Meet The Professors Live: Clinical Investigators Provide Perspectives on Actual Cases of Patients with Ovarian and Endometrial Cancer

Sunday, June 2, 2024
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Brian M Slomovitz, MD

Moderator

Angeles Alvarez Secord, MD, MHSc

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Faculty

Floor J Backes, MD
Professor
Fellowship Director
Division of Gynecologic Oncology
Department of Obstetrics and Gynecology
The Ohio State University College of Medicine
The James Cancer Hospital
and Solove Research Institute
Columbus, Ohio

Mansoor Raza Mirza, MD
Chief Oncologist, Rigshospitalet
Medical Director, NSGO-CTU (Nordic Society
of Gynaecological Oncology – Clinical Trial Unit)
Vice-President 2020-2024, ESGO (European Society of
Gynaecological Oncology)
Faculty, ESMO (European Society of Medical Oncology)
Scientific Chair, IGCS Congress 2024
Jury Member, Prix Galien Foundation
Copenhagen, Denmark

Ritu Salani, MD, MBA
Director, Division of Gynecologic Oncology
Professor, Department of Obstetrics and Gynecology
UCLA Health
Los Angeles, California

Brian M Slomovitz, MD
Professor, OB-GYN, Florida International University
Director, Gynecologic Oncology
Co-Chair, Cancer Research Committee
Mount Sinai Medical Center
Miami, Florida

Moderator
Angeles Alvarez Secord, MD, MHSc
Professor of Obstetrics and Gynecology
Gynecologic Oncology
Director of Gynecologic Oncology Clinical Trials
Duke Cancer Institute
Durham, North Carolina

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Contributing General Medical/Gynecologic Oncologists

Eric H Lee, MD, PhD
Compassionate Cancer Care Medical Group
Fountain Valley, California

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

Priya Rudolph, MD, PhD
Northside Hospital Cancer Institute
Georgia Cancer Specialists
Athens and Greensboro, Georgia

Neil Love, MD
Research To Practice
Miami, Florida

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Dr Backes — Disclosures
Faculty

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

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Dr Mirza — Disclosures
Faculty

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Stock Options/Stock — Public Company	Karyopharm Therapeutics

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Dr Salani — Disclosures
Faculty

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Dr Slomovitz — Disclosures
Faculty

Consulting Agreements	Aadi Bioscience, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, ImmunoGen Inc, Merck, Novocure Inc
Speakers Bureau	Seagen Inc
Nonrelevant Financial Relationship	GOG Foundation Inc

Dr Lee — Disclosures
Contributing General Medical/Gynecologic Oncologist

No relevant conflicts of interest to disclose.

Dr Rudolph — Disclosures
Contributing General Medical/Gynecologic Oncologist

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Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Gilead Sciences Inc, Lilly, Pfizer Inc, Puma Biotechnology Inc, Seagen Inc, Stemline Therapeutics Inc

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Dr Willmott — Disclosures
Contributing General Medical/Gynecologic Oncologist

Advisory Committee	OncoC4
Data and Safety Monitoring Board/Committee	Merck
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Eisai Inc, ImmunoGen Inc, Merck, Seagen Inc

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Dr Secord — Disclosures
Moderator

Clinical Trial Steering Committees (Uncompensated)	Aravive Inc (AXLerate trial), CanariaBio Inc (FLORA-5 trial, QPT-ORE-004 trial), F Hoffmann-La Roche Ltd (AtTEnd trial)
Contracted Research	AbbVie Inc, Aravive Inc, AstraZeneca Pharmaceuticals LP, CanariaBio Inc, Clovis Oncology, Eisai Inc, Ellipses Pharma, Genentech, a member of the Roche Group, GSK, I-Mab Biopharma, ImmunoGen Inc, Karyopharm Therapeutics, Merck, Mersana Therapeutics Inc, OncoQuest Inc, Seagen Inc, VBL Therapeutics, Zentalis Pharmaceuticals
Data and Safety Monitoring Board/Committee	CanariaBio Inc

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Dr Love — Disclosures

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Friday May 31	**Hepatobiliary Cancers** 11:45 AM – 12:45 PM CT (12:45 PM – 1:45 PM ET)
	Non-Small Cell Lung Cancer with an EGFR Mutation 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday June 1	**Antibody-Drug Conjugates in the Treatment of Lung Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday June 2	**Multiple Myeloma** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 3	**Colorectal Cancer (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 4	**Bispecific Antibodies in the Management of Lymphoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Exciting CME Events in Chicago You Do Not Want to Miss

A CME Hybrid Symposium Series Held in Conjunction with the 2024 ASCO® Annual Meeting

Multiple Myeloma

Sunday, June 2, 2024

6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Rafael Fonseca, MD
María-Victoria Mateos, MD, PhD
Elizabeth O'Donnell, MD

LIVE WEBCAST

Colorectal Cancer

Monday, June 3, 2024

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

Faculty

Scott Kopetz, MD, PhD
John Strickler, MD

Ovarian and Endometrial Cancer

Sunday, June 2, 2024

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

Faculty

Floor J Backes, MD
Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Angeles Alvarez Secord, MD, MHSc
Brian M Slomovitz, MD

Metastatic Breast Cancer

Monday, June 3, 2024

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

Faculty

Aditya Bardia, MD, MPH
Harold J Burstein, MD, PhD
Professor Giuseppe Curigliano, MD, PhD
Sara A Hurvitz, MD, FACP
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Exciting CME Events in Chicago You Do Not Want to Miss

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LIVE WEBCAST

Bispecific Antibodies in Lymphoma

Tuesday, June 4, 2024

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

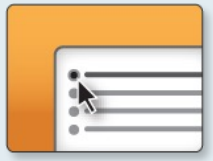
Faculty

Joshua Brody, MD
Ian W Flinn, MD, PhD
Tycel Phillips, MD

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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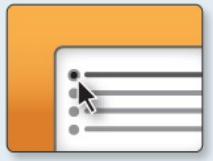
Clinicians Attending via Zoom

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



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

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

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

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About the Enduring Program

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

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Meet The Professors Live: Clinical Investigators Provide Perspectives on Actual Cases of Patients with Ovarian and Endometrial Cancer

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Mansoor Raza Mirza, MD
Ritu Salani, MD, MBA
Brian M Slomovitz, MD

Moderator

Angeles Alvarez Secord, MD, MHSc

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Agenda

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

Module 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr Backes

Module 3: First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Mirza

Module 4: Current Therapeutic Options for R/R EC; Novel Investigational Strategies — Dr Slomovitz

Module 5: Role of HER2-Targeted Therapy in the Management of Advanced OC, EC and Other Gynecologic Cancers — Dr Secord

Agenda

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Dr Eric Lee: Case Presentation

Clinical presentation: 64-year-old woman with mild dementia was admitted to the hospital with bowel obstruction and on lap found to have abdominal abscess and peritoneal carcinomatosis.

BRCA/HRD status: Somatic BRCA1 mutation

Treatment: Carboplatin, paclitaxel and bevacizumab x 7 cycles. Then switched to bevacizumab and olaparib maintenance.

Response: Complete response on PET-CT, normalization of tumor markers during chemotherapy portion. Developed appendiceal perforation after 3 months of maintenance therapy. Bevacizumab discontinued. Continued on olaparib x 3 months. Restaging PET-CT showed pelvic sidewall recurrence. Recommendation is to biopsy for folate receptor alpha testing.

Side effects/tolerability issues: GI perforation on bevacizumab. No significant cytopenias or GI toxicities while on PARP.

Dr Eric Lee: Case Questions

How would you have managed this patient postoperatively? What do you consider to be a contraindication to bevacizumab?

What would be your treatment approach for a patient who presents with ovarian cancer and a bowel obstruction?

How long would you continue olaparib in this situation?

In what situations should bevacizumab be included as part of neoadjuvant therapy?

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Dr Eric Lee: Questions for the Faculty

In what situations should bevacizumab be included as a component of front-line chemotherapy?

For patients who don't receive bevacizumab with chemotherapy, when should it be added to PARP maintenance?

How, if at all, do you factor in the KELIM score when deciding treatment approach?

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Dr Lyndsay Willmott: Case Presentation

Clinical presentation: 44-year-old woman with ovarian cancer who underwent immediate cytoreduction

BRCA/HRD status: gBRCA1 mutation

Treatment: Primary cytoreduction followed by chemotherapy and olaparib maintenance

Response: Complete response (subsequent platinum-sensitive recurrence)

Tolerability issues: Anemia that was resolved after dose reduction

Dr Lyndsay Willmott: Case Questions

What's your general approach to BRCA/homologous recombination deficiency (HRD) testing? How do you sequence germline, somatic and liquid assays?

How do you counsel family members who have a germline BRCA mutation?

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Dr Lyndsay Willmott: Questions for Faculty

Should PARP inhibitor maintenance be offered to all patients who do not experience disease progression on first-line platinum-based chemotherapy, or are there any situations in which you would not do so?

In general, what is your approach to primary PARP inhibitor maintenance for patients with a germline or somatic BRCA mutation?

What about patients without a BRCA mutation with HRD-positive disease?

Upfront Treatment of Advanced Ovarian Cancer

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

UCLA Health

Objectives

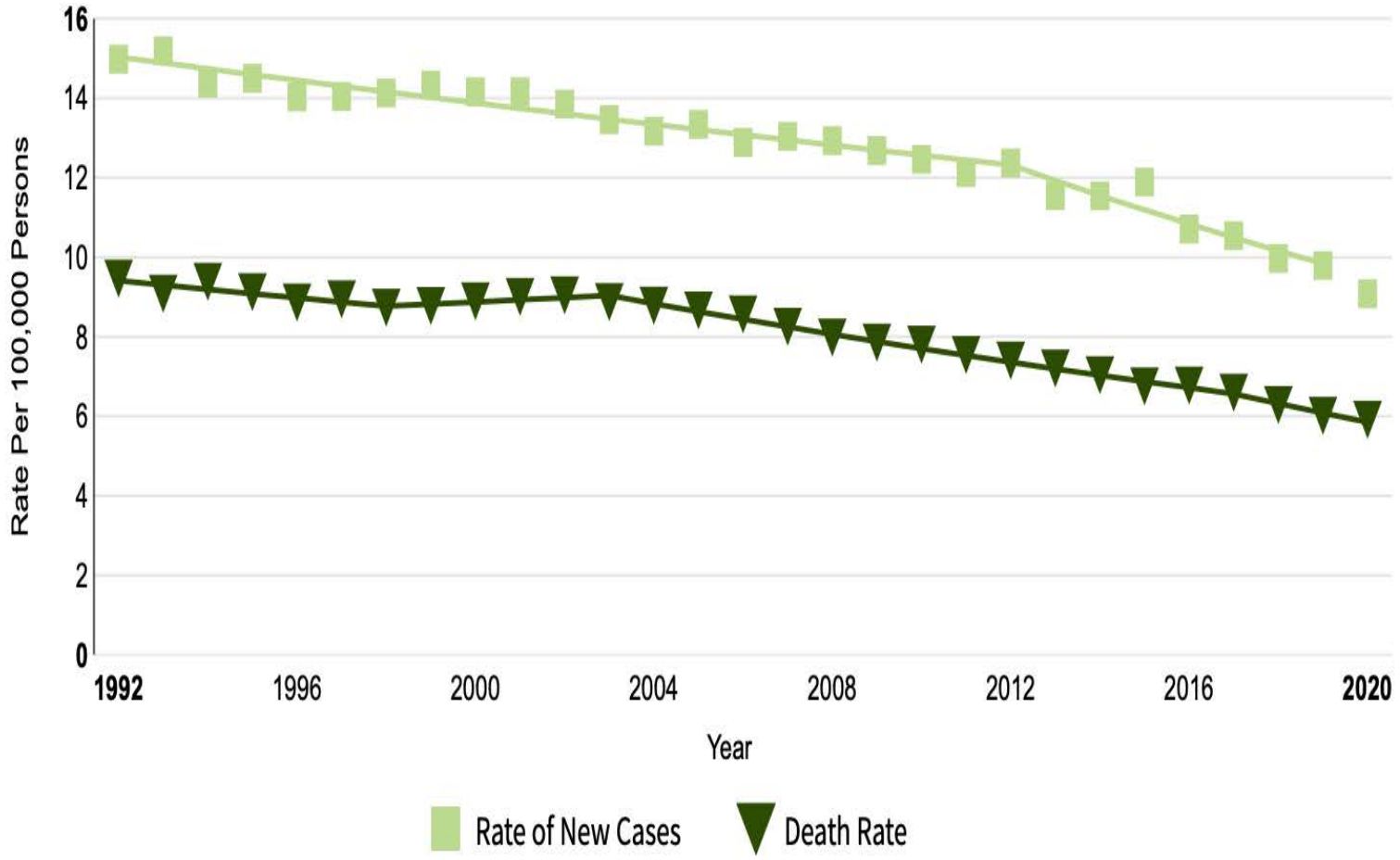
- Role of genetic testing and tumor biomarkers
  - BRCA and HRR/HRD testing
- Review frontline ovarian cancer treatment options
  - Bevacizumab
  - PARP inhibitors
  - Immunotherapy

Ovarian Cancer Statistics

Estimated New Cases in 2023	19,710
% of All New Cancer Cases	1.0%

Estimated Deaths in 2023	13,270
% of All Cancer Deaths	2.2%

5-Year Relative Survival
50.8%
2013–2019



https://seer.cancer.gov/statfacts/html/ovary.html

Genetic and Tumor Testing

NCCN Guidelines® for ovarian cancer

- At diagnosis, all patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should have genetic risk evaluation and germline and somatic testing (if not previously done)
  - Germline and somatic ***BRCA1/2*** status informs maintenance therapy; in the absence of a *BRCA1/2* mutation, **homologous recombination (HR) status** may provide information on the magnitude of the benefit of PARP inhibitor therapy
- Tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done
  - Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, ***BRCA1/2*, HR status, MSI, TMB, NRTK** if prior testing did not include these markers[b]

Society of Gynecologic Oncology

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

American Society of Clinical Oncology

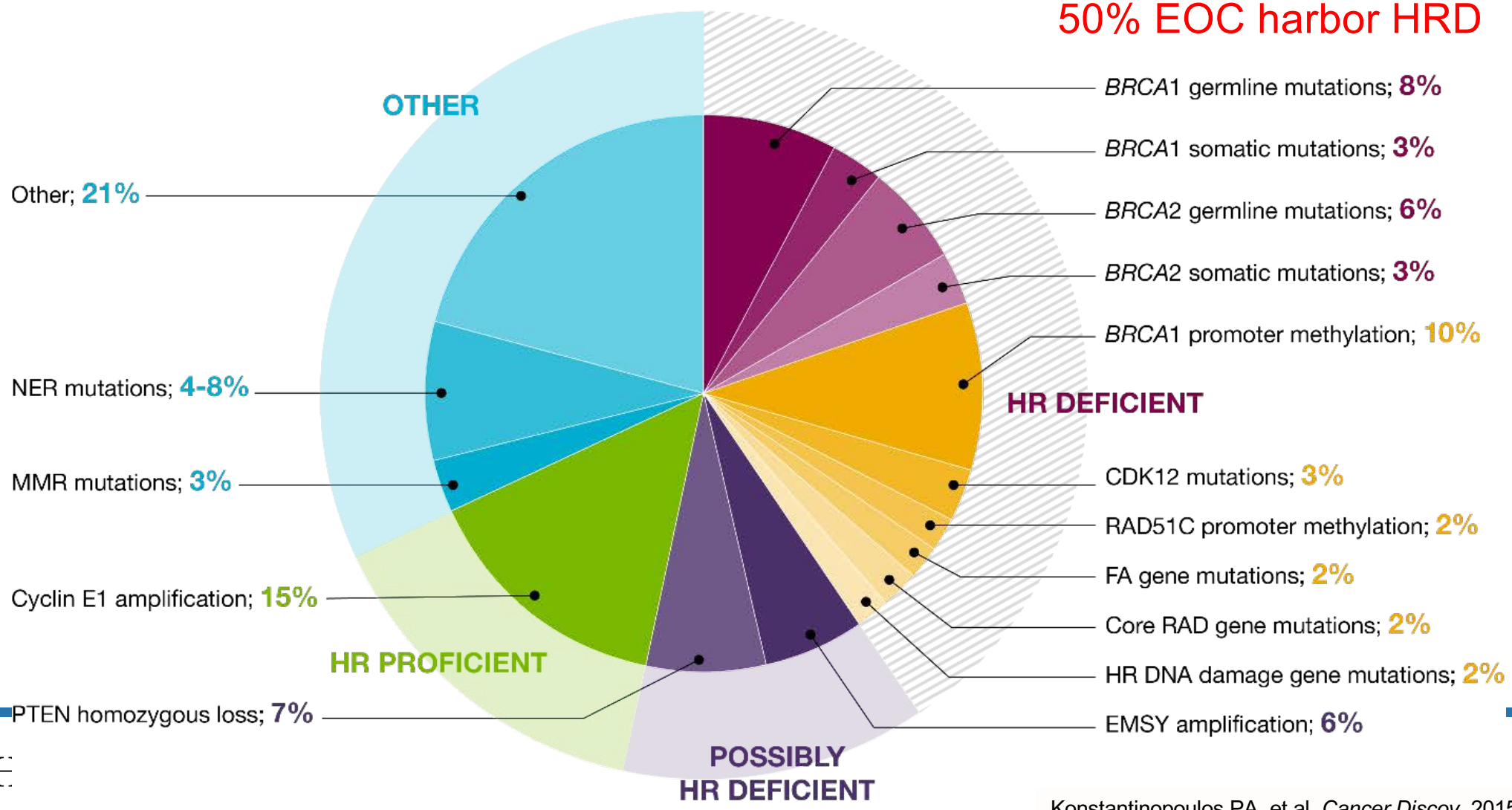
- All women diagnosed with epithelial ovarian cancer should be offered germline genetic testing for ***BRCA1/2*** and other ovarian cancer susceptibility genes, irrespective of their clinical features or family cancer history. Women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant should be offered somatic tumor testing for ***BRCA1/2***
- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for **mismatch repair (MMR) deficiency**

UCLA Health

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer. 2. Lancaster JM et al. *Gynecol Oncol.* 2015. Konstantinopoulos PA et al. *J Clin Oncol.* 2020.

Ovarian Cancer and Homologous Recombination

50% EOC harbor HRD



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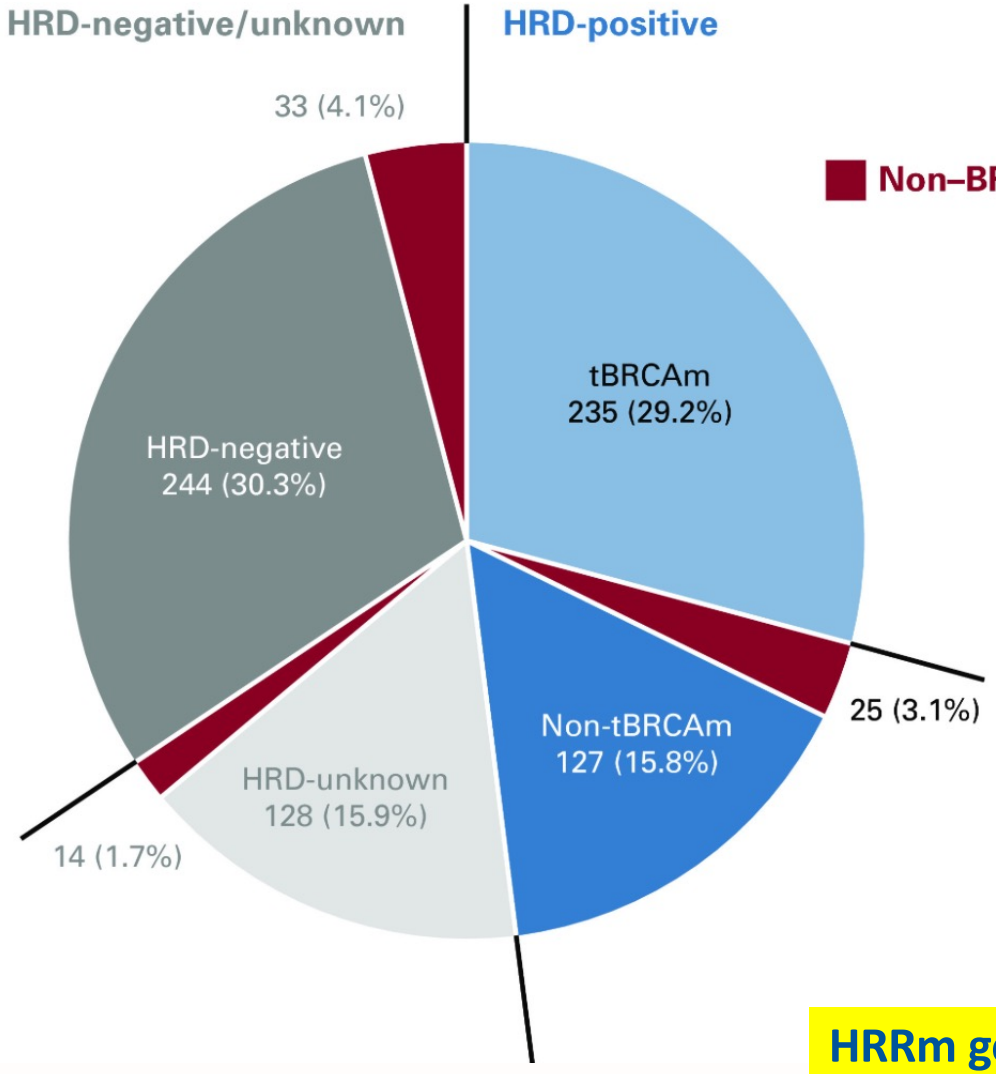
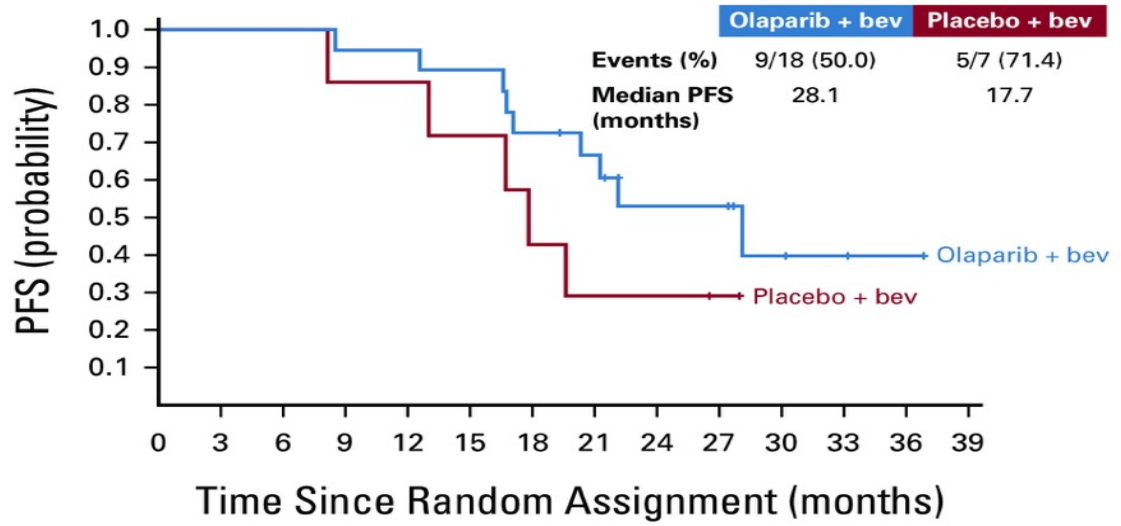
Konstantinopoulos PA, et al. *Cancer Discov*. 2015

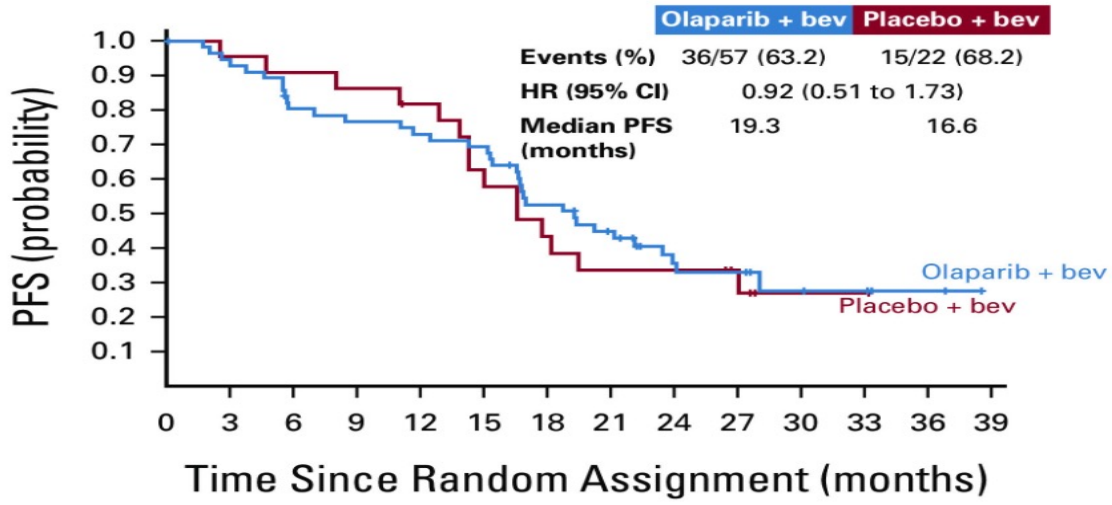
Tumor testing



HRD



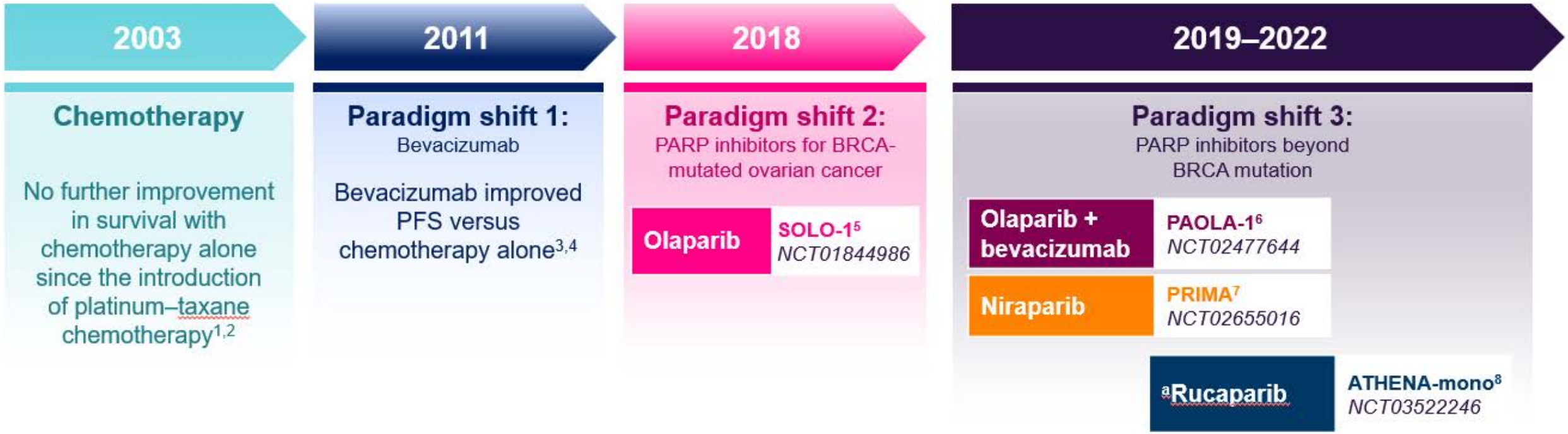
HRR



HRRm gene panel and HRD genomic instability tests are not interchangeable.

Pujade-Lauraine E, et al *JCO Precis Oncol*. 2023

Ovarian Cancer Landscape



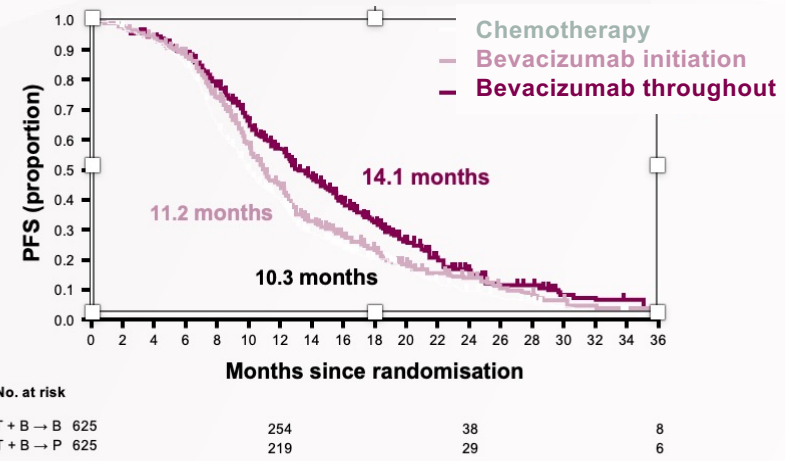
Frontline Bevacizumab: GOG 218 and ICON7

Significant improvement in PFS

GOG-0218[1]

Combination and maintenance bevacizumab with chemotherapy

PFS at the primary analysis[1]

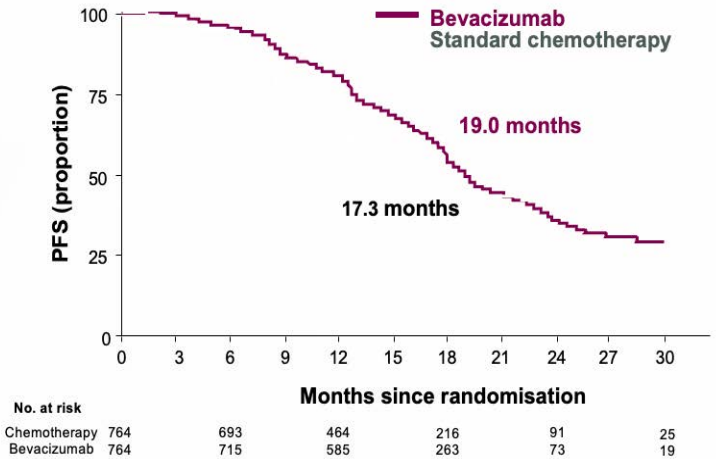


	Bevacizumab[a] (n=623)	
Median PFS, months	**14.1**	**10.3**
	HR 0.72 95% CI 0.63–0.82; p<0.0001	

ICON7[2]

Carboplatin & paclitaxel in combination with bevacizumab in patients with newly diagnosed OC

PFS[1]



	Bevacizumab (n=764)	
Events, n (%)	367 (48)	392 (51)
Median PFS, months	**19.0**	**17.3**
	HR 0.81 95% CI 0.70–0.94; p=0.004	

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Burger RA, et al. *N Engl J Med* 2011; Perren TJ, et al. *N Engl J Med* 2011.

SOLO-1: Olaparib

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCAm*
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib 300 mg bd (N=260)

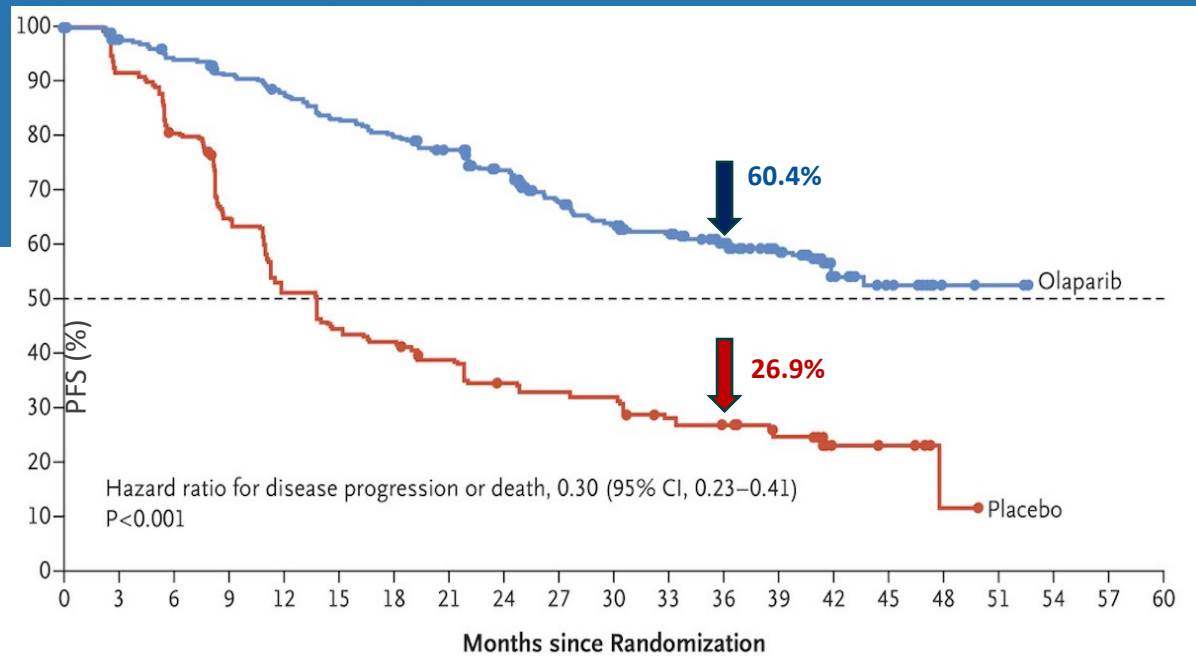
2:1 randomization

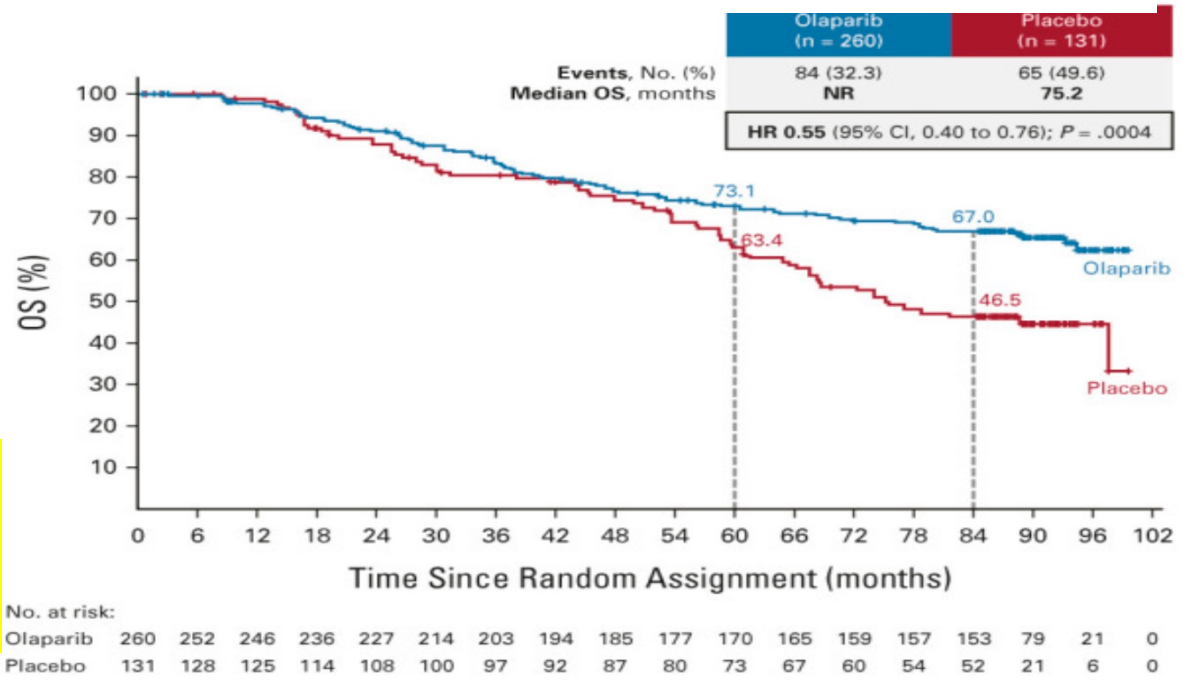
Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease





44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

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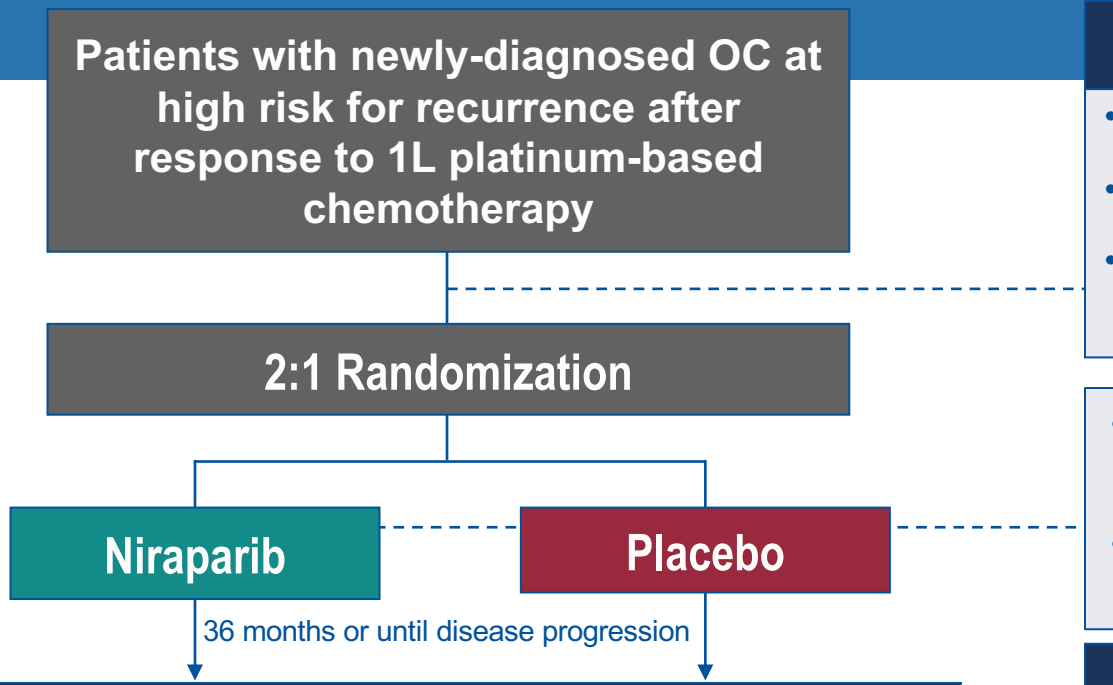
Moore K *N Engl J Med.* 2018; DiSilvestro P et al, *J Clin Oncol* 2023

PRIMA: Niraparib Trial Design



Endpoint assessment

Primary Endpoint: Progression-free survival by BICR

Key Secondary Endpoint: Overall Survival

Secondary Endpoints: PFS2, TFST, PRO, Safety

Stratification Factors

- Neoadjuvant chemotherapy administered: Yes or no
- Best response to first platinum therapy: CR or PR
- Tissue homologous recombination test status: deficient or proficient/not-determined

- Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD
- Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

Hierarchical PFS Testing

- **Patients with homologous recombination deficient tumors**, followed by the **overall population**.
- Statistical assumption: a hazard ratio benefit in PFS of
  - 0.5 in homologous recombination deficient patients
  - 0.65 in the overall population
- >90% statistical power and one-sided type I error of 0.025

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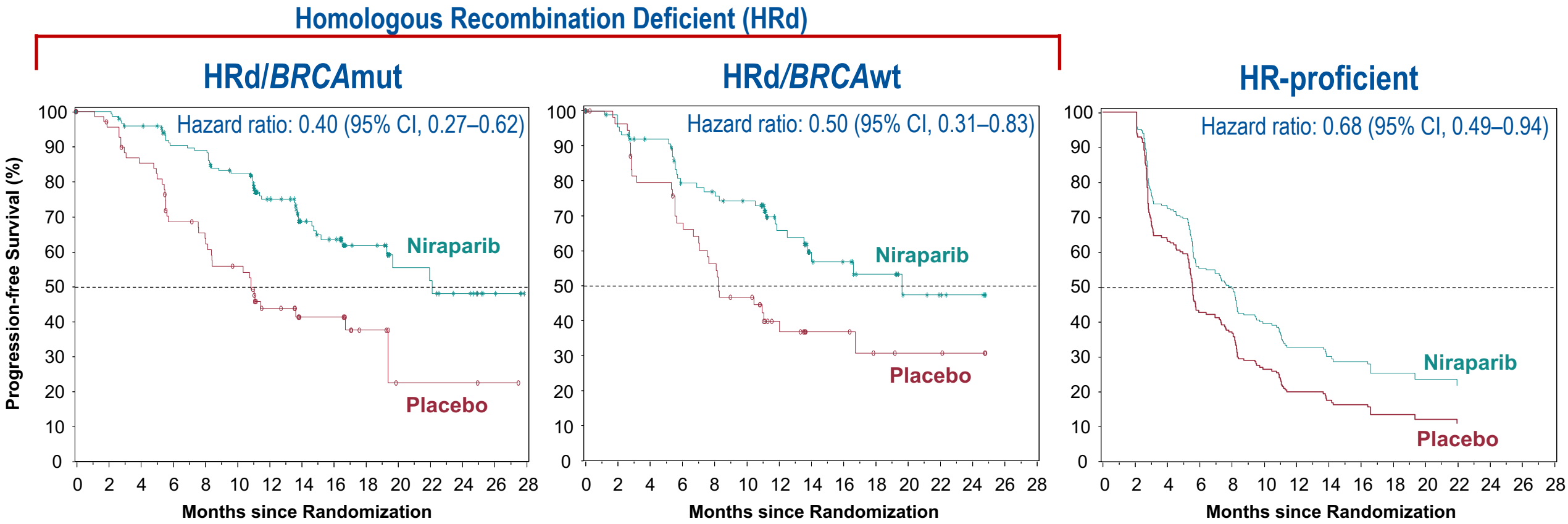
Gonzalez-Martin A *N Engl J Med.* 2019

PRIMA: PFS in Biomarker Subgroups



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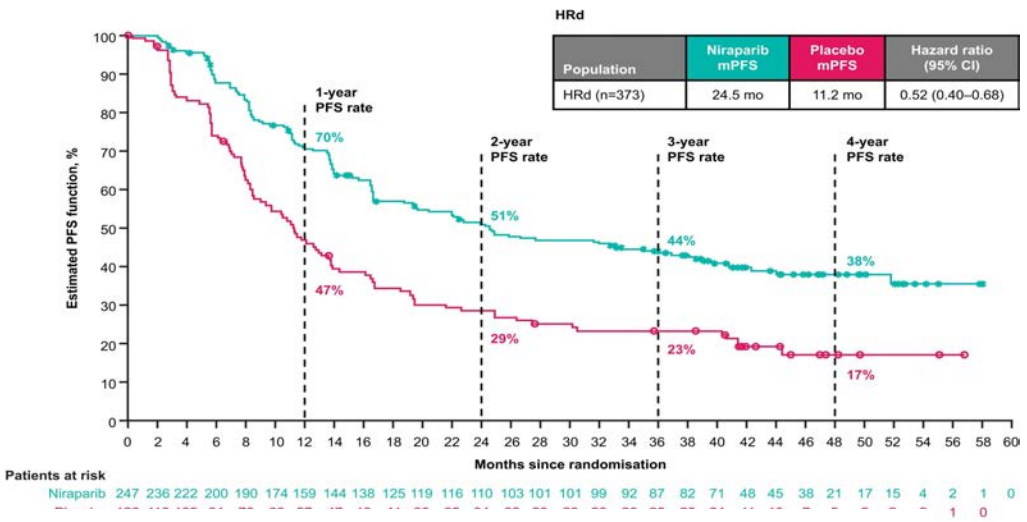
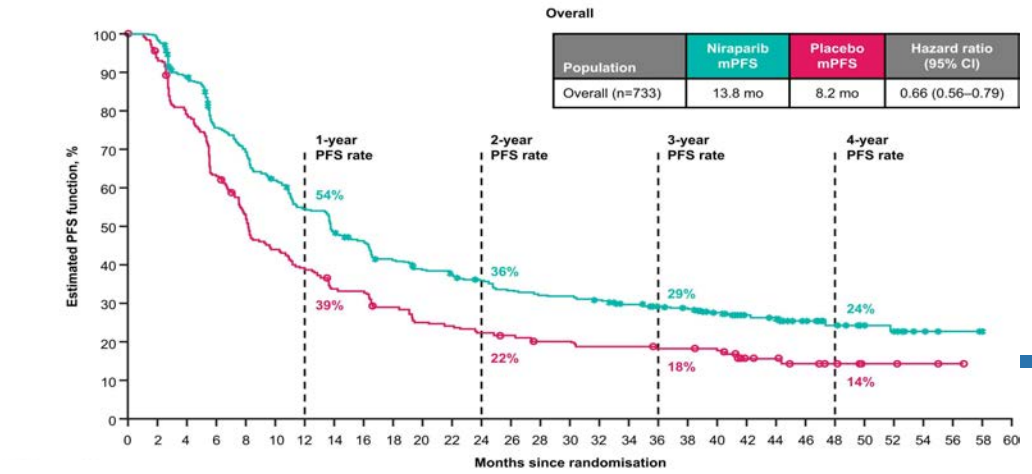
Gonzalez-Martin A *N Engl J Med.* 2019

PRIMA: Updated PFS Analysis

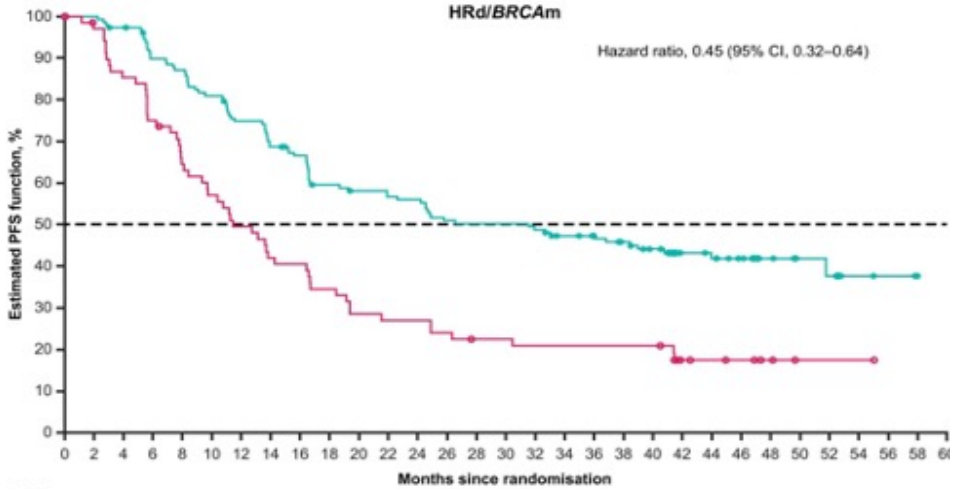
PFS in the HRD population



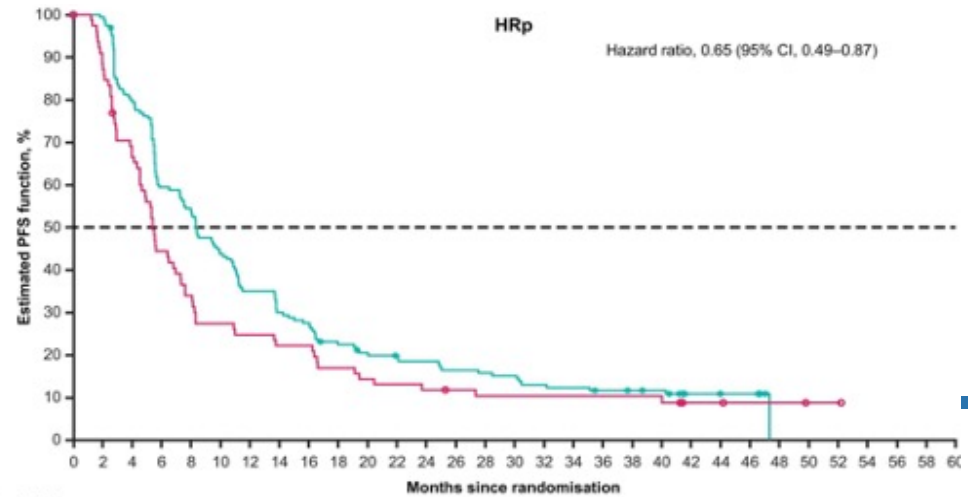
PFS in the Overall population



PFS in the HRD/BRCAm population



PFS in the HRP population



Gonzalez-Martin A *European J Cancer* 2023.

PAOLA-1 Trial Design

- **Newly diagnosed Stage III-IV EOC**
- **Surgery (upfront or interval)**
- **Platinum–taxane based chemotherapy**
- **≥3 cycles of bevacizumab**

NED/CR/PR

N=806

Randomization

Maintenance therapy

2:1

Olaparib (300 mg BID) x2 years
+
bevacizumab†

Placebo x2 years
+
bevacizumab†

Stratification
- Tumour *BRCA*m status‡
- First-line treatment outcome¶

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

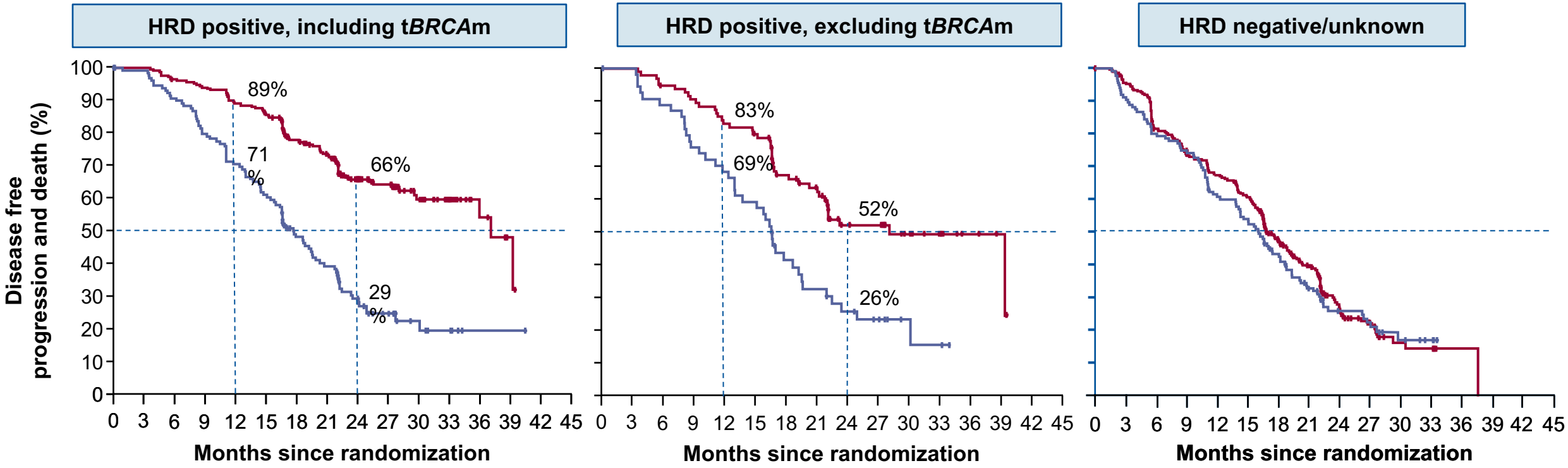
Sensitivity analysis
PFS by BICR

Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

UCLA Health

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

PAOLA-1: PFS in Biomarker Subgroups



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	**37.2***	**17.7**
	HR 0.33 (95% CI 0.25–0.45)	

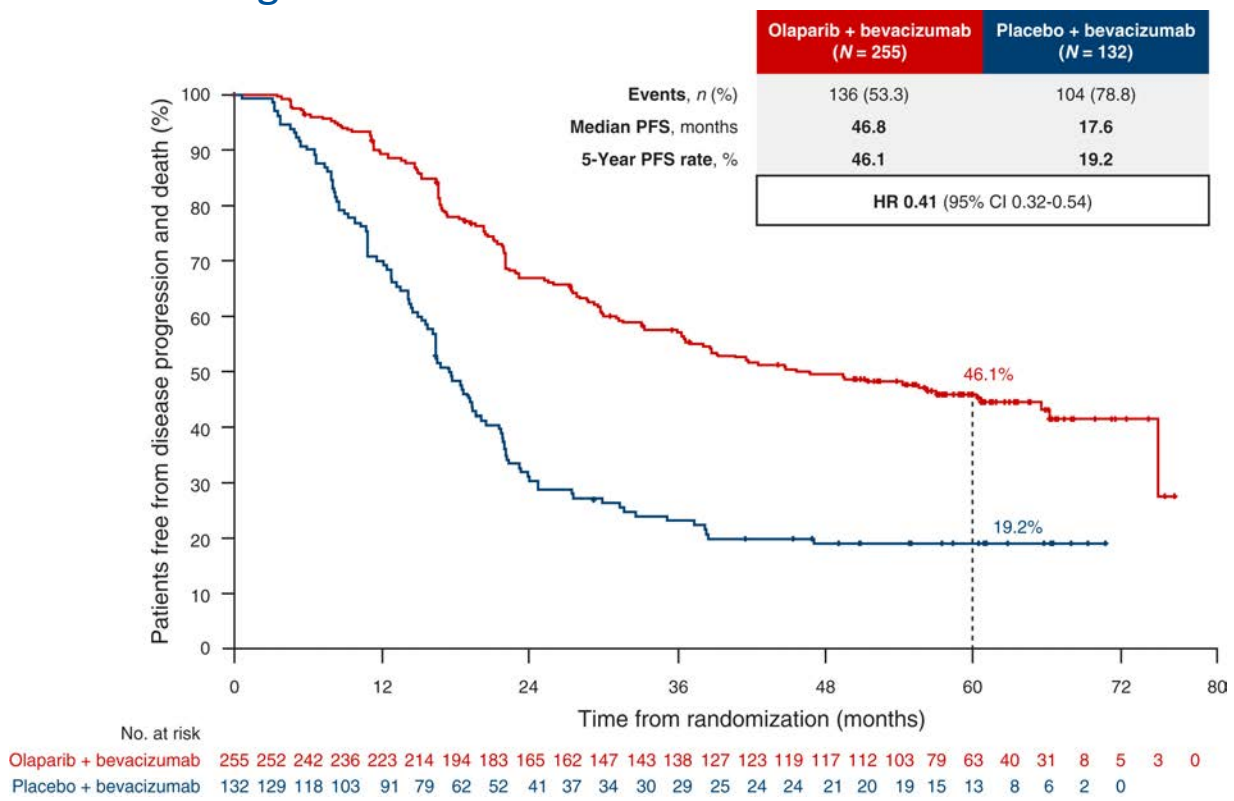
	Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
	43 (44)	40 (73)
	28.1*	**16.6**
	HR 0.43 (95% CI 0.28–0.66)	

	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)	

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

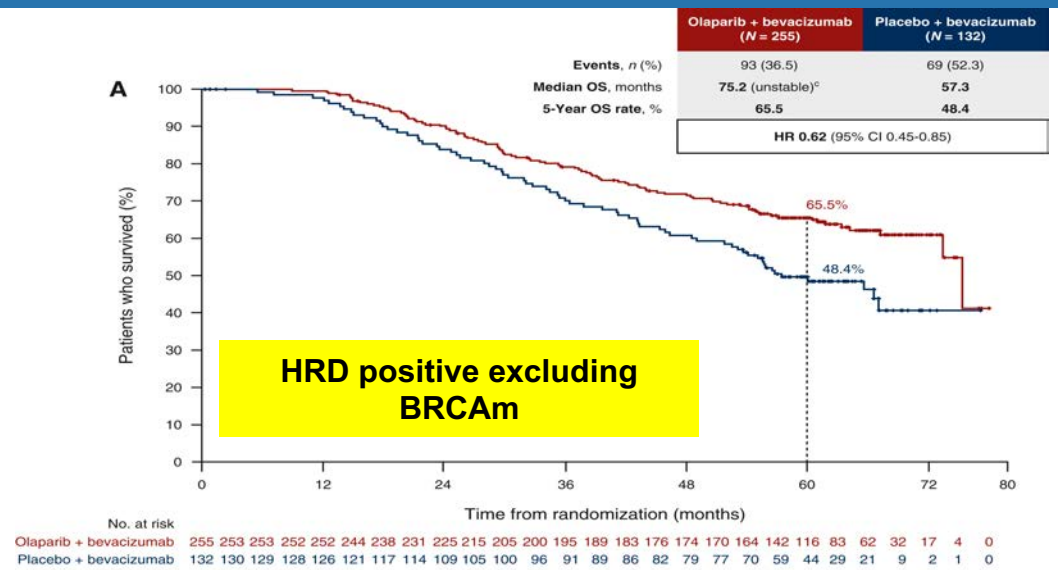
PAOLA-1: Updated PFS and OS

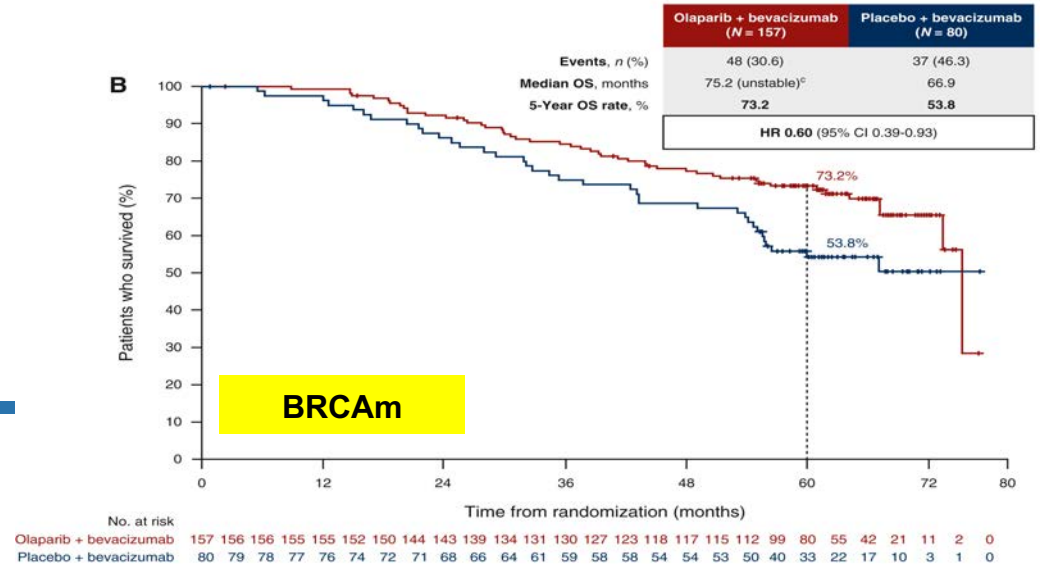
Progression-free Survival HRD+



No improvement in patients with HRD negative cancers

Overall Survival





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Ray-Coquard I, et al. *Annals Oncol* 2023

Phase II OVARIO: Niraparib and Bevacizumab

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

All patients underwent tissue testing for HRD status at enrollment

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

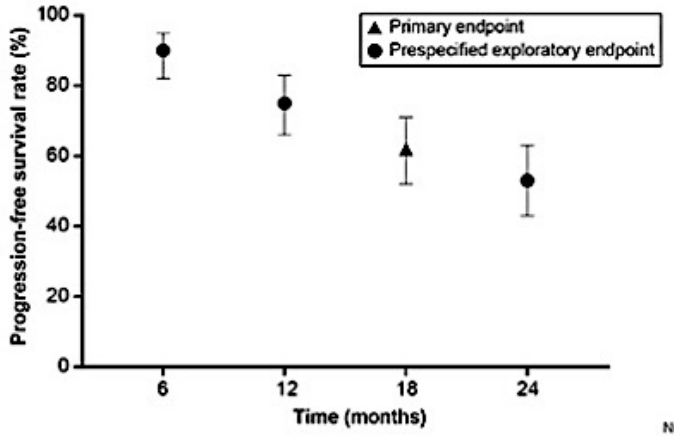
Niraparib starting dose	Bevacizumab
200 mg: <77 kg and/or platelet count <150,000/μL **300 mg:** All others	Maximum of 15 months, including first-line treatment

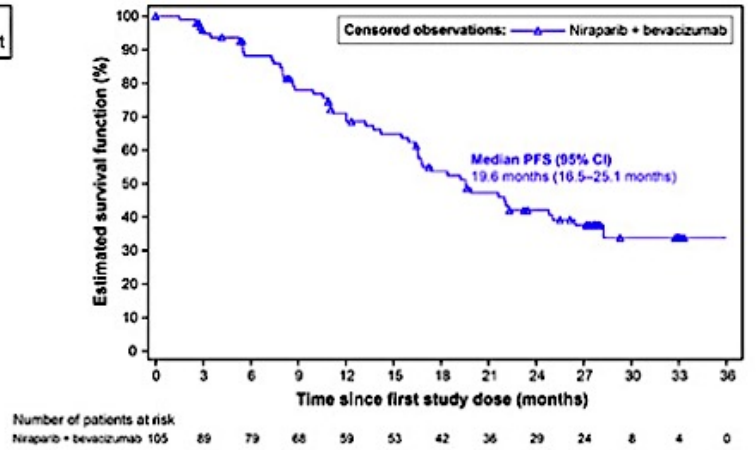
- Results were favorable compared with other upfront maintenance treatment trials
- At the 24 month analysis, 53% of patients in the overall population remained progression free
- No new safety signals were observed

PFS Rate as of December 24, 2020

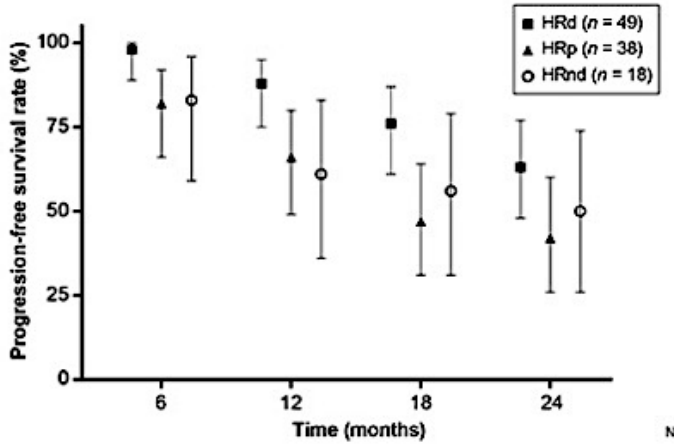
Median PFS as of June 16, 2021

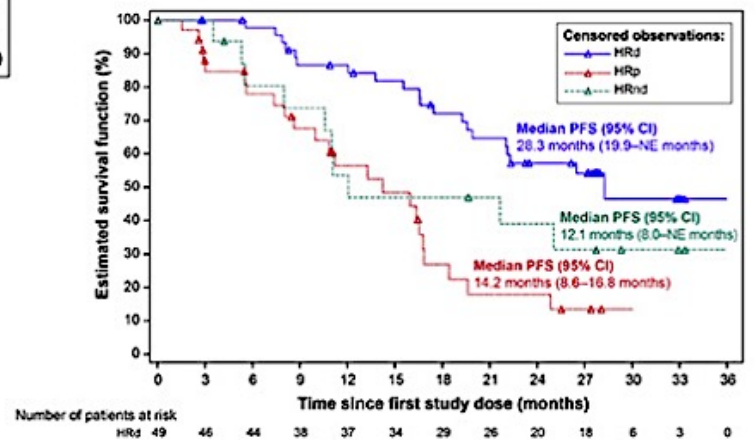
All patients





By HRD status





Hardesty MM. Gynecol Oncol 2022.

ATHENA MONO: Rucaparib

ATHENA–MONO Study Schema

Key Patient Eligibility

- Newly diagnosed, stage III–IV, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Completed frontline platinum-doublet chemotherapy and surgery
  - Achieved investigator-assessed CR or PR
  - Received cytoreductive surgery (primary or interval; R0/complete resection permitted)
- ECOG PS 0 or 1
- No prior frontline maintenance treatment for ovarian cancer

Randomization 4:4:1:1

Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Arm C (n≈100)
placebo PO + nivolumab 480 mg IV

Arm D (n≈100)
placebo PO + placebo IV

Randomization Stratification Factors
- Tumor HRD test status†
- Disease status post-chemotherapy
- Timing of surgery

Treatment for 24 months,* or until radiographic progression, unacceptable toxicity, or other reason for discontinuation

Study Analyses

ATHENA–MONO
Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

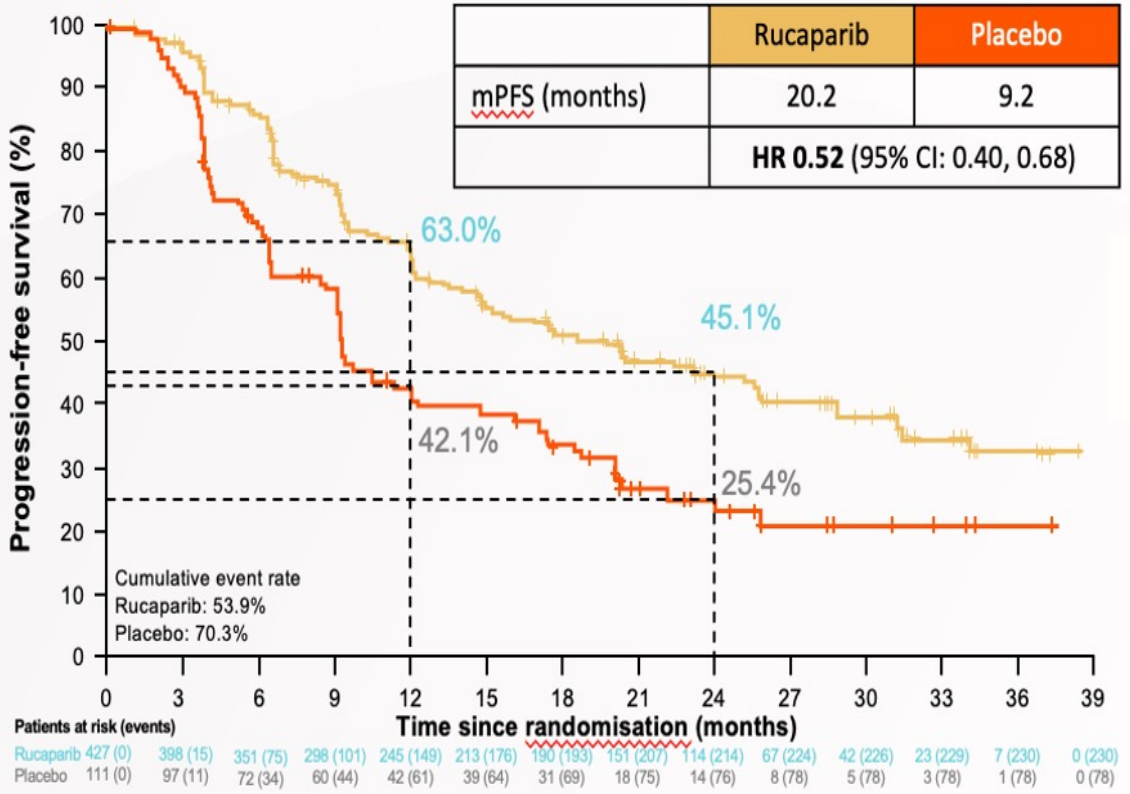
Arm D (n≈100)
placebo PO + placebo IV

ATHENA–COMBO
Arm A (n≈400)
rucaparib 600 mg BID PO + nivolumab 480 mg IV

Arm B (n≈400)
rucaparib 600 mg BID PO + placebo IV

Investigator-assessed PFS in the ITT population

	Rucaparib	Placebo
mPFS (months)	20.2	9.2
	HR 0.52 (95% CI: 0.40, 0.68)	



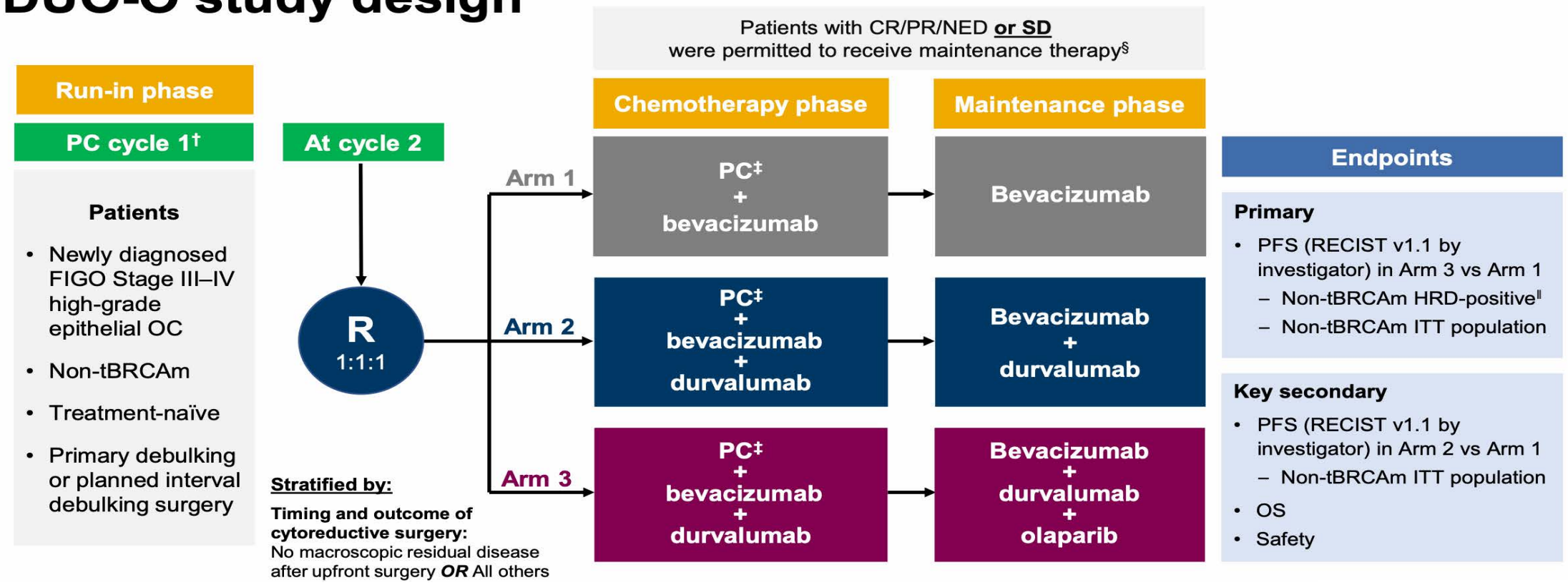
- Rucaparib reduced the risk of progression or death by 48% versus placebo
- Adverse event findings were consistent with the primary analysis, with no new safety signals

UCLA Health

Monk BJ, et al. *J Clin Oncol* 2022

DUO-O: Chemotherapy, Bevacizumab and Durvalumab

DUO-O study design*



- DUO-O met its primary endpoints at the planned interim PFS analysis (DCO1), demonstrating statistically significant and clinically meaningful improvement with Arm 3 versus Arm 1[1]

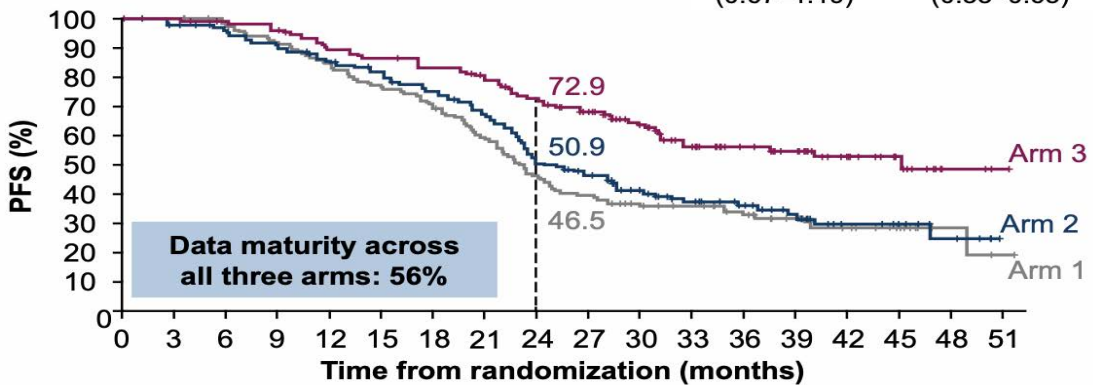
DUO-O also included an independent, single-arm, open-label, tBRCAm cohort – results not presented

Harter P, et al. ASCO 2023; Harter P, et al. SGO 2024

DUO-O: Final PFS

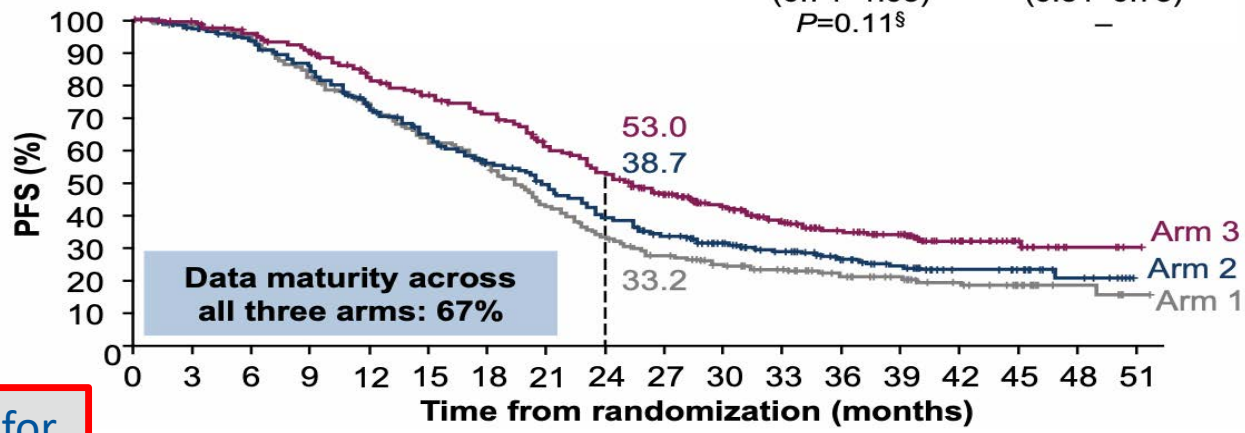
Non-tBRCAm HRD-positive

	Arm 1 PC + B N=143	Arm 2 PC + B + D N=148	Arm 3 PC + B + D + O N=140
Median follow-up,* months	38.4	33.1	34.6
Events, n (%)	94 (66)	89 (60)	57 (41)
mPFS,† months	**23.3**	**25.1**	**45.1**
HR (95% CI) vs Arm 1‡		**0.89** (0.67–1.19)	**0.46** (0.33–0.65)



Non-tBRCAm ITT

	Arm 1 PC + B N=378	Arm 2 PC + B + D N=374	Arm 3 PC + B + D + O N=378
Median follow-up,* months	34.5	33.1	32.0
Events, n (%)	283 (75)	257 (69)	221 (58)
mPFS,† months	**19.3**	**20.6**	**25.1**
HR (95% CI) vs Arm 1‡		**0.87** (0.74–1.03) *P*=0.11§	**0.61** (0.51–0.73) –



mPFS of 45.1 months in B+D+O arm is the longest observed for non-t*BRCA* mutation HRD+ patients in the first line setting

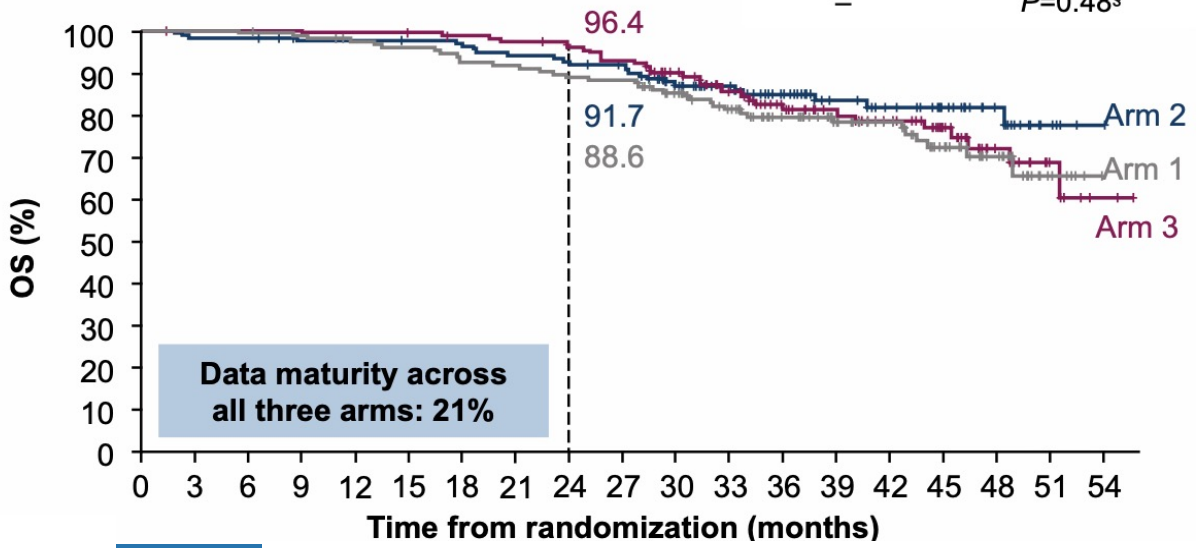
UCLA Health

Harter P, et al. ASCO 2023; Harter P, et al. SGO 2024

DUO-O: Interim OS

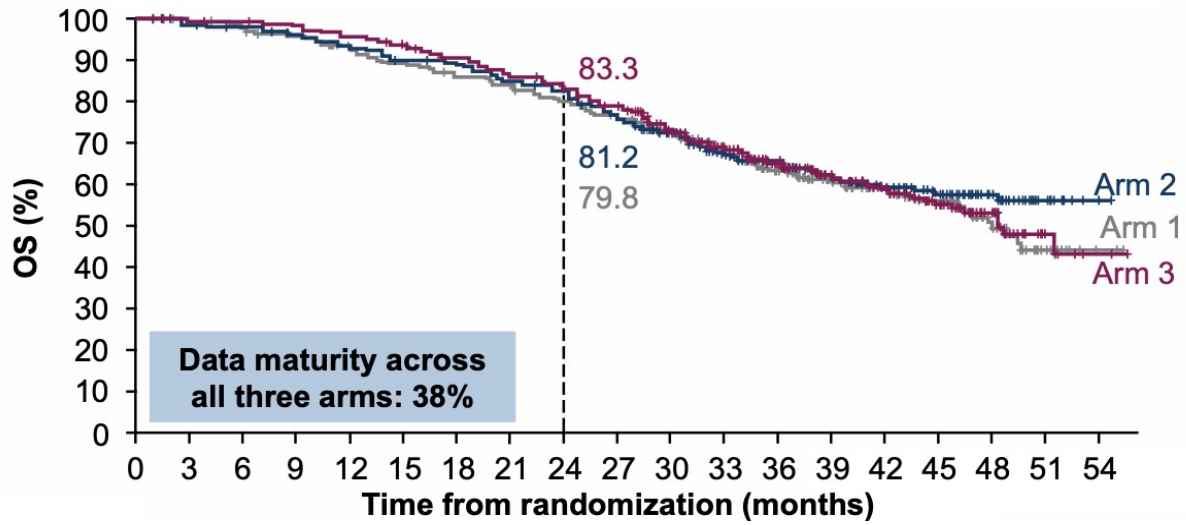
Non-tBRCAm HRD-positive

	Arm 1 PC + B N=143	Arm 2 PC + B + D N=148	Arm 3 PC + B + D + O N=140
Median follow-up,* months	40.7	36.5	38.0
Events, n (%)	35 (24)	24 (16)	30 (21)
mOS,† months	NR	NR	NR
HR (95% CI) vs Arm 1‡		**0.69** (0.41–1.15) –	**0.84** (0.51–1.37) *P*=0.48§



Non-tBRCAm ITT

	Arm 1 PC + B N=378	Arm 2 PC + B + D N=374	Arm 3 PC + B + D + O N=378
Median follow-up,* months	38.7	37.8	37.6
Events, n (%)	150 (40)	137 (37)	145 (38)
mOS,† months	48.0	NR	48.5
HR (95% CI) vs Arm 1‡		**0.92** (0.73–1.16) *P*=0.48§	**0.95** (0.76–1.20) *P*=0.68§



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Harter P, et al. ASCO 2023; Harter P, et al. SGO 2024

Future Directions: PARPi, Bev and CPI

Trial	Size	Anti VEGF	PARPi	ICI	Start	Estimated Primary Completion
FIRST[a] ENGOT OV-44	1405	± Bev	Niraparib	Dostarlimab	Oct 2018	Jan 2023
ATHENA GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43 KEYLYNK-001	~1086	± Bev	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

Agenda

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

Module 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr Backes

Module 3: First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Mirza

Module 4: Current Therapeutic Options for R/R EC; Novel Investigational Strategies — Dr Slomovitz

Module 5: Role of HER2-Targeted Therapy in the Management of Advanced OC, EC and Other Gynecologic Cancers — Dr Secord

Dr Priya Rudolph: Case Presentation

Clinical presentation: 49-year-old woman who presented a year ago with abdominal pain and distention due to ascites. CT — large volume ascites with scattered mesenteric edema, peritoneal nodularity and 3.6-cm L ovarian mass.

BRCA/HRD status: Fluid cytology/peritoneal biopsy c/w high-grade serous ca, germline BRCA2-positive

Treatment: Neoadjuvant carbo/paclitaxel/bevacizumab x 3

Interval TAH/BSO debulking path — 0.4-cm residual tumor L ovary; extensive treatment effect.

Completed 3 additional cycles post op.

Started on maintenance bevacizumab plus olaparib. Olaparib started 3 months ago.

Tolerability issues: Severe anemia despite dose reduction (300 mg BID to 250 mg BID), requiring transfusion. Plan to cut down to 200 mg BID.

Dr Priya Rudolph: Case Discussion Questions

Do you agree with the neoadjuvant approach that was taken here?

What is your approach to monitoring and mitigating the side effects associated with PARP inhibitors (eg, GI toxicity, anemia)?

How do you discuss the risk of developing acute myeloid leukemia or myelodysplastic syndromes with your patients with ovarian cancer who are receiving a PARP inhibitor?

Dr Priya Rudolph: Questions for the Faculty

Do you believe there is therapeutic synergy between PARP inhibitors and anti-PD-1/PD-L1 antibodies?

Based on available data from studies such as DUO-O, is there any current role for this strategy?

Dr Lyndsay Willmott: Case Presentation

Clinical presentation: 55-year-old woman with platinum sensitive-recurrent ovarian cancer who had not received a prior PARP inhibitor

BRCA/HRD status: Somatic BRCA2 mutation

Treatment: Chemotherapy followed by olaparib maintenance

Response: Complete response; currently on olaparib maintenance

Tolerability issues: No dose-limiting toxicities

Dr Lyndsay Willmott: Case Discussion Questions

How long would you continue olaparib for this patient?

Regulatory and reimbursement issues aside, what treatment would you recommend if she experiences disease progression?

Dr Lyndsay Willmott: Questions for Faculty

Under what circumstances, if any, would you use a PARP inhibitor for a patient with recurrent ovarian cancer?

What has been your clinical experience with efficacy and tolerability with mirvetuximab soravtansine?

What is the biological rationale for targeting human cadherin-6 in ovarian cancer?

Current Management of Relapsed/Refractory Ovarian Cancer

Promising Novel Agents and Strategies Under Investigation

Floor J. Backes, MD
Professor, Gynecologic Oncologist
Columbus, Ohio

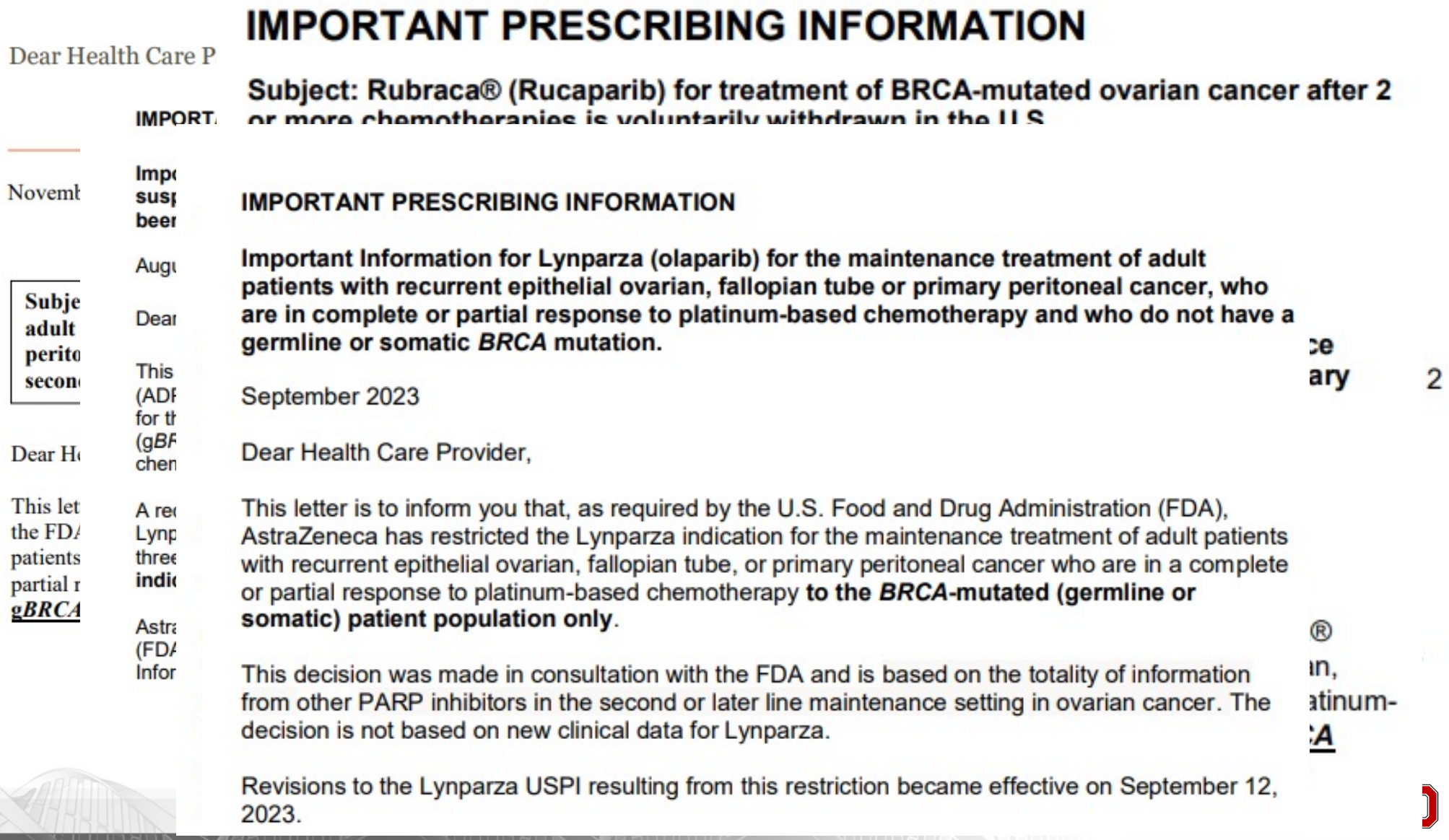
The James

The Ohio State University
Wexner Medical Center

Objectives

- Updated indications for PARP inhibitors in platinum sensitive and platinum resistant ovarian cancer
- PARP after PARP
- Key data on mirvetuximab soravtansine in platinum resistant ovarian cancer
- Early activity of raludotatug deruxtecan (R-DXd) in platinum resistant ovarian cancer

2022 : “Dear Health Care Provider….”



IMPORTANT PRESCRIBING INFORMATION

Subject: Rubraca® (Rucaparib) for treatment of BRCA-mutated ovarian cancer after 2 or more chemotherapies is voluntarily withdrawn in the U.S.

IMPORTANT PRESCRIBING INFORMATION

Important Information for Lynparza (olaparib) for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy and who do not have a germline or somatic *BRCA* mutation.

September 2023

Dear Health Care Provider,

This letter is to inform you that, as required by the U.S. Food and Drug Administration (FDA), AstraZeneca has restricted the Lynparza indication for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy **to the *BRCA*-mutated (germline or somatic) patient population only**.

This decision was made in consultation with the FDA and is based on the totality of information from other PARP inhibitors in the second or later line maintenance setting in ovarian cancer. The decision is not based on new clinical data for Lynparza.

Revisions to the Lynparza USPI resulting from this restriction became effective on September 12, 2023.

The James

The Ohio State University
Wexner Medical Center

2022: Dear Doctor Letters

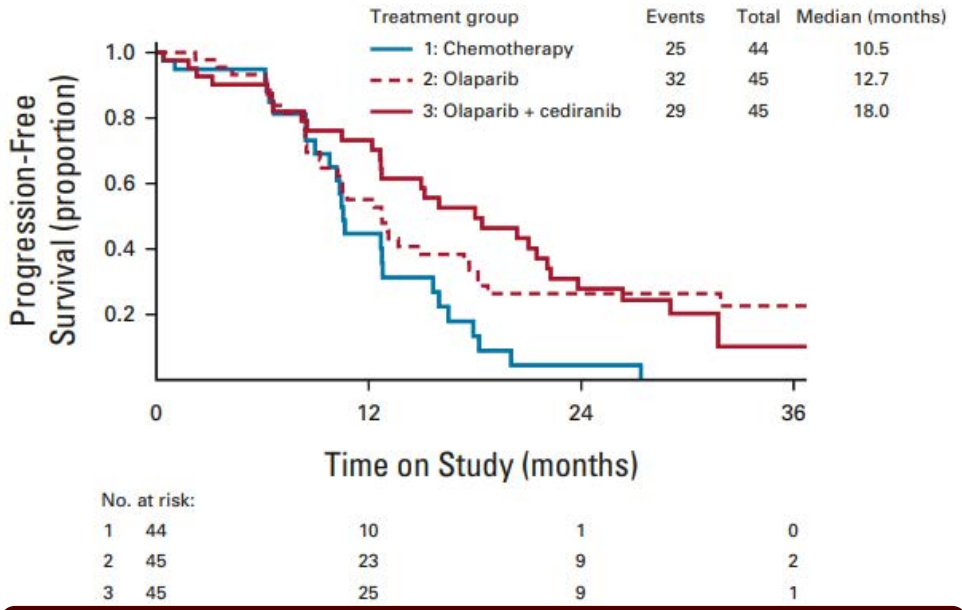
- Treatment of PSOC

Overall Survival	≥2 prior lines	≥3 prior lines
ARIEL4 (BRCAmut) Rucaparib vs chemo	5.4 months (ITT) %CI 1.0, 1.73]	m sensitive 7.6 (HR 1.07) esistant (HR 1.51)
SOLO-3 (BRCAmut) Olaparib vs chemo	HR	39.4 months = 1.33 95% CI = 0.84, 2.18
Quadra (HRD+) Niraparib (single arm trial)		months (95% CI 14.5–24.6)
GY004 Platinum doublet vs Olaparib vs Olaparib/cediranib	s and 33.5 mo 1.3, and 44.8 months (gBRCA)	

Liu, ESMO 2023; Kristeleit Lancet Oncol 2022; Oza, Annals of Oncol 2022; Penson Gynecol Oncol 2022; Moore Lancet Oncol 2019.

Table: 518O ARIEL4: OS

	n	PFS HR (95% CI)*	PFS2 HR (95% CI)†	Median OS, mo†	OS HR (95% CI)†
ITT					
Rucaparib	233	0.665	0.860	19.4	1.313 (0.999–1.725)
CT	116	(0.516–0.858); *P*=0.002	(0.674–1.098)	25.4	
ITT, excluding pts who crossed over to rucaparib					
Rucaparib	233	NA	NA	19.4	0.423 (0.276–0.650)
CT	36			9.1	
ITT, censoring pts who crossed over to rucaparib					
Rucaparib	233	NA	NA	19.4	1.059 (0.688–1.630)
CT	116			26.2	
Platinum-sensitive					
Rucaparib	113	0.502	0.737	29.4	1.071 (0.709–1.618)
CT	57	(0.343–0.733); *P*=0.0004	(0.512–1.060)	27.6	
Platinum-resistant					
Rucaparib	120	0.821	0.968	14.2	1.511 (1.053–2.170)
CT	59	(0.583–1.155); *P*=0.257	(0.697–1.344)	22.2	



GY004: Platinum sensitive gBRCA1/2

2022: Dear Doctor Letters

- PARP inhibitor maintenance after platinum-based therapy for platinum sensitive recurrence

Overall survival	gBRCA	Non-gBRCA	Non-gBRCA, HRD+	HRD+
NOVA Niraparib vs placebo	40.9 vs 38.1 months HR 0.85 [95% CI 0.61, 1.20]	31 vs 34.8 months HR 1.0 [95% 0.81,]	35.8 vs 41.4 months HR 1 [95 CI 0.8 95]	n/a
ARIEL3 Rucaparib vs placebo	45.9 vs 47.8 months HR 0.832 [95% CI 0.58, 1.19]	n/a	36 vs 44.7 months HR 1 [95 CI 0.84, 95]	40.5 vs 47.8 mon H 01 [95% CI 0.77,1.32]
SOLO-2 Olaparib vs placebo	51.7 vs 38.8 months HR 0.74 [95%CI 0.54,1.00]	n/a	n/a	n/a
NORA Niraparib vs placebo	56.0 vs 47.6 months HR 0.86 [95% CI, 0.46–1.58]	46.5 vs 46.9 HR 0.87 [95% CI 0.56,1.35]	Not assessed	Not assessed

Matulonis, Gynecol Oncol 2023; Coleman, Int J Gynecol Cancer 2022; Poveda, Lancet Oncol 2021; Wu, Lancet 2024

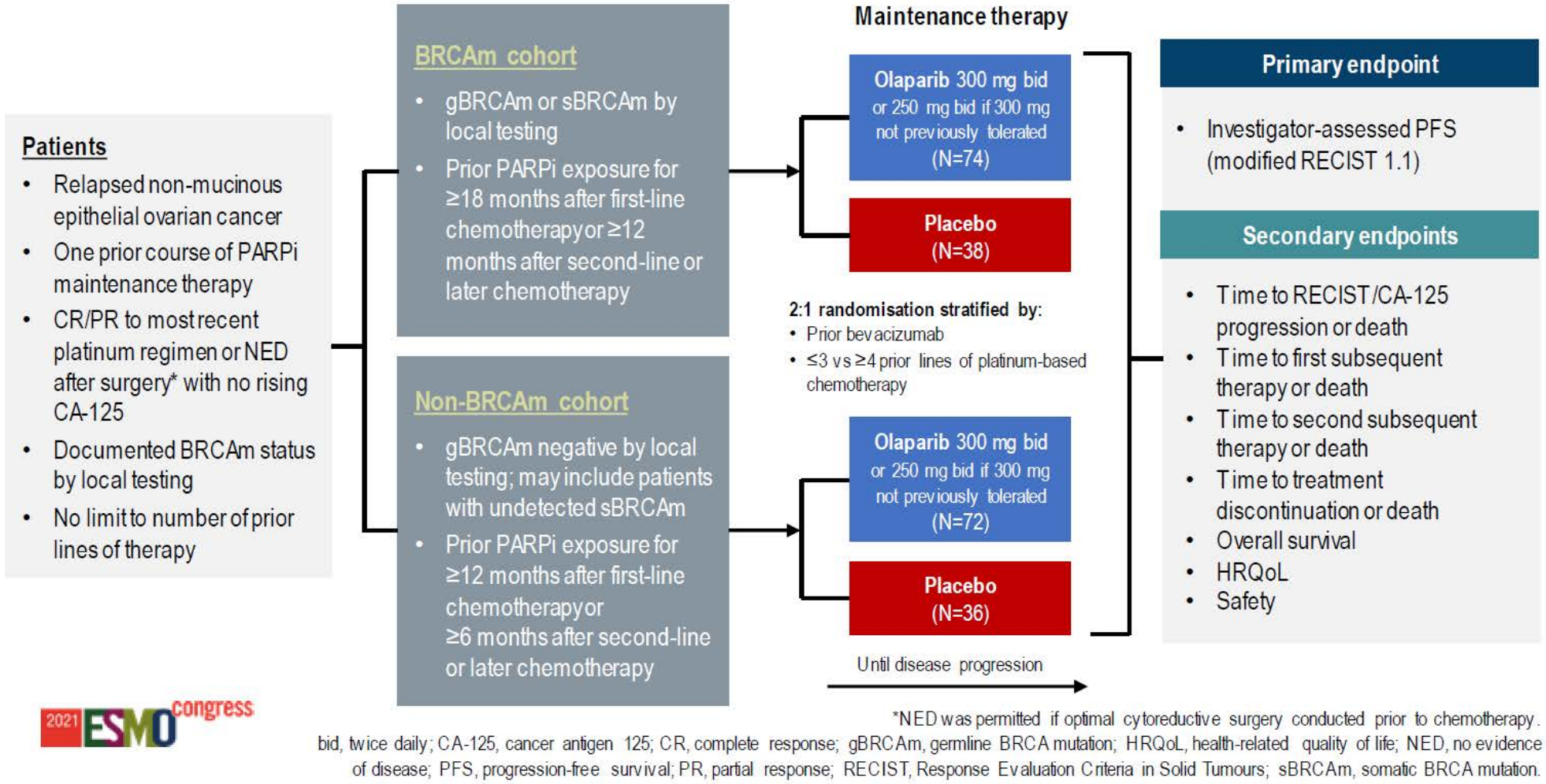
Summary PARP inhibitor FDA indications

Agent	First line	Second line (platinum sensitive)	Treatment of recurrence
Olaparib	gBRCA, sBRCA	gBRCA, sBRCA	none
Olaparib + bevacizumab	HRD+	n/a	n/a
Niraparib	All comers	gBRCA	none
Rucaparib	none	gBRCA, sBRCA	none

Prescribing information for niraparib, rucaparib, olaparib; https://ace.asco.org/guidelines/149680

PARP after PARP? Phase IIIb OReO/ENGOT-OV38 trial

Study design



2021 ESMO congress

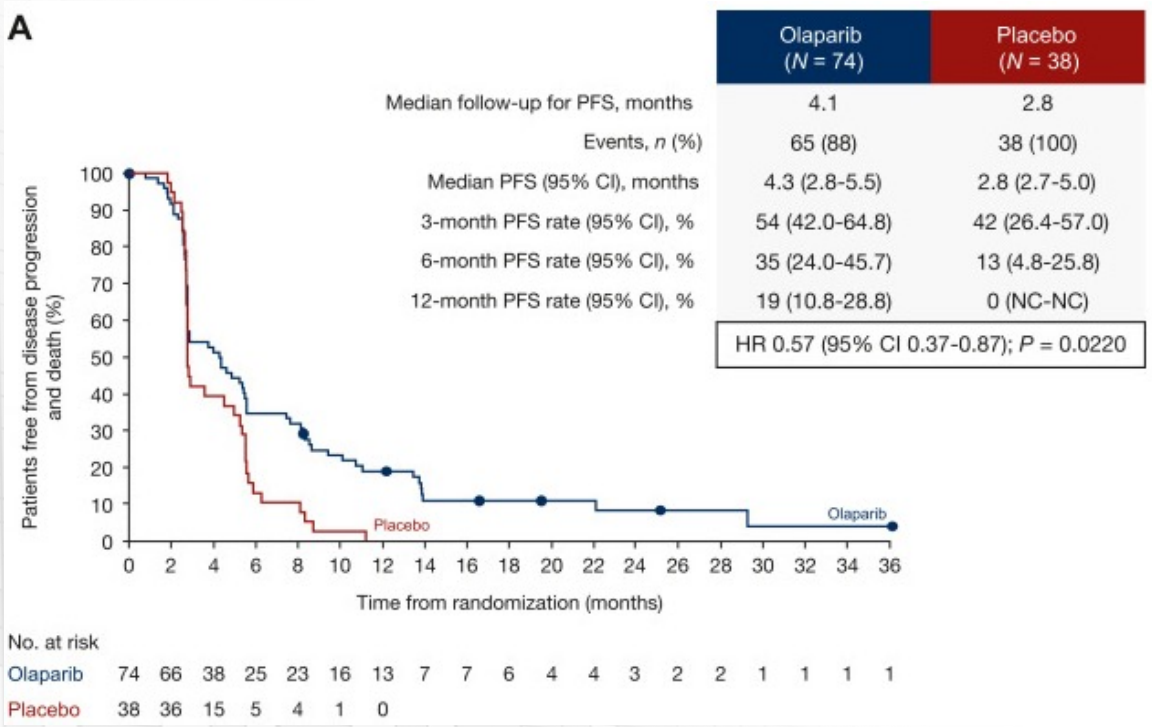
*NED was permitted if optimal cytoreductive surgery conducted prior to chemotherapy.
bid, twice daily; CA-125, cancer antigen 125; CR, complete response; gBRCAm, germline BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; sBRCAm, somatic BRCA mutation.

- >85% had ≥3 prior platinum
- 20-34% CR to last chemo
- BRCAwt: 40% HRD+
- 7% and 14% had first line maintenance PARP

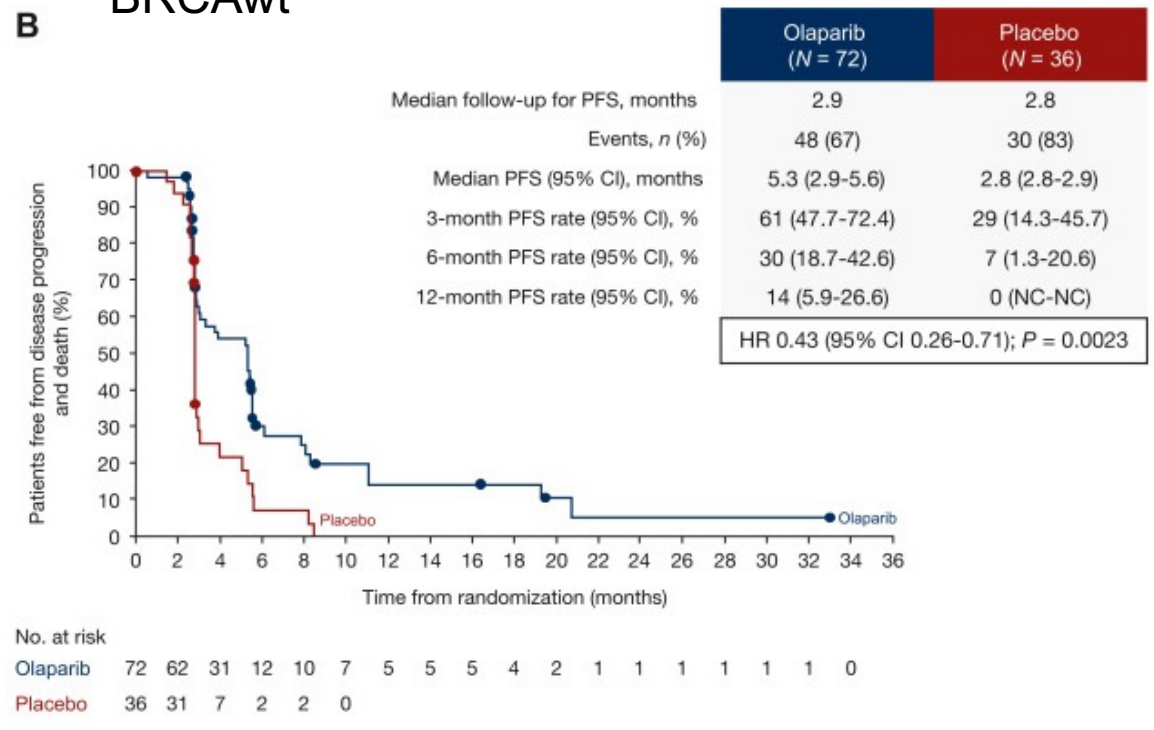
Pujade-Lauraine, Annals of Oncol 2023, ESMO 2021

PARP after PARP?

BRCAmut



BRCAwt



Median OS in the BRCAm cohort was 20.1 months with olaparib and 20.9 months with placebo (HR 0.88; 95% CI 0.52-1.53; P = 0.44) (at 54% OS maturity). OS data was immature for BRCAwt

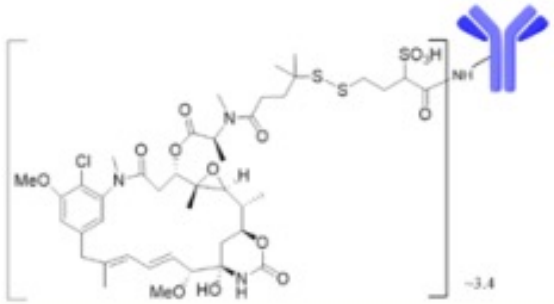
No new cases of MDS/AML in Olaparib group (1 (3%) in placebo group in BRCAm patient)

The James

THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

Pujade-Lauraine, Annals of Oncol 2023

Mirvetuximab Soravtansine vs Investigator Choice Chemo



MIRVETUXIMAB SORAVTANSINE
Folate receptor alpha-targeting ADC

ANTIBODY: Humanized monoclonal antibody which selectively binds to FRα

PAYLOAD: DM4 maytansinoid payload; potent tubulin-targeting agent

LINKER: Cleavable sulfo-SPDB linker

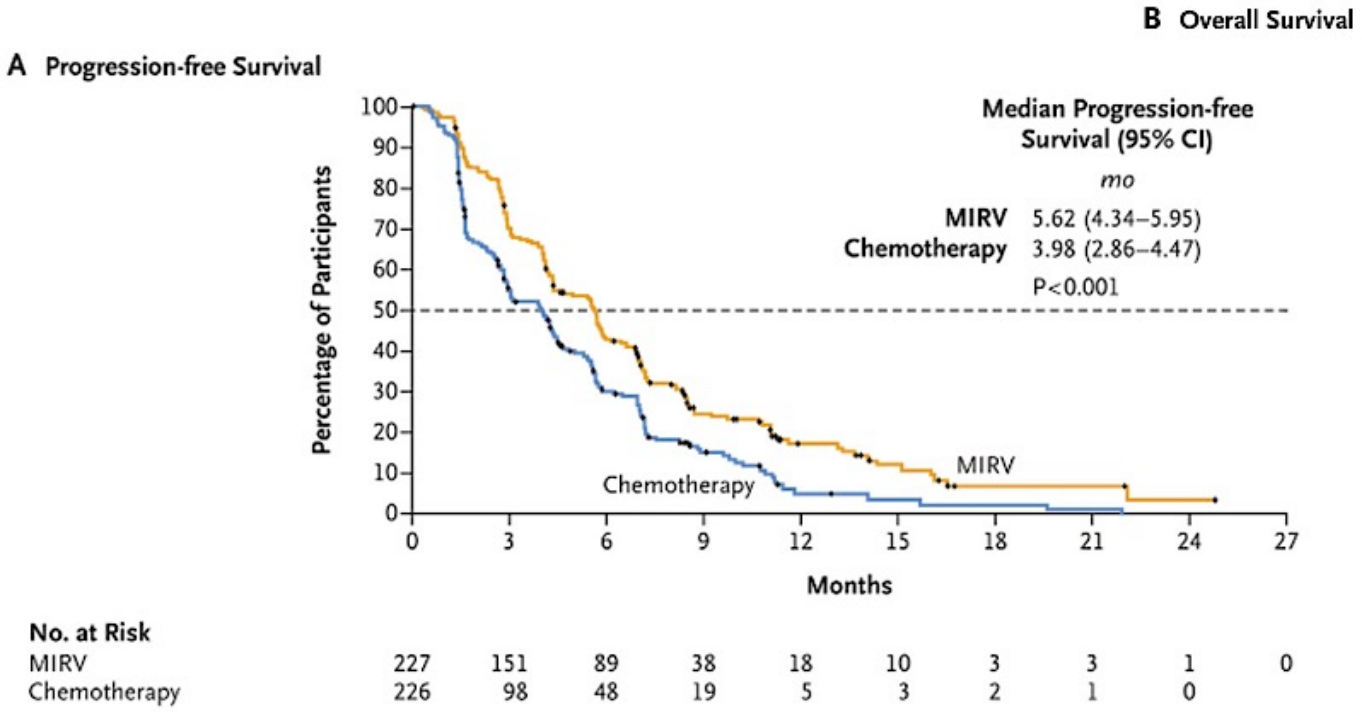
AVERAGE DAR: 3.4

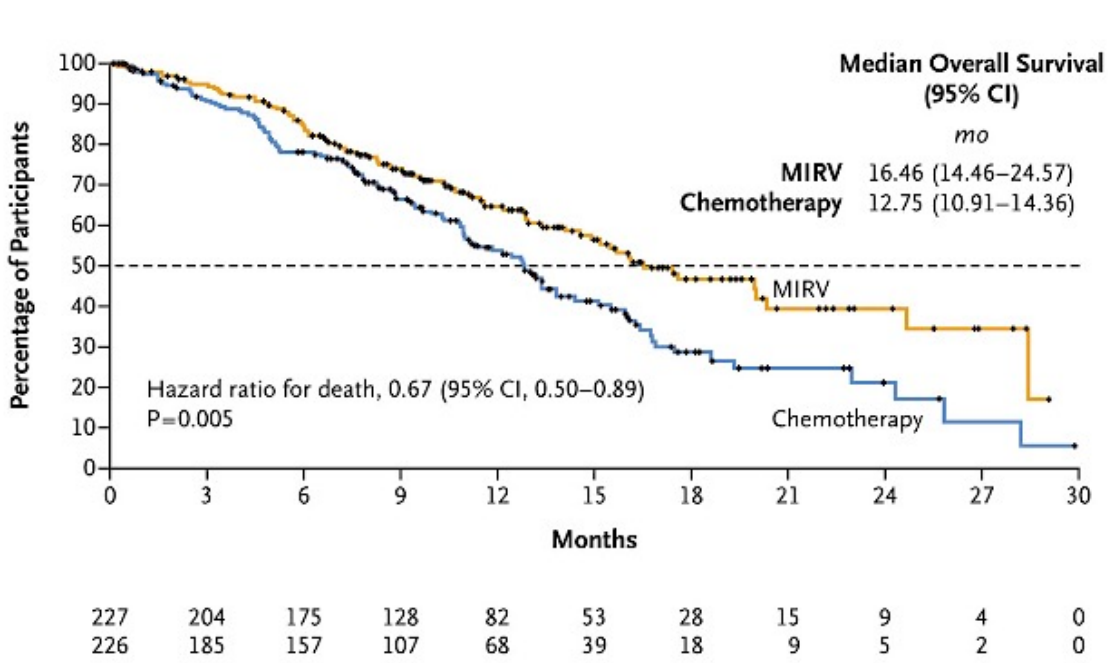
- Phase III RCT mirv vs SOC chemo
  - 2020-2023
  - N=453
- Platinum resistant ovarian cancer
- Folate Receptor Alpha “high”
  - ≥75% of viable cells with 2-3+ staining intensity
- 1-3 prior lines (47% had 3)
- >60% prior bev; >50% prior PARPi
- 40% platinum free interval < 3 months

- ORR: 42.3% vs 15.9%
  - DOR 6.77 vs 4.47 months

Moore, NEJM 2023;

Mirvetuximab Soravtansine





Moore, NEJM 2023

The James

The Ohio State University
Wexner Medical Center

MIRASOL Safety

FDA approves mirvetuximab soravtansine-gynx for FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

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On March 22, 2024, the Food and Drug Administration approved mirvetuximab soravtansine-gynx … for adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens. Patients are selected based on an FDA-approved test. Mirvetuximab soravtansine-gynx previously received accelerated approval for this indication.

Content current as of:
03/22/2024

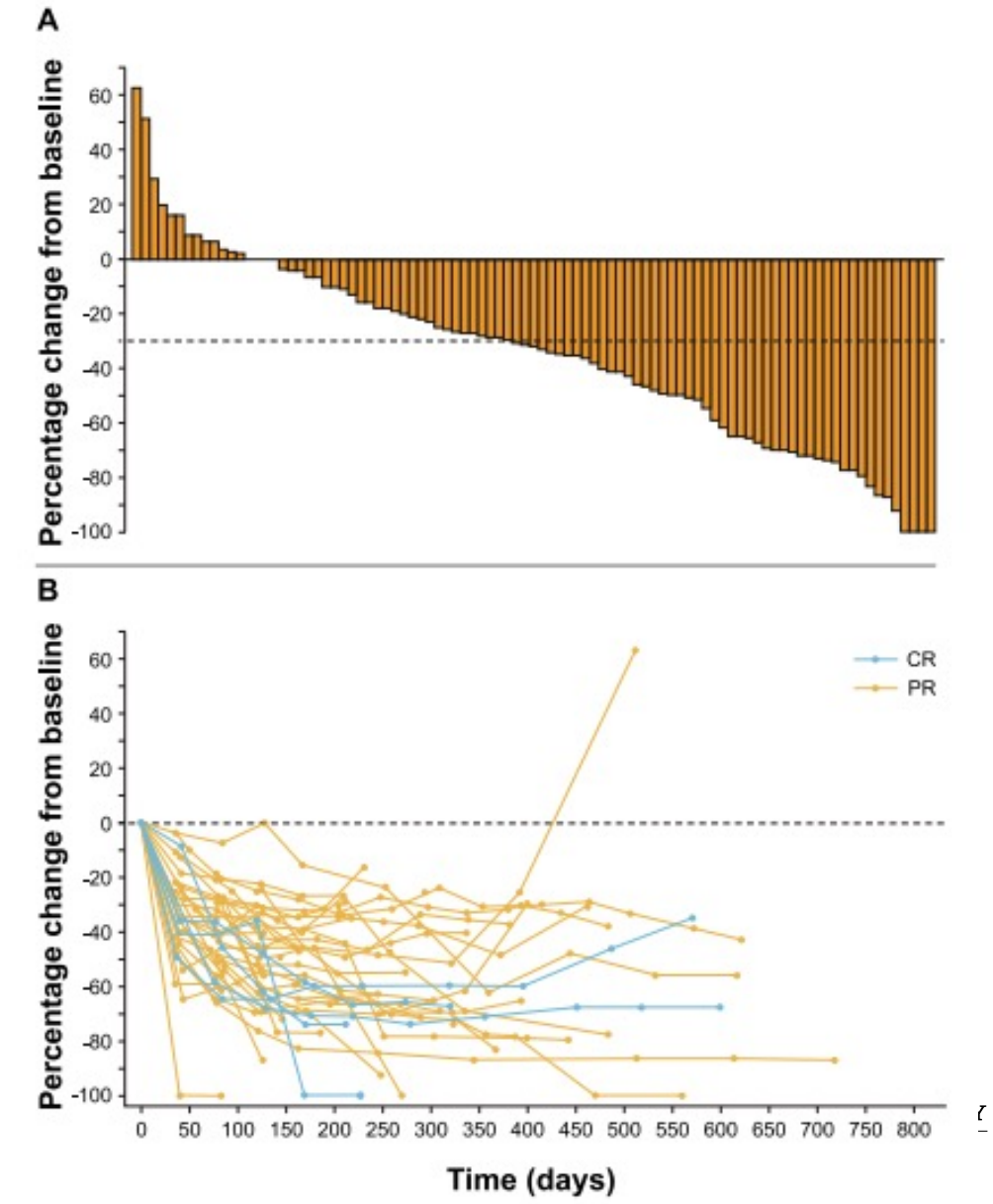
Moore, NEJM 2023

The James

The Ohio State University
Wexner Medical Center

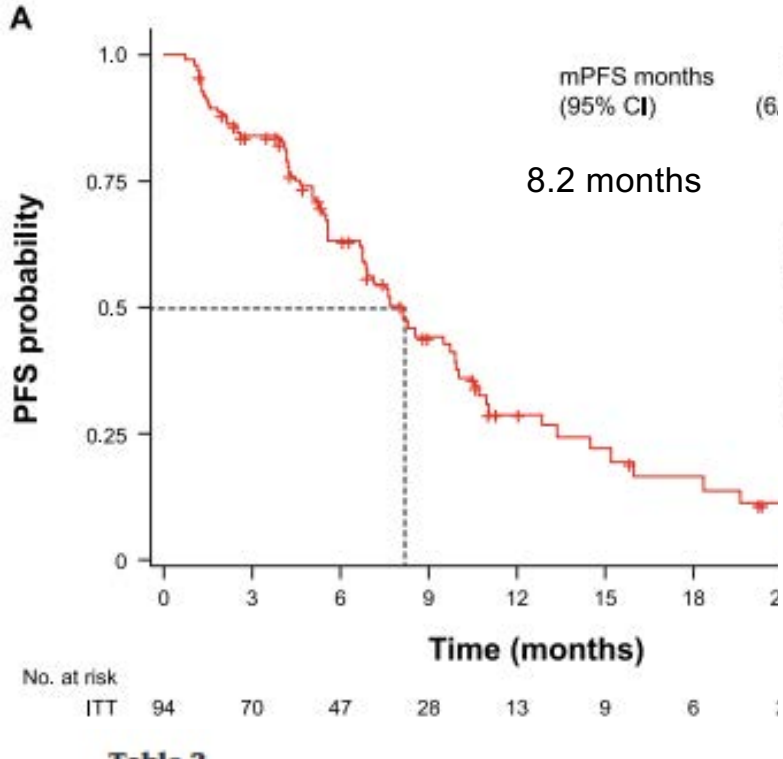
FORWARD II: Mirvetuximab with bevacizumab

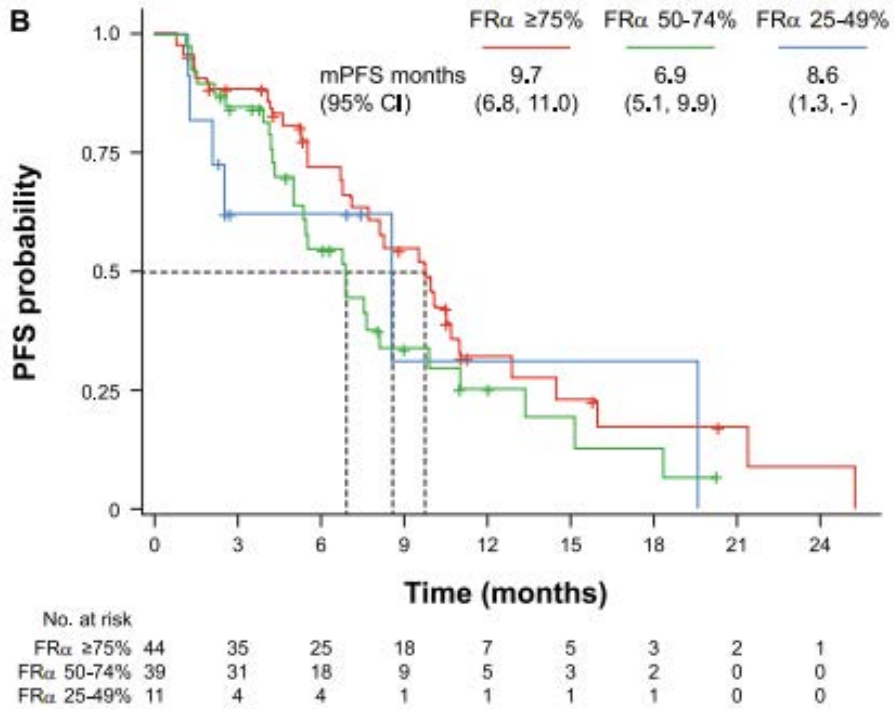
- Platinum resistant recurrent ovarian cancer
- FRα expression ≥25%
  - ≥75% FRa in 47%; 50-74% in 42%; 25-49% in 12%
- 1-3 prior lines
  - 52% had 3
- N=94
- ORR 44% (5% CR)
- mDOR 9.7 months



Gilbert, Gynecol Oncol 2023

Mirvetuximab with bevacizumab for PROC





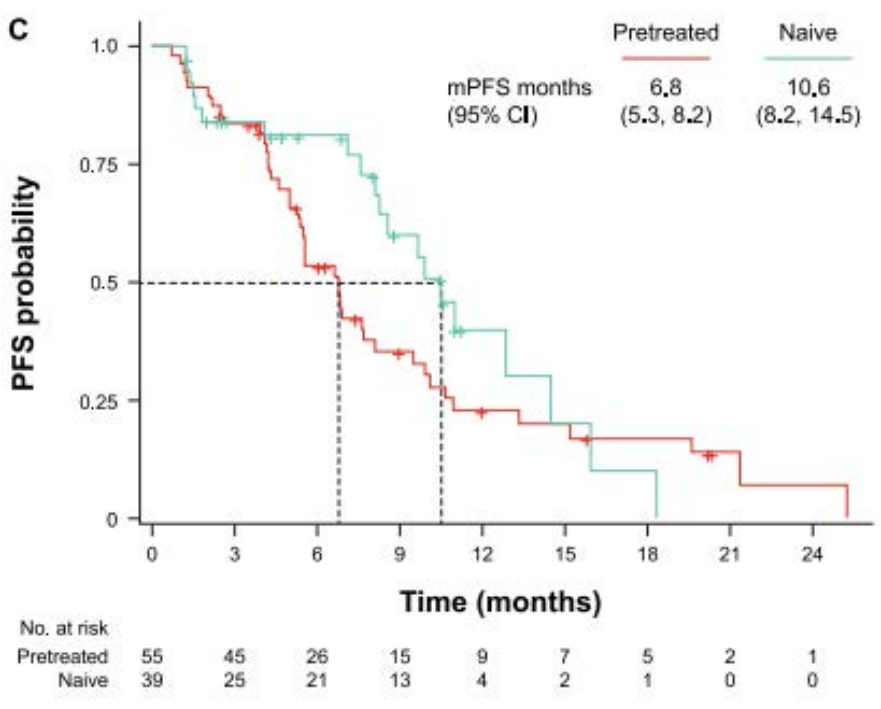


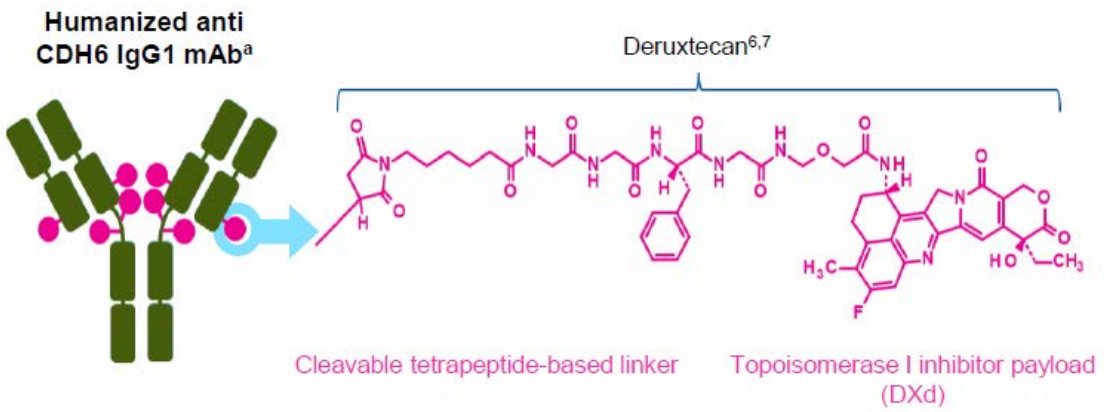
Table 3
Summary of efficacy in patients by subgroups.

Endpoint	FRα ≥ 75% (*n* = 44)	FRα 50–74% (*n* = 39)	FRα 25–49% (*n* = 11)	BEV-naïve (*n* = 39)	BEV-pretreated (*n* = 55)
Confirmed objective response rate, n (%)	21 (48)	16 (41)	4 (36)	22 (56)	19 (35)
95% CI	(33, 63)	(26, 58)	(11, 69)	(40, 72)	(22, 49)
Median duration of response, (months)	9.7	9.7	18.5	10.4	9.7
95% CI	(6.0, 12.0)	(3.0, NR)	(NE)	(6.9, 14.5)	(4.2, NR)
Median progression-free survival, (months)	9.7	6.9	8.6	10.6	6.8
95% CI	(6.8, 11.0)	(5.1, 9.9)	(1.3, NR)	(8.2, 14.5)	(5.3, 8.2)

BEV, bevacizumab; FRα, folate receptor alpha; NE, not evaluable; NR, not reached.

Gilbert, Gynecol Oncol 2023

Raludotatug deruxtecan (R-DXd) monotherapy in patients with previously treated ovarian cancer

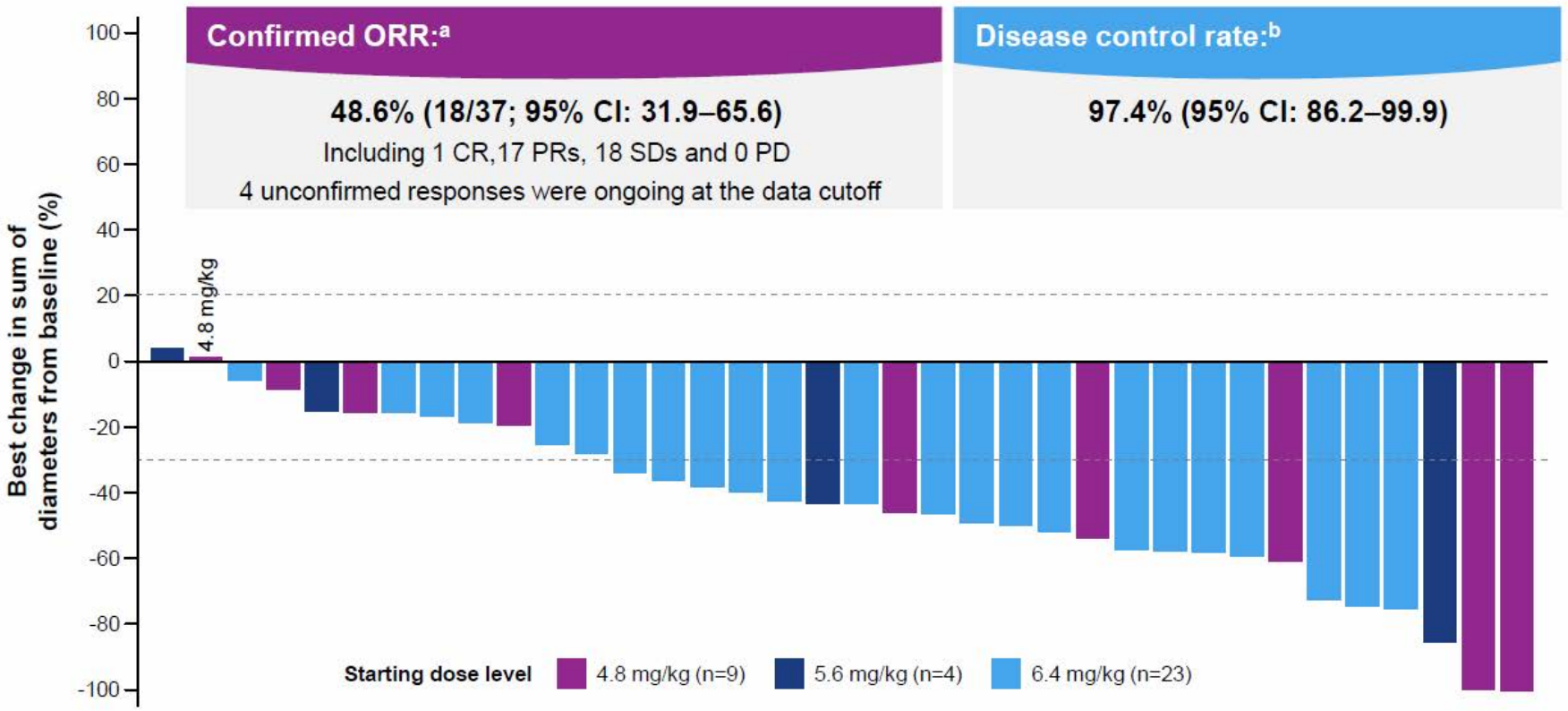


Payload mechanism of action: topoisomerase I inhibitor[4,b]
High potency of payload[5,8,b]
High drug-to-antibody ratio of ≈8[4,b]
Payload with short systemic half-life[5,b,c]
Stable linker-payload[5,8,b]
Tumor-selective cleavable linker[4,5,8,b]
Bystander antitumor effect[4,b]

- CDH6 expression in ~65 to 85% of patients with ovarian cancer
- First in Human Phase 1 study (NCT04707248)
- Ovarian cancer patients treated with R-DXd 4.8-6.4 mg/kg IV every 3 weeks
  - N=45
- Median prior lines : 4 (1-12)
- PROC 89%
- 64% prior bev; 64% prior PARPi

Courtesy of Dr Kathleen Moore, SGO Annual Meeting 2024

CDH6 targeting ADC: Raludotatug deruxtecan (R-DXd)



- Median DOR: 11.2 months
- Median PFS: 8.1 months
- No correlation between CDH6 expression and response
- Phase 2/3 REJOICE-Ovarian01 now open (NCT06161025)

Courtesy of Dr Kathleen Moore, SGO Annual Meeting 2024

The James

The Ohio State University
Wexner Medical Center

Raludotatug deruxtecan (R-DXd) Safety Profile

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. ESMO 2023;Abstract 745MO.

Conclusion

- Increased use of PARP inhibitors in first line; limited indications for PARP inhibitors in second line maintenance
  - Consider for patients with no prior progression on PARPi and long PARPi-free interval
- Many new exciting options for platinum resistant ovarian cancer
  - Antibody drug conjugates
    - Multiple different targets
    - Multiple different payloads
- Minimal activity of immunotherapy for PROC but novel immunotherapy strategies under development

Agenda

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

Module 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr Backes

Module 3: First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Mirza

Module 4: Current Therapeutic Options for R/R EC; Novel Investigational Strategies — Dr Slomovitz

Module 5: Role of HER2-Targeted Therapy in the Management of Advanced OC, EC and Other Gynecologic Cancers — Dr Secord

Dr Priya Rudolph: Case Presentation

Clinical presentation: 63-year-old woman diagnosed with Stage 1A Grade 1 endometrioid endometrial cancer w 35% myometrial involvement in 06/2015, s/p robotic TAH/BSO, no RT

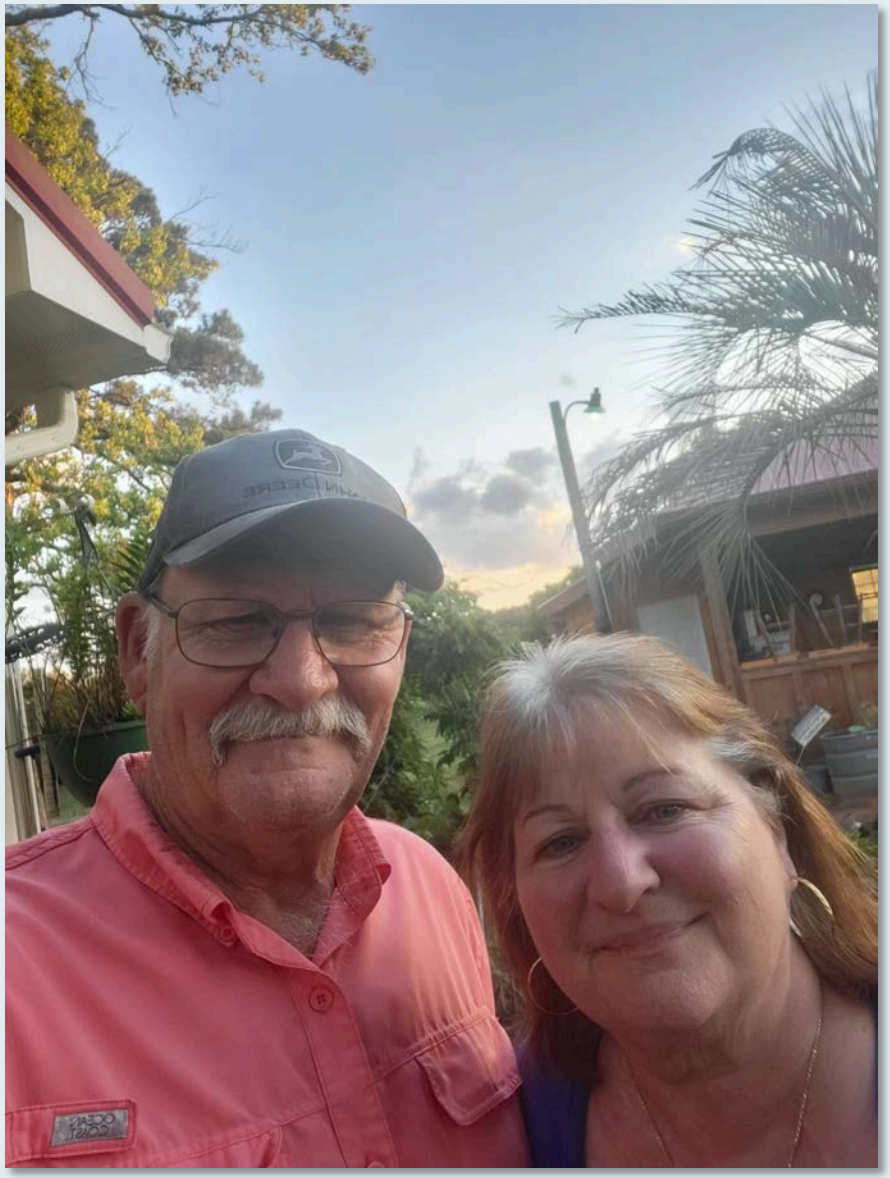
2 y later in 11/2017 — presented with abdominal pain and noted to have 15 x 12-cm mass in central pelvis and additional smaller masses in L pelvis with pelvic adenopathy, not amenable to resection

Biopsy: Endometrioid EC, MSI-H

Treatments to date: Carboplatin/paclitaxel/bevacizumab — 6 cycles with partial response followed by interval debulking w residual pelvic mass w endometrioid features with focal squamous differentiation and extensive necrosis. PET/CT — mass in vaginal cuff and upper vagina, pelvic adenopathy

Weekly cisplatin/RT x 6 weeks, then vaginal brachytherapy. Resumed carboplatin/paclitaxel/bevacizumab — neuropathy, cytopenias, bleeding. Bevacizumab held. CT 3 mo later — new soft tissue mass associated with rectovaginal fistula

Pembrolizumab x 2 y; well tolerated except for colitis, acute nephritis and hypothyroidism. PET/CT after 7 mo – NED. NED x 3 y



RTP
RESEARCH
TO PRACTICE

RTP
RESEARCH
TO PRACTICE

Dr Priya Rudolph: Case Discussion Questions

Have you seen cases of patients with endometrial cancer who experience a good response to anti-PD-1/PD-L1 antibodies?

How do you approach monitoring and management of side effects associated with immunotherapy?

What, if any, history of autoimmune disease is an absolute contraindication for immunotherapy?

Dr Priya Rudolph: Questions for the Faculty

What is your preferred first-line therapy for metastatic microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) EC? Is your approach any different for a younger patient with no comorbidities? Does PD-L1 status matter?

Do you have a preferred anti-PD-1/PD-L1 antibody for patients with MSI-H/dMMR EC?

Dr Lyndsay Willmott: Case Presentation

Clinical presentation: 73-year-old woman with Stage IV carcinosarcoma; MSI-H/dMMR

Treatment: Surgery followed by carboplatin/paclitaxel/dostarlimab → dostarlimab maintenance

Response: Complete response; currently on dostarlimab maintenance

Side effects/tolerability issues: No dose-limiting toxicities

Dr Lyndsay Willmott: Case Discussion Questions

How would you have treated this case of MSI-H/dMMR Stage IV carcinosarcoma?

Is immunotherapy as effective for patients with carcinomsarcomas as it is for patients with endometrioid EC?

Dr Lyndsay Willmott: Questions for Faculty

What is your preferred approach to the management of EC with a POLE mutation in the adjuvant and metastatic setting?

Do you expect ongoing clinical trials evaluating anti-PD-1/PD-L1 antibody-based strategies in the adjuvant and neoadjuvant settings to be positive?

In what situations, if any, are you currently employing adjuvant immunotherapy (IO) outside of a clinical trial setting?

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First-Line Therapy for Advanced Endometrial Cancer

Mansoor Raza Mirza

Chief Oncologist	Dept. of Oncology, Rigshospitalet, Copenhagen University Hospital, Denmark.
Medical Director	NSGO-CTU (Nordic Society of Gynaecological Oncology)
Chairman$_{2020\text{-}2022}$	ENGOT (European Network of Gynaecological Oncology Trials group)
Vice-President$_{2020\text{-}2024}$	ESGO (European Society of Gynaecological Oncology)
Faculty	ESMO (European Society of Medical Oncology)
Scientific Chair	IGCS Congress 2024
Congress Chair	ESGO Congress 2026
Prix Galien Foundation	Jury member

Rationale of combining Immune Checkpoint Inhibitor and PARP inhibitor with Chemotherapy

Immune Checkpoint Inhibitors:

- Durable activity in both dMMR/MSI-H and MMRp/MSS previously treated EC[1]
- dMMR/MSI-H EC is associated with:
  - High TMB/TILs[2]
  - Higher response rate to anti–PD-1[1]

Chemotherapy:

- Enhances immunogenic cell death[3,4]
- Reduces immunosuppression in TME[3,4]
- Broad clinical activity when combined with anti–PD-1 in several cancers[5–8]

Addition of PARP inhibitor:

- Adding a PARPi to immune checkpoint inhibitor may further improve outcomes, including in patients with MMRp/MSS disease, a population with high unmet need[9–12]

dMMR, mismatch repair deficient; EC, endometrial cancer; MMRp, mismatch repair proficient; MSI-H, microsatellite instability-high; MSS, microsatellite stable; PD-1, programmed death protein-1; TIL, tumor infiltrating lymphocytes; TMB, tumor mutational burden; TME, tumor microenvironment. CP, carboplatin-paclitaxel; OS, overall survival; PARPi, poly(ADP-ribose) polymerase inhibitor;

1. Oaknin A, Gilbert L, Tinker AV, et al. *J Immunother Cancer*. 2022;10:e003777. 2. Song Y, et al. *Onco Targets Ther*. 2021;14:4485-4497. 3. Emens LA, Middleton G. *Cancer Immunol*. 2015;3(5):436-443. 4. Hato SV, et al. *Clin Cancer Res.* 2014;20:2831-2837. 5. Gandhi L, et al. *N Engl J Med*. 2018;378:2078-92. 6. Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-51. 7. Janjigian YY, et al. *Lancet*. 2021;398:27-40. 8. Burtness B, et al. *Lancet*. 2019;394:1915-1928. 9. McGranahan N, et al. *Science.* 2016;351(6280):1463–1469. 10. Jiao S, et al. *Clin Cancer Res*. 2017;23(14):3711–3720. 11. Bang Y-J, et al. *J Clin Oncol*. 2019;37(suppl 4):140. 12. Westin SN, et al. *J Clin Oncol*. 2024;42(3):283–299.

Paradigm-shifting data in EC management

Different studies; cross-trial comparisons are not appropriate

Name	EN6-RUBY Part 1	EN7-AtTEnd	NRG018	EN11
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp
Investigational agent	Dostarlimab + chemo	Atezolizumab + chemo	Pembrolizumab + chemo	Pembro + chemo
N	494	550	775	990
Concomitant	+	+	+	+
Maintenance	+	+	+	
Expected readout	**NEJM 2023**	**ESMO 23**	**NEJM 2023**	**Negative**
☺	**Statistically significant PFS dMMR & ITT, OS ITT**	**Statistically significant PFS dMMR and ITT**	**Statistically significant PFS dMMR and pMMR**	?
☹	**Not powered for pMMR**	**OS immature**	**Not testing for OS**	**?**

dMMR = mismatch repair deficient; ITT = intent to treat population; MSI-H = microsatellite instability-high; PFS = progression free survival; pMMR = mismatch repair proficient; OS = overall survival.

1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.; 7. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132 ; 8. Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1; 9. Eskander RN, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2; 10. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40; 11. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V; 12. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2

Paradigm-shifting data in EC management

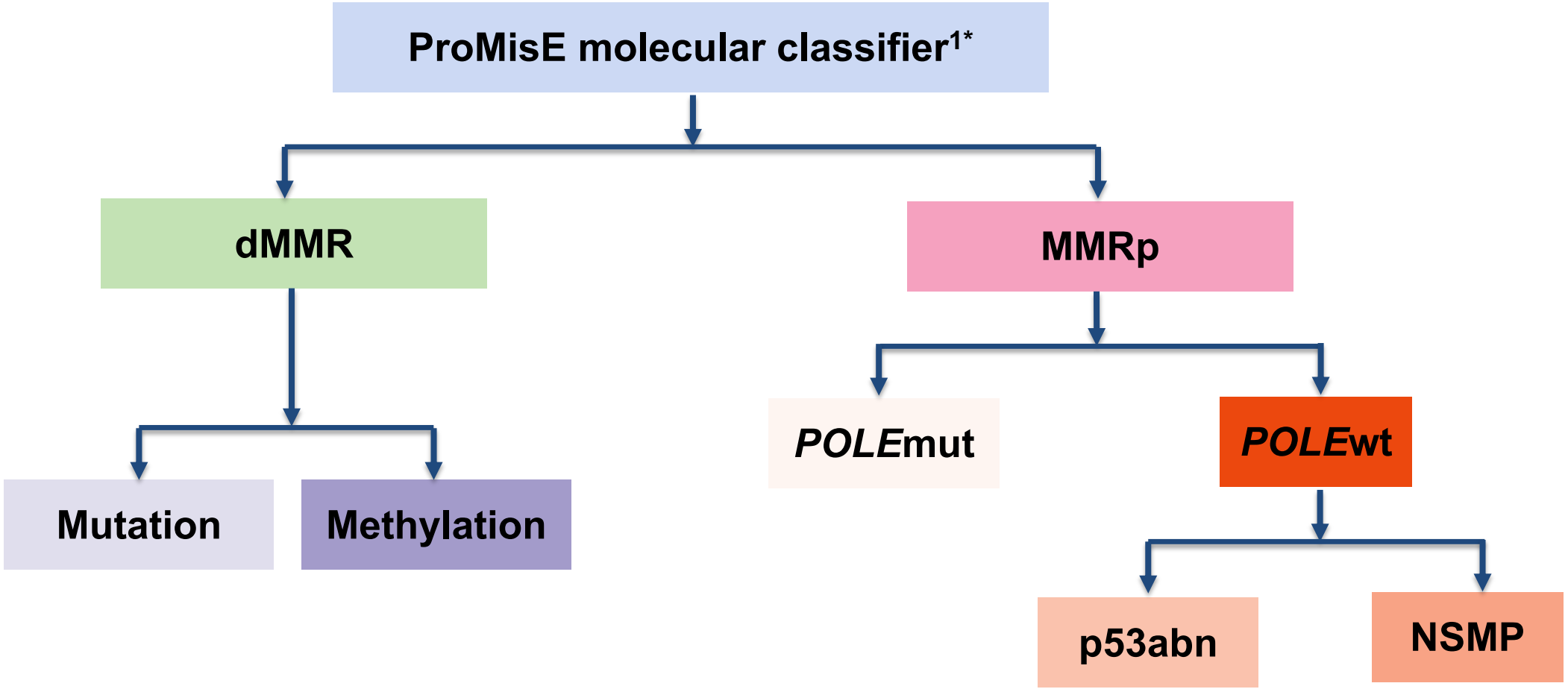
Different studies; cross-trial comparisons are not appropriate

Name	EN6-RUBY Part 1	EN7-AtTEnd	NRG018	EN11	EN6-RUBY Part 2	DUO-E
Lead group Study chair	NSGO-CTU Mirza	MaNGO Colombo	NRG Eskander	BGOG Van Gorp	NSGO-CTU Mirza	GOG-P Westin
Investigational agent	Dostarlimab + chemo	Atezolizumab + chemo	Pembrolizumab + chemo	Pembro + chemo	Dostarlimab + Niraparib + chemo	Durvalumab + Olaparib + chemo
N	494	550	775	990	270	699
Concomitant	+	+	+	+	+	+
Maintenance	+	+	+		+	+
Expected readout	**NEJM 2023**	**ESMO 23**	**NEJM 2023**	**Negative**	**SGO 24**	**JCO 2023**
☺	**Statistically significant PFS dMMR & ITT, OS ITT**	**Statistically significant PFS dMMR and ITT**	**Statistically significant PFS dMMR and pMMR**	?	**Statistically significant PFS ITT and PFS pMMR**	**Statistically significant PFS ITT for durvalumab and durvalumab + olaparib**
☹	**Not powered for pMMR**	**OS immature**	**Not testing for OS**	**?**	**Chemo + ICI arm is missing OS immature**	**Not powered for ICI + chemo +/- PARPi Not powered for pMMR or dMMR**

dMMR = mismatch repair deficient; ITT = intent to treat population; MSI-H = microsatellite instability-high; PFS = progression free survival; pMMR = mismatch repair proficient; OS = overall survival.

1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158. 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170. 4. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA. 5. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA.; 6. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40.; 7. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132 ; 8. Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1; 9. Eskander RN, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2; 10. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40; 11. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V; 12. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2

Patient characteristics in first-line EC trials



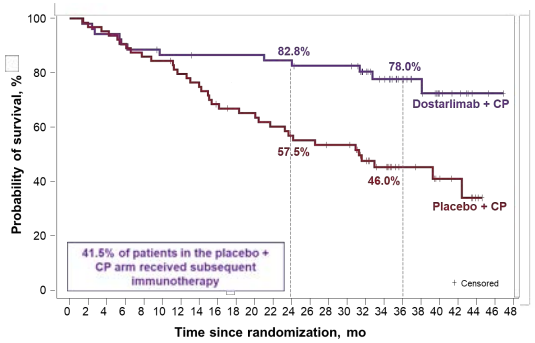
dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

1. Kommoss S, et al. Ann Oncol. 2018;29(5):1180–1188.

dMMR EC

Substantial and unprecedented PFS and OS benefit of ICI + chemotherapy

EN6-RUBY Part 1[1–4]

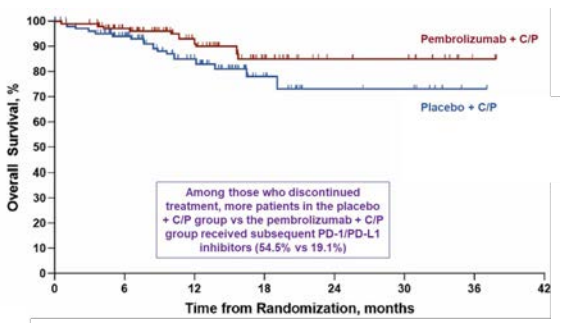


OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	22.6	NE (NE-NE)
Placebo + C/P	53.8	31.4 (20.3-NE)
OS data maturity	39.8%	
Median follow-up, mo	36.6	

PFS HR 0.28 (95% CI, 0.16-0.50); *P*<0.001

OS **HR 0.32** (95% CI, 0.17-0.63); *Nominal P*=0.0002

NRG-GY018[5–7]

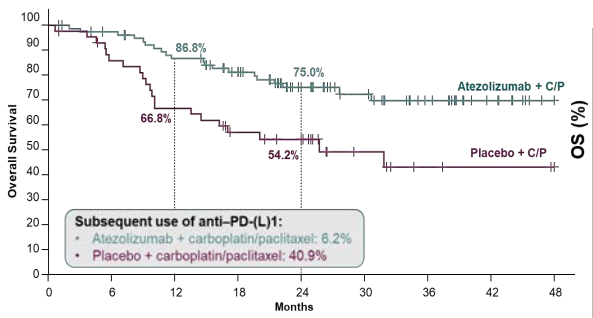


OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	9.1	NR (NR-NR)
Placebo + C/P	15.1	NR (NR-NR)
OS data maturity	18%	
Median follow-up, mo	13.3-13.7	

HR 0.30 (95% CI, 0.19-0.48); *P*<0.001

HR 0.55 (95% CI, 0.25-1.19)

EN7-AtTEnd[8]

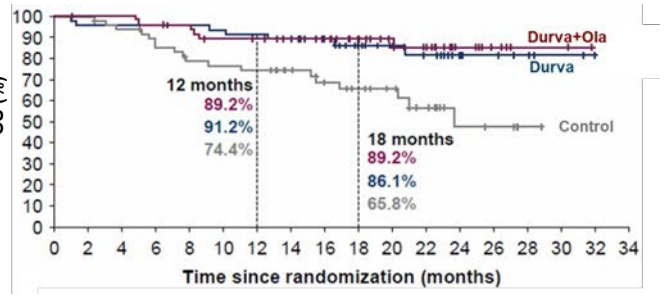


OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	24.7	NE (NE-NE)
Placebo + C/P	47.7	25.7 (13.5-NE)
OS data maturity	--	
Median follow-up, mo	--	

HR 0.36 (95% CI, 0.23-0.57); *P*=0.0005

HR 0.41 (95% CI, 0.22-0.76)

DUO-E[9–10]



OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	15.2	NR (NR-NR)
Placebo + C/P	36.7	23.7 (16.9-NR)
OS data maturity	21.7%	
Median follow-up, mo	--	

HR 0.42 (95% CI, 0.22-0.80); *Durva + C/P arm*

HR 0.34 (95% CI, 0.13-0.79) *Durva + C/P arm*

There are inherent limitations in cross-study comparisons and caution is needed when reviewing data across individual (non-comparative) trials.
This slide is for information purposes only and is not intended to imply or infer the noninferiority or superiority of any product, in terms of efficacy or safety.

dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; PFS = progression free survival; OS = overall survival.

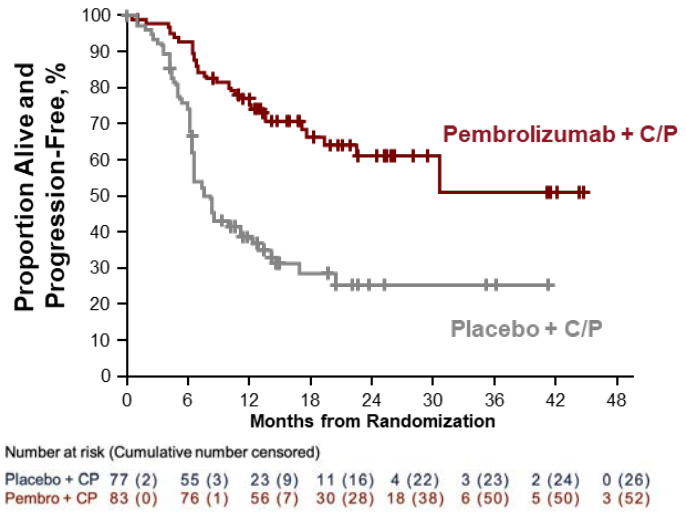
1. Mirza MR, et al. N Engl J Med. 2023;388:2145-2158; 2. Mirza MR, et al. Ann Oncol. 2023;34:500-501; 3. Eskander RN, et al. N Engl J Med. 2023;388:2159-2170; 4. Powell MA, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA1; 5. Eskander RN, et al. Presented at: SGO; March 25-28 2023; Tampa, FL, USA; 6. Arend RC, et al. Presented at: SGO; March 25-28, 2023; Tampa, FL, USA; 7. Eskander RN, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2; 8. Colombo N et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA40; 9. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132; 10. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V

No PFS difference seen in patients with dMMR EC based on mechanism of MMR loss

NRG-GY018: PFS by methylation status in the dMMR population

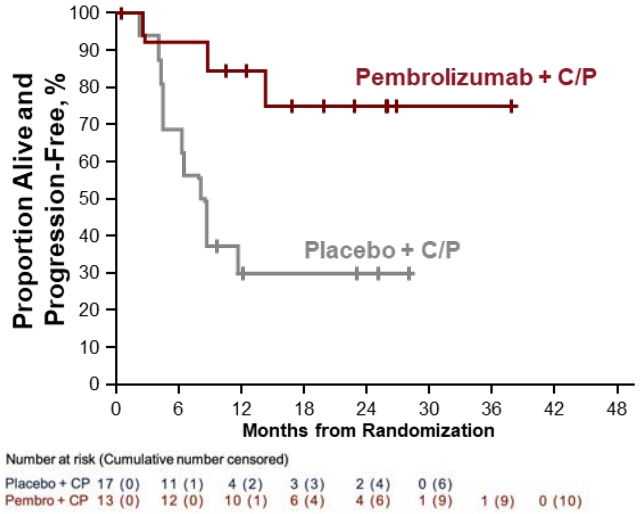
Methylation
Pembro + C/P vs Placebo + C/P

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + C/P	51/77	7.5 (6.4–11.3)	0.307 (0.19–0.49) *Nominal* P* <0.0001
Pembro + C/P	28/83	NR (22.3–NR)	



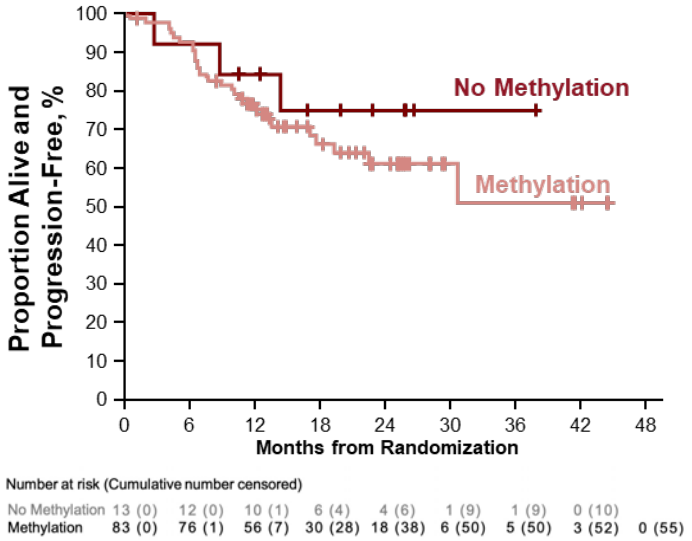
No methylation
Pembro + C/P vs Placebo + C/P

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + C/P	11/77	8.3 (4.4–NR)	0.263 (0.07–0.99) Nominal* P =0.0172
Pembro + C/P	3/13	NR (14.2–NR)	



Methylation status
Pembro + C/P arm

	Events n/N	Median (95% CI), mo
No Methylation	3/13	NR (14.2–NR)
Methylation	28/83	NR (22.3–NR)

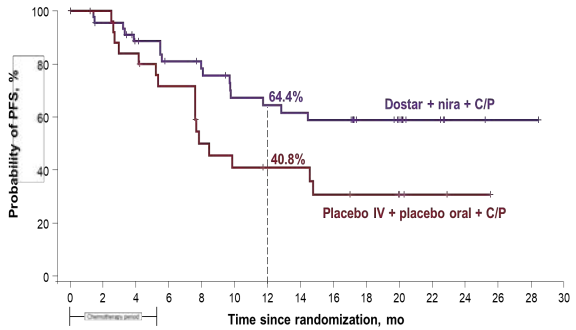
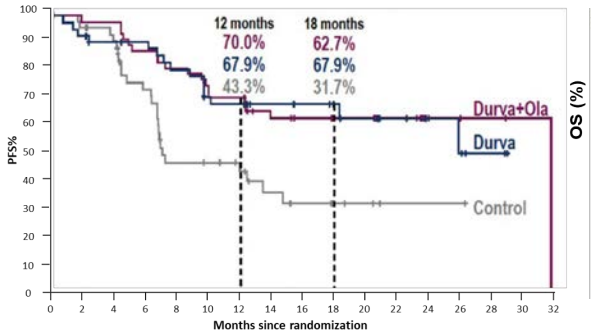
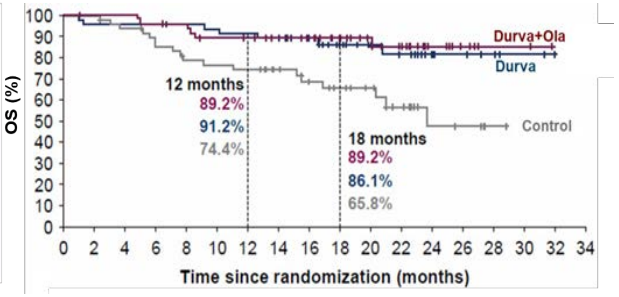


CP = carboplatin/paclitaxel; dMMR = mismatch repair deficient; MMR = mismatch repair; PFS = progression-free survival; OS = overall survival.
Data cut off date, August 18, 2023.

1. Eskander RN, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20–24, 2023; Madrid, Spain; Presentation #LBA43.

No additional benefit of PARPi in dMMR EC

The effect is predominantly driven by anti-PD-(L)1

EN6-RUBY Part 2[1]		DUO-E[2,3]	
PFS	**OS**	**PFS**	**OS**
	Not mature*		
HR 0.48 (95% CI, 0.27-0.96); *Nominal P*<0.0174 Dostar+Nira+C/P arm	HR 0.28 (95% CI, 0.16-0.50); *P*<0.001 Dostar+C/P arm	Not mature	HR 0.33 (95% CI, 0.17-0.63); *Nominal P*=0.0002 Dostar+C/P arm
HR 0.41 (95% CI, 0.21-0.75); Durva+Ola+C/P arm	HR 0.42 (95% CI, 0.22-0.80) Durva+C/P arm	HR 0.28 (95% CI, 0.10-0.68); *Durva+Ola+C/P arm*	HR 0.34 (95% CI, 0.13-0.79); *Durva+C/P arm*

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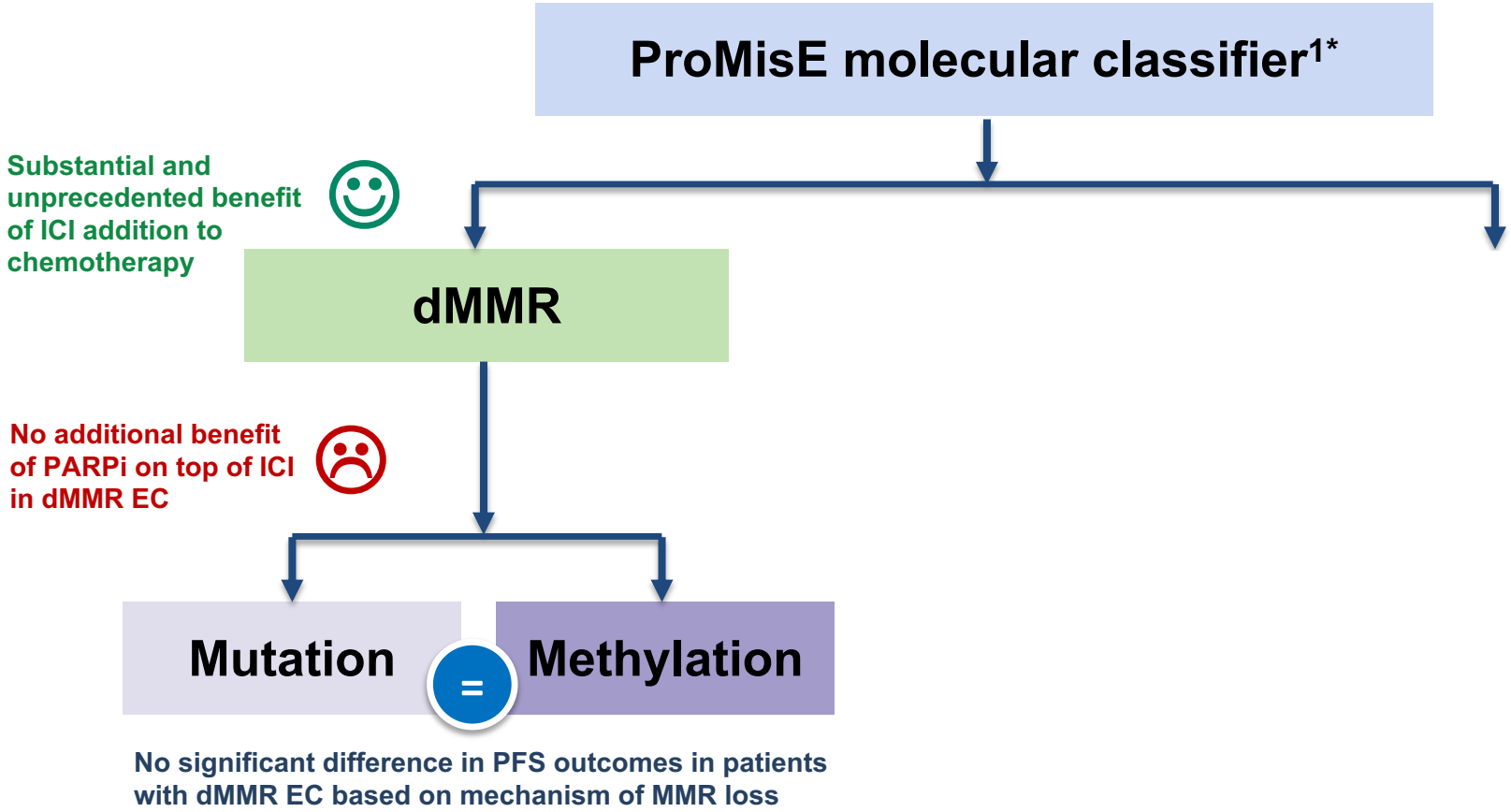
dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; OS = overall survival.

1. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.; 2. Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132; 3. Baurain JF, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Scientific Plenary V

Patient characteristics in first-line EC trials



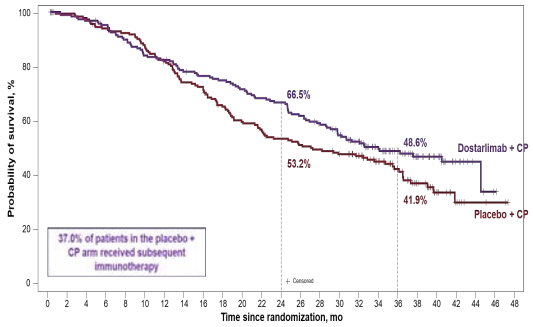
dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

1. Kommoss S, et al. Ann Oncol. 2018;29(5):1180–1188.

MMRp EC

Clinically meaningful PFS and OS benefit of ICI + chemotherapy

EN6-RUBY Part 1[1–4]

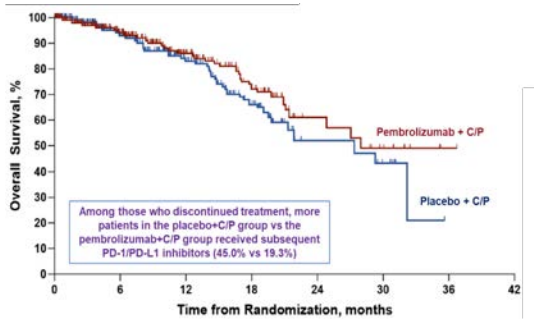


OS Data	Events, %	Median (95% CI), mo
Dostarlimab + C/P	50.5	34.0 (28.6-NE)
Placebo + C/P	59.2	27.0 (21.5-35.6)
OS data maturity	54.8%	
Median follow-up, mo	37.5	

PFS HR 0.76 (95% CI, 0.59-0.98);

OS **HR 0.79** (95% CI, 0.60-1.04); *Nominal p*=0.0493

NRG-GY018[5–7]

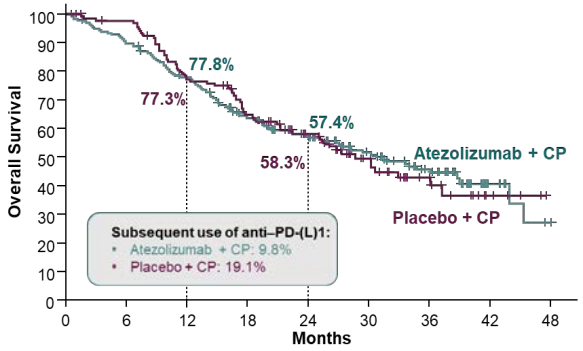


OS Data	Events, %	Median (95% CI), mo
Pembrolizumab + C/P	15.3	28.0 (21.4-NR)
Placebo + C/P	18.3	27.4 (19.5-NR)
OS data maturity	27.2%	
Median follow-up, mo	8.4-8.8	

PFS HR 0.54 (95% CI, 0.41-0.71); *P*<0.001

OS **HR 0.79** (95% CI, 0.53-1.17) *Nominal p=0.1157*

EN7-AtTEnd[8]

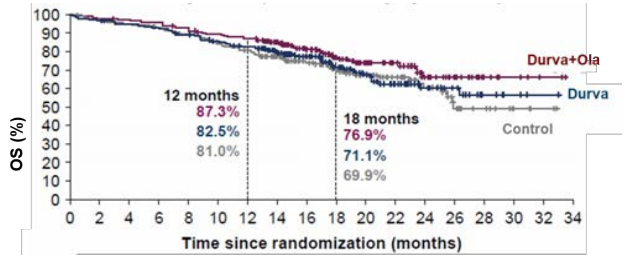


OS Data	Events, %	Median (95% CI), mo
Atezolizumab + C/P	47.2	31.5 (25.0-38.9)
Placebo + C/P	46.4	28.6 (22.4-37.2)
OS data maturity	--	
Median follow-up, mo	--	

PFS HR 0.92 (95% CI, 0.73-1.16);

OS **HR 1.00** (95% CI, 0.74-1.35)

DUO-E[9–10]



OS Data	Events, %	Median (95% CI), mo
Durvalumab + C/P	30.2	NR (NR-NR)
Placebo + C/P	33.3	25.9 (25.1-NR)
OS data maturity	29.2%	
Median follow-up, mo	--	

PFS HR 0.77 (95% CI, 0.60-0.97); *Durva + C/P arm*

OS **HR 0.91** (95% CI, 0.64-1.30) *Durva + C/P arm*

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dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high; PFS = progression free survival; OS = overall survival.

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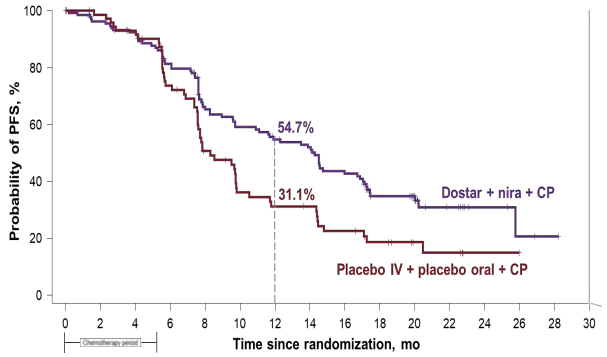
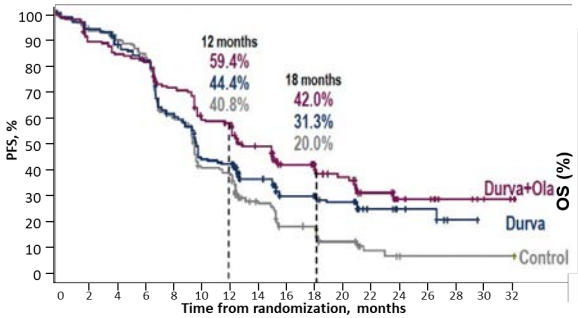
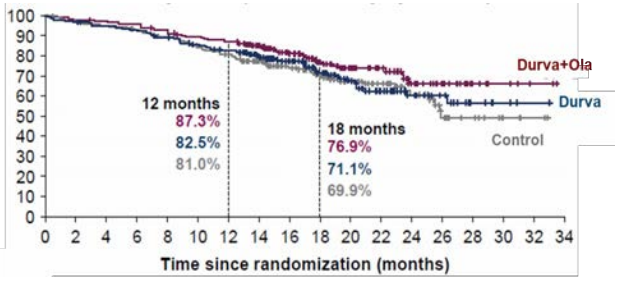
Potential benefit of PARPi addition to ICI + chemotherapy in MMRp EC

More analysis needed to identify which subgroup derives the most benefit

EN6-RUBY Part 2[1]		DUO-E[2,3]	
PFS	**OS**	**PFS**	**OS**
	Not mature*		
HR 0.63 (95% CI, 0.44-0.91); *P*=0.0060 Dostar+Nira+C/P arm	HR 0.76 (95% CI, 0.59-0.98); Dostar+C/P arm	Not mature	HR 0.79 (95% CI, 0.60-1.04); *Nominal P*=0.0493 Dostar+C/P arm	HR 0.57 (95% CI, 0.44-0.73); Durva+Ola+C/P arm	HR 0.77 (95% CI, 0.60-0.97) Durva+C/P arm	HR 0.69 (95% CI, 0.47-1.00); *Durva+Ola+C/P arm*	HR 0.91 (95% CI, 0.64-1.30); *Durva+C/P arm*

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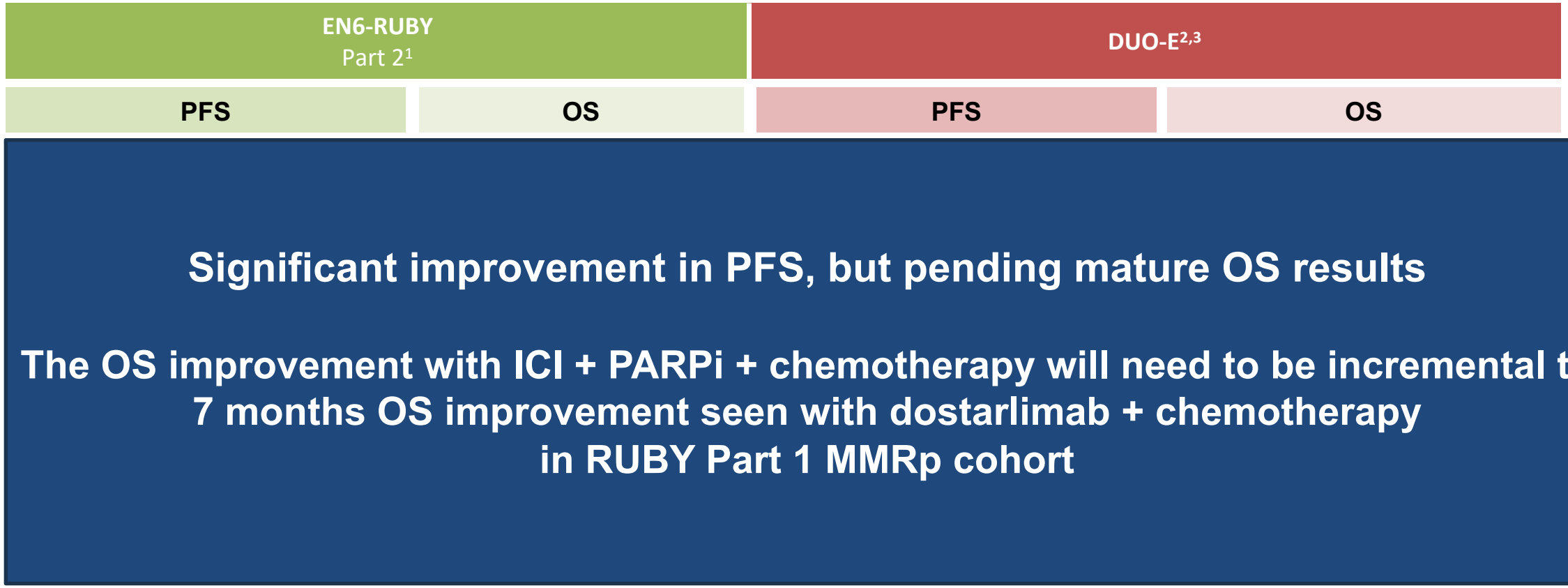
Potential benefit of PARPi addition to ICI + chemotherapy in MMRp EC

More analysis needed to identify which subgroup derives the most benefit



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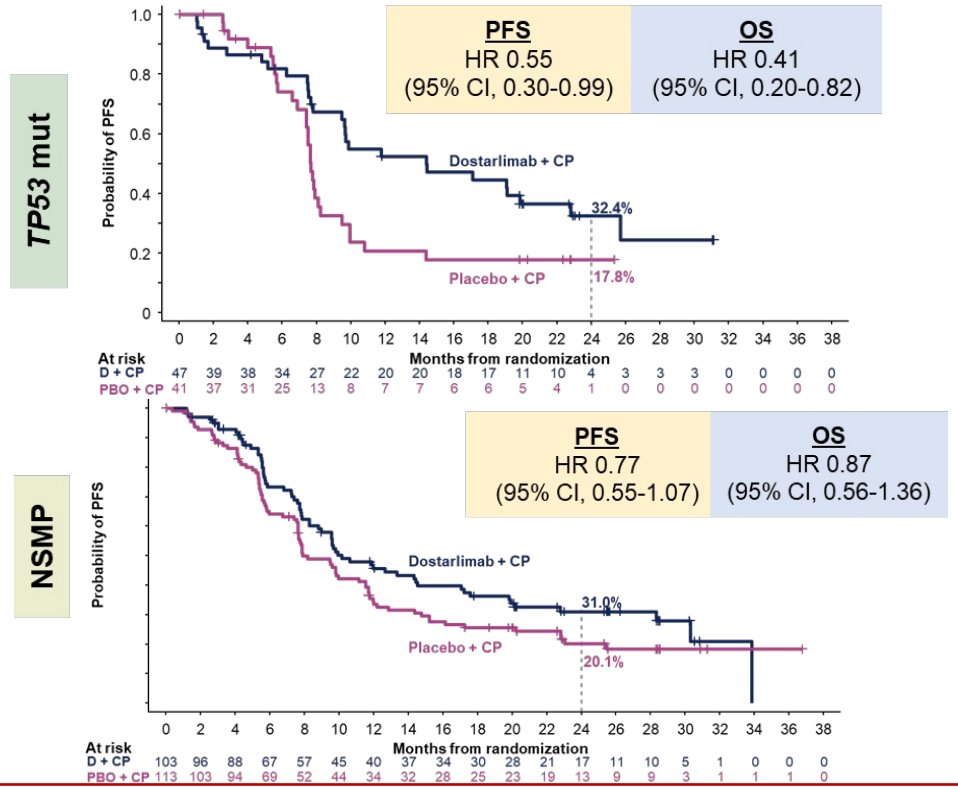
Which MMRp EC patients may benefit from ICI + chemotherapy (±) PARPi?

EC, endometrial cancer; ICI, immune checkpoint inhibitor; MMRp, mismatch repair proficient; PARPi, Poly (ADP-ribose) polymerase inhibitor.

Is TP53 or NSMP a potential biomarker to predict benefit from ICI + chemotherapy (±) PARPi?

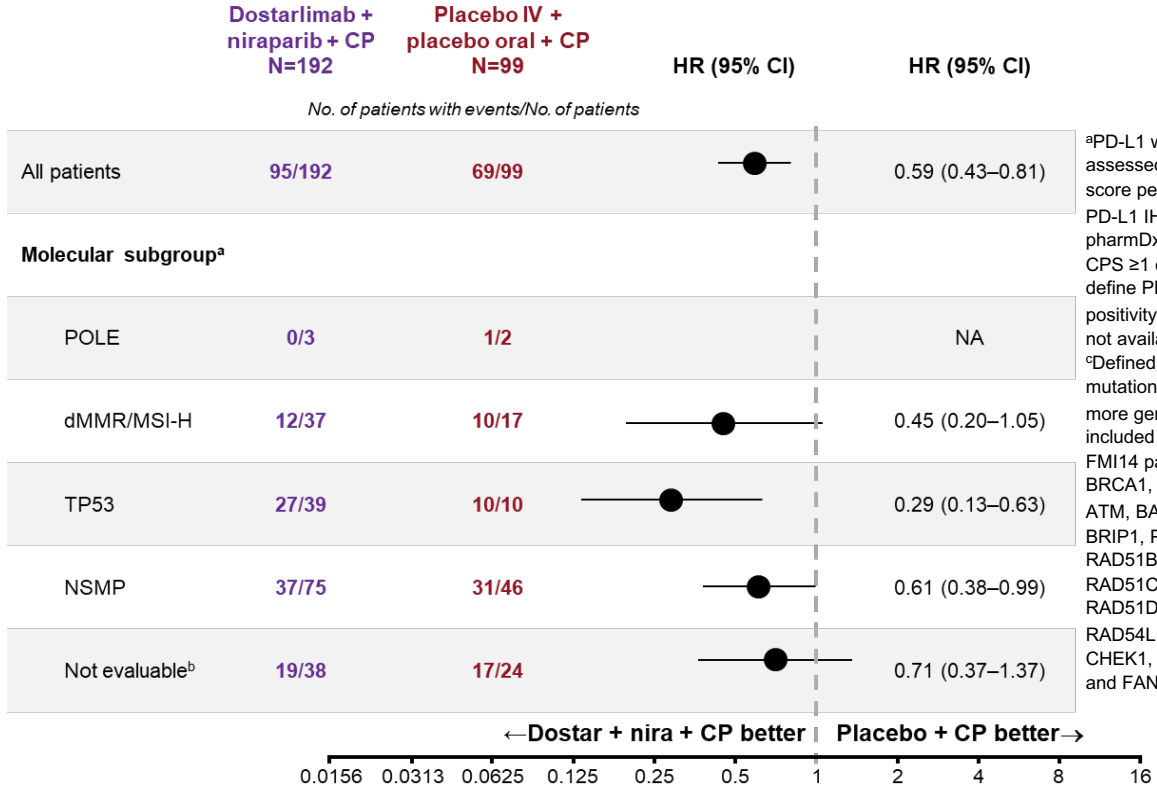
RUBY Part 1[1]

Molecular subgroup analysis based on 400/494 patients with known molecular classification per WES



RUBY Part 2[2]

Exploratory PFS molecular subgroup analyses in overall population



[a]PD-L1 was assessed by CPS score per Dako PD-L1 IHC 22C3 pharmDx with a CPS ≥1 cutoff to define PD-L1 positivity. [b]Sample not available. [c]Defined by a mutation in 1 or more genes included in the FMI14 panel: BRCA1, BRCA2, ATM, BARD1, BRIP1, PALB2, RAD51B, RAD51C, RAD51D, RAD54L, CDK12, CHEK1, CHEK2, and FANCL

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CI = confidence interval; C/P = carboplatin/paclitaxel; NA = not applicable; NSMP = no specific molecular profile; PFS = progression-free survival; POLε = polymerase epsilon; TP53 = tumor protein 53; WES = whole exome sequencing

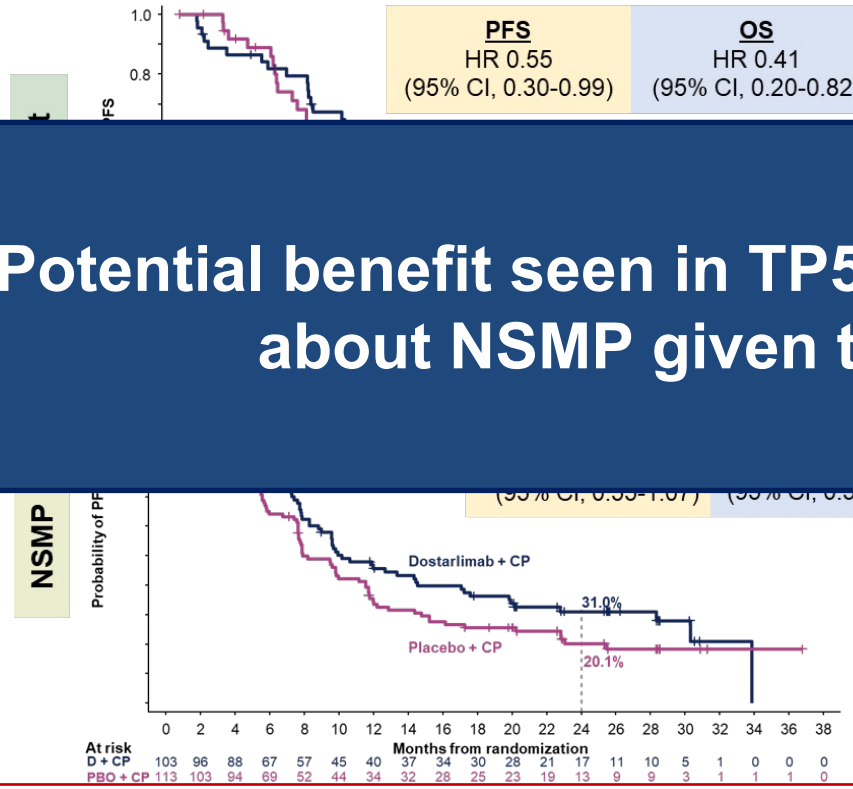
1. Adapted from Mirza MR, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #740MO;
2. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Is TP53 or NSMP a potential biomarker to predict benefit from ICI + chemotherapy (±) PARPi?

RUBY Part 1[1]

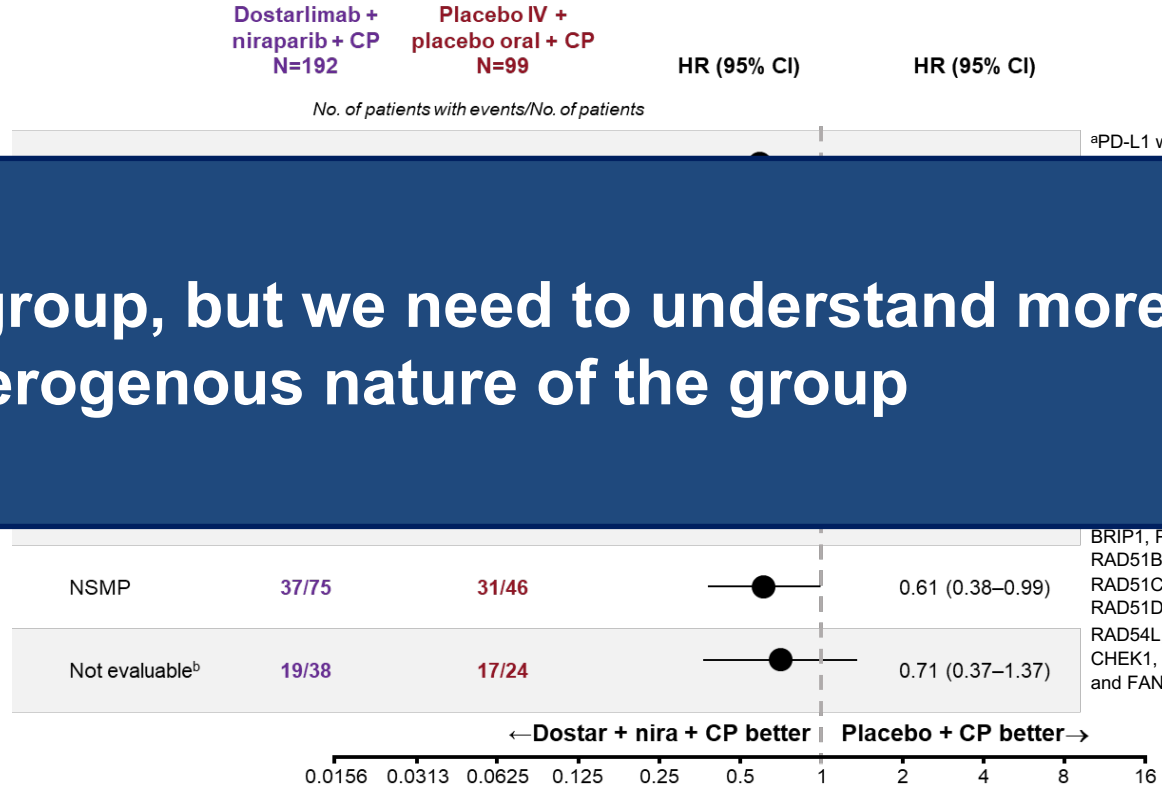
Molecular subgroup analysis based on 400/494 patients with known molecular classification per WES

PFS	OS
HR 0.55 (95% CI, 0.30-0.99)	HR 0.41 (95% CI, 0.20-0.82)



RUBY Part 2[2]

Exploratory PFS molecular subgroup analyses in overall population



Potential benefit seen in TP53mut group, but we need to understand more about NSMP given the heterogenous nature of the group

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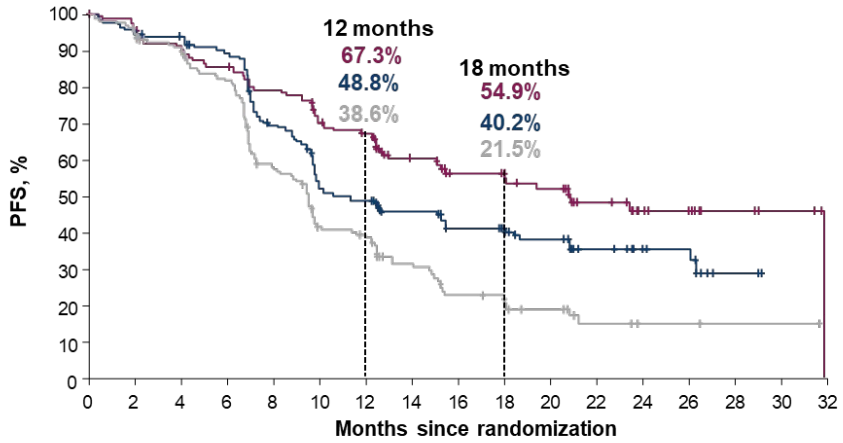
2. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

PD-L1 status is not a predictive biomarker for ICI (±) PARPi use in EC patients

DUO-E exploratory PFS analysis in PD-L1 + subgroup[1,2]

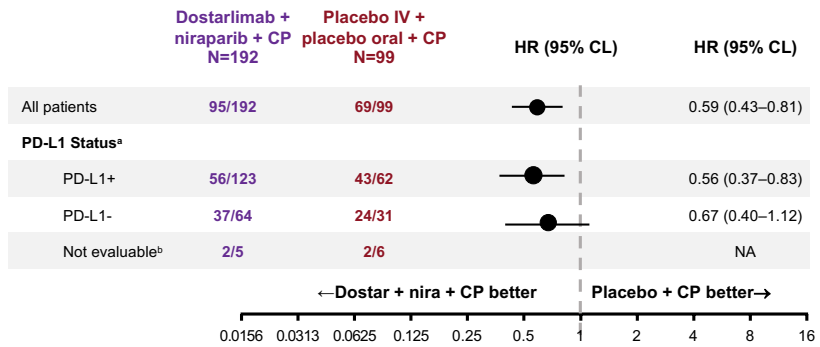


No. at risk																	
Durva+Ola	150	144	135	126	116	101	95	66	45	40	37	23	13	10	5	3	0
Durva	170	158	152	142	109	80	75	53	43	38	33	21	12	11	3	0	0
Control	163	149	139	122	85	58	53	33	22	17	13	7	3	3	1	1	0

	Control (N=163)	Durva (N=170)	Durva+Ola (N=150)
Events, n (%)	114 (69.9)	97 (57.1)	68 (45.3)
Median PFS (95% CI),[a] months	9.5	11.3	20.8
HR (95% CI) vs Control[b]		**0.63 (0.48–0.83)**	**0.42 (0.31–0.57)**
HR (95% CI) vs Durva[b]			**0.67 (0.49–0.91)**

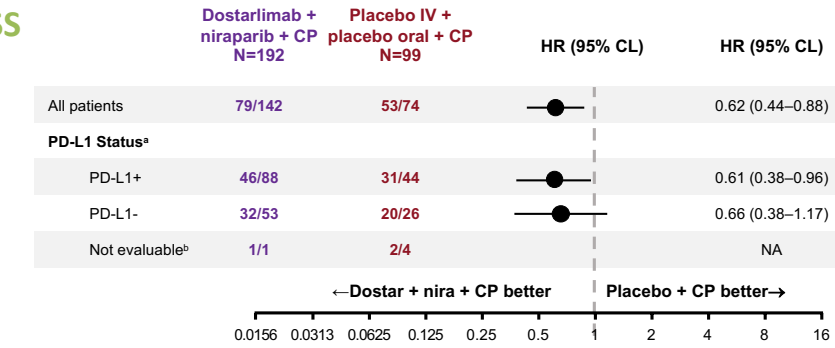
RUBY Part 2 exploratory analysis by PD-L1 status[3]

ITT



[a]PD-L1 was assessed by CPS score per Dako PD-L1 IHC 22C3 pharmDx with a CPS ≥1 cutoff to define PD-L1 positivity.
[b]Sample not available.

MMRp/MSS



[a]PD-L1 was assessed by CPS score per Dako PD-L1 IHC 22C3 pharmDx with a CPS ≥1 cutoff to define PD-L1 positivity.
[b]Sample not available.

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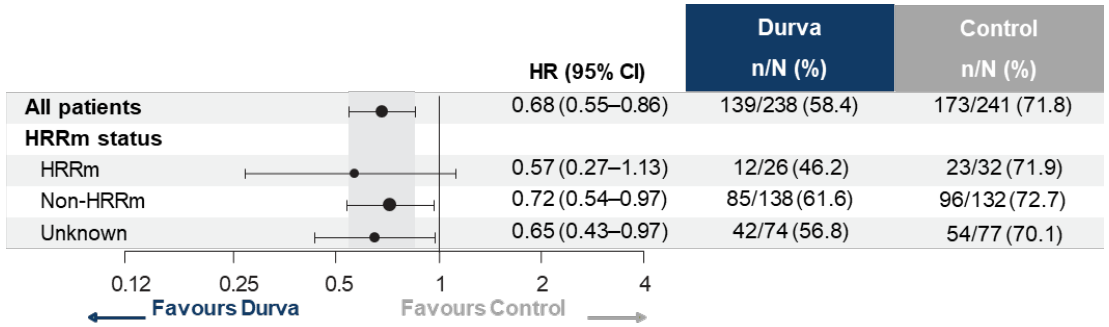
[a]CI for median PFS is derived based on the Brookmeyer–Crowley method; [b]The primary PFS analysis for each comparison was performed separately. The HR and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. The CI was calculated using a profile likelihood approach. The P value was calculated using a log-rank test stratified by MMR and disease status.

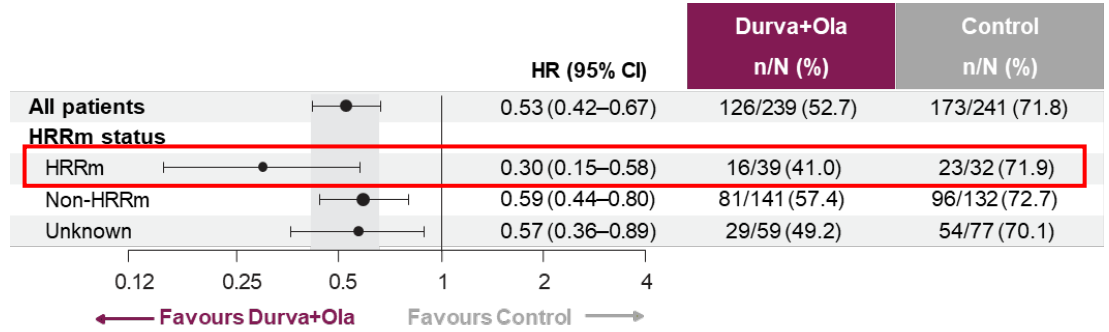
1. Westin SN, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA41. 2. Westin SN, et al. J Clin Oncol. 2023. DOI:10.1200/JCO.23.02132;
3. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Results by mutation status: Exploratory analyses, but some signal noted

DUO-E exploratory PFS subgroup analysis[1,2]

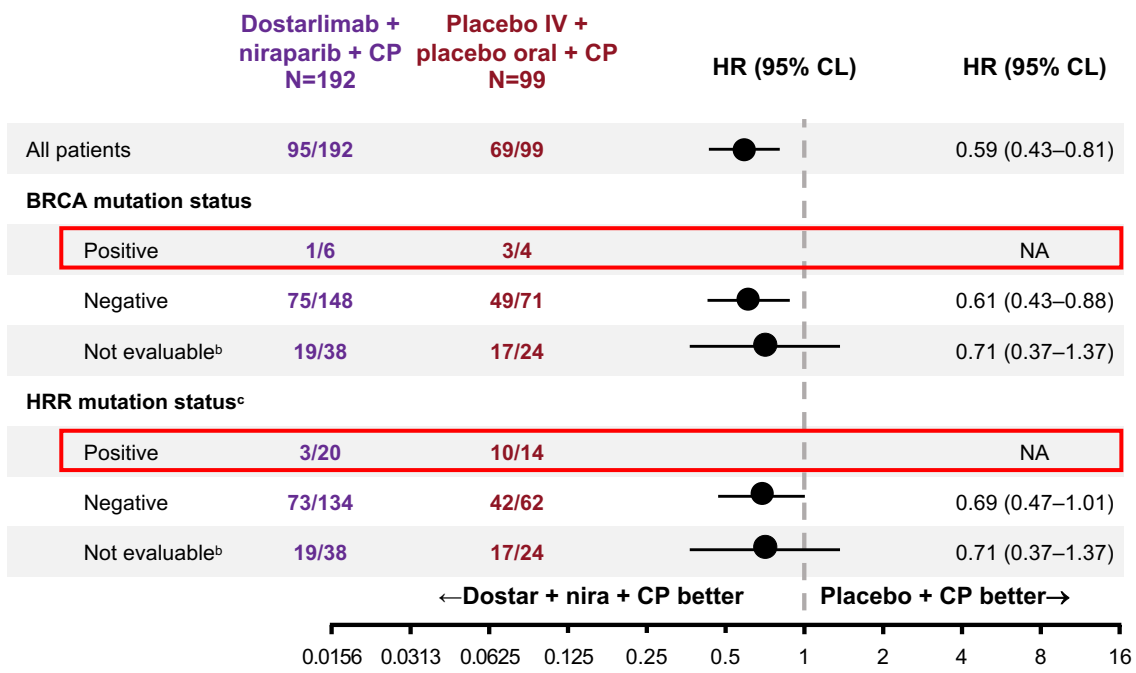
Overall population





RUBY Part 2 exploratory PFS analysis by mutation status[3]

Overall population



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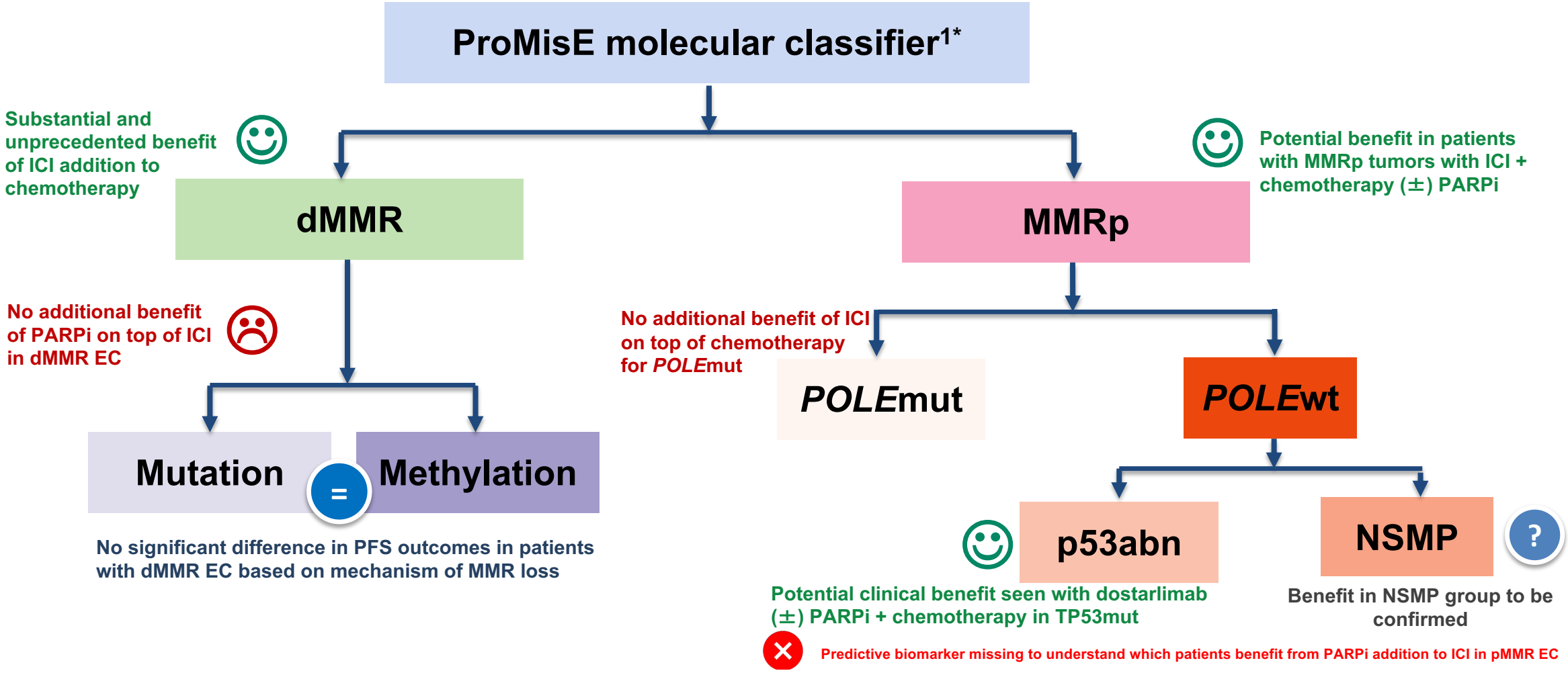
1. Westin SN, et al. Presented at European Society for Medical Oncology (ESMO) Annual Meeting. October 20-24, 2023; Madrid, Spain; Presentation #LBA41. 2. Westin SN, et al. J Clin Oncol. 2023. DOI:10.1200/JCO.23.02132;
3. Mirza MR, et al. Presented at the Society of Gynecologic Oncology Annual Meeting 2024. Presentation #LBA2.

Patient characteristics in first-line EC trials



dMMR = mismatch repair deficient; EC = endometrial cancer; HRneg = homologous recombinant deficient negative; HRpos = homologous recombinant deficient positive; MMRp = mismatch repair proficient; MSS = microsatellite stable; NSMP = non-specific molecular profile

1. Kommoss S, et al. Ann Oncol. 2018;29(5):1180–1188.

Safety
Example: DUO-E

AEs, n (%)	Overall (chemotherapy + maintenance phase)			Maintenance phase only		
	Control (N=236)	Durva (N=235)	Durva+Ola (N=238)	Control (N=169)	Durva (N=183)	Durva+Ola (N=192)
Any AEs	236 (100.0)	232 (98.7)	237 (99.6)	143 (84.6)	158 (86.3)	184 (95.8)
Grade ≥3 AEs	133 (56.4)	129 (54.9)	160 (67.2)	28 (16.6)	30 (16.4)	79 (41.1)
Serious AEs	73 (30.9)	73 (31.1)	85 (35.7)	19 (11.2)	22 (12.0)	42 (21.9)
AEs with outcome of death	8 (3.4)	4 (1.7)	5 (2.1)	2 (1.2)	0	3 (1.6)
AEs of special interest to olaparib						
MDS/AML*	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
New primary malignancies*	3 (1.3)	1 (0.4)§	2 (0.8)	2 (1.2)	1 (0.5)§	1 (0.5)
Pneumonitis†	1 (0.4)	4 (1.7)	12 (5.0)	0	3 (1.6)	8 (4.2)
Any immune-mediated AEs‡	16 (6.8)	66 (28.1)	56 (23.5)	6 (3.6)	27 (14.8)	27 (14.1)
AEs leading to discontinuation of study treatment	44 (18.6)	49 (20.9)	58 (24.4)	7 (4.1)	11 (6.0)	27 (14.1)
AEs leading to discontinuation of carboplatin/paclitaxel	32 (13.6)	31 (13.2)	31 (13.0)	–	–	–
AEs leading to discontinuation of durvalumab/placebo	19 (8.1)	26 (11.1)	22 (9.2)	4 (2.4)	9 (4.9)	16 (8.3)
AEs leading to discontinuation of olaparib/placebo	5 (2.1)	11 (4.7)	21 (8.8)	5 (3.0)	10 (5.5)	21 (10.9)
AEs leading to dose interruption/delay of study treatment‖	118 (50.0)	128 (54.5)	164 (68.9)	37 (21.9)	52 (28.4)	113 (58.9)
AEs leading to dose reduction of olaparib/placebo	5 (2.1)	14 (6.0)	65 (27.3)	4 (2.4)	13 (7.1)	63 (32.8)

Includes AEs with onset or worsening on or after the date of first dose of durvalumab/placebo or olaparib/placebo (overall) or first dose of olaparib/placebo (maintenance phase) until initiation of the first subsequent anticancer therapy following last dose of study treatment or until the end of the safety follow-up period, whichever occurs first. AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). *MDS/AML and new primary malignancies include AEs from first dose of investigational product (durvalumab/olaparib/placebo) until the end of the study (includes cases reported beyond the safety follow-up period); †Grouped term: includes pneumonitis, bronchiolitis, and interstitial lung disease; ‡As assessed by the investigator, and programmatically derived from individual causality assessments for combination studies. Missing responses are counted as related; §Excludes one event of basal cell carcinoma; ‖For durvalumab/placebo, this includes dose interruption during infusion as well as doses that were skipped or delayed. AE, adverse event; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome.

Westin SN, et al. J Clin Oncol. 2023; DOI: 10.1200/JCO.23.02132

Key takeaways

- Molecular profiling of this disease has completely transformed our therapeutic approach
- **ICI + C/P is the new standard of care for patients with advanced/recurrent endometrial cancer**
- **However,** this is just the beginning of an unprecedented improvement in the outcome of our patients. We need to understand:
  - Which are the dMMR patients that do not benefit from ICI + chemotherapy?
  - Can we replace chemotherapy in dMMR patients in view of ICI-only treatment? And in which patients?
  - How to treat patients who experience relapse post-chemotherapy + immunotherapy?
  - How do we further validate the prognostic value of molecular subgroups for identifying those patients who will benefit the most?
  - What are the predictive biomarkers to understand which patients benefit most from PARPi addition to ICI in MMRp EC?

Agenda

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

Module 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr Backes

Module 3: First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Mirza

Module 4: Current Therapeutic Options for R/R EC; Novel Investigational Strategies — Dr Slomovitz

Module 5: Role of HER2-Targeted Therapy in the Management of Advanced OC, EC and Other Gynecologic Cancers — Dr Secord

Dr Priya Rudolph: Case Presentation

Age: 60-year-old with a history of serous endometrial cancer s/p TAH/BSO followed by adjuvant chemotherapy/RT completed 2 y prior in a different state (details unavailable) presented with abdominal distention. CT with ascites, nodularity in omentum; cytology c/w serous endometrial adenocarcinoma.

Next-generation sequencing (NGS): MSS, HER2-negative IHC, TMB low.

Treatment, side effects and response: Carboplatin/docetaxel (due to Grade 2 baseline neuropathy). After 4 cycles, severe worsening of neuropathy.

Lenvatinib/pembrolizumab x 7 months — rash, severe fatigue, weight loss.

Carboplatin/liposomal doxorubicin — PD

Bevacizumab — PD

RTP
RESEARCH
TO PRACTICE

Dr Priya Rudolph: Case Discussion Questions

What is your treatment of choice for patients with recurrent EC and neuropathy if they are still platinum sensitive? (Liposomal doxorubicin is listed on NCCN as a single agent for second-line, not first-line recurrent/metastatic EC.)

What about the patient who received carboplatin/paclitaxel with an anti-PD-1 antibody and experienced progression 12 months later? Is there any data supporting the use of lenvatinib/pembrolizumab in this setting?

What starting dose of lenvatinib do you typically employ?

RTP
RESEARCH
TO PRACTICE

Dr Priya Rudolph: Questions for the Faculty

Do you believe the signal seen with the use of selinexor for patients with p53 wild-type disease is real?

At the current time, would you consider using selinexor for EC outside of a trial under any circumstances?

Are there any investigational agents — like antibody-drug conjugates — for patients with progressive EC that may be more attractive than currently available therapeutic options?

Dr Eric Lee: Case Presentation

Clinical presentation: 77-year-old diagnosed with endometrial cancer initially treated with total abdominal hysterectomy followed by adjuvant carboplatin and paclitaxel and vaginal brachytherapy

2 years later she developed a cough and weight loss and was found to have lung lesions, which biopsy showed was endometrial cancer. MSS/pMMR; PD-L1 CPS = 30

Treatment: Carboplatin, paclitaxel and dostarlimab, completed 6 cycles chemotherapy and IO and transitioned to dostarlimab maintenance

Response: Substantial response with complete resolution of peritoneal, mediastinal, and hilar disease; residual LLL disease

Side effects/tolerability issues: None, excellent tolerance

RTP
RESEARCH
TO PRACTICE

Dr Eric Lee: Case Discussion Questions

Beyond MSI-H status, are there other predictors of response to anti-PD-1/PD-L1 antibodies, such as PD-L1 combined positive score (CPS) and tumor mutational burden?

If this patient were younger and/or symptomatic, would you consider dual immunotherapy?

Dr Eric Lee: Questions for the Faculty

Regulatory and reimbursement issues aside, what would be your recommended first-line therapy for a patient with microsatellite-stable/mismatch repair-proficient metastatic EC?

How frequently are BRCA and other HRD pathway abnormalities seen in patients with EC? Do you believe these are driving the benefit seen with PARP inhibitors?

Based on findings from DUO-E and RUBY Part 2, are there any situations in which you would like to include a PARP inhibitor for any of your patients with EC? If yes, for which specific patient populations?

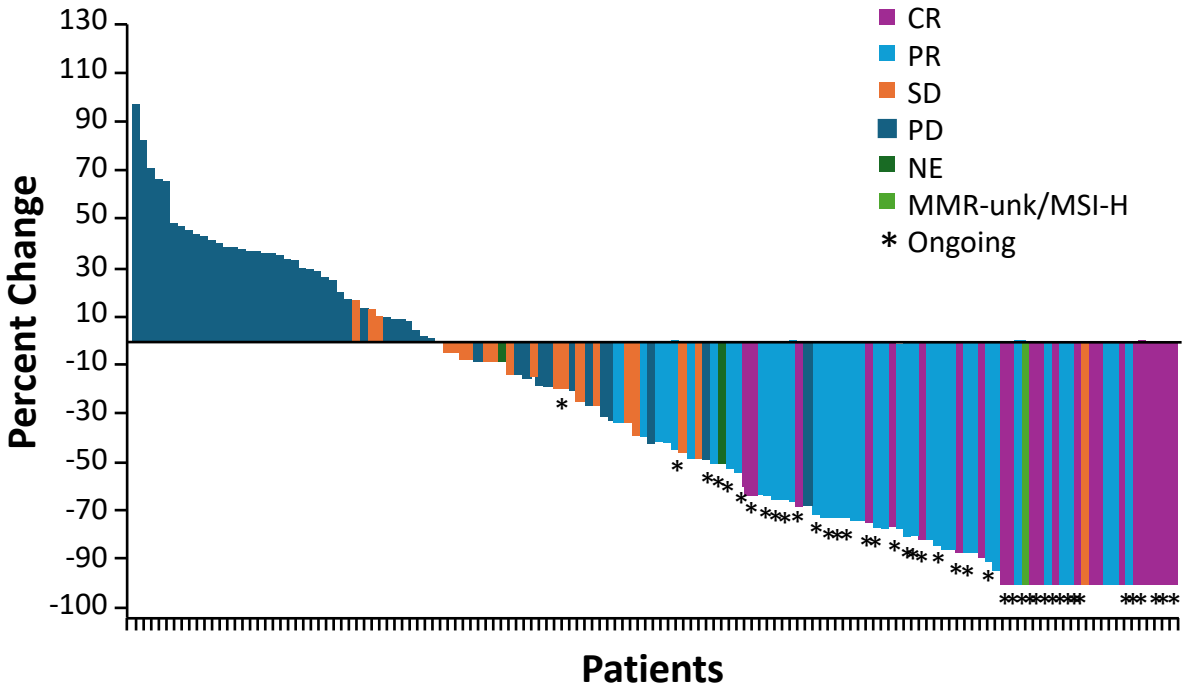
Current Options for Recurrent EC

Brian M Slomovitz, MD

GARNET: Dostarlimab in Previously Treated dMMR/pMMR EC

Dostarlimab (GARNET Cohorts A1 & A2): Clinical Benefit in dMMR and pMMR EC Patients

Variable	dMMR EC n = 103	pMMR EC n = 142
ORR % (95% CI)	**46** (34.9-54.8)	**19** (8.3-20.1)
Complete response	11 (10.7)	3 (2.1)
Partial response	35 (34.0)	16 (11.3)
Stable disease	13 (12.6)	31 (21.8)
Progressive disease	39 (37.9)	77 (54.2)
Not evaluable	3 (2.9)	0
Not done	2 (1.9)	15 (10.6)



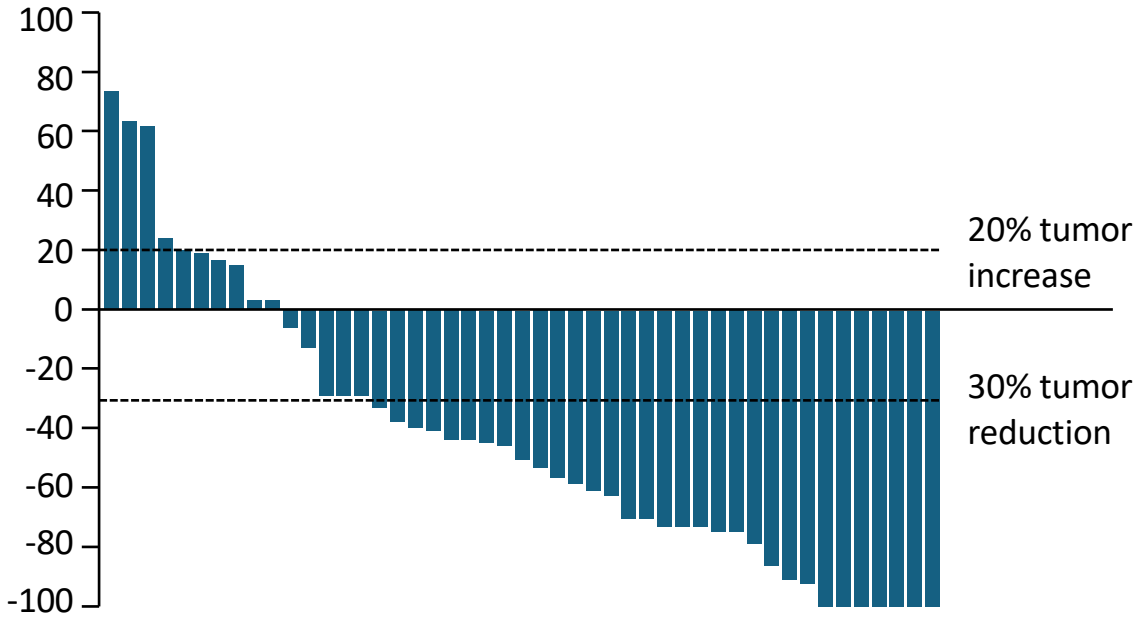
CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; pMMR, mismatch repair proficient; PR, partial response; SD, stable disease.

Oaknin A, et al. *J Immunother Cancer*. 2022;10:e003777.

KEYNOTE-158: Pembrolizumab in MSI-H Advanced EC

Pembrolizumab (KN-158): Robust Antitumor Activity in Patients With MSI-H Advanced EC

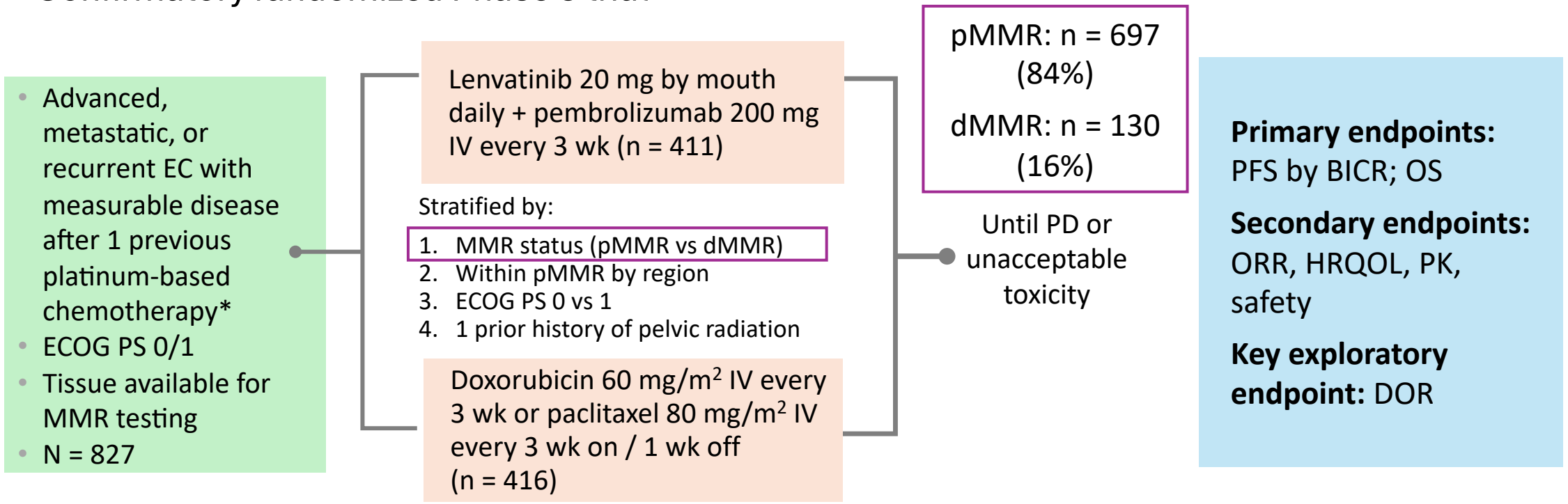
Variable	MSI-H EC n = 79	EC (Biomarker Unselected) n = 107
ORR % (95% CI)	**48** (37-60)	**11.2** (5.9-18.8)
Complete response	11 (14)	0
Partial response	27 (34)	12 (11.2)
Stable disease	14 (18)	26 (24.3)
Progressive disease	23 (29)	56 (52.3)
Not evaluable	1 (1)	2 (1.9)
Not assessed	3 (4)	11 (10.3)



O'Malley DM, et al. *J Clin Oncol*. 2022;40:752-761; Marabelle A, et al. *J Clin Oncol*. 2020;38:1-10.

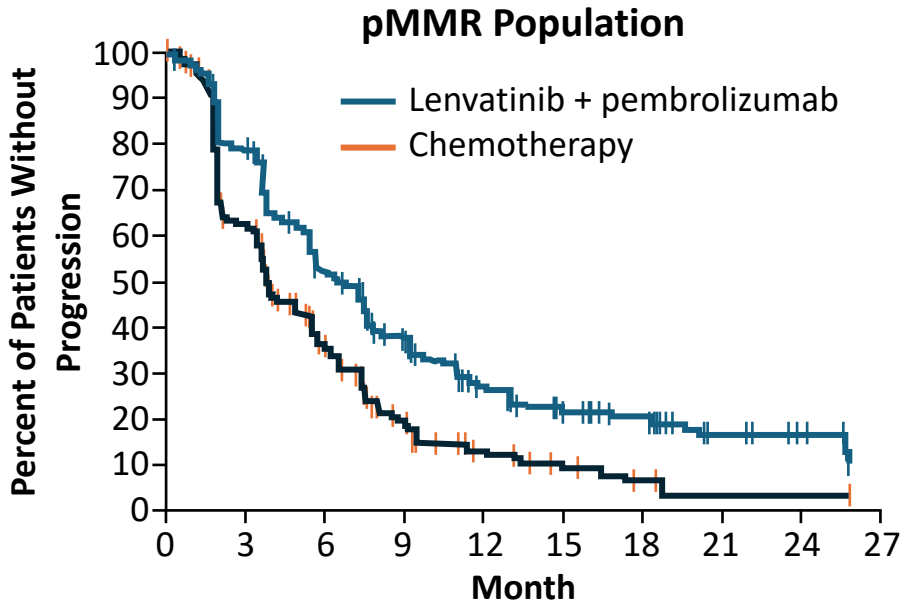
Study 309/KEYNOTE-775: Phase 3 Trial of TKI Lenvatinib + Pembrolizumab After Platinum for Advanced EC

- FDA-approved for patients with recurrent/advanced EC not MSI-H or dMMR
- Confirmatory randomized Phase 3 trial

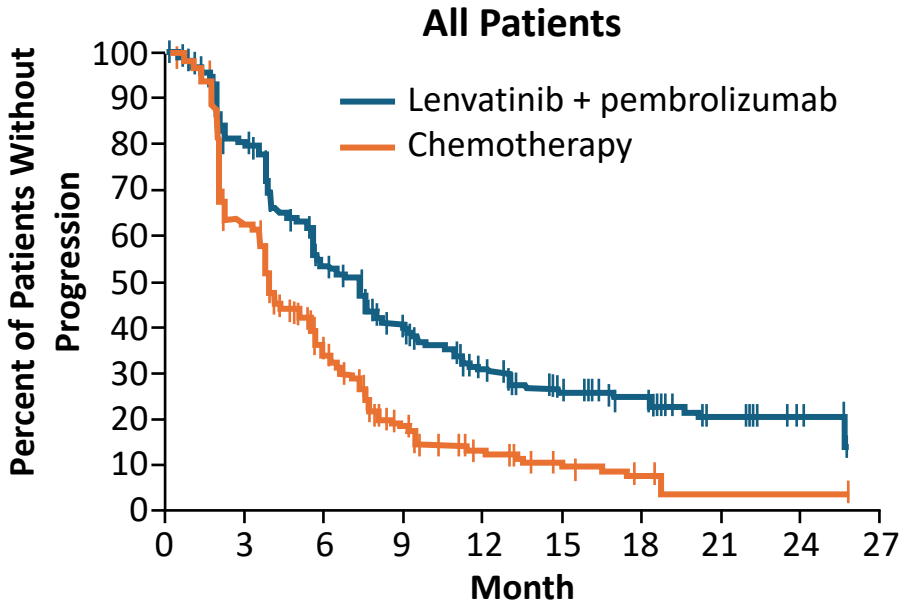


*2 prior regimens allowed if 1 regimen was in the neoadjuvant/adjuvant setting.
BICR, blinded independent central review; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQOL, health-related quality of life; IV, intravenous; OS, overall survival;
PK, pharmacokinetics; PS, performance status; TKI, tyrosine kinase inhibitor.
Makker V, et al. *N Engl J Med*. 2022;386:437-448.

Study 309/KEYNOTE-775: Lenvatinib + Pembrolizumab



	mPFS, mo (95% CI)
Len + pembro	6.6 (5.6, 7.4)
Chemotherapy	3.8 (3.6, 5.0)
HR for progression or death, 0.60 (95% CI, 0.50, 0.72) *P* < .001	

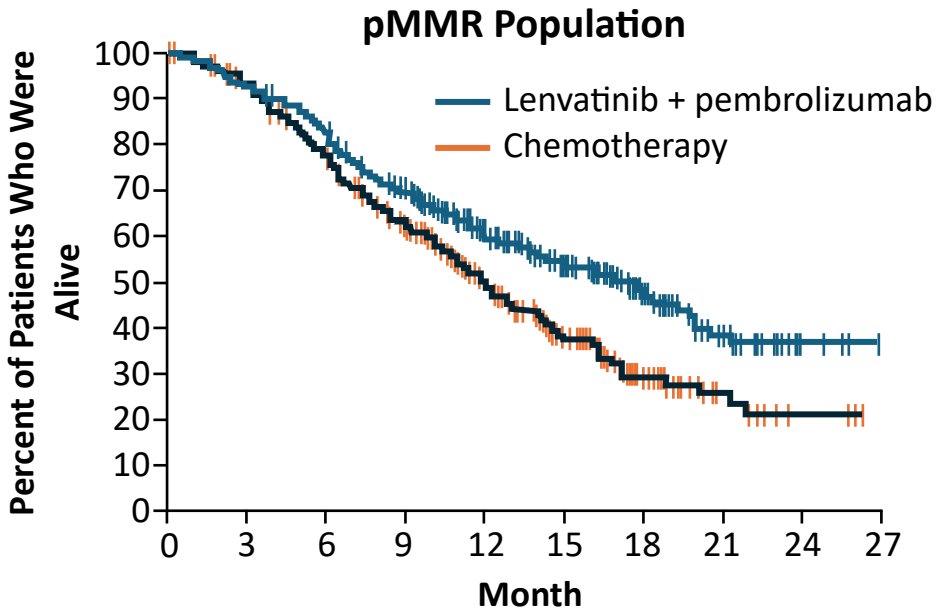


	mPFS, mo (95% CI)
Len + pembro	7.2 (5.7, 7.6)
Chemotherapy	3.8 (3.6, 4.2)
HR for progression or death, 0.56 (95% CI, 0.47, 0.66) *P* < .001	

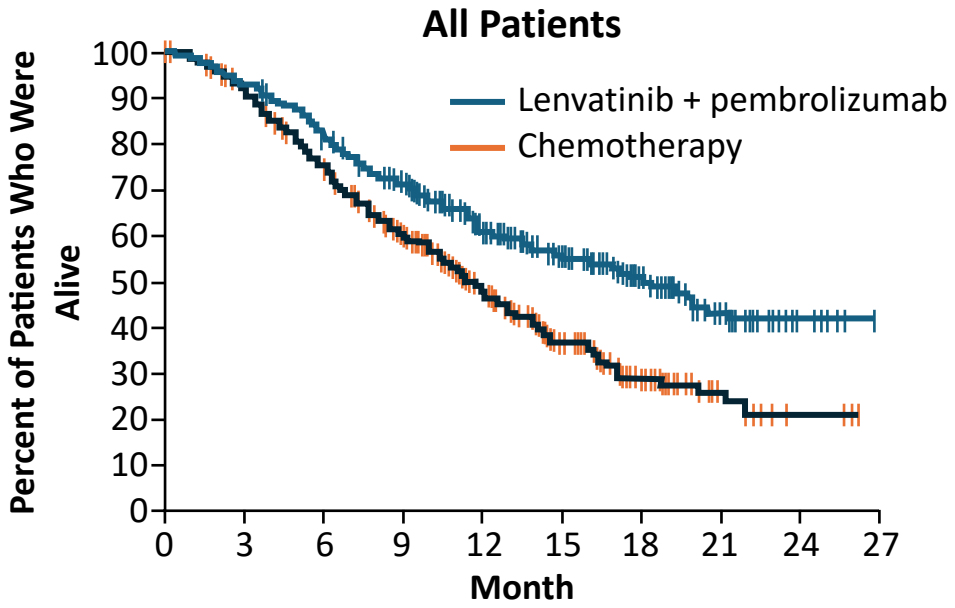
mPFS, median progression-free survival.

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

Study 309/KEYNOTE-775: Lenvatinib + Pembrolizumab (cont.)



	mOS, mo (95% CI)
Len + pembro	17.4 (14.2, 19.9)
Chemotherapy	12.0 (10.8, 13.3)
HR for death, 0.68 (95% CI, 0.56, 0.84) *P* < .001	



	mOS, mo (95% CI)
Len + pembro	18.3 (15.2, 20.5)
Chemotherapy	11.4 (10.5, 12.9)
HR for death, 0.62 (95% CI, 0.51, 0.75) *P* < .001	

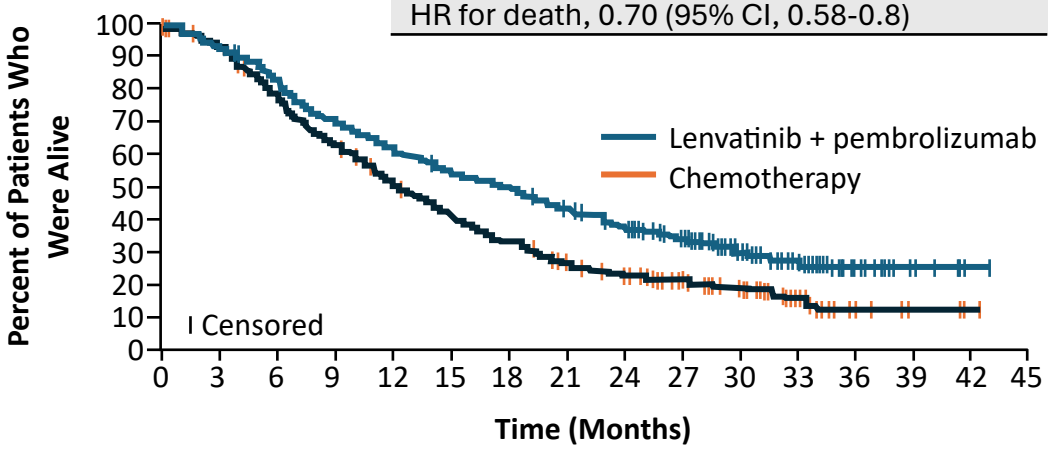
mOS, median overall survival.

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

Continued OS Benefit of Lenvatinib Plus Pembrolizumab vs Chemotherapy With Follow-Up Extended by Over 16 Months

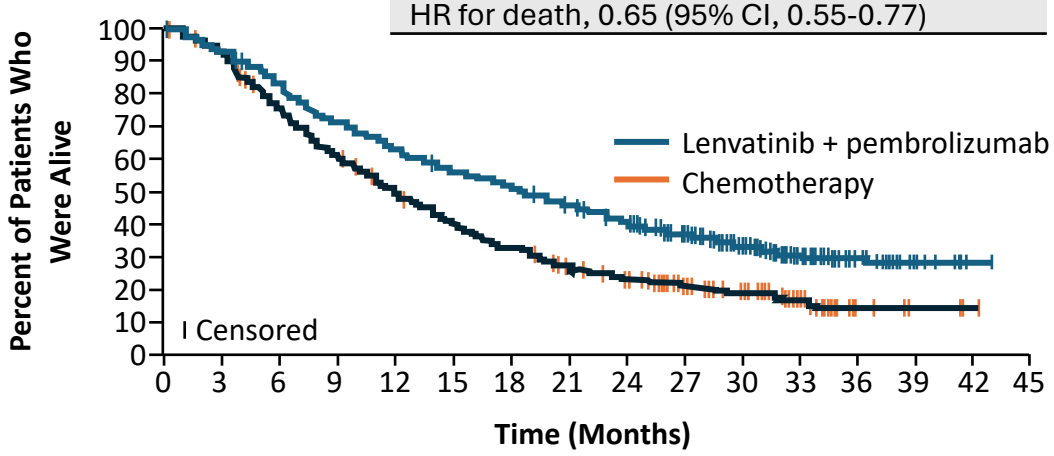
pMMR Population

	mOS, mo (95% CI)
Len + pembro	18.0 months (14.9-20.5)
Chemotherapy	12.2 months (11.0-14.1)
HR for death, 0.70 (95% CI, 0.58-0.8)	



All-Comer Population

	mOS, mo (95% CI)
Len + pembro	18.7 months (15.6-21.3)
Chemotherapy	11.9 months (10.7-13.3)
HR for death, 0.65 (95% CI, 0.55-0.77)	



- OS favored lenvatinib + pembrolizumab despite some pts in the chemotherapy arm receiving subsequent lenvatinib + pembrolizumab
- In the chemotherapy arm, 10.0% of pts in the pMMR population and 8.7% of pts in the all-comer population received subsequent lenvatinib + pembrolizumab
- After excluding these pts, the pMMR OS HR was 0.64 (95% CI, 0.54, 0.76); the all-comer OS HR was 0.60 (95% CI, 0.51, 0.71)

Makker V, et al. Presented at: ESMO 2022; Sept 9-13, 2022; Paris, France. Abstract 525MO. Makker V, et al. *J Clin Oncol*. 2023;41(16):2904-2910.

Pembrolizumab + Lenvatinib Safety Profile in Patients With Advanced EC Consistent With Individual Monotherapies

Safety	Pembrolizumab + lenvatinib n = 406	Physician's Choice n = 388
Median duration of treatment (range), days	231 (1-817)	104.5 (1-785)
TEAEs, %	99.8	99.5
Grade ≥3 TEAEs, %	88.9	72.7
TEAEs leading to dose reductions, %	66.5	12.9
Any-grade TEAEs leading to interruptions, %	69.2	27.1
Lenvatinib	58.6	--
Pembrolizumab	50.0	--
Pembrolizumab + lenvatinib	30.8	--
Any-grade TEAEs leading to discontinuation, %	33.0	8.0
Lenvatinib	30.8	--
Pembrolizumab	18.7	--
Pembrolizumab + lenvatinib	14.0	--

Most frequent TEAEs for pembrolizumab + lenvatinib (≥40% of all-comers) included:

- Hypertension (64%), hypothyroidism (57%), diarrhea (54%), nausea (50%), and decreased appetite (45%)

Most frequent (≥5%) Grade ≥3 TEAEs included:

- Hypertension (38%), weight decrease (10%), diarrhea (8%), decreased appetite (8%), anemia (6%), asthenia (6%), fatigue (5%), and proteinuria (5%)

Most frequent TEAEs for physician's choice (≥40% of all-comers) included:

- Anemia (49%) and nausea 46%

Most frequent (≥5%) Grade ≥3 TEAEs included:

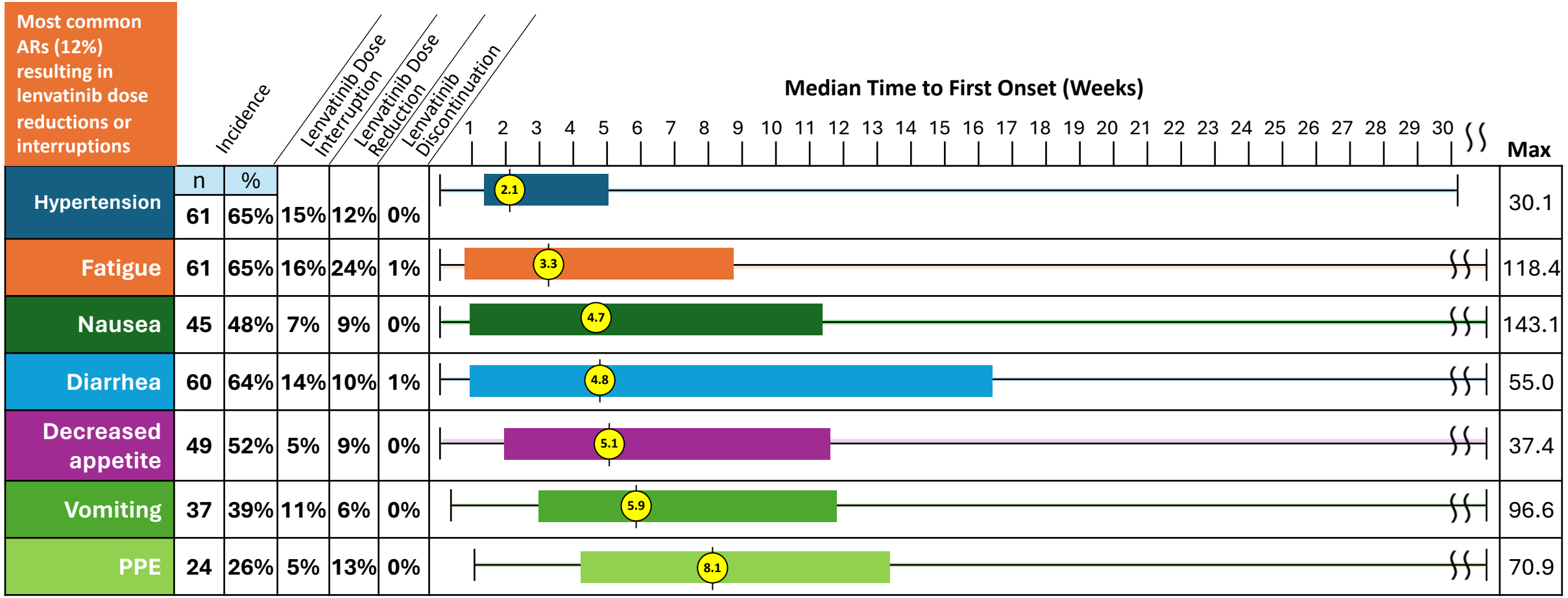
- Neutropenia (26%) and anemia (15%)

TEAE, treatment-emergent adverse event.

Makker V, et al. *Oncologist*. 2021;26:e1599-e1608.

Previously Treated pMMR Subgroup (n = 94), Study 111: Phase 2 Study of Lenvatinib Plus Pembrolizumab in Patients

Most Common Adverse Reactions, All Grades, Time to First Onset, Weeks



ARs, adverse reactions; PPE, palmar-plantar erythrodysesthesia.

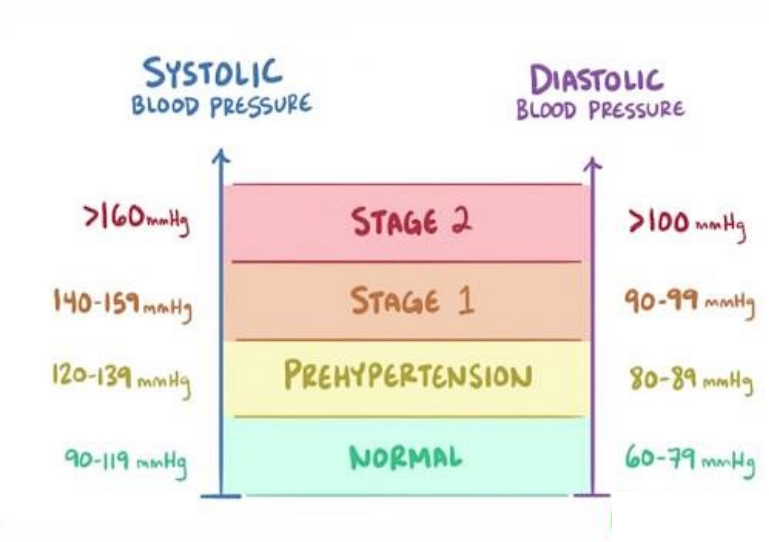
Makker V, et al. *Oncologist*. 2021;26:e1599-e1608.

Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions

1. Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a **hypertensive crisis or has uncontrolled hypertension** with significant risk factors for severe complications (eg, BP ≥160/100 mm Hg)

2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or **1 or more agents of a different class** of antihypertensive should be added. Study treatment can be continued without dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite **maximal antihypertensive therapy**, then **lenvatinib administration should be interrupted and restarted at 1 dose level reduction** only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.



Diarrhea: Pembrolizumab vs. Lenvatinib

- Immune-mediated diarrhea and colitis (IMDC) is among the common immune-related adverse events in patients with cancer treated with pembrolizumab (<4%)
- Preexisting inflammatory bowel disease significantly increases the risk of diarrhea and colitis with ICI treatment.
- Early endoscopic evaluation improves clinical outcome by identifying high-risk patients who will benefit from early add-on immunosuppressants. Inflammatory markers, including fecal lactoferrin and calprotectin, are good screening tools to predict which patients are at risk for colitis.
- Corticosteroids remain the first-line medical treatment of IMDC management, and add-on therapy with vedolizumab or infliximab should be considered in selected patients.

Lenvatinib-induced diarrhea is common

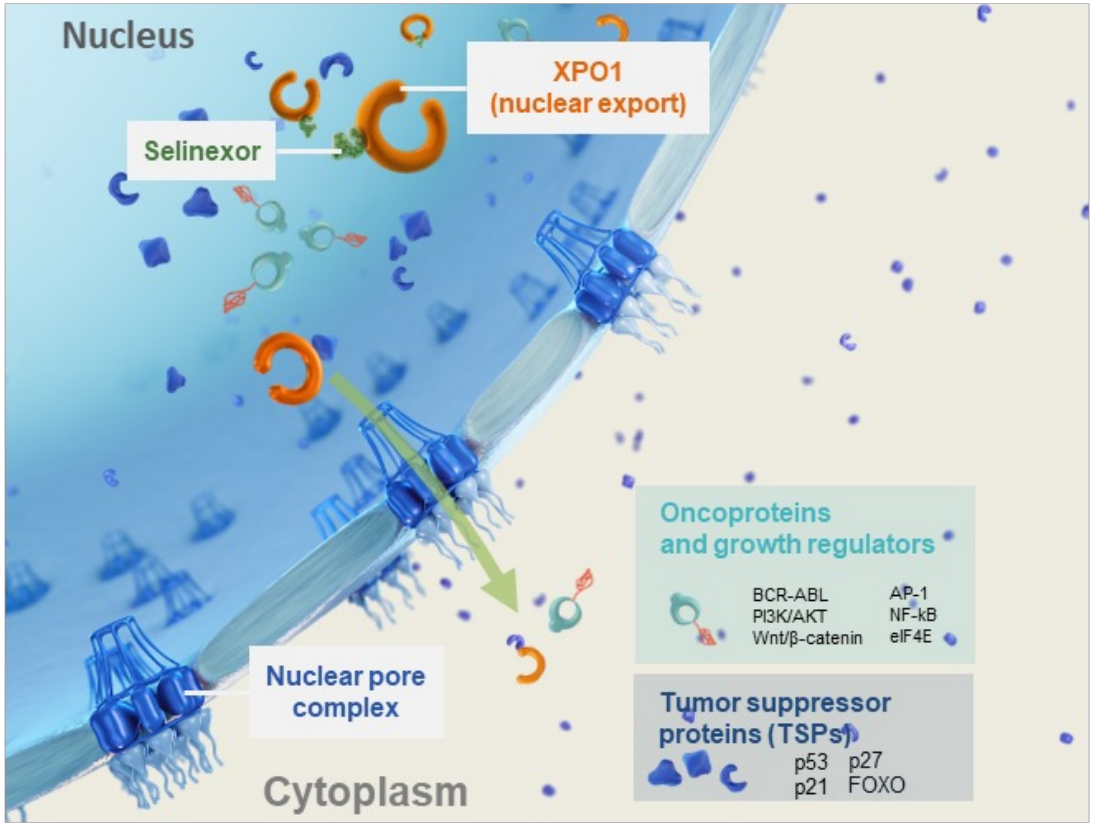
(<70% any-grade, <10% grade 3-4)

- Dose reductions (10%)
- Dose interruptions (14%)

Supportive care:

- Loperamide
- BRAT-diet

Selinexor - Background



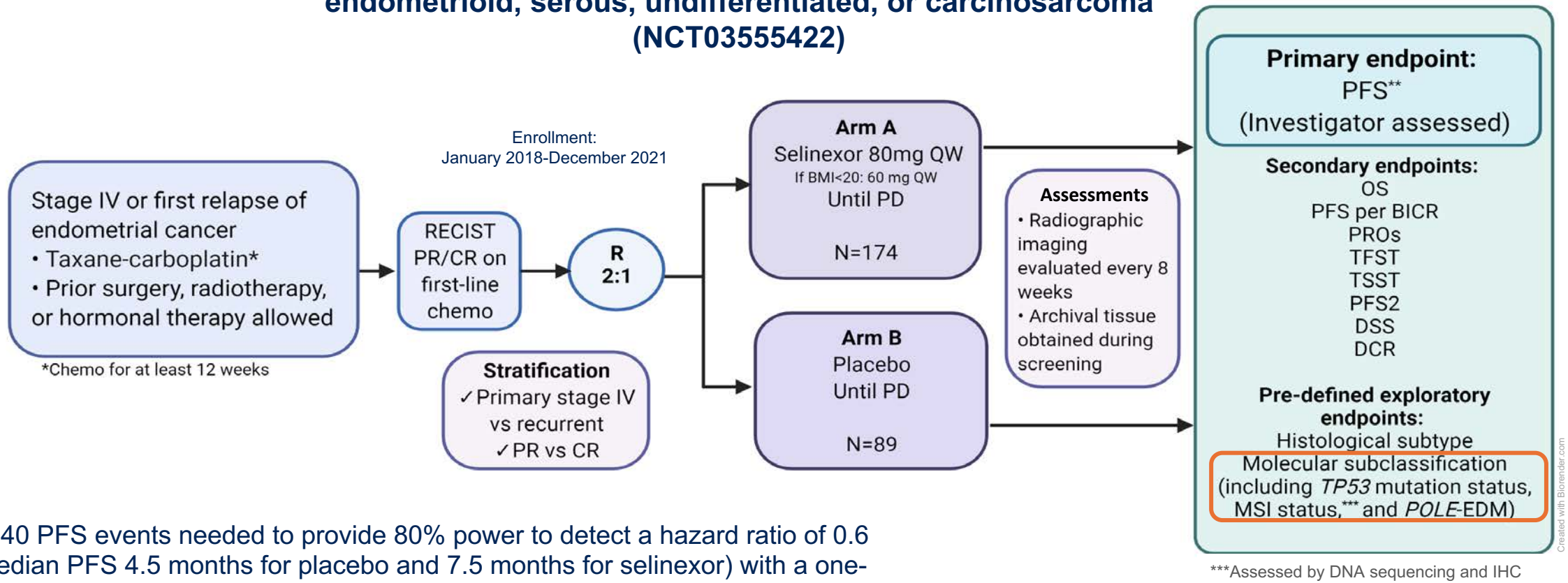
- While immune checkpoint inhibitors show a significant benefit in patients with dMMR (MSI-H) tumors, there is a high unmet need in those with *TP53wt* and pMMR (MSS) tumors for which there is limited evidence of benefit.[1,2,3]
- *TP53* is a well-recognized prognostic marker for EC.[4,5] Approximately >50% of advanced/recurrent EC tumors are *TP53*wt, of which 40-55% are also pMMR (MSS).[6,7,8]
- Selinexor is an investigational oral XPO1 inhibitor, that prevents the XPO1-mediated export of several tumor suppressor proteins (TSPs), including wild type p53.[9]
- At primary analysis of the phase 3 SIENDO study of selinexor maintenance therapy in patients with advanced/recurrent EC, the improvement in median PFS for the ITT population was not clinically meaningful, however an exploratory analysis in a pre-specified subgroup of patients with *TP53*wt EC showed a promising efficacy signal.[7]
- Here we report long-term follow up of the *TP53*wt subgroup and further subgroup analyses.

EC, endometrial cancer; ITT, intent-to-treat; dMMR, deficient mismatch repair; mRNA, messenger ribonucleic acid; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, proficient mismatch repair; mut, mutant; PFS, progression-free survival; *TP53*, tumor protein 53 gene; TSP, tumor suppressor protein; wt, wild-type; XPO1, exportin 1.

1. Mirza, MR, et al. *N Eng J Med* 2023;388:2145-2158. **2**. Eskander, RN, et al. *N Eng J Med 2023*; 388:2159-2170. **3**. JEMPERLI© USPI. 2021. Accessible at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761174s000lbl.pdf. **4**. Levine DA. *Nature.* 2013;497(7447):67–73. **5.** Oaknin, A., et al. *Annals of Oncology* 33.9 (2022): 860-877. **6**. Leslie KK, et al. *Gynecol Oncol*. 2021;161(1):113-121**. 7**. Vergote I, et *al J Clin Oncol* 41, 5400-5410(2023). **8.** Mirza M, et al. Presentation at: ESMO Congress Oct 20-24 2023, Abstract 740MO **9.** Tai Y-T, et al. *Leukemia*. 2014;28(1):155-165.

Trial Design **ENGOT-EN5/GOG-3055/SIENDO**

Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)



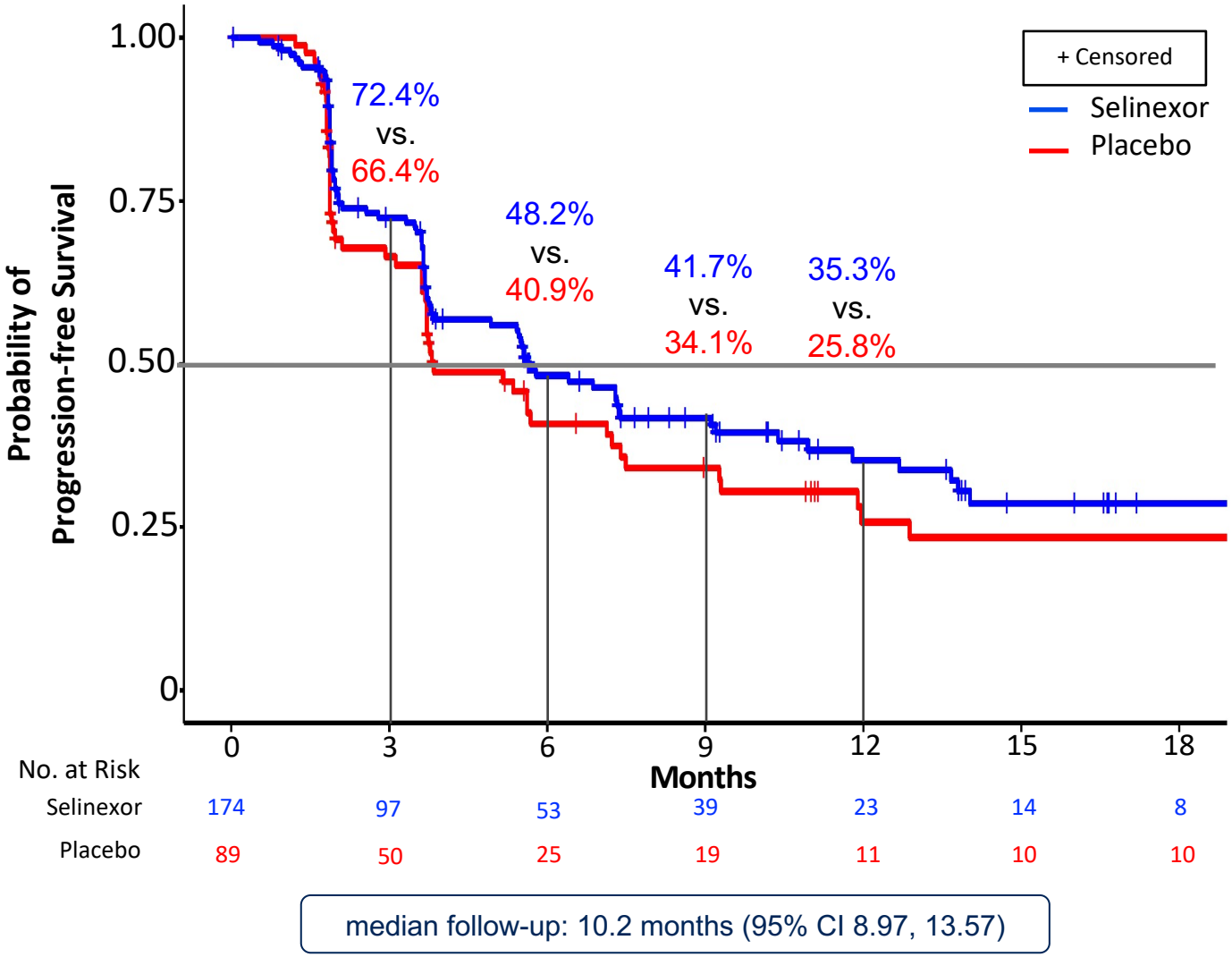
**140 PFS events needed to provide 80% power to detect a hazard ratio of 0.6 (median PFS 4.5 months for placebo and 7.5 months for selinexor) with a one-sided alpha of 0.025 and 2:1 randomization ratio favoring selinexor.

***Assessed by DNA sequencing and IHC

Data cutoff: January 18, 2022

BICR; blinded independent central review; BMI, body mass index; CR, complete response; DCR, disease control rate; DSS, disease-specific survival; EDM, exonuclease domain mutation; IHC, immunohistochemistry; MSI, microsatellite instability; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PFS2, progression-free survival on subsequent therapy; PR, partial response; PROs, patient-reported outcomes; QW, once weekly; R, randomized; RECIST, response evaluation criteria in solid tumors; TFST, time to first subsequent therapy; TSST, time to second subsequent treatment;

Primary Endpoint: PFS in ITT Population



median follow-up: 10.2 months (95% CI 8.97, 13.57)

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)

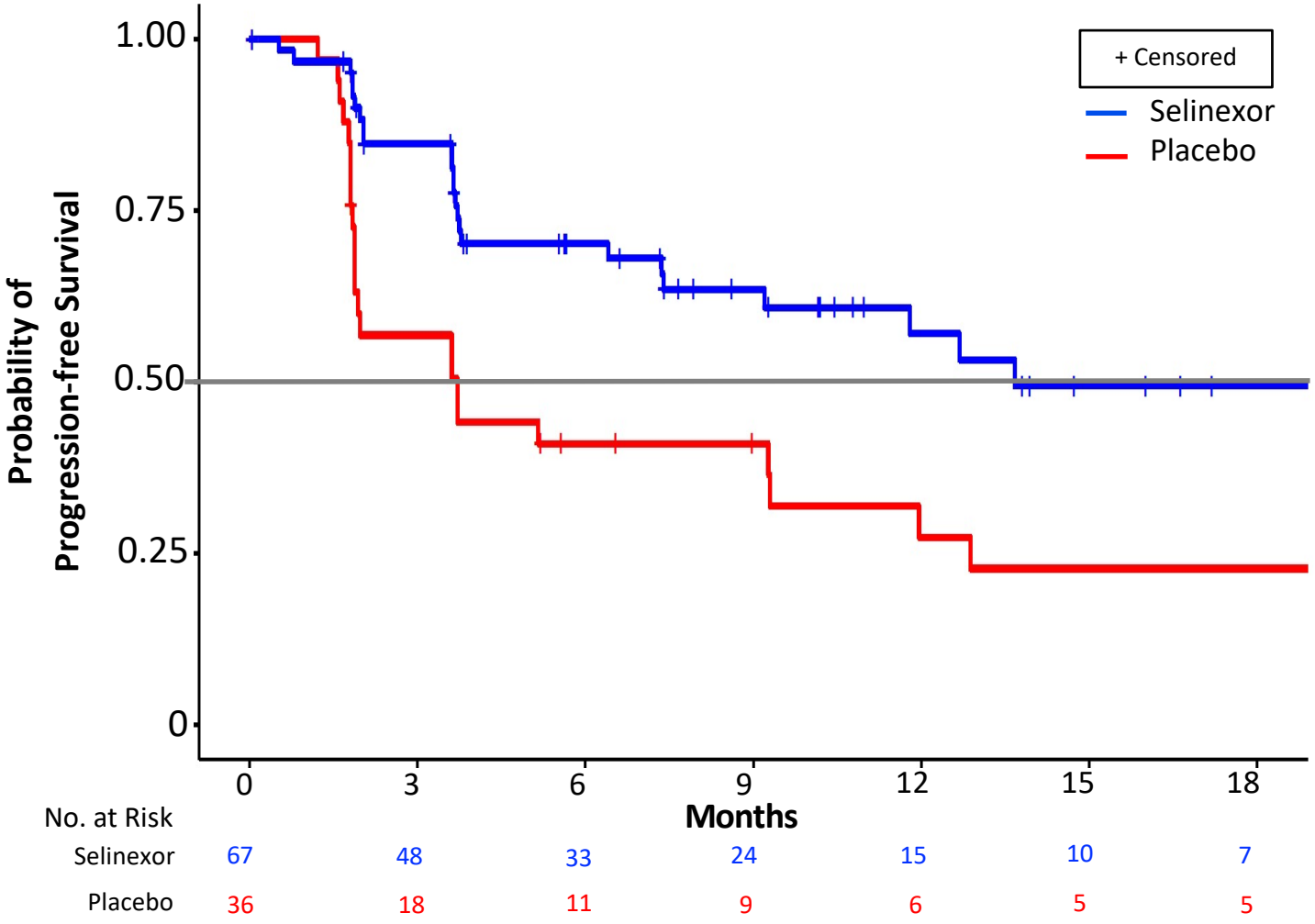
HR = 0.76 (95% CI 0.543-1.076)

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

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

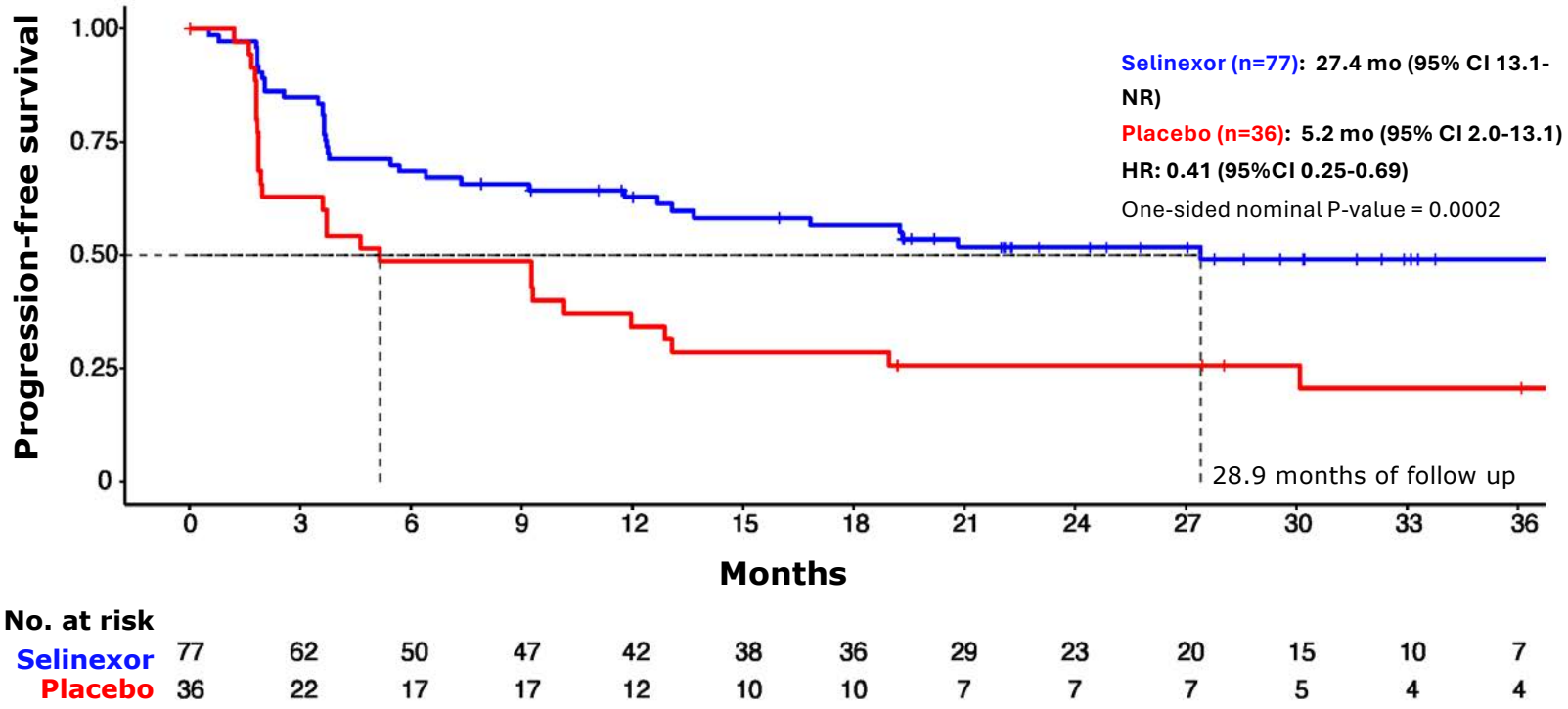
Unaudited

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

Long-term follow up: PFS in the *TP53*wt subgroup



PFS calculation begins at initiation of maintenance therapy and does not include duration of previous systemic chemotherapy.

Preliminary Overall Survival

	No. w/ events (%)	Median (95% CI), months	Overall Maturity (%)	HR (95% CI)
Selinexor	23.4%	NR (NR, NR)	26.6%	**0.76** (0.36-1.59)
Placebo	33.3%	NR (35.19, NR)		

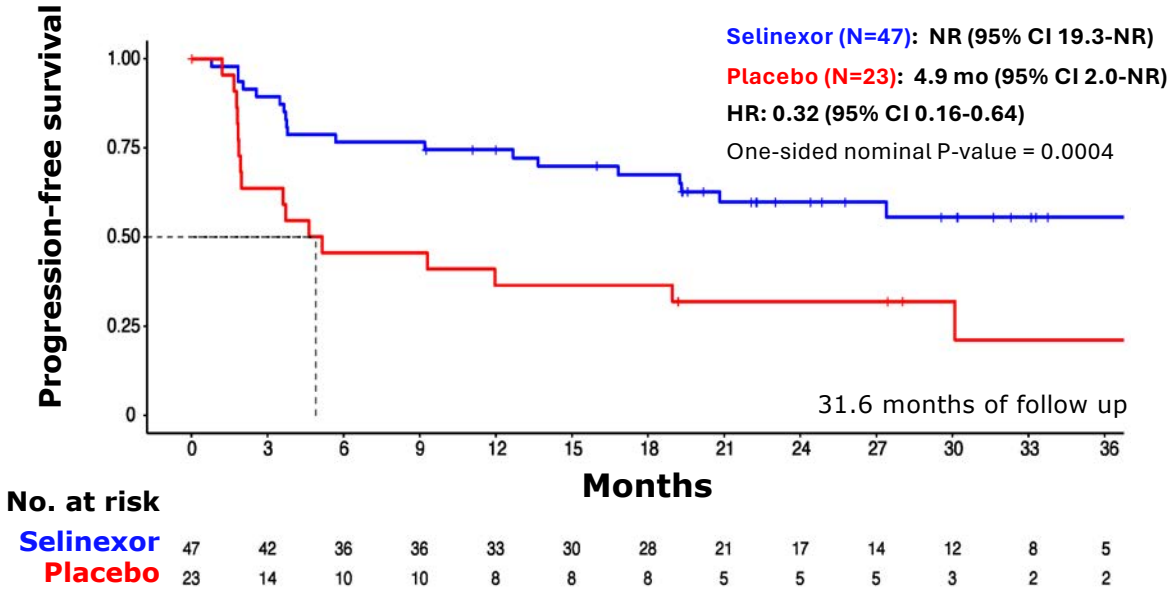
OS calculation begins at time randomization and does not include duration of previous systemic chemotherapy.

Data cut off date: Sept. 1, 2023

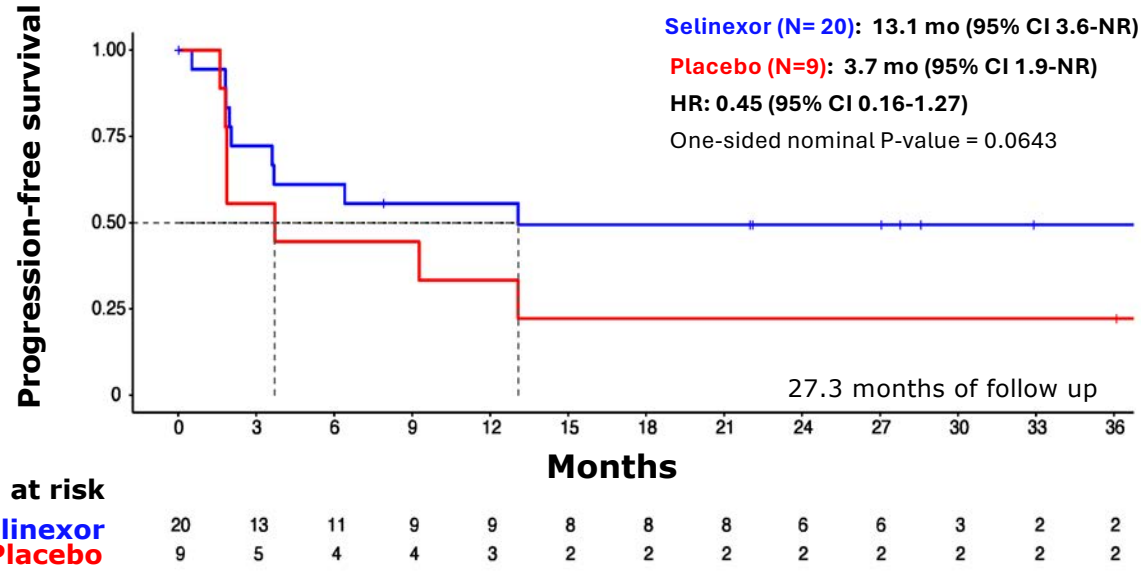
CI, confidence interval; HR, hazard ratio; mo, months; mut, mutant; NR, not reached.

Long-term follow up: PFS in additional subgroups

*TP53*wt/pMMR (MSS) subgroup



*TP53*wt/dMMR (MSI-H) subgroup



Preliminary Overall Survival

	No. w/ events (%)	Median (95% CI), months	Overall Maturity (%)	HR (95% CI)
Selinexor	23.4%	NR (NR, NR)	30.0%	**0.57** (0.24-1.35)
Placebo	43.5%	35.19 (28.68, NR)		

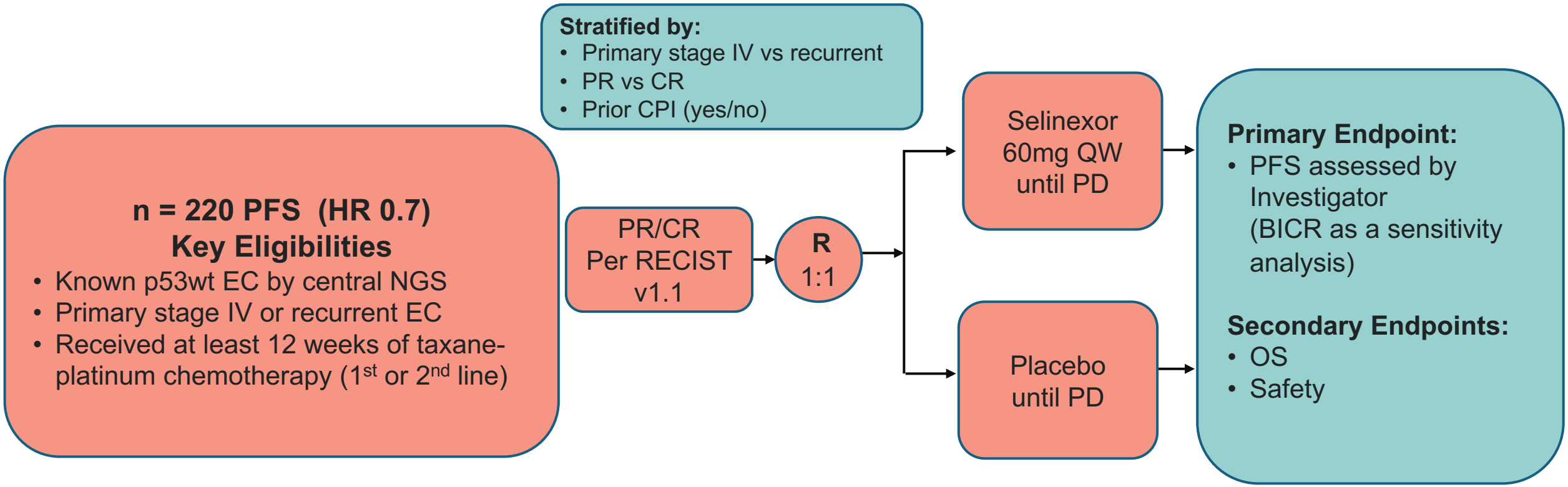
	No. w/ events (%)	Median (95% CI), months	Overall Maturity (%)	HR (95% CI)
Selinexor	10.0%	NR (NR, NR)	26.6%	**0.62** (0.06-6.81)
Placebo	11.1%	NR (NR, NR)		

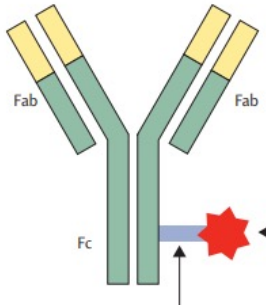
Data cut off date: Sept. 1, 2023

PFS calculation begins at initiation of maintenance therapy and does not include duration of previous systemic chemotherapy.
OS calculation begins at time randomization and does not include duration of previous systemic chemotherapy.

ENGOT-EN20/GOG-3083/XPORT-EC-042 Randomized, blinded Phase 3 international study of oral Selinexor once weekly versus placebo for maintenance therapy in patients with p53wt endometrial carcinoma responding to front line chemotherapy

Primary Objective: To evaluate the efficacy of selinexor compared to placebo as maintenance therapy in patients with p53wt advanced or recurrent endometrial cancer





ADCs under Development in Endometrial Cancer

Monoclonal antibody target	Drug Name	Payload	Ongoing trial
B7-H4	XMT-1660	Auristatin F-Hydroxypropylamide (microtubule inhibitor)	NCT05377996 (Phase I)
B7-H4	SGN-B7H4V (1 EC)	Monomethyl Auristatin E	NCT05194072 (Phase I)
B7-H4	AZD8205	Topoisomerase I inhibitor	NCT05123482 (Phase I)
Folate Receptor α	Farletuzumab ecteribulin (MORAb-202, FZEC) (3 EC)	Eribulin (microtubule inhibitor)	NCT04300556 (Phase I/II)
Folate Receptor α	Mirvetuximab Soravtansine	Maytansinoid (DM4)→ tubulin targeting	NCT03835819 (Phase II combination with pembro)
TROP2	Sacituzumab govitecan (IMMU-132) *approved in TNBC, urothelial	SN-38 (irinotecan metabolite) → Topoisomerase I inhibitor	NCT04251416 (Phase II) NCT03992131 (combination with rucaparib)
TROP2	Sacituzumab tirumotecan (SKB264/MK-2870)	Belotecan derivative → Topoisomerase I inhibitor	NCT04152499 (Phase I/II) NCT06132958 (Phase III)

TroFuse: Phase 3 ENGOT-en23/GOG-3095/MK-2870-005[1]

Key Eligibility Criteria

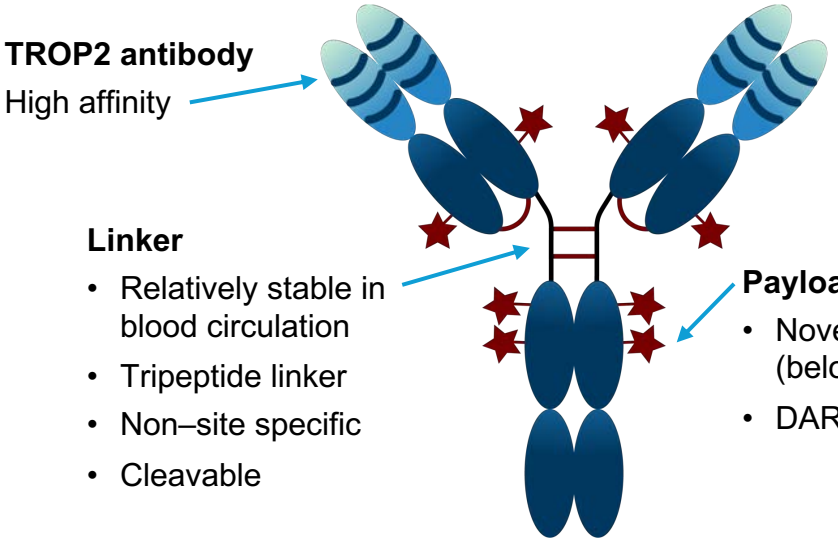
- Histologically confirmed endometrial carcinoma or carcinosarcoma
- Radiographically evaluable disease, either measurable or nonmeasurable per RECIST v1.1 (by BICR)
- Must have received prior platinum-based chemo and anti–PD-1/anti–PD-L1 therapy, either separately or in combination
- No neuroendocrine tumors or endometrial sarcoma, including stromal sarcoma, leiomyosarcoma, adenosarcoma, or other types of pure sarcomas
- Has not received >3 prior lines of therapy for endometrial carcinoma or carcinosarcoma
- Has not had a recurrence of endometrial carcinoma or carcinosarcoma >180 days after completing platinum-based therapy administered in the curative-intent or adjuvant setting without any additional platinum-based therapy received in the metastatic or recurrent setting

TROP2: transmembrane glycoprotein overexpressed by several gynecologic tumor types

R

Sacituzumab tirumotecan (SKB264/MK-2870) 4 mg/kg IV on day 1 of each 14-day cycle

Doxorubicin 60 mg/m^2 IV on day 1 of each 21-day cycle
or
Paclitaxel 80 mg/m^2 IV on days 1, 8, and 15 of each 28-day cycle



- Sacituzumab tirumotecan (SKB264/MK-2870) employs the same antibody as sacituzumab govitecan
- Its linker was designed to have higher stability
- Novel TOPO I inhibitor payload (KL610023) is a belotecan derivative/topoisomerase inhibitor that has similar in vitro activity to belotecan and SN-38 (sacituzumab govitecan's payload)

- **Primary endpoints**: PFS, OS
- **Secondary endpoints**: ORR, DOR, safety, HRQOL

1. https://clinicaltrials.gov/study/NCT06132958.

Agenda

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

Module 2: Current Management of Relapsed/Refractory (R/R) OC; Promising Novel Agents and Strategies Under Investigation — Dr Backes

Module 3: First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Mirza

Module 4: Current Therapeutic Options for R/R EC; Novel Investigational Strategies — Dr Slomovitz

Module 5: Role of HER2-Targeted Therapy in the Management of Advanced OC, EC and Other Gynecologic Cancers — Dr Secord

Dr Priya Rudolph: Case Presentation

Clinical presentation: 68-year-old with postmenopausal bleeding, endometrioid adenocarcinoma in 09/23, lost to follow-up, admitted with abdominal distention. CT — massive ascites, 14-cm central pelvic mass, large adnexal masses, omental caking, hydronephrosis.

Treatment: Carboplatin/paclitaxel/bevacizumab. She had LOC and low back pain with her second cycle. Continued with more premedication. Switched treatment to carboplatin/paclitaxel/trastuzumab due to HER2 positivity (3+ IHC).

Response assessment: PET pending; clinical improvement; drop in CA-125 from 772 to 228.

RTP
RESEARCH
TO PRACTICE

Dr Priya Rudolph: Case Discussion Questions

When are you generally conducting HER2 assessment for your patients with gynecologic cancers? Is the timing different for patients with OC versus EC versus cervical cancer?

Given the IHC 3+, would you offer trastuzumab deruxtecan (T-DXd) to this patient?

Do you prefer bevacizumab or trastuzumab for a patient with ascites and a HER2-positive tumor?

Would you consider maintenance trastuzumab, and for how long? What if they experience pathologic complete response by the time of surgery?

If disease recurs on trastuzumab and is MSS, what is your preferred treatment — lenvatinib/pembrolizumab or T-DXd?

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RESEARCH
TO PRACTICE

Dr Priya Rudolph: Questions for the Faculty

What would be your treatment approach for a patient with ascites and MSI-H, HER2-positive disease?

For a patient with ovarian cancer who is both folate receptor alpha and HER2-positive, how would you sequence T-DXd and mirvetuximab soravtansine?

Dr Eric Lee: Case Presentation

Clinical presentation: 36-year-old with mucinous adenocarcinoma of the ovary; 20-cm tumor encasing the L ovary. Total abdominal hysterectomy in 2023, delay of care due to insurance, did not receive HIPEC or adjuvant chemotherapy and was diagnosed with a liver metastasis in 2024.

Treatment: Given mucinous histology she was initially started on capecitabine, oxaliplatin and bevacizumab. Subsequent NGS showed ERBB2 amplification, KRAS G12V, TP53. BRCA 1- and 2-negative, HRD not detected, low TMB. CA125 elevated, CEA normal.

Response: Just started therapy. CA125 rising. Given KRAS mutation, may not benefit from HER2 targeted therapy. Pt is also pending endoscopy to rule out a GI primary although there was no obvious primary mass on imaging.

Side effects/tolerability issues: Baseline liver insufficiency 2/2 mets.

Dr Eric Lee: Case Discussion Questions

What treatment would you recommend for this patient?

What would be your next line of treatment if/when she experiences disease progression?

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Dr Eric Lee: Questions for the Faculty

Where in the treatment course are you typically offering T-DXd to your patients with OC, EC and cervical cancer?

Are you only offering T-DXd to patients with IHC 3+ disease per the indication, or would you consider it for a patient with no other options and lower levels of expression?

How, specifically, are you monitoring for interstitial lung disease (ILD) in your patients receiving T-DXd?

At what level of ILD are you permanently discontinuing treatment even after resolution of symptoms?

RTP
RESEARCH
TO PRACTICE

Role of HER2-Targeted Therapy in Advanced OC, EC and Other Gynecologic Cancers

Angeles Alvarez Secord, MD, MHSc
Director, Gynecologic Oncology Clinical Trials
Division of Gynecologic Oncology, Department Ob/Gyn
Duke Cancer Institute

DukeHealth

Objectives

- Discuss HER2 testing and frequency of high HER2 expression in advanced gynecologic cancers
  - When and how do/would you test for HER2?

- Review the use of HER2-targeted strategies such as trastuzumab and trastuzumab deruxtecan (T-DXd) in advanced gynecologic cancers

- Review safety profile of T-DXd toxicities and recommendations for monitoring and management

Case #1

A 56-y.o. woman with recurrent *BRCA*-wt/HRD+ high-grade serous ovarian cancer presents with extensive ascites, pleural effusion, hepatic mets, progressed on second-line PLD/platinum-based therapy.

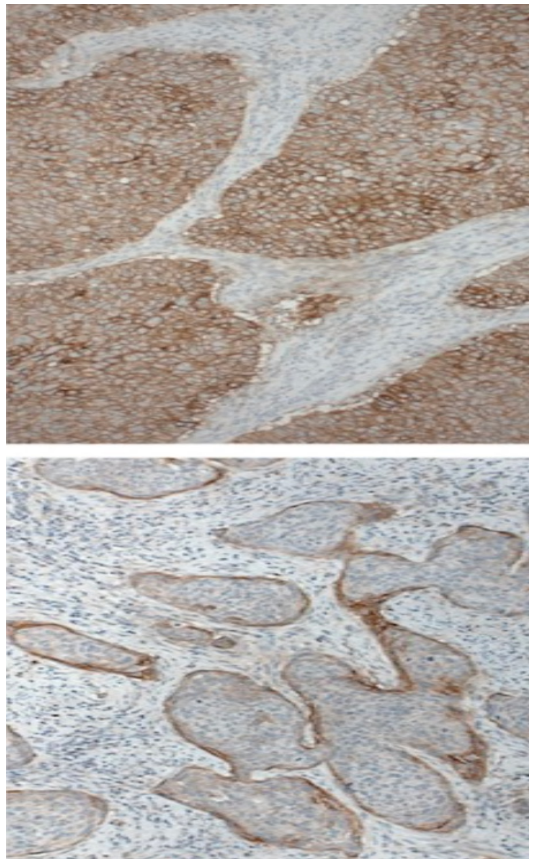
Treatment options:

- ❑ Mirvetuximab
- ❑ Paclitaxel with bevacizumab
- ❑ Trastuzumab deruxtecan
- ❑ Clinical trial

What do you need to know first?

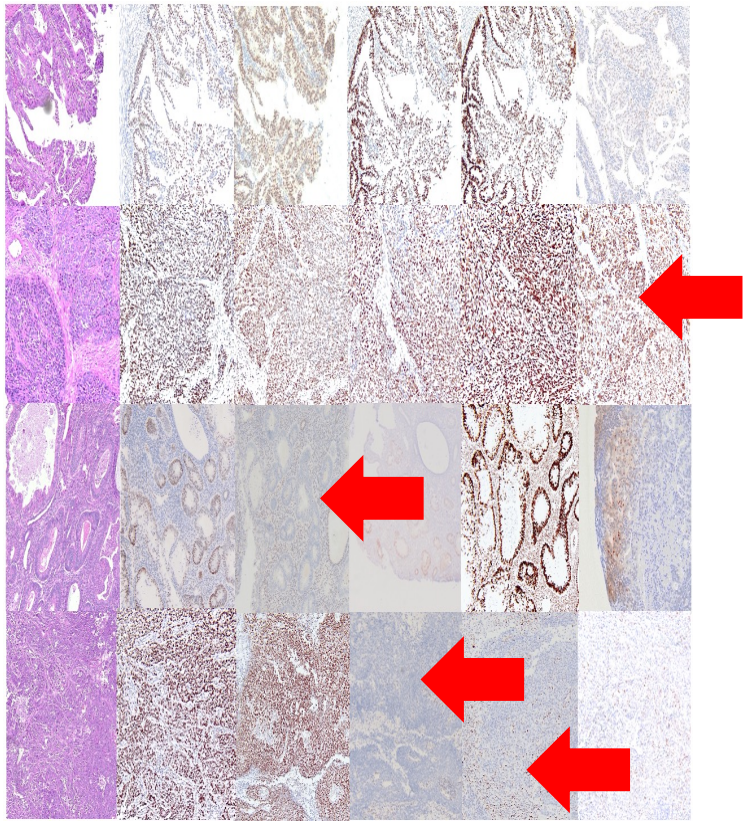
Testing is CRITICAL in gynecologic cancer

PD-L1



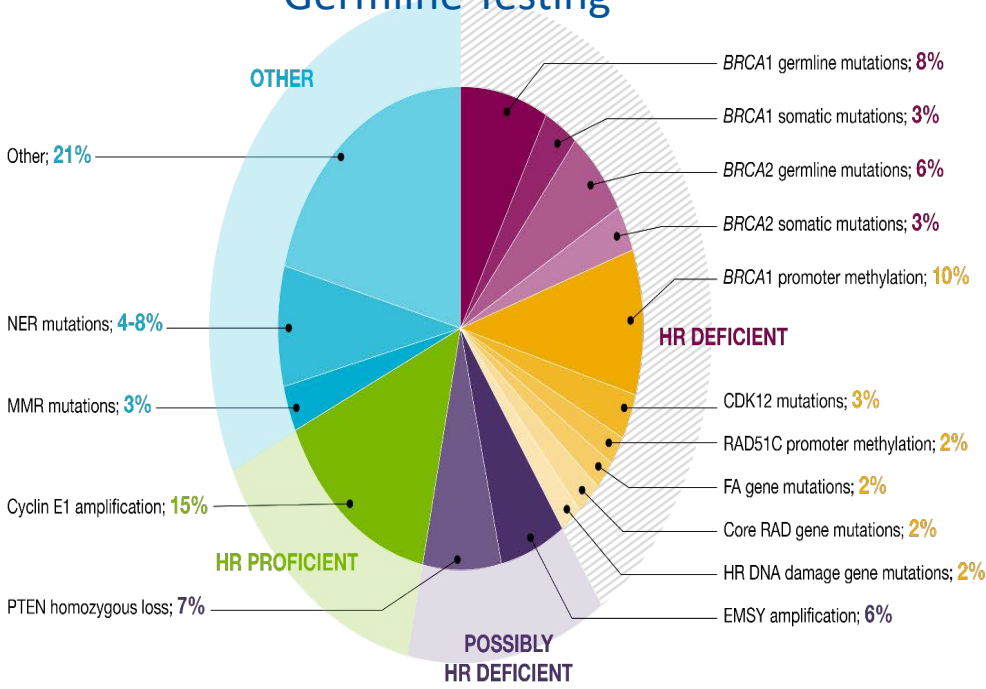
PD-L1 expression noted in high percentage of cervical cancers

H&E MLH1 PMS2 MSH2 MSH6 p53



Approximately 30% endometrial cancers have dMMR and 25% abnormal p53 expression

Germline Testing



Approximately 50% high grade epithelial ovarian cancers have homologous recombination deficiency and mutation in DNA repair gene pathway

Heeren AM, et al. *Mod Pathol* 2016; Alvarez Secord GOG249 MMR/p53 testing; Konstantinopoulos PA, et al. *Cancer Discov*. 2015

HER2 Testing – it's complicated

HER2	Breast (ASCO/CAP 2007)	Breast (ASCO/CAP 2013; 2018*)	Gastric (ASCO/CAP 2016)	Colorectal (HERACLES trial)	UPSC (Fader et al.) Endometrial
IHC 3+	>30% strong, uniform, complete	>10% circumferential, strong, complete	≥10%, strong complete or basolateral/lateral	≥50% strong, complete or basolateral/lateral	>30% strong complete or basolateral/lateral
FISH amplification	HER2/CEPT17 ratio >2.2 Patients with HER2/CEPT17 ratio 2-2.2 eligible	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus *(if IHC 2+ or 3+)	HER2/CEPT17 ratio ≥2.0 OR ratio <2.0 and HER2 signal ≥6.0/nucleus	HER2/CEPT17 ratio ≥2.0 in ≥50% of cells	HER2/CEPT17 ratio ≥2.0

Lassus H et al *Gynecol Onc* 2004; McCaughan H et al *J Clin Pathol* 2012; Hale RJ et al *Int J Gynecol Pathol* 2013; Bellone S et al *J Clin Pathol* 2003; Ersoy E et al *Gyn Path* 2022

HER2 expression in ovarian cancer

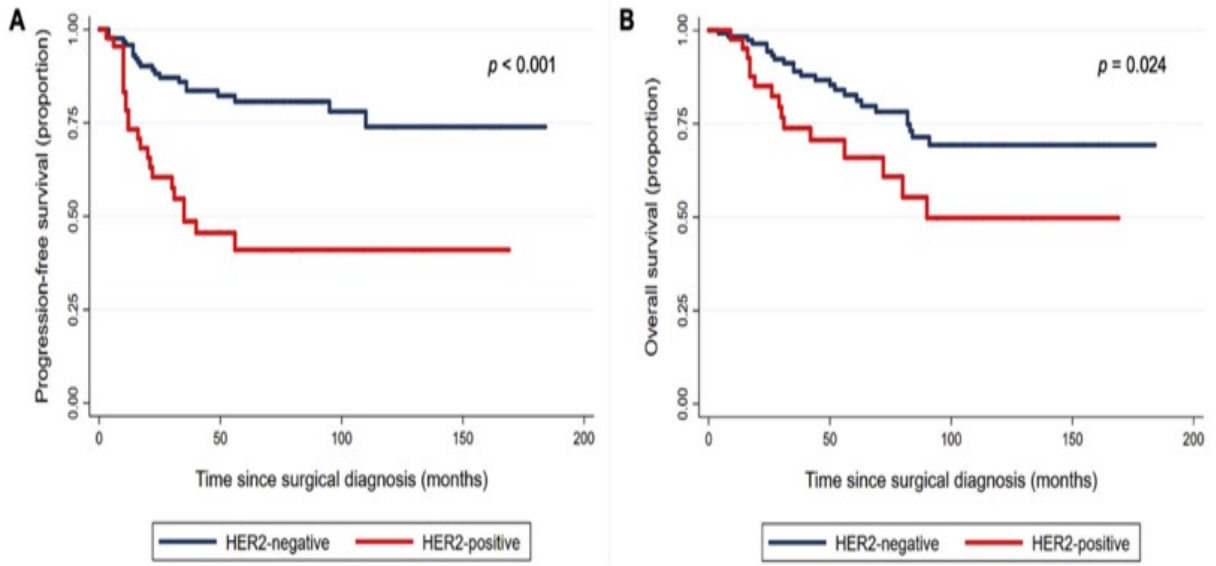
- HER2 overexpression/amplification highest in mucinous carcinomas
  - Protein overexpression 29.4%
  - Amplification 25-35.3%
- HER2 gene amplification in mixed-type carcinomas (11.9%), clear cell carcinomas (4%), serous papillary carcinomas (3%), and endometrioid carcinomas (2.1%)
- Intra-tumoral heterogeneity of HER2 protein expression seen in 20% of cases
- High HER2 expression and increased copy number associated with worse PFS and OS

- In GOG160, a phase II trial evaluating trastuzumab in patients with recurrent or refractory ovarian cancer had ORR of 7.3 % in patients with HER2 overexpression (n=41)
  - 837 tumor samples screened for HER2 expression; 95 patients (11.4%) exhibited 2+/3+

English D, et al. *Mol Diagn Ther*. 2013; Bookman, M, et al. J Clin Oncol 2003

HER2 expression in endometrial cancer

- HER2 overexpression and amplification 4% to 69%
  - Serous carcinomas: 43% overexpression and 29% amplification
  - Clear cell cancers: 38% HER2 amplification
  - Grade 1 endometrioid cancers: 3% overexpression and 1% amplification
- Higher frequency HER2 overexpression in Black compared to White patients
- HER2 expression associated with worse PFS and OS



HER2+ cancers had worse PFS (aHR 3.50; p < .001) and OS (aHR 2.00; p = .039) compared to HER2-negative tumors

English D, et al. *Mol Diagn Ther*. 2013; Erickson B et al *Gynecol Oncol* 2020.

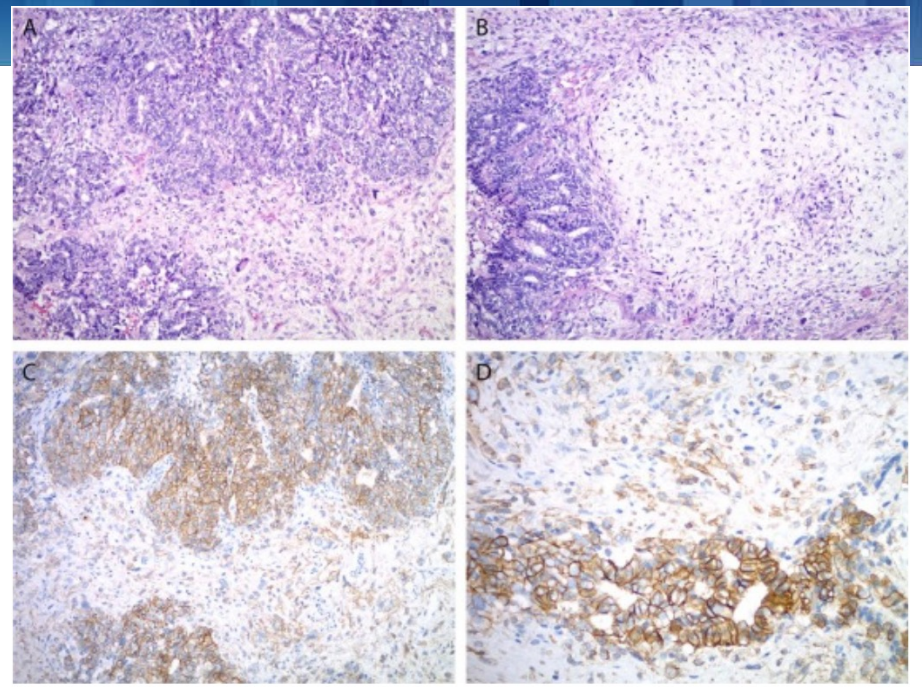
HER2 expression in cervical cancer

- HER2 protein expression in 38.7%; somatic *HER2* mutations occur in ~5%
  - IHC studies on biopsies from some recurrent lesions demonstrated a strong (3+) expression for HER2 even though primary were HER2 negative.
- Overexpression associated with poor survival ($p<0.0001$)
- Phase 2 SUMMIT basket trial of neratinib in patients with *HER2*-mutant, metastatic cervical cancer. (N=16)
  - ORR 25%; CBR 50% had stable disease ≥16 weeks
  - DOR for responders were 5.6, 5.9, and 12.3 months
  - Median PFS was 7.0 months; median OS was 16.8 months

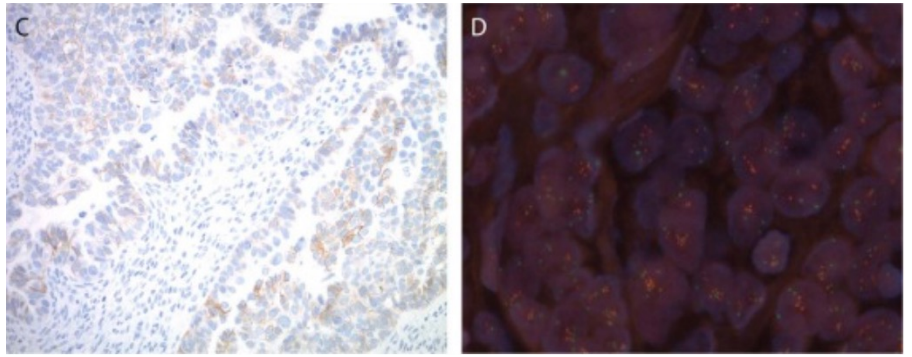
English D, et al. *Mol Diagn Ther*. 2013; Oaknin A et al *Gynecol Oncol* 2020.

HER2 expression in carcinosarcomas

- Conflicting data in the literature HER2+ IHC/FISH 3%-56%
- Using the 2013 ASCO/CAP criteria 16% HER2+ (13/80; 12 uterine and 1 ovarian)
- The HER2+ rate was higher in uterine vs ovarian cancers (14-19% vs 7%)
- All HER2+ tumors had either a serous or a mixed carcinomatous component.
- All tumors with endometrioid, clear cell, undifferentiated, or neuroendocrine carcinoma subtype were HER2 negative.



Uterine carcinosarcoma. HER2 3+ in the carcinoma and the sarcoma component



Ovarian carcinosarcoma. HER2 2+ in the carcinoma with amplification by FISH (HER2/CEP17 ratio = 2.3)

English D, et al. *Mol Diagn Ther*. 2013; Rottman D et al *Modern Pathology 2020*

Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Key eligibility criteria

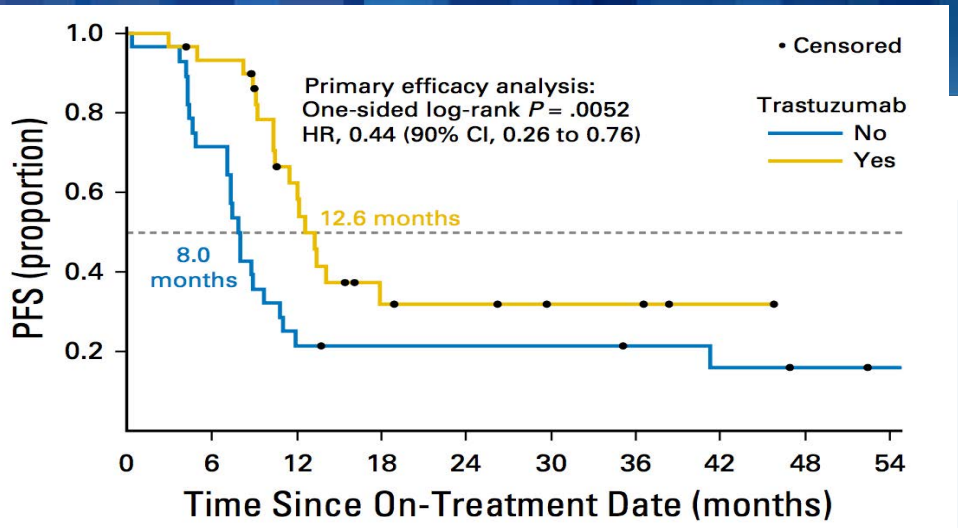
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- "platinum sensitive" recurrence (6 mo)

Investigator initiated study

Phase II

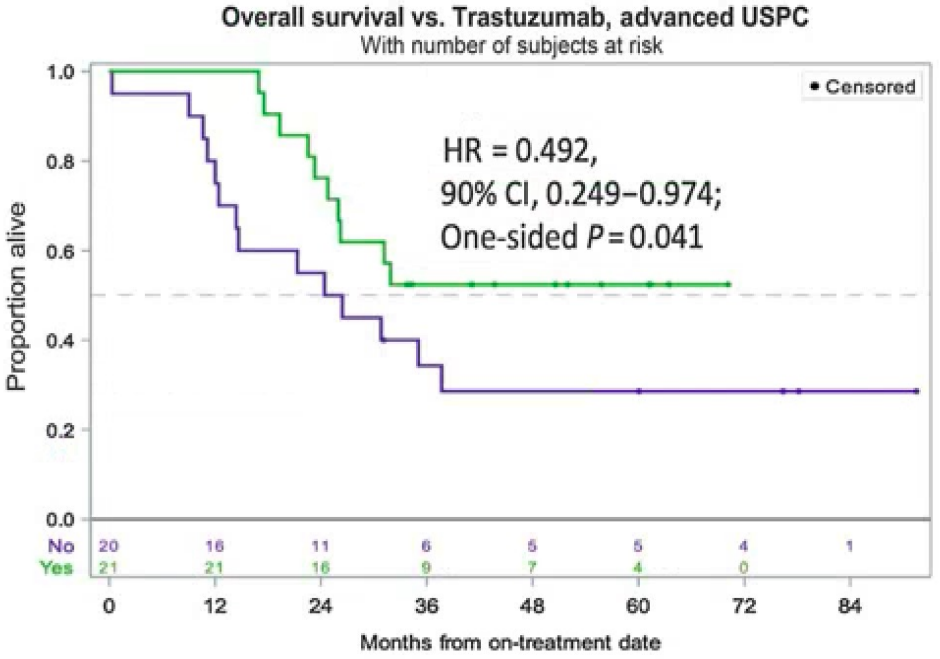
Open label

Investigator assessed PFS



No. at risk

No	28	20	6	5	5	5	4	3	2	1



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Endometrial Carcinoma

Primary or Adjuvant Therapy

Systemic Therapy

Preferred Regimens

- Carboplatin/paclitaxel[7]
- Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8]
- Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9]
- Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10]
- Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10]

Recurrent Disease

First-Line Therapy for Recurrent Disease[i]

Preferred

- Carboplatin/paclitaxel (category 1 for carcinosarcoma)[k,7]
- Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,c,d,8]
- Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,e,9]
- Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive uterine serous carcinoma)[d,10]
- Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive carcinosarcoma)[f,10]

Nickles-Fader A *J Clin Oncol* 2018; www.nccn.org

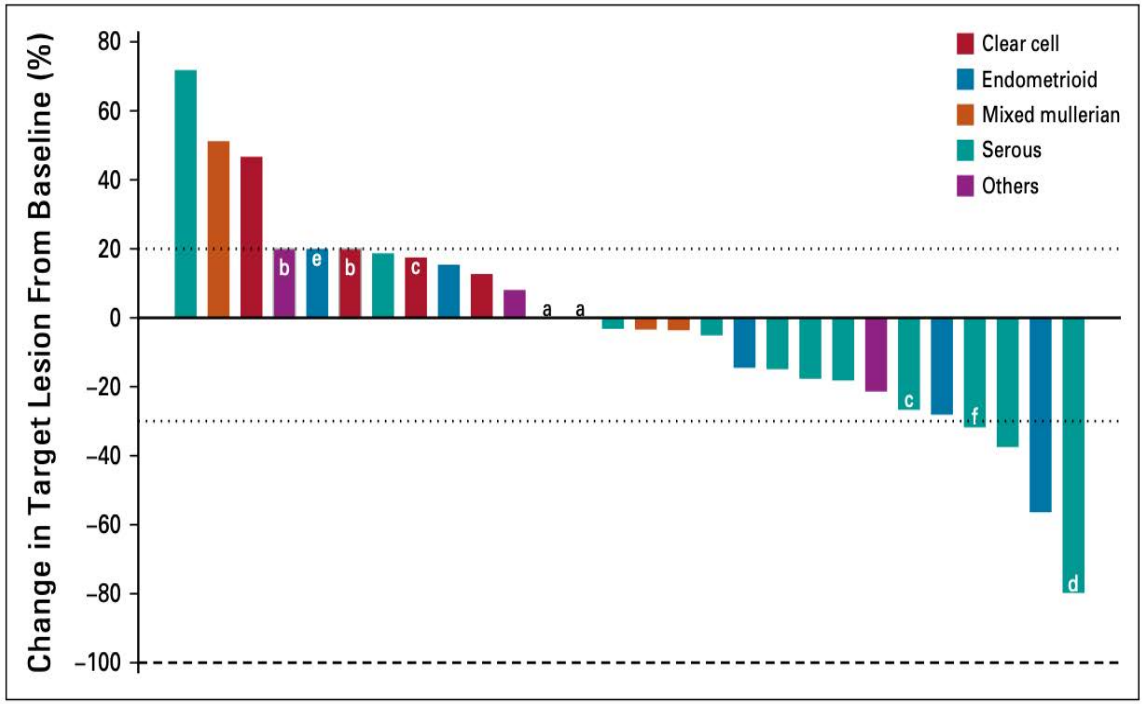
TAPUR Trial: Pertuzumab and Trastuzumab in Endometrial Cancer with ERBB2/3-Amplification, Overexpression, or Mutation

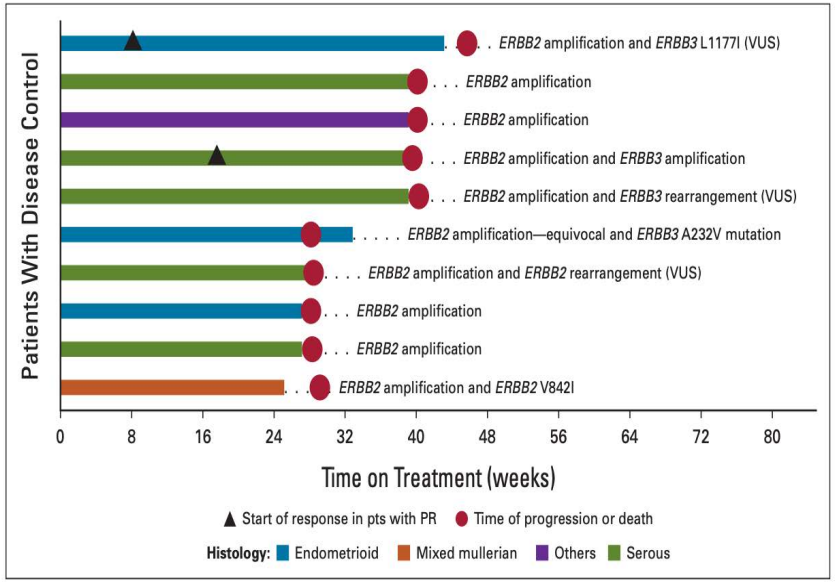
Pragmatic Basket Trial N=28

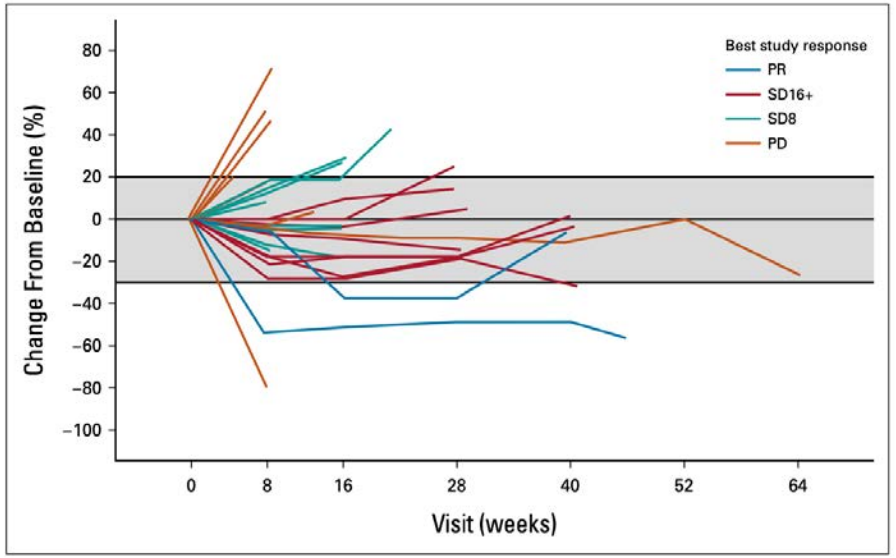
Disease control rate = 37%

2 Partial responses; 8 Stable Disease 16+ weeks

mPFS = 16 weeks; mOS = 61 weeks



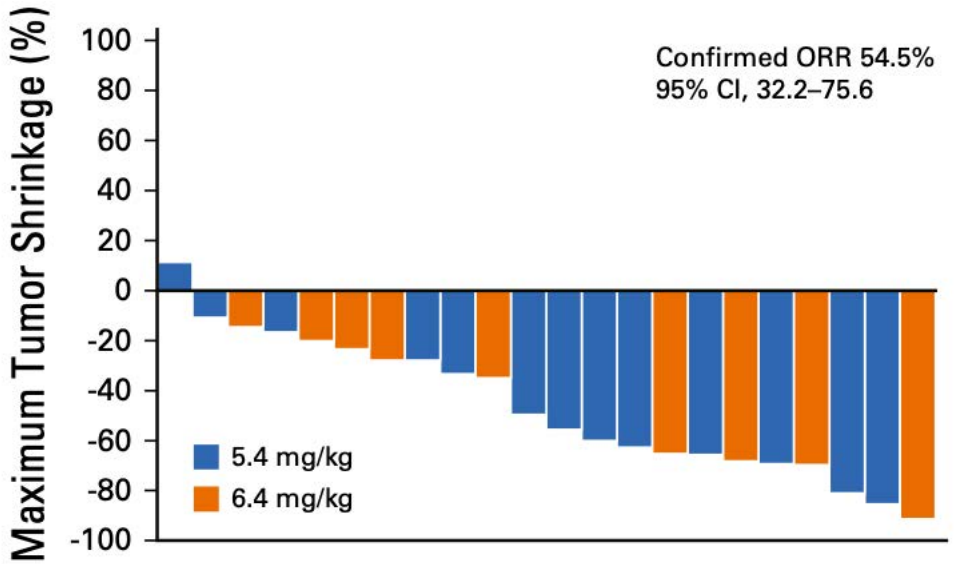


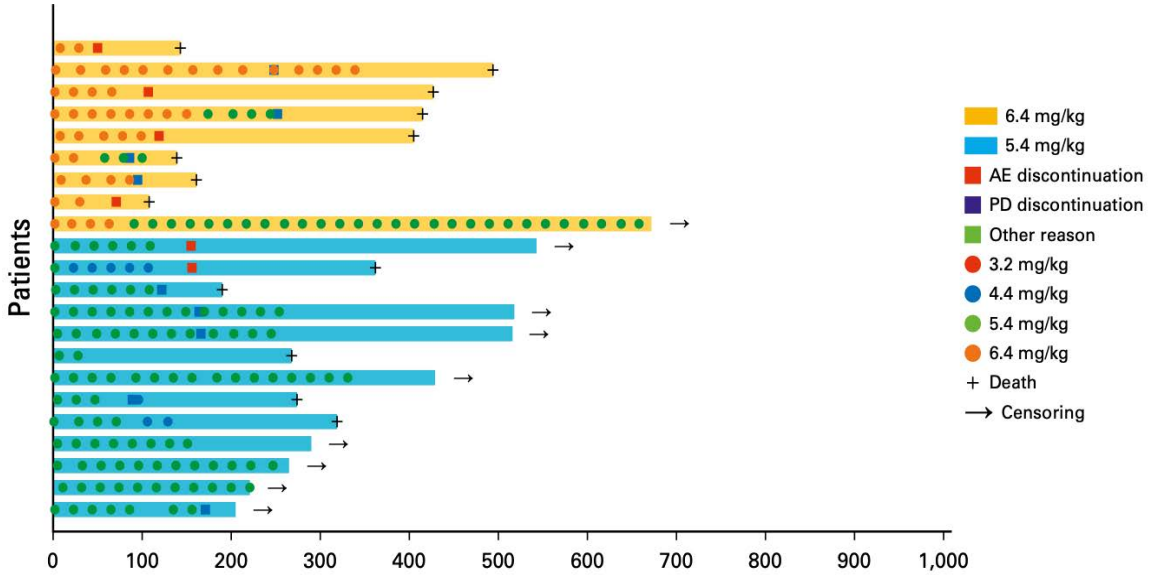


Ahn ER et al. Targeted Drug Therapy 2023

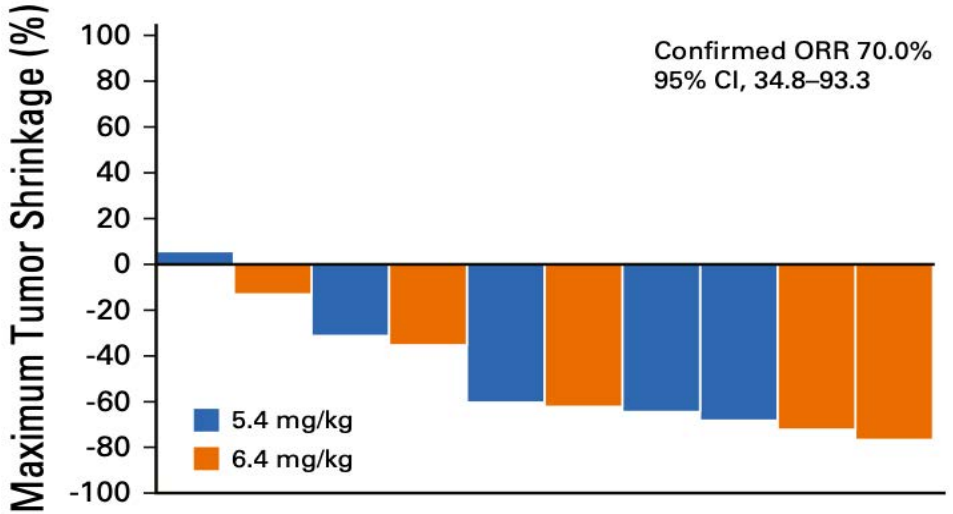
STATICE Trial: Trastuzumab deruxtecan for HER2-expressing Advanced or Recurrent Uterine Carcinosarcoma

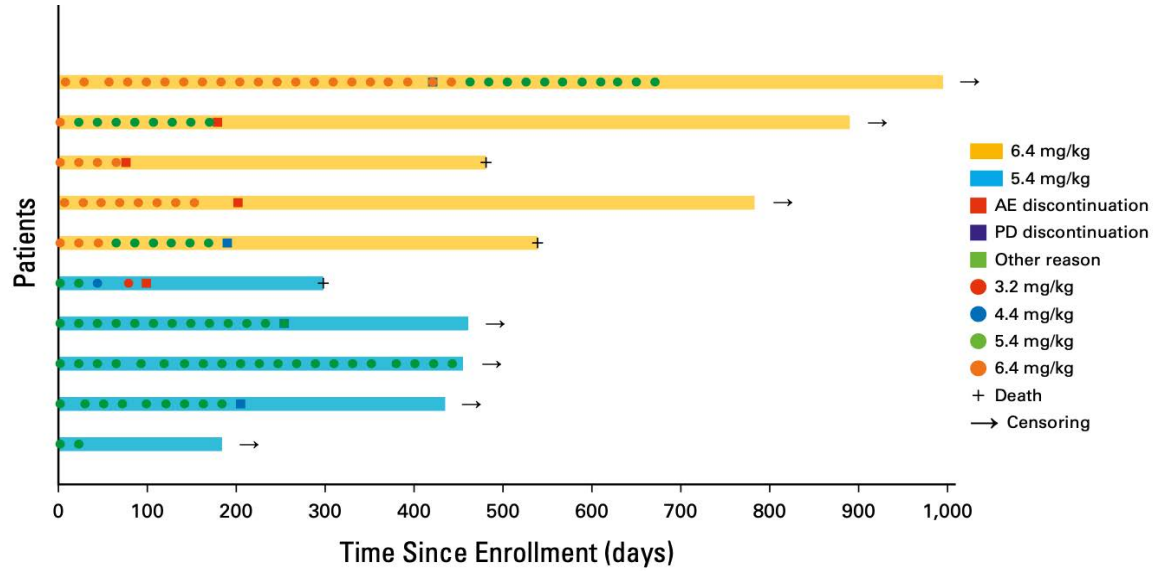
HER2-High





HER2-Low





Nishikawa T et al. J Clin Oncol 2023

STATICE Trial: Trastuzumab deruxtecan for HER2-expressing Advanced or Recurrent Uterine Carcinosarcoma

	All (N = 33), No. (%)			5.4 mg/kg (n = 19), No. (%)			6.4 mg/kg (n = 14), No. (%)		
Adverse Event	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Nausea	28 (84.8)	1 (3.0)	0	17 (89.5)	0	0	11 (78.6)	1 (7.1)	0
Anemia	18 (54.5)	8 (24.2)	0	8 (42.1)	2 (10.5)	0	10 (71.4)	6 (42.9)	0
Decreased white blood cell	17 (51.5)	3 (9.1)	0	6 (31.6)	0	0	11 (78.6)	3 (21.4)	0
Decreased neutrophil count	16 (48.5)	7 (21.2)	2 (6.1)	5 (26.3)	2 (10.5)	0	11 (78.6)	5 (35.7)	2 (14.3)
Malaise	14 (42.4)	2 (6.1)	0	10 (52.6)	0	0	4 (28.6)	2 (14.3)	0
Hypoalbuminemia	14 (42.4)	4 (12.1)	0	6 (31.6)	1 (5.3)	0	8 (57.1)	3 (21.4)	0
Vomiting	12 (36.4)	1 (3.0)	0	7 (36.8)	0	0	5 (35.7)	1 (7.1)	0
Diarrhea	12 (36.4)	1 (3.0)	0	4 (21.1)	0	0	8 (57.1)	1 (7.1)	0
Elevated ALT	12 (36.4)	0	0	7 (36.8)	0	0	5 (35.7)	0	0
Elevated AST	11 (33.3)	0	0	5 (26.3)	0	0	6 (42.9)	0	0
Constipation	11 (33.3)	0	0	7 (36.8)	0	0	4 (28.6)	0	0
Decreased lymphocyte count	10 (30.3)	5 (15.2)	2 (6.1)	6 (31.6)	3 (15.8)	0	4 (28.6)	2 (14.3)	2 (14.3)
Weight loss	9 (27.3)	0	0	3 (15.8)	0	0	6 (42.9)	0	0
Elevated ALP	9 (27.3)	0	0	6 (31.6)	0	0	3 (21.4)	0	0
Pneumonitis/interstitial lung disease	9 (27.3)	1 (3.0)	0	4 (21.1)	0	0	5 (35.7)	1 (7.1)	0
Decreased appetite	8 (24.2)	1 (3.0)	0	2 (10.5)	0	0	6 (42.9)	1 (7.1)	0
Decreased platelet count	7 (21.2)	2 (6.1)	0	1 (5.3)	0	0	6 (42.9)	2 (14.3)	0

Nishikawa Tet al. J Clin Oncol 2023

DESTINY-PanTumor02 Open-label Multicenter Study of Trastuzumab deruxtecan for HER2-expressing cancers

Key eligibility criteria

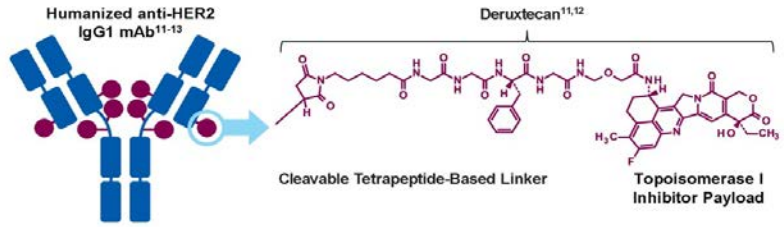
- Advanced solid tumors not eligible for curative therapy
- 2L+
- HER2 expression (IHC 3+ or 2+)
  - Local or central testing by HercepTest if local test not feasible
  - ASCO/CAP gastric cancer scoring
- Prior HER2-targeted therapy allowed
- PS 0-1

N=267

- 202 (75.7% based on local HER2 testing
- 111 (41.6%) HER2-3+ based on HER local or central test
- 75 (28.1%) were HER2-3+ based on central test

Meric-Bernstam F et al. J Clin Oncol 2024

Trastuzumab deruxtecan (T-DXd)

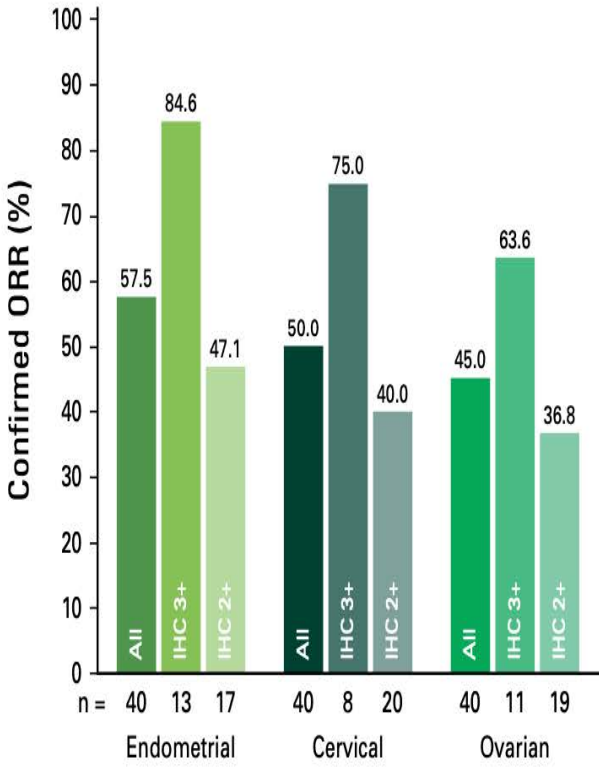


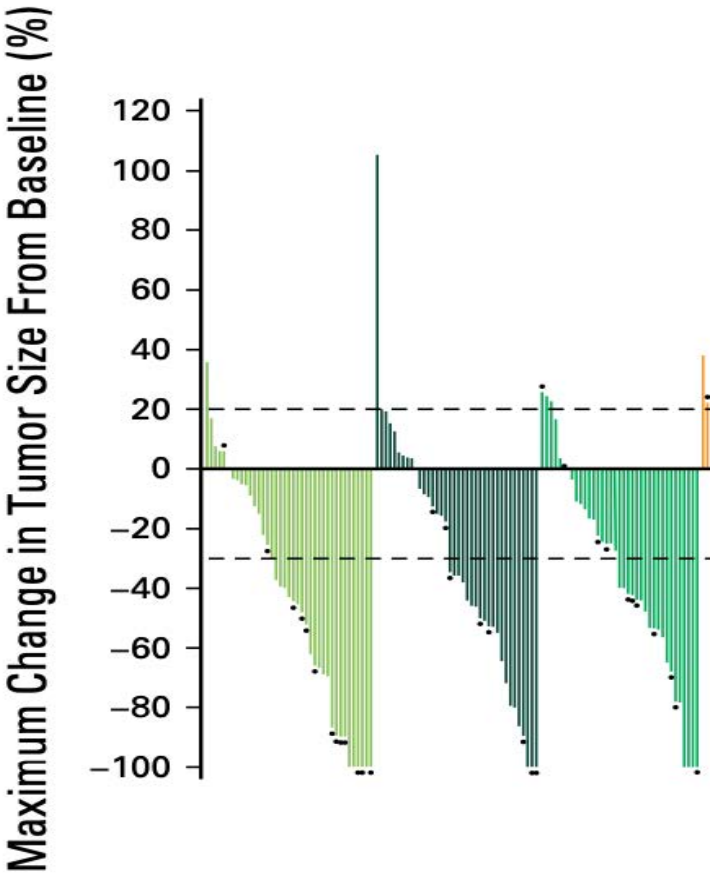
FDA grants accelerated approval to fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive solid tumors

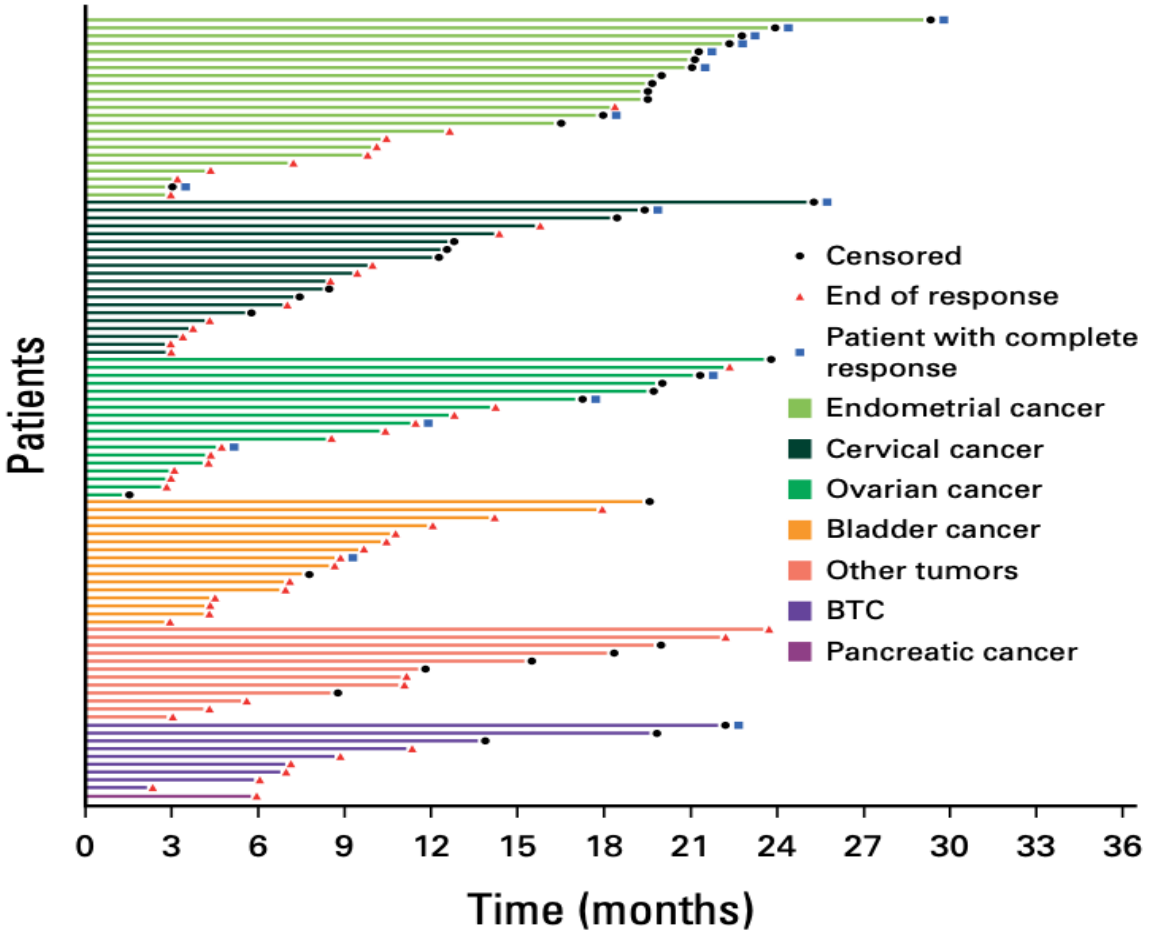
On April 5, 2024, the Food and Drug Administration granted accelerated approval to fam-trastuzumab deruxtecan-nxki ( ) for adult patients with unresectable or metastatic HER2-positive (IHC3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.

DESTINY-PanTumor02 Open-label Multicenter Study of Trastuzumab deruxtecan for HER2-expressing cancers

Confirmed ORR







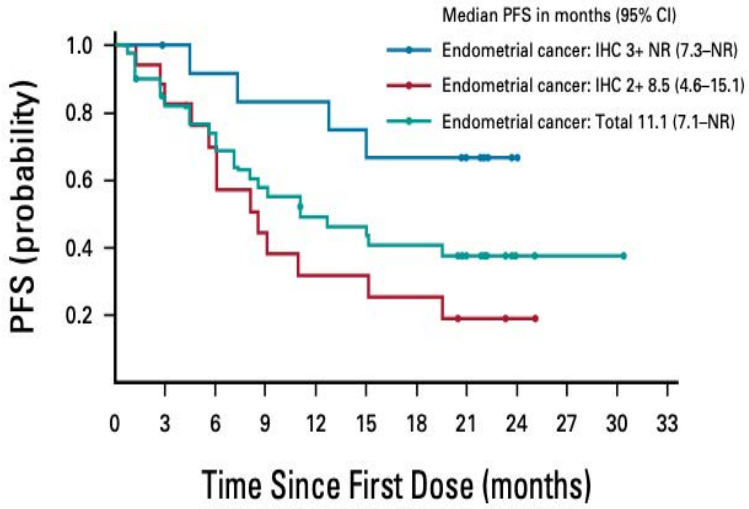
Outcome	Endometrial Cancer	Cervical Cancer	Ovarian Cancer
All patients	40	40	40
Confirmed ORR (investigator)	23 (57.5)	20 (50.0)	18 (45.0)
95% CI	40.9 to 73.0	33.8 to 66.2	29.3 to 61.5

Meric-Bernstam F et al. J Clin Oncol 2024

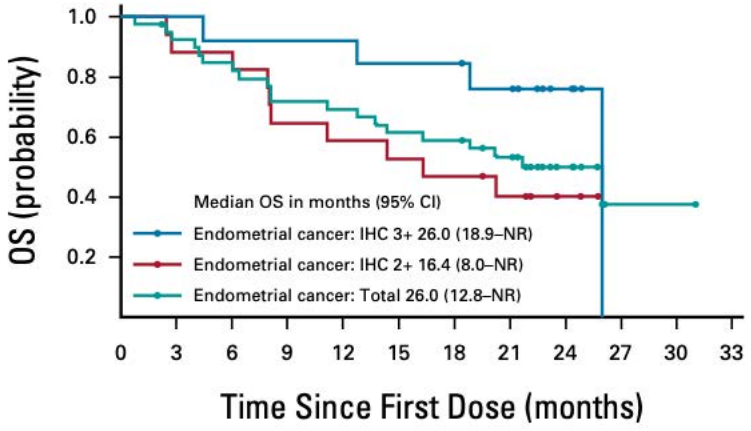
DESTINY-PanTumor02 Open-label Multicenter Study of Trastuzumab deruxtecan for HER2-expressing cancers

Endometrial Cancer

PFS

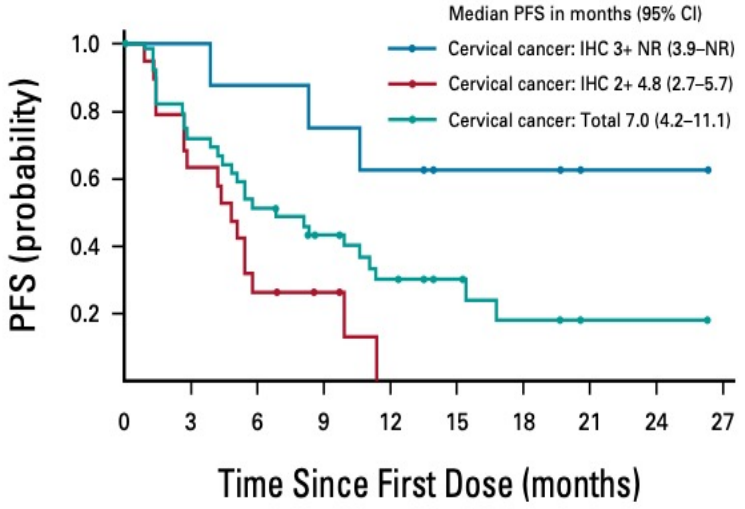


OS



Cervical Cancer

PFS



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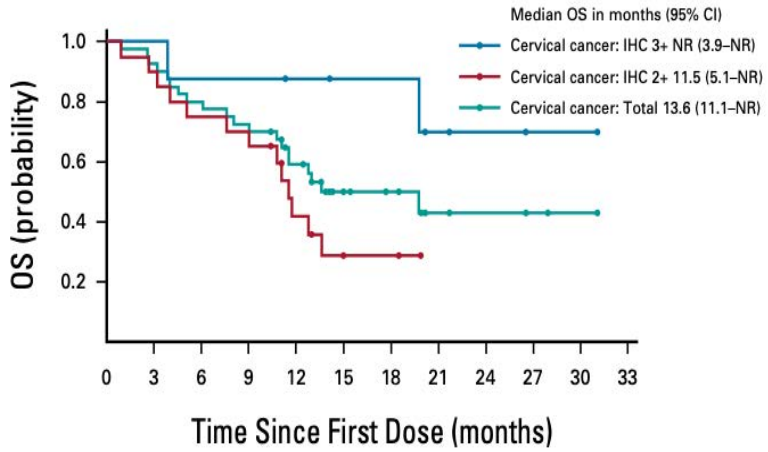

Ovarian Cancer

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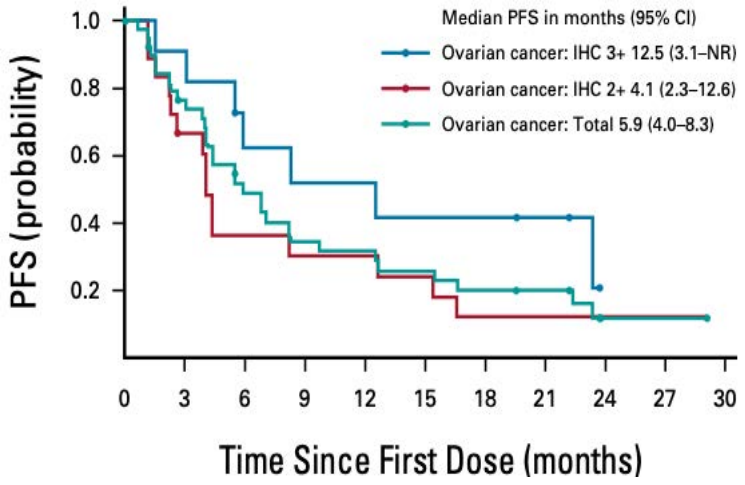

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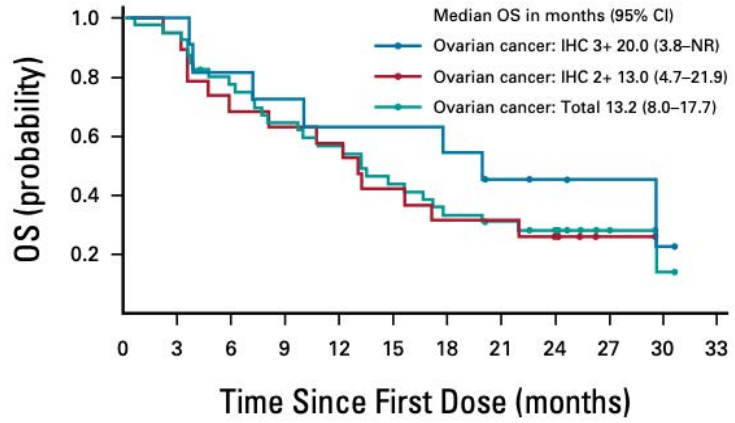


Meric-Bernstam F et al. J Clin Oncol 2024

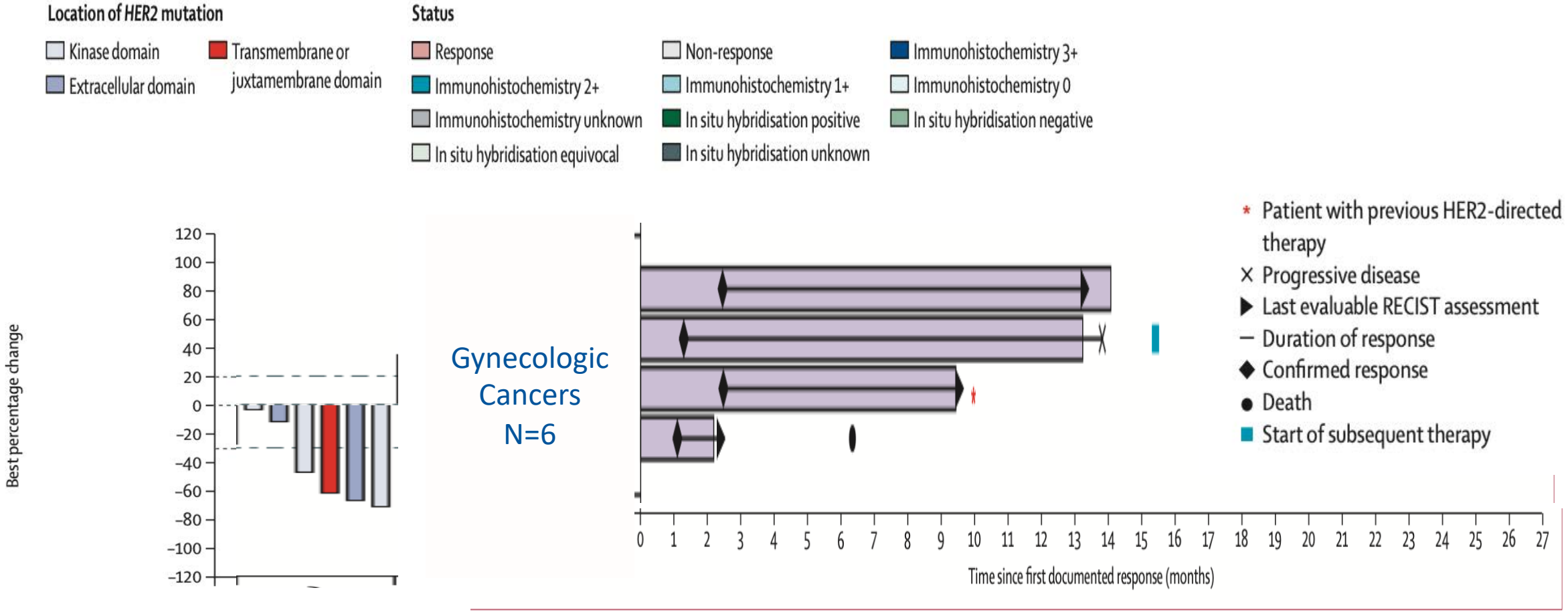
DESTINY-PanTumor02 Open-label Multicenter Study of Trastuzumab deruxtecan for HER2-expressing cancers

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)

- Adjudicated drug-related events of ILD/pneumonitis occurred in 28 (10.5%) patients, with the majority as low grade (grade 1, n 5 7 [2.6%]; grade 2, n 5 17 [6.4%]). There was one (0.4%) grade 3 event and three (1.1%) fatal adjudicated drug- related cases of ILD/ pneumonitis, one each in the biliary tract, endometrial, and other tumors cohorts.

Meric-Bernstam F et al. J Clin Oncol 2024

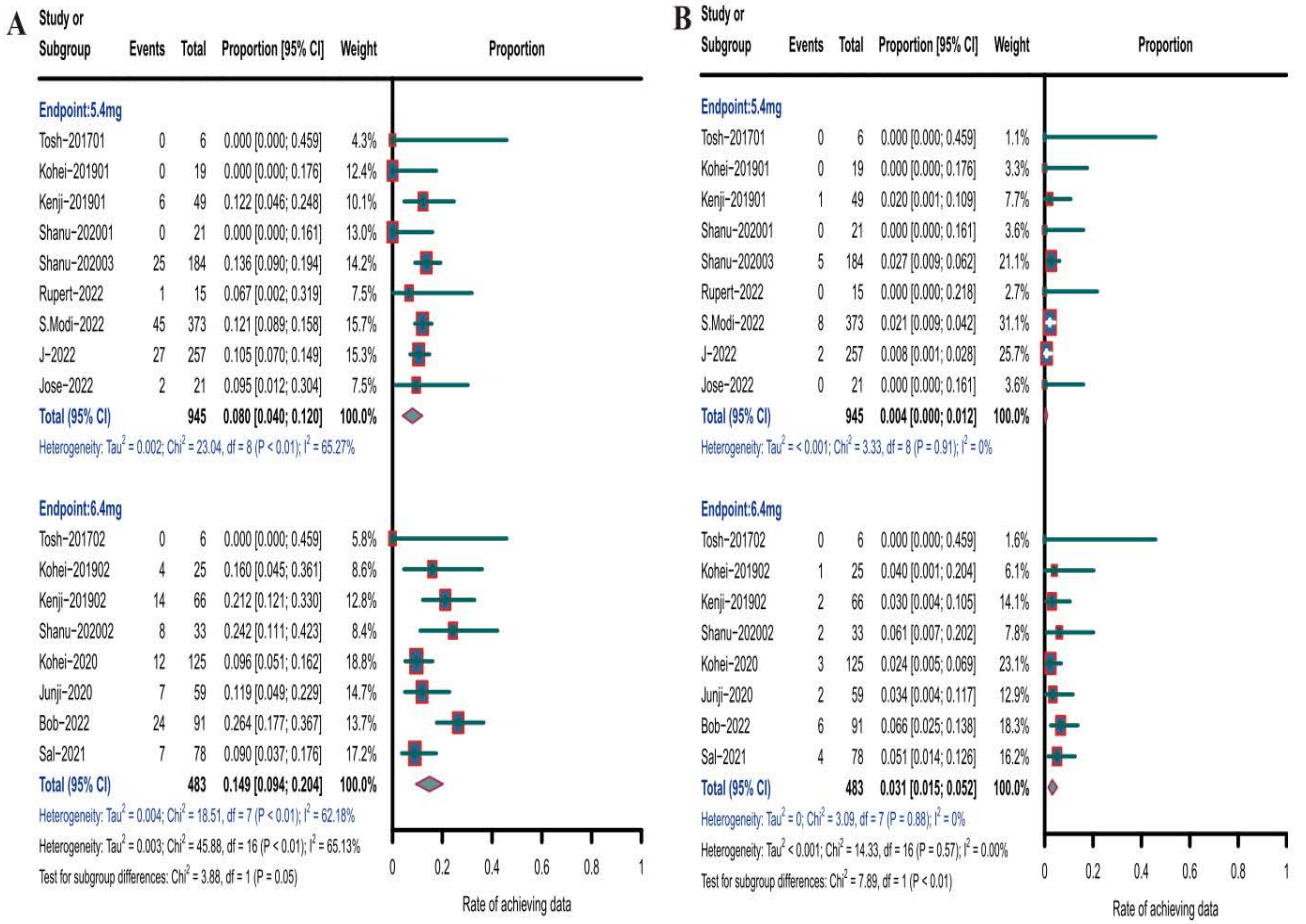
DESTINY-PanTumor01 Phase II Study of Trastuzumab deruxtecan: Efficacy in Activating *HER2* Mutated Cancers



Lee BT et al *Lancet Oncol* 2024

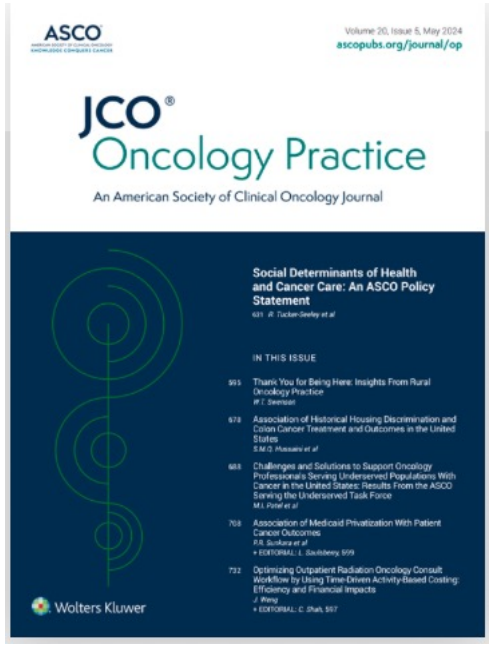
Trastuzumab deruxtecan and Interstitial Lung Disease

- Potential risk factors
  - Age
  - Enrollment in Japan
  - Dose
  - Oxygen saturation
  - Moderate/severe renal impairment
  - Lung comorbidities (other than lung cancer)
- Incidence ILD and/or pneumonitis higher for 6.4 vs 5.4 mg/kg dosage
  - All-grade: 14.9% vs. 8.0%
  - Grade≥3: 3.1% vs. 0.4%



Powell CA et al. *ESMO Open* 2022;7(4):100554.

Trastuzumab deruxtecan and Interstitial Lung Disease



Real-World Perspectives and Practices for Pneumonitis/Interstitial Lung Disease Associated With Trastuzumab Deruxtecan Use in Human Epidermal Growth Factor Receptor 2–Expressing Metastatic Breast Cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

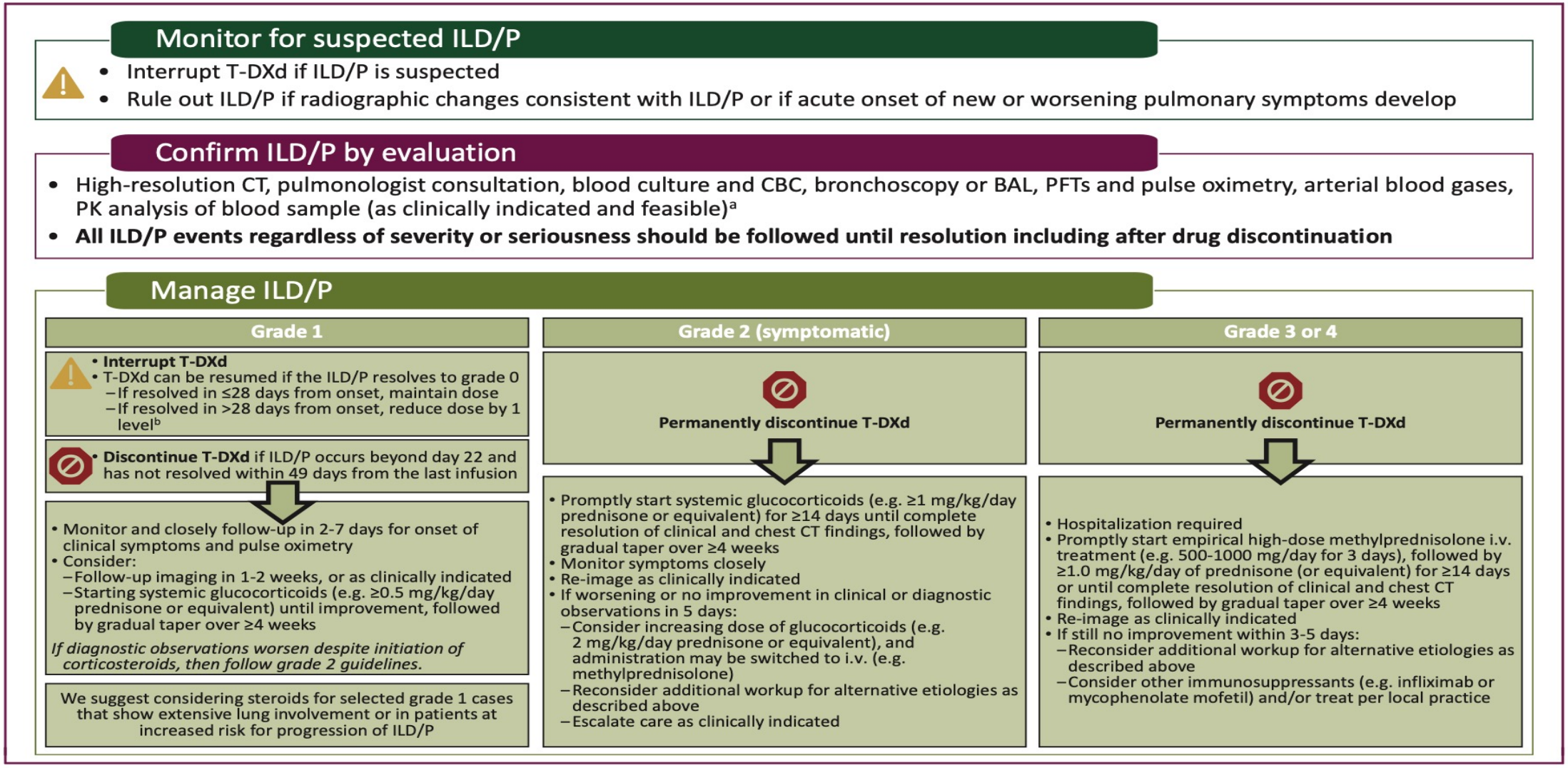
ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Optimizing treatment management of trastuzumab deruxtecan in clinical practice of breast cancer

Rugo HS et al *JCO Oncology Practice* 2023; Rugo HS et al *ESMO Open* 2022

Trastuzumab deruxtecan and Interstitial Lung Disease



Rugo HS et al *ESMO Open* 2022

NRG-GY026 Study Schema

Chemo-naïve, non-recurrent, stage I-IVB, HER2 positive endometrial serous carcinoma or carcinosarcoma

Randomization 1:1:1

Arm 1:
Paclitaxel/Carboplatin
every 3 weeks x 6 cycles

Arm 2:
Paclitaxel/Carboplatin/Trastuzumab and hyaluronidase-oysk every 3 weeks x 6 cycles

Maintenance Trastuzumab and hyaluronidase-oysk every 3 week for up to 1 year

Arm 3:
Paclitaxel/Carboplatin/Pertuzumab, Trastuzumab, and hyaluronidase-zzsf q 3 weeks x 6 cycles

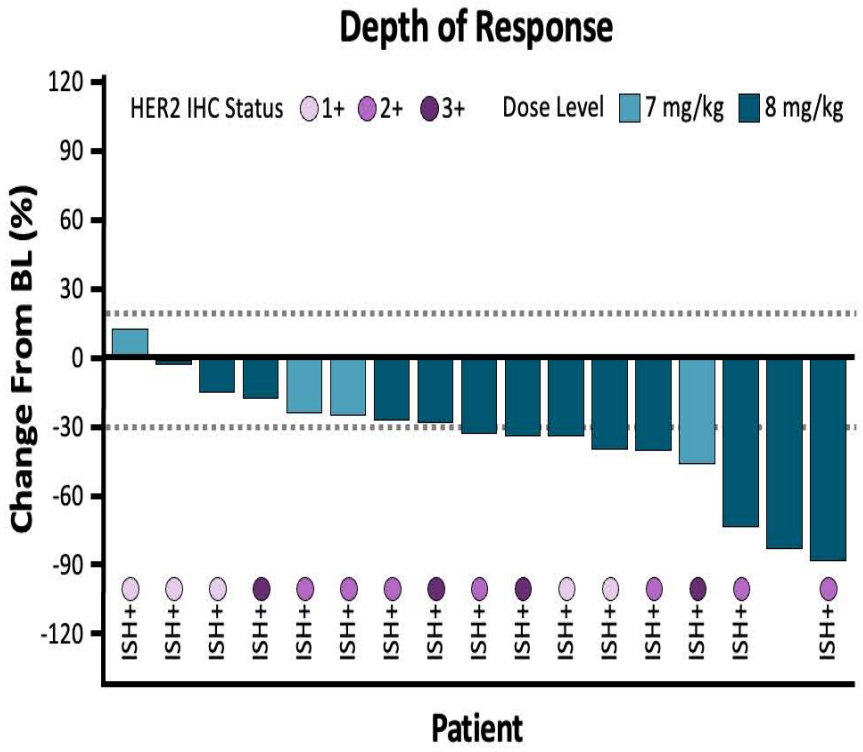
Maintenance Pertuzumab, Trastuzumab, and hyaluronidase-zzsf every 3 weeks for up to 1 year

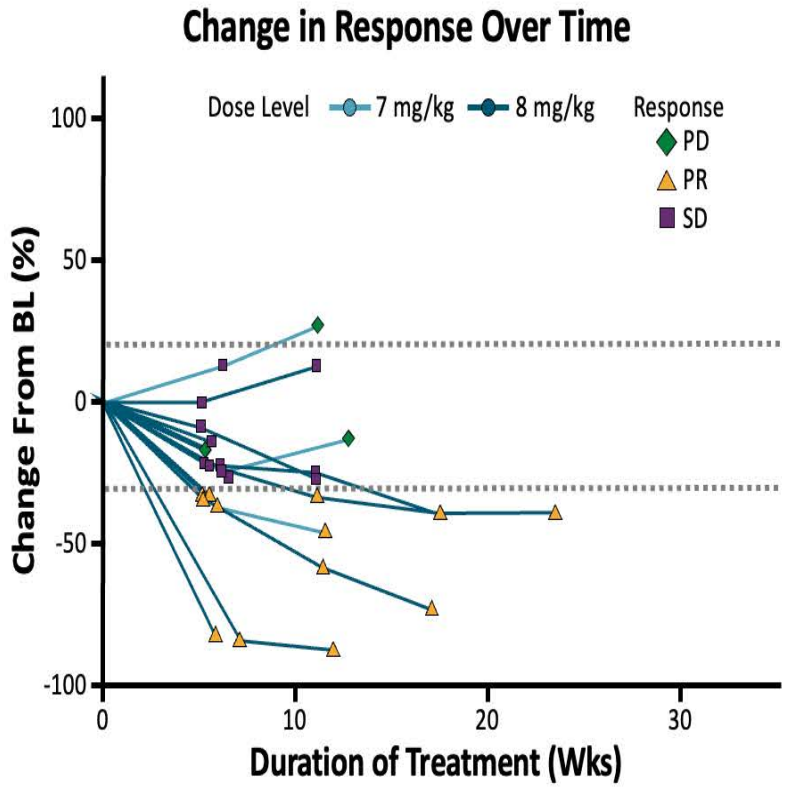
Stratification
- Stage I-II v. III-IV
- Histology (serous vs carcinosarcoma)
- Plan for vaginal brachytherapy (yes vs no)

Phase I/IIa of HER2-Targeting ADC (DB-1303) in Advanced Solid Tumors

Phase II: dose expansion cohorts

Cohort 2a: previous trastuzumab and HER2+ (IHC 3+,2+ and ISH-positive) gastric or GEJ adenocarcinoma, n = 30; HER2+ esophageal carcinoma, n = 10; and HER2+ CRC, n = 15
Cohort 2b: *HER2* overexpression + HER2-low EC* (UC+USC), n = 30 to 60
Cohort 2c: HR+/HER2-low (IHC 2+/ISH-negative, or 1+) BC, n = 30 to 50
Cohort 2d: HER2+ (IHC 3+, 2+/ISH-positive) BC, n = 20-40
Cohort 2e: NSCLC with activating *HER2* mutation, n = 15 to 30
Cohort 2f: HER2+ (n = 10) or HR+/HER2-low (n = 10) BC that failed previous treatment with trastuzumab deruxtecan (T-DXd)





Nineteen patients (59.4%) had prior IO; 17 patients were evaluable for response.
10 (58.8%) had PR (4 confirmed, and 6 requiring further confirmation). Overall DCR was 94.1%.

TEAEs occurred in 30 patients (93.8%); ≥G 3 in 10 patients (31.2%), hypokalaemia (12.5%), anemia (6.2%), and syncope (6.2%).
No ILD

Moore. K et al ESGO 2023. Abstr 430.

RTP Live from Chicago: Investigator Perspectives on Recent Advances and Challenging Questions in the Management of Colorectal Cancer

A CME-Accredited Virtual Event Held in Conjunction with the 2024 ASCO® Annual Meeting

Monday, June 3, 2024

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

Faculty

Scott Kopetz, MD, PhD

John Strickler, MD

Moderator

Neil Love, MD

RTP RESEARCH TO PRACTICE

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