Cases from the Community: Investigators Discuss Available Research Guiding the Care of Patients with Ovarian and Endometrial Cancer

Sunday, June 1, 2025

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Joyce F Liu, MD, MPH

David M O'Malley, MD

Ritu Salani, MD, MBA

Alessandro D Santin, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Faculty

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Dr Westin — Disclosures
Moderator

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Dr Love — Disclosures

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Commercial Support

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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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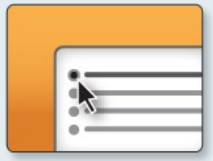
Clinicians in the Meeting Room

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 pre- and postmeeting surveys.

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.

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

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Clinicians Attending via Zoom

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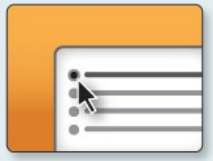

Answer Survey Questions: Complete the pre- and postmeeting surveys.

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 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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Agenda

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

MODULE 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr O'Malley

MODULE 3: Role of HER2-Targeted Therapy in Advanced OC, Endometrial Cancer (EC) and Other Gynecologic Cancers — Dr Santin

MODULE 4: First-Line Therapy for Advanced EC — Dr Westin

MODULE 5: Current Therapeutic Options for R/R EC; Novel Investigational Strategies for Newly Diagnosed and Recurrent Disease — Dr Salani

Agenda

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

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Upfront Treatment for Advanced Ovarian Cancer

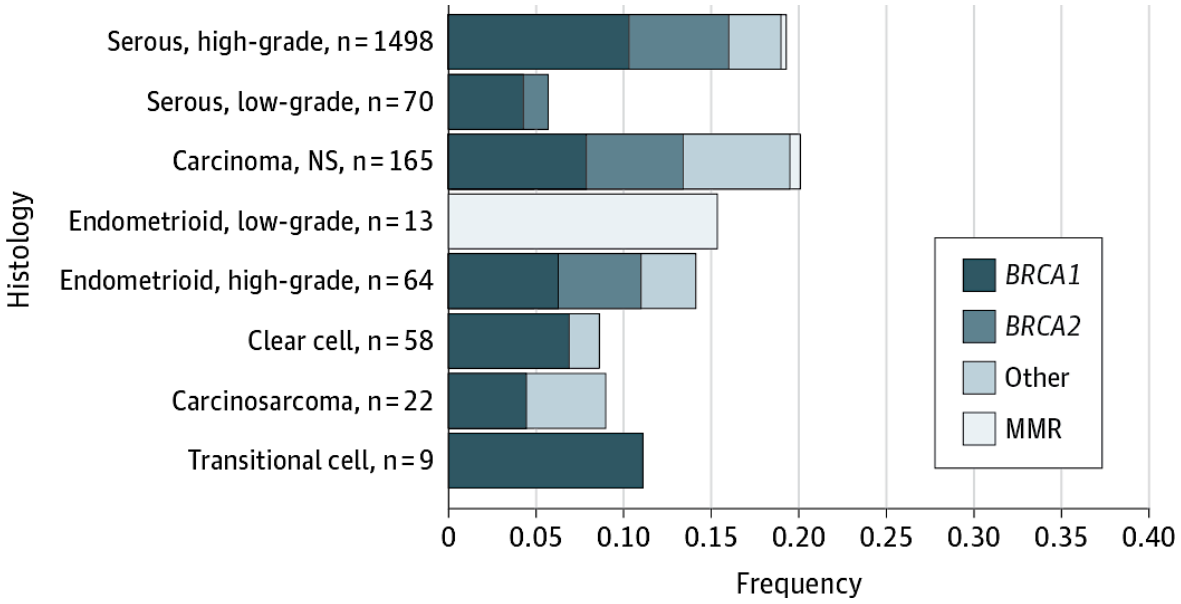
Joyce Liu, MD, MPH
Associate Chief and Director of Clinical Research
Division of Gynecologic Oncology
Dana-Farber Cancer Institute, Boston, MA

Agenda

- Biomarker testing in newly diagnosed ovarian cancer
- PARP inhibitors as 1L maintenance for ovarian cancer
- PARP inhibitors + IO therapy in 1L ovarian cancer maintenance
- Future considerations

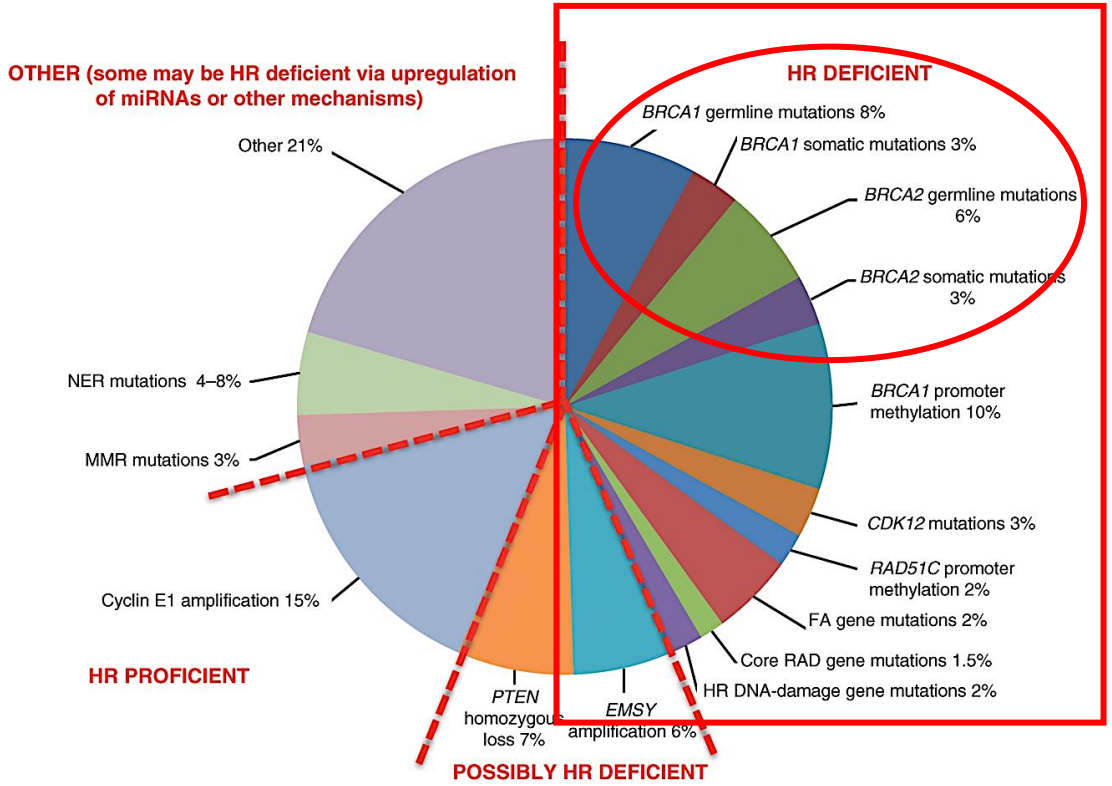
BRCA mutations and HRD are common in ovarian cancer

BRCA1/2 mutations occur across EOC subtypes



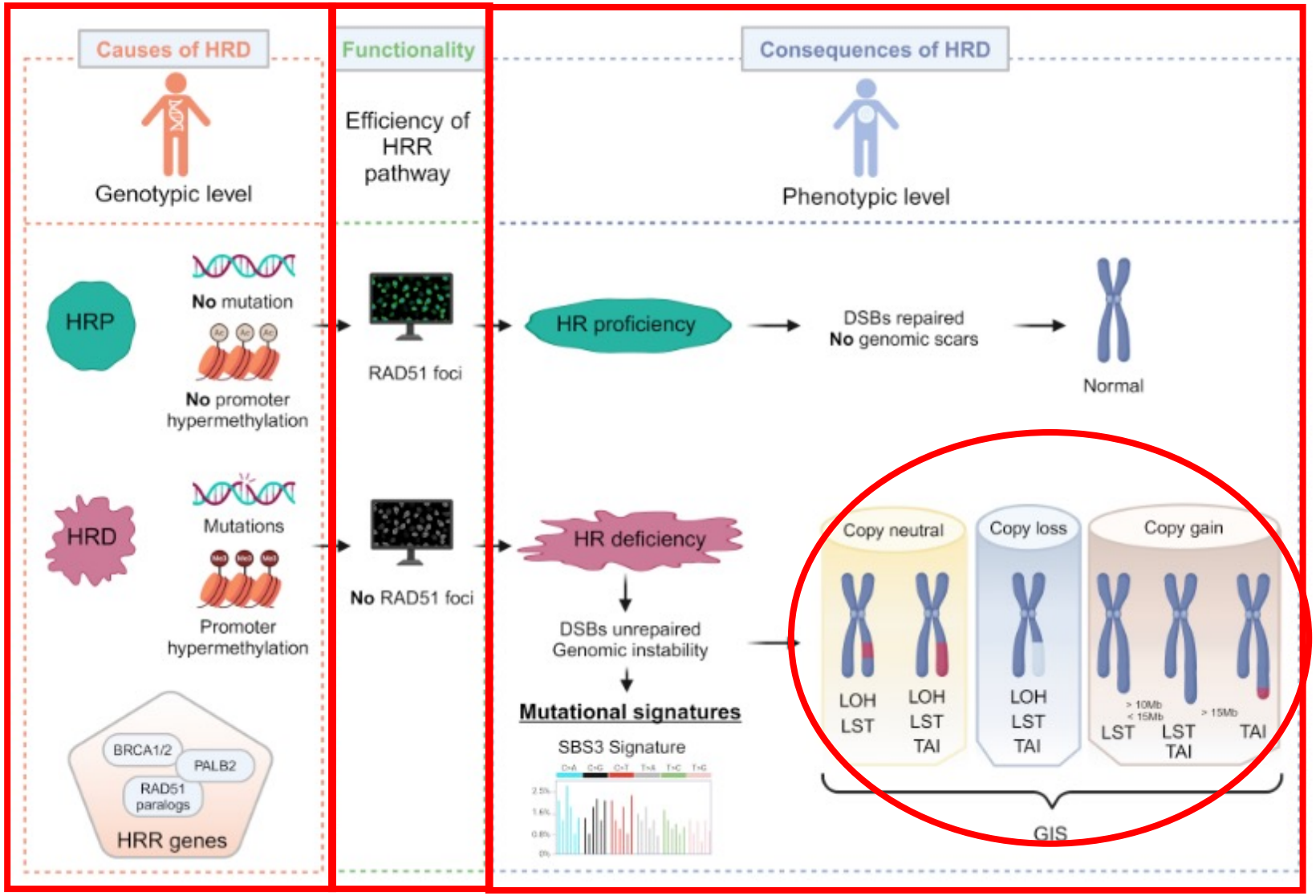
Norquist et al, *JAMA Oncol*, 2016

~50% of HGSOC have evidence of HR deficiency



Konstantinopoulos et al, *Cancer Discov*, 2015

Testing for Homologous Recombination Deficiency (HRD)



Witz et al, *Biomarker Research*, 2025

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	ATHENA-COMBO: Rucaparib + nivolumab	ATHENA-COMBO: Rucaparib + nivolumab DUO-O: Olaparib + bevacizumab + durvalumab KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab	ATHENA-COMBO: Rucaparib + nivolumab DUO-O: Olaparib + bevacizumab + durvalumab KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab

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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
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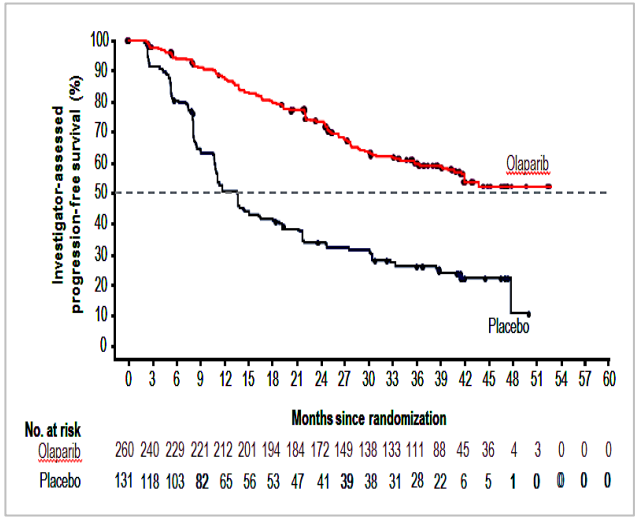
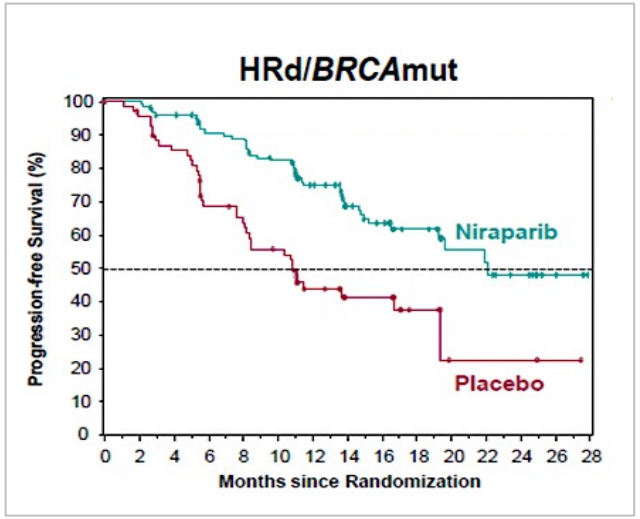
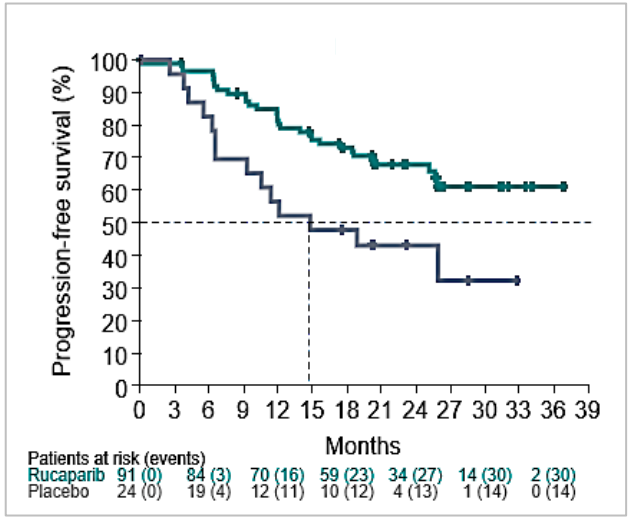
*BRCA*m tumors: PARP inhibitor monotherapy maintenance

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

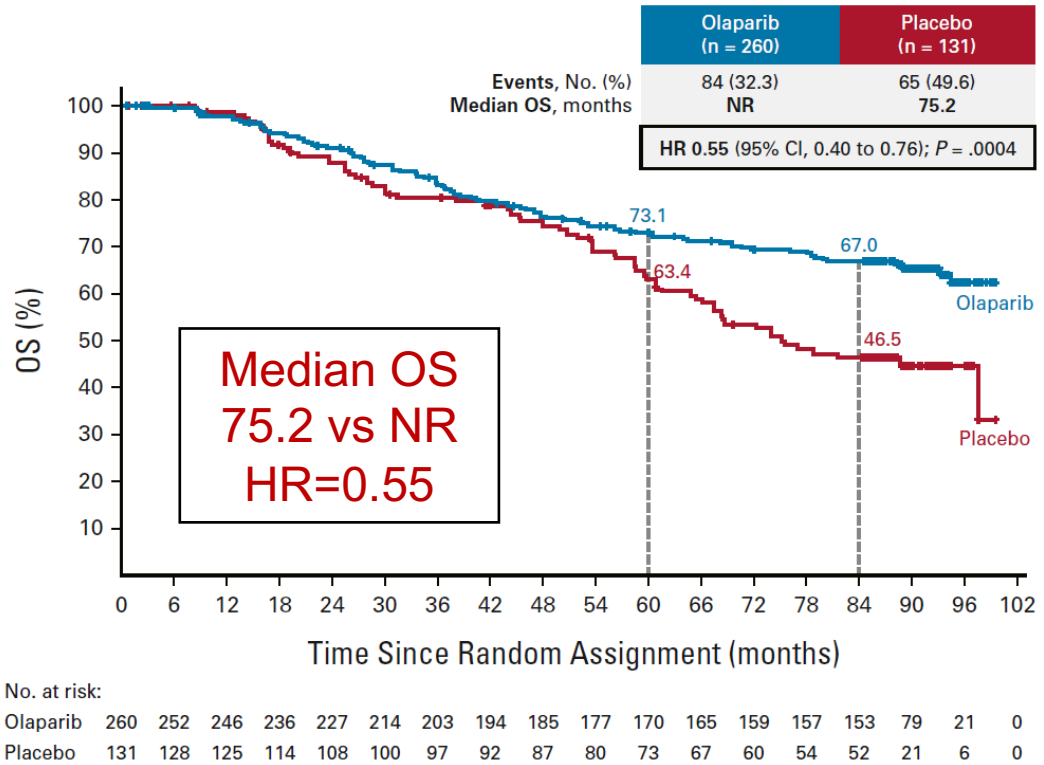
Dana-Farber Cancer Institute

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

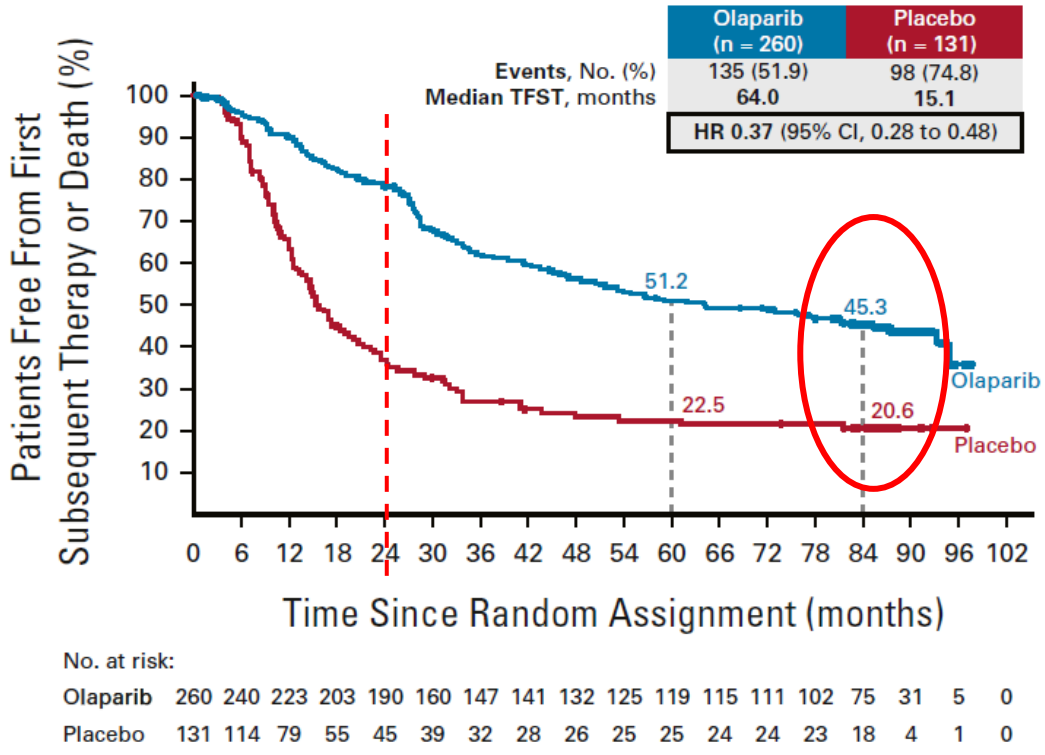
Olaparib maintenance demonstrates long-term benefit in individuals with *BRCA*m ovarian cancers

SOLO1: 7 year follow-up

Overall Survival



Time to First Subsequent Therapy

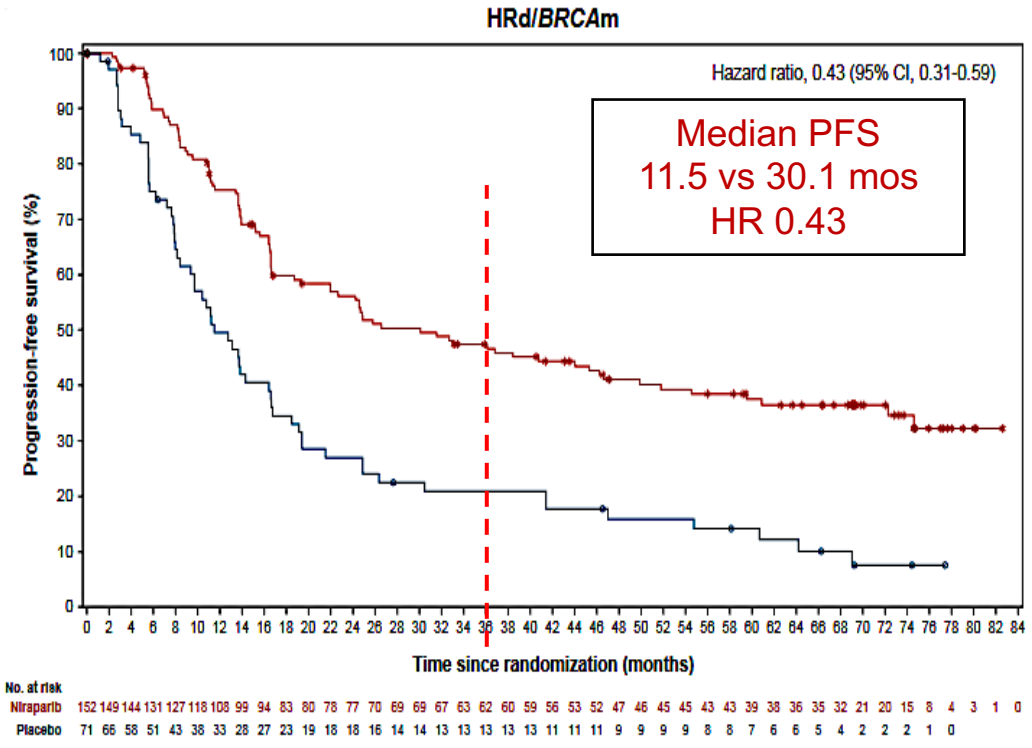


Disilvestro et al., *J Clin Oncol* 2022

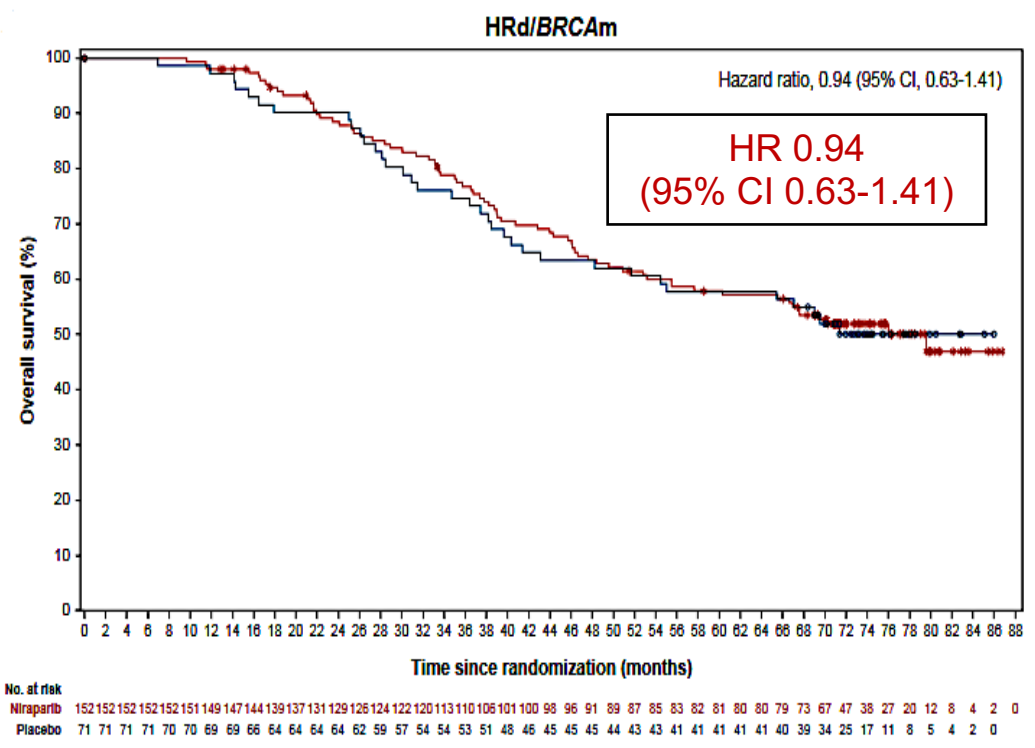
Niraparib maintenance demonstrates continued PFS benefit but no OS benefit in *BRCA*m ovarian cancers in final analysis

PRIMA Final OS Analysis: ~6.2 year follow-up

PFS HRD/*BRCA*m



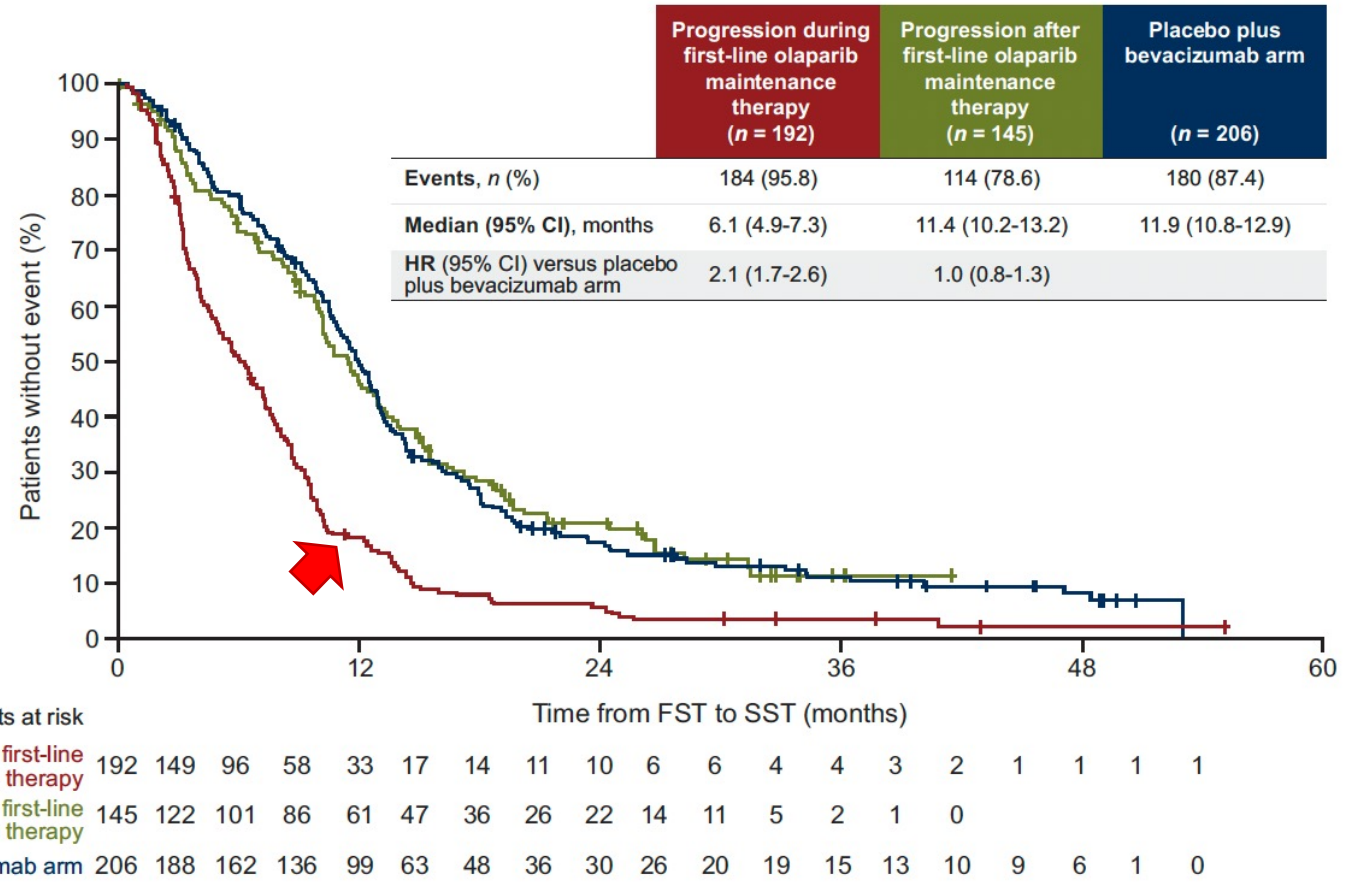
OS HRD/*BRCA*m



Gonzalez-Martin, 2024 ESMO Congress; Monk et al., *Ann Oncol* 2024

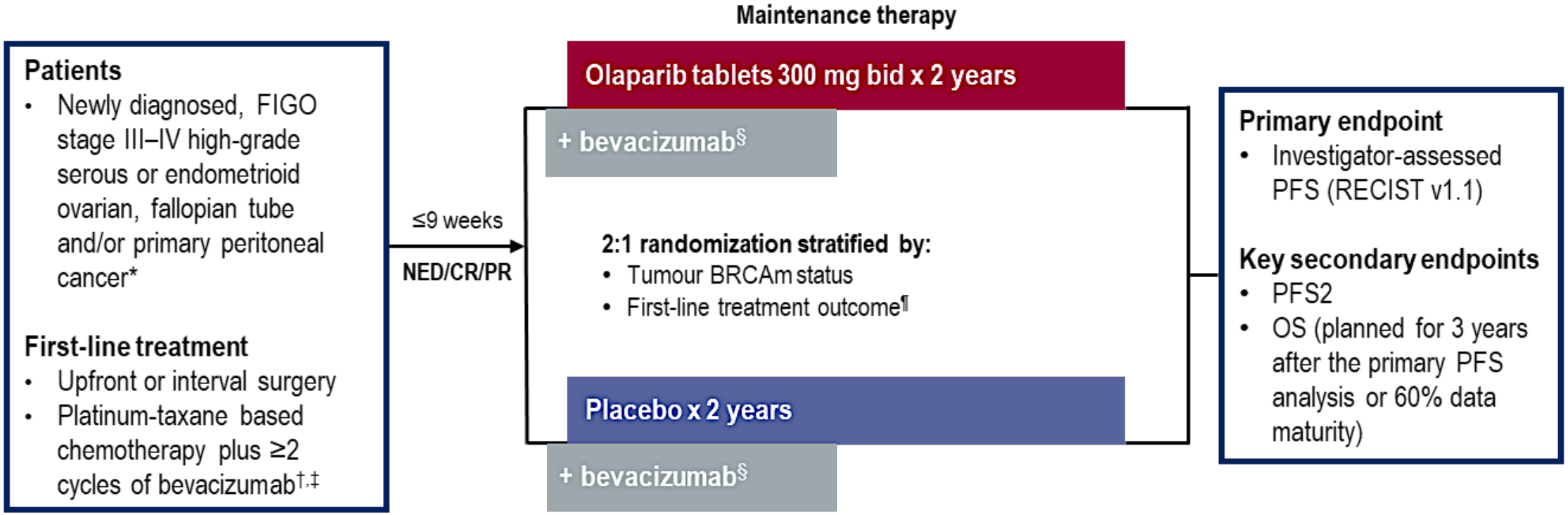
What happened?

- Different patient populations?
- Percentage cross-over to PARPi?
  - SOLO1 44.3% placebo; 14.6% olaparib
  - PRIMA 57.7% placebo; 19.1% niraparib
- Impact of PARPi on future therapies?



Harter et al., *Ann Oncol* 2025

PAOLA-1 trial design



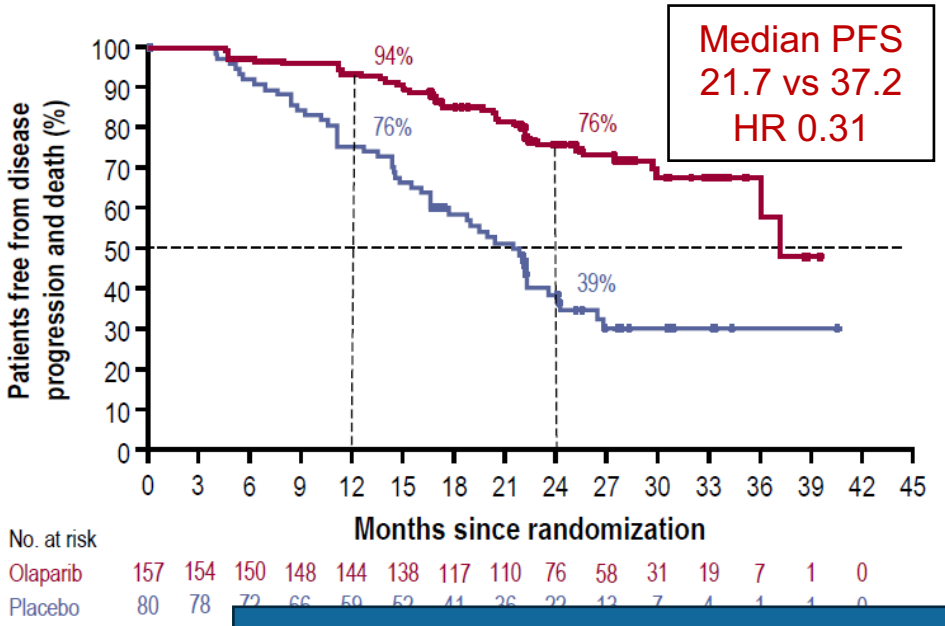
*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval 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, *N Engl J Med* 2019

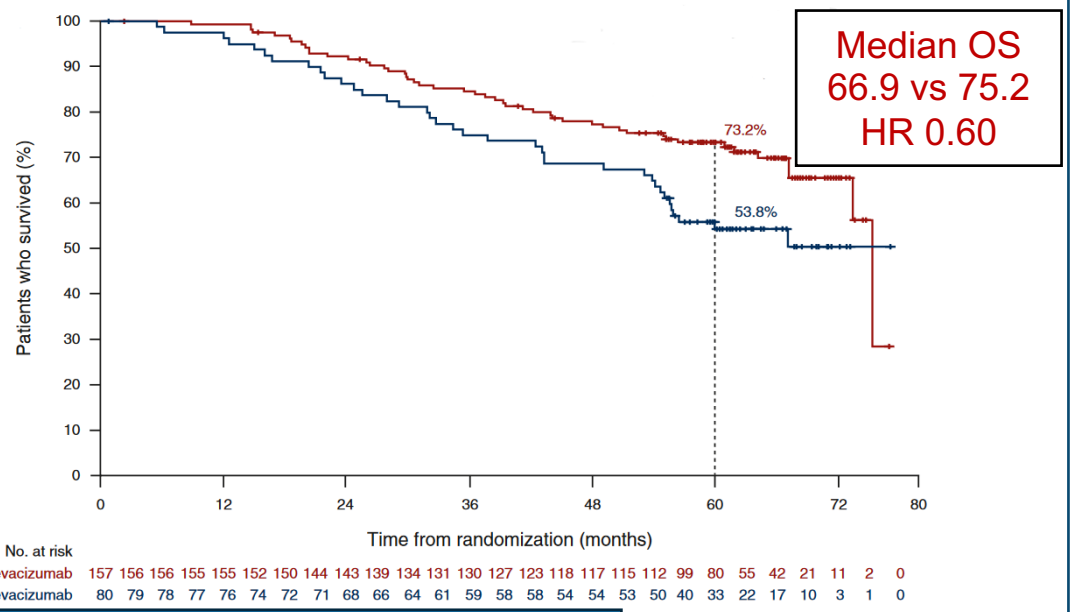
Olaparib/bevacizumab improves outcomes compared to bevacizumab in *BRCA*m ovarian cancer

PAOLA1: Primary PFS and Final OS analyses

Primary analysis PFS t*BRCA*m



Final OS analysis t*BRCA*m



But how does it compare to olaparib alone? Unknown.

Dana-Farber Cancer Institute

Ray-Coquard *N Engl J Med* 2019; Ray-Coquard *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	PRIMA: Niraparib
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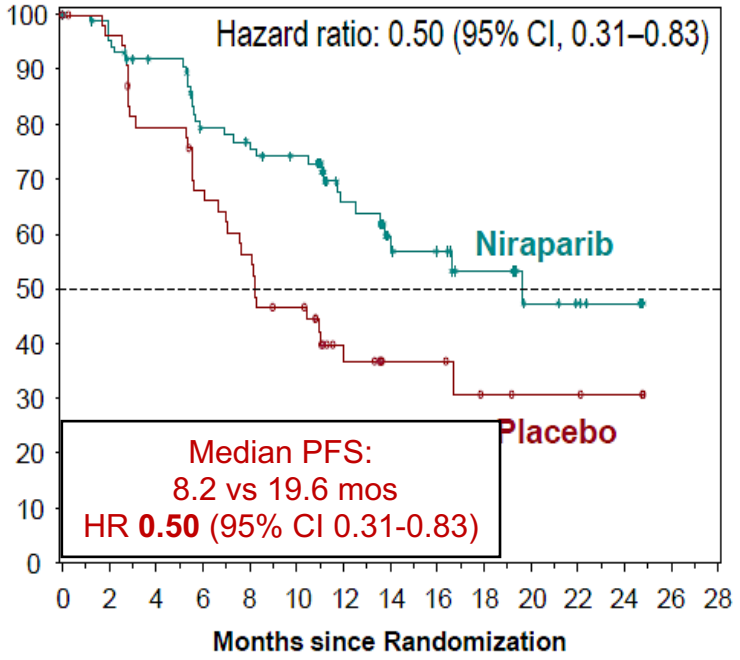
		KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab	KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab

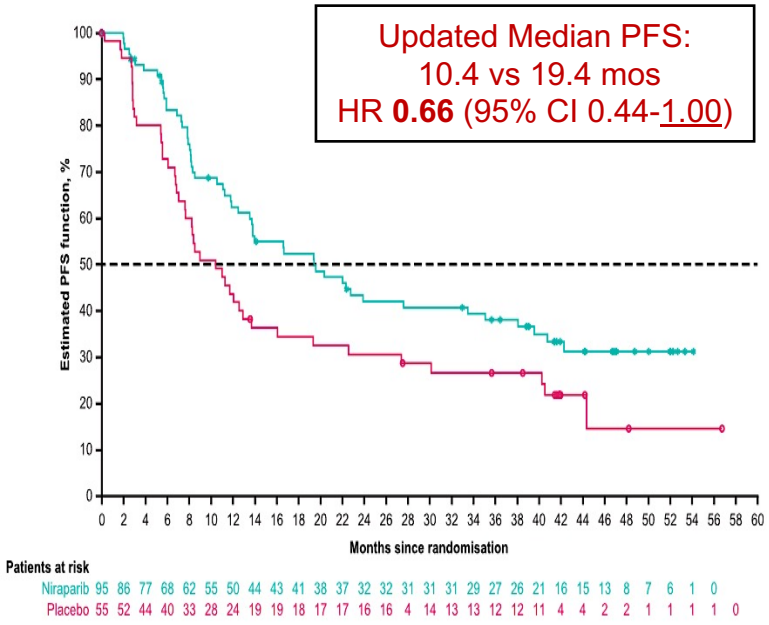
PARPi monotherapy maintenance results in PFS benefit in *BRCA*wt HRD test positive tumors

PRIMA (HRD by GIS ≥42)

Primary analysis

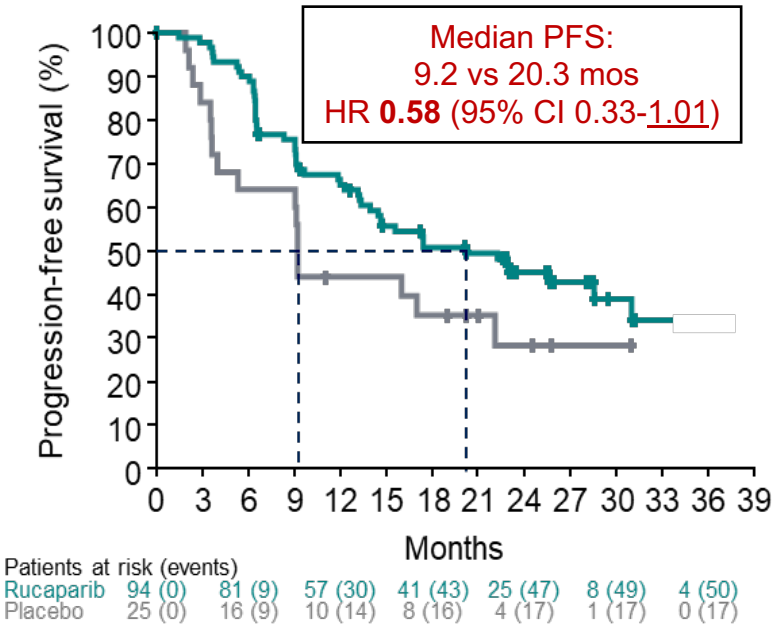


3.5 year follow-up



ATHENA-MONO (HRD by LOH ≥16%)

Primary analysis



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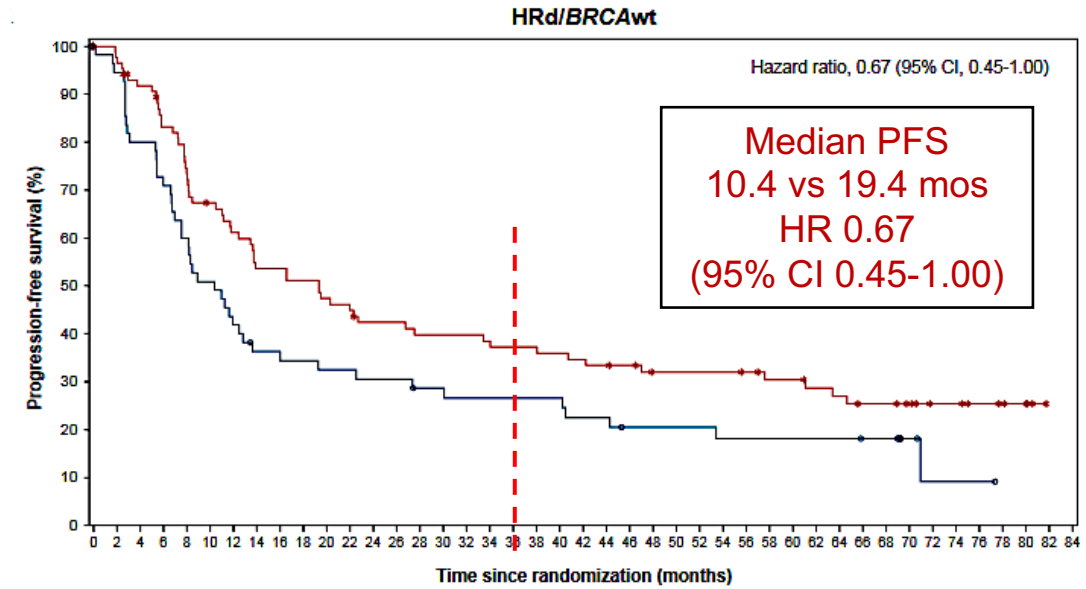
Gonzalez-Martin *N Engl J Med* 2019; Gonzalez-Martin *Eur J Cancer* 2023; Monk *J Clin Oncol* 2022

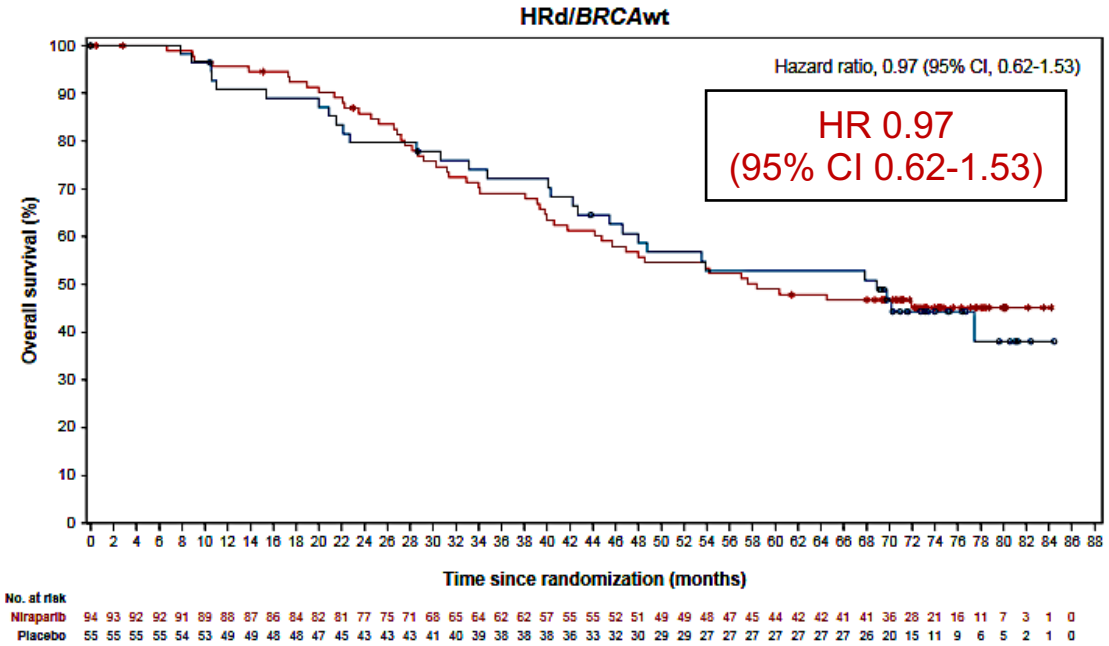
No OS benefit for niraparib maintenance in *BRCA*wt HRD test positive tumors

PRIMA Final OS Analysis: ~6.2 year follow-up

PFS HRD/*BRCA*wt



OS HRD/*BRCA*wt

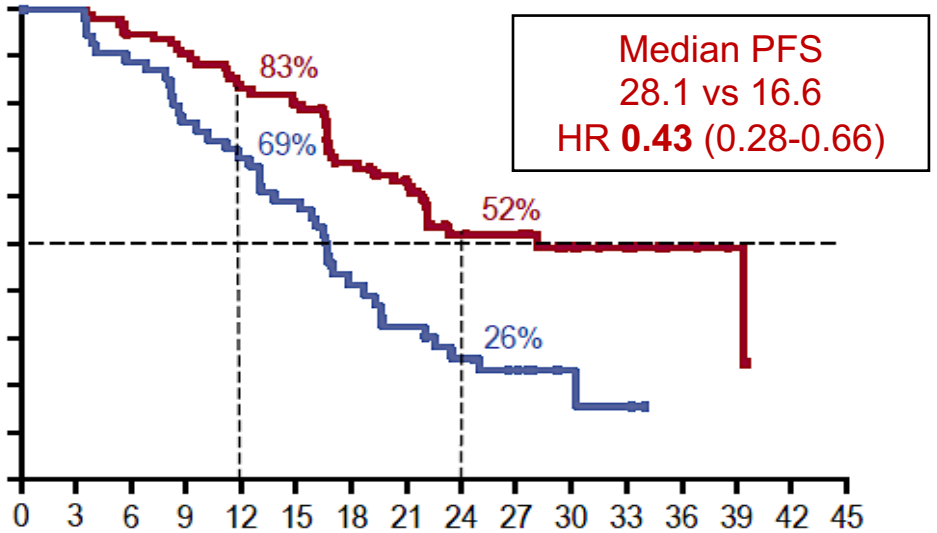


Gonzalez-Martin, 2024 ESMO Congress; Monk et al., *Ann Oncol* 2024

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

PAOLA1: Primary PFS and Final OS analyses

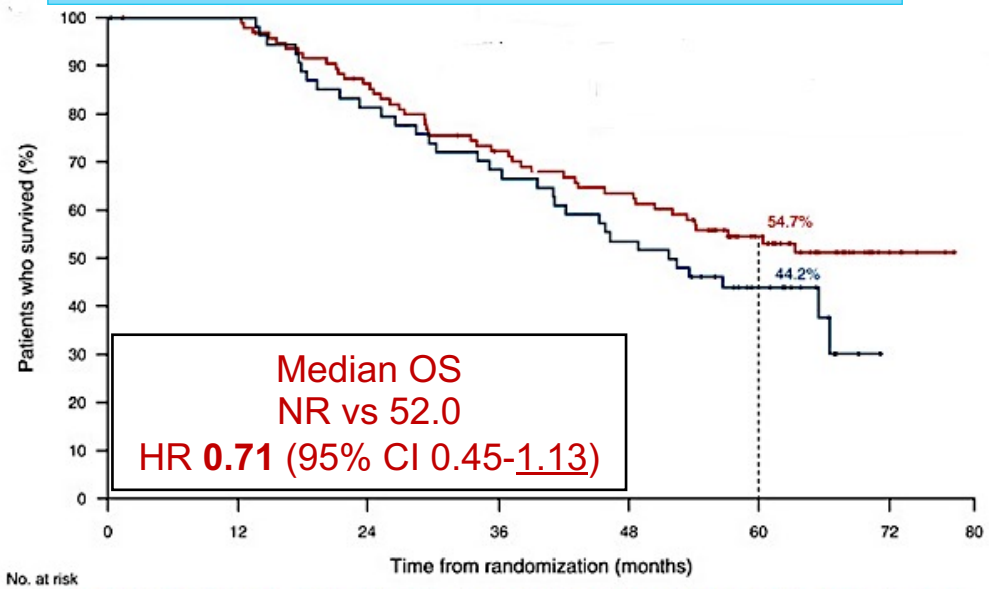
Primary analysis PFS *BRCA*wt, HRD+



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

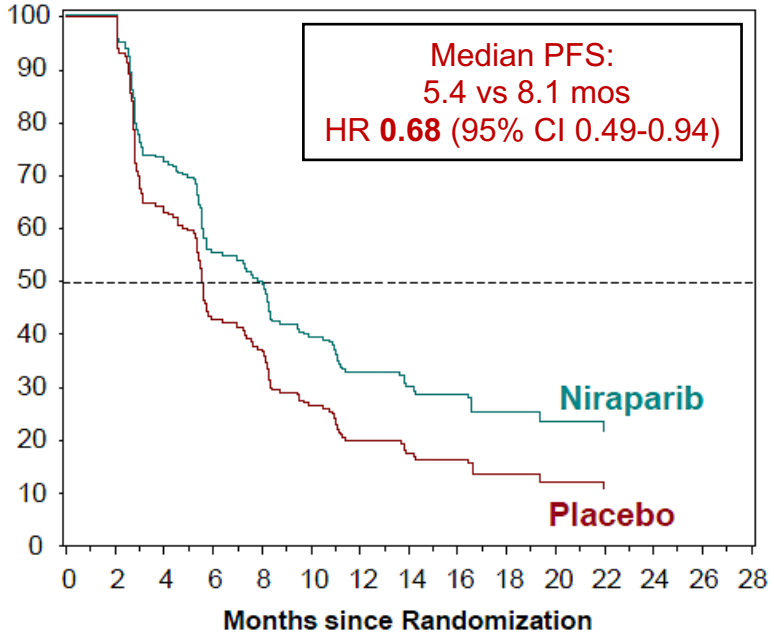
Randomized studies informing front-line PARPi maintenance

	*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	ATHENA-COMBO: Rucaparib + nivolumab	ATHENA-COMBO: Rucaparib + nivolumab DUO-O: Olaparib + bevacizumab + durvalumab KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab	ATHENA-COMBO: Rucaparib + nivolumab DUO-O: Olaparib + bevacizumab + durvalumab KEYLYNK-001: Olaparib + pembrolizumab +/- bevacizumab

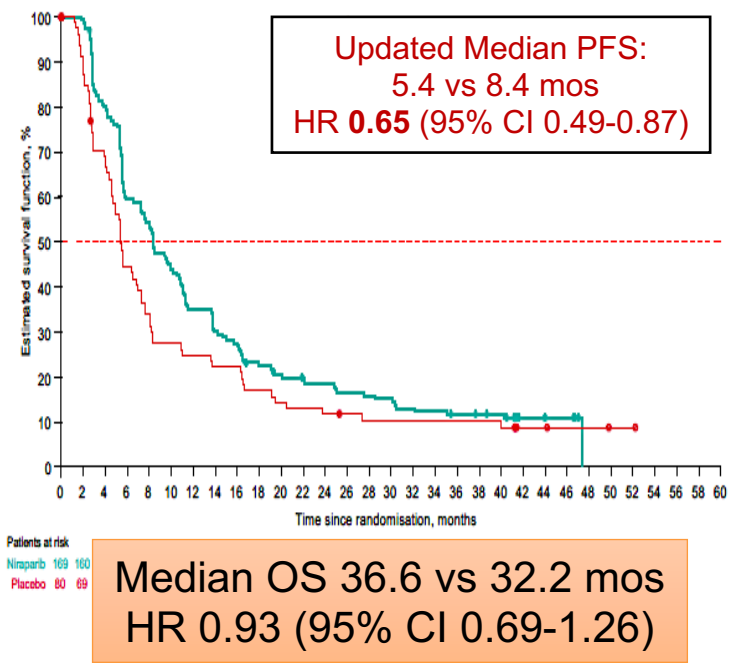
PARPi monotherapy maintenance has limited PFS benefit in *BRCA*wt HRD test negative tumors

PRIMA (HRD test neg; GIS <42)

Primary analysis



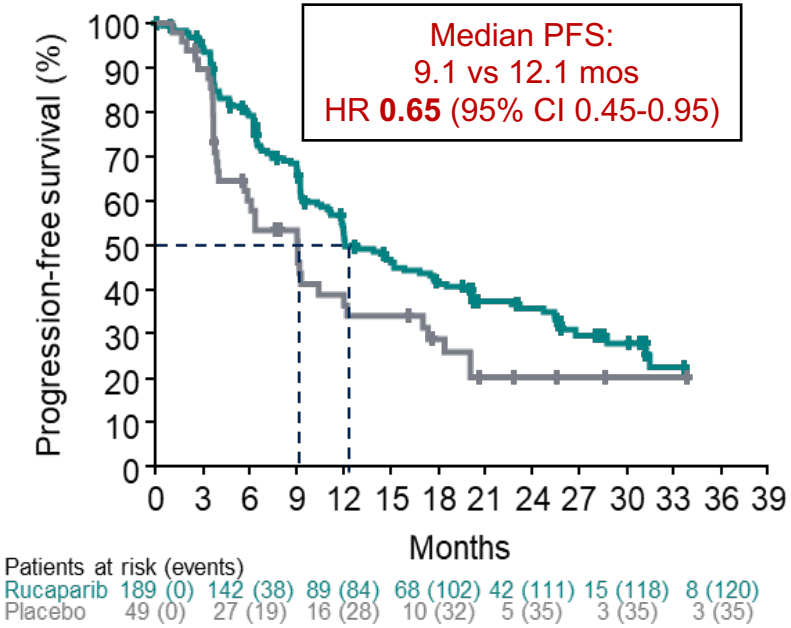
3.5 year follow-up



Median OS 36.6 vs 32.2 mos
HR 0.93 (95% CI 0.69-1.26)

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

Primary analysis



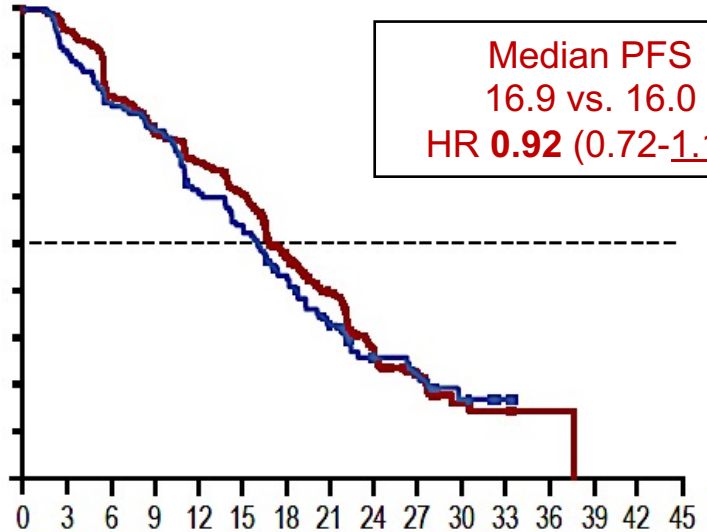
Dana-Farber Cancer Institute

Gonzalez-Martin *N Engl J Med* 2019; Gonzalez-Martin *Eur J Cancer* 2023; Monk *J Clin Oncol* 2022; Gonzalez-Martin 2024 ESMO Congress; Monk *Ann Oncol* 2024

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

PAOLA1: Primary PFS and Final OS analyses

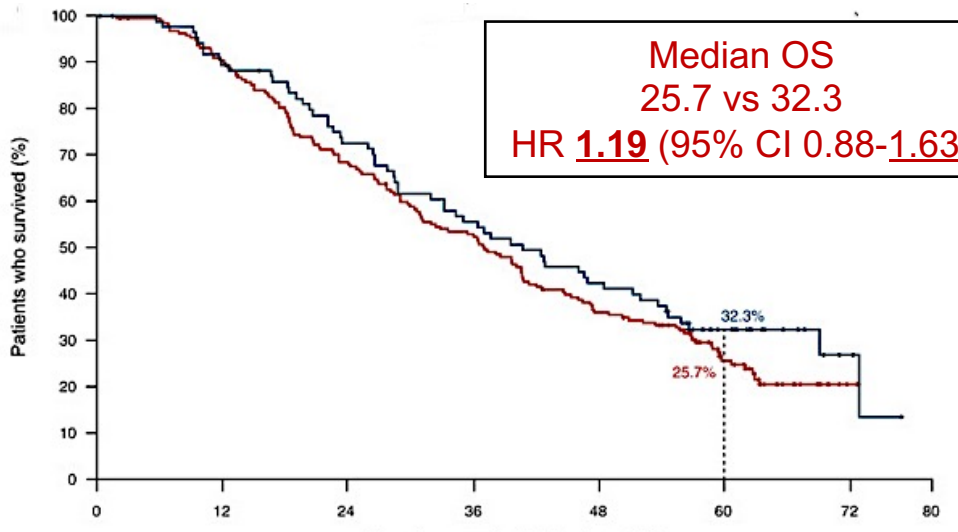
Primary analysis PFS *BRCA*wt, HRD test neg



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 *N Engl J Med* 2019; Ray-Coquard *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
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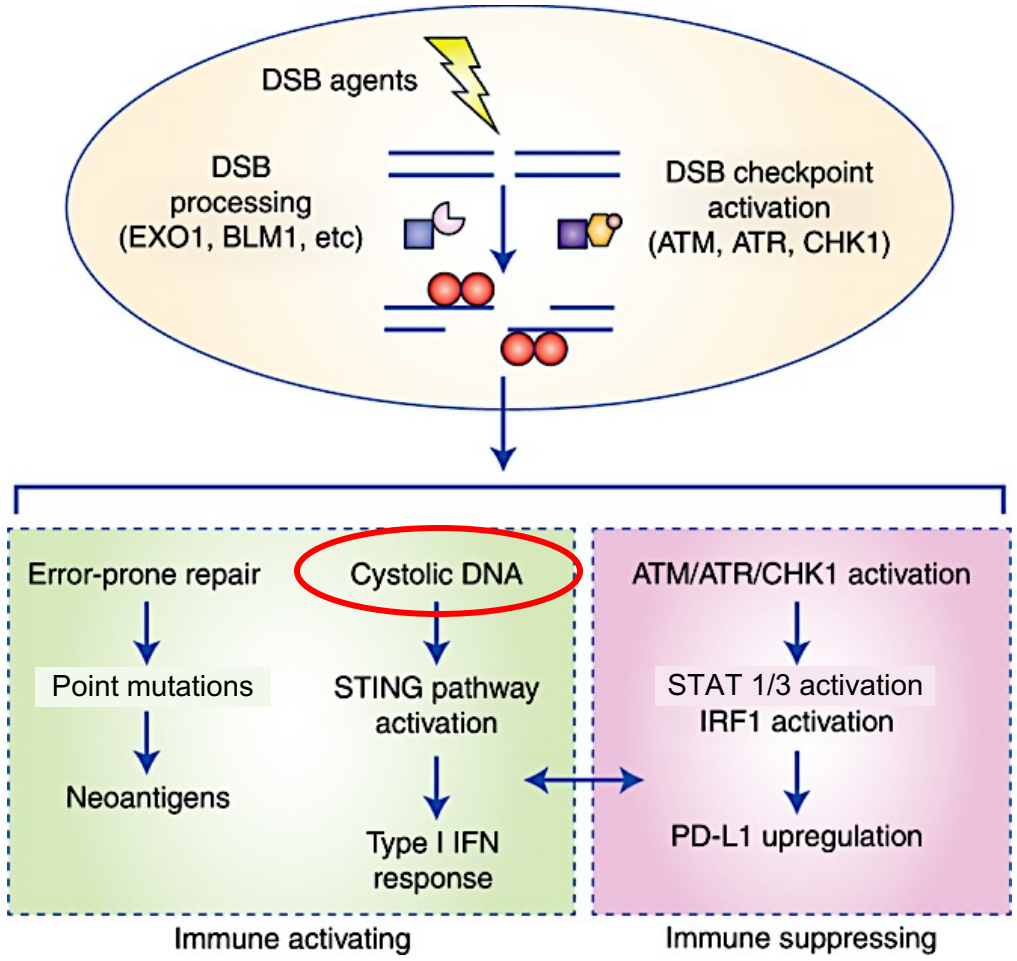
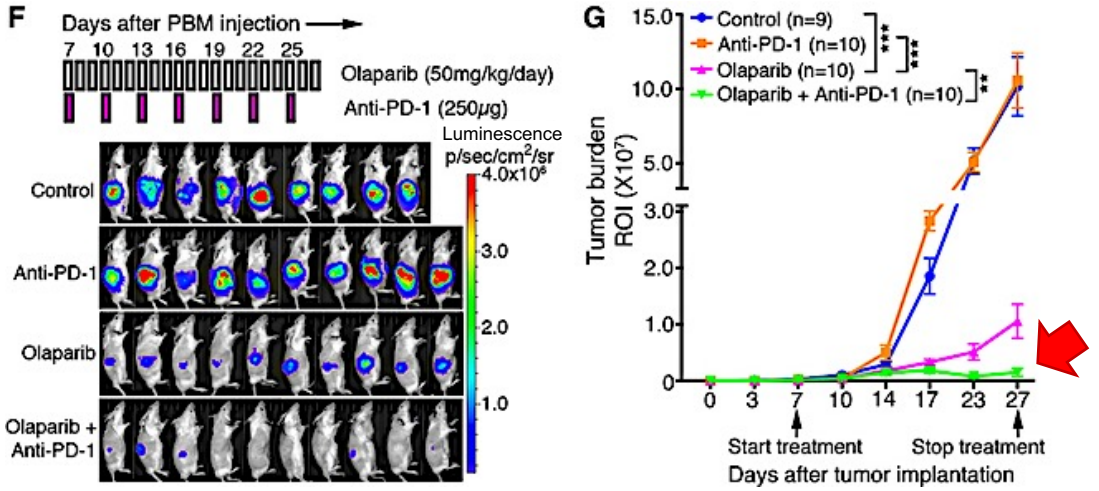
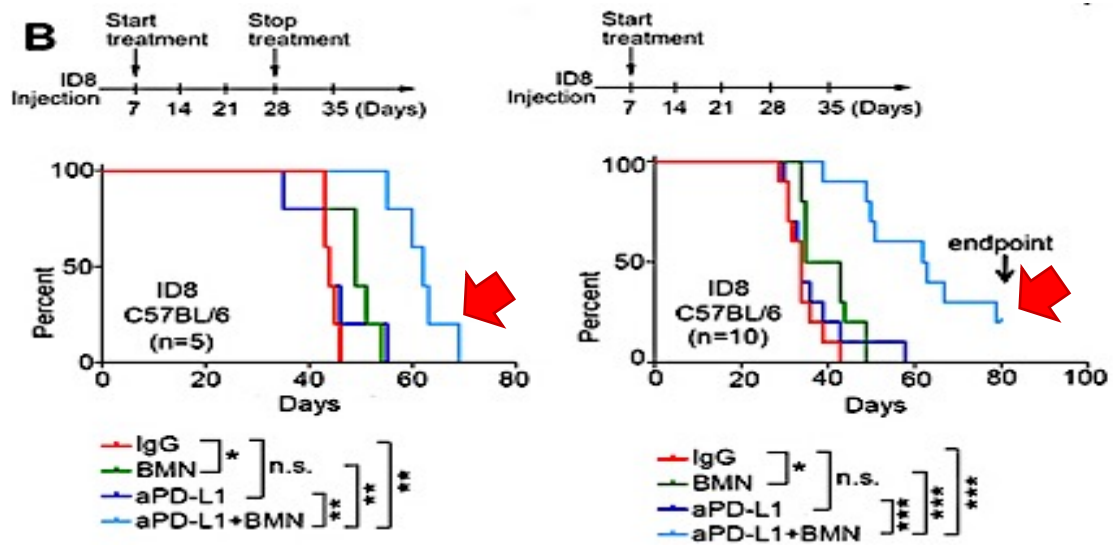
Immunotherapy + PARP inhibitors



Mouw and Konstantinopoulos, *Brit J Cancer* 2018



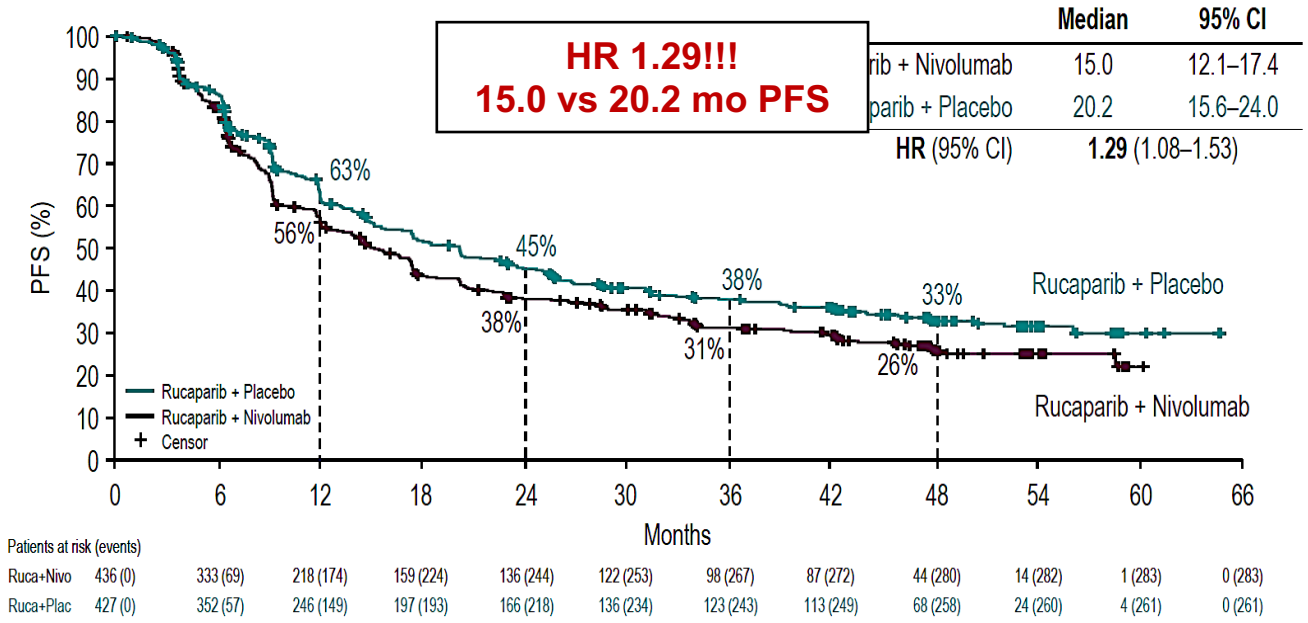
Ding L et al., *Cell Rep.* 2018



Shen et al., *Cancer Res* 2019

Rucaparib + nivolumab did not improve PFS compared to rucaparib alone

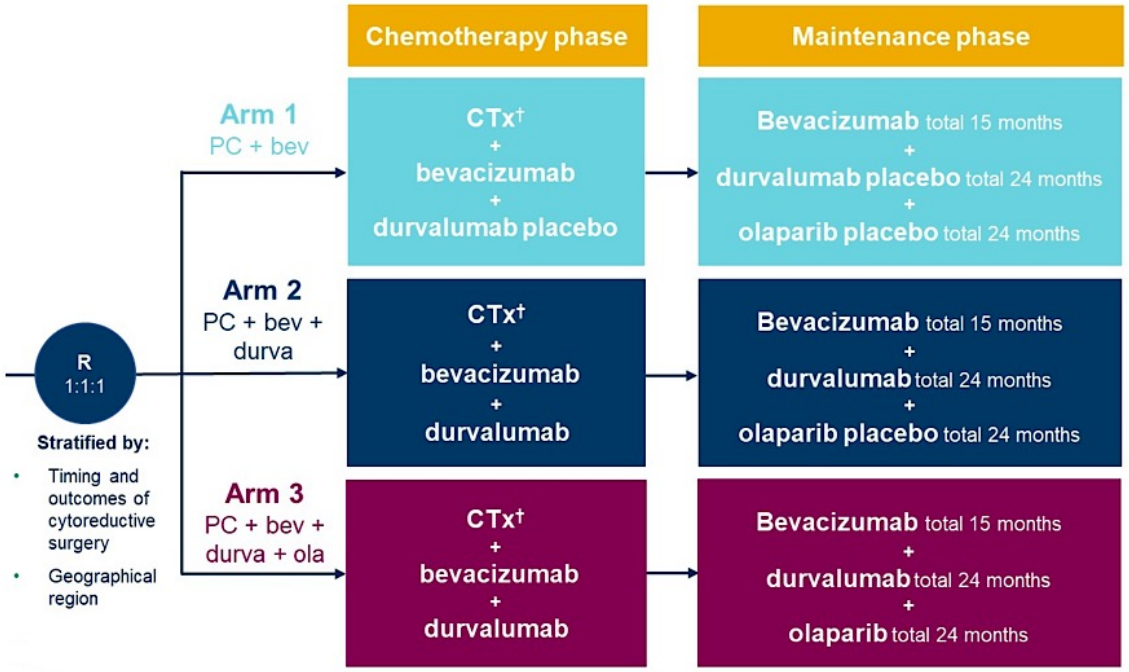
ATHENA-COMBO
PFS ITT



	Rucaparib/ Nivolumab (N=410)	Rucaparib/ Placebo (N=448)
Oral drug interruption and/or dose reduction for TEAE	321 (78.3)	283 (63.2)
Oral drug d/c for TEAE	104 (25.4)	66 (14.7)
IV drug d/c for TEAE	145 (35.4)	43 (9.6)
Oral and IV drug d/c for TEAE	63 (15.4)	19 (4.2)

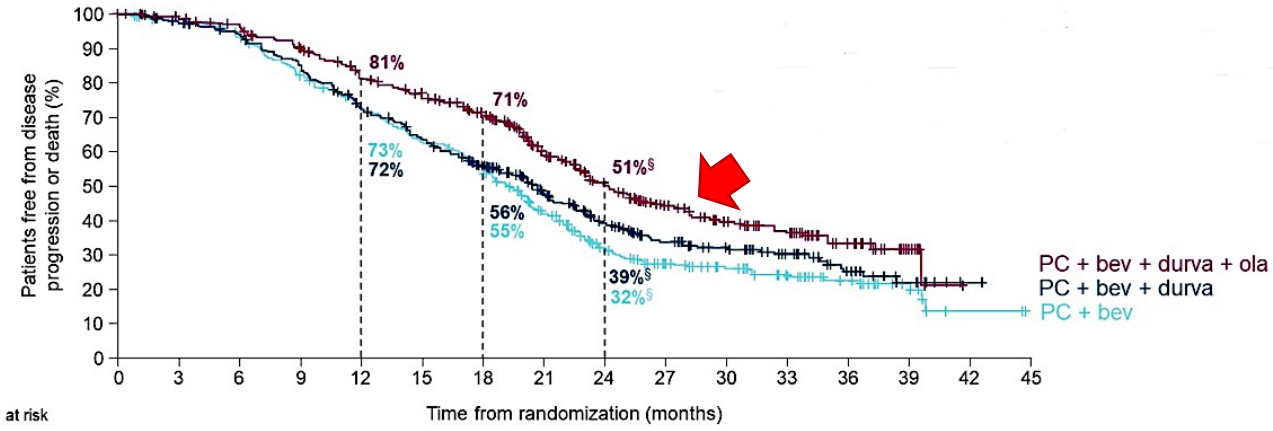
Monk et al., 2024 ESMO Congress

DUO-O demonstrated PFS improvement with olaparib + dostarlimab + bevacizumab



	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

HR 0.63

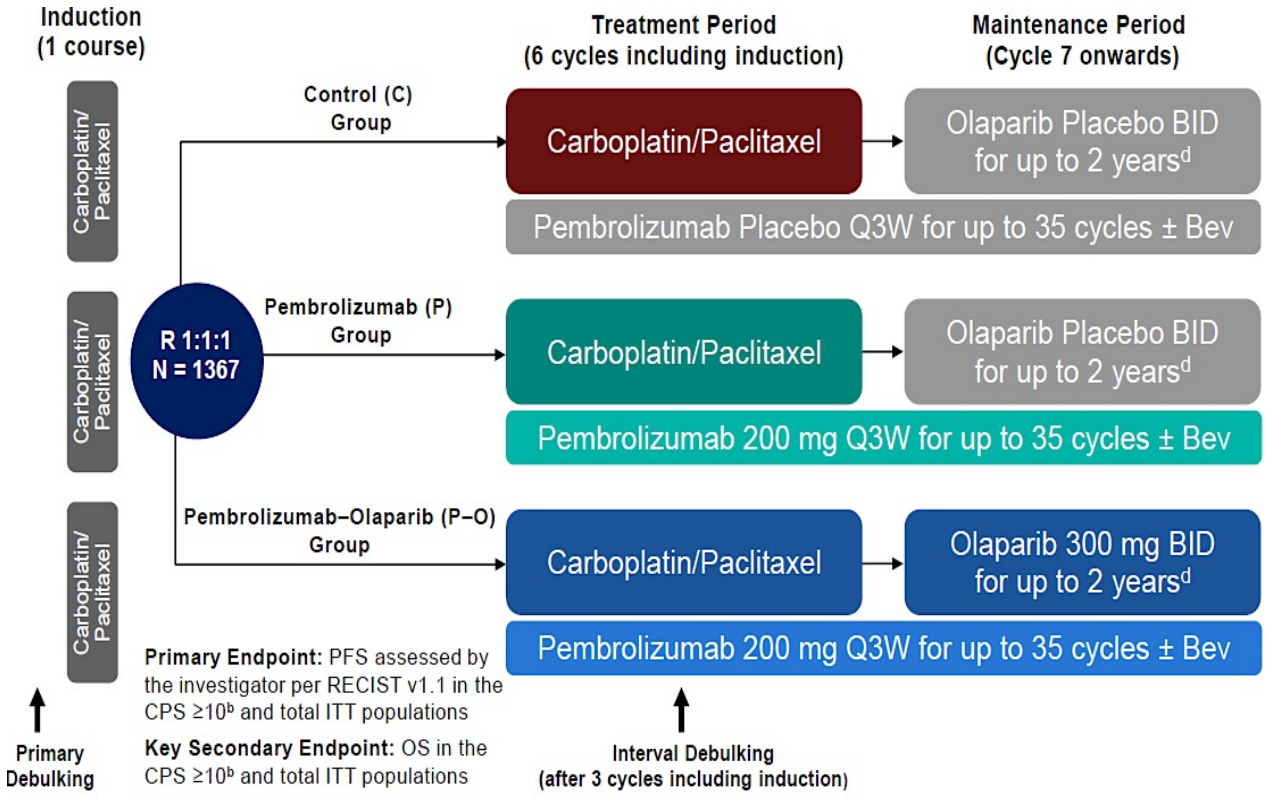


…but we do not have the control arms to tell us this could not be from olaparib or olaparib + bevacizumab

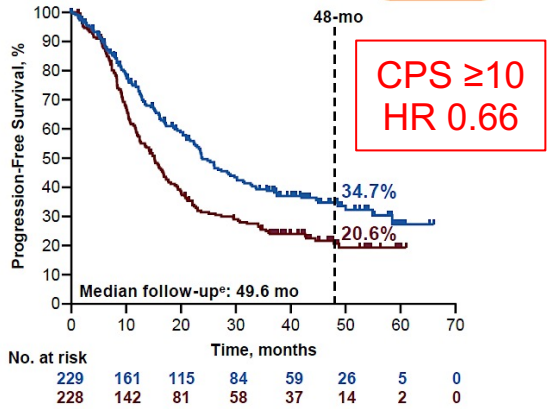
Dana-Farber Cancer Institute

Harter et al., 2023 ASCO Annual Meeting

KEYLYNK-001 demonstrated PFS improvement with olaparib + pembrolizumab (+/- bevacizumab)

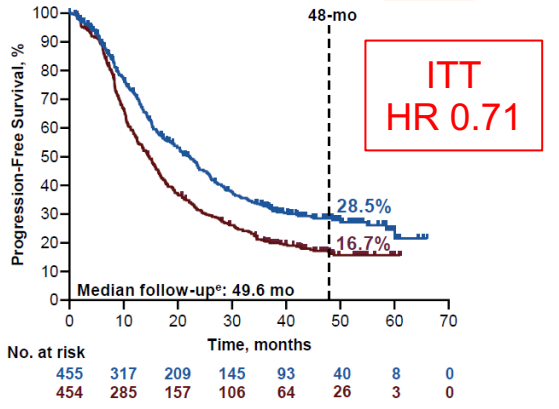


FA (Aug 2024)[b]	Median, months	Events	HR (95% CI)
P–O Group	23.9	58.5%	0.66[c] (0.53-0.83)
C Group	15.2	72.4%	



CPS ≥10
HR 0.66

FA (Aug 2024)[b]	Median, months	Events	HR (95% CI)
P–O Group	22.2	64.0%	0.71[c] (0.61-0.84)
C Group	14.6	77.5%	



ITT
HR 0.71

Overall Survival	P–O Group	C Group
CPS ≥10 Population		
Median, mo	50.2	51.6
HR (95% CI)	0.98 (0.75-1.27)	
Total ITT Population		
Median, mo	47.7	47.1
		1.25)

…but we still do not have the control arms to tell us this could not be from olaparib or olaparib + bevacizumab

Powell et al., 2025 SGO Annual Meeting

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

- Test for *BRCA* mutations and HRD status

The Present State

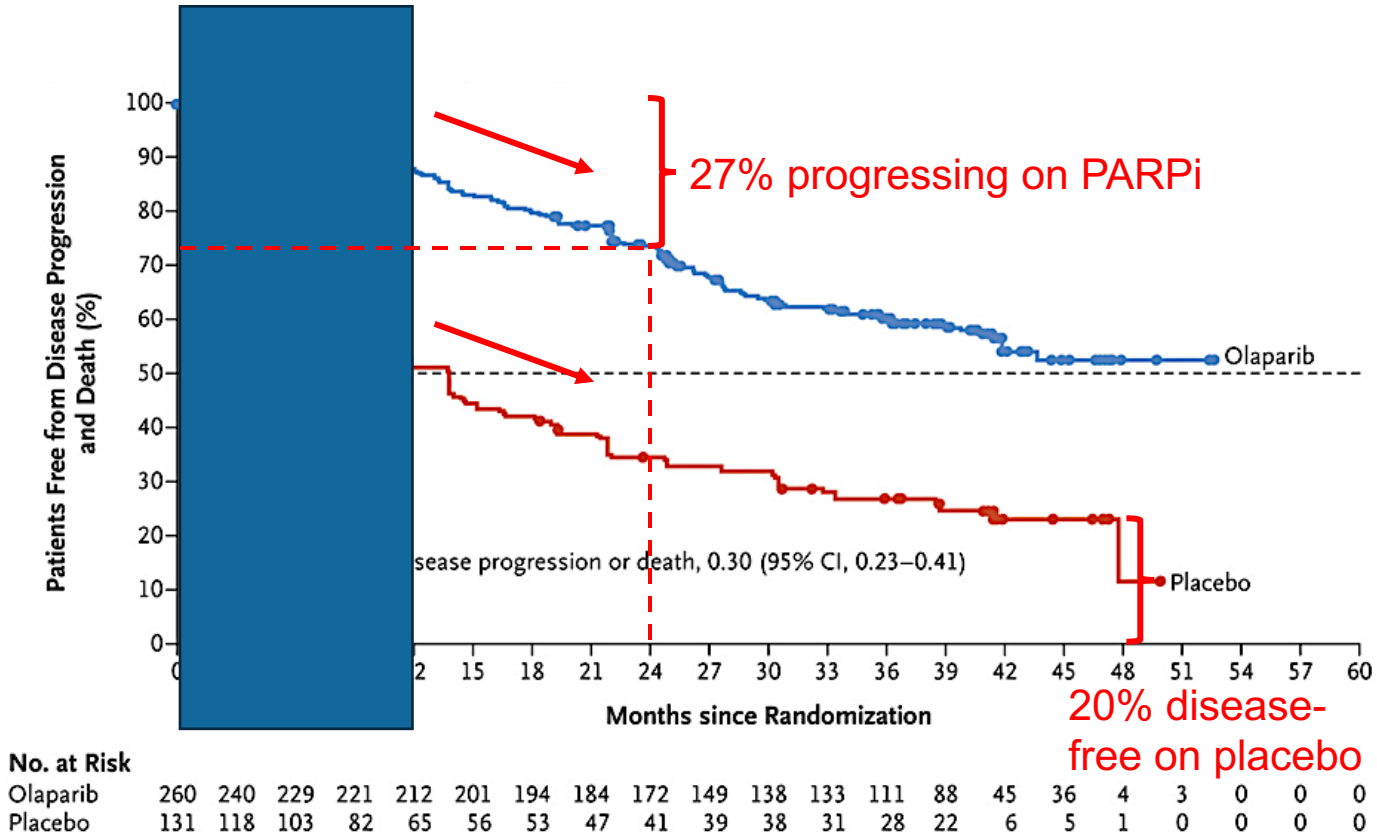
	PARPi monotherapy		PARPi + bevacizumab	
	PFS benefit	OS benefit	PFS benefit	OS benefit
*BRCA*m	YES!	YES! (Olap 7y) No (Nirap)	YES!	YES! (5 yr f/u)
*BRCA*wt HRD test pos	Yes	No (Nirap)	Yes	Trend (5 yr f/u)
*BRCA*wt HRD test neg	Yes, but very modest	No (Nirap)	No	No

Still to Come…

- PARPi monotherapy OS
  - ATHENA-MONO: Rucaparib
- PARPi vs. PARPi + bev
  - NIRVANA-1: Niraparib +/- bev
  - AGO-OVAR 28: Niraparib +/- bev
  - MITO25: Rucaparib +/- bev vs bev
- PARPi + ICI +/- bev
  - FIRST: Niraparib + dostarlimab +/- bev

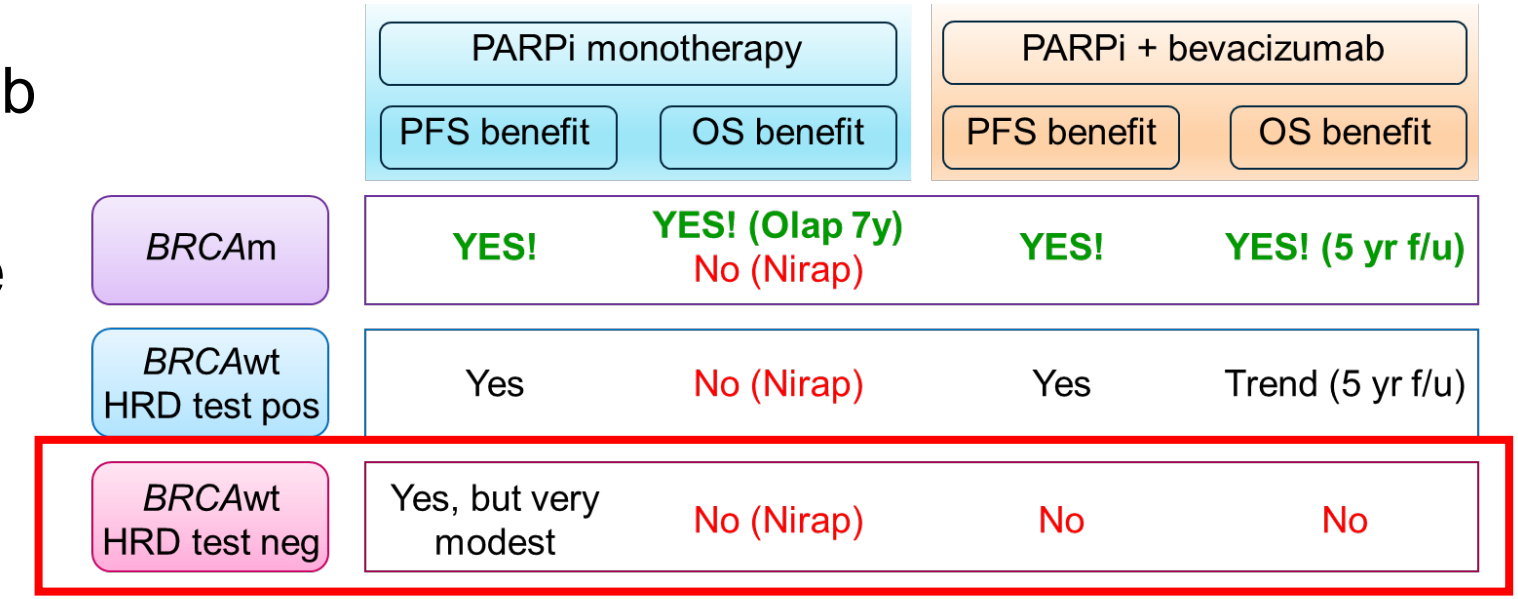
Where do we go from here?

- Optimal duration of therapy
  - NRG-GY036: One vs. two years of maintenance olaparib
- Identify patients at risk for early progression and those with exceptional prognosis



Where do we go from here?

- Optimal duration of therapy
  - NRG-GY036: One vs. two years of maintenance olaparib
- Identify patients at risk for early progression and those with exceptional prognosis
- Options for patients with HRP tumors
  - ADC maintenance?



Case Presentation: 65-year-old woman (PS 1) with moderate ascites and omental caking is diagnosed with HRD-positive, BRCA wild-type HGSOC

Dr Karim ElSahwi (Neptune City, New Jersey)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

How do you decide whether to start with neoadjuvant chemotherapy versus primary debulking surgery for patients with newly diagnosed advanced ovarian cancer?

If you opt for neoadjuvant chemotherapy, in which situations, if any, do you use HIPEC?

How much stock do you put in genomic testing platforms other than the companion diagnostics used in the pivotal clinical trials? Are they equally effective?

Questions for the Faculty

What maintenance therapy would you recommend for this patient? Which PARP inhibitor would you prefer? Would you continue bevacizumab in the maintenance setting? How long would you continue maintenance therapy?

How, if at all, would your approach to maintenance therapy differ if this patient had a germline or somatic BRCA mutation?

Do you think regimens combining PARP inhibitors with immune checkpoint inhibitors may eventually have a role in newly diagnosed advanced ovarian cancer? Are there any patient subsets for whom these strategies seem more promising?

Case Presentation: 73-year-old woman with BRCA wild-type Stage IIIC HGSOC (HRD status inconclusive twice) receives carboplatin/paclitaxel and interval debulking surgery

Dr Kellie Schneider (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

Have you encountered inconclusive HRD results? Are there any steps that can be taken to increase the likelihood of obtaining interpretable HRD test results?

Would you have recommended maintenance therapy for this patient, and if so, what?

How would you have managed this patient's thrombocytopenia? Would you have switched to another PARP inhibitor, continued niraparib at a lower dose or discontinued maintenance therapy?

Questions for the Faculty

How often do you order CBCs for patients receiving up-front PARP inhibitor maintenance? Is there any way to anticipate which patients will experience cytopenias?

Would you ever continue up-front PARP inhibitor maintenance beyond the recommended duration for patients who are tolerating therapy well and are nervous about stopping?

RTP
RESEARCH
TO PRACTICE

Agenda

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

MODULE 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr O'Malley

MODULE 3: Role of HER2-Targeted Therapy in Advanced OC, Endometrial Cancer (EC) and Other Gynecologic Cancers — Dr Santin

MODULE 4: First-Line Therapy for Advanced EC — Dr Westin

MODULE 5: Current Therapeutic Options for R/R EC; Novel Investigational Strategies for Newly Diagnosed and Recurrent Disease — Dr Salani

Current Management of Relapsed/Refractory Ovarian Cancer
Promising Novel Agents and Strategies Under Investigation

David M O'Malley, MD

The Ohio State University and
The James Comprehensive Cancer Center

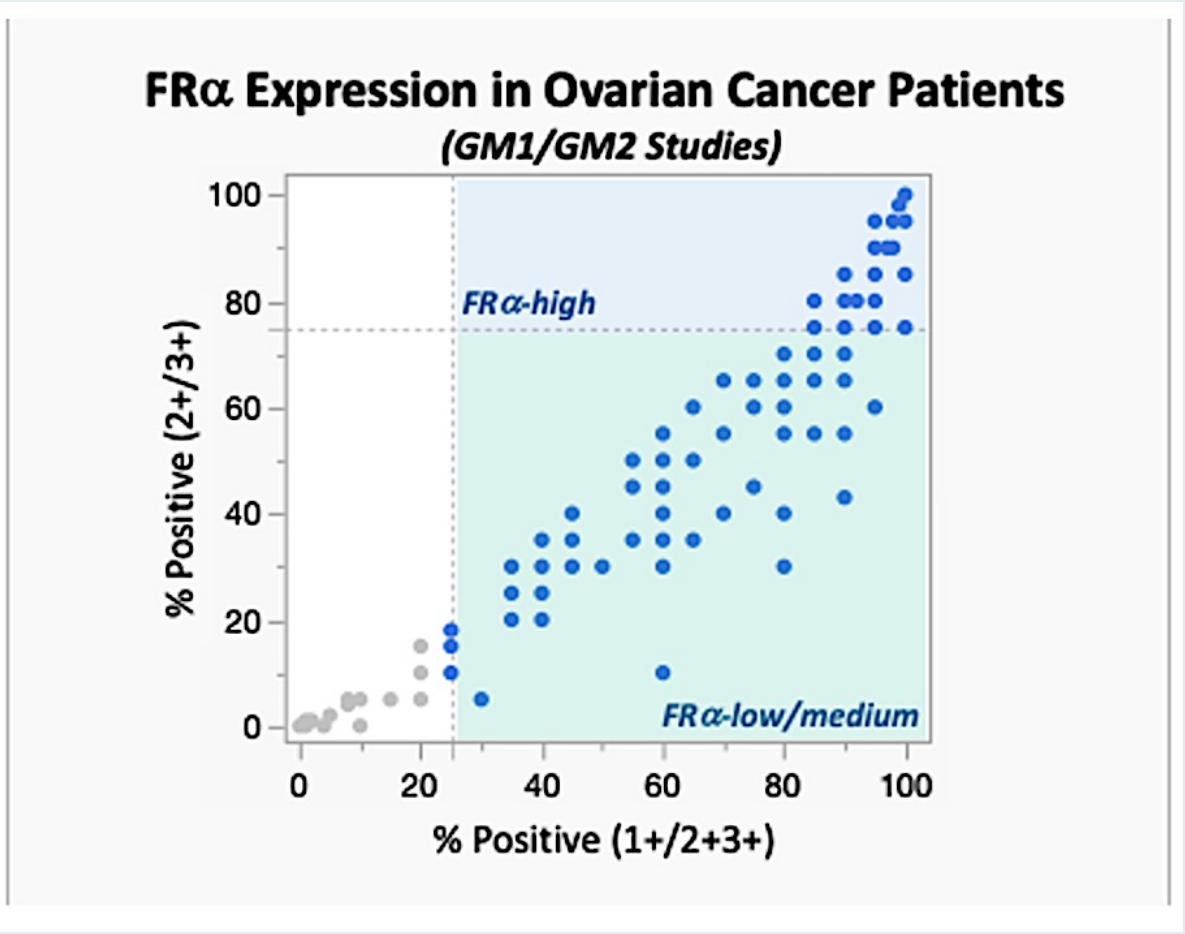
Columbus, Ohio

Agenda

- Antibody Drug Conjugates
  - Folate Receptor Alpha
  - CDH6
  - Others
- Glucocorticoid receptor antagonist
  - Relacorilant
  - Phase III ROSELLA trial of relacorilant in combination with *nab* paclitaxel
- Immune therapies
  - Phase 3 KEYNOTE-B96
- Post ADC World?

How common is FRα expressed in Ovarian Cancer?

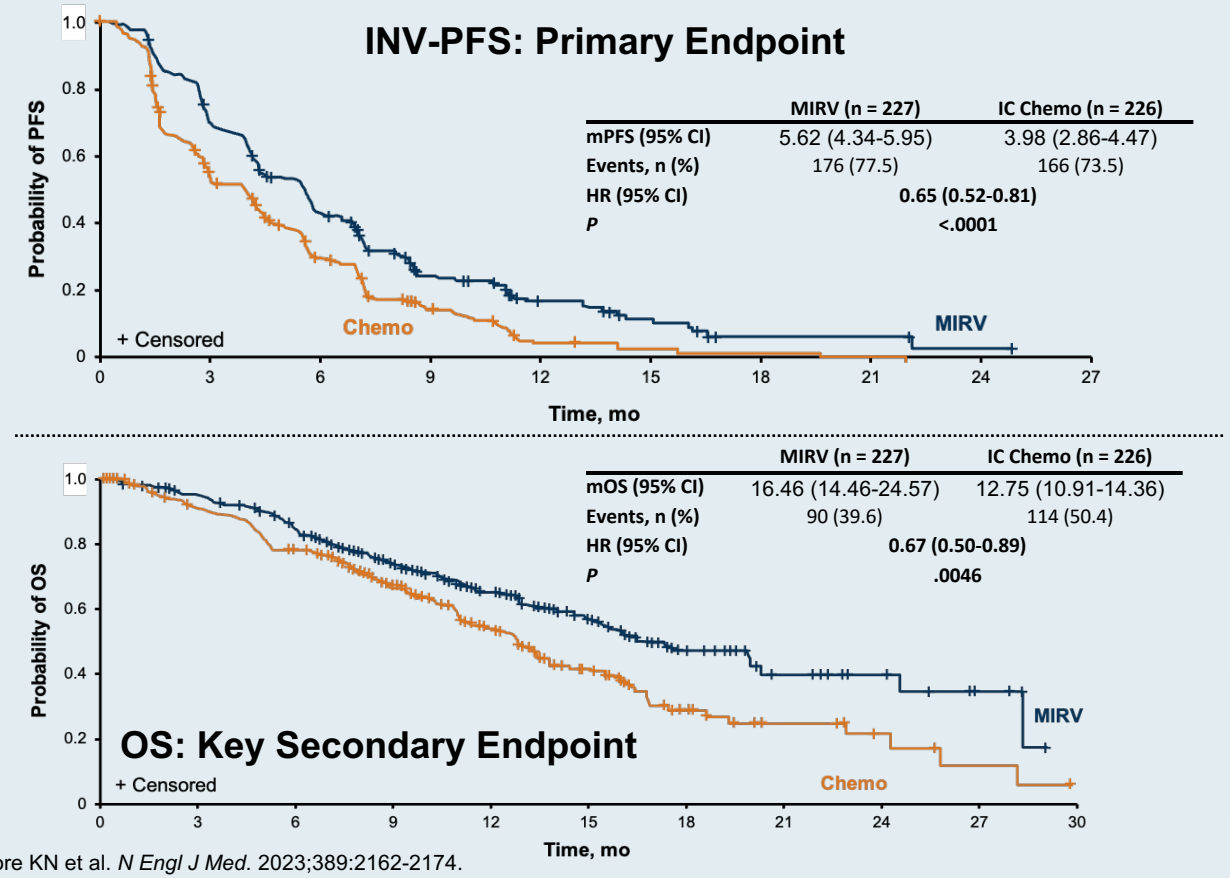
- **EOC expression from the STRO-002-GM1 and STRO-002-GM2 trials**
- **Approximately 40% will have high expression based PS2+ scoring (Abstract 5568, T. Krivak, et al) in real world analysis**
- **80%-90%+ will have some FRα expression**



T. Krivak, et al. Abstract 5568 ASCO 2025: Real-world analysis of folate receptor alpha (FRα; FOLR1) expression in pan-tumor samples from over 6000 patients in the US

A. Oakin et al 2023 "Luveltamab tazevibulin (STRO-002), an anti-folate receptor alpha (FolRα) antibody drug conjugate (ADC), safety and efficacy in a broad distribution of FolRα expression in patients with recurrent epithelial ovarian cancer (OC): Update of STRO-002-GM1 phase 1 dose expansion cohort. https://www.sutrobio.com/wp-content/uploads/2024/11/HP_Luvelta_ADC-World_11-07-2025_FINAL.pdf

Mirvetuximab Soravtansine Improved PFS and OS[1]



MIRASOL

- 35% improvement in PFS with MIRV vs chemotherapy
- 33% improvement in OS with MIRV vs chemotherapy
- ORR more than doubled: 42% vs 16% with MIRV vs chemotherapy (P < .0001; 12 CRs vs 0 CRs)

FDA Approval April 2024

1. Moore KN et al. *N Engl J Med.* 2023;389:2162-2174.

Safety and Tolerability of Mirvetuximab Soravtansine Monotherapy for Folate Receptor Alpha–Expressing Recurrent Ovarian Cancer: An Integrated Safety Summary

Objectives

Mirvetuximab soravtansine-gynx (MIRV) is a novel antibody-drug conjugate targeting folate receptor alpha (FRα), which is overexpressed in epithelial ovarian cancer (EOC), with limited expression on normal tissues

This integrated safety summary characterized the safety profile of MIRV monotherapy across 4 clinical trials among 682 participants with FRα-expressing recurrent EOC

Conclusions

As demonstrated among 682 participants, the safety profile of MIRV is well tolerated and consists primarily of resolvable ocular events, low-grade gastrointestinal events, fatigue, and peripheral neuropathy

Adverse events with MIRV were generally managed with supportive care and, if needed, dose modifications

The proven efficacy of MIRV along with the differentiated safety profile demonstrated here position MIRV as a new standard of care for patients with FRα-positive EOC

Integrated Safety Summary: Results from 4 clinical trials (N=682)

All participants received ≥1 dose of MIRV monotherapy at 6 mg/kg Q3W (using AIBW)

Phase 1 study N=113

- **Participants:** Relapsed/refractory or platinum-resistant/refractory EOC with ≥25% FRα expression
- **Design:** First in human, open-label, nonrandomized, dose-escalation and dose-expansion study

FORWARD I phase 3 study N=245

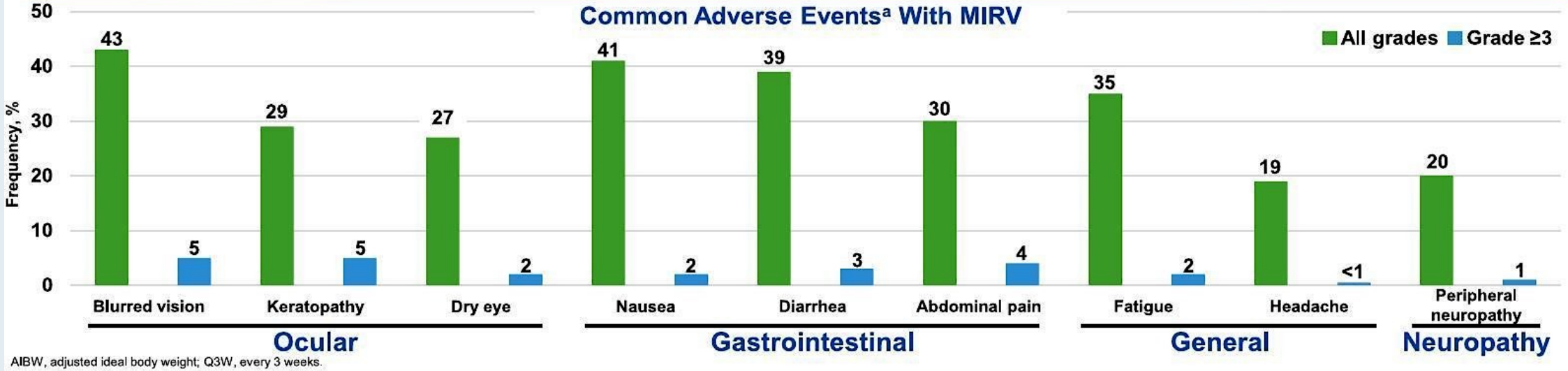
- **Participants:** Platinum-resistant EOC with ≥50% FRα expression and 1 to 3 previous systemic anticancer therapies
- **Design:** Open-label, randomized study

SORAYA phase 2 study N=106

- **Participants:** Platinum-resistant, advanced, high-grade serous EOC with ≥75% FRα expression and 1 to 3 previous systemic anticancer therapies
- **Design:** Open-label, nonrandomized, single-arm study

MIRASOL phase 3 study N=218

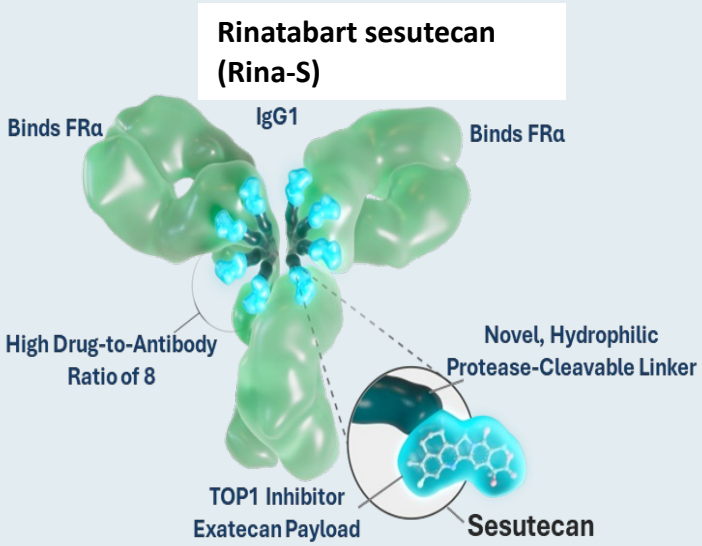
- **Participants:** Platinum-resistant, advanced, high-grade serous EOC with ≥75% FRα expression and 1 to 3 previous systemic anticancer therapies
- **Design:** Open-label, randomized study



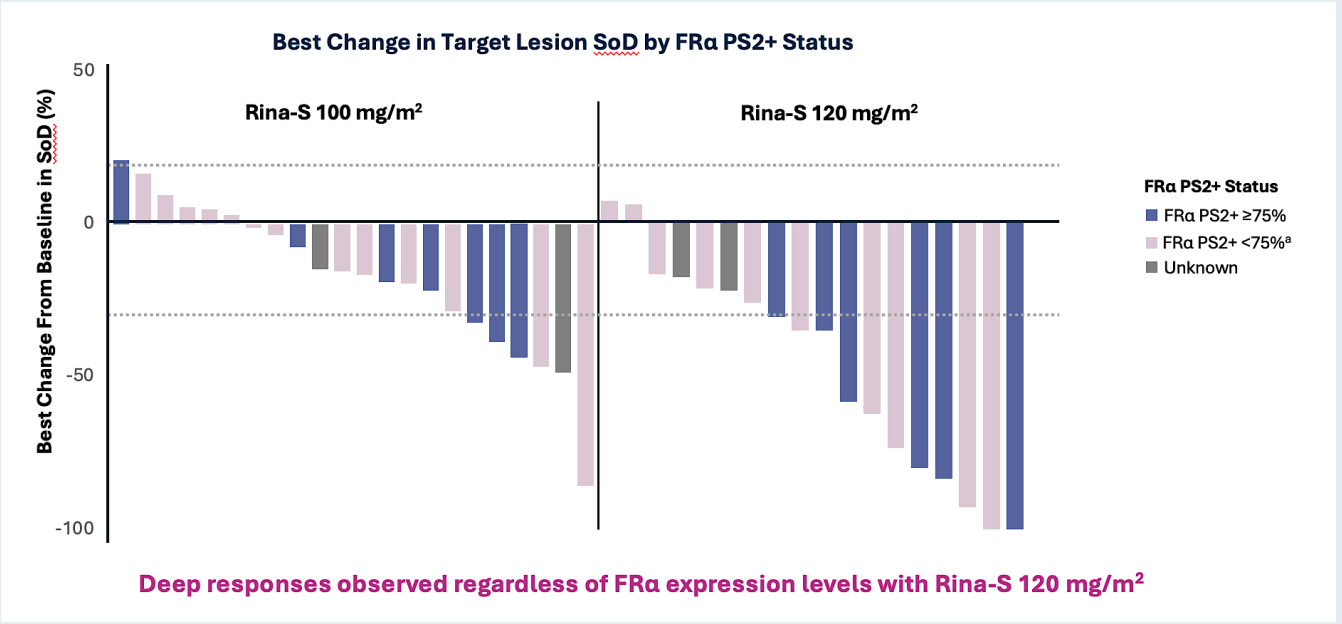
AIBW, adjusted ideal body weight; Q3W, every 3 weeks.
[a]Preferred terms (Medical Dictionary for Regulatory Activities version 24.0).

Safety and tolerability of mirvetuximab soravtansine monotherapy for folate receptor alpha–expressing recurrent ovarian cancer: An integrated safety summary. KN Moore, et al. Gynecologic Oncology 191, 249-258

Targeting FRα in Ovarian Cancer: What is next?



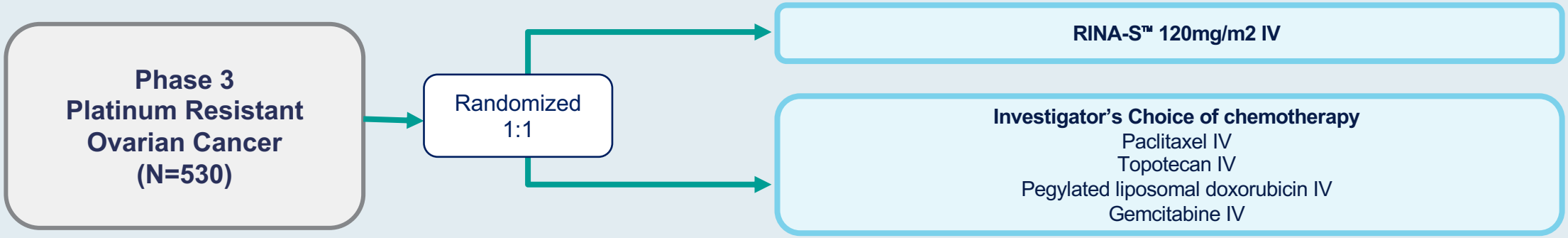
	Rina-S 100 mg/m² (n=22)[a]	Rina-S 120 mg/m² (n=18)[a]
Median on-study follow-up, weeks (range)	46.4 (6.6, 65.3)	48.1 (10.9-65.9)
Confirmed ORR[b], % (95% CI)	22.7 (7.8-45.4)	55.6 (30.8-78.5)
Confirmed response, n (%)		
CR	1 (4.5)	2 (11.1)
PR	4 (18.2)	8 (44.4)
SD	14 (63.6)	6 (33.3)
NE	0	1 (5.6)
Disease control rate, % (95% CI)	86.4 (65.1-97.1)	88.9 (65.3-98.6)



Deep responses observed regardless of FRα expression levels with Rina-S 120 mg/m²

Lee, EK, SGO 2025

Efficacy of Rina-S Compared to Treatment of Investigator's Choice in Participants with PROC: ENGOT-OV86/GOG-3107/RAINFOL-OV2



Evaluation of Study Objectives*

Primary Outcome Measure

- Progression-Free Survival

Secondary Outcome Measures

- Overall Survival
- Objective Response Rate
- Duration of Response
- CA-125 response by GCIG criteria
- Adverse Events
- GHS/QoI (EORTC-QLQ-C30)

Key Inclusion Criteria*

- Histologically or cytologically confirmed high grade serous or endometrioid epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer
- Received 1 to 4 prior lines of therapy with the following therapies:
- Platinum chemotherapy
- Bevacizumab (if applicable)
- Poly-ADP ribose polymerase (PARP) inhibitor (if applicable)
- MIRV (if eligible based on FRα expression test)
- Platinum-resistant disease
- No prior ADC therapy containing a topoisomerase 1 inhibitor
- No known active central nervous system metastases or carcinomatous meningitis

NCT06619236

NCT06619236. Accessed from: https://clinicaltrials.gov/study/NCT06619236.

Other FRα targeted ADC presented at ASCO 2025

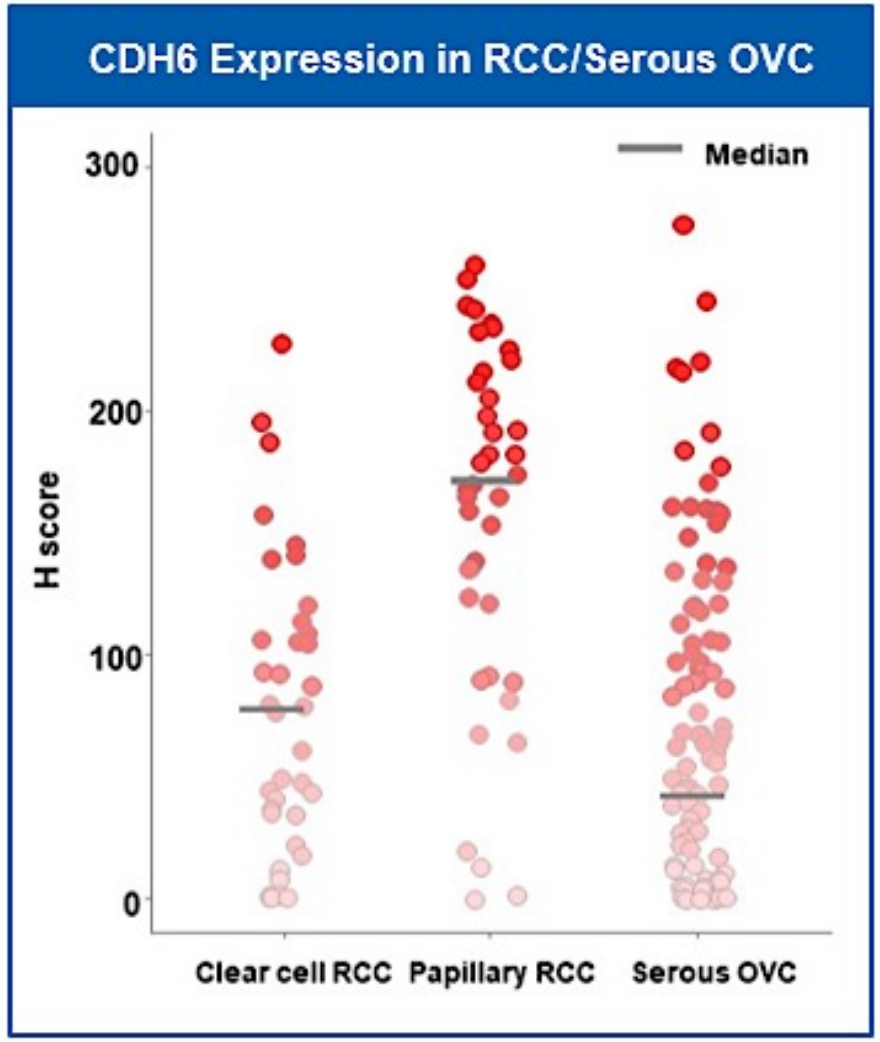
- **BAT8006**
- **LY4170156**

Songling Zhang, et al. **Safety and efficacy of BAT8006, a folate receptor α (FRα) antibody drug conjugate, in patients with platinum-resistant ovarian cancer: Update on the dose optimization/expansion cohort of BAT-8006-001-CR trial.**

Isabelle Ray-Coquard, David O'Malley, et al. **Initial results from a first-in-human phase 1 study of LY4170156, an ADC targeting folate receptor alpha (FRα), in advanced ovarian cancer and other solid tumors.**
ASCO 2025

Targeting Cadherin 6 (CDH6)

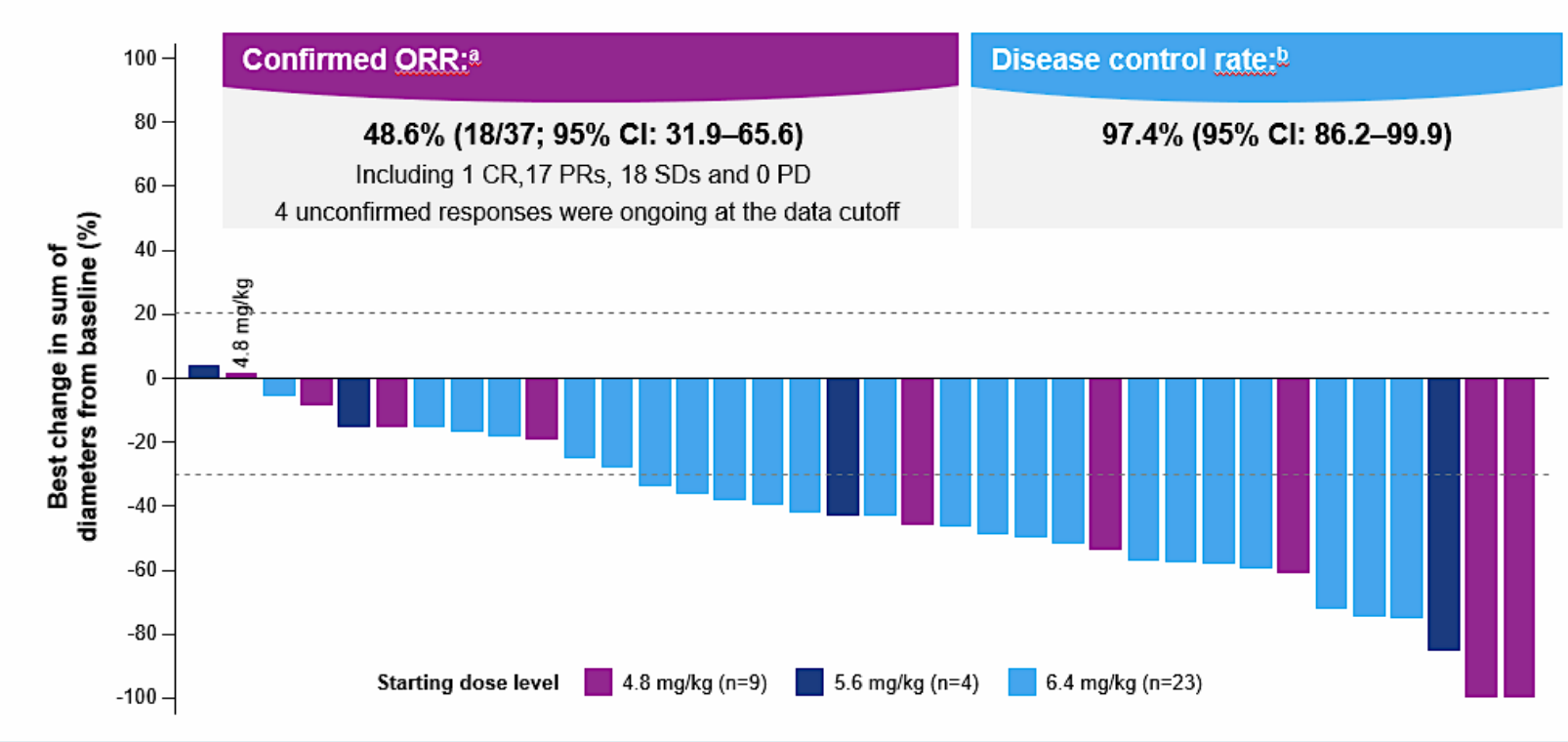
Targeting Cadherin 6 (CDH6) in Ovarian Cancer: Why?



- **CDH6 is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition**
- **Function of CDH6 has yet to be fully elucidated**
- **CDH6 is overexpressed in various cancers, particularly EOC**
- **Expression of CDH6 is observed in ~65–85% of patients with OVC**

Hirokazu S, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 16-21 September 2021; Paris, France. [Abstract 10P].
Bartolomé RA, et al. Mol Oncol. 2021;15:1849–1865;
Shintani D, et al. Gynecol Oncol. 2022;166(Suppl. 1):S116;

Targeting CDH6



	Raludotatug deruxtecan (DS-6000)[1,2]
Payload	Topoisomerase 1 inhibitor (DXd)
DAR	8
Linker	Cleavable tetrapeptide based linker
Trial	**NCT04707248**

Median DOR:[a]

11.2 months (95% CI: 3.1–NE)
Median (range) FU: 6.7 months (1.4–16.8)

Median TTR:[a]

5.7 weeks (95% CI: 5.3–11.4)

Median PFS:[b]

8.1 months (95% CI: 5.3–NE)
Median (range) FU: 4.0 months (0–25.1)

1. Moore K, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.;
2. NCT04707248. Accessed from: https://clinicaltrials.gov/study/NCT04707248?cond=NCT04707248&rank=1.

Raludotatug Deruxtecan Safety Profile

Patients with OVC who received R-DXd at 4.8–8.0 mg/kg

Overview of TEAEs

	n (%) N=60
Any TEAEs	57 (95.0)
TEAE with CTCAE Grade ≥3	31 (51.7)
TEAE associated with drug discontinuation	9 (15.0)
TEAE associated with dose interruption	22 (36.7)
TEAE associated with dose reduction	15 (25.0)
Any treatment-related CTCAE Grade ≥3 TEAE	22 (36.7)
Treatment-related TEAE associated with death	2 (3.3)[a]

- 3.3% (2/60) of patients in the 4.8–8.0 mg/kg cohort experienced Grade 5 ILD; both occurred in the 8.0 mg/kg cohort and were adjudicated as treatment-related
- 8.9% (4/45) of patients in the 4.8–6.4 mg/kg cohort experienced ILD (all Grade 2), of which 2 were adjudicated as treatment-related
- As of October 2022, the 8.0 mg/kg cohort was closed due to a higher incidence of serious and Grade ≥3 TEAEs and lack of a favorable benefit/risk ratio[b]
- Further dose assessment is ongoing at three doses: 4.8, 5.6 and 6.4 mg/kg

Data cutoff: July 14, 2023.

[a]Grade 5 ILD. [b]6/15 (40.0%) patients in the 8.0-mg/kg OVC cohort experienced serious and Grade ≥3 TEAEs.

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; OVC, ovarian cancer; TEAE, treatment-emergent adverse event.

Most common (≥10%) treatment-related TEAEs

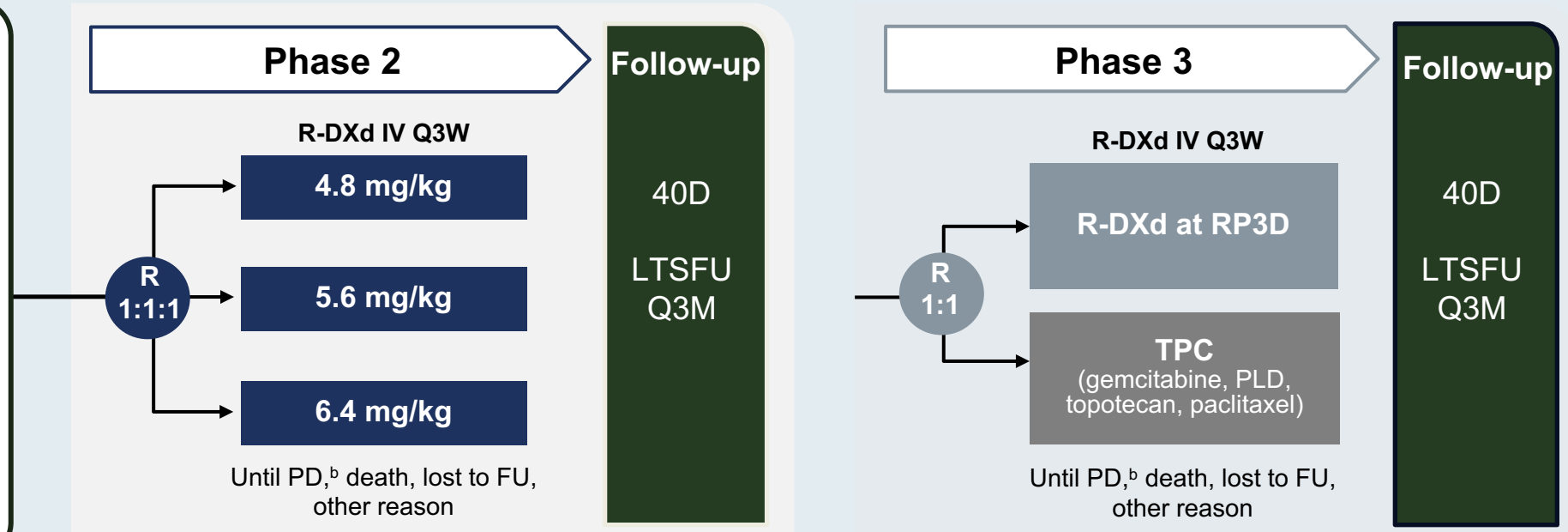
Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)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

Moore K, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting; 20-24 October 2023; Madrid, Spain.

REJOICE-Ovarian01/GOG-3096: Phase 2/3 Randomized Study of R-DXd in Platinum-Resistant EOC

Key eligibility criteria:

- High-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer
- 1−3 prior LOT (inc. bevacizumab)
- Platinum-resistant disease
- Prior MIRV if high FRα[a]
- ECOG PS 0−1
- No prior CDH6-targeting agents or ADCs with linked TOPO I inhibitor
- Patients with primary platinum-refractory disease are not eligible



Stratification:

- Number of prior LOT (1 vs 2/3)
- CDH6 expression (high vs low)
- TPC (paclitaxel vs others; *Ph 3 only*)

Primary endpoint:

- ORR per BICR[b]

Key secondary endpoints:

- ORR per inv[b]
- DOR

Primary endpoints:

- ORR per BICR[b]
- PFS per BICR[b]

Key secondary endpoints:

- OS
- QOL

NCT06161025

NCT06161025. Accessed from: https://clinicaltrials.gov/study/NCT06161025?term=NCT06161025&rank=1.

Glucocorticoid receptor antagonist

Primary Endpoint Met in the Pivotal Phase 3 ROSELLA Trial of Relacorilant Patients with Platinum-Resistant Ovarian Cancer

March 31, 2025 at 8:00 AM EDT

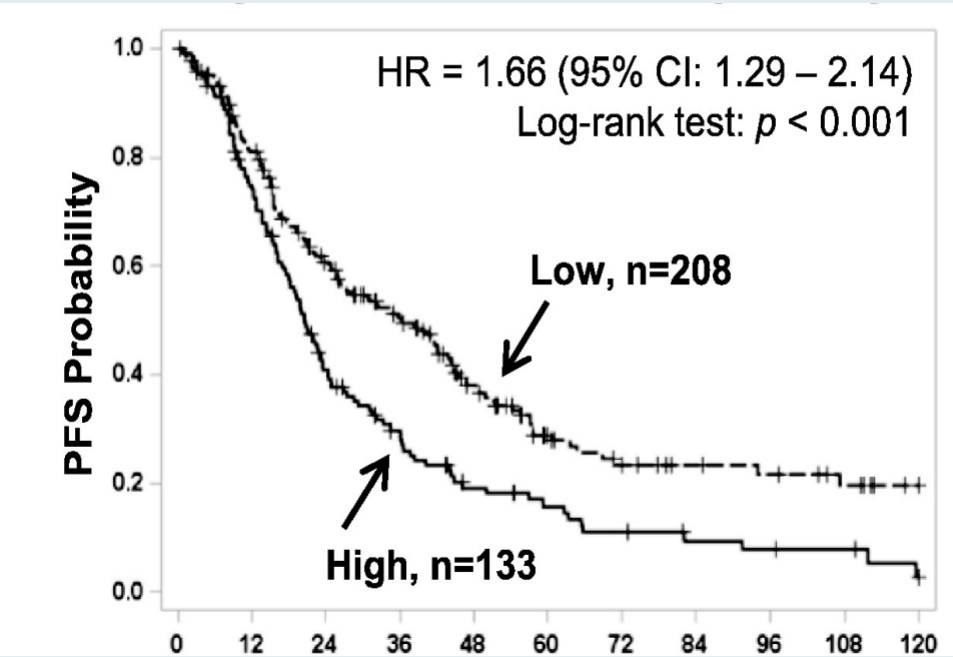
- Relacorilant plus nab-paclitaxel improved progression-free and overall survival and did not increase side effect burden
- Results will support a New Drug Application (NDA) in the United States and a Marketing Authorization Application (MAA) in Europe
- Relacorilant plus nab-paclitaxel has the potential to become a new standard of care for patients with platinum-resistant ovarian cancer

ROSELLA, a pivotal Phase 3 trial of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer, met its primary endpoint of improved progression-free survival, as assessed by blinded independent central review (PFS-BICR).

In ROSELLA, patients treated with relacorilant in addition to nab-paclitaxel chemotherapy experienced a 30 percent reduction in risk of disease progression compared to patients treated with nab-paclitaxel alone (hazard ratio: 0.70; p-value: 0.008). Their median PFS-BICR was 6.5 months, compared to 5.5 months in patients who received nab-paclitaxel alone. At an interim evaluation of overall survival (OS), patients treated with relacorilant plus nab-paclitaxel had a significant improvement in OS, with a median OS of 16.0 months, compared to 11.5 months for patients receiving nab-paclitaxel alone (hazard ratio: 0.69; p-value: 0.012). Relacorilant was well-tolerated and no new safety signals were observed. As was the case in the company's Phase 2 trial, safety and tolerability were comparable in the two groups.

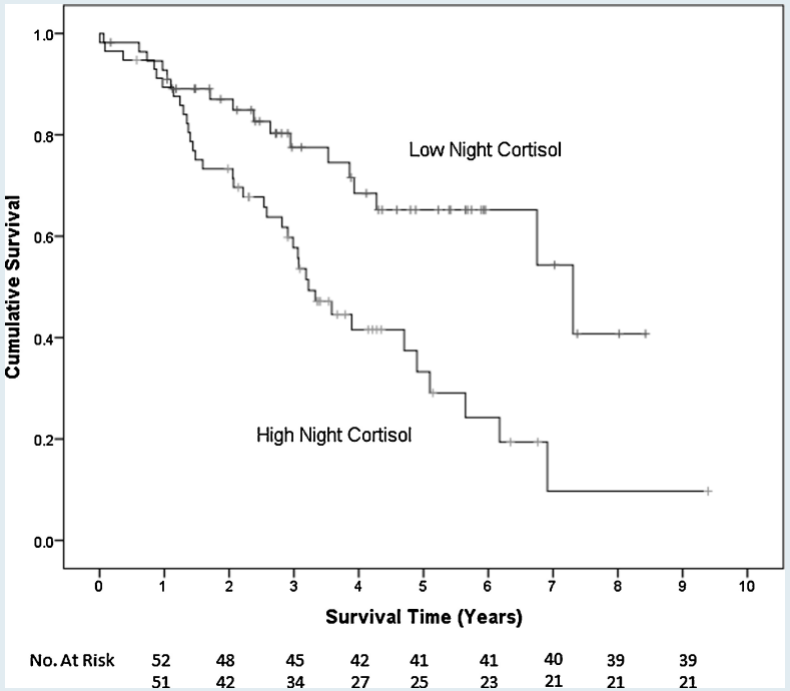
https://ir.corcept.com/news-releases/news-release-details/primary-endpoint-met-corcepts-pivotal-phase-3-rosella-trial

Outcomes are Poorer in Patients with Ovarian Cancer when GR is High or when Nocturnal Cortisol is High



Median PFS was 15 months shorter in patients with high tumor GR expression compared to those with low tumor GR expression (p < 0.001)

Veneris, Gynecol Oncol 2017

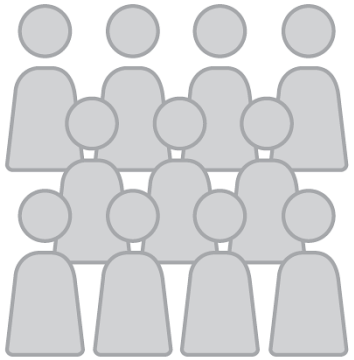


Median survival for patients with **high nocturnal cortisol (3.3 years**, 95% CI=2.6, 3.8 years) vs. with **low nocturnal cortisol (7.3 years**, 95% CI =3.8, 10.8 years). Cox regression adjusted for covariates indicates that patients with lower nocturnal cortisol had longer survival times (*p*=.021).

Schrepf, Psychoneuroendocrinology, 2015

Relacorilant + Nab-paclitaxel Phase 2 Study Design

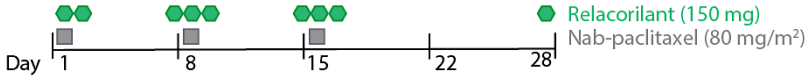
178 patients with ovarian, primary peritoneal, or fallopian tube cancer



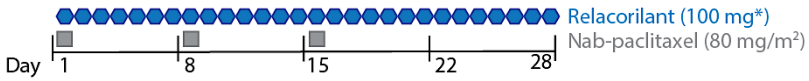
Randomized 1:1:1

- Treatment-free interval after platinum-based therapy <6 mo or disease progression during platinum-based therapy
- Measurable or non-measurable disease by RECIST v1.1
- Up to 4 prior chemotherapeutic regimens

INTERMITTENT relacorilant + nab-paclitaxel
N=60

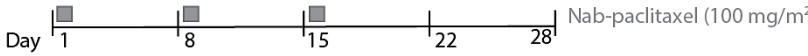


CONTINUOUS relacorilant + nab-paclitaxel
N=58



*Discretionary relacorilant escalation to 150 mg allowed

COMPARATOR nab-paclitaxel
N=60



CONTINUOUS vs COMPARATOR

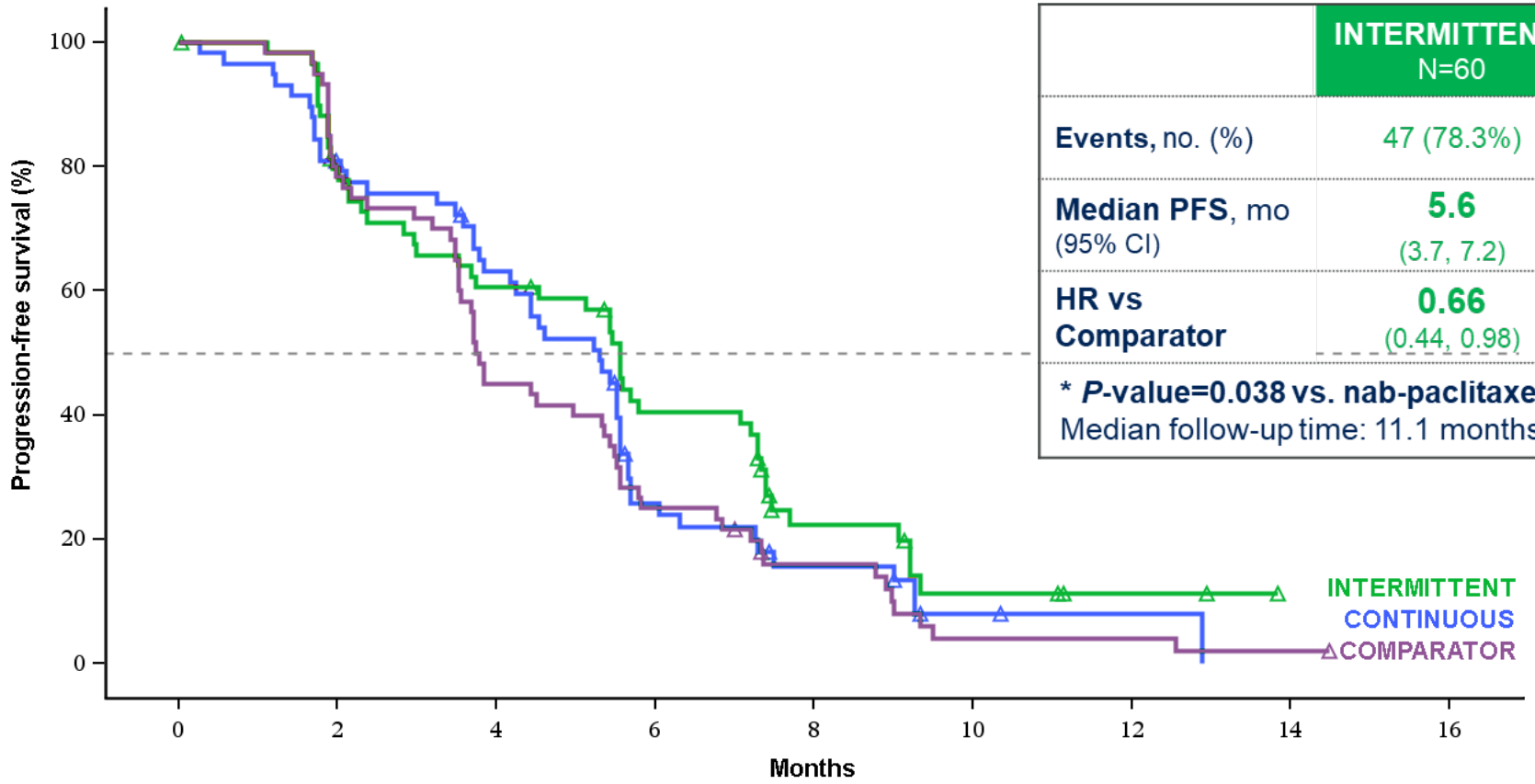
INTERMITTENT vs COMPARATOR

Primary endpoint:
- Progression-free survival (PFS) by RECIST v1.1

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

D Lorusso Previously reported at ESMO 2021

INTERMITTENT Relacorilant + Nab-paclitaxel Improved Progression-Free Survival



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

* ***P*-value=0.038 vs. nab-paclitaxel alone**; no multiplicity adjustment

Median follow-up time: 11.1 months Data cutoff: March 22, 2021

CONTINUOUS	58 (0/0)	46 (11/11)	35 (10/21)	13 (20/41)	7 (5/46)	2 (3/49)	1 (0/49)	0 (1/50)	
INTERMITTENT	60 (0/0)	46 (12/12)	35 (11/23)	22 (11/34)	9 (9/43)	4 (4/47)	2 (0/47)	0 (0/47)	
COMPARATOR	60 (0/0)	47 (13/13)	27 (20/33)	15 (12/45)	8 (5/50)	2 (6/56)	2 (0/56)	1 (1/57)	0 (0/57)

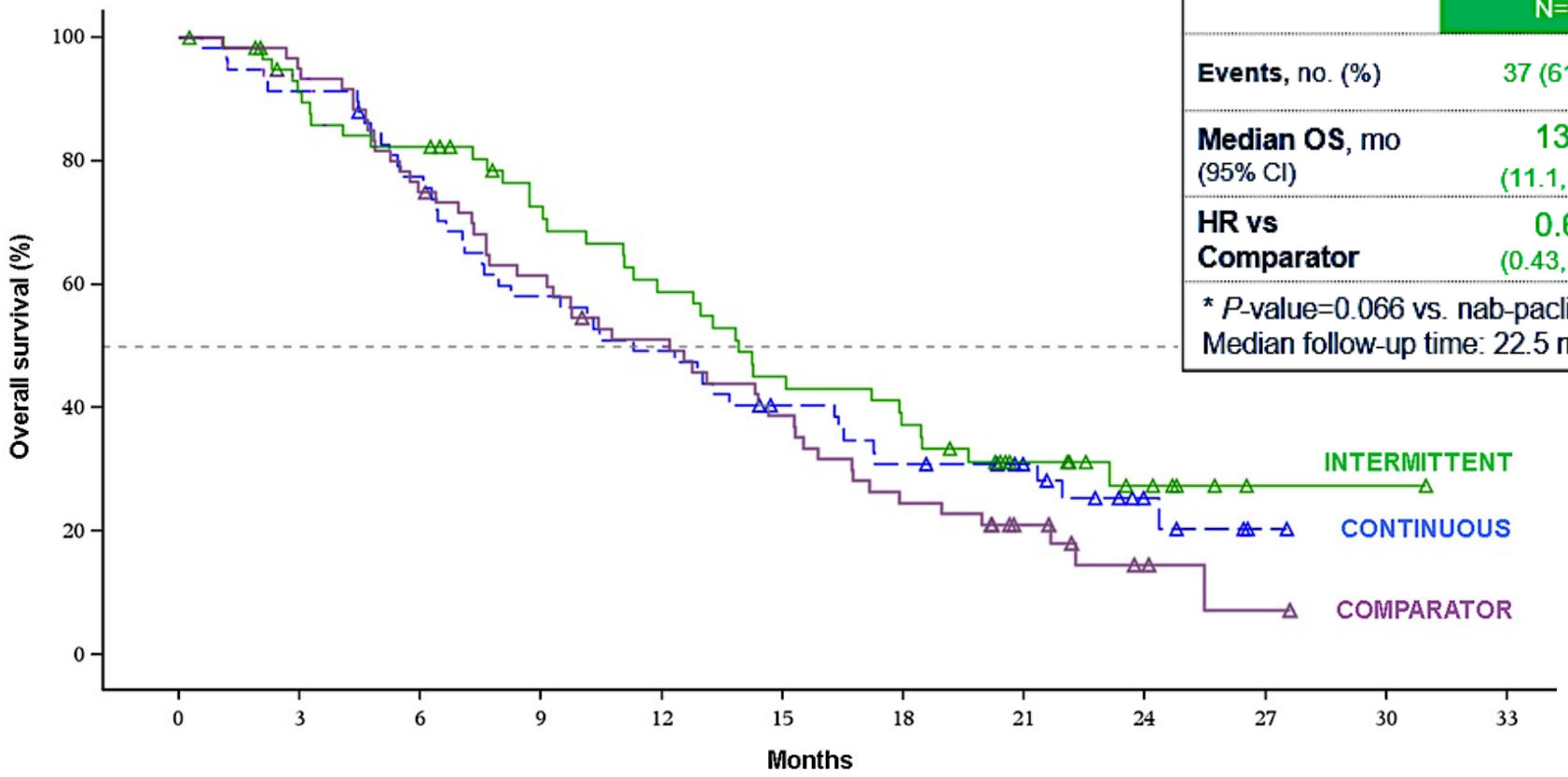
While ORR was similar, **DoR** was **significantly improved in the INTERMITTENT** vs the COMPARATOR arm.

HR 0.36, 95% CI (0.16-0.77), *P*=0.006

CONTINUOUS: once-daily relacorilant + nab-paclitaxel; INTERMITTENT: intermittent relacorilant + nab-paclitaxel; COMPARATOR: nab-paclitaxel monotherapy

D Lorusso Previously reported at ESMO 2021

INTERMITTENT Relacorilant + Nab-Paclitaxel Improved OS



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

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

CONTINUOUS	58 (0/0)	53 (5/5)	44 (8/13)	33 (11/24)	28 (5/29)	21 (5/34)	16 (5/39)	12 (0/39)	5 (2/41)	1 (1/42)	0 (0/42)	
INTERMITTENT	60 (0/0)	51 (5/5)	46 (5/10)	37 (5/15)	30 (7/22)	23 (7/29)	19 (4/33)	11 (3/36)	6 (1/37)	1 (0/37)	1 (0/37)	0 (0/37)
COMPARATOR	60 (0/0)	57 (3/3)	45 (12/15)	36 (8/23)	29 (6/29)	22 (7/36)	14 (8/44)	8 (2/46)	3 (2/48)	1 (1/49)	0 (0/49)	

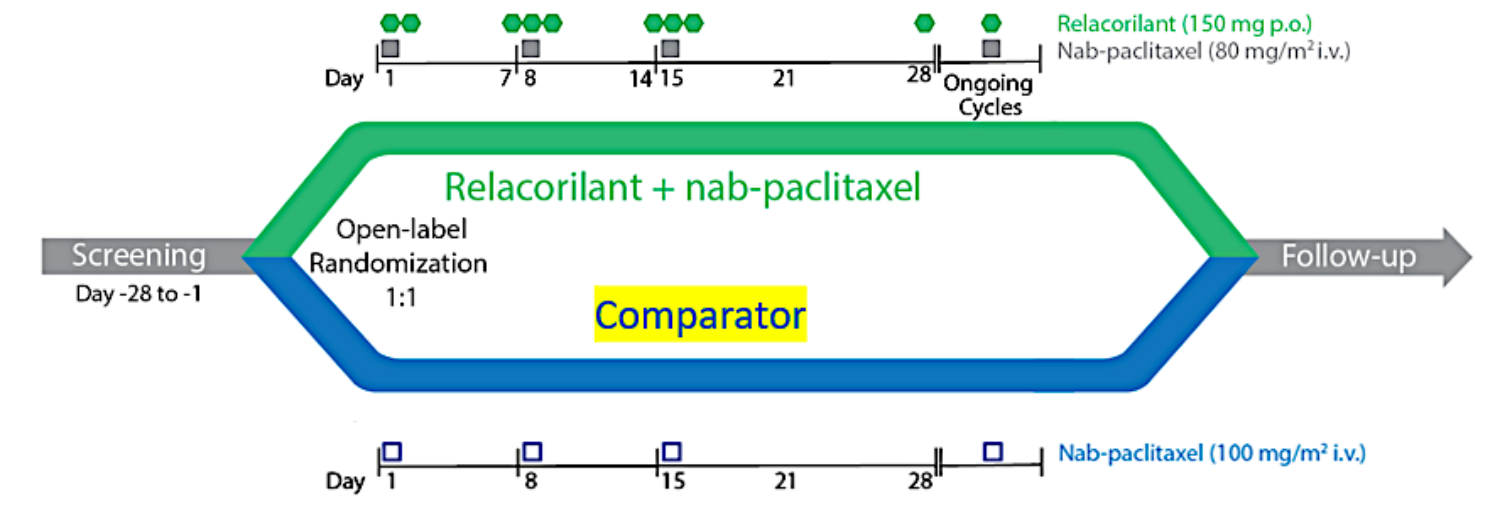
In the **INTERMITTENT arm, 27% of patients were still alive at 24 months** compared to **14% in the COMPARATOR arm**.

Trend toward **improved OS** consistent at interim and final analyses.

CONTINUOUS: once-daily relacorilant + nab-paclitaxel; INTERMITTENT: intermittent relacorilant + nab-paclitaxel; COMPARATOR: nab-paclitaxel monotherapy

D Lorusso Previously reported at ESMO 2021

ROSELLA Phase 3 Study Schema



Patient Population:

- HG serous, Endometrioid epithelial ovarian, primary peritoneal, or fallopian tube cancer
- Progression ≤ 6 months after last dose of plat-based therapy (exclude primary-platinum refractory)
- **Have received prior bevacizumab**

- **Primary Endpoint:**
  - **Progression free survival (BICR) per RECIST v1.1**
- **Secondary Endpoints:**
  - **Overall Survival**
  - **Progression-Free Survival (by INV) per RECIST v1.1**
  - **Overall Response Rate per RECIST v1.1, BOR**
  - **Duration of Response per RECIST v1.1**
  - **Clinical Benefit Rate per RECIST v1.1**
  - **Combined response according to RECIST v1.1 + GCIG criteria**
- **Safety Endpoints:**
  - **QOL, CA125, PD, PK**

BICR: Blinded Independent Central Review; INV: Investigator; RECIST: Response Evaluation Criteria in Solid Tumors;
GCIG: Gynecologic Cancer Intergroup

Collaborative Group Collaboration:

- Gynecologic Oncology Group (GOG)
- European Network of Gynecological Oncology Trial groups (ENGOT)

NCT05257408

Primary Endpoint Met in the Pivotal Phase 3 ROSELLA Trial of Relacorilant Patients with Platinum-Resistant Ovarian Cancer

March 31, 2025 at 8:00 AM EDT

- Relacorilant plus nab-paclitaxel improved progression-free and overall survival and did not increase side effect burden
- Results will support a New Drug Application (NDA) in the United States and a Marketing Authorization Application (MAA) in Europe
- Relacorilant plus nab-paclitaxel has the potential to become a new standard of care for patients with platinum-resistant ovarian cancer

ROSELLA, a pivotal Phase 3 trial of relacorilant plus nab-paclitaxel in patients with platinum-resistant ovarian cancer, met its primary endpoint of improved progression-free survival, as assessed by blinded independent central review (PFS-BICR).

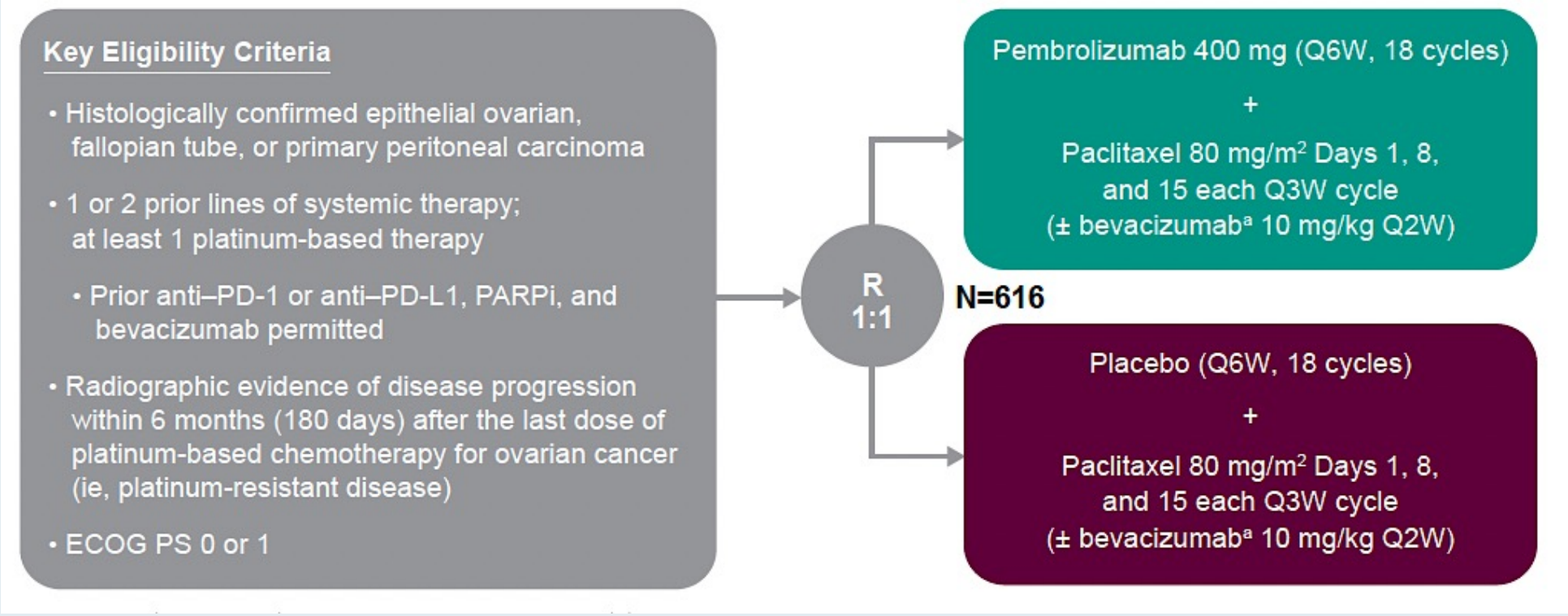
In ROSELLA, patients treated with relacorilant in addition to nab-paclitaxel chemotherapy experienced a 30 percent reduction in risk of disease progression compared to patients treated with nab-paclitaxel alone (hazard ratio: 0.70; p-value: 0.008). Their median PFS-BICR was 6.5 months, compared to 5.5 months in patients who received nab-paclitaxel alone. At an interim evaluation of overall survival (OS), patients treated with relacorilant plus nab-paclitaxel had a significant improvement in OS, with a median OS of 16.0 months, compared to 11.5 months for patients receiving nab-paclitaxel alone (hazard ratio: 0.69; p-value: 0.012). Relacorilant was well-tolerated and no new safety signals were observed. As was the case in the company's Phase 2 trial, safety and tolerability were comparable in the two groups.

https://ir.corcept.com/news-releases/news-release-details/primary-endpoint-met-corcepts-pivotal-phase-3-rosella-trial

Immune Therapy

A road for IO in PROC?

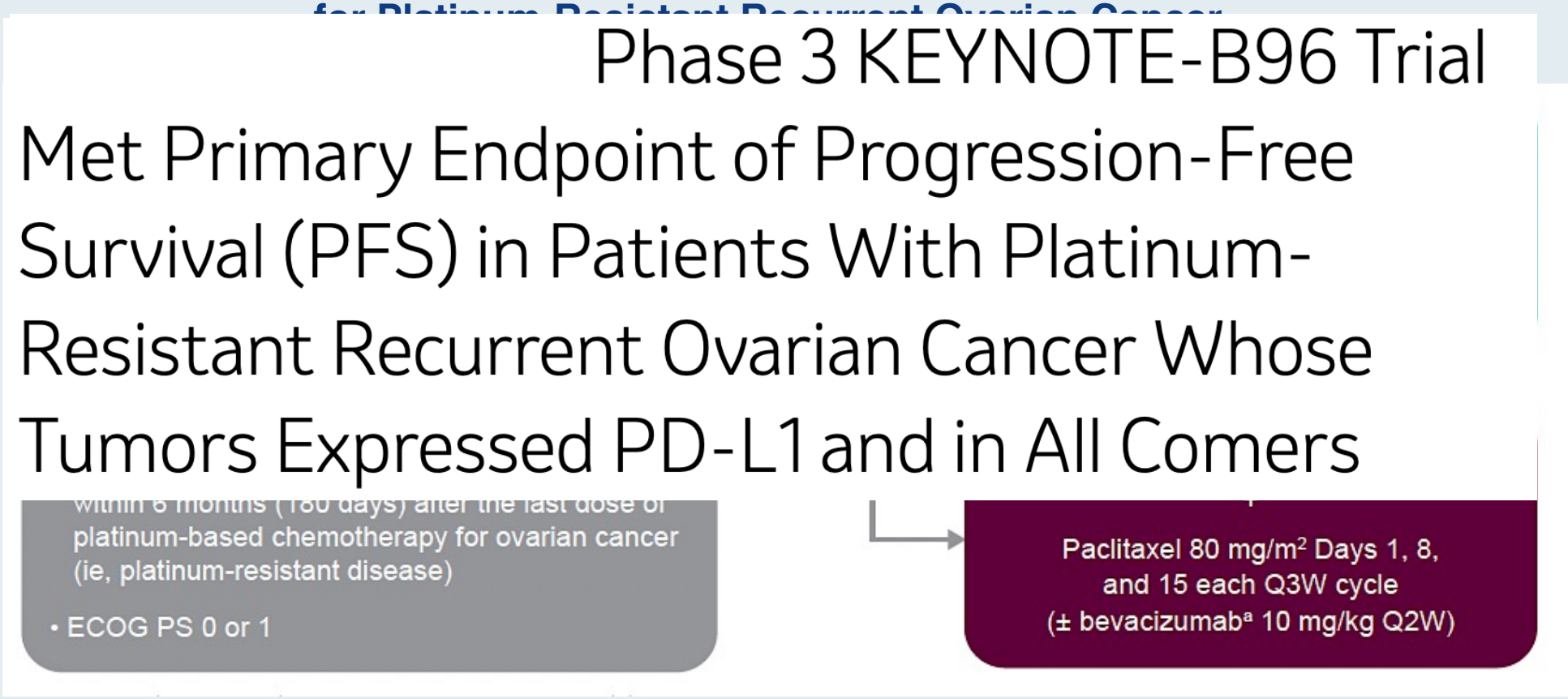
ENGOT-ov65/KEYNOTE-B96: Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo Plus Paclitaxel With Optional Bevacizumab for Platinum-Resistant Recurrent Ovarian Cancer



N. Colombo, ESGO 2022

A road for IO in PROC?

ENGOT-ov65/KEYNOTE-B96: Phase 3, Randomized, Double-Blind Study of Pembrolizumab Versus Placebo Plus Paclitaxel With Optional Bevacizumab

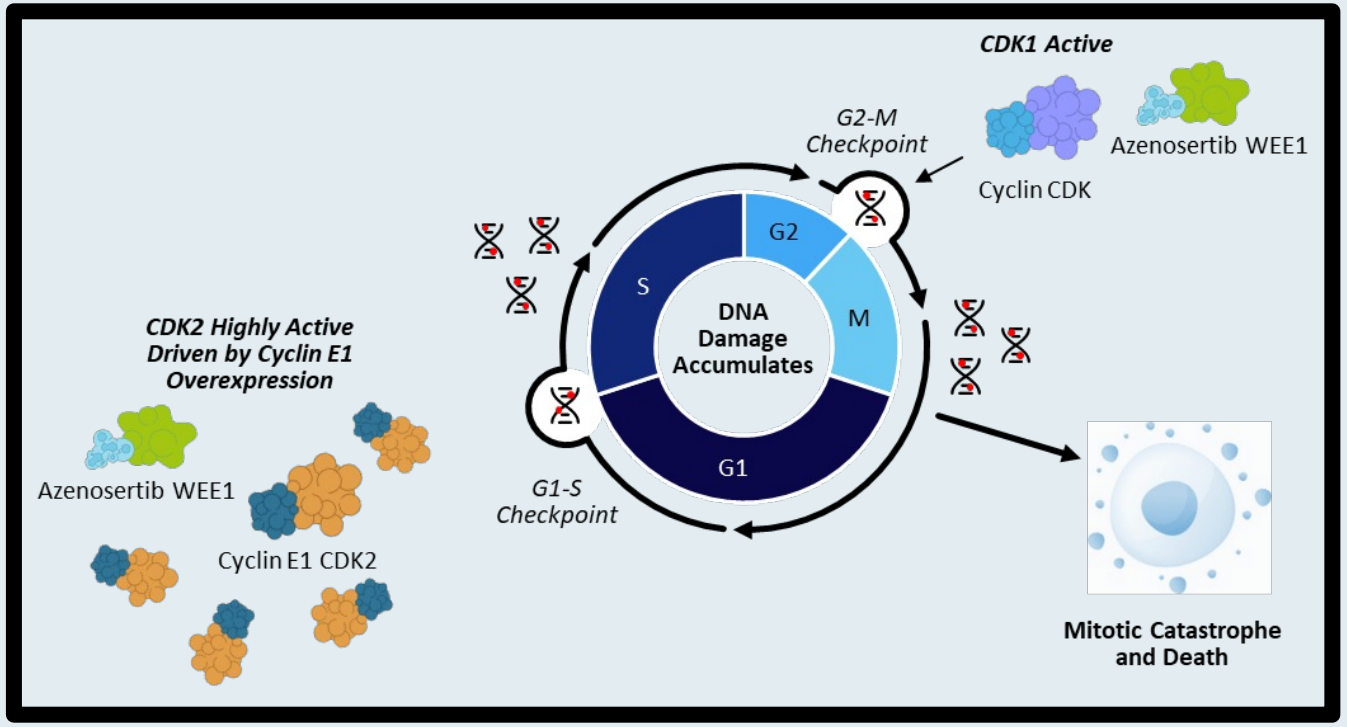


N. Colombo, ESGO 2022

What about the post ADC world?

Targeting WEE1 with Azenosertib Exploits Critical Cell Cycle Checkpoints that Cyclin E1 Overexpressing Cells Require for Survival

- Cyclin E1 protein overexpression results in cells moving prematurely from G1 to S, there by increasing reliance on the G2-M checkpoint to allow DNA repair[1,2]
- WEE1 is a master regulator of the cell cycle acting as a brake at G1-S and G2-M to allow DNA repair[3]
- Targeting WEE1 with azenosertib ultimately leads to mitotic catastrophe[4]



CDK, cyclin-dependent kinase; G1-S, Gap 1-Synthesis; G2-M, Gap 2-Mitosis; HGSOC, high-grade serous ovarian cancer.

1. Vriend LE, et al. *Biochim Biophys Acta*. 2013; 1836(2):227-335. **2.** Esposito F, et al. *Int J Mol Sci*. 2021;22(19):10689. **3.** Gorski JW, et al. Diagnostics (Basel). 2020;10(5):279. **4.** Kim D, et al. *NPJ Precis Oncol*. 2025;9(3).

F. Simpkins, SGO 2025

DENALI (GOG-3066): Phase 2, Open-Label, Multicenter Study of Azenosertib in PROC (Part 1 and 2)

Part 1b: Study design

Enrollment complete

Key eligibility criteria

- ✓ PROC
- ✓ 1-5 prior lines of therapy
- ✓ Prior bevacizumab
- ✓ **All comers** (irrespective Cyclin E1 status)

NCT05128825

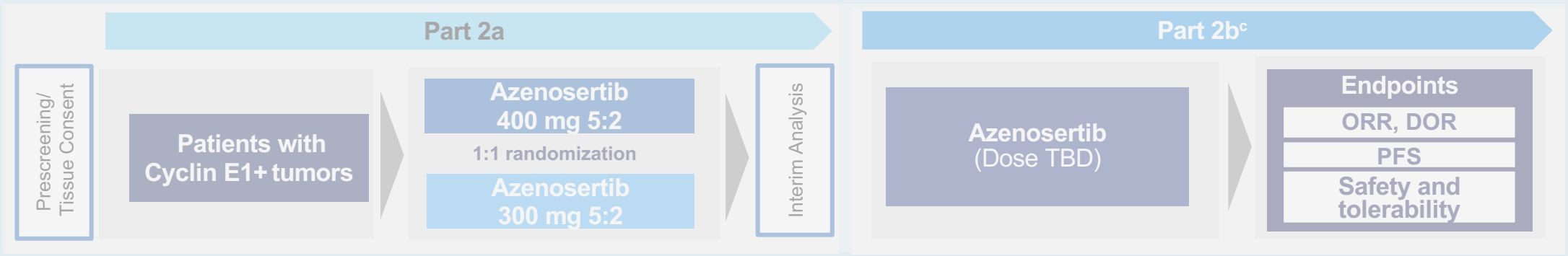
Enrollment (N=102)

Azenosertib 400 mg QD 5:2

Endpoints

- **Safety and tolerability**
- **ORR, DOR[a]**
- **PFS[b]**

Data cut-off Jan, 2025

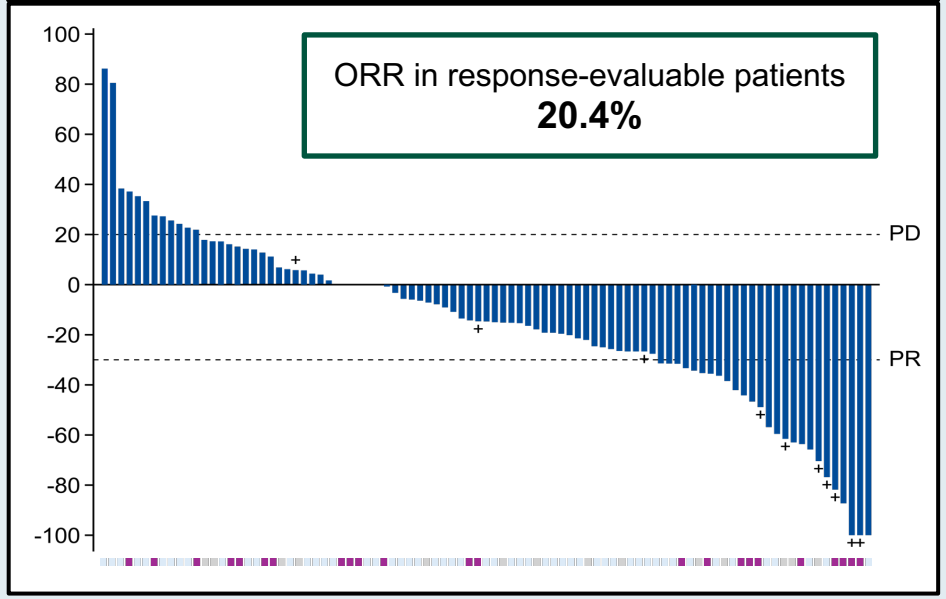


[a]Per RECIST v1.1 by ICR and investigator every 6 weeks until disease progression, death from any cause (ORR: up to 12 months; DOR: up to 60 months). [b]Per RECIST v1.1 by ICR and investigator every 6 weeks until disease progression, death from any cause up to 12 months. [c]Subject to FDA feedback. 5:2, 5 days on, 2 days off; DOR, duration of response; ICR, independent committee review; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TBD, to be determined. ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05128825

F. Simpkins, SGO 2025

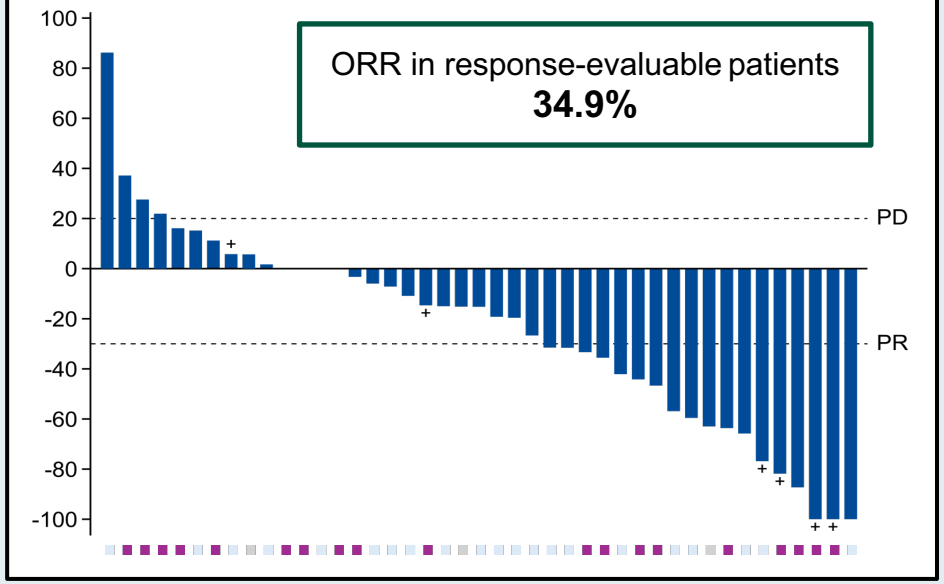
DENALI (GOG-3066) Part 1b: Cyclin E1+ by IHC is a Biomarker Predicting Response to Azenosertib

All treated patients[a] (N=102)



Cyclin E1 IHC+

Biomarker positive: Cyclin E1 IHC[b] (n=48)



+ Treatment ongoing

CCNE1 Status:

- Amplified
- Non-amplified
- Not evaluable

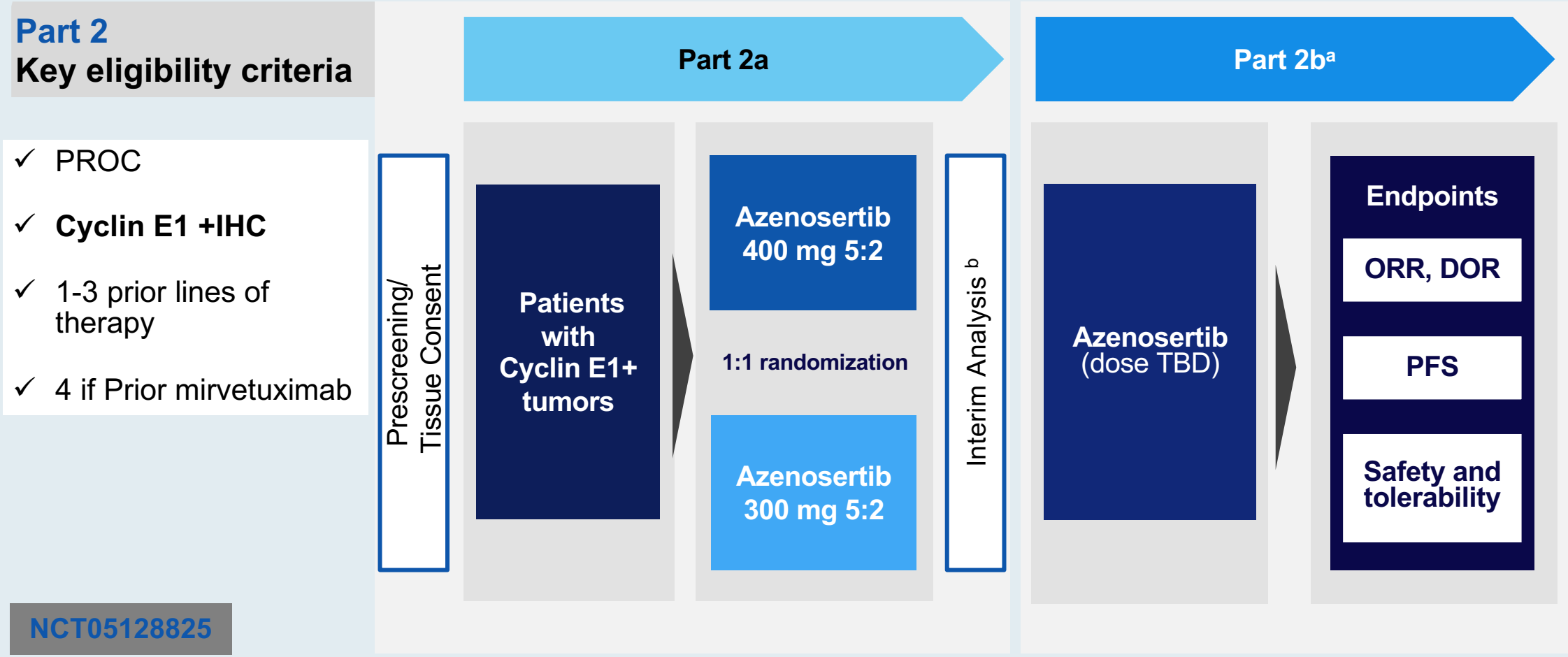
	All treated patients (N=102)
ORR in response-evaluable[c] patients, % (n/N; 95% CI)	**20.4** (19/93; 12.8-30.1)
ORR, ITT % (n/N; 95% CI)	**18.6** (19/102; 11.6-27.6)

	Cyclin E1 IHC+ (n=48)
ORR in response-evaluable[c] patients, % (n/N; 95% CI)	**34.9** (15/43; 21.0-50.9)
ORR, ITT % (n/N; 95% CI)	**31.3** (15/48; 18.7-46.3)

Data cutoff date: January 13, 2025. [a]Full analysis set: all treated patients. [b]Biomarker dataset: all treated patients with evaluable tissue and Cyclin E1 IHC status. [c]Includes patients who received at least one post-treatment scan. Amp, amplified; IHC, immunohistochemistry; ORR, objective response rate; PD, progressive disease; PR, partial response.

F. Simpkins, SGO 2025

DENALI (GOG-3066): Phase 2, Open-Label, Multicenter Study Investigating Azenosertib in Cyclin E1+ PROC



[a]Subject to FDA feedback. [b]Enrollment will continue through the interim analysis
5:2, 5 days on, 2 days off; DOR, duration of response; FRa, folate receptor alpha; ORR, objective response rate; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; TBD, to be determined.
ClinicalTrials.gov: https://clinicaltrials.gov/study/NCT05128825.

F. Simpkins, SGO 2025

Key Takeaways

- **ADCs are here to stay**
- **Sequencing, cross resistance, biomarker status continues to be unanswered**
- **Positive Phase 3 trials will markedly impact the PROC landscape**
  - **Sequencing**
  - **Clinical trial design**
  - **Weekly taxane + ?**
    - **Bev**
    - **Relacorilant**
    - **Pembro**
    - **Combination (e.g. BELLA -** NCT06906341**)**
    - **Other options**
- **What about the post ADC world?**

Case Presentation: 44-year-old woman with germline BRCA1 mutation and HGSOC receives treatment in 2018 with chemotherapy followed by olaparib maintenance and recurrence 1 year ago

Dr Lyndsay Willmott (Phoenix, Arizona)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

In which patients, if any, would you attempt to rechallenge with a PARP inhibitor after disease progression on up-front PARP inhibitor maintenance?

How long do you continue PARP inhibitor maintenance for patients with recurrent advanced ovarian cancer?

What do you quote patients in terms of the risk of AML/MDS associated with PARP inhibitor therapy? Does this risk increase with longer exposure?

Case Presentation: 78-year-old woman with germline BRCA1 mutation and recurrent folate receptor alpha-positive HGSOC receives mirvetuximab soravtansine with CR but develops interstitial pneumonitis

Dr Spencer Bachow (Boca Raton, Florida)

Questions for the Faculty

How long would you continue mirvetuximab soravtansine for this patient who is in a complete response?

How often do patients receiving mirvetuximab soravtansine develop toxicity resulting in discontinuation? What are the most common toxicities that prompt you to discontinue mirvetuximab soravtansine?

What degree of interstitial lung disease/pneumonitis would prompt you to permanently discontinue mirvetuximab soravtansine? Is this the same paradigm that you employ for T-DXd?

Do you have any tricks of the trade for mitigating and managing the ocular toxicities associated with mirvetuximab soravtansine?

Agenda

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

MODULE 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr O'Malley

MODULE 3: Role of HER2-Targeted Therapy in Advanced OC, Endometrial Cancer (EC) and Other Gynecologic Cancers — Dr Santin

MODULE 4: First-Line Therapy for Advanced EC — Dr Westin

MODULE 5: Current Therapeutic Options for R/R EC; Novel Investigational Strategies for Newly Diagnosed and Recurrent Disease — Dr Salani

Role of HER2-Targeted therapy in Advanced Gynecologic Cancers

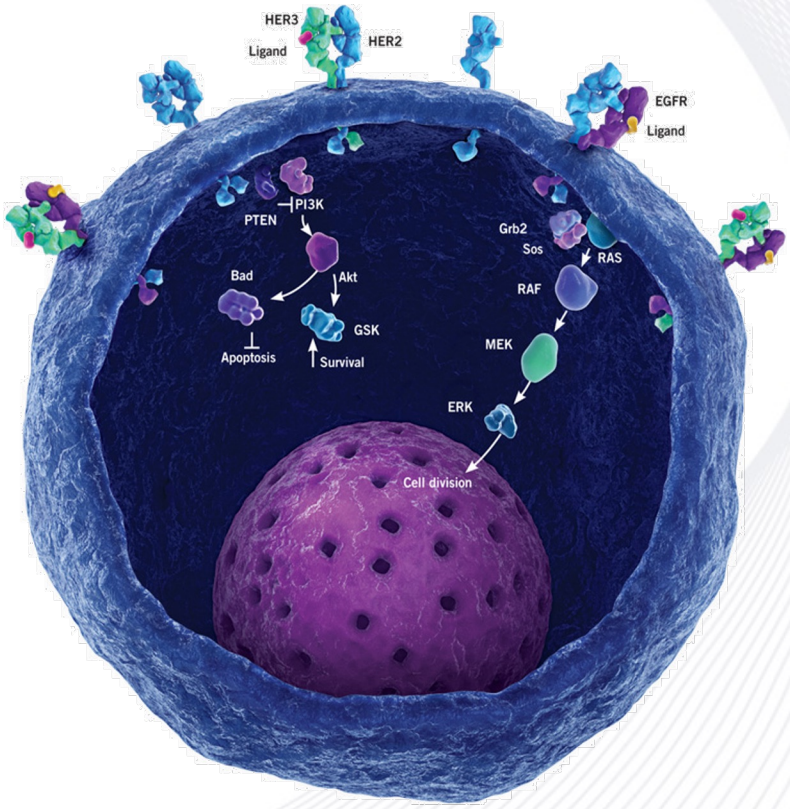
Alessandro D. Santin, MD
Professor of Gynecologic Oncology
Department of Obstetrics, Gynecology & Reproductive Sciences
Yale University School of Medicine
New Haven, CT

HER2/neu in Gynecologic Cancers

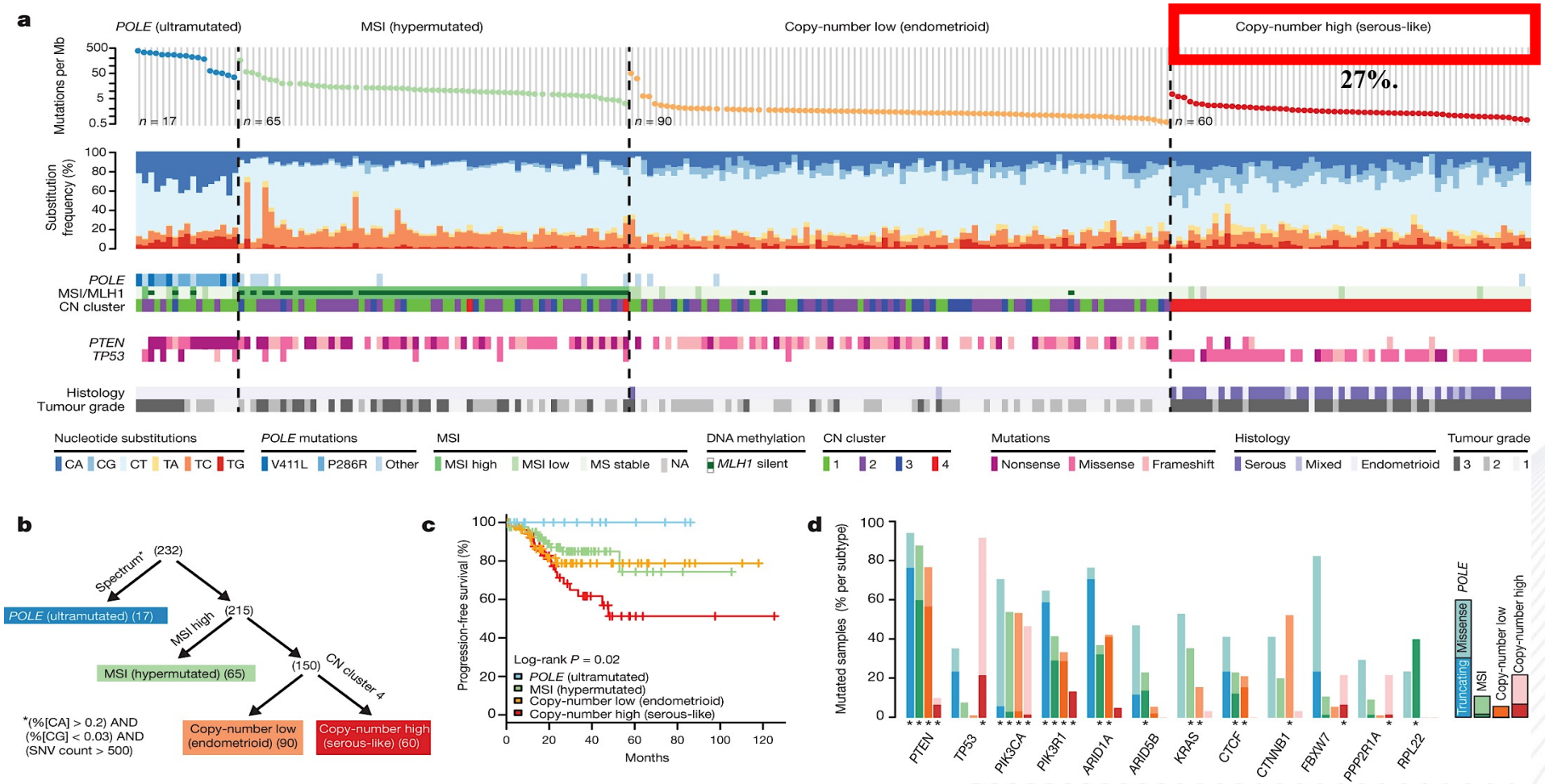
- The Human Epidermal Growth Factor Type II receptor (i.e., HER2/neu, encoded by the c-ErbB2 gene) is a transmembrane RECEPTOR protein including an **extracellular** ligand-binding domain, **a membrane spanning region** and an **intracellular** TYROSINE KINASE domain.

- HER2/neu functions as a **preferred partner for heterodimerisation** with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and thus plays an important role in coordination of the complex c-ErbB2 signaling network that is responsible for regulating cell growth and differentiation.

- HER2/neu overexpression is thought to result in the **tyrosine kinase becoming constitutively activated** causing dysregulated gene transcription through activation of downstream protein pathways such as the PIK3CA/AKT/mTOR and RAS/RAF/MAPK.

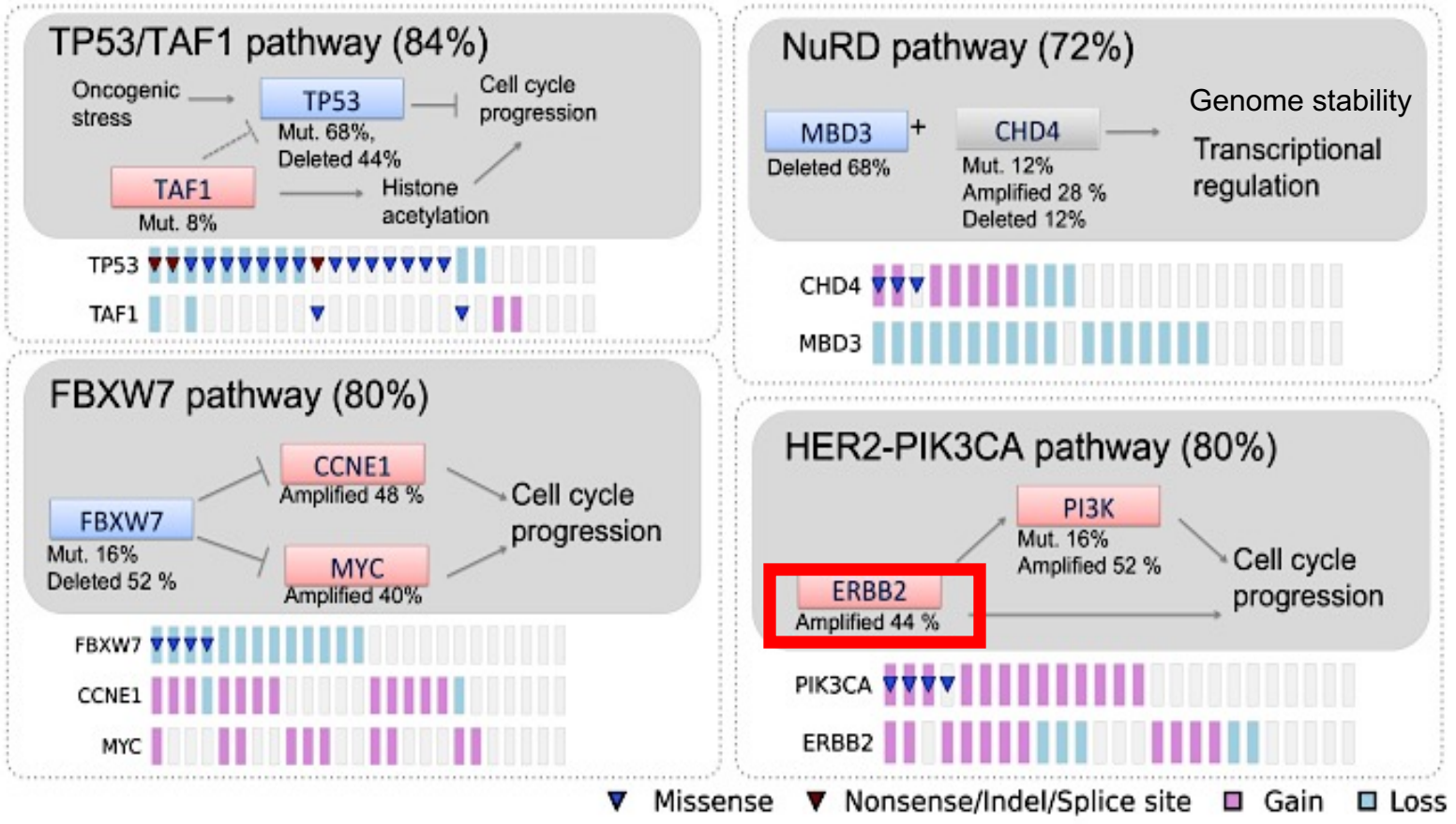


Frequency of HER2 expression amplification/mutations among Uterine Cancers



Levine DA. Nature 2013

Incidence of HER2 amplification in USC



PNAS

Landscape of somatic single-nucleotide and copy-number mutations in uterine serous carcinoma

Siming Zhao[a], Murim Choi[a], John D. Overton[a], Stefania Bellone[b], Dana M. Roque[b], Emiliano Cocco[b], Federica Guzzo[b], Diana P. English[b], Joyce Varughese[b], Sara Gasparrini[b], Ileana Bortolomai[b], Natalia Buza[c], Pei Hui[c], Maysa Abu-Khalaf[d], Antonella Ravaggi[e], Eliana Bignotti[e], Elisabetta Bandiera[e], Chiara Romani[e], Paola Todeschini[e], Renata Tassi[e], Laura Zanotti[e], Luisa Carrara[e], Sergio Pecorelli[e], Dan-Arin Silasi[b], Elena Ratner[b], Masoud Azodi[b], Peter E. Schwartz[b], Thomas J. Rutherford[b], Amy L. Stiegler[f], Shrikant Mane[a], Titus J. Boggon[f], Joseph Schlessinger[f], Richard P. Lifton[a,1], and Alessandro D. Santin[b]

[a]Department of Genetics, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510; [b]Departments of Obstetrics, Gynecology, and Reproductive Sciences, [c]Pathology, [d]Internal Medicine and Oncology, and [f]Pharmacology, Yale University School of Medicine, New Haven, CT 06510; and [e]Department of Obstetrics, and Gynecology, "Angelo Nocivelli" Institute of Molecular Medicine, University of Brescia, 25123 Brescia, Italy

Zhao S. PNAS 2013

Incidence of HER2 amplification in Uterine and Ovarian Carcinosarcomas (CS)

PNAS 130.132.173.125

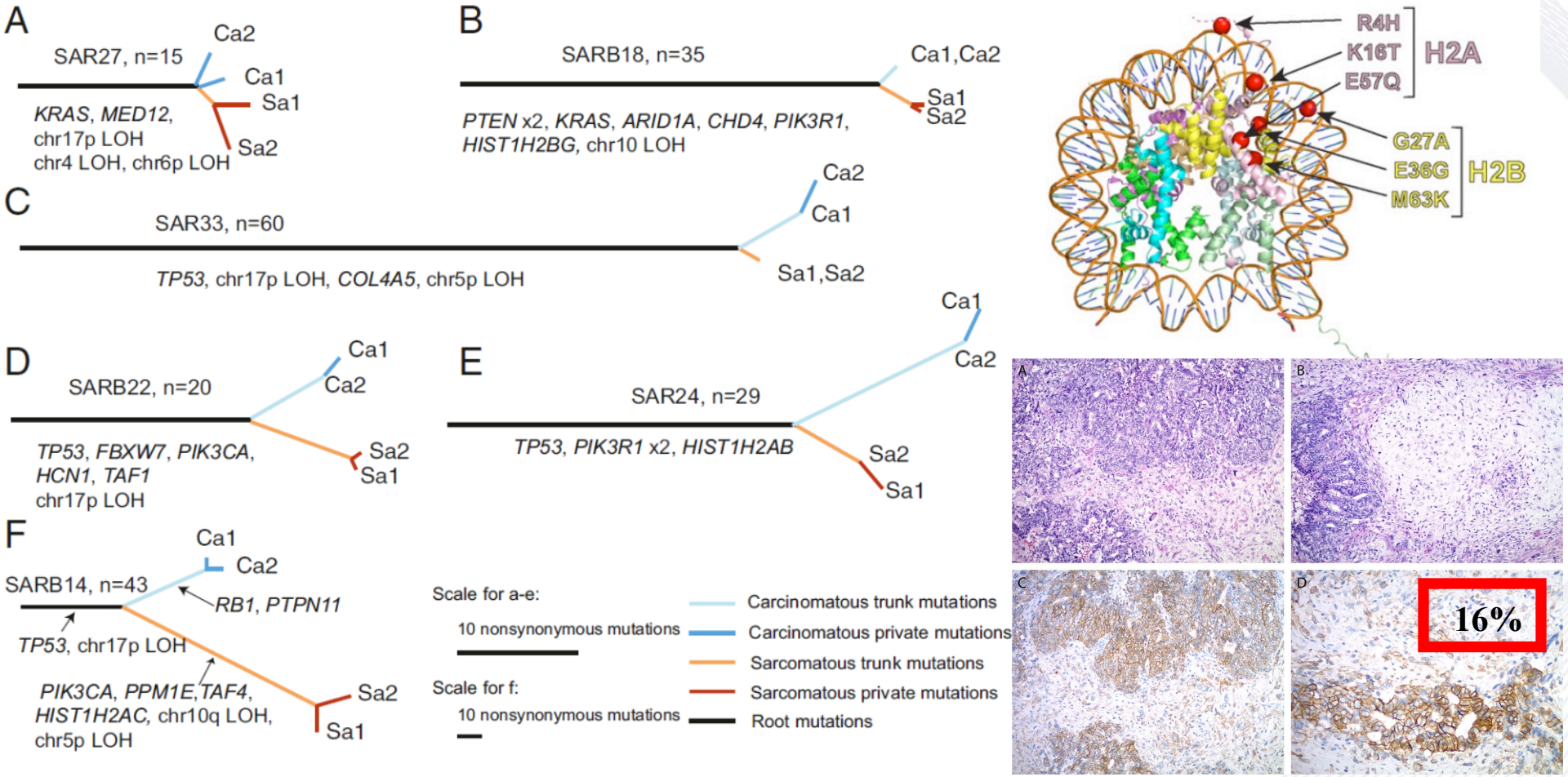
Mutational landscape of uterine and ovarian carcinosarcomas implicates histone genes in epithelial–mesenchymal transition

Siming Zhao[a,b], Stefania Bellone[c], Salvatore Lopez[c], Durga Thakral[a,b], Carlton Schwab[c], Diana P. English[c], Jonathan Black[c], Emiliano Cocco[c], Jungmin Choi[a,b], Luca Zammataro[c], Federica Predolini[c], Elena Bonazzoli[c], Mark Bi[a,b], Natalia Buza[d], Pei Hui[d], Serena Wong[d], Maysa Abu-Khalaf[e], Antonella Ravaggi[f], Eliana Bignotti[f], Elisabetta Bandiera[f], Chiara Romani[f], Paola Todeschini[f], Renata Tassi[f], Laura Zanotti[f], Franco Odicino[f], Sergio Pecorelli[f], Carla Donzelli[g], Laura Ardighieri[g], Fabio Facchetti[g], Marcella Falchetti[g], Dan-Arin Silasi[c], Elena Ratner[c], Masoud Azodi[c], Peter E. Schwartz[c], Shrikant Mane[a,b], Roberto Angioli[h], Corrado Terranova[h], Charles Matthew Quick[i], Babak Edraki[j], Kaya Bilgüvar[a,b], Moses Lee[k], Murim Choi[k], Amy L. Stiegler[l], Titus J. Boggon[l], Joseph Schlessinger[l], Richard P. Lifton[a,b,m,1], and Alessandro D. Santin[c]

[a]Department of Genetics, Yale University School of Medicine, New Haven, CT 06510; [b]Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT 06510; [c]Department of Obstetrics, Gynecology & Reproductive Sciences, Yale University School of Medicine, New Haven, CT 06510; [d]Department of Pathology, Yale University School of Medicine, New Haven, CT 06510; [e]Internal Medicine & Oncology, Yale University School of Medicine, New Haven, CT 06510; [f]"Angelo Nocivelli" Institute of Molecular Medicine, Department of Obstetrics & Gynecology, University of Brescia, 25100 Brescia, Italy; [g]Department of Pathology, University of Brescia, 25100 Brescia, Italy; [h]Division of Gynecologic Oncology, Universita' Campus Bio-Medico di Roma, 00128 Rome, Italy, [i]Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, AR 72205; [j]Division of Gynecologic Oncology, John Muir Health Clinical Research Center, Concord, CA 94598; [k]Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul 110-799, Korea; [l]Department of Pharmacology, Yale University School of Medicine, New Haven, CT 06510; and [m]Laboratory of Human Genetics and Genomics, The Rockefeller University, New York, NY 10065

12238–12243 | PNAS | 25, 2016 | vol. 113 | no. 43

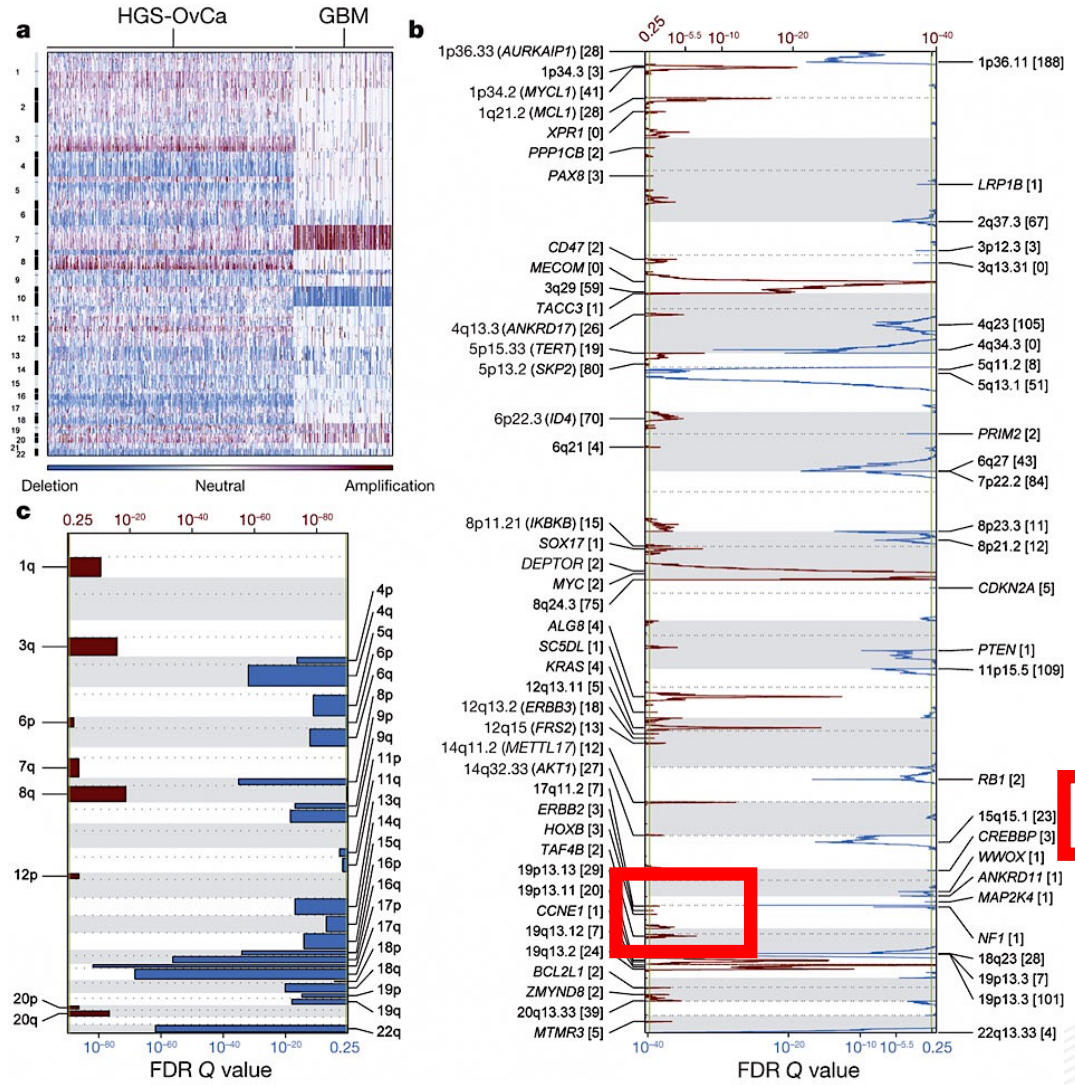
Incidence of HER2 amplification in CS



To resolve the evolutionary history and heterogeneity of CSs, we performed multi-region WES comprising four to five **carcinoma and sarcoma areas** from multiple tumors. Our NGS results **unequivocally demonstrated that carcinomatous and sarcomatous elements derive from a common precursor having mutations typical of carcinomas.** With the use of phylogenetic trees, we also demonstrated that divergence between carcinomatous and sarcomatous elements may happen at different time points during evolution of CSs, with some tumors diverging relatively late while others diverge early. Stable transgenic expression of The **Histone core genes H2A and H2B** in a uterine serous carcinoma cell line demonstrated that mutant, but not wild-type, histones **increased expression of markers of epithelial–mesenchymal transition (EMT)** as well as tumor migratory and invasive properties, suggesting a role in sarcomatous transformation.

Zhao S. PNAS 2016

HER2 amplification in Ovarian Cancer



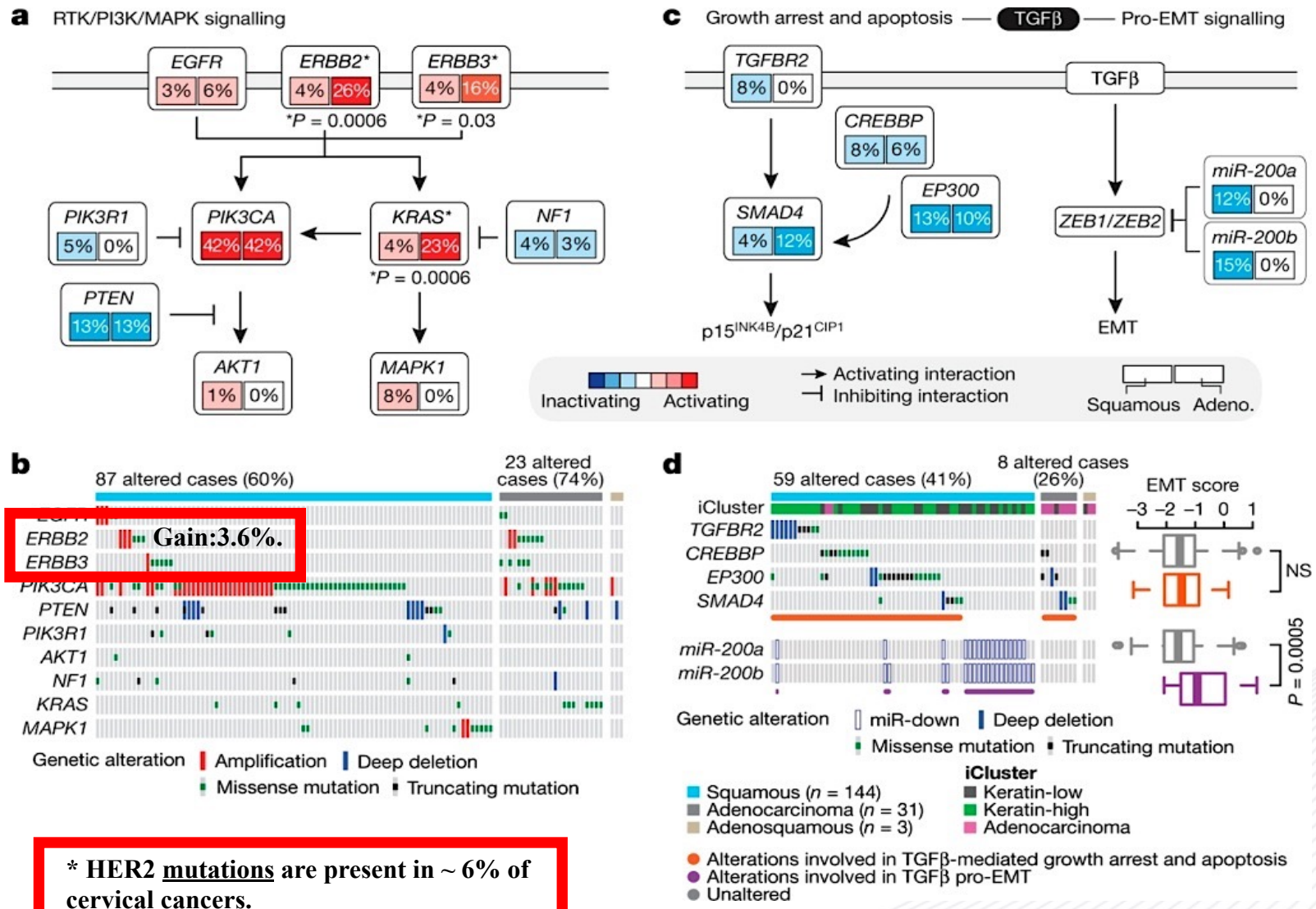
Genome copy number abnormalities

c-erbB2 CNV gains: ~5%

D Bell *et al. Nature* **474**, 609-615 (2011) doi:10.1038/nature10166

nature

HER2 amplification in Cervical Cancer



*** HER2 <u>mutations</u> are present in ~ 6% of cervical cancers.**

R D Burk *et al. Nature* **543,** 378–384 (2017) doi:10.1038/nature21386

Optimal source material for and timing of HER2 testing in advanced gynecologic cancers

HER2/neu testing Guidelines for Gynecologic tumors

Clinicians should request **HER2 testing** on tumor tissue in the biopsy or resection specimens (primary or metastasis) prior to the initiation of trastuzumab/ADC therapy.

When HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first, followed by ISH/FISH when IHC result is 2+ (equivocal). **Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH/FISH testing**.

Pathologists should identify and **mark areas with strongest intensity** of HER2 expression by IHC in the specimen for subsequent ISH/FISH scoring when required.

The prevalence of HER2 status may be discordant between the primary tumor and metastases in **approximately 25% of cases**, especially after treatment.

Per **NCCN guidelines** treating clinicians should offer **combination chemotherapy and HER2-targeted therapy** as the initial treatment for appropriate patients harboring HER2 positive advanced/recurrent USC and for any gynecologic cancer patient with recurrent tumors demonstrating HER2 2+/3+ expression by IHC.

Published research studies with the use of HER2-targeted strategies in advanced EC

GOG 181B

Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study.

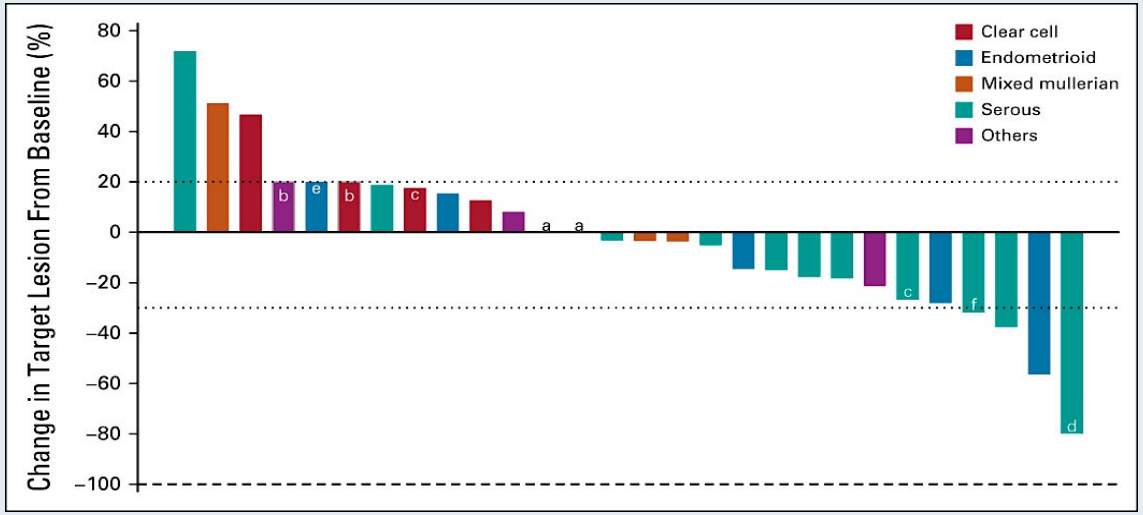
The trial opened in 2000 to women with IHC-positive tumors and was later amended to include women with FISH-positive tumors.

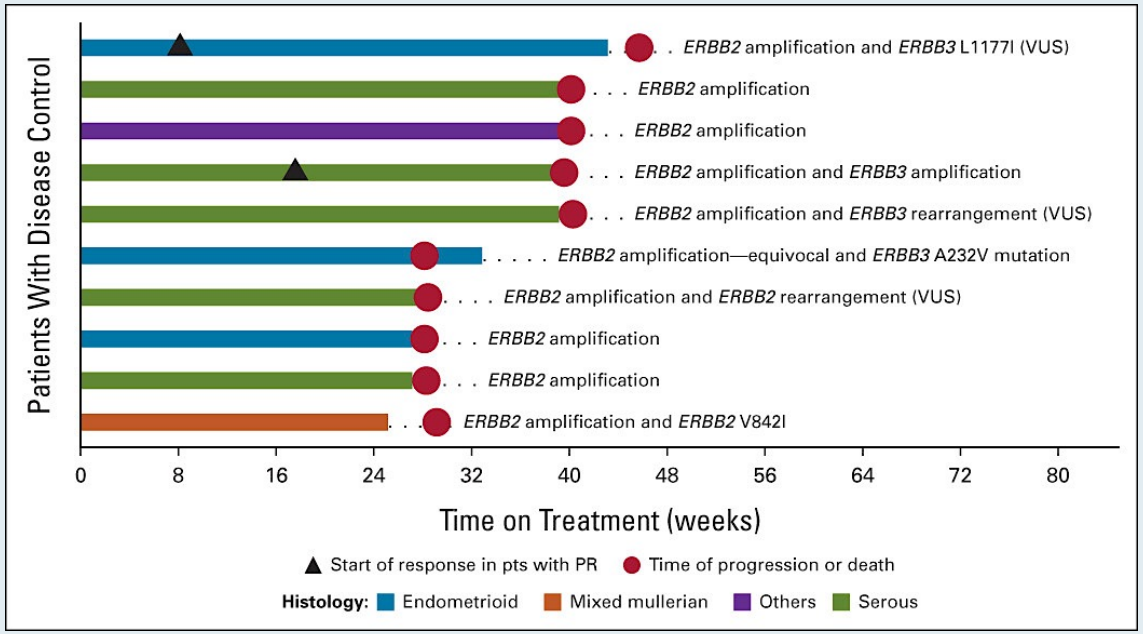
Of the 286 tumors centrally screened 11.5% (33) were HER2-amplified. Of the 33 evaluable patients only 52% has c-erbB2 amplification by FISH and the majority had endometrial histology. **No CR/PR detected.**

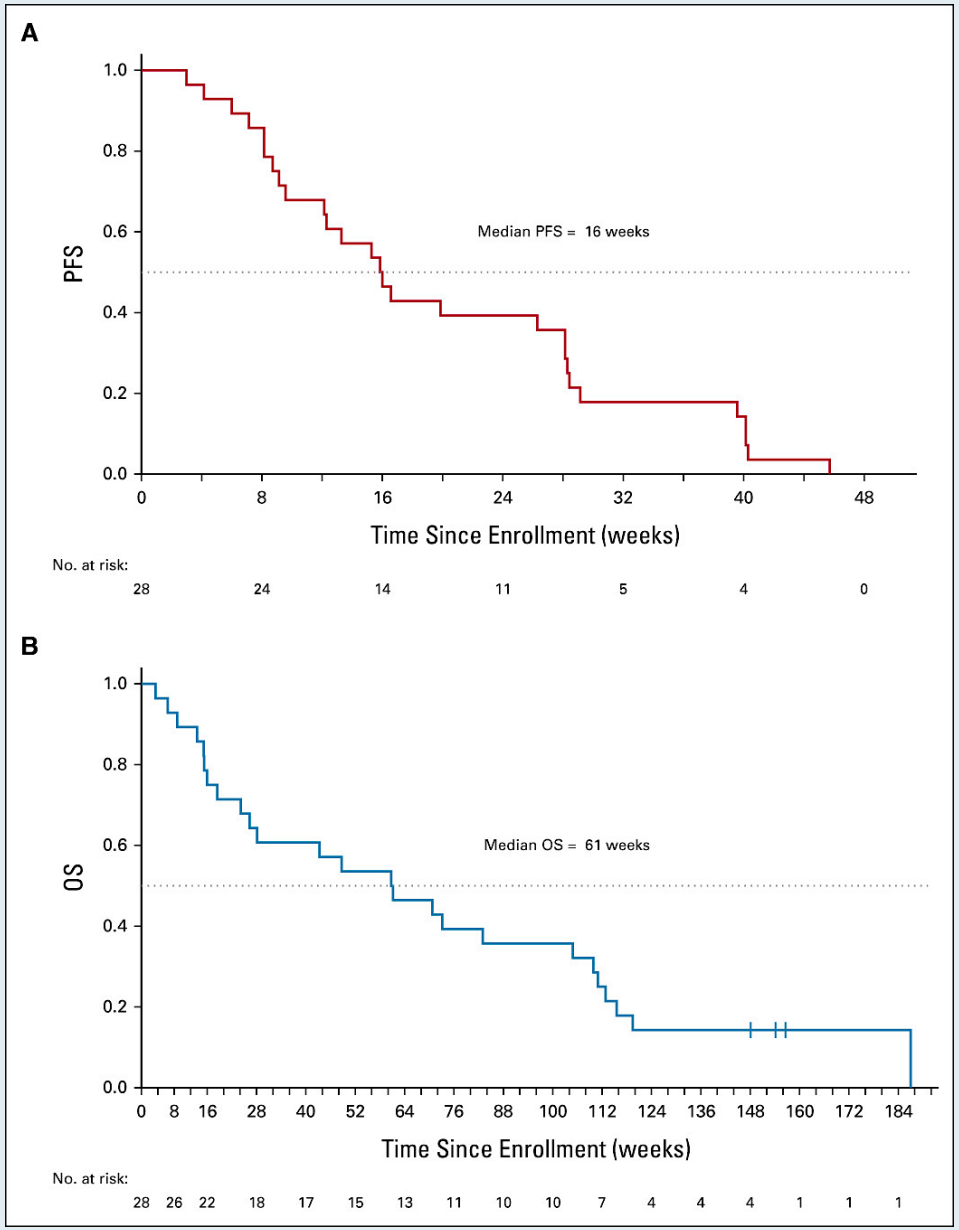
Conclusion: Trastuzumab as a single agent did not demonstrate activity against endometrial carcinomas with HER2 overexpression or HER2 amplification.

Fleming G., et al., PMID: 19840887 PMCID: PMC2804260 DOI: 10.1016/j.ygyno.2009.09.025

Phase II TAPUR Trial: Endometrial Cancer Cohort
Pertuzumab + Trastuzumab for HER2/HER3-Amplified EC







Ahn ER et al. *JCO Precis Oncol* 2023

PR = partial response; PFS = progression-free survival; OS = overall survival

RTP RESEARCH TO PRACTICE

Clinical and Molecular characteristics associated with HER2-positive gynecologic malignancies

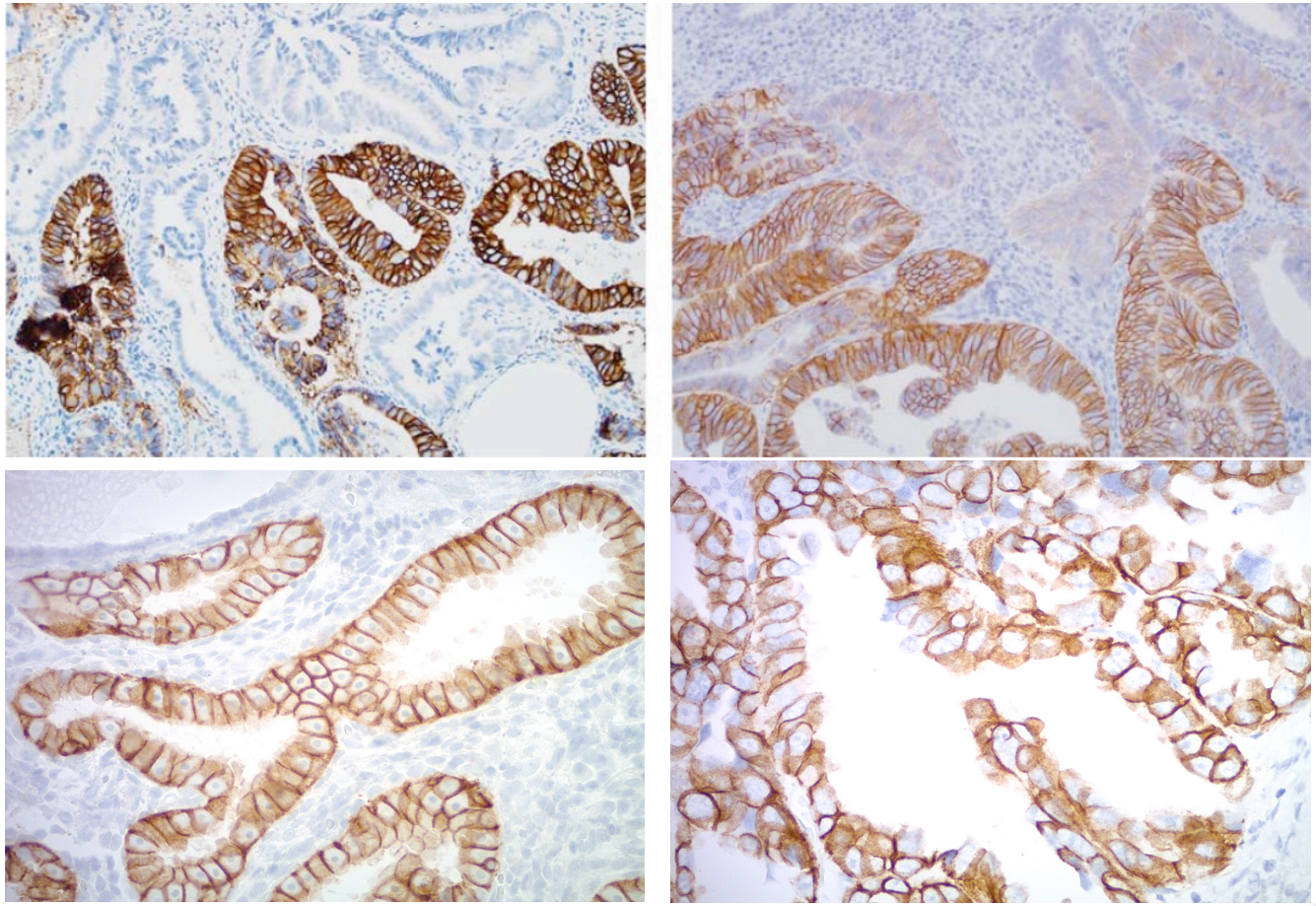
Solid tumors from different organs **have unique characteristics of HER2 protein expression and gene amplification**. Accordingly, different/specific HER2 scoring criteria should apply.

Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice

Natalia Buza[1], Diana P English[2], Alessandro D Santin[2] and Pei Hui[1]

Natalia Buza, MD.
HER2 Testing in Endometrial Serous Carcinoma
Time for Standardized Pathology Practice to Meet the Clinical Demand
Arch Pathol Lab Med. 2021;145:687–691

Molecular characteristics of HER2 protein expression and gene amplification in USC



Unlike breast cancer, **USC is highly heterogeneous in HER2/neu expression** with up to **53%** of HER2/neu 3+ by IHC demonstrating at least two-degree difference in staining intensity in tumor cells. **Lack of Apical Her2 Staining: ~75% of Her2 positive cases.**

CLINICAL CANCER RESERACH

Randomized Phase II Trial of Carboplatin-Paclitaxel Compared with Carboplatin-Paclitaxel-Trastuzumab in Advanced (Stage III-IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis

Amanda N Fader[1], Dana M Roque[2], Eric Siegel[3], Natalia Buza[4], Pei Hui[4], Osama Abdelghany[4], Setsuko Chambers[5], Angeles Alvarez Secord[6], Laura Havrilesky[6], David M O'Malley[7], Floor J Backes[7], Nicole Nevadunsky[8], Babak Edraki[9], Dirk Pikaart[10], William Lowery[11], Karim ElSahwi[12], Paul Celano[13], Stefania Bellone[4], Masoud Azodi[4], Babak Litkouhi[14], Elena Ratner[4], Dan-Arin Silasi[4], Peter E Schwartz[4], **Alessandro D Santin**[15]

PMID: 32601075 PMCID: PMC8792803 DOI: 10.1158/1078-0432.CCR-20-0953 2020 Aug 1;26(15):3928-3935.

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

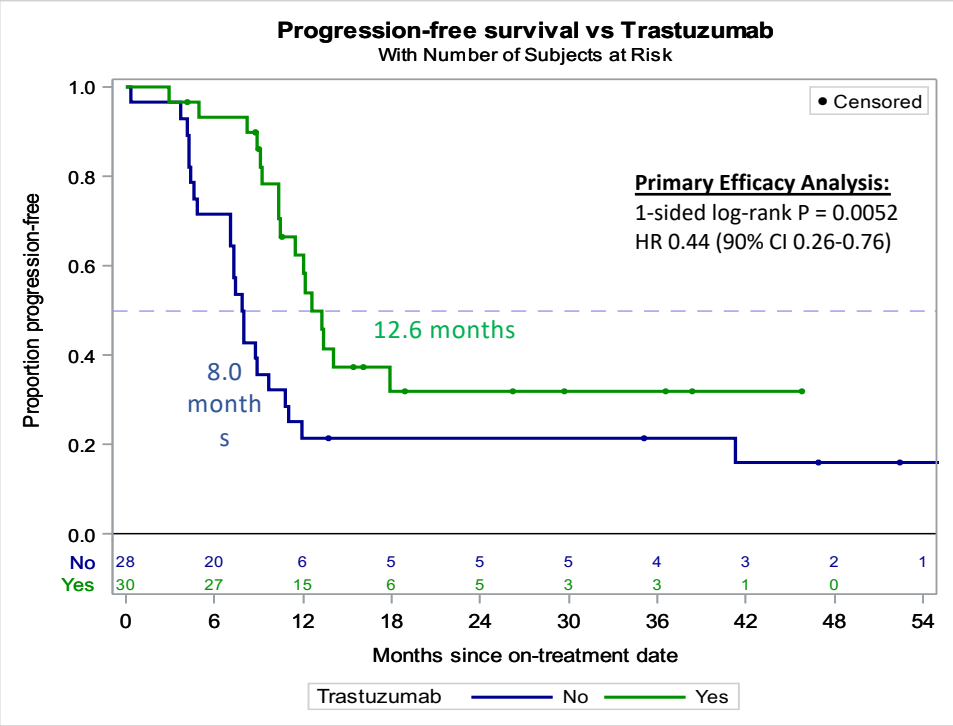
Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

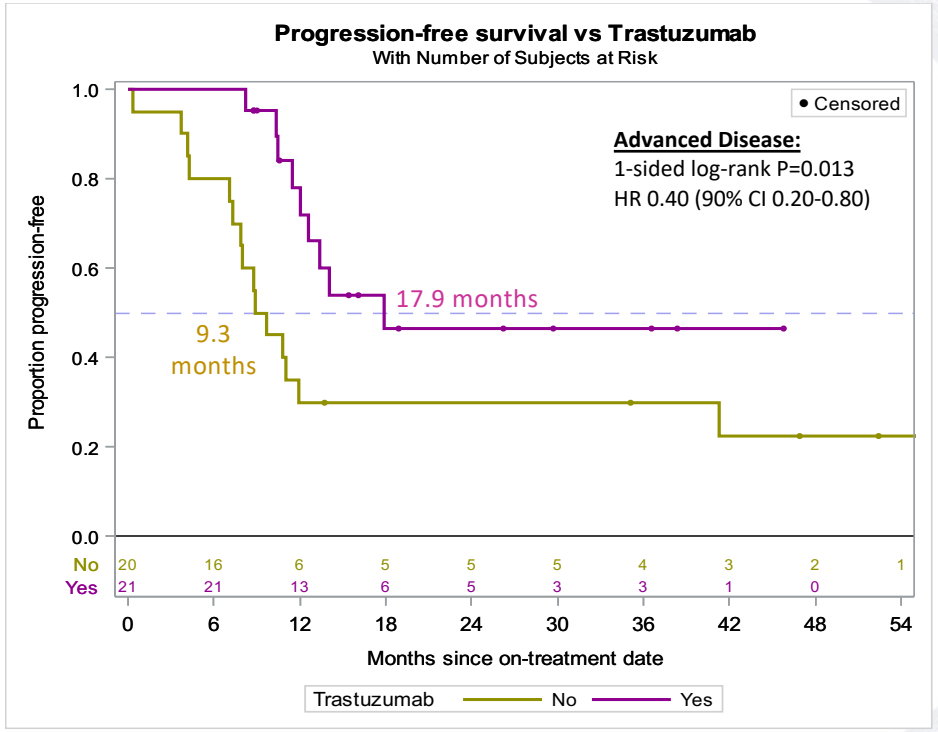
Amanda N. Fader, Dana M. Roque, Eric Siegel, Natalia Buza, Pei Hui, Osama Abdelghany, Setsuko K. Chambers, Angeles Alvarez Secord, Laura Havrilesky, David M. O'Malley, Floor Backes, Nicole Nevadunsky, Babak Edraki, Dirk Pikaart, William Lowery, Karim S. ElSahwi, Paul Celano, Stefania Bellone, Masoud Azodi, Babak Litkouhi, Elena Ratner, Dan-Arin Silasi, Peter E. Schwartz, and Alessandro D. Santin

Revision of the National Comprehensive Cancer Network (NCCN) guidelines, which are widely recognized and used as the standard for clinical policy in oncology by clinicians and payers, adding carboplatin/paclitaxel trastuzumab (**2A category recommendation**) as the **preferred regimen** for women with **HER2+, advanced or recurrent USC** (http://www.jnccn.org).

NRG-GY026: in HER2 positive, stage I-IV **initially only USC and CS and now amended to any histology.**

Progression-Free Survival by Treatment Arm



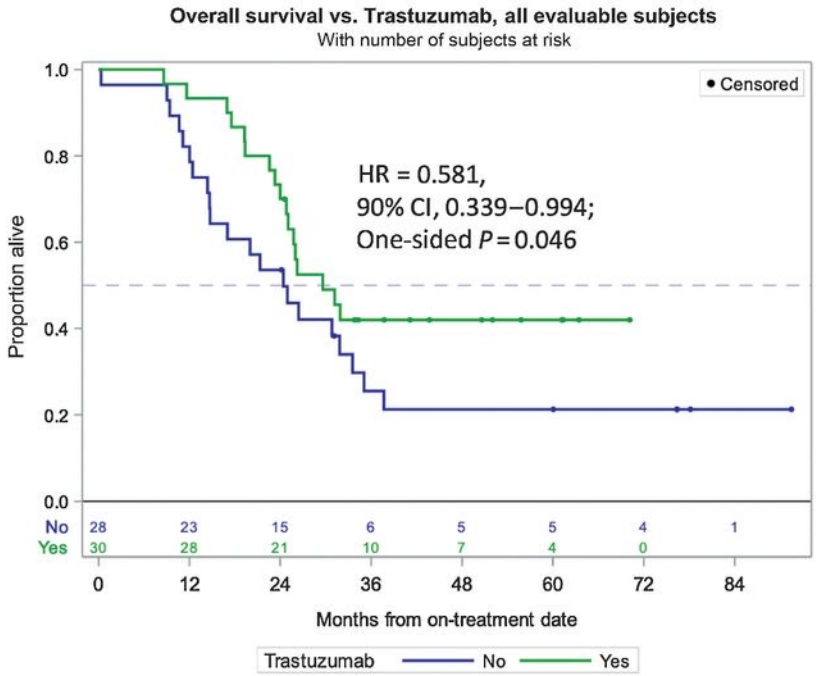


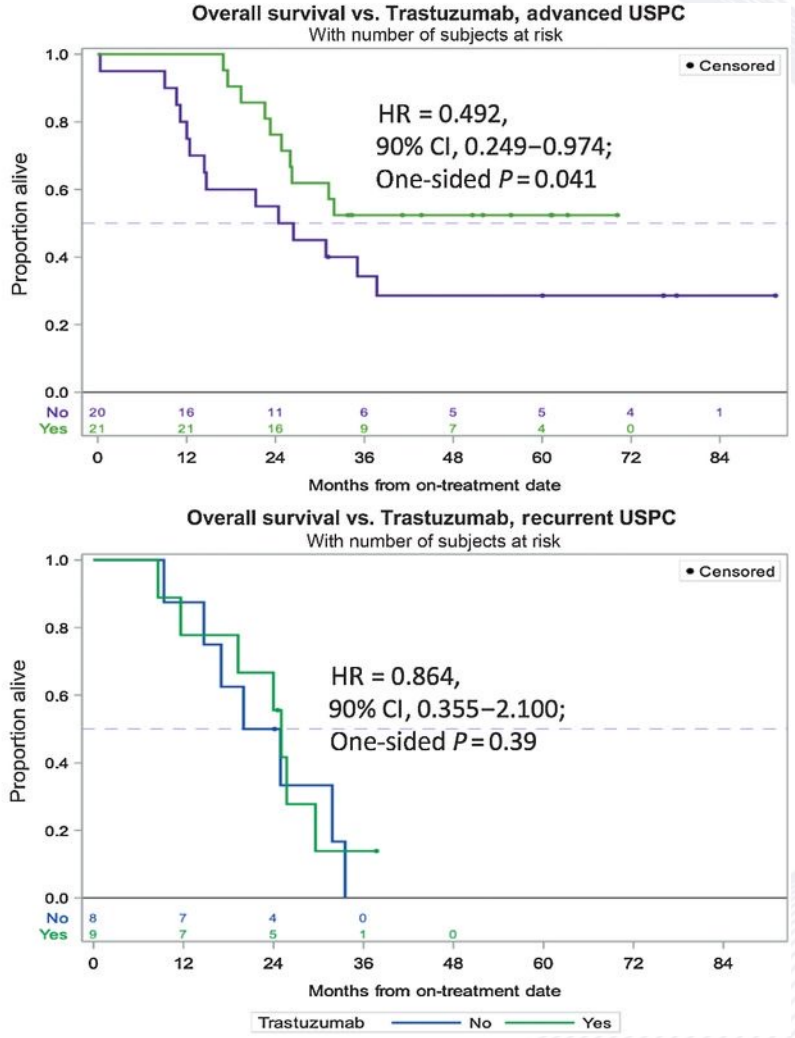
Advanced/recurrent patients:
Median progression-free survival was improved by **4.6 months** in patients who received trastuzumab with carboplatin-paclitaxel (12.6 months) compared to those who received carboplatin-paclitaxel alone (8.0 months) (p=0.005; hazard ratio [HR] 0.44 with 90% confidence interval [CI] of 0.26-0.76).

Advanced (stage III/IV) patients only:
Median progression-free survival was improved by **8.6 months** in patients who received trastuzumab with carboplatin-paclitaxel (17.9 months) compared to those who received carboplatin-paclitaxel alone (9.3 months) (HR 0.40, 90% CI 0.20-0.80, p=0.013).

Fader AN et al. *J Clin Oncol*. 2018 Jul 10;36(20):2044-2051.

Overall Survival by Treatment Arm





Left: Among all patients, OS was 24.4 (CP) versus 29.6 (CP+T) months (HR = 0.581; 90% CI, 0.339–0.994; *P* = 0.0462). Right-top: Benefit was greatest in those undergoing primary therapy with advanced disease (OS 25.4 months vs. not reached; HR = 0.492; 90% CI, 0.249–0.974; *P* = 0.0406). Right-bottom: Benefit was not apparent in the recurrent setting (22.5 months vs. 25.0 months; HR = 0.864; 90% CI, 0.355–2.100; *P* = 0.3929).

Fader AN et al. *Clin Cancer Res*. 2020 Jun 29;26(15):3928–3935.

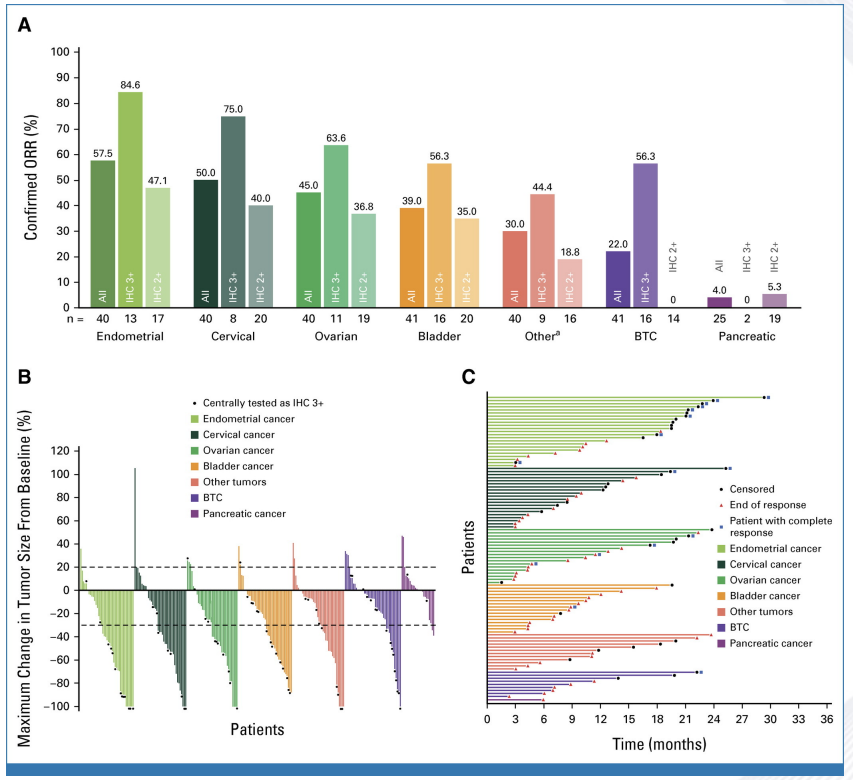
Efficacy outcomes with T-DXd among patients with advanced OC, EC and other gynecologic cancers in the DESTINY-PanTumor02 study

HER2/neu as Target unconjugated Antibody vs ADC

- **Main Mechanisms of action of Trastuzumab (unconjugated Ab)** include:
- 1) Inhibition of tumor cell proliferation/induction of apoptosis (secondary to **decreased** HER2/neu receptor **dimerization**).
- 2) **ADCC** secondary to engagement of Fc receptors on effector cells (NK) (Dominant component of in vivo activity).

- **Main Mechanisms of action of ADC (T-DXd, T-DM1)** include:
- 1) tumor cell killing directly related to its **"toxic payload,"** which is a highly potent cytotoxic drug specifically delivered to cancer cells by the attached antibody.
- 2) **Bystander effect:** Once processed by the Tumor HER2/neu + cells, ADCs can release cytotoxic drug molecules that can diffuse out of Ag+ cells into the neighboring antigen-negative (Ag−) cells to induce their cytotoxicity.

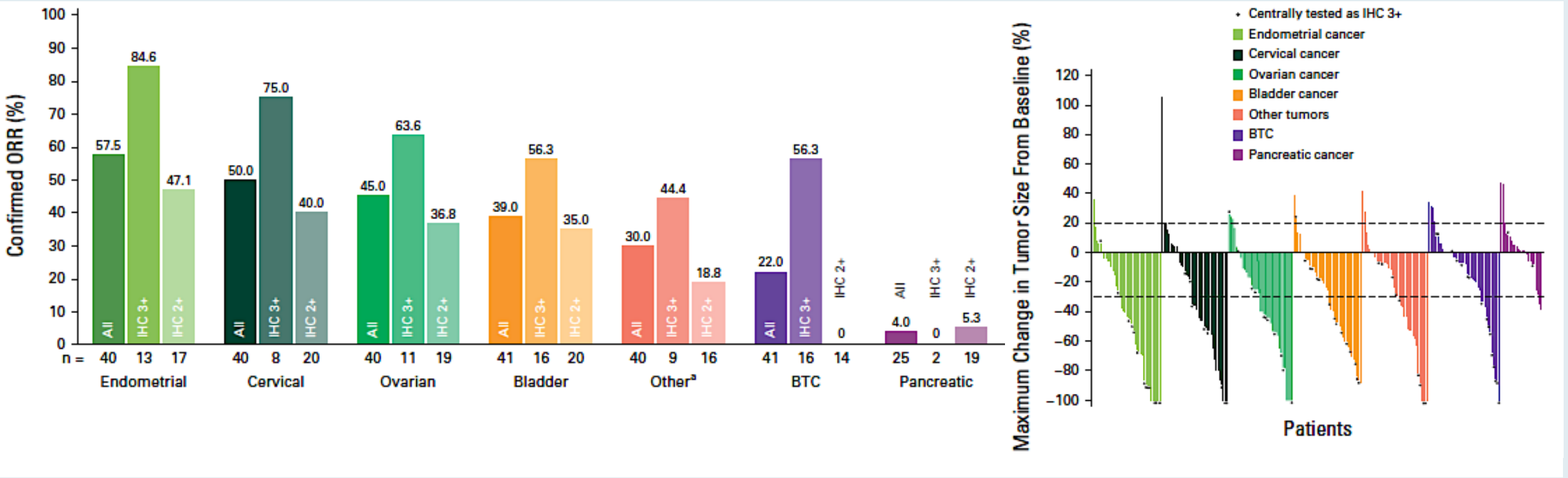
- **DESTINY TRIAL**: New category of targetable patients: **HER2/neu 2+ FISH- patients**.



Meric-Bernstam F., et al. Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the **DESTINY-PanTumor02 Phase II Trial**. J Clin Oncol. 2024 Jan 1;42(1):47-58.

*HER2 IHC status was assessed centrally using HER2 HercepTest (DAKO) and scored according to gastric-specific criteria

DESTINY-PanTumor02: Phase II Trial of Trastuzumab Deruxtecan for Patients with HER2-Expressing Solid Tumors



IHC = immunohistochemistry; BTC = biliary tract cancer

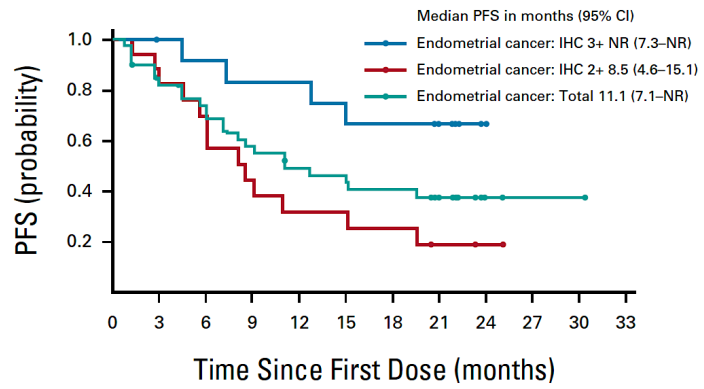
Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

RTP RESEARCH TO PRACTICE

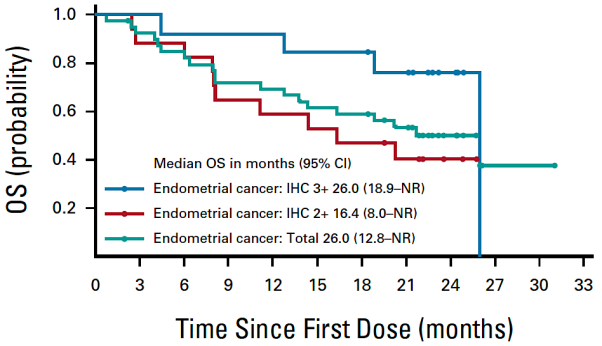
DESTINY-PanTumor02: Survival

Endometrial

PFS

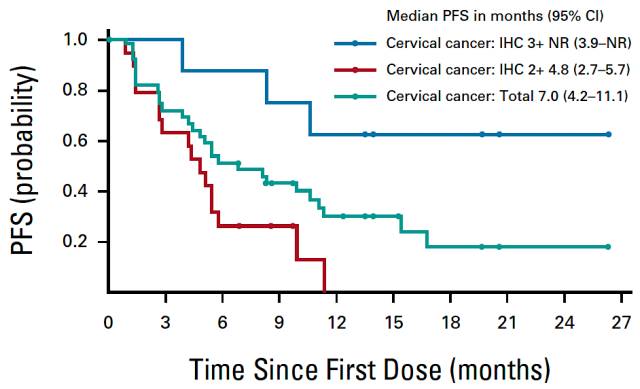


OS



Cervical

PFS



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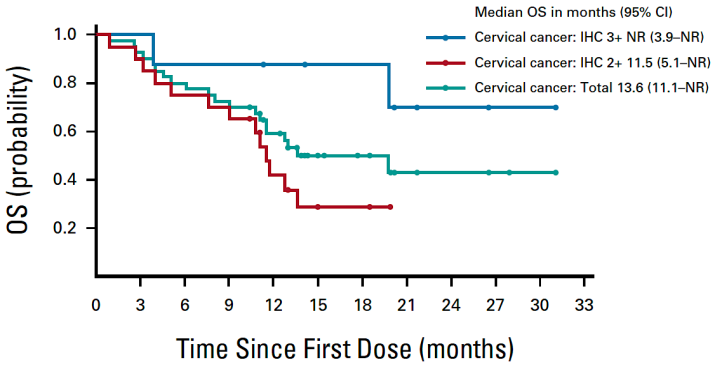
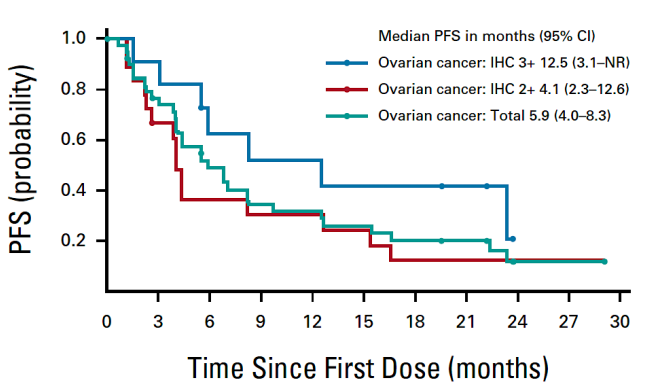
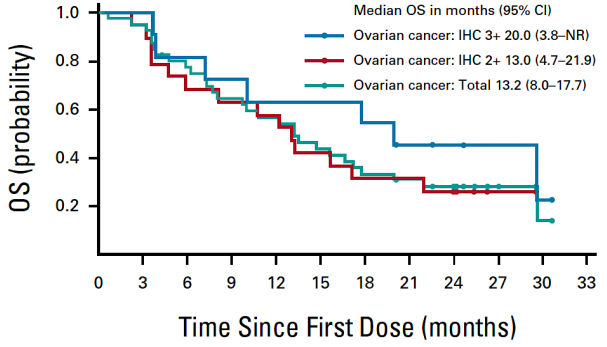


Ovarian

PFS



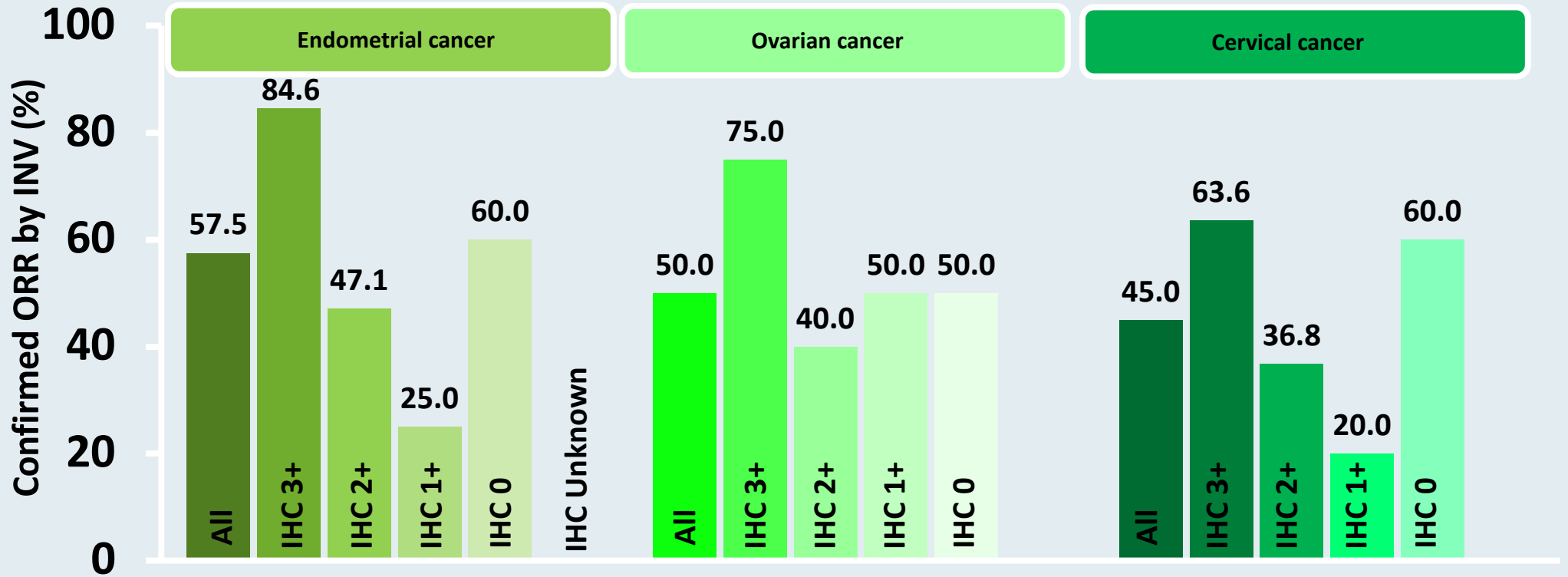
OS



Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

RTP RESEARCH TO PRACTICE

DESTINY-PanTumor02: Response by HER2 Expression Level (Central)



	Endometrial cancer						Ovarian cancer					Cervical cancer				
	All	IHC 3+	IHC 2+	IHC 1+	IHC 0	IHC Unknown	All	IHC 3+	IHC 2+	IHC 1+	IHC 0	All	IHC 3+	IHC 2+	IHC 1+	IHC 0
Total n in subgroup	40	13	7	4	5	1	40	8	20	8	4	40	11	19	5	5
n of responders	23	11	8	1	3	0	20	6	8	4	2	18	7	7	1	3
Median DOR, months	NR	NR	18.2	NR	9.9	–	14.2	NR	3.8	14.2	NR		11.3	22.1	11.3	8.3	4.5
95% CR	9.9, NE	9.6, NE	3.0, NE	–	2.8, NE	–		4.1, NE	9.3, NE	2.8, NE	8.3, NE	6.8, NE	4.4, 22.1	4.2, NE	2.8, NE	–	2.6, NE

ORR = objective response rate; INV = investigator; DOR = duration of response; CR = complete response; NE = not estimable; NR = not reached

Lee J-Y et al. International Gynecological Cancer Society (IGCS) 2023.

DESTINY-PanTumor02: Adverse Events

Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)
Associated with death	2 (5.0)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)			
Nausea	29 (72.5)	26 (65.0)	22 (55.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)

Meric-Bernstam F et al. *J Clin Oncol* 2024;42(1):47-58.

Incidence of ILD and other toxicities with T-DXd in DESTINY-PanTumor02; recommendations for monitoring and management

In DESTINY-PanTumor02, ILD incidence with T-DXd was **5.9% at 5.4 mg/kg** and 14% at 6.4 mg/kg.

TABLE 1. T-DXd Prescribing Information and DESTINY-Breast03 and DESTINY-Breast04 Protocol-Recommended Dose Modifications for Pneumonitis/ILD[4,7,9]

Severity	Treatment	
Asymptomatic pneumonitis/ILD (grade 1)	Interrupt T-DXd until resolved to grade 0, then If resolved in 28 days or less from date of onset, maintain dose If resolved in >28 days from date of onset, reduce dose 1 level per the recommendations below However, if the grade 1 pneumonitis/ILD event occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued Consider corticosteroid treatment (eg, ≥0.5 mg/kg/d prednisolone or equivalent) as soon as pneumonitis/ILD is suspected	
	Dose reduction schedule	Breast cancer
	Recommended starting dose	5.4 mg/kg
	First dose reduction	4.4 mg/kg
	Second dose reduction	3.2 mg/kg
	Requirement for further dose reduction	Discontinue treatment
Symptomatic pneumonitis/ILD (grade 2 or greater)	Permanently discontinue T-DXd Promptly initiate corticosteroid treatment (eg, ≥1 mg/kg/d prednisolone or equivalent and continue for ≥14 days, followed by gradual taper for ≥4 weeks) as soon as pneumonitis/ILD is suspected	

Abbreviations: ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

Early diagnosis and prompt treatment are crucial for managing T-DXd-related ILD and potentially allowing for continued treatment with T-DXd.

Rugo et al., JCO Oncol. Pract. 2023 May 19;19(8):539–546. doi: 10.1200/OP.22.00480

Case Presentation: 75-year-old woman with HER2-positive (IHC 3+) recurrent ovarian cancer (HRD-negative, PD-L1-positive, folate receptor alpha-positive) receives T-DXd

Dr Kellie Schneider (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

In general, for a patient with FRα-positive, HER2-positive (IHC 3+) recurrent ovarian cancer, would you recommend mirvetuximab soravtansine or T-DXd first? What about for a patient like this who is concerned about peripheral neuropathy?

Given the emerging results from the KEYNOTE-B96 trial, do you expect that pembrolizumab will soon be a consideration for patients with platinum-resistant recurrent ovarian cancer? If so, how do you envision sequencing it relative to other currently available strategies? Would PD-L1 expression have any bearing on your decision?

Questions for the Faculty

What other novel investigational strategies are you excited about for patients with advanced ovarian cancer? Given what we currently know about raludotatug deruxtecan, would you like to have access to it at the current time? If so, for which types of patients would you like to employ it?

Case Presentation: 80-year-old woman with MSS HER2-positive (IHC 3+), TP53-mutant metastatic recurrent uterine carcinosarcoma

Dr Spencer Bachow (Boca Raton, Florida)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

How do you currently approach first-line therapy for patients with HER2-positive advanced endometrial cancer? Do you combine an anti-PD-1/PD-L1 antibody with carboplatin/paclitaxel/trastuzumab?

If this patient's disease recurrence were diagnosed today, what second-line treatment would you recommend — T-DXd or pembrolizumab/lenvatinib?

Questions for the Faculty

What is your approach to the management of the acute nausea and vomiting associated with T-DXd? How do you manage breakthrough nausea and vomiting despite guideline-directed antiemetic prophylaxis?

How are you monitoring for ILD in your patients receiving T-DXd? Is ILD unlikely after a certain point? Can the frequency of monitoring be reduced after a particular duration of treatment?

Agenda

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

MODULE 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr O'Malley

MODULE 3: Role of HER2-Targeted Therapy in Advanced OC, Endometrial Cancer (EC) and Other Gynecologic Cancers — Dr Santin

MODULE 4: First-Line Therapy for Advanced EC — Dr Westin

MODULE 5: Current Therapeutic Options for R/R EC; Novel Investigational Strategies for Newly Diagnosed and Recurrent Disease — Dr Salani

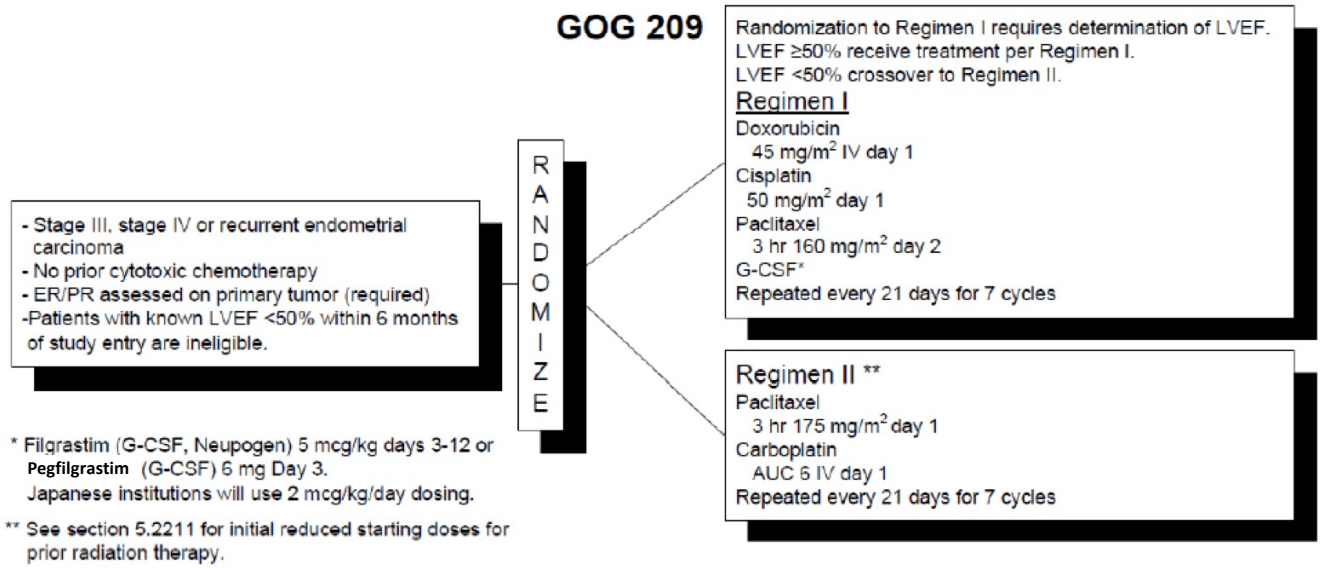
First-Line Therapy for Advanced Endometrial Cancer

Shannon N. Westin, MD, MPH
Professor
University of Texas MD Anderson Cancer Center

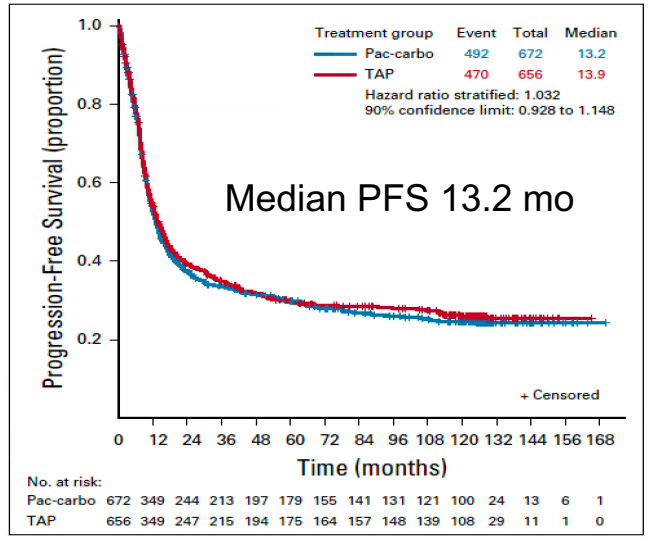
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

GOG 209

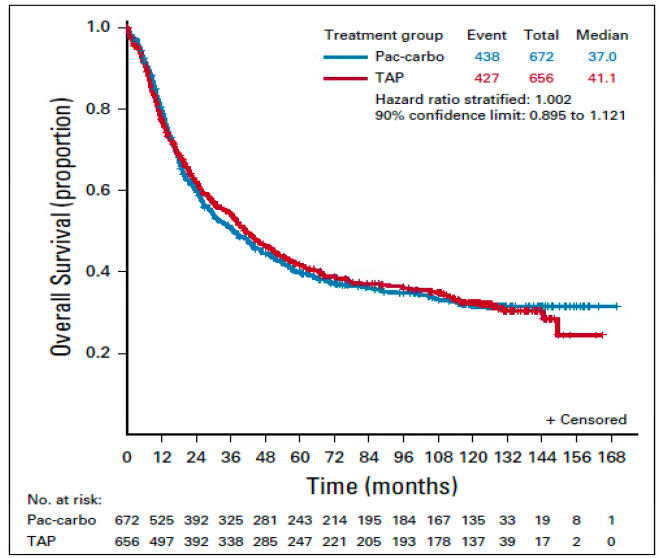
Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease



Progression Free Survival



Overall Survival



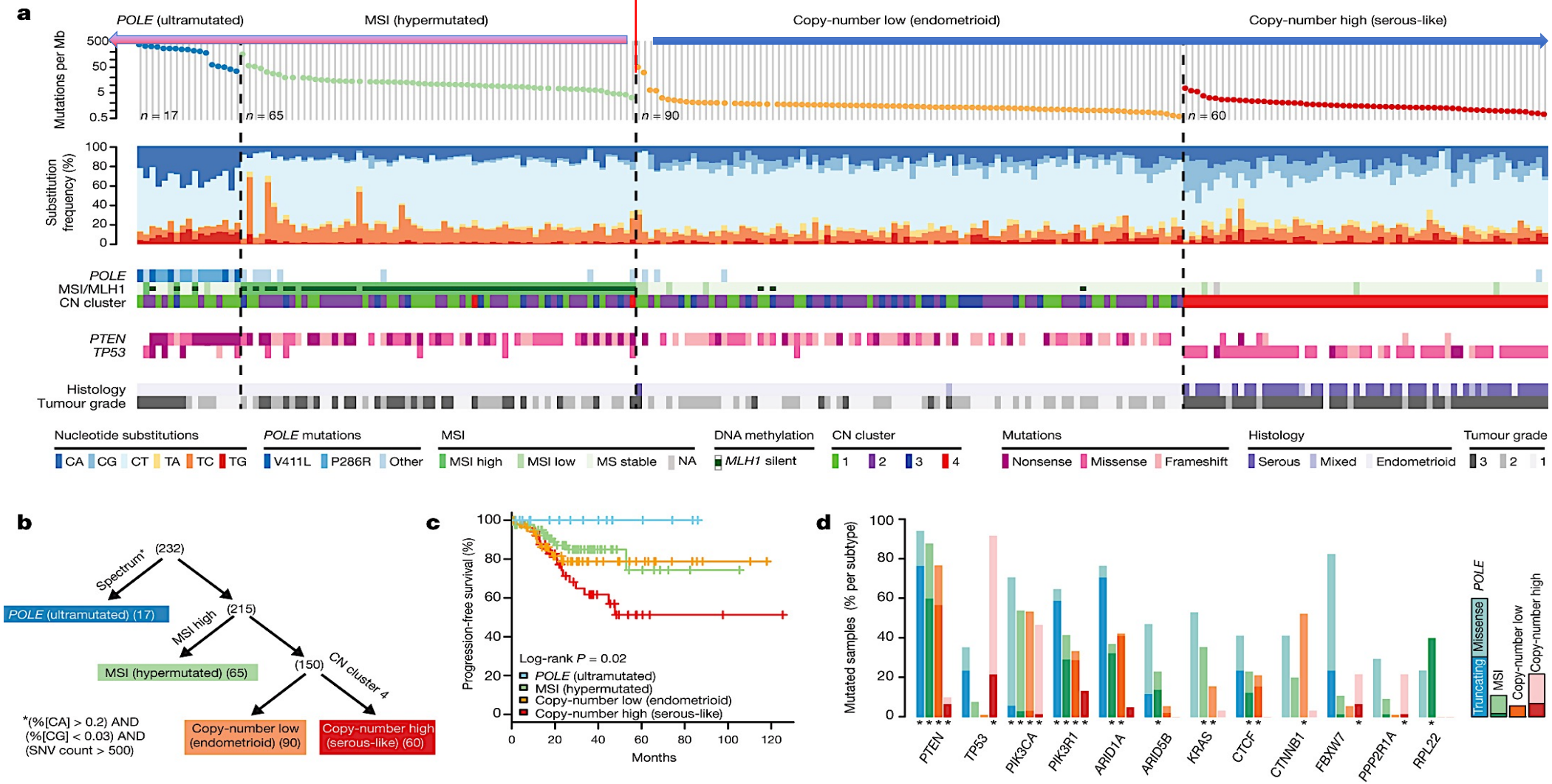
Key eligibility criteria

- Stage III, Stage IV or recurrent endometrial carcinoma. **NO mandate for measurable disease**
- **NO prior cytotoxic chemotherapy**, including chemotherapy used for radiation sensitization
- GOG PS 0,1 or 2

Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

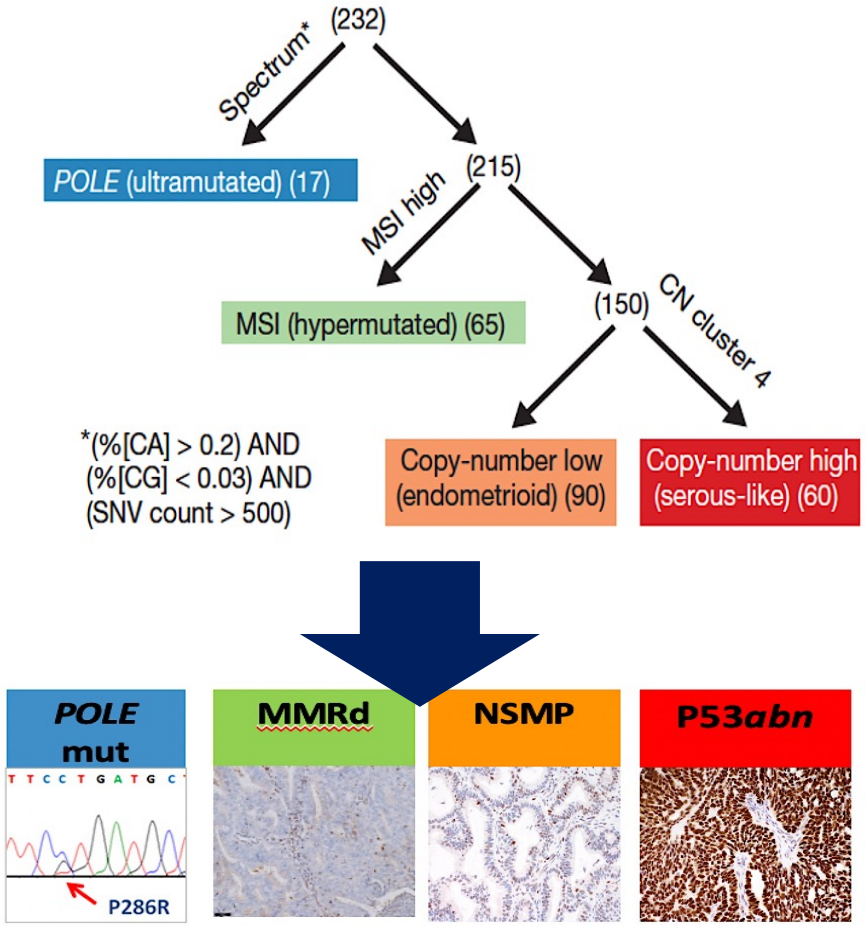
Shifting the Paradigm: Lumping to Splitting

Immunologically Responsive | Immunologically Non-Responsive

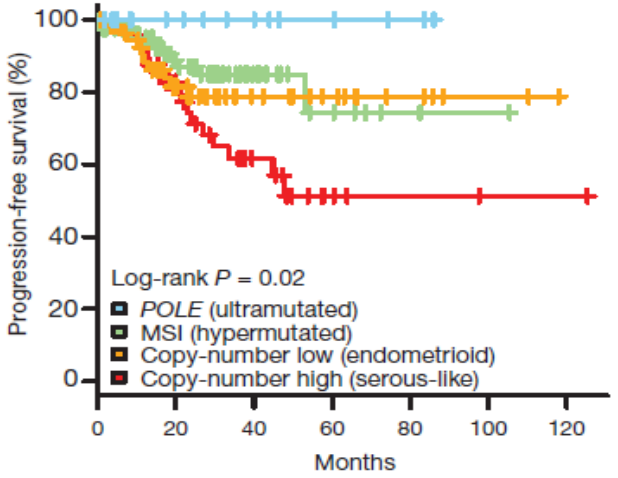


G Getz *et al. Nature* **497**, 67-73 (2013)

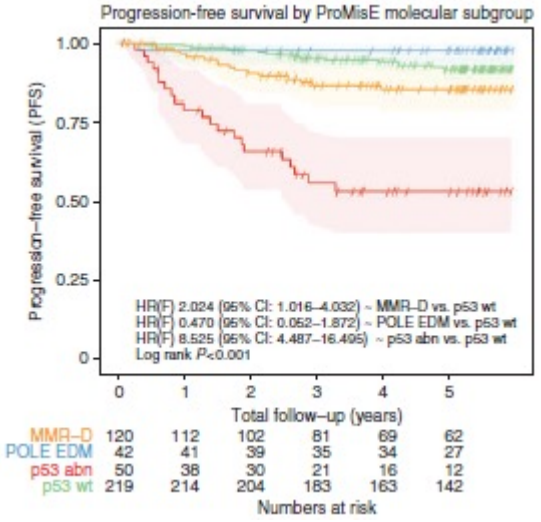
The Tipping Point: Bringing Biology Into the Clinic



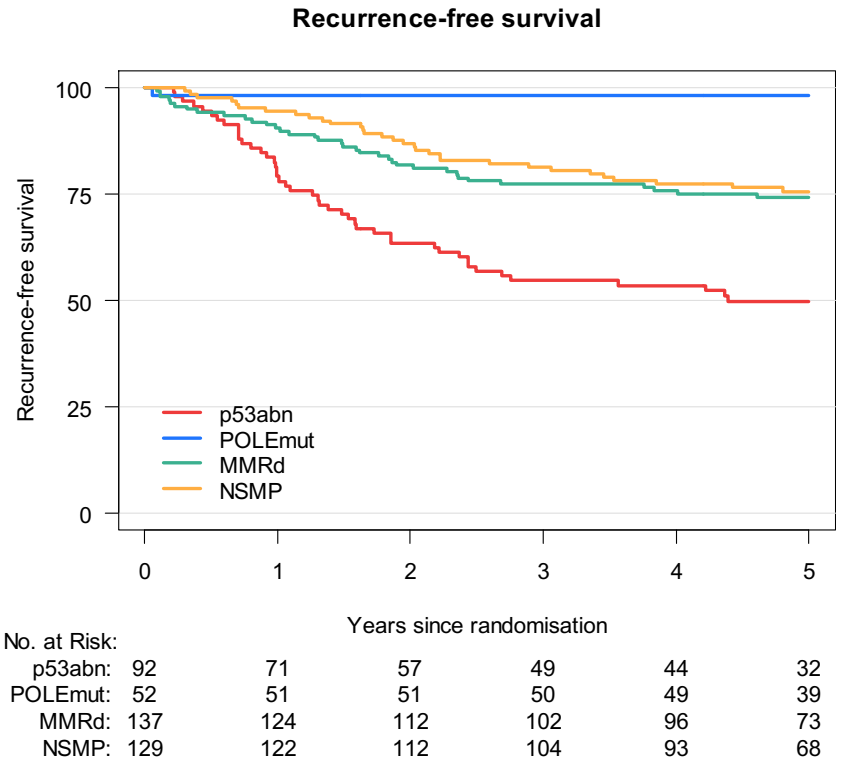
TCGA[1]



ProMisE[2]

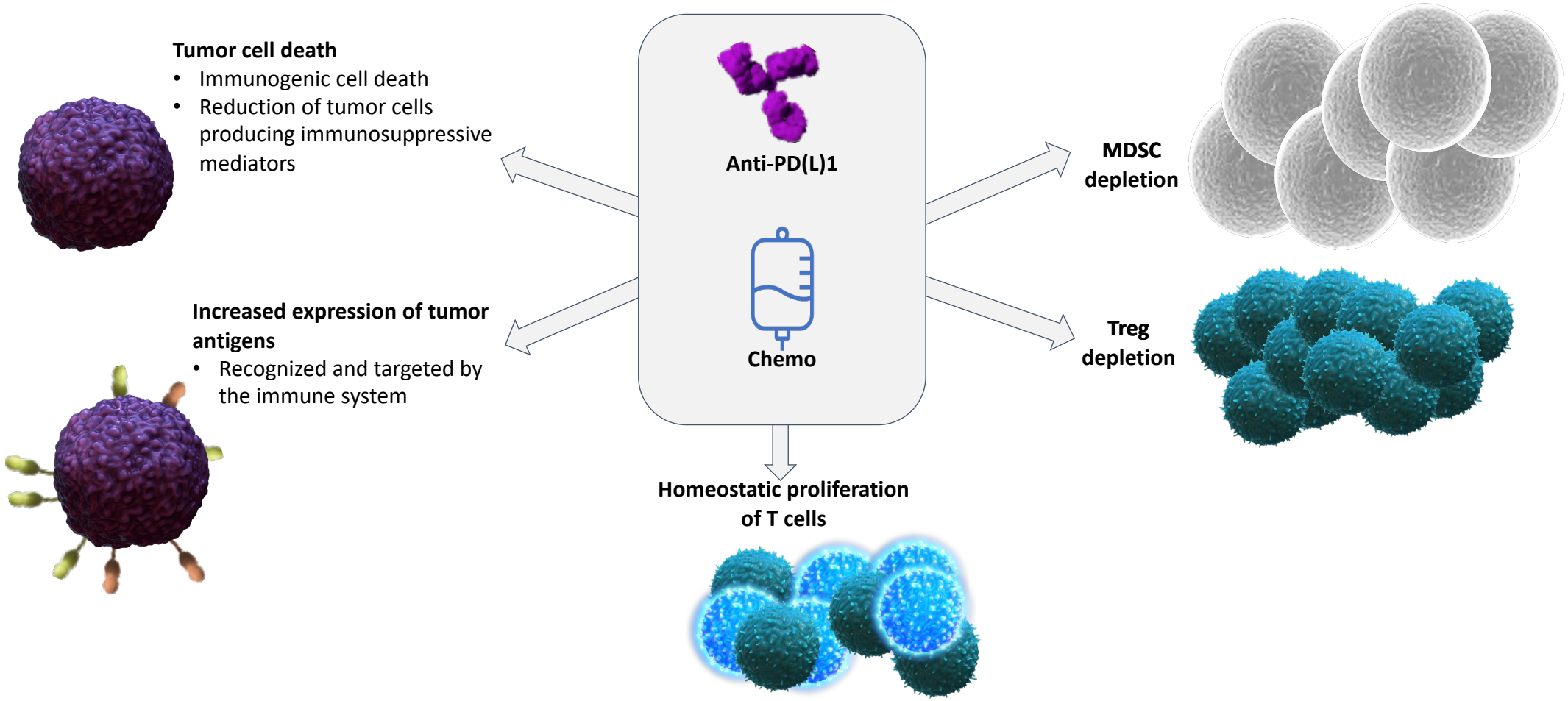


PORTEC-3[3]



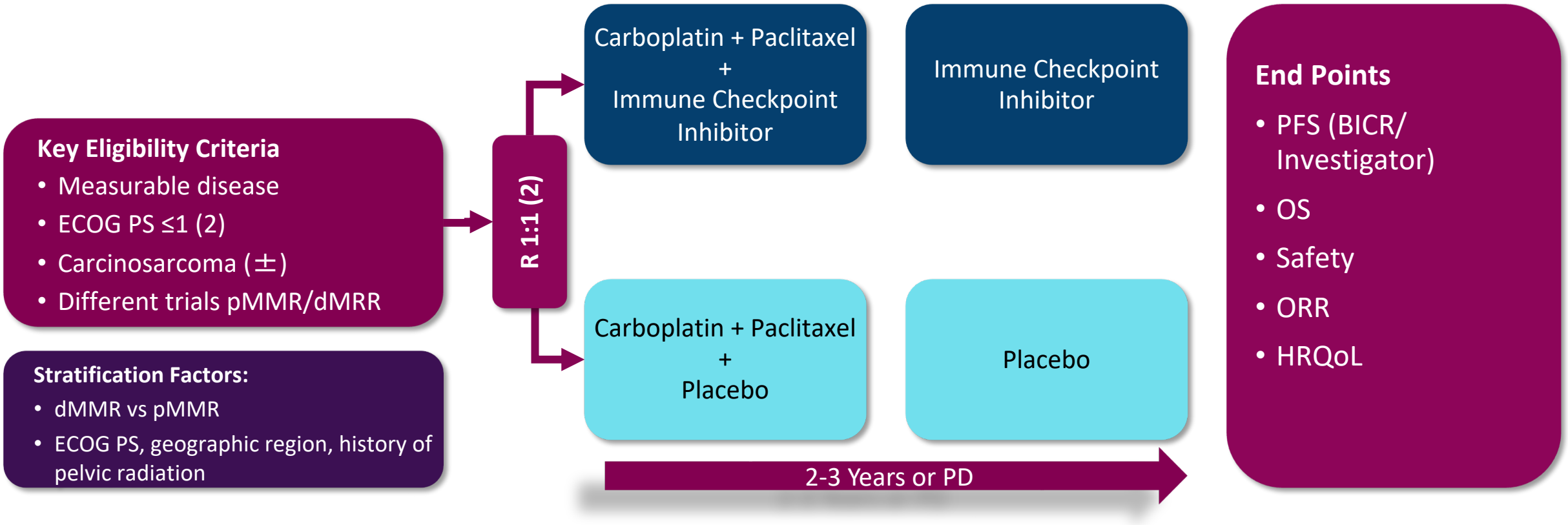
1.Levine DA, et al. *Nature.* 2013;497:67–73. doi:10.1038/nature12113; 2. Kommoss F, et al. *Annals of Oncology.* 2018;29:1180–1188; 3. León-Castillo A, et al. *J Clin Oncol.* 2020; 4. Cosgrove CM, et al. *Gynecol Oncol.* 2018;148:174–180.

Rationale for Combinatorial Approach with Chemo + IO



Hato SV *Clin Cancer Res.* 2014, Chen Y*Am J Cancer Res*. 2021, Pfannenstiel T *Cell Immunol*. 2010, Sevko A *J Immunol*. 2013.

Benefit of IO + Chemo in EC: 1L Studies in Patients with Advanced Stage or Recurrent EC



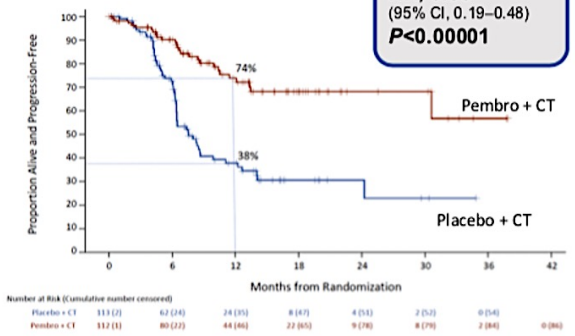
BICR=blinded independent central review; dMMR=deficient mismatch repair; ECOG PS=Eastern Cooperative Oncology Group Performance Status; HRQoL=health-related quality of life; ORR=overall response rate; OS=overall survival; pMMR=proficient mismatch repair; PD=progressive disease; PFS=progression-free survival; R=randomized.

1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Colombo N, et al. *Lancet Oncol.* 2024,Sep;25(9):1135-1146. doi: 10.1016/S1470-2045(24)00334-6; 5. Marth C, et al. *J Clin Oncol.* 2024;00:1-18. doi: 10.1200/JCO-24-0132.

Benefit of IO + Chemo in the dMMR EC Population

dMMR population

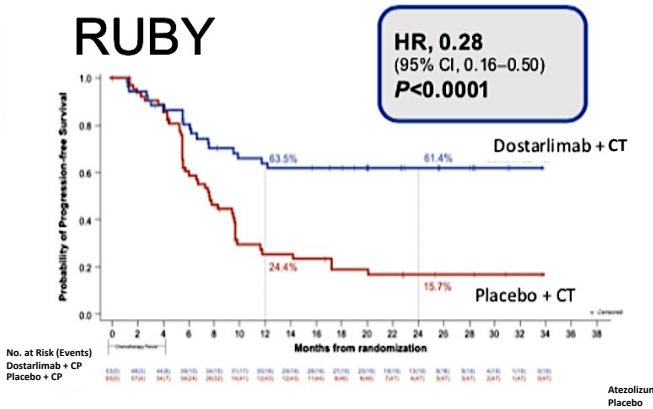
GY018



PFS	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

dMMR/MSI-H population

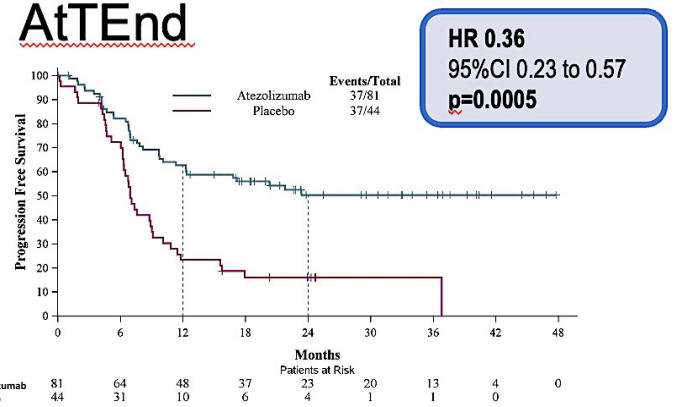
RUBY



PFS	No with events%	Median
Dostar + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

dMMR population

AtTEnd

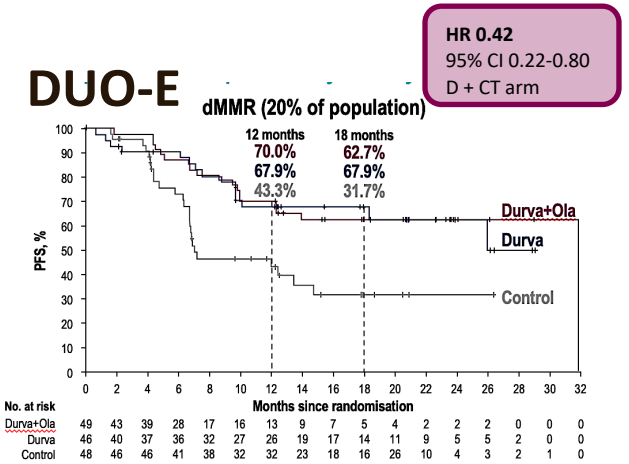


PFS	No with events%	Median
Atezo + CT	45.7	NR (12.3-NR)
Placebo + CT	84.1	6.9 (6.2-9.0)

AtTEnd data refers to investigational uses of treatments that are not yet licensed for use by regulatory authorities.

dMMR population

DUO-E



PFS	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo + CT	51	7.0 (6.7-14.8)

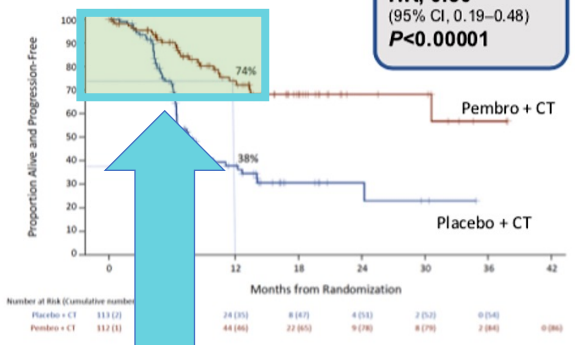
Please note that head-to-head studies were not conducted between these products.
These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

1. Mirza MR, et al. *N Engl J Med.* 2023;388(23):2145-2158. doi:10.1056/nejmoa2216334; 2. Eskander RN, et al. *N Engl J Med.* 2023;388(23):2159-2170. doi:10.1056/NEJMoa2302312; 3. Westin SN, et al. *J Clin Oncol.* 2024;42(3):283-299. doi: 10.1200/JCO.23.02132; 4. Colombo N, et al. *Lancet Oncol.* 2024,Sep;25(9):1135-1146. doi: 10.1016/S1470-2045(24)00334-6.

Benefit of IO + Chemo in the dMMR EC Population

dMMR population

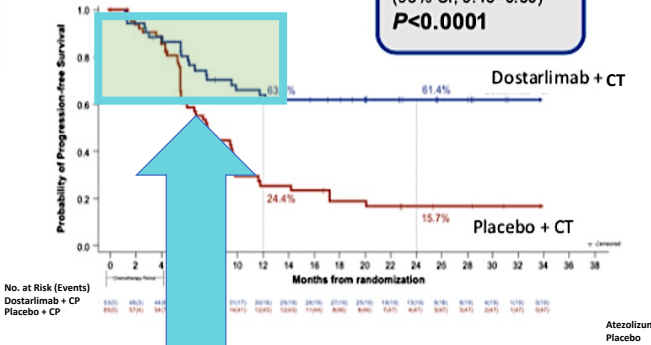
NRG-GY018



	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

dMMR/MSI-H population

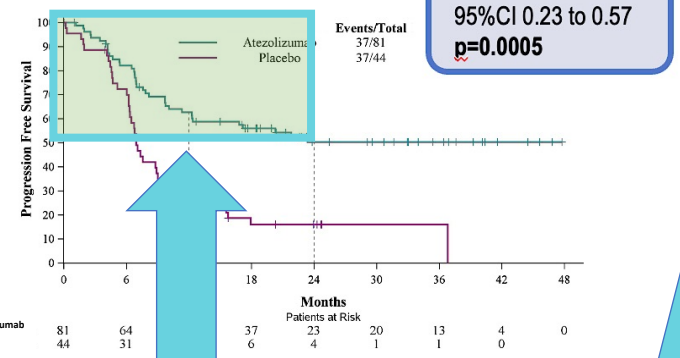
RUBY



	No with events%	Median
Dostar + CT	35.8	NR (11.8-NR)
Placeb + CT	72.3	7.7 (5.6-9.7)

dMMR population

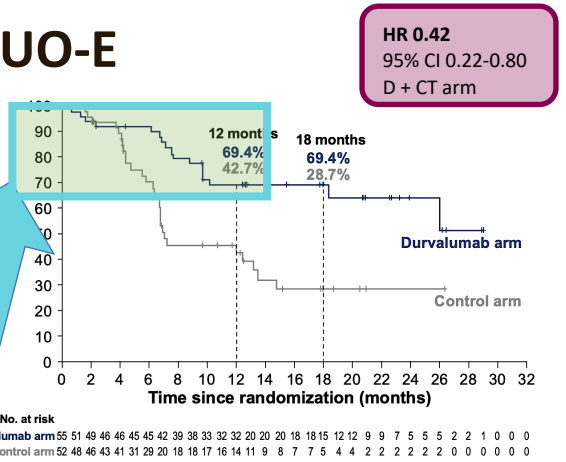
AtTEnd



	No with events%	Median
Atezo CT	45.7	NR (12.3-NR)
Placeb + CT	84.1	6.9 (6.2-9.0)

dMMR/MSI-H population

DUO-E



	No with events %	Median
Durva + CT	32.6	NR (NR-NR)
Placebo + CT	51	7.0 (6.7-14.8)

Who are these 25-30% of dMMR patients who progress on immune checkpoint inhibition?

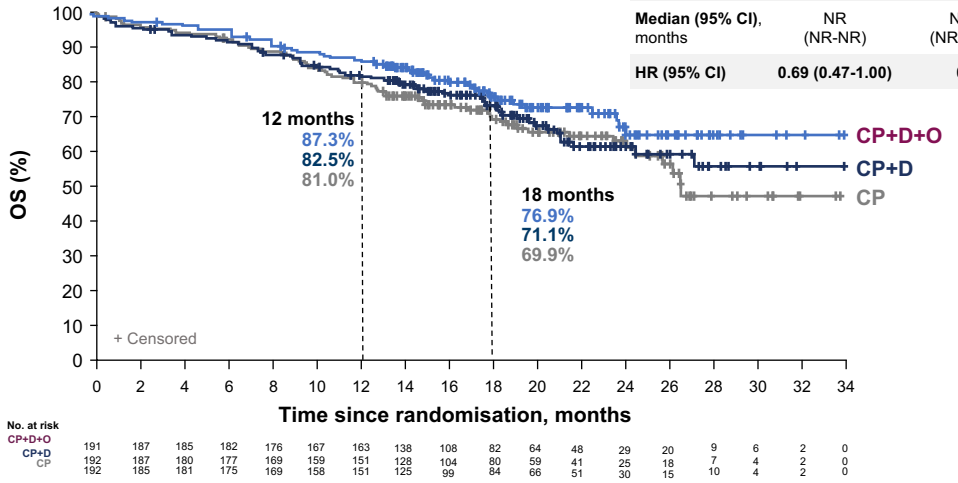
- **dMMR but TMB low…**

Mirza NEJM 2023, Eskander NEJM 2023, Westin JCO 2024, Colombo Lancet Oncology 2024

Chemotherapy + ICI OS Results in pMMR

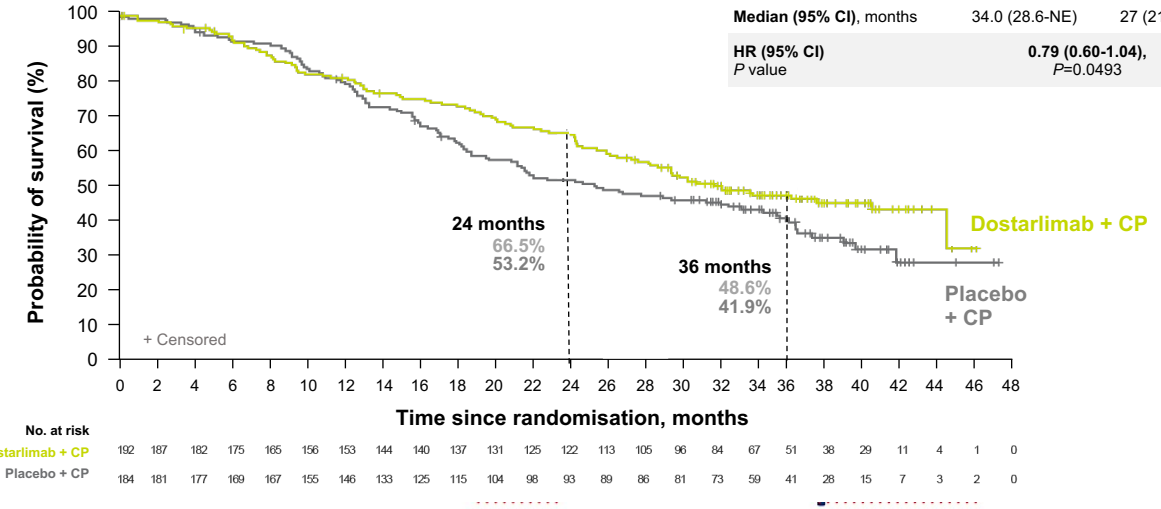
ENGOT-EN10/DUO-E

	CP+D+O (n=191)	CP+D (n=192)	CP (n=192)
Events, n (%)	46 (24.1)	58 (30.2)	64 (33.3)
Median (95% CI), months	NR (NR-NR)	NR (NR-NR)	25.9 (25.1-NR)
HR (95% CI)	**0.69 (0.47-1.00)**	**0.91 (0.64-1.30)**	



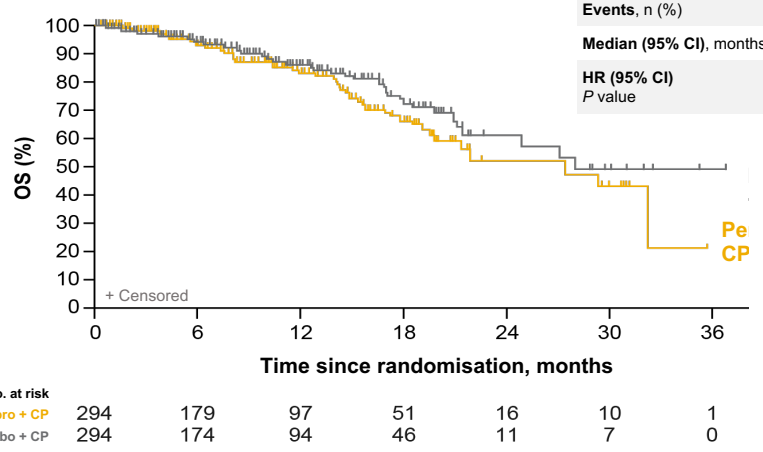
ENGOT-EN6/RUBY Part 1

	Dostarlimab + CP n=192	Placebo + CP n=184
Events, n (%)	97 (50.5)	109 (59.2)
Median (95% CI), months	34.0 (28.6-NE)	27 (21.5-35.6)
HR (95% CI) *P* value	**0.79 (0.60-1.04)**, *P*=0.0493	

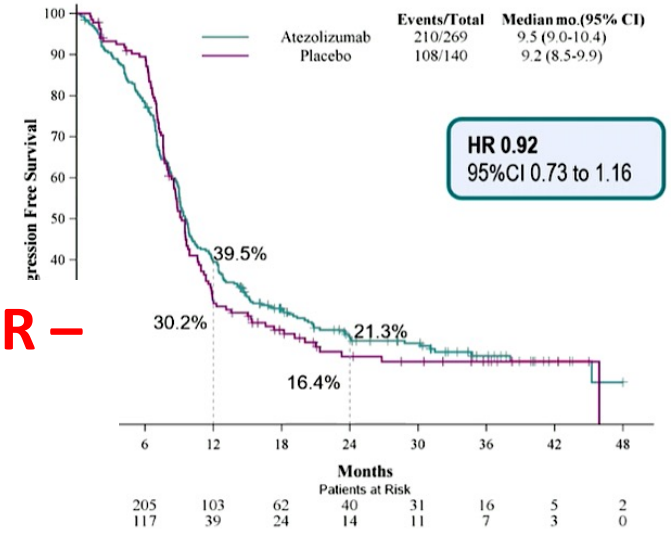


NRG-GY018

	Pembro + CP (n=294)	Placebo + CP (n=294)
Events, n (%)	45 (15.3)	54 (18.4)
Median (95% CI), months	27.96 (21.42-NR)	27.37 (19.52-NR)
HR (95% CI) *P* value	**0.79 (0.53-1.17)** *P*=0.1157	



AtTEnd

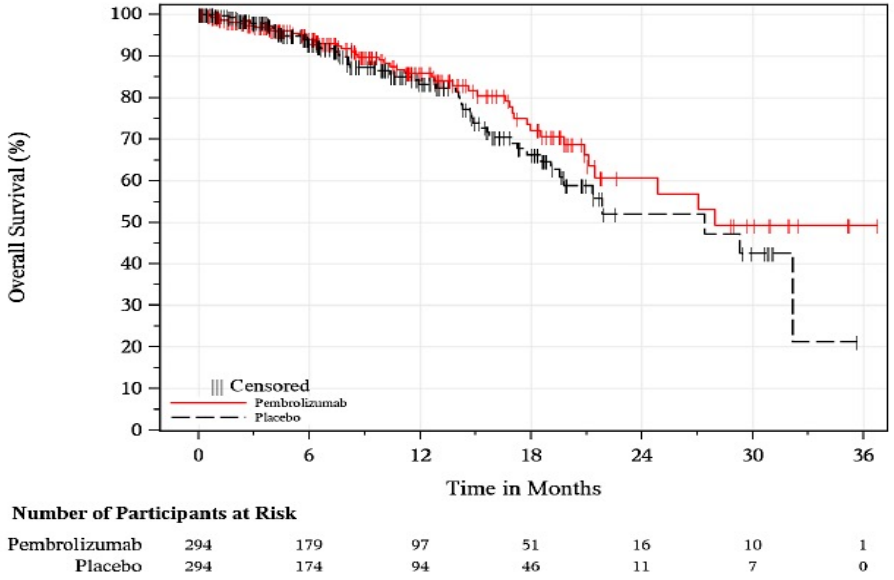


Benefit much lower in pMMR – UNMET NEED AND OPPORTUNITY

Mirza NEJM 2023, Eskander NEJM 2023, Westin JCO 2024, Colombo Lancet Oncology 2024

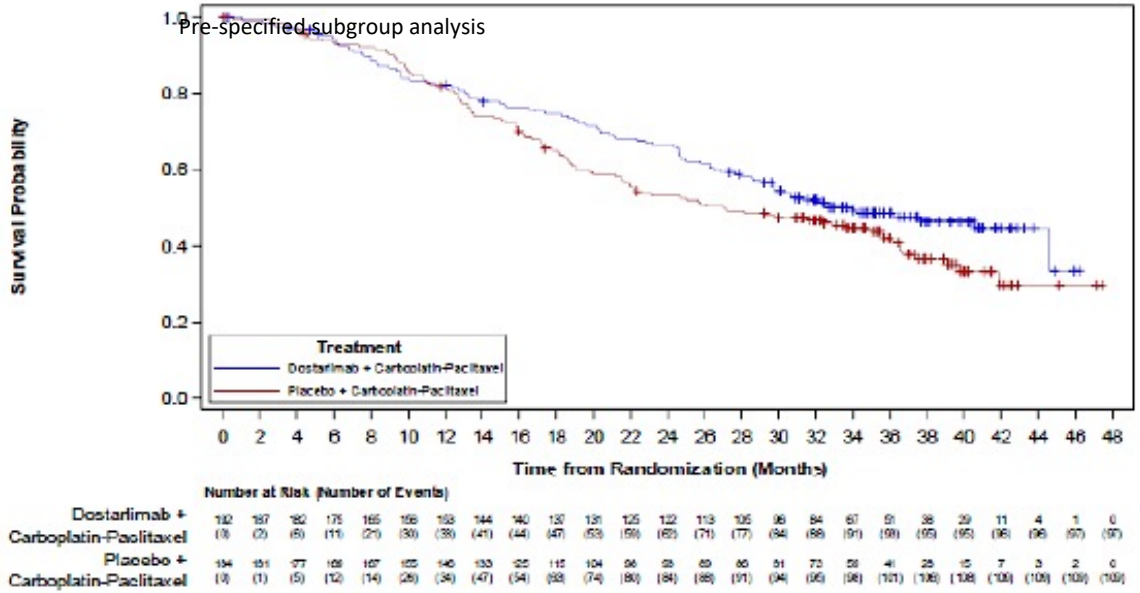
Chemotherapy + ICI Options - OS Results in pMMR

NRG-GY018[1]



	Pembrolizumab + CP (n=294)	Placebo + CP (n=294)
Events, n (%)	45 (15.3%)	54 (18.4%%)
Data Maturity	**17%**	
DCO	06/12/2022	
Median, (95% CI), mos	28 (21.4, NR)	27.4 (19.5, NR)
HR (95% CI) *p* value	**0.79** (0.53, 1.17) *p*<0.0001	

ENGOT-EN6/RUBY Part 1[2]

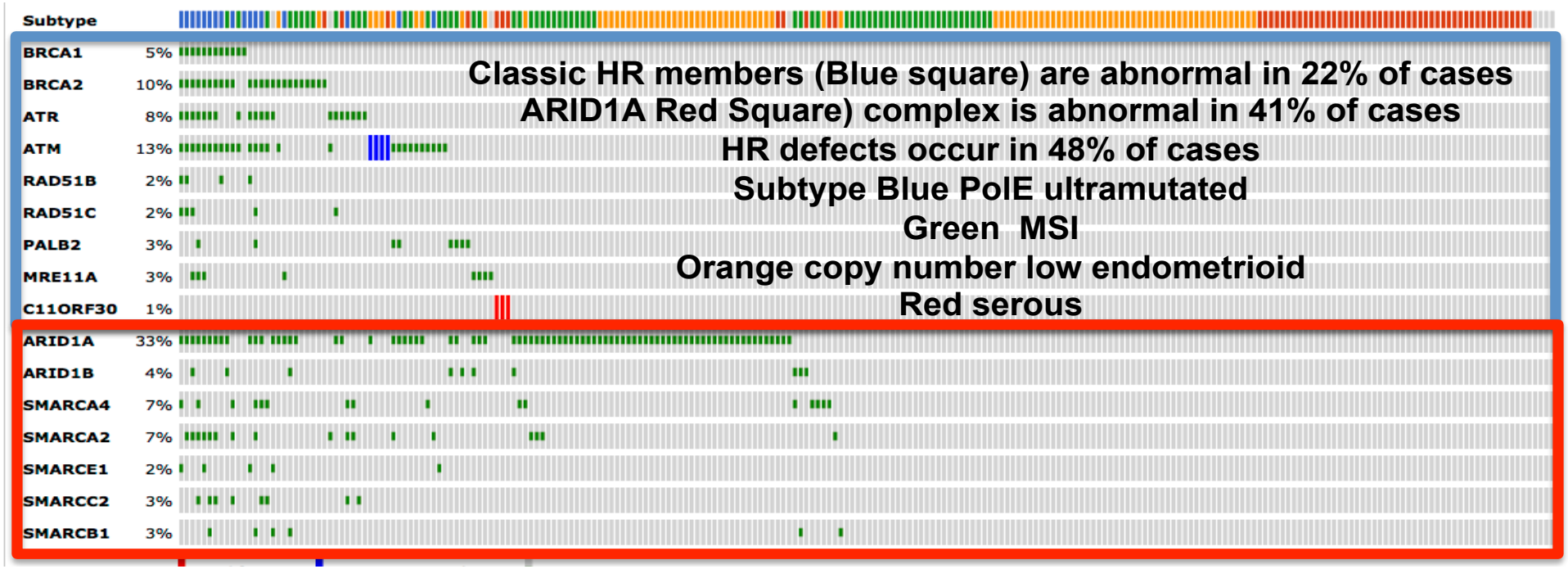


	Dostarlimab + CP n=192	Placebo + CP n=184
Events, n (%)	97 (50.5%)	109 (59.2%)
Data Maturity	**55%**	
DCO	22/09/2023	
Median (95% CI), **mos**	34.0 (28.6-NR)	27 (21.5-35.6)
HR (95% CI)	**0.79** (0.60-1.04)	

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. Some of the therapeutic approaches discussed are currently under investigational use and do not yet have licensed therapeutic treatments available.

1. European Medicines Agency (EMA). *Keytruda-H-C-003820-II-0153: EPAR – Assessment Report – Variation.* Reference Number: EMA/480904/2024. First published: 06/11/2024. https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0153-epar-assessment-report-variation_en.pdf.; 2. EMA. *Jemperli-H-C-005204-II-0032: EPAR – Assessment Report – Variation.* Reference Number: EMA/4794/2025. First published: 21/01/2025. https://www.ema.europa.eu/en/documents/variation-report/jemperli-h-c-005204-ii-0032-epar-assessment-report-variation_en.pdf.

Homologous Recombination Defects in EC

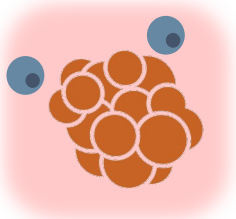


- Classic HRD members: 22%
- ARID1A: 41%
- HRD + ARID1A: 48%
- HRD, ARID1A, PTEN: 77%

Liang H, et al. *Genome Res*. 2012.

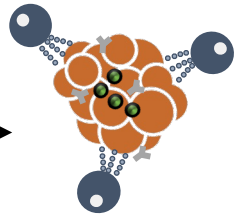
Addition of Olaparib to Durvalumab Enhanced PFS Benefit in pMMR Subpopulation

pMMR endometrial cancer



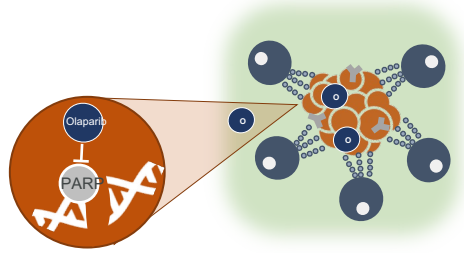
Biologically heterogeneous population – diverse genomic drivers and variable immune priming[2-4]

INDUCTION: CP + durvalumab

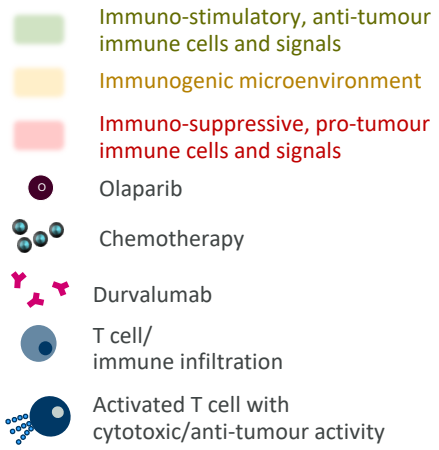


CP + durvalumab drives direct tumour killing, which may promote immune priming[3-8]

MAINTENANCE: durvalumab + olaparib



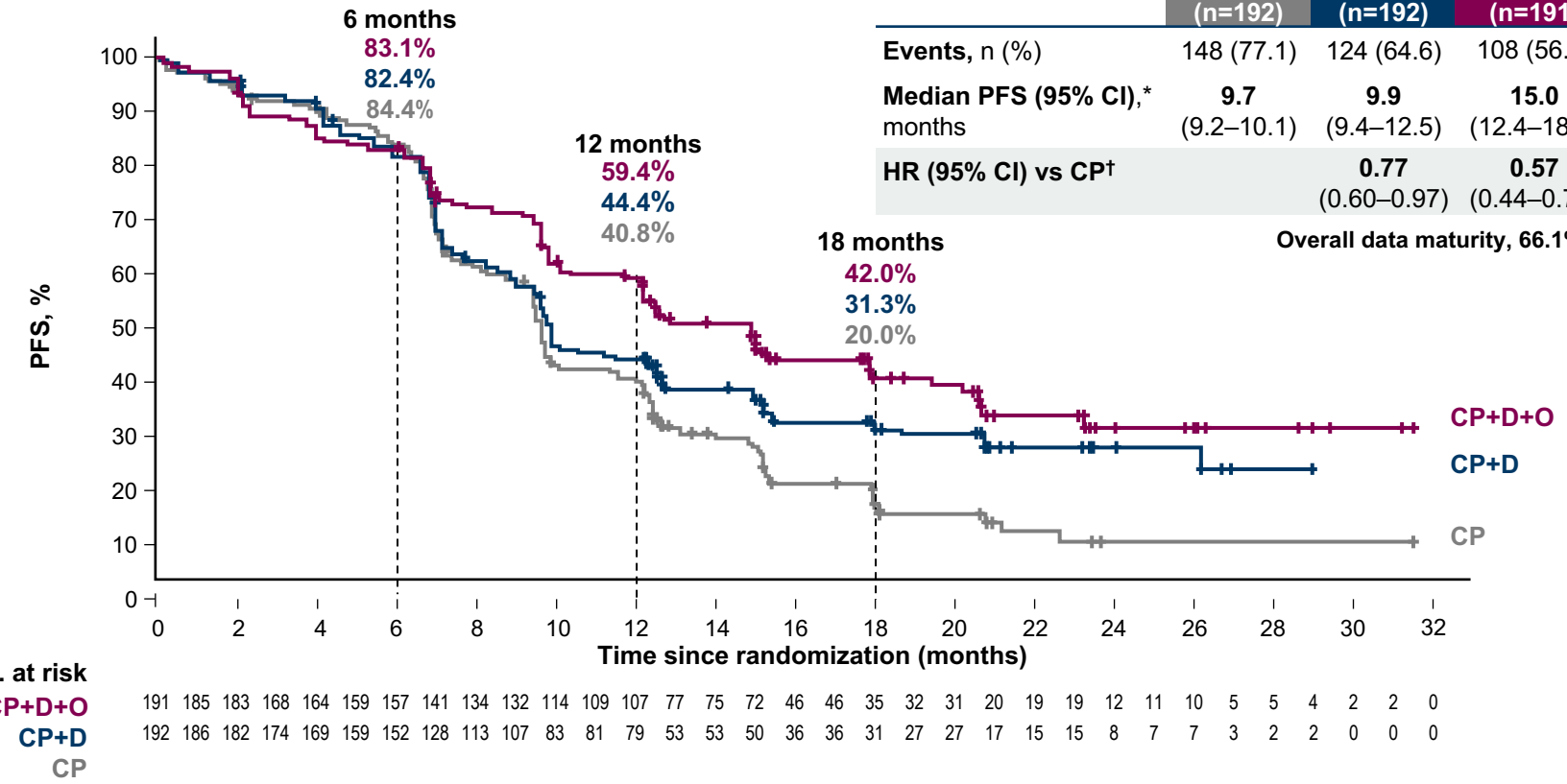
Olaparib induces DNA damage and further immune priming, which may promote more robust anti-tumour immunity and potentially more durable benefit for the **durvalumab + olaparib** combination[9-11]



prespecified exploratory analysis – PFS in pMMR[1]

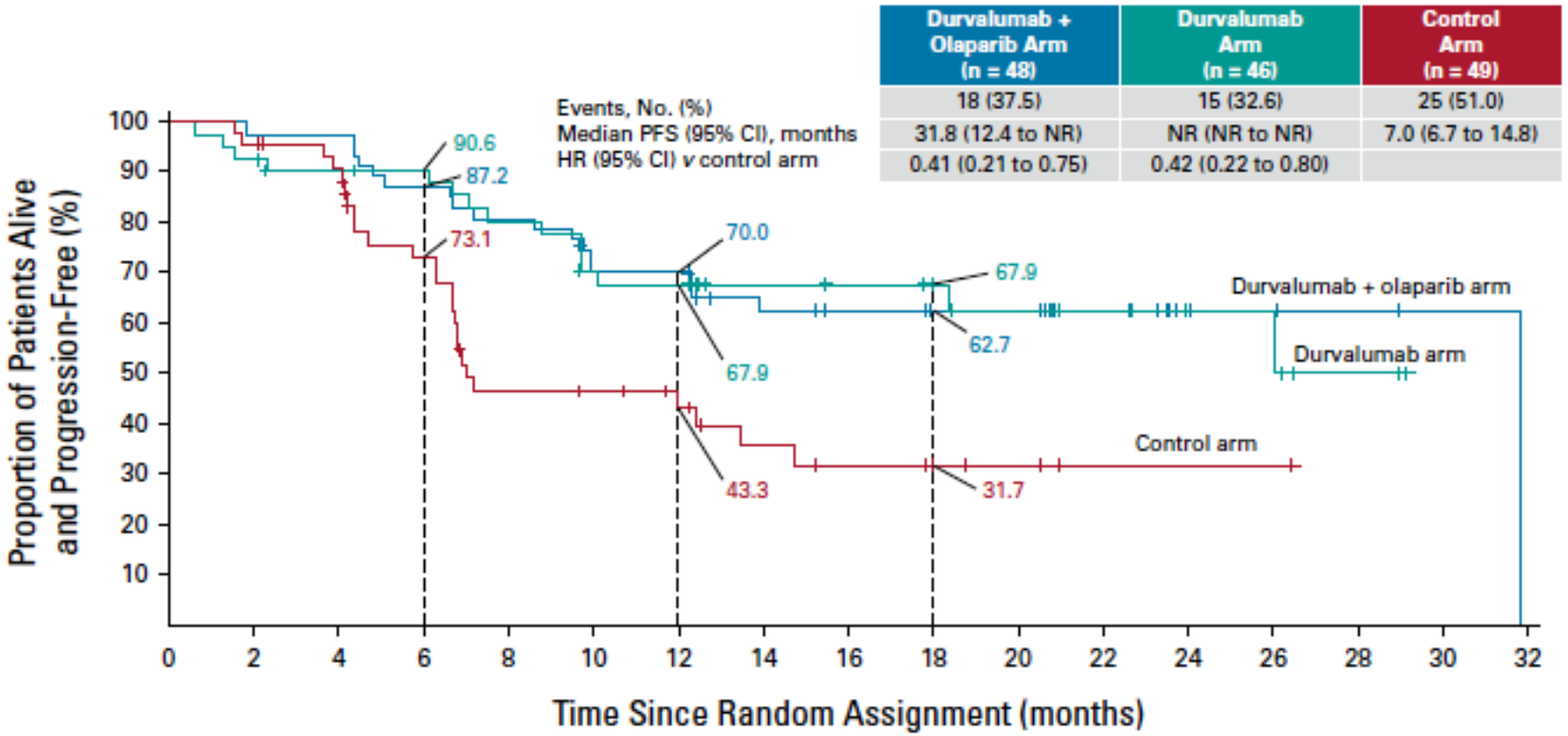
	CP (n=192)	CP+D (n=192)	CP+D+O (n=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	**9.7** (9.2–10.1)	**9.9** (9.4–12.5)	**15.0** (12.4–18.0)
HR (95% CI) vs CP†		**0.77** (0.60–0.97)	**0.57** (0.44–0.73)

Overall data maturity, 66.1%



Westin SN *J Clin Oncol* 2024, Rizzo A *J Clin Med.* 2022; Yang Y *Int J Gynaecol Obstet.* 2024; Antill Y *Cancer.* 2022 Corr B, *BMJ Med.* 2022; Eskander RN & Powell MA. *Ther Adv Med Oncol.* 2021; Liu T-Y *Theranostics.* 2021; El-ghazzi N *Onco Targets Ther.* 2023; Stewart RA *Cancer Res.* 2018; Musacchio L *Cancer Manag Res.* 2020; Post CCB, *Crit Rev Oncol Hematol.* 2020

dMMR Subpopulation PFS Results

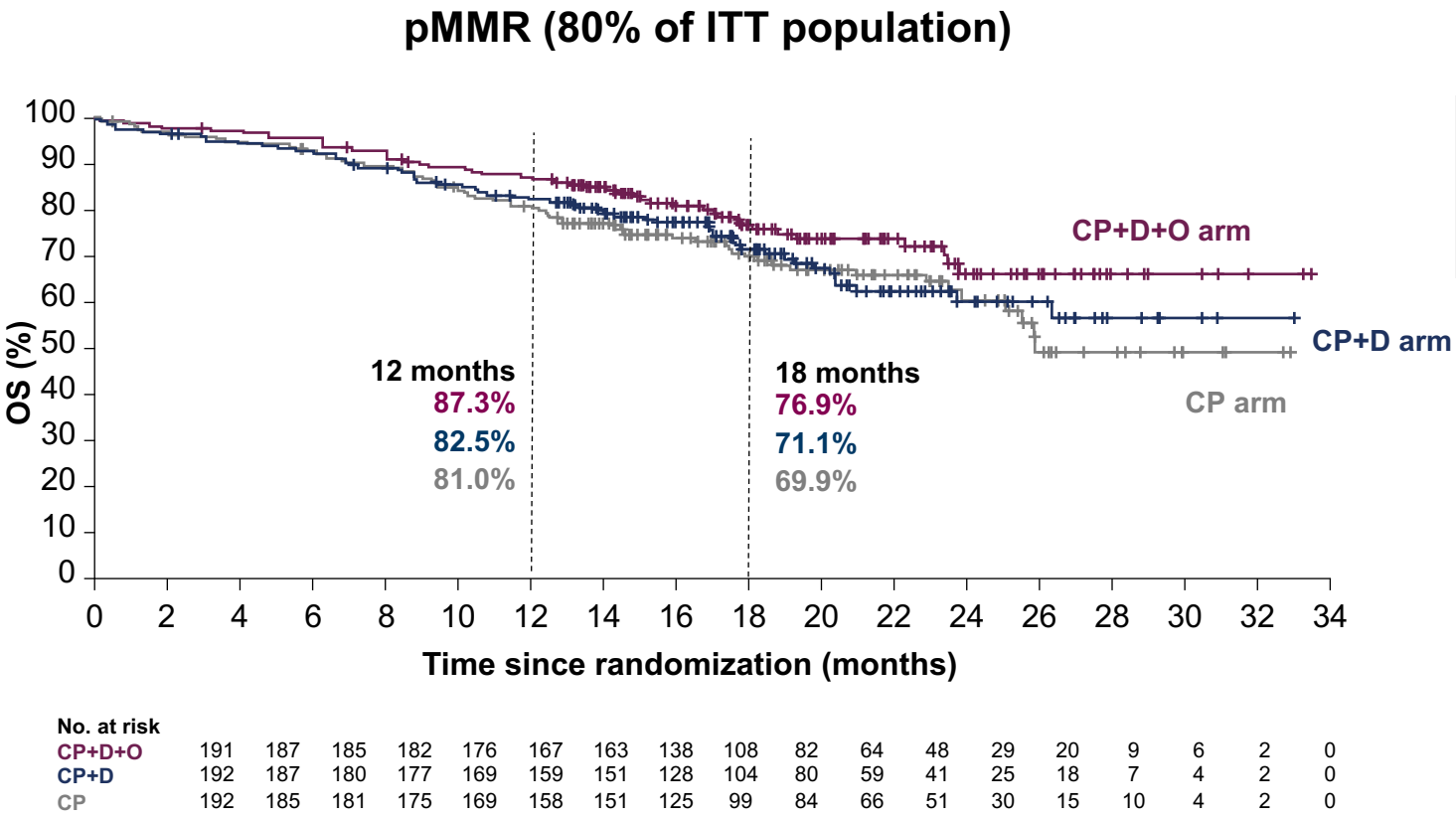


No. at risk:

Durvalumab + olaparib arm	48	47	46	46	46	41	41	39	38	37	32	32	32	24	23	23	18	18	16	16	16	10	10	9	4	3	3	2	2	1	1	1	0
Durvalumab arm	46	42	40	37	37	36	36	34	32	31	27	26	26	19	19	19	17	17	14	11	11	9	9	7	5	5	5	2	2	1	0	0	0
Control arm	49	45	43	41	39	29	28	19	17	17	16	15	13	10	9	8	7	7	5	4	4	2	2	2	2	2	2	0	0	0	0	0	0

Westin SN *J Clin Oncol* 2024.

Post-hoc Exploratory Analysis: Interim OS Data – Adding Olaparib Maintenance to Durvalumab + Chemotherapy in Patients with pMMR EC



	CP arm (n=192)	CP+D arm (n=192)	CP+D+O arm (n=191)
Events, n (%)	64 (33.3)	58 (30.2)	46 (24.1)
Median OS (95% CI), months	25.9 (25.1–NR)	NR (NR–NR)	NR (NR–NR)
HR (95% CI) vs CP arm*		0.91 (0.64–1.30)	0.69 (0.47–1.00)
HR (95% CI) vs CP+D arm*			**0.75 (0.51–1.11)**

Overall data maturity: 29.2%

DCO: April 12, 2023. For dMMR subpopulation, median duration of follow-up for OS was 18.4 (CP), 19.1 (CP+D) and 19.9 months (CP+D+O) in censored patients; for pMMR subpopulation, median duration of follow-up was 18.6 (CP), 18.2 (CP+D) and 18.4 months (CP+D+O) in censored patients. MMR status was evaluated using the Ventana MMR immunohistochemistry panel. OS rates were estimated by the Kaplan–Meier method.
***HRs and CIs were estimated from an unstratified Cox proportional hazards model.**

1. Westin SN, et al. *J Clin Oncol*. 2024;42:283–99. doi/full/10.1200/JCO.23.02132.; 2. European Medicines Agency (EMA). *Summary of product characteristics: durvalumab.* Last updated: 23/10/2024; https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf.

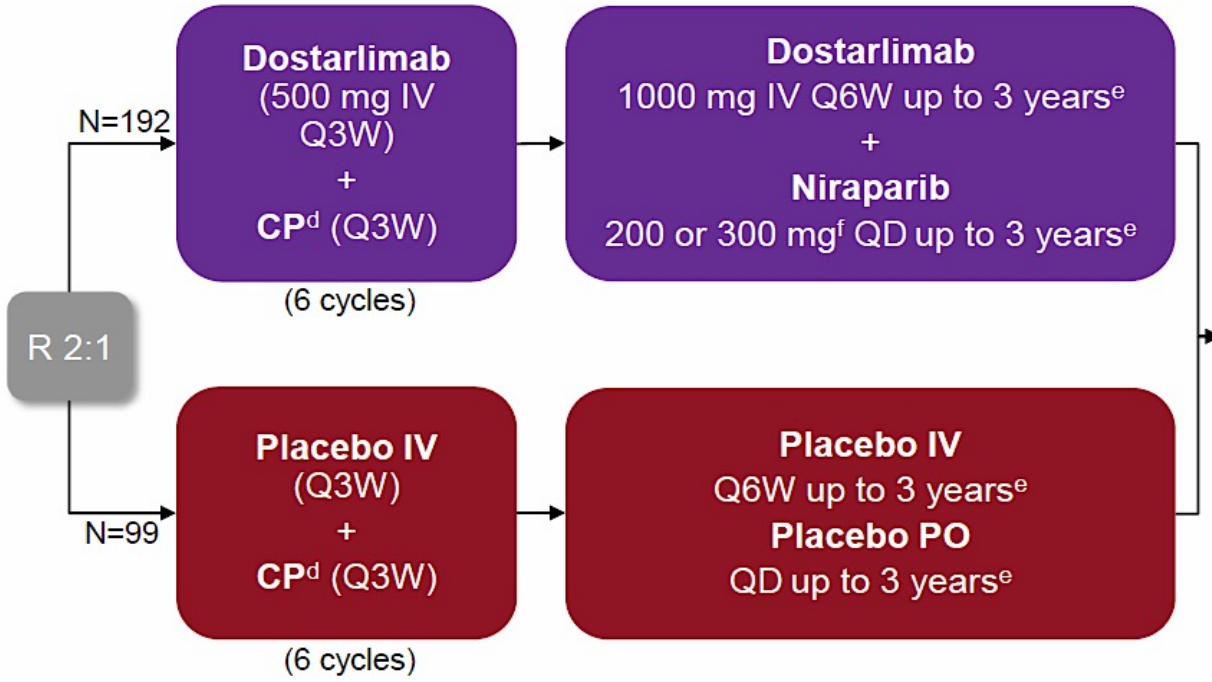
ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2 Study Design

Eligible patients

- Stage III/IV disease or first recurrent EC[a]
  - All histologies except sarcomas[b]
- Naive to systemic anticancer therapy or had a recurrence or PD ≥6 months after completing systemic anticancer therapy
- Naive to PARP inhibitor therapy

Stratification

- MMR/MSI status[c]
  - 25% dMMR/MSI-H
  - 75% MMRp/MSS
- Prior external pelvic radiotherapy
- Disease status



Primary endpoint

- PFS by INV per RECIST v1.1
  - Overall
  - MMRp/MSS

Secondary endpoints

- OS
- PFS by BICR
- ORR
- DOR
- DCR (BOR of CR, PR, or SD)
- PFS2
- HRQOL/PRO
- PK

Dostarlimab + CT + niraparib is not indicated in pMMR

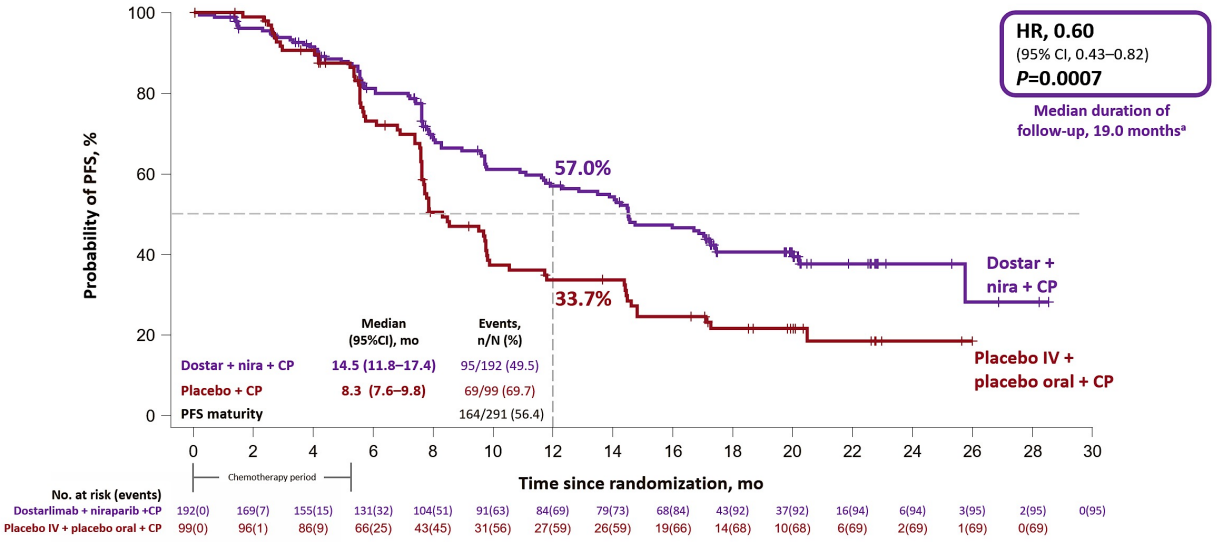
[a]Histologically/cytologically proven advanced or recurrent EC; stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination. [b]Carcinoma, clear cell, serous, or mixed histology permitted. [c]Patients were randomized based on either local or central MMR/MSI testing results. [d]carboplatin AUC 5mg/mL/min and paclitaxel 175 mg/m^2. [e]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigators decision, or death, whichever occurs first.

BOR, best overall response; CP, carboplatin/paclitaxel; CR, complete response; DCR, disease control rate; DOR, duration of response; EC, endometrial cancer; HRQOL, health related quality of life; MSI, microsatellite stability; (d)(p)MMR, mismatch repair (deficient) (proficient); ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression free survival; PK, pharmacokinetics; PR, partial response; PRO, patient reported outcome; QD, once a day; SD, stable disease

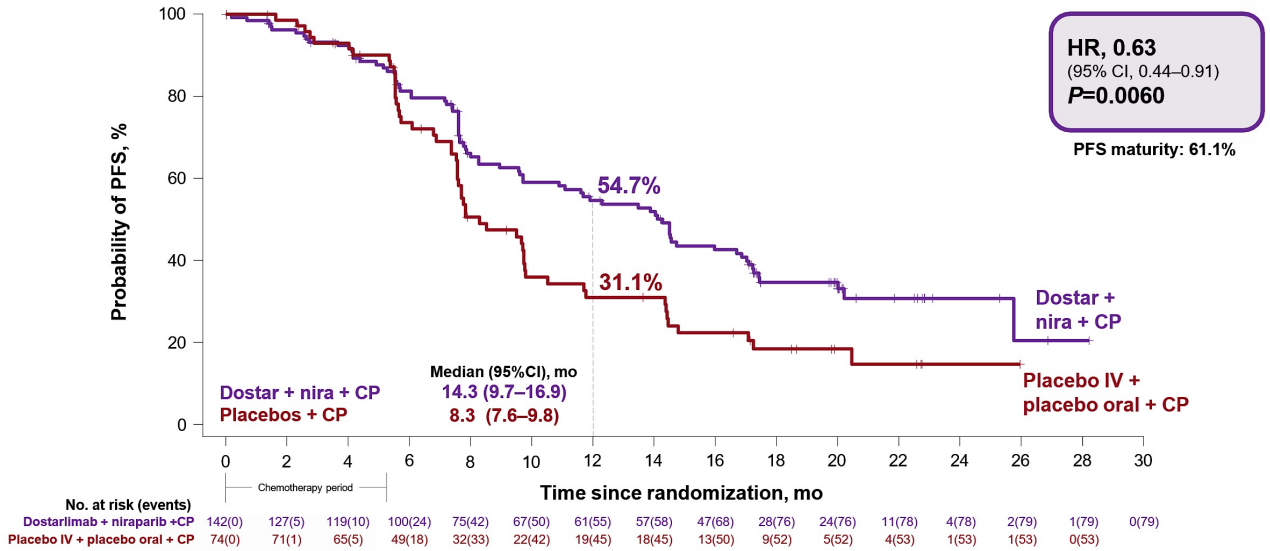
Mirza MR, et al. Presented at Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, California USA.

RUBY Part 2 Demonstrated Statistically Significant PFS Benefit in the Overall and pMMR Populations

Overall population



MMRp/MSS population



[a]Median expected duration of follow-up.
CP, carboplatin-paclitaxel; dostar, dostarlimab; HR, hazard ratio; nira, niraparib; PFS, progression-free survival.

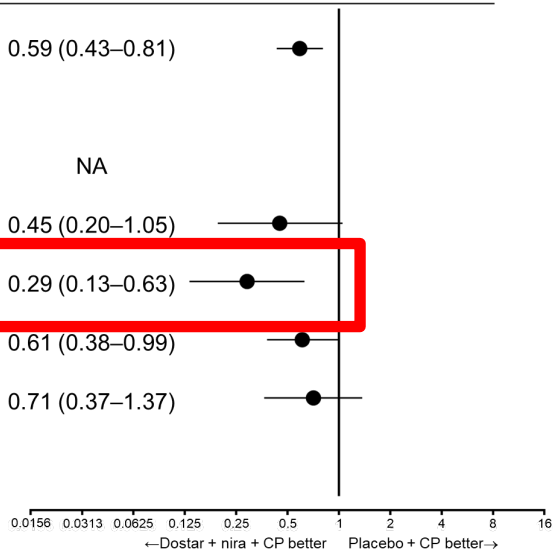
Mirza MR, et al. Presented at Society of Gynecologic Oncology (SGO) Annual Meeting on Women's Cancer; 16-18 March 2024; San Diego, California USA.

RUBY Part 2 PFS Analyses of Exploratory Biomarkers

Exploratory PFS Subgroup Analyses in Overall and pMMR Populations

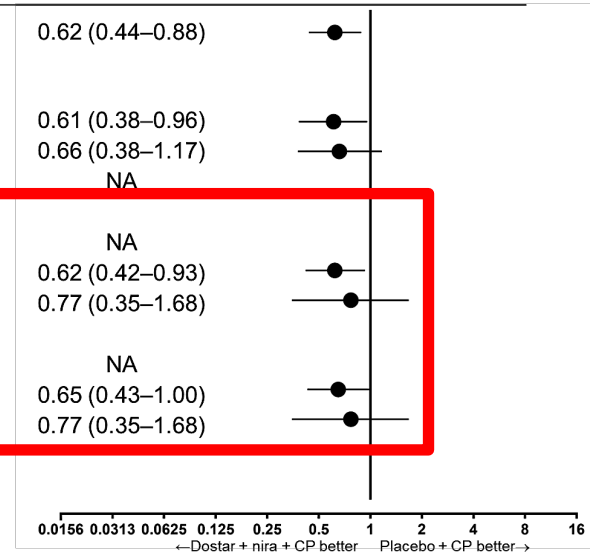
Overall Population by Molecular Subgroup

	Dostarlimab + niraparib + CP N=192	Placebo IV + placebo oral + CP N=99	HR (95%CI)
	No. of patients with events/No. of patients		
All patients	95/192	69/99	0.59 (0.43–0.81)
Molecular subgroup[a]			
POLE	0/3	1/2	NA
dMMR/MSI-H	12/37	10/17	0.45 (0.20–1.05)
TP53mut	27/39	10/10	0.29 (0.13–0.63)
NSMP	37/75	31/46	0.61 (0.38–0.99)
Not evaluable[b]	19/38	17/24	0.71 (0.37–1.37)



MMRp/MSS Population

	Dostarlimab + niraparib + CP N=142	Placebo IV + placebo oral + CP N=74	HR (95%CI)
	No. of patients with events/No. of patients		
All patients	79/142	53/74	0.62 (0.44–0.88)
PD-L1 Status[a]			
PD-L1+	46/88	31/44	0.61 (0.38–0.96)
PD-L1-	32/53	20/26	0.66 (0.38–1.17)
Not evaluable[b]	1/1	2/4	NA
BRCA mutation status			
Positive	1/4	2/3	NA
Negative	63/113	40/55	0.62 (0.42–0.93)
Not evaluable[b]	15/25	11/16	0.77 (0.35–1.68)
HRR mutation status[c]			
Positive	3/10	8/11	NA
Negative	61/107	34/47	0.65 (0.43–1.00)
Not evaluable[b]	15/25	11/16	0.77 (0.35–1.68)

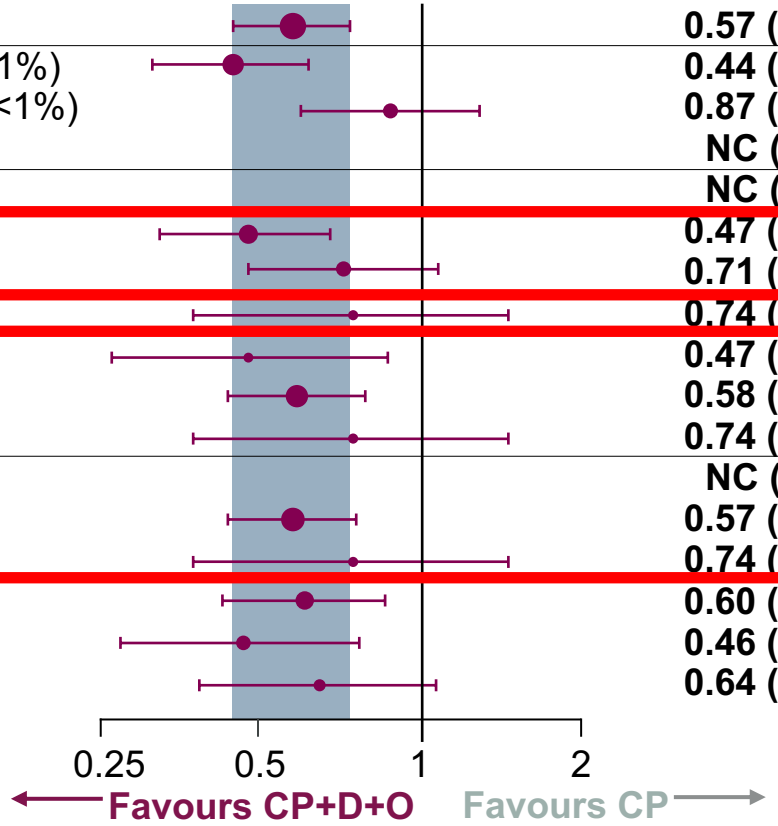


Mirza. SGO 2024

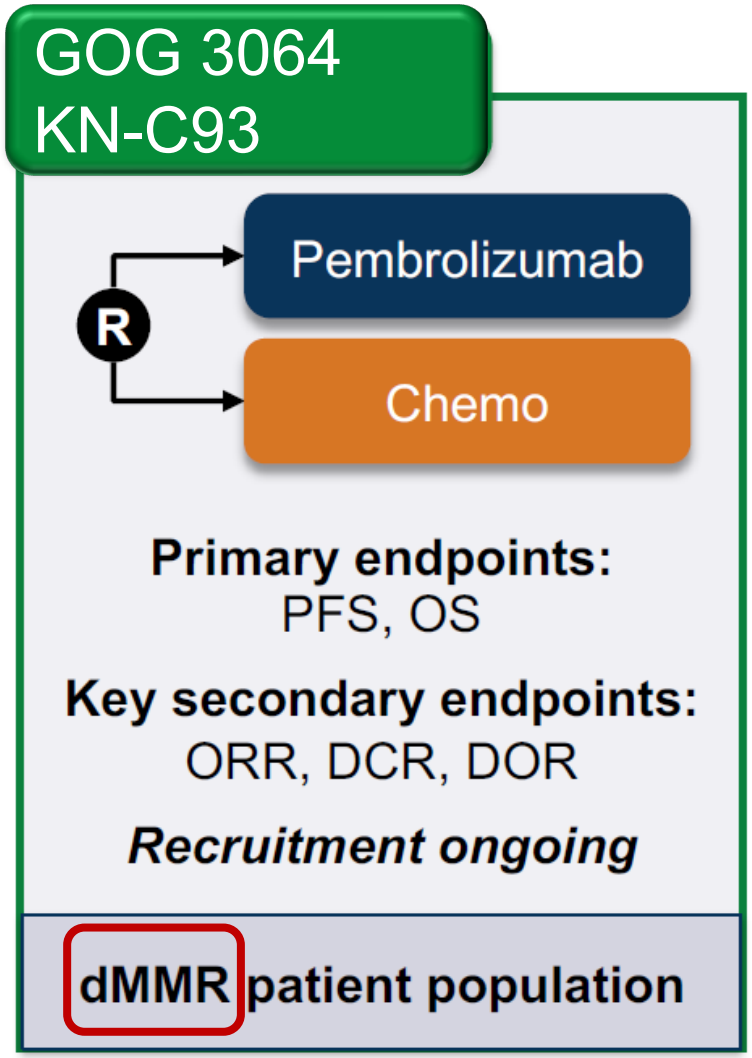
pMMR Subpopulation: PFS by Biomarker Subgroup
CP + Durvalumab + Olaparib vs CP

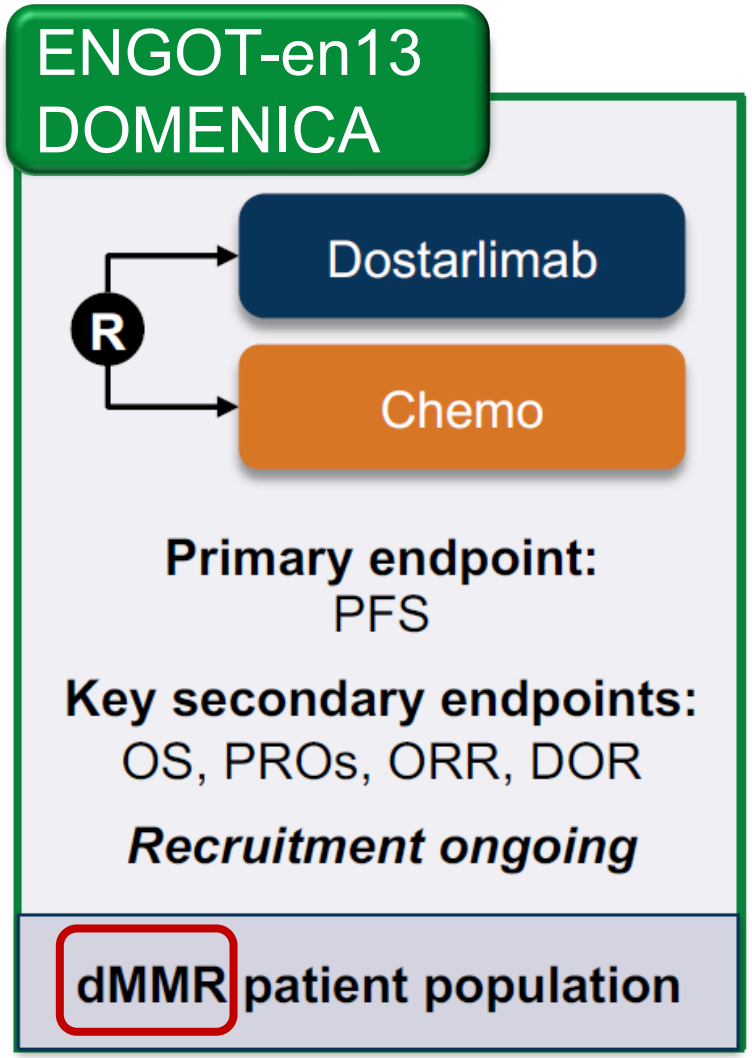
***Post hoc* exploratory analysis**

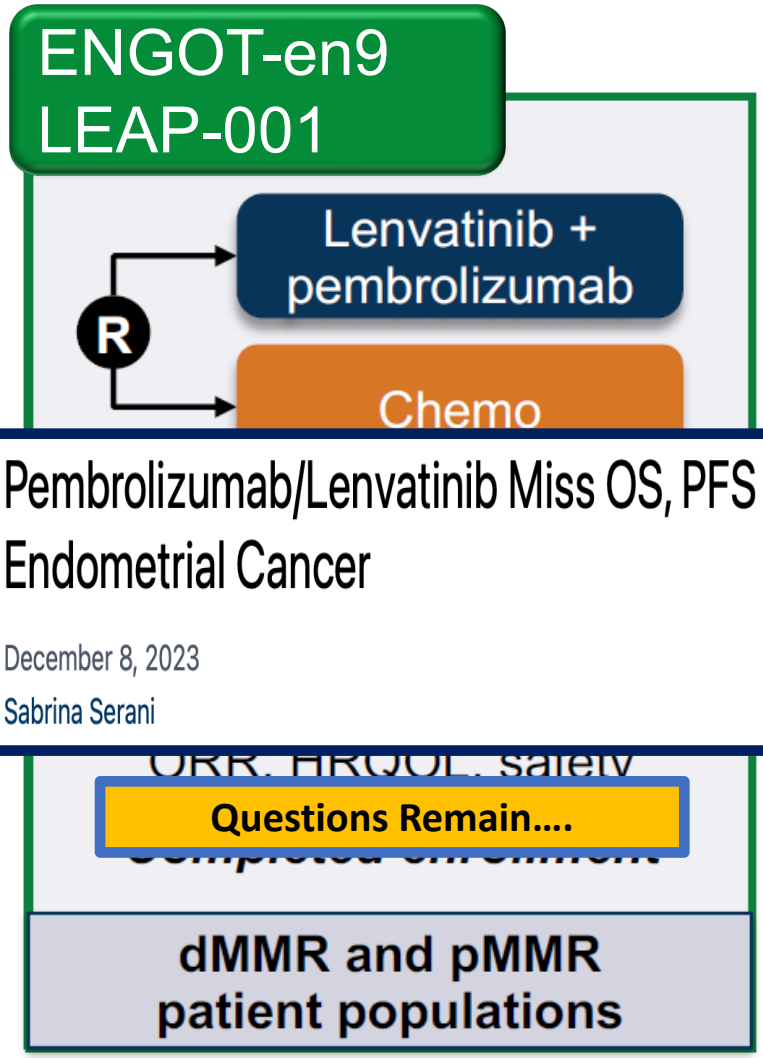
		HR (95% CI)	CP+D+O n/N	CP n/N
All pMMR patients		**0.57 (0.44–0.73)**	108/191	148/192
PD-L1 expression*	Positive (TAP score ≥1%)	**0.44 (0.31–0.61)**	54/112	94/124
	Negative (TAP score <1%)	**0.87 (0.59–1.28)**	52/73	53/67
	Unknown	**NC (NC–NC)‖**	2/6	1/1
***POLE*m and *TP53*m status†,‡**	*POLE*m	**NC (NC–NC)‖**	1/5	0/1
	*TP53*m	**0.47 (0.32–0.67)**	52/89	73/90
	TP53 wild-type	**0.71 (0.47–1.07)**	41/72	54/71
	Unknown	**0.74 (0.37–1.45)**	14/25	21/30
HRRm status†,§	HRRm	**0.47 (0.26–0.86)**	22/40	22/27
	Non-HRRm	**0.58 (0.43–0.78)**	72/126	105/135
	Unknown	**0.74 (0.37–1.45)**	14/25	21/30
BRCAm status†	BRCAm	**NC (NC–NC)‖**	7/14	11/13
	Non-BRCAm	**0.57 (0.43–0.75)**	87/152	116/149
	Unknown	**0.74 (0.37–1.45)**	14/25	21/30
Histology	Endometrioid	**0.60 (0.42–0.85)**	56/107	71/98
	Serous	**0.46 (0.27–0.76)**	24/42	43/52
	Other¶	**0.64 (0.38–1.06)**	28/42	34/42



Moving Immunotherapy Efforts into the Frontline as Chemotherapy Replacement…







Pembrolizumab/Lenvatinib Miss OS, PFS in Endometrial Cancer

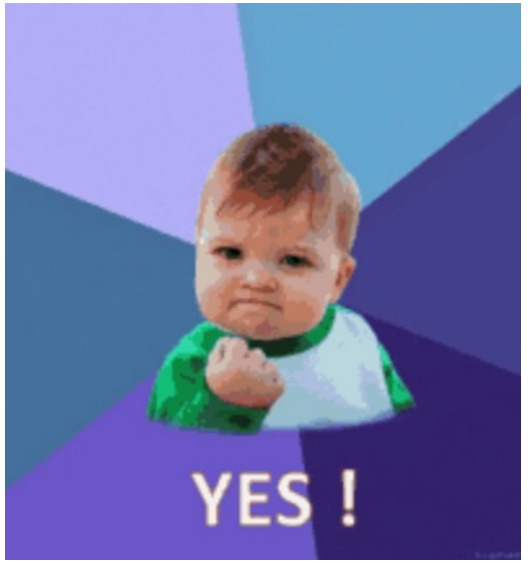
December 8, 2023

Sabrina Serani

Questions Remain….

Conclusions

- Clear role for immunotherapy in endometrial cancer, especially in MMRd
  - Will single agent IO overthrow chemotherapy + IO?
- Evolving understanding of the best treatment of MMRp – need to further split this subtype
  - P53, NSMP, HER2, ER/PR+
  - PARPi appears to provide benefit – do we tease out or just treat everyone right now?
- 2nd line – can we use IO after IO?



Case Presentation: 61-year-old woman with Stage IIIC dMMR endometrial cancer and Lynch syndrome undergoes debulking surgery and receives carboplatin/docetaxel/pembrolizumab followed by pembrolizumab maintenance

Dr Gigi Chen (Walnut Creek, California)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

How do you decide whether to incorporate an anti-PD-1/PD-L1 antibody for a patient such as this? Would you prefer a specific anti-PD-1/PD-L1 antibody, or do you consider them essentially equivalent in terms of efficacy and tolerability?

Have you encountered increased GI toxicity when anti-PD-1/PD-L1 antibodies are administered during radiation therapy? For your patients with Stage III/IV endometrial cancer who are going to receive chemoimmunotherapy and radiation therapy, do you hold the anti-PD-1/PD-L1 antibody during the radiation therapy?

How do you approach first-line therapy for patients with endometrial cancer who develop metastatic disease after adjuvant chemotherapy?

RTP
RESEARCH
TO PRACTICE

Case Presentation: 67-year-old woman with MSS high-grade serous endometrial cancer and recurrence in vaginal cuff after hysterectomy receives carboplatin/paclitaxel/pembrolizumab

Dr Erik Rupard (Hershey, Pennsylvania)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

For patients with advanced endometrial cancer who are receiving up-front chemotherapy in combination with an anti-PD-1/PD-L1 antibody, how long do you continue the anti-PD-1/PD-L1 antibody in the maintenance setting?

In general, how does the addition of anti-PD-1/PD-L1 antibodies to up-front chemotherapy affect tolerability for patients with advanced endometrial cancer? What are the most common tolerability issues that you encounter with these combinations?

Do you believe there is the potential for cure or long-term survivorship for patients with advanced endometrial cancer who receive up-front therapy with chemotherapy and an anti-PD-1/PD-L1 antibody?

Questions for the Faculty

Does histologic subtype (pure endometrioid carcinoma, endometrial carcinoma, high- or low-grade serous, etc) affect the likelihood of response to first-line anti-PD-1/PD-L1 antibody-containing regimens? What about level of PD-L1 expression? Are there any situations in which you still prefer chemotherapy alone?

Do you think regimens combining PARP inhibitors with immune checkpoint inhibitors may eventually have a role in newly diagnosed advanced endometrial cancer? If these regimens were to become available, in which patients can you envision prioritizing their use?

What would you recommend next for this patient at the time of disease progression? Is there any role for anti-CTLA-4 antibodies in this setting?

RTP
RESEARCH
TO PRACTICE

Agenda

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

MODULE 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr O'Malley

MODULE 3: Role of HER2-Targeted Therapy in Advanced OC, Endometrial Cancer (EC) and Other Gynecologic Cancers — Dr Santin

MODULE 4: First-Line Therapy for Advanced EC — Dr Westin

MODULE 5: Current Therapeutic Options for R/R EC; Novel Investigational Strategies for Newly Diagnosed and Recurrent Disease — Dr Salani

RTP RESEARCH TO PRACTICE

Therapeutic Options for Endometrial Cancer: Current and Novel Investigational Strategies

Ritu Salani, M.D., M.B.A.
Professor

UCLA Health

Objectives

- Review up to date management of recurrent endometrial cancer, pMMR with lenvatinib and pembrolizumab
- Discuss emerging targeted therapy options
  - Selinexor
  - TROP2 ADC
  - FOLR1 ADC
  - Non-ADC options

Advanced Endometrial Cancer

- 2000s: Chemotherapy became standard of care
  - 2010: Carboplatin and paclitaxel became the preferred regimen
- 80% will experience recurrence within first 2 years

Study (control arm)	Median PFS, mo
GOG 209	13
GY018	8.7
RUBY	7.9
MITO END-2	10.5
FANDANGO	7.2

Miller DS, et al. *J Clin Oncol*. 2020;38:3841-3850.

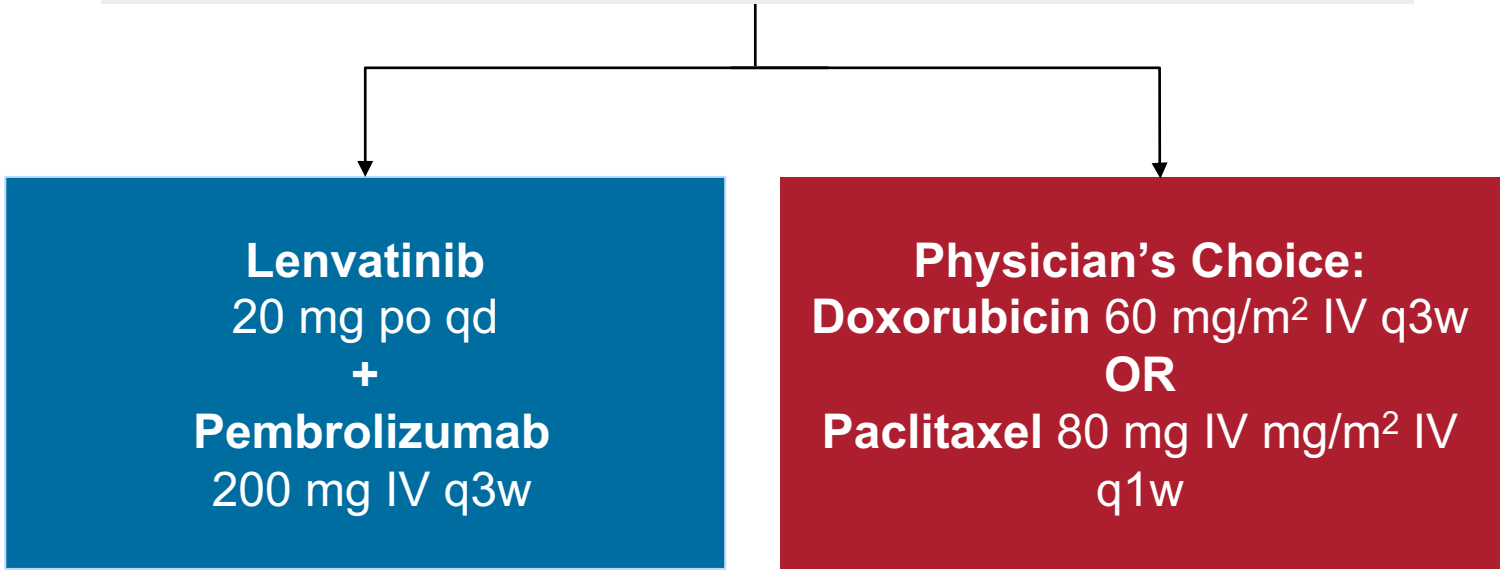
KEYNOTE-775: Recurrent Endometrial Cancer

Key Eligibility Criteria

- Advanced, metastatic, or recurrent EC
- Measurable disease by BICR
- 1 prior platinum-based chemotherapy regimen
- ECOG PS 0–1

Stratification Factors

- MMR status (dMMR vs MMRp)
- ECOG PS
- Geographic region
- Prior pelvic radiation



Primary Endpoints

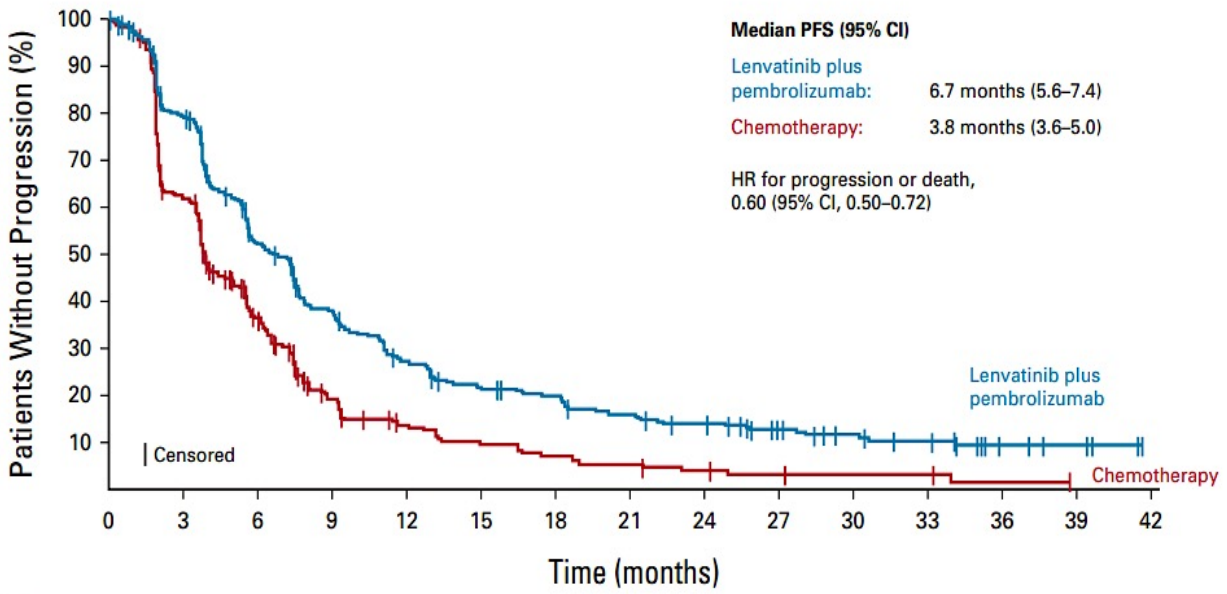
- PFS by BICR and OS

UCLA Health

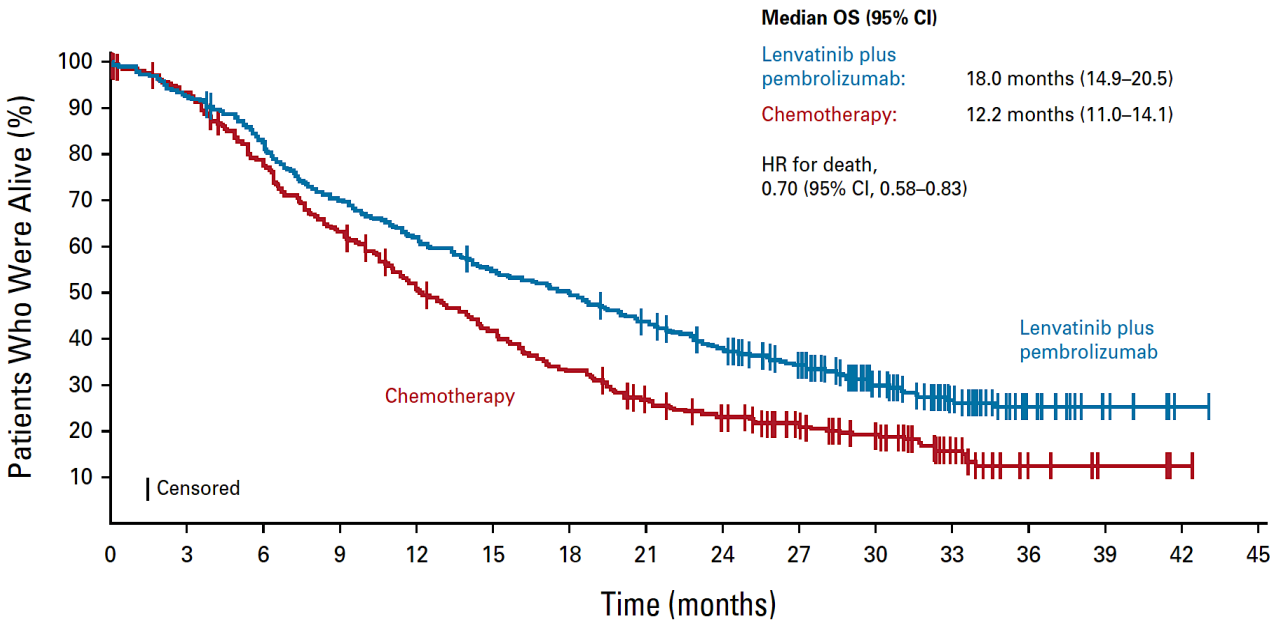
Makker V, et al. *N Engl J Med*. 2022;386:437-448.

KEYNOTE-775: Survival Outcomes pMMR

Progression Free Survival



Overall Survival



pMMR Population	ORR, (95% CI)	mDOR, mo (range)	mOS, mo (95% CI)	HR
Len + Pem	32.4% (27.5–37.6)	9.3 (1.6+ to 39.5+)	18.0 (14.2–19.)	0.70 (0.56–0.83)
Chemotherapy	15.1% (11.5–19.3)	5.7 (0.0+ to 37.1+)	12.2 (11.0–14.1)	

UCLA Health

Makker V. *J Clin Oncol*. 2023;41:2904-2910.

TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 388)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hypertension	65.0	39.2	5.2	2.6
Hypothyroidism	58.9	1.5	0.8	0
Diarrhea	55.7	8.1	20.4	2.1
Nausea	51.7	3.4	46.4	1.3
Decreased appetite	46.6	7.6	21.4	0.5
Vomiting	37.7	3.0	21.1	2.6
Weight decrease	35.5	10.8	5.9	0.3
Fatigue	34.0	5.4	27.6	3.1
Arthralgias	32.3	1.7	8.0	0

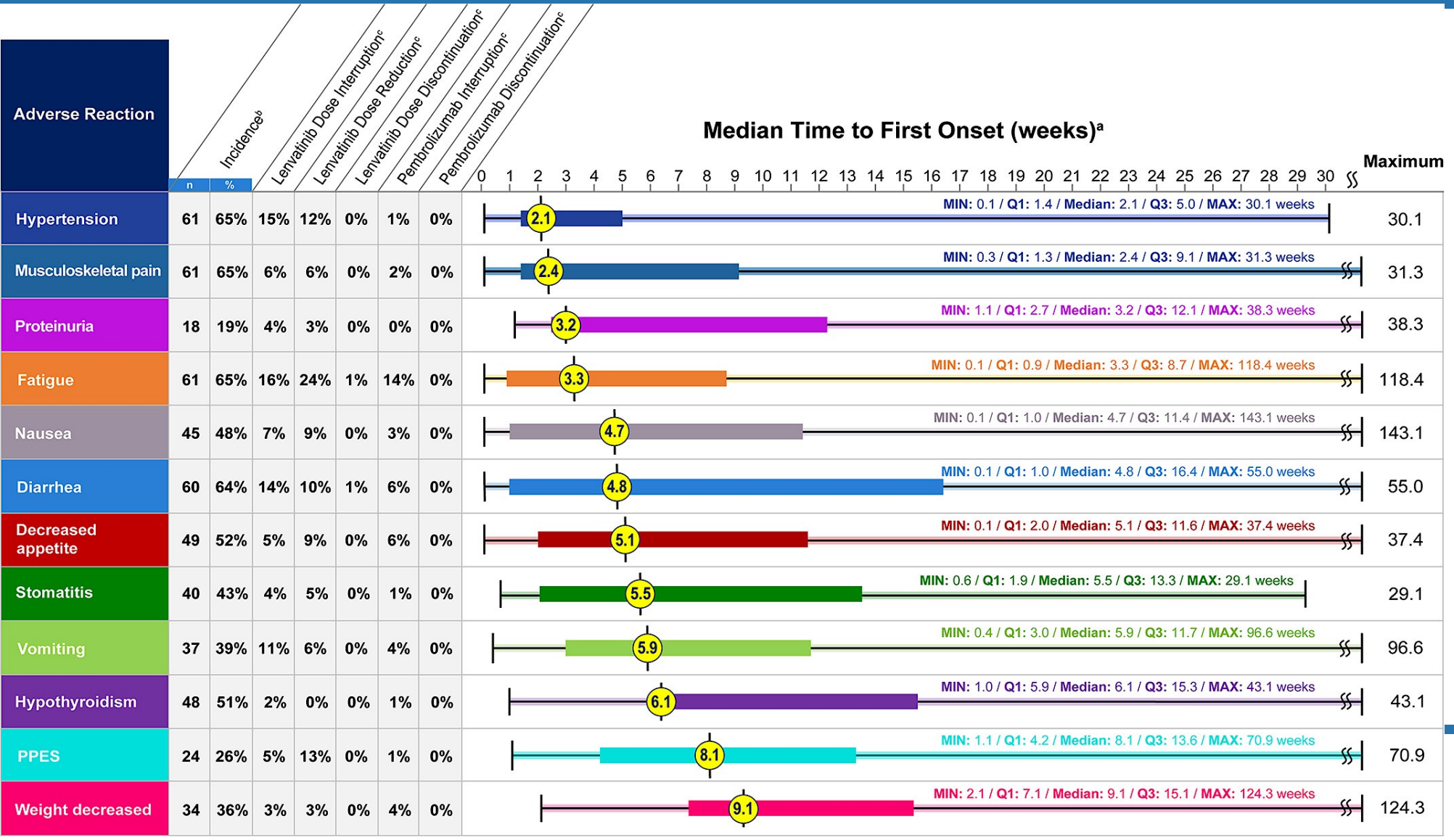
TEAE, %	Lenvatinib + Pembrolizumab (n = 406)		Doxorubicin or Paclitaxel (n = 388)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Proteinuria	30.5	5.2	3.4	0.3
Constipation	28.3	0.7	24.5	0.5
Anemia	28.1	6.9	48.7	15.5
UTI	27.6	4.2	10.3	1.0
Headache	26.4	0.5	9.0	0.3
Neutropenia	9.1	2.0	34.0	26.0
Alopecia	5.9	0	30.9	0.3

*In the lenvatinib and pembrolizumab arm, 6.4% of patients suffered grade 5 AEs, and 5.2% of patients in the TPC arm suffered grade 5 AEs.

Dose reductions 66.5%
Dose interruptions 69.2%
Discontinuation secondary to AE 33.0%

Makker V, et al. *N Engl J Med*. 2022;386:437-448;
Makker V, et al. *J Clin Oncol*. 2023;41:2904-2910.

Lenvatinib and Pembrolizumab: Adverse Events



Makker V, et al. *Oncologist.* 2021.

Maintenance Therapy in Endometrial Cancer

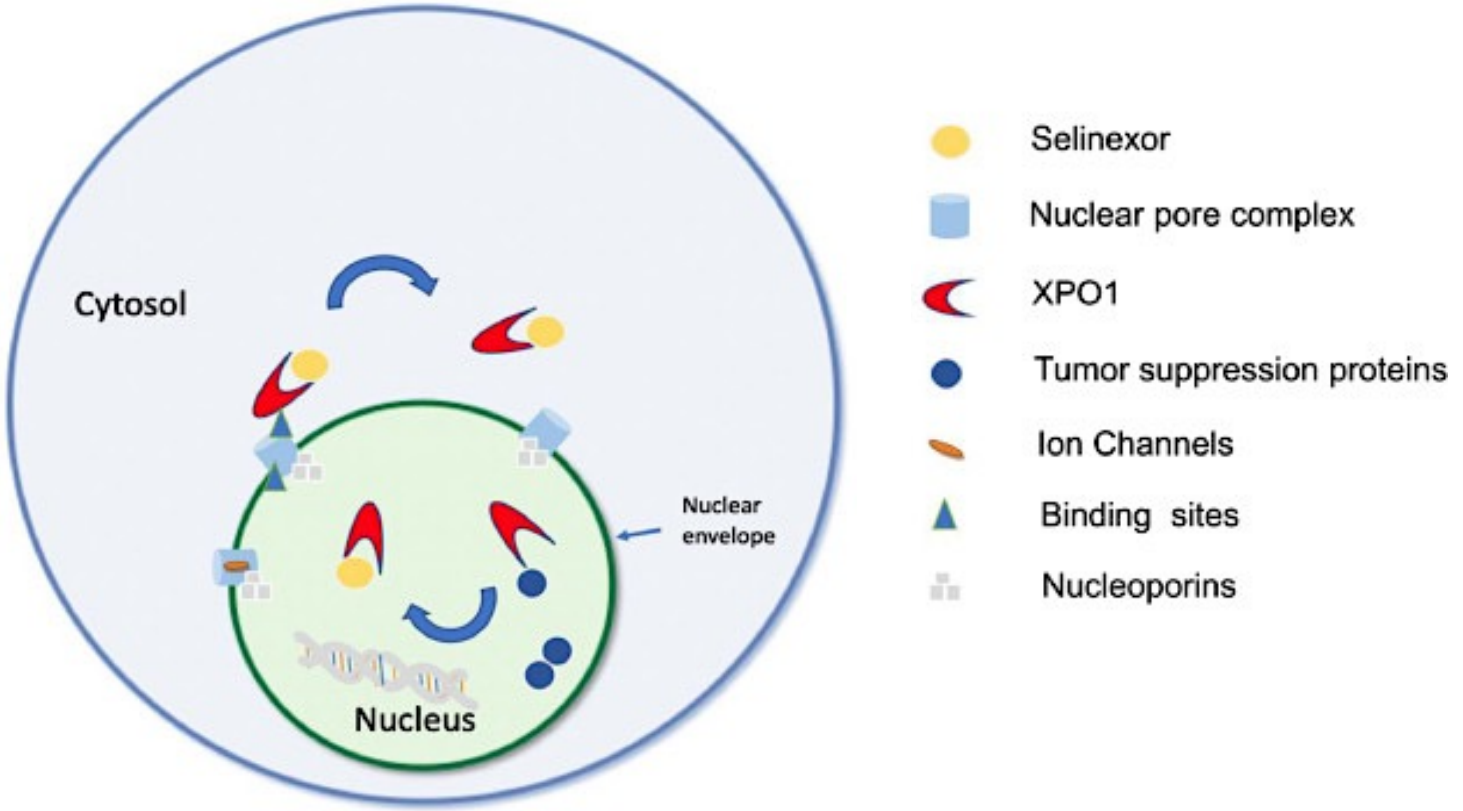
UCLA Health

Selinexor

- Frontline EC treatment includes checkpoint inhibitors and maintenance
  - Highest benefit in dMMR EC
  - Modest benefit in pMMR tumors
- Over 50% of advanced/recurrent EC are TP53wt
  - 40-55% are TP53 and pMMR

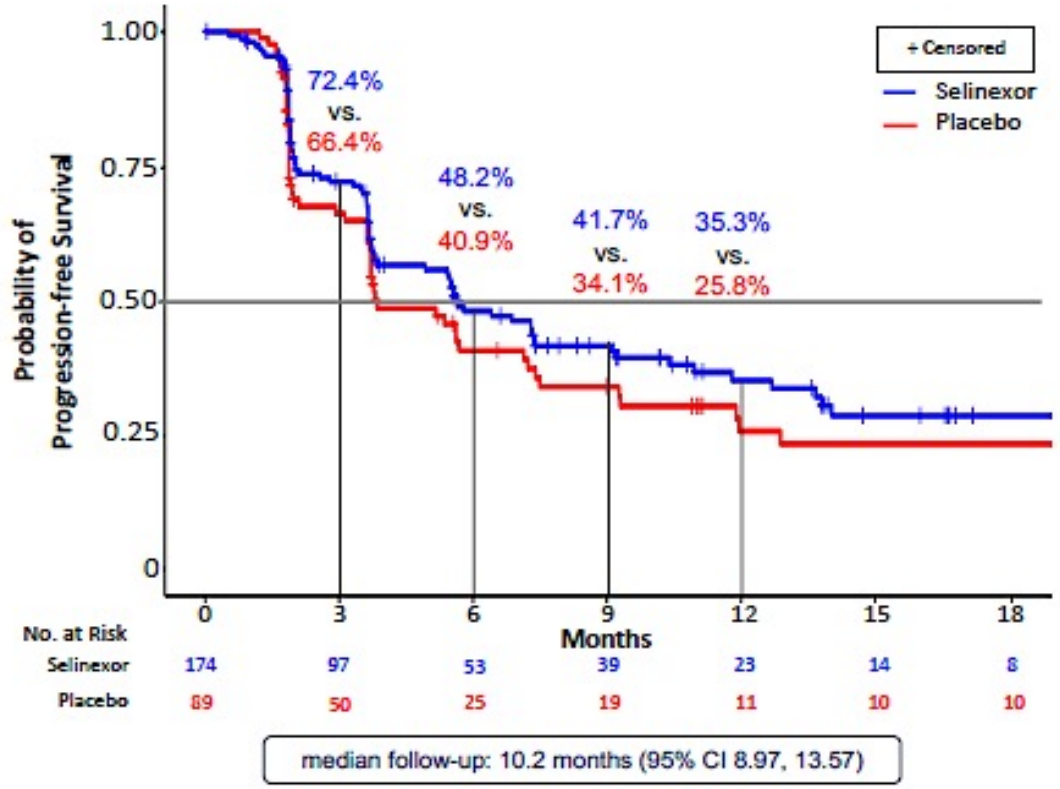
Bogani G. Curr Prob in Cancer 2023

- Selinexor is an oral XPO1 inhibitor
  - Prevents XPO1 mediated export of several tumor suppressor proteins
    - Including TP53



Phase II SIENDO Trial: Selinexor Maintenance

Primary Endpoint: PFS in ITT Population



Median PFS

Selinexor (n=174): 5.7 mo (95% CI 3.81-9.20)

Placebo (n=89): 3.8 mo (95% CI 3.68-7.39)

Audited* (by electronic case report form)

HR = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Unaudited* (by interactive response technology)

HR = 0.76 (95% CI 0.543-1.076)

One-sided P value = 0.063

*In 7 patients (2.7% of 263), the stratification factor of CR/PR was incorrect and was corrected by the Investigators prior to database lock and unblinding. The statistical analysis was validated by the independent ENGOT statistician and approved by the IDMC.

CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

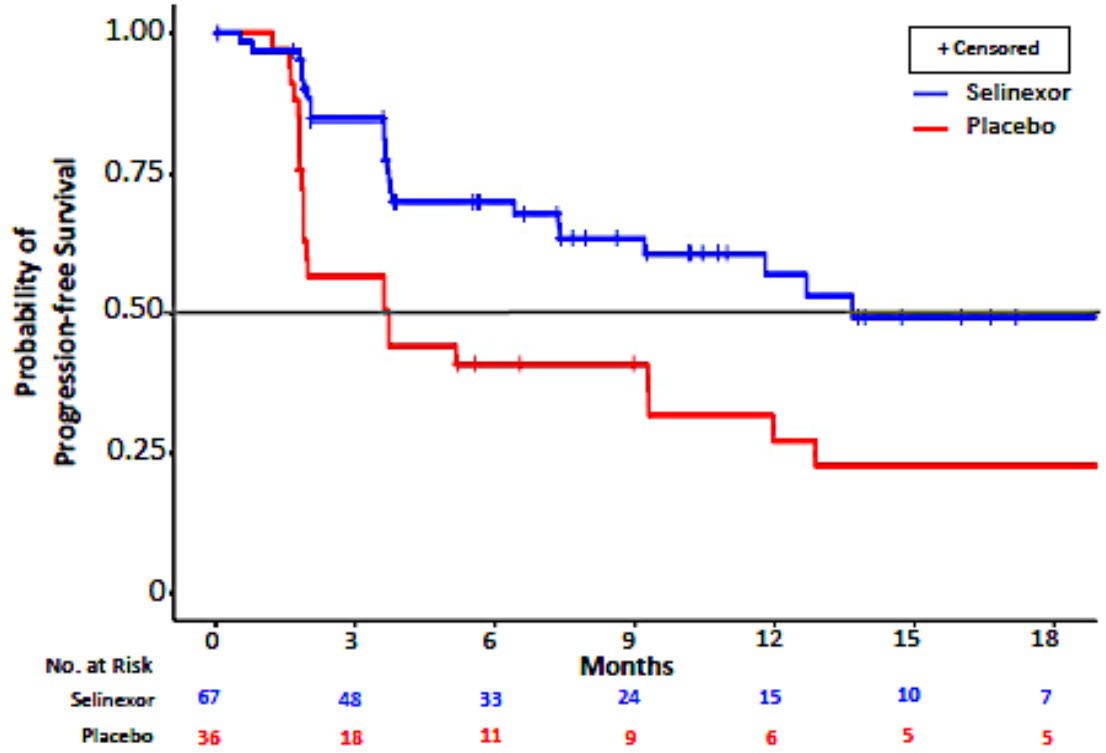
Vicky Makker, M.D., ENGOT-EN5/GOG-3055/SIENDO

UCLA Health

Makkar V. Gynecol Oncol 2024.

Phase II SIENDO Trial: Selinexor Maintenance

Preliminary Analysis of a Prespecified Exploratory Subgroup PFS: Patients with p53 wild-type EC



Median PFS

Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

Placebo (n=36): 3.7 mo (95% CI 1.87-12.88)

Audited

HR = 0.375 (95% CI 0.210-0.670)

Nominal one-sided P value = 0.0003

Unaudited

HR = 0.407 (95% CI 0.229-0.724)

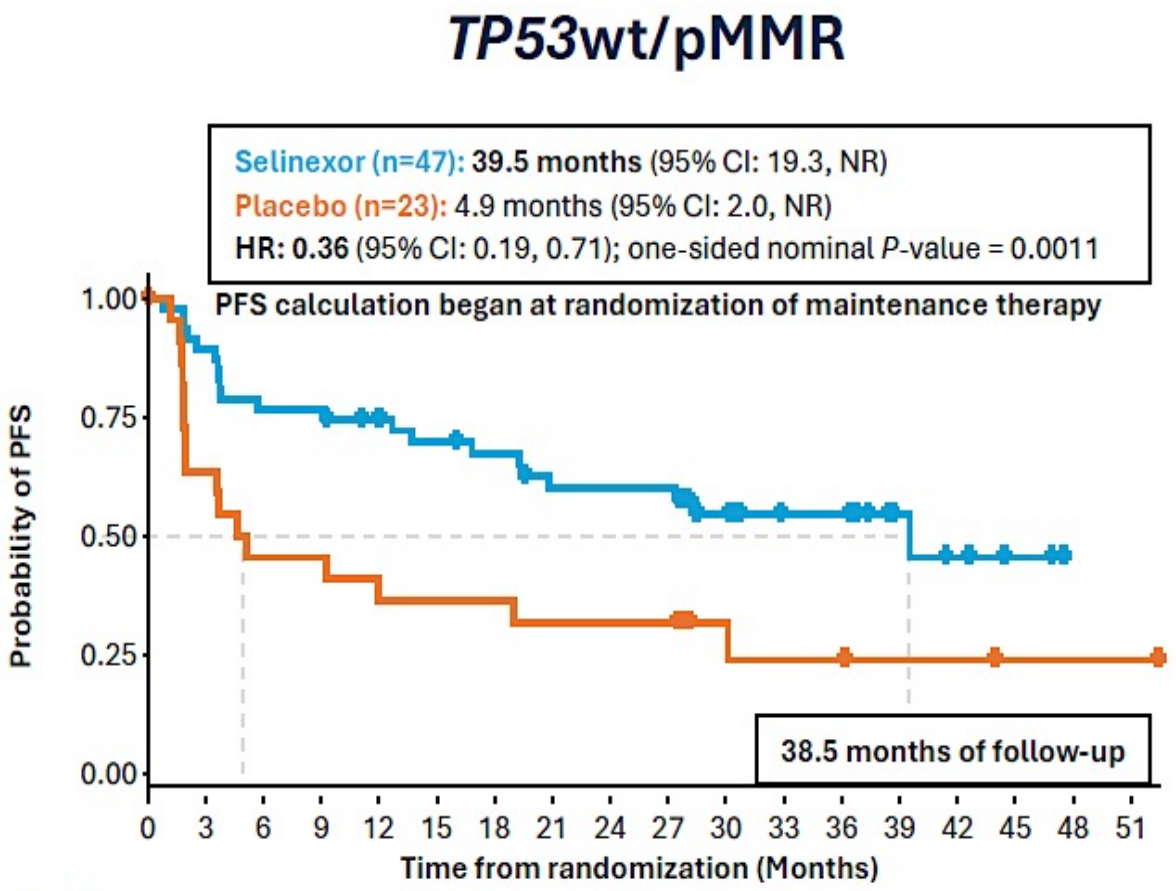
Nominal one-sided P value = 0.0008

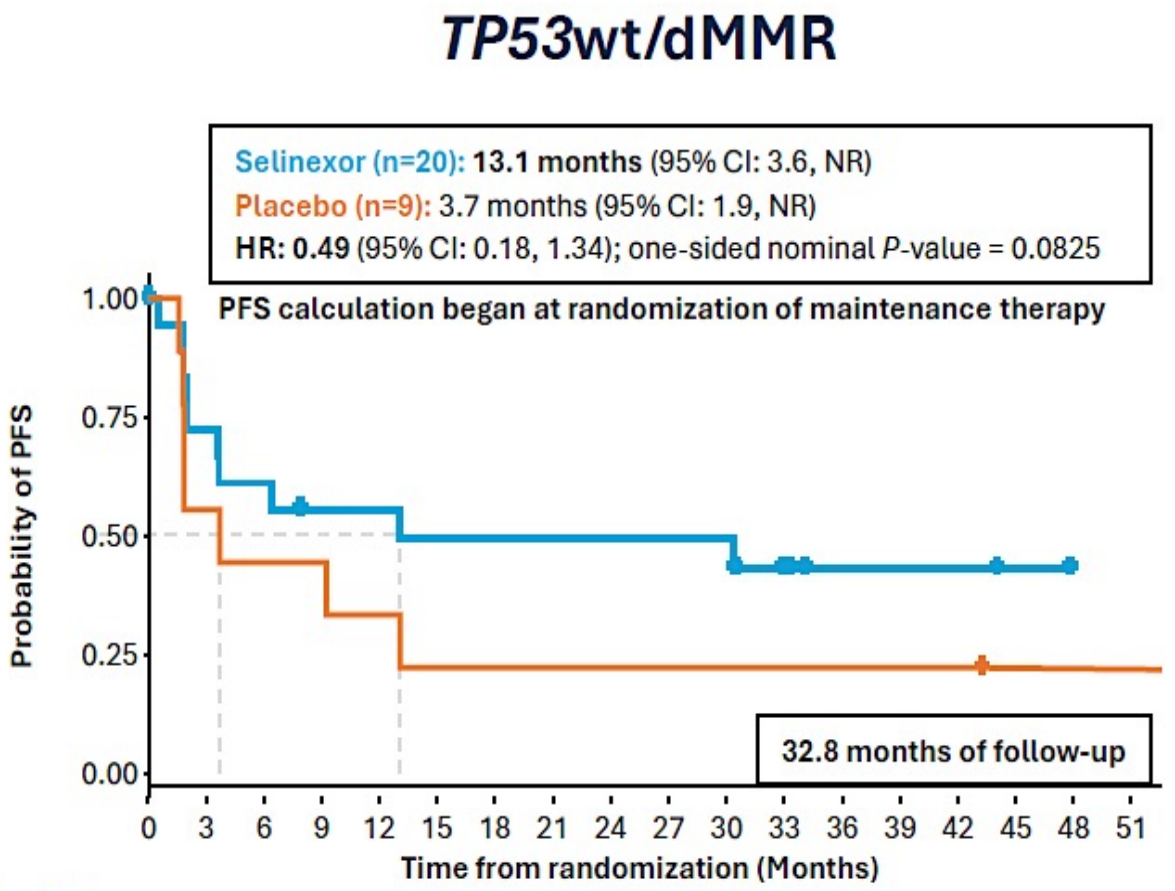
CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival

UCLA Health

Makkar V. Gynecol Oncol 2024.

Phase II SIENDO Trial: Selinexor Maintenance



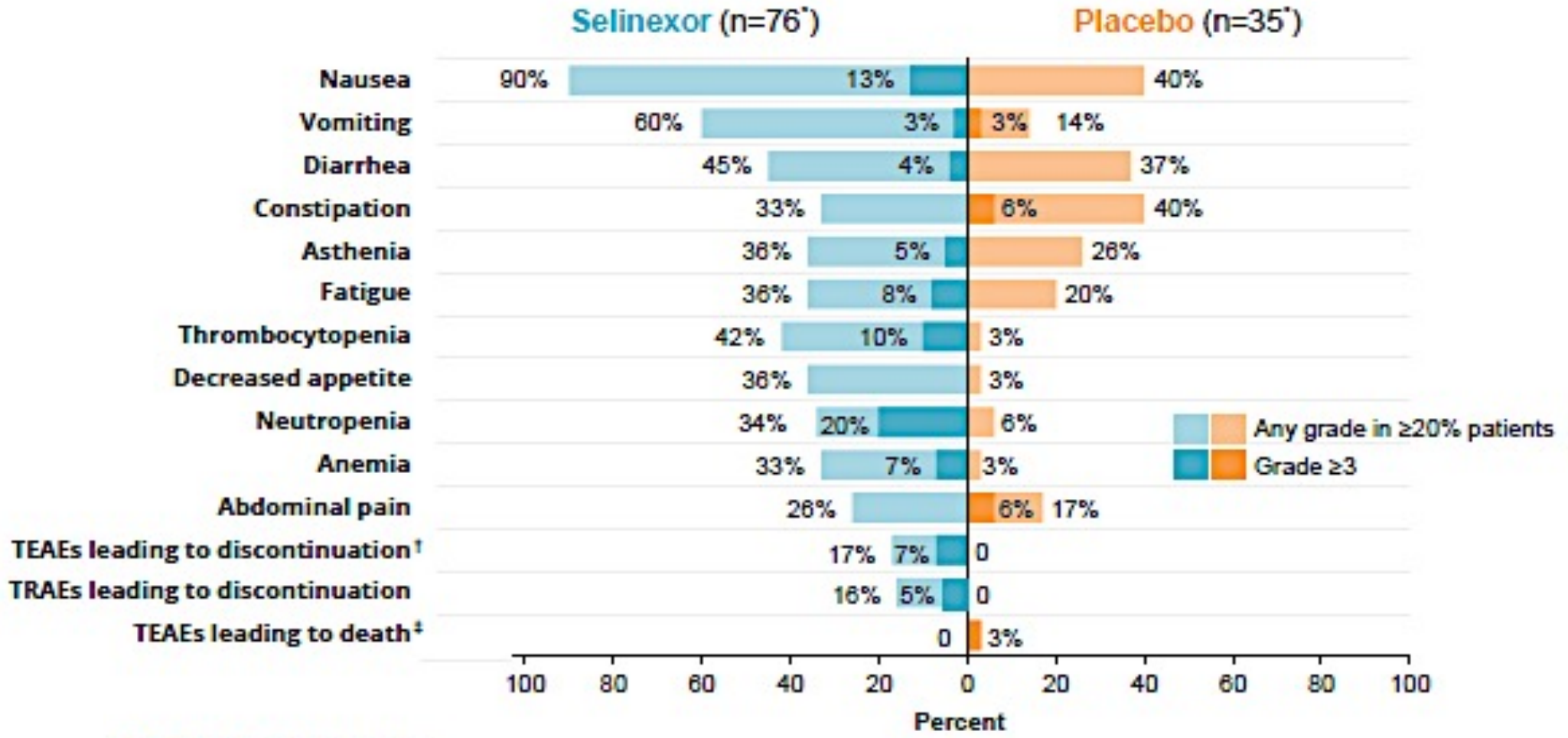


Benefits in TFST, PFS2, TSST

UCLA Health

Makker V. ASCO 2024. Richardson D. SGO 2025.

SIENDO: Adverse Events



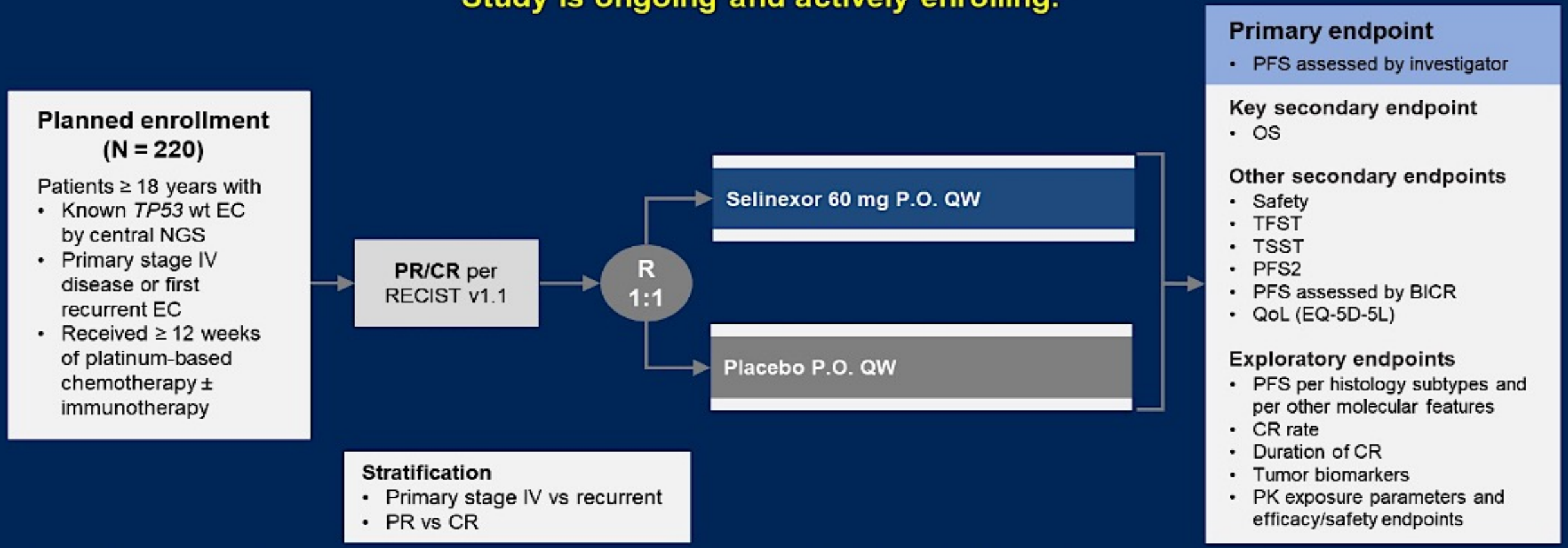
UCLA Health

Richardson D. SGO 2025.

Phase 3 Confirmatory Trial: XPORT-EC-042

ENGOT-EN20/GOG-3083/XPORT-EC-042 (NCT05611931)
Selinexor in Maintenance Therapy After Systemic Therapy for Participants With p53 Wild-Type, Advanced or Recurrent Endometrial Carcinoma

Study is ongoing and actively enrolling.



Emerging Therapies

TROP-2 ADCs

	Sacituzumab Govitecan	Datopotamab Deruxtecan	Sacituzumab Tirumotecan
Payload	SN-38 (metabolite of Topo-I inhibitor)	Deruxtecan (Topo-I payload)	Novel Topo-I inhibitor (KL610023)
DAR	7.6	4	7.4
Study Size	N=21	N=40	N=44
Patient Population	- 47% with >3 prior lines	- 73% with 1 prior line - 22.5% prior IO	- 48% with 1 prior line - 36% prior IO
Region Trial conducted	United States	- EU (45%) - Asia (45%)	- Almost entirely China
Efficacy	ORR 33%	ORR 27.5%	ORR 27.3% (41.7% H-score>200)
SAEs	- Neutropenia - Diarrhea	- Stomatitis - Anemia - Amylase Increase	- Stomatitis - Anemia - Neutropenia

UCLA Health

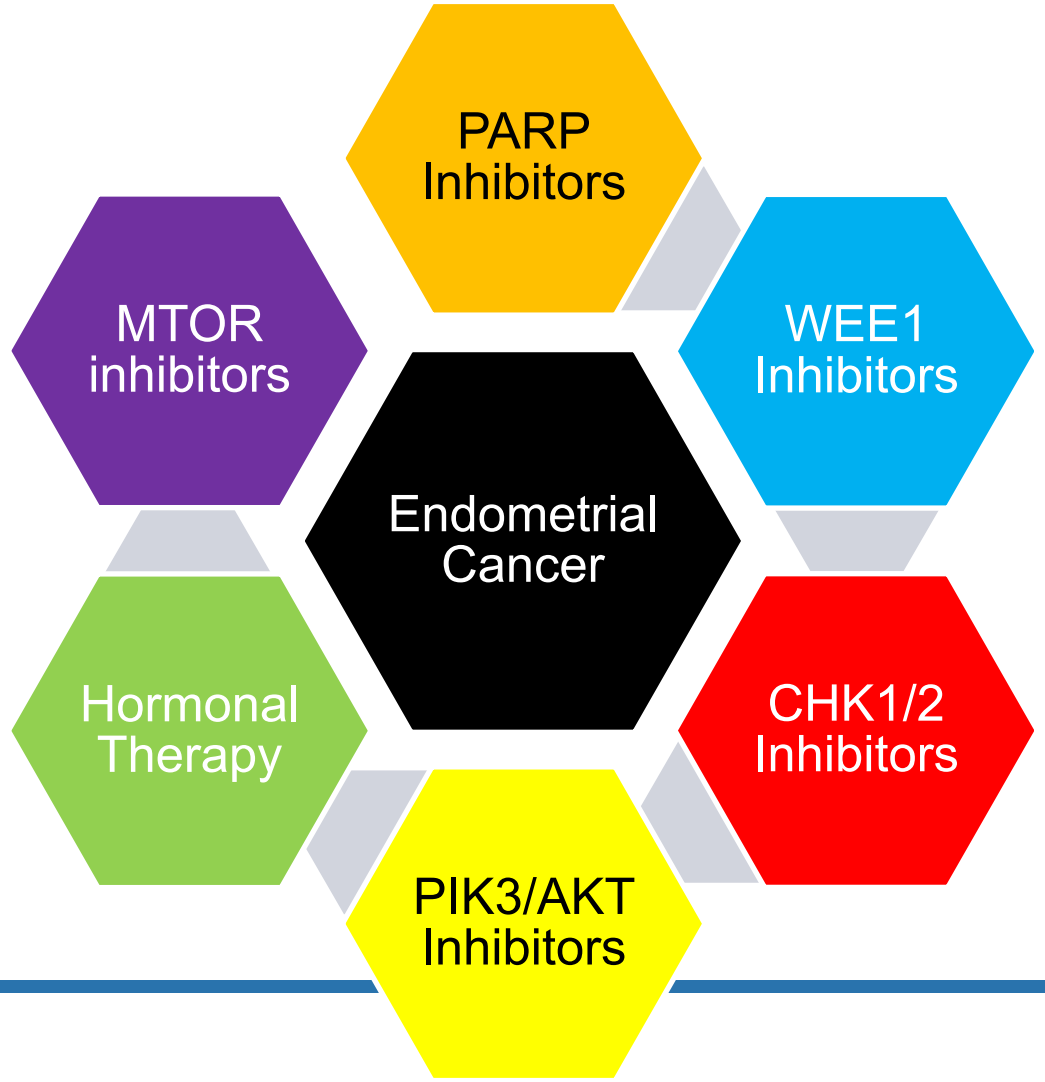
Santin A. ASCO 2023. Oaknin A. ESMO 2024. Wang. ESMO 2024. Lee. ESMO 2024.

ADCs in Development for Endometrial Cancer

HER2	Trastuzumab deruxtecan DB-1303/BNT323	HER2: 18-80%	T-DXd: ORR 3+: 56% BNT-323: ORR: 59%
TROP2	Sacituzumab govitecan Sacituzumab tirumotecan Datopotamab Deruxtecan	TROP2: ~50% high expression	Sac-Gov: ORR: 22-33% Sac-TMT: ORR: 34% Dato-DXd: ORR: 28%
FRα	Mirvetuximab IMGN-151 Rinatabart Sesutecan	FRα: 33% high expression (PS2+ ≥50%)	Mirv: ORR: 38% IMGN-151: Pending Rina-S: Pending

…and many others on the horizon!
B7H4, CDH6, CLDN6

Non-ADC Targeted Therapies



Conclusions

- Recent FDA approvals
  - Lenvatinib and Pembrolizumab
  - Trastuzumab deruxtecan (accelerated)
- The potential landscape for management is rapidly evolving
  - Strategies to determine the most efficacious therapy are needed
    - Biomarker directed versus all-comer options
  - Ideal sequencing of therapies remains unclear

Case Presentation: 79-year-old woman with Stage IV MSI-H endometrial cancer receives 1 cycle of carboplatin/paclitaxel/ pembrolizumab with poor tolerance

Dr Victoria Giffi (Hagerstown, Maryland)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

For a patient like this with MSI-high disease for whom chemotherapy might be problematic, would it be reasonable to administer anti-PD-1/PD-L1 monotherapy in the front-line setting? Would you ever employ first-line lenvatinib/pembrolizumab for a patient who wasn't fit enough for chemotherapy?

How do you approach initial dosing of the lenvatinib for patients receiving lenvatinib/pembrolizumab? Do you prefer to start at the recommended dose and dose-reduce as needed or start at a lower dose and increase it if it is well tolerated?

What strategies would you recommend to prevent or manage mucositis in patients receiving lenvatinib?

Case Presentation: 63-year-old woman with recurrent POLE-mutant, TP53-mutant endometrial cancer receives pembrolizumab/lenvatinib

Dr Kellie Schneider (Charlotte, North Carolina)

RTP
RESEARCH
TO PRACTICE

Questions for the Faculty

If this patient with a POLE mutation presented with newly diagnosed disease today, how would you think through initial treatment?

What would you recommend at this point? Would you be comfortable discontinuing lenvatinib/pembrolizumab?

Questions for the Faculty

What novel investigational strategies are you excited about for patients with advanced endometrial cancer? How optimistic are you that selinexor will eventually be an option for TP53 wild-type disease? If selinexor were available, would you add it for a patient who received up-front chemoimmunotherapy followed by anti-PD-1/PD-L1 antibody maintenance? If so, would you administer selinexor and the anti-PD-1/PD-L1 antibody concurrently or sequentially?

Do you see TROP2-targeted antibody-drug conjugates playing a role in advanced endometrial cancer in the future?

Contributing General Medical Oncologists

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John Muir Health
Walnut Creek, California

Karim ElSahwi, MD
Hackensack Meridian Health
Neptune City, New Jersey

Victoria Giffi, MD
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Oncology Specialists
Hagerstown, Maryland

Erik Rupard, MD
Penn State Cancer Institute
Hershey, Pennsylvania

Kellie E Schneider, MD
Novant Health Cancer Institute
Charlotte, North Carolina

Lyndsay J Willmott, MD
Virginia G Piper Cancer Care Network
Phoenix, Arizona

Neil Love, MD
Research To Practice
Miami, Florida

Thank you

RTP Live from Chicago: Investigator Perspectives on Available Research Findings and Challenging Questions in the Management of Renal Cell Carcinoma

A CME-Accredited Virtual Event Held in Conjunction with the 2025 ASCO® Annual Meeting

Monday, June 2, 2025

7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

Faculty

Professor Laurence Albiges, MD, PhD

Tian Zhang, MD, MHS

Moderator

Neil Love, MD

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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