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

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

Monday, March 18, 2024

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

Faculty

Nicoletta Colombo, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Faculty

Nicoletta Colombo, MD
Director, Gynecologic Oncology Program
European Institute of Oncology IRCCS
University of Milano-Bicocca
Milan, Italy

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

Matthew A Powell, MD
Professor, Department of Obstetrics and Gynecology
Washington University School of Medicine
St Louis, Missouri

Moderator
Shannon N Westin, MD, MPH, FASCO, FACOG
Professor
Medical Director, Gynecologic Oncology Center
Director, Early Drug Development
Department of Gynecologic Oncology and Reproductive Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

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Prof Colombo — Disclosures
Faculty

Advisory Committees	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GSK, ImmunoGen Inc, Merck, Mersana Therapeutics Inc, MSD, Novocure Inc, Nuvation Bio, OncXerna Therapeutics Inc, Pieris Pharmaceuticals Inc, Roche Laboratories Inc
Consulting Agreements	MSD, Roche Laboratories Inc
Contracted Research	AstraZeneca Pharmaceuticals LP, GSK
Speakers Bureaus	AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc, GSK, Merck, MSD

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Dr Powell — Disclosures
Faculty

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Eisai Inc, GSK, ImmunoGen Inc, Merck, Seagen Inc

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 Westin — Disclosures
Moderator

Consulting Agreements	AstraZeneca Pharmaceuticals LP, Caris Life Sciences, Clovis Oncology, Eisai Inc, EQRx, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Immunocore, ImmunoGen Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Mereo BioPharma, Mersana Therapeutics Inc, NGM Biopharmaceuticals, Nuvectis Pharma Inc, pharmaand GmbH, Seagen Inc, Verastem Inc, Vincerx Pharma, Zentalis Pharmaceuticals, ZielBio
Contracted Research	AstraZeneca Pharmaceuticals LP, Avenge Bio, Bayer HealthCare Pharmaceuticals, Bio-Path Holdings, Clovis Oncology, Genentech, a member of the Roche Group, GSK, Jazz Pharmaceuticals Inc, Mereo BioPharma, Novartis, Nuvectis Pharma Inc, pharmaand GmbH, Zentalis Pharmaceuticals

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Dr Backes — Disclosures
Video Participant

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

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Dr Salani — Disclosures
Video Participant

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

Commercial Support

This activity is supported by educational grants from AstraZeneca Pharmaceuticals LP, GSK, and Karyopharm Therapeutics.

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

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

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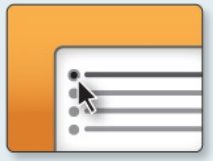
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the premeeting survey.

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

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

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

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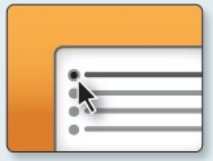
Clinicians Attending via Zoom

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



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

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

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

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About the Enduring Program

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

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JOIN US IN MARCH FOR THE RETURN OF

The Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, ACPE- and NCPD-Accredited Educational Conference Developed in Partnership with Florida Cancer Specialists & Research Institute

MARCH 22-24, 2024

JW Marriott Miami Turnberry

To Learn More or to Register, Visit
www.ResearchToPractice.com/Meetings/GMO2024

Third Annual **National General Medical Oncology Summit**

Friday, March 22, 2024

6:30 PM – 7:00 PM

Welcome Reception

7:00 PM – 9:00 PM

Keynote Session: ER-Positive Metastatic Breast Cancer

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Special Feature: Clinicians with Breast Cancer

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

7:30 AM – 9:10 AM

Hodgkin and Non-Hodgkin Lymphoma

Ann S LaCasce, MD, MMSc
Matthew Lunning, DO
Kami Maddocks, MD
Andrew D Zelenetz, MD, PhD

9:30 AM – 10:20 AM

Gynecologic Cancers

Bradley J Monk, MD
David M O'Malley, MD

10:20 AM – 11:10 AM

Localized Breast Cancer; SABCS 2023 Review

Virginia Kaklamani, MD, DSc
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD

11:10 AM – 12:00 PM

Metastatic Breast Cancer, Triple-Negative Breast Cancer, HER2-Positive Breast Cancer; SABCS 2023 Review

Erika Hamilton, MD
Virginia Kaklamani, MD, DSc
Hope S Rugo, MD

Third Annual **National General Medical Oncology Summit**

Saturday, March 23, 2024

12:30 PM – 1:20 PM

Prostate Cancer

Emmanuel S Antonarakis, MD
Rana R McKay, MD

1:20 PM – 2:10 PM

Urothelial Bladder Cancer

Matthew D Galsky, MD
Jonathan E Rosenberg, MD

2:10 PM – 3:00 PM

Renal Cell Carcinoma

Eric Jonasch, MD
Brian Rini, MD

3:20 PM – 4:10 PM

Targeted Therapy for Non-Small Cell Lung Cancer

Ibiayi Dagogo-Jack, MD
Helena Yu, MD

4:10 PM – 5:00 PM

Nontargeted Treatments for Lung Cancer

Edward B Garon, MD, MS
Corey J Langer, MD

Third Annual **National General Medical Oncology Summit**

Sunday, March 24, 2024

7:30 AM – 8:20 AM

Multiple Myeloma

Natalie S Callander, MD
Paul G Richardson, MD

8:20 AM – 9:10 AM

Gastroesophageal Cancers

Yelena Y Janjigian, MD
Samuel J Klempner, MD

9:30 AM – 10:20 AM

Hepatobiliary Cancers

Ghassan Abou-Alfa, MD, MBA
Richard S Finn, MD

10:20 AM – 11:10 AM

Colorectal Cancer

Kristen K Ciombor, MD, MSCI
John Strickler, MD

11:10 AM – 12:00 PM

Pancreatic Cancer

Andrew H Ko, MD
Eileen M O'Reilly, MD

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Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Agenda

Module 1: Current Approaches to First-Line Therapy for Advanced Endometrial Cancer (EC) — Prof Colombo

Module 2: Novel Investigational Strategies for Newly Diagnosed EC — Dr Westin

Module 3: Current Options for Relapsed/Refractory EC — Dr Slomovitz

Module 4: Role of HER2-Targeted Therapy in the Management of Advanced EC — Dr Powell

Consulting Faculty

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

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

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MODULE 1: Current Approaches to First-Line Therapy for Advanced Endometrial Cancer (EC) — Dr Colombo

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Consulting Faculty Questions

Perspective on current first-line treatment landscape; response to dostarlimab with chemotherapy in a p53 wild-type subgroup of patients

Neil Love, MD

Floor J Backes, MD

Ritu Salani, MD, MBA

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QUESTIONS FOR THE FACULTY

Floor J Backes, MD

What is your preferred first-line therapy for metastatic MSI-H/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?

Ritu Salani, MD, MBA

What is your preferred first-line therapy for metastatic MSS/pMMR EC? Are you any more inclined to use an anti-PD-1/PD-L1 antibody if the patient has p53-mutated disease?

Do you have a preferred anti-PD-1/PD-L1 antibody for patients with MSS/pMMR EC?

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Consulting Faculty Questions

Potential use of immunotherapy combined with chemotherapy in the adjuvant setting; management of EC with a POLE mutation

Neil Love, MD

Floor J Backes, MD

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QUESTIONS FOR THE FACULTY

Floor J Backes, MD

What is your preferred approach to the management of POLE-mutated EC 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 setting to be positive?

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

What is your usual first-line therapy for a patient with MSS/pMMR metastatic EC? In general, do you prefer a specific anti-PD-1/PD-L1 antibody in this setting?

	First-line treatment	Anti-PD-1/PD-L1 antibody preference
 Prof Colombo	Carboplatin/paclitaxel	I would not offer an anti-PD-1/PD-L1 antibody in the above setting
 Dr Powell	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	Yes, pembrolizumab or dostarlimab
 Dr Slomovitz	Carboplatin/paclitaxel + pembrolizumab	Yes, pembrolizumab
 Dr Westin	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	No preference
 Dr Backes	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	No preference
 Dr Salani	Carboplatin/paclitaxel	I would not offer an anti-PD-1/PD-L1 antibody in the above setting

MSS = microsatellite stable; pMMR = mismatch repair proficient

What is your usual first-line therapy for a patient with MSI-high/dMMR metastatic EC? In general, do you prefer a specific anti-PD-1/PD-L1 antibody in this setting?

	First-line treatment	Anti-PD-1/PD-L1 antibody preference
 Prof Colombo	Carboplatin/paclitaxel + anti-PD-1/PD-L1 antibody*	No preference
 Dr Powell	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	Yes, pembrolizumab or dostarlimab
 Dr Slomovitz	Carboplatin/paclitaxel + pembrolizumab	Yes, pembrolizumab
 Dr Westin	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	No preference
 Dr Backes	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	No preference
 Dr Salani	Carboplatin/paclitaxel + dostarlimab	No preference

MSI = microsatellite instability; dMMR = mismatch repair deficient
*Pembrolizumab, dostarlimab or atezolizumab

Which adjuvant systemic treatment, if any, would you recommend for a patient with localized EC who has undergone hysterectomy and has 2 positive lymph nodes whose disease is …?

	MSS/pMMR	MSI high/dMMR
 Prof Colombo	Carboplatin/paclitaxel + radiation therapy	Carboplatin/paclitaxel + anti PD-1/PD-L1 antibody*
 Dr Powell	Carboplatin/paclitaxel	Carboplatin/paclitaxel ± either pembrolizumab or dostarlimab
 Dr Slomovitz	Carboplatin/paclitaxel + pembrolizumab	Carboplatin/paclitaxel + pembrolizumab
 Dr Westin	Carboplatin/paclitaxel	Carboplatin/paclitaxel
 Dr Backes	Carboplatin/paclitaxel	Carboplatin/paclitaxel
 Dr Salani	Carboplatin/paclitaxel ± either pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

*Pembrolizumab, dostarlimab or atezolizumab

Which “adjuvant” systemic treatment, if any, would you recommend for a patient with EC who has undergone hysterectomy and is found to have 1 isolated lung metastasis that is resected whose disease is …?

	MSS/pMMR	MSI-high/dMMR
 Prof Colombo	Carboplatin/paclitaxel	Carboplatin/paclitaxel + anti PD-1/PD-L1 antibody*
 Dr Powell	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Slomovitz	Carboplatin/paclitaxel + pembrolizumab	Carboplatin/paclitaxel + pembrolizumab
 Dr Westin	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Backes	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Salani	Carboplatin/paclitaxel ± either pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

*Pembrolizumab, dostarlimab or atezolizumab

Current Approaches to First-Line Therapy for Advanced Endometrial Cancer (EC)

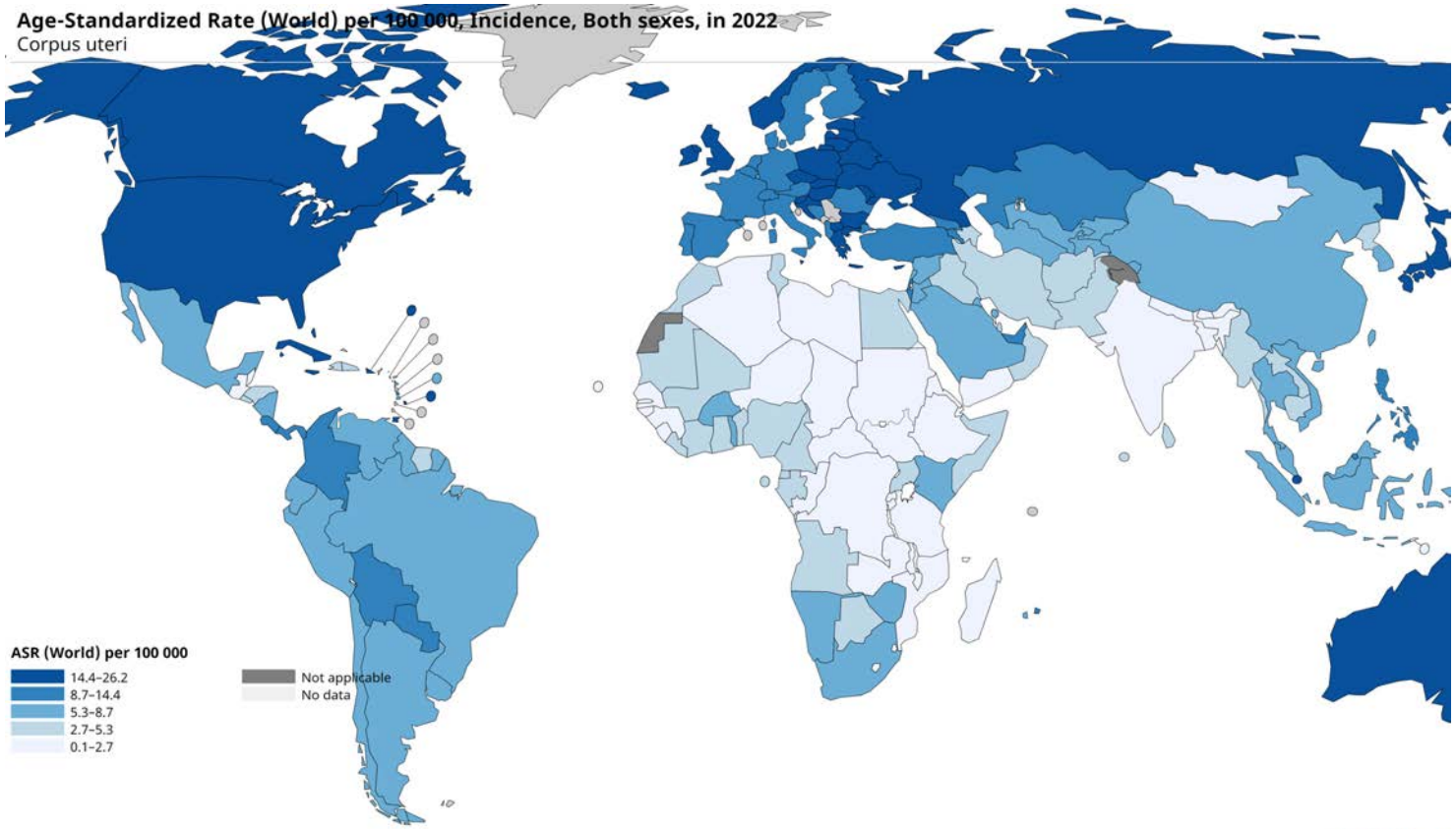
Nicoletta Colombo
University Milano-Bicocca
European Institute of Oncology, Milan, Italy

Endometrial Cancer 2023

The only Gynecologic Cancer with rising incidence and mortality

Incidence		
Rank	Cases	ASR (World)
15	420 368	8.4

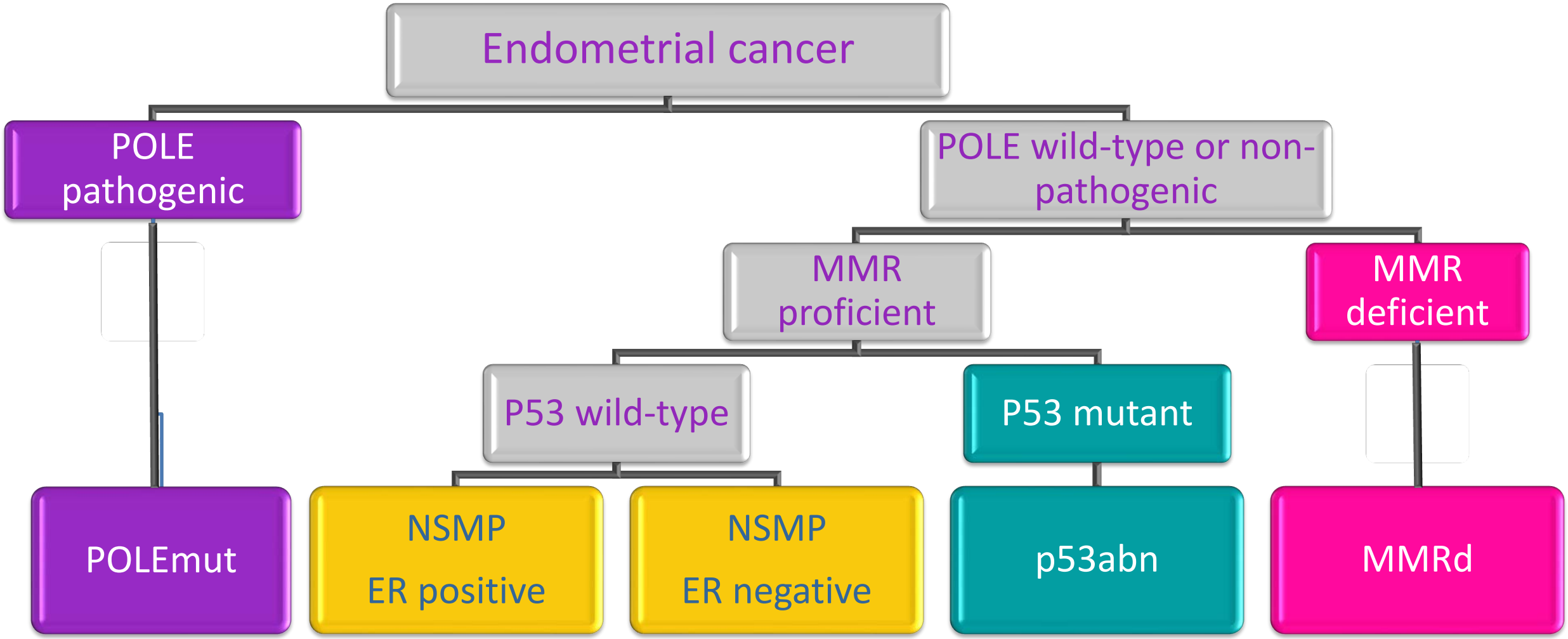
Mortality		
Rank	Deaths	ASR (World)
19	97 723	1.7



Cancer TODAY | IARC
https://gco.iarc.who.int/today
Data version: Globocan 2022 - 08.02.2024

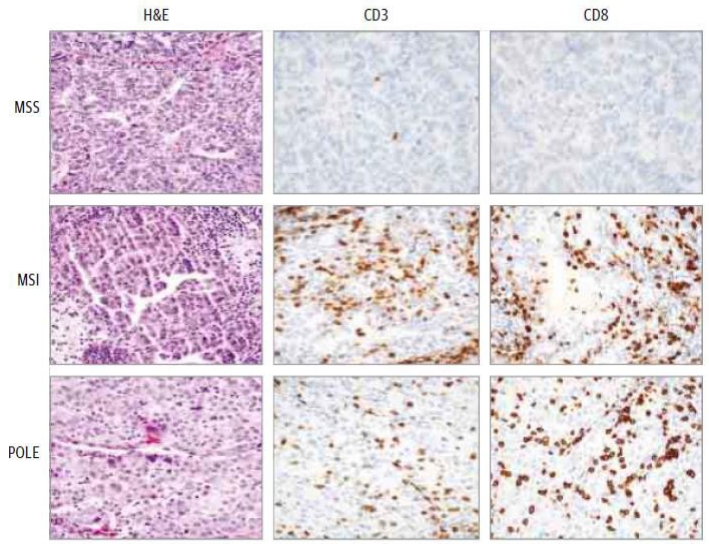
International Agency for Research on Cancer
World Health Organization

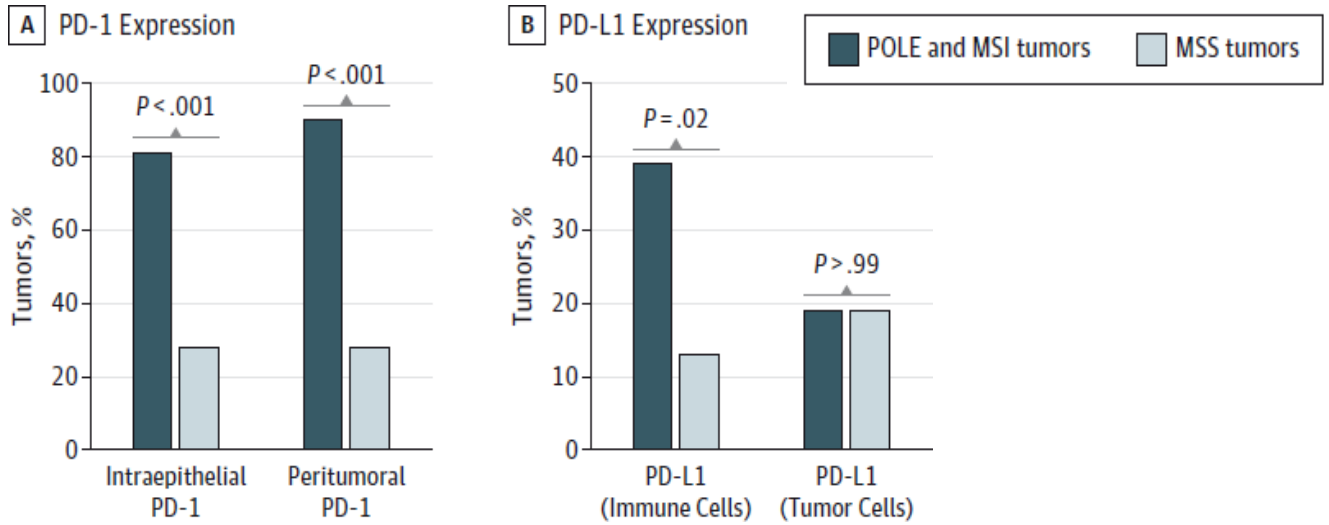
Molecular classification of endometrial cancer: FIGO staging 2023
Prognostic, risk assessment, predictive, genetic screening

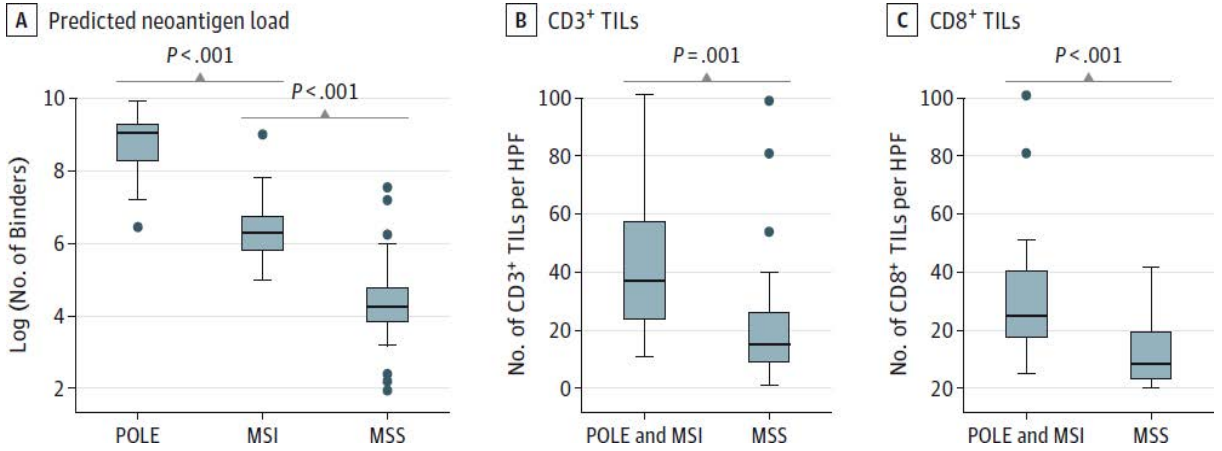


Vermij et al., British Journal of Cancer (2023) 128:1360 – 1368

MSI-high and POLE mutated Endometrial Cancers display increased Neoantigen load, more TILs, and higher PD1/PD-L1 Expression: Great benefit from ICIs!!

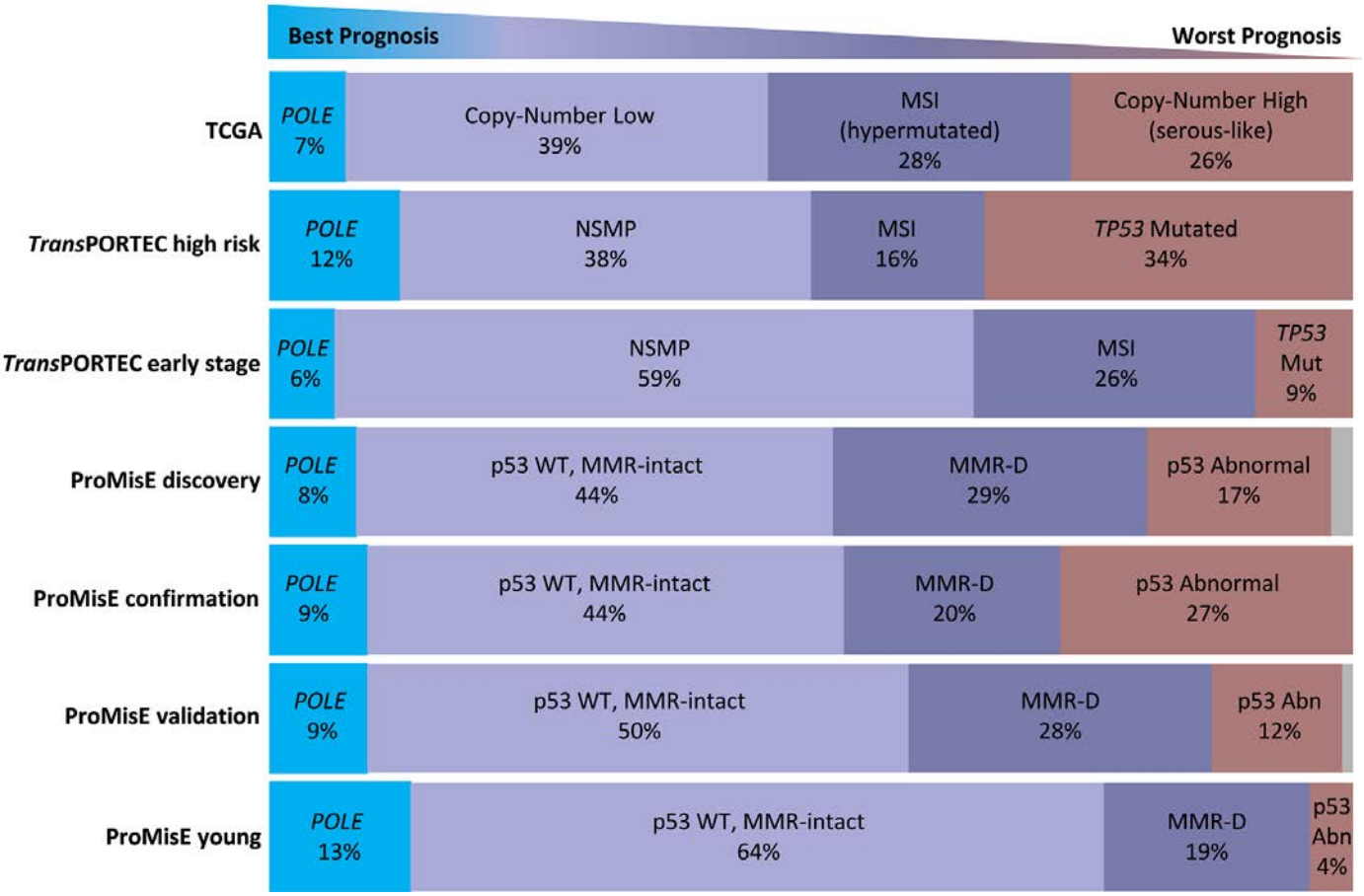


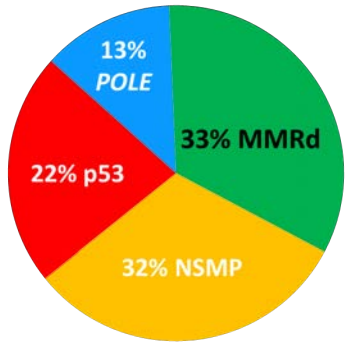




Howitt BE, Konstantinopoulos PA. Association of Polymerase e-Mutated and Microsatellite-Instable Endometrial Cancers With Neoantigen Load, Number of Tumor-Infiltrating Lymphocytes, and Expression of PD-1 and PD-L1. JAMA Oncol. 2015 Dec;1(9):1319-23

How many endometrial cancers are dMMR?





PORTEC-3 HR-EC trial N=410

Germline mutation mismatch repair proteins (Lynch Syndrome)

Somatic mutation mismatch repair proteins

Epigenetic loss (*MLH1, MSH2*)

~ 75% all dMMR

Stelloo et al, CCR 2016

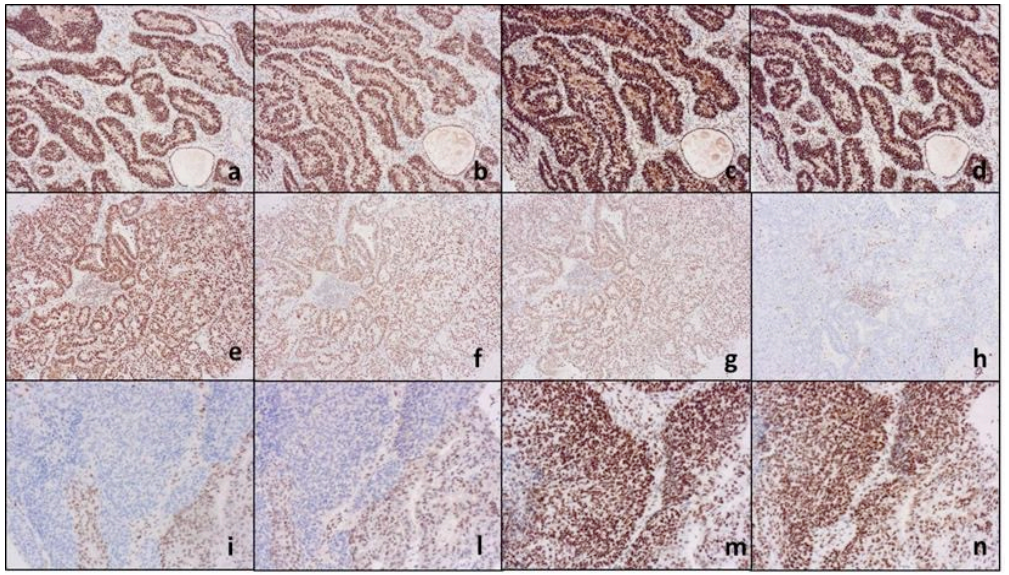
Leon-Castillo et al, J Pathol 2020

Urick ME, Bell DW. Nat Rev Cancer. 2019 Sep;19(9):510-521.

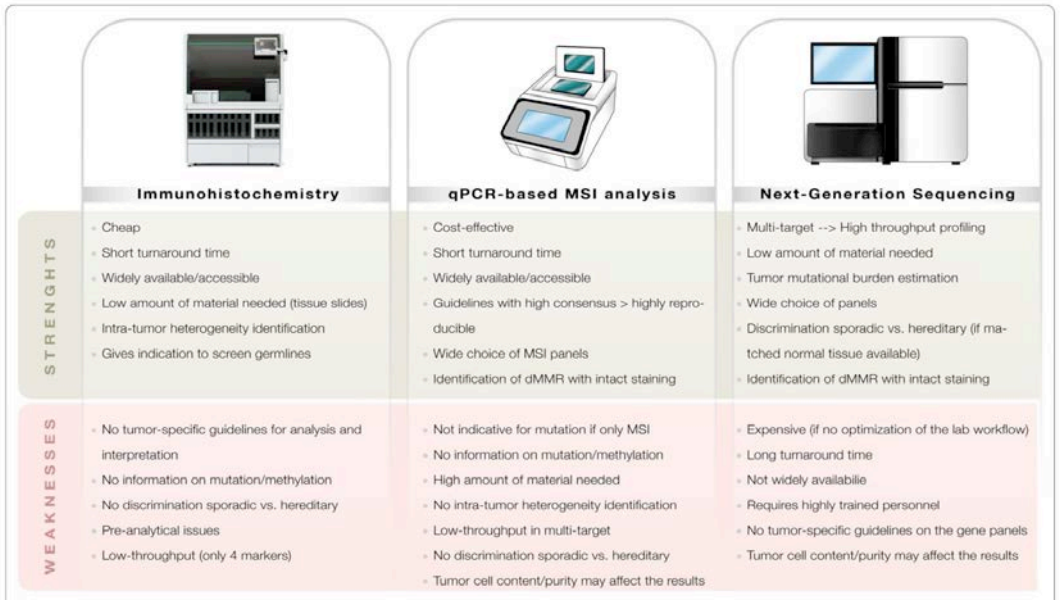
How to test ?

MMR/MSI TESTING: HOW

- The first test of choice is IHC for the four MMR proteins
- Widely available/accessible
- Relatively cheap
- Short turnaround time
- Low amount of material required
- Higher sensitivity (for MSH6 mutation)
- Identification of defective protein/gene
- Identification of intra-tumor heterogeneity
- In case of doubt of IHC, confirmatory molecular analysis is mandatory



MLH1 PMS2 MSH2 MSH6



asco special articles

Mismatch Repair and Microsatellite Instability Testing for Immune Checkpoint Inhibitor Therapy: ASCO Endorsement of College of American Pathologists Guideline

Praveen Vikas, MD[1]; Hans Messersmith, MPH[2]; Carolyn Compton, MD, PhD[3]; Lynette Sholl, MD[4]; Russell R. Broaddus, MD[5]; Anjee Davis, MPPA[6]; Maria Estevez-Diz, MD, PhD[7]; Rohan Garje, MD[8]; Panagiotis A. Konstantinopoulos, MD[9]; Aliza Leiser, MD[10]; Anne M. Mills, MD[11]; Barbara Norquist, MD[12]; Michael J. Overman, MD[13]; Davendra Sohal, MD[14]; Richard C. Turkington, MD, PhD[15]; and Tyler Johnson, MD[16]

Vikas P, et al. J Clin Oncol. 2023 Apr1;41(10):1943-1948.

Phase III trials of chemotherapy and ICIs in endometrial Cancer

NRG-GY018/KEYNOTE-868 (NCT03914612)

Key Eligibility Criteria
- Measurable stage III/IVA or measurable/nonmeasurable stage IVB or recurrent endometrial cancer
- Pathology report showing results of institutional MMR IHC testing
- ECOG PS 0, 1, or 2
- No prior chemo except prior adjuvant chemo if completed ≥12 mo before study

N = 816 (591 pMMR, 225 dMMR)

R 1:1

Arm 1
Placebo IV Q3W + Paclitaxel 175 mg/m² IV Q3W + Carboplatin AUC 5 IV Q3W
for 6 cycles

Arm 1
Placebo IV Q6W
for up to 14 additional cycles

Arm 2
Pembrolizumab 200 mg IV Q3W + Paclitaxel 175 mg/m² IV Q3W + Carboplatin AUC 5 IV Q3W
for 6 cycles

Arm 2
Pembrolizumab 400 mg IV Q6W
for up to 14 additional cycles

Stratification Factors
- dMMR vs pMMR
- ECOG PS (0 or 1 vs 2)
- Prior adjuvant chemo (yes vs no)

Endpoints
- **Primary:** PFS per RECIST v1.1 by investigator in pMMR and dMMR populations
- **Secondary:** Safety, ORR/DOR per RECIST v1.1 by BICR or investigator by treatment arm and MMR IHC status, OS in pMMR and dMMR populations, PRO/QoL in pMMR population, and concordance of institutional vs central MMR IHC testing results

BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient; PRO, patient-reported outcomes; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

ENGOT-EN6-NSGO/GOG-3031/RUBY (NCT03981796)

Phase 3, randomized, double-blind, multicenter study of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin/paclitaxel in patients with primary advanced or recurrent EC

Eligible patients
- Histologically/cytologically proven advanced or recurrent EC
- Stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination
  - Carcinosarcoma, clear cell, serous, or mixed histology permitted[a]
- Naïve to systemic therapy or systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment
- ECOG PS 0-1
- Adequate organ function

Stratification
- MMR/MSI status[b]
- Prior external pelvic radiotherapy
- Disease status

R1:1

Dostarlimab IV 500 mg Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m² Q3W for 6 cycles → **Dostarlimab IV 1000 mg** Q6W up to 3 years[c]

Placebo Carboplatin AUC 5 mg/mL/min Paclitaxel 175 mg/m² Q3W for 6 cycles → **Placebo IV** Q6W up to 3 years[c]

Follow -up

Primary endpoint
- PFS by INV
- OS

Secondary endpoints
- PFS by BICR
- PFS2
- ORR
- DOR
- DCR
- HRQOL/PRO
- Safety

On-study imaging assessments are to be performed Q6W (±7 days) from the randomization date until Week 25 (Cycle 8), followed by Q9W (±7 days) until Week 52. Subsequent tumor imaging is to be performed every 12 weeks (±7 days) until radiographic PD is documented by investigator assessment per RECIST v1.1 followed by one additional imaging 4-6 weeks later, or subsequent anticancer therapy is started, whichever occurs first. Thereafter, scans may be performed per standard of care.
[a]Mixed histology containing at least 10% carcinosarcoma, clear cell, or serous histology. [b]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [c]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the Sponsor and the investigator. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response. EC, endometrial cancer; IV, administered intravenously; INV, investigator assessment; MMR, mismatch repair; MSI, microsatellite instability; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome.

ENGOT-EN6-NSGO/GOG-3031/RUBY presented by Mansoor R Mirza

Scan for slides

AtTEnd Study Design

- Endometrial carcinoma or carcinosarcoma
- Patients with advanced (stage III-IV) newly diagnosed or recurrent disease with no prior systemic chemotherapy for recurrence.
- In recurrent patients, one prior line of systemic platinum-based regimen is permitted with a platinum-free interval ≥ 6 months.
- ECOG 0-2
- Normal organ and bone marrow function

R 2:1

Paclitaxel 175mg/m² carboplatin AUC 5 or 6 atezolizumab 1200mg → Maintenance atezolizumab 1200mg

Paclitaxel 175mg/m² carboplatin AUC 5 or 6 placebo → Maintenance placebo

Confirmed PD

Stratified by:
- Country
- Endometrioid vs. other histotypes
- Recurrent disease vs newly diagnosed
- pMMR vs dMMR vs non evaluable *(centrally evaluated)*

Endpoints

Hierarchical order

PFS dMMR	IF POSITIVE	PFS All comers	IF POSITIVE	OS* All comers
α (two-sided) 4%	α=4%	α (two-sided) 4%	α=4%	α (two-sided) 5%
HR: 0.5		HR: 0.7		HR: 0.7

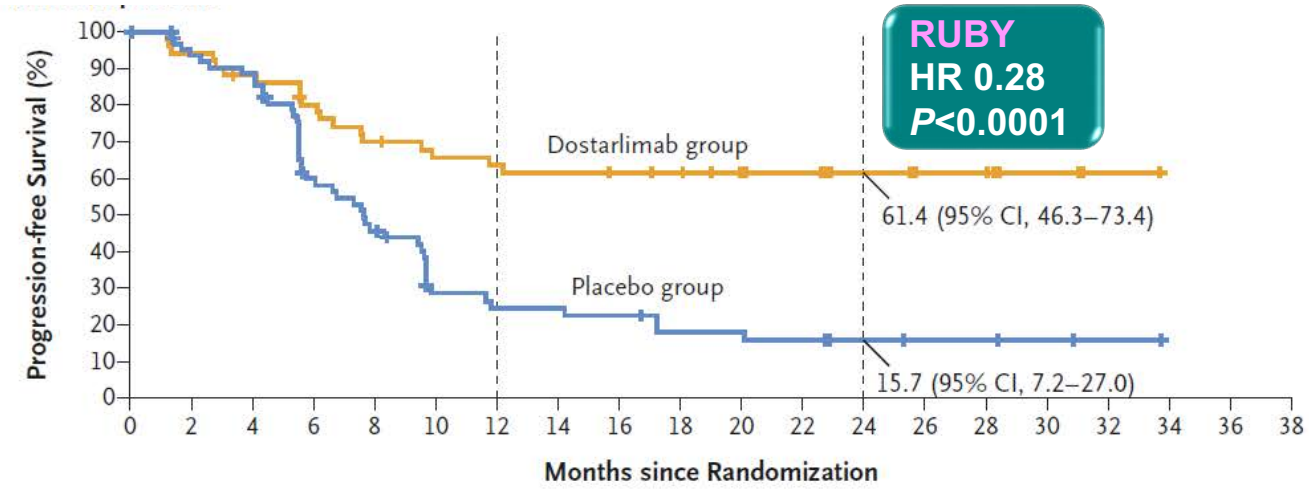
ECOG: Eastern Cooperative Oncology Group. pMMR: mismatch repair proficient. dMMR: mismatch repair deficient. AUC: area under the curve. PD: progressive disease. PFS: Progression free survival. OS: overall survival. HR: hazard ratio.

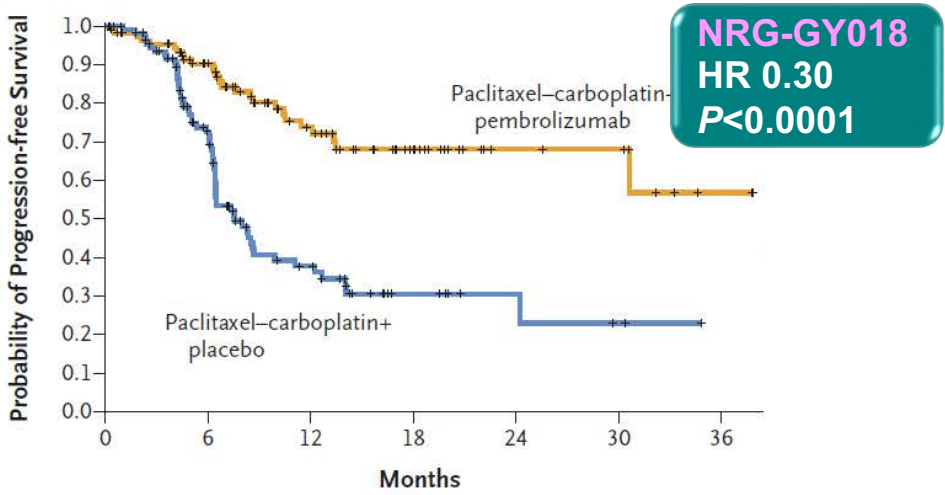
*OS interim analysis planned with a 63% power

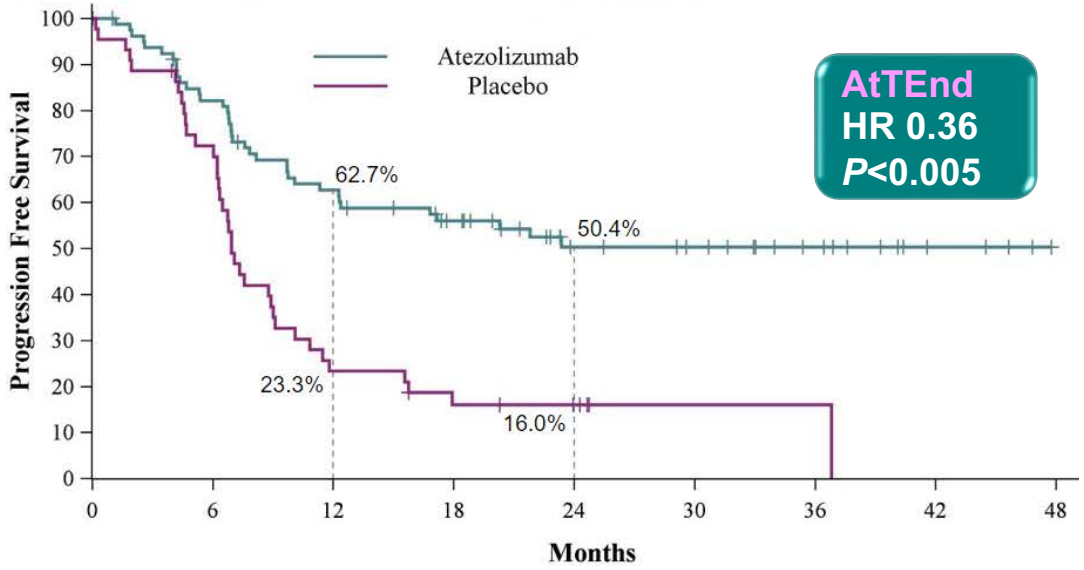
Nicoletta Colombo, MD

First-line Phase III trials	RUBY Dostarlimab	GY018 pembrolizumab	AtTEnd Atezolizumab
Patients d-MMR	494 91 (22.75%)	816 225 (27.6%)	549 125 (22.8%)
Asian population	3%	4%	**20%**
Primary Stage III Primary Stage IV Recurrent	**92 (18.6%)** 166 (33.6%) **236 (47.8)**	NR	**31 (5.6%)** 148 (26.9%) **369 (67.2%)**
Carcinosarcoma	**10%**	**NO**	**9%**
Non-endometrioid histology	45%	20%	34%
Time since completion of adjvant CT	≥6 months	≥ 12 months	≥ 6 months
Median follow up	**24.5 months**	**12 (dMMR)** **7.9 (pMMR)**	**28.3 months**
Duration of treatment	3 years	2 years	Until PD
Randomization	1:1	1:1	1:2
Statistical design	Hierarchical PFS dMMR-all comers **OS all comers**	dMMR pMMR PFS	Hierarchical PFS dMMR-all comers **OS all comers**

Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in dMMR Tumors



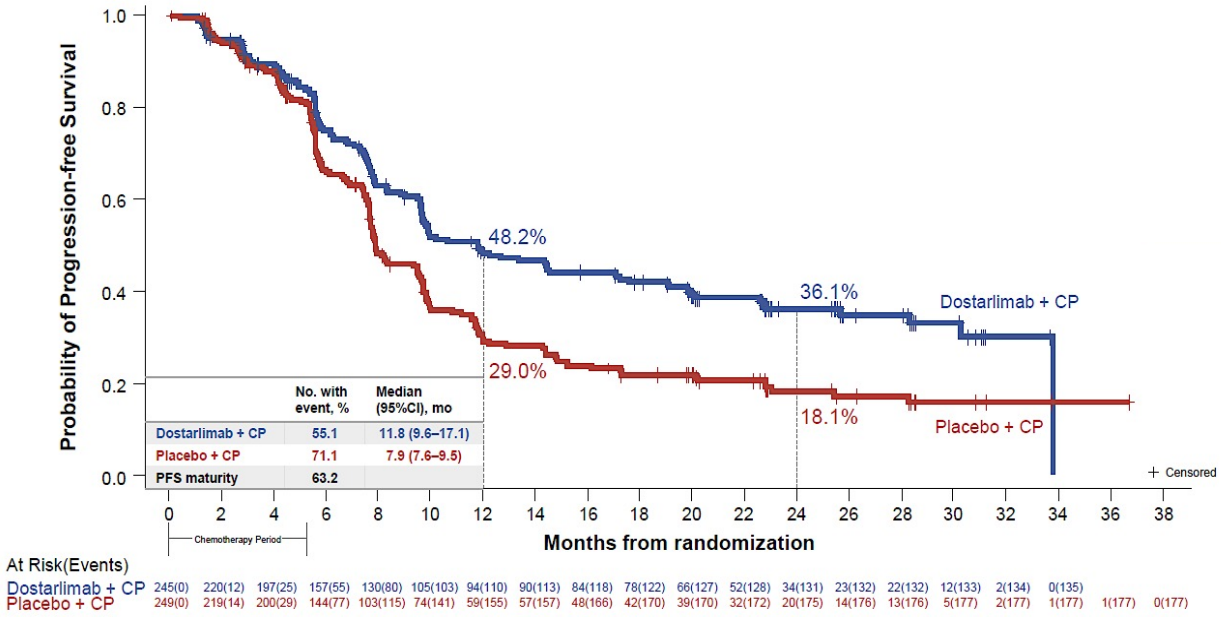




Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Nicoletta Colombo et al., ESMO 2023

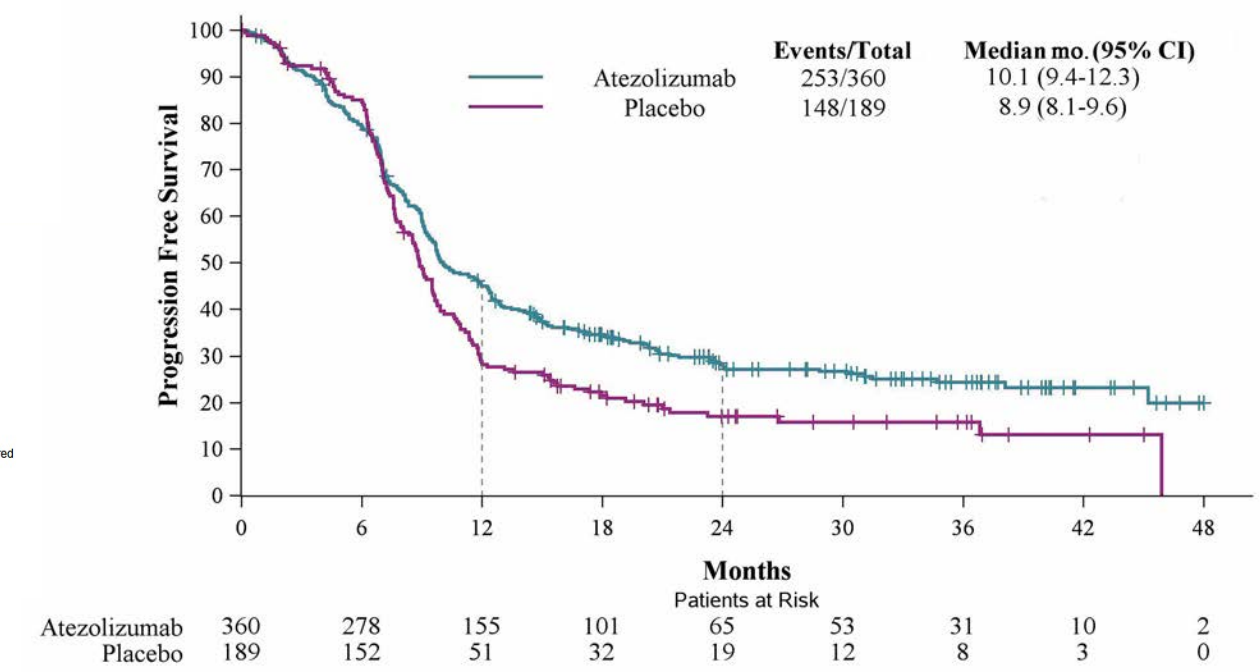
RUBY and AtTEnd
Primary endpoint: PFS in all comers

RUBY: all comers



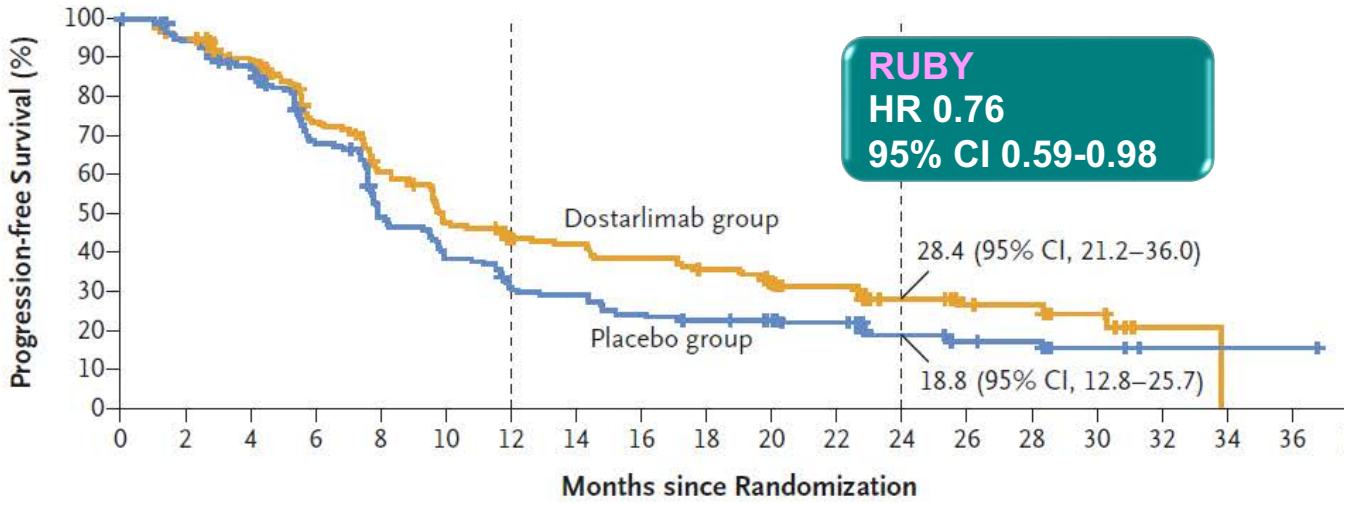
Logrank test
P<0.0001
HR 0.64
95%CI 0.507 to 0.800

AtTEnd: all comers

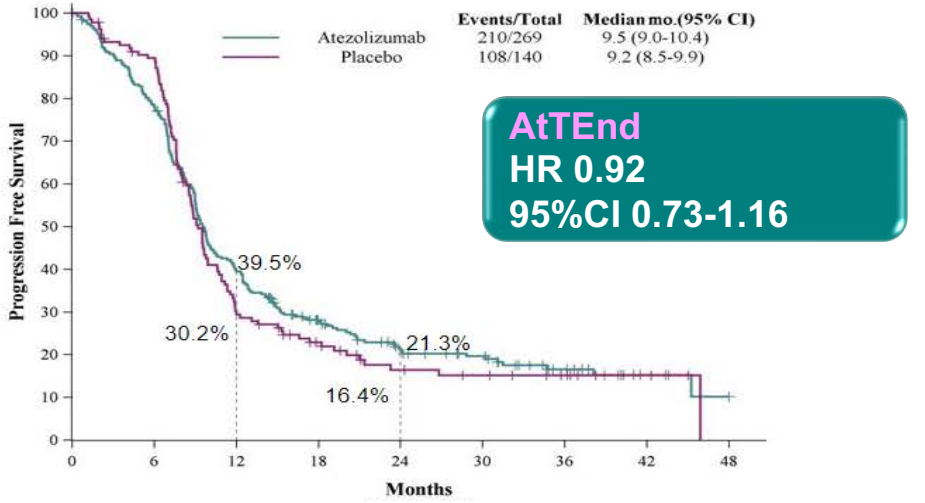


Logrank test
p=0.0219
HR 0.74
95%CI 0.61 to 0.91

Immune Checkpoint Inhibitor plus Chemotherapy in First-line Endometrial Cancer: PFS in pMMR Tumors

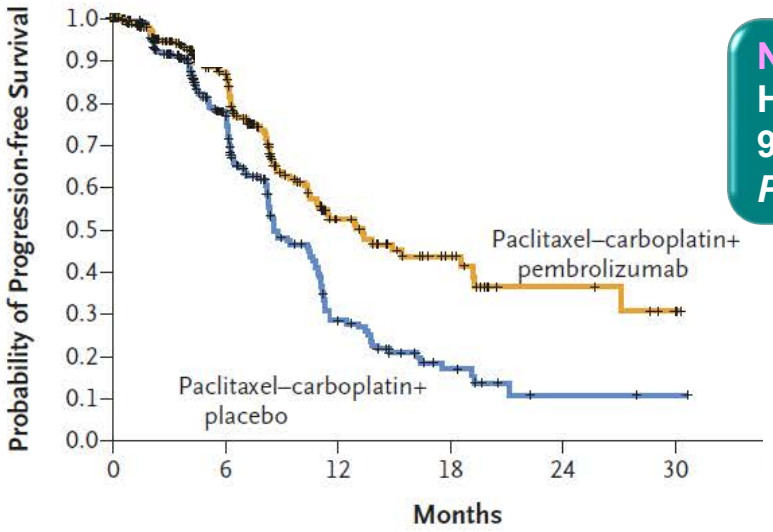


RUBY
HR 0.76
95% CI 0.59-0.98



AtTEnd
HR 0.92
95%CI 0.73-1.16

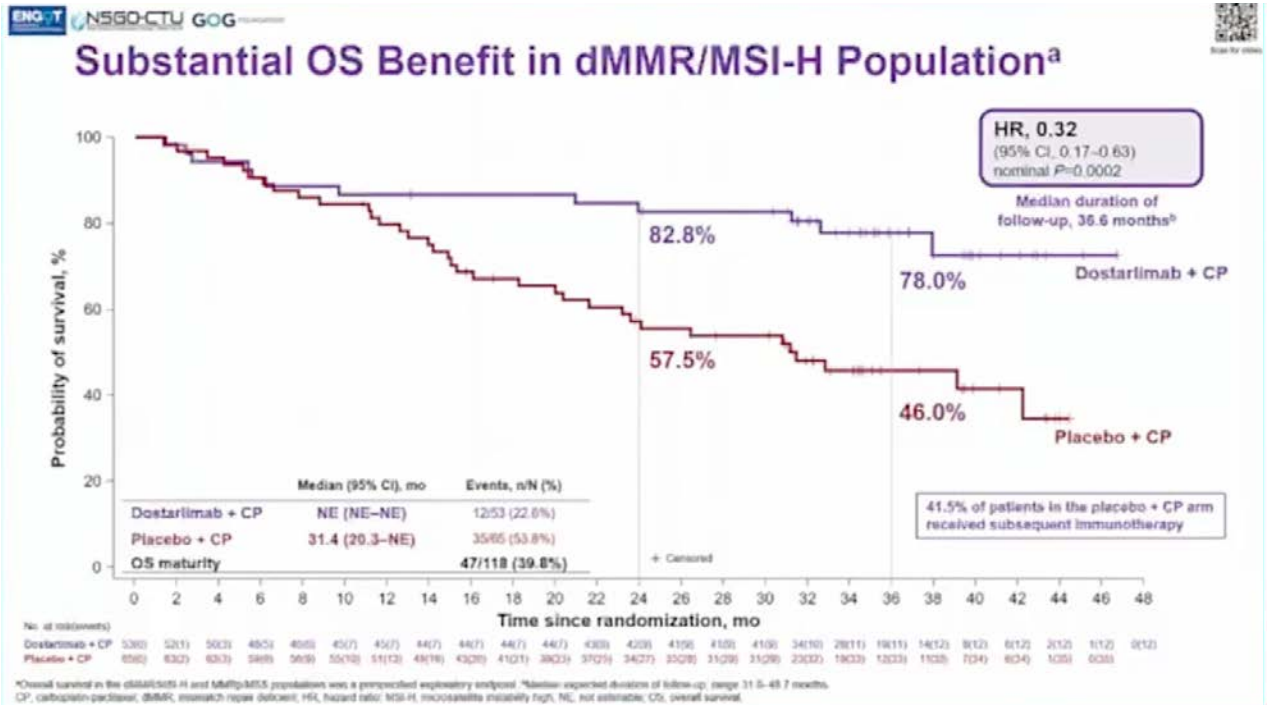
GY018 only study powered to examine the pMMR cohort independently

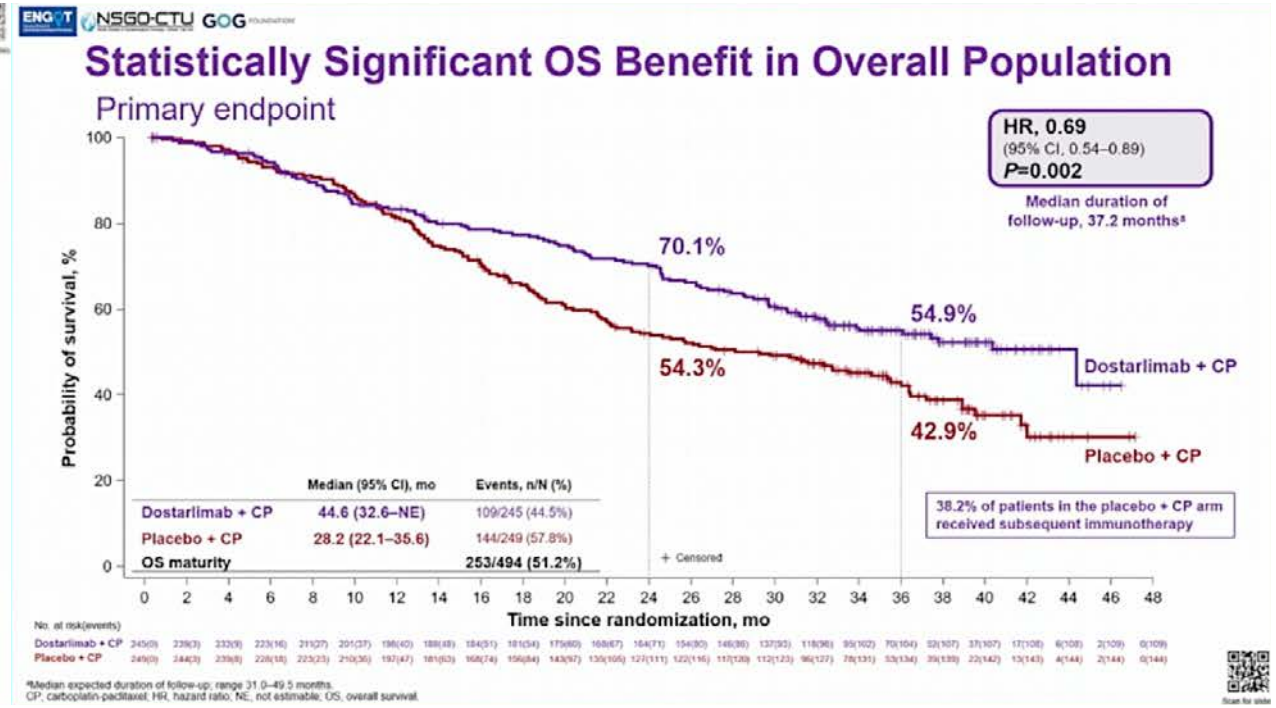


NRG-GY018
HR 0.54
95% CI 0.41-0.71
***P*<0.0001**

Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Nicoletta Colombo et al., ESMO 2023

GOG-3031/RUBY: Updated OS Outcomes





OS in dMMR/MSI-H
HR=0.32 (95% CI: 0.17-0.63)
P=0.0002

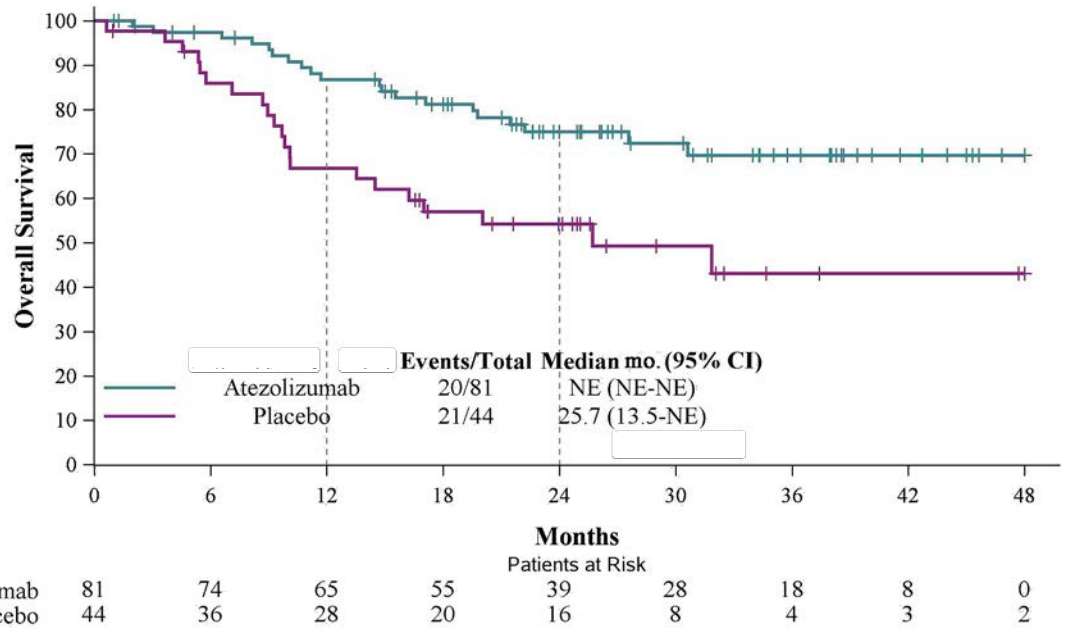
Received subsequent immunotherapy:
- ~40% of patients on placebo arm

OS in Overall Population
HR=0.69 (95% CI: 0.54-0.89)
P=0.002

Powell M et al. Presented at SGO 2024.

AtTEnd: Overall survival in all comers and d-MMR

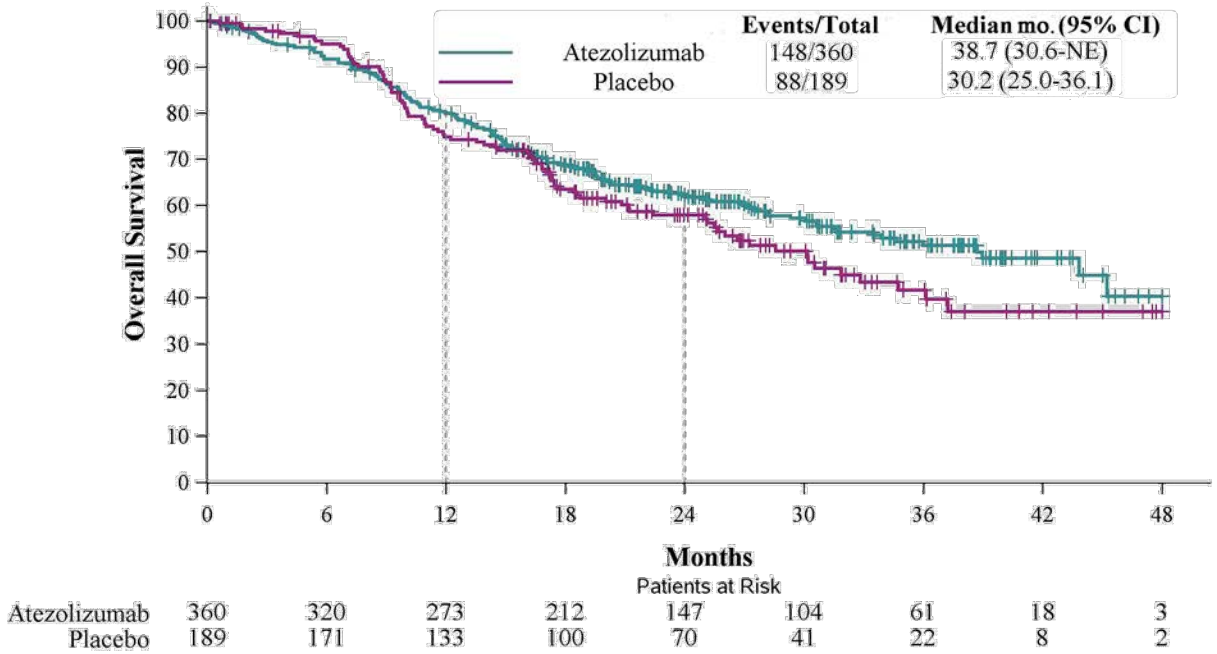
OS in dMMR/MSI-H Population



HR=0.41 (95% CI: 0.22-0.76)

Received subsequent immunotherapy:
- 40.9% of patients on placebo arm
- 6.2% of patients on dostarlimab arm

OS in Overall Population (43% Maturity)



HR=0.82 (95% CI: 0.63-1.07)
P=0.0483[a]

Received subsequent immunotherapy:
- 24.3% of patients on placebo arm
- 9% of patients on atezolizumab arm

N.Colombo ESMO 2023

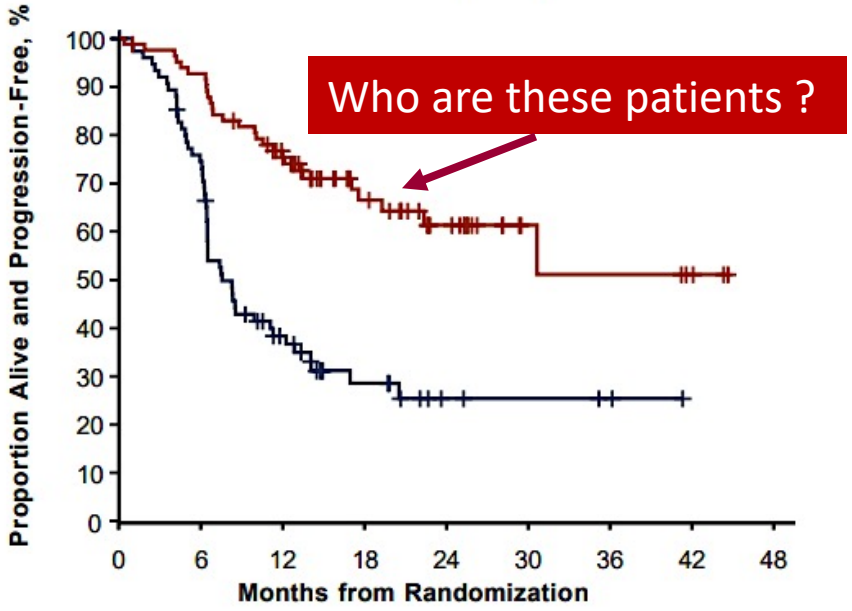
[a] *P*≤0.024 required to declare statistical significance at first interim analysis.

Will Chemotherapy + ICIs replace chemotherapy alone also in p-MMR?
How to select the good p-MMR and the bad d-MMR?

NRG-GY018: Outcome by Methylation Status in dMMR

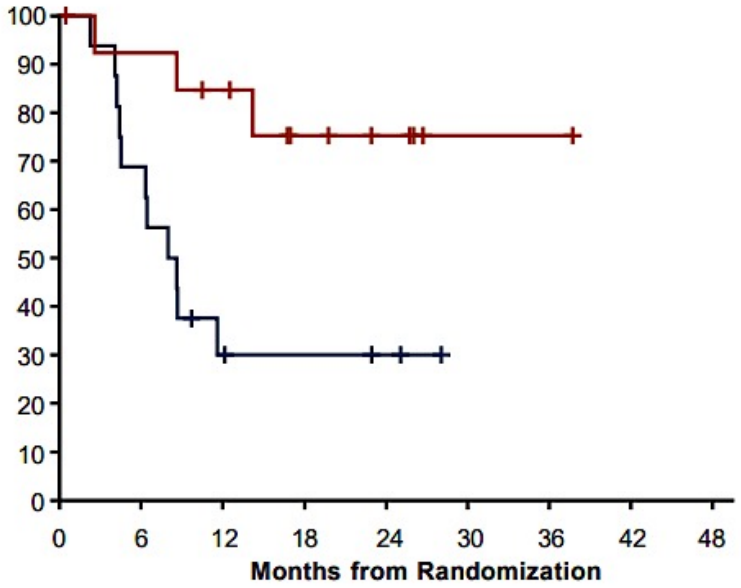
Methylation
Pembro + CP vs Placebo + CP

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



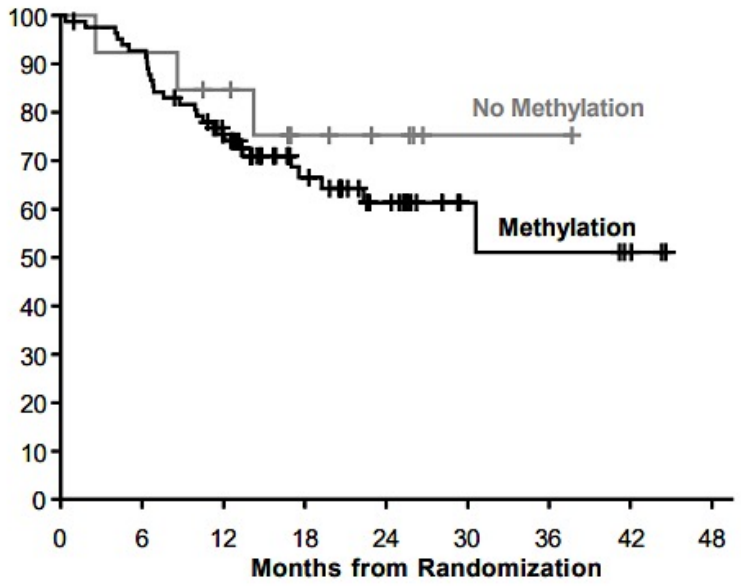
No Methylation
Pembro + CP vs Placebo + CP

	Events n/N	Median (95% CI), mo	HR (95% CI)
Placebo + CP	11/17	8.3 (4.4–NR)	0.263 (0.07–0.99) *P* = 0.0172
Pembro + CP	3/13	NR (14.2–NR)	



Methylation Status
Pembro + CP Arm

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



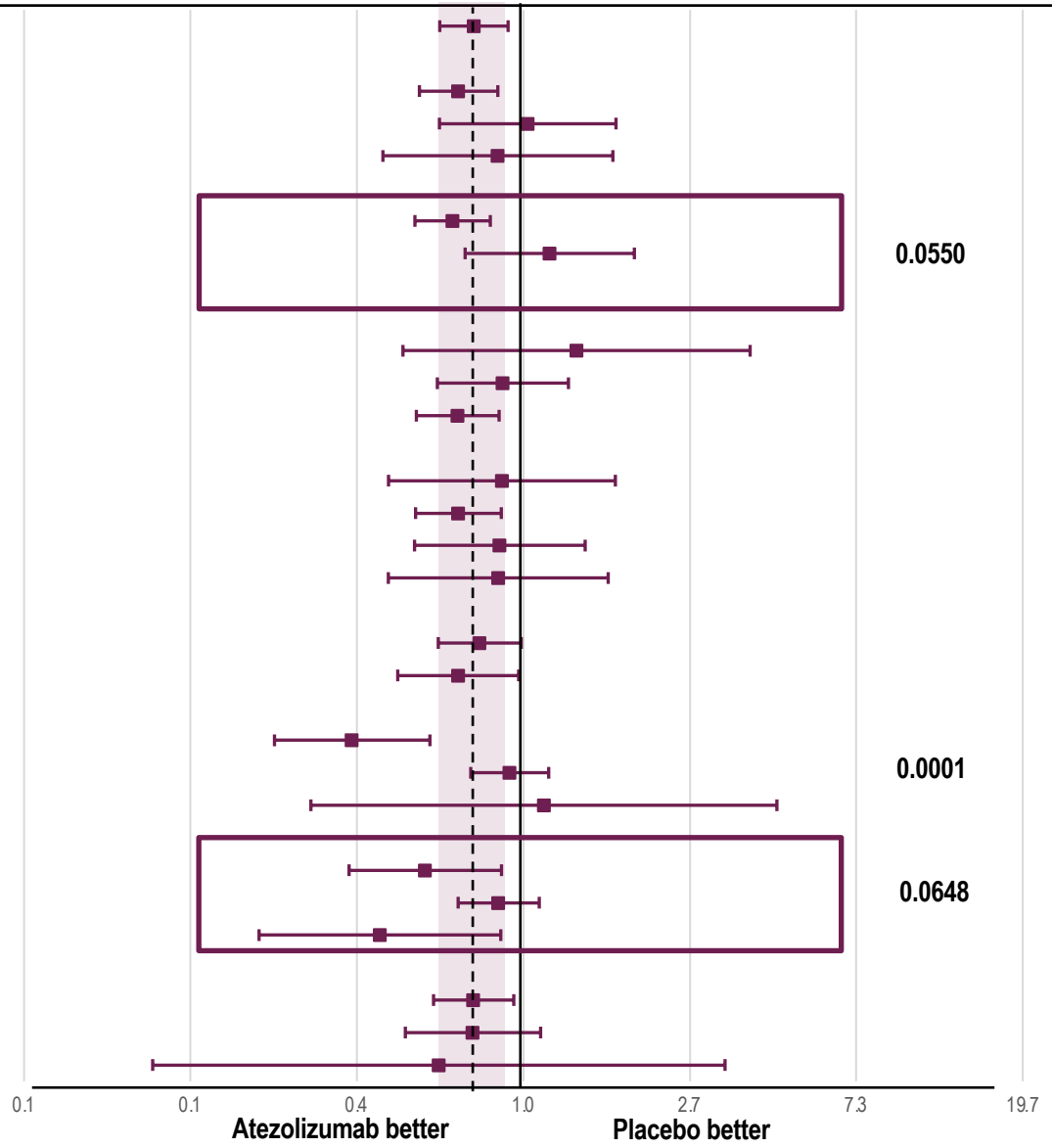
Eskander, ESMO 2023

P-MMR who will benefit?

- Discrepancy among trials:
  - PD1-PD-L1-i?
  - Racial/ethnicity?
  - Prior treatment interval
  - Recurrent/metastatic
  - Adjuvant vs measurable disease
  - Histotypes (carcinosarcoma?)
- How to select the good p-MMR?
  - PDL1?
  - TMB?
  - P53m?
  - Composite biomarkers?

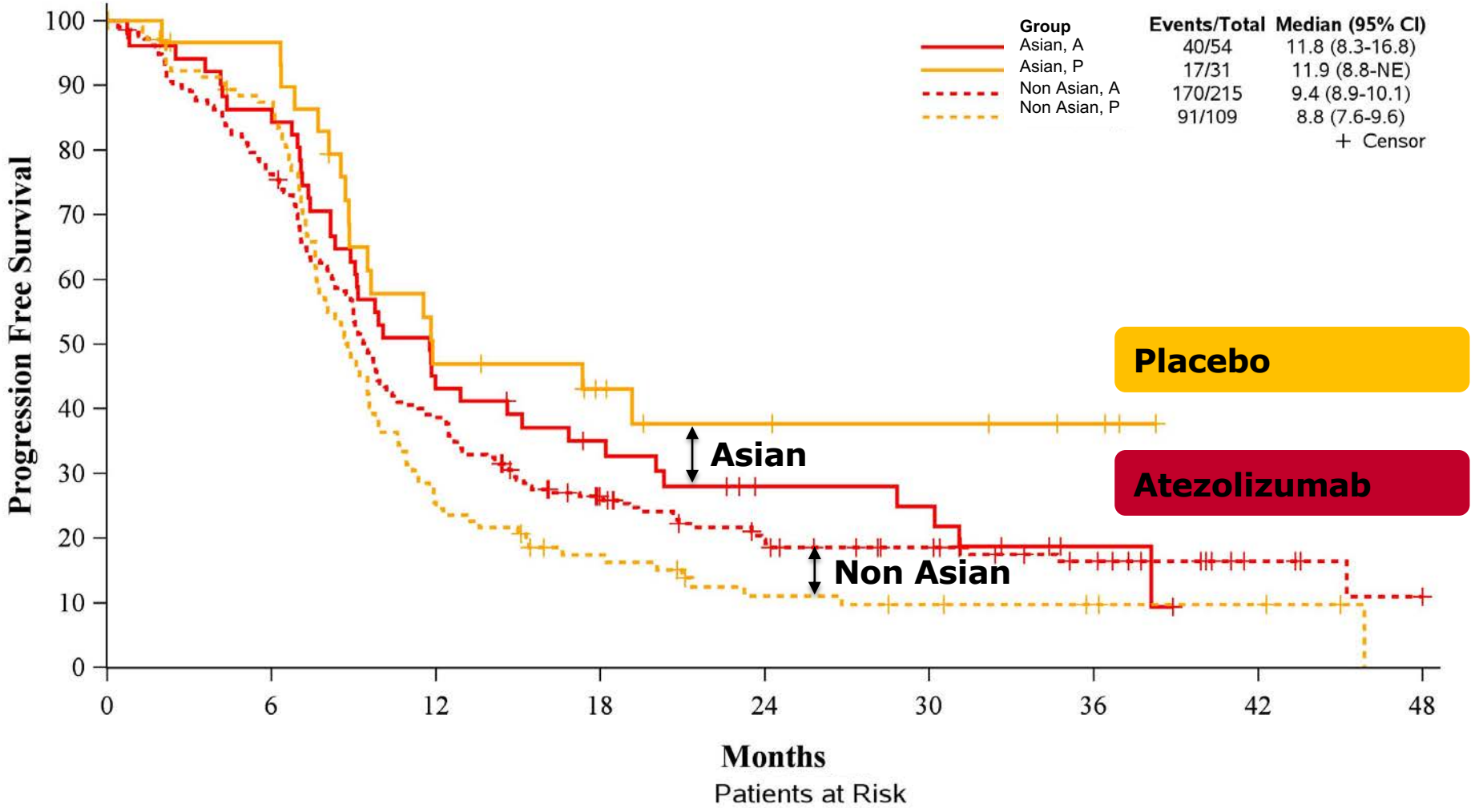
Impact of PD-L1 expression and ethnicity: AtTEnd all comers

Subgroup	Placebo no. events/no. pts	Atezolizumab no. events/no. pts	HR (95% CI)
Overall	148/189 (78%)	253/360 (70%)	0.74 (0.61-0.91)
Geographic region			
Europe	114/134 (85%)	189/264 (72%)	0.68 (0.54-0.86)
Asia	21/37 (57%)	41/66 (62%)	1.03 (0.61-1.74)
Australia/New Zealand	13/18 (72%)	23/30 (77%)	0.86 (0.43-1.71)
Race			
Caucasian	123/143 (86%)	207/289 (72%)	0.66 (0.52-0.82)
Asian	23/43 (53%)	44/69 (64%)	1.17 (0.71-1.94)
Other	2/3 (67%)	2/2 (100%)	NE
Status of disease*			
Newly diagnosed-Stage III	5/10 (50%)	13/21 (62%)	1.37 (0.49-3.87)
Newly diagnosed-Stage IV	39/52 (75%)	72/96 (75%)	0.88 (0.60-1.31)
Recurrent	103/126 (82%)	168/243 (69%)	0.68 (0.53-0.87)
Histological type			
Carcinosarcoma	12/15 (80%)	30/35 (86%)	0.88 (0.45-1.73)
Endometrioid	99/125 (79%)	150/227 (66%)	0.68 (0.53-0.88)
Papillary serous	23/29 (79%)	47/59 (80%)	0.87 (0.52-1.45)
Other	14/20 (70%)	26/39 (67%)	0.86 (0.45-1.66)
Pre-treated with chemotherapy			
No	100/129 (78%)	172/253 (68%)	0.77 (0.60-0.99)
Yes	48/60 (80%)	81/107 (76%)	0.68 (0.47-0.97)
Mismatch repair status			
Deficient	37/44 (84%)	37/81 (46%)	0.36 (0.23-0.57)
Proficient	108/140 (77%)	210/269 (78%)	0.92 (0.73-1.16)
Not evaluable	3/5 (60%)	6/10 (60%)	1.13 (0.28-4.54)
PD-L1 (IC) expression			
Positive	32/44 (73%)	49/86 (57%)	0.56 (0.35-0.88)
Negative	102/129 (79%)	186/247 (75%)	0.86 (0.68-1.10)
Not evaluable	14/16 (88%)	18/27 (67%)	0.42 (0.21-0.87)
ARID1A expression			
Intact	107/131 (82%)	188/248 (76%)	0.74 (0.58-0.94)
Loss	39/55 (71%)	61/104 (59%)	0.74 (0.49-1.11)
Not evaluable	2/3 (67%)	4/8 (50%)	0.60 (0.11-3.33)



Colombo N, ESMO 2023

AtTEnd: PFS in pMMR according to ethnicity



Asian
Logrank test
P=0.1042

HR 1.42
95%CI 0.80 to 2.50

Non Asian
Logrank test
P=0.0849

HR 0.82
95%CI 0.63 to 1.05

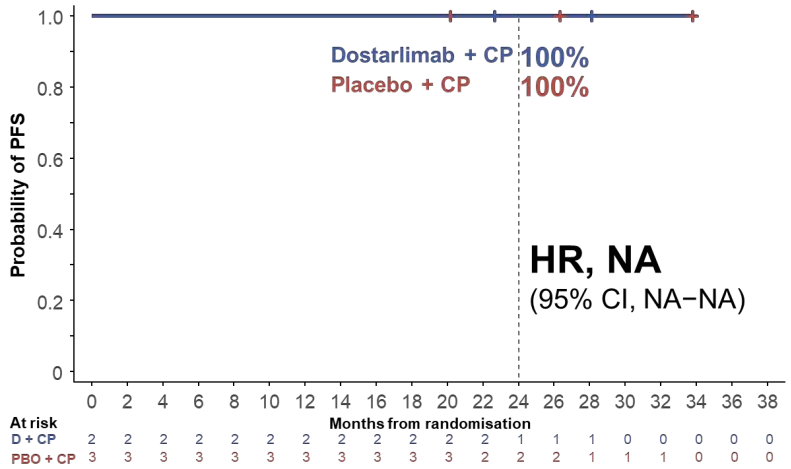
Interaction test
P=0.071

Shin Nishio, ESGO 2024

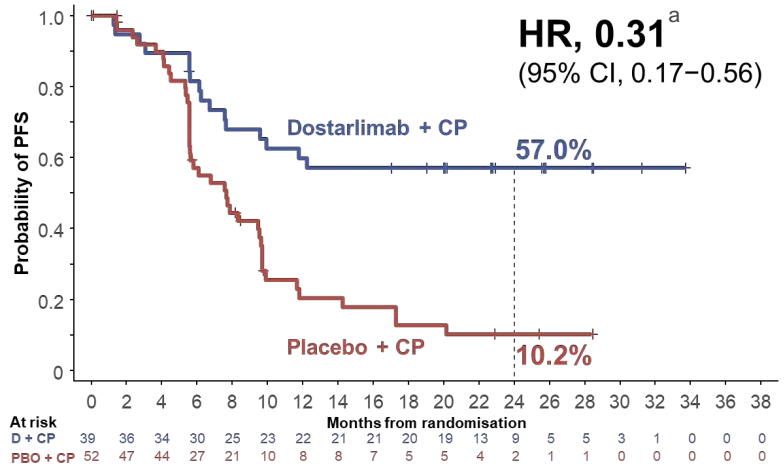
GOG-3031/RUBY: PFS according to molecular subgroup

Based on 400/494 patients with known molecular classification per whole exome sequencing

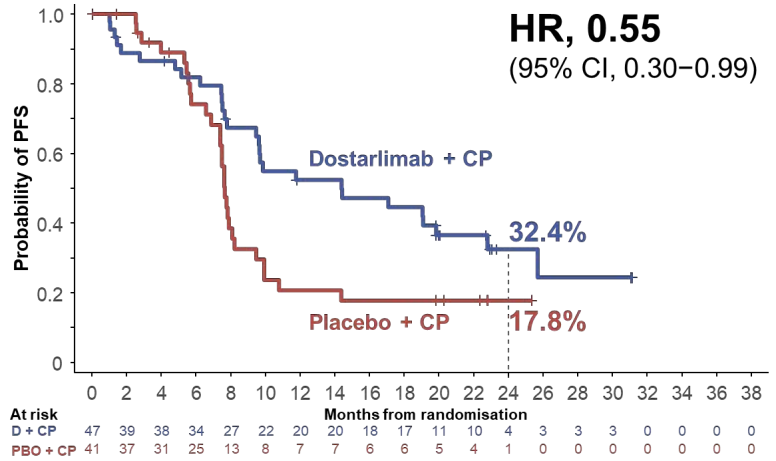
POLε mut



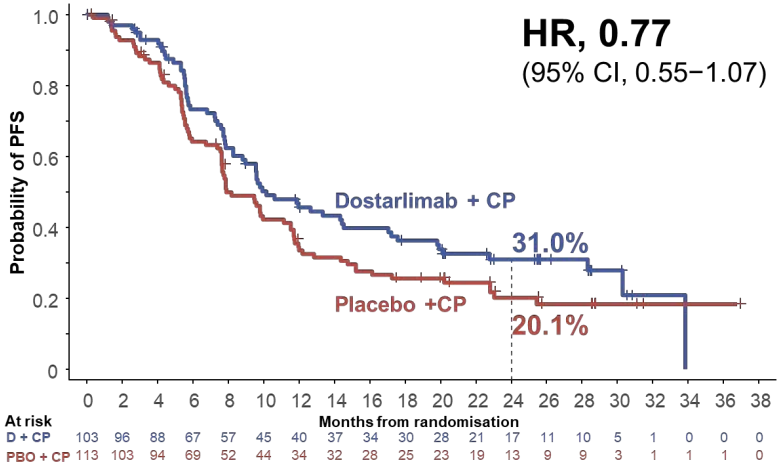
dMMR/MSI-H



TP53 mut



NSMP



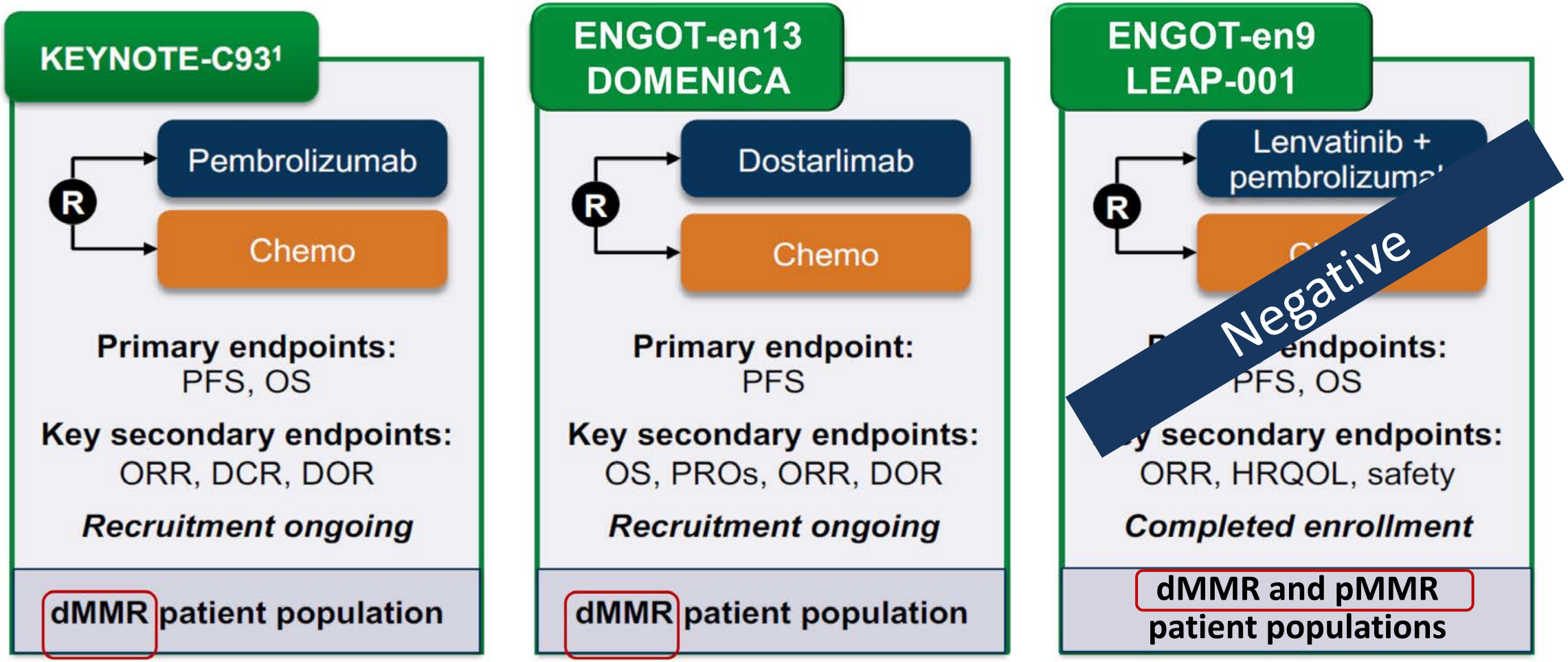
[a]Primary endpoint of PFS in dMMR/MSI-H patients (n=118) showed HR, 0.28; *P*<0.0001

CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; PBO, placebo; PFS, progression-free survival; POLε , polymerase epsilon; TP53, tumor protein 53.

Mirza MR, et al. ESMO 2023.

WILL ICIs alone replace chemotherapy in the front-line setting of dMMR EC?

Do you need chemo in this group?



ENGOT-en9/LEAP-001 Study: Summary

- LEN/PEMBRO did not meet the prespecified statistical criteria for OS or PFS vs TC in patients with pMMR advanced/recurrent endometrial cancer in the first-line setting
  - HR 1.02 (95% CI, 0.83-1.26), non-inferiority p = 0.246
  - In dMMR subgroup, LEN/PEMBRO prolonged PFS and OS vs TC
    - HRs 0.61 (95% CI, 0.40-0.92) and 0.57 (95% CI, 0.36-0.91), respectively
- ORR generally similar in pMMR population, while higher in dMMR subgroup for LEN/PEMBRO vs TC
- DOR was longer with LEN/PEMBRO vs TC in both the pMMR population and dMMR subgroup

C. Marth, ESGO 2024

Summary

- The incorporation of ICIs into first line treatment provided a substantial PFS improvement in patients with advanced/recurrent endometrial cancer, particularly for those exhibiting mismatch repair deficiency (MMRd/MSI-H)
- One trial (RUBY) showed benefit in overall survival (all comers)
- Many open questions remain:
  - WILL ICIs completely replace chemotherapy in the front line setting of dMMR EC ?
  - How to identify patients with non responding dMMR tumors and how to treat them?
  - pMMR/MSS is a heterogeneous population: which patients will benefit from the addition of IO to chemotherapy? How to develop the right biomarkers?

Immunotherapy has transformed the endometrial cancer treatment landscape and changed the first line standard of care of patients with advanced/metastatic endometrial cancer

MODULE 2: Novel Investigational Strategies for Newly Diagnosed EC— Dr Westin

Consulting Faculty Questions

Available efficacy data with selinexor and perspective on the multiple myeloma experience

Neil Love, MD

Ritu Salani, MD, MBA

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Ritu Salani, MD, MBA

How do you explain the differential outcomes observed among patients with p53 wild-type and p53-mutant EC in clinical trials evaluating selinexor?

What tolerability concerns, if any, do you have about the use of maintenance selinexor in EC?

Consulting Faculty Questions

HRR status and PD-L1 as potential biomarkers for response

Neil Love, MD

Floor J Backes, MD

QUESTIONS FOR THE FACULTY

Floor J Backes, MD

Based on recent findings from studies such as DUO-E and RUBY Part 2, what role, if any, do you see for PARP inhibitors in the future management of EC?

Do you believe the benefit of PARP inhibitors will be confined to those patients with BRCA and other HRD abnormalities, or do you think a wider population will benefit?

Based on the results of the Phase III DUO-E trial evaluating durvalumab in combination with chemotherapy followed by durvalumab/olaparib maintenance for patients with newly diagnosed advanced or recurrent EC, would you like to be able to use this strategy in your practice?

 Prof Colombo	No
 Dr Powell	Yes, especially when we learn which is the appropriate patient and the effect on overall survival
 Dr Slomovitz	No
 Dr Westin	Yes, for patients with MSS disease
 Dr Backes	Yes, for patients who are positive for BRCA or other HRR mutations
 Dr Salani	Yes, for patients with BRCA mutation or potentially for patients with HRD tumor status

HRR = homologous recombination repair; HRD = homologous recombination deficient

What is your global view of the antitumor efficacy of selinexor for patients with p53 wild-type metastatic EC?

 Prof Colombo	Selinexor was used in the maintenance setting. We can discuss PFS prolongation but not response
 Dr Powell	Likely an important addition that needs to be confirmed on subsequent studies
 Dr Slomovitz	It's a maintenance drug
 Dr Westin	Improved PFS in subset
 Dr Backes	Interesting and exciting and would like to try; I want to see Phase III confirmatory results
 Dr Salani	We have the trial open and I am very excited about this agent in this setting

PFS = progression-free survival

RTP RESEARCH TO PRACTICE

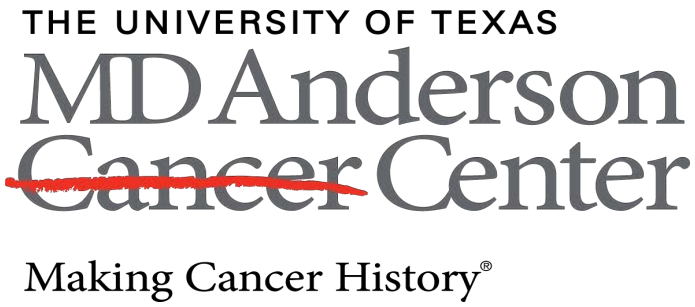
What is your global view of the tolerability of selinexor for patients with p53 wild-type metastatic EC?

 Prof Colombo	Nausea, decreased appetite and thrombocytopenia can lead to discontinuation or interruption in few patients. However, the dose used in the current trial is lower and we may expect better tolerance
 Dr Powell	At a lower dose, this is manageable 20%-25%
 Dr Slomovitz	Overall, it is well tolerated
 Dr Westin	Low rates of discontinuation (< 10%) but approximately 50% of patients require dose reduction
 Dr Backes	I have not used it as the trial is in process of being opened at our institution
 Dr Salani	Because it is maintenance and earlier than other disease sites, I think side effects will be well managed

RTP RESEARCH TO PRACTICE

Novel Investigational Strategies for Newly Diagnosed Endometrial Cancer

Shannon N. Westin, MD, MPH
Professor
Medical Director, Gynecologic Oncology Center
Department of Gynecologic Oncology and Reproductive Medicine



Shifting the Paradigm: Changing the Focus to Molecular Classification

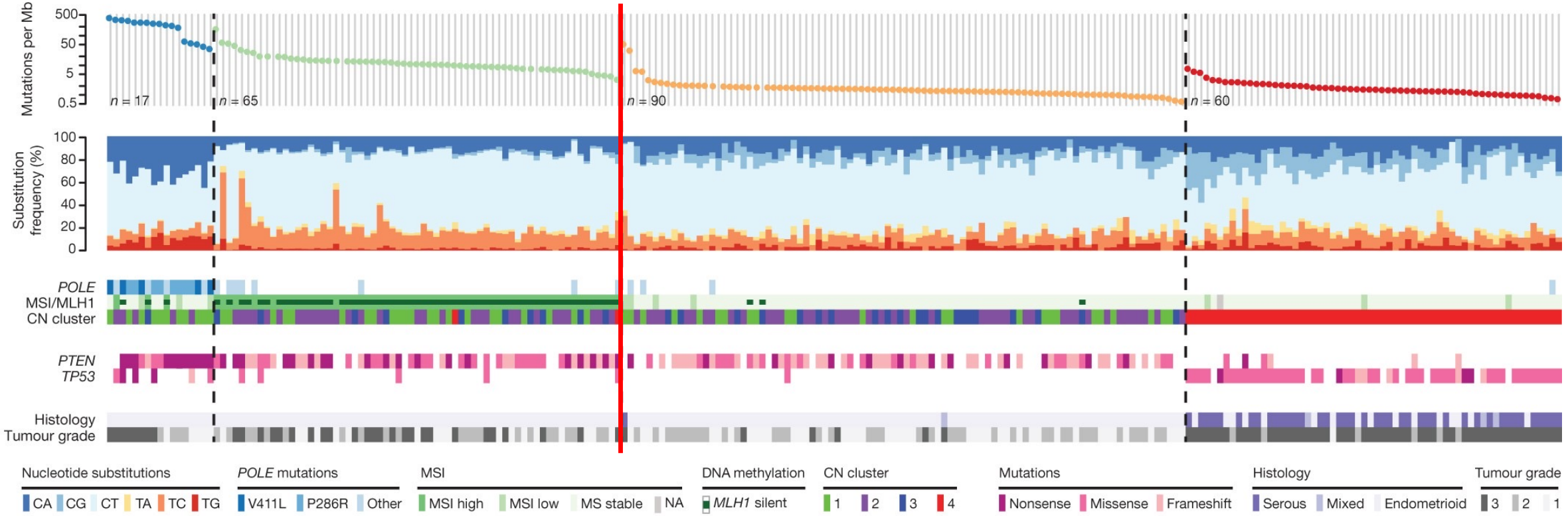
POLE: 100-500 mutations/ Mb, endometrioid, *PTEN* mutations

MSI-high: 10-20 mutations/Mb, endometrioid, *PTEN* mutations, mixed grade

CN-low: 2-3 mutations/Mb, endometrioid, *PTEN* and *CTNNB1* mutations, G1

CN-high: 2-3 mutations/Mb, endometrioid, *TP53* mutations, high grade

Ultramutated (*POLE*) | **Hypermutated (MSI/*MLH1*)** | **Copy number-low** | **Copy number-high**



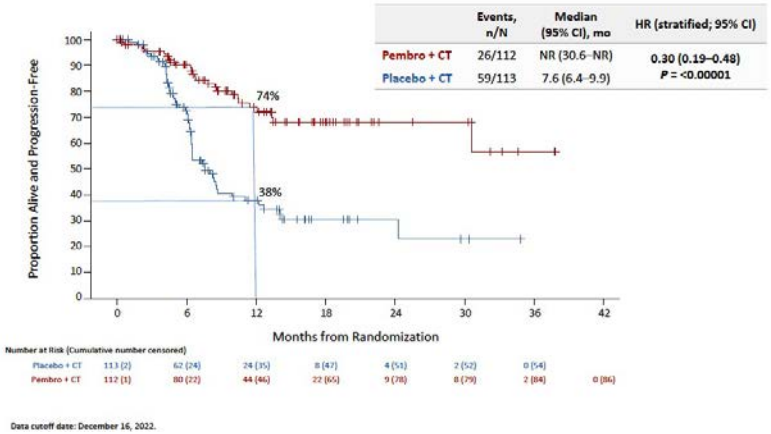
HOT TUMORS **COLD TUMORS**

Levine DA. *Nature*. 2013;497.

Checkpoint Inhibitors Improve PFS

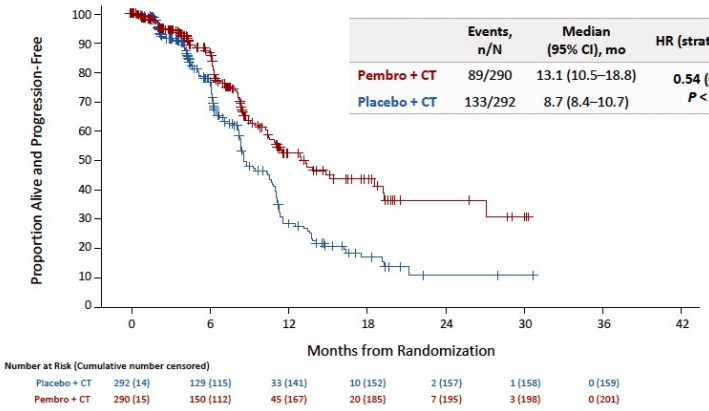
GY018

PFS per RECIST v1.1: dMMR Population



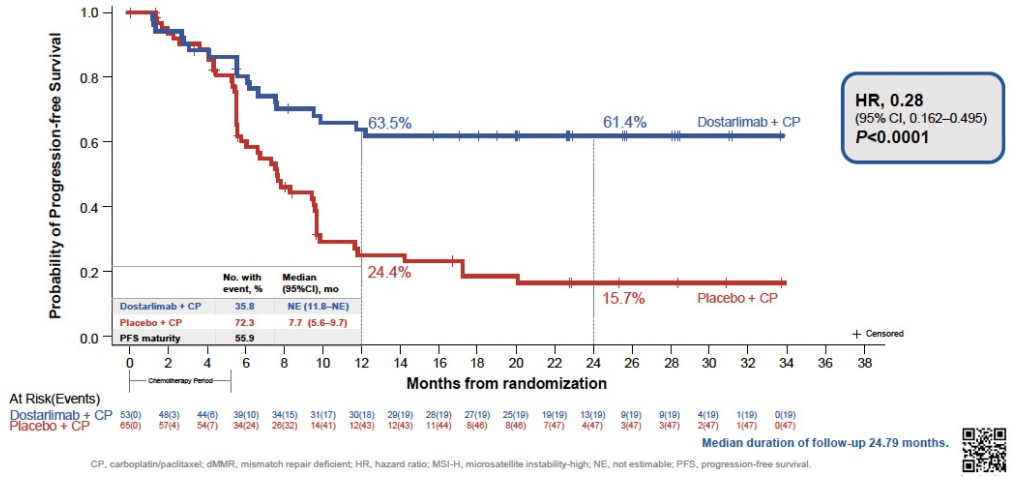
Data cutoff date: December 16, 2022.

PFS per RECIST v1.1: pMMR Population



RUBY

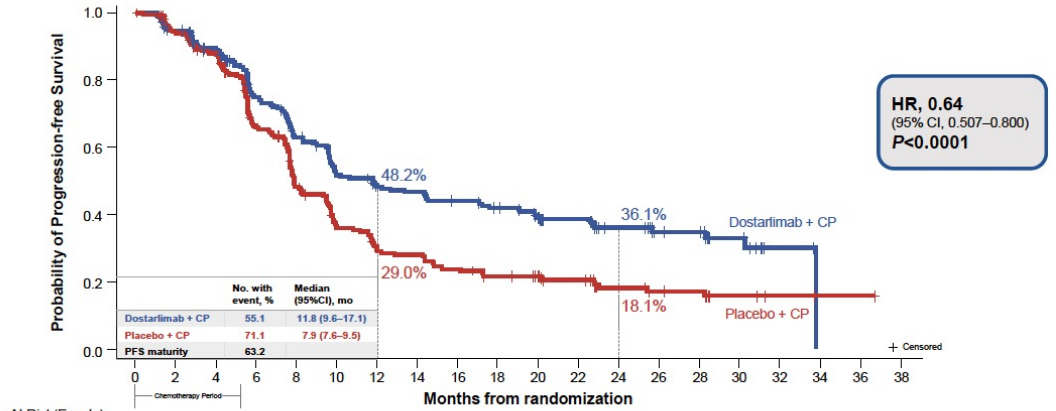
Primary Endpoint: PFS in dMMR/MSI-H Population



Median duration of follow-up 24.79 months.

CP, carboplatin/paclitaxel; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability-high; NE, not estimable; PFS, progression-free survival.

Primary Endpoint: PFS in Overall Population



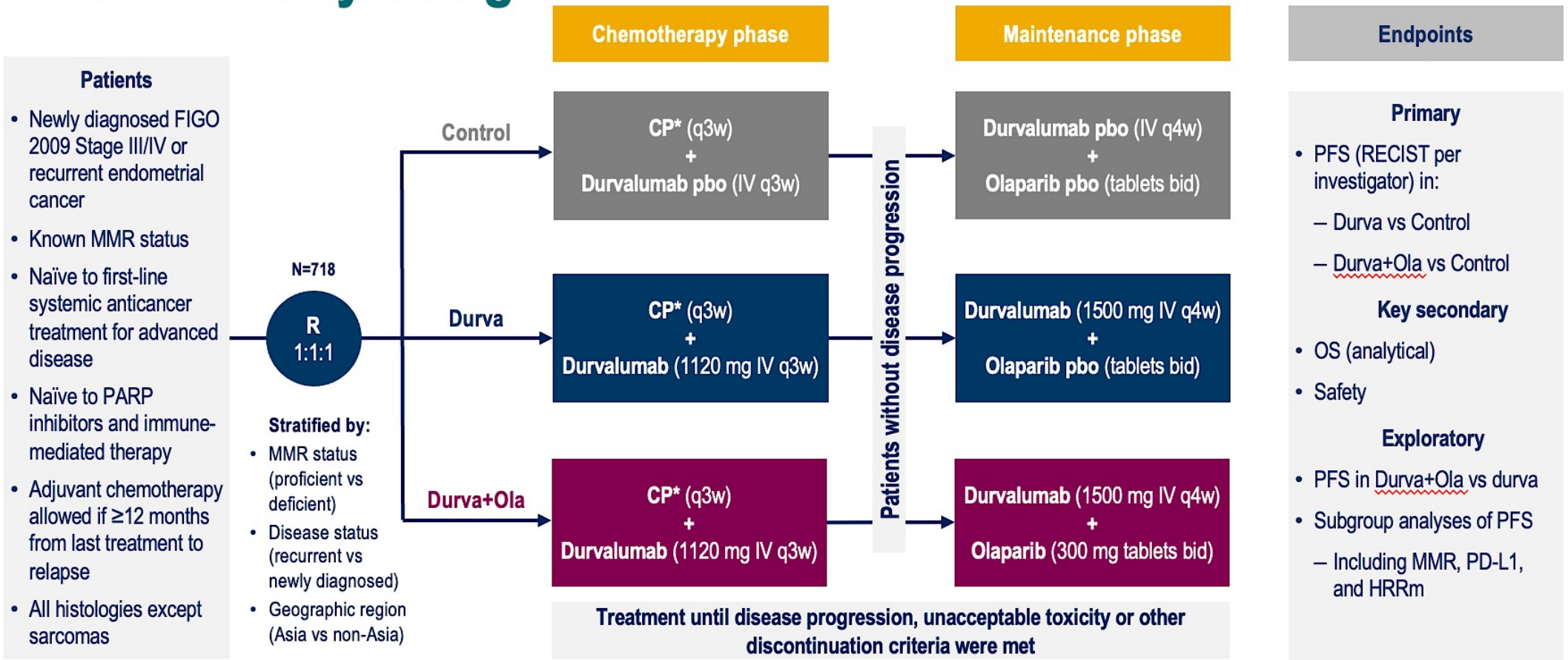
Median duration of follow-up 25.38 months.

CP, carboplatin/paclitaxel; HR, hazard ratio; PFS, progression-free survival.

Eskander NEJM 2023 Mirza NEJM 2023

DUO-E: Combination of durvalumab and olaparib

DUO-E study design



*Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg per mL/min and paclitaxel 175 mg/m^2.
bid, twice daily; CP, carboplatin/paclitaxel; durva, durvalumab; FIGO, International Federation of Gynaecology and Obstetrics; HRRm, homologous recombination repair mutation; IV, intravenously; ola, olaparib; pbo, placebo; q3(4)w, every 3(4) weeks; R, randomisation; RECIST, Response Evaluation Criteria for Solid Tumours.

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DUO-E patient characteristics

Characteristics		Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Age, years	Median (range)	64 (31–85)	64 (22–84)	63 (27–86)
Geographic region,* %	Asia	28	29	28
	Non-Asia	72	71	72
Race, %	White	59	57	56
	Asian	30	30	29
	Black/African American	4	5	6
	American Indian/Alaska Native	0	3	3
	Other or not reported	6	5	7
Ethnicity, %	Not Hispanic or Latino	90	87	86
	Hispanic or Latino	8	12	13
Disease status, %	Newly diagnosed*	48	47	48
	FIGO Stage III	5	7	5
	FIGO Stage IV	42	40	41
	Recurrent*	52	53	52
ECOG PS, %	(0) Normal Activity	65	66	69
	(1) Restricted Activity	35	34	31
Measurable disease at baseline, %		82	85	77

Characteristics		Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
MMR status,*,† %	Proficient	80	81	80
	Deficient	20	19	20
PD-L1 status,‡ %	Positive (TAP score ≥1%)	68	71	63
	Negative (TAP score <1%)	31	26	34
	Unknown	1	3	3
HRRm status,§ %	HRRm	13	11	16
	Non-HRRm	55	58	59
	Unknown	32	31	25
Histology type at diagnosis, %	Endometrioid	58	59	64
	Serous	22	24	18
	Carcinosarcoma	9	5	8
	Mixed, epithelial	5	4	4
	Clear cell	3	2	3
	Undifferentiated	1	2	2
	Mucinous or other	2	4	2
Previous chemotherapy, %		21	21	23
Previous radiotherapy, %		29	31	36
Prior surgery, %		84	86	87

Percentages may not total 100 because of rounding. *Stratification factors (MMR status [proficient vs deficient], disease status [newly diagnosed vs recurrent], and geographic region [Asia vs non-Asia]) are per the randomisation code. Two patients with 'unknown' MMR status per central laboratory were randomised as 'deficient' per interactive voice response system, based on local testing. Asia included China, Hong Kong, India, Japan, Singapore and South Korea; †MMR status evaluated using the Ventana immunohistochemistry MMR panel; ‡PD-L1 expression evaluated using Ventana SP263; § HRRm status evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L*. HRRm status unknown includes patients recruited in China where HRR testing was not performed and patients with samples that were unavailable for testing. ECOG PS, Eastern Cooperative Oncology Group performance status; TAP, tumour area positivity.

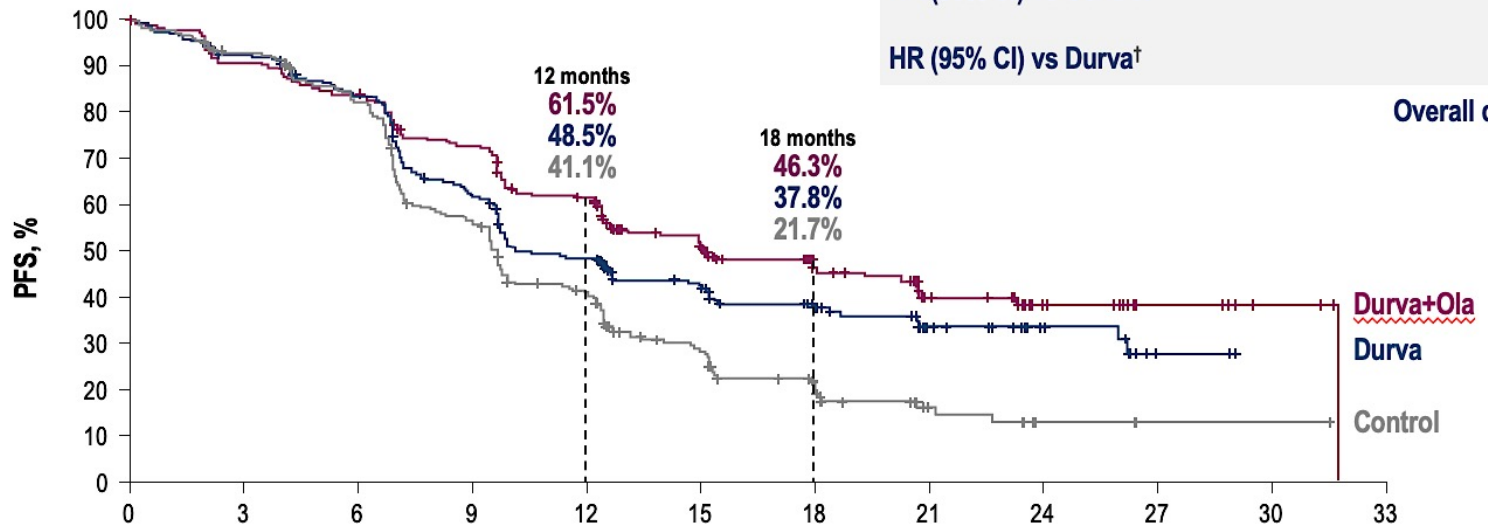
Durva and Durva + Olaparib Improve PFS in EC

PFS: ITT population

Primary endpoint

	Control (N=241)	Durva (N=238)	Durva+Ola (N=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS (95% CI),* months	9.6 (9.0–9.9)	10.2 (9.7–14.7)	15.1 (12.6–20.7)
HR (95% CI) vs Control†		**0.71** (0.57–0.89); *P*=0.003	**0.55** (0.43–0.69); *P*<0.0001
HR (95% CI) vs Durva†			0.78 (0.61–0.99)

Overall data maturity 61.0%



No. at risk												
Durva+Ola	239	214	198	169	139	95	51	30	16	7	3	0
Durva	238	211	188	138	105	69	45	26	13	5	0	0
Control	241	213	184	125	86	45	26	10	3	1	1	0

The median (range) duration of follow-up for PFS was 12.6 (0.0–31.6), 15.4 (0.0–29.1), and 15.4 (0.0–31.7) months in censored patients for the Control, Durva, and Durva+Ola arms, respectively. PFS rates were estimated by the KM method. *CI for median PFS is derived based on the Brookmeyer–Crowley method; †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. ITT, intent-to-treat; KM, Kaplan–Meier.

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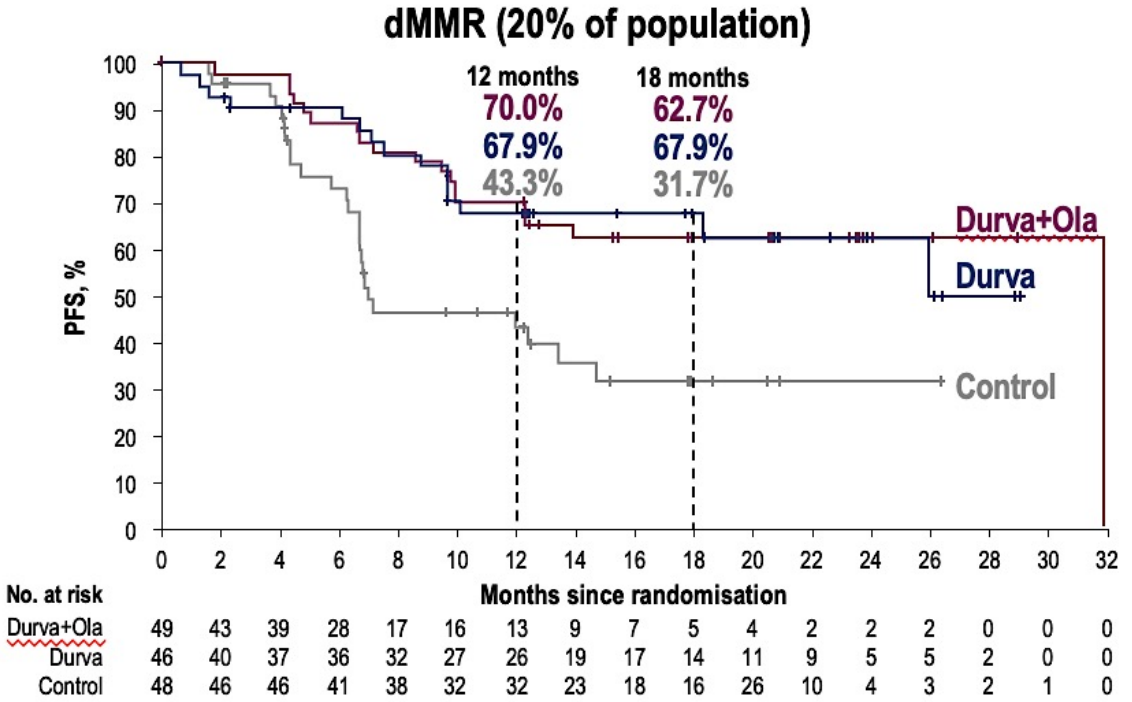
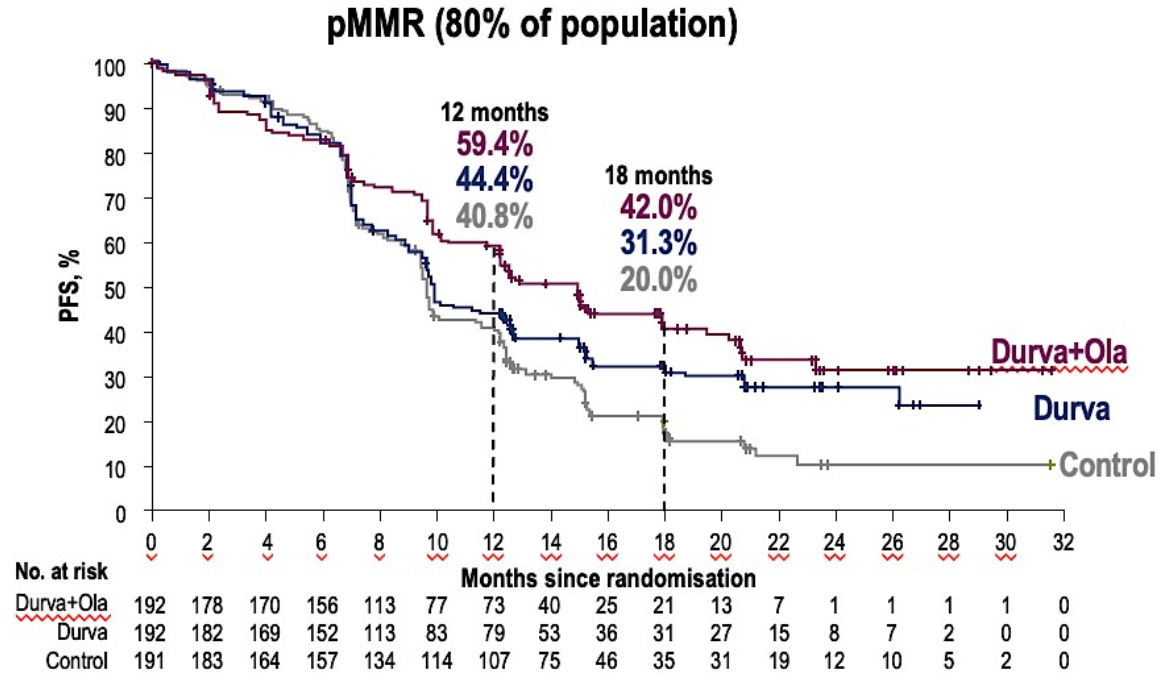
DUO-E subgroup analyses by biomarkers: Mismatch repair



	Control (N=49)	Durva (N=46)	Durva+Ola (N=48)
Events, n (%)	25 (51.0)	15 (32.6)	18 (37.5)
Median PFS (95% CI),* months	7.0 (6.7–14.8)	NR (NR–NR)	31.8 (12.4–NR)
HR (95% CI) vs Control†		**0.42 (0.22–0.80)**	**0.41 (0.21–0.75)**
HR (95% CI) vs Durva†			**0.97 (0.49–1.98)**



	Control (N=192)	Durva (N=192)	Durva+Ola (N=191)
Events, n (%)	148 (77.1)	124 (64.6)	108 (56.5)
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		**0.77 (0.60–0.97)**	**0.57 (0.44–0.73)**
HR (95% CI) vs Durva†			**0.76 (0.59–0.99)**

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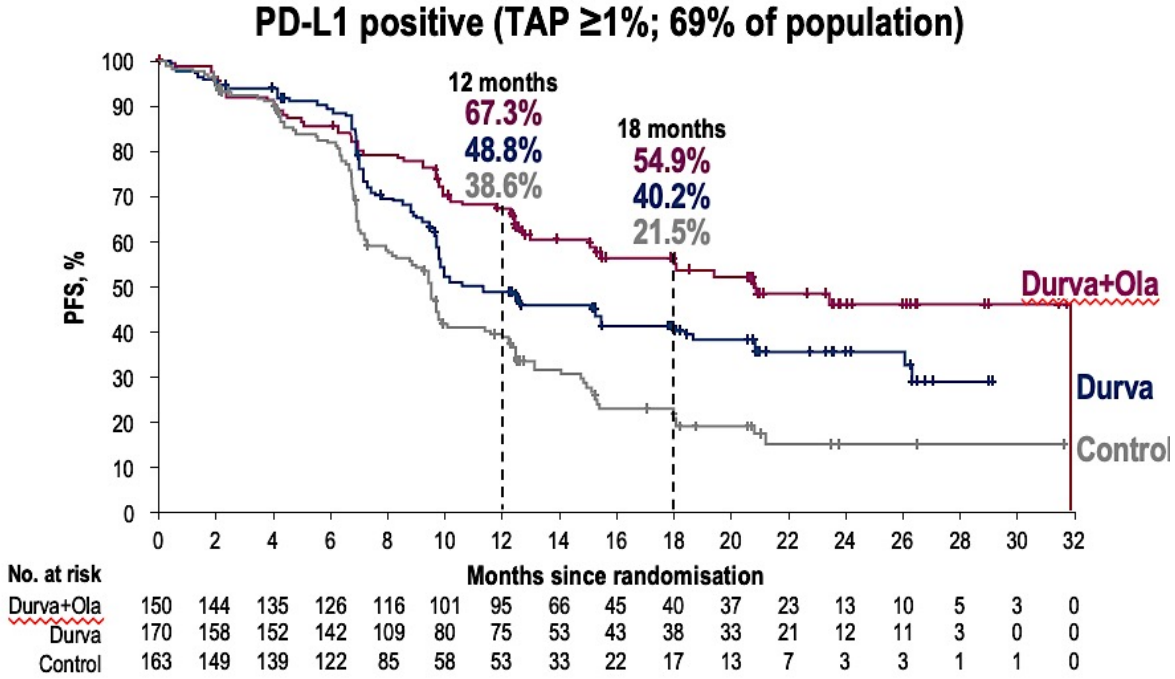
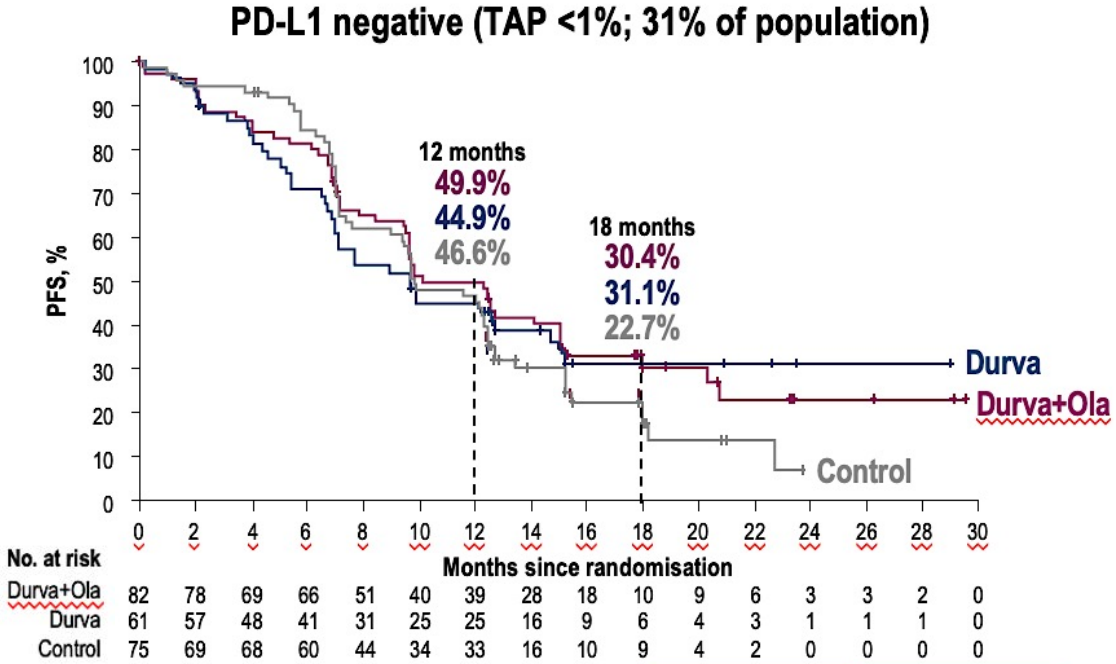
DUO-E subgroup analyses by biomarkers: PD-L1



	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),* months	9.5	11.3	20.8
HR (95% CI) vs Control†		**0.63 (0.48–0.83)**	**0.42 (0.31–0.57)**
HR (95% CI) vs Durva†			**0.67 (0.49–0.91)**



	Control (N=75)	Durva (N=61)	Durva+Ola (N=82)
Events, n (%)	57 (76.0)	38 (62.3)	55 (67.1)
Median PFS (95% CI),* months	9.9	9.7	10.1
HR (95% CI) vs Control†		**0.89 (0.59–1.34)**	**0.80 (0.55–1.16)**
HR (95% CI) vs Durva†			**0.93 (0.61–1.41)**

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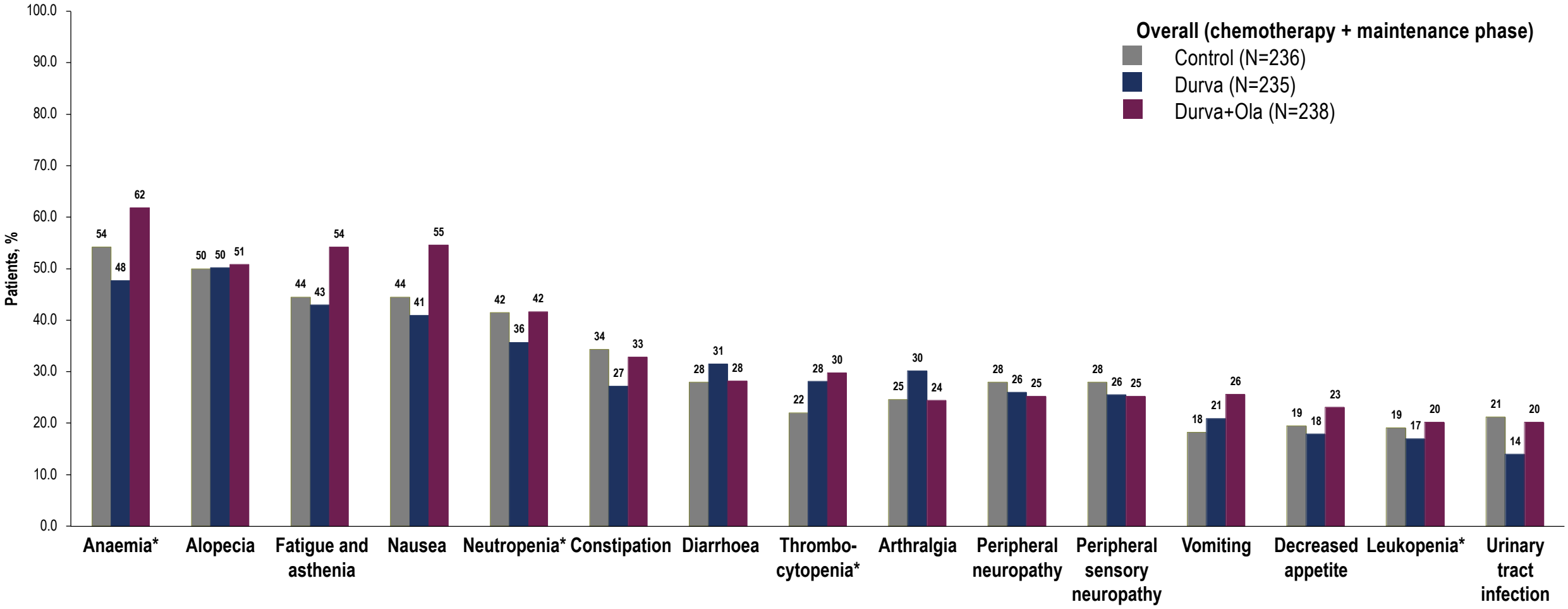
DUO-E Safety Summary

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.

Any grade AEs with a frequency of ≥20% in any arm



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. In addition to AEs shown, COVID-19 was reported in 32 (14%) patients in the Control arm, 36 (15%) patients in the Durva arm, and 48 (20%) patients in the Durva+Ola arm overall, and in 20 (12%), 21 (11%), and 34 (18%) patients, respectively, during the maintenance phase.

*Grouped terms: anaemia includes anaemia and haemoglobin decreased; neutropenia includes agranulocytosis, febrile neutropenia, neutropenia, neutropenic infection, neutropenic sepsis, and neutrophil count decreased; thrombocytopenia includes platelet count decreased and thrombocytopenia; leukopenia includes leukopenia and white blood cell count decreased.

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

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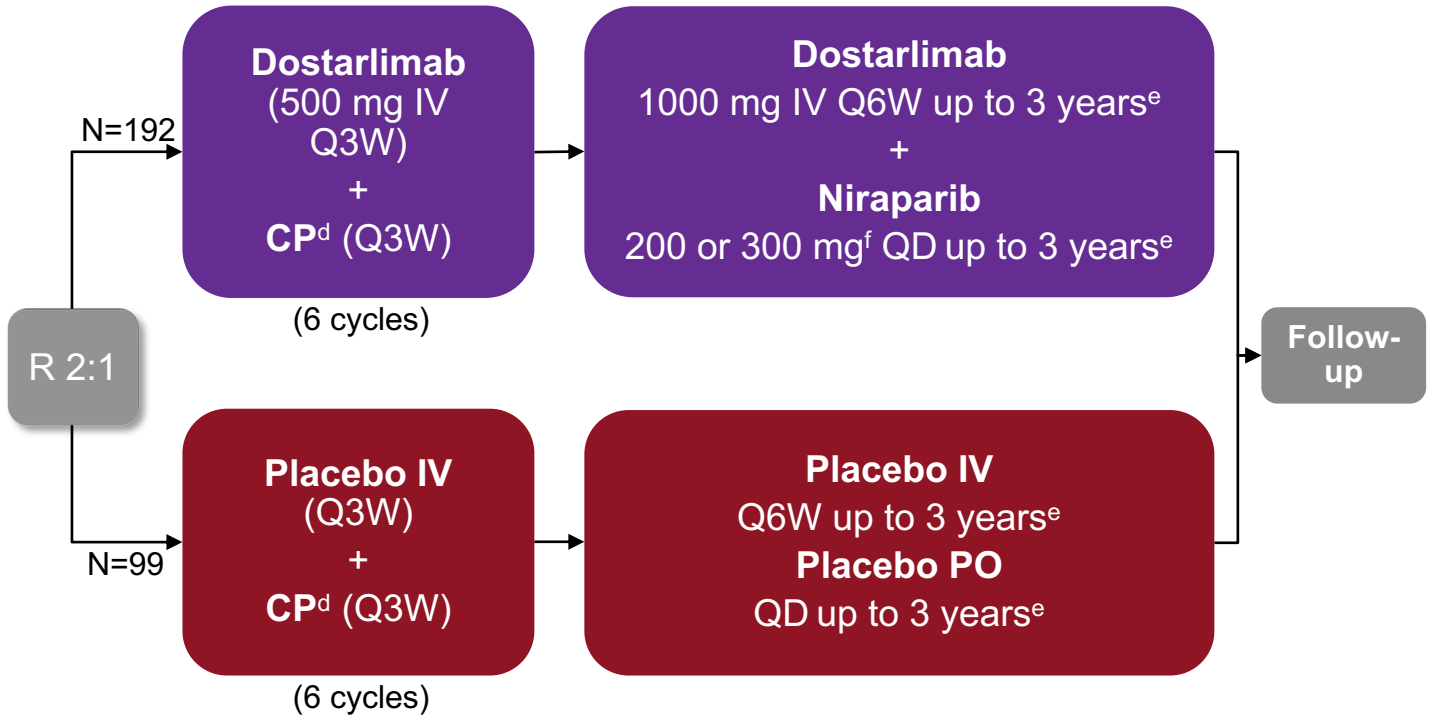
Eligible patients

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

Stratification

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



Primary endpoint

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

Secondary endpoints

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

On-study imaging assessments were performed Q6W (±7 days) from the randomization date until week 25 (cycle 8), followed by Q9W (±7 days) until week 52. Subsequent tumor imaging was performed every 12 weeks (±7 days) until radiographic PD was documented by investigator assessment per RECIST v1.1 followed by 1 additional imaging 4–6 weeks later, or subsequent anticancer therapy was started, whichever occurred first. Thereafter, scans were performed per standard of care.
[a]Histologically/cytologically proven advanced or recurrent EC; stage III/IV disease or first recurrent EC with low potential for cure by radiation therapy or surgery alone or in combination. [b]Carcinosarcoma, clear cell, serous, or mixed histology permitted (mixed histology containing ≥10% carcinosarcoma, clear cell, or serous histology). [c]Patients were randomized based on either local or central MMR/MSI testing results. Central testing was used with local results were not available. For local determination of MMR/MSI status, IHC, next-generation sequencing, and polymerase chain reaction assays were accepted. For central determination of MMR/MSI status IHC per Ventana MMR RxDx panel was used. [d]Carboplatin AUC 5 mg/mL/min and paclitaxel 175 mg/m^2. [e]Treatment ends after 3 years, PD, toxicity, withdrawal of consent, investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo beyond 3 years may be considered following discussion between the sponsor and the investigator. [f]Dose of 300 mg in patients with body weight ≥77 kg and platelet count ≥150,000/μL and 200 mg in patients with body weight <77 kg or platelet count <150,000/μL or both. AUC, area under the plasma or serum concentration-time curve; BICR, blinded independent central review; BOR, best overall response; CP, carboplatin-paclitaxel; CR, complete response; DCR, disease control rate; dMMR, MMR deficient; DOR, duration of response; EC, endometrial cancer; HRQOL, health-related quality of life; IHC, immunohistochemistry; INV, investigator assessment; MMR, mismatch repair; MMRp, MMR proficient; MSI, microsatellite instability; MSI-H, MSI high; MSS, microsatellite stable; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic; PO, by mouth; PR, partial response; PRO, patient-reported outcome; Q3W, every 3 weeks; Q6W, every 6 weeks; Q9W, every 9 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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Baseline Characteristics

Variable	Overall		MMRp/MSS	
	Dostar + CP followed by dostar + nira (N=192)	Placebo + CP followed by placebo (N=99)	Dostar + CP followed by dostar + nira (N=142)	Placebo + CP followed by placebo (N=74)
Age				
Median (range), y	65.0 (36–86)	64.0 (40–83)	65.0 (36–84)	64.5 (40–83)
≥65 y, % (n)	54.7 (105)	49.5 (49)	52.8 (75)	50.0 (37)
Race, % (n)				
White	84.9 (163)	77.8 (77)	85.2 (121)	77.0 (57)
Black	8.9 (17)	9.1 (9)	9.9 (14)	10.8 (8)
Asian	1.6 (3)	1.0 (1)	1.4 (2)	1.4 (1)
Other[a]	4.7 (9)	12.1 (12)	3.5 (5)	10.8 (8)
ECOG PS, % (n)[b]				
0	62.2 (117)	65.7 (65)	65.5 (91)	71.6 (53)
1	37.2 (70)	34.3 (34)	34.5 (48)	28.4 (21)
2	0.5 (1)[c]	0	0	0
BMI				
Median (range), kg/m^2	30.1 (17.0–56.2)	30.7 (1.6–70.2)	30.1 (17.4–56.2)	30.5 (1.6–70.2)

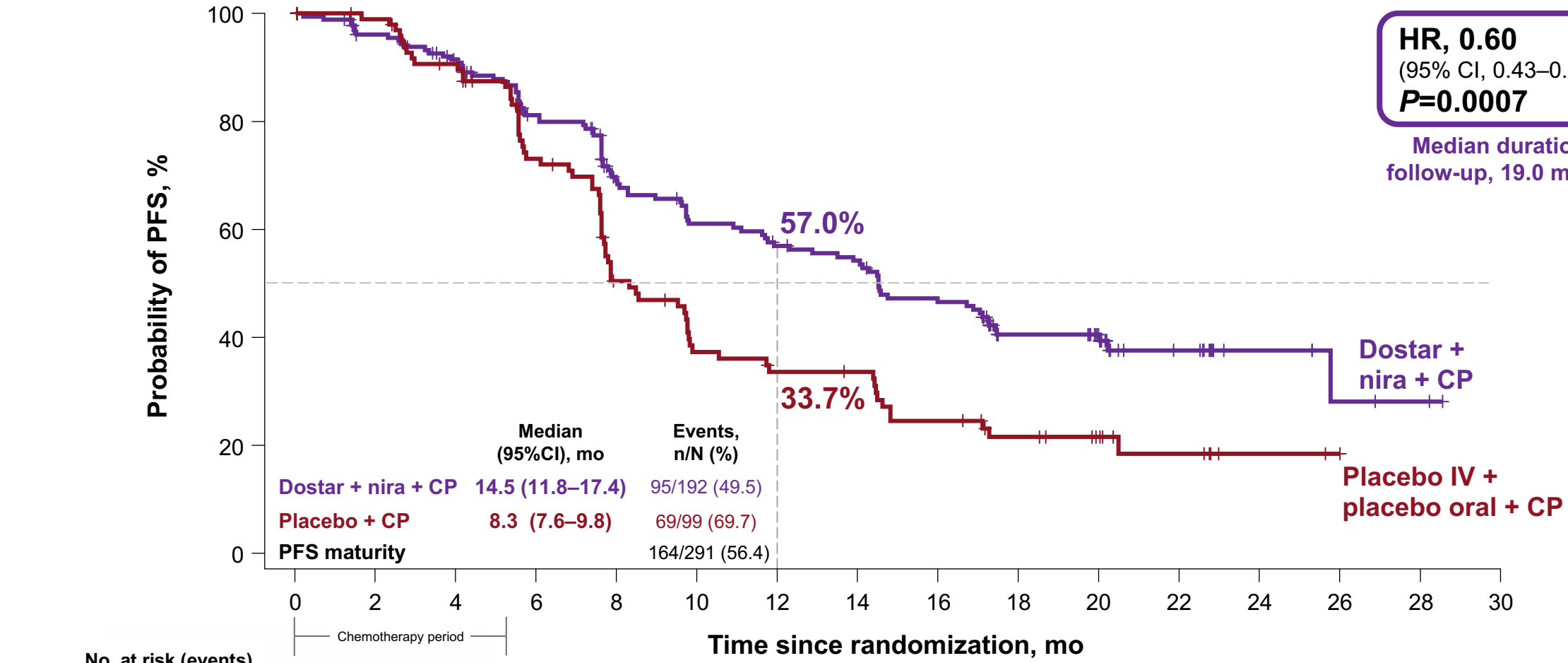
Variable	Overall		MMRp/MSS	
	Dostar + CP followed by dostar + nira (N=192)	Placebo + CP followed by placebo (N=99)	Dostar + CP followed by dostar + nira (N=142)	Placebo + CP followed by placebo (N=74)
Histology type, % (n)[d]				
Carcinosarcoma	9.4 (18)	10.1 (10)	12.0 (17)	12.2 (9)
Endometrioid[e]	63.0 (121)	69.7 (69)	54.2 (77)	62.2 (46)
Mixed carcinoma[f]	5.2 (10)	3.0 (3)	7.0 (10)	4.1 (3)
Serous adenocarcinoma	15.1 (29)	13.1 (13)	19.7 (28)	16.2 (12)
Clear cell adenocarcinoma	4.2 (8)	3.0 (3)	5.6 (8)	4.1 (3)
Mucinous adenocarcinoma	0.5 (1)	0	0	0
Undifferentiated carcinoma	1.6 (3)	0	0.7 (1)	0
Other	1.0 (2)	1.0 (1)	0.7 (1)	1.4 (1)
Evaluable disease at baseline, % (n)[g]				
Patients	84.4 (162)	86.9 (86)	84.5 (120)	85.1 (63)

[a]Other includes patients identifying as mixed race, unknown, or not reported. [b]Patients with ECOG score: 188 dostar + CP followed by dostar + nira overall, 99 placebo + CP followed by placebo overall, 139 dostar + CP followed by dostar + nira MMRp/MSS, 74 placebo + CP followed by placebo MMRp/MSS. [c]One patient had an ECOG PS of 2, and 1 patient had an ECOG PS of 2 or greater. [d]At diagnosis. [e]Adenocarcinoma or adenocarcinoma variants. [f]Mixed carcinoma ≥10% of carcinosarcoma, clear cell, or serous histology. [g]Includes patients with target or non-target lesions.

BMI, body mass index; CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; ECOG PS, Eastern Cooperative Oncology Group performance status; MMRp, mismatch repair proficient; MSS, microsatellite stable; nira, niraparib.

Statistically Significant PFS Benefit in Overall Population

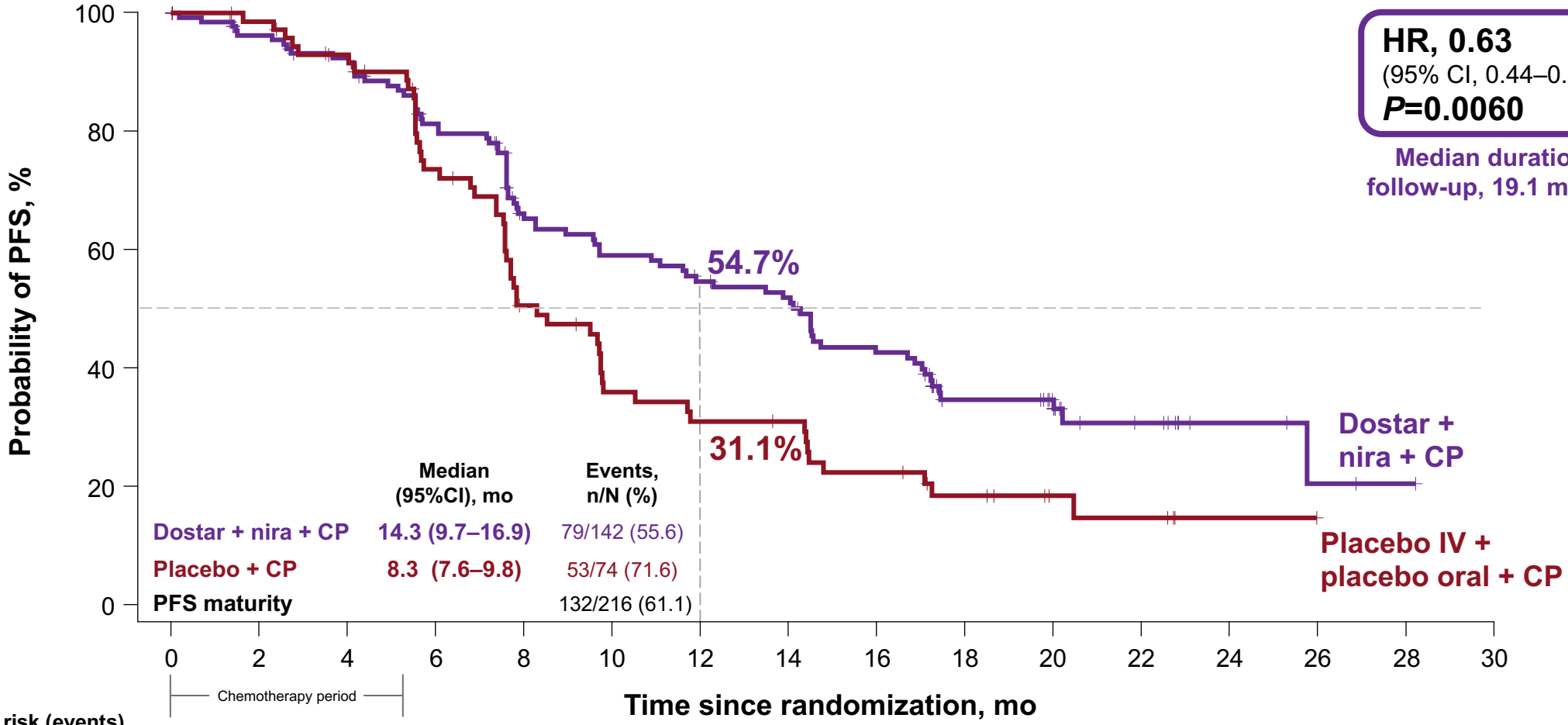
Primary endpoint



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

Statistically Significant PFS Benefit in MMRp/MSS Population

Primary endpoint

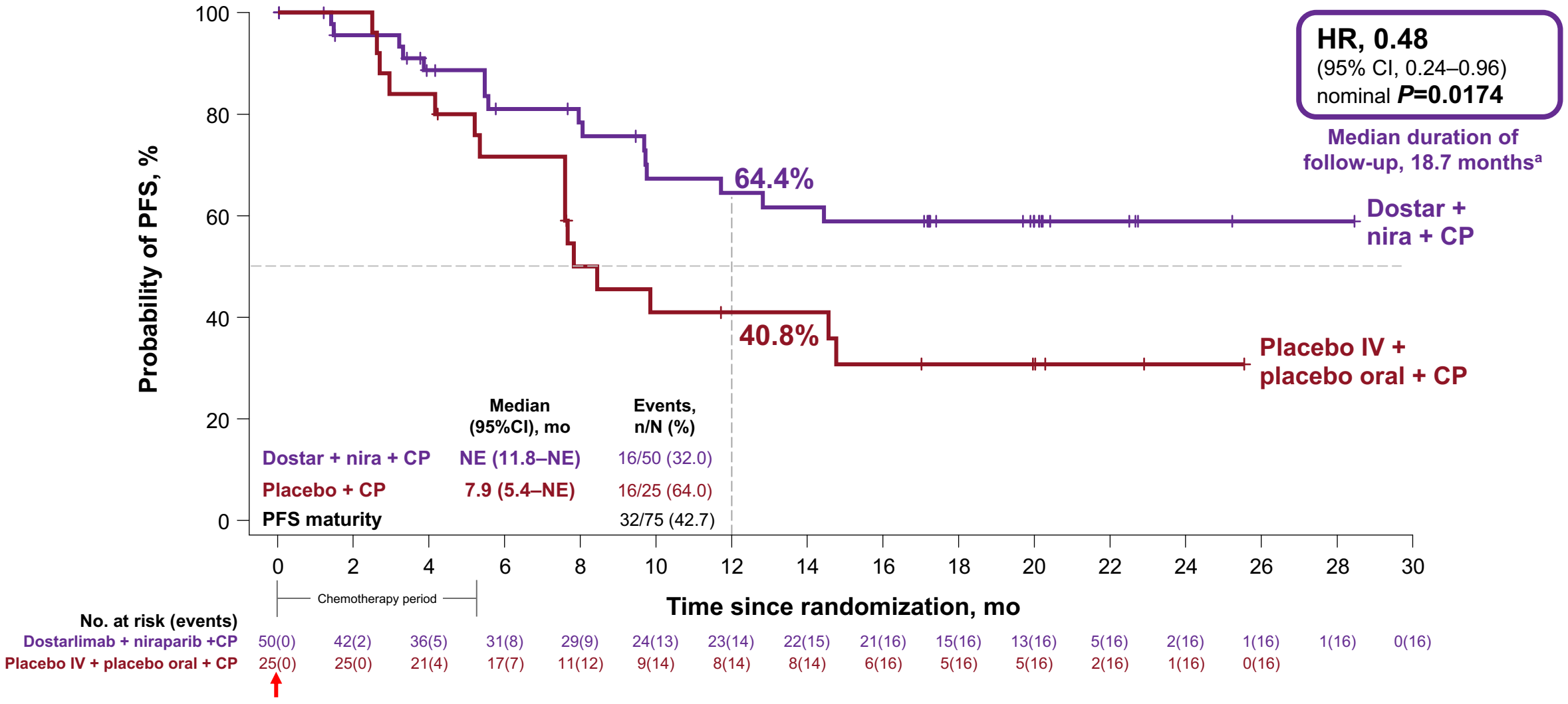


No. at risk (events)															
Dostarlimab + niraparib +CP	142(0)	127(5)	119(10)	100(24)	75(42)	67(50)	61(55)	57(58)	47(68)	28(76)	24(76)	11(78)	4(78)	2(79)	1(79)	0(79)
Placebo IV + placebo oral + CP	74(0)	71(1)	65(5)	49(18)	32(33)	22(42)	19(45)	18(45)	13(50)	9(52)	5(52)	4(53)	1(53)	1(53)	0(53)	

[a]Median expected duration of follow-up.
CP, carboplatin-paclitaxel; dostar, dostarlimab; HR, hazard ratio; MMRp, mismatch repair proficient; MSS, microsatellite stable; nira, niraparib; PFS, progression-free survival.

Clinically Relevant PFS Difference in dMMR/MSI-H Population

Prespecified exploratory analysis



[a]Median expected duration of follow-up.
CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; MSI-H, microsatellite instability high; NE, not estimable; nira, niraparib; PFS, progression-free survival.

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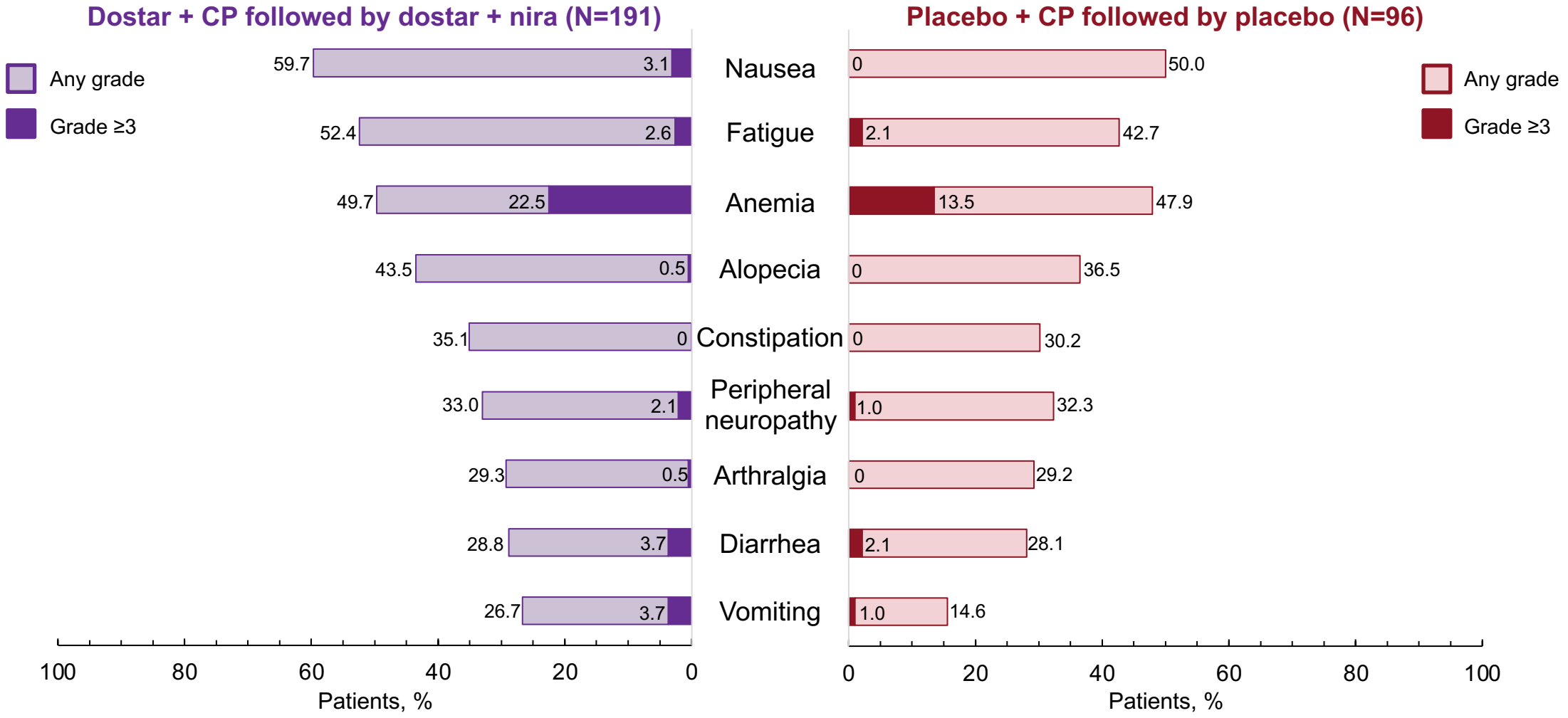
Safety Summary[a]

Parameter, % (n)	Overall	
	Dostar + CP followed by dostar + nira (N=191)	Placebo + CP followed by placebo (N=96)
Any TEAE	**99.5** (190)	**100** (96)
Any treatment-related TEAE	**96.3** (184)	**97.9** (94)
Any grade ≥3 TEAE	**84.8** (162)	**49.0** (47)
Any grade ≥3 treatment-related TEAE	**70.7** (135)	**36.5** (35)
Any serious TEAE	**44.0** (84)	**19.8** (19)
Any treatment-related serious TEAE	**23.6** (45)	**9.4** (9)
Any dostarlimab-/placebo-related irAE[b]	**36.6** (70)	**6.3** (6)
Any TEAE leading to discontinuation	**36.6** (70)	**13.5** (13)
Any TEAE leading to discontinuation of dostarlimab or placebo	**24.1** (46)	**5.2** (5)
Any TEAE leading to discontinuation of carboplatin	**13.6** (26)	**4.2** (4)
Any TEAE leading to discontinuation of paclitaxel	**18.3** (35)	**7.3** (7)
Any TEAE leading to discontinuation of niraparib or placebo	**15.7** (30)	**4.2** (4)
Any TEAE leading to death	**2.1** (4)	**0**
Any treatment-related TEAE leading to death	**0**	**0**
Duration of overall treatment, median (range), weeks	45.0 (0.9–136.3)	36.8 (6.0–115.9)

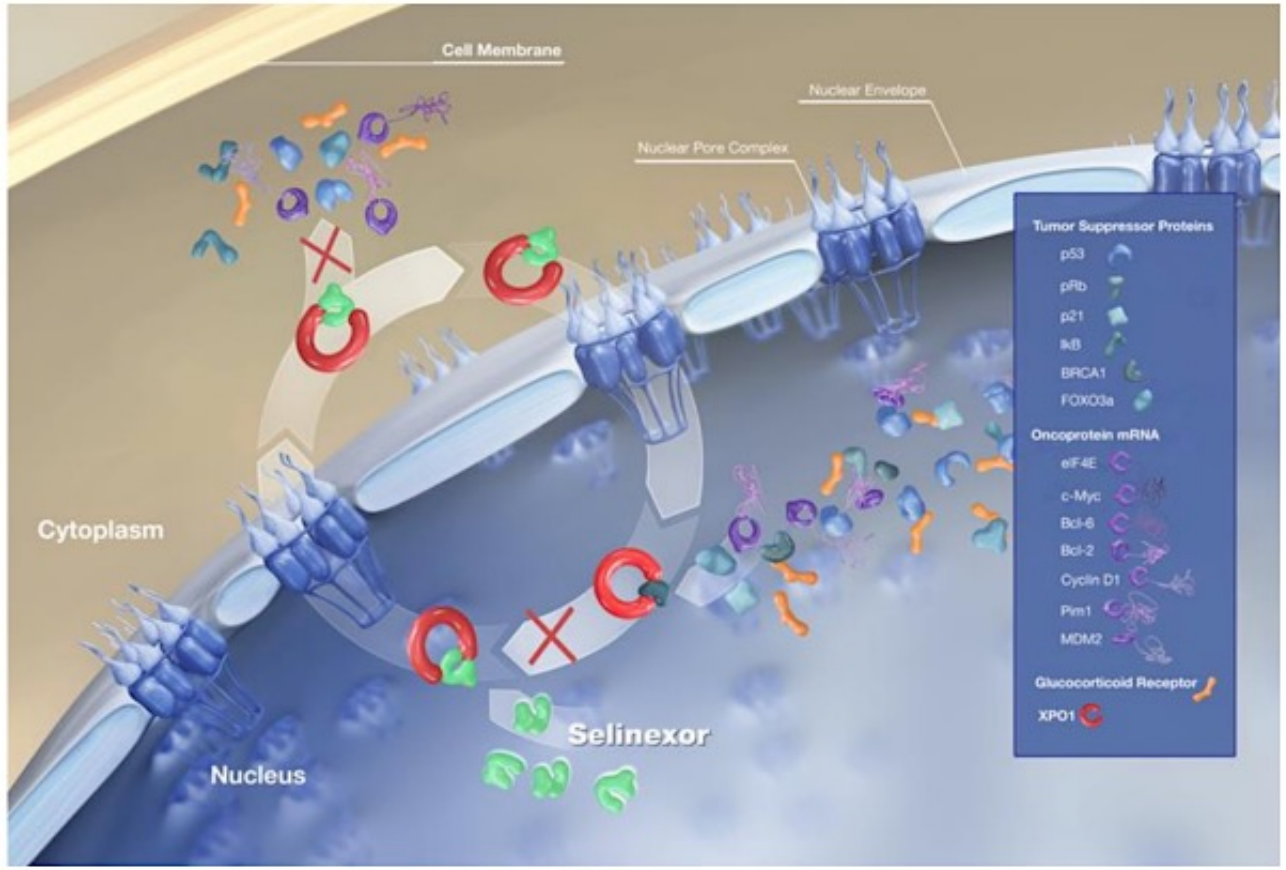
[a]Analyzed in the safety population, defined as all patients who received any amount of study drug.
[b]Grade ≥2 AEs from a prespecified list.
AE, adverse event; CP, carboplatin-paclitaxel; dostar, dostarlimab; irAE, immune-related AE; nira, niraparib; TEAE, treatment-emergent AE.

TEAEs in ≥25% of Patients in Either Arm



CP, carboplatin-paclitaxel; dostar, dostarlimab; nira, niraparib; TEAE, treatment-emergent adverse event.

Selinexor: XPO1 inhibition



Exportin 1 (XPO1) is the major nuclear export protein for:[1]

- Tumor suppressor proteins (TSPs, e.g., p53, IkB, PTEN, and FOXO1)

Inhibition of XPO1 results in:[1]

- The increase in nuclear levels and activation of TSPs
- Reduction of oncoprotein levels

Selinexor is an oral selective XPO1 inhibitor

Preclinical data for selinexor:[2]

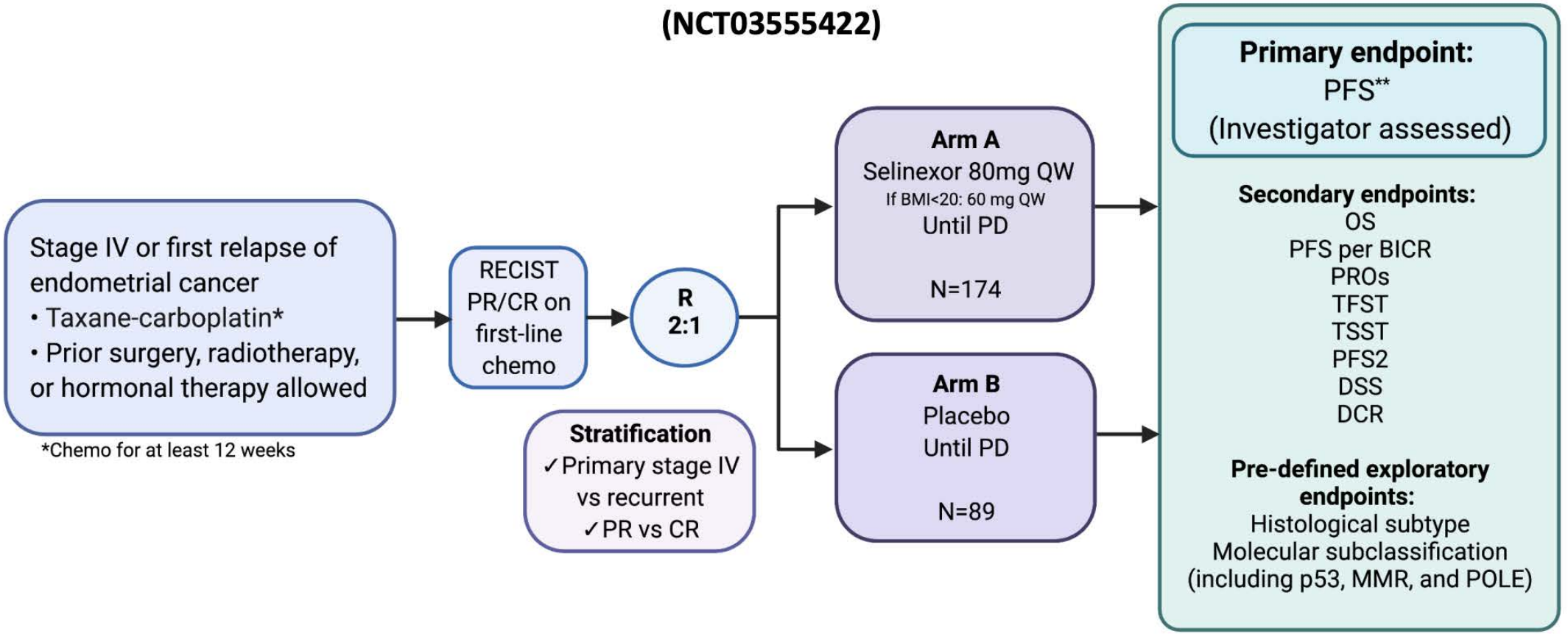
- Reactivates multiple TSPs, including p53 wild type, by preventing nuclear export

1. Fung HY, Chook YM. Atomic basis of CRM1-cargo recognition, release and inhibition. Semin Cancer Biol. 2014;27:52–61.
2. Tai YT, Landesman Y, Acharya C, et al. CRM1 inhibition induces tumor cell cytotoxicity and impairs osteoclastogenesis in multiple myeloma: molecular mechanisms and therapeutic implications. Leukemia. 2014;28(1):155–165.

Vergote JCO 2023

ENGOT-EN5/GOG-3055/SIENDO

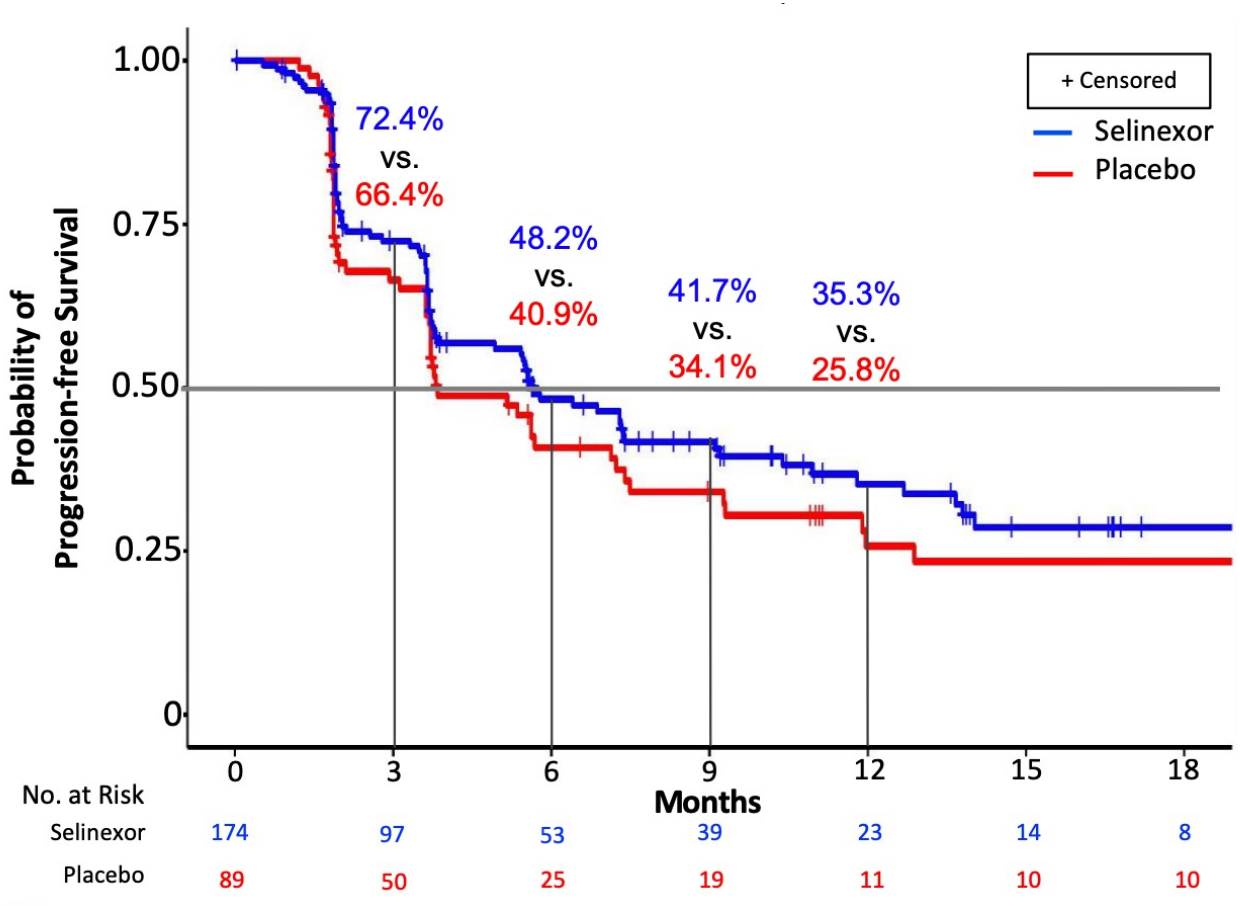
Stage IV or first relapse of endometrial cancer endometrioid, serous, undifferentiated, or carcinosarcoma (NCT03555422)



**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.

Vergote JCO 2023

SIENDO PFS in ITT



ITT Population

Median PFS (Investigator assessed)

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

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

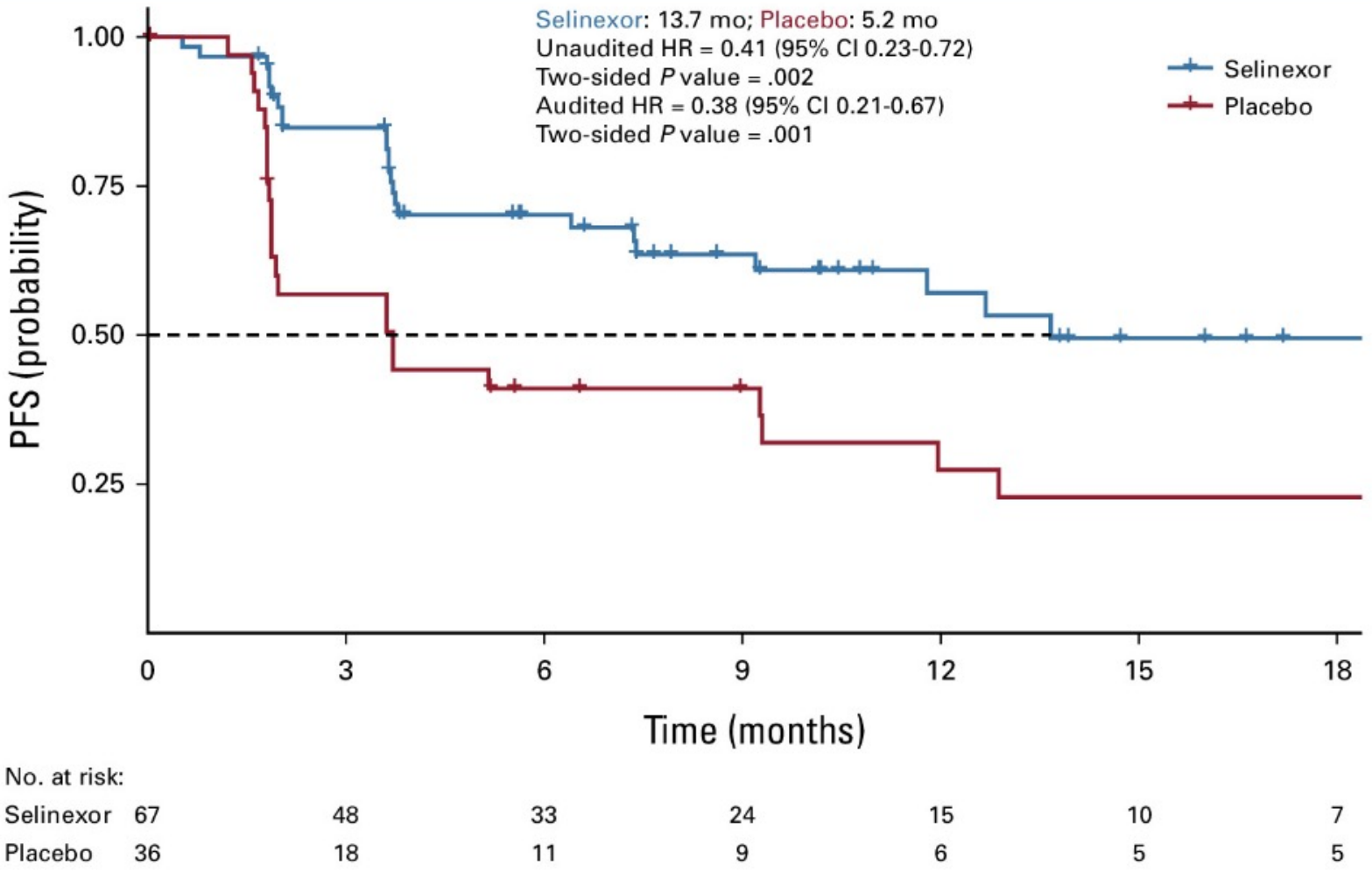
HR* = 0.705 (95% CI 0.499-0.996)

One-sided P value = 0.024

Vergote JCO 2023

SIENDO PFS in P53wt

P53wt Population



Vergote JCO 2023

GOG-3083/ENGOT-EN20/XPORT-EC-042
A Phase 3, Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With p53 Wild-Type Advanced or Recurrent Endometrial Carcinoma (GOG PI: Robert Coleman, MD)

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

Key Eligibilities
- Known p53wt EC by central NGS
- Primary stage IV or recurrent EC
- Received at least 12 weeks of taxane-platinum chemotherapy +/- immunotherapy

N = 220

PLEASE ENROLL

Stratified by:
- Primary stage IV vs recurrent
- PR vs CR

PR/CR Per RECIST v1.1

R 1:1

Selinexor 60mg QW until PD, unacceptable toxicity, or withdrawal of consent

Placebo until PD, unacceptable toxicity, or withdrawal of consent

Primary Endpoint:
- PFS assessed by Investigator

Secondary Endpoint:
- OS
- Safety
- BICR as a sensitivity analysis

NCT05611931

GOG PARTNERS

The Future is Bright!

- Maintenance is the place to be in endometrial cancer
- Still a work in progress regarding positioning and sequencing the right option for each individual patient
- Translational work and molecular testing will be critical to answer existing questions

MODULE 3: Current Options for Relapsed/Refractory EC — Dr Slomovitz

Consulting Faculty Questions

Managing toxicities associated with lenvatinib/pembrolizumab

Neil Love, MD

Ritu Salani, MD, MBA

RTP
RESEARCH
TO PRACTICE

QUESTIONS FOR THE FACULTY

Ritu Salani, MD, MBA

What preemptive strategies, if any, do you use to minimize the toxicities related to lenvatinib/pembrolizumab, and how do other multidisciplinary team members assist?

RTP
RESEARCH
TO PRACTICE

Consulting Faculty Questions

Treatment approach for patients with an isolated recurrence on or after treatment with immunotherapy

Neil Love, MD

Floor J Backes, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Floor J Backes, MD

How would you approach the treatment of a patient with MSI-H/dMMR metastatic EC who experienced a CR with front-line chemotherapy combined with an anti-PD-1/PD-L1 antibody but, while still receiving maintenance therapy, was found to have an isolated lung metastasis that is removed? What if the patient developed an isolated recurrence 6 months after completing maintenance therapy?

RTP
RESEARCH
TO PRACTICE

What is your usual second-line treatment for a patient with metastatic EC who experiences disease progression on carboplatin/paclitaxel and whose disease is …?

	MSS/pMMR	MSI-high/dMMR
 Prof Colombo	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab
 Dr Powell	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab
 Dr Slomovitz	Lenvatinib/pembrolizumab	Lenvatinib/pembrolizumab
 Dr Westin	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab
 Dr Backes	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab
 Dr Salani	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

What is your usual second-line treatment for a patient with metastatic EC who experiences disease progression on carboplatin/paclitaxel/anti-PD-1/PD-L1 antibody and whose disease is …?

	MSS/pMMR	MSI-high/dMMR
 Prof Colombo	Doxorubicin, weekly paclitaxel	Doxorubicin, weekly paclitaxel
 Dr Powell	Will consider lenvatinib/pembrolizumab	Will consider lenvatinib/pembrolizumab or nivolumab/ipilimumab
 Dr Slomovitz	Switch chemotherapy and add bevacizumab	Switch chemotherapy and add bevacizumab
 Dr Westin	Switch chemo and add bevacizumab or lenvatinib/pembrolizumab	Switch chemo and add bevacizumab or lenvatinib/pembrolizumab
 Dr Backes	Lenvatinib/pembrolizumab	Lenvatinib/pembrolizumab
 Dr Salani	It depends on interval, but would challenge with platinum-based chemotherapy	Switch chemotherapy and add bevacizumab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

For a patient with recurrent metastatic EC to whom you are about to administer second-line lenvatinib/pembrolizumab, in general, what is your usual starting dose of lenvatinib? Approximately what proportion of patients with EC who receive your usual starting dose of lenvatinib require dose modification?

	Lenvatinib starting dose	Proportion of patients requiring dose reduction
 Prof Colombo	20 mg	80%
 Dr Powell	14 mg	25%
 Dr Slomovitz	20 mg	60%
 Dr Westin	20 mg	50%
 Dr Backes	20 mg	75%
 Dr Salani	20 mg	60%

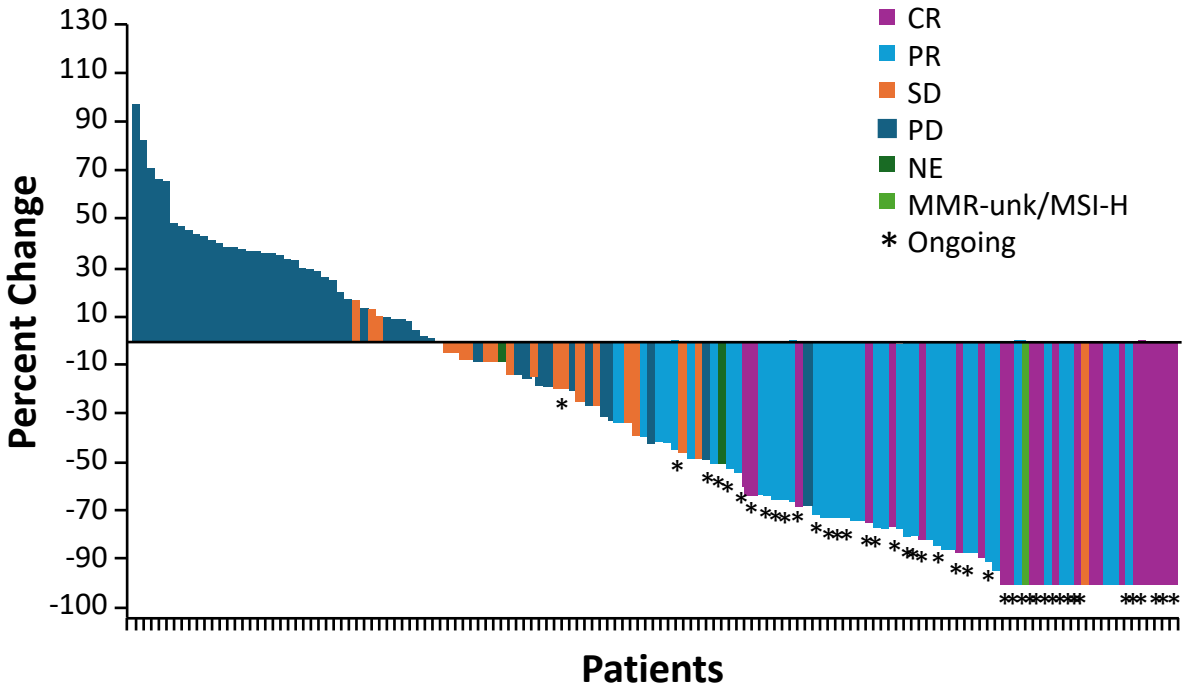
Current Options for Relapsed/Refractory EC

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)



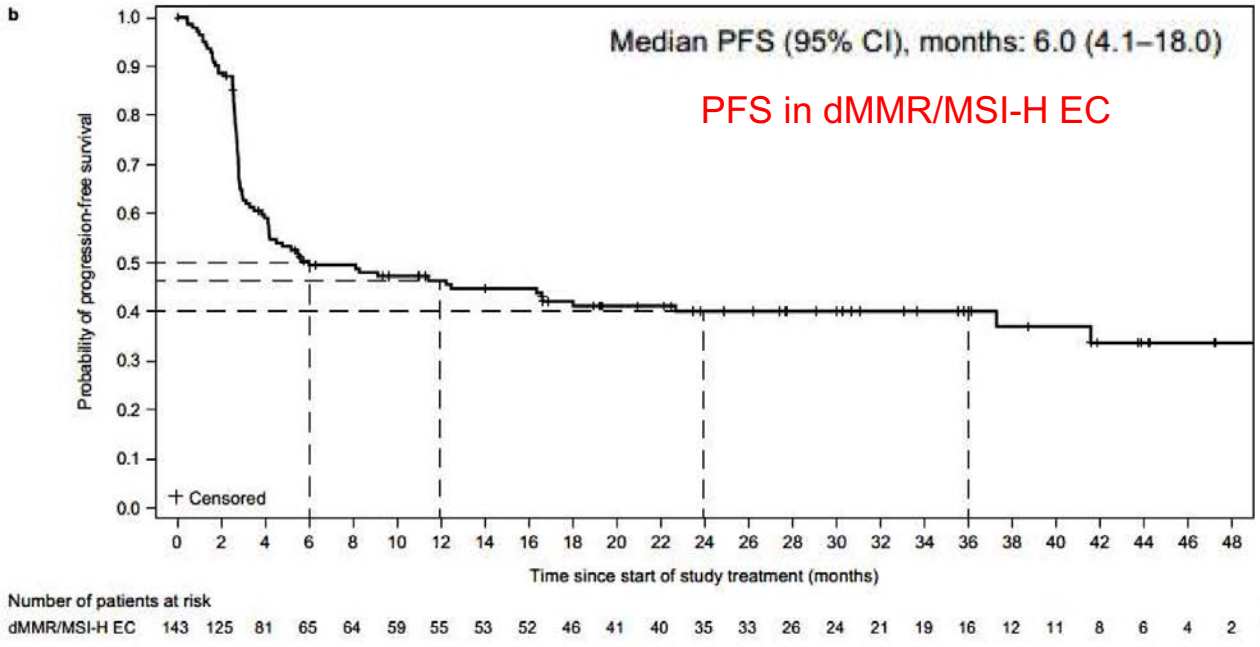
CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; pMMR, mismatch repair proficient; PR, partial response; SD, stable disease.

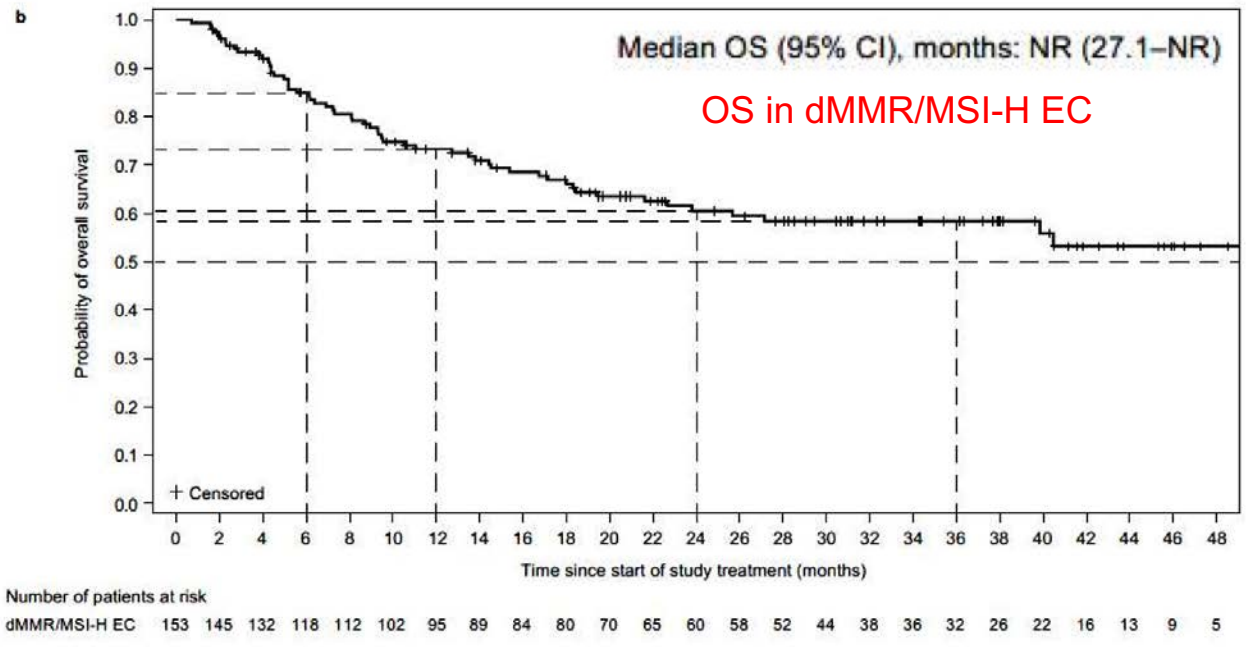
Oaknin A, et al. *J Immunother Cancer*. 2022;10:e003777.

GARNET: Dostarlimab in dMMR/MSI-H EC

Table 2. Efficacy Results by Tumor Type for Patients With dMMR and MSI-H or POLE-Altered Tumors in the Efficacy Population

Tumor type	Patients, No.	No. (%) CR	No. (%) PR	ORR, % (95% CI)	mDOR (95% CI), mo	mPFS (95% CI), mo	mOS (95% CI), mo
Overall	347	46 (13.3)	107 (30.8)	44.1 (38.8-49.5)	NR (NR-NR)	7.0 (4.2-13.8)	NR (39.9-NR)
dMMR overall	327	43 (13.1)	101 (30.9)	44.0 (38.6-49.6)	NR (NR-NR)	6.9 (4.2-13.6)	NR (31.6-NR)
EC	143	23 (16.1)	42 (29.4)	45.5 (37.1-54.0)	NR (38.9-NR)	6.0 (4.1-18.0)	NR (25.7-NR)





dMMR = mismatch repair deficient; MSI-H = microsatellite instability-high

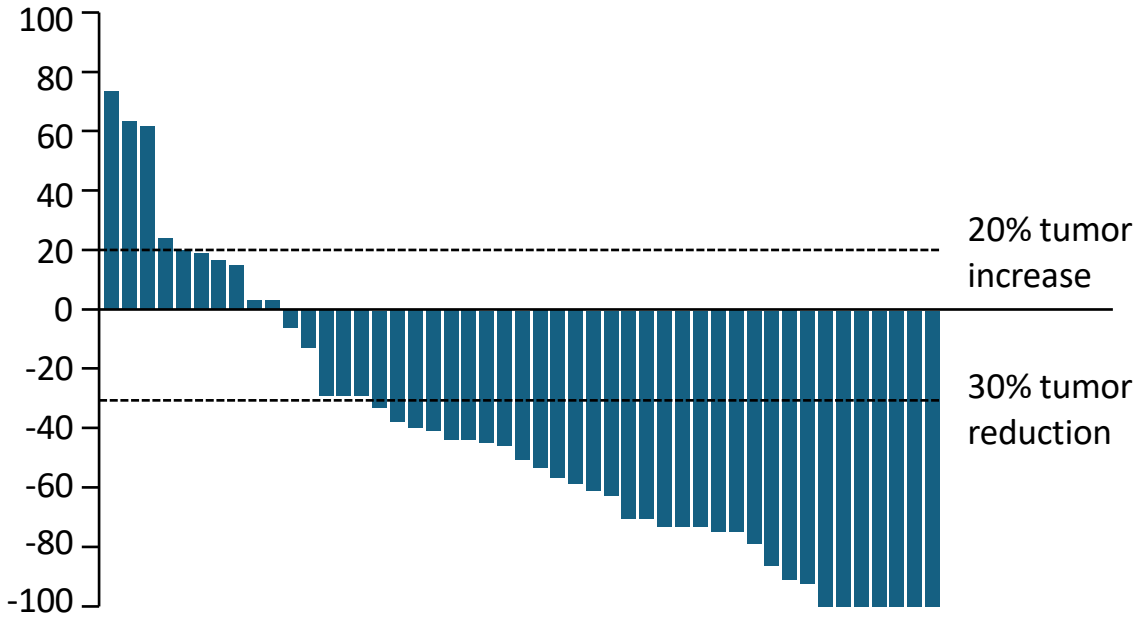
André T et al. *JAMA Netw Open* 2023;6(11):e2341165.

RTP RESEARCH TO PRACTICE

KEYNOTE-158: Pembrolizumab in MSI-H Advanced EC

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

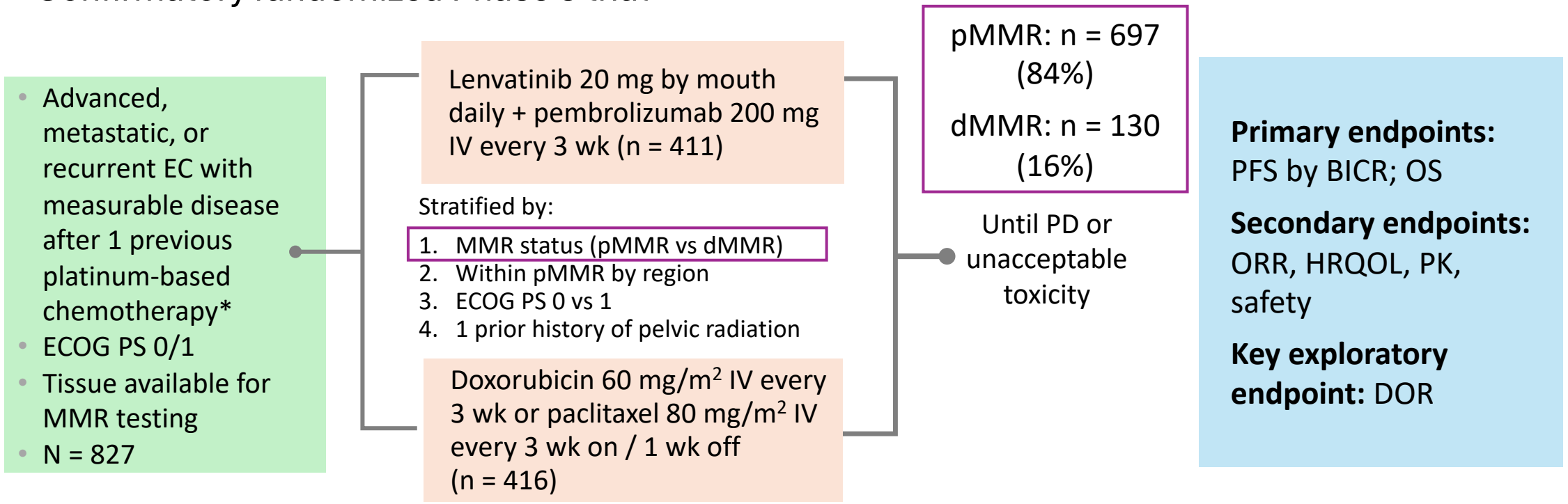
Variable	MSI-H EC n = 79	EC (Biomarker Unselected) n = 107
ORR % (95% CI)	**48** (37-60)	**11.2** (5.9-18.8)
Complete response	11 (14)	0
Partial response	27 (34)	12 (11.2)
Stable disease	14 (18)	26 (24.3)
Progressive disease	23 (29)	56 (52.3)
Not evaluable	1 (1)	2 (1.9)
Not assessed	3 (4)	11 (10.3)



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

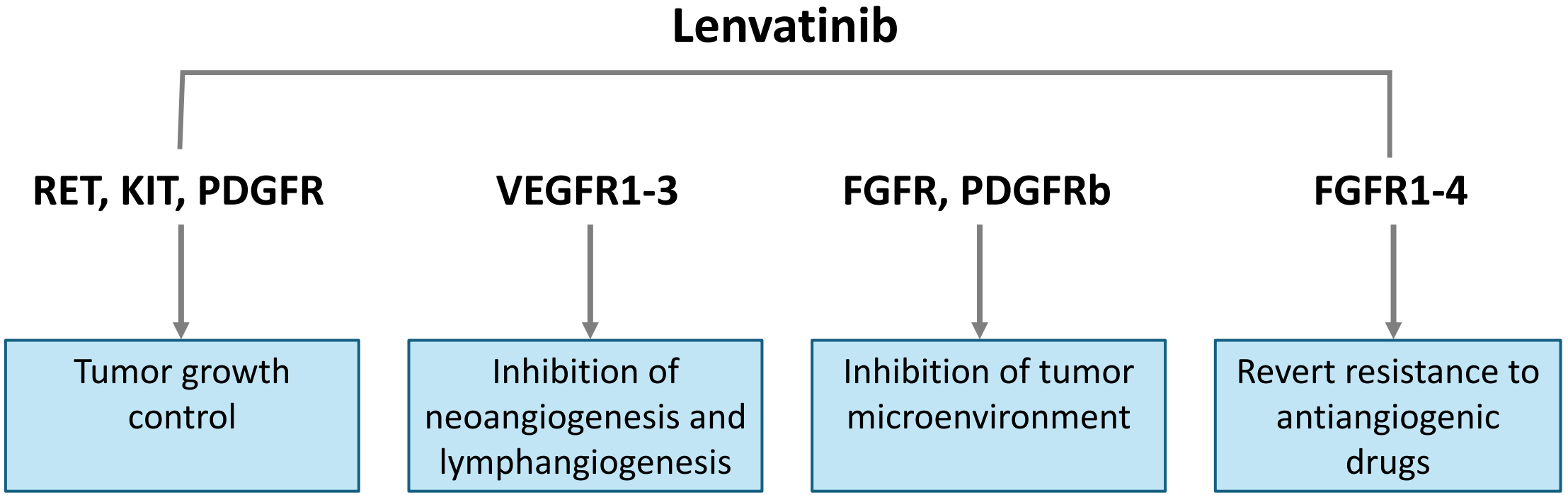
Study 309/KEYNOTE-775: Phase 3 Trial of TKI Lenvatinib + Pembrolizumab After Platinum for Advanced EC

- 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.

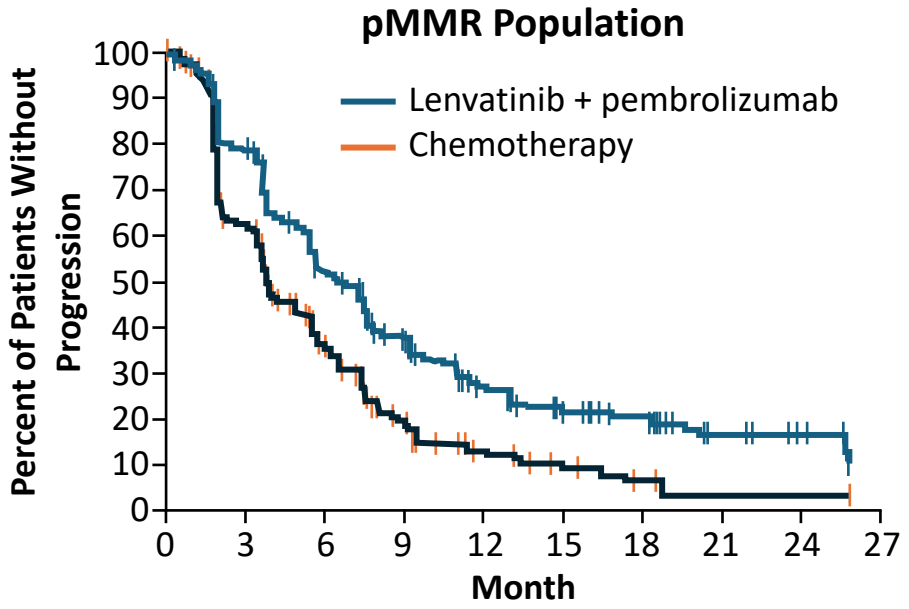
Study 309/KEYNOTE-775



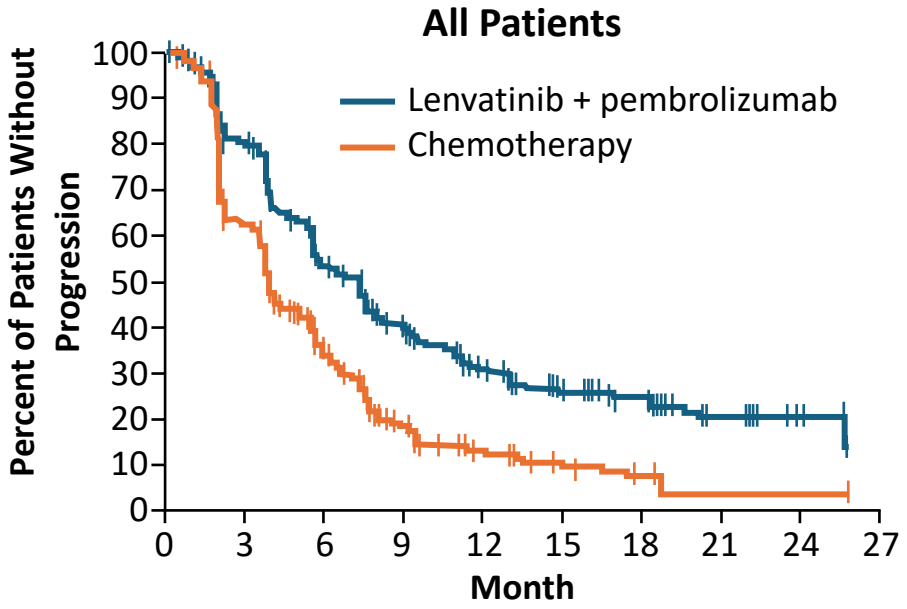
FGFR, fibroblast growth factor receptor; KIT, proto-oncogene, receptor tyrosine kinase; PDGFR, platelet-derived growth factor receptor alpha; RET, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.

Stjepanovic N, Capdevila J. *Biologics*. 2014;8:129-139.

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	

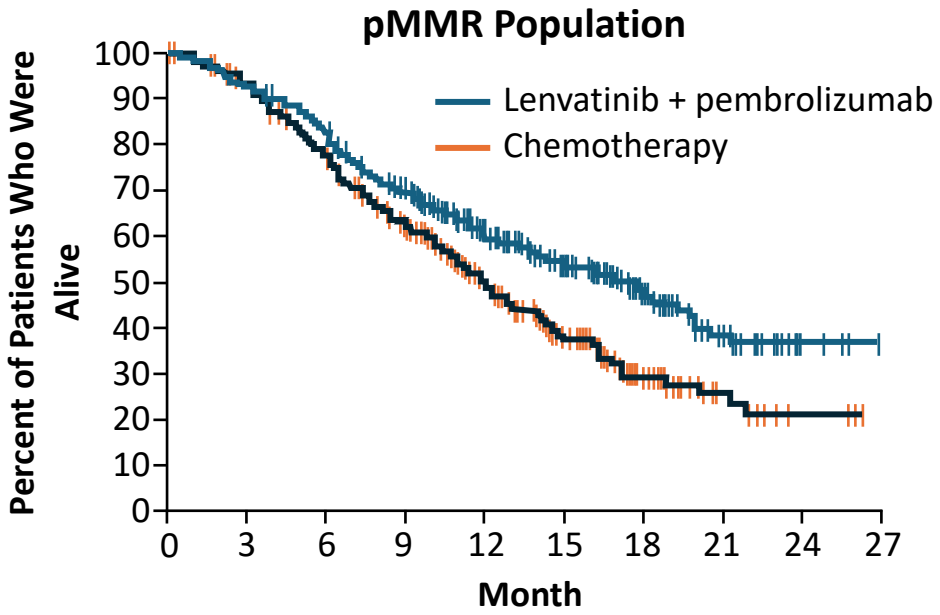


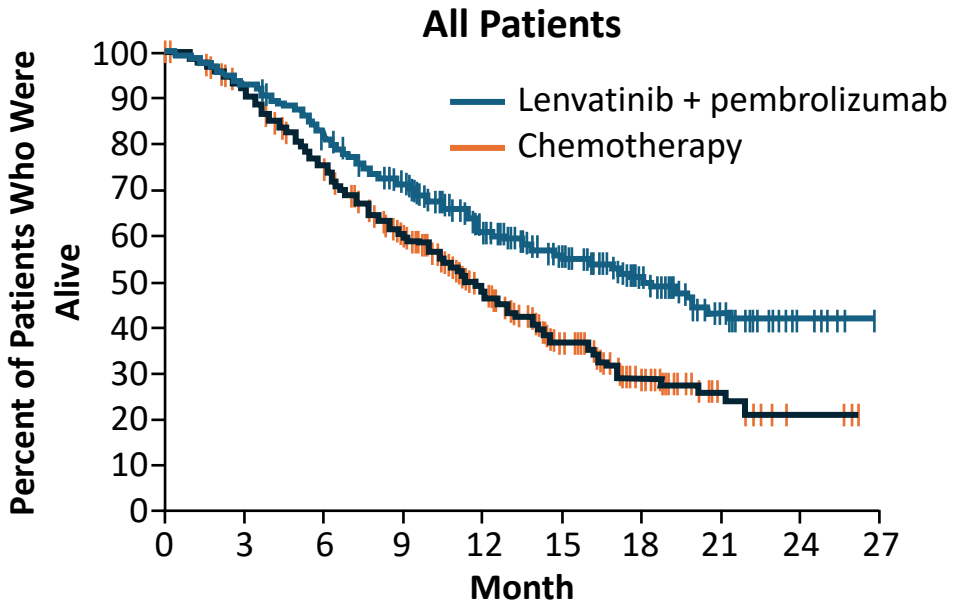
	mPFS, mo (95% CI)
Len + pembro	7.2 (5.7, 7.6)
Chemotherapy	3.8 (3.6, 4.2)
HR for progression or death, 0.56 (95% CI, 0.47, 0.66) *P* < .001	

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	

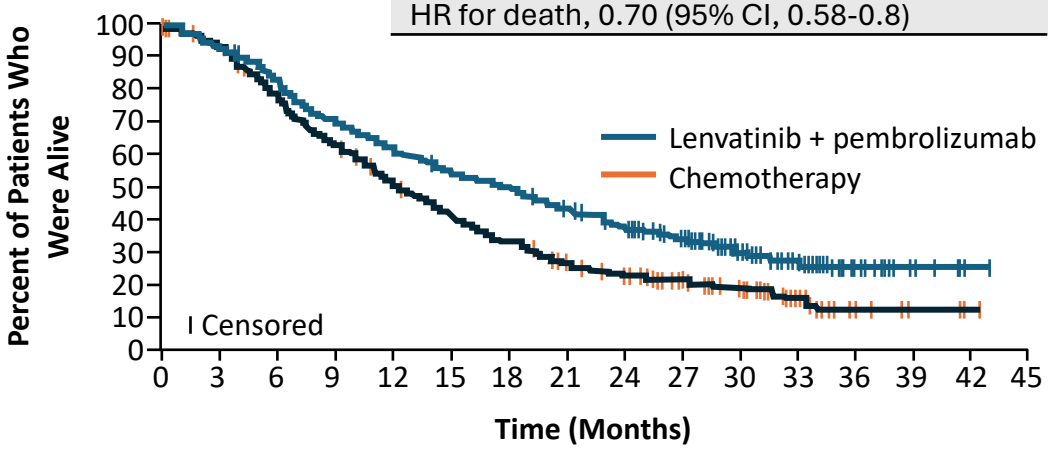
mOS, median overall survival.

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

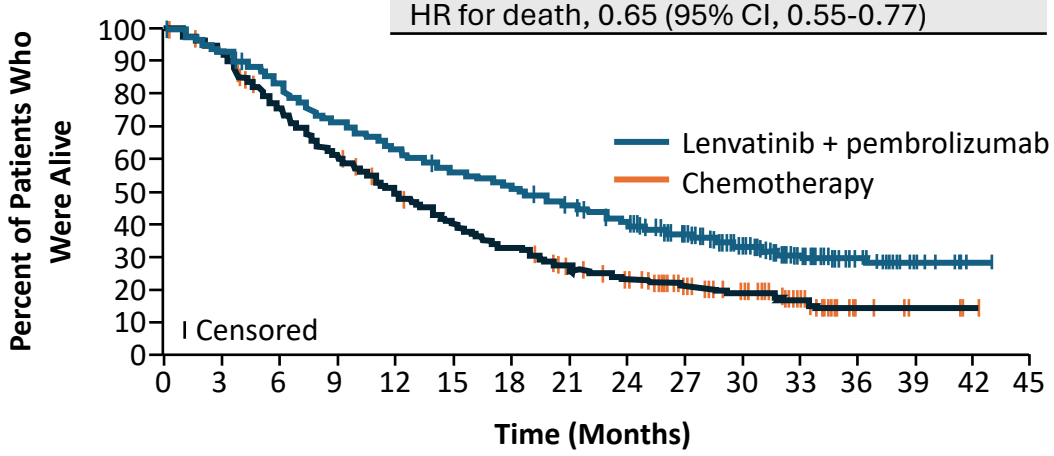
pMMR Population

	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:

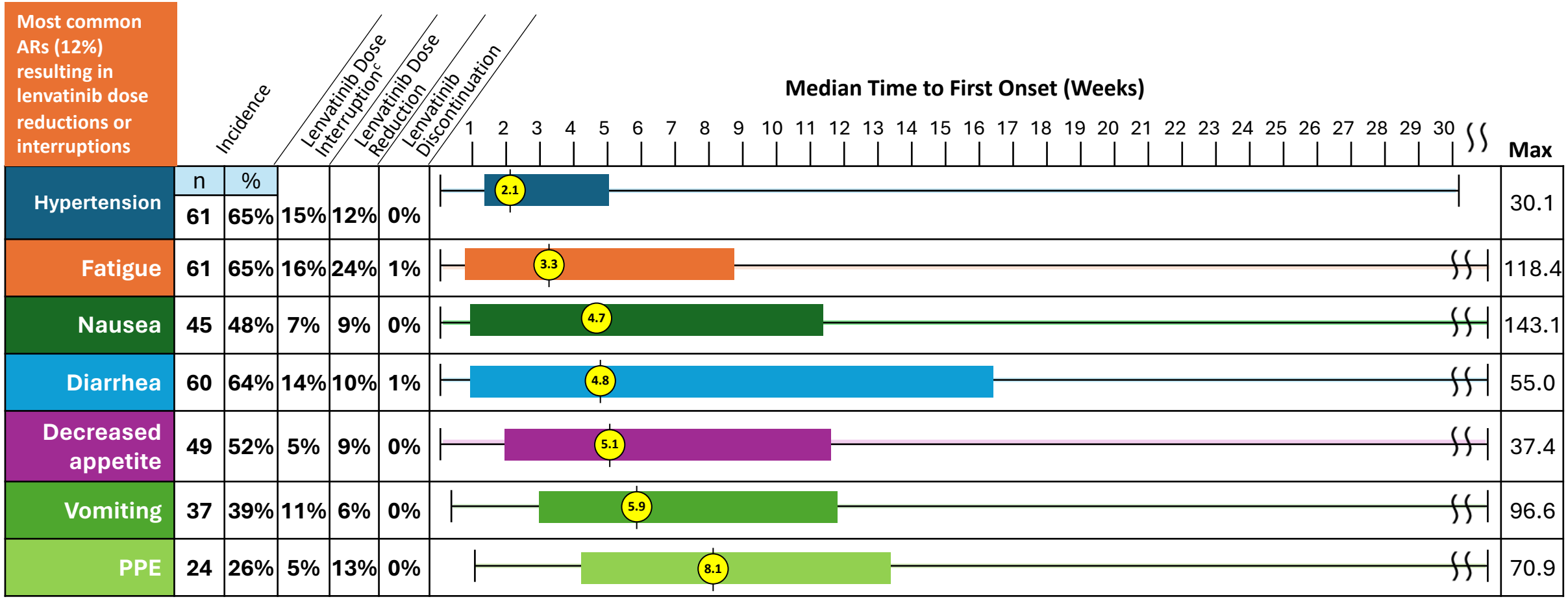
- Neutropenia (26%) and anemia (15%)

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

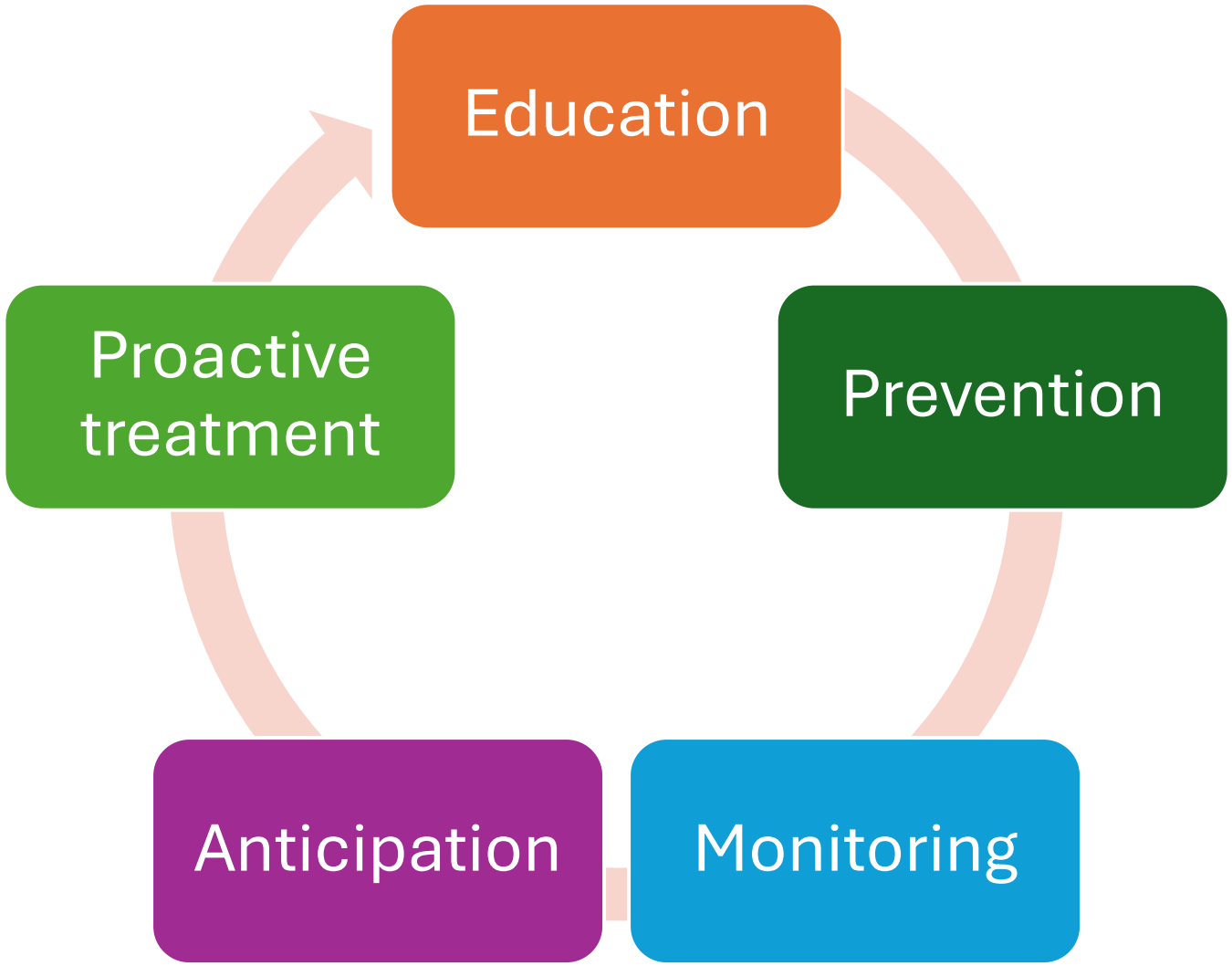
Most Common Adverse Reactions, All Grades, Time to First Onset, Weeks



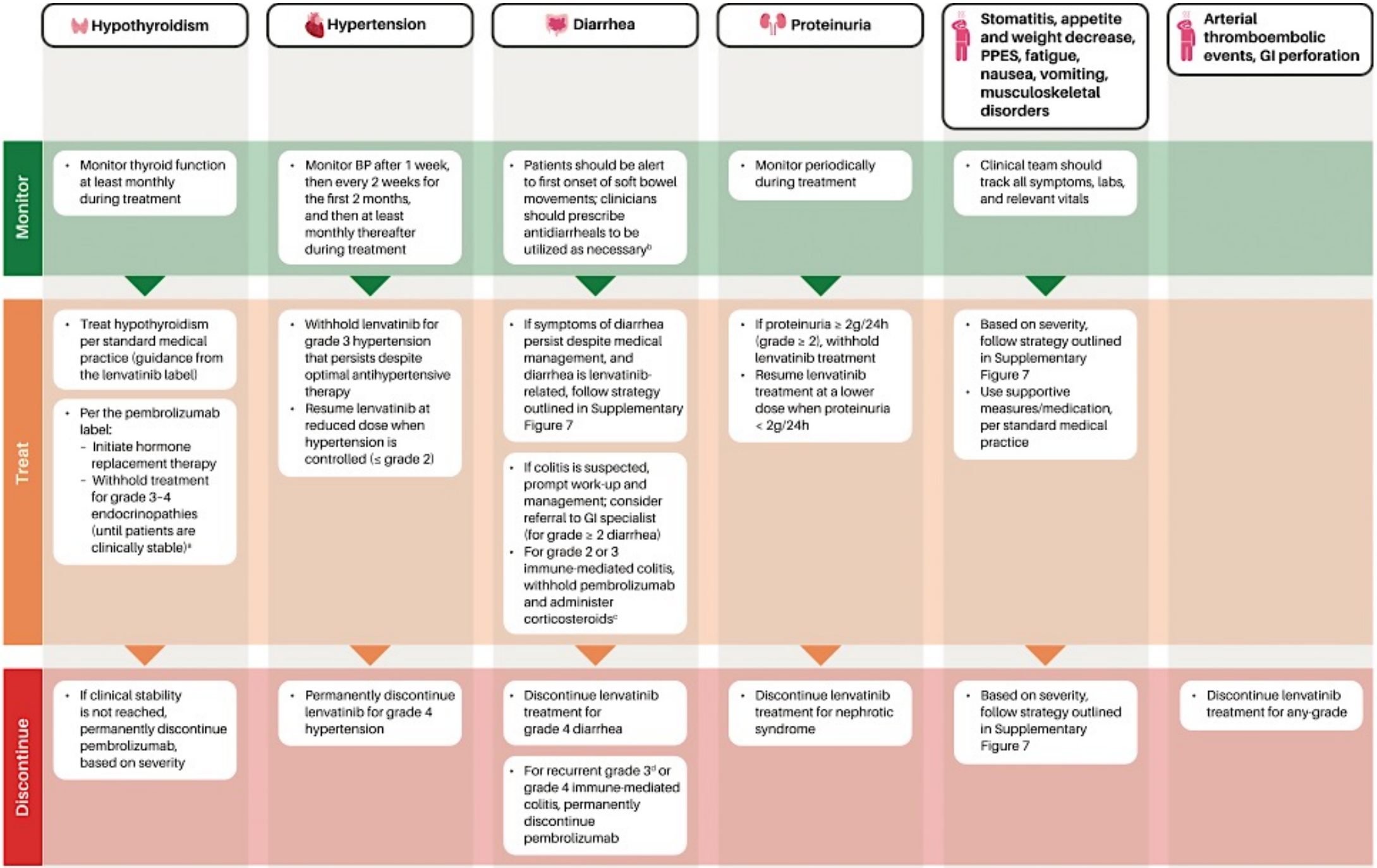
ARs, adverse reactions; PPE, palmar-plantar erythrodysesthesia.

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

Key points for toxicity management



- Increase awareness about toxicity/efficacy of lenvatinib among patients, caregivers and physicians
- Working on prevention and prehabilitation (when possible)
- Management of side effects as early as possible (don’t wait for Grade 3 toxicity!)
- Increase and ameliorate the adherence to treatment

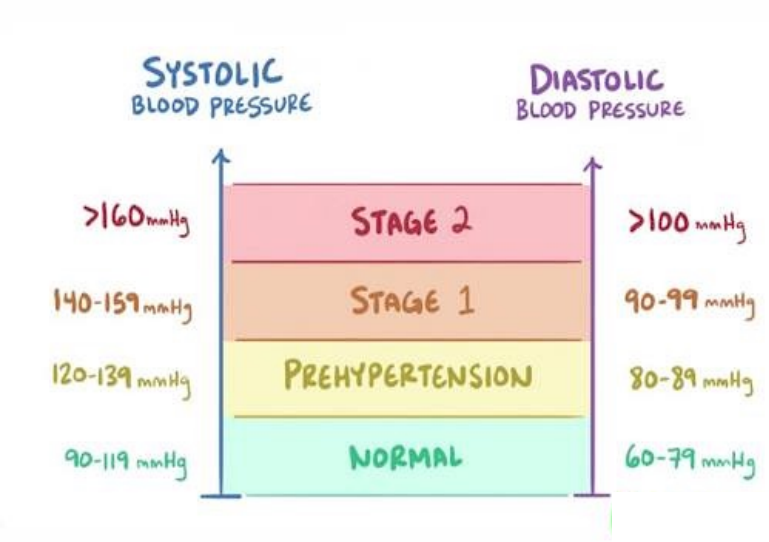

Hypothyroidism
Hypertension
Diarrhea
Proteinuria
Stomatitis, appetite and weight decrease, PPES, fatigue, nausea, vomiting, musculoskeletal disorders
Arterial thromboembolic events, GI perforation
Monitor
Monitor thyroid function at least monthly during treatment
Monitor BP after 1 week, then every 2 weeks for the first 2 months, and then at least monthly thereafter during treatment
Patients should be alert to first onset of soft bowel movements; clinicians should prescribe antidiarrheals to be utilized as necessary[b]
Monitor periodically during treatment
Clinical team should track all symptoms, labs, and relevant vitals
Treat
Treat hypothyroidism per standard medical practice (guidance from the lenvatinib label)
Per the pembrolizumab label:
- Initiate hormone replacement therapy
- Withhold treatment for grade 3–4 endocrinopathies (until patients are clinically stable)[a]
Withhold lenvatinib for grade 3 hypertension that persists despite optimal antihypertensive therapy
Resume lenvatinib at reduced dose when hypertension is controlled (≤ grade 2)
If symptoms of diarrhea persist despite medical management, and diarrhea is lenvatinib-related, follow strategy outlined in Supplementary Figure 7
If colitis is suspected, prompt work-up and management; consider referral to GI specialist (for grade ≥ 2 diarrhea)
For grade 2 or 3 immune-mediated colitis, withhold pembrolizumab and administer corticosteroids[c]
If proteinuria ≥ 2g/24h (grade ≥ 2), withhold lenvatinib treatment
Resume lenvatinib treatment at a lower dose when proteinuria < 2g/24h
Based on severity, follow strategy outlined in Supplementary Figure 7
Use supportive measures/medication, per standard medical practice
Discontinue
If clinical stability is not reached, permanently discontinue pembrolizumab, based on severity
Permanently discontinue lenvatinib for grade 4 hypertension
Discontinue lenvatinib treatment for grade 4 diarrhea
For recurrent grade 3[d] or grade 4 immune-mediated colitis, permanently discontinue pembrolizumab
Discontinue lenvatinib treatment for nephrotic syndrome
Based on severity, follow strategy outlined in Supplementary Figure 7
Discontinue lenvatinib treatment for any-grade

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

Wee-1 Inhibitors in Endometrial Cancer

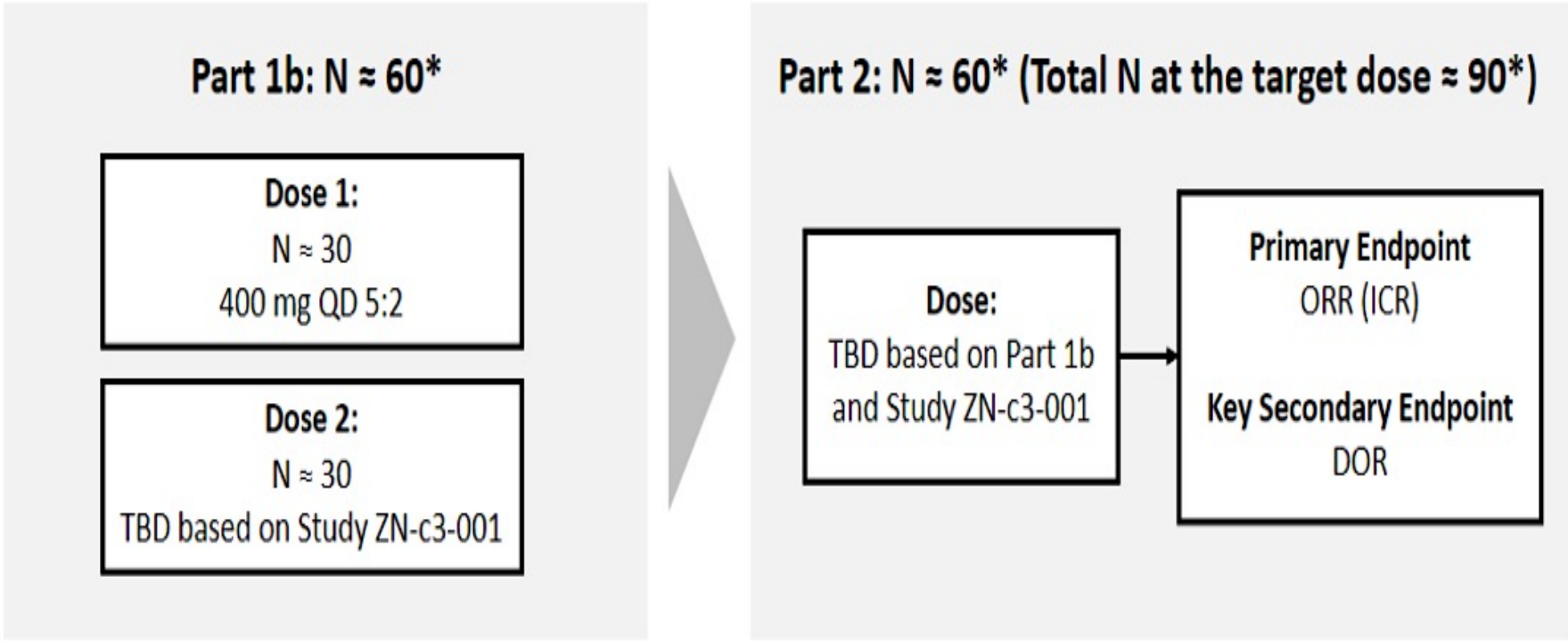
Trial Name	Phase	Publication/ Presentation	Number of patients	Median Duration of Response	Overall Response Rate	Median Progression-Free Survival
A phase II study of the WEE1 inhibitor adavosertib in recurrent uterine serous carcinoma	II	JCO 2021	34	9.0 months	29.4%	6.1 months
ADAGIO: A phase IIb international study of the Wee1 inhibitor adavosertib in women with recurrent or persistent uterine serous carcinoma	IIb	JCO 2023	167	-	24.2%	5.3 months
ZN-c3 Phase 1 Monotherapy Expansion Cohort in Patients with Advanced/Recurrent Uterine Serous Carcinoma	I	AACR 2022	43	-	27.3%	9.9 months

GOG-3065/Zn-c3-004/TETON

A Phase 2 Open-Label, Multicenter Study to Evaluate Efficacy and Safety of ZN-c3 in Adult Women with Recurrent or Persistent Uterine Serous Carcinoma (GOG PI: Shannon Westin, MD)

Key Eligibility Criteria:

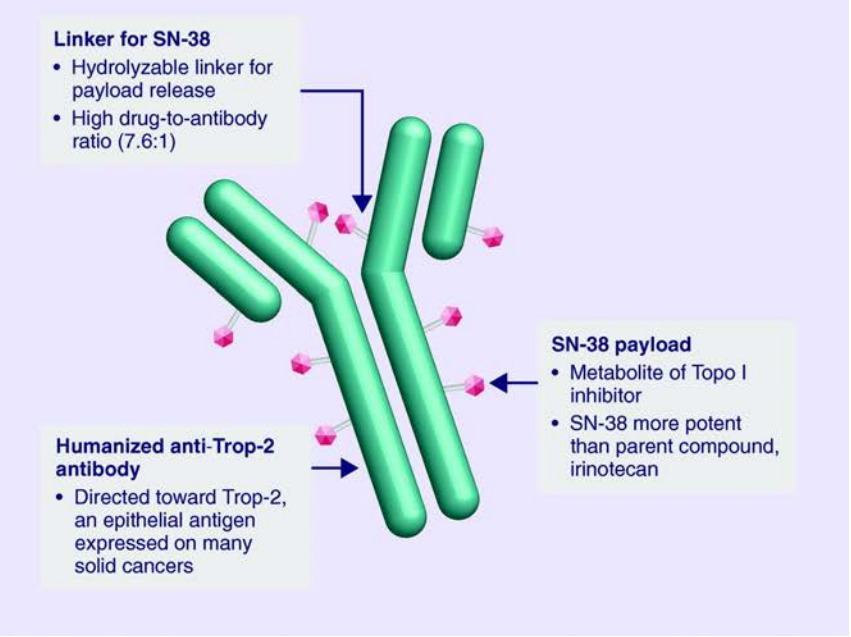
- Histologically confirmed recurrent or persistent USC
  - Subjects with endometrial carcinoma of mixed histology where the serous component comprises at least 5% of the tumor will be considered eligible.
  - Subjects with carcinosarcomas (even if there is a serous component) are not eligible.
- Measurable disease per RECIST 1.1
- Required prior therapy for endometrial cancer;
  - Treatment with a platinum-based chemotherapy regimen
  - Treatment with a PD-(L)1 inhibitor
  - Known HER2-positive tumors: treatment with at least 2 HER2-targeted therapies



Note: Part 1a (not shown) is described in Section 12.4. In Part 1b, Dose 2 may not be evaluated.
*Response-evaluable subjects

Sacituzumab govitecan (SG) in patients (pts) with previously treated metastatic endometrial cancer (mEC): results from a phase I/II study.

ORR 33% in mEC



Sacituzumab govitecan ADC: anti–Trop-2 antibody linked to drug SN-38.
Future Medicine. 2020 Mar.

Table 1. Demographics and clinical characteristics	SG (n = 21)
Median age at study entry, y (range)	63 (47-77)
Race, n (%)	
White	15 (71.4)
Black or African-American	0
Asian	2 (9.5)
Other	4 (19.0)
Histological/cytological diagnosis, n (%)	
Serous	10 (47.6)
Endometrioid	6 (28.6)
Carcinosarcoma	3 (14.3)
Other	2 (9.5)
Number of prior anticancer regimens, n (%)	
1-3	11 (52.4)
> 3	10 (47.6)
Median prior anticancer regimens, n (range)	3 (1-6)
Median follow up duration, m (IQR)	17 (7.6-35.2)

Table 2. Overall response rate and durable disease control	SG (n = 21) n (%)
Best overall response	
Confirmed complete response (CR)	1 (4.8)
Confirmed partial response (PR)	6 (28.5)
Stable disease	11 (47.6)
Progressive disease	3 (14.3)
Objective response rate (confirmed CR + PR)	7 (33.3)
Durable disease control (confirmed CR + PR + SD ≥ 6 months)	7 (35.0)*

*Out of 20 patients evaluable for durable disease control

Table 3. Most Common Treatment-Related Adverse Events	Grade ≥ 3 (≥ 10% of patients)
Neutropenia	9 (43%)
Fatigue	4 (19%)
Anemia	3 (14%)
Diarrhea	3 (14%)
Febrile neutropenia	2 (10%)

Santin A et al. ASCO 2023;Abstract 5599.

Study Schema: ENGOT-en23/GOG-3095/ MK-2870-005

ClinicalTrials.gov ID NCT06132958

A Phase 3, Randomized, Active-controlled, Open-label, Multicenter Study to Compare the Efficacy and Safety of MK-2870 Monotherapy Versus Treatment of Physician's Choice in Participants With Endometrial Cancer Who Have Received Prior Platinum-based Chemotherapy and Immunotherapy (PI: Monk; co-PI: Lightfoot)

Key Eligibility Criteria:

- ✓ Histologically-confirmed endometrial carcinoma or carcinosarcoma
- ✓ Radiologically apparent measurable or non-measurable disease per RECIST 1.1, as assessed by BICR
- ✓ Prior platinum exposure AND prior anti-PD-1/anti-PD-L1 exposure (given separately or in combination), in any setting including neoadjuvant or adjuvant therapy

RAND
1:1
N=710

MK-2870
4 mg/kg IV Q2W

Treatment of Physician's Choice (TPC)
Doxorubicin 60mg/m² IV Q3W
or
Paclitaxel 80mg/m² IV on Days 1, 8 and 15 of each 28-day cycle

Dual Primary Endpoints
- PFS (BICR)
- OS

Secondary Endpoints
- ORR (BICR)
- DOR (BICR)
- QoL
- Safety/Tolerability

Stratification: 4 Factors
- ❖ MMR (dMMR or pMMR)
- ❖ TROP2 expression (low vs medium + high)
- ❖ Number of prior lines of therapy (≤ 2 vs 3)
- ❖ Disease status at baseline per RECIST 1.1 as assessed by BICR (measurable vs non-measurable)

Lead Group: ENGOT
N = 142
GOG Accrual: 0
Global Enrollment: 4
GOG Activated Sites: 0/42
Study Start-up

MODULE 4: Role of HER2-Targeted Therapy in the Management of Advanced EC — Dr Powell

Consulting Faculty Questions

Approach to HER2 testing in endometrial cancer; incorporating trastuzumab deruxtecan into the treatment armamentarium and monitoring for associated toxicities

Neil Love, MD

Ritu Salani, MD, MBA

Floor J Backes, MD

RTP RESEARCH TO PRACTICE

QUESTIONS FOR THE FACULTY

Floor J Backes, MD

Ritu Salani, MD, MBA

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

In what situations, if any, would you currently use trastuzumab deruxtecan (T-DXd)?

How do you approach GI prophylaxis with T-DXd?

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

RTP RESEARCH TO PRACTICE

What is your usual first-line therapy for a patient with HER2-positive metastatic EC whose disease is …?

	MSS/pMMR	MSI-high/dMMR
 Prof Colombo	Carboplatin/paclitaxel + trastuzumab	Carboplatin/paclitaxel + anti-PD-1/PD-L1 antibody*
 Dr Powell	Carboplatin/paclitaxel + trastuzumab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Slomovitz	Carboplatin/paclitaxel + trastuzumab	Carboplatin/paclitaxel + pembrolizumab
 Dr Westin	Carboplatin/paclitaxel + either trastuzumab, pembrolizumab or dostarlimab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Backes	Carboplatin/paclitaxel + trastuzumab	Carboplatin/paclitaxel + either pembrolizumab or dostarlimab
 Dr Salani	Carboplatin/paclitaxel + trastuzumab	Carboplatin/paclitaxel + dostarlimab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

*Pembrolizumab, dostarlimab or atezolizumab

What is your usual second-line treatment for a patient with HER2-positive metastatic EC who experiences disease progression on carboplatin/paclitaxel/trastuzumab and whose disease is …?

	MSS/pMMR	MSI-high/dMMR
 Prof Colombo	Doxorubicin, weekly paclitaxel	Pembrolizumab or dostarlimab
 Dr Powell	Trastuzumab deruxtecan	Pembrolizumab or dostarlimab
 Dr Slomovitz	Lenvatinib/pembrolizumab	Lenvatinib/pembrolizumab
 Dr Westin	Trastuzumab deruxtecan	Trastuzumab deruxtecan
 Dr Backes	Trastuzumab deruxtecan	Pembrolizumab or dostarlimab
 Dr Salani	Lenvatinib/pembrolizumab	Pembrolizumab or dostarlimab

MSS = microsatellite stable; pMMR = mismatch repair proficient; MSI = microsatellite instability; dMMR = mismatch repair deficient

*Pembrolizumab, dostarlimab or atezolizumab

What is your usual third-line treatment for a patient with MSS/pMMR, HER2-positive metastatic EC who experiences disease progression on first-line carboplatin/paclitaxel/trastuzumab and second-line lenvatinib/pembrolizumab?

 Prof Colombo	Doxorubicin, weekly paclitaxel
 Dr Powell	Trastuzumab deruxtecan
 Dr Slomovitz	Trastuzumab deruxtecan
 Dr Westin	Trastuzumab deruxtecan
 Dr Backes	Trastuzumab deruxtecan
 Dr Salani	Trastuzumab deruxtecan

What is your usual third-line treatment for a patient with MSI-high/dMMR, HER2-positive metastatic EC who experiences disease progression on first-line carboplatin/paclitaxel/trastuzumab and second-line anti-PD-1/PD-L1 monotherapy?

 Prof Colombo	Doxorubicin, weekly paclitaxel
 Dr Powell	Trastuzumab deruxtecan
 Dr Slomovitz	Trastuzumab deruxtecan
 Dr Westin	Trastuzumab deruxtecan
 Dr Backes	Trastuzumab deruxtecan
 Dr Salani	Trastuzumab deruxtecan

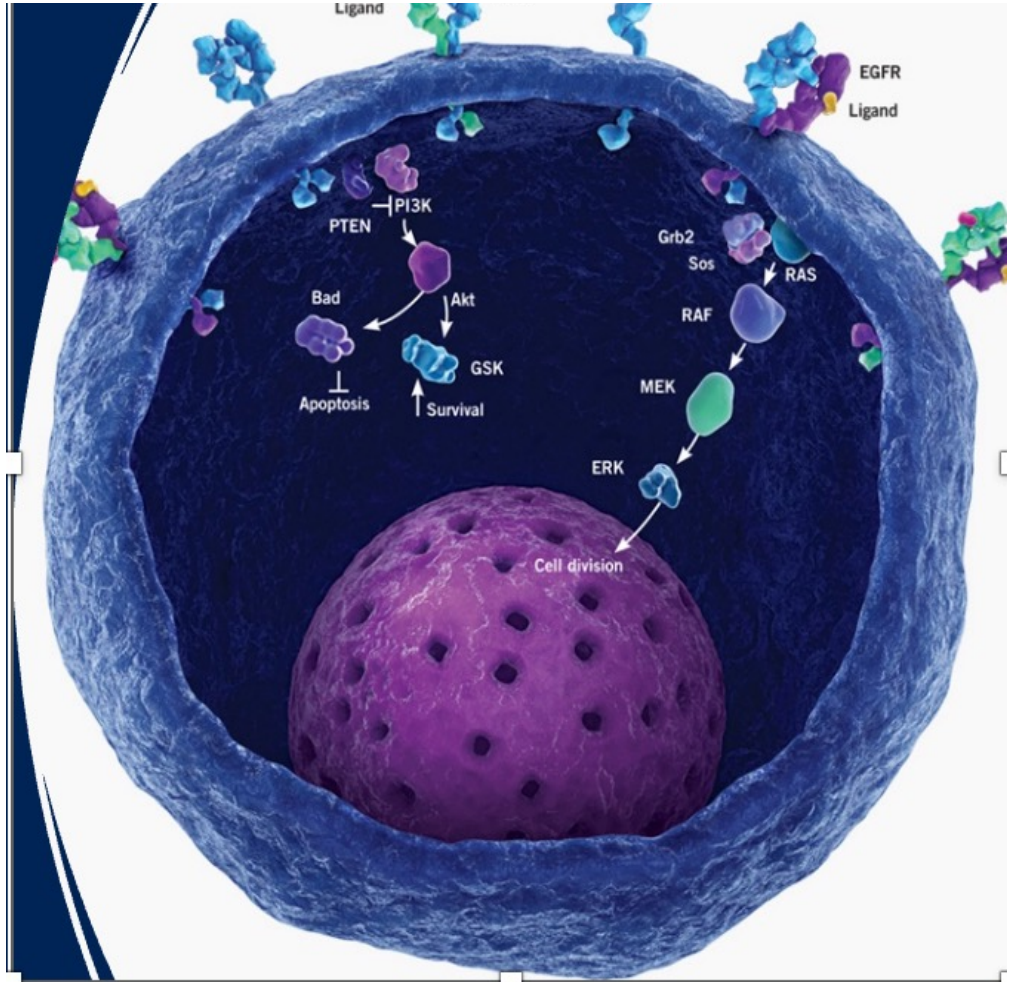
RTP RESEARCH TO PRACTICE

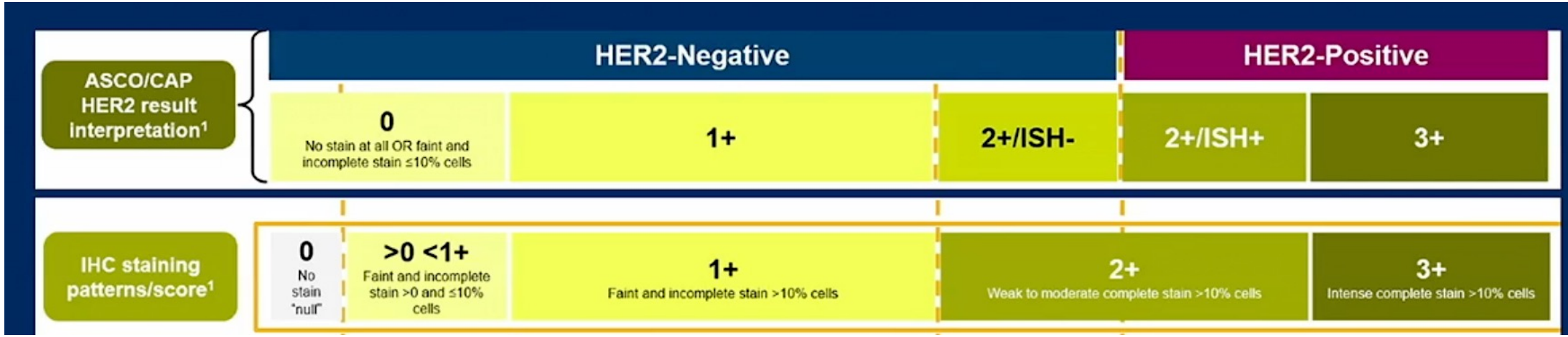
Role of HER2-Targeted Therapy in the Management of Advanced EC

Dr. Matthew A. Powell
Professor, Div. Gynecologic Oncology
Washington University School of Medicine

HER2/neu in Endometrial Cancer

- *Her2/neu* overexpression by IHC demonstrated in 14-60% of USC. Estimates vary widely due to lack of standardized algorithms for interpretation and scoring of Her2 immunostains in endometrial cancer
- Dysregulation of *Her2/neu oncogene* reported in 27% of USC in Whole Exome Sequencing (WES) studies performed by TCGA network (Levine DA , Nature 2013)
- HER2/neu functions as preferred partner for heterodimerisation with any of the other members of the EGF receptor family (HER1, HER3 and HER4) and responsible for regulating cell growth and differentiation





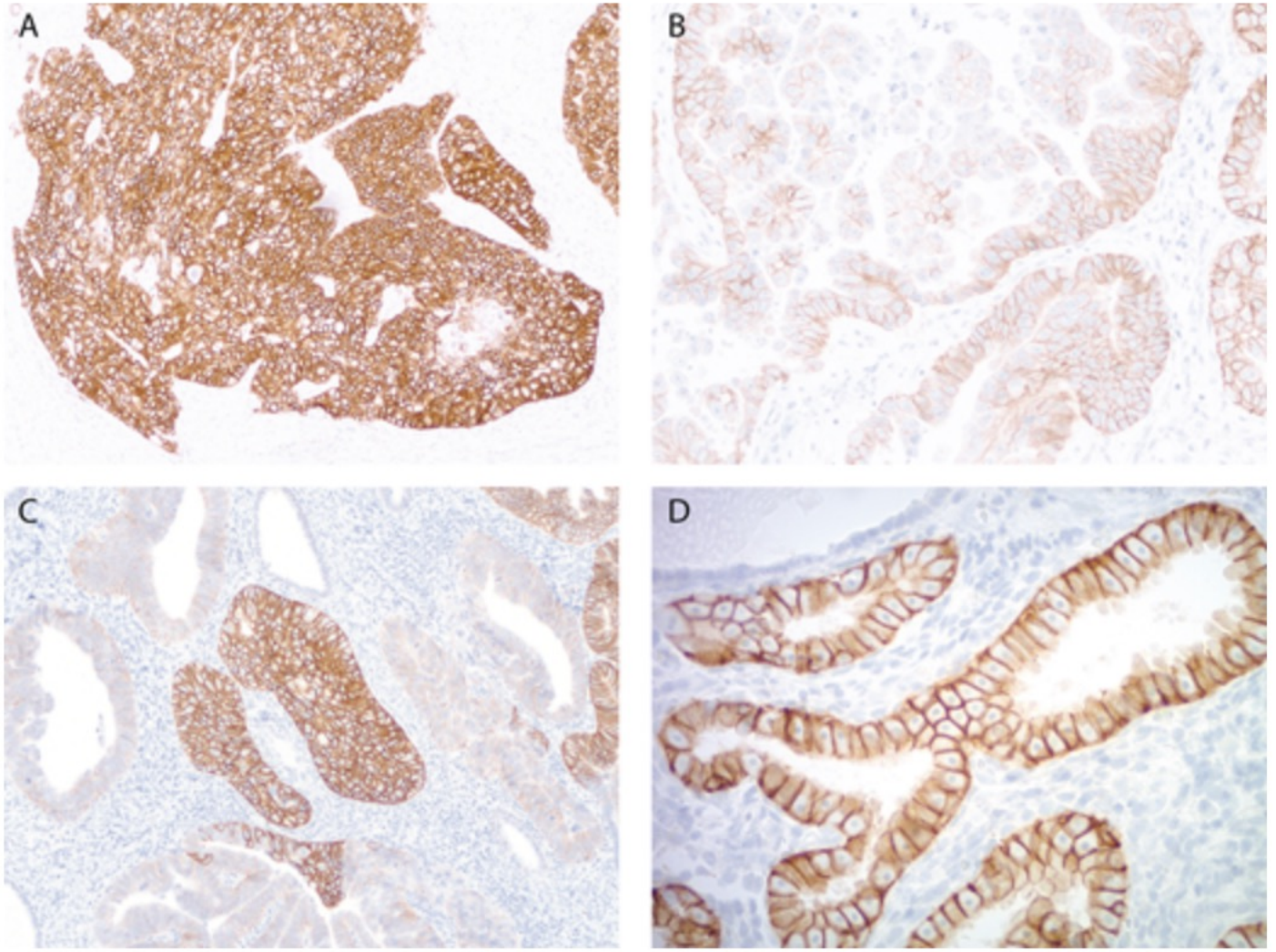
	Breast (ASCO/CAP 2018)[23]	Gastric (ASCO/CAP 2016)[36]	Colorectal (HERACLES Trial)[39]	Endometrial Serous (Fader et al Clinical Trial)[21]
HER2 IHC 3+	>10% circumferential, strong, complete	≥10%, strong complete, or basolateral/lateral	≥50% strong complete, or basolateral/lateral	>30% strong complete or basolateral/lateral
HER2 FISH amplification	*HER2*/CEP17 ratio ≥2.0 and *HER2* signal ≥4.0 per nucleus OR ratio <2.0 and *HER2* signal ≥6.0 per nucleus (if IHC score 2+ or 3+)	*HER2*/CEP17 ratio ≥2.0 OR ratio <2.0 and *HER2* signal >6.0 per nucleus	*HER2*/CEP17 ratio ≥2.0 in ≥50% of cells	*HER2*/CEP17 ratio ≥2.0

Abbreviations: ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists.

HER2 Staining

strong, complete membranous staining in >30% of tumor cells

HER2 2+ score membranous staining basolateral pattern in ≥10% of tumor cells



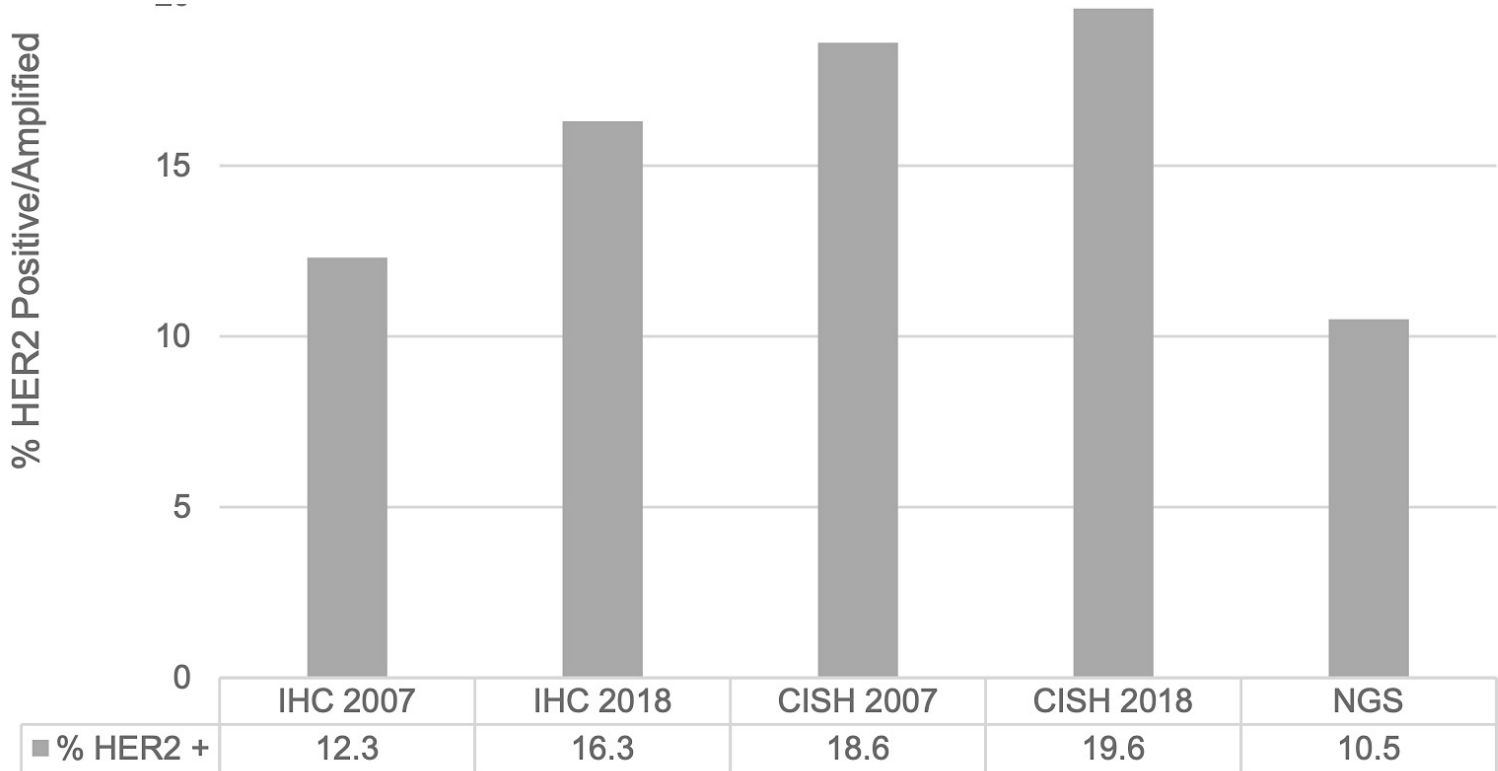
Heterogeneity

lack of apical membrane staining

HER2 in Uterine Serous Carcinoma: Testing platforms and implications for targeted therapy

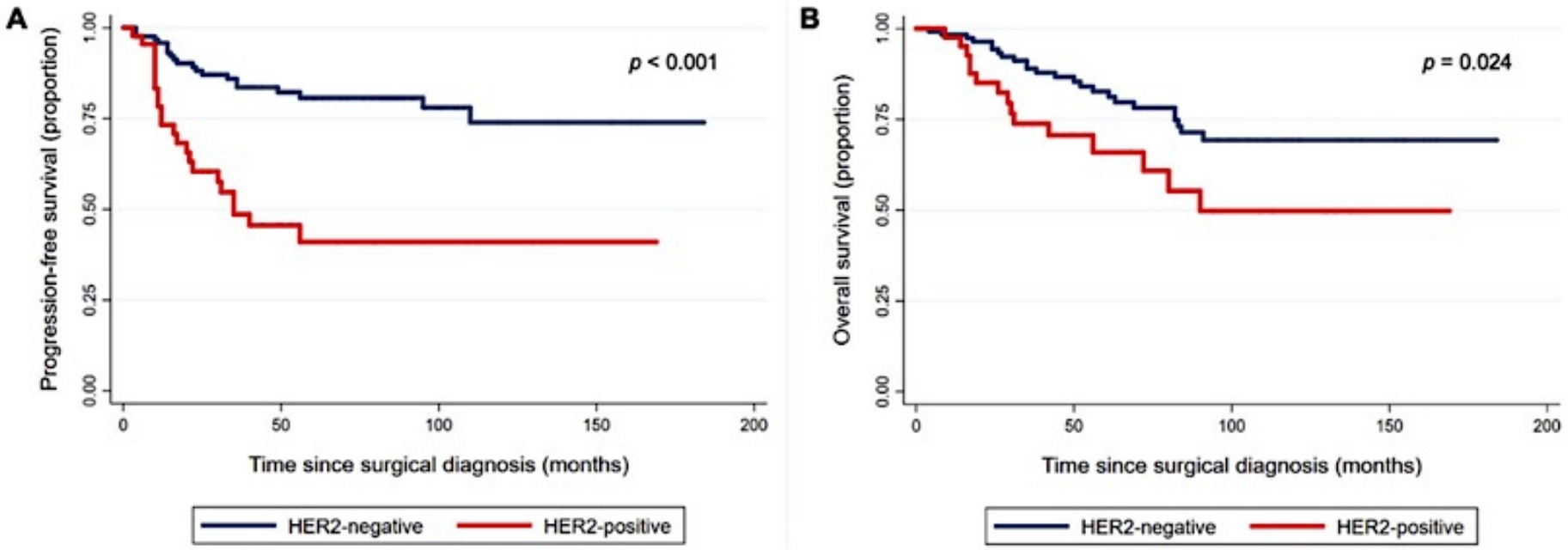
Gynecologic Oncology 167 (2022) 289–294

Tenley R. Klc [a], Sharon Wu [b], Annelise M. Wilhite [c], Nathaniel L. Jones [c], Matthew A. Powell [d], Alex Olawaiye [e], Eugenia Girda [f], Jubilee Brown [g], Allison Puechl [g], Rouba Ali-Fehmi [h], Ira S. Winer [h], Thomas J. Herzog [i], W. Michael Korn [b], Britt K. Erickson [a]



Support for HER2 testing even in early stage

Human Epidermal Growth Factor 2 (HER2) in Stage1 Uterine Serous Carcinoma (Outcomes 2X worse!)



HER2 positive tumors were associated with inferior PFS (aHR 3.50, 95%CI 1.84-6.67; p < .001) and OS (aHR 2.00, 95%CI 1.04-3.88; p = .039) compared to HER2-negative tumors even when given Carbo/Pac

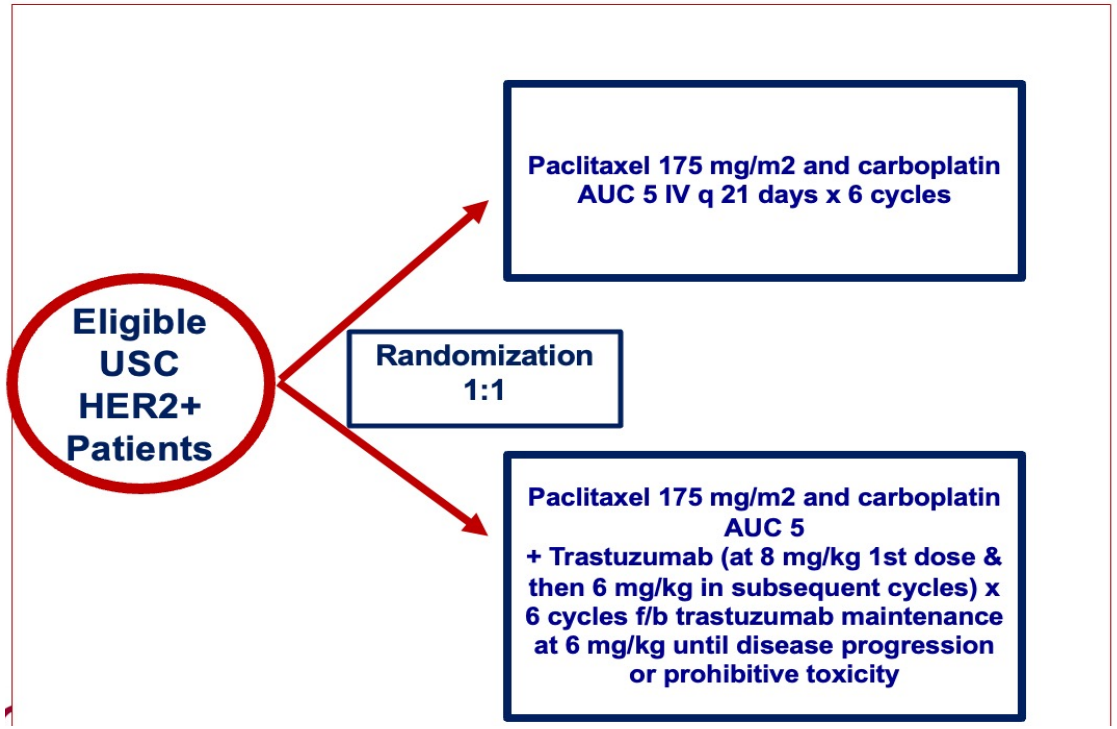
Erickson et al *Gynecol Oncol* 2020.

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

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

Study Design

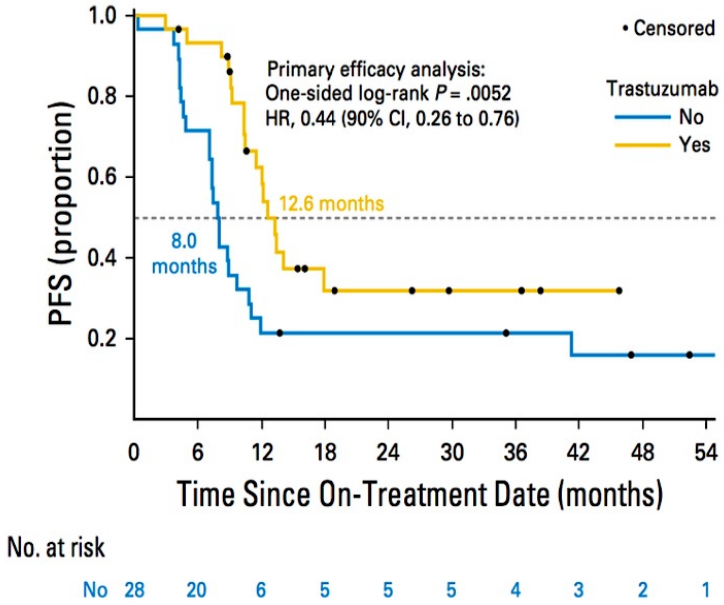


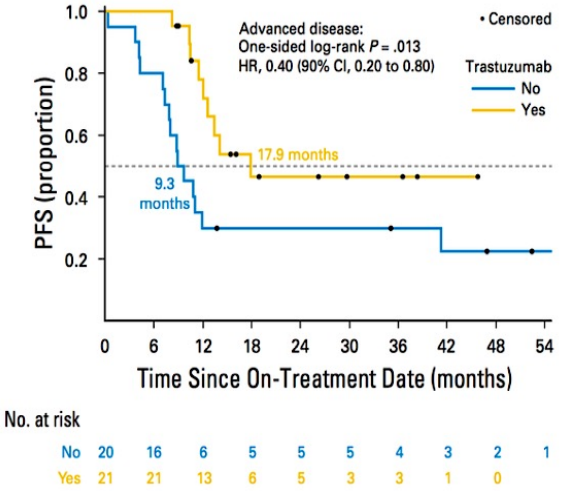
- 61 patients with advanced stage/recurrent HER2+ USC
- 3+ IHC, or 2+ with FISH + (modified 2007 ASCO/CAP)
- Measurable/non-measurable disease

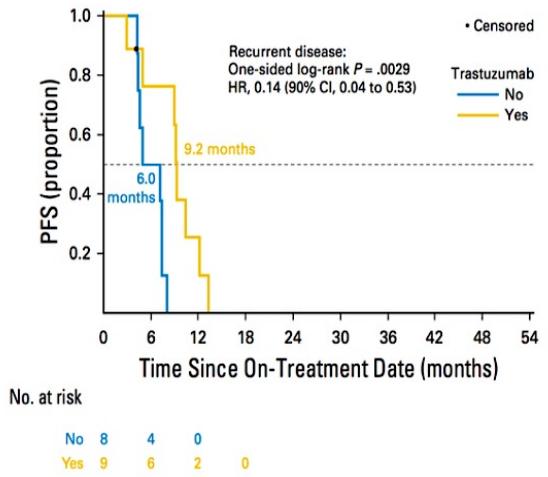
JCO, 2018

Key eligibility criteria

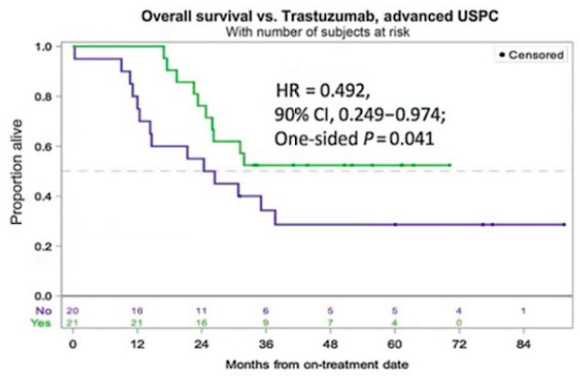
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)

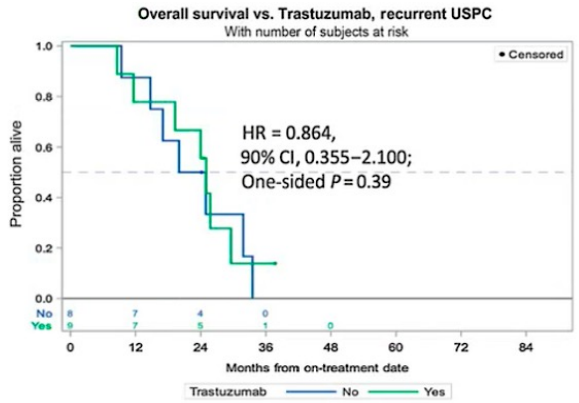






<u>OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).</u>



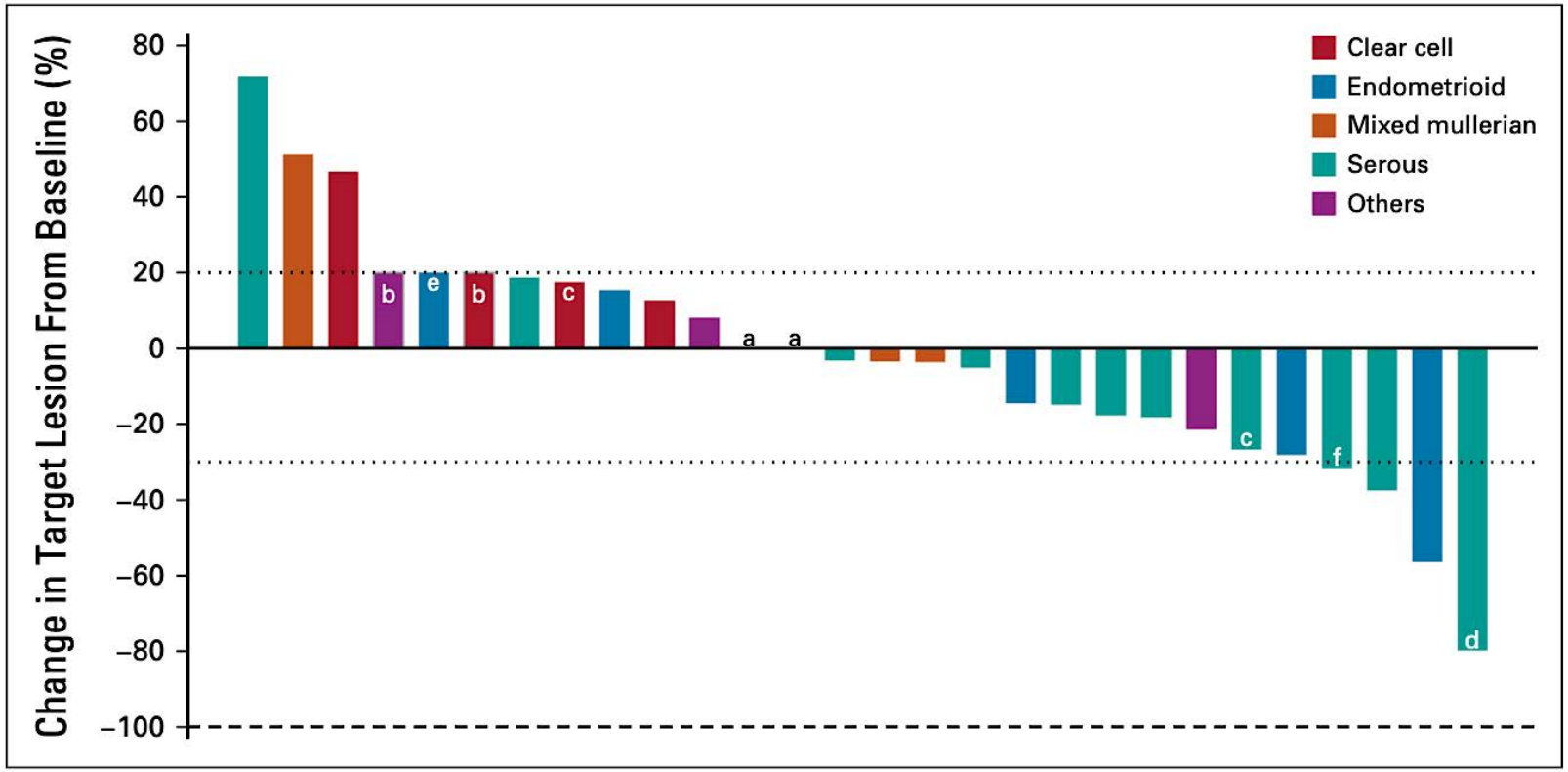


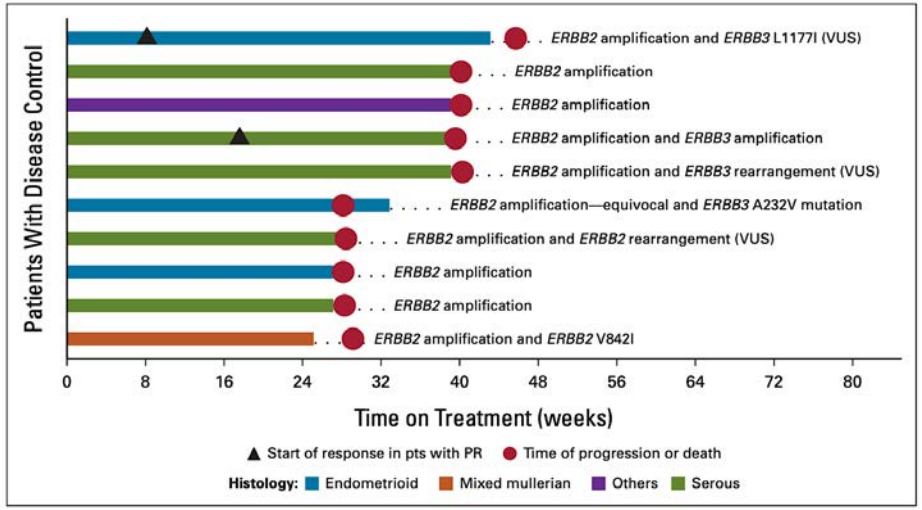
JCO, 2018; Clin Cancer Res 2020

Pertuzumab Plus Trastuzumab in Patients With Endometrial Cancer With *ERBB2/3* Amplification, Overexpression, or Mutation: Results From the TAPUR Study

Eugene R. Ahn, MD[1]; Michael Rothe, MS[2]; Pam K. Mangat, MS[2]; Elizabeth Garrett-Mayer, PhD[2]; Hussein M. Ali-Ahmad, MD[3]; John Chan, MD[4]; Michael L. Maitland, MD, PhD[5,6]; Sapna R. Patel, MD[7]; Zachary Reese, MD[8]; Ani S. Balmanoukian, MD[9]; Charles W. Drescher, MD[10]; Rui Li, MD, PhD[11]; Apostolia M. Tsimberidou, MD, PhD[12]; Charles A. Leath III, MD, MSPH[13]; Raegan O'Lone, PhD[2]; Gina N. Grantham, BS[2]; Susan Halabi, PhD[14]; and Richard L. Schilsky, MD[2]

N=28
DCR=37%
ORR=7%
Well tolerated





JCO Precis Oncol, 2023

NRG GY-026

PI: Britt Erickson
Co-PI: Amanda Fader
Intl Co-PI: Clare Scott
TransIx PI: Alessandro Santin

Newly Diagnosed, Stage I-IVB, HER2 positive uterine serous or carcinosarcoma

Randomize 1:1:1

Arm 1:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles (may continue to 10 cycles if measurable disease and SD or PR)

Arm 2:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + trastuzumab 8 mg/kg IV loading dose f/b 6 mg/kg IV q 21 days

Maintenance trastuzumab 6mg/kg IV every 21 days x 1 year (or progression/ prohibitive toxicity)

Safety Lead-In (n=45)

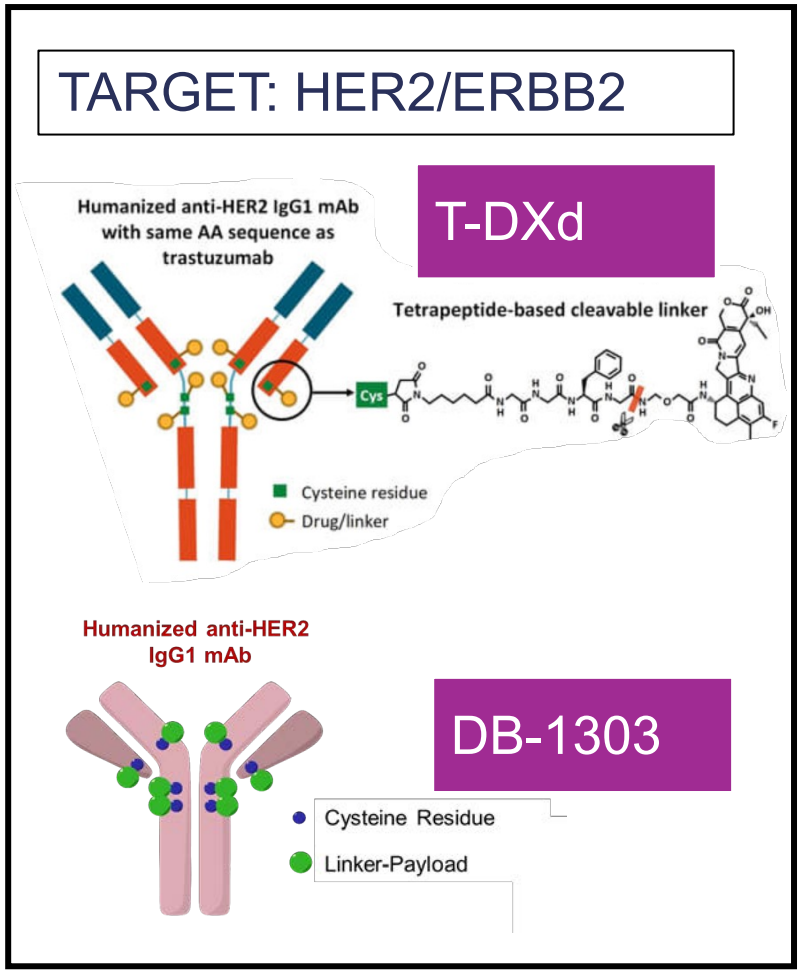
Arm 3:
Carboplatin AUC 5 + paclitaxel 175 mg/m2 q 21 days x 6 cycles + fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ (with initial 1200 mg SQ pertuzumab loading dose w 1st cycle)

Maintenance fixed dose trastuzumab 600 mg/ pertuzumab 600 mg SQ q 21 days for 1 year (or until disease progression or prohibitive toxicity)

Strata:

- Stage (I-II vs III-IV)
- Measurable vs. non-measurable dz
- Histology (serous vs carcinosarcoma)

Targeting HER2 with ADCs



Drug Name	Payload
Trastuzumab deruxtecan (DS-8201a or T-DXd)	Topoisomerase I inhibitor
BNT232/DB-1303	Topoisomerase I inhibitor

IHC = immunohistochemisty.

Erickson BK, et al. *Gynecol Oncol*. 2020;159(1):17-22. Erickson BK, et al. *Curr Opin Obstet Gynecol.* 2020;32(1):57-64.
Lin et al. Gynecol Oncol 2022.

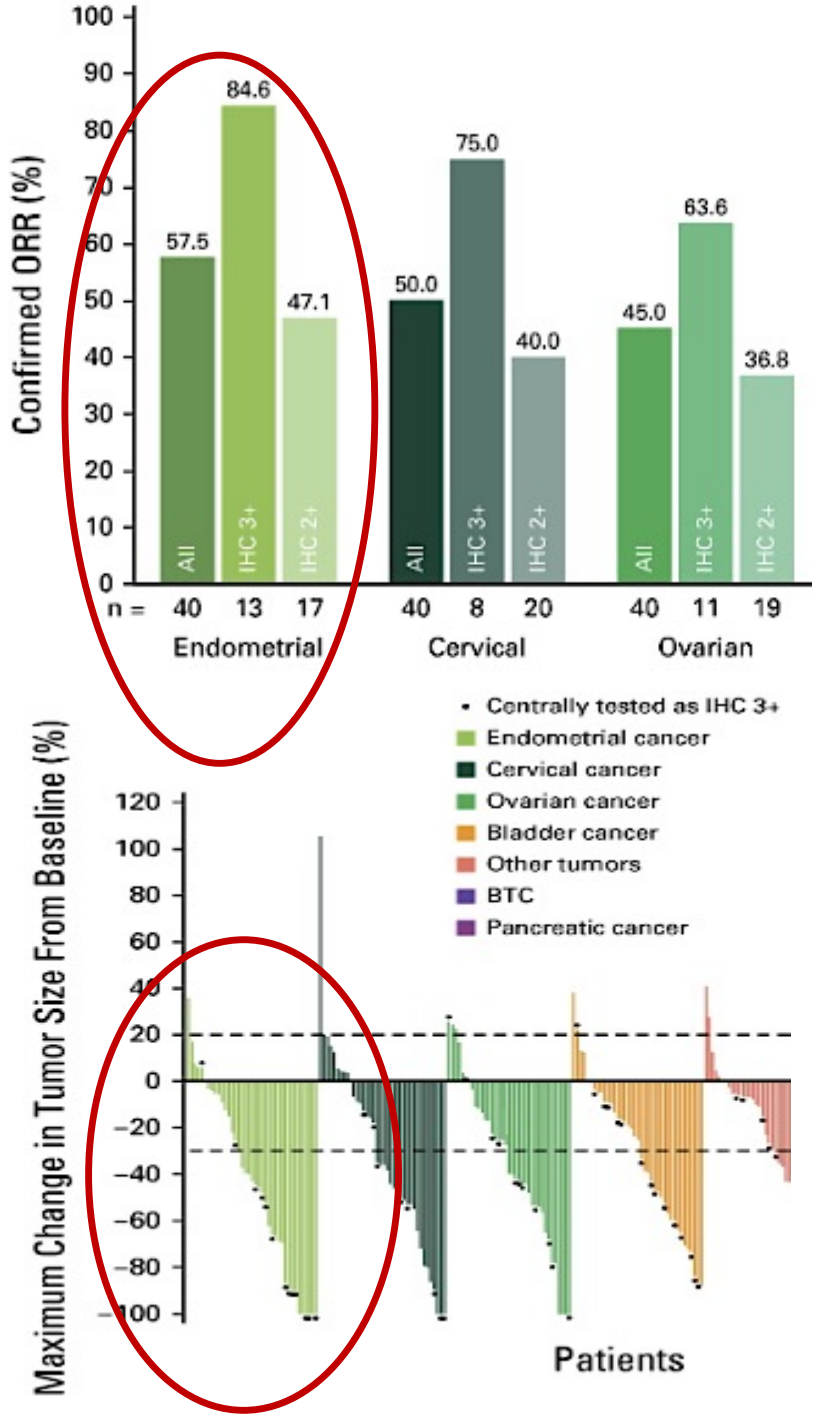
Trastuzumab Deruxtecan (T-DXd) DESTINY-PanTumor02 Phase II Trial

- N=40 endometrial cancer
- 22% prior anti-HER2
- 1/3 ≥ 3 prior lines (median 2)
- 10% Black, 25% Asian
- IHC: 3+ 33%, 2+ 43%, 1+ 10%, 0/unk 15%
- ORR 57.5%, DCR 94%

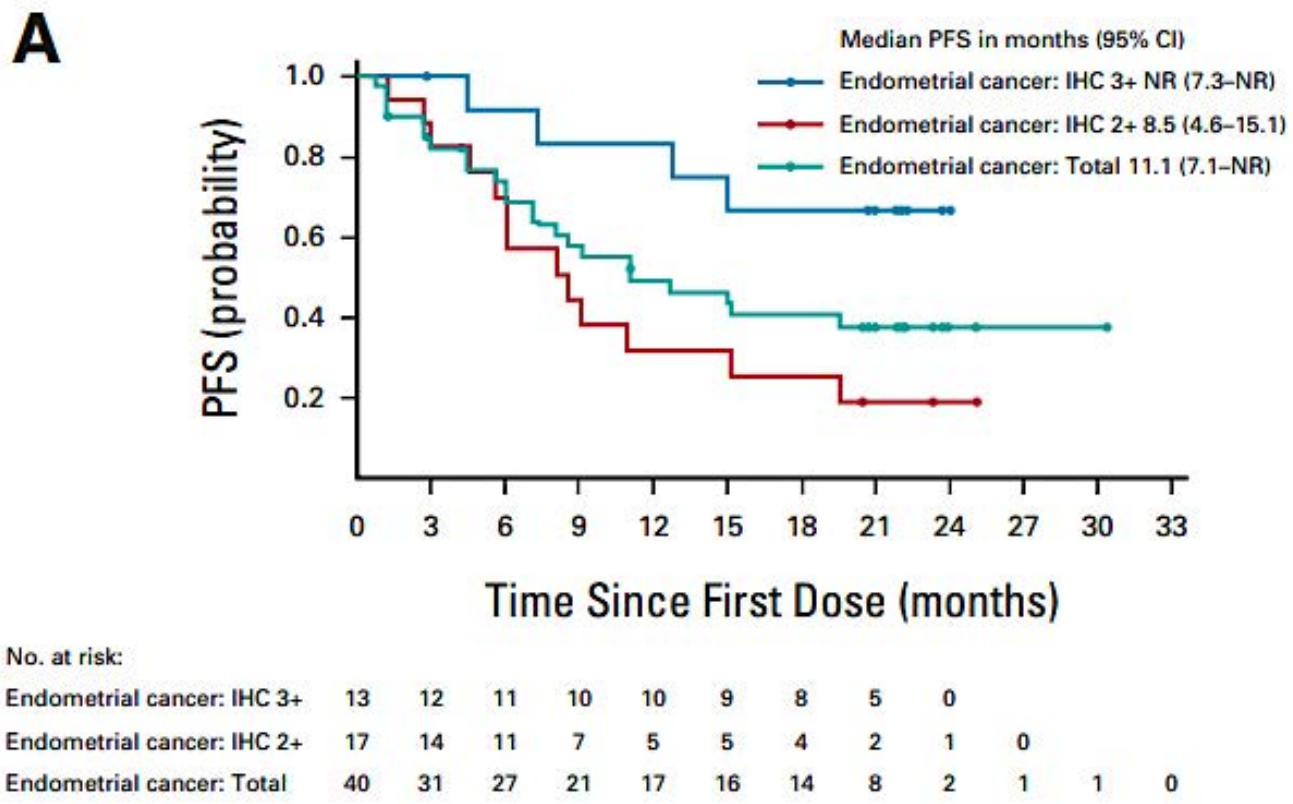
- The most frequent TEAEs of any grade were nausea, vomiting, diarrhea, fatigue.
- Grade 3 or greater was rare (neutropenia, anemia). ILD/pneumonitis 10.5% (0.4% grade 3, 1.1% grade 5)
- Alopecia 22%

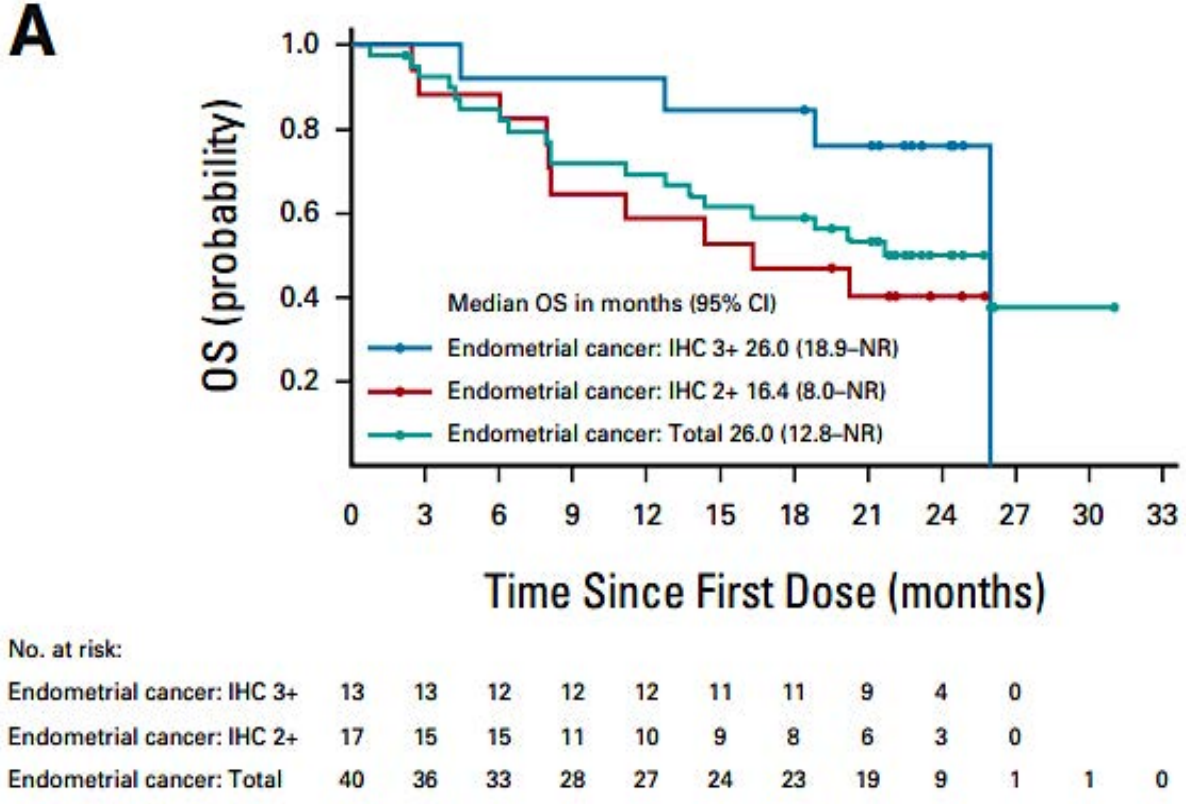
NCCN: listed version 2.2024

Meric-Bernstam, F. JCO 2023



Trastuzumab Deruxtecan (T-DXd): DESTINY-PanTumor02 Phase II Trial





Meric-Bernstam, F. JCO 2023

Trastuzumab Deruxtecan (T-DXd): DESTINY-PanTumor02 Phase II Trial

TABLE 2. Incidence of Drug-Related Adverse Events

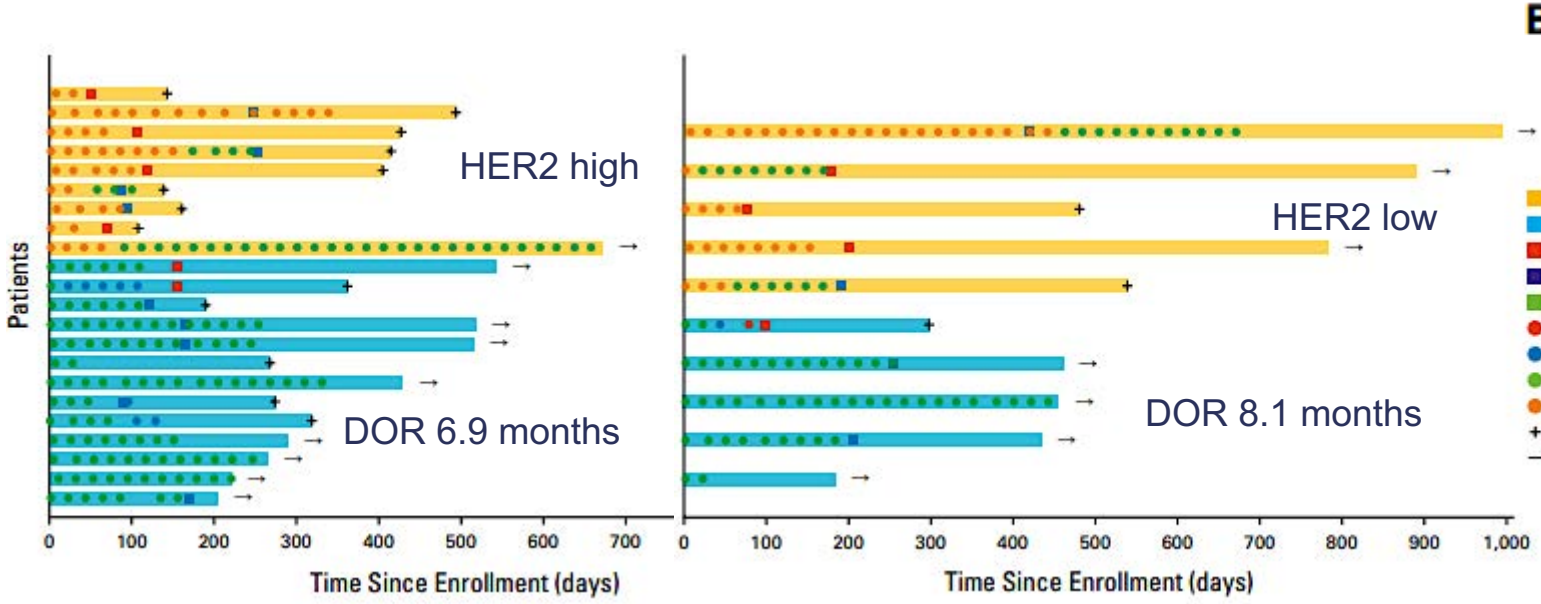
Adverse Event	Endometrial Cancer (n = 40)
Drug-related adverse events, No. (%)	36 (90.0)
Grade ≥3	14 (35.0)
Serious adverse events	4 (10.0)
Leading to discontinuation	3 (7.5)
Loading to dose modification	13 (32.5)
Associated with death	2 (5.0)
Most common drug-related adverse events (>10% of total patients), No. (%)	
Nausea	29 (72.5)
Anemia	7 (17.5)
Diarrhea	16 (40.0)
Fatigue	10 (25.0)
Vomiting	16 (40.0)
Neutropenia	4 (10.0)
Decreased appetite	8 (20.0)
Asthenia	11 (27.5)
Alopecia	9 (22.5)
Thrombocytopenia	2 (5.0)

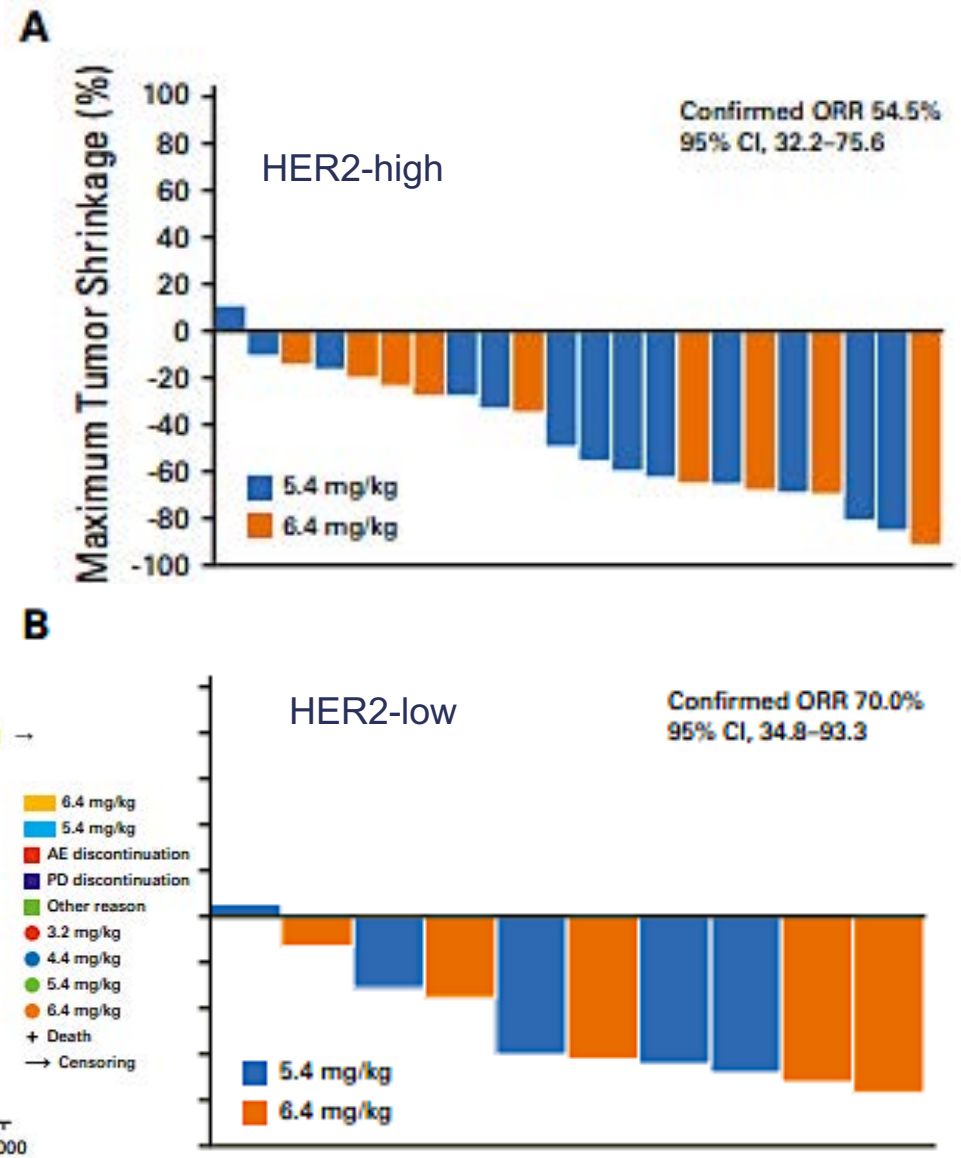
NCCN: listed version 2.2024

Meric-Bernstam, F. JCO 2023

STATICE TRIAL: Trastuzumab deruxtecan (T-DXd): Uterine Carcinosarcoma patients

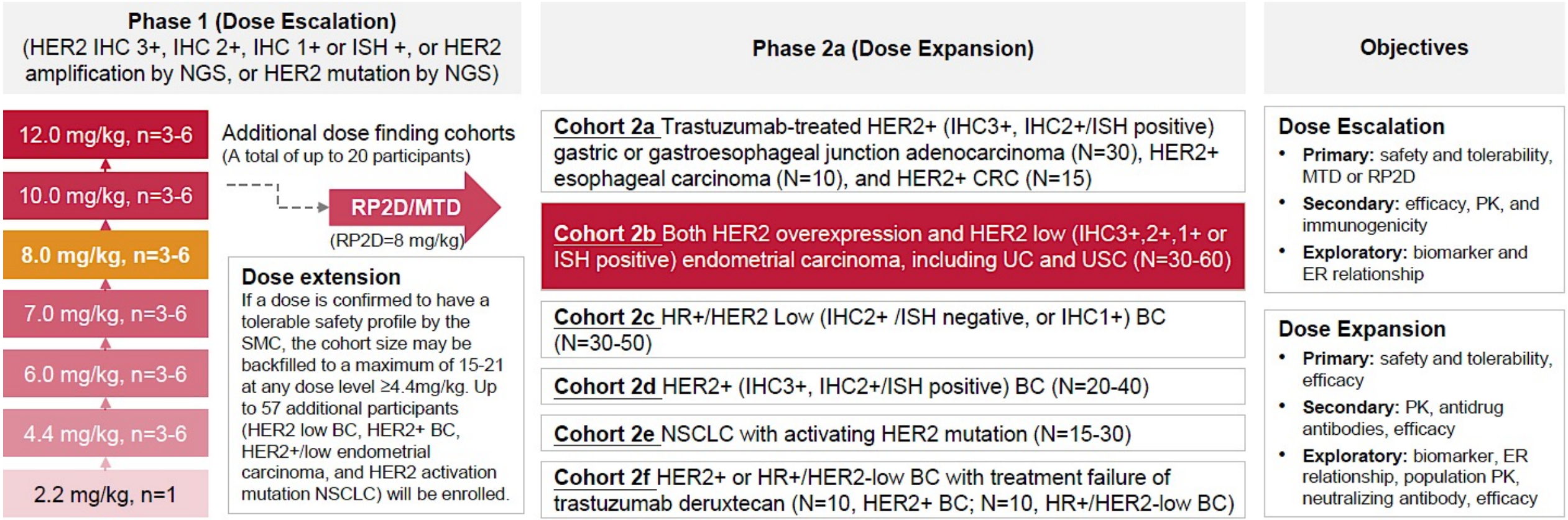
- HER2 targeting; topoisomerase I inhibitor
- Phase II, N= 34 (22 high, 10 low), Japan
- Carcinosarcoma, HER2 IHC score ≥1+ , >1 prior line
- 6.4 mg/kg → 5.4 mg/kg
- Median PFS 6.7 months (95% CI, 5.4 to 8.8)
- Pneumonitis/ILD in 9 (27%)





Nishikawa T, JCO 2023

BNT232/DB-1303: Phase I/2a



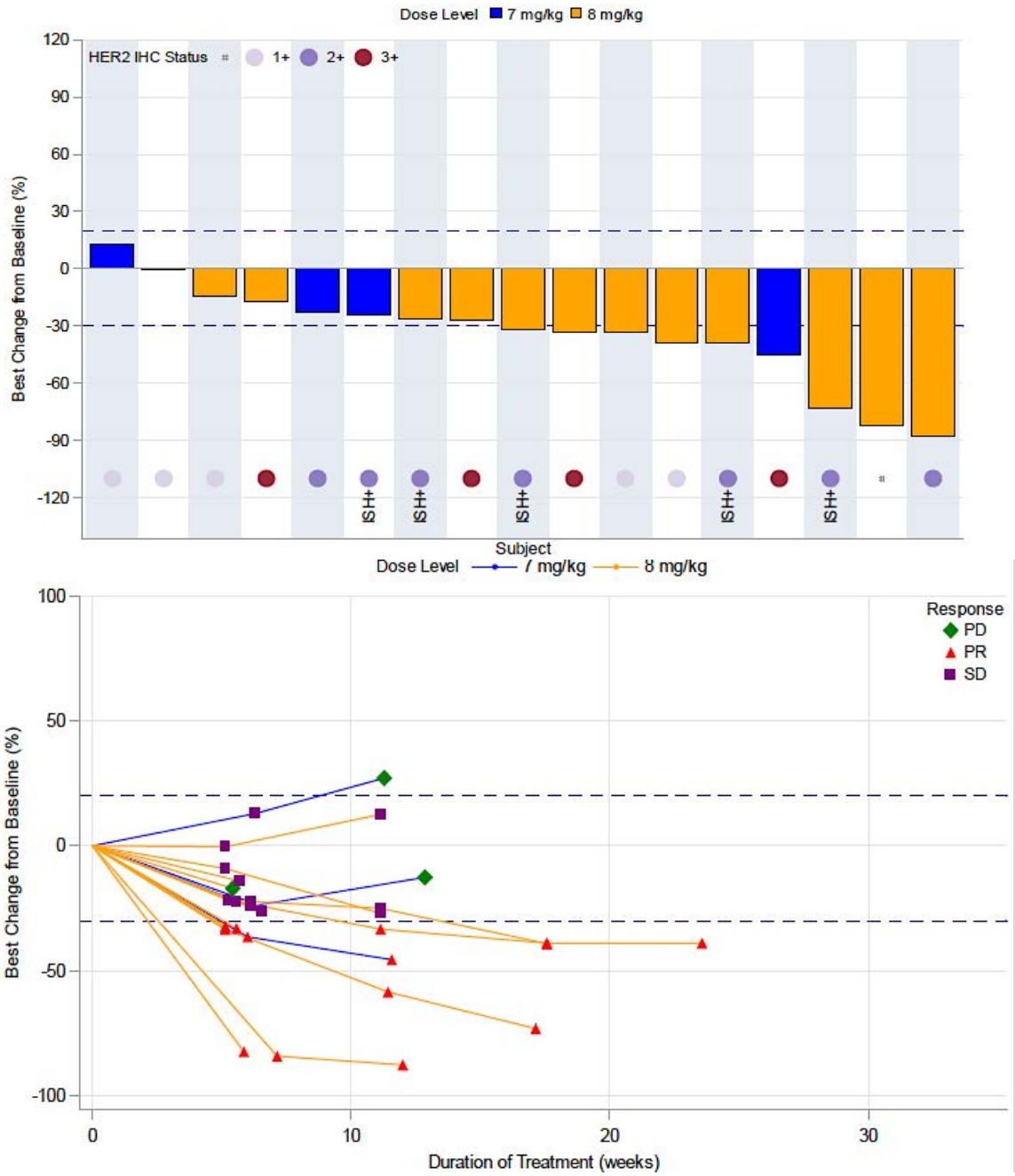
>1 prior line. NCT05150691

Moore, K. ESGO 2023

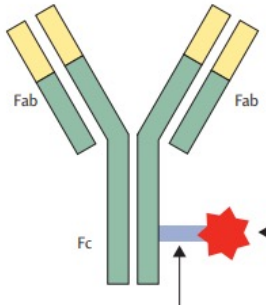
DB-1303/BNT232

- HER2 targeting; topoisomerase I inhibitor
- N=32
- 59% prior IO
- 38% prior Anti-HER2
- 1/3≥3 prior lines
- 34% Black, 6% Asian
- ORR 10/17 (58.8%) (unconfirmed), DCR 94%

- The most frequent TEAEs of any grade were nausea, fatigue, and vomiting, grade 3 or greater was rare.
- Alopecia 3.1%



Moore, K. ESGO 2023



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	SKB264/MK-2870	Belotecan derivative → Topoisomerase I inhibitor	NCT04152499 (Phase I/II) NCT06132958 (Phase III)

Summary Role of HER2-Targeted Therapy in EC

- HER2 important biomarker in endometrial cancer
  - Controversary remains as to most appropriate method of reporting
  - Worse outcomes
- Efficacy with trastuzumab + chemo in RP2 in advanced stage pts
- Testing Anti-HER2 therapy with trastuzumab +- pertuzumab + chemotherapy in both early and advanced stage patients (GY026)
- ADCs showing promise in both serous and carcinosarcoma
- NCCN listing of trastuzumab deruxtecan (T-DXd) second-line/ subsequent therapy (Useful in Certain Circumstances) 2.2024

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

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

Monday, March 18, 2024

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

Faculty

Nicoletta Colombo, MD

Matthew A Powell, MD

Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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

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

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

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