Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

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Faculty

Joyce F Liu, MD, MPH
Associate Chief and Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

David M O'Malley, MD
Director and Professor
Division of Gynecologic Oncology in Obstetrics and Gynecology
John G Boutselis Chair in Gynecologic Oncology
The Ohio State University and The James Comprehensive Cancer Center
Columbus, Ohio

Mansoor Raza Mirza, MD
Chief Oncologist
Copenhagen University Hospital
Medical Director
Nordic Society of Gynaecological Oncology – Clinical Trial Unit
Vice President, European Society of Gynaecological Oncology
Copenhagen, Denmark

Moderator
Kathleen N Moore, MD, MS
Deputy Director
Associate Director, Clinical Research
Virginia Kerley Cade Chair in Developmental Therapeutics
Co-Director, Cancer Therapeutics Program
Stephenson Cancer Center at the University of Oklahoma HSC
Associate Director, GOG Partners
Board of Directors, GOG Foundation
Oklahoma City, Oklahoma

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Dr Liu — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Eisai Inc, Genentech, a member of the Roche Group, GSK, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Regeneron Pharmaceuticals Inc, Zentalis Pharmaceuticals
Consulting Agreement	Bristol Myers Squibb
Trial Support to My Institution for Study Conduct	Aravive Inc, Arch Oncology, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Clovis Oncology, GSK, Impact Therapeutics, Regeneron Pharmaceuticals Inc, Seagen Inc, Vigeo Therapeutics, Volastra Therapeutics Inc, Zentalis Pharmaceuticals

Dr Mirza — Disclosures
Faculty

Advisory Committees	Allarity Therapeutics, BIOCAD, BioNTech SE, Daiichi Sankyo Inc, Eisai Inc, GSK, Karyopharm Therapeutics, Merck, Mersana Therapeutics Inc, MSD, Zai Lab
Consulting Agreements	Allarity Therapeutics, AstraZeneca Pharmaceuticals LP, BIOCAD, BioNTech SE, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Eisai Inc, Genmab US Inc, GSK, ImmunoGen Inc, Incyte Corporation, Karyopharm Therapeutics, Merck, Mersana Therapeutics Inc, MSD, Novartis, Regeneron Pharmaceuticals Inc, Roche Laboratories Inc, Seagen Inc, Takeda Pharmaceuticals USA Inc, Zai Lab
Stock Options/Stock — Public Companies	Karyopharm Therapeutics, Sera Prognostics

Dr O'Malley — Disclosures
Faculty

Advisory Committees and Consulting Agreements (Personal Fees)	AbbVie Inc, Adaptimmune, Agenus Inc, Arcus Biosciences, Arquer Diagnostics, AstraZeneca Pharmaceuticals LP, Atossa Therapeutics, Cardiff Oncology, Celcuity, Clovis Oncology, Corcept Therapeutics, Duality Biologics, Eisai Inc, Elevar Therapeutics, Exelixis Inc, F Hoffmann-La Roche Ltd, Genelux Corporation, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Imvax Inc, InterVenn Biosciences, InxMed, Iovance Biotherapeutics, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Laekna Therapeutics, Leap Therapeutics Inc, Luzsana Biotechnology, Merck, Mersana Therapeutics Inc, MSD, Myriad Genetic Laboratories Inc, Novartis, Novocure Inc, OncoC4, Onconova Therapeutics Inc, Regeneron Pharmaceuticals Inc, Replimune, Roche Diagnostics, R-Pharm US, Seagen Inc, Sorrento Therapeutics, Sumitomo Dainippon Pharma Oncology Inc, Sutro Biopharma, Tarveda Therapeutics, Toray Industries Inc, Trillium Therapeutics Inc, Umoja Biopharma, VBL Therapeutics, Verastem Inc, Vincerx Pharma, Xencor, Zentalis Pharmaceuticals
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Dr Moore — Disclosures
Moderator

Advisory Committees	Aadi Bioscience, Aravive Inc, AstraZeneca Pharmaceuticals LP, Blueprint Medicines, Caris Life Sciences, Clovis Oncology, Duality Biologics, Eisai Inc, Genentech, a member of the Roche Group, GSK, ImmunoGen Inc, Janssen Biotech Inc, Lilly, Merck, Mersana Therapeutics Inc, Myriad Genetic Laboratories Inc, Panavance Therapeutics, Regeneron Pharmaceuticals Inc, VBL Therapeutics, Verastem Inc, Zentalis Pharmaceuticals
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Contracted Research	Genentech, a member of the Roche Group, GSK, Lilly, PTC Therapeutics

Dr Armstrong — Disclosures
Video Participant

Consulting Agreement (Uncompensated Consulting)	Janssen Biotech Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, Eisai Inc
Data and Safety MonitoringBoard/Committee	AstraZeneca Pharmaceuticals LP

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Dr Backes — Disclosures
Video Participant

Advisory Committees and Consulting Agreements	AstraZeneca Pharmaceuticals LP, BioNTech SE, Clovis Oncology, Daiichi Sankyo Inc, Eisai Inc, EMD Serono Inc, GSK, ImmunoGen Inc, Merck

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Dr Grisham — Disclosures
Video Participant

Consulting Agreements	AstraZeneca Pharmaceuticals LP, GSK, Myriad Genetic Laboratories Inc, Natera Inc
Contracted Research	Context Therapeutics, Corcept Therapeutics, Pfizer Inc, SpringWorks Therapeutics Inc, Verastem Inc

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Dr Salani — Disclosures
Video Participant

Advisory Committees	Eisai Inc, GSK, ImmunoGen Inc, Merck, Regeneron Pharmaceuticals Inc, Seagen Inc

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, GSK, Merck, and Mural Oncology Inc.

Research To Practice CME Planning Committee Members, Staff and Reviewers

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This program will contain discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer®

Monday, March 18, 2024

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Nicoletta Colombo, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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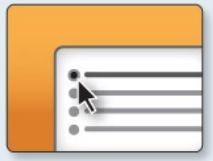
Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

Complete Your Evaluation: Tap the CME Evaluation button to complete your evaluation electronically to receive credit for your participation.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

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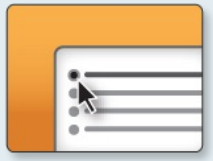
Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.



Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CME Credit: A CME credit link will be provided in the chat room at the conclusion of the program.

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Ovarian Cancer

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Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

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Agenda

Module 1: Current Up-Front Treatment for Advanced Ovarian Cancer (OC) — Dr Liu

Module 2: Potential Role of Immunotherapeutic Strategies for Advanced OC — Dr O'Malley

Module 3: Incorporation of Novel Therapies into the Management of Relapsed/Refractory OC — Dr Moore

Module 4: Diagnosis and Management of Adverse Events Associated with Commonly Employed Therapies for Advanced OC — Dr Mirza

Consulting Faculty

Deborah K Armstrong, MD
The Sidney Kimmel Comprehensive Cancer Center
Baltimore, Maryland

Rachel N Grisham, MD
Memorial Sloan Kettering Cancer Center
New York, New York

Floor J Backes, MD
The James Cancer Hospital and Solove Research Institute
Columbus, Ohio

Ritu Salani, MD, MBA
UCLA Health
Los Angeles, California

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MODULE 1: Current Up-Front Treatment for Advanced Ovarian Cancer (OC) — Dr Liu

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Consulting Faculty Questions

Integration of bevacizumab into neoadjuvant therapy; quality of tissue testing specimens to inform neoadjuvant therapy selection

Neil Love, MD

Deborah K Armstrong, MD

Rachel N Grisham, MD

QUESTIONS FOR THE FACULTY

Deborah K Armstrong, MD

Rachel N Grisham, MD

What criteria do you use to select patients for neoadjuvant systemic therapy?

In what situations do you use bevacizumab in the neoadjuvant setting? In what situations, if any, will you add bevacizumab after surgery for a patient who did not receive it as a component of neoadjuvant therapy?

Should genomic analysis be conducted prior to neoadjuvant treatment, and if so, what assays should be employed (eg, next-generation sequencing, germline, liquid biopsy)?

Are there clinical situations in which you could envision the potential benefit of neoadjuvant PARP inhibition?

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Consulting Faculty Questions

First-line maintenance therapy options; potential utility of ctDNA assays

Neil Love, MD

Ritu Salani, MD, MBA

Deborah K Armstrong, MD

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QUESTIONS FOR THE FACULTY

Ritu Salani, MD, MBA

What is your preferred initial therapy for a patient with advanced ovarian cancer and a BRCA mutation? Do you have a preferred PARP inhibitor for these patients? Do you typically employ bevacizumab? How long would you continue treatment with a PARP inhibitor for these patients?

Deborah K Armstrong, MD

What is your preferred initial therapy for a patient with HRD-positive, BRCA-negative advanced ovarian cancer? What about for a patient with HRD-negative, BRCA-negative disease? Do you have a preferred PARP inhibitor for these patients? Do you typically employ bevacizumab? How long would you continue treatment with a PARP inhibitor for these patients?

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A 65-year-old woman with no comorbidities presenting with OC with extensive intra-abdominal disease and ascites (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 you most likely recommend as maintenance therapy and for what duration if genetic testing revealed a BRCA1/2 mutation?

	Maintenance therapy	Duration of maintenance
 Dr Liu	Olaparib/bevacizumab	2 years; 15 cycles
 Dr Mirza	Olaparib/bevacizumab	2 years
 Dr Moore	Olaparib/bevacizumab	2 years
 Dr O'Malley	Olaparib/bevacizumab	2 years; 1 year
 Dr Armstrong	Olaparib	2 years
 Dr Grisham	Olaparib/bevacizumab	2 years; 1 year

A 65-year-old woman with no comorbidities presenting with OC with extensive intra-abdominal disease and ascites (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 you most likely recommend as maintenance therapy and for what duration if genetic testing revealed the tumor to be BRCA wild type, HR deficient (LOH high)?

	Maintenance therapy	Duration of maintenance
 Dr Liu	Olaparib/bevacizumab	2 years; 15 cycles
 Dr Mirza	Olaparib/bevacizumab	2 years
 Dr Moore	Olaparib/bevacizumab (if HRD)	2 years
 Dr O'Malley	Olaparib/bevacizumab	2 years; 1 year
 Dr Armstrong	Olaparib/bevacizumab	2 years
 Dr Grisham	Olaparib/bevacizumab	2-3 years; 1 year

A 65-year-old woman with no comorbidities presenting with OC 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 and for what duration if genetic testing revealed a BRCA1/2 mutation?

	Maintenance therapy	Duration of maintenance
 Dr Liu	Olaparib	2 years
 Dr Mirza	Niraparib	3 years
 Dr Moore	Olaparib	2 years
 Dr O'Malley	Rucaparib	2 years
 Dr Armstrong	Olaparib	2 years
 Dr Grisham	Olaparib	2 years

A 65-year-old woman with no comorbidities presenting with OC 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 and for what duration if genetic testing revealed the tumor to be BRCA wild type, HR deficient (LOH high)?

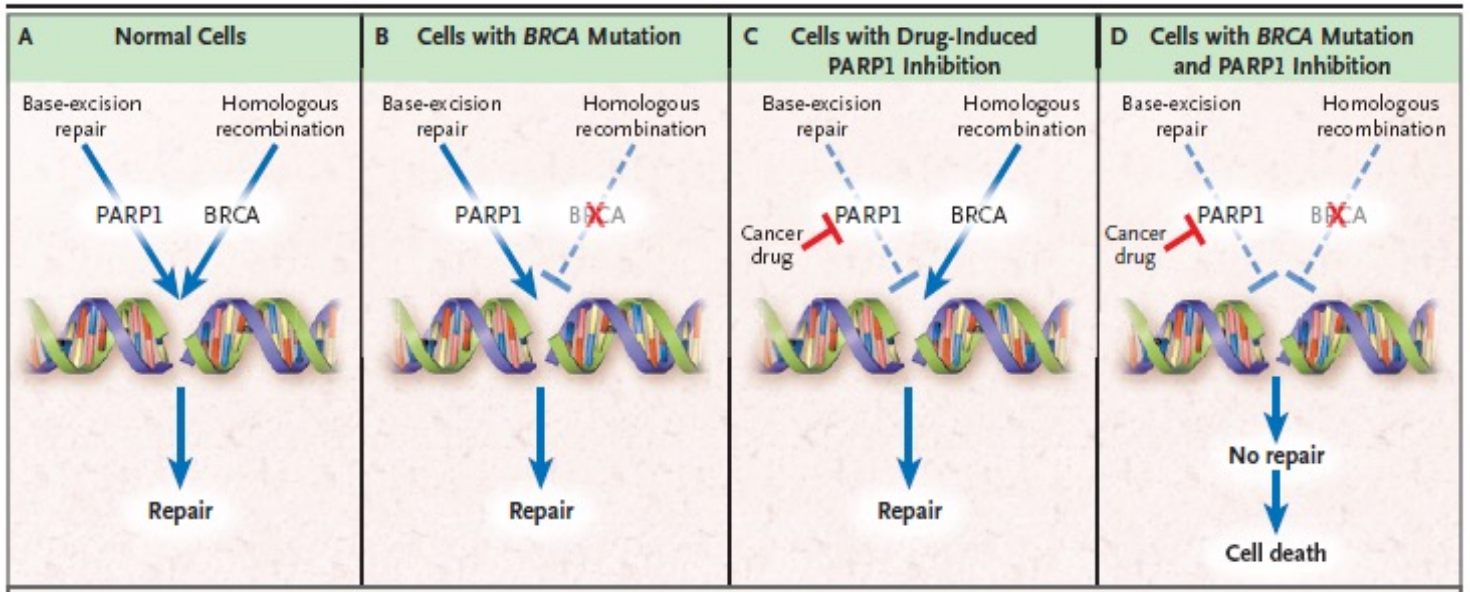
	Maintenance therapy	Duration of maintenance
 Dr Liu	Niraparib	3 years
 Dr Mirza	Niraparib	3 years
 Dr Moore	Olaparib/bevacizumab (if HRD)	2 years
 Dr O'Malley	Rucaparib	2 years
 Dr Armstrong	Niraparib	2 years
 Dr Grisham	Niraparib	2 to 3 years

Current Upfront Treatment for Ovarian Cancer

Joyce Liu, MD, MPH
Associate Chief and Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute, Boston, MA

Implications of *BRCA* and homologous recombination (HR) status in ovarian cancer

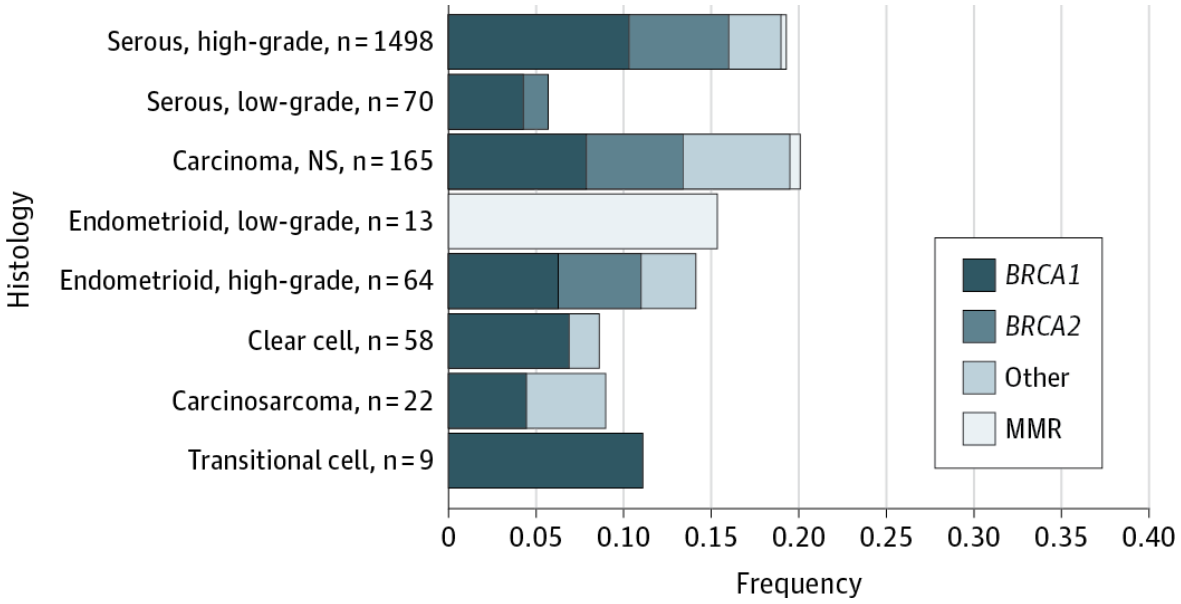
- Clinical testing for germline *BRCA* and other genetic susceptibility genes with implications for cascade testing
- Somatic testing for *BRCA* and HR deficiency with clinical decision-making implications in the era of PARP inhibitors
- Homologous recombination deficiency is a state where a cell cannot perform homologous recombination
  - Can be caused by loss of function in genes in HR pathway (e.g., *BRCA1/2*)
  - Leads to increased vulnerability to drugs such as PARP inhibitors



Silver and Iglehart, *N Engl J Med*, 2009

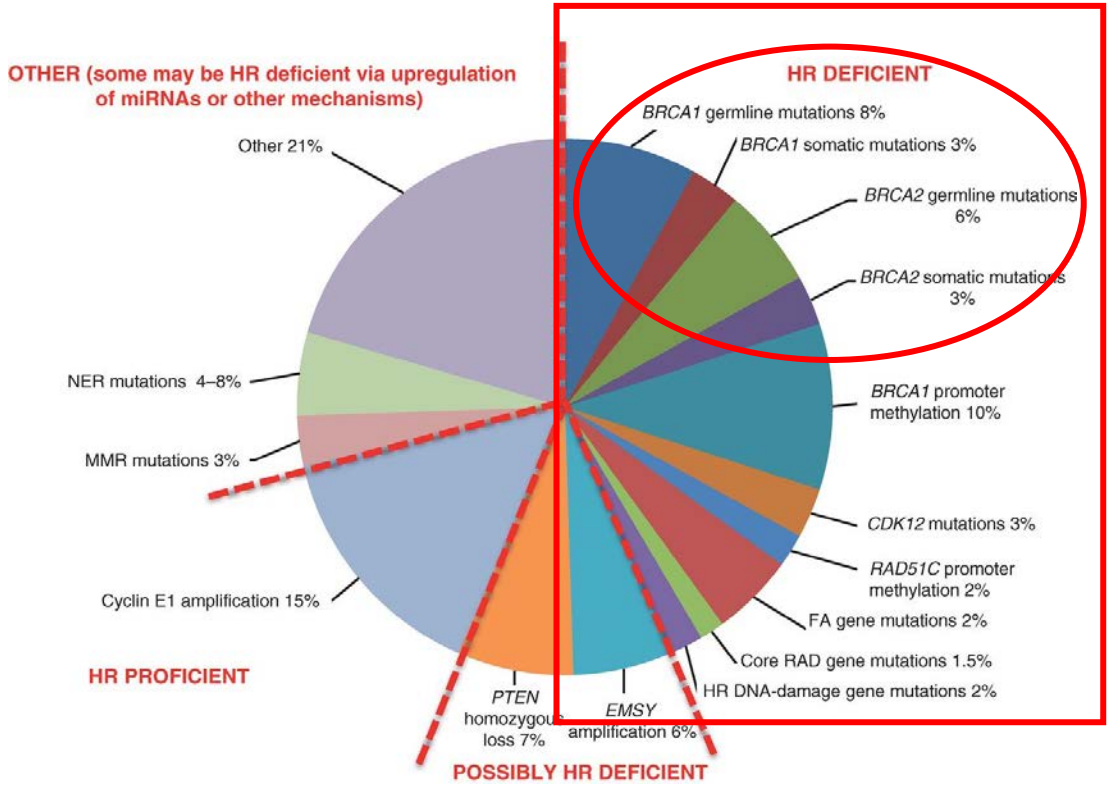
BRCA mutations and HRD are common in ovarian cancer

BRCA1/2 mutations occur across EOC subtypes



Norquist et al, *JAMA Oncol*, 2016

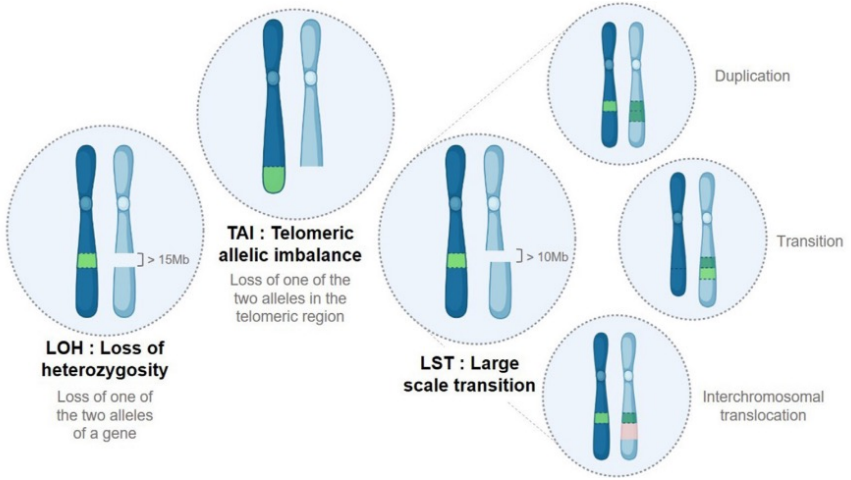
~50% of HGSOC have evidence of HR deficiency



Konstantinopoulos et al, *Cancer Discov*, 2015

Testing for Homologous Recombination Deficiency (HRD)

- Homologous recombination (HR) is one of the primary pathways by which cells repair double-strand DNA breaks
- Current commercial assays of HRD use patterns of DNA damage to indirectly predict whether a cell is HR deficient or HR proficient



Paulet et al, *Eur J Cancer*, 2022

Assays of HRD in Ovarian Cancer used in randomized Phase 3 trials

Test	Measurement	Studies Used
Myriad MyChoice HRD	Combination of 3 types of DNA change: • Loss of heterozygosity (LOH) • Telomeric allelic imbalance • Large-scale state transitions Also includes all deleterious *BRCA1/2* mutations	VELIA PRIMA PAOLA-1 NOVA
FoundationOne LOH	Loss of heterozygosity	ARIEL3 ATHENA-MONO

Additional proposed assays for HRD

Test	Measurement	
HRR mutations	Identify pathogenic mutations in selected HRR genes	Non-BRCA HRR genes not predictive biomarker in PAOLA-1
Functional HRD assays (e.g., RAD51 foci)	Detection RAD51 foci formation by IHC or IF	

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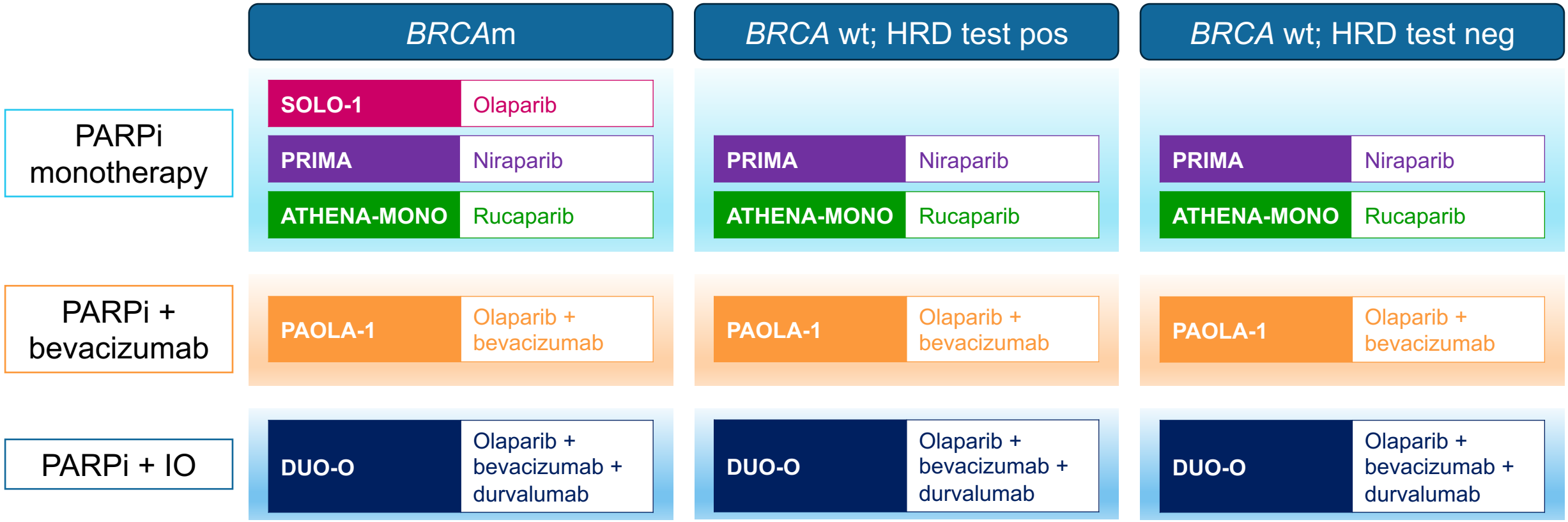
Randomized studies informing front-line PARPi maintenance

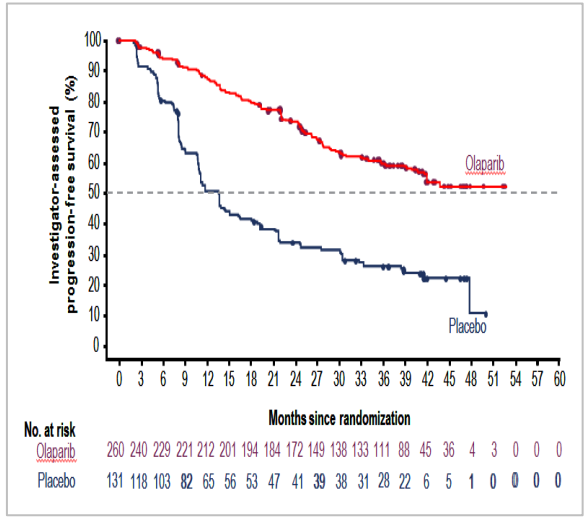
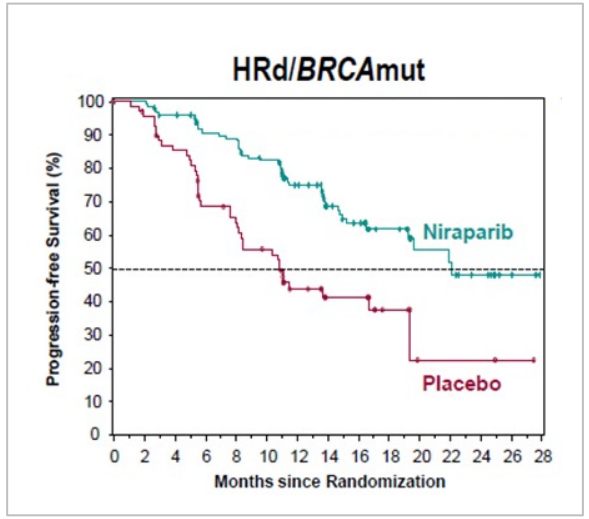
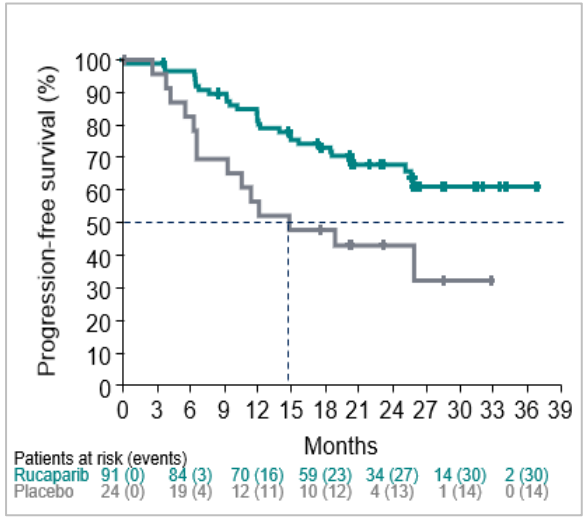


Additional studies performed in China: PRIME (niraparib); FLAMES (senaparib)
Non-randomized studies: OVARIO (niraparib + bevacizumab)

Randomized studies informing front-line PARPi maintenance

	*BRCA*m	*BRCA* wt; HRD test pos	*BRCA* wt; HRD test neg
PARPi monotherapy	SOLO-1: Olaparib PRIMA: Niraparib ATHENA-MONO: Rucaparib	PRIMA: Niraparib ATHENA-MONO: Rucaparib	PRIMA: Niraparib ATHENA-MONO: Rucaparib
PARPi + bevacizumab	PAOLA-1: Olaparib + bevacizumab	PAOLA-1: Olaparib + bevacizumab	PAOLA-1: Olaparib + bevacizumab
PARPi + IO	DUO-O: Olaparib + bevacizumab + durvalumab	DUO-O: Olaparib + bevacizumab + durvalumab	DUO-O: Olaparib + bevacizumab + durvalumab

*BRCA*m tumors: PARP inhibitor monotherapy maintenance

SOLO-1 Olaparib	PRIMA Niraparib	ATHENA-MONO Rucaparib
		
N = 391	**N = 223**	**N = 235**
HR 0.30 95% CI 0.23-0.41	**HR 0.40** 95% CI 0.27-0.62	**HR 0.40** 95% CI 0.21-0.75
13.8 mos vs NR	10.9 vs 22.1 mos	14.7 mos vs NR

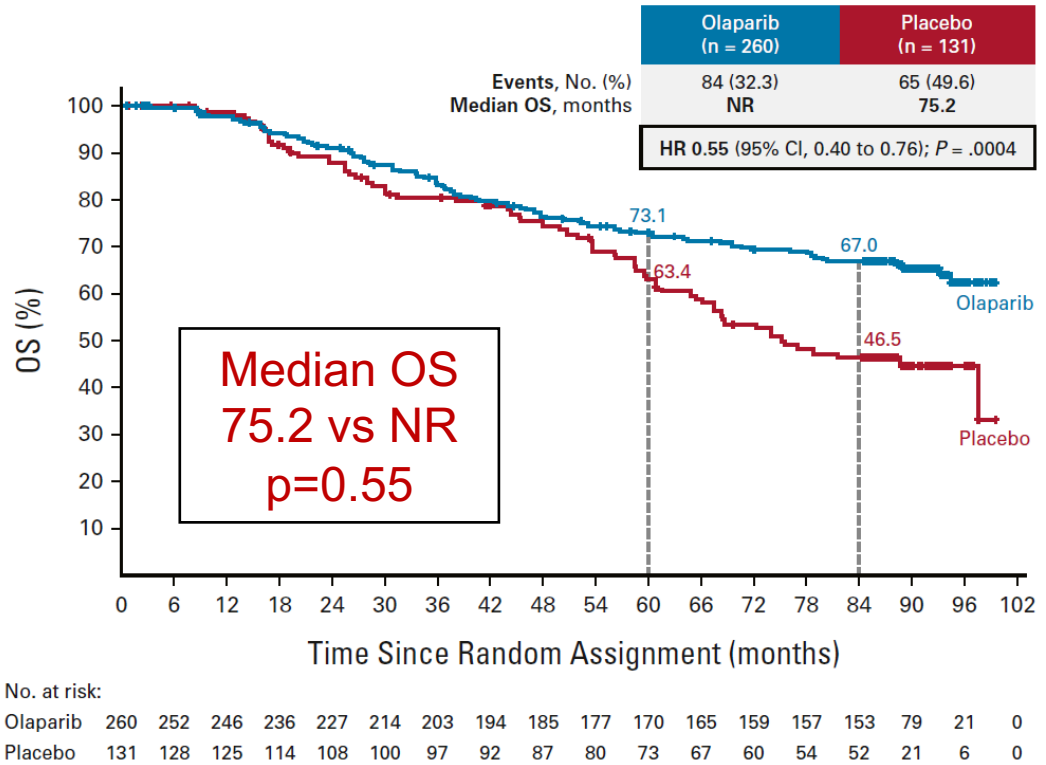
Dana-Farber Cancer Institute

Moore et al. *N Engl J Med* 2018; Gonzalez-Martin et al. *N Engl J Med* 2019; Monk et al. *J Clin Oncol* 2022

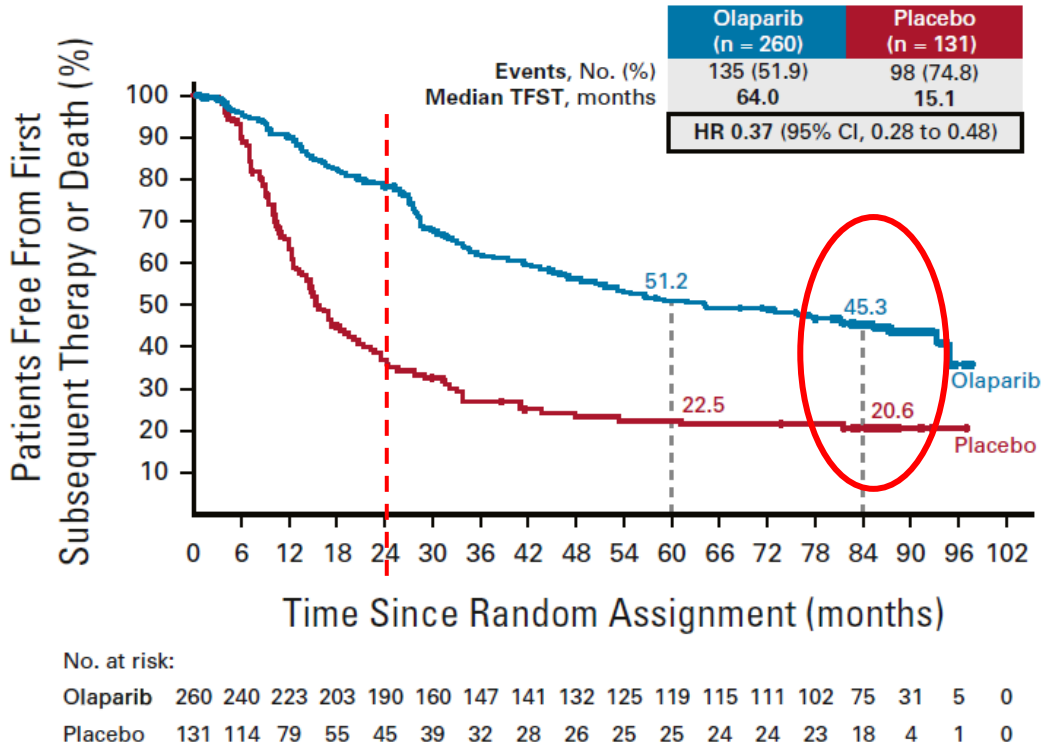
Olaparib maintenance demonstrates long-term benefit in individuals with *BRCA*mt ovarian cancers

SOLO-1: 7 year follow-up

Overall Survival



Time to First Subsequent Therapy



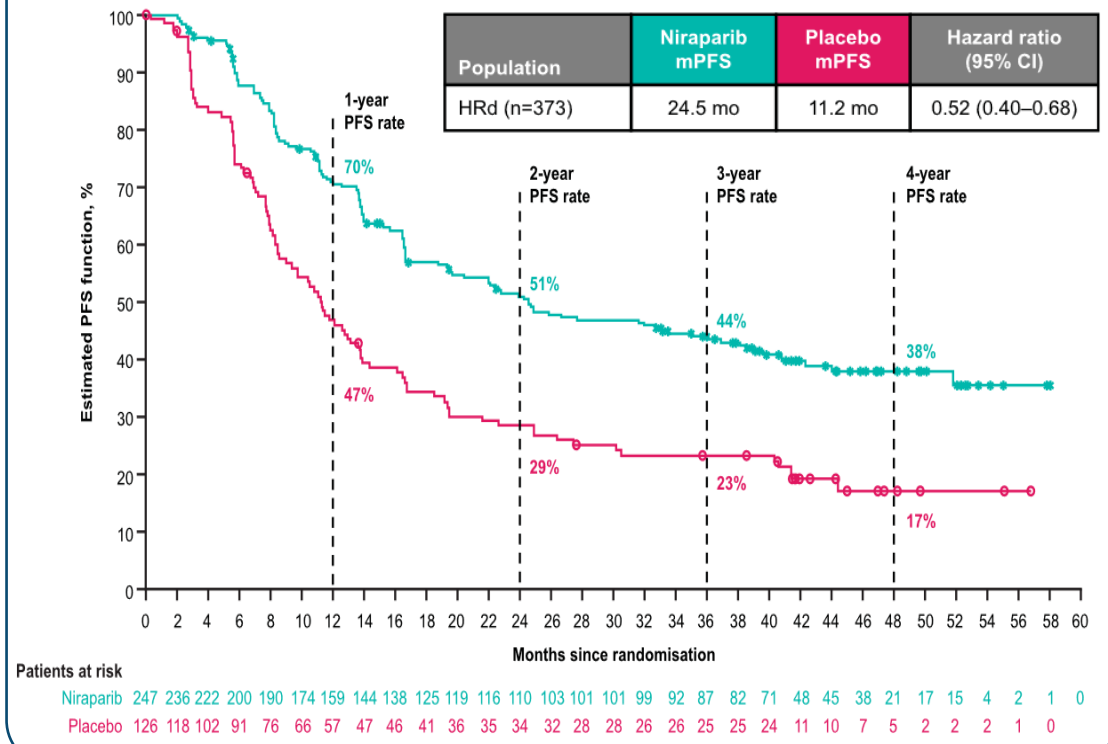
Dana-Farber Cancer Institute

Disilvestro et al. *J Clin Oncol* 2023

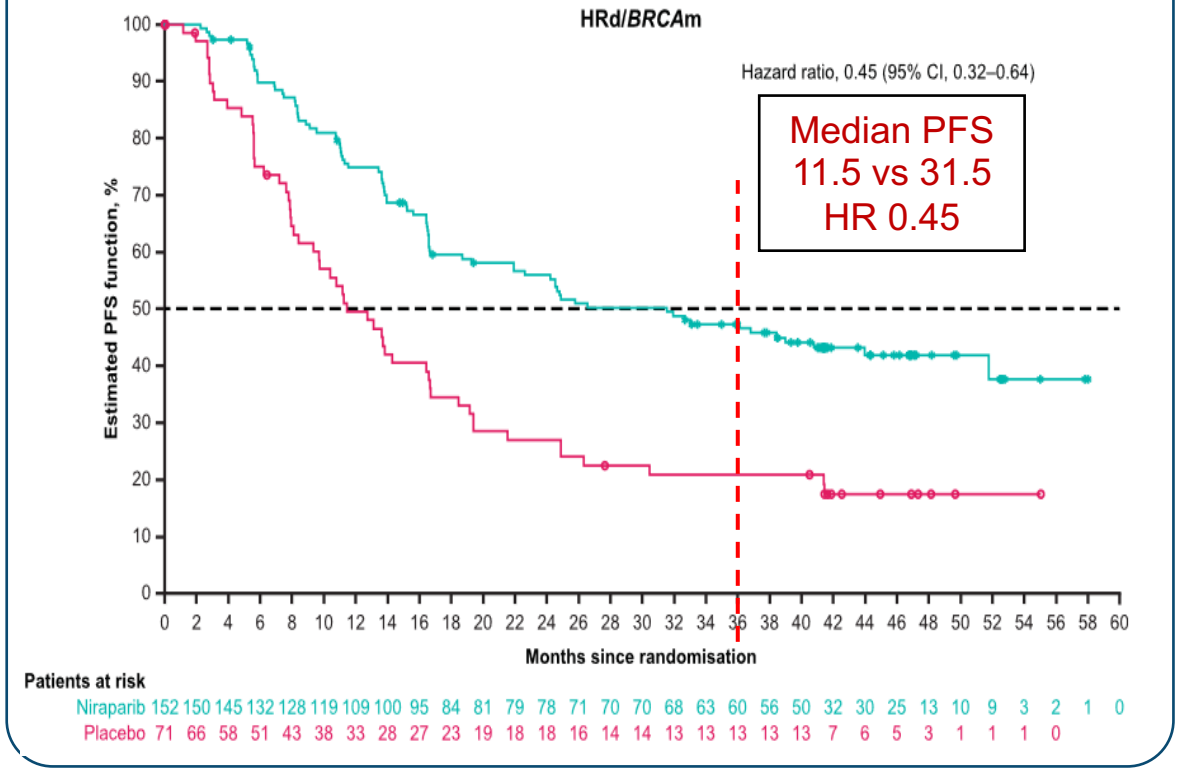
Niraparib maintenance with continued PFS benefit in *BRCA*m ovarian cancers with 3.5 years follow-up

PRIMA: 3.5 year follow-up

HRD population (inc. *BRCA*m)

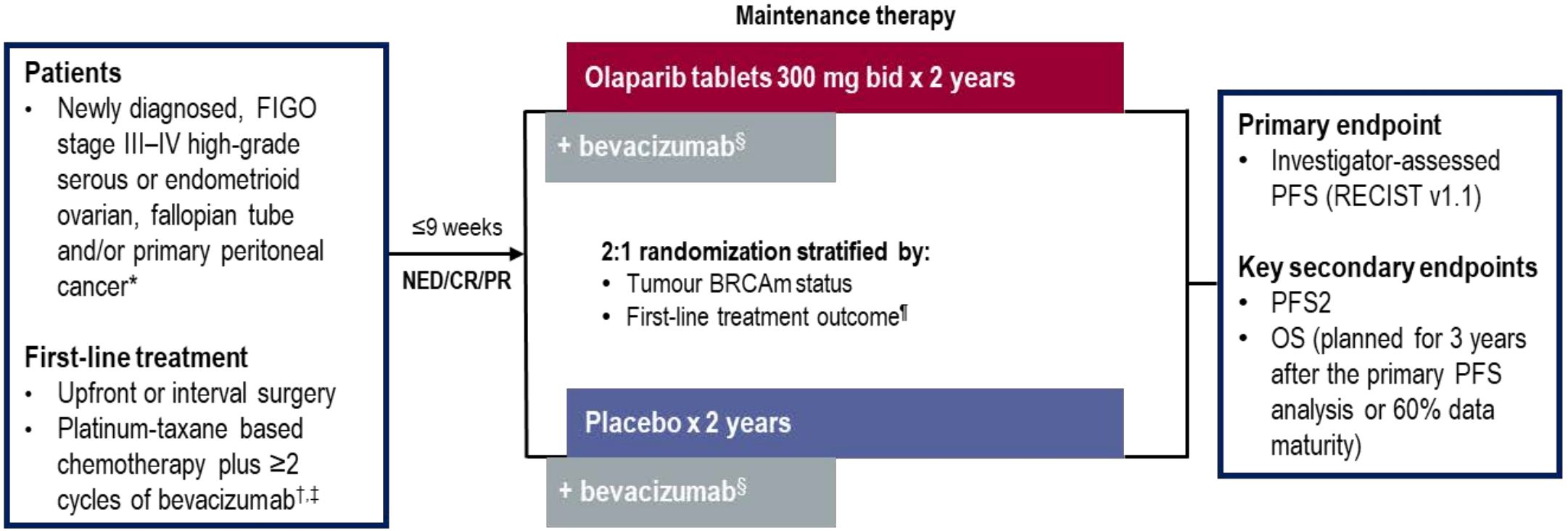


*BRCA*m



Gonzalez-Martin et al. *Eur J Cancer* 2023

PAOLA-1 trial design



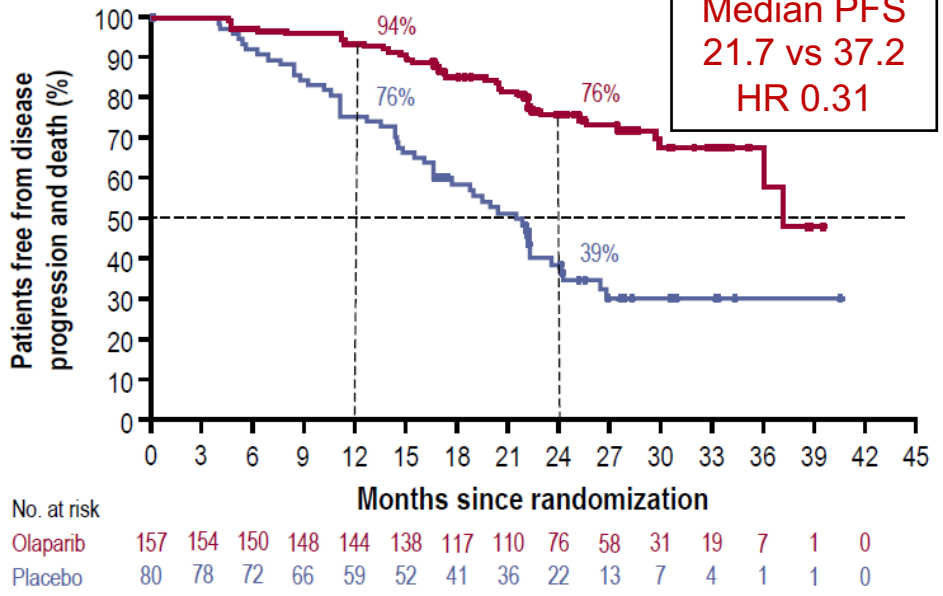
*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; §Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; ¶According to timing of surgery and NED/CR/PR. bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

Ray-Coquard et al. *N Engl J Med* 2019

Olaparib/bevacizumab improves outcomes compared to bevacizumab in *BRCA*m ovarian cancer

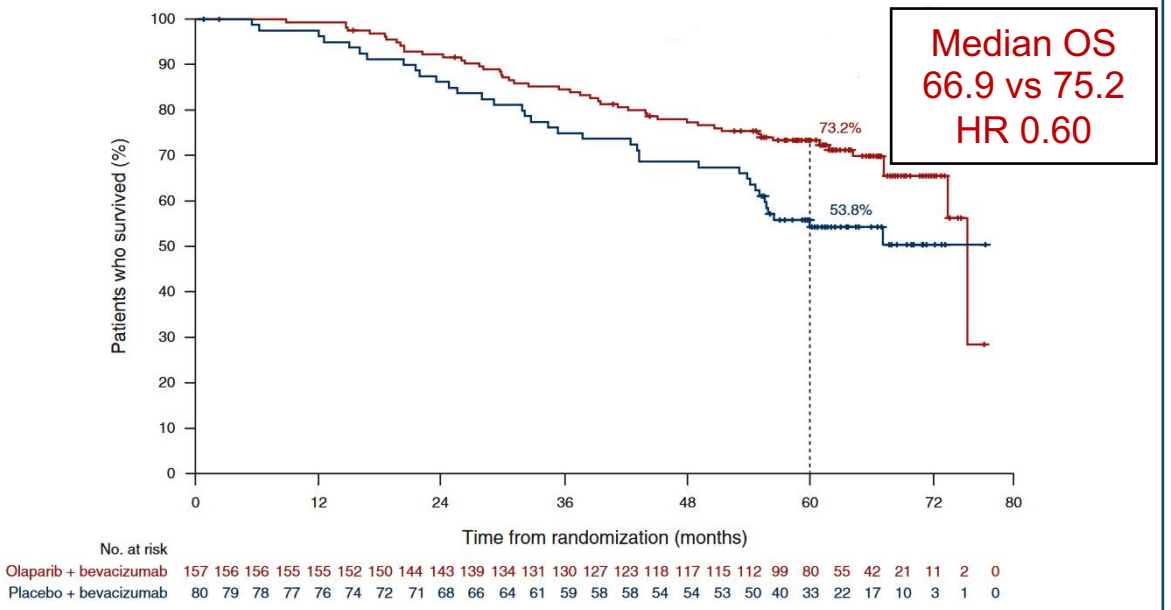
PAOLA-1: Primary PFS and Final OS analyses

Primary analysis PFS t*BRCA*m



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

Final OS analysis t*BRCA*m

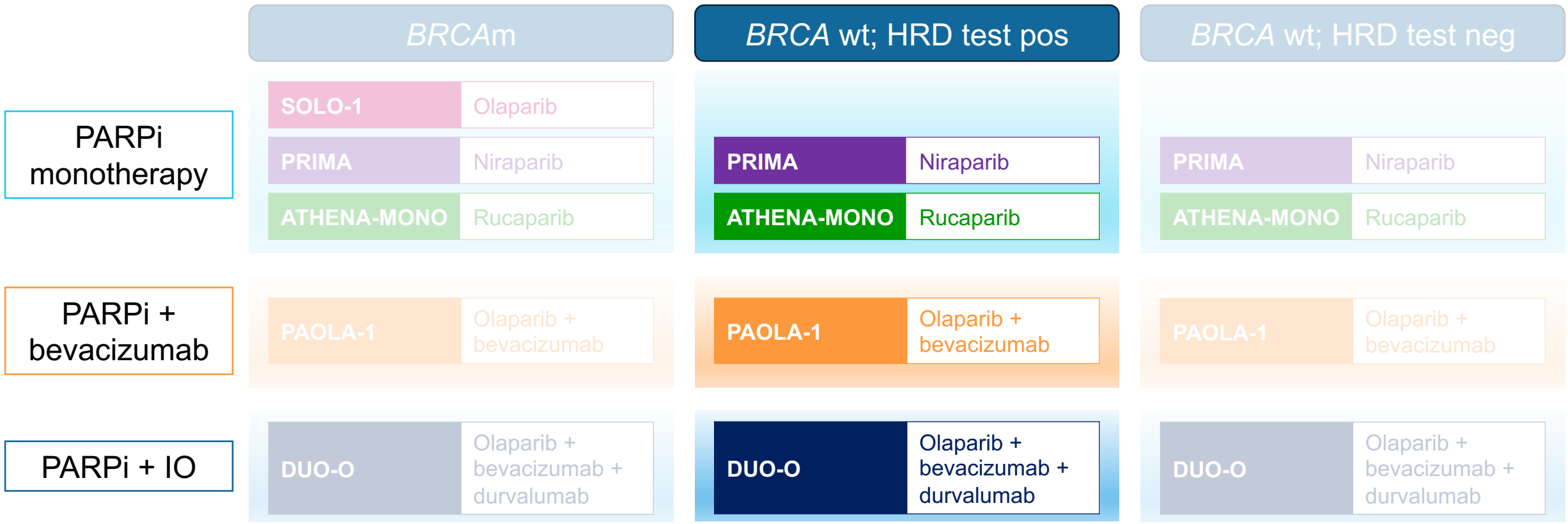


	Olaparib + bevacizumab (*N* = 157)	Placebo + bevacizumab (*N* = 80)
Events, *n* (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)[c]	66.9
5-Year OS rate, %	**73.2**	**53.8**
	HR 0.60 (95% CI 0.39-0.93)	

Dana-Farber Cancer Institute

Ray-Coquard et al. *N Engl J Med* 2019; Ray-Coquard et al. *Ann Oncol* 2023

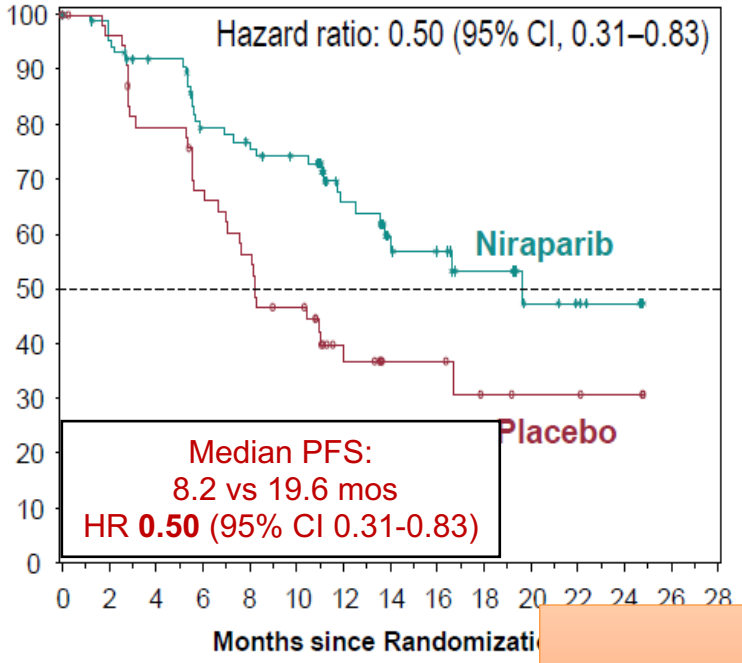
Randomized studies informing front-line PARPi maintenance



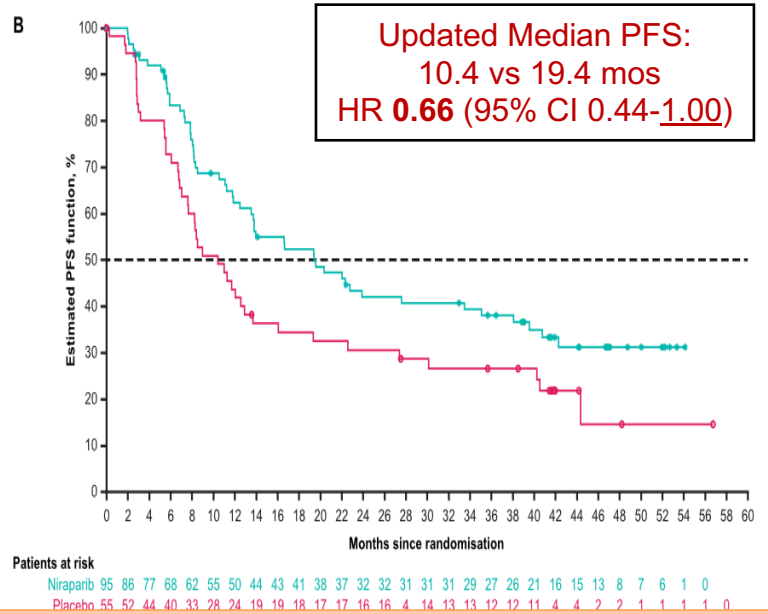
PARPi monotherapy maintenance results in PFS benefit in *BRCA*wt HRD test positive tumors

PRIMA (HRD by GIS ≥42)

Primary analysis

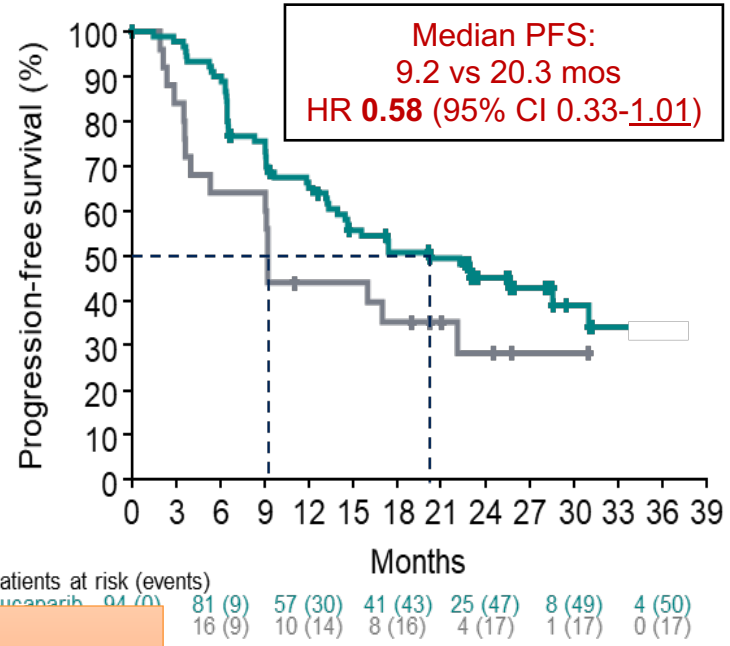


3.5year follow-up



ATHENA-MONO (HRD by LOH ≥16%)

Primary analysis



OS outcomes still maturing

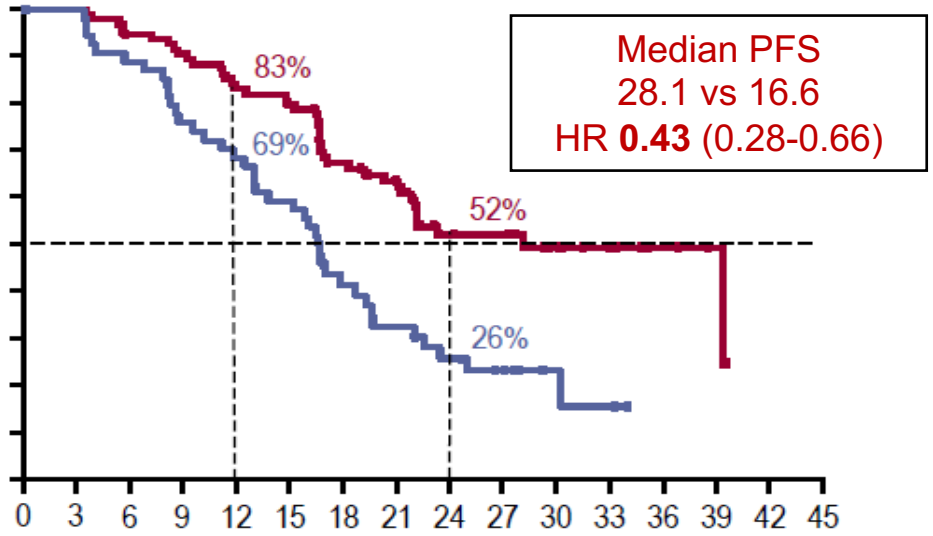
Dana-Farber Cancer Institute

Gonzalez-Martin et al. *N Engl J Med* 2019; Gonzalez-Martin et al. *Eur J Cancer* 2023; Monk et al. *J Clin Oncol* 2022

Olaparib/bevacizumab improves outcomes compared to bevacizumab in *BRCA*wt HRD test positive ovarian cancer

PAOLA-1: Primary PFS and Final OS analyses

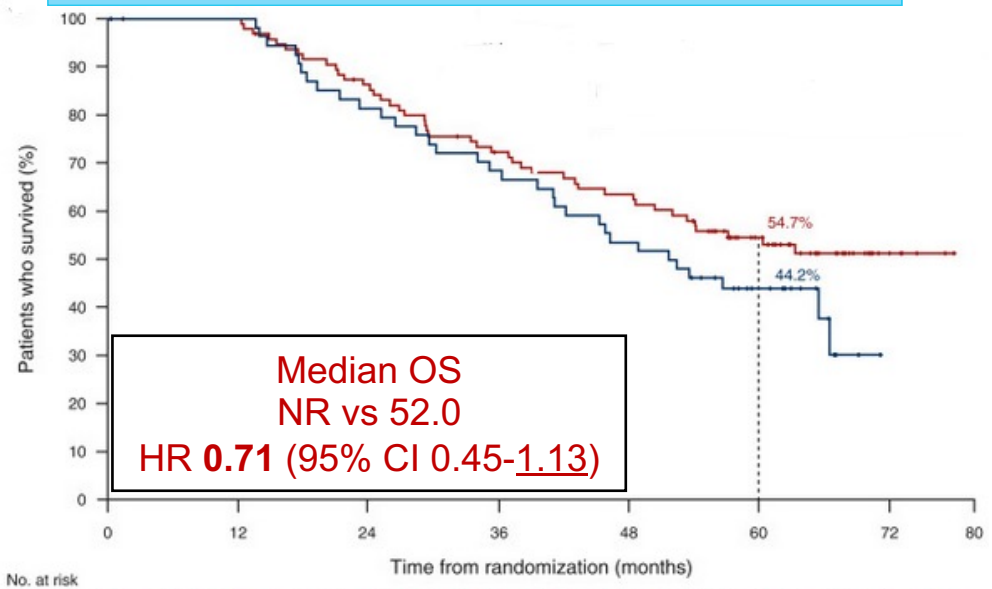
Primary analysis PFS *BRCA*wt, HRD+



Median PFS
28.1 vs 16.6
HR **0.43** (0.28-0.66)

Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
43 (44)	40 (73)
28.1*	**16.6**
HR 0.43 (95% CI 0.28–0.66)	

Final OS analysis *BRCA*wt, HRD+



Median OS
NR vs 52.0
HR **0.71** (95% CI 0.45-1.13)

	Olaparib + bevacizumab (*N* = 97)	Placebo + bevacizumab (*N* = 55)
Events, *n* (%)	44 (45.4)	32 (58.2)
Median OS, months	NR	52.0
5-Year OS rate, %	**54.7**	**44.2**
	HR 0.71 (95% CI 0.45-1.13)	

Dana-Farber Cancer Institute

Ray-Coquard et al. *N Engl J Med* 2019; Ray-Coquard et al. *Ann Oncol* 2023

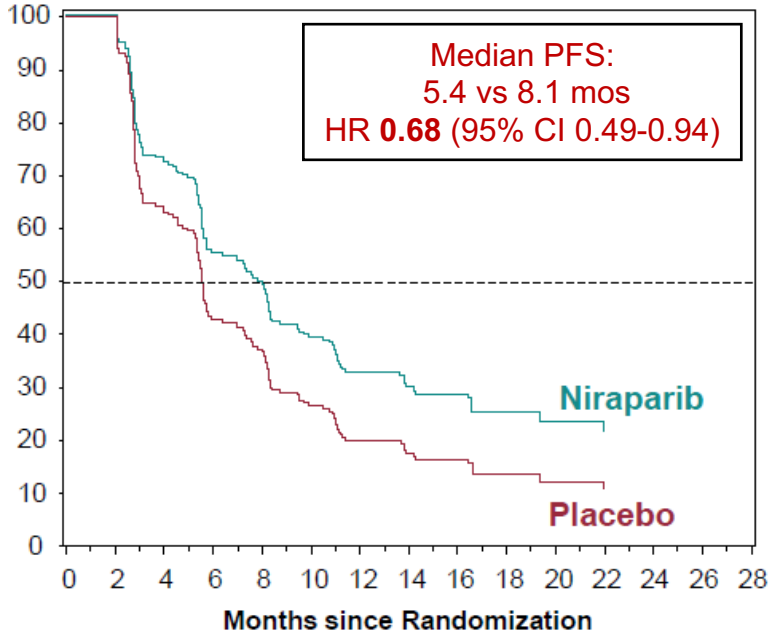
Randomized studies informing front-line PARPi maintenance

	*BRCA*m	*BRCA* wt; HRD test pos	*BRCA* wt; HRD test neg
PARPi monotherapy	SOLO-1: Olaparib PRIMA: Niraparib ATHENA-MONO: Rucaparib	PRIMA: Niraparib ATHENA-MONO: Rucaparib	PRIMA: Niraparib ATHENA-MONO: Rucaparib
PARPi + bevacizumab	PAOLA-1: Olaparib + bevacizumab	PAOLA-1: Olaparib + bevacizumab	PAOLA-1: Olaparib + bevacizumab
PARPi + IO	DUO-O: Olaparib + bevacizumab + durvalumab	DUO-O: Olaparib + bevacizumab + durvalumab	DUO-O: Olaparib + bevacizumab + durvalumab

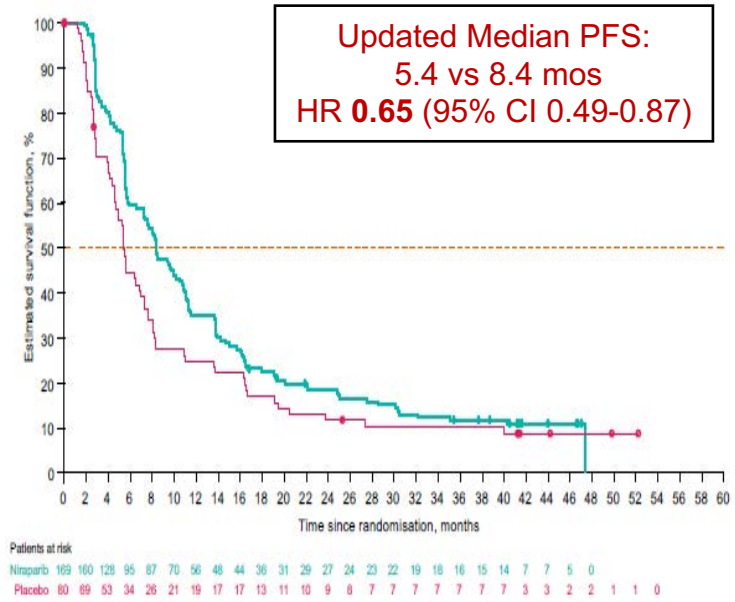
PARPi monotherapy maintenance has limited PFS benefit in *BRCA*wt HRD test negative tumors

PRIMA (HRD test neg; GIS <42)

Primary analysis

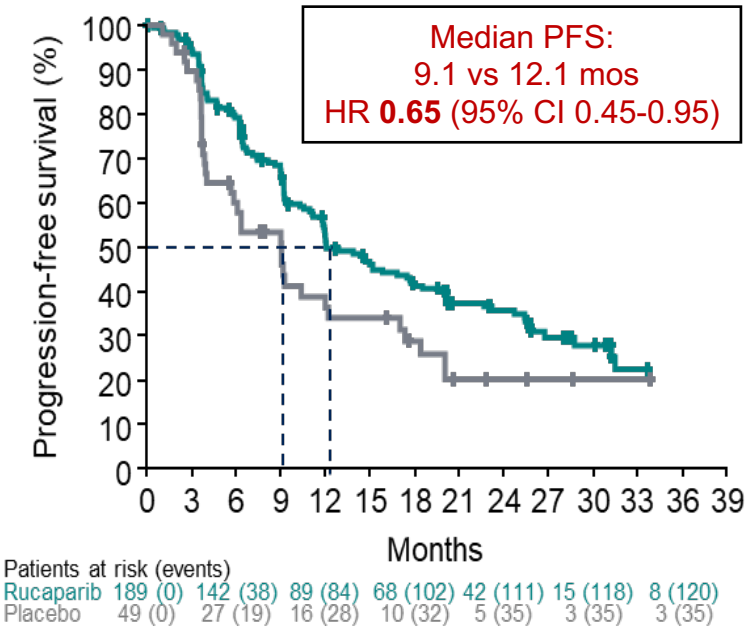


3.5year follow-up



ATHENA-MONO (HRD test neg; LOH <16%

Primary analysis



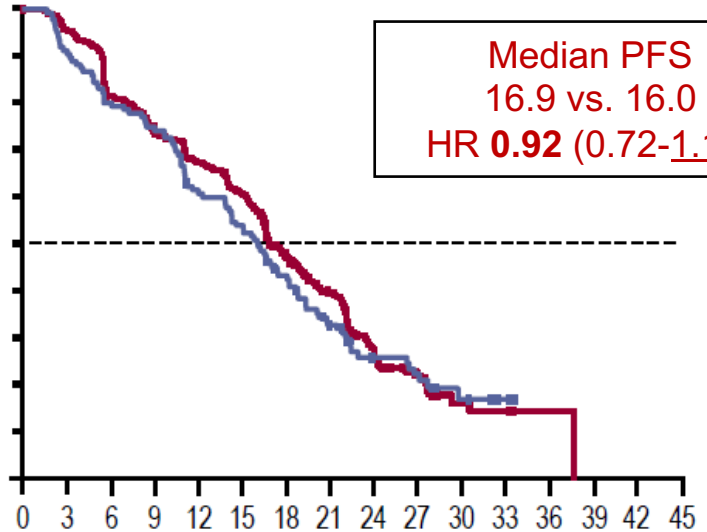
Dana-Farber Cancer Institute

Gonzalez-Martin et al. *N Engl J Med* 2019; Gonzalez-Martin et al. *Eur J Cancer* 2023; Monk et al. *J Clin Oncol* 2022

Olaparib/bevacizumab does not improve outcomes compared to bevacizumab in *BRCA*wt, HRD test negative ovarian cancer

PAOLA-1: Primary PFS and Final OS analyses

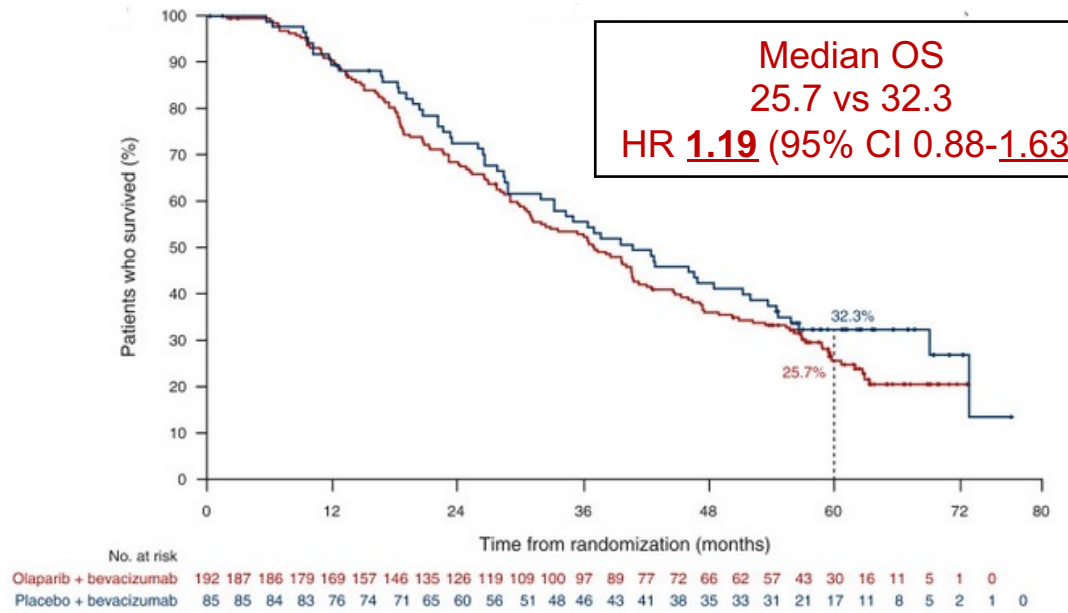
Primary analysis PFS *BRCA*wt, HRD test neg



Median PFS
16.9 vs. 16.0
HR **0.92** (0.72-1.17)

Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
193 (68)	102 (74)
16.9	**16.0**
HR 0.92 (95% CI 0.72–1.17)	

Final OS analysis *BRCA*wt, HRD test neg



Median OS
25.7 vs 32.3
HR **1.19** (95% CI 0.88-1.63)

	Olaparib + bevacizumab (*N* = 192)	Placebo + bevacizumab (*N* = 85)
Events, *n* (%)	140 (72.9)	58 (68.2)
Median OS, months	36.8	40.4
5-Year OS rate, %	**25.7**	**32.3**
	HR 1.19 (95% CI 0.88-1.63)	

Dana-Farber Cancer Institute

Ray-Coquard et al. *N Engl J Med* 2019; Ray-Coquard et al. *Ann Oncol* 2023

OVARIO: Niraparib/bevacizumab as 1L maintenance

Design: Phase II, Single-Arm, Open-Label Study

Patients with newly diagnosed high-grade serous or endometrioid stage IIIB or IV epithelial ovarian, fallopian tube, or peritoneal cancer who achieved a CR, PR, or NED result after front-line platinum-based chemotherapy + bevacizumab (N=105)

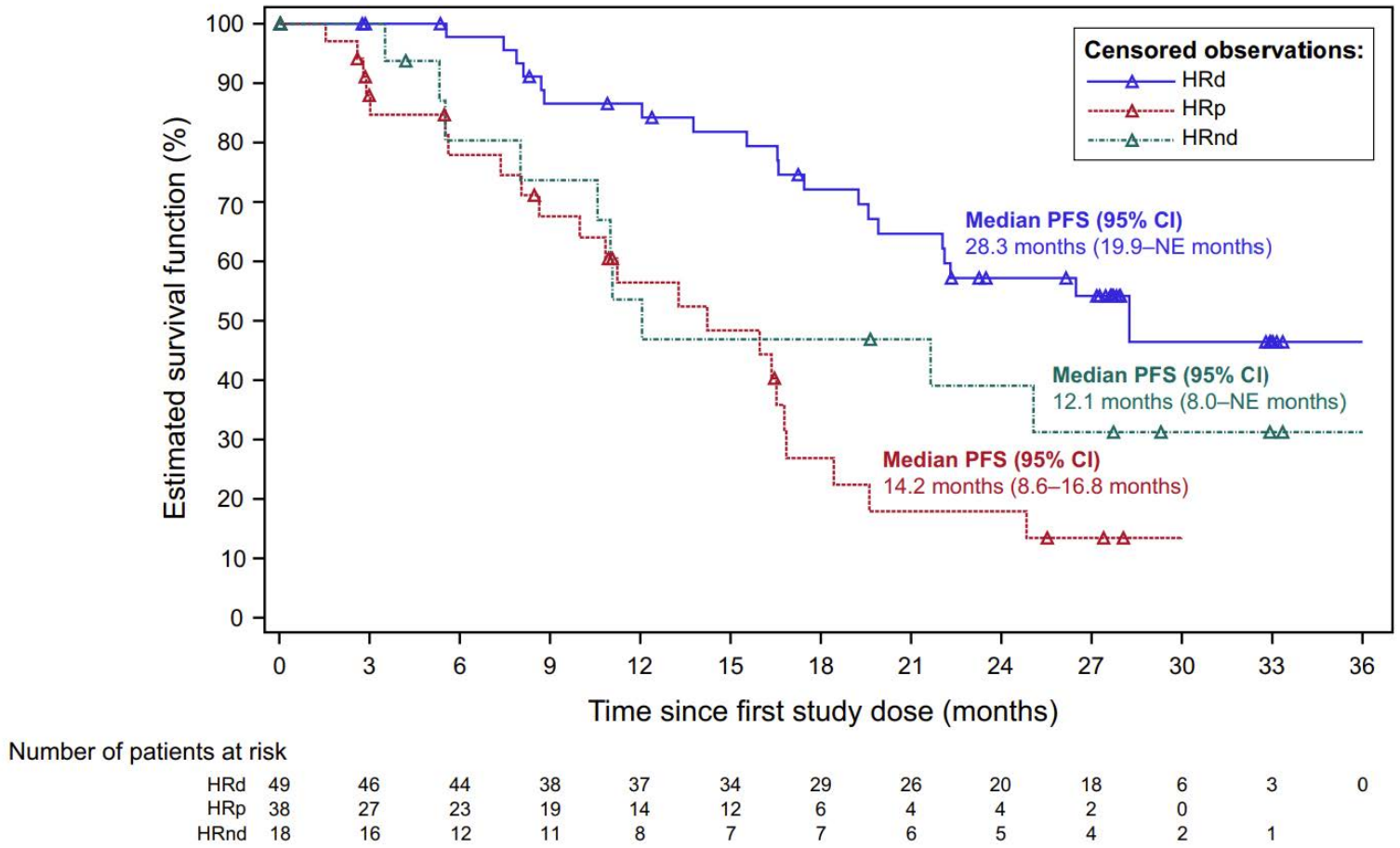
All patients underwent tissue testing for HRD status at enrollment

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

Niraparib starting dose	Bevacizumab
200 mg: <77 kg and/or platelet count <150,000/μL **300 mg:** All others	Maximum of 15 months, including first-line treatment

Endpoint		Data cutoff
Efficacy	PFS rate at 18 months[a]	December 24, 2020
	Median PFS	June 16, 2021
Safety	Treatment-related AEs	December 24, 2020

[a]Primary endpoint.



Hardesty et al. *Gynecol Oncol* 2022

Front-line maintenance: where are we, and what's still ahead?

- Test for *BRCA* mutations and HRD status

The Present State

	PARPi monotherapy		PARPi + bevacizumab	
	PFS benefit	OS benefit	PFS benefit	OS benefit
*BRCA*m	YES!	YES! (7 yr f/u)	YES!	YES! (5 yr f/u)
*BRCA*wt HRD test pos	Yes	Unknown	Yes	Trend (5 yr f/u)
*BRCA*wt HRD test neg	Yes, but very modest	Unknown	No	No

Still to Come…

- PARPi monotherapy OS
  - PRIMA — Niraparib
  - ATHENA-MONO — Rucaparib
- PARPi vs. PARPi + bev
  - NIRVANA-1 — Niraparib +/- bev
  - AGO-OVAR 28 — Niraparib +/- bev
  - MITO 25 — Rucaparib +/- bev vs bev
- PARPi + ICI +/- bev

MODULE 2: Potential Role of Immunotherapeutic Strategies for Advanced OC — Dr O'Malley

Consulting Faculty Questions

FDA withdrawal of PARP indications in the recurrent setting; Duration of PARP inhibition in patients with recurrent OC

Neil Love, MD

Ritu Salani, MD, MBA

Rachel N Grisham, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Ritu Salani, MD, MBA

Rachel N Grisham, MD

Do you believe immune checkpoint inhibitors in combination with PARP inhibitors will eventually be a part of standard ovarian cancer management? Are there any situations in which you will currently employ an anti-PD-1/PD-L1 antibody in combination with a PARP inhibitor for a patient with advanced ovarian cancer?

Which of the novel immunotherapeutic strategies (eg, adoptive cell therapy, oncolytic viruses, cancer vaccines) being evaluated do you believe offer the most promise?

In what situations, if any, will you recommend a PARP inhibitor for a patient with recurrent ovarian cancer? If you were to use a PARP inhibitor in the recurrent setting, which agent would you select and how long would you continue it?

RTP
RESEARCH
TO PRACTICE

Outside of a protocol setting, in what clinical situations would you administer a PARP inhibitor to a patient with relapsed advanced OC?

 Dr Liu	Maintenance after response to platinum for BRCAm cancer that has not previously progressed on PARP inhibitor
 Dr Mirza	All regardless of HRD (if patient is platinum sensitive and in response to platinum)
 Dr Moore	PARP inhibitor-naïve PS OC or as re-treatment for BRCAm with long PARP inhibitor-free interval
 Dr O'Malley	PS OC with CR after platinum doublet only if no progression on prior PARP inhibitor
 Dr Armstrong	Maintenance, PS BRCAm (germline or somatic), niraparib/bev in PS based on AVANOVA, PARP inhibitor-naïve patient with BRCA mutation
 Dr Grisham	BRCA mutant after CR or PR to platinum-based therapy

PS = platinum-sensitive

Outside of a protocol setting, in what situations, if any, would you administer a PARP inhibitor as a component of later-line treatment for a patient whose disease has progressed on or after first-line maintenance with a PARP inhibitor?

 Dr Liu	I may consider for a patient with PS disease, a BRCAm tumor, long platinum-free interval, response to platinum, and no progression on prior PARP inhibitor
 Dr Mirza	BRCA mutation
 Dr Moore	If disease progression > 12 months after completion of PARP inhibitor therapy
 Dr O'Malley	Only if no progression on prior PARP inhibitor
 Dr Armstrong	Very selectively, with careful discussion of MDS/AML risks
 Dr Grisham	None

PS = platinum-sensitive

How would you rate your enthusiasm for enrolling a patient on the Phase III ARTISTRY-7 trial of nemvaleukin alfa in combination with pembrolizumab for patients with platinum-resistant epithelial OC?

	Enthusiasm*	Comments
 Dr Liu	1	No comment
 Dr Mirza	1	Not certain about activity
 Dr Moore	1	No comment
 Dr O'Malley	2	No comment
 Dr Armstrong	4	Takes me back to when we used IP IL-2 in ovarian cancer (I AM that old!)
 Dr Grisham	4	Combination may show promise

* 1 = not at all enthusiastic, 4 = very enthusiastic

Potential Role of Immunotherapeutic Strategies for Advanced Ovarian Cancer

David O'Malley, MD
Director & Professor, Division of Gynecologic Oncology
in Obstetrics and Gynecology
John G. Boutselis Chair in Gynecologic Oncology
Ovarian Cancer Clinical Trial Advisor, GOG Partners

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

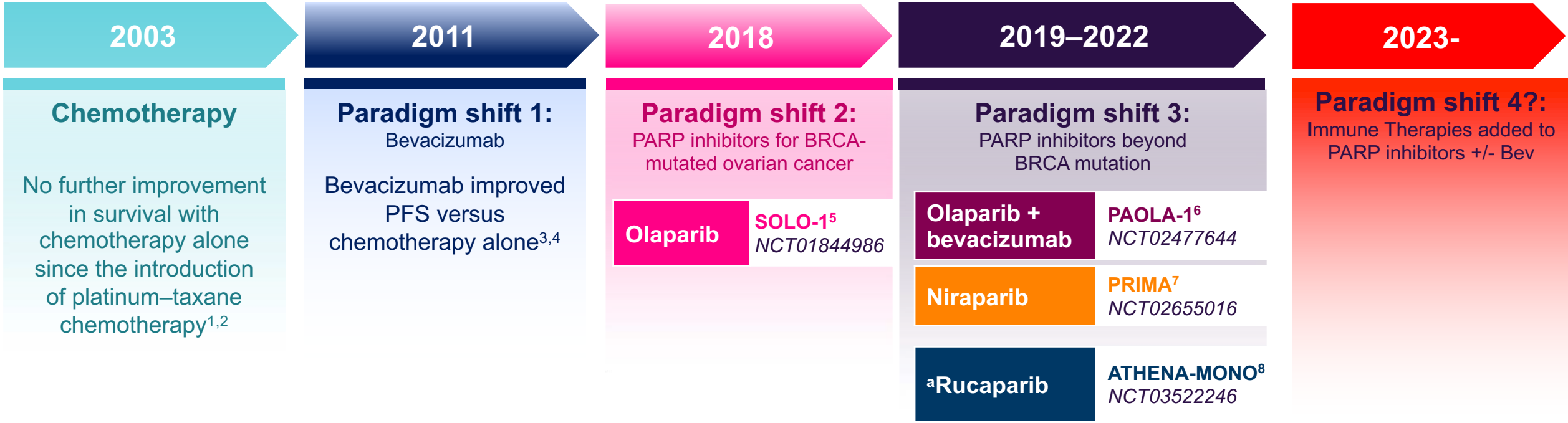
Creating a cancer-free world. One person, one discovery at a time.




Agenda

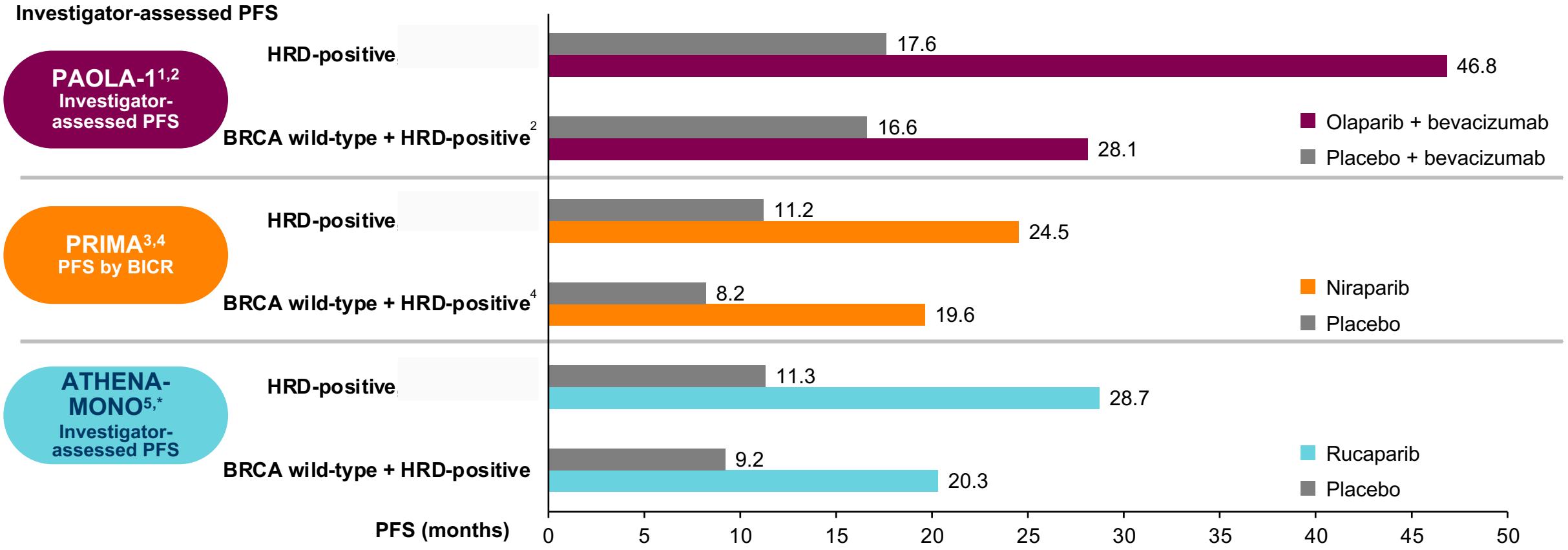
- First Line Therapy
  - Current Standard
  - Role of IO?
  - DUO-O
  - Ongoing Trials
- PROC
  - Novel Immune Strategies

Significant progress has been made in the first-line management of ovarian cancer over the past decade



1. McGuire WP, et al. *N Engl J Med* 1996;334:1–6; 2. du Bois A, et al. *J Natl Cancer Inst* 2003;95:1320–1329; 3. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483; 4. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496; 5. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01844986 (Accessed March 2022); 6. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed March 2022); 7. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016 (Accessed March 2022); 8. Monk JM, et al. *J Clin Oncol* 2022. doi: http://ascopubs.org/doi/full/10.1200/JCO.22.01003 [Epub ahead of print]

PARPi clearly benefit HRD+



1. Ray-Coquard I, et al. Presented at European Society for Medical Oncology Congress; 9th–13th September 2022; Paris, France; 2. Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–2428;
3. Gonzales-Martin A, et al. Presented at European Society for Medical Oncology Congress; 9th–13th September 2022; Paris, France; abstract #530P; 4. González-Martín A, et al. Presented at European Society of Gynaecological Oncology Congress; 2nd–5th November 2019; Athens, Greece; abstract #4627; 5. Monk JM, et al. *J Clin Oncol* 2022.
doi: http://ascopubs.org/doi/full/10.1200/JCO.22.01003 [Epub ahead of print]

Missing Arms of Reported Trials – Some Answers Coming

No olaparib monotherapy arm in

PAOLA-1[1]

No bevacizumab combination arm in

SOLO-1[2]

PRIMA[3]

ATHENA-MONO[4]

Ongoing trials will allow a direct comparison of 1L PARPi with and without bevacizumab

NIRVANA-1[5]

Niraparib ± bevacizumab as maintenance after complete cytoreduction

AGO-OVAR 28[6]

Niraparib vs niraparib + bevacizumab as maintenance after platinum + bevacizumab

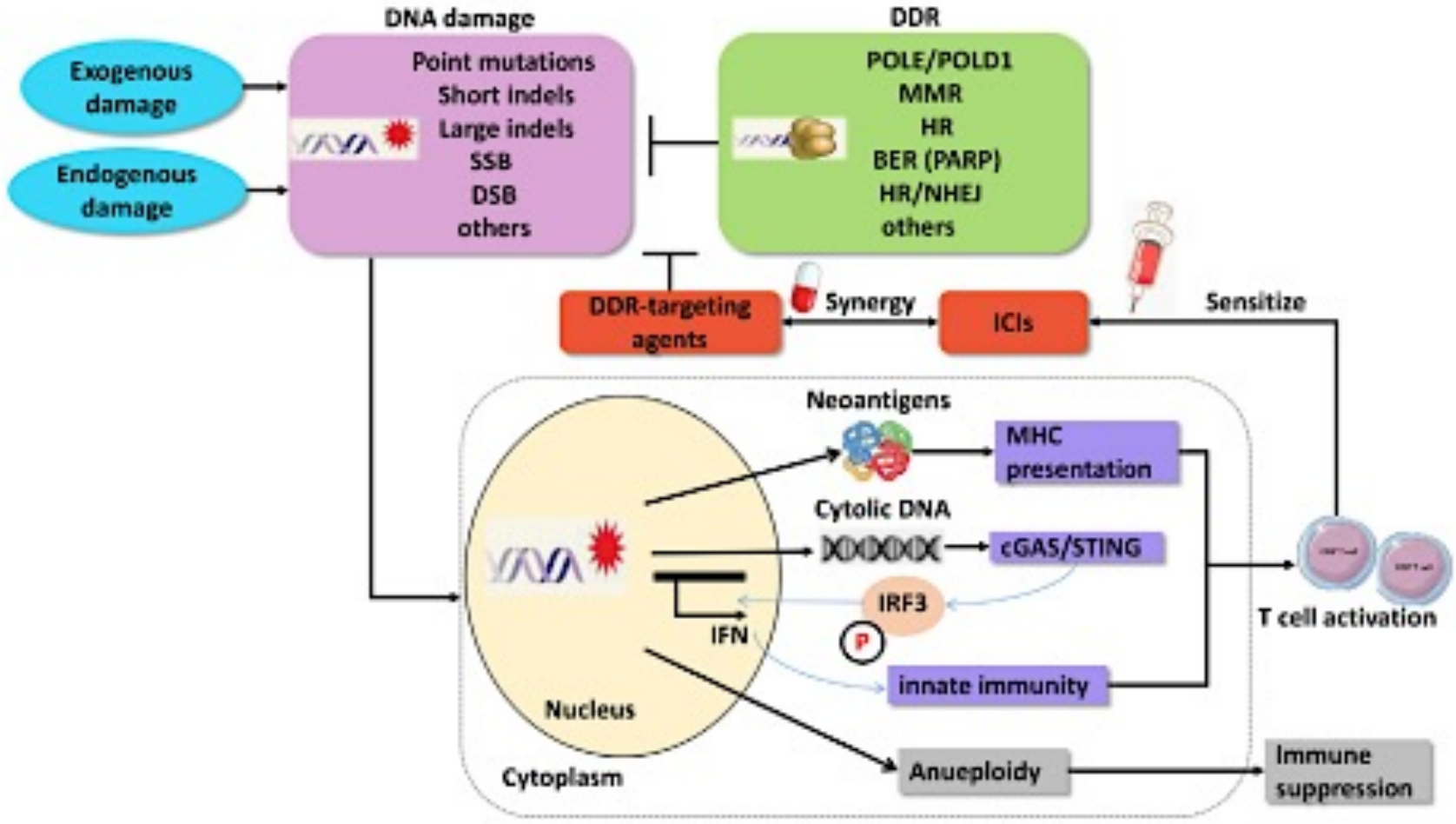
MITO25[7]

Chemotherapy ± bevacizumab followed by rucaparib maintenance ± bevacizumab or bevacizumab alone

1. Ray-Coquard I, et al. *N Engl J Med* 2019;381:2416–242; 2. Moore K, et al. *N Engl J Med* 2018;379:2495–2505. 3. Gonzalez-Martin A, et al. *N Engl J Med* 2019;381:2391–2402; 4. Monk BJ, et al. *Int J Gynecol Cancer* 2021;31:1589–1594; 5. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05183984; 6. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT05009082; 7. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03462212

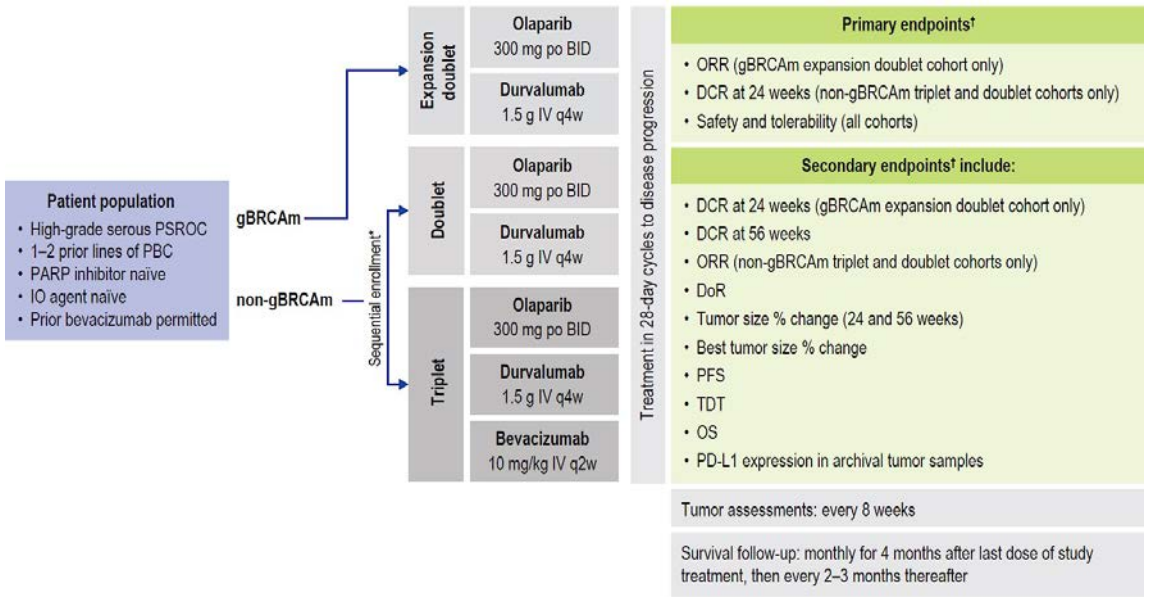
Does the addition of immune therapy to PARPi improve outcomes?

- DDR deficiency/synthetic lethality leads to neoantigens resulting in an immune response
- DNA damage activates STING (stimulator of interferon genes) pathway triggering an immune response



Sun W et al. Frontiers in Oncology. 2021

MEDIOLA - olaparib tablets (300 mg twice daily) plus durvalumab (1.5 g IV every 4 weeks); the triplet cohort also received bevacizumab (10 mg/kg IV every 2 weeks) in 28-day cycles



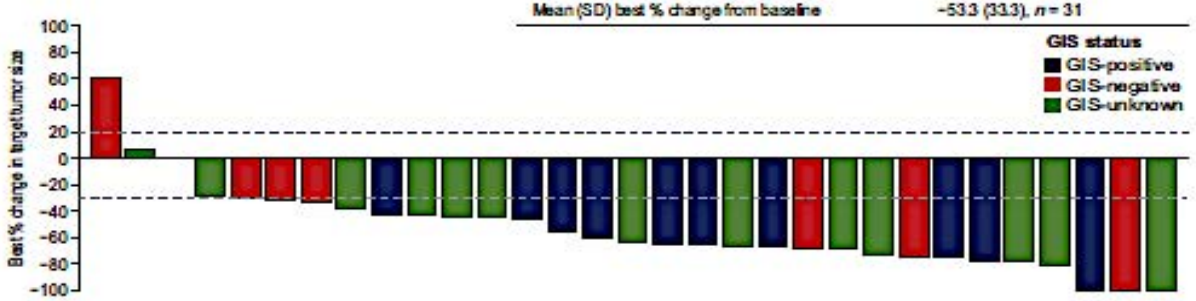
	gBRCAm expansion doublet cohort (*N* = 51)		Non-gBRCAm doublet cohort (*N* = 32)		Non-gBRCAm triplet cohort (*N* = 31)	
	PD-L1 staining	ORR (%)†	PD-L1 staining	ORR (%)†	PD-L1 staining	ORR (%)†
Tumor cells						
	<1% (*N* = 34)	30 (88.2)	<1% (*N* = 20)	7 (35.0)	<1% (*N* = 21)	17 (81.0)
	≥1% (*N* = 12)	12 (100)	≥1% (*N* = 8)	3 (37.5)	≥1% (*N* = 6)	6 (100)
Immune cells						
	<1% (*N* = 14)	13 (92.9)	<1% (*N* = 12)	5 (41.7)	<1% (*N* = 8)	7 (87.5)
	≥1% (*N* = 32)	29 (90.6)	≥1% (*N* = 16)	5 (31.3)	≥1% (*N* = 19)	16 (84.2)

B

Target tumor size	Non-gBRCAm doublet cohort (*N* = 32)
Mean (SD) % change from baseline	
At 24 weeks	−35.6 (34.0), *n* = 15
At 56 weeks	−39.5 (33.7), *n* = 5
Mean (SD) best % change from baseline	−20.4 (41.2), *n* = 32

C

Target tumor size	Non-gBRCAm triplet cohort (*N* = 31)
Mean (SD) % change from baseline	
At 24 weeks	−43.0 (32.4), *n* = 27
At 56 weeks	−60.0 (29.1), *n* = 15
Mean (SD) best % change from baseline	−53.3 (33.3), *n* = 31

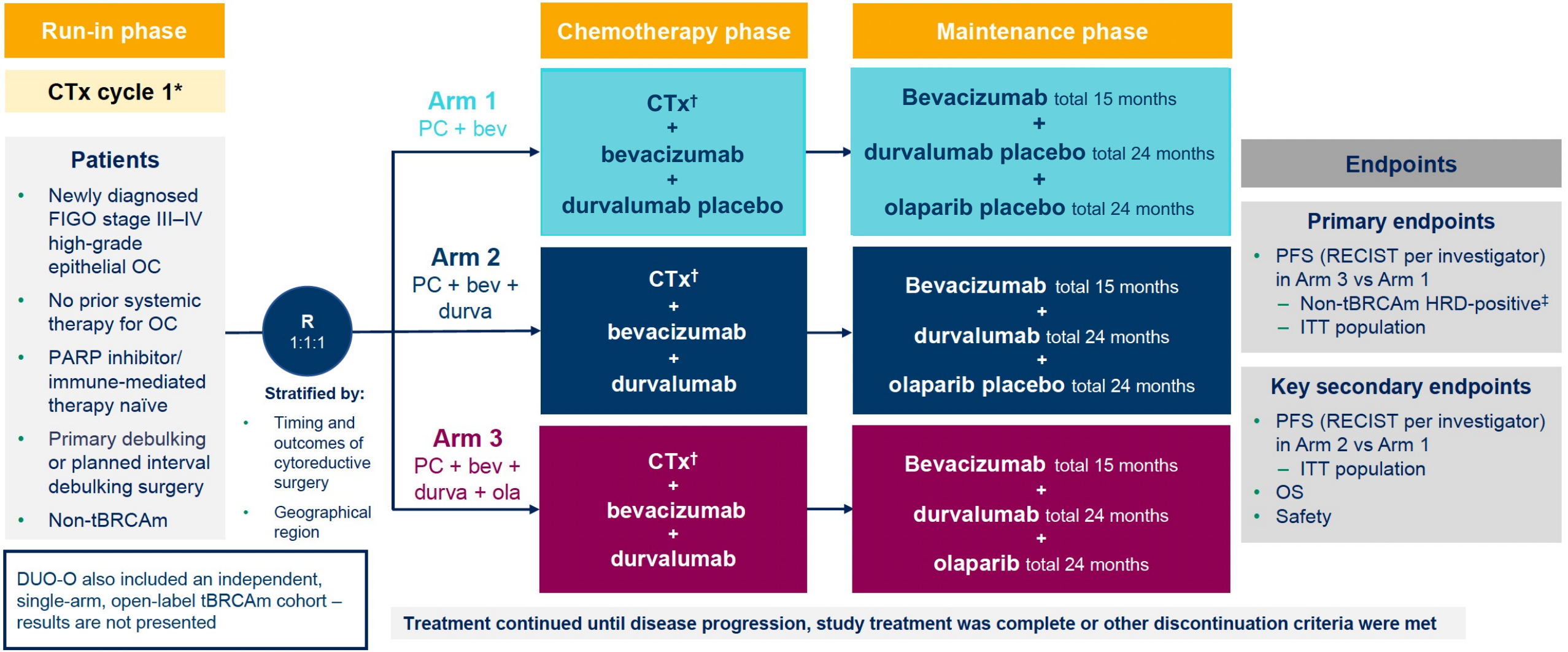


D

	Non-gBRCAm doublet cohort		Non-gBRCAm triplet cohort	
GIS* subgroup	ORR (95% CI), %	*n*/*N* patients	ORR (95% CI), %	*n*/*N* patients
GIS-positive	50.0 (18.7–81.3)	5/10	100.0 (69.2–100.0)	10/10
GIS-negative	16.7 (0.4–64.1)	1/6	75.0 (34.9–96.8)	6/8
GIS-unknown	31.3 (11.0–58.7)	5/16	84.6 (54.6–98.1)	11/13

Y Drew, J W Kim, RT. Penson, D M O'Malley, C Parkinson, P Roxburgh, R Plummer, SA Im, M Imbimbo, M Ferguson, O Rosengarten, N Steeghs, MH Kim, E Gal-Yam, D Tsoref, JH Kim , B You, M Fe Jonge, R Laisang, E Gort, S Bastian, K Meyer, L Fenny, N Backer, MW Ah-See, S Domchek, S Banerjee. Olaparib plus durvalumab, with or without bevacizumab, in platinum-sensitive relapse high-grade serous ovarian cancer: a phase II multi-cohort study (MEDIOLA). CCR 2024

GOG-3025 DUO-O: C/T/Bev +/- Durva +/- Olaparib



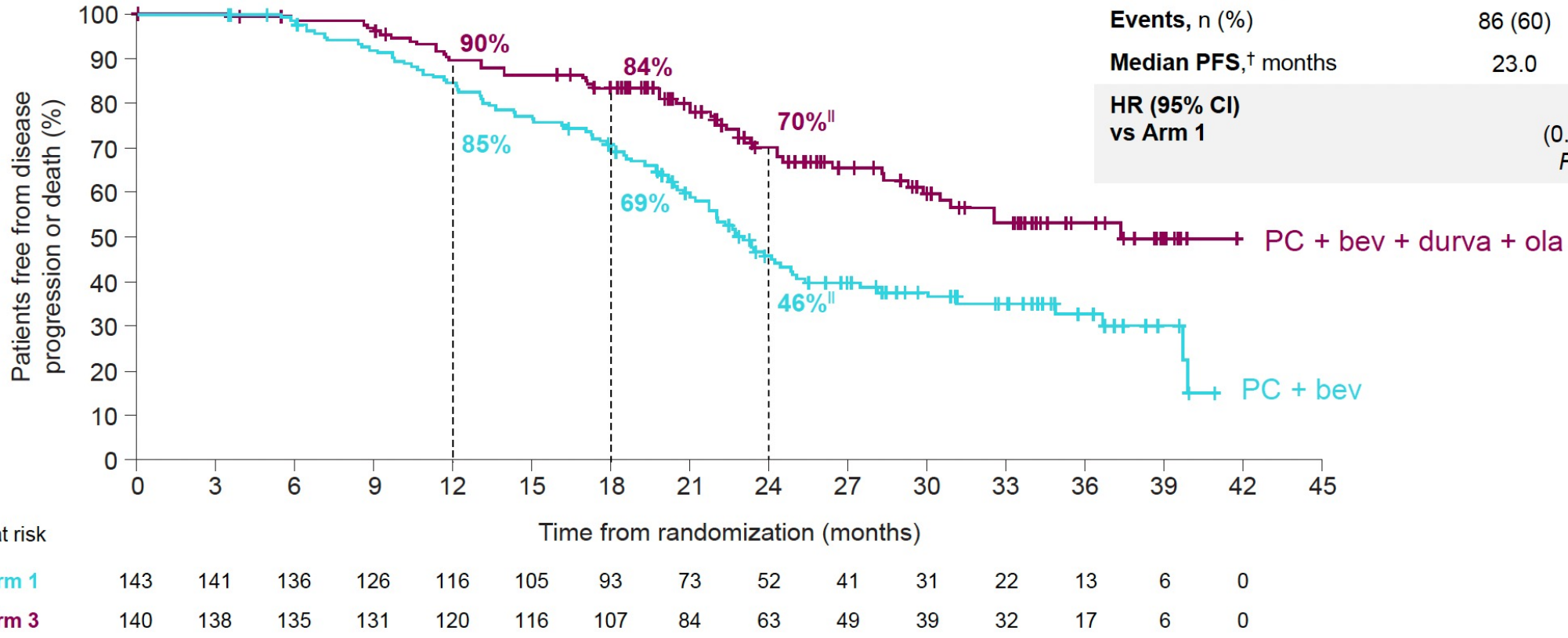
Dosing and schedule: bevacizumab (15 mg/kg IV q3w); durvalumab (1120 mg IV q3w); olaparib (300 mg po bid); chemotherapy: paclitaxel 175 mg/m^2 IV q3w and carboplatin at AUC5 or AUC6 IV q3w. PFS interim analysis DCO: December 5, 2022.
*With or without bevacizumab according to local practice; †Cycles 2–6; ‡Genomic instability score ≥42 assessed prospectively by Myriad MyChoice CDx assay.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; ola, olaparib; OS, overall survival; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors.

P Harter, et al. Presented at ASCO 2023, Chicago, IL

PFS: Non-tBRCAm HRD-positive population

Arm 3 vs Arm 1

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Median follow-up,* months	28.8	25.6
Events, n (%)	86 (60)	49 (35)
Median PFS,† months	23.0	37.3‡
HR (95% CI) vs Arm 1	**0.49** (0.34–0.69)§ *P*<0.0001	



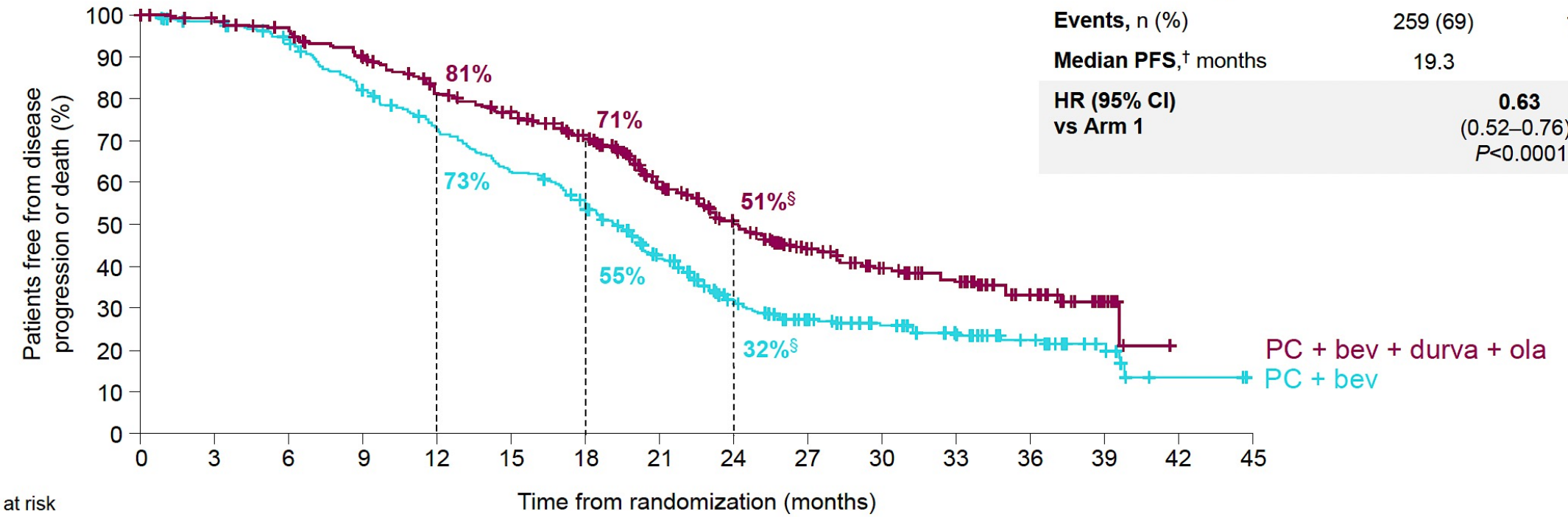
Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

*In censored patients; †Medians and rates were estimated by KM method; ‡Median PFS in Arm 3 unstable; §HR and CI were estimated from a stratified Cox proportional hazards model. *P* value from a stratified log rank text. Model stratified by timing and outcome of cytoreductive surgery; ‖24-month PFS rates unstable.
CI, confidence interval; HR, hazard ratio; KM, Kaplan–Meier.

PFS: ITT population
Arm 3 vs Arm 1

	Arm 1 PC + bev N=378	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.3
Events, n (%)	259 (69)	193 (51)
Median PFS,† months	19.3	24.2
HR (95% CI) vs Arm 1	**0.63** (0.52–0.76)‡ *P*<0.0001	



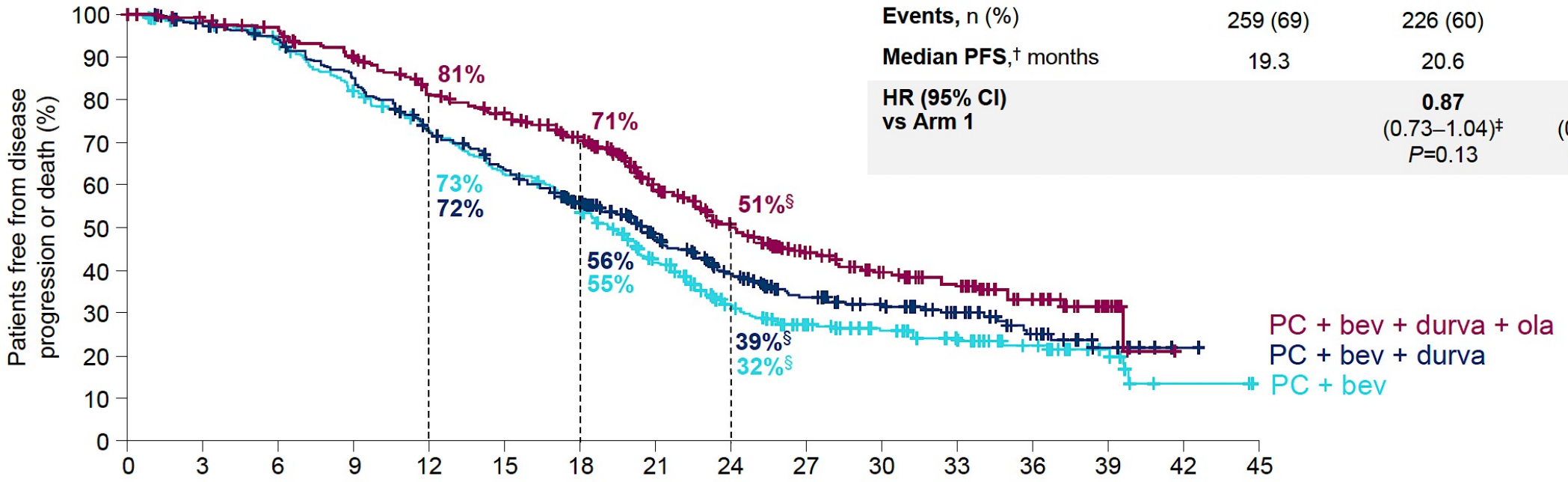
Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

PFS: ITT population

	Arm 1 PC + bev N=378	Arm 2 PC + bev + durva N=374	Arm 3 PC + bev + durva + ola N=378
Median follow-up,* months	25.5	23.1	23.3
Events, n (%)	259 (69)	226 (60)	193 (51)
Median PFS,† months	19.3	20.6	24.2
HR (95% CI) vs Arm 1		**0.87** (0.73–1.04)‡ *P*=0.13	**0.63** (0.52–0.76)‡ *P*<0.0001



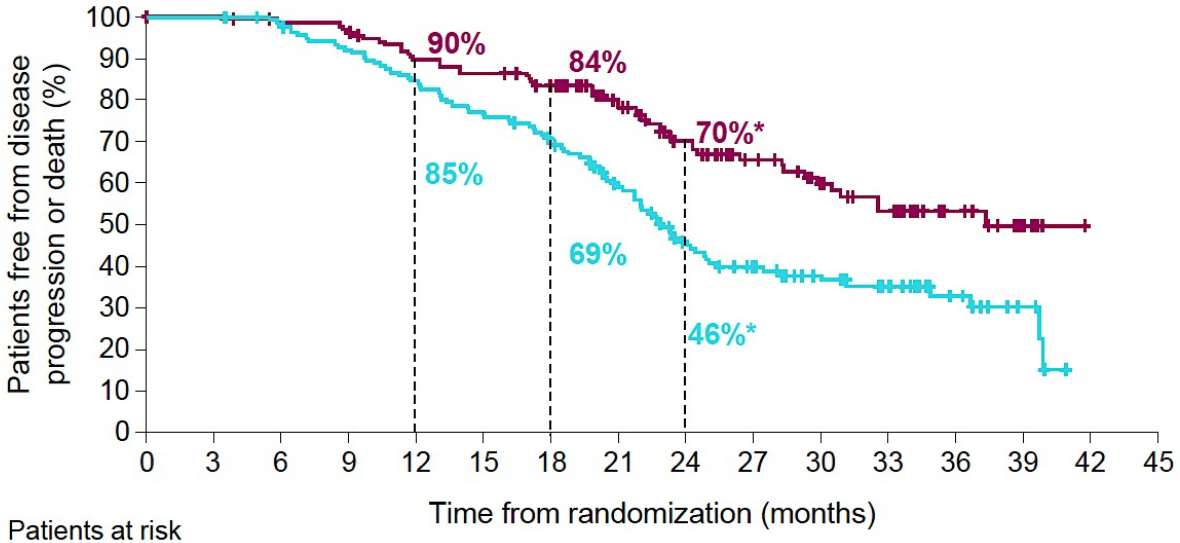
Patients at risk

Arm 1	378	363	341	297	260	223	189	130	87	63	51	35	23	11	2	0
Arm 2	374	354	336	301	254	221	180	130	93	70	54	39	23	11	1	0
Arm 3	378	366	351	323	286	266	228	163	123	84	65	52	27	9	0	

*In censored patients; †Medians and rates were estimated by KM method; ‡HR and CI were estimated from a stratified Cox proportional hazards model. Model stratified by timing and outcome of cytoreductive surgery and geographical region. *P* value from a stratified log rank text; §24-month PFS rates unstable.

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

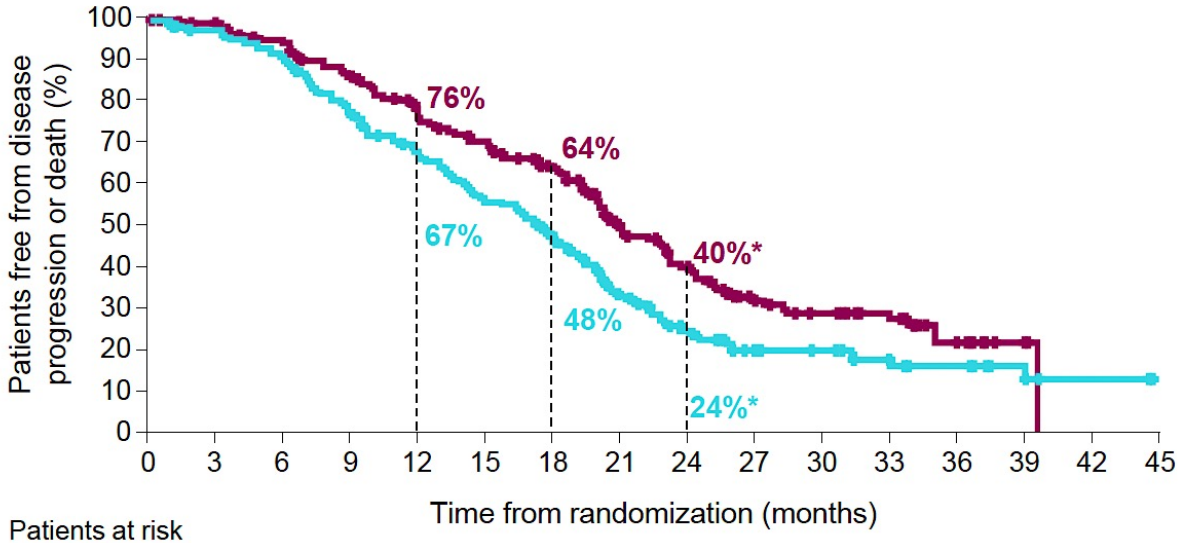


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	49 (35)
Median PFS, months†	23.0	37.3‡
HR (95% CI) vs Arm 1		**0.51** (0.36–0.72)§

HRD-negative



Patients at risk

Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

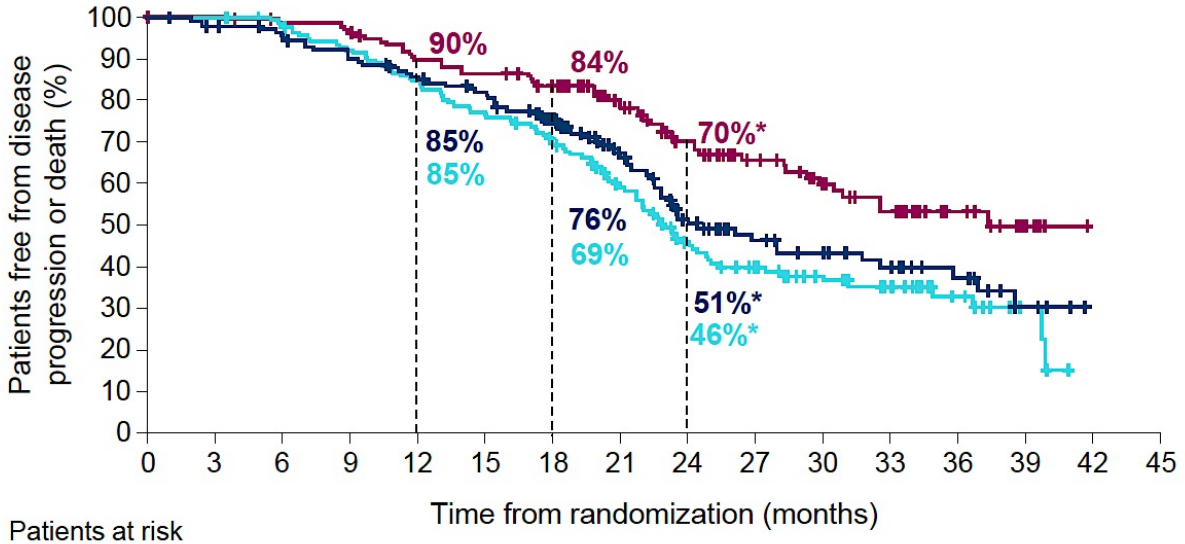
	Arm 1 PC + bev N=216	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	127 (60)
Median PFS, months†	17.4	20.9
HR (95% CI) vs Arm 1		**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

P Harter, et al. Presented at ASCO 2023, Chicago, IL

Subgroup analysis of PFS by HRD status

Non-tBRCAm HRD-positive

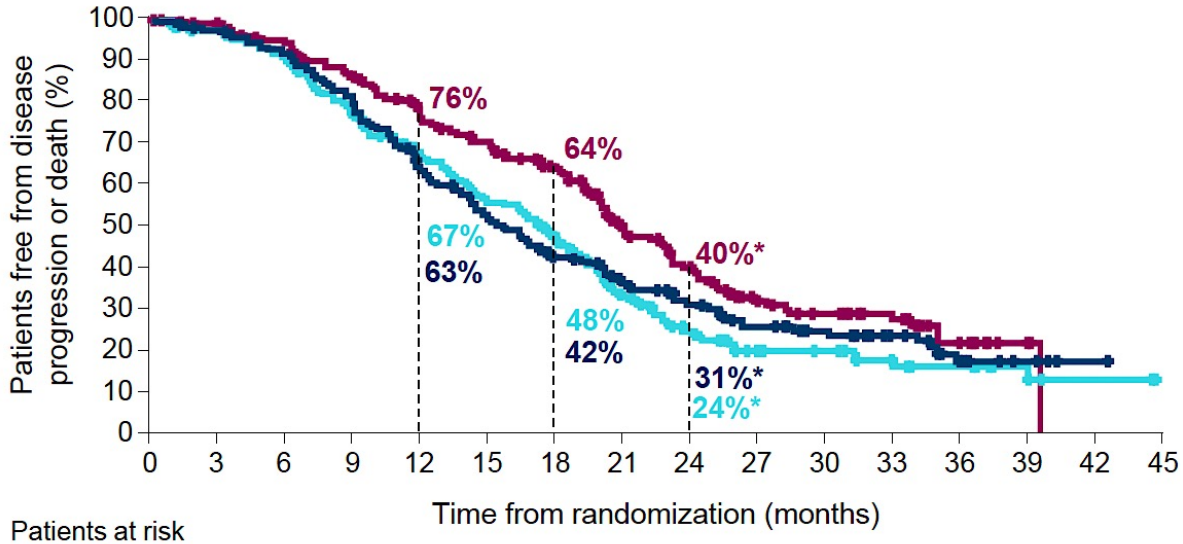


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



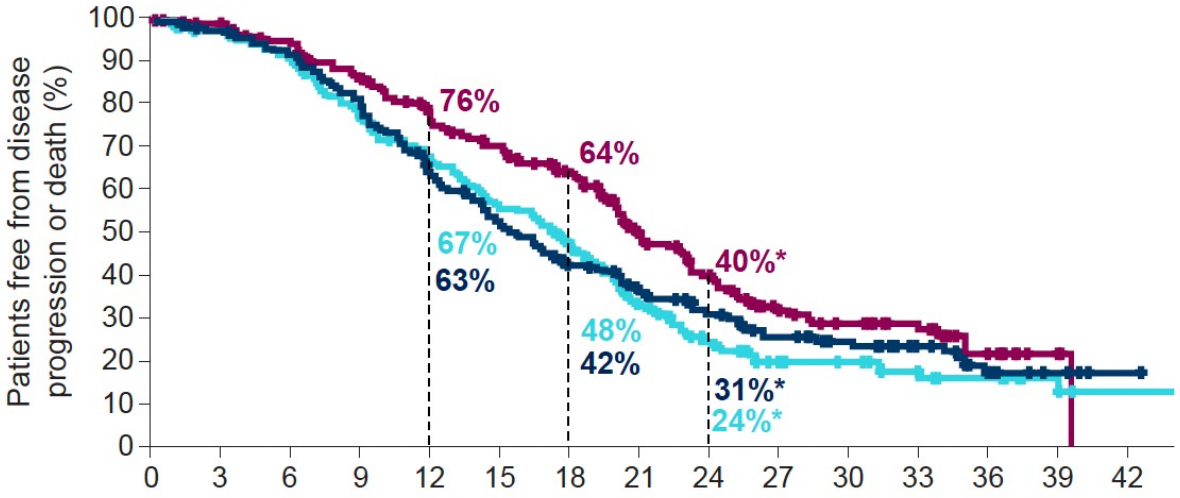
Patients at risk

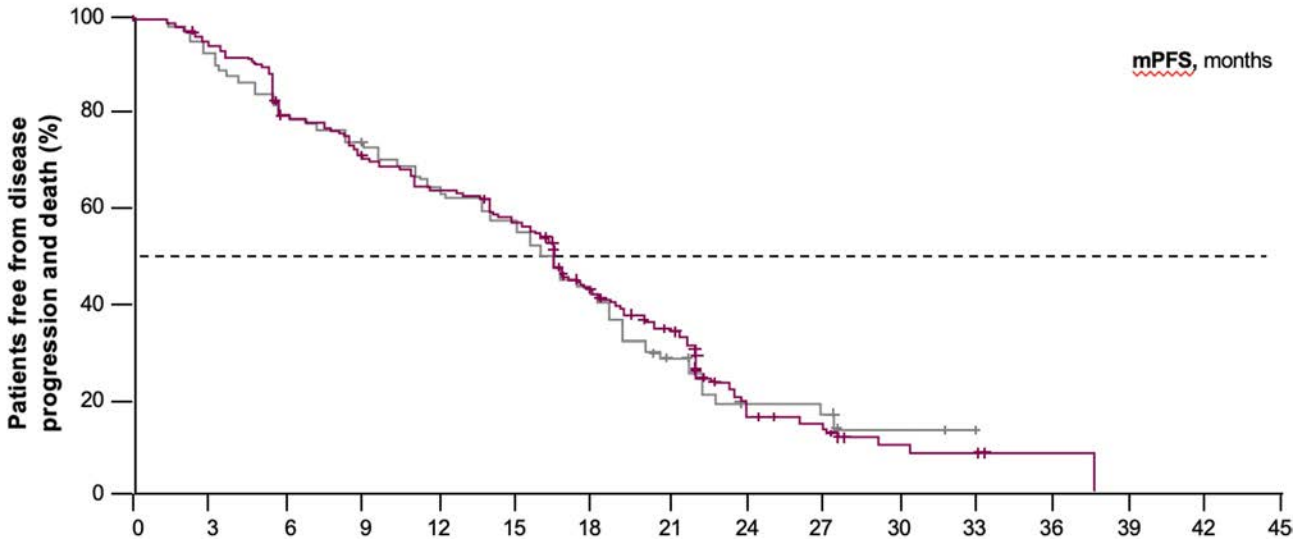
Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

*24-month PFS rates unstable; †Medians and rates were estimated by KM method; ‡Median PFS in HRD-positive subgroup Arm 3 and Arm 2 unstable; §HR and CI were estimated from an unstratified Cox proportional hazards model.

Cross Trial Comparison is not valid BUT…
DUO-O (arms 1&3) & PAOLA-1 HRD





Is this a single????

P Harter, et al. Presented at ASCO 2023, Chicago, IL

The James
The Ohio State University
Wexner Medical Center

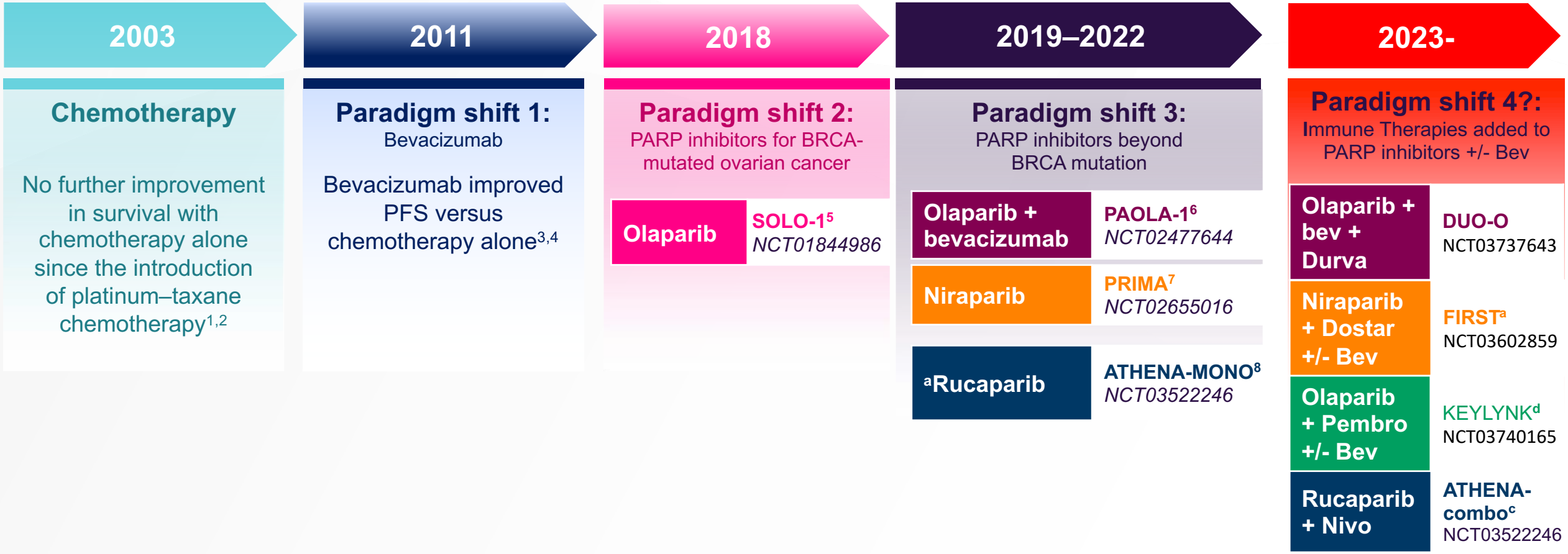
Completed Front Line Trials with IO

Trial	Size	Anti-angiogenic	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	29 MAR 2024
ATHENA-COMBO[c] GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	30 DEC 2024
KEYLYNK-001[d] ENGOT OV-43 GOG-3036	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	30 AUG 2024

Optional Bev

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

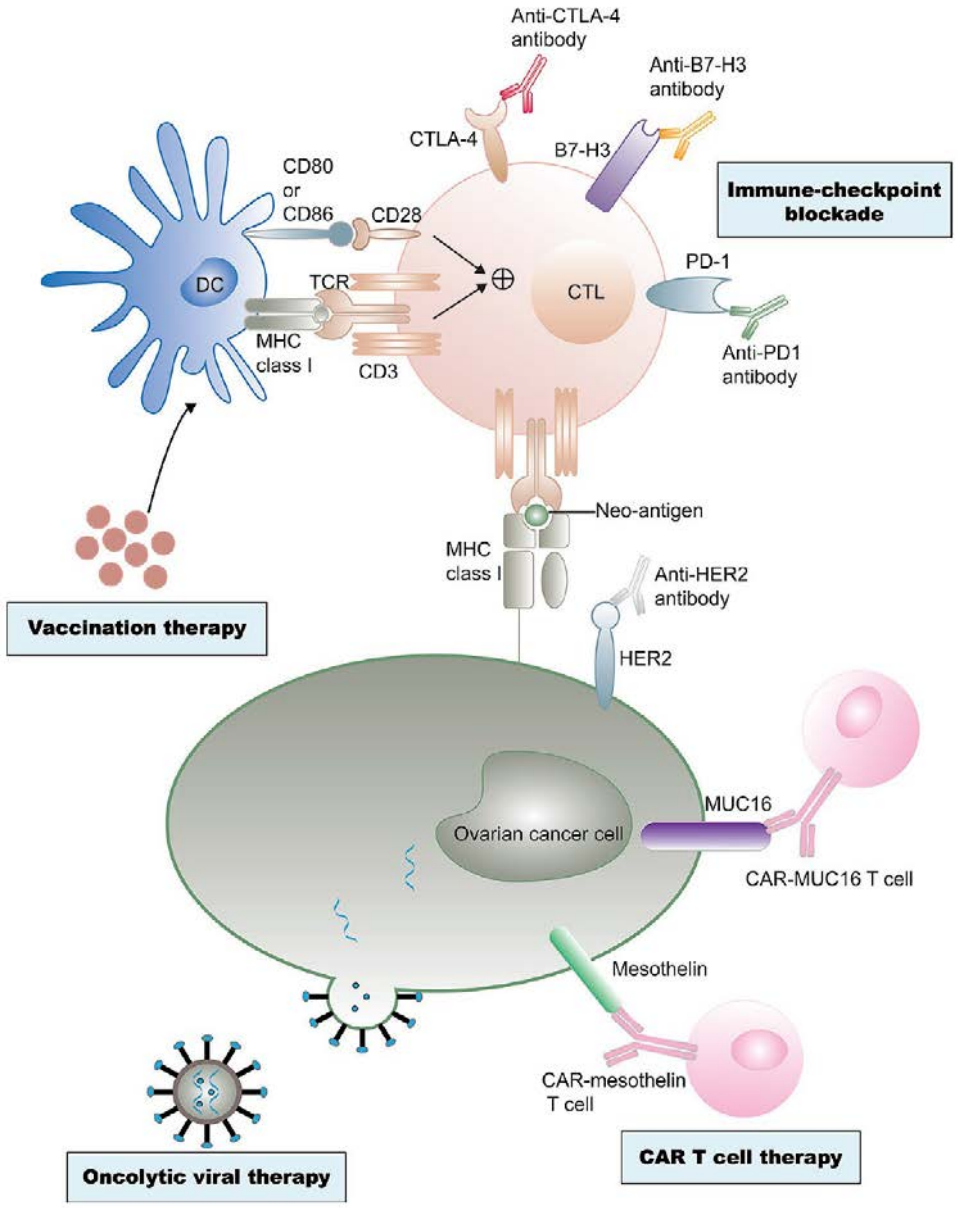
Significant progress has been made in the first-line management of ovarian cancer over the past decade



1. McGuire WP, et al. *N Engl J Med* 1996;334:1–6; 2. du Bois A, et al. *J Natl Cancer Inst* 2003;95:1320–1329; 3. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483;
4. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496; 5. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT01844986 (Accessed March 2022);
6. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed March 2022); 7. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02655016 (Accessed March 2022); 8. Monk JM, et al. *J Clin Oncol* 2022. doi: http://ascopubs.org/doi/full/10.1200/JCO.22.01003 [Epub ahead of print]

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

Platinum-Resistant Ovarian Cancer – Role of Immune Therapy



Cancer immunotherapy encompasses a variety of approaches, including[2]:

- **Immune checkpoint inhibitors**
- **Adoptive cell therapy**
- **Cancer vaccines**
- **Oncolytic viruses**

1. Chen DS, Mellman I. *Immunity*. 2013;39(1):1–10.
2. Yang C et al. *Front Immunol*. 2020;11:577869.

Efficacy of Immune Checkpoint Inhibitors

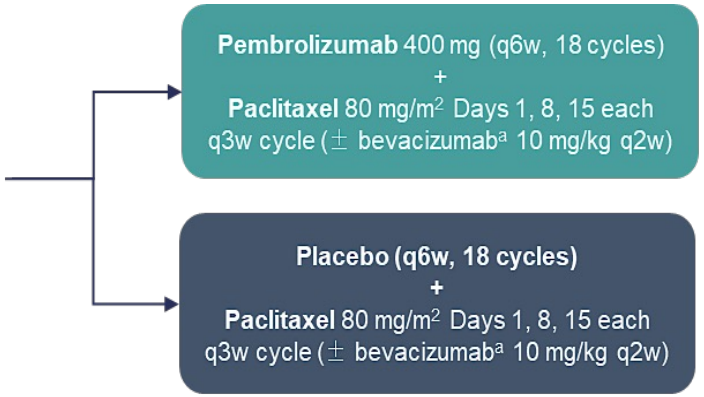
	Trial name (NCT number) / patient population (N)	Prior lines of anticancer treatment	Study design/treatments	
Phase III	JAVELIN Ovarian 200 (NCT02580058) (N = 566)	1: 48% for each arm 2–3: 52% for each arm	Open-label randomized: PLD or Ave or PLD + Ave	Co-primary end points: mPFS: 3.5 mo (95% CI: 2.1–4.0) for PLD, 1.9 mo (95% CI, 1.8–1.9) for Ave, 3.7 mo (95% CI: 3.3–5.1) for PLD + Ave [no significant differences between treatment arms] mOS: 13.1 mo (95% CI: 11.8–15.5) for PLD, 11.8 mo (95% CI: 8.9–14.1) for Ave, 15.7 mo (95% CI: 12.7–18.7) for PLD + Ave [no significant differences between treatment arms]
	NINJA (JapicCTI153004) (N = 316)	Nivo vs Chemo: 1: 24% vs 20% 2: 42% vs 41% ≥3: 34% vs 39%	Open-label randomized: Chemo (Gem or PLD) or Nivo	Primary end point: mOS: 10.1 mo (95% CI: 8.3–14.1) for Nivo; 12.1 mo (95% CI: 9.3–15.3) for chemo (no significant differences between treatment arms) Secondary end points: mPFS: 2.0 mo (95% CI: 1.9–2.2) for Nivo; 3.8 mo (95% CI: 3.6–4.2) for chemo (HR 1.5, 95% CI: 1.2–1.9; p = 0.002); **ORR: 7.6% for Nivo, 13.2% for chemo** [no significant differences between treatment arms]; mDOR: 18.7 mo (95% CI: 2.5–NE) for Nivo, 7.4 mo (3.0–10.3) for chemo
Phase II	NCT02853318 (N = 30)	Median: 3.8 (SD 2.6)	Open-label single arm: Bev + Cyc + Pembro	Co-primary end points: **ORR: 43.3%** (90% CI: 29.6–58.2); PFS: 7.6 mo (90% CI: 5.7–10.3)
	NCT02865811 (N = 26)	1: 38.5% 2: 38.5% 3: 23.1%	Open-label single arm: PLD + Pembro	Primary end point: CBR: 52.2% (95% CI: 30.6–73.2) Secondary end point: **ORR: 26.1%** (95% CI; 10.2–48.4)
	KEYNOTE-100 (NCT02674061) (N = 376)	1: 23% 2: 32% ≥3: 45%	Open-label single arm: Pembro	Primary end point: **ORR by BICR overall: 8%** (95% CI: 5.4–11.2) Secondary end points: DCR overall: 37.2% (95% CI: 32.3–42.3); DOR: 8.2 mo (range: 3.9–18.6) for cohort A; mPFS: 2.1 mo (95% CI: 2.1–2.2) for cohort A, 2.1 mo (95% CI: 2.1–2.6) for cohort B
	NCT02873962 (N = 18)	1: 27.8% 2: 33.3% 3: 38.9%	Open-label single arm: Bev + Nivo	Primary end point: **ORR: 16.7%** (95% CI: 3.6–41.4) Secondary end points: mPFS: 7.7 mo (95% CI: 4.7–NA)
	NRG-GY003 (NCT02498600) (N = 100)	Nivo vs Nivo + Ipi: 1: 29% vs 20% 2: 47% vs 43% 3: 25% vs 37%	Open-label randomized: Nivo or Nivo + Ipi	**Primary end point: ORR: 12.2% for Nivo, 31.4% for Nivo + Ipi** (odds ratio 3.28, 85% CI: 1.5–infinity; p = 0.034) Secondary end points: mPFS: 2.0 mo for Nivo, 3.9 mo for Nivo + Ipi (95% CI: 0.339–0.821); (HR 0.528, 95% CI: 0.339–0.821; 2-sided p = 0.004); mOS: 21.8 mo for Nivo, 28.1 mo for Nivo + Ipi [no sig difference b/t arms]
	TOPACIO (NCT02657889) (N=62)	Median: 3 (range: 1–5)	Open-label single arm: Nira + Pembro	**Primary end point: ORR: 18%** (90% CI: 11–29) Secondary end points: DCR: 65% (90% CI: 54–75); mPFS: 3.4 mo (95% CI: 2.1–5.1)

Pujade-Lauraine E, Fujiwara K, Ledermann JA *et al.* Avelumab alone or in combination with chemotherapy versus chemotherapy alone in platinum-resistant or platinum-refractory ovarian cancer (JAVELIN Ovarian 200): an open-label, three-arm, randomised, Phase III study. **Lancet Oncol.** 22(7), 1034–1046 (2021).
Hamanishi J, Takeshima N, Katsumata N *et al.* Nivolumab versus gemcitabine or pegylated liposomal doxorubicin for patients with platinum-resistant ovarian cancer: open-label, randomized trial in Japan (NINJA). **J. Clin. Oncol.** 39(33), 3671–3681 (2021).
Zsiros E, Lynam S, Attwood KM *et al.* Efficacy and safety of pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide in the treatment of recurrent ovarian cancer: a phase 2 nonrandomized clinical trial. **JAMA Oncol.** 7(1), 78–85 (2021).
Lee EK, Xiong N, Cheng S-C *et al.* Combined pembrolizumab and pegylated liposomal doxorubicin in platinum resistant ovarian cancer: a phase 2 clinical trial. **Gynecol. Oncol.** 159(1), 72–78 (2020).
Matulonis UA, Shapira-Frommer R, Santin AD *et al.* Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. **Ann. Oncol.** 30(7), 1080–1087 (2019).
Liu JF, Herold C, Gray KP *et al.* Assessment of combined nivolumab and bevacizumab in relapsed ovarian cancer: a phase 2 clinical trial. **JAMA Oncol.** 5(12), 1731–1738 (2019).
Zamarin D, Burger RA, Sill MW *et al.* Randomized phase II trial of nivolumab versus nivolumab and ipilimumab for recurrent or persistent ovarian cancer: an NRG Oncology study. **J. Clin. Oncol.** 38(16), 1814–1823 (2020).
Konstantinopoulos PA, Waggoner S, Vidal GA *et al.* Single-arm phases 1 and 2 trial of niraparib in combination with pembrolizumab in patients with recurrent platinum-resistant ovarian carcinoma. **JAMA Oncol.** 5(8), 1141–1149 (2019).

Thomas J Herzog, et al. ARTISTRY-7: phase III trial of nemvaleukin alfa plus pembrolizumab vs chemotherapy for platinum-resistant ovarian cancer. Future Oncology 2023 19:23, 1577-1591

CPI, Anti-Angiogenics & Chemotherapy into PROC: Randomized Phase 3 Studies

ENGOT-OV65/KEYNOTE-B96: Phase 3 pembrolizumab vs placebo plus paclitaxel with optional bevacizumab for PROC

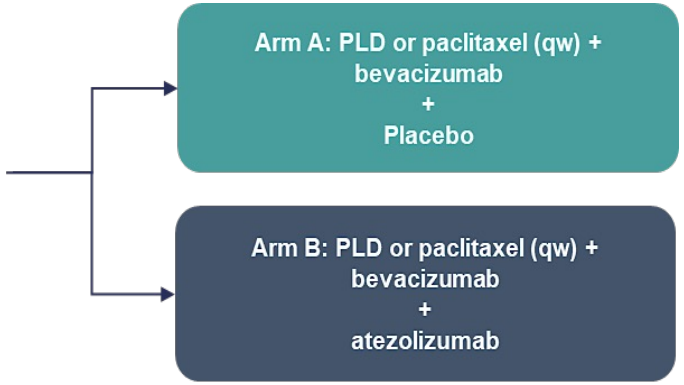


Endpoints

Primary: PFS - Investigator

NCT05116189

AGO-OVAR 2.29 (ENGOT-OV34): atezolizumab + bevacizumab + chemotherapy vs bevacizumab + chemotherapy in recurrent OC

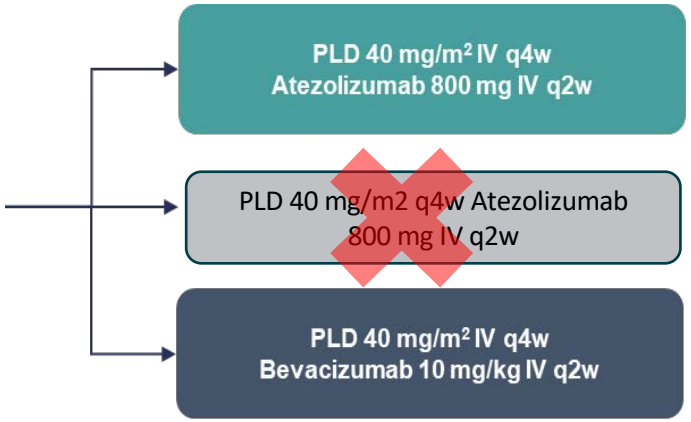


Endpoints

Co-Primary: OS, PFS

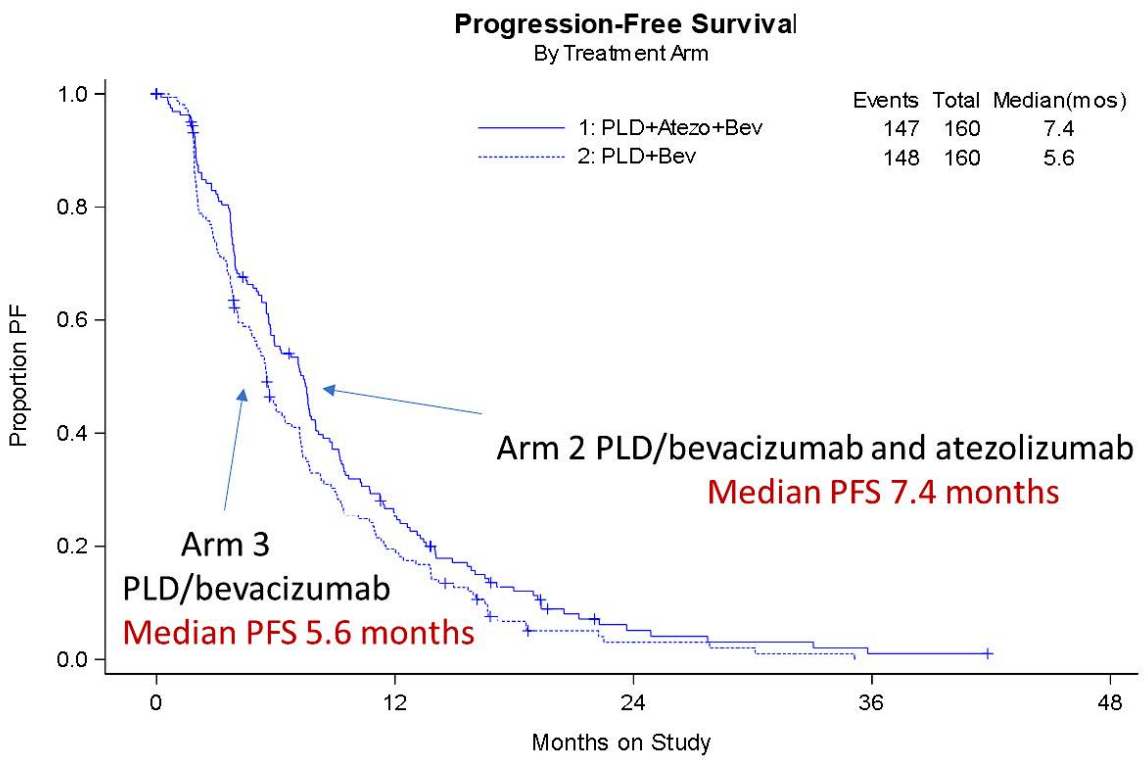
NCT03353831

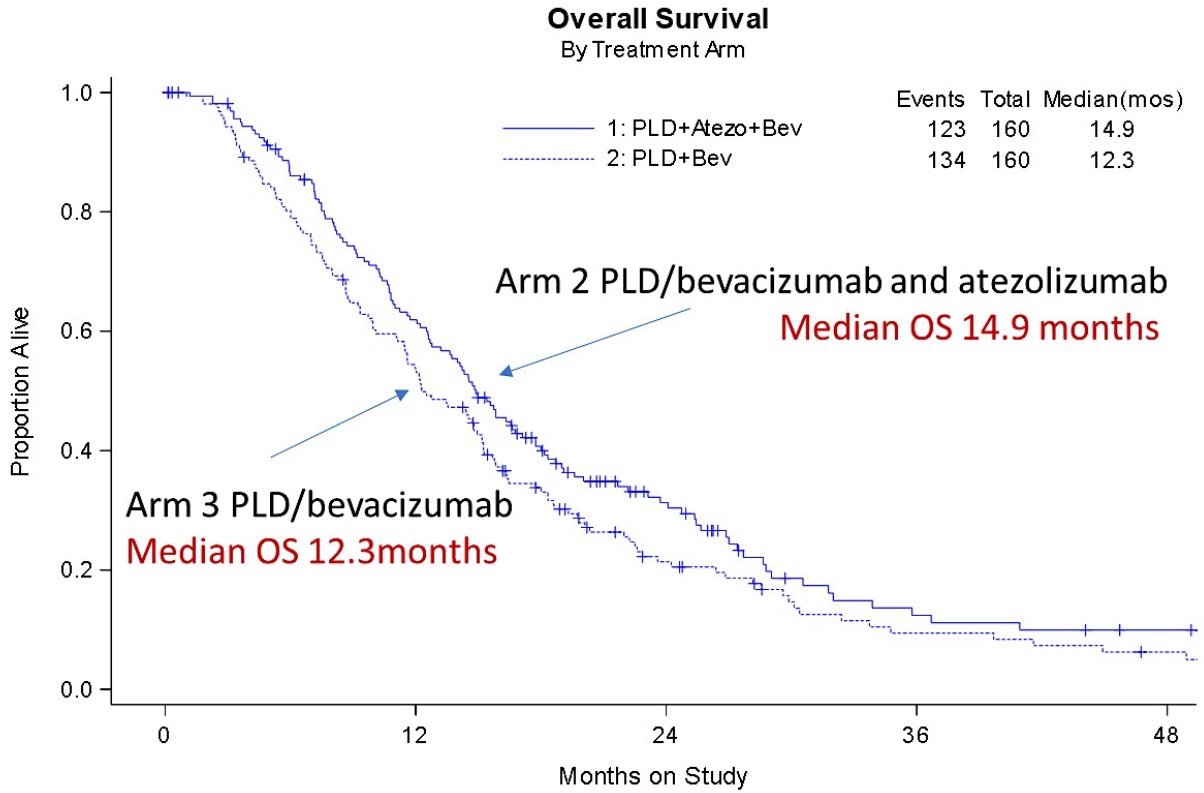
NRG GY009: Phase 2/3 study of PLD + atezolizumab ± bevacizumab in patients with PROC



NCT03353831

NRG GY009: A RPh2/3 STUDY OF PLD AND ATEZOLIZUMAB VS PLD, BEVACIZUMAB AND ATEZOLIZUMAB VS PLD AND BEVACIZUMAB IN PLATINUM-RESISTANT OVARIAN CANCER





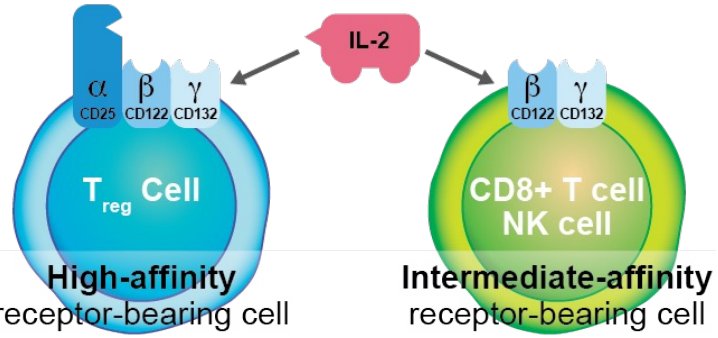
HR (95% CI): 0.79 (0.62, 0.99)
Did not reject null of no difference

HR (95% CI): 0.8 (0.63, 1.03)
Did not reject null of no difference

- Roisin O'Cearbhaill, et al. IGCS 2023

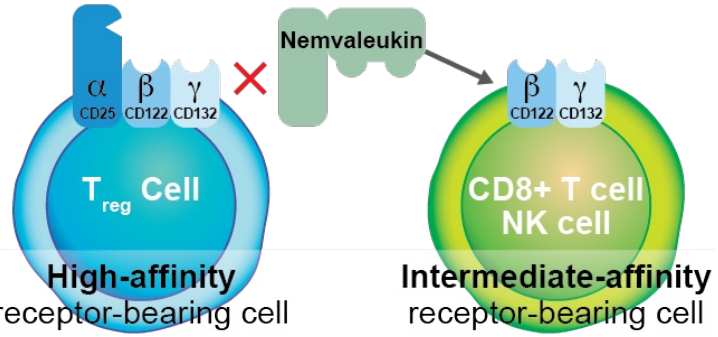
ARTISTRY-1: A Phase I/II Study of Nemvaleukin Alfa Alone and in Combination With Pembrolizumab

Cell activation by IL-2



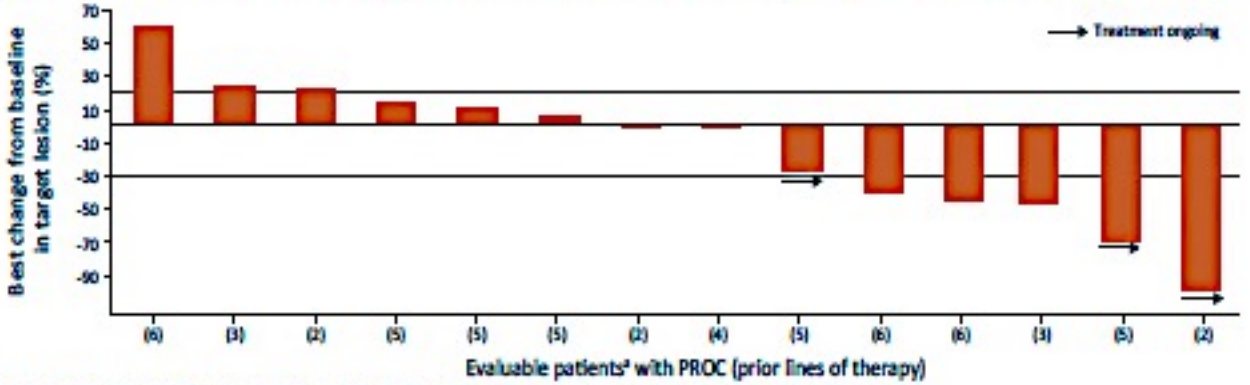
- Preferential activation of high-affinity IL-2R by high-dose IL-2 leads to expansion of T_{regs}, which may counteract antitumor activity as well as stimulate vascular endothelial cells
- Activation of vascular endothelial cells is associated with high incidence of acute toxicities, including capillary leak syndrome

Nemvaleukin is a stable fusion of IL-2 and IL-2α



- Stable fusion protein designed to harness the validated IL-2 pathway biology
- Intrinsically active immediately upon systemic entry; does not degrade to native IL-2
- Designed to selectively bind the immediate-affinity IL-2R to:
  - Preferentially activate memory cytotoxic $CD8^+$ T cells and NK cells without expanding $CD4^+$ T_{regs}
  - Mitigate toxicities associated with preferential binding of IL-2 to high-affinity IL-2R

Figure 3: ARTISTRY-1 best change from baseline in sum of target lesions with nemvaleukin plus pembrolizumab in patients with PROC



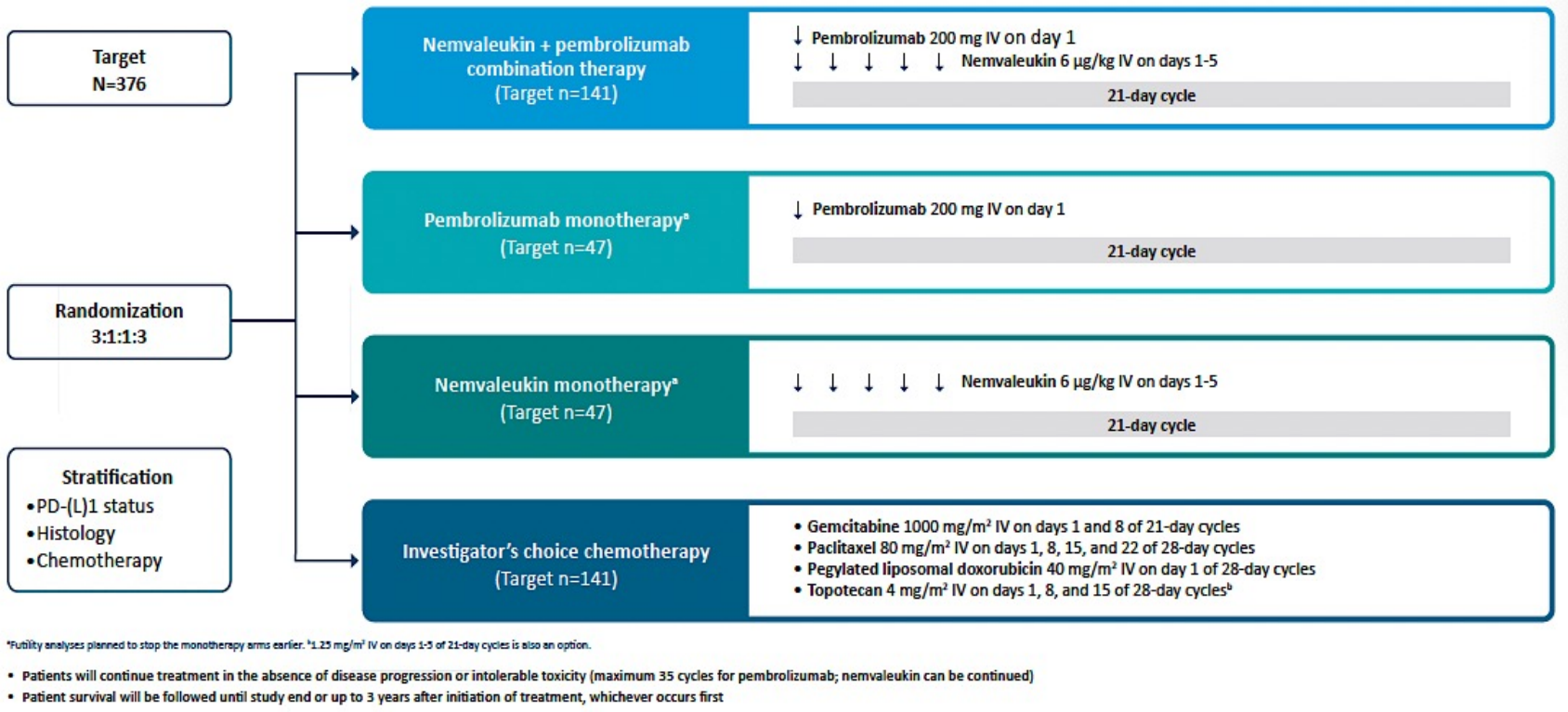
*N=14 evaluable patients with PROC who received nemvaleukin 3 µg/kg IV + pembrolizumab and ≥1 postbaseline scan.
Response per Response Evaluation Criteria in Solid Tumors v1.1. Data cutoff October 29, 2021.
IV, intravenous.

Winer I et al, SGO 2022; Herzog et al, SGO 2023 TiP abstract

The James
The Ohio State University
Wexner Medical Center

ARTISTRY-7: A Phase 3, Multicenter Study of Nemvaleukin Alfa in Combination With Pembrolizumab Versus Chemotherapy in Patients With Platinum-Resistant Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (GOG-3063; ENGOT-OV68)

- Recent Changes Announced*
  - OS primary endpoint
  - 56 additional patients
  - Closure of Single agent Pembro & Nemvaleukin arms



Thomas J Herzog, John L Hays, Joyce N Barlin, Joseph Buscema, Noelle G Cloven, Lynn R Kong, Nidhi Kumar Tyagi, Grainger S Lanneau, Beverly J Long, Robert L Marsh, Shelly M Seward, David C Starks, Stephen Welch, Kathleen N Moore, Panagiotis A Konstantinopoulos, Lucy Gilbert, Bradley J Monk, David M O'Malley, Xiwei Chen, Rita Dalal, Robert L Coleman, and Jalid Sehouli. ARTISTRY-7: phase III trial of nemvaleukin alfa plus pembrolizumab vs chemotherapy for platinum-resistant ovarian cancer. Future Oncology 2023 19:23, 1577-1591

* https://ir.muraloncology.com/news-releases/news-release-details/mural-oncology-announces-enhancements-late-stage-clinical-trials

ARTISTRY-7: Updated Study Design (Protocol v5)

Approximately 450 participants

Further enrollment in Arm 1 and 4 only
Randomization 1:1

No further enrollment in monotherapy arms

Key eligibility criteria [2]

- Platinum-resistant/ refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer
- At least 1L of systemic platinum therapy and ≤5L of systemic platinum-resistant therapy
- Prior bevacizumab treatment
- Measurable disease by RECIST v1.1

Arm 1 and Arm 4: 183 patients each

Arm 1
Nemvaleukin IV +
Pembrolizumab IV

Pembrolizumab dosing

Nemvaleukin dosing

Arm 4
Investigator's Choice
Single-Agent Chemotherapy

PLD IV, 40 mg/m² (Day 1 of 28-day cycle)
Paclitaxel IV, 80 mg/m² (Days 1, 8, 15, and 22 of 28-day cycle)
Topotecan IV, 4 mg/m² (Days 1, 8, and 15 of 28-day cycle)[a]
Gemcitabine IV, 1000 mg/m² (Days 1 and 8 of 21-day cycle)

Key Endpoints

Primary endpoint: OS

Secondary outcome measures:

- PFS, PFS2, ORR, DCR, DOR, and TTR[b]
- CA-125 response[c]
- TEAEs

Clinical trial and supply agreement with MSD (a tradename of Merck & Co., Inc. Kenilworth, NJ, USA)

Conduct of trial is in association with The GOG Foundation, Inc. (GOG), the European Network of Gynaecological Oncological Trial groups (ENGOT), and the Asia-Pacific Gynecologic Oncology Trials Group (APGOT)

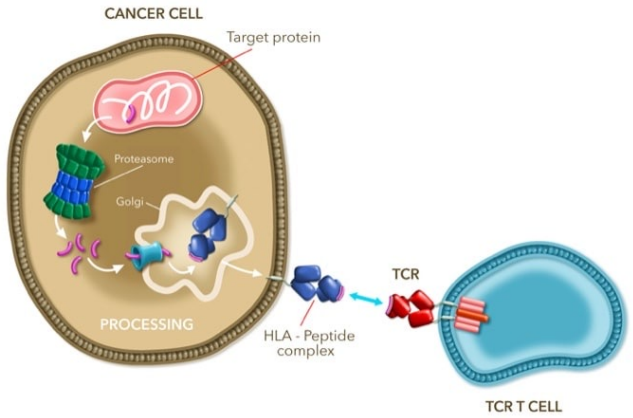
Arm 2 (Pembrolizumab Monotherapy) and Arm 3 (Nemvaleukin Monotherapy) met enrollment goals and closed to further enrollment.

[a] Alternative topotecan regimen: 1.25 mg/m² on Days 1-5 of 21-d cycles
[b] Response per RECIST v1.1
[c] Response per GCIG

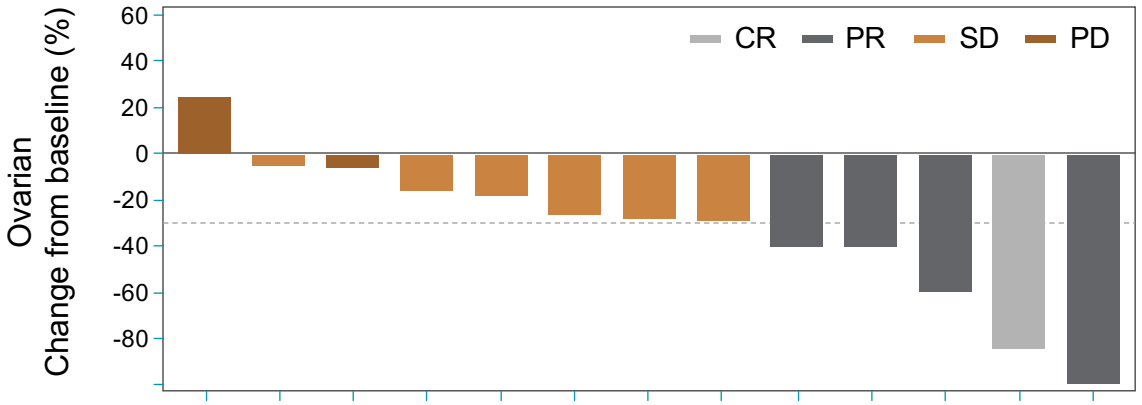
1. Herzog T et al. Poster presented at the Society for Gynecologic Cancers Annual Meeting (SGO), Phoenix, AZ, March 18-21, 2022
2. https://clinicaltrials.gov, NCT05092360

Abbrev.: **CA-125**: cancer antigen-125; **DCR**: disease control rate; **DOR**: duration of response; **GCIG**: Gynecologic Cancer InterGroup; **IV**: intravenous; **ORR**: objective response rate; **OS**: overall survival; **PFS**: progression-free survival; **PLD**: pegylated liposomal doxorubicin; **RECIST**: Response Evaluation Criteria in Solid Tumors; **TEAE**: treatment-emergent adverse event; **TTR**: time to response

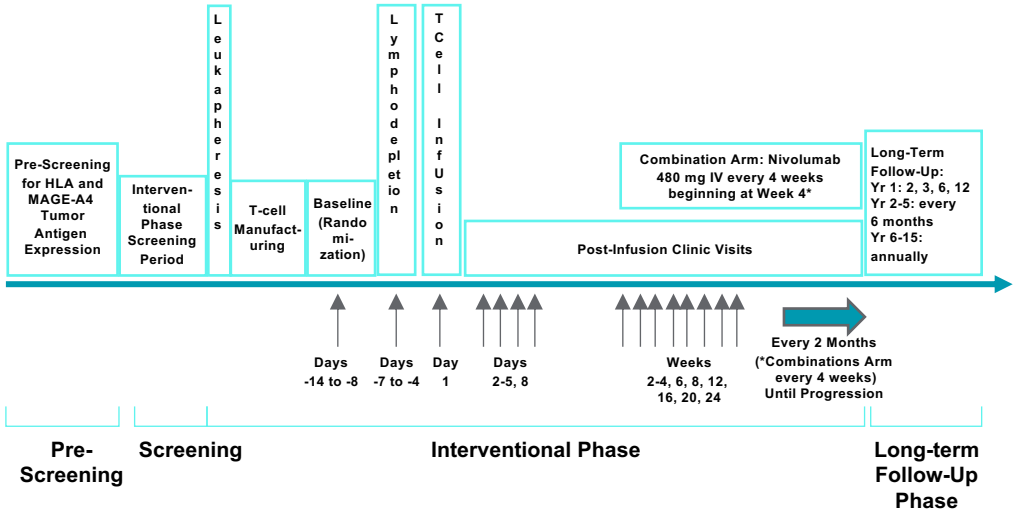
SURPASS-3: Phase 2 study of ADP-A2M4CD8 as monotherapy or in combination with nivolumab in HLA-A2+ patients with MAGE-A4–positive tumors



The HLA peptide complex presents peptides that are derived from intracellular target proteins. TCRs target and bind to a specific HLA peptide complex, resulting in the targeting and destruction of the relevant cell.



SURPASS-1: SPEAR T-cell therapy supplemented with CD8 alpha co-receptor. ORR of 36% with favorable benefit to risk profile.



NCT04044859: Recruiting

- Estimated enrollment: 120 participants
- Estimated primary completion date: September 2023

- 1. Van Tine BA et al. ESMO 2019. Abstract 5471. 2. Hong DS et al. ESMO 2022. Abstract 735MO. 3. ClinicalTrials.gov. NCT04044859.

Phase 3 OnPrime/GOG-3076 trial in PROC

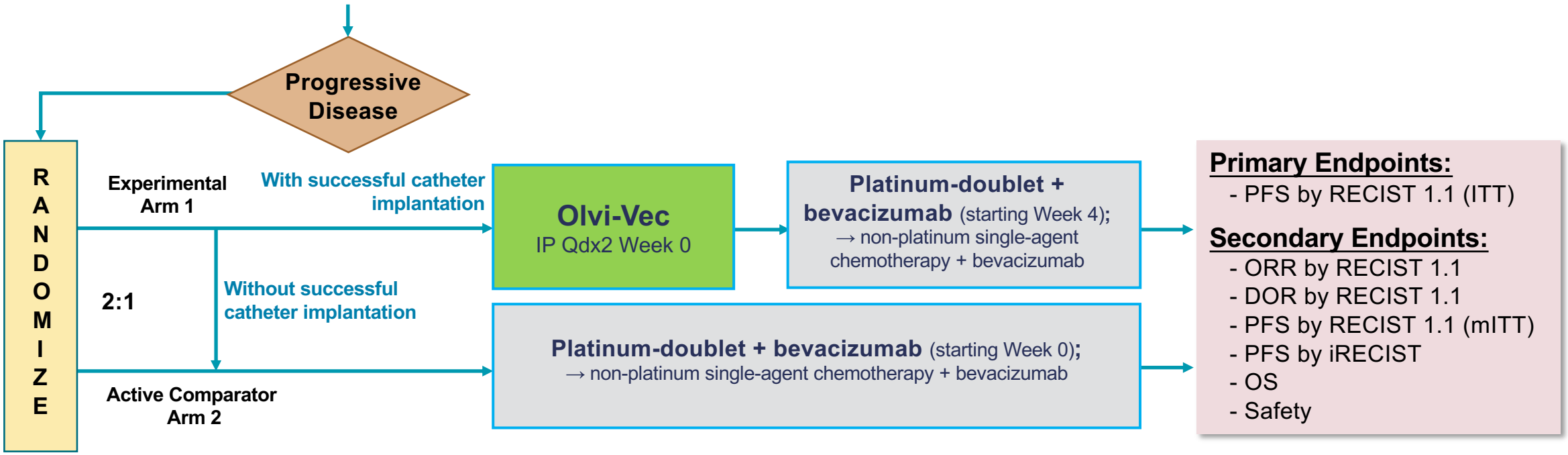
Oncolytic Vaccinia Virus Olvi-Vec (Modified oncolytic vaccinia virus (LIVP strain) with mutations that enhance tumor targeting

Platinum-resistant/refractory ovarian cancer (PRROC)

- Number of prior lines: ≥3
- Had prior bevacizumab or biosimilar
- Platinum-free interval (PFI): 0-1 month or 1-6 months
- Time from last platinum (TFLP) dose: 3-15 months

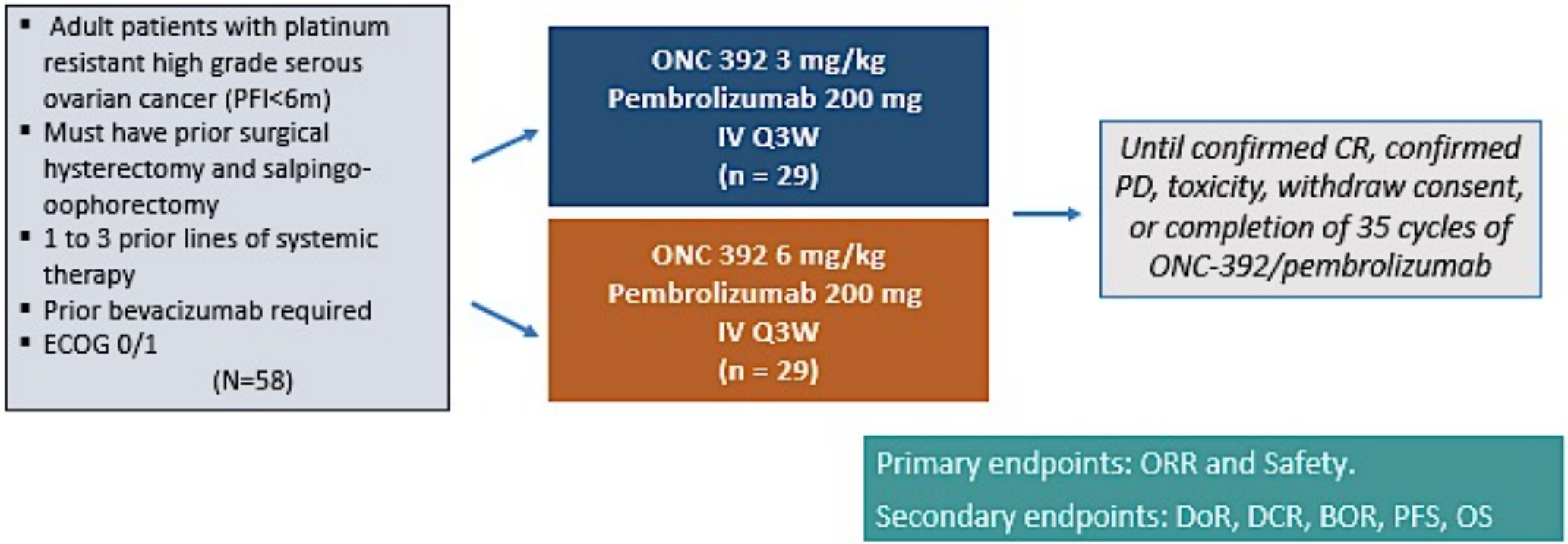
Stratification at Enrollment Prior to Randomization

- PFI after most recent platinum-based therapy: <1 month vs. 1-6 months
- Baseline germline *BRCA*1/2 mutation status: positive vs. negative



Holloway R et al. IGCS 2022. Abstract TP026

GOG-3081/ONC-392-005/PRESERVE-004
Phase 2 Randomized Open-label Multicenter Study of Combination of ONC-392 and Pembrolizumab for the Treatment of Patients with Platinum Resistant Ovarian Cancer (PI: Joyce Barlin/Brad Monk)



Summary

- First Line Therapy
  - Multiple Phase III trials will read out which will help to define the impact of IO in the first line
  - The impact of DUO-O remains unclear
- PROC
  - Multiple Opportunities for Novel Immune Strategies
  - Optimism persists
  - Challenging group of patients for IO therapies

MODULE 3: Incorporation of Novel Therapies into the Management of Relapsed/Refractory OC — Dr Moore

Consulting Faculty Questions

Mirvetuximab soravtansine: Repeat testing for folate receptor alpha on disease progression; monitoring for ocular toxicities

Neil Love, MD

Deborah K Armstrong, MD

Rachel N Grisham, MD

QUESTIONS FOR THE FACULTY

Deborah K Armstrong, MD

Rachel N Grisham, MD

What is your clinical experience with mirvetuximab soravtansine? How are you typically using this agent, and how frequently do you see antitumor benefit?

In general, how is mirvetuximab soravtansine tolerated? Are the ophthalmologic requirements associated with this agent challenging for you or your patients?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Screening patients for ILD associated with trastuzumab deruxtecan

Neil Love, MD

Rachel N Grisham, MD

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Rachel N Grisham, MD

How are you currently approaching HER2 testing for patients with ovarian cancer? When are you typically testing, and how do you define HER2 positivity?

In what situations, if any, would you currently use trastuzumab deruxtecan (T-DXd)? How do you approach GI prophylaxis with T-DXd?

How do you screen for ILD in patients receiving T-DXd? How would you manage Grade 1 ILD with the agent? What about Grade 2? In what situations, if any, will you consider reintroducing T-DXd in a patient for whom ILD symptoms have resolved?

What other novel approaches, including antibody-drug conjugates, in development appear most promising?

RTP
RESEARCH
TO PRACTICE

Should HER2 testing be ordered for patients with advanced OC? Have you offered or would you offer HER2-targeted therapy to your patients with HER2-positive advanced OC outside of a protocol setting?

	Order HER2 testing?	Offer HER2-targeted therapy?
 Dr Liu	Yes	I have
 Dr Mirza	Yes	I have not but would for the right patient
 Dr Moore	Yes	I have not but would for the right patient
 Dr O'Malley	Yes	I have
 Dr Armstrong	Yes	I have
 Dr Grisham	Yes	I have not but would for the right patient

In general how do you manage the nausea and vomiting associated with T-DXd?

 Dr Liu	Premedication with 5-HT3 antagonist, neurokinin antagonist and steroids
 Dr Mirza	NK1 inhibitors. We usually use aprepitant
 Dr Moore	Premedication with antiemetics and good rescue for home
 Dr O'Malley	Prophylactic regimen prior to infusion; if delayed nausea, then dexamethasone and prochlorperazine +/- olanzapine
 Dr Armstrong	Ondansetron, prochlorperazine
 Dr Grisham	Aprepitant with infusion, dexamethasone taper for 3 days post, ondansetron and lorazepam as needed

How would you rate your enthusiasm for enrolling a patient on the Phase II/III REJOICE-Ovarian01 study of raludotatug deruxtecan for patients with platinum-resistant, high-grade ovarian, primary peritoneal or fallopian tube cancer?

	Enthusiasm*	Comments
 Dr Liu	4	Based on Phase I data, rationale, and mechanism of action, I am enthusiastic
 Dr Mirza	4	Active drug
 Dr Moore	4	Phase I expansion data is very strong – drug is very well tolerated
 Dr O'Malley	4	No comment
 Dr Armstrong	3	Always excited about a new therapeutic target
 Dr Grisham	4	ADCs have been encouraging

* 1 = not at all enthusiastic, 4 = very enthusiastic

Considerations for the treatment of recurrent ovarian cancer

Kathleen N. Moore, MD, MS

Deputy Director and Associate Director Clinical Research

Stephenson Cancer Center at OU Health

Oklahoma City, OK

GOG F BOD

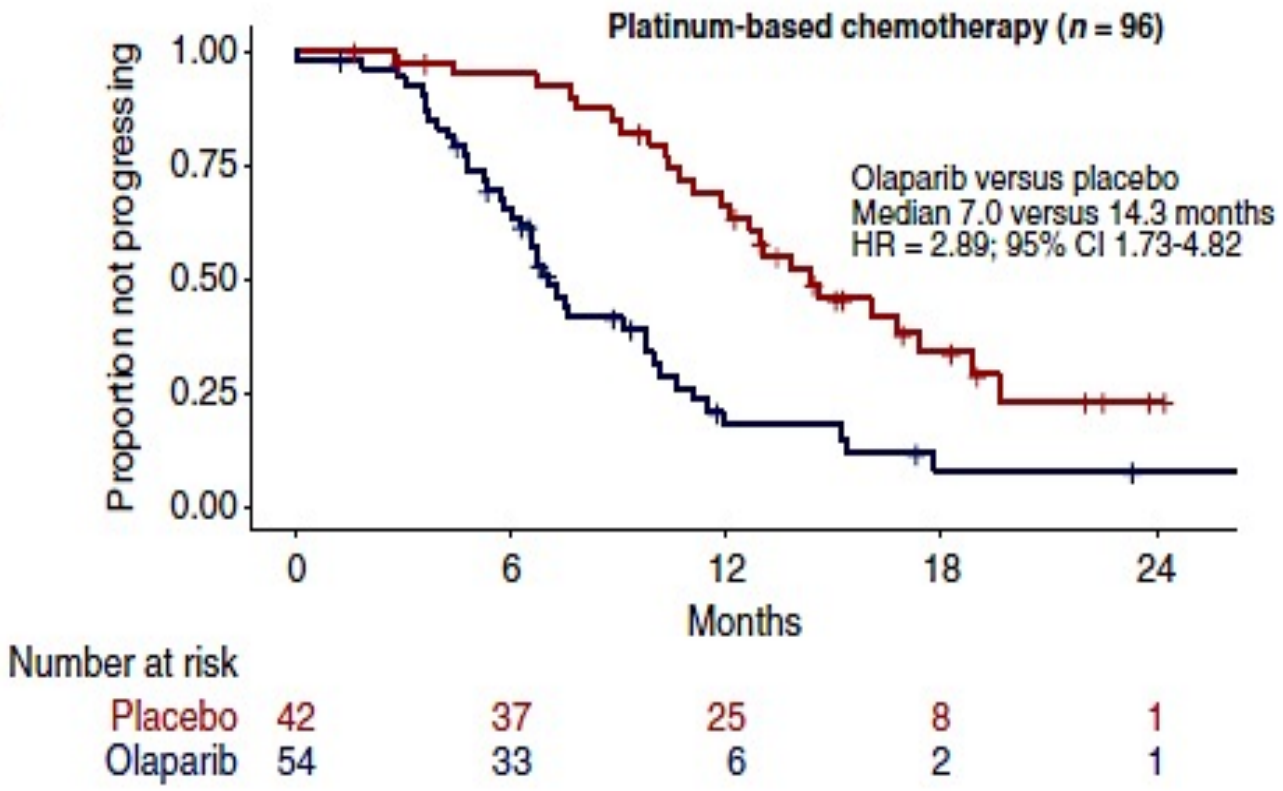
ASCO BOD

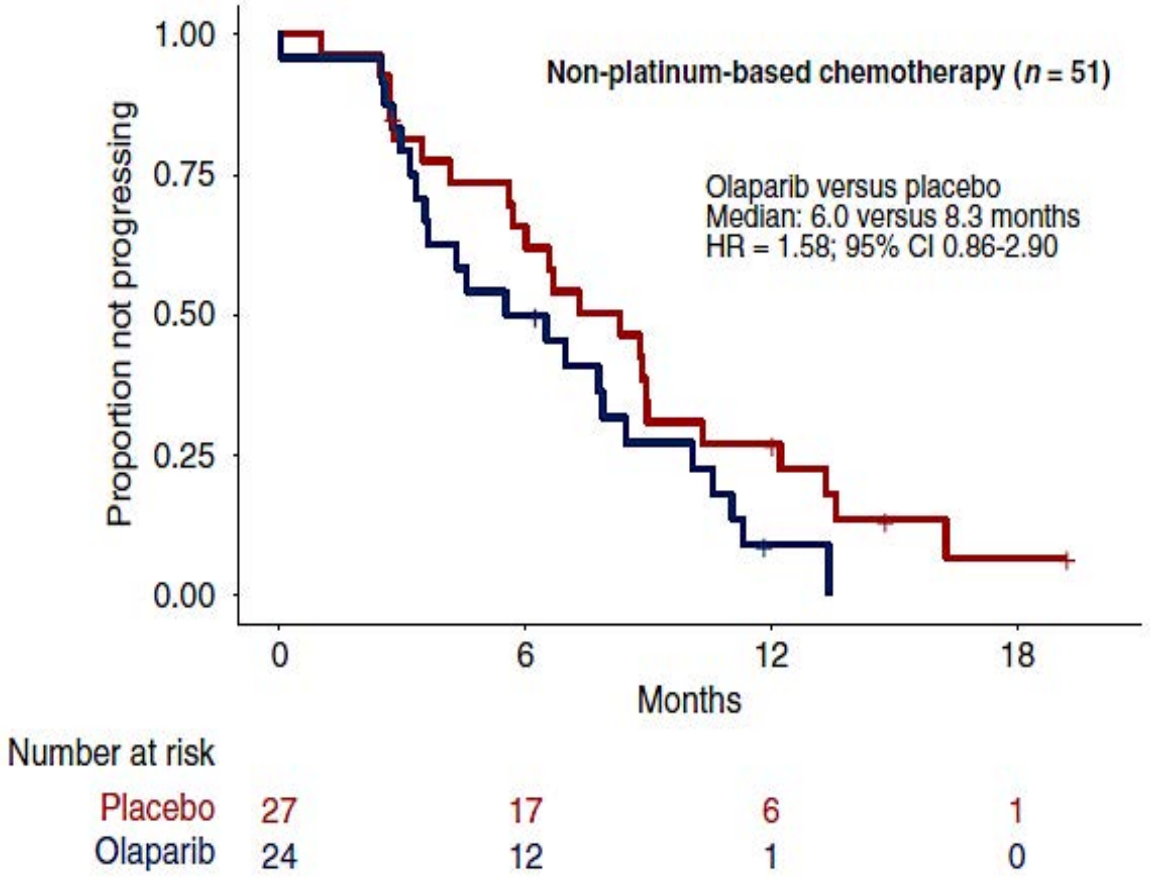
Objectives

- Role of PARP inhibition in recurrent disease
- Role of Antibody Drug Conjugates
  - Folate receptor alpha
  - Cadherin 6 (CDH6)
  - ERBB2/HER2

Overlap of Platinum & PARPi Resistance

Time to second progression according to subsequent therapy type

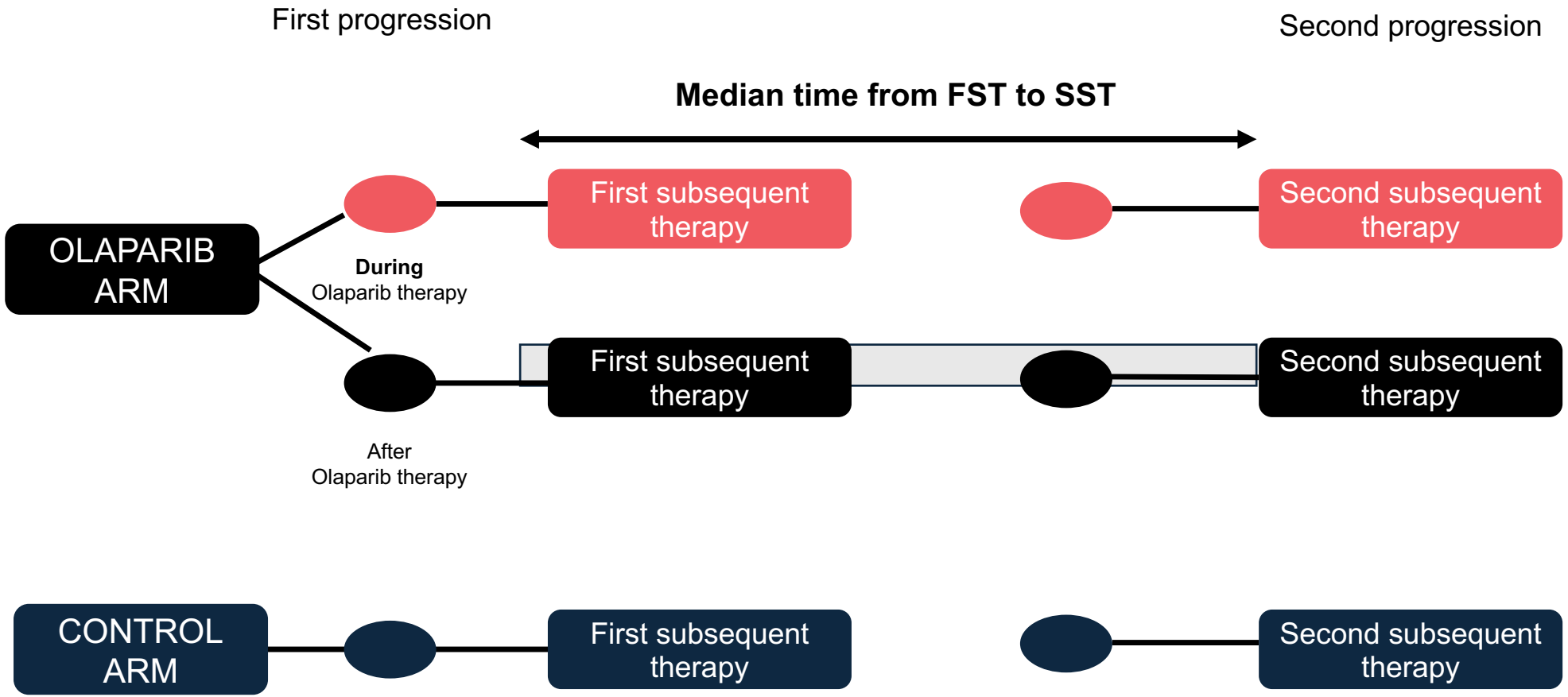




Frenel JS, et al. Ann Oncol. 2022;33(10):1021-8.

Resistance to PARPi = Resistance to Platinum?

Post hoc exploratory analysis:
Time from first subsequent therapy to second subsequent therapy

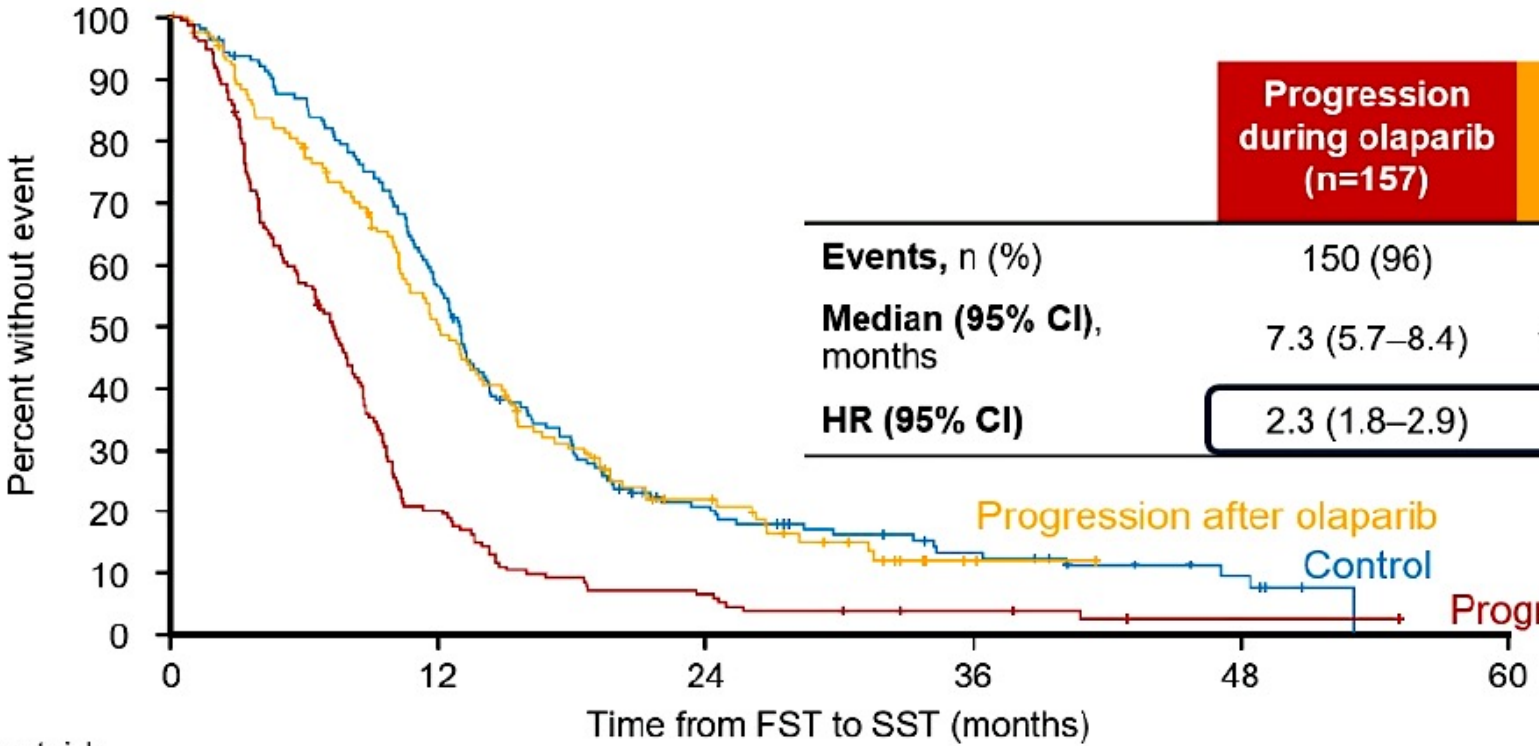


FST, First Subsequent Treatment; SST, Second Subsequent Treatment

Ray Coquard et al NEJM 2019 & Harter et al ASCO 2023

Resistance to PARPi = Resistance to Platinum?

A *post hoc* exploratory PAOLA-1 analysis suggested the efficacy of subsequent chemotherapy at first relapse was reduced in patients with disease progression during vs after Olaparib plus bevacizumab maintenance[1]



	Progression during olaparib (n=157)	Progression after olaparib (n=132)	Control (n=162)
Events, n (%)	150 (96)	103 (78)	139 (86)
Median (95% CI), months	7.3 (5.7–8.4)	12.0 (10.3–14.8)	12.9 (11.8–14.1)
HR (95% CI)	2.3 (1.8–2.9)	1.1 (0.8–1.4)	Ref

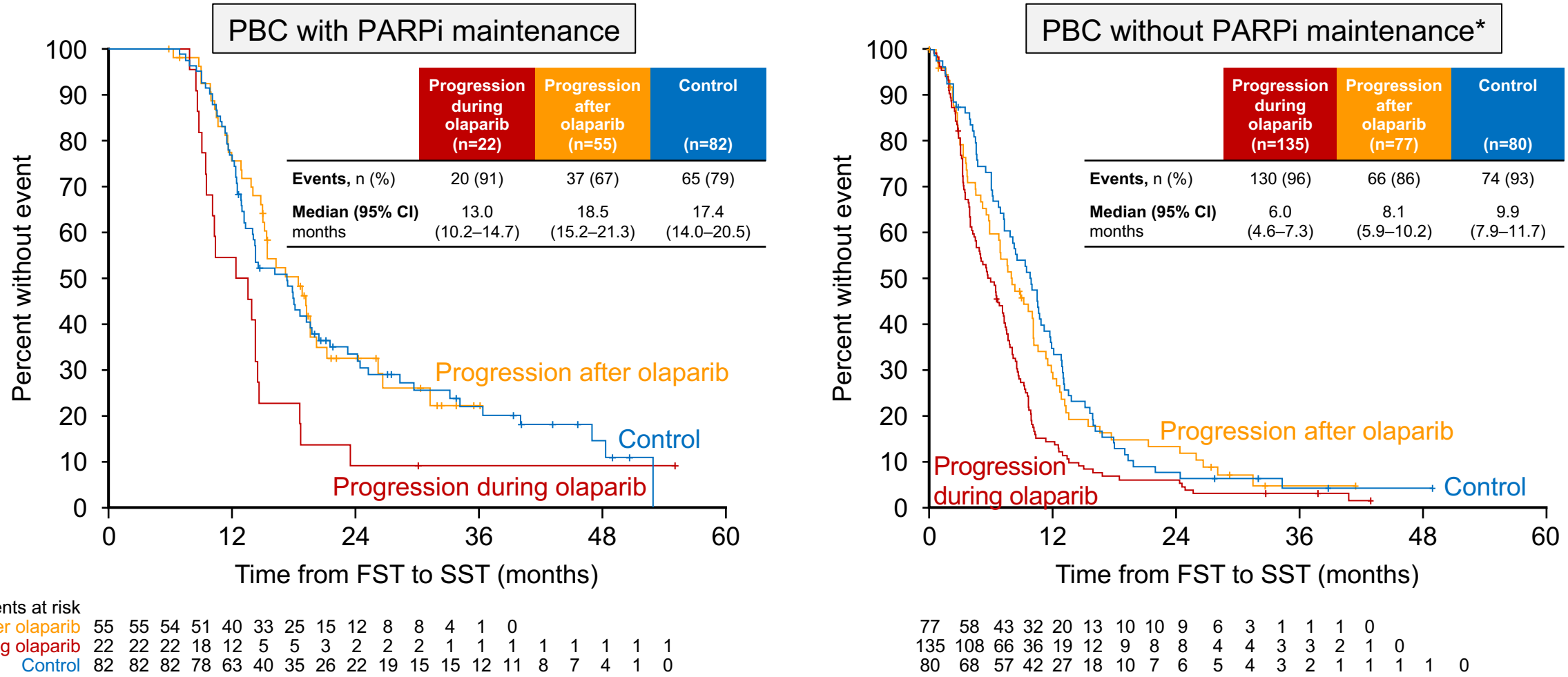
Patients at risk

Progression after olaparib	132	113	97	83	60	46	35	25	21	14	11	5	2	1	0				
Progression during olaparib	157	130	88	54	31	17	14	11	10	6	6	4	4	3	2	1	1	1	1
Control	162	150	139	120	90	58	45	33	28	24	19	18	14	12	9	8	5	1	0

One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

Ray Coquard et al NEJM 2019 & Harter et al ASCO 2023

Does exposure to PARPi in FL = Resistance to PARPi in 2L?



*One patient in the olaparib arm did not receive study treatment and is not included in this analysis.

Marth C et al. ESGO 2023, Istanbul

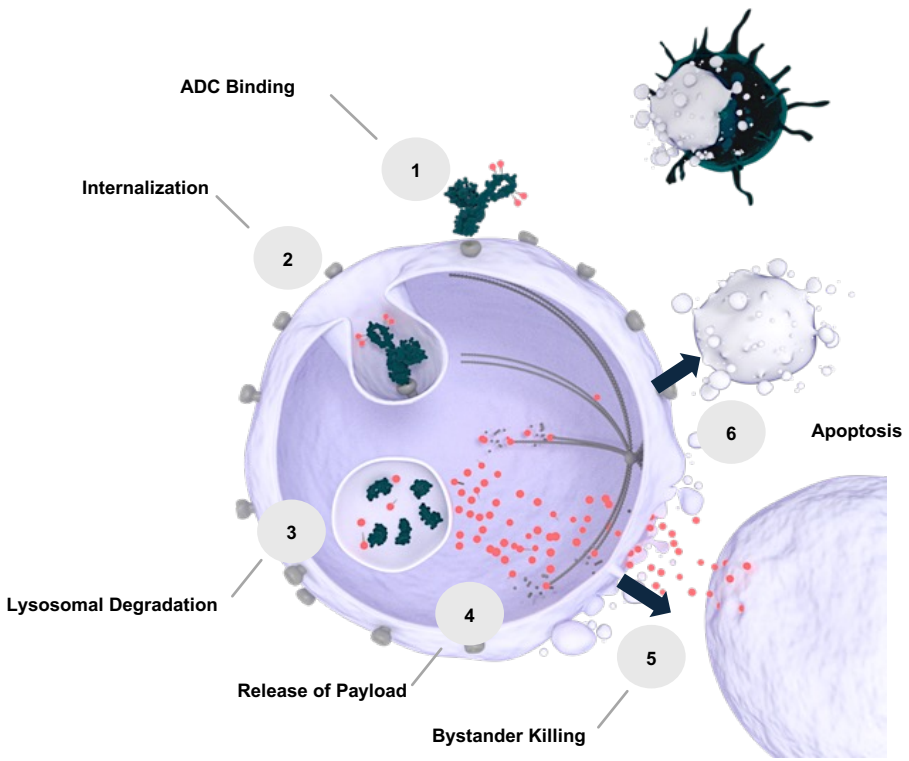
Select ADCs under clinical development in gynecologic oncology indications

Target	Drug	DAR	Tumor type
B7-H4	XMT-1660[1]	6	Ovarian, endometrial
	SGN-B7H4V[2–4]	4	Ovarian, endometrial
	AZD8205[5,6]	8	Ovarian, endometrial
CDH6	**DS-6000a[7,8]**	**~8**	Ovarian
FRα	**Luveltamab tazevibulin (STRO-002)[9,10]**	**4**	Ovarian, endometrial
	Farletuzumab ecteribulin (MORAb-202)[11,12]	**4**	Ovarian, endometrial
HER2	**SYD985[13,14]**	**2.7**	Ovarian, endometrial
	T-DXd[15,16]	**7–8**	Cervical, ovarian, endometrial
	DB-1303/BNT323[17,18]	**~8**	Endometrial
Mesothelin	**BMS-986148[19,20]**	**3**	Ovarian
Tissue factor	XB002[21,22]	4	Cervical, ovarian
TROP2	Sacituzumab govitecan[23, 24]	7.5	Cervical, ovarian, endometrial
	DB-1305[25, 26]	~4	Ovarian, endometrial

ADC, antibody-drug conjugate; CDH6, cadherin 6; DAR, drug-antibody ratio; FRα, folate receptor alpha; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell surface antigen 2.

1. Hamilton E et al. Poster presented at IGCS Annual Meeting 2022; Abstract 1420. 2. Gray E et al. *J Immunother Cancer.* 2021;9(Suppl 2):A1–A1054. 3. Patnaik A et al. Poster presented at ASCO Annual Meeting 2022; Abstract TPS3155. 4. ClinicalTrials.gov. NCT05194072. Accessed March 17, 2023. 5. Meric-Berstam F et al. Poster presented at ASCO Annual Meeting 2022; Abstract TPS3153. 6. ClinicalTrials.gov. NCT05123482. Accessed March 17, 2023. 7. Hamilton EP et al. Oral Presentation at ASCO Annual Meeting; Abstract 3002. 8. ClinicalTrials.gov. NCT04707248. Accessed March 17, 2023. 9. Li X et al. AACR Annual Meeting 2018; Poster Presentation. 10. ClinicalTrials.gov. NCT03748186. Accessed March 17, 2023. 11. Cheng X et al. *Mol Cancer Ther.* 2018;17(12):2665–2675. 12. ClinicalTrials.gov. NCT04300556. Accessed November 16, 2022. 13. Yao. *Drug Discov Today.* 2021;26(8):1857–1874. 14. ClinicalTrials.gov. NCT04602117, NCT04205630, NCT04235101. Accessed November 16, 2022. 15. Takegawa N et al. *Int J Cancer.* 2017;141(8):1682–1689. 16. ClinicalTrials.gov. NCT04585958, NCT04482309, NCT04639219. Accessed March 17, 2023. 17. Swain et al. *Nat Rev Drug Discov.* 2023;22(2):101–126. 18. ClinicalTrials.gov. NCT05150691. Accessed October 10, 2023. 19. Rottey S et al. *Clin Cancer Res.* 2022;28(1):95-105. 20. ClinicalTrials.gov. NCT02341625. Accessed October 2, 2023. 21. Tolcher A et al. Poster presentation at SGO Annual Meeting on Women's' Cancer; Poster 301. 22. Barnscher S et al. *Cancer Res.* 2017;77(13 Suppl):61. 23. Saxena A et al. Poster presentation at ASCO Annual Meeting 2020; Abstract TPS3648. 24. ClinicalTrials.gov. NCT04251416, NCT05119907, NCT03964727. Accessed March 17, 2023; 25. A Phase 1 study of DB-1305 in people with advanced ovarian, endometrial, cervical, or lung cancers. Memorial Sloan Kettering Cancer Center. Accessed October 30, 2023. https://www.mskcc.org/cancer-care/clinical-trials/23-059. 26. ClinicalTrials.gov. NCT05438329. Accessed October 30, 2023

Mirvetuximab Soravtansine



MIRV is an ADC comprising an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload[2]

SORAYA (NCT04296890) was a global, single-arm pivotal study evaluating mirvetuximab soravtansine in adult patients with FRα-positive platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer[3–5]

Key eligibility criteria[3–5]

- Platinum-resistant ovarian cancer
- Prior bevacizumab required, prior PARPi allowed
- 1–3 prior lines of therapy
- Patients with *BRCA* mutations allowed
- FRα-positive (≥75% of cells staining positive with ≥2+ staining intensity)

Mirvetuximab soravtansine (N=106)[3]
6.0 mg/kg adjusted ideal body weight (AIBW) q3w

Primary endpoint[3]
- ORR per Investigator

Secondary endpoints[2]
- DOR, PFS, OS, CA-125 response by GCIG criteria, safety

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ADC, antibody-drug conjugate; BRCA breast cancer gene; CA-125, cancer antigen 125; DM4, maytansine 4; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynaecologic Cancer Intergroup; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; q3w, every 3 weeks.

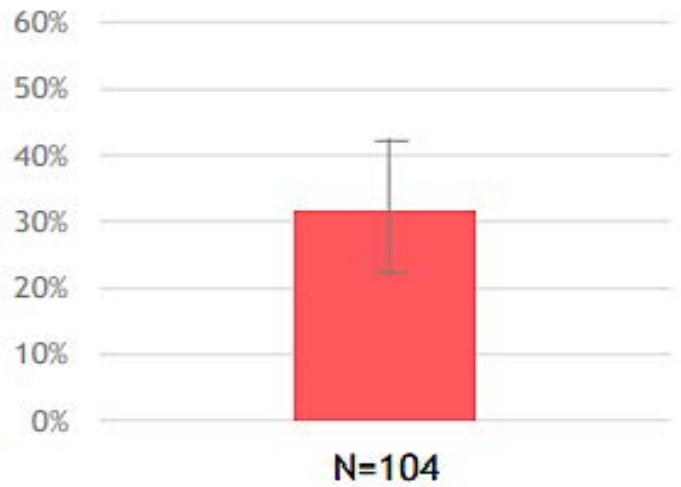
1. FDA. Published November 14, 2022. Accessed March 3, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mirvetuximab-soravtansine-gynx-fra-positive-platinum-resistant. 2. Moore KN et al. *Cancer*. 2017;123(16):3080–3087. 3. Matulonis UA et al. *J Clin Oncol*. 2023;JCO2201900. 4. Matulonis UA et al. Poster presentation at ASCO Annual Meeting 2022; Abstract 5512. 5. Mirvetuximab soravtansine-gynx package insert.; November 2022.

SORAYA

ORR% BY INVESTIGATOR[1]

31.7%

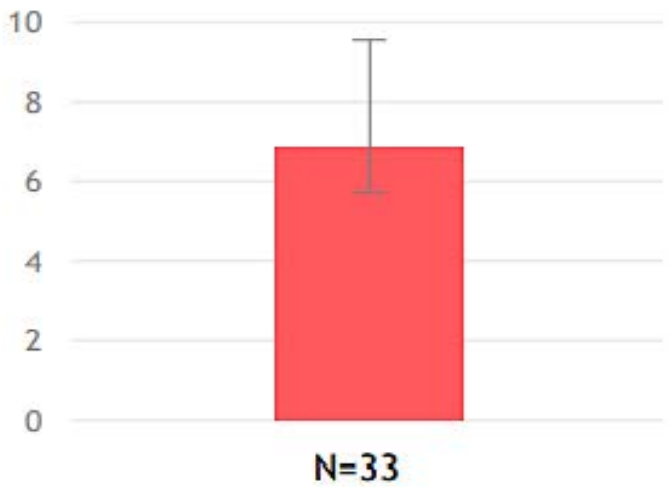
(22.9, 41.6)*



DOR BY INVESTIGATOR[1]

6.9 months

95% CI: (5.6, 9.7)



	Mirvetuximab soravtansine (n=104)
Confirmed ORR, n (%) [95% CI][a]	31.7 [22.9, 41.6]
Complete response, %	4.8
Partial response, %	26.9
mDOR, months [95% CI]	6.9 [5.6, 9.7]

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[a]Data shown from SORAYA safety population are derived from a separate data cutoff of April 29, 2022.[3]
DOR, duration of response; mDOR, median duration of response; ORR, objective response rate;.
. Matulonis et al. J Clin Oncol. 2023 41(13): 2436-2445

An open-label, phase 3 randomized trial of MIRV vs investigator's choice chemotherapy in patients with FRα-high platinum-resistant ovarian cancer

Patient Population (N=453)

Enrollment and Key Eligibility

Platinum-resistant disease (PFI ≤6 mo)

FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells

1º platinum-refractory disease excluded (primary PFI <3 mo)

1-3 prior lines of therapy

Prior BEV and PARPi allowed

Patients with BRCA mutations allowed

1:1 Randomization

MIRV
(6 mg/kg AIBW Q3W)

Investigator's Choice Chemotherapy
(Paclitaxel, PLD, or Topotecan)

Stratification Factors

IC chemo: paclitaxel, PLD, or topotecan

Prior lines of therapy: 1 vs 2 vs 3

Primary Endpoint

PFS by INV
(BICR for sensitivity analysis)

Secondary Endpoints

ORR by INV
OS
PROs[a]
Safety and tolerability
DOR
CA-125 response[b]
PFS2

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.

[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.

[b]Gynecological Cancer InterGroup (GCIG) criteria.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855

2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

MIRASOL

Baseline Demographics (N=453)

Characteristics		MIRV (n=227)	IC Chemo (n=226)
Age, median (range)	Age in years	63 (32-88)	62 (29-87)
Stage at initial diagnosis, n (%)[a]	I-II III IV	9 (4) 137 (60) 76 (33)	9 (4) 147 (65) 65 (29)
BRCA mutation, n (%)	Yes No/Unknown	29 (13) 198 (87)	36 (16) 190 (84)
No. of prior systemic therapies, n (%)	1 2 3	29 (13) 90 (40) 108 (48)	34 (15) 88 (39) 104 (46)
Prior exposure, n (%)	Bevacizumab PARPi Taxanes	138 (61) 124 (55) 227 (100)	143 (63) 127 (56) 224 (99)
Primary platinum-free interval, n (%)[b]	≤ 12 months > 12 months	146 (64) 80 (35)	142 (63) 84 (37)
Platinum-free interval, n (%)[c]	≤ 3 months > 3 - ≤6 months	88 (39) 138 (61)	99 (44) 124 (55)

Data cutoff: March 6, 2023

BRCA, BReast cancer gene; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor.

[a]Five patients (2%) in the MIRV arm and five patients in the IC chemo arm (2%) were missing information for stage at initial diagnosis. [b]One patient (<1%) in the MIRV arm was missing information on primary platinum-free interval.

[c]One patient (<1%) in the MIRV arm and 3 patients (1%) in the IC chemo arm enrolled with platinum-free interval of >6 months

Moore KN, Angelergues A, Konecny GE, et al: Phase III MIRASOL (GOG 3045/ENGOT-ov55) study: Initial report of mirvetuximab soravtansine vs. investigator's choice of chemotherapy in platinum-resistant, advanced, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor–alpha expression. 2023 ASCO Annual Meeting. Abstract LBA5507. Presented June 4, 2023.

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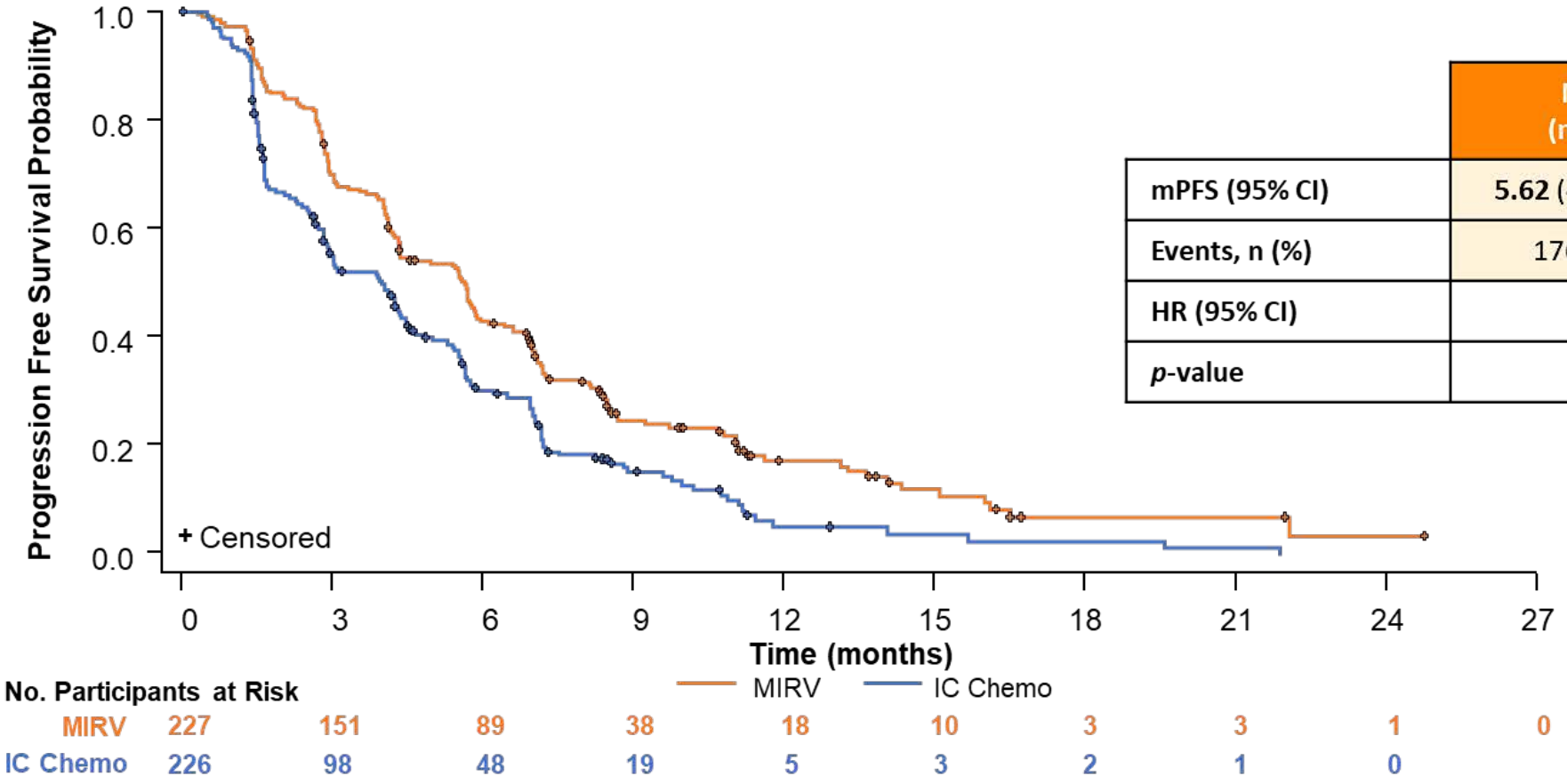
Primary Endpoint: Progression-Free Survival by investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	**5.62** (4.34, 5.95)	**3.98** (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
p-value	**<0.0001**	

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Moore et al. N Engl J Med 2023 De 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio

Best Overall Response by Investigator (N=453)

	MIRV (n=227)	IC Chemo (n=226)
ORR, n (%) [95% CI]	96 **(42)** [35.8, 49.0]	36 **(16)** [11.4, 21.4]
Best overall response, n (%)		
CR	12 **(5)**	0
PR	84 **(37)**	36 **(16)**
SD	86 (38)	91 (40)
PD	31 (14)	62 (27)
Not evaluable	14 (6)	37 (16)

Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease

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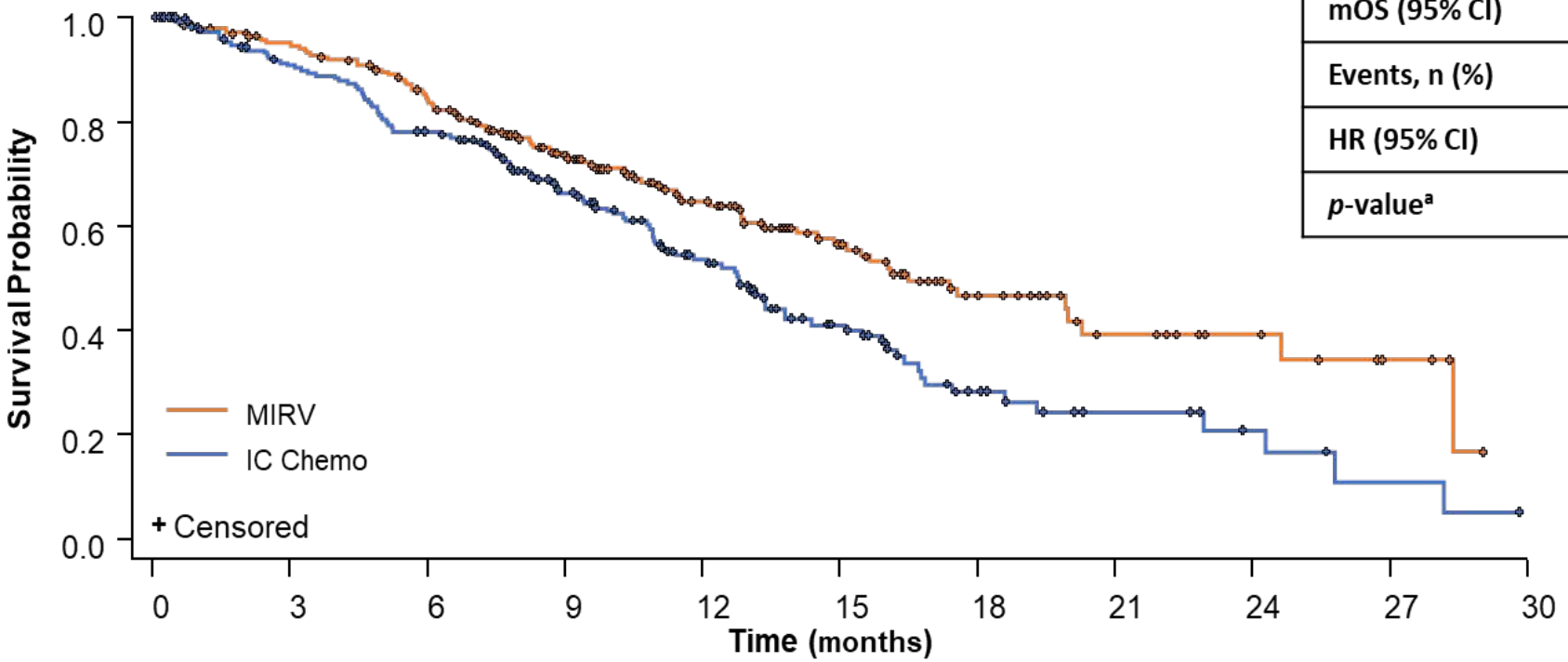
Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Overall Survival

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	**16.46** (14.46, 24.57)	**12.75** (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
p-value[a]	**0.0046**	

[a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313



No. Participants at Risk

MIRV 227	204	175	128	82	53	28	15	9	4	0
IC Chemo 226	185	157	107	68	39	18	9	5	2	0

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Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo, investigator choice chemotherapy; mOS, median overall survival; CI, confidence interval; HR, hazard ratio. [a]Overall survival is statistically significant based on pre-specified boundary p-value at interim analysis = 0.01313

Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Safety Summary (N=425)

MIRV demonstrated a tolerable safety profile compared with IC Chemo

	MIRV (n=218)	IC Chemo (n=207)
Any TEAE, n (%)	210 (96)	194 (94)
Grade 3+ TEAEs, n (%)	91 (42)	112 (54)
SAEs, n (%)	52 (24)	68 (33)
Deaths on study drug or within 30 days of last dose, n (%)	5 (2)	5 (2)
Dose reductions due to TEAEs, n (%)	74 (34)	50 (24)
Dose delays due to TEAEs, n (%)	117 (54)	111 (54)
Discontinuations due to TEAEs, n (%)	20 (9)	33 (16)

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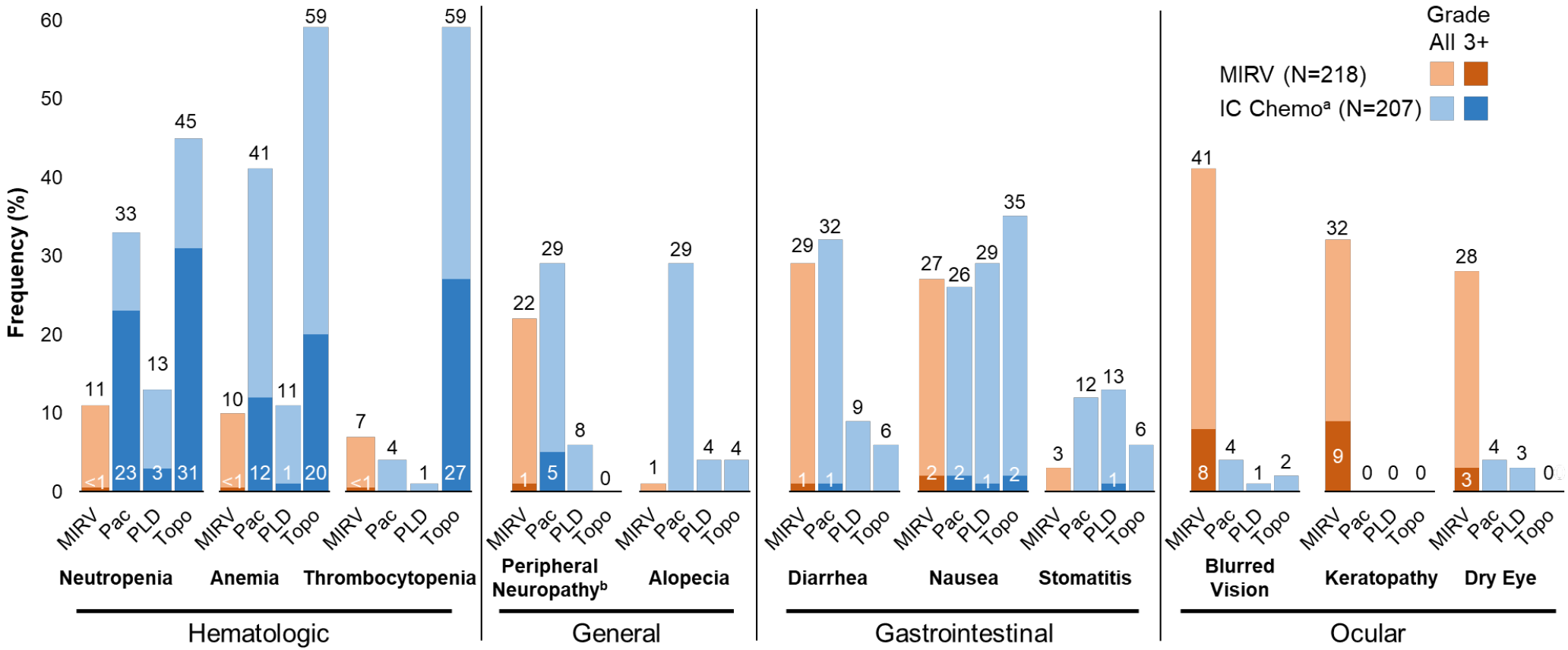
Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice of chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

aPac n=82, PLD n=76, Topo n=49. bGrade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

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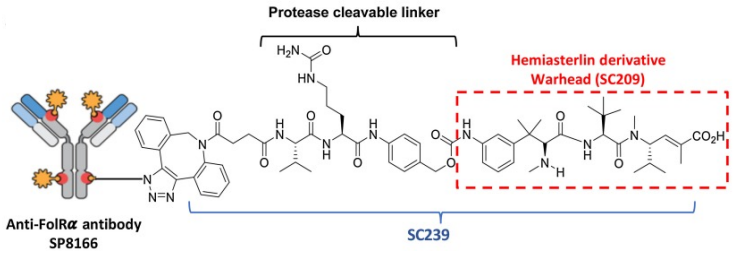
Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Other FRα ADCs:
Luveltamab tazevibulin (STRO-002) FRα-targeted ADC

Luveltamab



- Luveltamab (STRO-002) is a homogenous ADC targeting FRα
- Cathepsin B linker, which is a stable protease-cleavable linker
- Hemiasterlin-derivative[a] cytotoxic payload
- DAR=4

Efficacy Related Outcomes

Phase 1 dose-expansion study (NCT03748186)

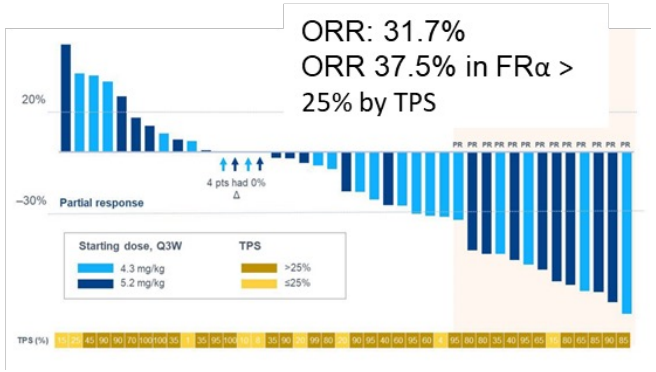
- Recurrent disease
  - Platinum resistant 1–3 prior regimens or platinum-sensitive 2–3 prior regimens
- Fresh or archival tissue required
- No mandate for FolRα expression
- At least 1 target lesion

N=44

R 1:1

Luveltamab 4.3 mg/kg Q3W n=23

Luveltamab 5.2 mg/kg Q3W n=21



Safety Related Outcomes

Phase 1 dose-expansion study

TRAEs leading to dose reduction in 61.4%

- Neutropenia[a] in 17 patients (39%)
  - Primarily G3/4 uncomplicated (abnormal lab value only)
  - Febrile neutropenia in 2 patients (4.5%)
  - Resolved without growth factor support in most patients
  - Median duration of G3+ AEs, 8 days
- Arthralgia in 8 patients (18%)
- Peripheral neuropathy in 3 patients (6.8%)
  - Most G1/2

TEAEs leading to dose discontinuation in 3 patients (6.8%)

- G3 fatigue
- G2 neuropathy
- G5 Sepsis

Currently moving to late phase trial

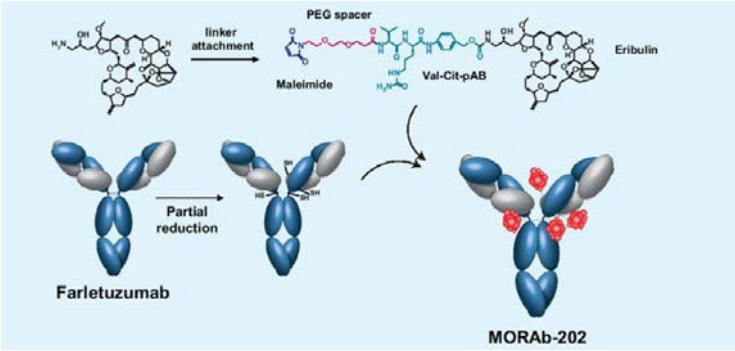
[a]Sutro-proprietary tubulin-targeting 3-aminophenol hemiasterlin warhead, SC209.

ADC, antibody-drug conjugate; AE, adverse event; DAR, drug-to-antibody ratio; FRα, folate receptor alpha; G, grade; ORR, objective response rate; PD, progressive disease; PR, partial response; R, randomization; TPS, tumor proportion score; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

1. Oaknin et al. Poster presented at ASCO 2023; Abstract 5508. 2. Sutro Biopharma. Accessed March 2, 2023. https://www.sutrobio.com/wp-content/uploads/2023/01/Sutro-STRO-002-Luvelta-update-Jan-9-2023-FINAL.pdf

Other FRα ADCs: Farletuzumab ecteribulin (MORAb-202) FRα-targeted ADC

MORAb-202[1,2]

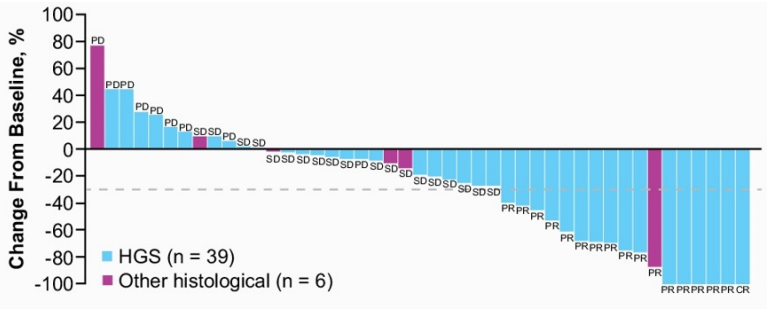


MORAb-202 is an ADC consisting of:

- Antibody: farletuzumab
- Linker: cathepsin B cleavable linker
- Payload: eribulin, microtubule inhibitor
- DAR=4

Efficacy Related Outcomes[1,2]

Phase 1 dose-expansion study



Data cutoff date: October 31, 2021.

Parameter	Cohort 1: MORAb-202 0.9 mg/kg (n=24)	Cohort 2: MORAb-202 1.2 mg/kg (n=21)
CR, n (%)	1 (4.2)	0
PR, n (%)	5 (20.8)	11 (52.4)
SD, n (%)	10 (41.7)	9 (42.9)
PD, n (%)	8 (33.3)	1 (4.8)
~~ORR, n (%), (95% CI)[a]~~	~~5 (25.0), (9.8–46.7)~~	~~11 (52.4), (29.8–74.3)~~
DCR, n (%), (95% CI)[a]	**16 (66.7), (44.7–84**	**20 (95.2), (76.2–99.9)**
~~mPFS, mo (95% CI)[a]~~	~~6.7 (1.5–12)~~	~~8.2 (4.2–10.4)~~
mOS, mo (95% CI)[a]	10.5 (6.4–15.1)	NE (12.5–NE)

Safety Related Outcomes[1]

Phase 1 dose-expansion study

- The most common TEAE was interstitial lung disease (ILD)/pneumonitis at both dose levels
  - Cohort 1: 37.5% (n=9; 8 with Gr 1; 1 with Gr 2)
  - Cohort 2: 66.7% (n=14; 6 with Gr 1; 7 with Gr 2, 1 with Gr 3)
- Other common TEAEs of any grade, in Cohorts 1 and 2, respectively, were:
  - Nausea (25.0%; 33.3%)
  - Pyrexia (33.3%; 42.9%)
  - Malaise (16.7%; 28.6%)
  - Headache (12.5%; 47.6%)

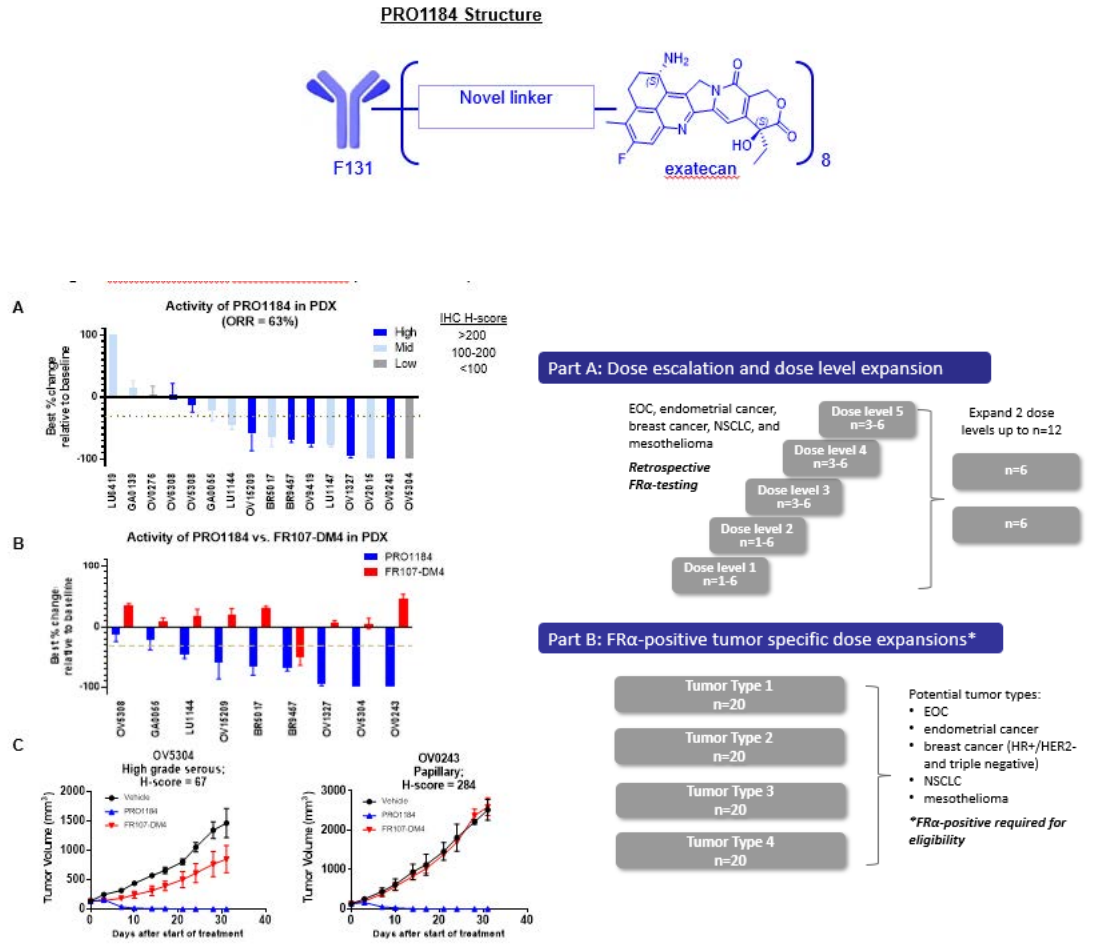
[a] CI calculations: ORR, DRC–Clopper-Pearson's exact method; PFS, OS–Kaplan-Meier estimate and Greenwood Formula.

ADC, antibody-drug conjugate; CI, confidence interval; CR, complete response; DAR, drug-to-antibody ratio; DCR, disease control rate; Gr, grade; HGS, high-grade serous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

1. Nishio S et al. ASCO 2022. Abstract 5513. 2. Shimizu T et al. ASCO 2019. Abstract 5544

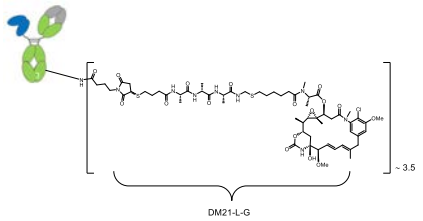
Other Antibody Drug Conjugates (ADCs) Targeting FRα
PRO1184 & IMGN151 (Phase I Studies)

PRO1184 (NCT05579366)[1] – Phase 1/2

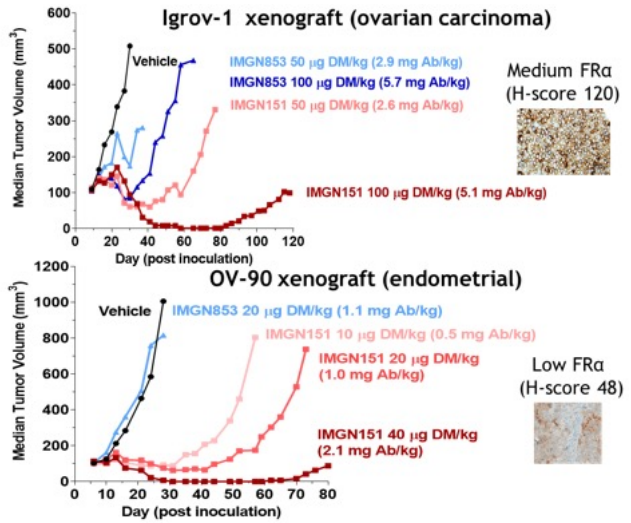


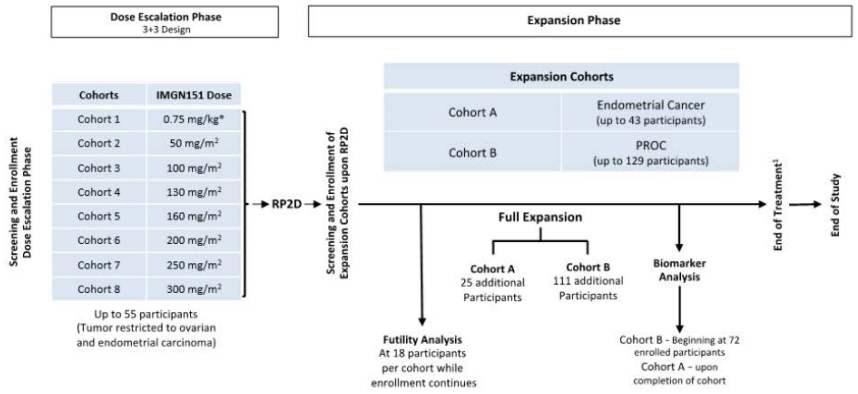
1. Call et al. AACR 2023 Abstract #9329

IMGN151 (NCT04209855)[2,3] – Phase 1/2



- B5327A: asymmetric biparatopic anti-FRα antibody comprised of IMGN853 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-L-G: maytansine-derived payload/linker

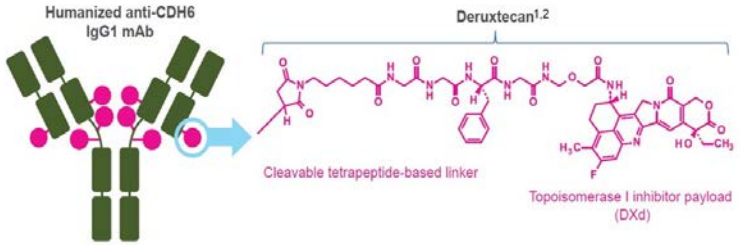




2. Ab O et al. AACR 2020 Abstract # 2829; 3. Study Details | First in Human Study of IMGN151 in Recurrent Endometrial Cancer and Recurrent, High-grade Serous Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancers | ClinicalTrials.gov (accessed March 2024)

Raludotatug deruxtecan (DS-6000a), CDH6-directed ADC[1,2]

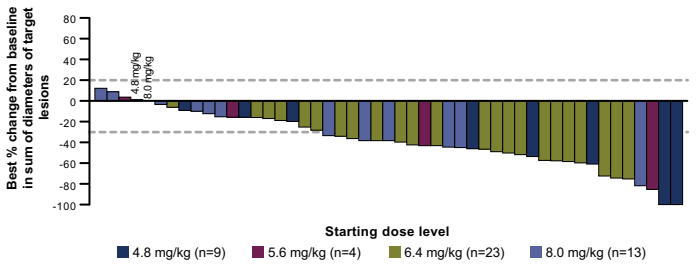
DS-6000[1,2]

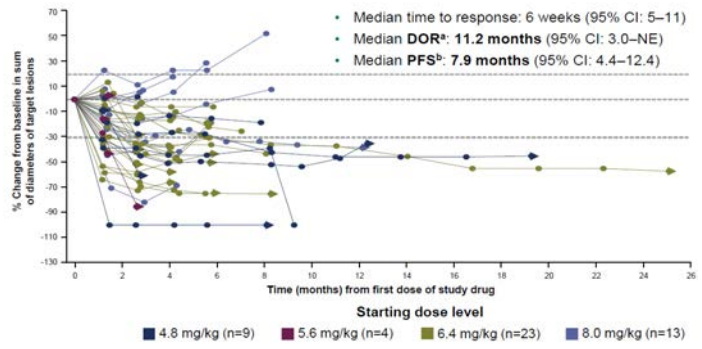


- A humanized anti-CDH6 IgG1 monoclonal antibody
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker
- DAR ~8

Efficacy Related Outcomes

- **Confirmed ORR: 46%** in the 4.8–8.0 mg/kg OVC cohort (23/50; 95% CI: 32–61); one CR and 22 PRs
  - 4 unconfirmed responses were ongoing at data cutoff
- **Disease control rate**[a]: **98%**





Safety Related Outcomes

Most common (≥10%)TEAEs

	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

NCT04707248: Recruiting

- Estimated enrollment: 140 participants
- Estimated primary completion date: October 31, 2024

Data cutoff: July 14, 2023

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1.

Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall or spider plots. DCR: CR + PR + stable disease.

[a]Median f/u for DOR: 5.8 months (range: 1.4-16.8). [b]Median f/u for PFS: 5.6 months (range 0.03-25.1)

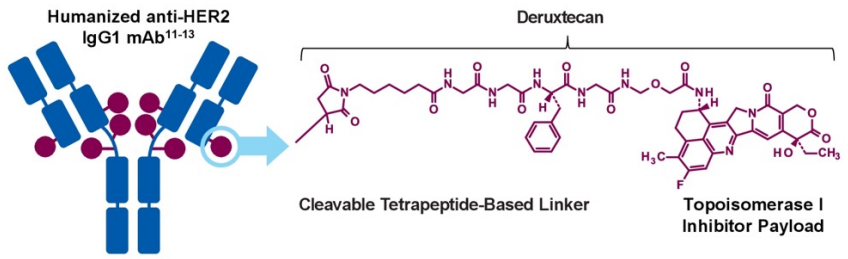
ADC, antibody-drug conjugate; CDH6, cadherin-6; cORR, confirmed overall response rate; CR, complete response; DAR, drug-to-antibody ratio; DCR, disease control rate; DOR, duration of response; f/u, follow-up; IgG1, immunoglobulin G1; NE, not estimable; ORR, overall response rate; OVC, serous ovarian cancer; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant ovarian cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

1. Moore KN et al. Poster presented at ESMO 2023; Abstract 3002. 2. ClinicalTrials.gov. NCT04707248. Accessed March 1, 2023.

Trastuzumab deruxtecan (T-DXd), HER2-targeted ADC for patients with HER2-expressing tumors including OC

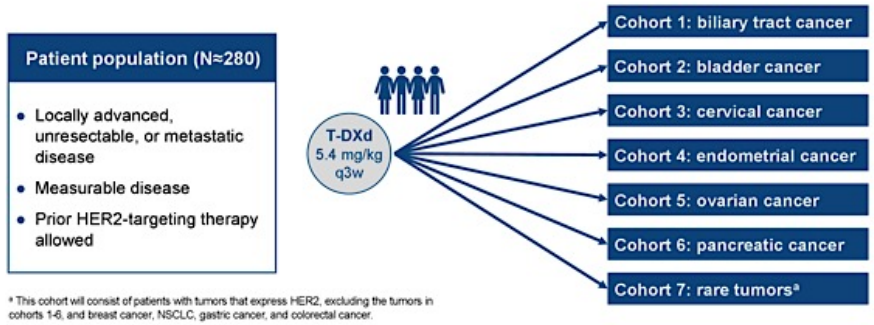
DESTINY-PanTumor02 (NCT04482309), phase 2, T-DXd in select advanced HER2-expressing tumors (including GYN tumors)[1,2]

Trastuzumab deruxtecan (T-DXd)[1]



- ADC targeting ERBB2 (HER2)
- Conjugated to a topoisomerase inhibitor
- DAR=8

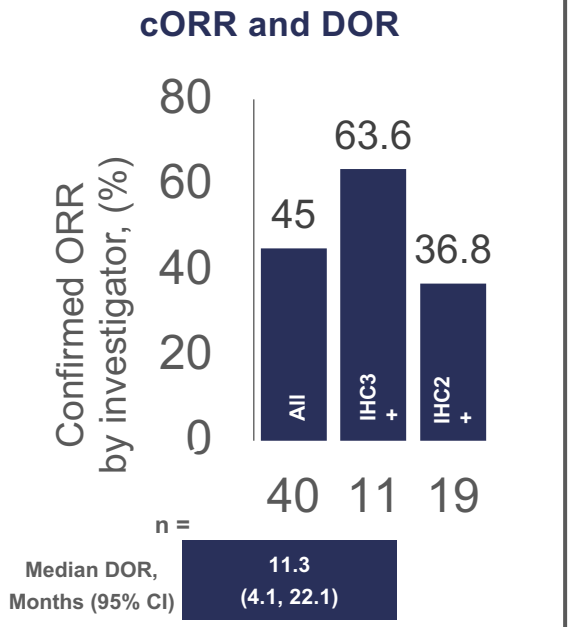
Study design and population



NCT04482309: Active, not recruiting

- Actual enrollment: 468 participants
- Estimated primary completion date: March 2027

Objective response and duration of response in ovarian cancer cohort



ADC, antibody-drug conjugate; cORR, confirmed overall response rate; DAR, drug-to-antibody ratio; DOR, duration of response; ERBB2, erb-b2 receptor tyrosine kinase 2; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OC, ovarian cancer; q3w, every 3 weeks.

1. ClinicalTrials.gov. NCT04482309. Accessed March 1, 2023; 2. Meric-Bernstam F et al. J Clin Oncol. 2024 42(1): 4758

Prevalence of HER2 expression in Ovarian Cancer

- Largest study GINECO study of 320 patients (Tuefferd M, et al. PLoS One 2007)
  - Evaluated with IHC and FISH, using breast criteria (complete membrane staining)
  - HER2 2+ or 3+ was 13%
  - Potentially under-representation given breast criteria used

- Additional studies estimate up to ~20% prevalence of HER2 2+/3+
  - Chao WR, et al. Virchows Arch 2022 – HER2 in mucinous ovarian carcinoma
    - HER2 positive 18.2% by gastric criteria, 14.2% by breast criteria
  - Ersoy E, et al. Int J Gynecol Pathol 2022 – 100 cases high-grade serous carcinoma
    - 81 cases HER2 0/1+ and 18 were 2+ and 1 was 3+
  - Bookman MA, et al. J Clin Oncol 2003 – phase II GOG study of trastuzumab
    - Utilized complete membrane staining criteria
    - 11.4% were HER2 2+/3+ and 19% were HER2 1+

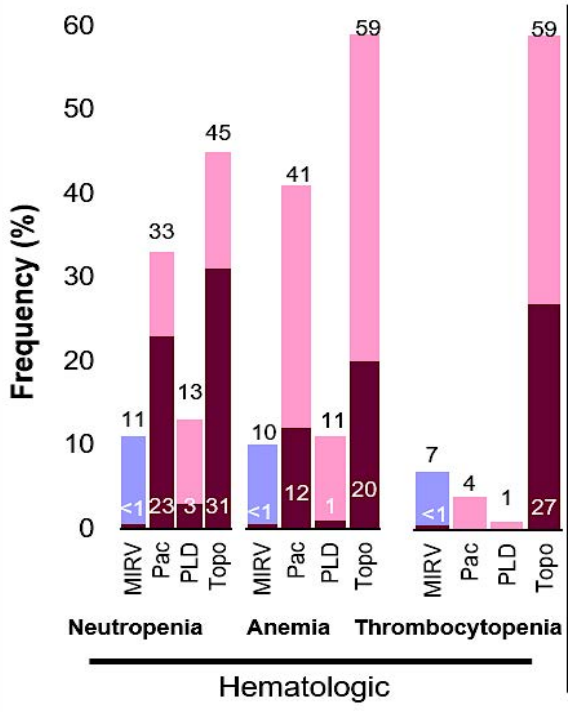
Antibody Drug Conjugates (ADCs) Treatment Related Adverse Events: Hematologic

Raludotatug deruxtecan

	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

Moore et al. ESMO 2023

Mirvetuximab soravtansine



Moore et al. N Engl J. Med 2023

Trastuzumab deruxtecan

	All grades N=40 N(%)
Nausea	22 (55)
Anemia	15 (37.5)
Diarrhea	8(20)
Fatigue	11(27.5)
Anorexia	8 (20)
Vomiting	7 (15)
Neutropenia	5 (12.5)
Thrombocytopenia	5 (12.5)

Meric-Berstam et al. J Clin Oncol 2024

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Antibody Drug Conjugates (ADCs)
Treatment Related Adverse Events: Non-Hematologic

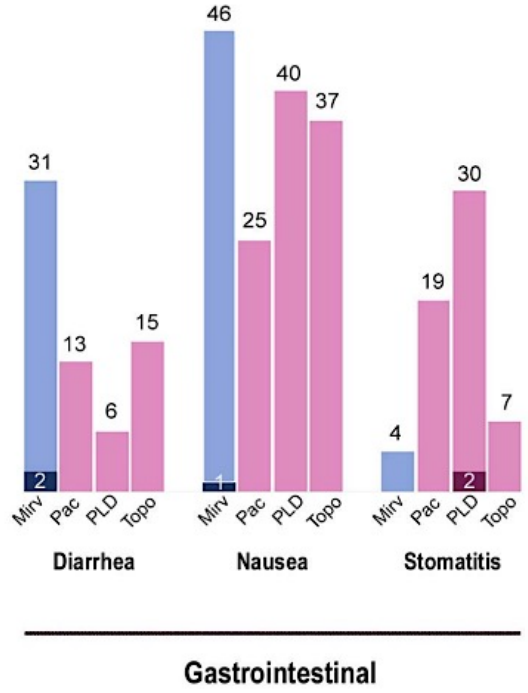
Raludotatug deruxtecan

Most common (≥10%) treatment-related TEAEs

Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

Moore et al. ESMO 2023

Mirvetuximab soravtansine



Moore et al. N Engl J. Med 2023

Trastuzumab deruxtecan

	All grades N=40 N(%)
Nausea	22 (55)
Anemia	15 (37.5)
Diarrhea	8(20)
Fatigue	11(27.5)
Anorexia	8 (20)
Vomiting	7 (15)
Neutropenia	5 (12.5)
Thrombocytopenia	5 (12.5)

Meric-Berstam et al. J Clin Oncol 2024

Nausea, vomiting and fatigue can be common across agents and standard pre-medications are recommended for mitigation. Pneumonitis is seen across all programs (MIRV 10%; T-DXd 10.5%) the majority of which is low grade

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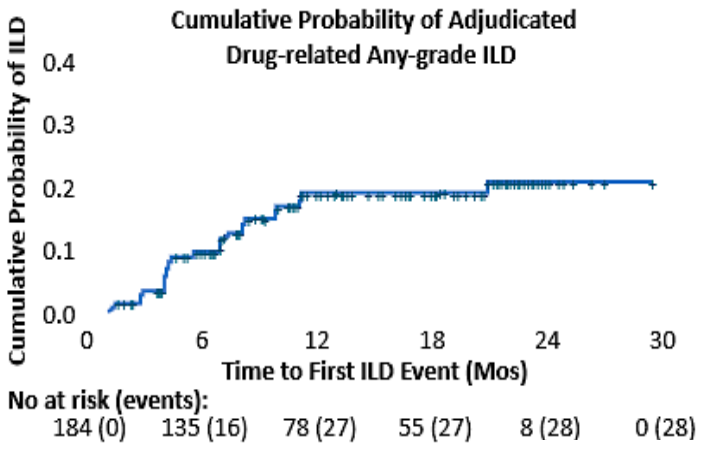
Antibody Drug Conjugates (ADCs)
Mitigation of Treatment Related Adverse Events: Pneumonitis

Incidence over time



Modi et al, SABCS 2020

Mitigation Strategy

Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Results of Mitigation

Updated toxicity Management guidelines implemented (Dec 2019

Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**

Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade > 3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years

MODULE 4: Diagnosis and Management of Adverse Events Associated with Commonly Employed Therapies for Advanced OC — Dr Mirza

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Management of PARP-associated toxicities

Neil Love, MD

Ritu Salani, MD, MBA

Floor J Backes, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Ritu Salani, MD, MBA

Floor J Backes, MD

What is your experience with PARP inhibitor-related fatigue, and what approaches are available to help patients overcome this toxicity?

For a patient experiencing anemia while receiving a PARP inhibitor, what comes first — dose reduction or transfusion?

When using the "weights and plates" dosing strategy with niraparib, how do you approach re-treatment and dosing for a patient who develops Grade 4 thrombocytopenia?

RTP
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TO PRACTICE

Consulting Faculty Questions

Educating patients on the risk of AML/MDS associated with PARP inhibitor therapy

Neil Love, MD

Deborah K Armstrong, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Deborah K Armstrong, MD

Do you discuss the potential risk of AML/MDS with all of your patients receiving PARP inhibitors?

How would you counsel an educated and interested patient (eg, a physician) regarding the risk of AML/MDS with the use of chemotherapy and PARP inhibitor maintenance? What specific estimates would you provide?

How would you respond to a 65-year-old woman with advanced OC and a germline BRCA mutation who undergoes resection and receives adjuvant carboplatin/paclitaxel and asks you to estimate the chance that she will develop myelodysplastic syndromes (MDS)/acute myeloid leukemia (AML) …

	Without further therapy	With maintenance PARPi x 2 years
 Dr Liu	<1%	1%-2%
 Dr Mirza	0%	1%
 Dr Moore	0.5%	1.5%
 Dr O'Malley	1% +/- 0.5%	1.5% +/- 0.5%
 Dr Armstrong	0.8%	1.5%
 Dr Grisham	0.8%	1.5%

PARPi = PARP inhibitor

Based on your personal clinical experience and/or knowledge of available data, please estimate the chance that a patient receiving up-front olaparib maintenance will experience toxicity during treatment that will require withholding administration. What are the primary toxicities patients experience that lead to withholding this strategy?

	Chance of withholding	Primary toxicities
 Dr Liu	5%	Fatigue, anemia
 Dr Mirza	5%	Nausea, fatigue
 Dr Moore	24%	Anemia
 Dr O'Malley	<10%	GI, fatigue, anemia
 Dr Armstrong	20%	GI, fatigue, anemia
 Dr Grisham	15%	Fatigue, anemia

Would you recommend transfusion or dose reduction first for a patient with advanced OC who is experiencing PARP inhibitor-related anemia?

 Dr Liu	Dose reduction
 Dr Mirza	Transfusion
 Dr Moore	Usually transfusion
 Dr O'Malley	Dose reduction
 Dr Armstrong	Dose reduction
 Dr Grisham	Transfusion concurrent with anemia work-up and then dose reduction if reversible cause not found

RTP RESEARCH TO PRACTICE

Based on your personal clinical experience and/or knowledge of available data, please estimate the chance that a patient receiving up-front niraparib maintenance will experience toxicity during treatment that will require withholding administration. What are the primary toxicities patients experience that lead to withholding this strategy?

	Chance of withholding	Primary toxicities
 Dr Liu	5%	Anemia, thrombocytopenia, fatigue
 Dr Mirza	10%	Hematologic
 Dr Moore	60%	Thrombocytopenia
 Dr O'Malley	<10%	GI, fatigue, anemia
 Dr Armstrong	10%-20%	Platelets, HTN
 Dr Grisham	30%	Cytopenia

Diagnosis and Management of Adverse Events Associated with Commonly Employed Therapies for Advanced Ovarian Cancer

Mansoor Raza Mirza

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PARP inhibitors

Summary of toxicity of maintenance PARPi trials (first-line)

	GOG-218	SOLO-1	PAOLA-1	PRIMA
Administration	IV q3weeks 15 months	Oral BID 2 years	Oral BID 2y + IV q3w 15m	Oral QD 3 years
% dose reduction	-	28.5	41	70.9
% dose interruption	-	51.9	54	79.5
% discontinuation	**17**	**11.5**	**20**	**12**
Most frequent Grade ≥ 3 AE	Neut. G4 (64%) HT G ≥2 (23%)	Anaemia (22%) Neut. (9%) Asthenia (4%)	HT (19%) Anaemia (17%) Lymph (7%)	Anaemia (31%) Plates. (28%) Neut. (12.8%)

Burger. NEJM 2011; Moore. NEJM 2018; Ray-Coquard. NEJM 2019; Gonzalez-Martin. NEJM 2019

Summary of toxicity of maintenance PARPi trials (relapsed disease)

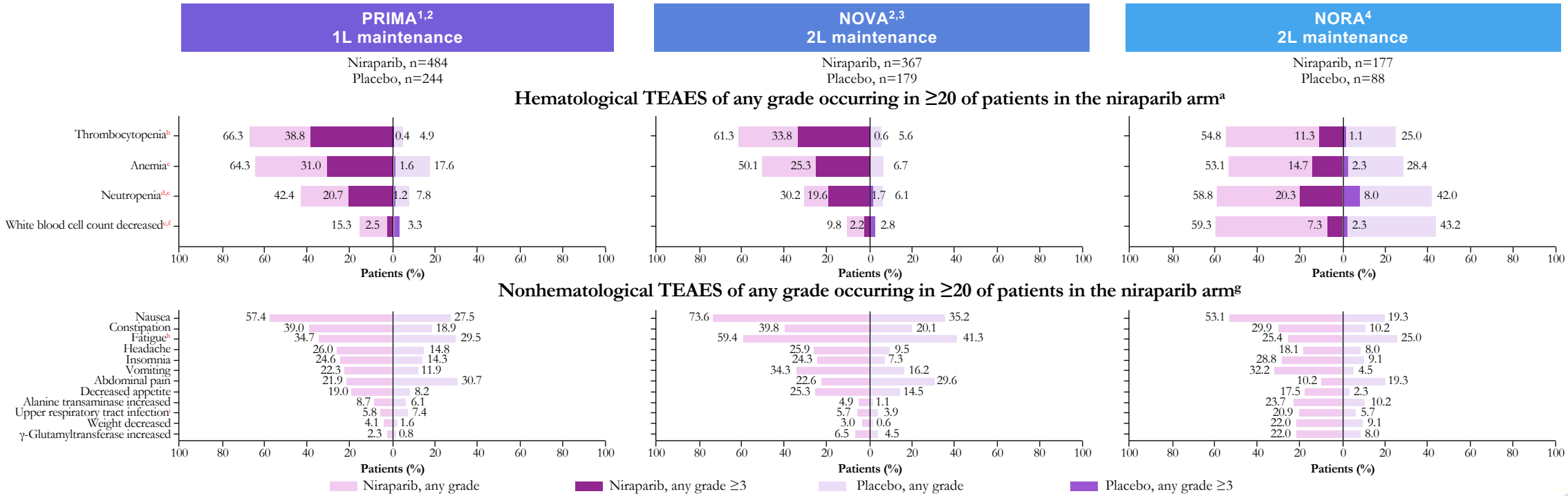
Treatment Related Dose Discontinuations

Rucaparib	Olaparib	Niraparib
13.4%	17%	14.7%
Coleman RL et al. *Lancet 2017*	Poveda et al. *ASCO 2020*	Mirza MR et al. *N Engl J Med 2016*

Niraparib safety in patients with *BRCA*-mutated ovarian cancer: results from three phase 3 niraparib trials

Summary of the safety of niraparib in patients with *BRCA*m ovarian cancer across three phase 3 trials: no new safety signals were identified

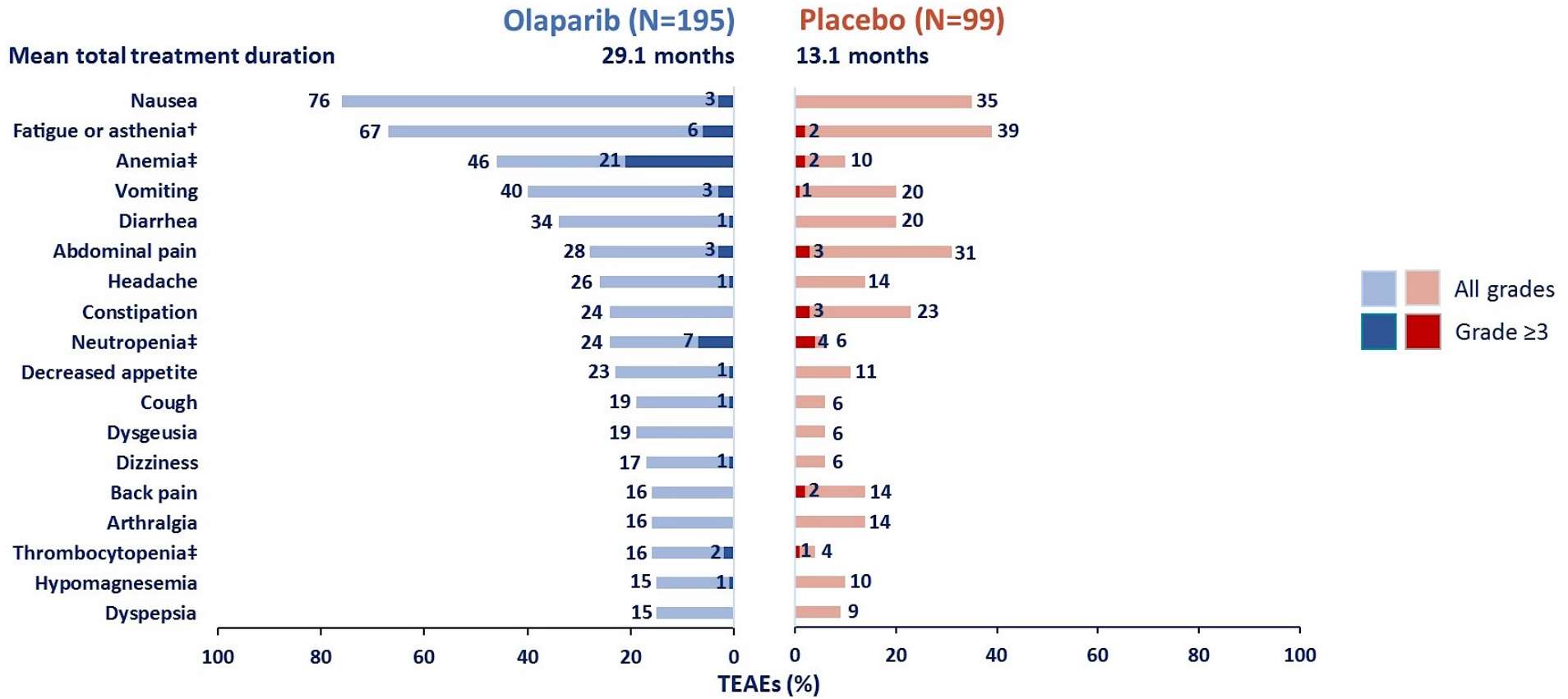
TEAEs in the overall population for PRIMA, NOVA, and NORA



[a]Hematologic TEAEs of any grade occurring in ≥20% of patients in the niraparib arm of PRIMA, NOVA, or NORA. Grade ≥3 TEAEs are also reported for each event; [b]Thrombocytopenia: PRIMA, NOVA, and NORA: thrombocytopenia and platelet count decreased; [c]Anemia: PRIMA, anemia; NOVA, anemia and decreased hemoglobin count; NORA, anemia; [d]Neutropenia: PRIMA, neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis; NOVA, neutropenia, neutrophil count decreased, and febrile neutropenia; NORA, neutropenia and neutrophil count decreased; [e]NORA: In the niraparib group, among 105 patients who experienced white blood cell count decreased and 104 patients who experienced neutrophil count decreased, 94 patients had both events reported with overlapping duration, and among 13 patients who experienced grade 3 white blood cell count decreased, 11 patients also had grade 3 neutrophil count decreased reported with overlapping duration. In the placebo group, among the 38 patients who experienced white blood cell count decreased of any grade and 37 patients who experienced neutrophil count decreased, 32 patients reported both events with overlapping duration, and 2 patients who experienced grade 3 white blood cell count decreased also reported grade 3 neutrophil count decreased with overlapping duration; [f]White blood cell decreased: PRIMA and NOVA, white blood cell decreased; NORA, white blood cell decreased and leukopenia; [g]Nonhematologic TEAEs of any grade occurring in ≥20 of patients in the niraparib arm of PRIMA, NOVA, or NORA; [h]Fatigue: PRIMA, fatigue; NOVA, fatigue, asthenia, malaise, and lethargy; NORA, asthenia; [i]Did not include viral upper respiratory tract infection for PRIMA or NOVA.

SOLO-2: most common TEAEs – final analysis*

Small increase in TEAEs in the olaparib group, compared with the primary analysis, despite longer treatment duration



*Frequency ≥15%; †Includes patients with fatigue and patients with asthenia; ‡Grouped terms

Poveda A et al. ASCO 2020; Abstract 6002.

Patterns of Toxicity of PARP Inhibitors

	OLAPARIB	NIRAPARIB	RUCAPARIB
Fatigue	+++	++	+++
Nausea/Vomiting	+++	++	+++
Anaemia	+++	+++	+++
Neutropenia	+	++	+
Thrombocytopenia	+	+++	++
Diarrhoea	++	+	++
Headache	++	+	+
Insomnia	+	-	-
Dysgeusia	++	-	++
Raised ALT/AST	-	-	++
Photosensitive rash	-	-	+
Hypertension	-	++	-

Poveda et al. *ASCO 2020* Mirza MR et al. *N Engl J Med 2016* Coleman RL et al. *Lancet 2017*

SOLO-2: AEs of special interest – primary and final analyses*, †

	Olaparib (N=195)		Placebo (N=99)	
	Primary	Final	Primary	Final
Mean total treatment duration (SD), months	17.4 (9.8)	**29.1 (24.7)**	9.0 (8.1)	**13.1 (18.6)**
MDS/AML, n (%)	4 (2)	**16 (8)**	4 (4)	**4 (4)**
During the safety follow-up period (TEAE)		**7 (4)**		**0**
After the safety follow-up period (non-TEAE)		**9 (5)**		**4 (4)**
Pneumonitis, n (%)	3 (2)	**3 (2)**	0	**0**

MDS/AML

- **Actively solicited throughout study treatment and follow-up**
- **Incidences should be interpreted in the context of their late onset‡ and the longer OS observed with olaparib vs placebo**
- **Association with the number of prior platinum regimens, olaparib treatment and other potential risk factors is being explored**

In patients with newly diagnosed ovarian cancer and a BRCAm, at median follow-up of 65 months, MDS/AML occurred in 1% of olaparib patients and no placebo patients[1]

*Includes AEs that occurred outside safety follow-up period (during treatment and up to 30 days after discontinuation); †New primary malignancies (excluding hematologic malignancies) occurred in one olaparib patient (1%) and one placebo patient (1%) in the primary analysis, and in eight olaparib patients (4%) and two placebo patients (2%) in the final analysis; ‡After the safety follow-up period
AML, acute myeloid leukemia; MDS, myelodysplastic syndrome

1. AstraZeneca data on file for the SOLO-1 trial (NCT01844986)

Poveda et al. ASCO 2020; Abstract 6002.

NOVA: Summary of MDS/AML

- At the time of the primary analysis, incidence of MDS/AML was 1.4% (5/367) in the niraparib arm vs. 1.1% (2/179) in the placebo arm[1]
- With long-term follow-up and administration of subsequent therapies, 3.5% (13/367) of patients in the niraparib arm vs. 1.7% (3/179) in the placebo arm developed MDS/AML[2]

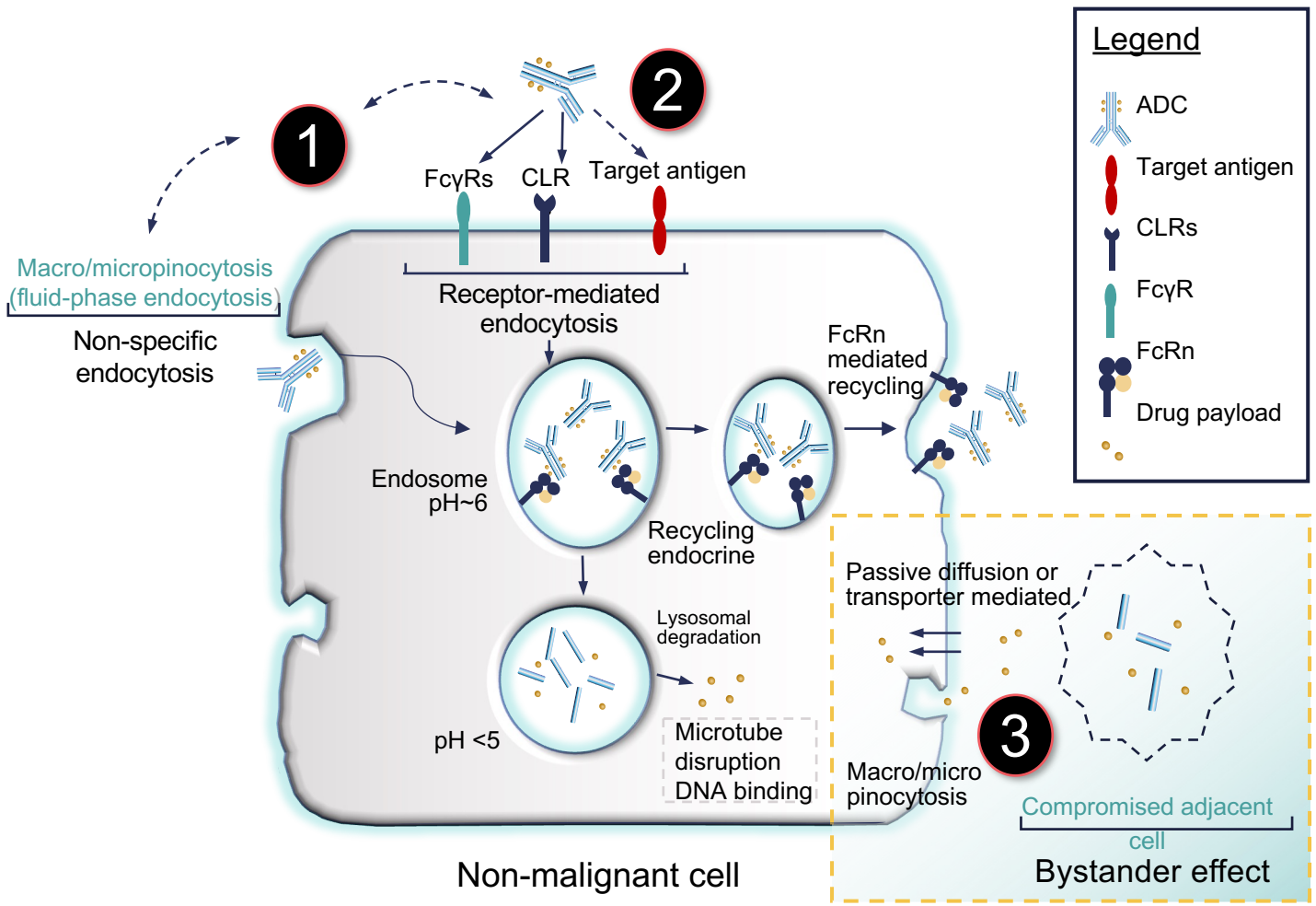
	Niraparib arm			Placebo arm		
Adverse event, n (%)	**All (N=367)**	**g*BRCA*m (n=136)**	**Non-g*BRCA*m (n=231)**	**All (N=179)**	**g*BRCA*m (n=65)**	**Non-g*BRCA*m (n=114)**
MDS/AML all	**13[a] (3.5)**	9 (6.6)	4 (1.7)	**3 (1.7)**	2 (3.1)	1 (0.9)
TEAE (treatment)	9 (2.5)	7 (5.1)	2 (0.9)	0	0	0
TEAE (follow-up)	4 (1.1)	2 (1.5)	2 (0.9)	3 (1.7)	2 (3.1)	1 (0.9)

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.
Final data cutoff date was October 1, 2020 (average duration of follow-up for OS was 67 months).
[a]A total of 16 events of MDS/AML were reported in 13 patients treated with niraparib: 1 patient had MDS then AML; 1 patient had MDS grade 1, then MDS grade 4, then AML.

1. Mirza MR et al. *N Engl J Med* 2016;375:2154–2164.
2. Matulonis U et al. SGO 2021;Abstract 11139.

Antibody Drug Conjugates
Mirvetuximab soravtansine

Potential mechanisms of toxicity associated with ADCs



1. **Target-independent toxicity:** ADC uptake into nonmalignant cells
   - Nonspecific endocytosis
   - Macropinocytosis and micropinocytosis
   - Binding to Fc receptors
2. **On-target, off-tumor toxicity:** target antigen may be expressed on normal cells and contribute to target antigen–dependent uptake of ADCs
3. **Bystander effect (off-target, off-tissue toxicity):** membrane-permeable drug payloads diffuse from target cell into neighboring cells
   - May be beneficial if the neighboring cell is cancerous, or detrimental if neighboring cell is healthy

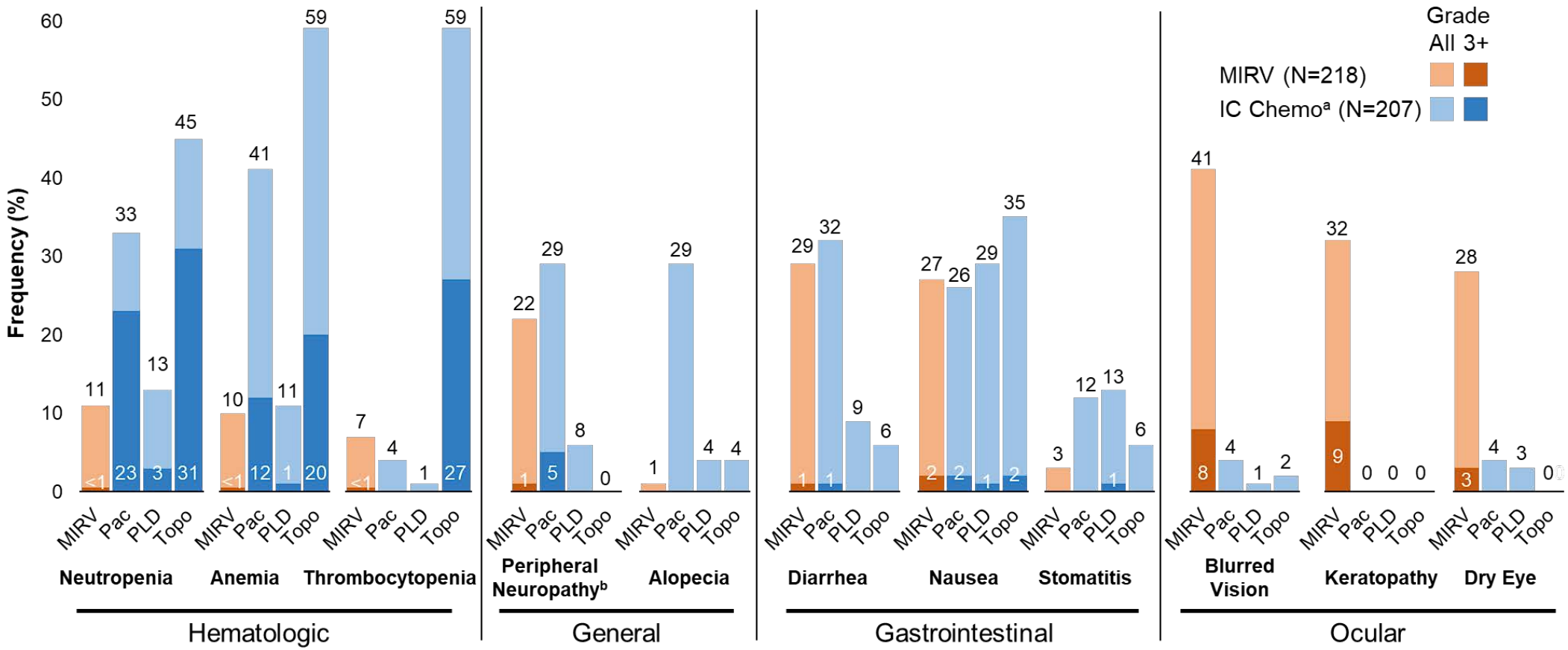
Microtubule inhibitor	Commonly reported clinical toxicity
MMAE	Anemia, neutropenia, and peripheral neuropathy
DM1	Thrombocytopenia and hepatotoxicity
MMAF and DM4	Ocular toxicity

ADC, antibody-drug conjugate; CLR, C-type leptin receptor; DM1, maytansine 1; DM4, maytansine 4; FcRn, neonatal Fc receptor; FcγR, Fc gamma receptor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

Mahalingaiah PK et al. *Pharmacol Ther*. 2019;200:110–125.

Courtesy K Moore

Differentiated Safety Profile: Treatment-Emergent Adverse Events



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MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice of chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

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Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

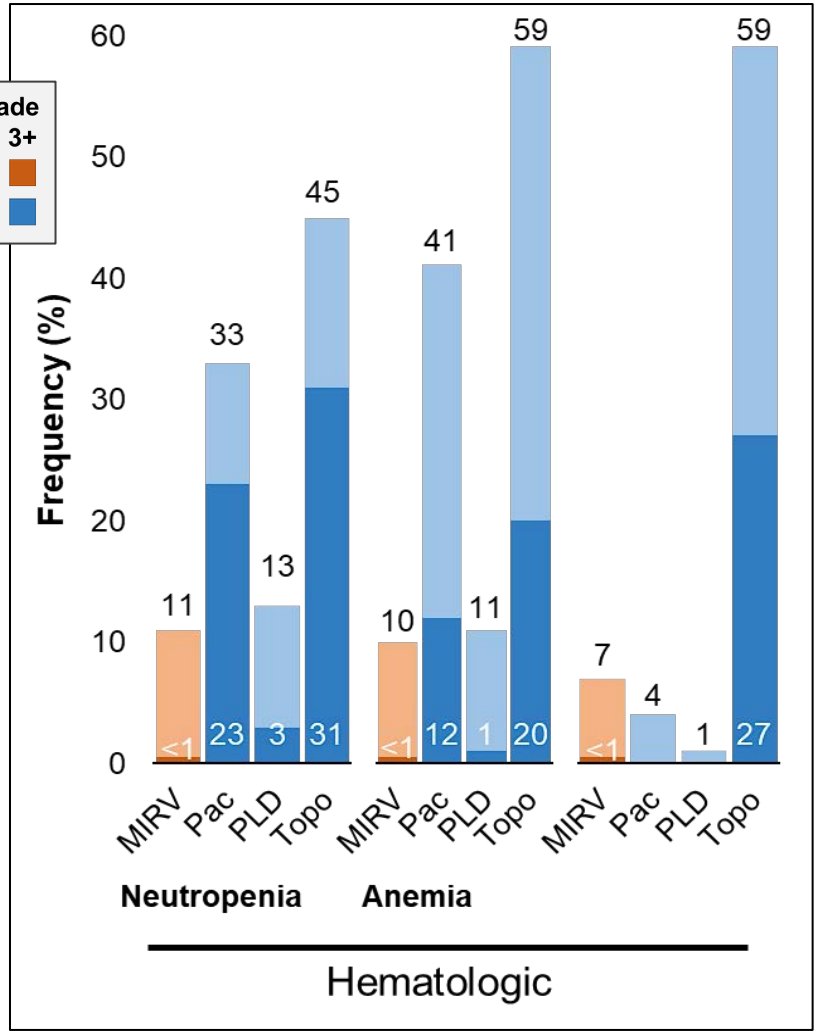
Safety Profile

Hematologic

Off-target cytotoxic damage into hematopoietic stem cells of the bone marrow

Incidence < 12%
Mostly Grade 1-2

Criteria to receive MIRV:
- ANC must be ≥ 1.5x10^9/L (1,500/µL)
- Platelet count must be ≥ 80 x 109/L (80,000/µL)



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aPac n=82, PLD n=76, Topo n=49. bGrade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

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Safety Profile

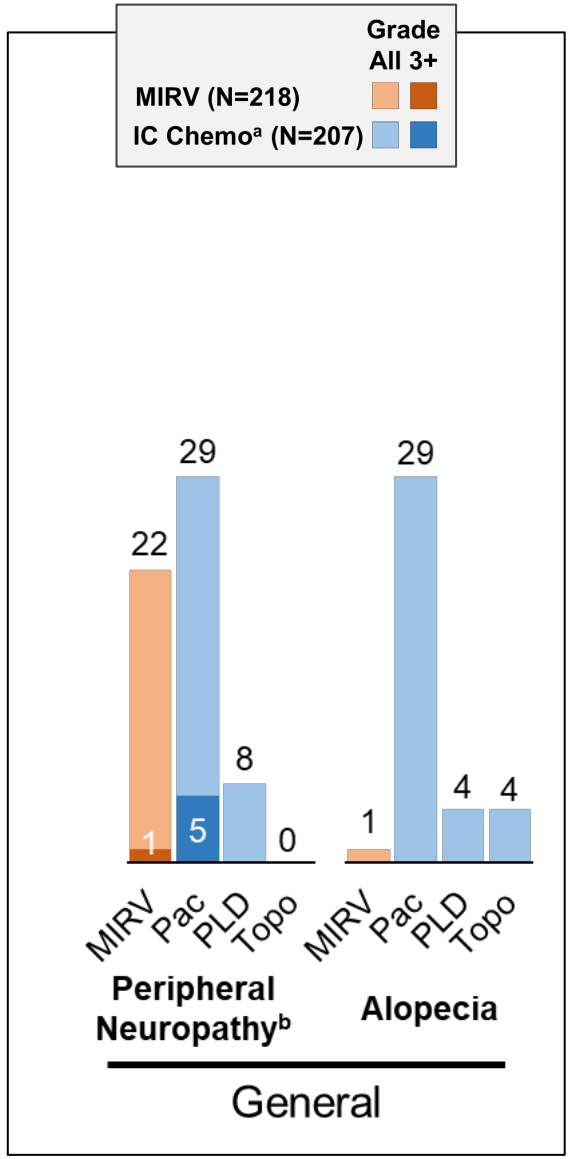
Peripheral neuropathy

Off-target neurological effect associated to anti-microtubule activity

Incidence 22 % ←→ 29% with Pac

Mostly Grade 1-2
Only 1% G3+ ←→ 5% with Pac

Dose reduction was considered in the case of Grade 2 peripheral neuropathy interfering with patient's normal life



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Moore et al. N Engl J Med 2023 Dec 7;380(23):31622174. doi: 10.1056/NEJMoa2309169

Safety Profile

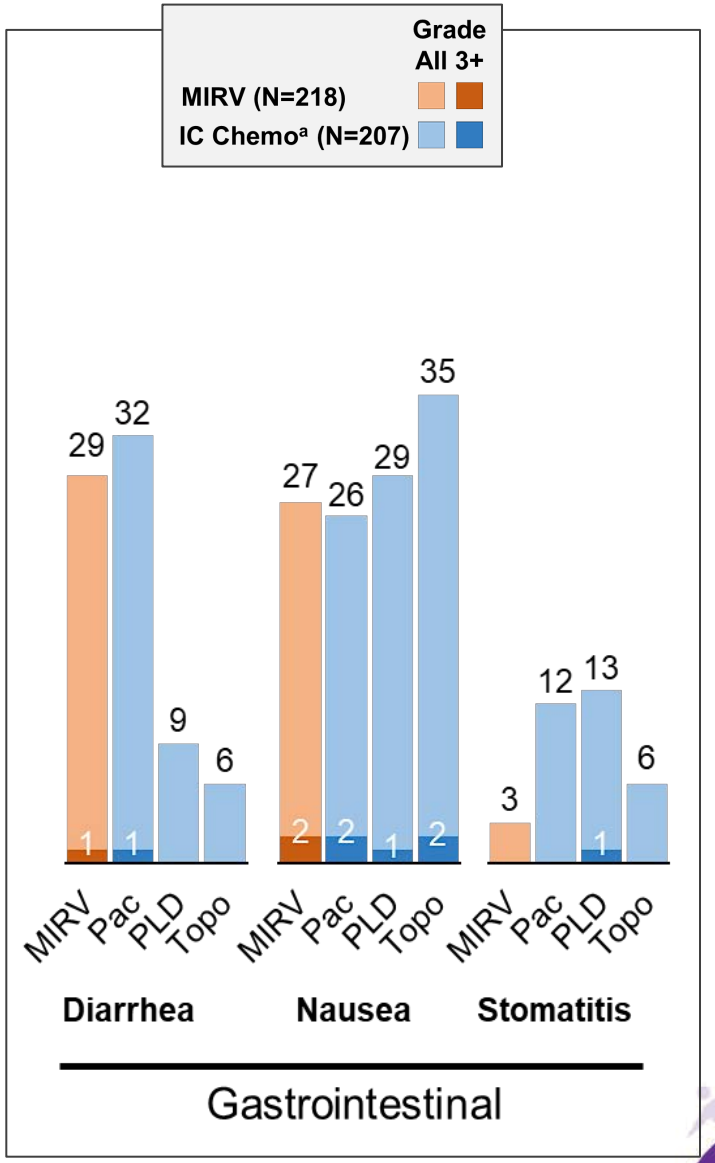
Gastrointestinal

Off-target effect

Incidence 27-29 %

Mostly Grade 1-2 (only 1-2% G3+)

In the case of grade 3 despite optimal use of anti-emetic or anti-diarrheal treatment: Drug was held until resolution to < grade 1, then resumed at a lower level



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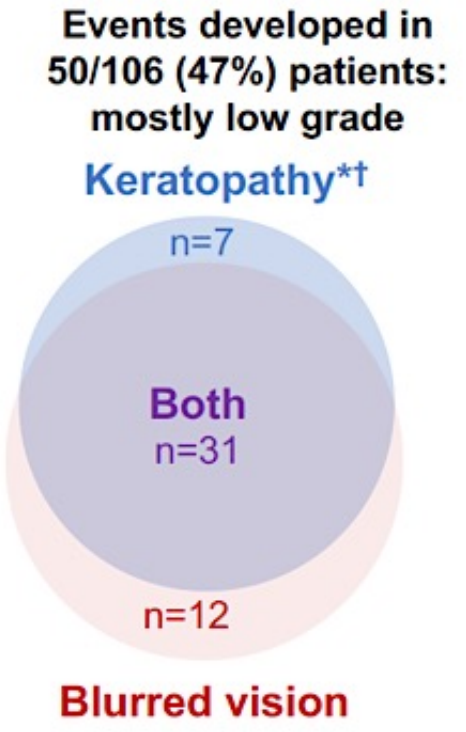
Safety Profile

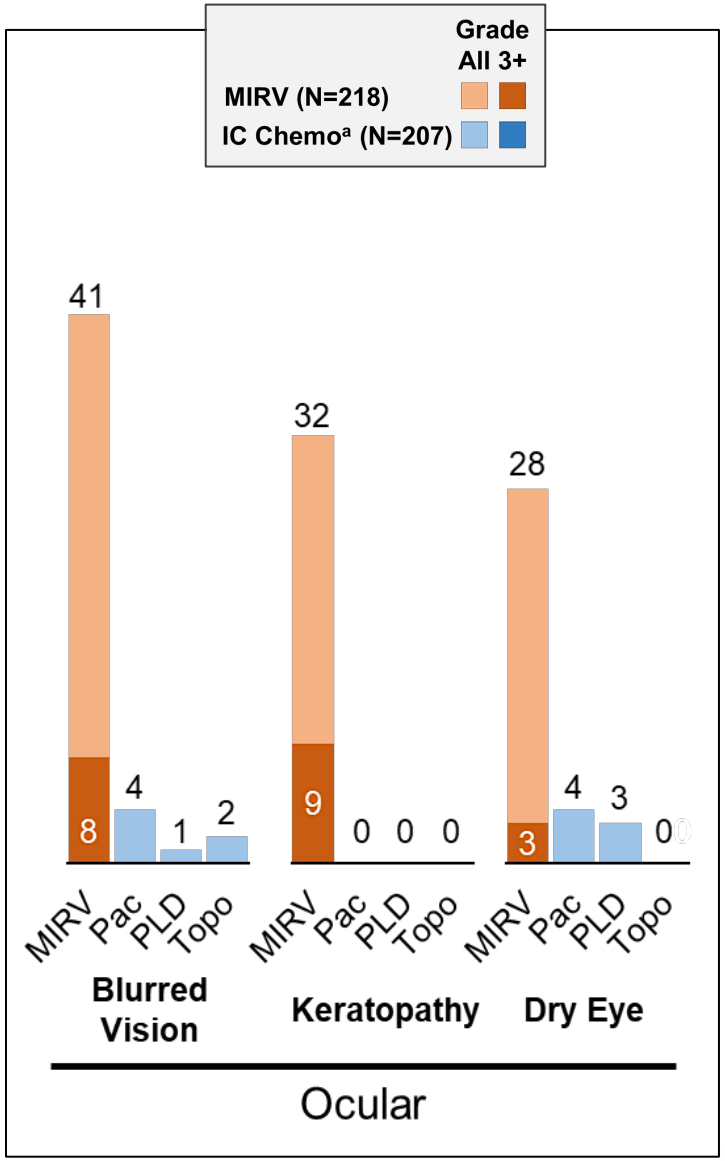
Ocular

Significantly more frequent with MIRV compared to IC Chemo

Predominantly Grade 1-2



Matulonis et al. SGO 2022
Matulonis et al. J Clin Oncol 2023;41(13):2436-45



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

Review article

Strategies for prevention and management of ocular events occurring with mirvetuximab soravtansine

Andrew Hendershot [a,*], Mark Slabaugh [a], Kamran M. Riaz [b], Kathleen N. Moore [c], David M. O'Malley [d], Ursula Matulonis [e], Gottfried E. Konecny [f]

Summary of the Grading of Key Ocular Adverse Events in MIRV Clinical Trials (NCI CTCAE v5.0, 2017).

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4
Blurred vision[a]	Intervention not indicated	Symptomatic; moderate decrease in visual acuity; limiting instrumental ADL[b]	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[c]	Best corrected visual acuity of **20/200 or worse** in the affected eye
Keratitis[d] *(Included in keratopathy group term)*	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; corneal ulcer; limiting self-care ADL[c]	Perforation; best corrected visual acuity of **20/200 or worse** in the affected eye
Dry eye[e]	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity	Symptomatic, with marked decrease in visual acuity; limiting self-care ADL[c]	
Photophobia[f]	Symptomatic but not limiting ADL	Limiting instrumental ADL[b] **Definition: "Moderate decrease in visual acuity"** Best corrected visual acuity 20/40 and better or ≤3 lines of decreased vision from known baseline	Limiting self-care ADL[c] **Definition: "Marked decrease in visual acuity"** Best corrected visual acuity worse than 20/40 or >3 lines of decreased vision from known baseline, up to 20/200	

ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; MIRV, mirvetuximab soravtansine; NCI, National Cancer Institute.

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Consulting Faculty Questions

Strategies to prevent peripheral neuropathy associated with taxane chemotherapy

Neil Love, MD

Rachel N Grisham, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Rachel N Grisham, MD

What approaches do you employ in your practice to prevent and/or ameliorate taxane-related neuropathy? Do you use extremity cooling? If so, how effective does it seem to be?

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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Ovarian Cancer

Part 1 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer®

Monday, March 18, 2024

6:30 AM – 8:00 AM PT (9:30 AM – 11:00 AM ET)

Faculty

Joyce F Liu, MD, MPH

Mansoor Raza Mirza, MD

David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Management of Endometrial Cancer

Part 2 of a 2-Part CME Symposium Series Held in Conjunction with the 2024 Society of Gynecologic Oncology Annual Meeting on Women's Cancer®

Monday, March 18, 2024

12:15 PM – 1:45 PM PT (3:15 PM – 4:45 PM ET)

Faculty

Nicoletta Colombo, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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