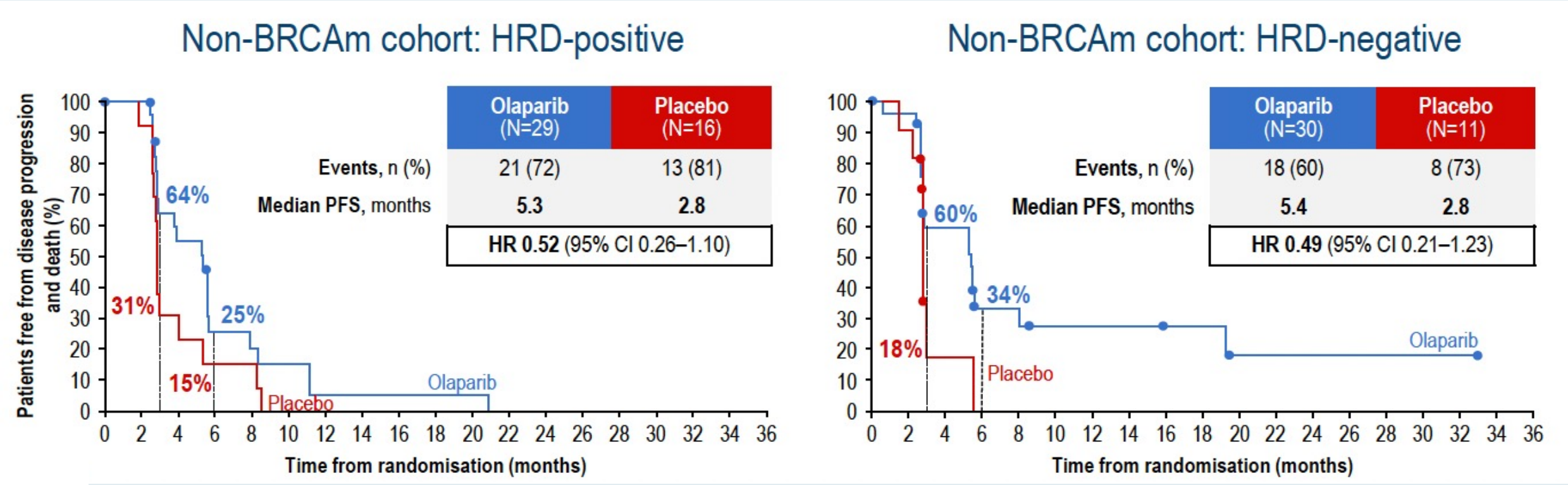


Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	**5.3**	**2.8**

HR 0.43 (95% CI 0.26–0.71); *P*=0.0023

Pujade-Lauraine E et al. ESMO 2021;Abstract LBA33.

OReO: Progression-Free Survival in the Non-BRCAm Cohort by Homologous Recombination Deficiency (HRD) Status



Pujade-Lauraine E et al. ESMO 2021;Abstract LBA33.

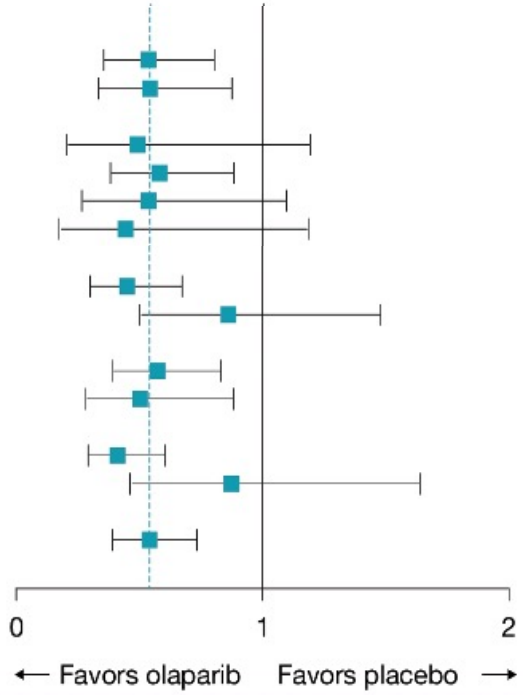
OReO/ENGOT Ov-38 Trial: Impact of Maintenance Olaparib Rechallenge According to Ovarian Cancer Patient Prognosis — An Exploratory Joint Analysis of the BRCA and Non-BRCA Cohorts

Selle F et al.

ASCO 2022;Abstract 5558.

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

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



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

Selle F et al. ASCO 2022;Abstract 5558.

RTP RESEARCH TO PRACTICE

Research

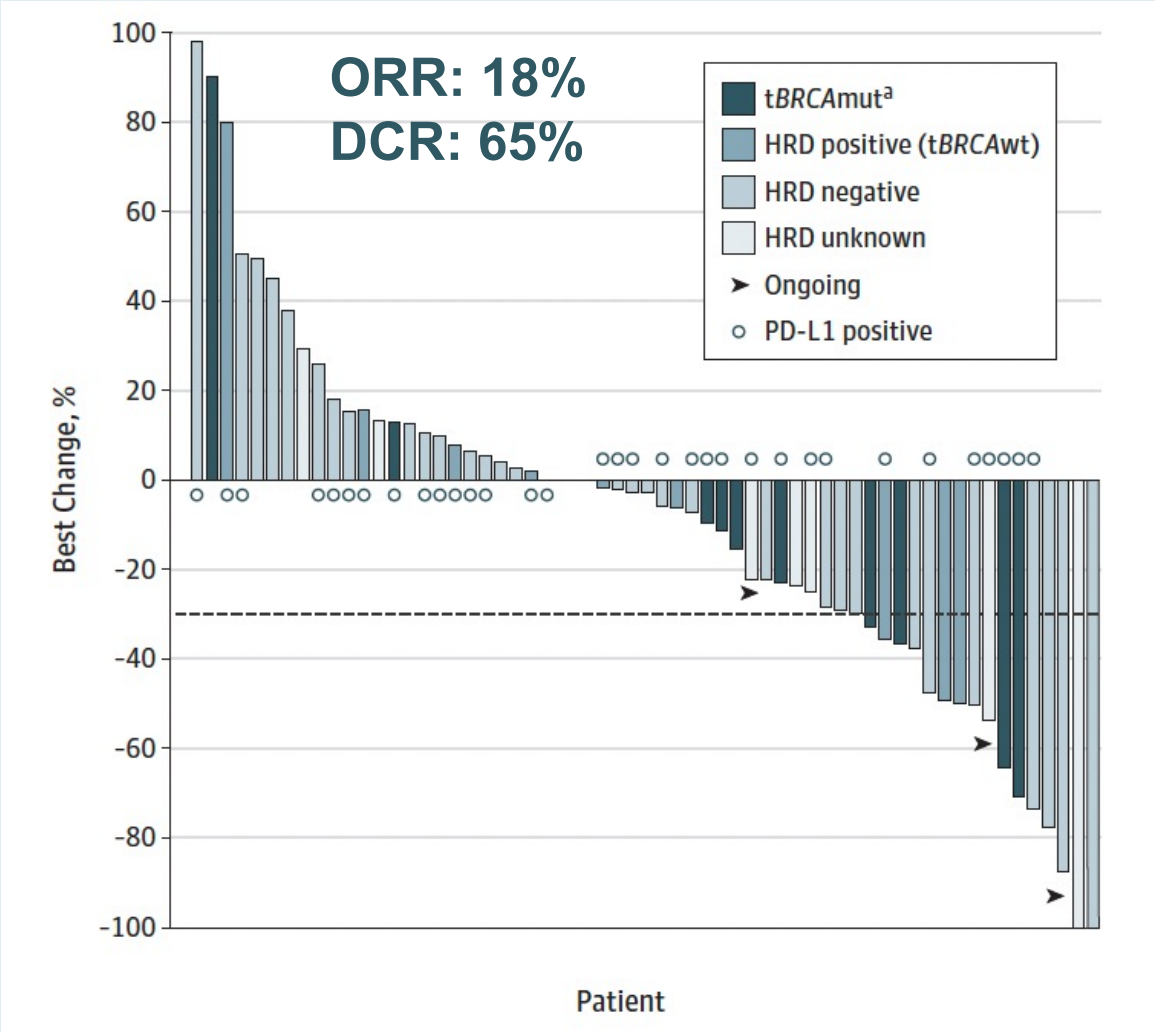
JAMA Oncol 2019;5(8):1141-9.

JAMA Oncology | Original Investigation

Single-Arm Phases 1 and 2 Trial of Niraparib in Combination With Pembrolizumab in Patients With Recurrent Platinum-Resistant Ovarian Carcinoma

Panagiotis A. Konstantinopoulos, MD, PhD; Steven Waggoner, MD; Gregory A. Vidal, MD; Monica Mita, MD; John W. Moroney, MD; Robert Holloway, MD; Linda Van Le, MD; Jasgit C. Sachdev, MD; Eloise Chapman-Davis, MD; Gerardo Colon-Otero, MD; Richard T. Penson, MD; Ursula A. Matulonis, MD; Young Bae Kim, MD; Kathleen N. Moore, MD; Elizabeth M. Swisher, MD; Anniina Färkkilä, MD; Alan D'Andrea, MD; Erica Stringer-Reasor, MD; Jing Wang, PhD; Nathan Buerstatte, MPH; Sujata Arora, MS; Julie R. Graham, PhD; Dmitri Bobilev, MD; Bruce J. Dezube, MD; Pamela Munster, MD

TOPACIO/KEYNOTE-162: Antitumor Activity of Niraparib in Combination with Pembrolizumab



ORR = overall response rate; DCR = disease control rate

Konstantinopoulos PA et al. *JAMA Oncol* 2019;5(8):1141-9.

RTP RESEARCH TO PRACTICE

VIRTUAL 2020 ESMO congress

Abstract 814MO.

Phase II study of olaparib plus durvalumab and bevacizumab (MEDIOLA): initial results in patients with non-germline BRCA-mutated platinum sensitive relapsed ovarian cancer

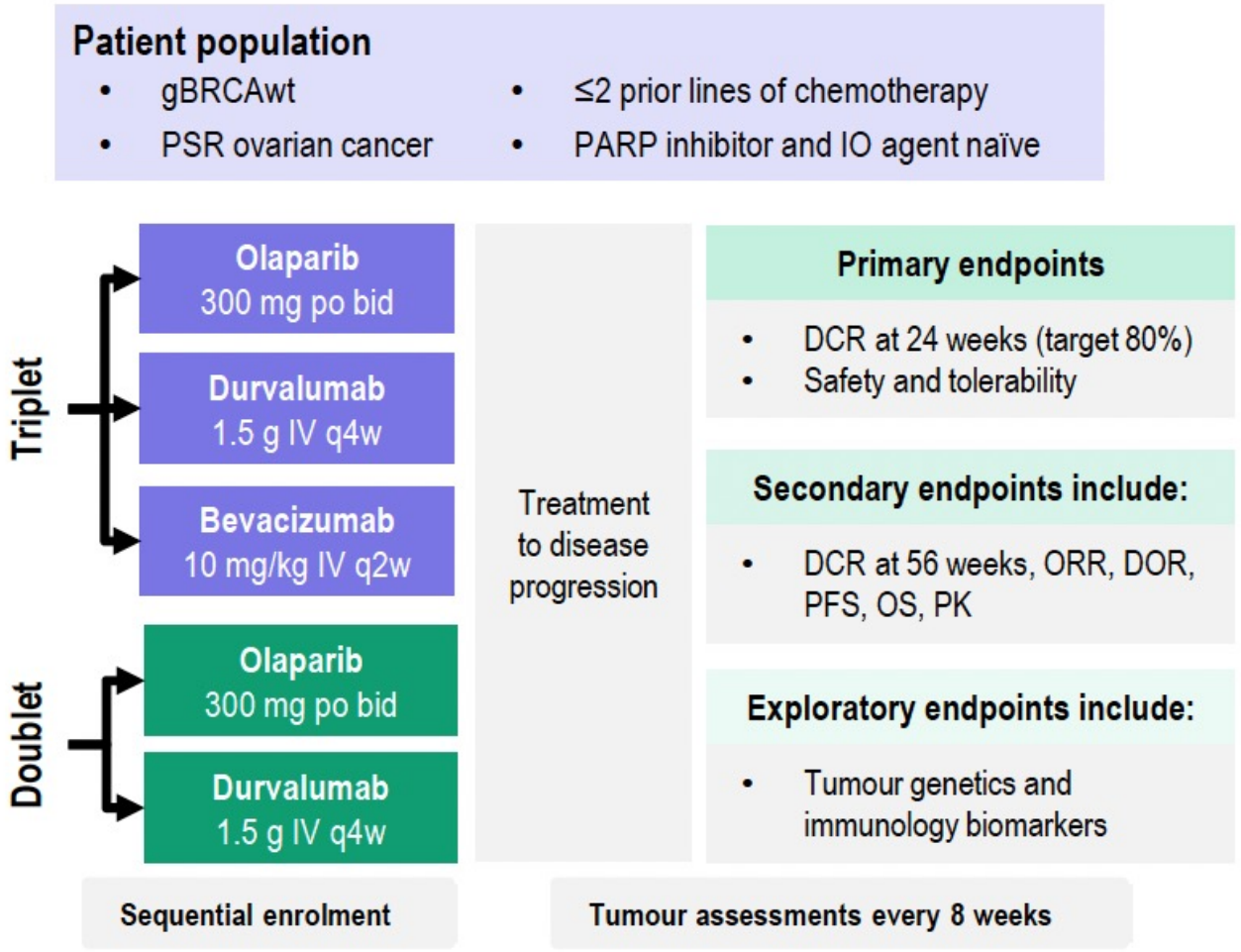
Yvette Drew,[1] Richard Penson,[2] David M O'Malley,[3] Jae-Weon Kim,[4] Stefan Zimmermann,[5] Patricia Roxburgh,[6] Joohyuk Sohn,[7] Salomon M Stemmer,[8] Sara Bastian,[9] Michelle Ferguson,[10] Benoit You,[11] Susan Domchek,[12] Haiyan Gao,[13] Helen K Angell,[13] Kassondra Meyer,[14] Laura Opincar,[14] Lone Ottesen,[13] Susana Banerjee[15]

[1]Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust, and Newcastle University, Newcastle upon Tyne, UK; [2]Massachusetts General Hospital, Boston, MA, USA; [3]The Ohio State University – James Comprehensive Cancer Center, Columbus, OH, USA; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [6]Beatson West of Scotland Cancer Centre, and Institute of Cancer Sciences, University of Glasgow, Glasgow, UK, [7]Yonsei Cancer Centre, Yonsei University, Sinchon-dong, Republic of Korea; [8]Rabin Medical Center-Beilinson Campus, Petach Tikva and Tel-Aviv University, Tel-Aviv, Israel; [9]Kantonsspital Graubuenden, Chur, Switzerland; [10]NHS Tayside, Dundee, UK; [11]Institut de Cancérologie des Hospices Civils de Lyon, CITOHL, GINECO, Université Claude Bernard Lyon 1, Lyon, France; [12]Basser Center for BRCA University of Pennsylvania, Philadelphia, PA, USA; [13]AstraZeneca, Cambridge, UK; [14]AstraZeneca, Gaithersburg, MD, USA; [15]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK

ClinicalTrials.gov identifier: NCT02734004
This study was sponsored by AstraZeneca

RTP RESEARCH TO PRACTICE

MEDIOLA gBRCA Wild Type Study Schema

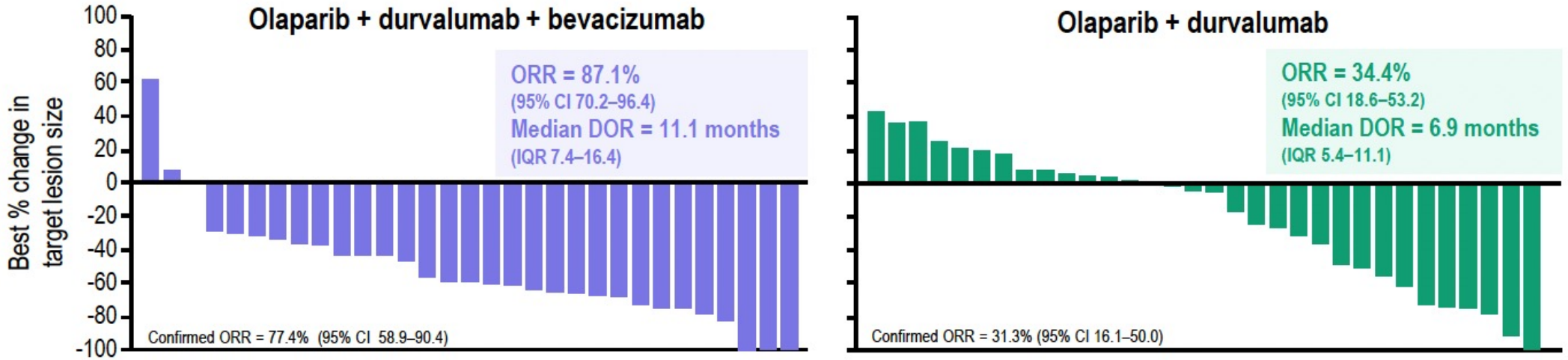


	Olap + durva + bev (N=31)	Olap + durva (N=32)
Median age, years	64.0	68.5
Age group (years), n (%)		
<50	3 (9.7)	4 (12.5)
≥50–<65	14 (45.2)	8 (25.0)
≥65	14 (45.2)	20 (62.5)
Race, n (%)		
White	20 (64.5)	24 (75.0)
Asian	10 (32.3)	3 (9.4)
Other	1 (3.2)	5 (15.6)
Platinum sensitivity, n (%)		
>6–12 months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

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

RTP RESEARCH TO PRACTICE

MEDIOLA gBRCA Wild Type: Antitumor Activity



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 Y et al. ESMO 2020;Abstract 814MO.

RTP RESEARCH TO PRACTICE

BARCELONA 2019 ESMO congress

Poster board number: 1190PD

Phase II study of olaparib + durvalumab (MEDIOLA): Updated results in the germline BRCA-mutated platinum-sensitive relapsed ovarian cancer cohort

Yvette Drew,[1] Bella Kaufman,[2] Susana Banerjee,[3] Alain Lortholary,[4] Sook Hee Hong,[5] Yeon Hee Park,[6] Stefan Zimmermann,[7] Patricia Roxburgh,[8] Michelle Ferguson,[9] Ricardo H Alvarez,[10] Susan Domchek,[11] Christopher Gresty,[12] Helen K Angell,[12] Vidalba Rocher Ros,[13] Kassondra Meyer,[13] Mark Lanasa,[13] Pia Herbolsheimer,[13] Maja de Jonge[14]

[1]Northern Centre for Cancer Care, Newcastle upon Tyne Hospitals NHS Foundation Trust Newcastle upon Tyne, UK; [2]Chaim Sheba Medical Center, Tel Hashomer, Israel; [3]The Royal Marsden Hospital, London, UK; [4]Centre Catherine de Sienne, Nantes, France; [5]Seoul St Mary's Hospital, Catholic University of Korea, Seoul, South Korea; [6]Samsung Medical Center, Seoul, Republic of Korea; [7]Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland; [8]University of Glasgow and Beatson West of Scotland Cancer Centre, Glasgow, UK; [9]NHS Tayside, Dundee, UK; [10]Cancer Treatment Centers of America-Atlanta and Augusta University, Augusta, GA, USA; [11]Basser Center for BRCA University of Pennsylvania, Philadelphia, PA, USA; [12]AstraZeneca, Cambridge, UK; [13]AstraZeneca, Gaithersburg, MD, USA and [14]Erasmus MC Daniel den Hoed Cancer Center, Rotterdam, Netherlands

esmo.org

MEDIOLA mBRCA Cohort Study Schema

- MEDIOLA is a multi-cohort, Phase I/II study
- The design of the BRCAm ovarian cohort is presented below; other ovarian cancer cohorts are ongoing

N=34*

- Platinum-sensitive relapsed ovarian cancer†
- Germline mutation in *BRCA1* or *BRCA2*
- ≥1 previous platinum-based therapy
- PARP inhibitor and immunotherapy naïve

Olaparib monotherapy 300 mg bid PO for 4 weeks

then

Olaparib 300 mg bid PO plus **durvalumab** IV 1.5 g every 4 weeks

Treatment until disease progression or intolerable toxicity

Primary endpoints

- Disease control rate at 12 weeks
- Safety and tolerability

Secondary endpoints

- Disease control rate at 28 weeks
- Objective response rate
- Duration of response
- Progression-free survival
- Overall survival
- PD-L1 expression in tumour samples

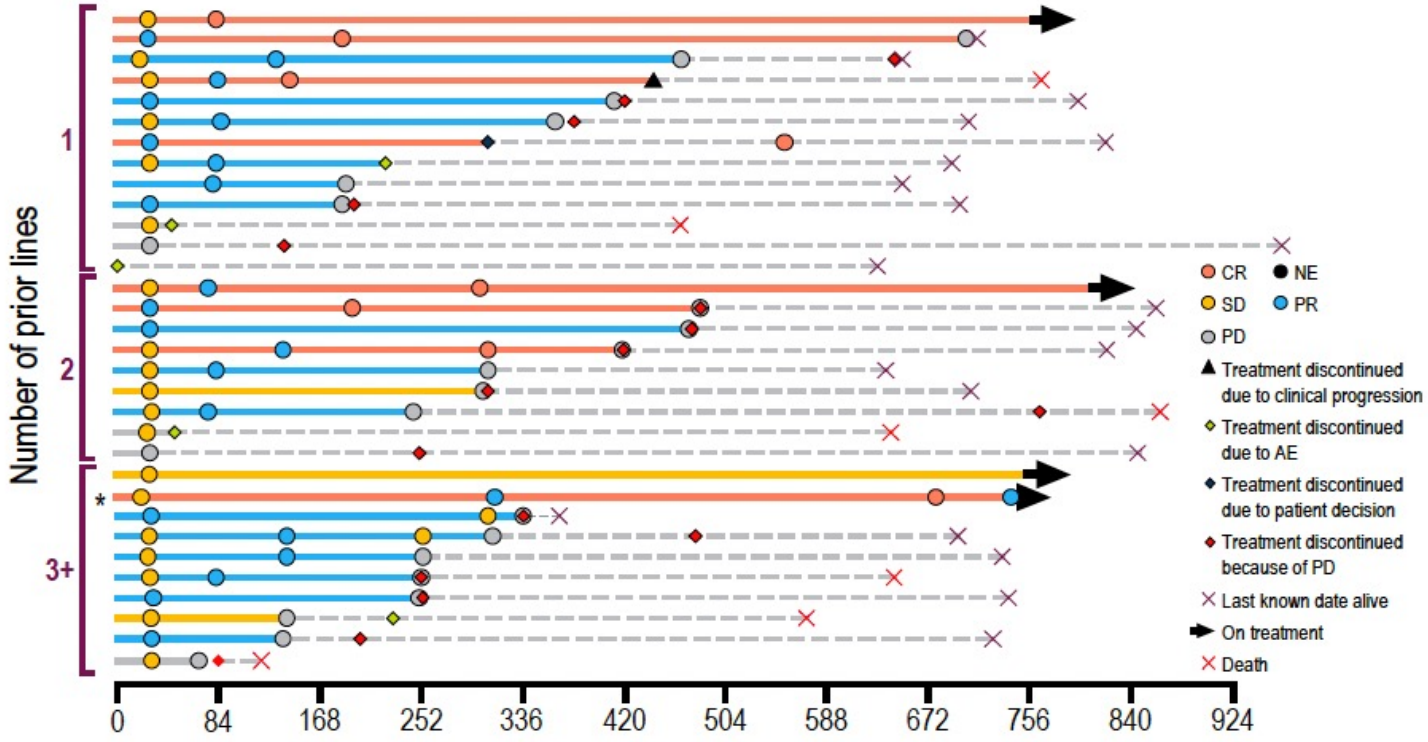
Drew Y et al. ESMO 2019;Abstract 1190PD.

MEDIOLA mBRCA Cohort: Efficacy

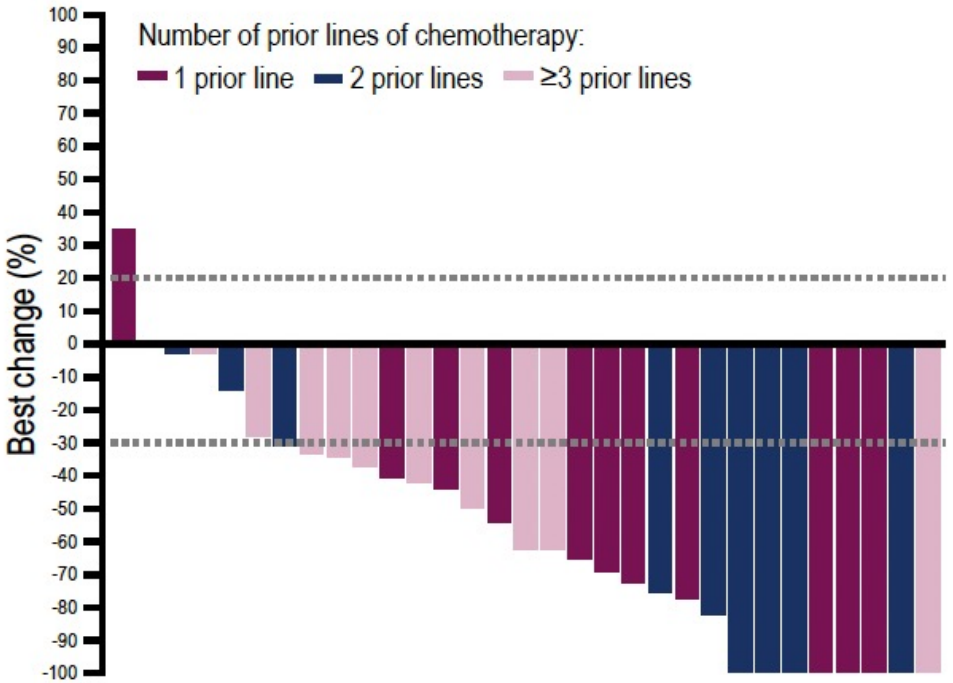
- DCR at 12 weeks: 81.3% (90% CI 66.3, 91.5)
- DCR at 28 weeks: 65.6% (90% CI 49.6, 79.4)
- Unconfirmed ORR: 71.9% (95% CI 53.3, 86.3)
- mPFS: 11.1 months (95% CI 8.2, 15.6)

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

Time to progression or treatment discontinuation



Best percentage change in target lesion size†



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

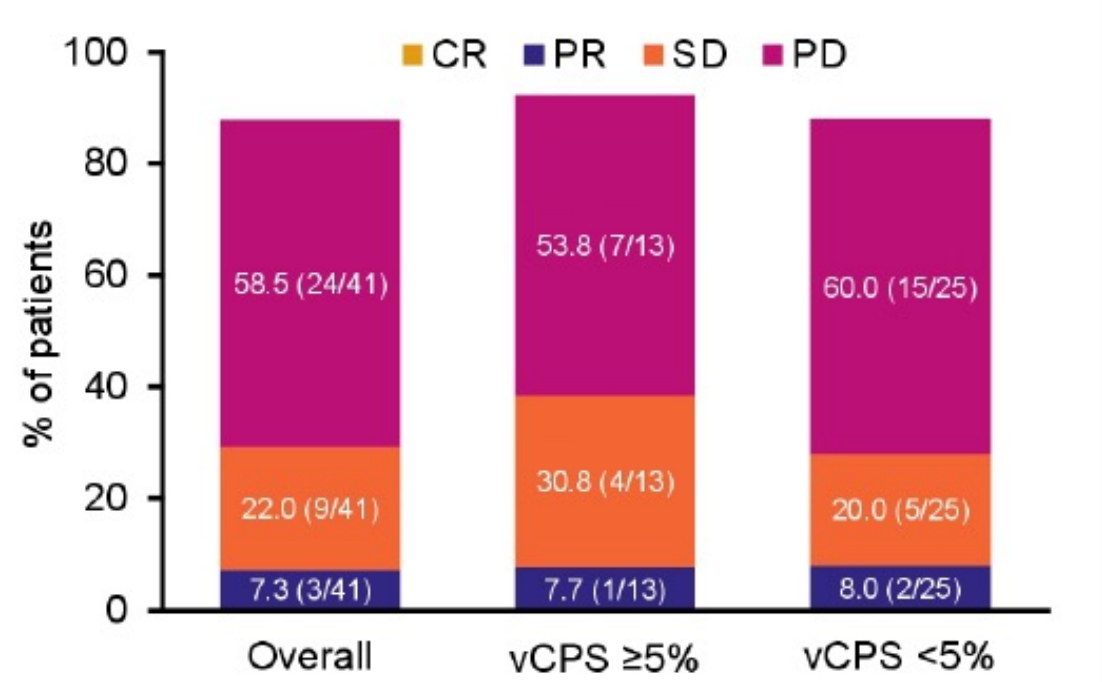
RTP RESEARCH TO PRACTICE

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

Randall LM et al.

ASCO 2022;Abstract 5573.

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



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

Randall LM et al. ASCO 2022;Abstract 5573.

MOONSTONE: Select Treatment-Related Adverse Events in >10% of Patients

Adverse event n (%)	Related to either niraparib or dostarlimab	Related to niraparib	Related to dostarlimab
Nausea	23 (56.1)	21 (51.2)	11 (26.8)
Fatigue	14 (34.1)	13 (31.7)	13 (31.7)
Vomiting	13 (31.7)	13 (31.7)	7 (17.1)
Anemia	13 (31.7)	13 (31.7)	7 (17.1)
Platelet count decreased	11 (26.8)	11 (26.8)	0 (0)
Thrombocytopenia	8 (19.5)	8 (19.5)	0 (0)

Randall LM et al. ASCO 2022;Abstract 5573.

An Open-Label Phase 2 Study of Dostarlimab, Bevacizumab, and Niraparib Combination in Patients with Platinum-Resistant Ovarian Cancer: Cohort A of the OPAL Trial

Joyce F. Liu,[1] Stéphanie Gaillard,[2] Andrea E. Wahner Hendrickson,[3] John W. Moroney,[4] Oladapo Yeku,[5] Elisabeth Diver,[6] Camille Gunderson,[7] Rebecca Arend,[8] Elena Ratner,[9] Vivek Samnotra,[10] Divya Gupta,[10] Lena Evilevitch,[10] Zebin Wang,[10] Ping Wang,[10] Joseph Tang,[10] Emeline Bacqué,[10] Xiaohong Liu,[10] Gottfried E. Konecny[11]

Poster #23

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [3]Mayo Clinic Rochester, Rochester, NY, USA; [4]University of Chicago Medicine Comprehensive Cancer Center, Chicago, IL, USA; [5]Massachusetts General Cancer Center, Boston, MA, USA; [6]Stanford Women's Cancer Center, Palo Alto, CA, USA; [7]University of Oklahoma Stephenson Cancer Center, Oklahoma City, OK, USA; [8]The University of Alabama at Birmingham, UAB Comprehensive Cancer Center, Birmingham, AL, USA; [9]Yale University, New Haven, CT, USA; [10]GlaxoSmithKline, Waltham, MA, USA; [11]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA.

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

Abstract 10415

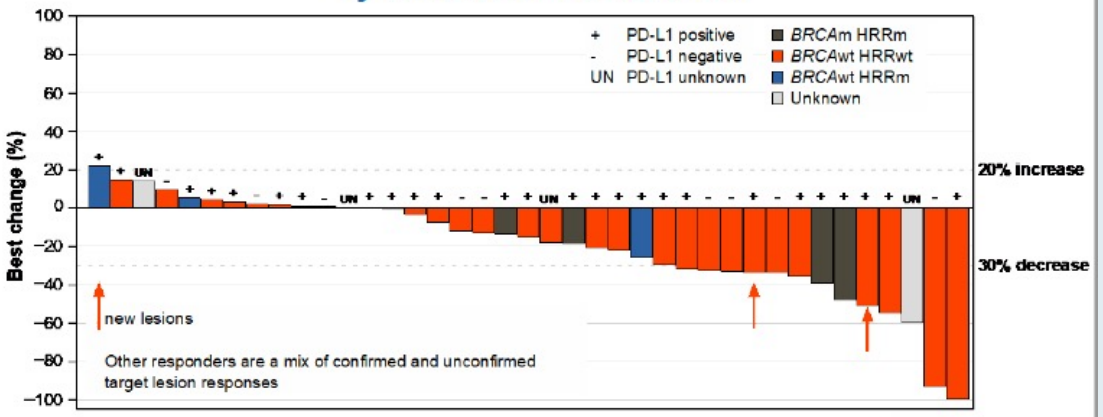
SGO Society of Gynecologic Oncology

Antitumor Activity

- Antitumor activity was assessed in the response-evaluable population (n=39)
  - 2 patients in the safety population did not have a postbaseline scan and were excluded from the response-evaluable population
- Response data required that patients with a best response of complete response or partial response had a confirmation scan ≥4 weeks after the first scan in which a response was observed

Antitumor Activity per RECIST v1.1	
Variable, n (%)	**Response-evaluable population (n=39)**
Complete response	0
Partial response	7 (17.9)
Stable disease	23 (59.0)
Progressive disease	8 (20.5)
Inconclusive	1 (2.6)
ORR (90% CI), %	17.9 (8.7–31.1)
DCR (90% CI), %	76.9 (63.2–87.4)

Best Percent Change from Baseline Sum of Target Lesions by HRR and PD-L1 Status



*BRCA*m, *BRCA* mutation; *BRCA*wt, *BRCA* wild type; HRRm, homologous recombination repair mutation; HRRwt, homologous recombination repair wild type; PD-L1, programmed death ligand 1.

SGO 2021 VIRTUAL ANNUAL MEETING ON WOMEN'S CANCER®

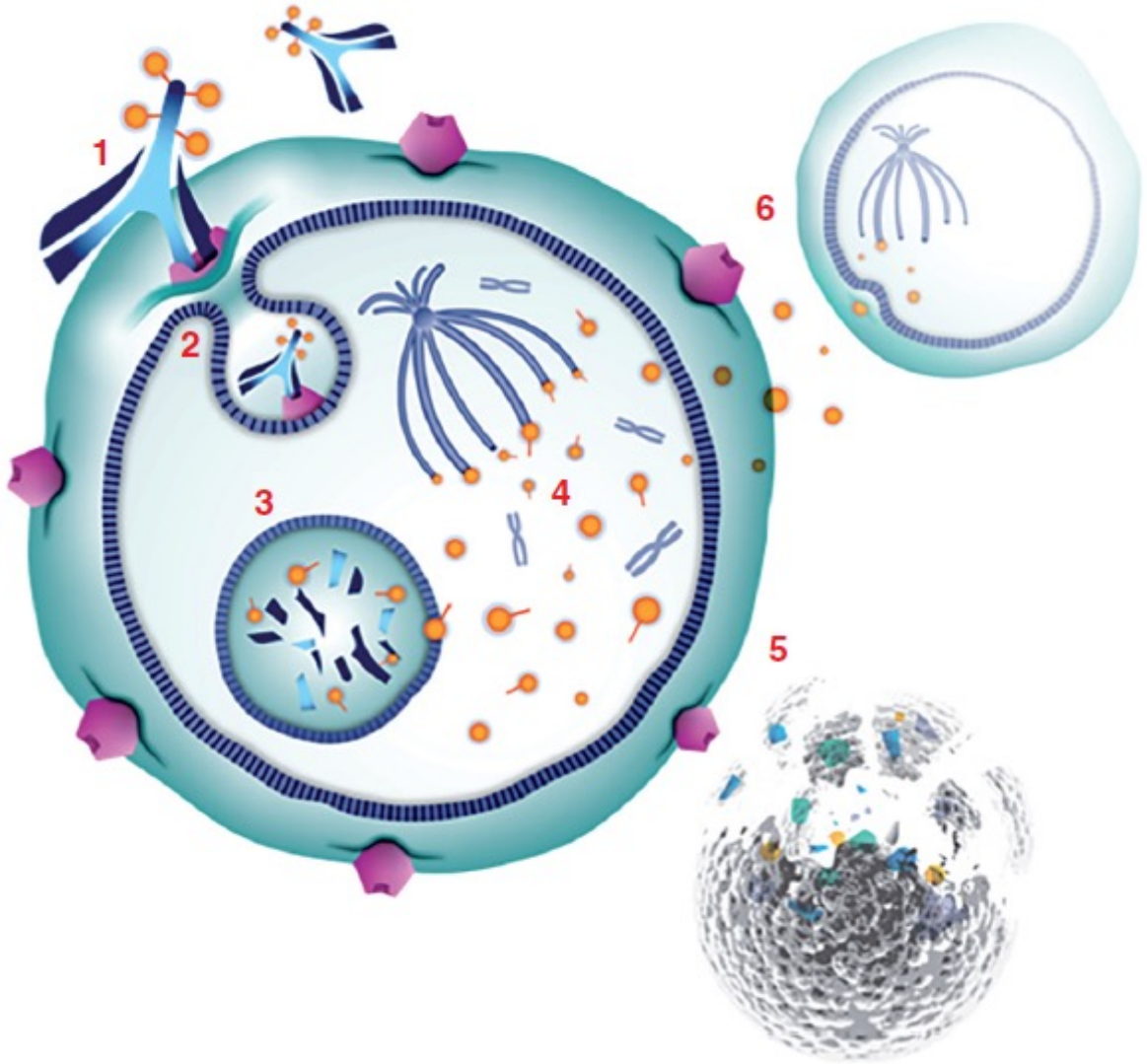
Society of Gynecologic Oncology

Liu JF et al. SGO 2021;Abstract 10415.

RTP RESEARCH TO PRACTICE

Novel Investigational Agents and Strategies

Mirvetuximab Soravtansine: Mechanism of Action



(1) Mirvetuximab soravtansine binds with high affinity to FRα expressed on the tumor cell surface

(2) The antibody-drug conjugate (ADC)/receptor complex becomes internalized via antigen-mediated endocytosis

(3) Lysosomal processing releases active DM4 catabolites from the ADC molecule

(4) These maytansinoid derivatives inhibit tubulin polymerization and microtubule assembly

(5) The potent antimitotic effects result in cell-cycle arrest and apoptosis

(6) Active metabolites can also diffuse into neighboring cells and induce further cell death — in other words, bystander killing

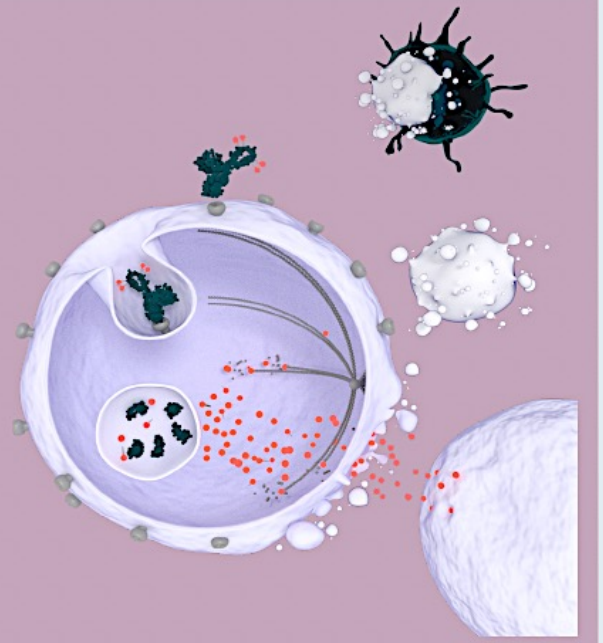
Moore K et al. *Future Oncol* 2018:14(2);123-36.

RTP RESEARCH TO PRACTICE

Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study

Ursula A. Matulonis,[1] Domenica Lorusso,[2] Ana Oaknin,[3] Sandro Pignata,[4] Hannelore Denys,[5] Nicoletta Colombo,[6] Toon Van Gorp,[7] Jason A. Konner,[8] Margarita Romeo Marin,[9] Philipp Harter,[10] Conleth G. Murphy,[11] Jiuzhou Wang,[12] Elizabeth Noble,[12] Brooke Esteves,[12] Michael Method,[12] Robert L. Coleman[13]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Fondazione Policlinico Universitario A. Gemelli, IRCCS and Catholic University of Sacred Heart, Rome, Italy; [3]Gynaecologic Cancer Programme, Vall d'Hebron Institute of Oncology (VHIO), Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [4]Istituto Nazionale Tumori di Napoli Fondazione G Pascale IRCCS, Naples, Italy; [5]Ghent University Hospital, Ghent, Belgium; [6]European Institute of Oncology IRCCS, Milan, Italy and University of Milan-Bicocca, Milan, Italy; [7]University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; [8]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [9]Institut Català d'Oncologia, Badalona, Spain; [10]Ev. Kliniken Essen-Mitte, Essen, Germany; [11]Bon Secours Hospital and Cancer Trials, Cork, Ireland; [12]ImmunoGen, Inc., Waltham, MA, USA; [13]US Oncology Research, Texas Oncology, The Woodlands, TX, USA



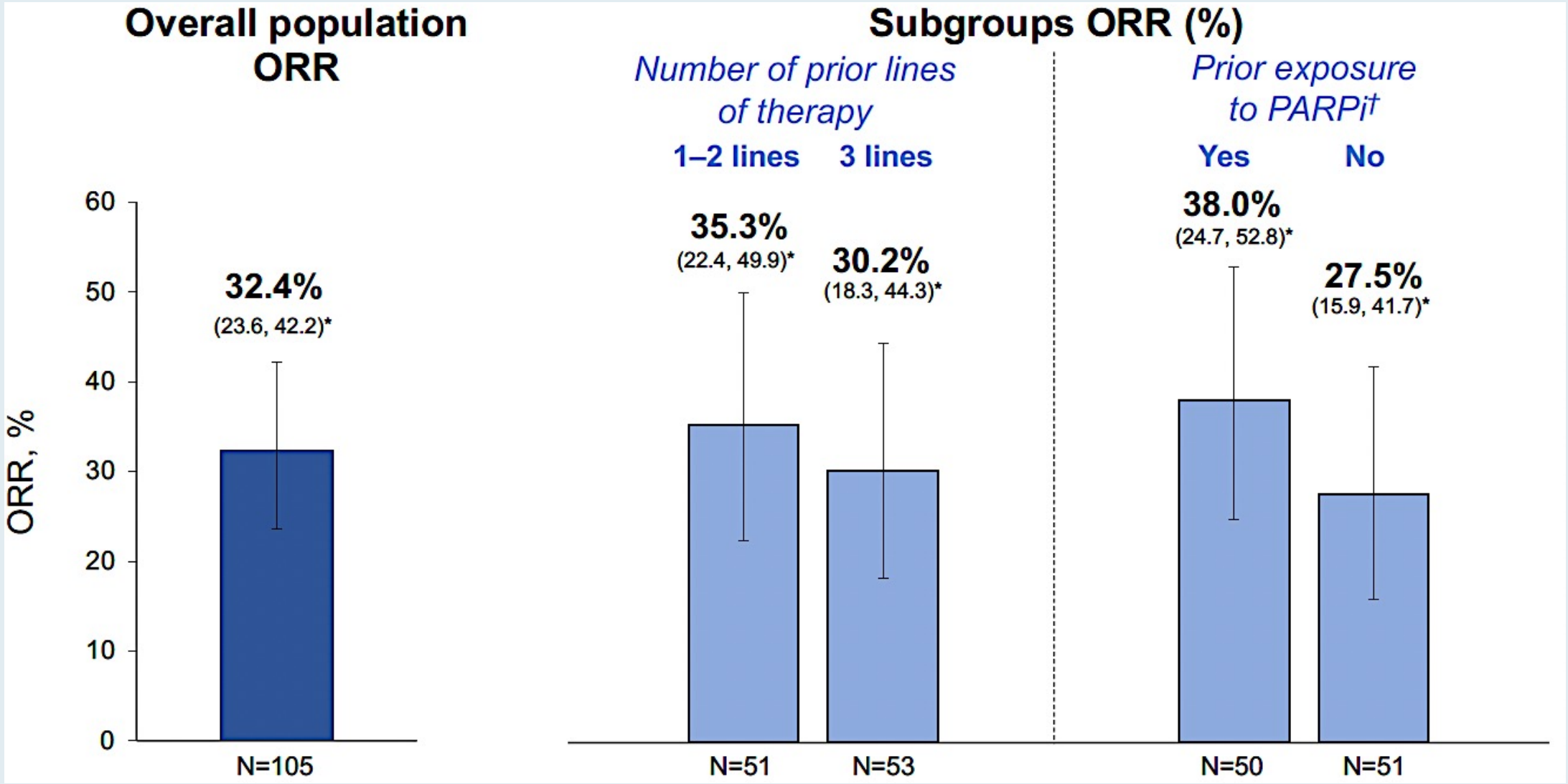
SORAYA

ANNUAL MEETING ON WOMENS' CANCER®
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 18 - 21, 2022

SGO 2022;Abstract LBA4.

Society of Gynecologic Oncology

SORAYA: Investigator-Assessed Objective Response Rate by Prior Therapy



Matulonis UA et al. SGO 2022;Abstract LBA4.

RTP RESEARCH TO PRACTICE

SORAYA: Treatment-Related Adverse Events (≥10%)

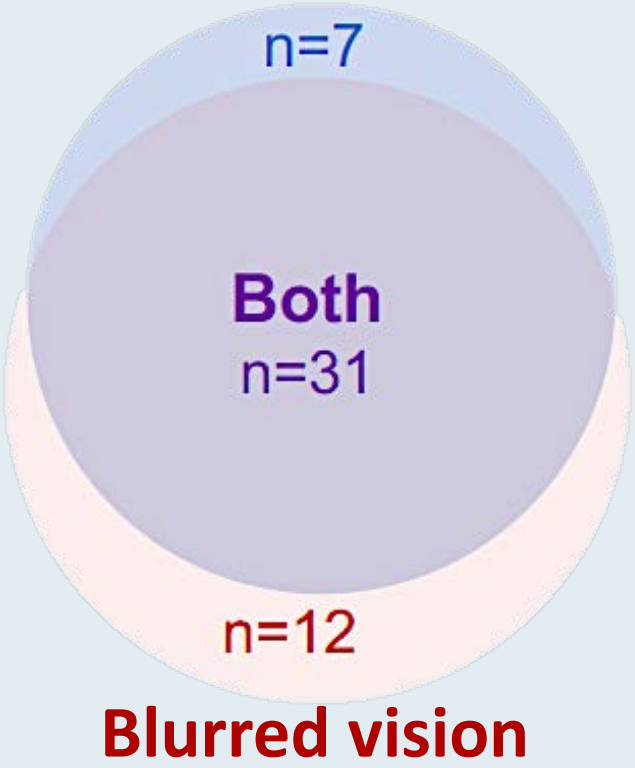
TRAEs, n (%)	All Grades	Grade 3	Grade 4
Patients with any event	91 (86)	29 (27)	1 (1)
Blurred vision	43 (41)	6 (6)	0 (0)
Keratopathy*†	38 (36)	8 (8)	1 (1)
Nausea	31 (29)	0 (0)	0 (0)
Dry eye	24 (23)	2 (2)	0 (0)
Fatigue	24 (23)	1 (1)	0 (0)
Diarrhea	23 (22)	2 (2)	0 (0)
Asthenia	16 (15)	1 (1)	0 (0)
Photophobia	15 (14)	0 (0)	0 (0)
Peripheral neuropathy	13 (12)	0 (0)	0 (0)
Decreased appetite	13 (12)	1 (1)	0 (0)
Vomiting	12 (11)	0 (0)	0 (0)
Neutropenia	11 (10)	1 (1)	0 (0)

- Most adverse events (AEs) were low-grade, reversible ocular and GI events
- Serious Grade ≥3 treatment-related AEs (TRAEs) were reported in 8% of patients
- TRAEs led to dose delay in 32% and dose reduction in 19%
- 7 patients (7%) discontinued treatment due to TRAEs
- 1 death was recorded as possibly related to study drug
  - Respiratory failure
  - Autopsy: No evidence of drug reaction; lung metastases

Matulonis UA et al. SGO 2022;Abstract LBA4.

Unique Events Associated with Mirvetuximab Soravtansine: Keratopathy and Blurred Vision

Events developed in 50/106 (47%) patients: mostly low grade



Proactive supportive care
– Lubricating artificial tears
– Corticosteroid eye drops

Predictable
– Median time to onset: cycle 2 (~1.5 months)

Manageable with dose modifications, if needed
– 22% of patients (23/106) had dose delay and/or reduction

Reversible
– At data cutoff: >80% of Grade 2-3 events had resolved to Grade 0-1
  – 9 patients still receiving mirvetuximab soravtansine or being followed up for resolution

<1% discontinuation due to ocular events
– 1 of 106 patients discontinued due to Grade 4 keratopathy, which resolved within 15 days

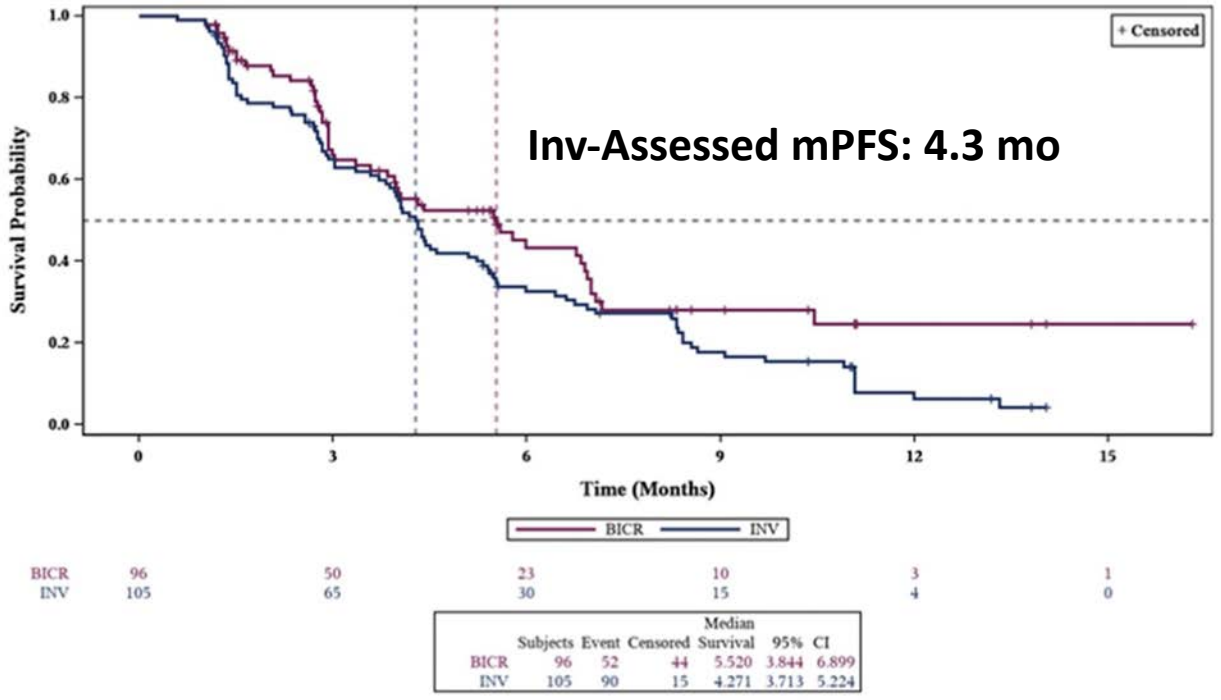
Matulonis UA et al. SGO 2022;Abstract LBA4.

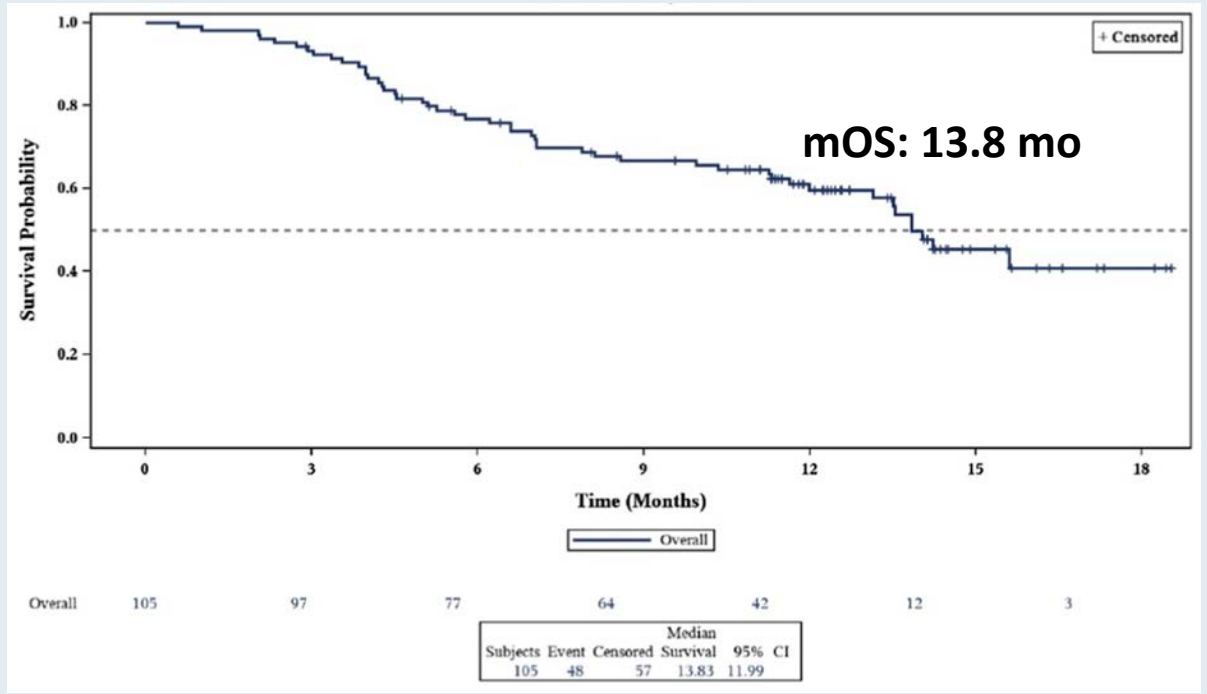
Mirvetuximab Soravtansine (MIRV) in Patients with Platinum-Resistant Ovarian Cancer with High Folate Receptor Alpha (FRα) Expression: Characterization of Antitumor Activity in the SORAYA Study

Matulonis UA et al.

ASCO 2022;Abstract 5512.

SORAYA: Overall Response Rate in the BRCA Mutation-Positive Subgroup





Matulonis UA et al. ASCO 2022;Abstract 5512.

RTP RESEARCH TO PRACTICE

SORAYA: Overall Response Rate in the BRCA Mutation-Positive Subgroups

	BRCAmt with prior PARPi (n=16)	*BRCAmt* without prior PARPi (n=4)
Responders, n	6	3
ORR	38%	75%

Matulonis UA et al. ASCO 2022;Abstract 5512.

MIRASOL Phase III Study Schema

MIRASOL

Enrollment and Key Eligibility

- Platinum-resistant disease (PFI ≤ 6 mo)
  - 1° platinum refractory disease excluded (primary PFI < 3 mo)
- Prior bevacizumab and PARPi allowed
- 1-3 prior lines of therapy
- Patients with BRCA mutations allowed
- FRα-high by PS2+ scoring (≥75% PS2+)

Statistical Assumptions

- 430 patients/ 330 events for PFS by INV
- α=0.05 (two-sided)
- Power=90%; HR=0.7; control arm mPFS 3.5 mo

Mirvetuximab Soravtansine
6 mg/kg AIBW (calculated using adjusted ideal body weight) intravenously once every 3 weeks

1:1 Randomization
STRATIFICATION FACTORS
Investigator's Choice (IC) Chemotherapy
(Paclitaxel, PLD, Topotecan)
Prior Therapies
(1 vs 2 vs 3)

Investigator's Choice (IC) Chemotherapy
Paclitaxel, PLD,† or Topotecan
Paclitaxel: 80 mg/m2 weekly; PLD: 40 mg/m² every 4 weeks;
Topotecan: 4 mg/m² on days 1, 8, and 15 every four weeks;
or 1.25 mg/m² on days 1-5 every 3 weeks

Moore KN et al. SGO 2022;Abstract 297.

PICCOLO Phase II Trial Schema

PICCOLO

Enrollment and Key Eligibility

- Platinum-sensitive disease (PFI >6 mo)
- At least 2 prior lines of platinum-based therapy
  - Patients with documented platinum allergy require only 1 prior line of platinum
- FRα-high by IHC scoring (≥75% PS2+)
- Appropriate for single agent therapy as next line of therapy as determined by investigator

Statistical Assumptions

- N=75
- Null hypothesis: ORR is ≤ 28% tested using an optimal Simon's two-stage design w/o pause in enrollment

→

Mirvetuximab Soravtansine

6 mg/kg AIBW (calculated using adjusted ideal body weight) intravenously once every 3 weeks

Alvarez Secord A et al. SGO 2022;Abstract 300.

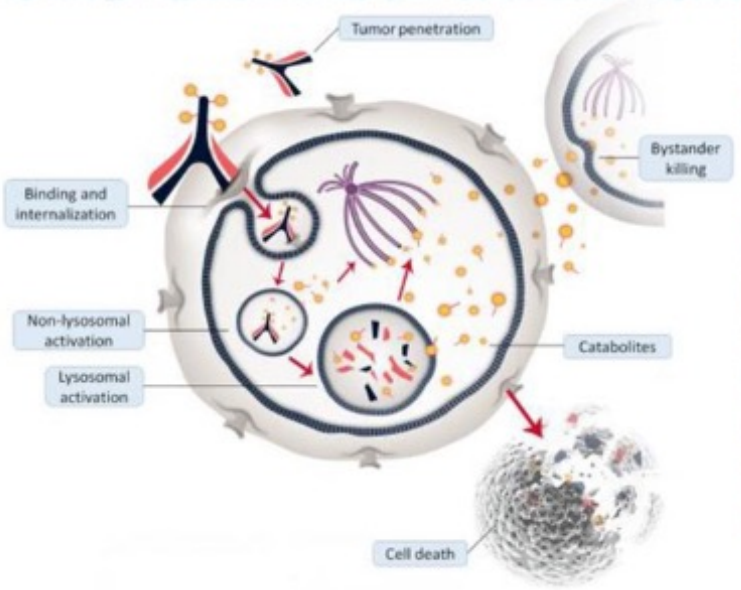
2021 ASCO ANNUAL MEETING

Abstract 5504

Mirvetuximab Soravtansine, a folate receptor alpha-targeting antibody drug conjugate, in combination with bevacizumab in patients with platinum-agnostic ovarian cancer: final analysis

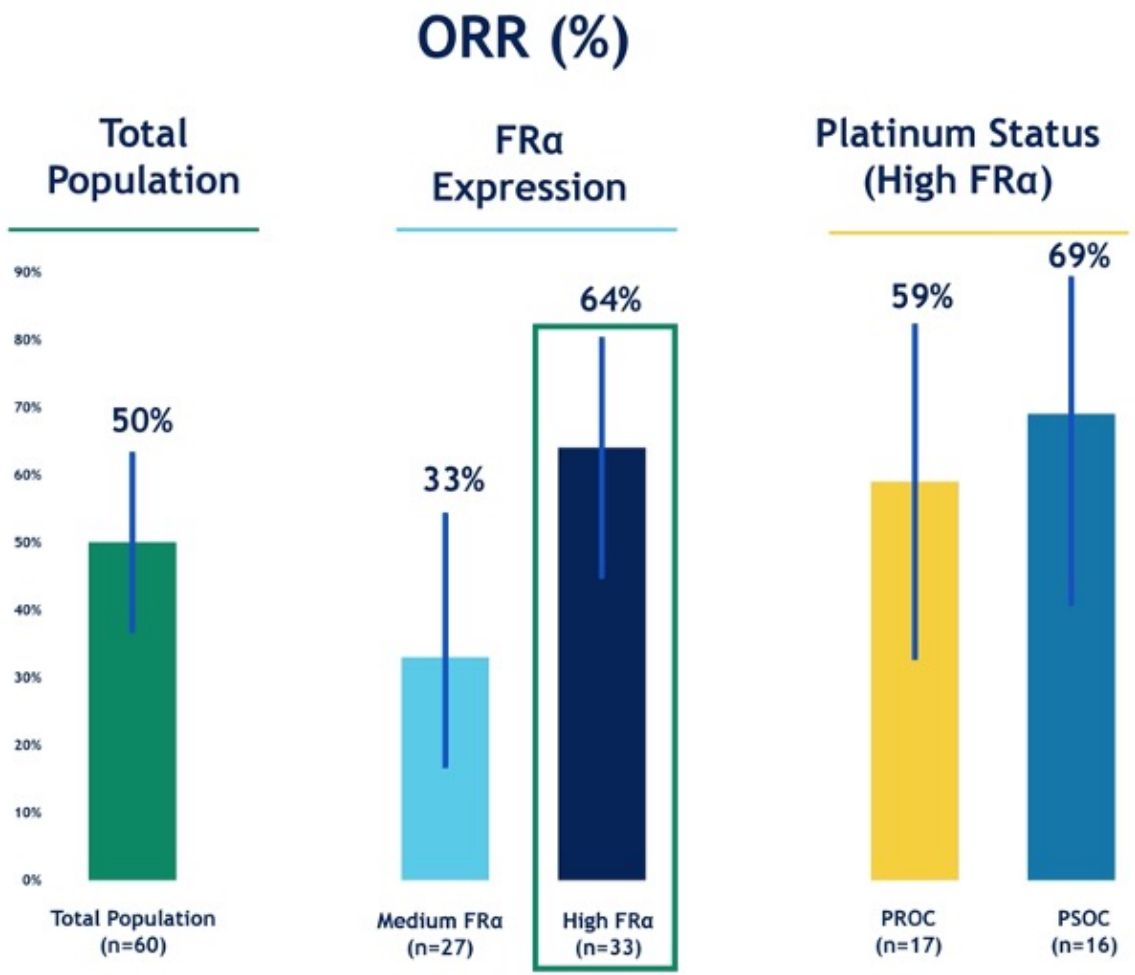
David M. O'Malley[1], Ana Oaknin[2], Ursula A. Matulonis[3], Gina M. Mantia-Smaldone[4], Peter Lim[5], Cesar Castro[6], Diane Provencher[7], Sanaz Memarzadeh[8], Patrick Zweidler-McKay[9], Jiuzhou Wang[9], Brooke Esteves[9], Kathleen N. Moore[10] Lucy Gilbert[11]

[1]Ohio State University, Columbus, OH; [2]Vall D´Hebron University Hospital, Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [3]Dana Farber Cancer Institute, Boston, MA; [4]Fox Chase Cancer Center, Philadelphia, PA; [5]The Center of Hope Renown Regional Medical Center, Reno, NV; [6]Massachusetts General Hospital, Boston, MA; [7]Institute du Cancer de Montreal, Montreal, Canada; [8]Ronald Reagan UCLA Medical Center UCLA Medical Center, Santa Monica; [9]ImmunoGen, Inc., Waltham, MA; [10]University of Oklahoma Health Sciences Center, Oklahoma City, OK/Sarah Cannon Research Institute, Nashville, TN; [11]McGill University Health Center-RI, Montreal, Canada



RTP RESEARCH TO PRACTICE

Confirmed ORR by FRα Expression and Platinum Status

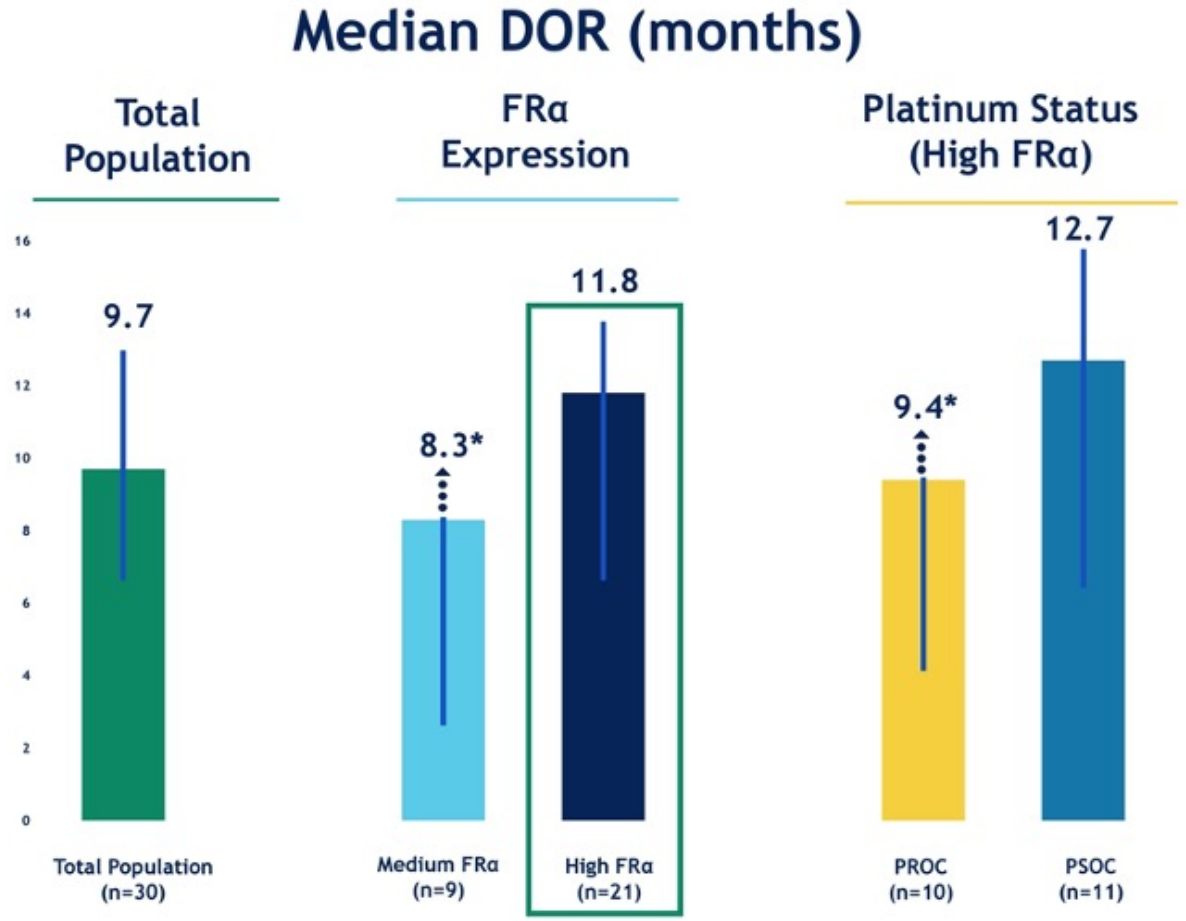


- **50% ORR** (30/60) for overall cohort
- **64% ORR** (21/33) in high FRα tumors
  - **59% ORR** (10/17) in PROC subset
  - **69% ORR** (11/16) in PSOC subset

ORR = overall response rate; PROC = platinum-resistant ovarian cancer; PSOC = platinum-sensitive ovarian cancer

O'Malley DM et al. ASCO 2021;Abstract 5504.

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

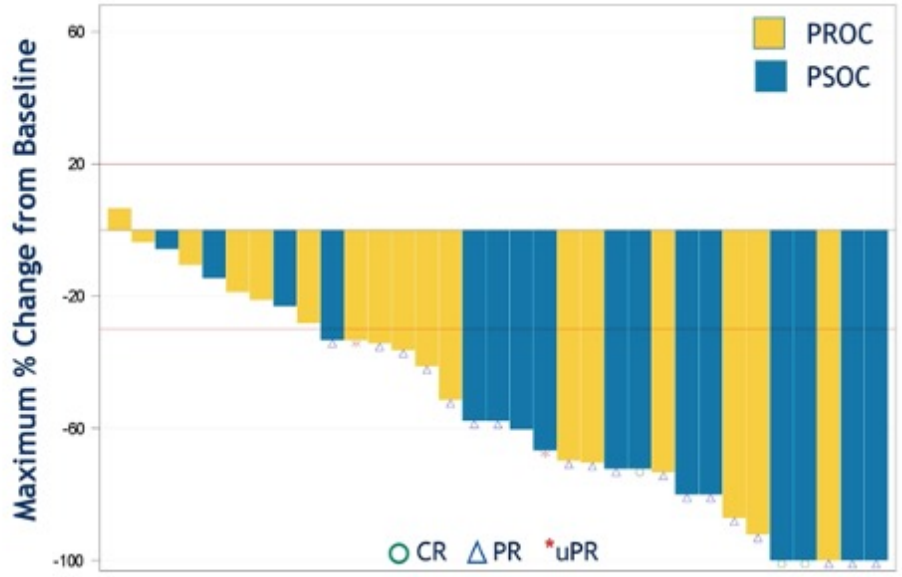
*Upper limit of 95% confidence interval not reached

O'Malley DM et al. ASCO 2021;Abstract 5504.

RTP RESEARCH TO PRACTICE

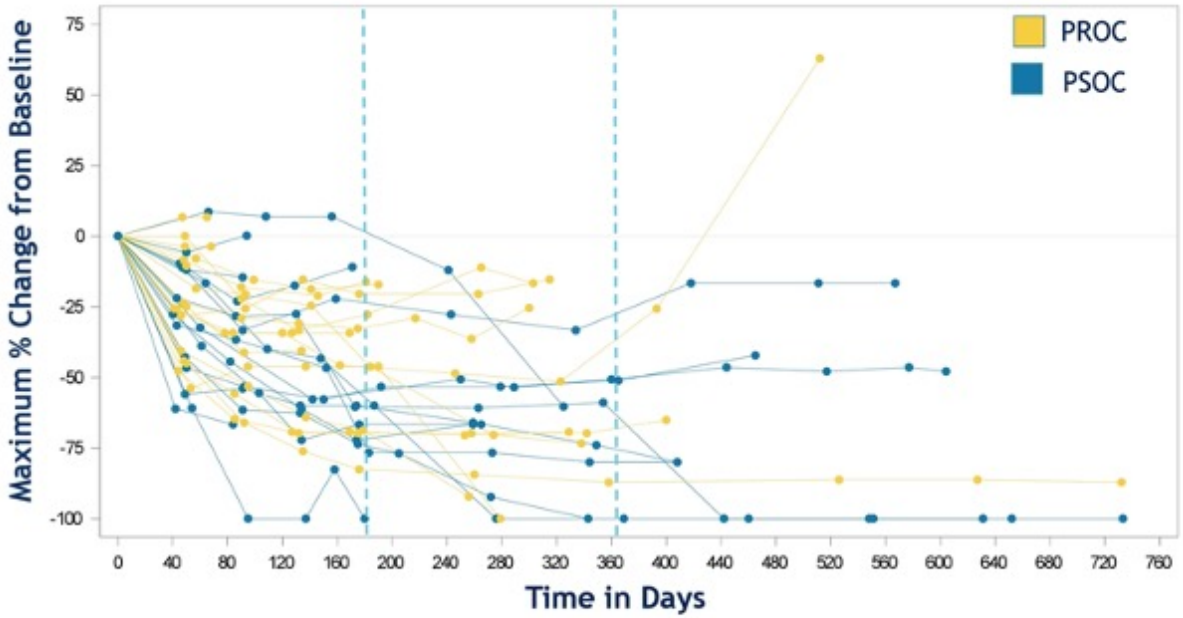
High FRα Tumors Showed a Deep Response and Durable Benefit

Maximum % Change from Baseline



- **97% (32/33)** of patients demonstrated tumor burden reduction

Percent Change and Duration from Baseline



- Rapid tumor shrinkage, with early responses
- Durable benefit in both PSOC and PROC

O'Malley DM et al. ASCO 2021;Abstract 5504.

Updated Results From the Phase 1b Expansion Study of Upifitamab Rilsodotin (UpRi; XMT-1536), a NaPi2b-directed Dolaflexin Antibody Drug Conjugate (ADC) in Ovarian Cancer

Richardson, Debra L[1]; Hamilton, Erika P[2]; Barve, Minal[3]; Anderson, Charles K[4]; Taylor, Sara K[5]; Lakhani, Nehal[6]; Buscema, Joseph[7]; Tolcher, Anthony W[8]; Zarwan, Corrine[9]; Werner, Theresa L[10]; Hays, John L[11]; Richards, Paul[12]; Arend, Rebecca[13]; Edenfield, Jeffery[14]; Putiri, Emily[15]; Bernardo, Patricia[15]; Burger, Robert A[15]; Matulonis, Ursula A[16]

[1]Stephenson Cancer Center, University of Oklahoma Health Sciences Center and the Sarah Cannon Research Institute, Oklahoma City, OK; [2]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [3]Mary Crowley Cancer Research, Dallas, TX; [4]Willamette Valley Cancer Institute and Research Center, Eugene, OR; [5]BC Cancer - Kelowna, Kelowna BC, Canada; [6]START Midwest, Grand Rapids, MI; [7]Arizona Oncology, Tucson, AZ; [8]NEXT Oncology, San Antonio, TX; [9]Lahey Clinic, Burlington, MA; [10]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; [11]Arthur James Cancer Hospital, Ohio State University, Columbus, OH; [12]US Oncology, Oncology and Hematology Assoc. of Southwest VA, Salem, VA; [13]University of Alabama at Birmingham, Birmingham, AL; [14]Prisma Health Cancer Institute, Greenville, SC; [15]Mersana Therapeutics, Inc, Cambridge, MA; [16]Dana-Farber Cancer Institute, Boston, MA

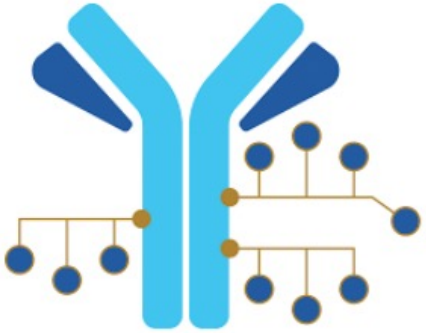
Abstract 76

ANNUAL MEETING ON WOMENS' CANCER®
BUILDING BRIDGES // BREAKING BARRIERS
SGO // PHOENIX, ARIZONA // MARCH 18 - 21, 2022

SGO 2022;Abstract 76.

Society of Gynecologic Oncology

Upifitamab Rilsodotin (UpRi): First-in-Class ADC Targeting NaPi2b



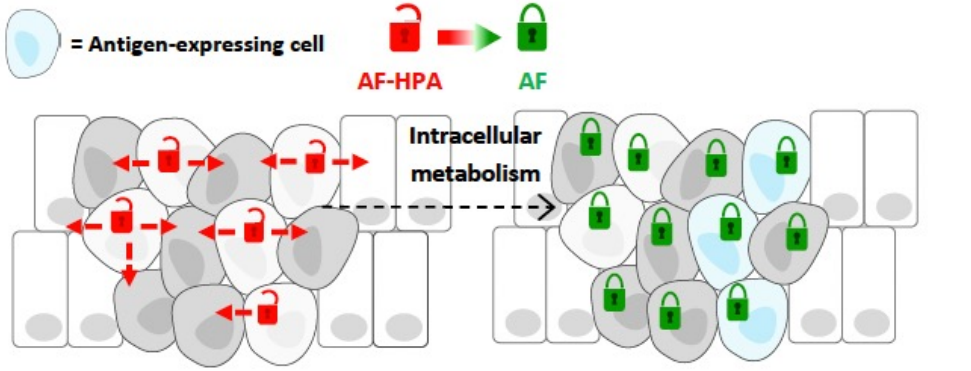
UpRi

Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

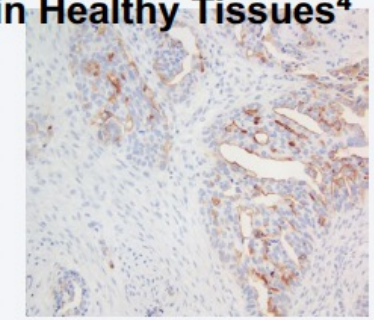
Drug-to-Antibody Ratio: ~10



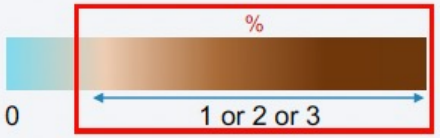
Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy cells[2,3]

NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[4]

- NaPi2b expressed by tumor cells in two-thirds of patients with high-grade serous ovarian cancer[2]
- NaPi2b is a lineage antigen (not an oncogene)[1]



NaPi2b IHC assay in development *– an optimal diagnostic assay would be robust, predictive, reproducible, easily able to distinguish a wide range of expression using* ***TPS scoring method***[2]



Richardson DL et al. SGO 2022;Abstract 76.

RTP RESEARCH TO PRACTICE

UpRi Phase Ib Study Schema

Patient Population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1

Ovarian Cancer Cohort
- 1–3 prior lines in platinum-resistant
- 4 prior lines regardless of platinum status
- High-grade serous histology
- Archived tumor and fresh biopsy (if medically feasible) for NaPi2b
- Exclusion: Primary platinum-refractory disease

UpRi IV Q4W until disease progression or unacceptable toxicity

36 mg/m² cohort initiated in August 2019

43 mg/m² to a max of ~80 mg cohort initiated in December 2019

Primary Objectives
- Evaluate safety and tolerability of MTD or RP2D
- Assess preliminary efficacy (ORR, DCR)

Secondary Objectives
- Association of tumor NaPi2b expression and objective tumor response using an IHC assay with a broad dynamic range to distinguish tumors with high and low NaPi2b expression
- Further assessment of preliminary anti-neoplastic activity (DoR)

Assessment: Tumor imaging (MRI or CT) at baseline and every 2nd cycle; response assessed per RECIST v1.1

Richardson DL et al. SGO 2022;Abstract 76.

Expansion Cohort Experience Across a Range of Doses Allowed for Further Optimization of UpRi Profile

Updated Analysis of Phase 1b PROC Expansion Cohort to Evaluate Safety and ORR Based on UpRi Dose Levels[a]

Dose Group 36 (33–38 mg/m²) (n=29)

12 patients at **36 mg/m²** starting dose (all BSA levels)

+

17 patients at ~80 mg starting dose with BSA ≥1.8 who received an actual dose of **33 to 38 mg/m²**

Dose Group 43 (>38–43 mg/m²) (n=66)

39 patients at **43 mg/m²** starting dose with BSA <1.8

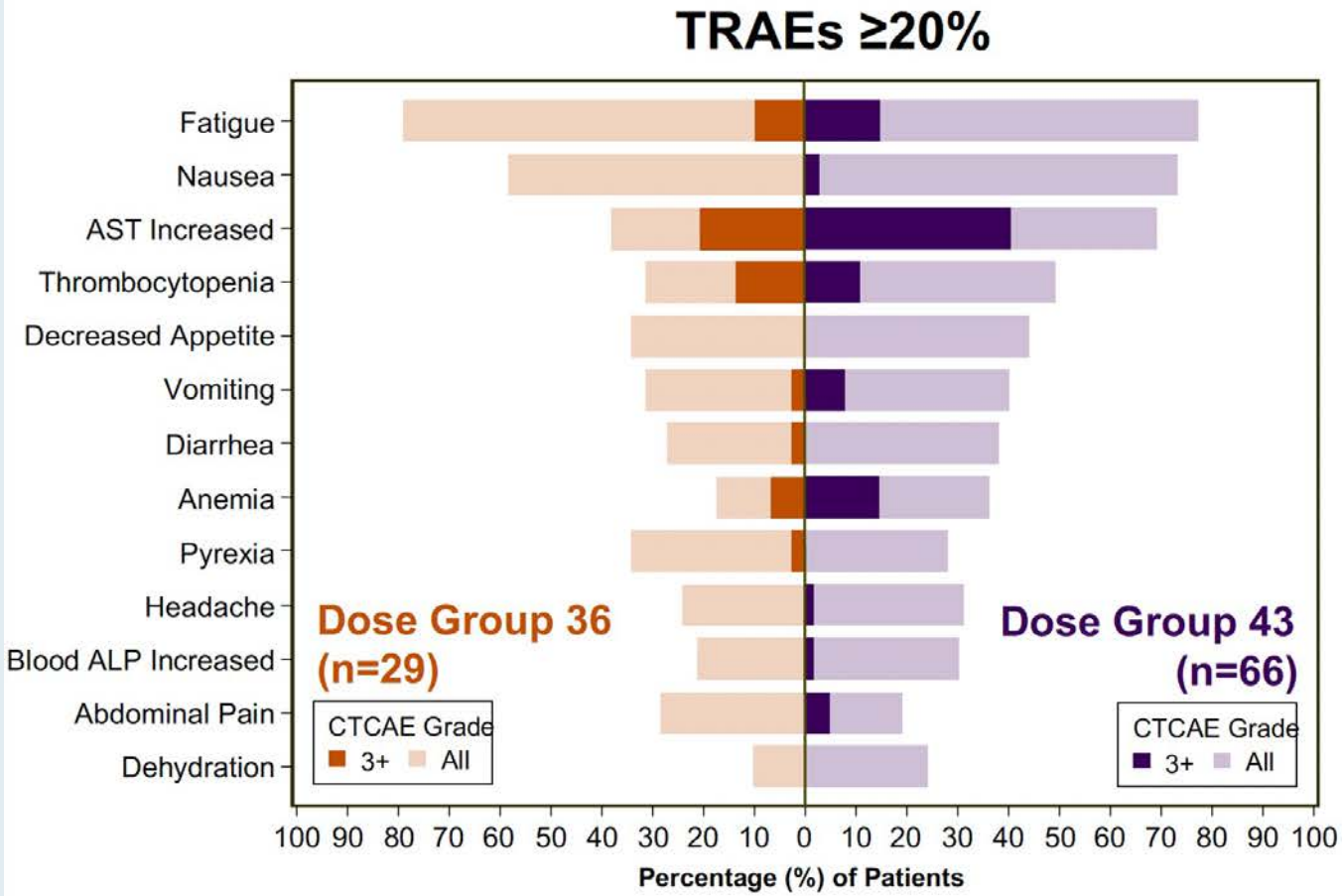
+

27 patients at ~80 mg starting dose with BSA ≥1.8 who received an actual dose of **>38 mg/m²**

Richardson DL et al. SGO 2022;Abstract 76.

TRAEs by UpRi Dose Group

Dose Group 36 Had a More Favorable Safety Profile Compared to Dose Group 43



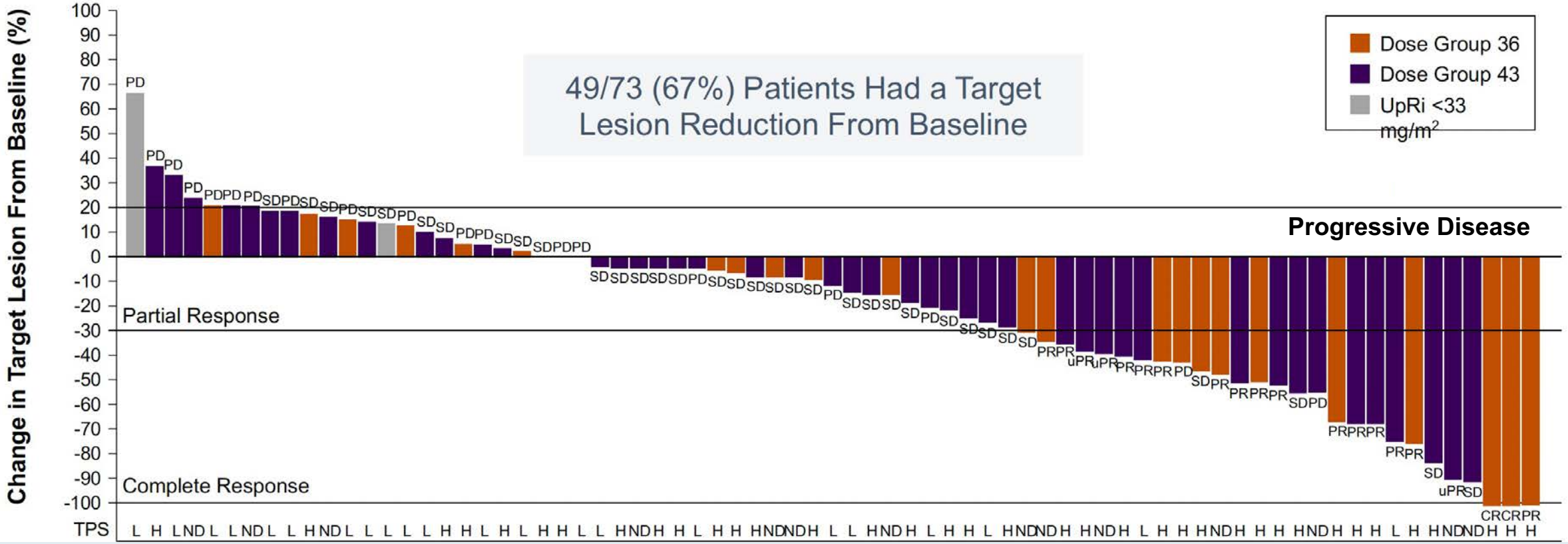
- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43[a]

Richardson DL et al. SGO 2022;Abstract 76.

RTP RESEARCH TO PRACTICE

Best Response by UpRi Dose Group

Similar Tumor Reduction in Both Dose Groups: Two-thirds of Patients Had Reductions in Target Tumor Lesions by RECIST 1.1



Richardson DL et al. SGO 2022;Abstract 76.

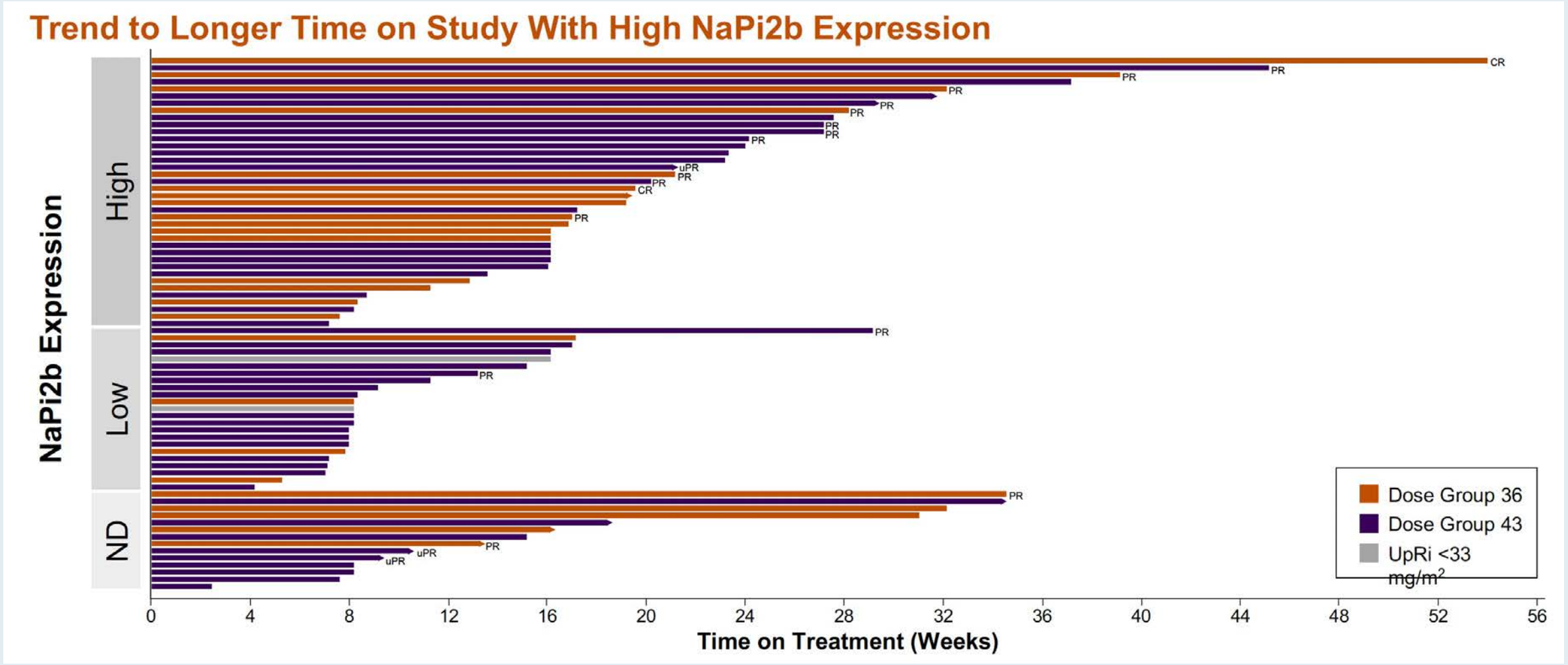
Confirmed ORR by UpRiDose Group and NaPi2b Level and Duration of Response (DoR)

		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

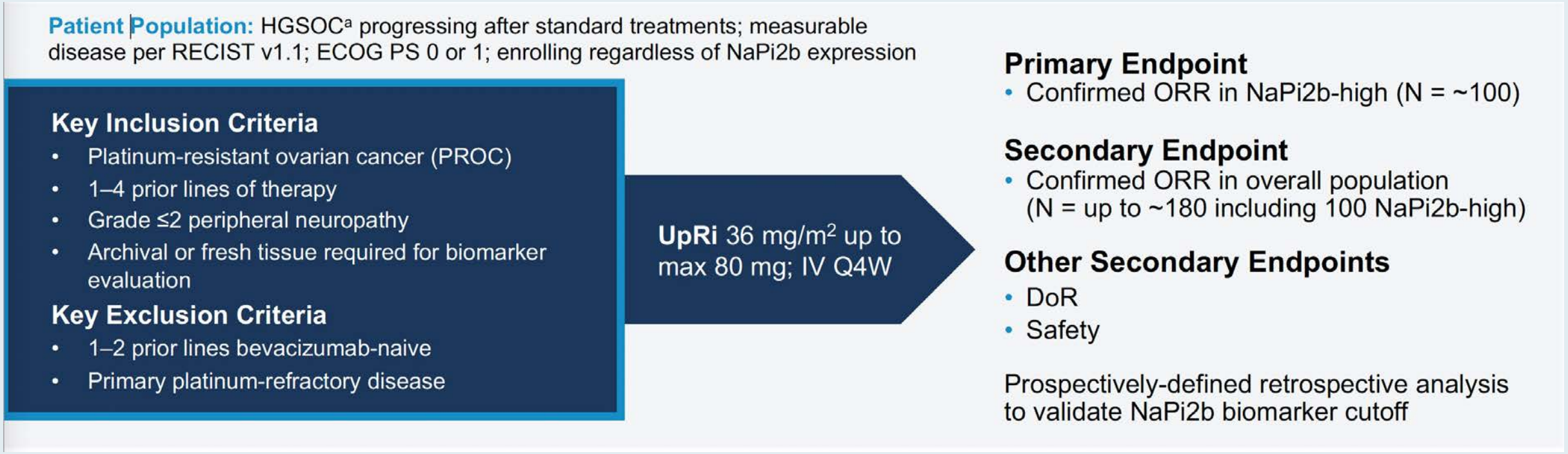
Richardson DL et al. SGO 2022;Abstract 76.

Time on UpRi Study in Evaluable Patients



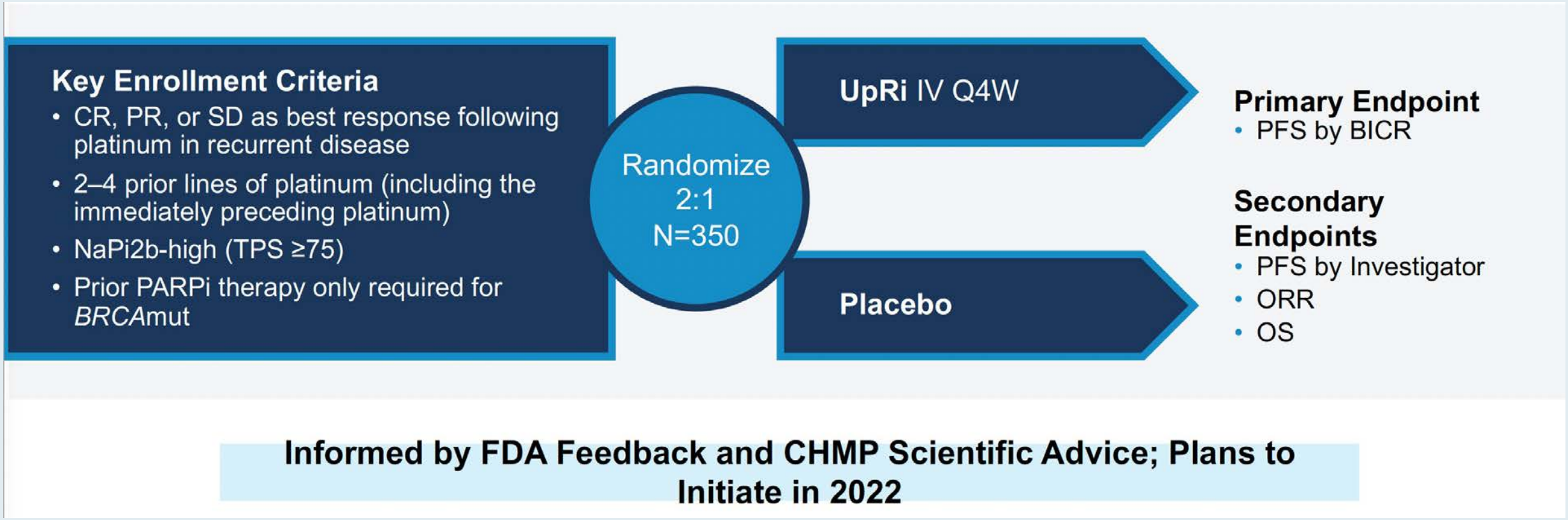
Richardson DL et al. SGO 2022;Abstract 76.

Ongoing UPLIFT (ENGOT-OV67/GOG-3048) Study Schema



Richardson DL et al. SGO 2022;Abstract 76.

Ongoing UP-NEXT Phase III (ENGOT-OV71-NSGO-CTU/GOG-3049) Study Schema



Richardson DL et al. SGO 2022;Abstract 76.

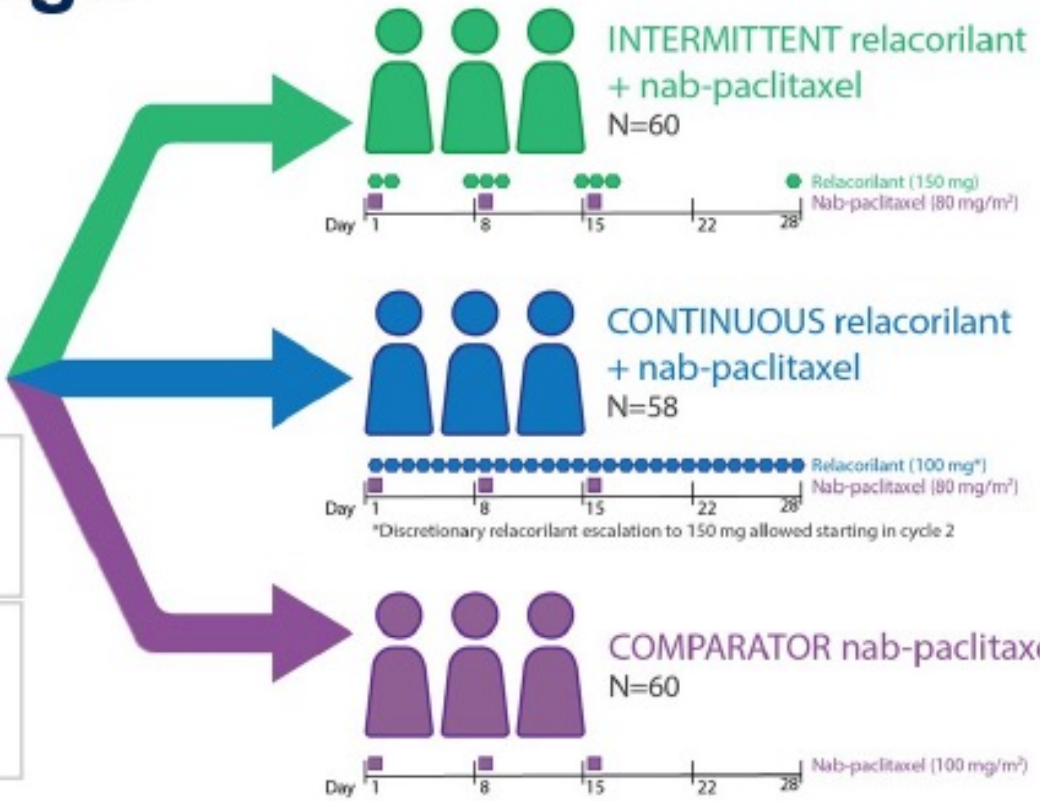
Relacorilant + Nab-paclitaxel Phase 2 Study Design

Randomized 1:1:1

- Measurable or non-measurable disease by RECIST v1.1
- Up to 4 prior chemotherapeutic regimens

Stratification factors:

- Relapse within 6 months of most recent taxane
- Presence of ascites



Primary endpoint:

- Progression-free survival (PFS) by investigator and RECIST v1.1

Secondary endpoints:

- Objective response rate (ORR)
- Duration of response (DoR)
- Overall survival (OS)
- Safety of the relacorilant + nab-paclitaxel combination

Statistical assumptions:

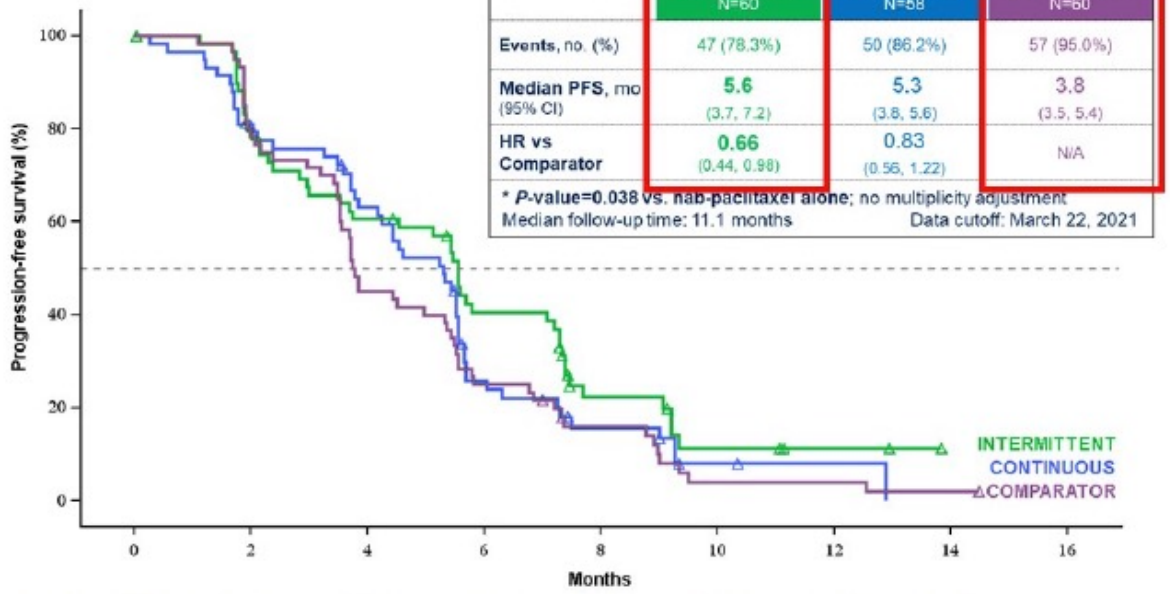
- **CONTINUOUS vs COMPARATOR**: 91 PFS events to detect a HR=0.56 (median PFS increase from 3.8 to 6.8 mo)
- **INTERMITTENT vs COMPARATOR**: 92 PFS events to detect a HR=0.7 (median PFS increase from 3.8 to 5.4 mo)

PFS analysis reported at ESMO 2021

Colombo N et al. ASCO 2022;Abstract LBA5503; Liu N. ASCO 2022;Highlights of the Day: Gynecologic Cancers.

Investigator assessed PFS and OS of relacorilant + nab-paclitaxel

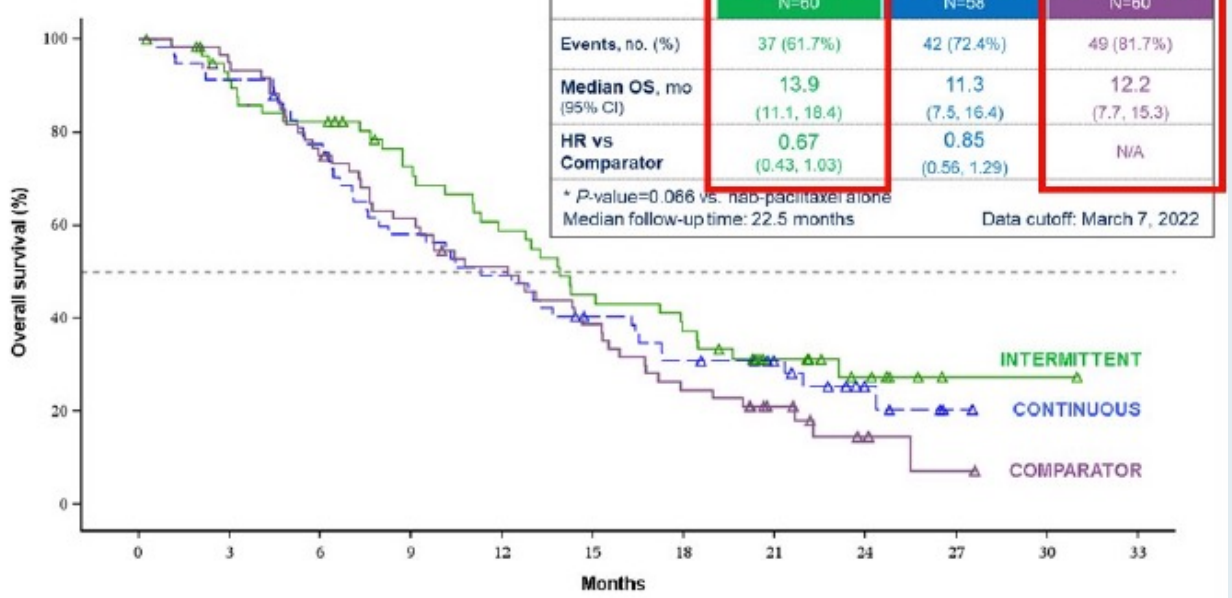
Progression free survival



	INTERMITTENT* N=60	CONTINUOUS N=58	COMPARATOR N=60
Events, no. (%)	47 (78.3%)	50 (86.2%)	57 (95.0%)
Median PFS, mo (95% CI)	5.6 (3.7, 7.2)	5.3 (3.8, 5.6)	3.8 (3.5, 5.4)
HR vs Comparator	0.66 (0.44, 0.98)	0.83 (0.56, 1.22)	N/A

* *P*-value=0.038 vs. nab-paclitaxel alone; no multiplicity adjustment
Median follow-up time: 11.1 months
Data cutoff: March 22, 2021

Overall survival



	INTERMITTENT* N=60	CONTINUOUS N=58	COMPARATOR N=60
Events, no. (%)	37 (61.7%)	42 (72.4%)	49 (81.7%)
Median OS, mo (95% CI)	13.9 (11.1, 18.4)	11.3 (7.5, 16.4)	12.2 (7.7, 15.3)
HR vs Comparator	0.67 (0.43, 1.03)	0.85 (0.56, 1.29)	N/A

* *P*-value=0.066 vs. nab-paclitaxel alone
Median follow-up time: 22.5 months
Data cutoff: March 7, 2022

Colombo N et al. ASCO 2022;Abstract LBA5503; Liu N. ASCO 2022;Highlights of the Day: Gynecologic Cancers.

Recent Advances in Medical Oncology:
A daylong CME hybrid (live/online) event

Saturday, August 6, 2022

9:00 AM – 4:30 PM PT (12:00 PM – 7:30 PM ET)

Bellagio Las Vegas | Las Vegas, Nevada

Faculty

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Harold J Burstein, MD, PhD
Ibiayi Dagogo-Jack, MD
Rafael Fonseca, MD
Brad S Kahl, MD
Rutika Mehta, MD, MPH
Craig Moskowitz, MD
Joyce O'Shaughnessy, MD
Krina Patel, MD, MSc
Philip A Philip, MD, PhD, FRCP
Suresh S Ramalingam, MD
Sandy Srinivas, MD

Moderator

Neil Love, MD

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

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