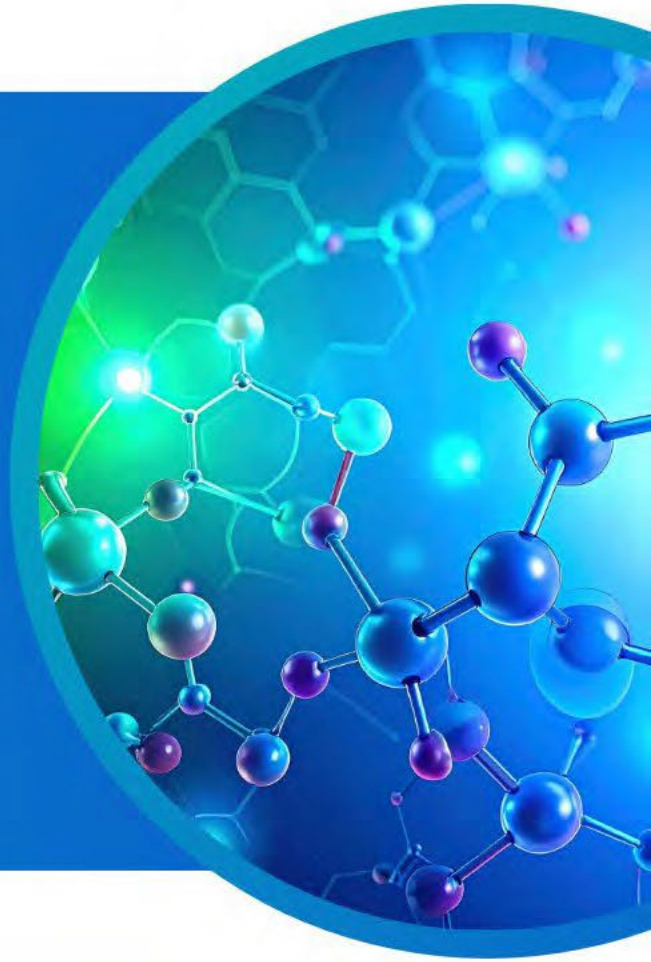
An Industry Supported Symposium at the IGCS 2025 Annual Global Meeting

Precision in Endometrial Cancer: Personalized Treatment Strategies for pMMR and dMMR Endometrial

This session is not included in the main event CME/CPD credit.



Cape Town, South Africa

Thursday, November 6, 2025

11:55 - 13:25 (GMT+2)

Eisai has sponsored this initiative with IGCS and had no input into or influence over the content

Eisai

Welcome & Opening Remarks

Christian Marth, MD, PhD
Innsbruck Medical University
Innsbruck, Austria

MODERATOR

Christian Marth, MD, PhD

Innsbruck Medical University
Innsbruck, Austria

FACULTY

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University of California San Diego
Moores Cancer Center
San Diego, California, USA

Alexander Olawaiye, MD

University of Pittsburgh
Magee-Womens Hospital of UPMC
Pittsburgh, Pennsylvania, USA

Leslie Randall, MD

Inova Health
Fairfax, Virginia, USA

Faculty Disclosures

Name	Role in Activity	Disclosures
Christian Marth, MD, PhD	Moderator	
Ramez N. Eskander, MD	Speaker	**Consultant/Advisory Board: AstraZeneca:** Clovis Oncology; Daiichi Sankyo, Inc.; Eisai Inc.; Elevar Therapeutics; GSK; ImmunoGen, Inc.; Mersana Therapeutics; Myriad Genetics, Inc.; Novocure GmbH; Onconova Therapeutics; Nuvectis; PMV Pharmaceuticals; Regeneron; Lilly; AbbVie; Pfizer; BeOne Medicine. Other Financial or Material Support for GOG P Associate Clinical Trial Advisor
Alexander Olawaiye, MD	Speaker	**Scientific Advisory Board Engagement:** AstraZeneca, GSK, Genentech, Corcept, Merck, Eli Lilly
Leslie Randall, MD	Speaker	**Consultant:** AstraZeneca; Genmab; Pfizer; GSK, Eisai; Merck; Abbvie; GOG Foundation **Research Funding**: Merck; AbbVie; GOG Foundation

Learning Objectives

Upon completion of the activities in this series, learners will demonstrate increased knowledge regarding:

1. Differentiate endometrial cancer across molecular classifications in terms of biology, clinical behavior, and treatment outcomes.

2. Evaluate current evidence and clinical considerations for treatment of, primary advanced and recurrent endometrial cancer.

3. Discuss therapeutic sequencing strategies in advanced/recurrent endometrial cancer, especially in the context of disease progression.

4. Apply real-world patient case scenarios to guide treatment decisions, manage toxicities, and address gaps in sequencing data.

Agenda

11:55 - 12:00: **Welcome & Opening Remarks**
Christian Marth, MD, PhD, Innsbruck Medical University, Innsbruck, Austria

12:00 – 12:20: **Decoding Endometrial Cancer: The Role of Molecular Profiling**
Alexander Olawaiye, MD, University of Pittsburgh, Magee-Womens Hospital of UPMC, Pittsburgh, Pennsylvania, USA

12:20 – 12:40: **Charting the Course: Treatment Approaches for dMMR Endometrial Cancer**
Ramez N. Eskander, MD, UC San Diego, Moores Cancer Center, San Diego, California, USA

12:40 – 13:00: **Charting the Course: Treatment Approaches for pMMR Endometrial Cancer**
Leslie Randall, MD, Inova Health, Fairfax, Virginia, USA

13:00 – 13:20: **Panel Discussion**
All Faculty

13:20 -13:25: **Closing & Key Takeaways**
Christian Marth, MD, PhD, Innsbruck Medical University, Innsbruck, Austria

Decoding Endometrial Cancer: The Role of Molecular Profiling

Alexander Olawaiye, MD
University of Pittsburgh,
Magee-Womens Hospital of UPMC
Pittsburgh, Pennsylvania, USA

Genomic Characterization of EC

Nature

Nature Publishing Group

THIS ARTICLE HAS BEEN CORRECTED.

See the correction in volume 500 on page 242.

Integrated genomic characterization of endometrial carcinoma

Douglas A. Levine and The Cancer Genome Atlas Research Network

Nature **497**, 67–73 (2013)

Genomic Characterization of EC

Using a combination of:

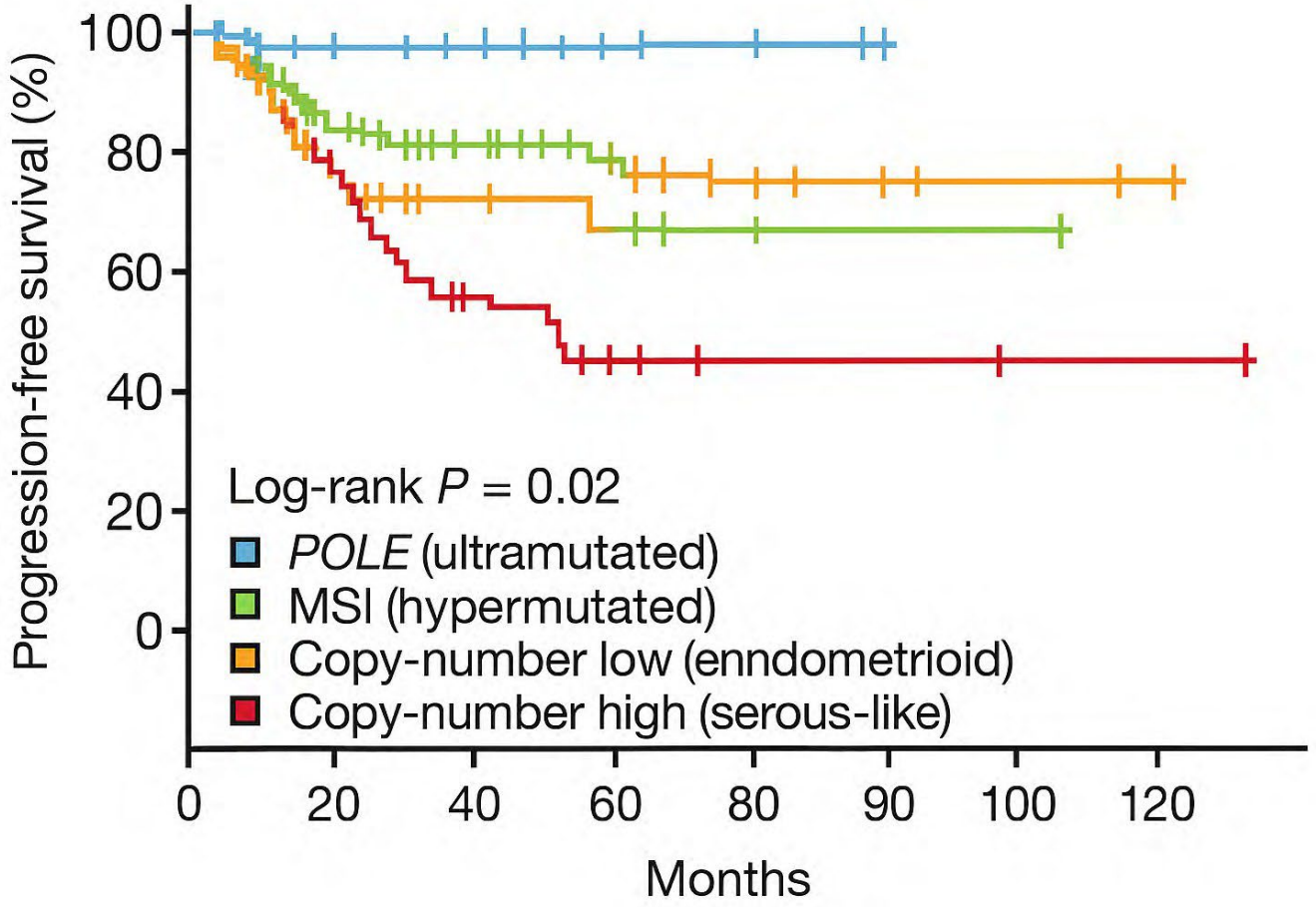
- nucleotide substitutions
- MSI
- SCNAs

Endometrial carcinomas were characterized into 4 groups:

1. Ultramutated group (*POLE*-EDM)
2. Hypermutated group (MSH)
3. Copy number low (NSMP)
4. Copy number high (Serous-like)

Genomic Characterization of EC

Genomic Characterization of EC



Key Research Finding

Approximately 25% of endometrioid endometrial adenocarcinomas classified as grade 3 and 5% classified as grade 1&2 tumors by pathologists have a molecular phenotype similar to uterine serous carcinomas.

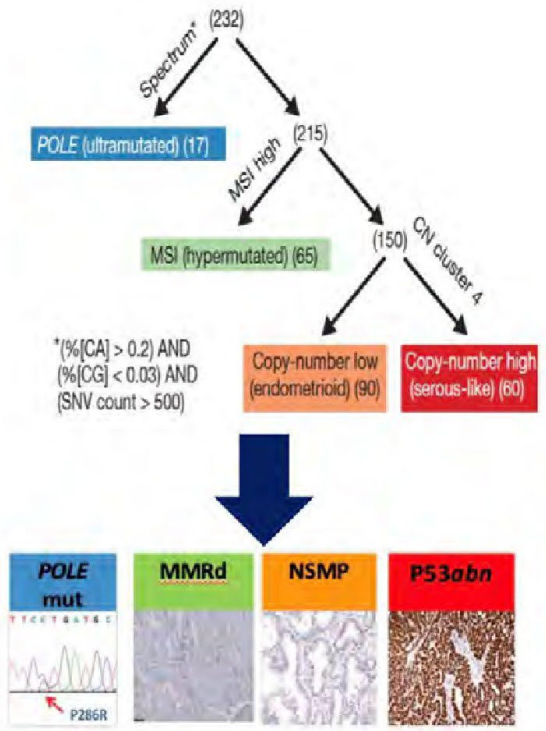
Tests

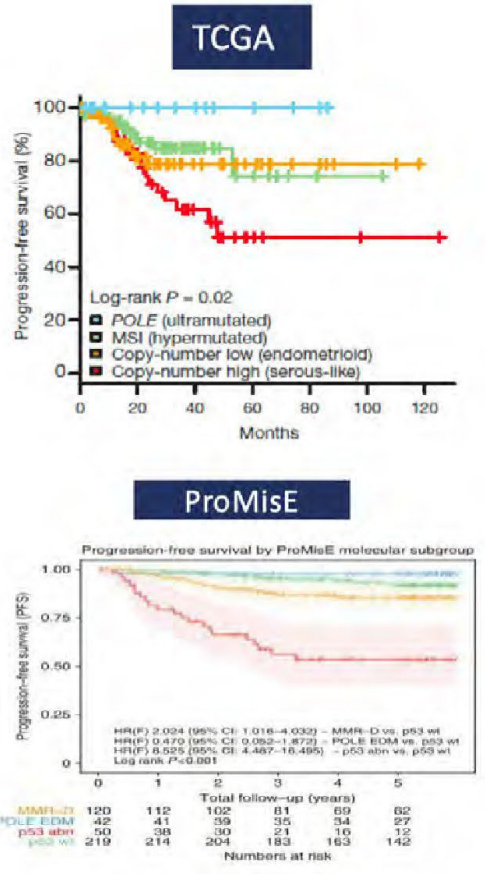
- Immunohistochemistry (p53, MSH-6, PMS-2)
- Somatic mutation analysis of *POLE* (exons 9, 11, 13, 14)

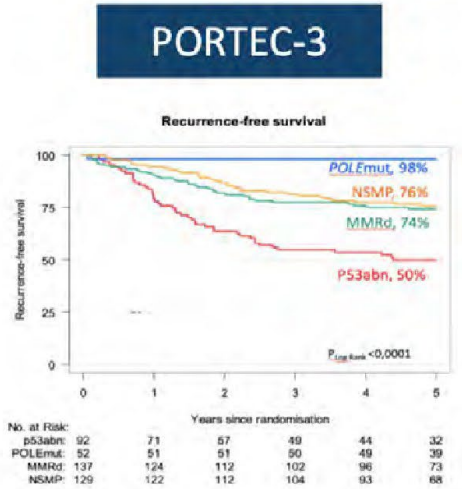
Groups

1. Ultramutated (Pathogenic *POLE* mutations)
2. Hypermutated with MSI/MMRd (loss of MMR protein immunoreactivity)
3. High copy number p53abn (p53 mutant immunoreactive pattern)
4. Low copy number/NSMP (retained MMR protein immunoreactivity, and p53 wild-type immunoreactive pattern

Bringing Biology into the Clinic







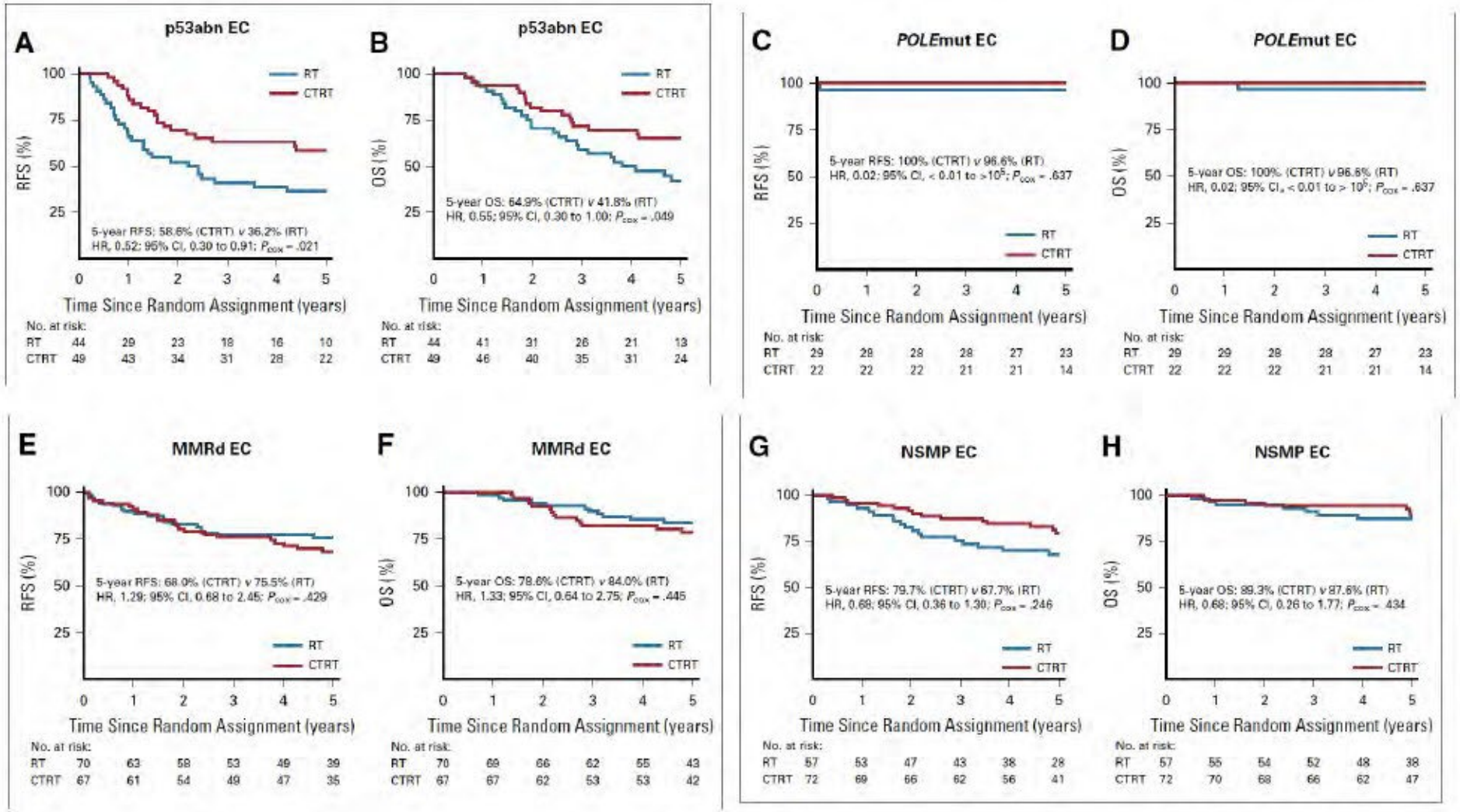
Nature 2013; 497: 67–73; 3. Kommoss et al. Annals of Oncology 2018; 29: 1180–1188; León-Castillo A. et al J Clin Oncol, 2020; C.M. Cosgrove et al, Gynecologic Oncology 148 (2018) 174–180; León-Castillo A. et al J Clin Oncol, 2020

Endometrial Cancer: Molecular Subtypes

***POLE* ultramutated**	• Ultra-high somatic mutation frequency; MSS; frequent mutations in the exonuclease domain of *POLE*; high ASNS and CCNB1 expression • Represents ~4% of endometrioid tumors* • Best prognosis	Clear IO Efficacy
MSI hypermutated	• High mutation rate and few copy number alterations; high rate of *MLH1* promoter methylation; high phospho-AKT; low PTEN expression; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations • Represents ~39% of endometrioid tumors*†	Clear IO Efficacy
Copy-number low‡	• High frequency of mutations in *CTNNB1*, *KRAS*, *SOX17*; frequent *PIK3CA* and *PIK3R1* mutations co-occurring with *PTEN* mutations; elevated levels of progesterone receptor and RAD50 expression • Represents ~49% of endometrioid tumors*	Unclear IO Efficacy?
Copy-number high‡	• Greatest transcriptional activity; frequent *TP53* mutations; decreased levels of phospho-AKT; mutually exclusive *PIK3CA*, *PIK3R1*, and *PTEN* mutations • Represents ~9% of endometrioid tumors* • Worst prognosis	Unclear IO Efficacy?

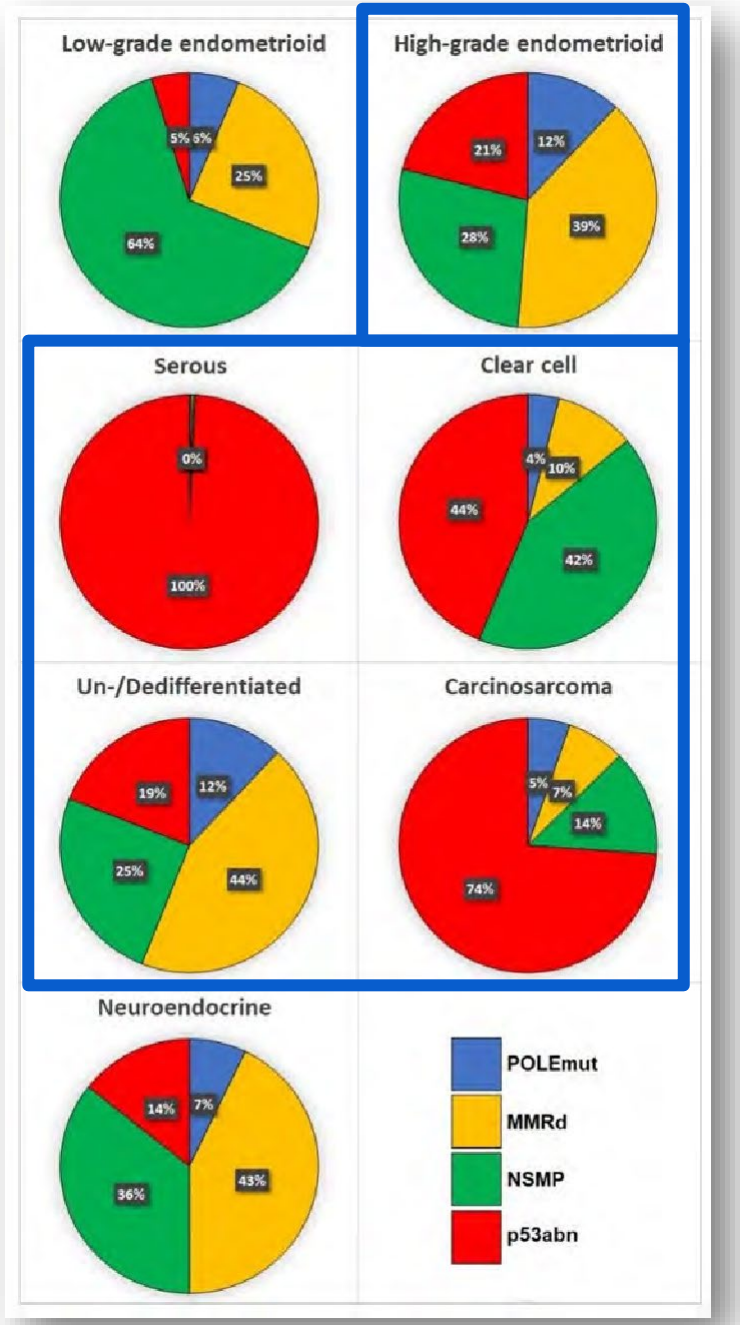
*G Getz et al. Nature **497**, 67-73 (2013)*

Endometrial Cancer: Molecular Subtypes are Important & Relevant



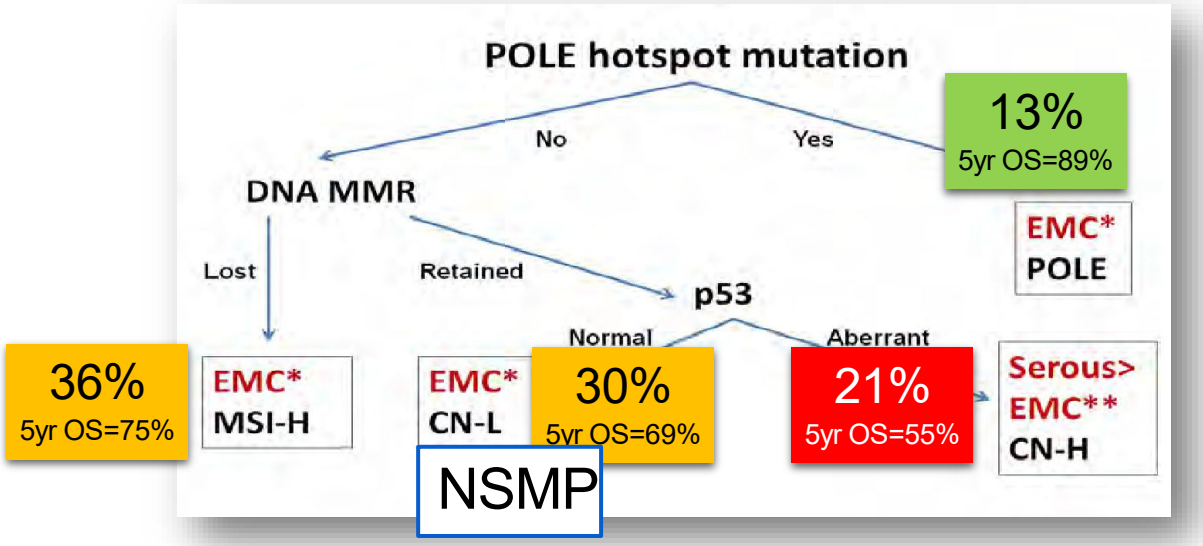
Leon-Castillo et al, JCO 2020.

TCGA Molecular Classification According to Endometrial Cancer Histotype

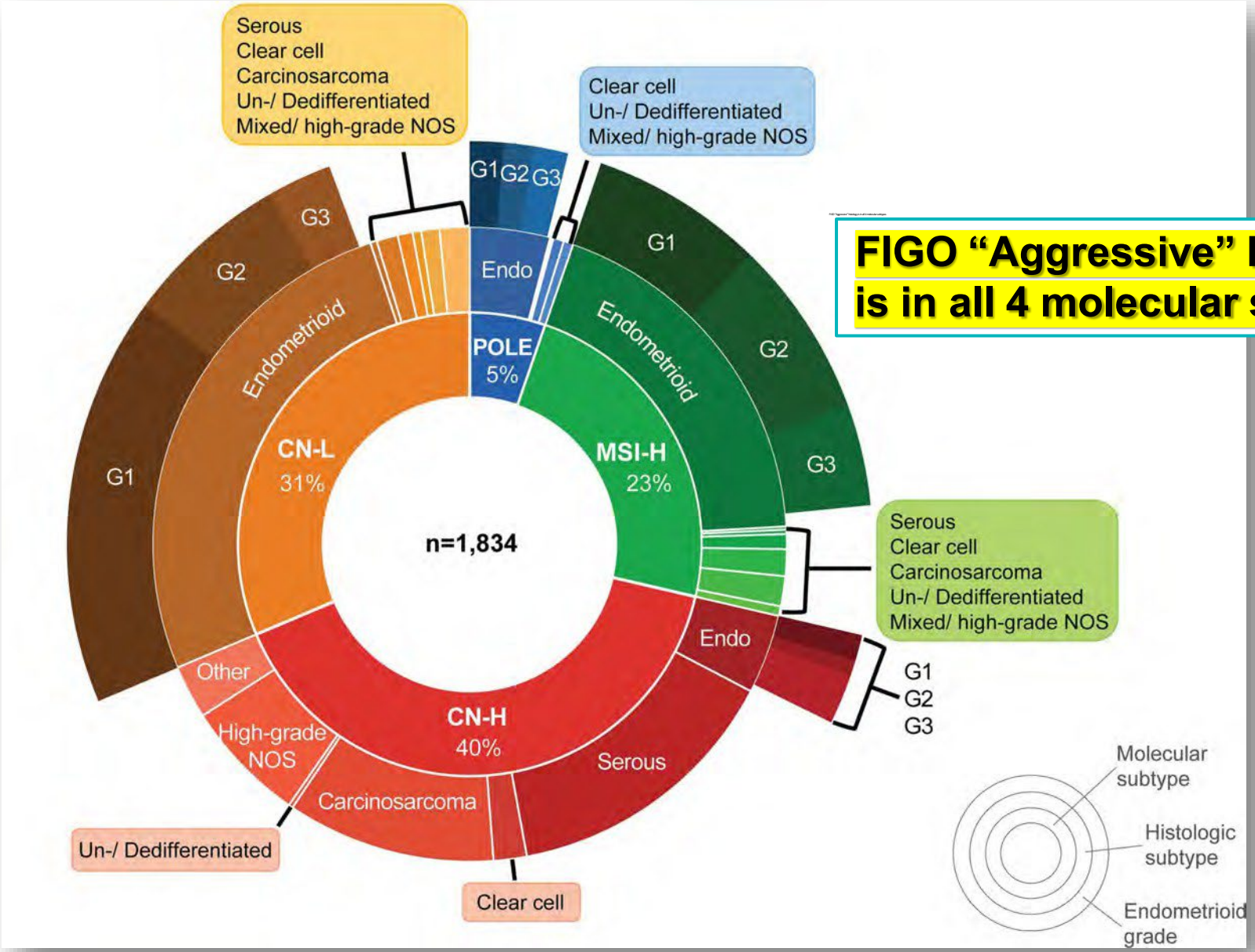


Santoro A. Zannoni GF. Cancers 2021

Molecular Classification of 381 Patients G3 Endometrioid Endometrial Ca “2023 FIGO Aggressive Histology



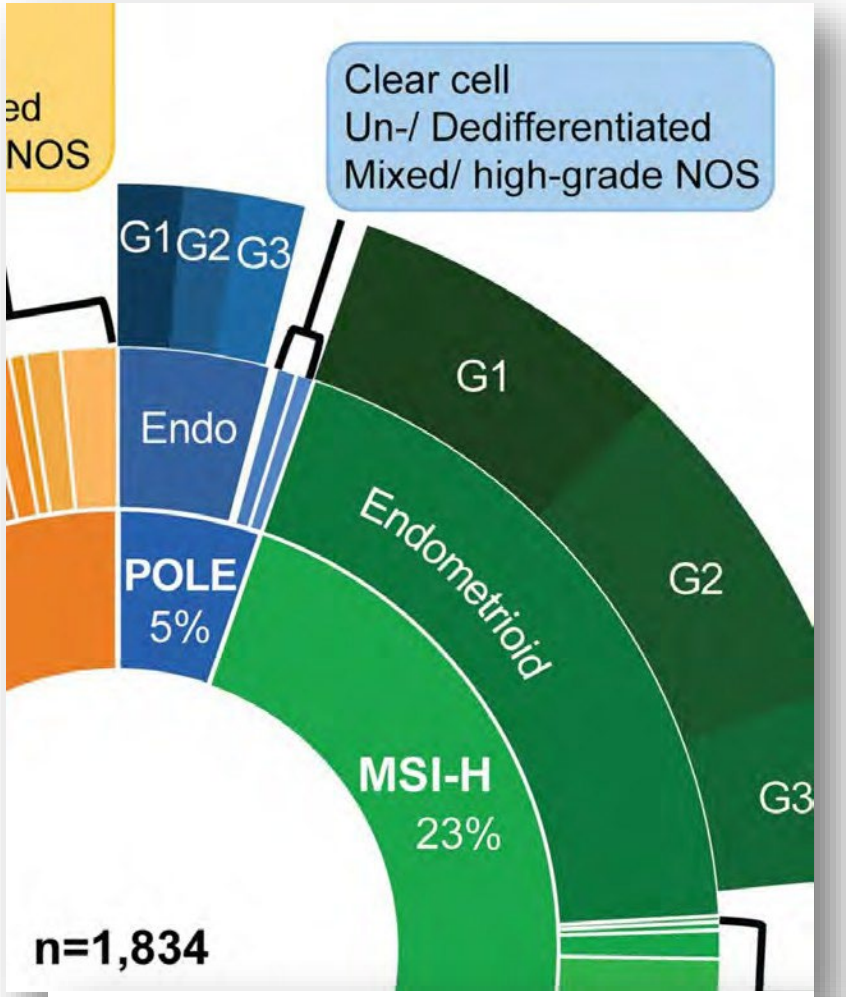
Tjalling Bosse, et al. Am J Surg Path 2018



FIGO "Aggressive" histology is in all 4 molecular subtypes

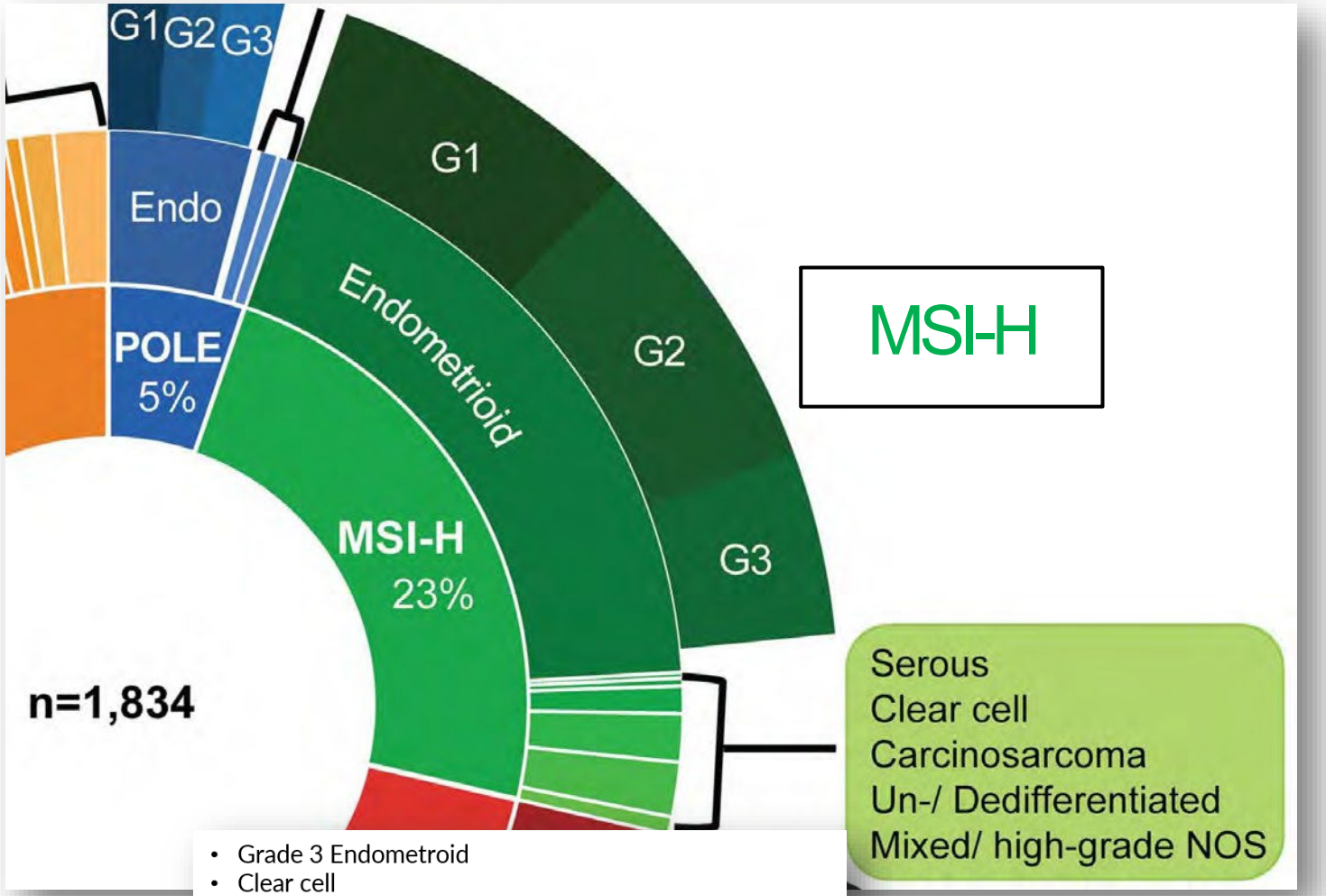
Rios-Doria E, et al. (MSKCC) Gynecol Oncol 2023

POLE



- Grade 3 Endometroid
- Clear cell
- Mixed
- Serous
- Undifferentiated
- Mesonephric-like and gastrointestinal type mucinous
- Carcinosarcoma

Rios-Doria E, et al. (MSKCC) Gynecol Oncol 2023



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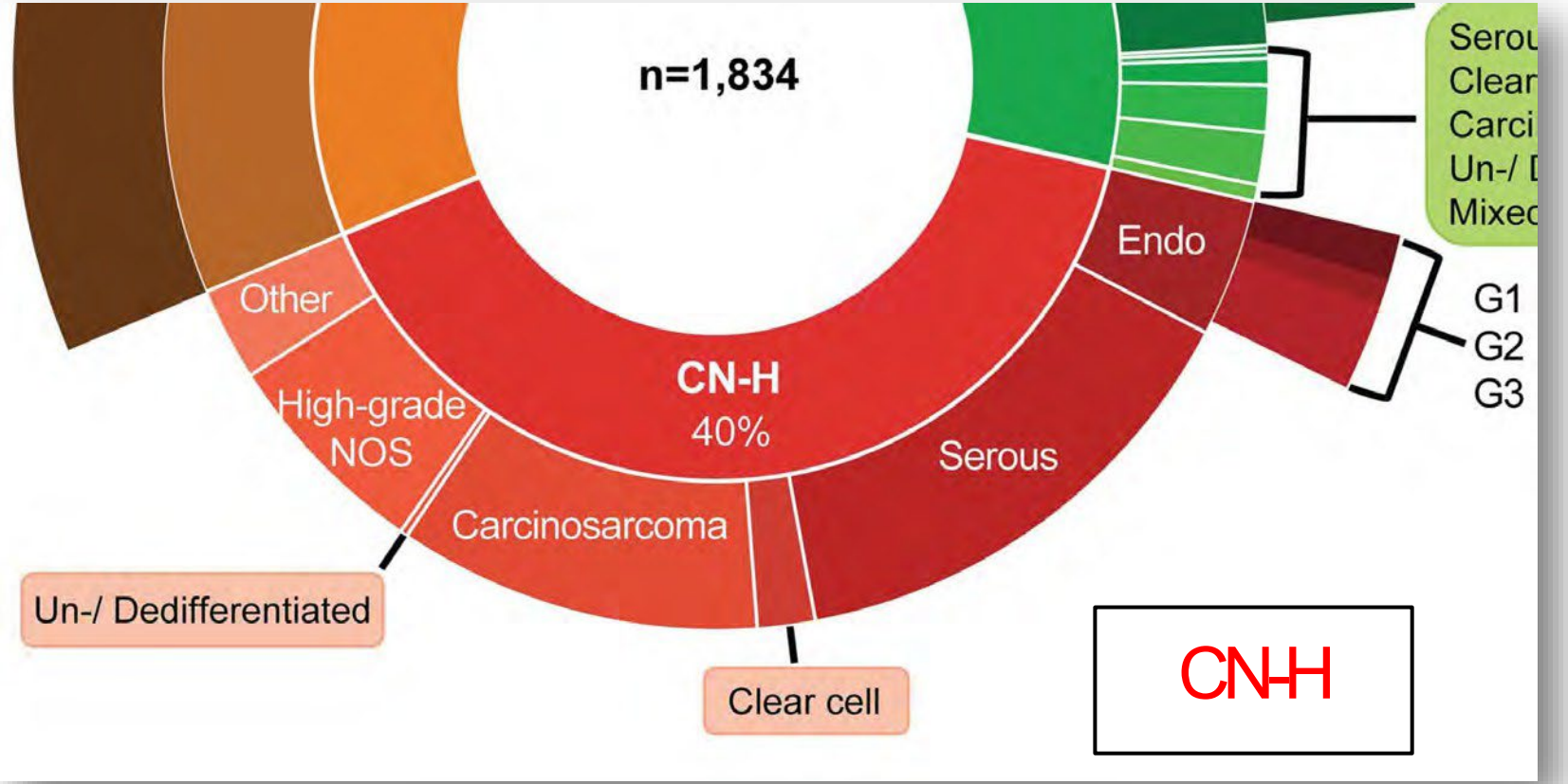
Rios-Doria E, et al. (MSKCC) Gynecol Oncol 2023



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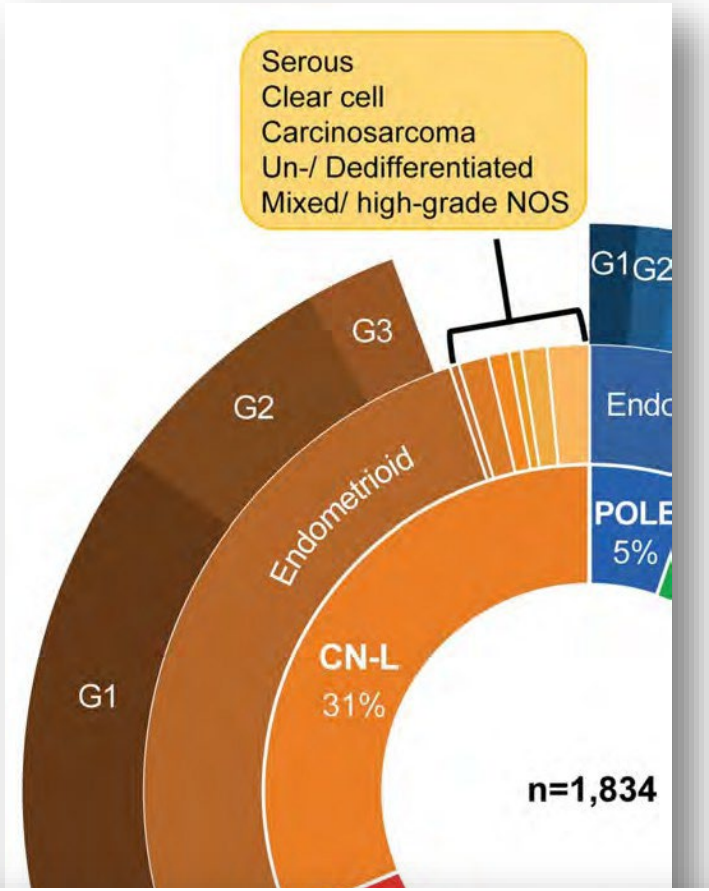
Rios-Doria E, et al. (MSKCC) Gynecol Oncol 2023

NSMP CN-L



- Grade 3 Endometroid
- Clear cell
- Mixed
- Serous
- Undifferentiated
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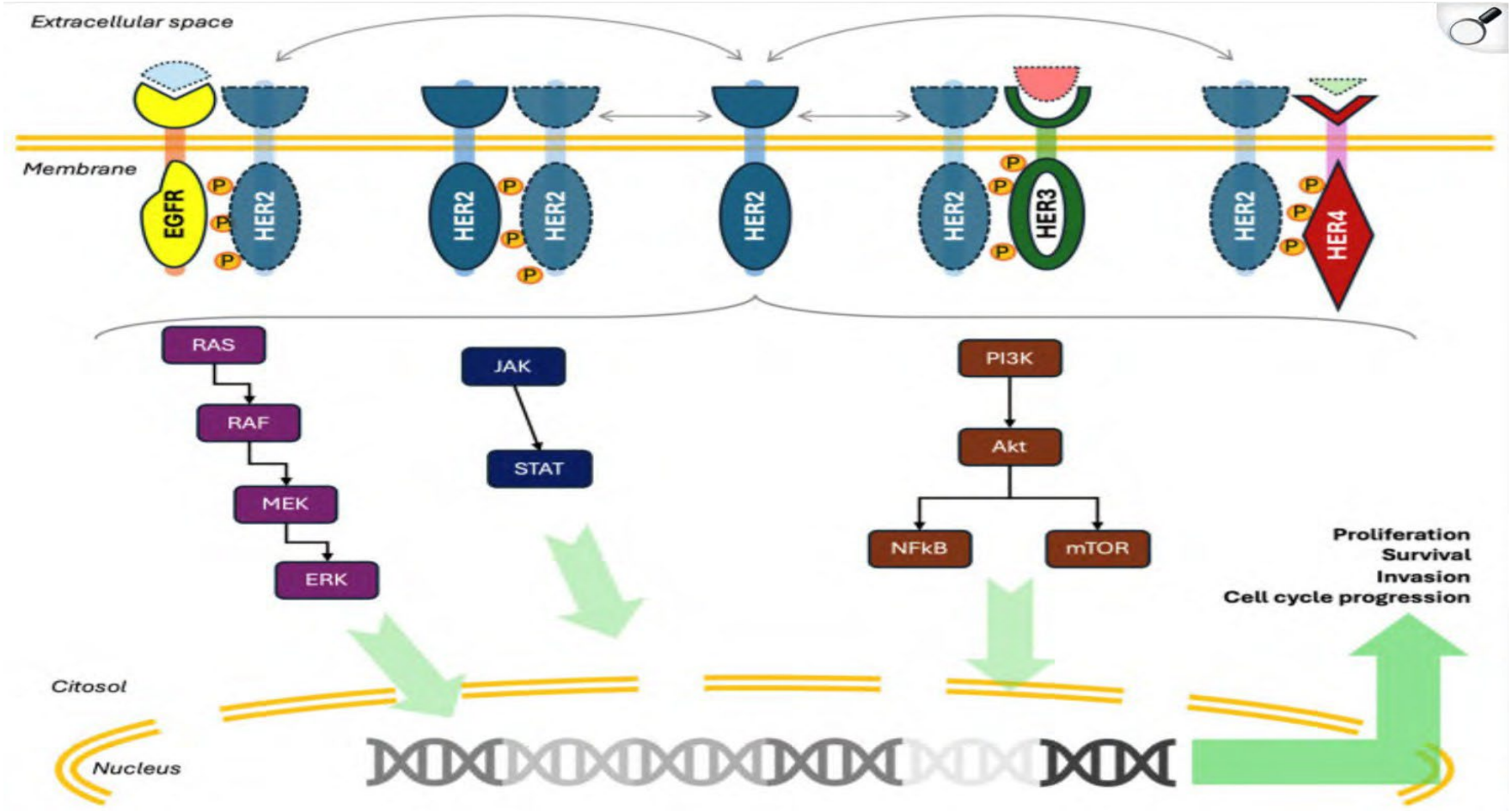
- Carcinosarcoma

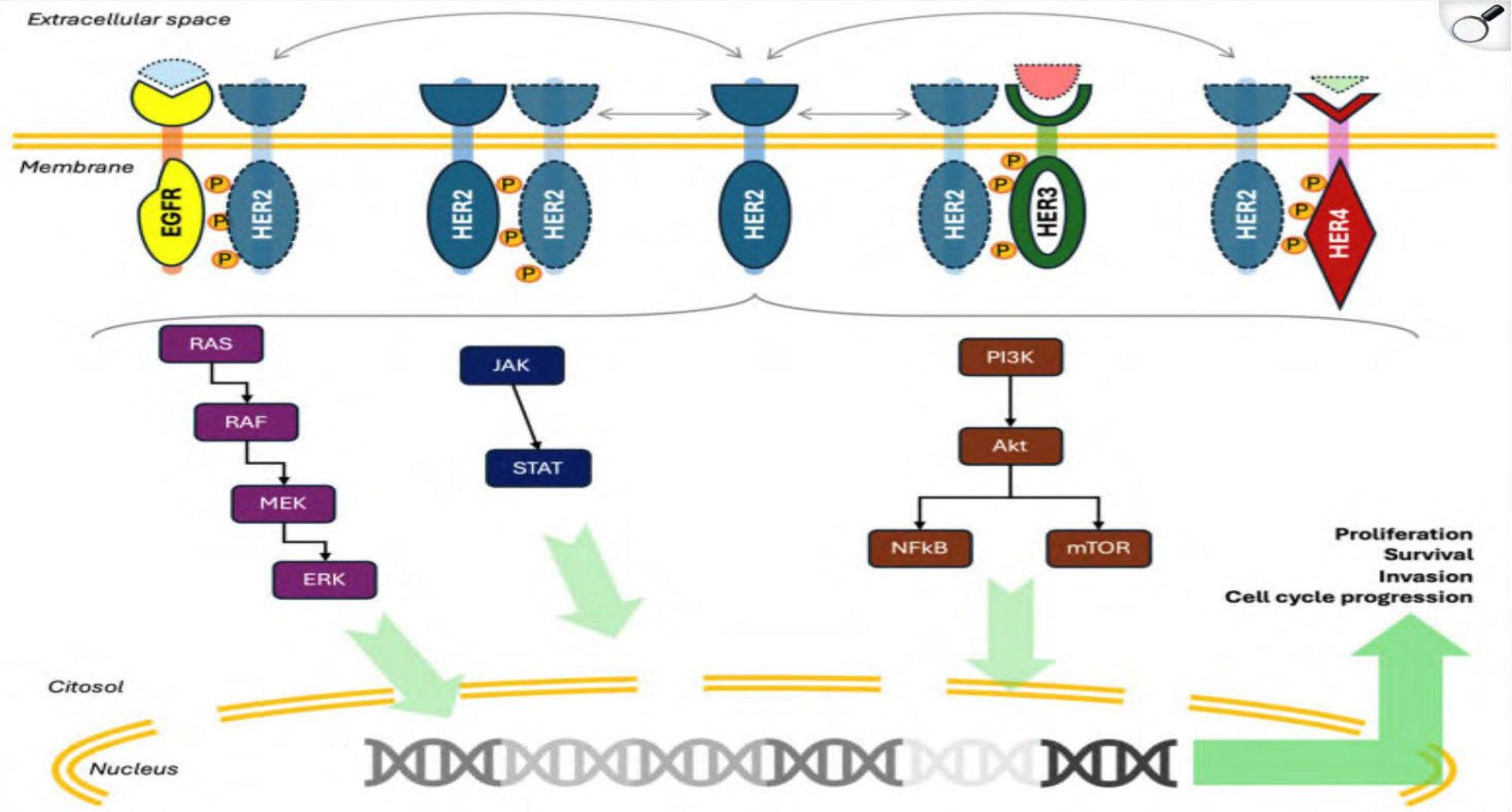
Eric Rios-Doria, et al. (MSKCC) Gynecol Oncol 2023

HER2 Signaling in EC



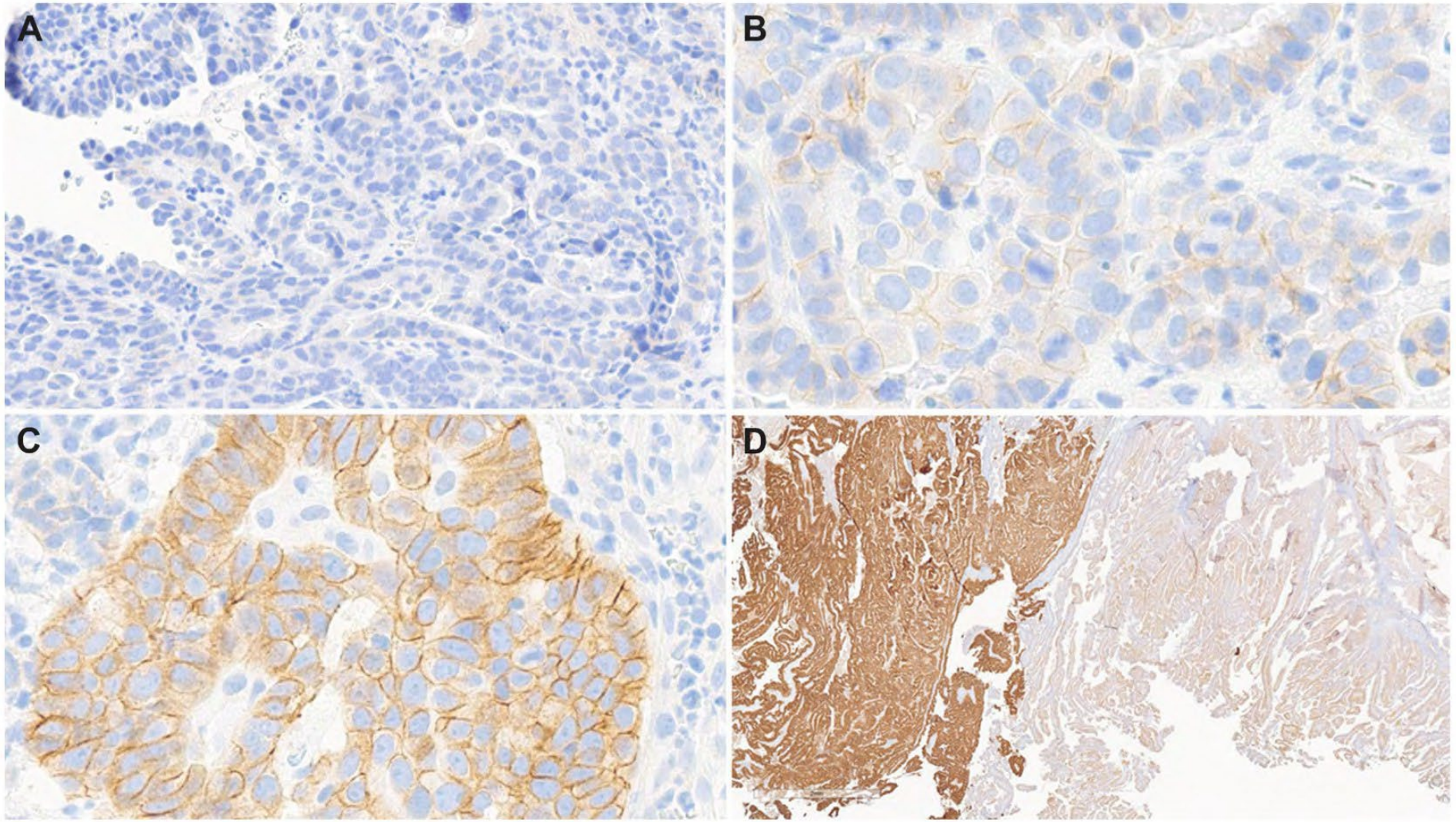
Ettore et. al. Cells. 2025 Aug 19;14(16):1282.

HER2 Signaling in EC



Ettore et. al. Cells. 2025 Aug 19;14(16):1282.

HER2 Immunohistochemical categories, EC criteria

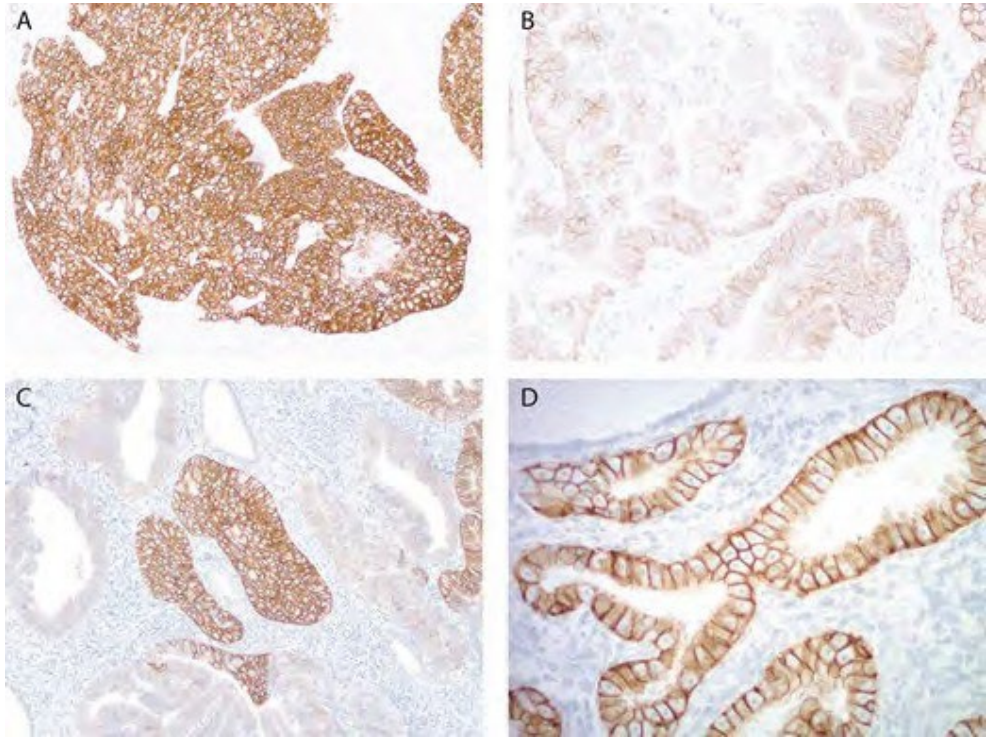


Ekaterina Menshikova et al. / Lab Invest 105 (2025) 104240

HER2 and Trastuzumab

	Endometrial Serous (Fader et al Clinical Trial)[21]
HER2 IHC 3+	>30% strong complete or basolateral/lateral
HER2 FISH amplification	*HER2*/CEP17 ratio ≥2.0

If 2+ staining, then should reflex to FISH to see if *HER2* gene is amplified



- A: HER2 3+ score with strong, complete membranous staining in >30% of tumor cells.
- B: HER2 2+ score showing weak to moderate membranous staining in a basolateral pattern in ≥10% of tumor cells
- C and D: Heterogeneity of HER2 protein expression (C) and lack of apical membrane staining (D) are often present

Arch Pathol Lab Med. 2021 Jun 1;145(6):687-691.

Clinical Trial > J Clin Oncol. 2018 Jul 10;36(20):2044-2051. doi: 10.1200/JCO.2017.76.5966.
Epub 2018 Mar 27.

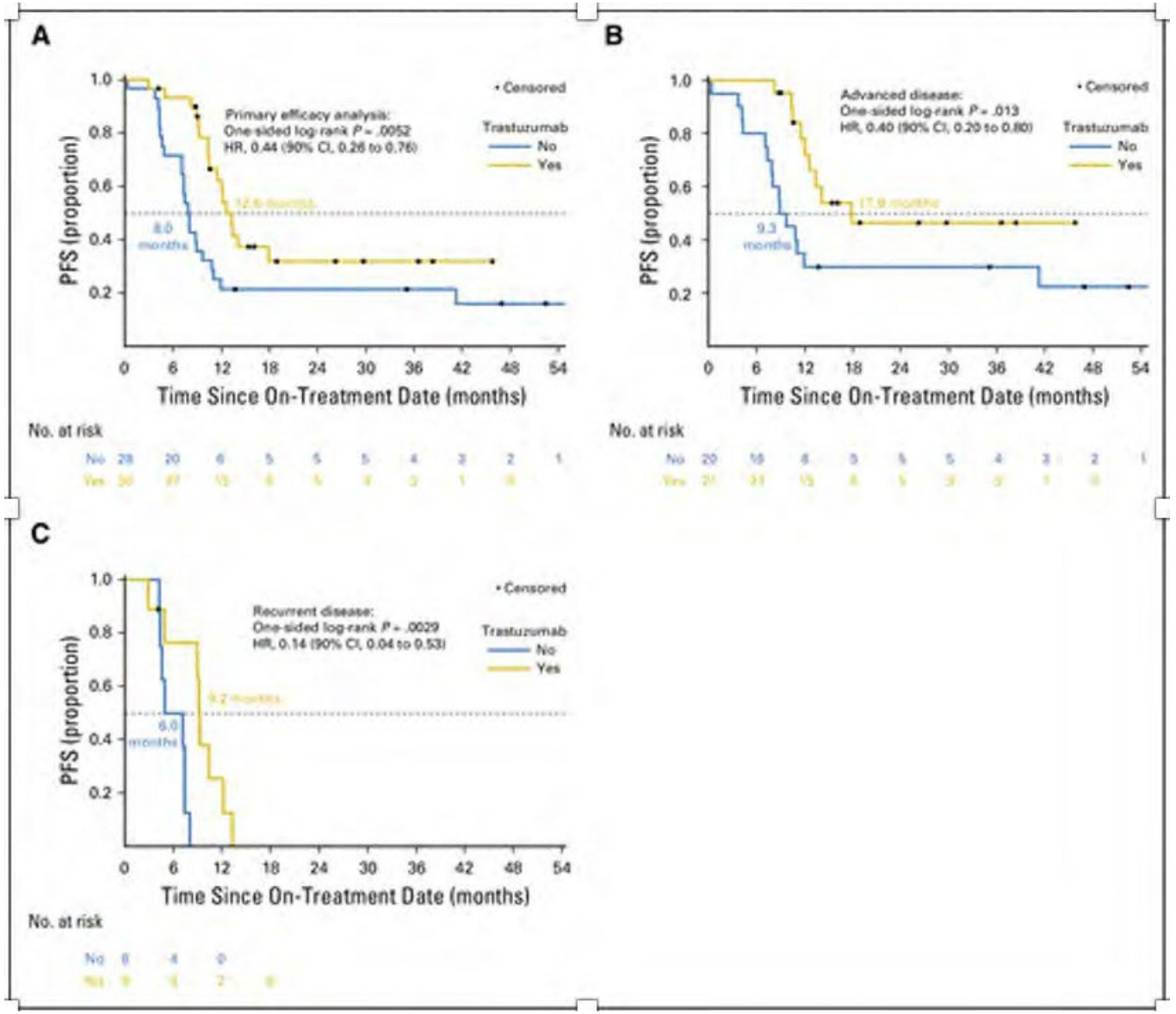
Randomized Phase II Trial of Carboplatin–Paclitaxel Versus Carboplatin–Paclitaxel–Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

Amanda N Fader [1], Dana M Roque [1], Eric Siegel [1], Natalia Buza [1], Pei Hui [1], Osama Abdelghany [1], Setsuko K Chambers [1], Angeles Alvarez Secord [1], Laura Havrilesky [1], David M O'Malley [1], Floor Backes [1], Nicole Nevadunsky [1], Babak Edraki [1], Dirk Pikaart [1], William Lowery [1], Karim S ElSahwi [1], Paul Celano [1], Stefania Bellone [1], Masoud Azodi [1], Babak Litkouhi [1], Elena Ratner [1], Dan-Arin Silasi [1], Peter E Schwartz [1], Alessandro D Santin [1]

Affiliations + expand

PMID: 29584549 DOI: 10.1200/JCO.2017.76.5966

Trastuzumab + Chemotherapy in Serous EC



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

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

DESTINY-PanTumor02

Funda Meric-Bernstam
The University of Texas MD Anderson Cancer Center, Houston, TX, USA

June 5, 2023

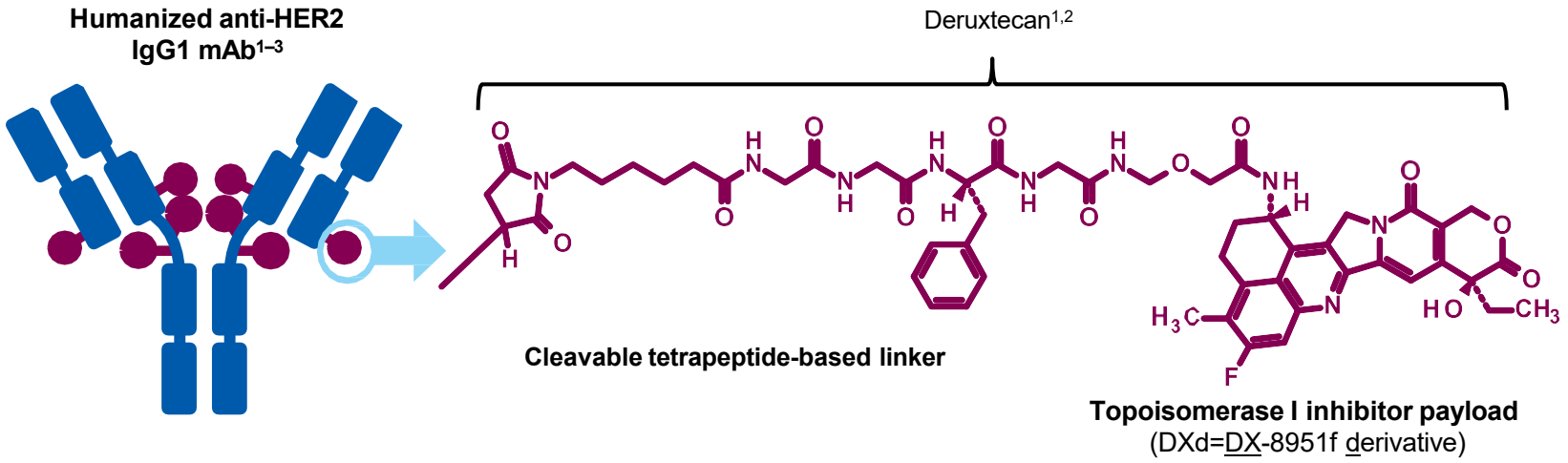
Additional authors: Vicky Makker, Ana Oaknin, Do-Youn Oh, Susana Banerjee, Antonio González-Martín, Kyung Hae Jung, Iwona Ługowska, Luis Manso, Aránzazu Manzano, Bohuslav Melichar, Salvatore Siena, Daniil Stroyakovskiy, Chiedozie Anoka, Yan Ma, Soham Puvvada, Jung-Yun Lee

On behalf of the DESTINY-PanTumor02 investigators

Trastuzumab Deruxtecan (T-DXd) was Designed with Seven Key Attributes

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

[a]*The clinical relevance of these features is under investigation.*

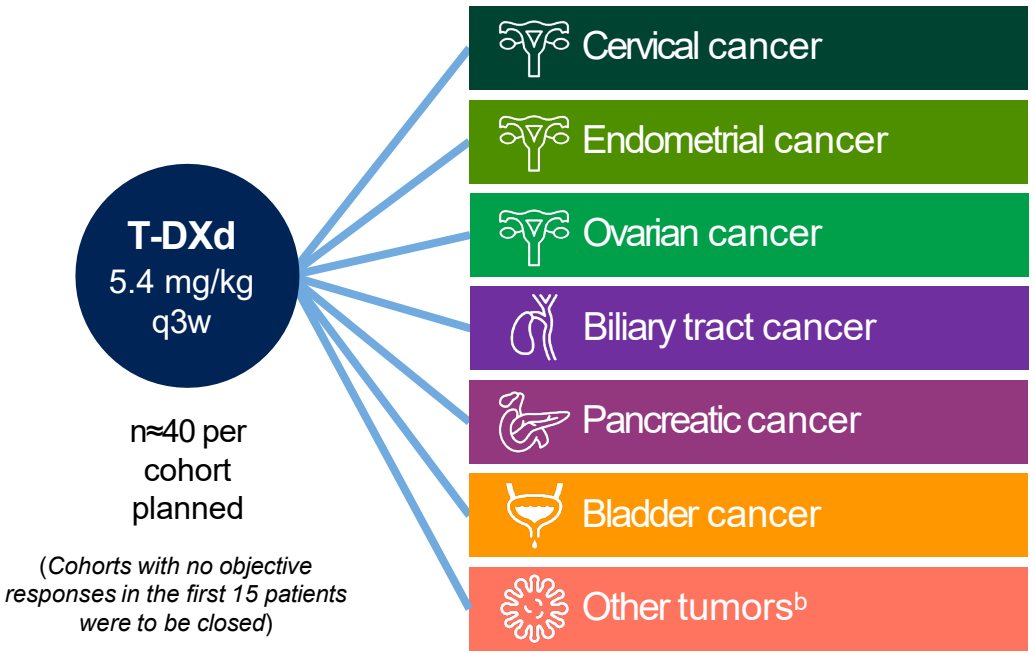
ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):173–185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097–5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126–142. 4. Okamoto H, et al. Xenobiotica. 2020;50(10):1242–1250. 5. Nagai Y, et al. Xenobiotica. 2019;49(9):1086–1096.

DESTINY-PanTumor02: A Phase 2 Study of T-DXd for HER2-Expressing Solid Tumors

An open-label, multicenter study (NCT04482309)

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1



n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

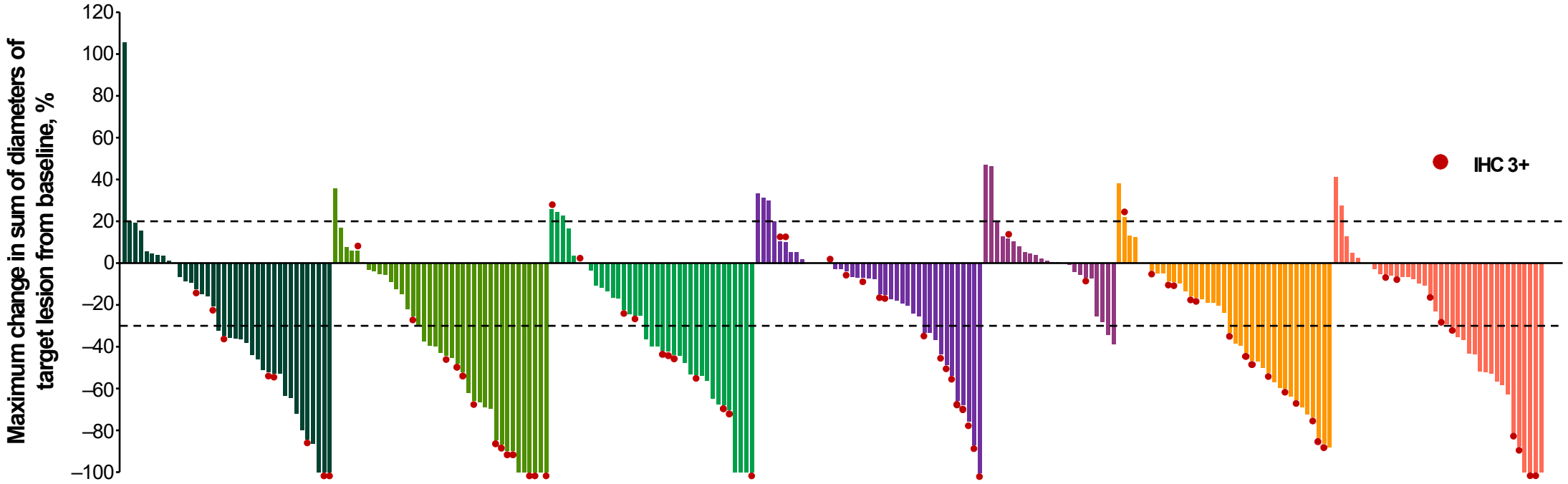
- Nov 16, 2022

[a]*Patients were eligible for either test. All patients were centrally confirmed.* [b]*Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer.*
[c]*Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.*
2L, second-line; ASCO, American Society of Clinical Oncology; DCR, disease control rate; CAP, College of American Pathologists; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. Histopathology 2008;52(7):797–805.

Funda Meric-Bernstam, MD

Best Percentage Change in Target Lesion From Baseline

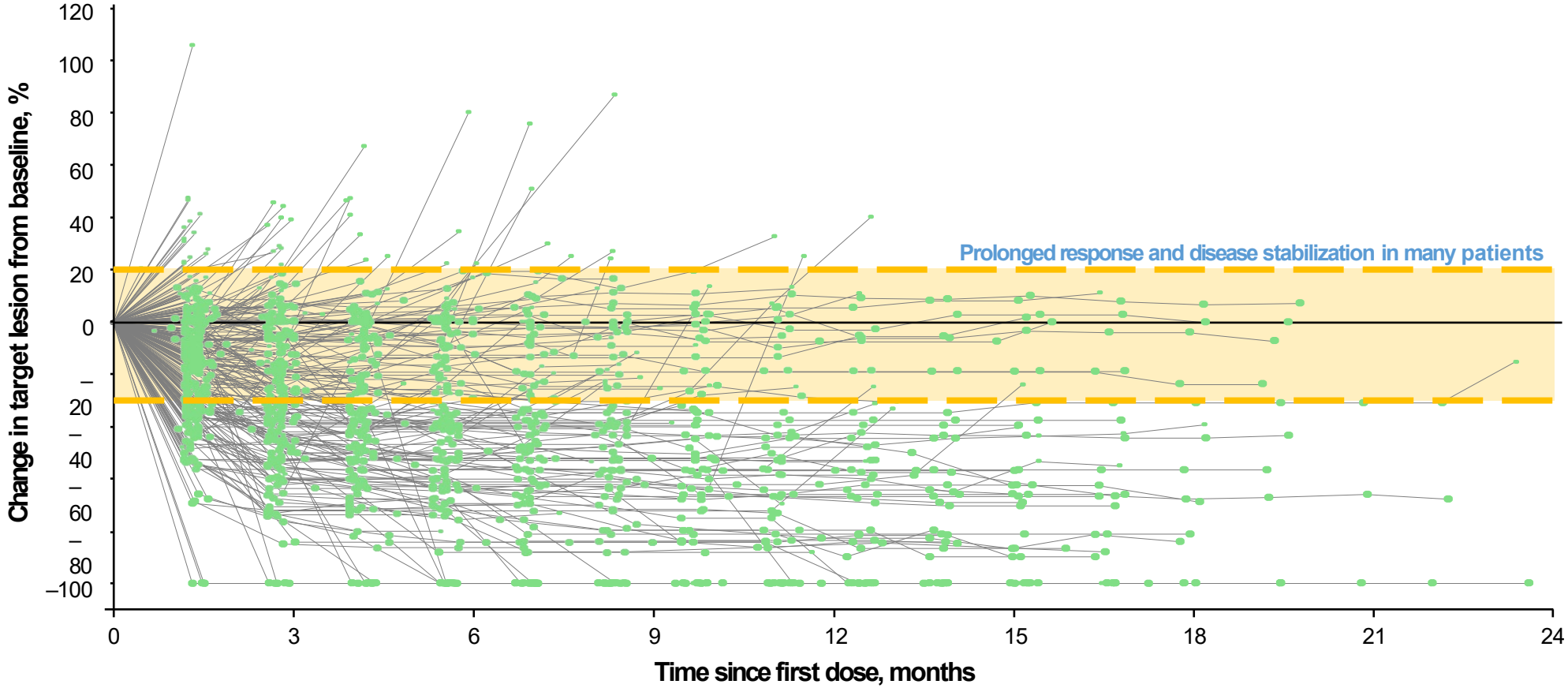


ORR in IHC 3+	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
n (%)	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

Funda Meric-Bernstam, MD

Percentage Change in Target Lesions Over Time



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267).

- *Funda Meric-Bernstam, MD*

Biomarkers play a key role in cancer care

- **Diagnostic biomarkers:** used to detect the presence of cancer
- **Prognostic biomarkers:** provide information about likely disease course
- **Predictive biomarkers:** help determine the likely response to treatment
- **Monitoring biomarkers:** used to track the progress of the disease and assess effectiveness of treatment

MMR deficiency predicts for response to ICI in recurrent endometrial cancer

MSI-H/dMMR

Agent	N	Target	ORR (%)	PFS (mos)	OS (mos)	DOR (mos)
Pembrolizumab[1,2]	79	PD-1	48	13.1	NR	NR
Avelumab[3]	15	PD-L1	26.7	4.4	NR	--
Durvalumab[4]	35	PD-L1	43	8.3*	NR	NR
Dostarlimab[5]	103	PD-1	44.7	--	--	NR

MSS/pMMR

Agent	N	Target	ORR (%)	PFS (mos)	OS (mos)	DOR (mos)
Avelumab[1]	15	PD-L1	6.25	1.9	6.6	--
Durvalumab[2]	35	PD-L1	3	1.8*	12.1	--
Dostarlimab[3]	142	PD-1	13.4	--	--	NR

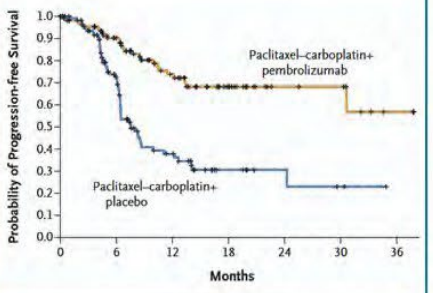
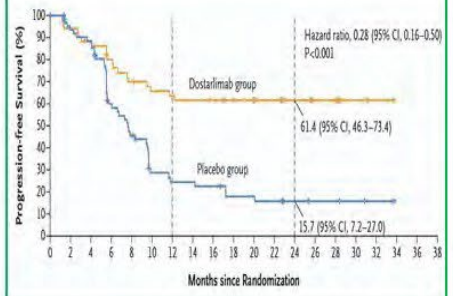
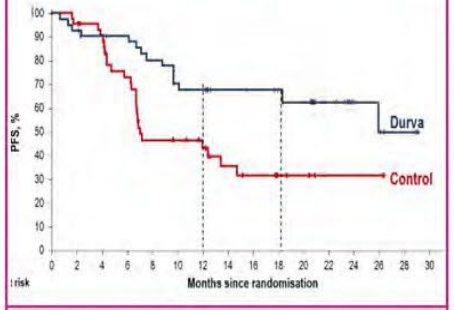
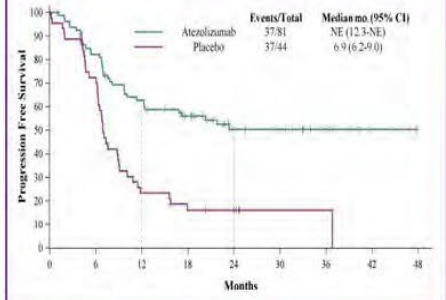
[1]Marabelle et al., *J Clin Oncol* 2020; [2]O'Malley et al., *J Clin Oncol* 2022; [3]Konstantinopoulos et al., *J Clin Oncol* 2019; [4]Antill et al., *J Immunother Cancer* 2021; [5]Oaknin et al., ESMO Annual Meeting 2020; [6]Oaknin et al., SGO Annual Meeting 2021

1L immunotherapy + chemotherapy for metastatic or recurrent endometrial cancer

	NRG-GY018 (N=816)	RUBY Part 1 (N=494)	DUO-E (N=718)	AtTEnd (N=551)
IO agent	Pembrolizumab	Dostarlimab	Durvalumab	Atezolizumab
Primary endpoint	PFS (separately powered dMMR and pMMR)	PFS and OS (hierarchical)	PFS (each exp arm against control)	PFS and OS (hierarchical)
Arms	1. Carbo/pac 2. Carbo/pac/pembro → pembro maintenance	1. Carbo/pac 2. Carbo/pac/dostarlimab → dostarlimab maintenance	1. Carbo/pac 2. Carbo/pac/durvalumab → durvalumab maintenance 3. Carbo/pac/durvalumab → durvalumab + olaparib maintenance	1. Carbo/pac 2. Carbo/pac/atezolizumab → atezolizumab maintenance
Length of IO	2 years	3 years	Until progression/toxicity	Until progression/toxicity
Patient population	Stage III measurable and Stage IV or recurrent	Stage III measurable and Stage IV or recurrent; high-risk stage III non-measurable (~15%)	Stage III measurable and Stage IV or recurrent	Stage III measurable and Stage IV or recurrent

Eskander et al., *N Engl J Med* 2023; Mirza et al., *N Engl J Med* 2023; Westin et al., *J Clin Oncol* 2024; Colombo et al., *Lancet Oncol* 2024

Immunotherapy + chemotherapy with significant PFS benefit in dMMR endometrial cancer

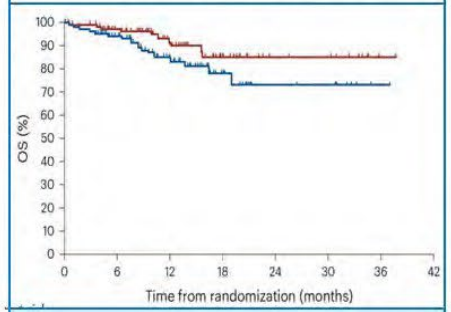
NRG-GY018	RUBY	DUO-E	AtTEnd
Pembrolizumab	Dostarlimab	Durvalumab	Atezolizumab
			
HR 0.30 95% CI 0.19-0.48 7.6 mos vs NR p<0.001	**HR 0.28** 95% CI 0.16-0.50 PFS24 15.7% vs 61.4% p<0.001	**HR 0.42** 95% CI 0.22-0.80 7.0 mos vs NR (exploratory)	**HR 0.36** 95% CI 0.23-0.57 6.9 mos vs NE p=0.0005

Eskander et al., *N Engl J Med* 2023; Mirza et al., *N Engl J Med* 2023; Westin et al., *J Clin Oncol* 2024; Colombo et al., *Lancet Oncol* 2024

Immunotherapy + chemotherapy with potential OS benefit in dMMR endometrial cancer

NRG-GY018

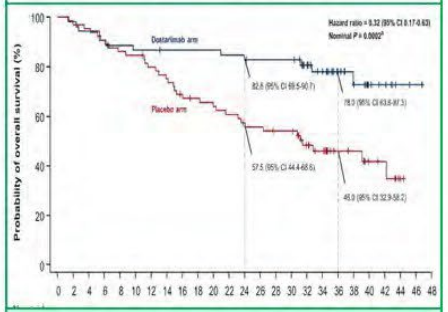
Pembrolizumab



HR 0.55
95% CI 0.25-1.19
NR vs NR
P=0.0617

RUBY

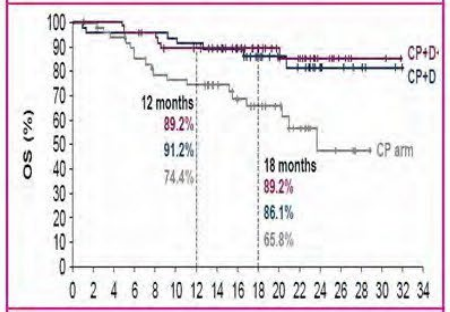
Dostarlimab



HR 0.32
95% CI 0.17-0.63
nominal p<0.0002

DUO-E

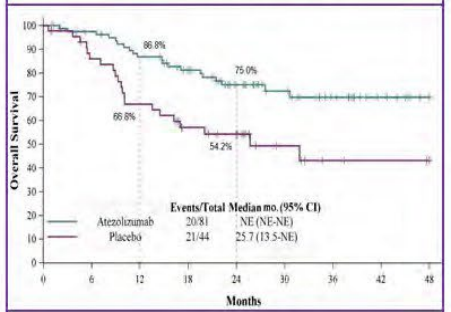
Durvalumab



HR 0.34
95% CI 0.13-0.79
23.7 mos vs NR

AtTEnd

Atezolizumab



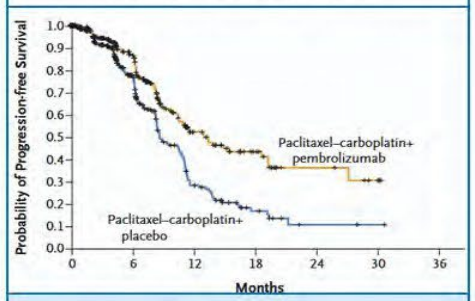
HR 0.41
95% CI 0.22-0.76
25.7 mos vs NE

Eskander et al., *Nat Med* 2025; Powell et al., *Ann Oncol* 2024; Sato et al., 2024 ESMO Congress; Colombo et al., *Lancet Oncol* 2024

Immunotherapy + chemotherapy with some PFS benefit in pMMR endometrial cancer

NRG-GY018

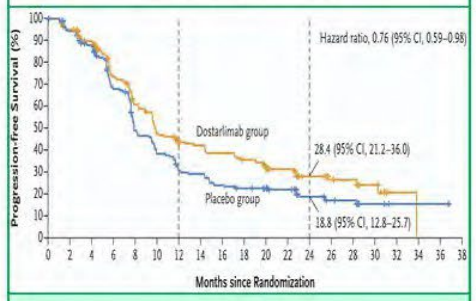
Pembrolizumab



HR 0.54
95% CI 0.41-0.71
8.7 vs 13.1 mos
p<0.001

RUBY

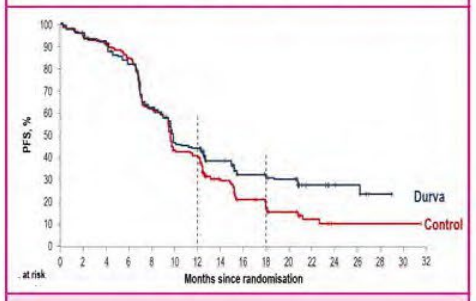
Dostarlimab



HR 0.76
95% CI 0.59-0.98
PFS24 18.8% vs 28.4%

DUO-E

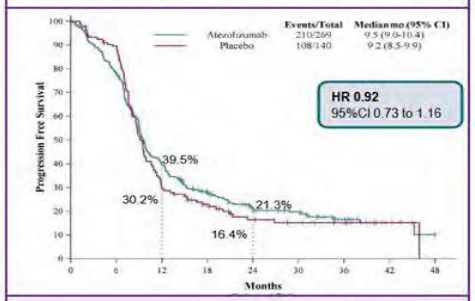
Durvalumab



HR 0.77
95% CI 0.60-0.97
9.7 vs 9.9 mos

AtTEnd

Atezolizumab



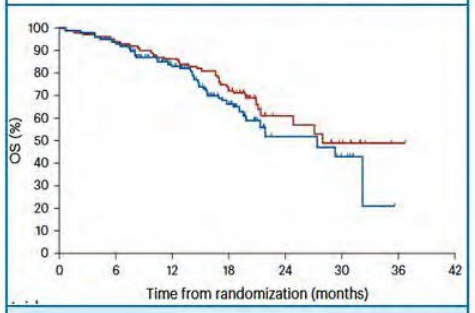
HR 0.92
95% CI 0.73-1.16
9.2 vs 9.5 mos

Eskander et al., *N Engl J Med* 2023; Mirza et al., *N Engl J Med* 2023; Westin et al., *J Clin Oncol* 2024; Colombo et al., *Lancet Oncol* 2024

Immunotherapy + chemotherapy with uncertain OS effect in pMMR endometrial cancer

NRG-GY018

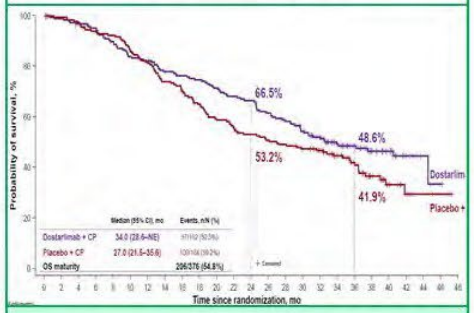
Pembrolizumab



HR 0.79
95% CI 0.53-1.17
27.4 vs 28.0 mos
(27.2% maturity)

RUBY

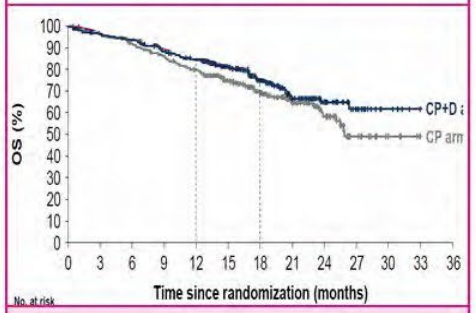
Dostarlimab



HR 0.79
95% CI 0.60-1.04
27.0 vs 34.0 mos
(54.8% maturity)

DUO-E

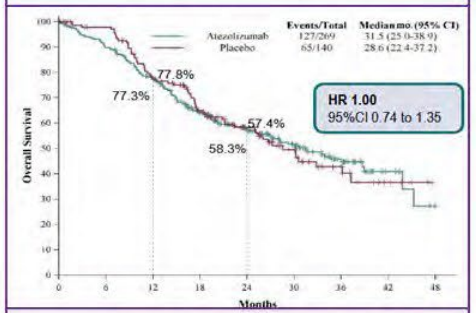
Durvalumab



HR 0.77
95% CI 0.56-1.07
25.9 mos vs NR
(27.7% maturity)

AtTEnd

Atezolizumab



HR 1.00
95% CI 0.74-1.35
28.6 vs 31.5 mos
(~50% maturity)

Eskander et al., *Nat Med* 2025; Powell et al., *Ann Oncol* 2024; Sato et al., 2024 ESMO Congress; Colombo et al., *Lancet Oncol* 2024

Conclusions

- Molecular profiling is critical in endometrial cancer management
- MMR deficiency is an established predictive marker in EC
- High expression of HER2neu is a predictive biomarker in EC
- Precision therapy is expanding in EC and should be embraced by all

Charting the Course: Treatment Approaches for dMMR Endometrial Cancer

Ramez N. Eskander, MD
University of California San Diego
Moores Cancer Center
San Diego, California, USA

Endometrial Cancer 2025

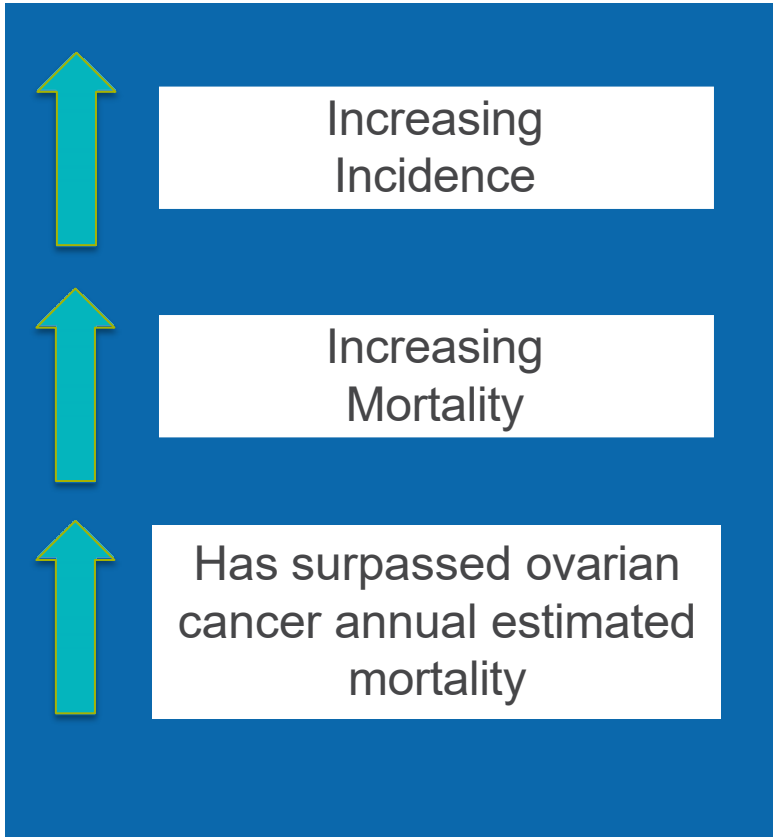
- **Only gynecologic cancer with rising incidence and mortality**
- **Now exceeds ovarian cancer in annual estimated deaths**

69,1200 new cases | **13,860 deaths**

~2/3 of these will be early stage and low grade with excellent prognosis

~1/3 will have high grade or advanced stage disease

Population of interest



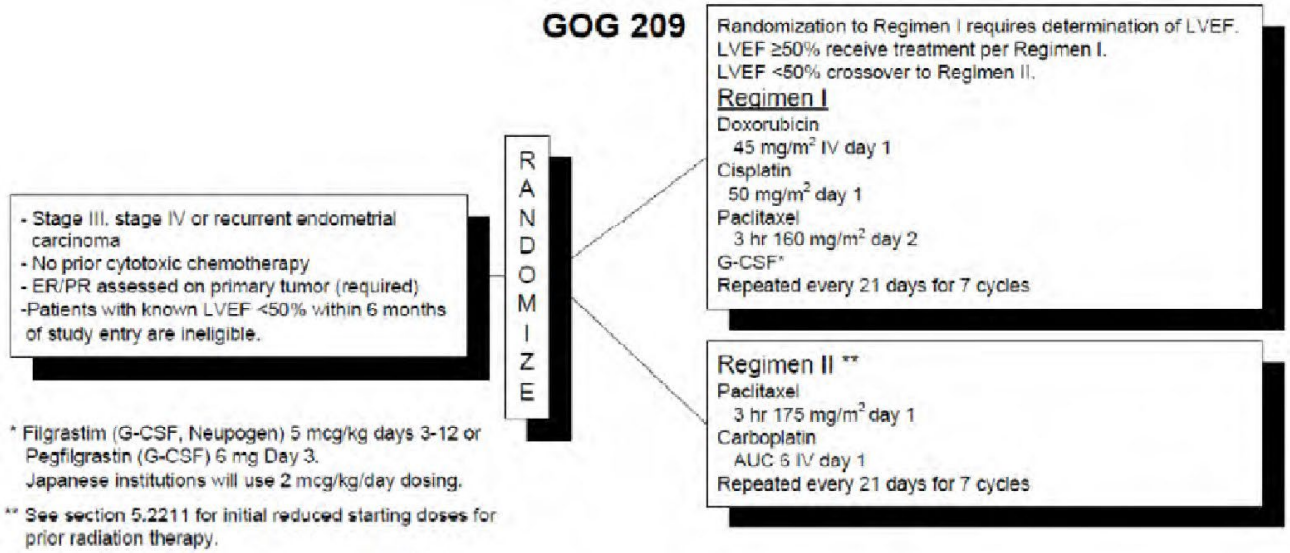
Siegel et al. Cancer Statistics 2025

Treatment of advanced stage/recurrent Endometrial Cancer

	RT agent vs. Doublet	Single agent vs. Doublet		Doublet vs. Doublet	Doublet vs. Triplet	TAP vs. TC
	GOG 122 Randall et al. JCO '06	**EORTC55872** Van Wijk Ann Onc '03	**GOG 107** Thigpen JCO '04	**GOG 163** Fleming. Ann Onc '04	**GOG 177** Fleming JCO '03	**GOG 209** Miller SGO ´12
Population (Stage)	III-IV	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4 & Relapsed	Stage 3-4
n	396	177	299	317	273	
Regimen	WART vs Dox-Cis	Dox vs. Dox-Cis	Dox (A) vs. Dox-Cis (AC)	Dox-Cisplat vs. Dox-Paclitax	Dox-Cisplat vs. Dox-Cisplat-Tax	Carbo-Tax vs. Dox-Cisplat-Tax
PFS	Signif HR 0.71	NS	Signif HR 0.73	NS	Signif P < 0.01	NS
OS	Signif HR 0.68	NS	NS	NS	Signif P < 0.037	NS

GOG 209

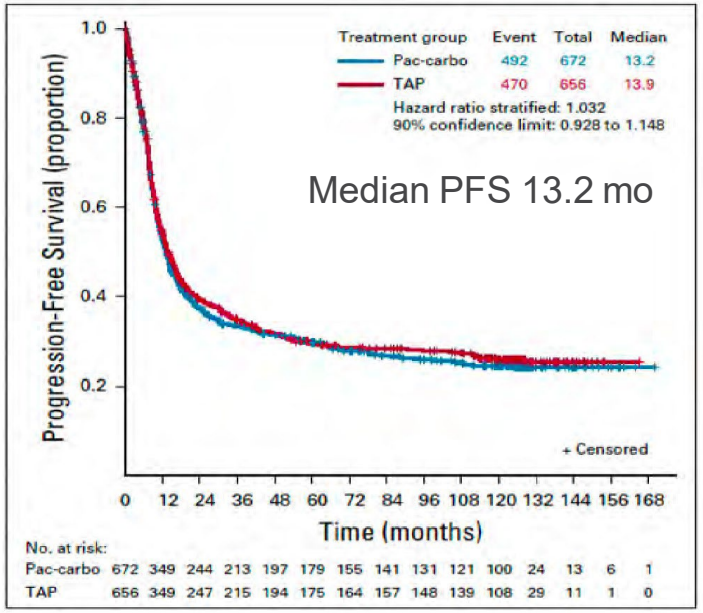
Established carboplatin and paclitaxel as the chemotherapy backbone for patients with advanced stage or recurrent disease



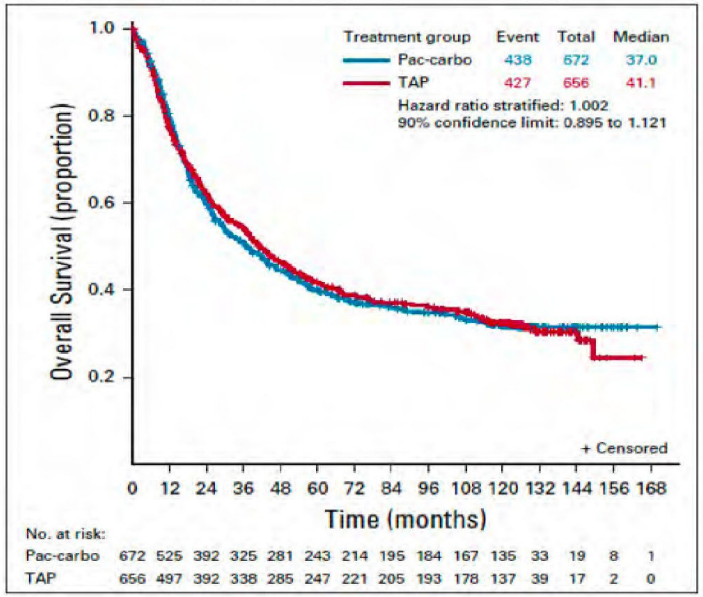
Key eligibility criteria

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

Progression Free Survival



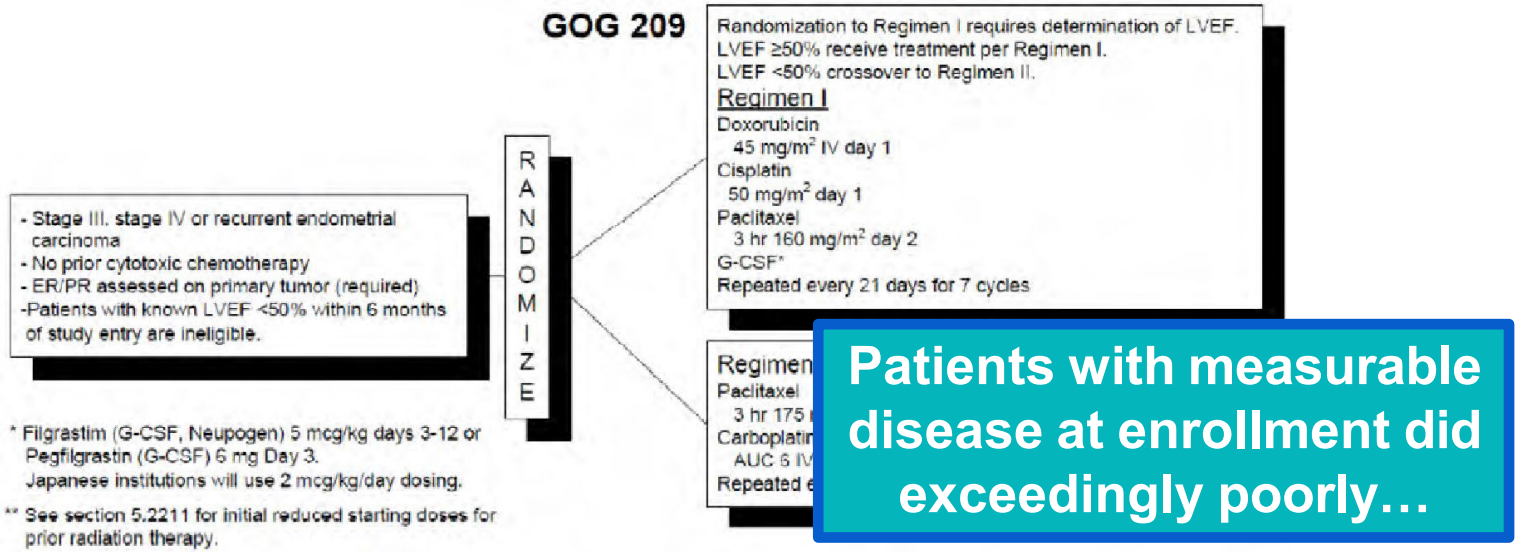
Overall Survival



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

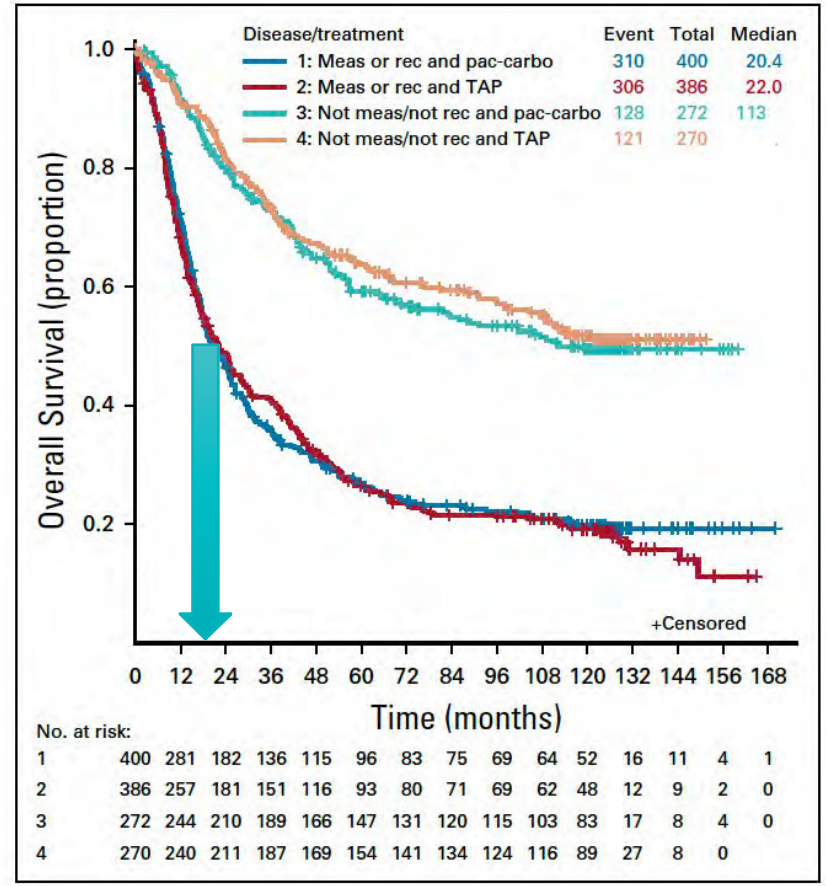
GOG 209

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



Patients with measurable disease at enrollment did exceedingly poorly…

Overall Survival



Key eligibility criteria

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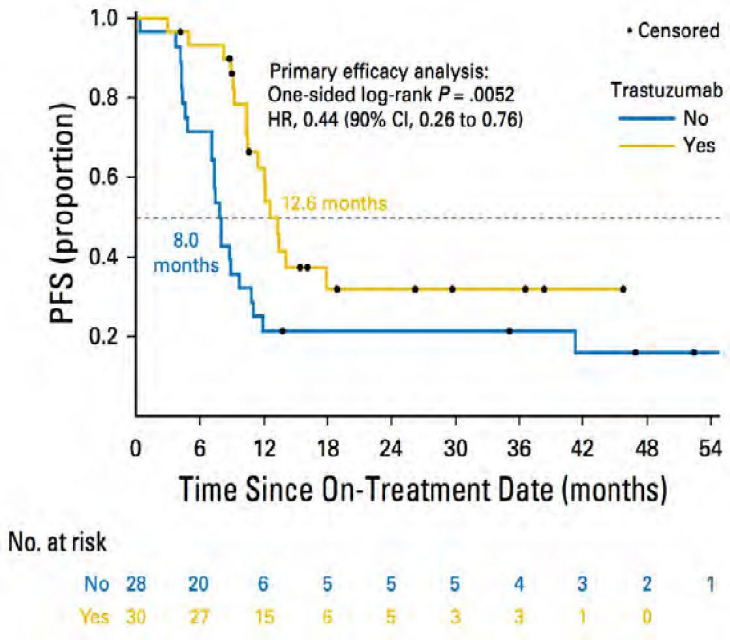
- **NO prior cytotoxic chemotherapy**, including chemotherapy used for radiation sensitization
- GOG PS 0,1 or 2

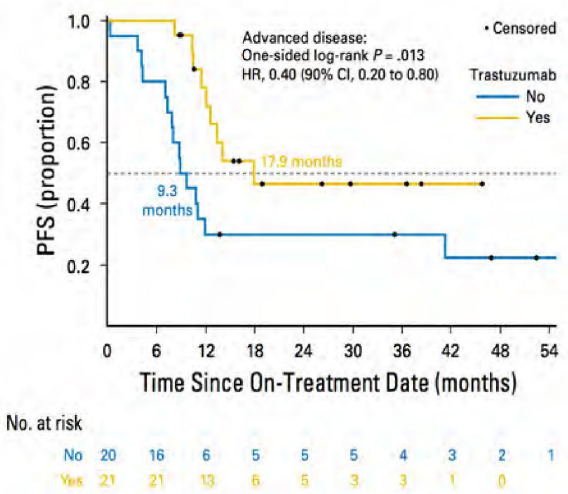
Miller DS, et al. J Clin Oncol. 2020 Nov 20;38(33):3841-3850.

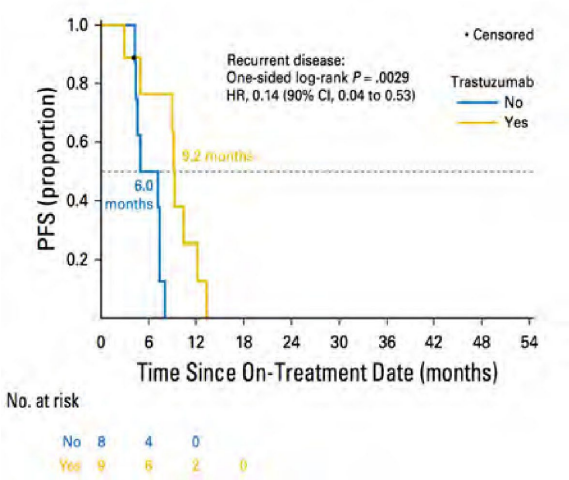
Incorporation of anti-HER-2 treatment: Trastuzumab with Chemotherapy

Key eligibility criteria

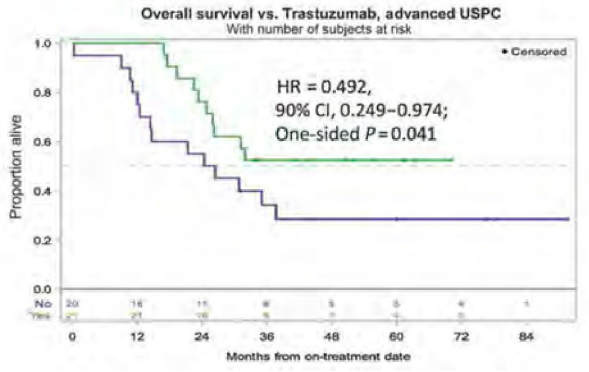
- Primary stage III or IV or recurrent HER2/neu-positive USC: IHC score 3+, or 2+ with + FISH
- ECOG 0-2
- ≤3 prior lines of therapy
- “platinum sensitive” recurrence (6 mo)

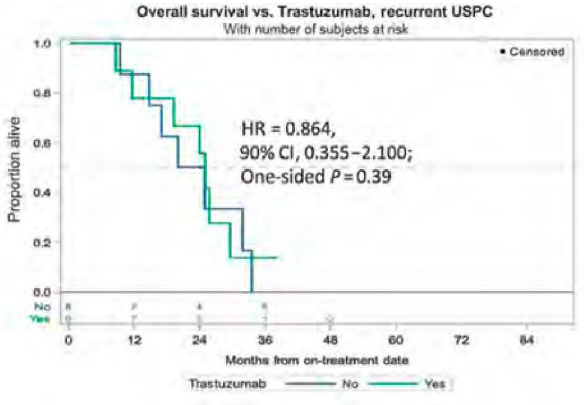






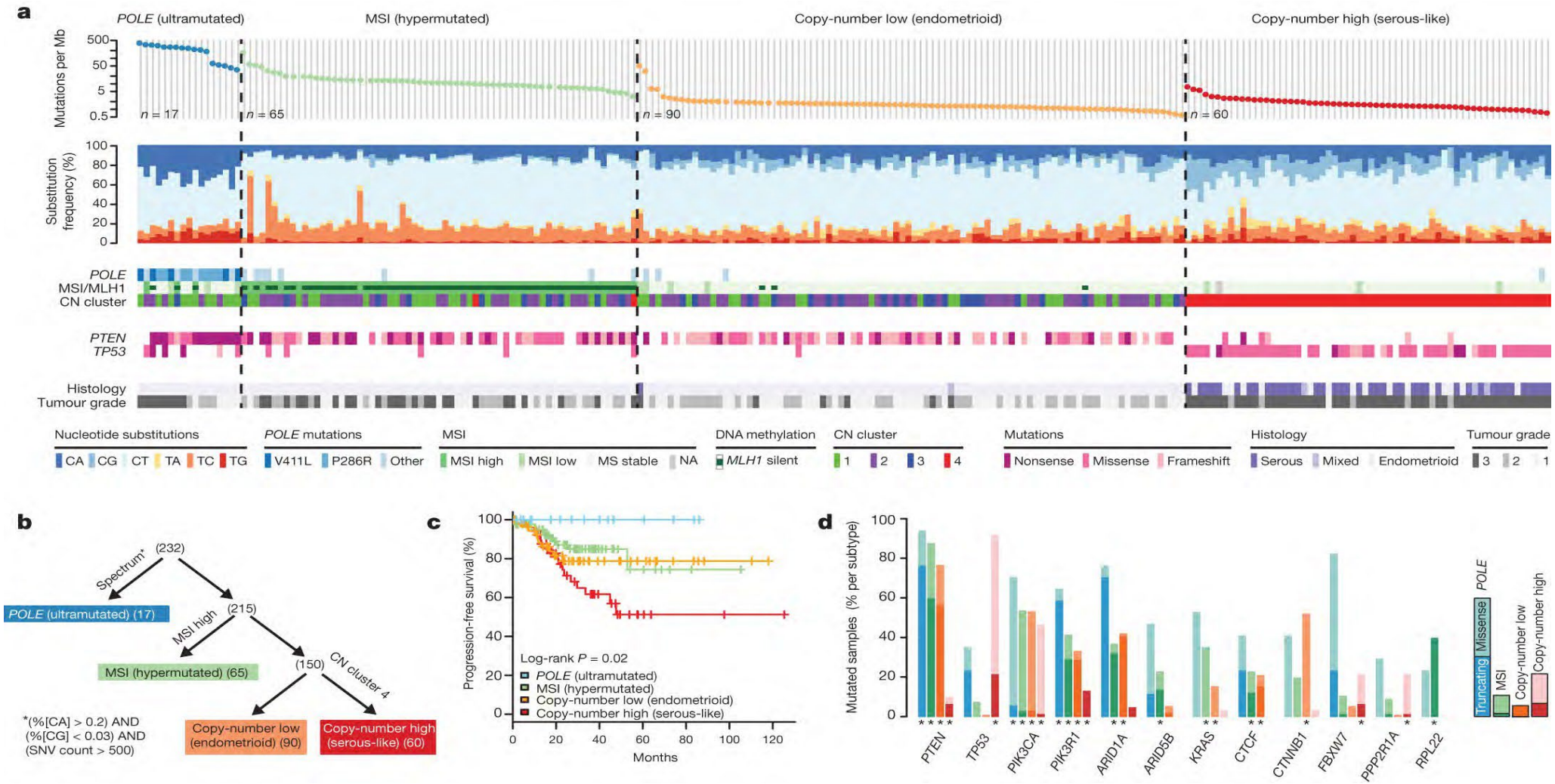
OS benefit particularly striking in stage III–IV patients, OS median of 25.4 months (control) versus NR (p = 0.041, HR = 0.49, 90% CI 0.25–0.97).





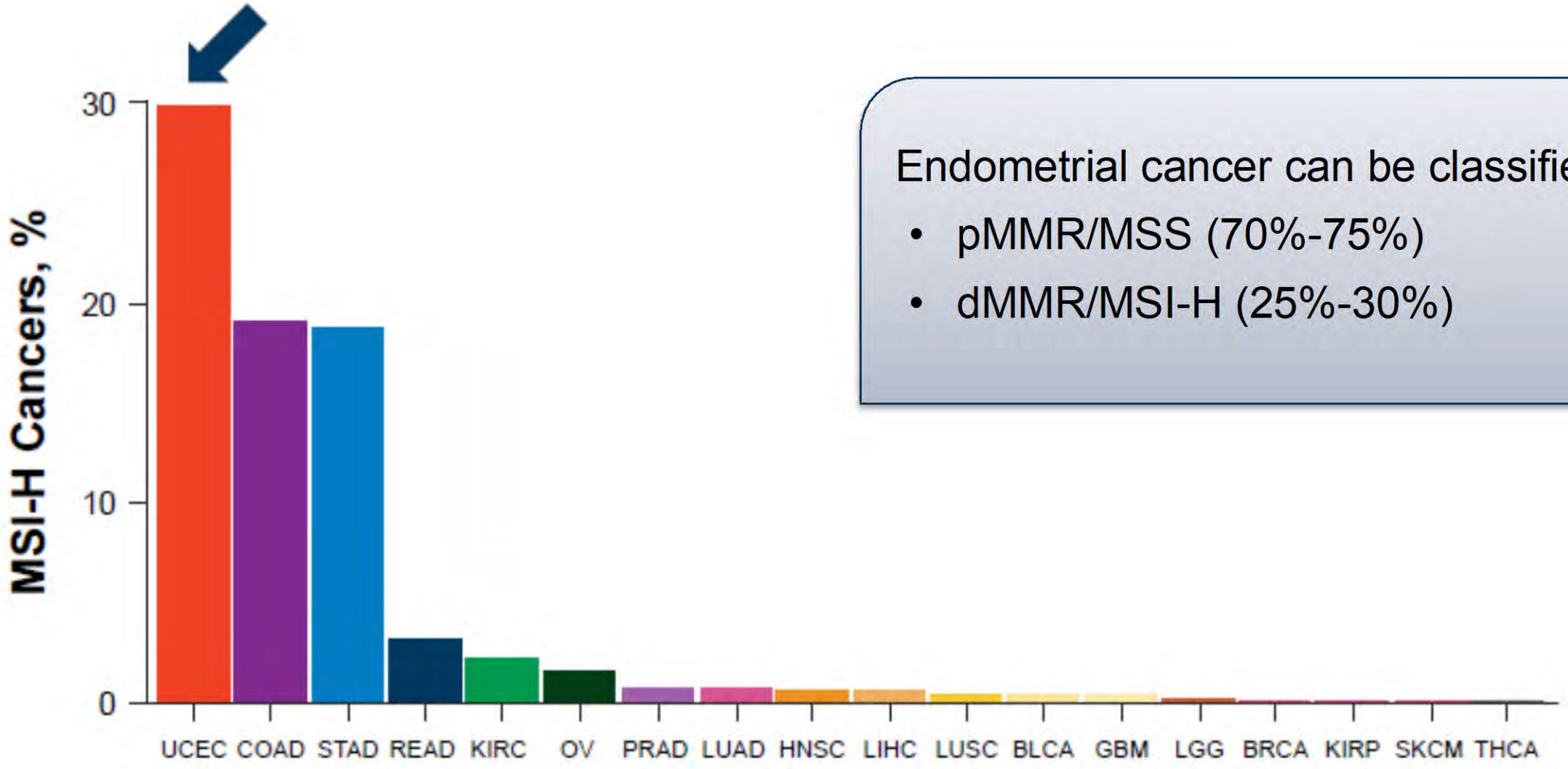
Nickles-Fader J Clin Oncol 2018

Disease Homogeneity to Molecular Granularity



G Getz et al. Nature **497**, 67-73 (2013) doi:10.1038/nature12113

Frequency of dMMR in Endometrial Cancer



Endometrial cancer can be classified as

- pMMR/MSS (70%-75%)
- dMMR/MSI-H (25%-30%)

[a] UCEC (n = 437); COAD (n = 294); STAD (n = 278); READ (n = 96); KIRC (n = 279); OV (n = 63); PRAD (n = 463); LUAD (n = 480); HNSC (n = 506); LIHC (n = 338); LUSC, (n = 443); BLCA (n = 253); GBM (n = 262); LGG (n = 513); BRCA (n = 266); KIRP (n = 207); SKCM (n = 268); THCA (n = 484).

1. Hause RJ et al. *Nat Med.* 2016;22:1342-1350.

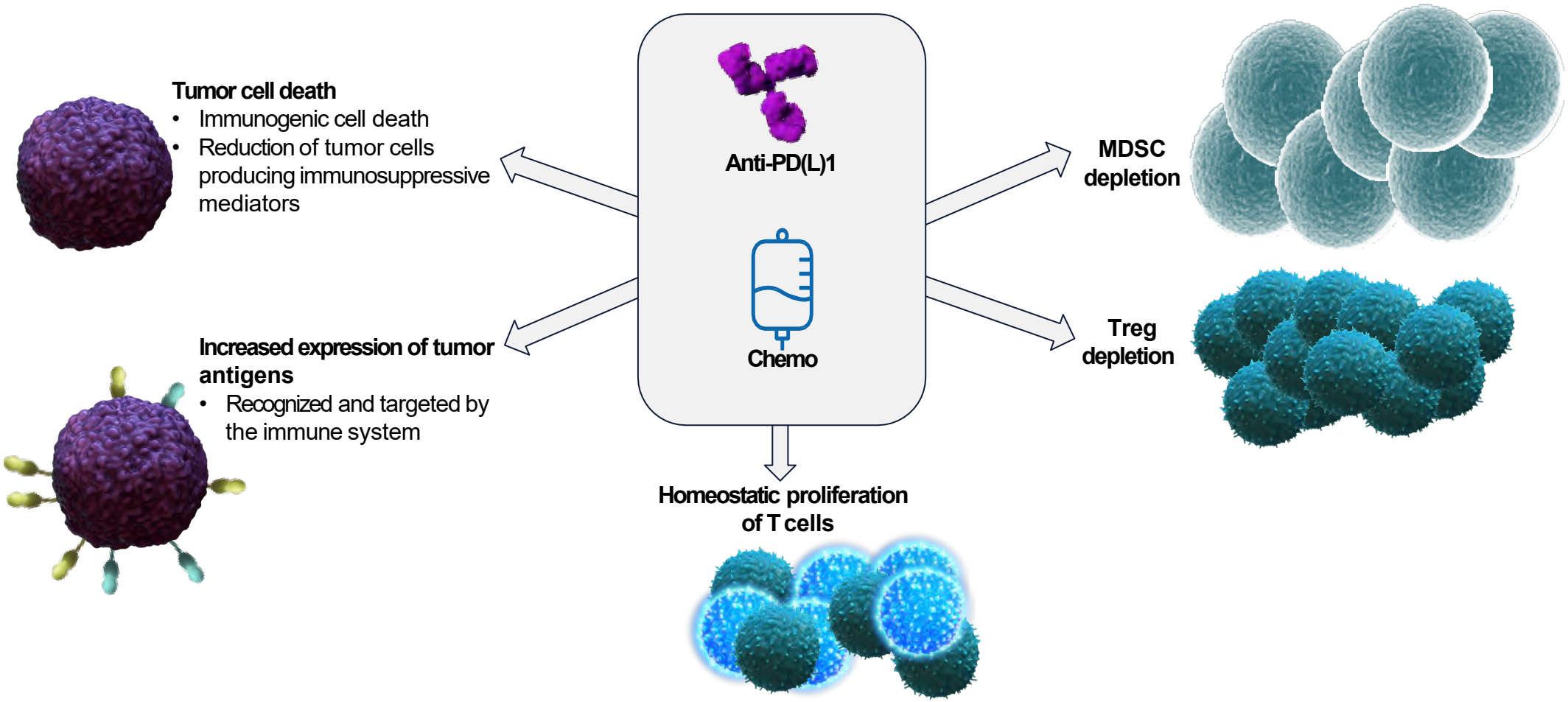
Single Agent IO in “biomarker” Selected Endometrial Cancer Populations (Recurrent dMMR EC)

Response to single agent IO in **recurrent dMMR or MSI-high endometrial**

Study & Drug	Patient Population	Outcome
Keynote 158: Pembrolizumab (N=90)	Advanced stage or metastatic dMMR endometrial cancer	ORR: 48%
PHAEDRA trial: Durvalumab (N=35 dMMR)	Advanced stage or metastatic endometrial cancer	ORR in dMMR: 43%
GARNET study: Dostarlimab (N=129)	Previously treated, recurrent advanced stage endometrial cancer	ORR in dMMR: 43.5%
Ph II Avelumab study (N= 15 dMMR)	Advanced stage or metastatic endometrial cancer	ORR: 26.7%

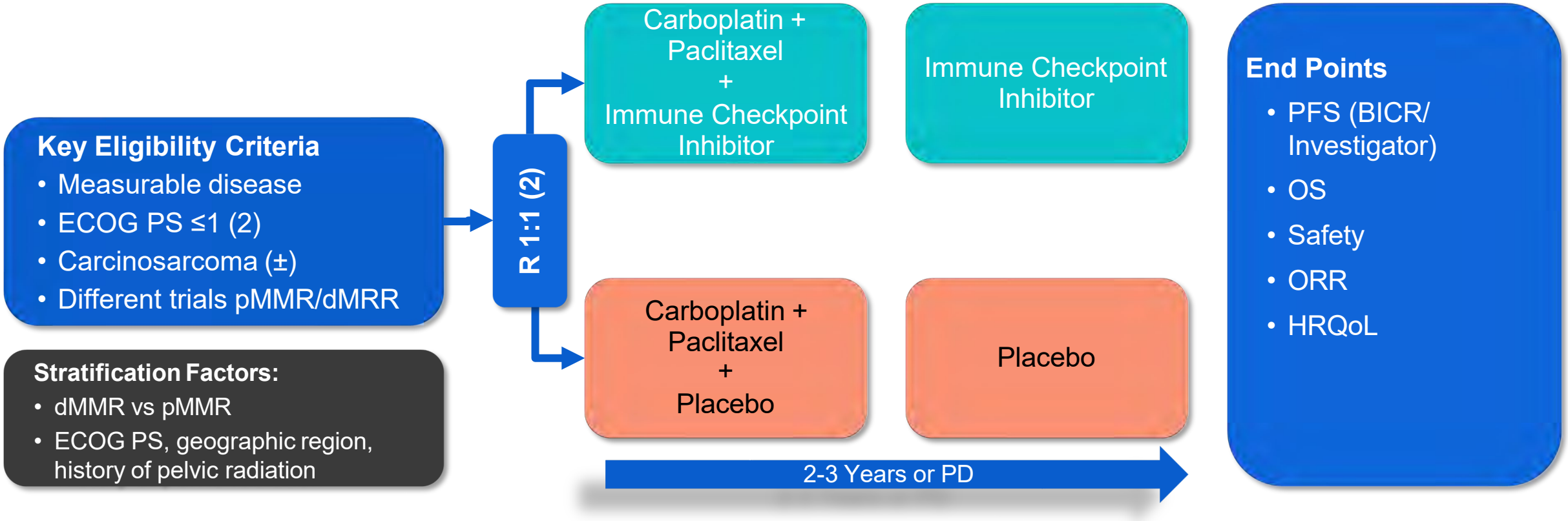
O’Malley D, et al. J Clin Oncol, 2022
Antill PSK et al. J Clin Oncol 2019
Oaknin A et al. Journal for ImmunoTherapy of Cancer 2022
Konstantinopoulos PA et al. J Clin Oncol 2019

Rational for Combinatorial Approach with Chemotherapy + IO



1. Hato SV et al. Clin Cancer Res. 2014. 2. Chen Y et al. Am J Cancer Res. 2021. 3. Pfannenstiel T et al. Cell Immunol. 2010. 4. Sevko A et al. J Immunol. 2013.

Benefit of IO + Chemo in EC: 1L studies in patients with advanced stage or recurrent EC Benefit of IO + Chemo in EC: 1L studies in patients with advanced stage or recurrent EC



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

Mirza M et al. NEJM March 2023
Eskander et al. NEJM March 2023
Colombo N, et al. Lancet Oncol Sept 2024
Marth C, et al. SGO 2024 Annual Meeting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M. Tian, Z. He, S. Stevens, E. Zografos, R.L. Coleman, and M.A. Powell, for the RUBY Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

ASCO Journal of Clinical Oncology®

Durvalumab Plus Carboplatin/Paclitaxel Followed by Maintenance Durvalumab With or Without Olaparib as First-Line Treatment for Advanced Endometrial Cancer: The Phase III DUO-E Trial

Shannon N. Westin, MD, MPH[1]; Kathleen Moore, MD[2]; Hye Sook Chon, MD[3]; Jung-Yun Lee, MD[4]; Jessica Thomes Pepin, MD[5]; Michael Sundborg, MD[6]; Ayelet Shai, MD, PhD[7]; Joseph de la Garza, MD[8]; Shin Nishio, MD[9]; Michael A. Gold, MD[10]; Ke Wang, MD[11]; Kristi McIntyre, MD[12]; Todd D. Tillmanns, MD[13]; Stephanie V. Blank, MD[14]; Ji-Hong Liu, MD[15]; Michael McCollum, MD[16]; Fernando Contreras Mejia, MD[17]; Tadaaki Nishikawa, MD[18]; Kathryn Pennington, MD[19]; Zoltan Novak, MD, PhD[20]; Andreia Cristina De Melo, MD[21]; Jalid Sehouli, MD[22]; Dagmara Klasa-Mazurkiewicz, MD[23]; Christos Papadimitriou, MD[24]; Marta Gil-Martin, MD[25]; Birute Brasiuniene, MD, PhD[26]; Conor Donnelly, PhD[27]; Paula Michelle del Rosario, MD[28]; Xiaochun Liu, MD, PhD[29]; and Els Van Nieuwenhuysen, MD[30]; on behalf of the DUO-E Investigators

DOI https://doi.org/10.1200/JCO.23.02132

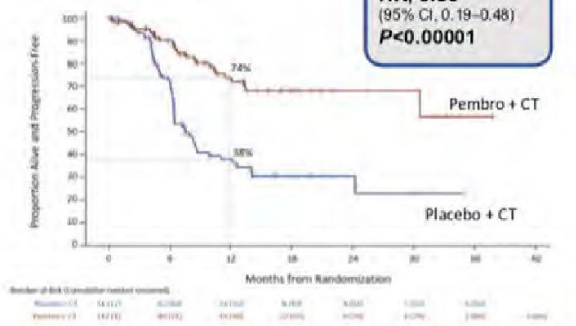
Atezolizumab and chemotherapy for advanced or recurrent endometrial cancer (AtTEnd): a randomised, double-blind, placebo-controlled, phase 3 trial

*Nicoletta Colombo, Elena Biagioli, Kenichi Harano, Francesca Galli, Emma Hudson, Yoland Antill, Chel Hun Choi, Manuela Rabaglio, Frederic Marmé, Christian Marth, Gabriella Parma, Lorena Fariñas-Madrid, Shin Nishio, Karen Allan, Yeh Chen Lee, Elisa Piovano, Beatriz Pardo, Satoshi Nakagawa, John McQueen, Claudio Zamagni, Luis Manso, Kazuhiro Takehara, Giulia Tasca, Annamaria Ferrero, Germana Tognon, Andrea Alberto Lissoni, Mariacristina Petrella, Maria Elena Laudani, Eliana Rulli, Sara Uggeri, M Pilar Barretina Ginesta, and AtTEnd study group**

Lancet Oncol 2024; 25: 1135–46

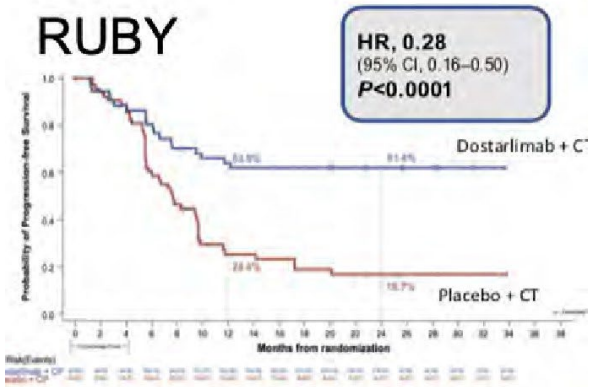
Benefit of IO + Chemo in the dMMR EC population

GY018



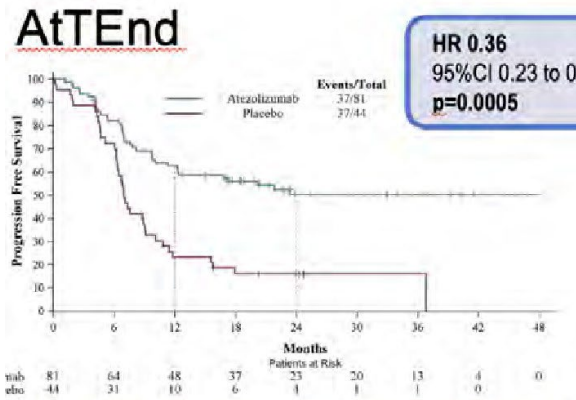
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



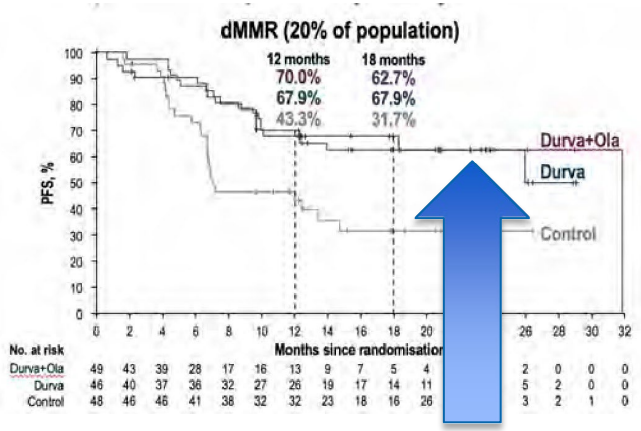
	No with events%	Median
Dorsta + CT	35.8	NR (11.8-NR)
Placebo + CT	72.3	7.7 (5.6-9.7)

AtTEnd



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

DUO-E



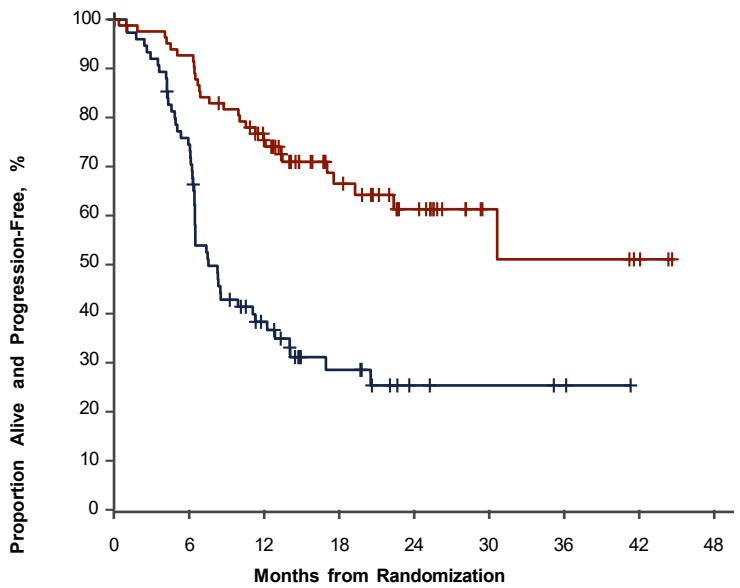
There is no role for PARPi in the dMMR population

CT		
Placebo + CT	51	7.0 (6.7-14.8)

Slide courtesy of Dr. David Tan ESMO 2023 - Revised

NRG GY018: PFS by MMR methylation status in the dMMR EC cohort

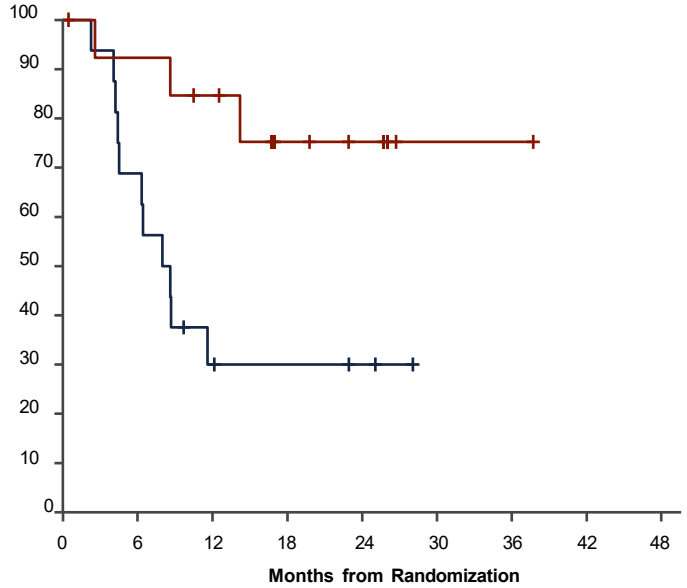
Methylation
Pembro + CP vs Placebo + CP



Number at risk (Cumulative number censored)

Placebo + CP	77 (2)	55 (3)	23 (9)	11 (16)	4 (22)	3 (23)	2 (24)	0 (26)	
Pembro + CP	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

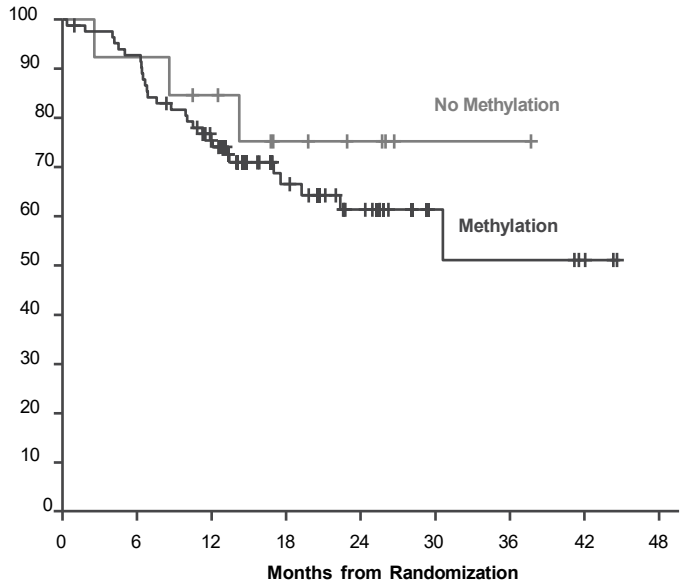
No Methylation
Pembro + CP vs Placebo + CP



Number at risk (Cumulative number censored)

Placebo + CP	17 (0)	11 (1)	4 (2)	3 (3)	2 (4)	0 (6)			
Pembro + CP	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	

Methylation Status
Pembro + CP Arm



Number at risk (Cumulative number censored)

No Methylation	13 (0)	12 (0)	10 (1)	6 (4)	4 (6)	1 (9)	1 (9)	0 (10)	
Methylation	83 (0)	76 (1)	56 (7)	30 (28)	18 (38)	6 (50)	5 (50)	3 (52)	0 (55)

Data cutoff: Aug 18, 2023

Eskander R, et al. ESMO 2023; Eskander R et al. Nature Medicine 2025

Benefit of IO + Chemo in the dMMR EC population

Immune Checkpoint Inhibition + CT is the new standard of care in advanced stage or recurrent dMMR EC…

July 31, 2023

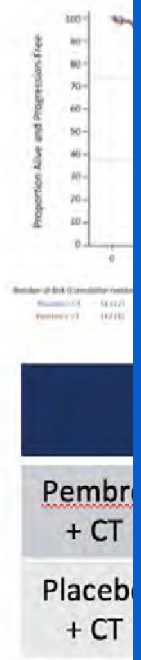
FDA approves dostarlimab-gxly with chemotherapy for endometrial cancer

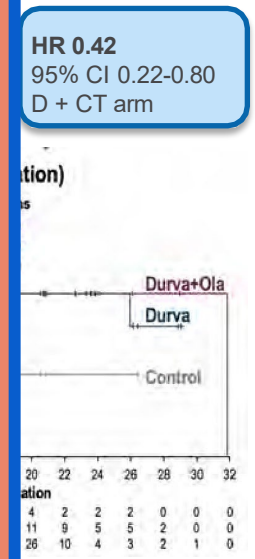
June 14, 2024

FDA approves durvalumab with chemotherapy for mismatch repair deficient primary advanced or recurrent endometrial cancer

June 17, 2024

FDA approves pembrolizumab with chemotherapy for primary advanced or





approved test, or microsatellite instability-high (MSI-H).

		Median
	32.6	NR (NR-NR)
Durva + O + CT	37.5	31.8 (12.4-NR)
Placebo + CT	51	7.0 (6.7-14.8)

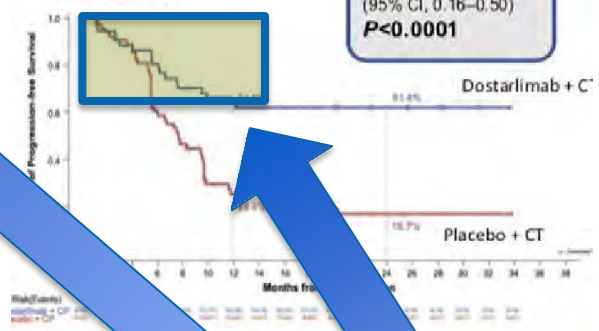
Slide courtesy of Dr. David Tan ESMO 2023 - Revised

Benefit of IO + Chemo in the dMMR EC population

GY018

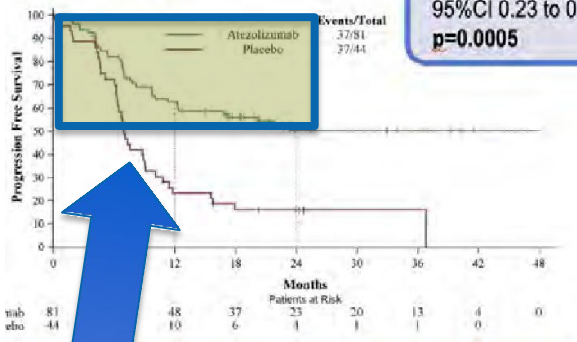
	No with events%	Median
Pembro + CT	23.2	NR (30.6-NR)
Placebo + CT	52.2	7.6 (6.4-9.9)

RUBY



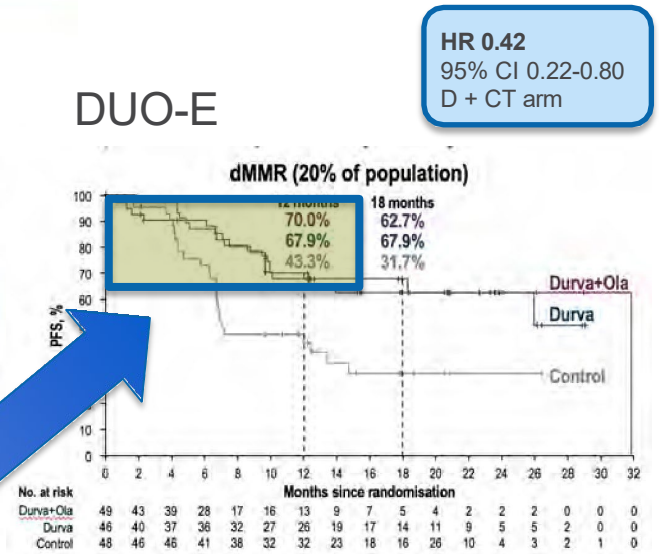
	No with events%	Median
Dorsta + CT	35.8	
Placebo + CT	72.3	7.7

AtTEnd



	No with events%	Median
zo + T	45.7	NR (12.3-NR)
cebo + CT	84.1	6.9 (6.2-

DUO-E



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

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

- I suspect dMMR but TMB low

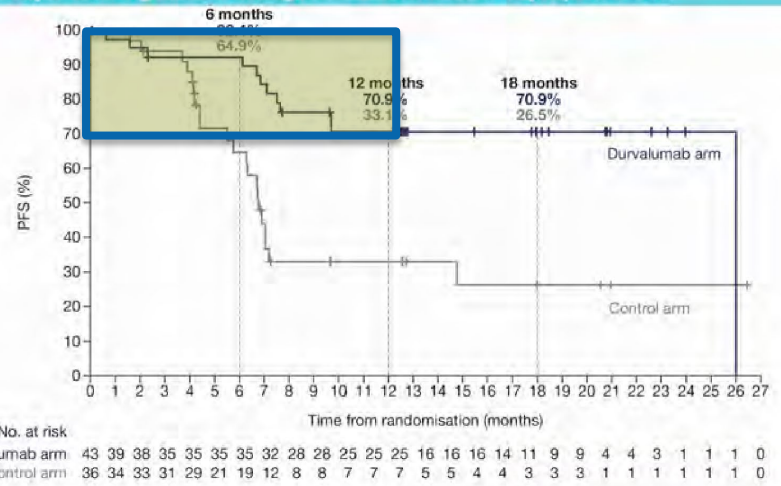
Recent Data…DUO-E (Westin et al. 1117P ESMO 2025)

Concordance between MMR and TMB status (concordance analysis set; N=479)

Subpopulation, n (%)	dMMR	pMMR	
TMB-H	92 (19.2%)	32 (6.7%)	124/479 (25.9%)
TMB-L	14 (2.9%)	341 (71.2%)	
	106/479 (22.1%)		433/479 (90.4%)

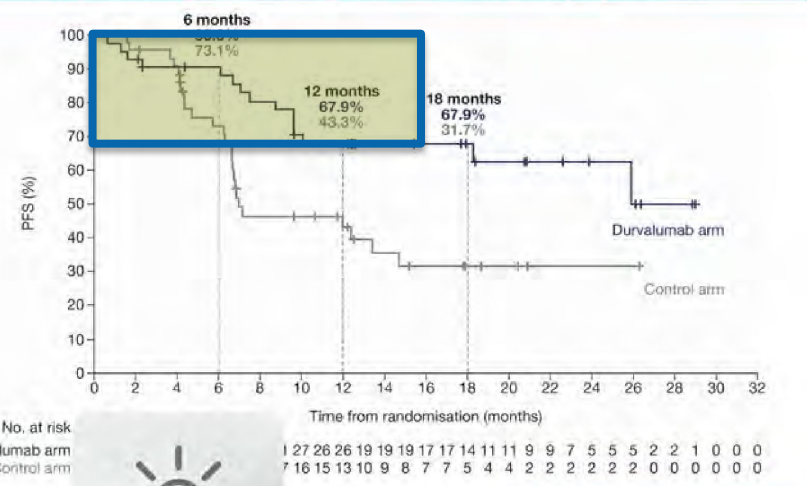
Concordance TMB & MMR status: 90.4% (95% CI 87.4–92.7)
Positive concordance between TMB-H & dMMR: 86.8% (95% CI 79.0–92.0)

Post hoc exploratory PFS analyses – TMB-H subpopulation



	Control arm (N=36)	Durvalumab arm (N=43)
Events, n (%)	21 (58.3)	12 (27.9)
Median PFS (95% CI), months	**6.8** (5.5–14.8)	**26.0** (NR–NR)
HR (95% CI) vs control	**0.30** (0.14–0.60)	

Prespecified exploratory PFS analyses – dMMR subpopulation



	ntrol arm (N=49)	Durvalumab arm (N=46)
Events, n (%)	25 (51.0)	15 (32.6)
Median PFS (95% CI)	**7.0** (6.7–14.8)	**NR** (NR–NR)
HR (95% CI) vs control	**0.42** (0.22–0.80)	

Progression does not appear to be associated with TBM status…

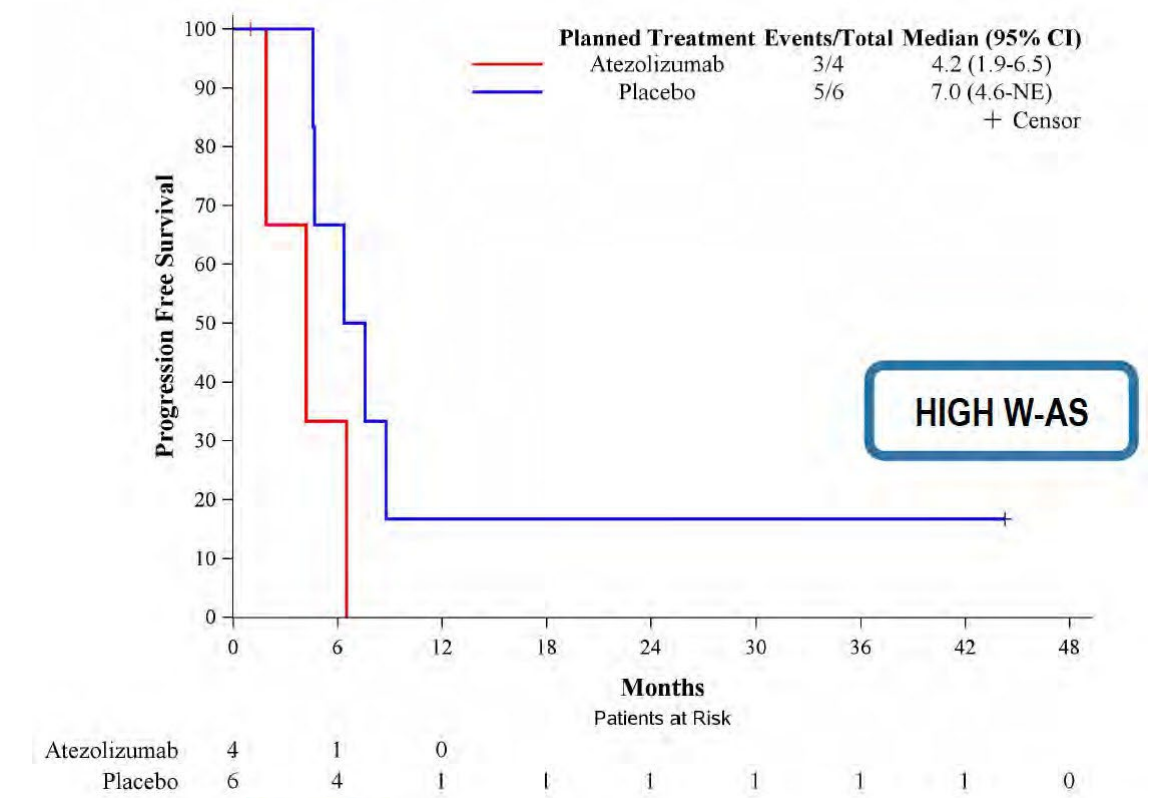
Recent Data…Attend (Mazzarella et al. ESMO 2025)

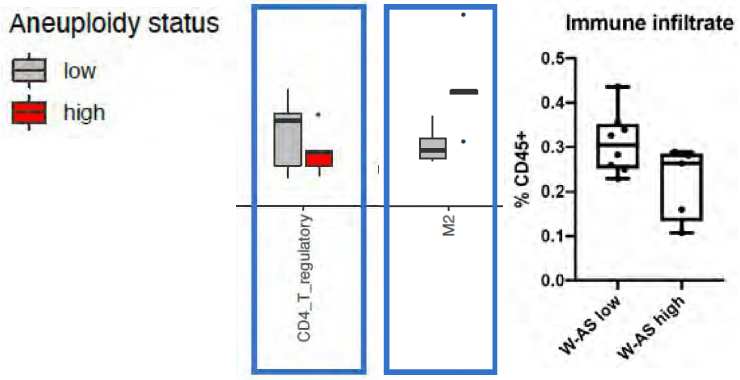
WES analysis on 110/125 dMMR tumors (88%)

WES-ANEUPLOIDY SCORE IN MMRd POPULATION	Overall (N=110)	Placebo arm (N=40)	Atezolizumab arm (N=70)
Low score	100 (90.9)	34 (85.0)	66 (94.3)
High score	10 (9.1)	6 (15.0)	4 (5.7)

WES-ANEUPLOIDY SCORE IN NON-MMRd POPULATION	Overall (N=121)	Placebo arm (N=41)	Atezolizumab arm (N=80)
Low score	57 (47.1)	24 (58.5)	33 (41.3)
High score	64 (52.9)	17 (41.5)	47 (58.7)

9% dMMR tumors were aneuploid





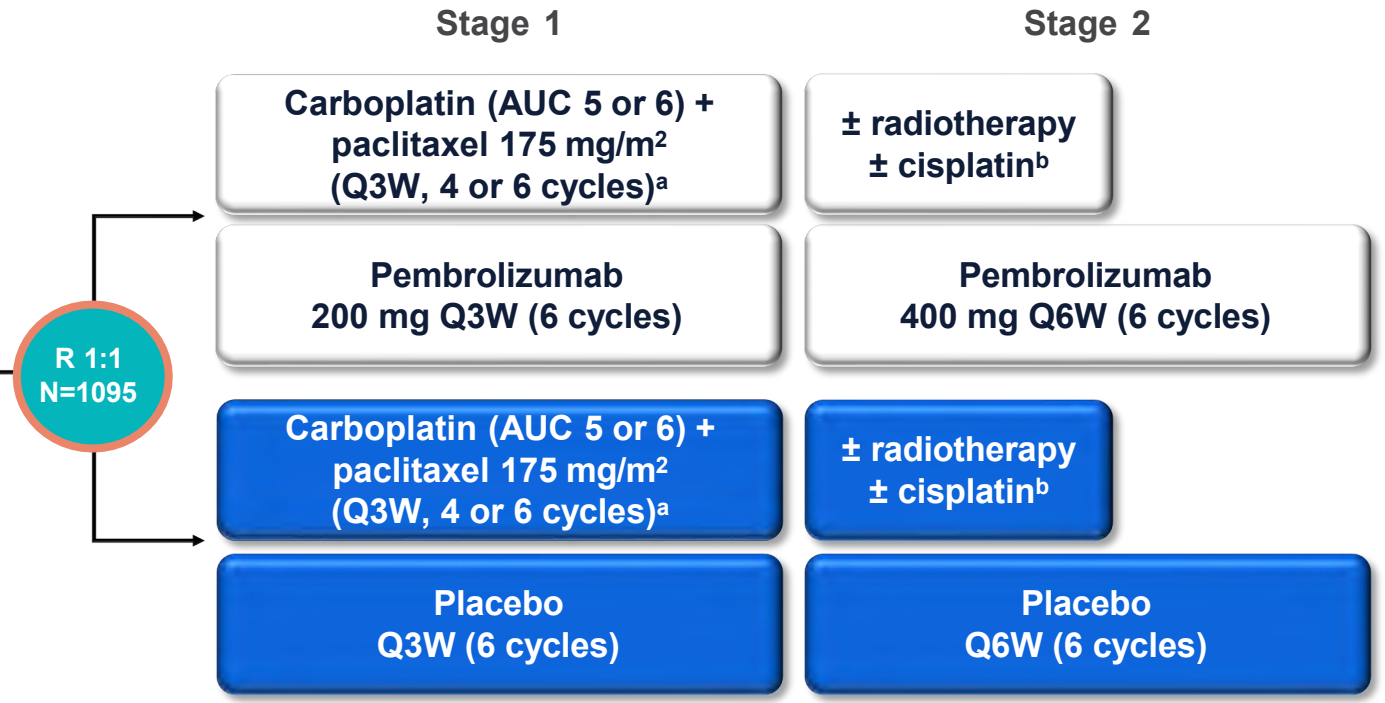
What about IO in early stage completely resected dMMR EC: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)

Key Eligibility Criteria

- Newly diagnosed EC or carcinosarcoma
- Curative surgery with no residual disease
- At high risk for recurrence:
  - FIGO (2009) surgical stage I/II, non-endometrioid with myometrial invasion
  - FIGO (2009) surgical stage I/II of any histology with known aberrant p53 expression or *TP53* mutation with myometrial invasion
  - FIGO (2009) surgical stage III/IVA of any histology
- No prior radiation or systemic therapy (including neoadjuvant) for EC

Stratification Factors

- **MMR status (pMMR vs dMMR)**, and within pMMR stratum:
  - Planned radiation (chemo-EBRT vs EBRT vs no EBRT)
  - Histology (endometrioid vs non-endometrioid)
  - FIGO (2009) surgical stage (I/II vs III/IVA)



Dual primary endpoints

- DFS as assessed radiographically by the investigator or by histopathologic confirmation
- OS

Van Gorp et al. ESMO 2024

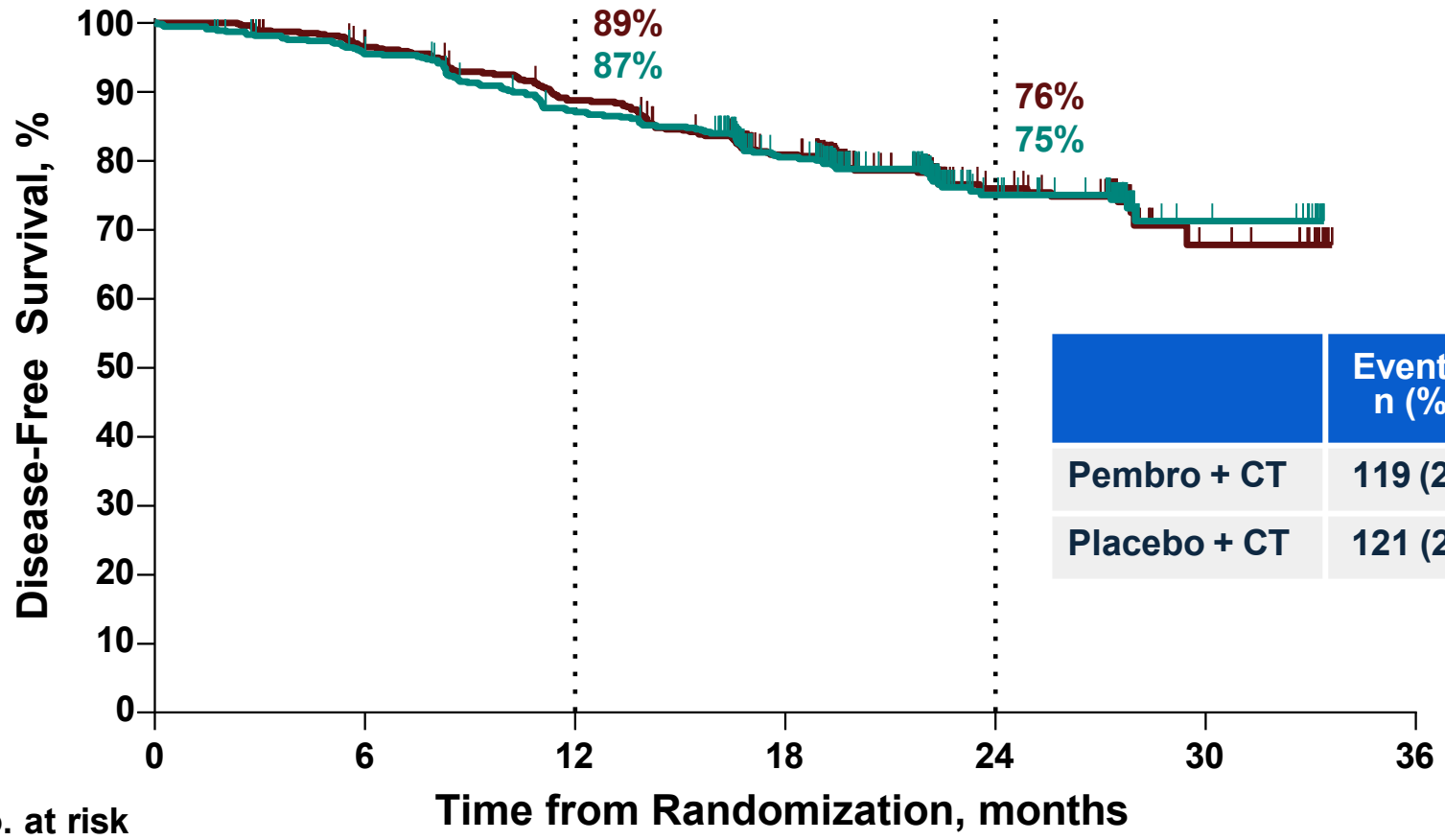
What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)

Characteristic	Pembro + Chemo (n = 545)	Placebo + Chemo (n = 550)
Age, median (range), y	62 (29–95)	62 (27–89)
ECOG PS 0	409 (75%)	416 (76%)
Race		
White	315 (58%)	362 (66%)
Asian	189 (35%)	157 (29%)
Multiple	23 (4%)	10 (2%)
Black or African American	11 (2%)	13 (2%)
American Indian or Alaska Native	2 (<1%)	3 (<1%)
Missing	5 (<1%)	5 (<1%)
Lymph node dissection	483 (89%)	502 (91%)
Lymph node status		
Lymph node involvement	223 (41%)	250 (45%)
No lymph node involvement	300 (55%)	284 (52%)
Not evaluable	22 (4%)	16 (3%)
MMR status at study entry		
dMMR	141 (26%)	140 (25%)
pMMR	404 (74%)	410 (75%)

Characteristic	Pembro + Chemo (n = 545)	Placebo + Chemo (n = 550)
FIGO 2009 stage at study entry		
IA/B	146 (27%)	144 (26%)
II	40 (7%)	41 (7%)
IIIA	109 (20%)	94 (17%)
IIIB	20 (4%)	19 (3%)
IIIC1	144 (26%)	169 (31%)
IIIC2	78 (14%)	81 (15%)
IVA/B[a]	8 (1%)	2 (<1%)
Planned radiation therapy at study entry		
EBRT[b] with cisplatin	94 (17%)	95 (17%)
EBRT[b] without cisplatin	256 (47%)	246 (45%)
Brachytherapy only	49 (9%)	52 (9%)
No EBRT or brachytherapy	146 (27%)	157 (29%)
Histology subtype		
Endometrioid	297 (54%)	297 (54%)
Non-endometrioid	248 (46%)	253 (46%)

Van Gorp et al. ESMO 2024

What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)



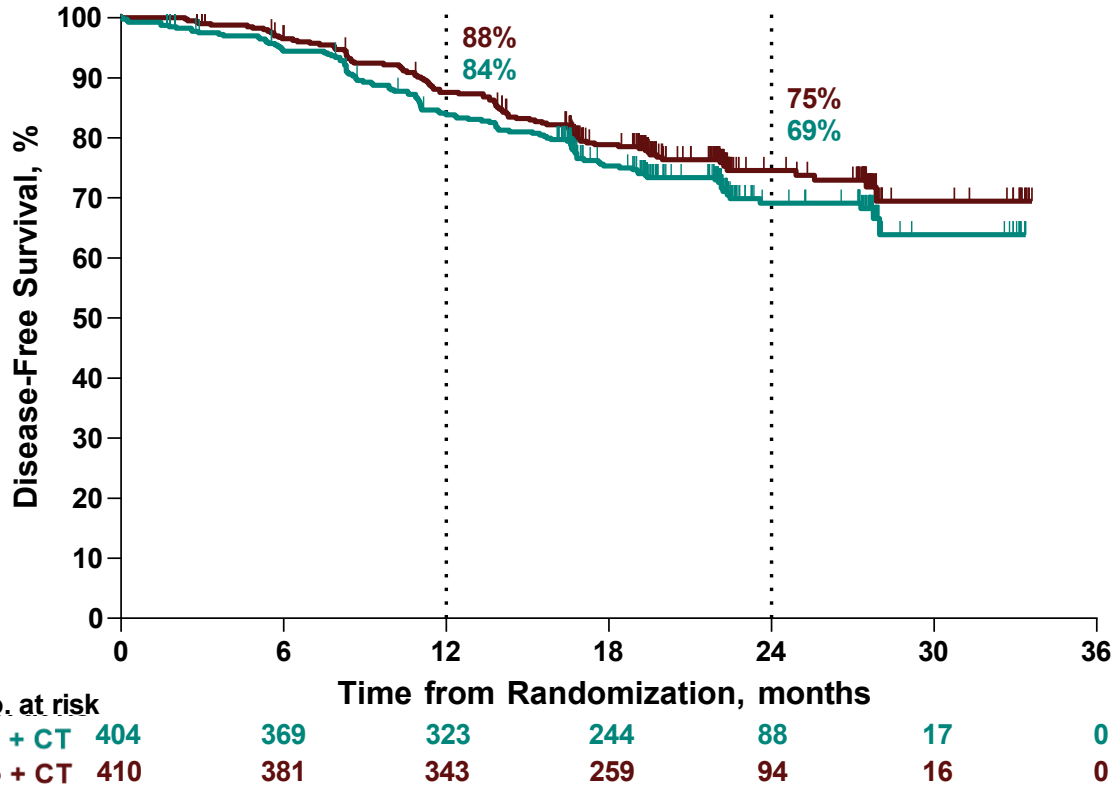
	Events, n (%)	Median (95% CI), mo	HR (95% CI)	*P* value
Pembro + CT	119 (22)	NR (NR–NR)	1.02 (0.79–1.32)	0.570
Placebo + CT	121 (22)	NR (NR–NR)		

Van Gorp et al. ESMO 2024

What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)

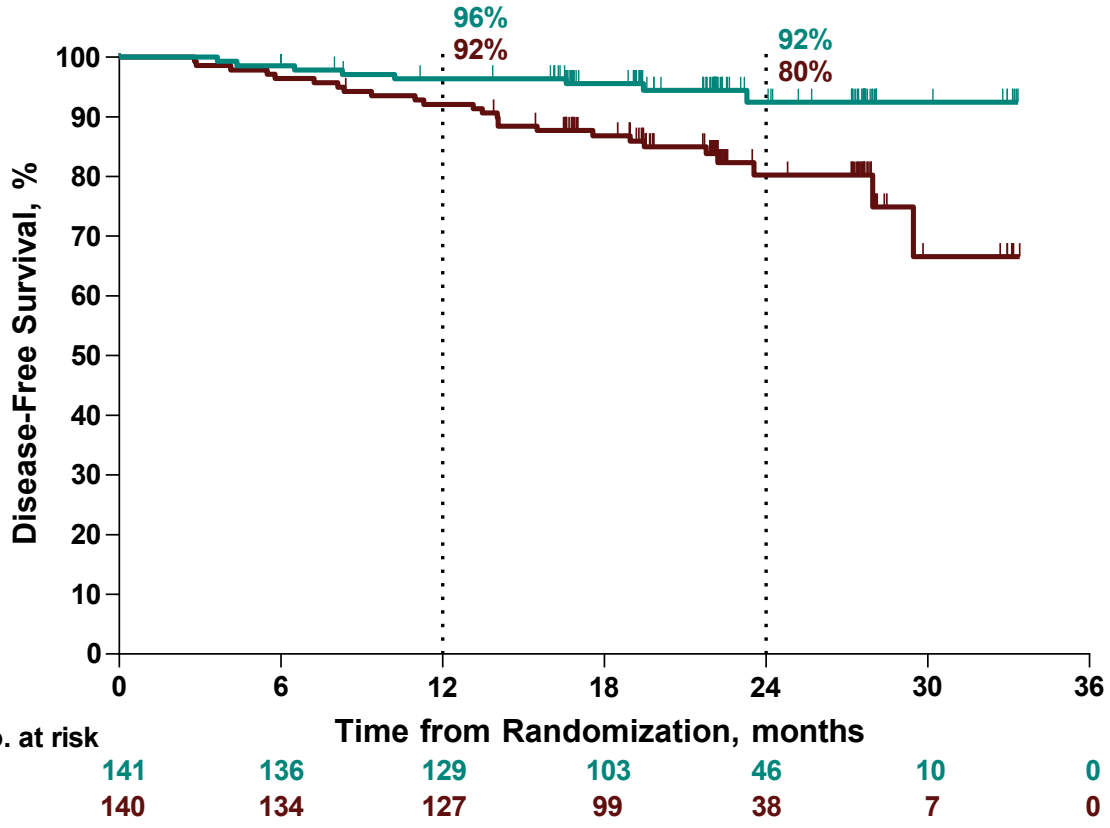
pMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	



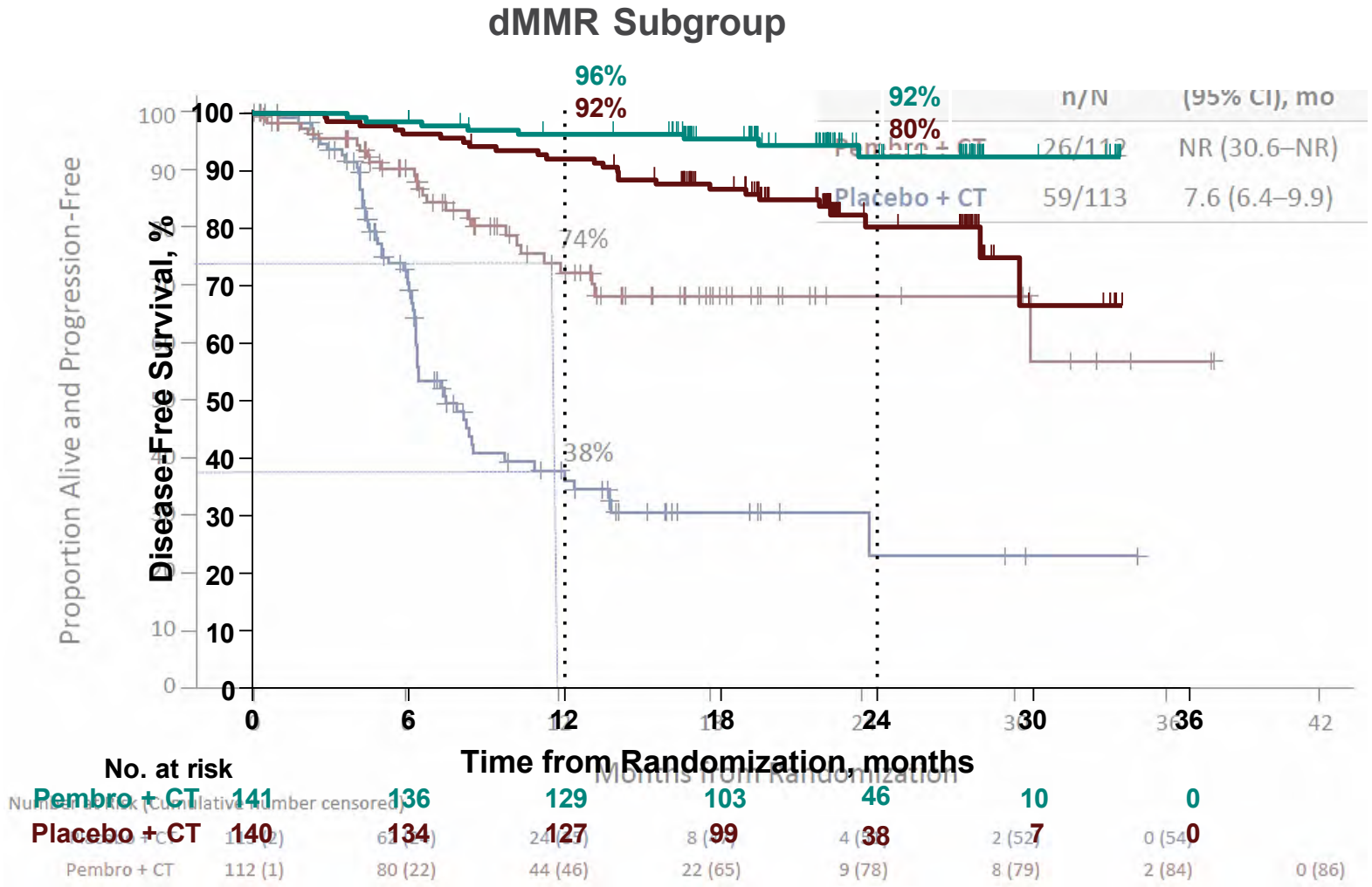
dMMR Subgroup

	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	8 (6)	NR (NR–NR)	0.31 (0.14–0.69)
Placebo + CT	25 (18)	NR (29.5–NR)	



Van Gorp et al. ESMO 2024

What about IO in early stage completely resected dMMR: (ENGOT-EN11/GOG-3053/KEYNOTE-B21)



Van Gorp et al. ESMO 2024

Moving Immunotherapy Efforts into the Frontline as Chemotherapy replacement…

GOG 3064 KN-C93

R → Pembrolizumab
R → Chemo

Primary endpoints:
PFS, OS

Key secondary endpoints:
ORR, DCR, DOR

Recruitment ongoing

dMMR patient population

ENGOT-en13 DOMENICA

R → Dostarlimab
R → Chemo

Primary endpoint:
PFS

Key secondary endpoints:
OS, PROs, ORR, DOR

Recruitment ongoing

dMMR patient population

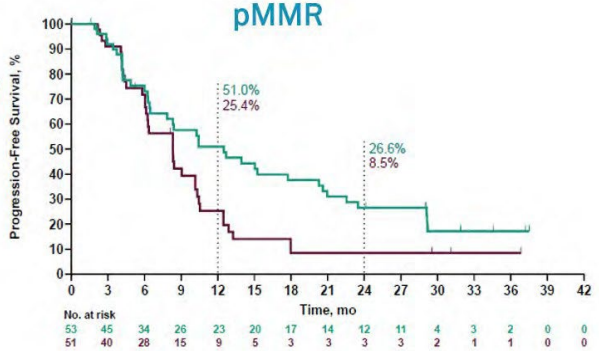
ENGOT-en9 LEAP-001

R → Lenvatinib + pembrolizumab

Pembrolizumab/Lenvatinib Miss OS, PFS in Endometrial Cancer

December 8, 2023
Sabrina Serani

PFS in Prior Neo/Adjuvant Chemotherapy Subgroup



patient populations

LEAP-001: Lenvatinib Plus Pembrolizumab vs Chemo

Key Eligibility Criteria

- Stage III, Stage IV or recurrent endometrial carcinoma[a]
- Radiographically apparent disease - either measurable or nonmeasurable
- No prior chemotherapy except in the neo/adjuvant setting[b]
- ECOG PS 0-1
- Tumor tissue sample for MMR testing

Stratification Factors

MMR status (pMMR vs dMMR),

- If pMMR
  - ECOG PS (0 vs 1)
  - Measurable disease (yes vs no)
  - Prior chemotherapy and/or chemoradiation (yes vs no)

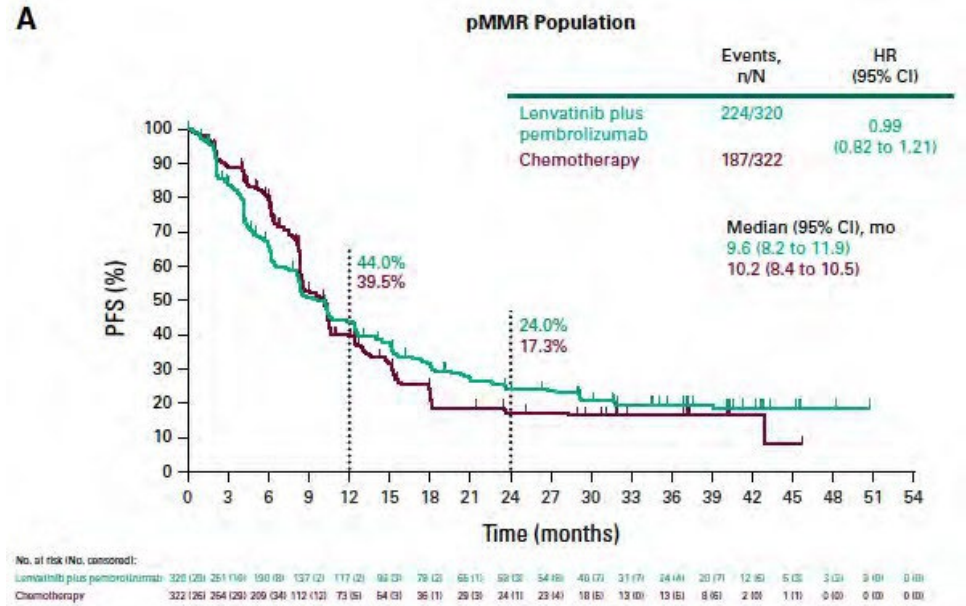
R (1:1)
N = 842

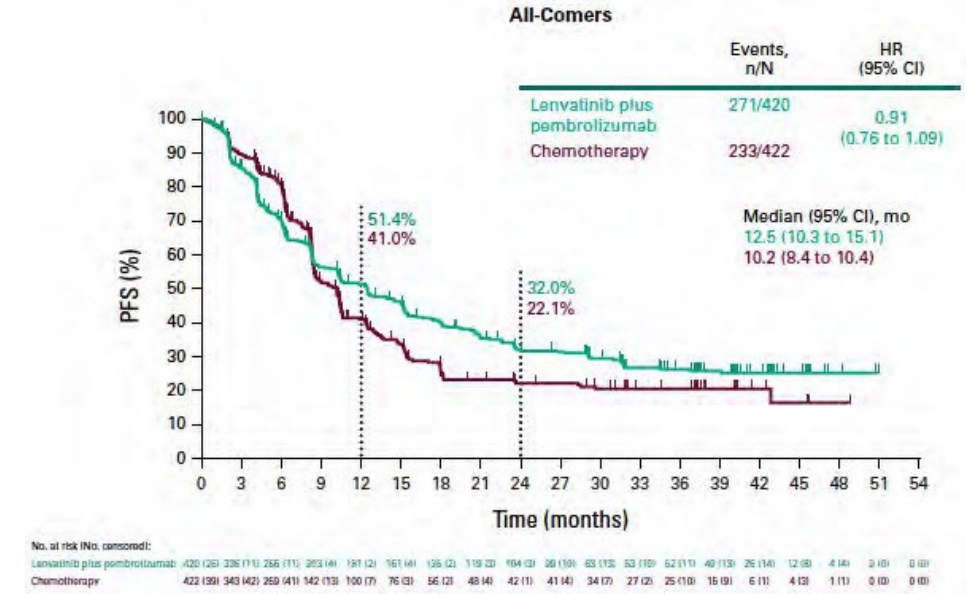
Lenvatinib 20 mg orally QD until PD
+
Pembrolizumab 200 mg IV Q3W
until PD or x35 cycles

Paclitaxel 175 mg/m^2 IV
+
Carboplatin AUC 6 IV Q3W
x7 cycles[c]

Endpoints

- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR





NCT04865289

Marth C et al. J Clin Oncol 2024

LEAP-001: Lenvatinib Plus Pembrolizumab vs Chemo

OS - pMMR Population

	Events/Patients	HR (95% CI)
Overall	366/642	1.02 (0.83-1.26)
Prior neo/adjuvant chemo		
Yes	64/104	0.67 (0.41-1.11)
No	302/538	1.11 (0.88-1.39)

OS - All-comers

	Events/Patients	HR (95% CI)
Overall	442/842	0.93 (0.77-1.12)
Prior neo/adjuvant chemo		
Yes	70/121	0.64 (0.40-1.03)
No	372/721	0.96 (0.79-1.18)

PFS - pMMR Population

	Events/Patients	HR (95% CI)
Overall	411/642	0.99 (0.82-1.21)
Prior neo/adjuvant chemo		
Yes	72/104	0.60 (0.37-0.97)
No	339/538	1.09 (0.88-1.35)

PFS - All-comers

	Events/Patients	HR (95% CI)
Overall	504/842	0.91 (0.76-1.09)
Prior neo/adjuvant chemo		
Yes	81/121	0.52 (0.33-0.82)
No	423/721	0.94 (0.78-1.14)

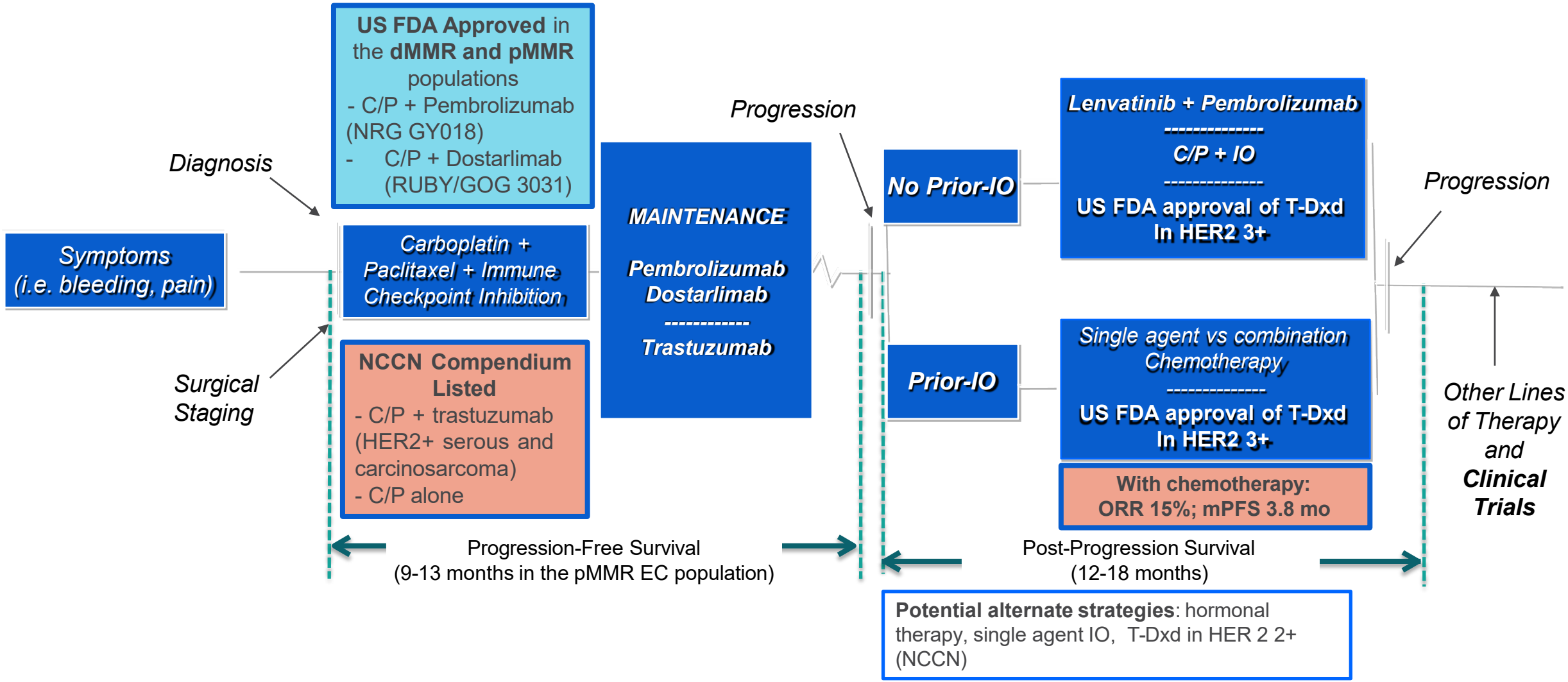
- OS and PFS were similar between arms for the pMMR and All-Comer populations
- **Numerical increases in OS and PFS were observed with lenvatinib/pembrolizumab among patients with prior neoadjuvant/adjuvant chemotherapy**

NCT04865289

1. https://clinicaltrials.gov/study/NCT03884101. 2.Marth C et al. ESGO 2024. 3. Marth C et al. SGO 2024. 4. Pignata S et al ESMO-GYN 2024 Abstract 39O.

Management of Recurrent Disease

Evolving Treatment Landscape for the Management of Advanced Stage or Recurrent Endometrial Cancer



Keynote 775 (NCT03517449) : Lenvatinib + Pembrolizumab

- Advanced, recurrent or metastatic endometrial
- Progressive disease 1-2 prior platinum regimens
- Measurable disease per RECIST 1.1
- Available archival tumor tissue
- Performance status of 0 to1
- Adequate organ function

Stratification:
1. MMR status (pMMR or dMMR)
2. ECOG performance status (0 or 1)
3. Geographic region
4. Prior history of pelvic radiation (yes or no)

R

1:1

Pembrolizumab 200 mg IV q 3 weeks plus **lenvatinib** 20 mg PO once daily (QD) during each 21-day cycle for up to 35 cycles.

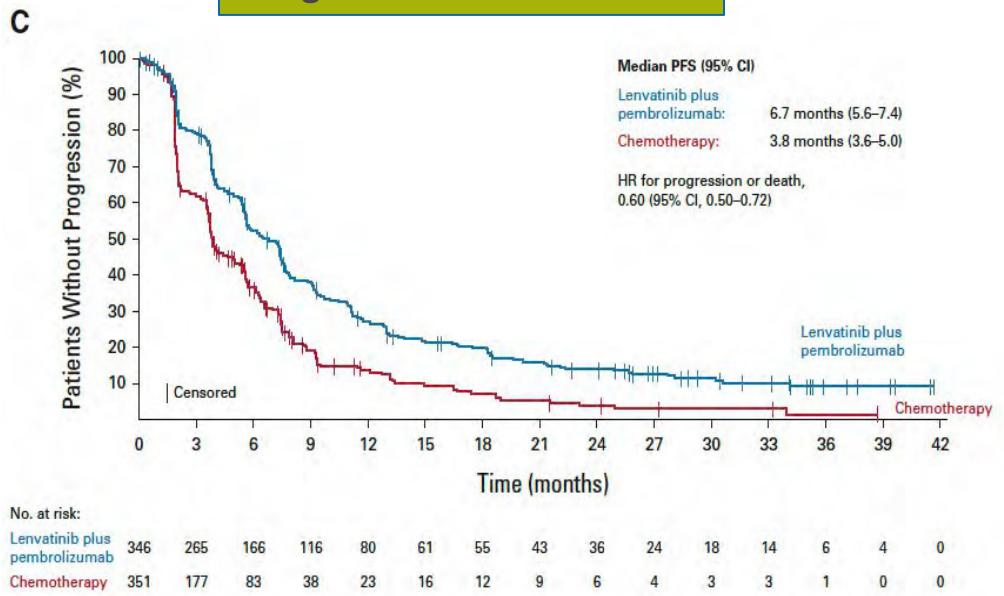
EITHER: **Doxorubicin** 60 mg/m2 IV q 3 weeks (max cumulative dose of 500 mg/m2) OR **Paclitaxel** 80 mg/m2 administered by IV on a 28-day cycle: 3 weeks receiving paclitaxel once a week and 1 week not receiving paclitaxel.

Primary endpoints:
1) Progression-free Survival (PFS) by RECIST 1.1 by BICR
2) Overall Survival (OS).

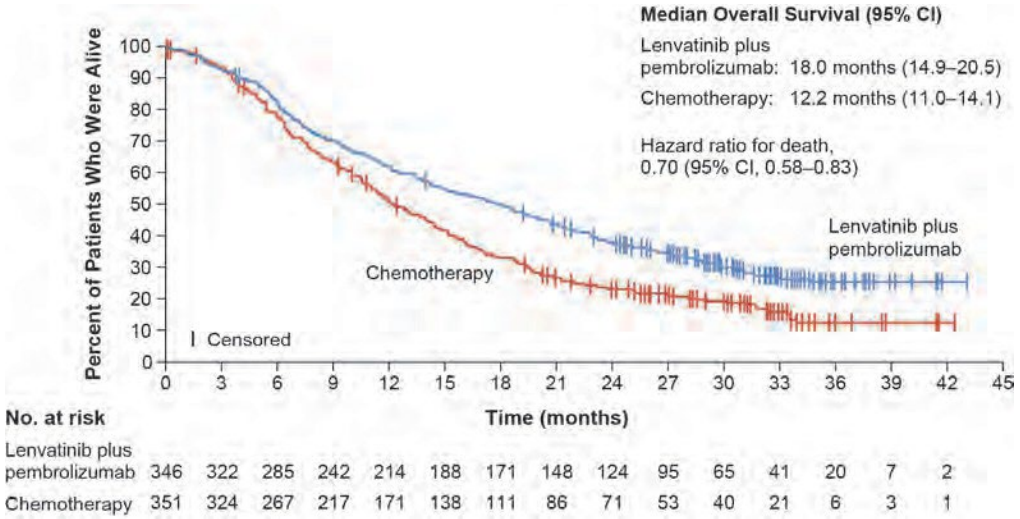
Secondary endpoints:
1) ORR, DOR, TTF, AEs, PK, PROs

ORR 30.3% (Lenvatinib + Pembrolizumab) versus 15.1% (PCC)
mPFS in the control arm 3.8 months

Progression Free Survival

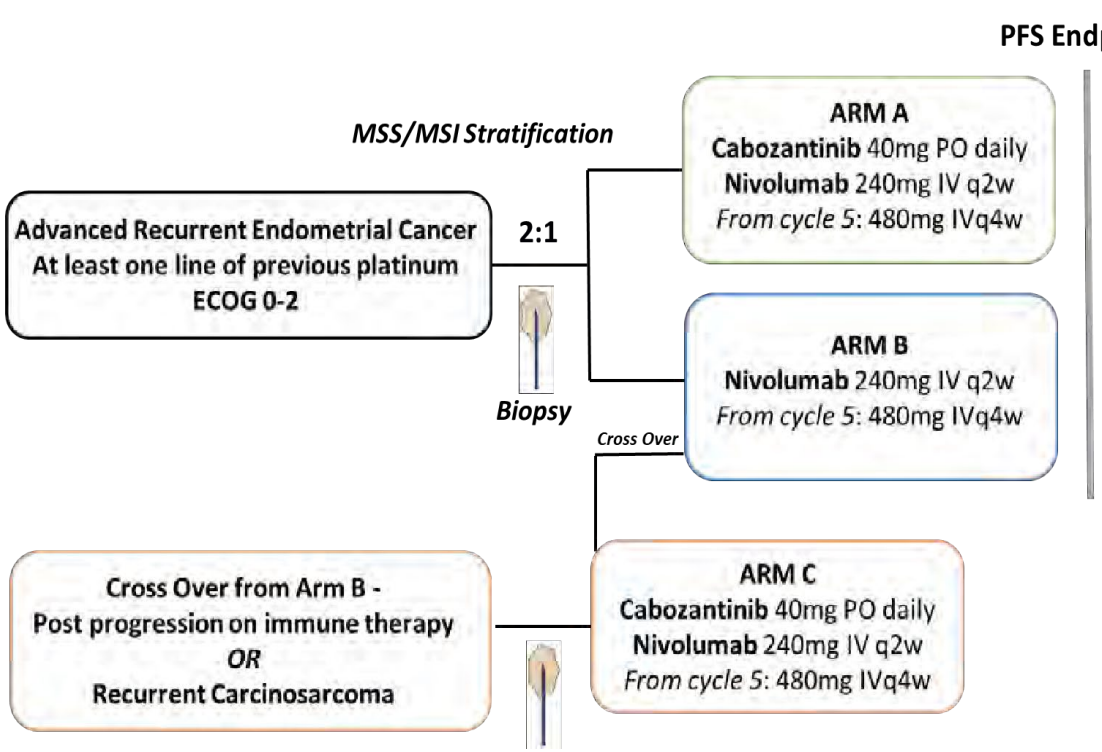


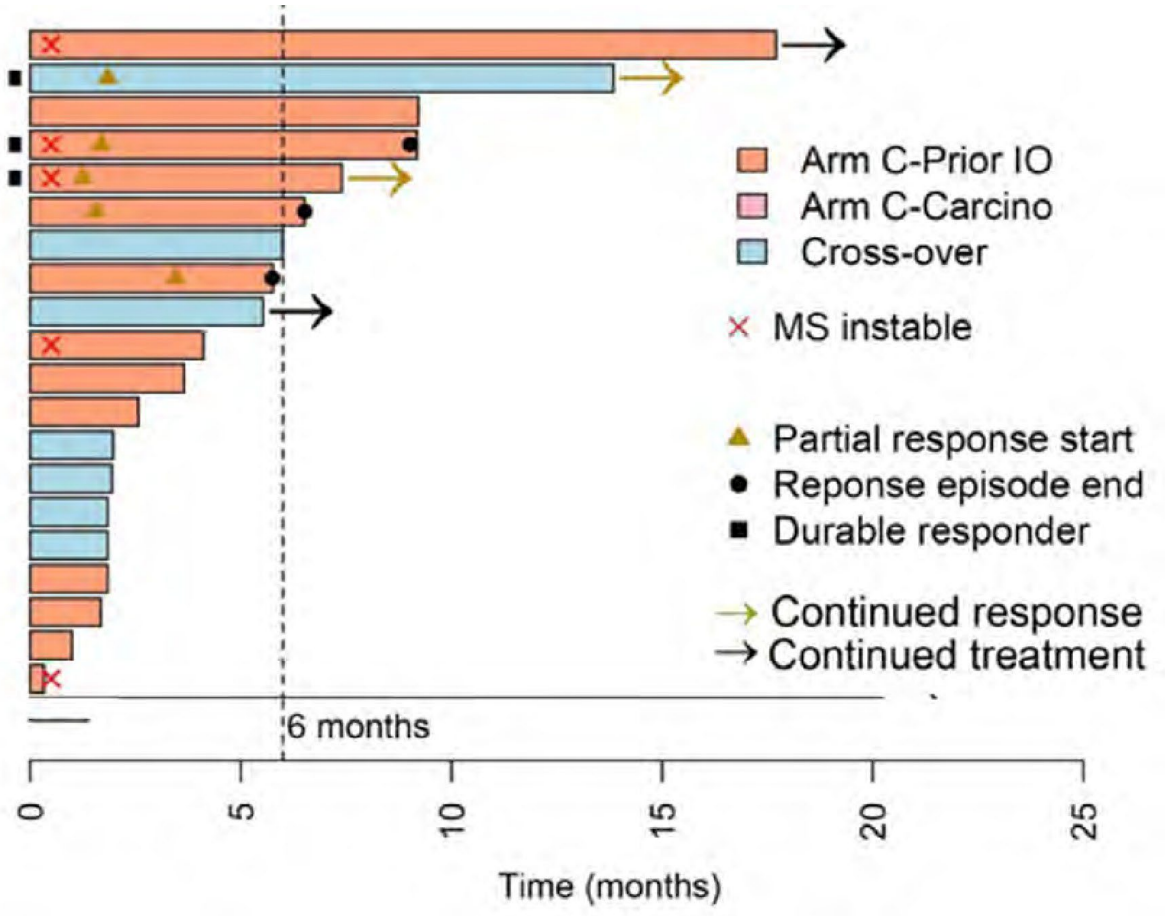
Overall Survival



Makker et al. J Clin Oncol Apr 2023

IO after IO in Endometrial Cancer





Lheureux S et al, JITC 2022

IO after IO in Endometrial Cancer

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Case series

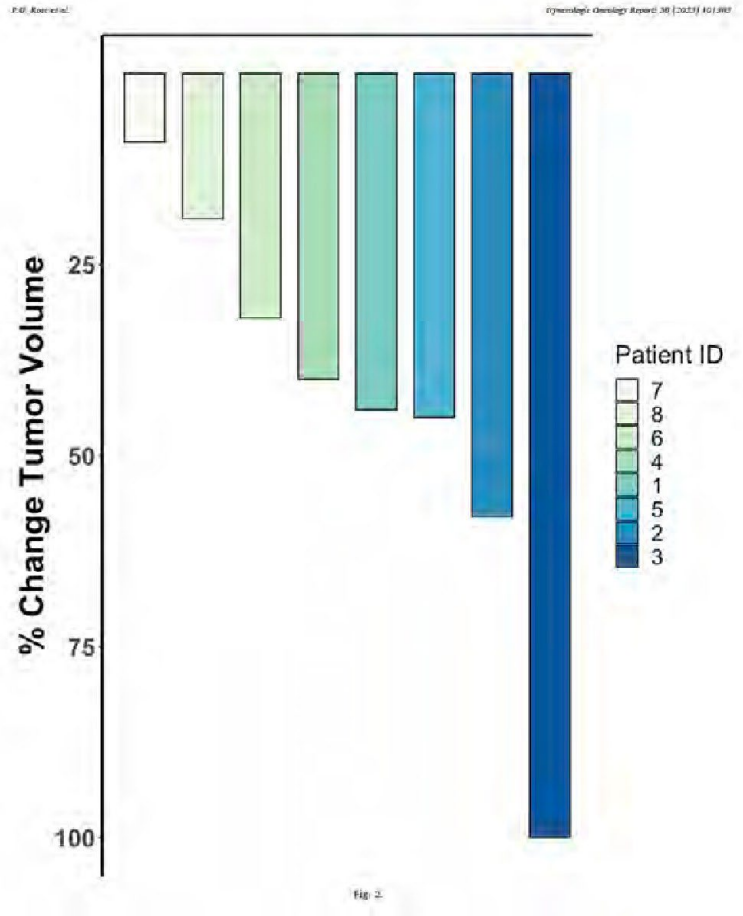
Activity of pembrolizumab and lenvatinib in mismatch repair deficient (dMMR) endometrial cancer patients who have failed pembrolizumab monotherapy: A case series

Peter G. Rose [a,*], Myra Feldman [b], Iwona Podzielinski [c], Aaron P. Petty [d], Roberto Vargas [a]

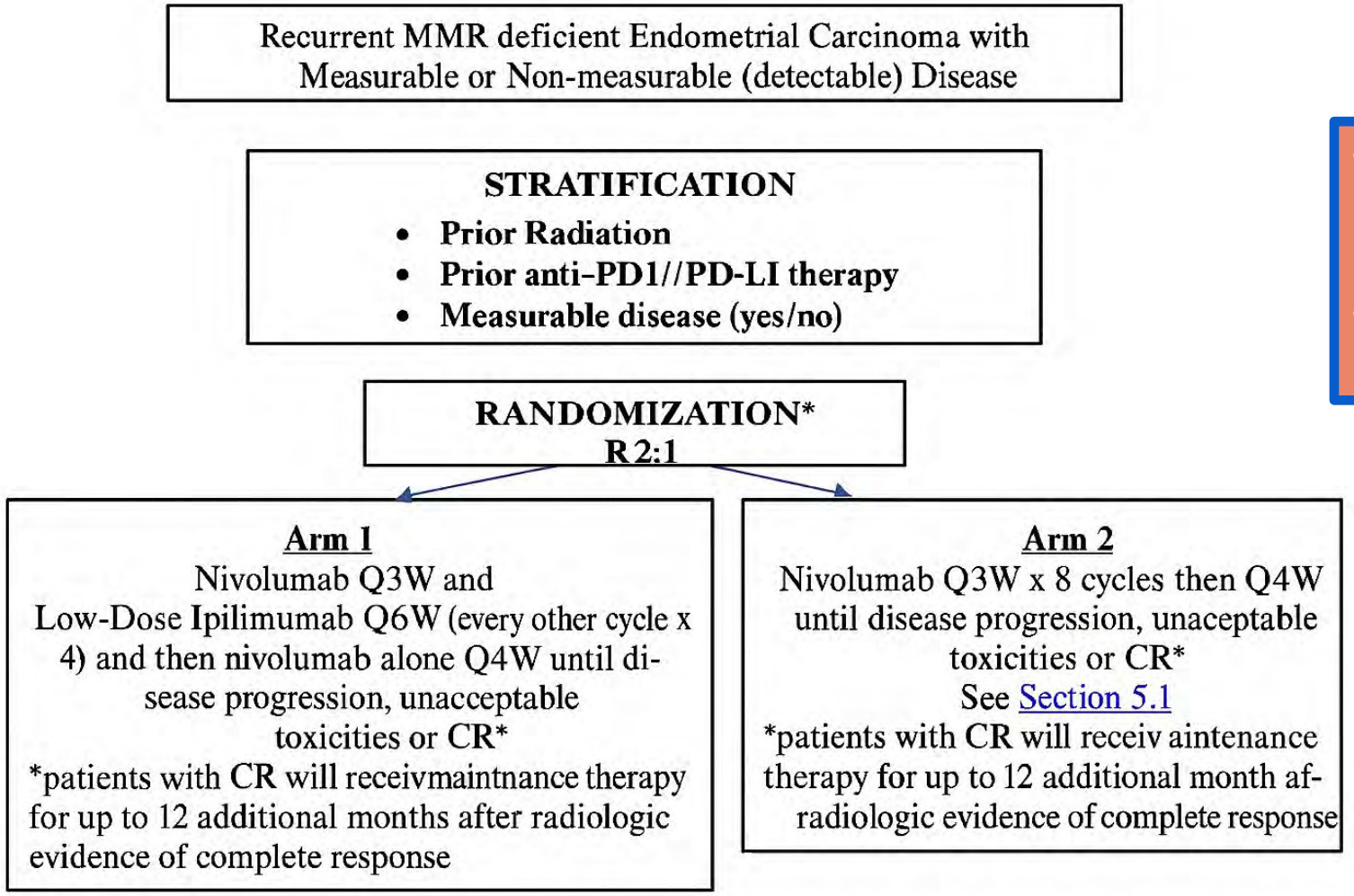
Table 1
Patient Tumor and Treatment Characteristics.

Patient number	MMRd	MLH 1 methyl	Age*	Stage FIGO 2009	Grade	Prior Systemic Therapy	Duration of Pembro	Response to Pembro	Duration of Pembro/ lenvima	Date initiated Lenvima Dose Starting/Final (# courses)	Response
1	MLH1/ PMS2	Present	54	IIIC1 Recurrent	FIGO 2	CP x 6	3 Cycles	Stable	25 cycles	7/1/2021 20 (1) 10 (24)	Radiologic PR (↓ 44 %)
2	MLH1/ PMS2	Present	56	IVB	FIGO G2	CPB x 9 B x 4	5 cycles	Progression	39 cycles+	7/23/2021 20 (6) 10 (33)	Radiologic PR (↓ 58 %)
3	MLH1/ PMS2	Present	73	IVB	FIGO G1	CP x 6 Letro x3	3 Cycles	Stable CA125 Progression	22 cycles +	7/11/2022 10 (2) 4 (20)	Radiologic CR ↓ CA125 396 to 9 U/ml
4	MLH1/ PMS2	Present	71	IIIC2 recurrent	FIGO G3	CA x 4 Letro x 13 B x 45	47 cycles	Progression	1 cycle	8/5/2022 10 (1)	Radiologic PR (40 %) ↓ CA125 59.6 to 44.4 U/ml
5	MLH1/ PMS2	Present	52	IIIC1 recurrent	FIGO G2	CDDP x 1CX1 CP X4	9 cycles	Progression	8 cycles	9/26/2022 10 (7) 4 (1)	Radiologic PR (45 %)
6	MLH1/ PMS2	Present	71	IB Recurrent	FIGO G3	CP x 7 Letro x 7	5 cycles	Progression	15 cycles +	10/31/2022 10 (15)	Radiologic PR (↓ 32 %)
7	PMS2	Lynch testing - Present	30	IB Recurrent	FIGO G3	CIS x 2 CP x 4	3 cycles	Progression	3 cycles	11/7/2022 14 (3)	Radiologic Stable (↓ 9 %)
8	MLH1/ PMS2	Present	79	IB Recurrent	FIGO G1	CPx6	11 cycles	Progression	13 cycles +	1/5/2023 14 (12) 10 (1)	Radiologic Stable (↓ 10 %)

Abbreviations: * Ag when Pembo lenvima started, A = Abraxane, B = Bevacizumab, C = arboplatin, C = Cisplatin, Lenvima = Lenvatinib, Letro = Letrozole MLH1Methyl = MLH1 promoter hypermethylation, P = Paclitaxel, Pembro = Pembrolizumab, -=negative, + currently in active treatment.



NRG GY025: Efficacy of ICI after ICI in Previously Treated dMMR EC (NCT0511260)



*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.

- Prior IO but mandates at least 12 month "IO free interval"
- 12-months of maintenance – "de-escalation"

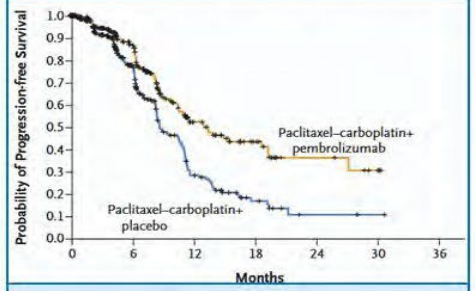
Charting the Course: Treatment Approaches for pMMR Endometrial Cancer

Leslie Randall, MD
Inova Health
Fairfax, Virginia, USA

Immunotherapy + chemotherapy with some PFS benefit in pMMR endometrial cancer

NRG-GY018

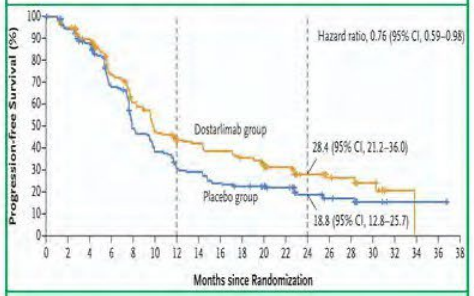
Pembrolizumab



HR 0.54
95% CI 0.41-0.71
8.7 vs 13.1 mos
p<0.001

RUBY

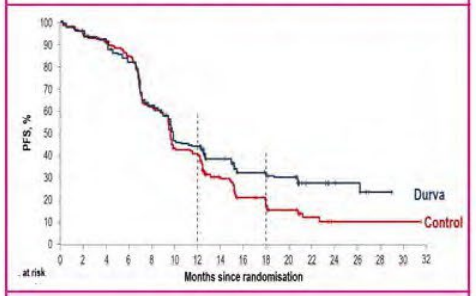
Dostarlimab



HR 0.76
95% CI 0.59-0.98
PFS24 18.8% vs 28.4%

DUO-E

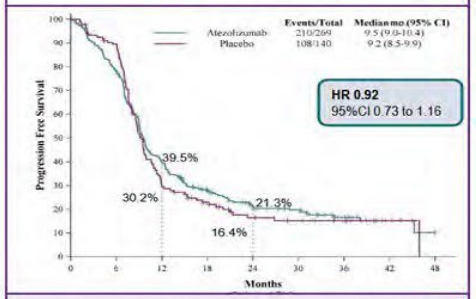
Durvalumab



HR 0.77
95% CI 0.60-0.97
9.7 vs 9.9 mos

AtTEnd

Atezolizumab



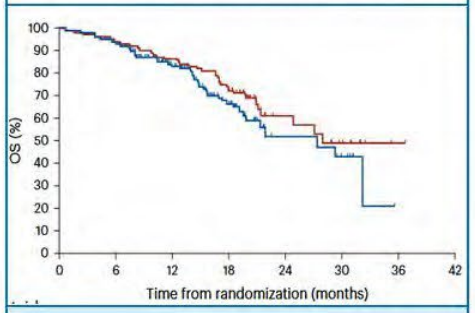
HR 0.92
95% CI 0.73-1.16
9.2 vs 9.5 mos

Eskander et al., *N Engl J Med* 2023; Mirza et al., *N Engl J Med* 2023; Westin et al., *J Clin Oncol* 2024; Colombo et al., *Lancet Oncol* 2024

Immunotherapy + chemotherapy with uncertain OS effect in pMMR endometrial cancer

NRG-GY018

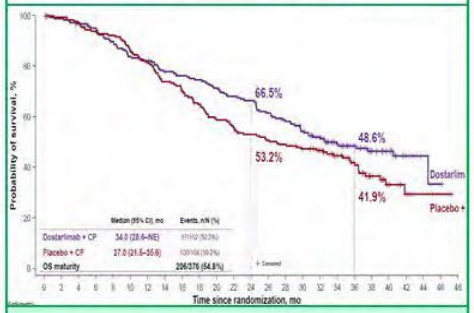
Pembrolizumab



HR 0.79
95% CI 0.53-1.17
27.4 vs 28.0 mos
(27.2% maturity)

RUBY

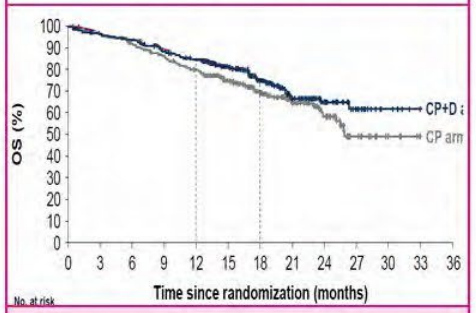
Dostarlimab



HR 0.79
95% CI 0.60-1.04
27.0 vs 34.0 mos
(54.8% maturity)

DUO-E

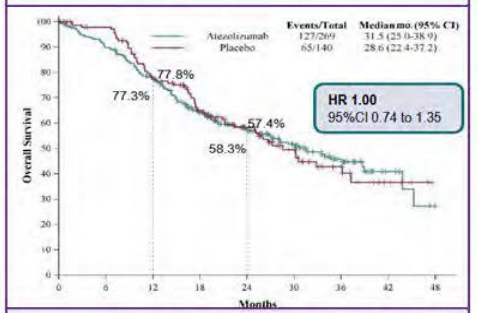
Durvalumab



HR 0.77
95% CI 0.56-1.07
25.9 mos vs NR
(27.7% maturity)

AtTEnd

Atezolizumab

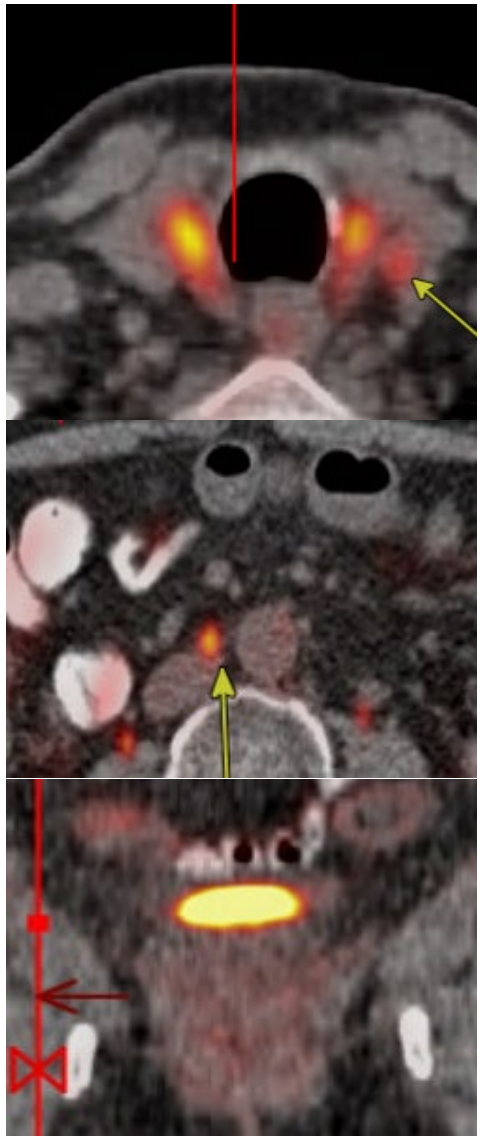


HR 1.00
95% CI 0.74-1.35
28.6 vs 31.5 mos
(~50% maturity)

Eskander et al., *Nat Med* 2025; Powell et al., *Ann Oncol* 2024; Sato et al., 2024 ESMO Congress; Colombo et al., *Lancet Oncol* 2024

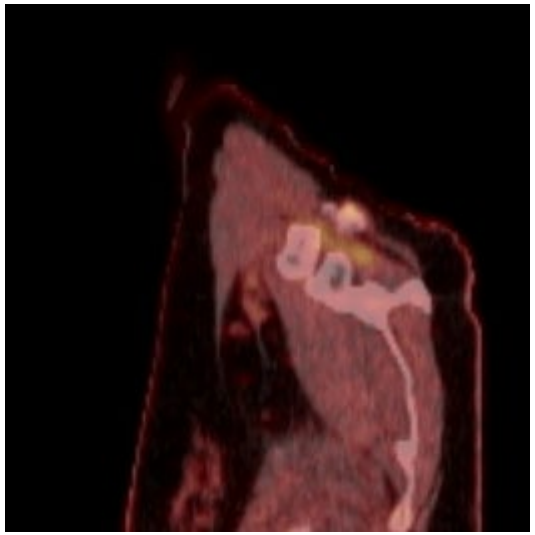
Case Study: Recurrent, metastatic endometrial cancer

- 73 y.o with IIIC1 carcinosarcoma
- MRH/BSO/SNB on 3/9/23
- NGS p53 mut, PIK3R1, pMMR
- Adjuvant carboplatin/paclitaxel x 6
- PET/CT in 4/2024 avid masses: paratracheal, paraaortic, vaginal
- Retx with carboplatin/paclitaxel/dostarlimab until 7/2025



Recurrent, metastatic endometrial cancer continued…

- 7/2025 PET/CT with new axillary nodal and pre-trapezial avid masses
- Perc biopsy trapezius mass confirmed metastatic high-grade endometrial carcinoma.
- NGS testing was same as at diagnosis: p53 mut, PIK3R1, pMMR
- What did we give her???



What are the options?

- Add to single agent IO
  - Anti-VEGF
    - Lenvatinib/pembrolizumab
    - Bevacizumab/pembrolizumab
  - IO/PARPi
    - Olaparib/durvalumab
    - Niraparib/dostarlimab
  - IO/ADC
    - Trop2
    - Her2
- Non-IO, ADC
- Non-IO, Non-ADC

DUO-E study design

Patients

- Newly diagnosed FIGO 2009 Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment for advanced disease
- Naïve to PARP inhibitors and immune-mediated therapy
- Adjuvant chemotherapy allowed if ≥12 months from last treatment to relapse
- All histologies except sarcomas

N=718

R 1:1:1

Stratified by:

- MMR status (proficient vs deficient)
- Disease status (recurrent vs newly diagnosed)
- Geographic region (Asia vs non-Asia)

	Chemotherapy phase	Maintenance phase
Control	CP* (q3w) + Durvalumab pbo (IV q3w)	Durvalumab pbo (IV q4w) + Olaparib pbo (tablets bid)
Durva	CP* (q3w) + Durvalumab (1120 mg IV q3w)	Durvalumab (1500 mg IV q4w) + Olaparib pbo (tablets bid)
Durva+Ola	CP* (q3w) + Durvalumab (1120 mg IV q3w)	Durvalumab (1500 mg IV q4w) + Olaparib (300 mg tablets bid)

Patients without disease progression

Treatment until disease progression, unacceptable toxicity or other discontinuation criteria were met

Endpoints

Primary

- PFS (RECIST per investigator) in:
  - Durva vs Control
  - Durva+Ola vs Control

Key secondary

- OS (analytical)
- Safety

Exploratory

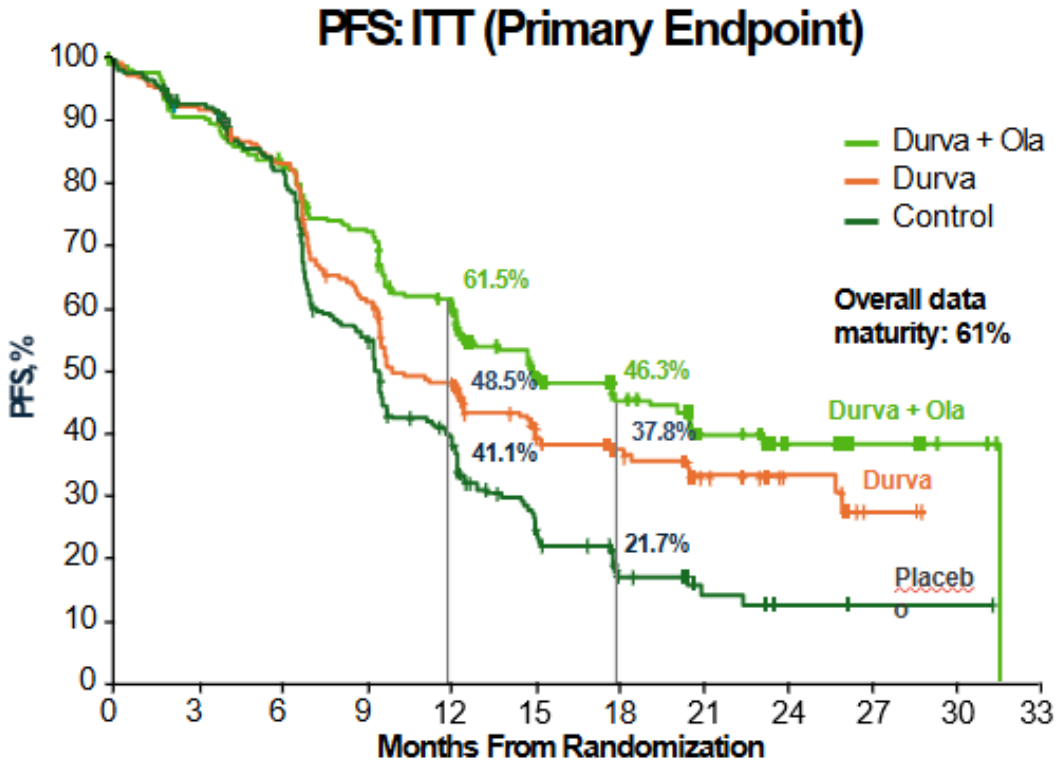
- PFS in Durva+Ola vs durva
- Subgroup analyses of PFS
  - Including MMR, PD-L1, and HRRm

*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.

Westin, S et al. ESMO 2023.

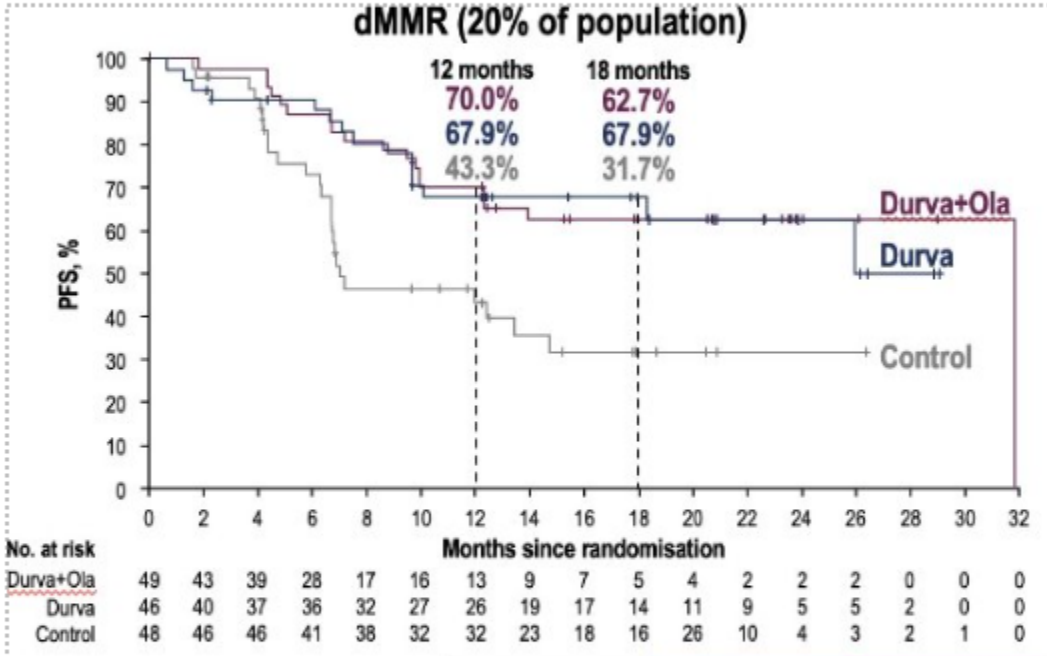
DUO-E: Maintenance Durvalumab ± Olaparib on PFS in ITT Population



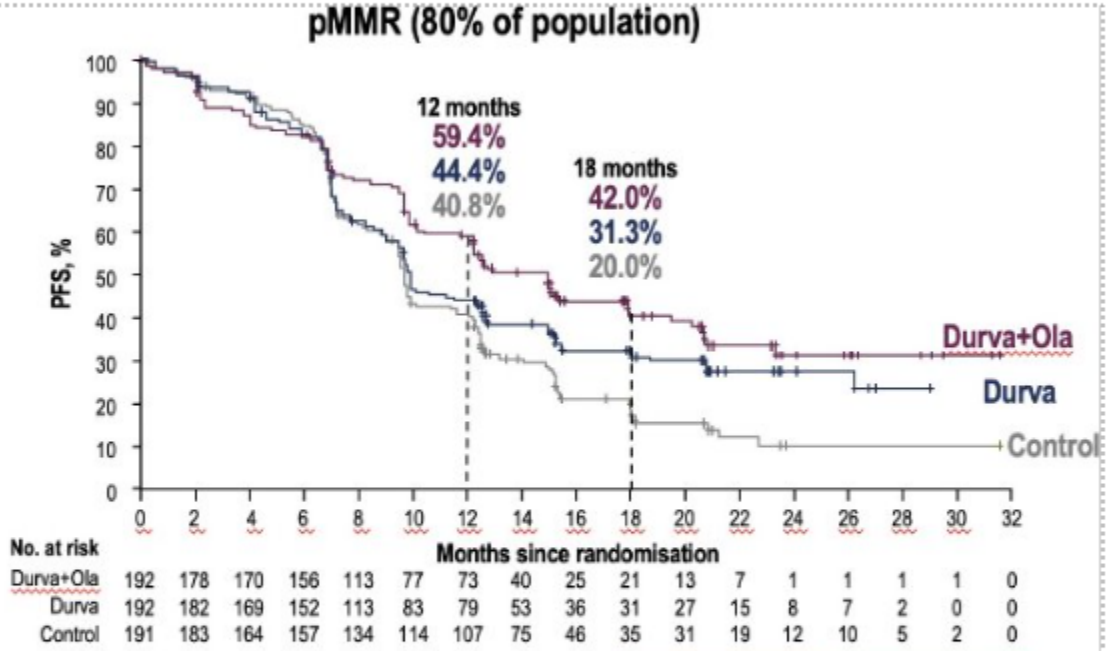
	Control (n=241)	Durva (n=238)	Durva + Ola (n=239)
Events, n (%)	173 (71.8)	139 (58.4)	126 (52.7)
Median PFS, mo (95% CI)	9.6 (9.0-9.9)	10.2 (9.7-14.7)	15.1 (12.6-20.7)
HR (95% CI) vs control		**0.71 (0.57-0.89); *P* = .003**	**0.55 (0.43-0.69); *P* < .0001**
HR (95% CI) vs durva			**0.78 (0.61-0.99)**

Westin, S et al. ESMO 2023.

DUO-E: Subgroup analysis of PFS by MMR status



	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)**

Westin, S et al. ESMO 2023.

Addition of PARPi: RUBY Pt2

Table. Progression-free survival.

	Dostarlimab + CP followed by dostarlimab + niraparib	Placebo + CP followed by placebo
Overall population, N	192	99
PFS, HR (95% CI)[a]	0.60 (0.43–0.82)	
P value	0.0007	
PFS, median (95% CI), mo	14.5 (11.8–17.4)	8.3 (7.6–9.8)
MMRp/MSS population, N	142	
PFS, HR (95% CI)[a]	0.63 (0.44–0.91)	
P value	0.0060	
PFS, median (95% CI), mo	14.3 (9.7–16.9)	8.3 (7.6–9.8)

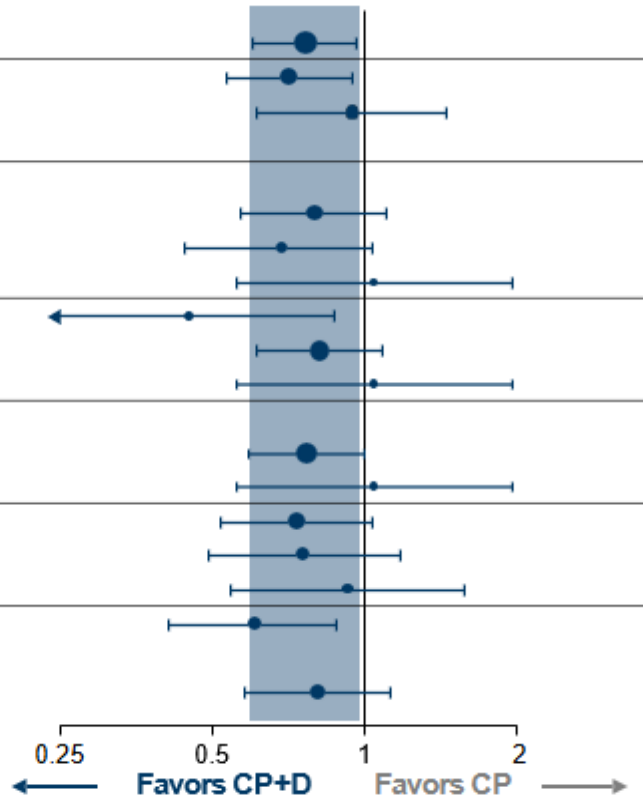
[a]Per RECIST v1.1 based on investigator assessment and primary censoring rule using stratification factors from randomization list.
CP, carboplatin-paclitaxel; HR, hazard ratio; MMRp, mismatch repair-proficient; MSS, microsatellite stable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Mirza et al SGO 2024

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab vs CP

Post hoc exploratory analysis



		HR (95% CI)
All pMMR patients		**0.77 (0.60–0.97)**
PD-L1 expression*	Positive (TAP score ≥1%)	**0.71 (0.53–0.95)**
	Negative (TAP score <1%)	**0.95 (0.61–1.45)**
	Unknown¶	**NC (NC–NC)††**
***POLE*m and *TP53*m status†,‡**	*POLE*m	**NC (NC–NC)††**
	*TP53*m	**0.80 (0.57–1.11)**
	TP53 wild-type	**0.69 (0.44–1.04)**
	Unknown¶	**1.05 (0.56–1.96)**
HRRm status†,§	HRRm	**0.45 (0.23–0.87)**
	Non-HRRm	**0.82 (0.61–1.08)**
	Unknown¶	**1.05 (0.56–1.96)**
BRCAm status†	BRCAm	**NC (NC–NC)††**
	Non-BRCAm	**0.77 (0.59–1.00)**
	Unknown¶	**1.05 (0.56–1.96)**
Histological type at diagnosis	Endometrioid	**0.74 (0.52–1.04)**
	Serous	**0.76 (0.49–1.18)**
	Other**	**0.93 (0.54–1.58)**
Baseline ctDNA‖	Detected	**0.61 (0.41–0.88)**
	Not detected	**NC (NC–NC)††**
	Unknown¶	**0.81 (0.58–1.13)**

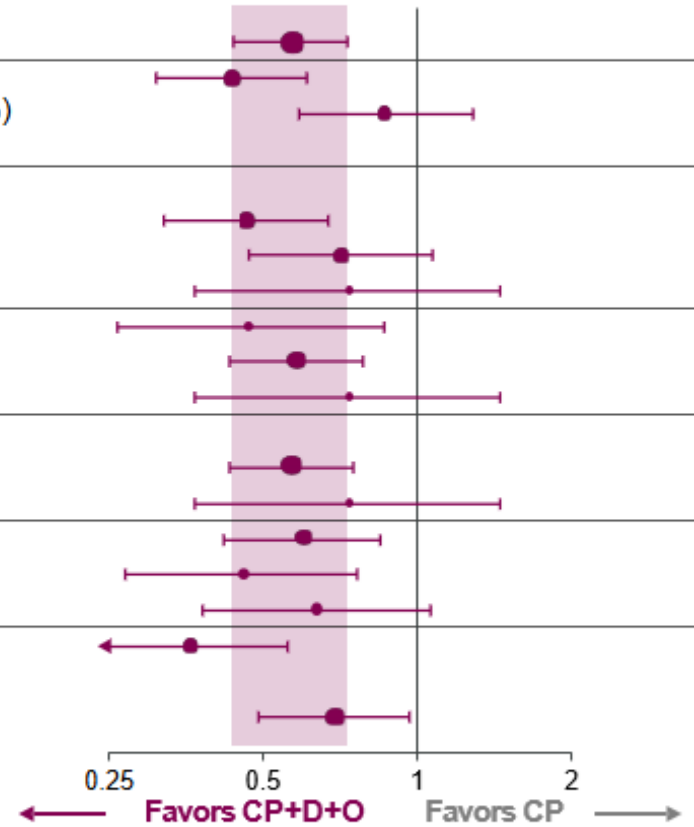
DCO: April 12, 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wild-type status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1,-CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; ‖ctDNA was analyzed using the methylation-based Guardant Infinity assay (Guardant Health, Palo Alto, CA); ¶'Unknown' status included patients recruited in China (where molecular testing was not performed) and/or patients who withdrew consent and/or those without available samples; **'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other; ††Not calculated due to low event numbers. NC, not calculable.

Westin, S et al. ESMO 2023.

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib vs CP

Post hoc exploratory analysis



		HR (95% CI)
All pMMR patients		**0.57 (0.44–0.73)**
PD-L1 expression*	Positive (TAP score ≥1%)	**0.44 (0.31–0.61)**
	Negative (TAP score <1%)	**0.87 (0.59–1.28)**
	Unknown¶	**NC (NC–NC)††**
***POLE*m and *TP53*m status†,‡**	*POLE*m	**NC (NC–NC)††**
	*TP53*m	**0.47 (0.32–0.67)**
	TP53 wild-type	**0.71 (0.47–1.07)**
	Unknown¶	**0.74 (0.37–1.45)**
HRRm status†,§	HRRm	**0.47 (0.26–0.86)**
	Non-HRRm	**0.58 (0.43–0.78)**
	Unknown¶	**0.74 (0.37–1.45)**
BRCAm status†	BRCAm	**NC (NC–NC)††**
	Non-BRCAm	**0.57 (0.43–0.75)**
	Unknown¶	**0.74 (0.37–1.45)**
Histological type at diagnosis	Endometrioid	**0.60 (0.42–0.85)**
	Serous	**0.46 (0.27–0.76)**
	Other**	**0.64 (0.38–1.06)**
Baseline ctDNA‖	Detected	**0.36 (0.23–0.56)**
	Not detected	**NC (NC–NC)††**
	Unknown¶	**0.69 (0.49–0.96)**

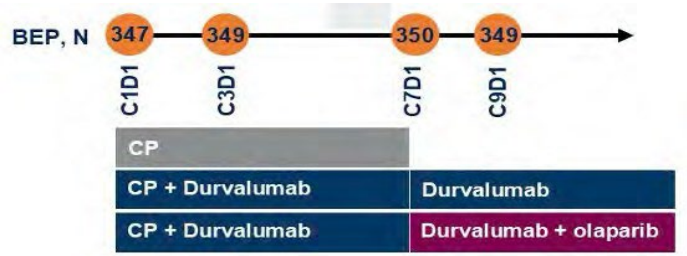
DCO: April 12, 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%; †Status determined retrospectively in two ways: from tissue samples (FoundationOne®CDx assay; Foundation Medicine, Inc.), and by molecular profiling of ctDNA (FoundationOne®Liquid CDx; Foundation Medicine, Inc.) from blood samples; ‡*TP53*m status defined as a sample with a deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; *TP53* wild-type status defined as a sample with no deleterious or suspected deleterious mutation in *TP53* excluding samples with a deleterious or suspected deleterious mutation in *POLE*; §Positive HRRm status defined as a sample with a deleterious or suspected deleterious mutation in any of the following prespecified genes: *ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D,* and *RAD54L*; negative HRRm status (non-HRRm) defined as a sample with no deleterious or suspected deleterious mutations in any of the prespecified genes; ‖ctDNA was analyzed using the methylation-based Guardant Infinity assay (Guardant Health, Palo Alto, CA); ¶'Unknown' status included patients recruited in China (where molecular testing was not performed) and/or patients who withdrew consent and/or those without available samples; **'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other; ††Not calculated due to low event numbers. NC, not calculable.

Westin, S et al. ESMO 2023.

ctDNA in EC: DUO-E/GOG-3041/ENGOT-En10

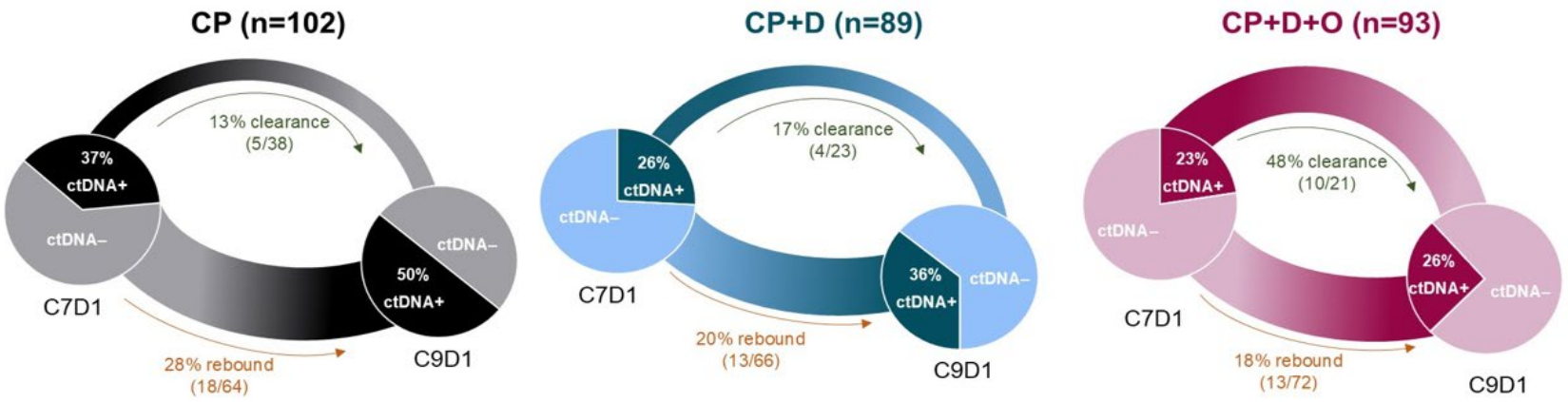
(post-hoc exploratory, longitudinal ctDNA analysis)

N=718 in ITT
N=341 (47.5%) with ctDNA at all 4 time points



DUO-E: durvalumab and olaparib mediated ctDNA changes during the maintenance phase (C7D1–C9D1) in pMMR patients

Addition of olaparib may be driving novel anti-tumor activity in pMMR tumors not seen with durvalumab alone

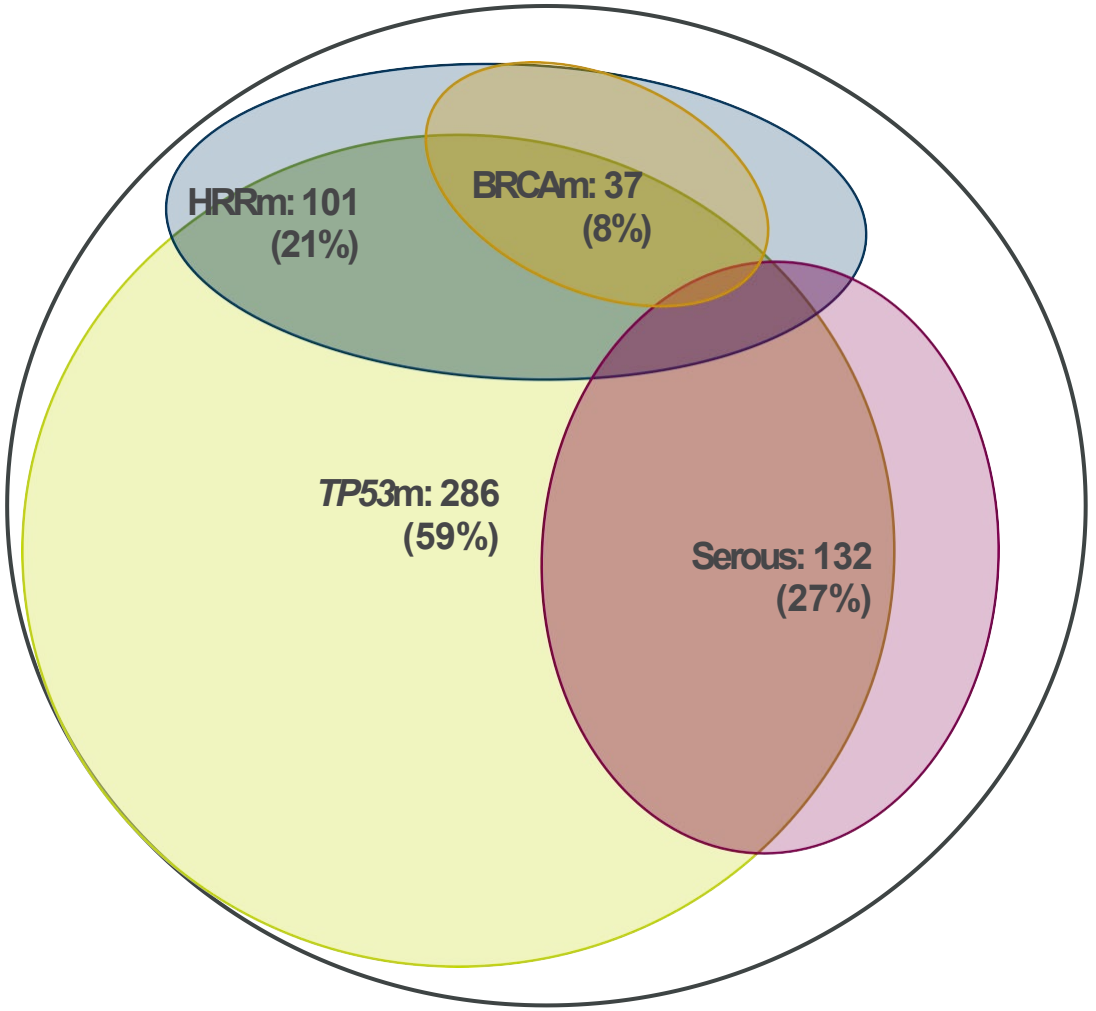


- Durvalumab led to 4% more clearance of ctDNA and 8% less rebound, vs CP arm
- Addition of olaparib to durvalumab led to 35% more clearance of ctDNA and 10% less rebound, vs CP arm

Westin et al. ASCO 2025

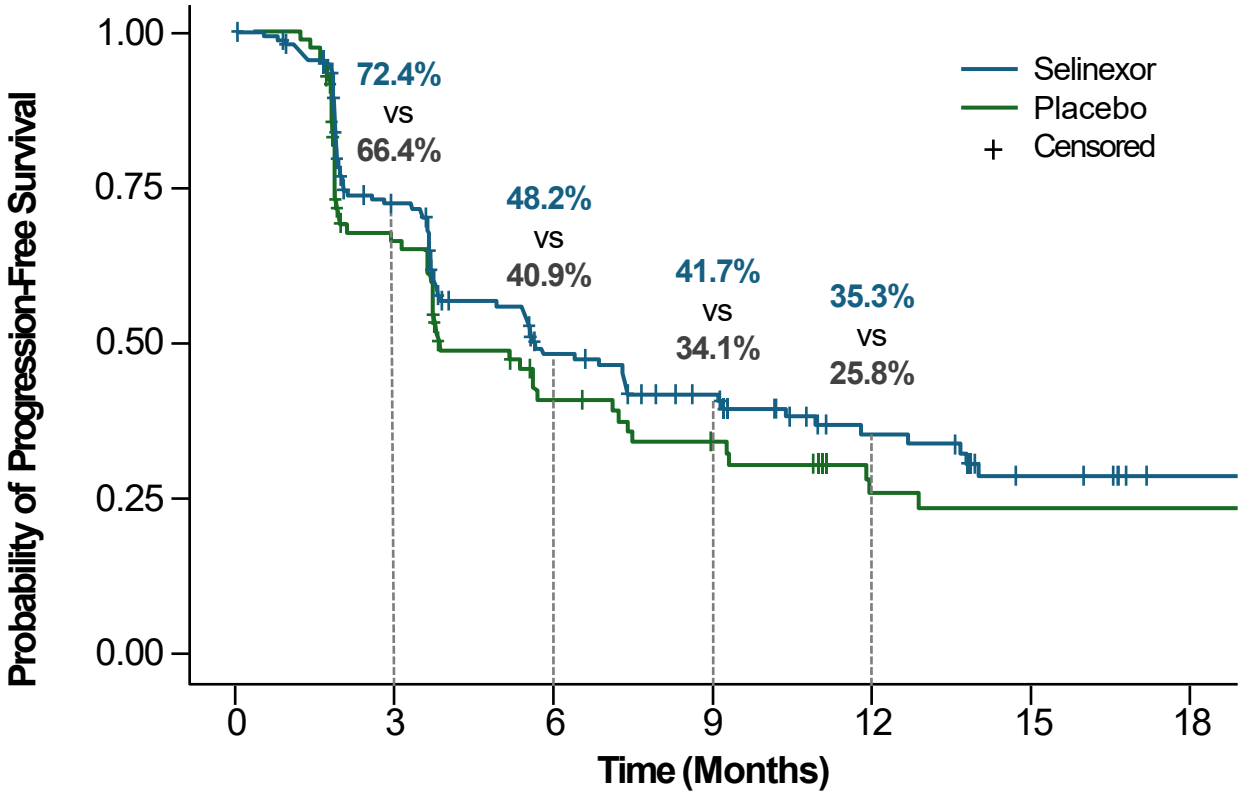
Translational markers in DUO-E: What is best alternate target?

	PD-L1 positive	*TP53*m	HRRm	BRCAm	*POLE*m	Serous
PD-L1 positive	67%	44%	16%	6%	2%	20%
*TP53*m	44%	59%	14%	6%	2%	24%
HRRm	16%	14%	21%	8%	2%	6%
BRCAm	6%	6%	8%	8%	1%	3%
*POLE*m	2%	2%	2%	1%	2%	0%
Serous	20%	24%	6%	3%	0%	27%

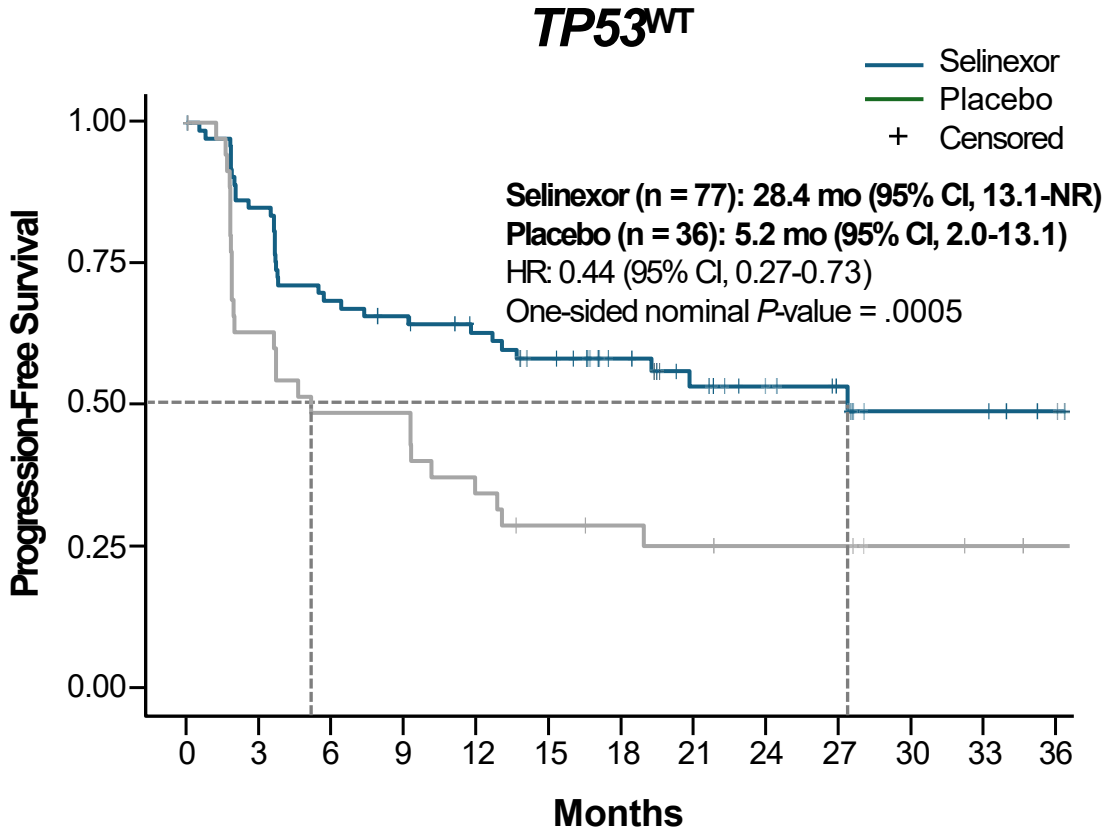


Westin et al IGCS 2024, Moore et al SGO 2025

Selinexor Is a Targeted Oral XPO1 Inhibitor
ENGOT-EN5/GOG-3055/SIENDO



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



Median follow-up: 36.8 months

Vergote I, et al. J Clin Oncol. 2023; Makker V, et al. Gynecol Oncol. 2024; Slomovitz BM, et al. J Clin Oncol. 2023

ENGOT
European Network of Gynaecological Oncological Trial groups

XPORT-EC-042/GOG-3083

A Phase 3 of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With TP53 Wild-type, Advanced, or Recurrent EC

Prescreening Consent
Tissue Sent to Foundation

Study Consent

Key Eligibility

- ***TP53* wild-type endometrial cancer testing by FMI**
- Primary stage IV or first recurrent EC
- Received at least 12 weeks of platinum-based chemotherapy +/- immunotherapy
- Carcinosarcomas allowed; clear cell/small cell carcinoma excluded

N=220

PR/CR per RECIST v1.1

R 1:1

Stratification:
- Primary Stage IV vs recurrent disease after platinum-based treatment
- PR vs CR

Selinexor 60mg PO QW until PD
n = 110

Treat until progression or intolerability

Placebo weekly until PD
n = 110

Primary Endpoint
- PFS assessed by Investigator

Key Secondary Endpoint
- OS

Secondary Endpoints
- Safety
- TFST
- TSST
- PFS2
- PFS as assessed by BICR
- HR-QoL

Exploratory Endpoints
- PFS per histology subtypes
- PFS per other molecular features
- CR rate among patients with PR as best response
- Duration of CR among patients who enter study as PR and achieve CR during study
- analysis of tumor biomarkers
- PK analysis

*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05.

CT.gov:NCT05611931

LEAP-001: Lenvatinib/Pembrolizumab vs Chemo

Key Eligibility Criteria

- Stage III, Stage IV or recurrent endometrial carcinoma[a]
- Radiographically apparent disease - either measurable or nonmeasurable
- No prior chemotherapy except in the neo/adjuvant setting[b]
- ECOG PS 0-1
- Tumor tissue sample for MMR testing

Stratification Factors

MMR status (pMMR vs dMMR),

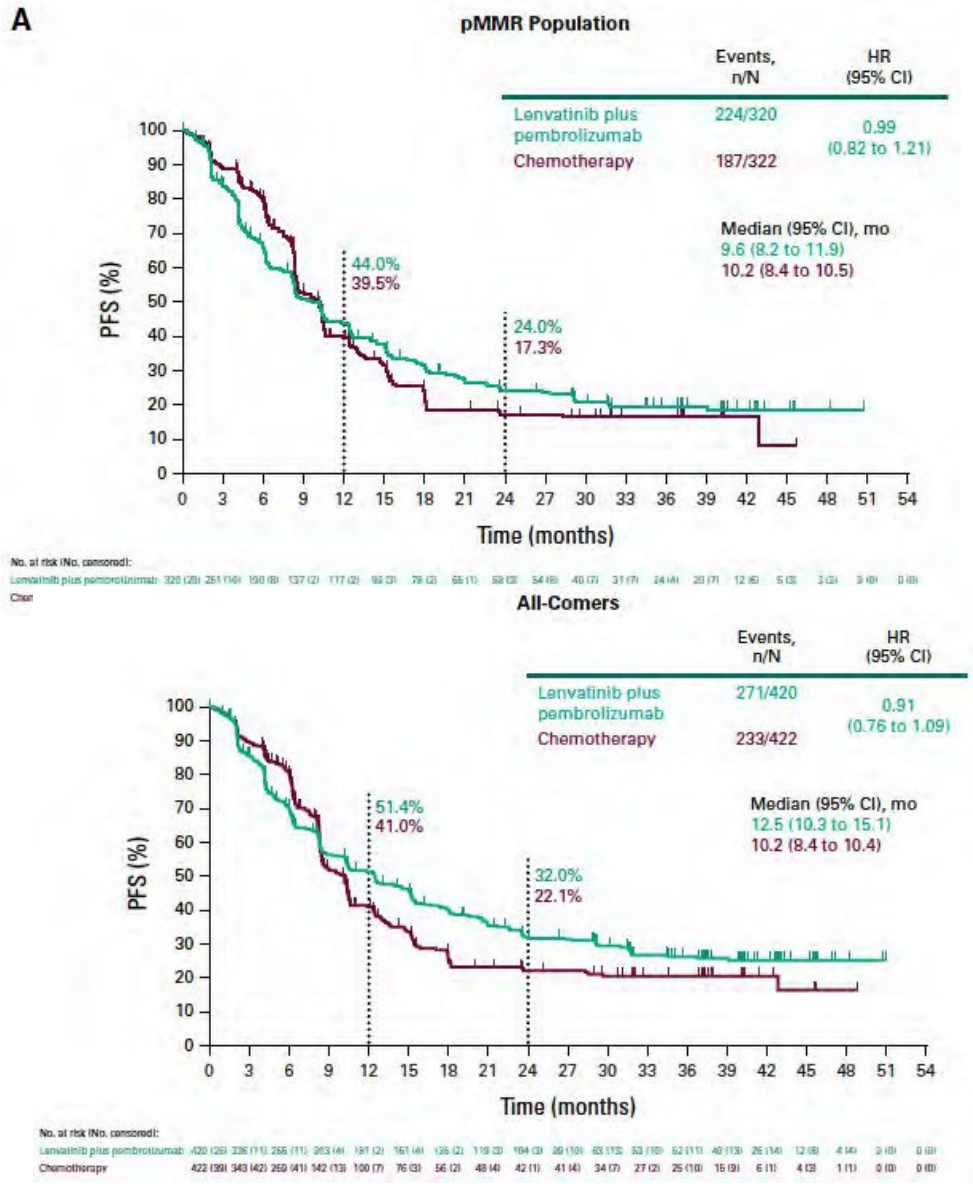
- If pMMR
  - ECOG PS (0 vs 1)
  - Measurable disease (yes vs no)
  - Prior chemotherapy and/or chemoradiation (yes vs no)

R (1:1)
N = 842

- Lenvatinib 20 mg orally QD until PD
  +
  Pembrolizumab 200 mg IV Q3W until PD or x35 cycles
- Paclitaxel 175 mg/m^2 IV
  +
  Carboplatin AUC 6 IV Q3W x7 cycles[c]

Endpoints

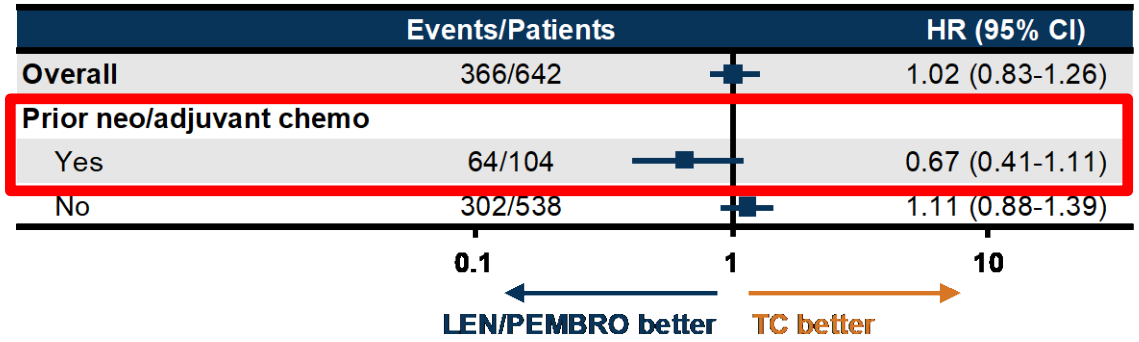
- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR



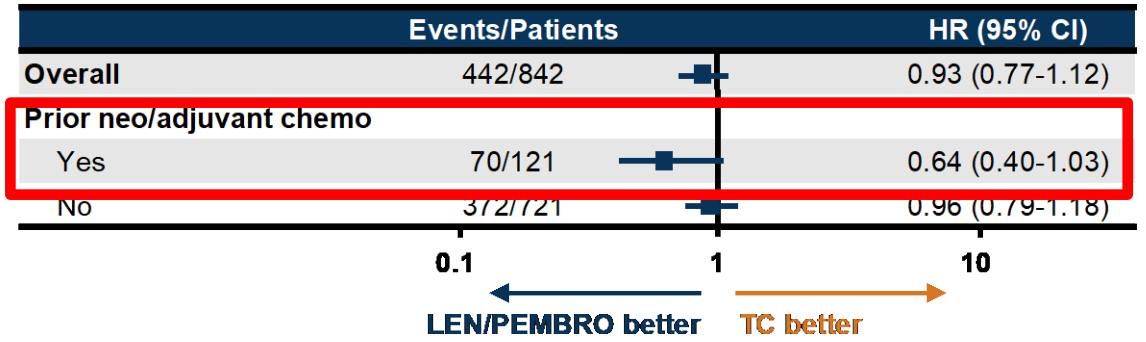
Marth C et al. J Clin Oncol 2024

LEAP-001: Lenvatinib/Pembrolizumab vs Chemo

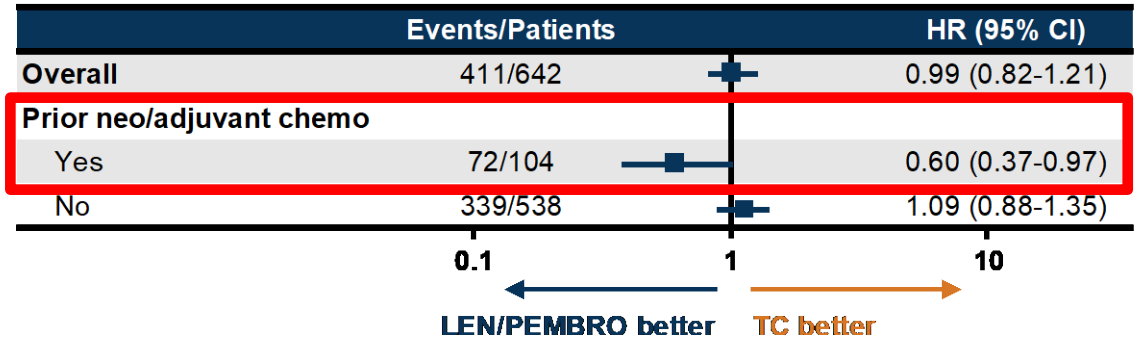
OS - pMMR Population



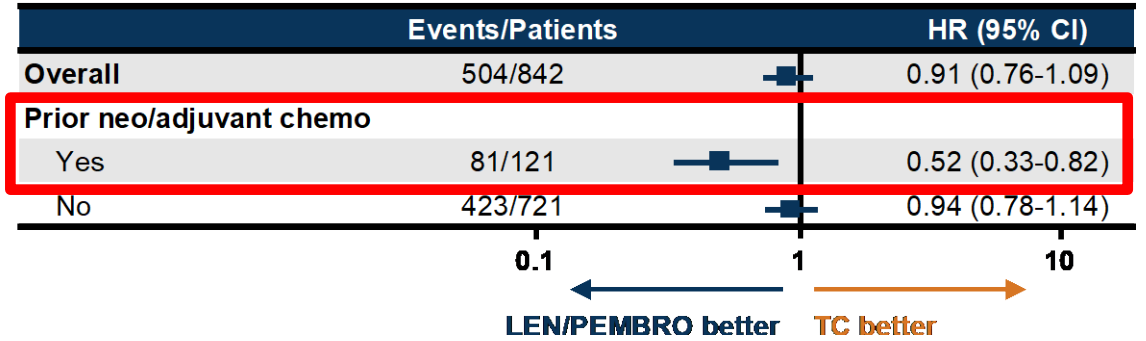
OS - All-comers



PFS - pMMR Population



PFS - All-comers



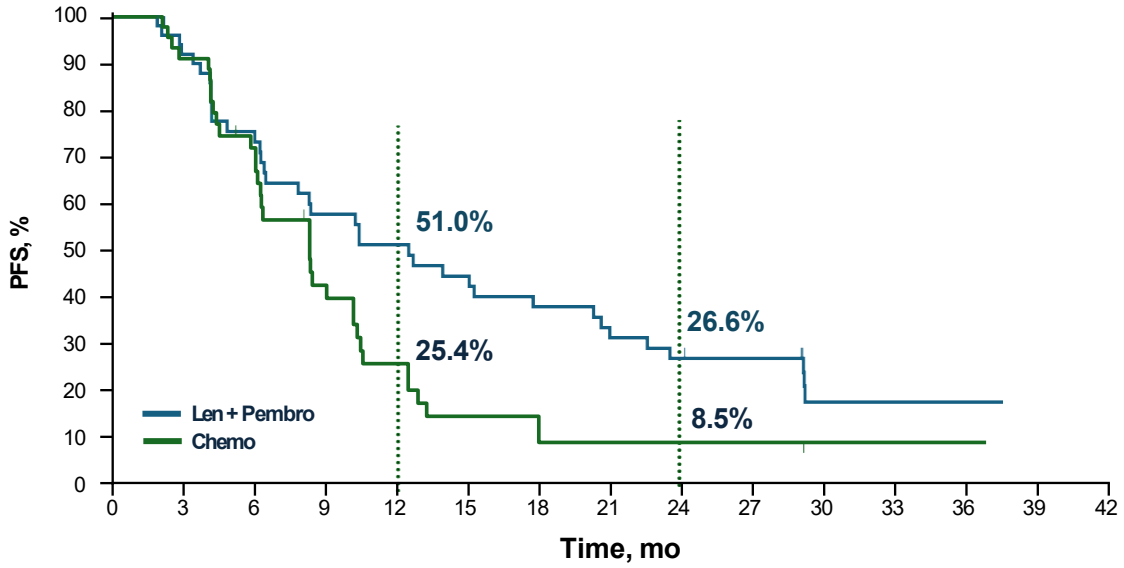
1. https://clinicaltrials.gov/study/NCT03884101. 2.Marth C et al. ESGO 2024. 3. Marth C et al. SGO 2024. 4. Pignata S et al ESMO-GYN 2024 Abstract 39O.

LEAP-001: Lenvatinib/Pembrolizumab vs Chemo

Lenvatinib + Pembrolizumab vs Chemotherapy – PFS in Patients with Prior Neoadjuvant/Adjuvant Chemotherapy

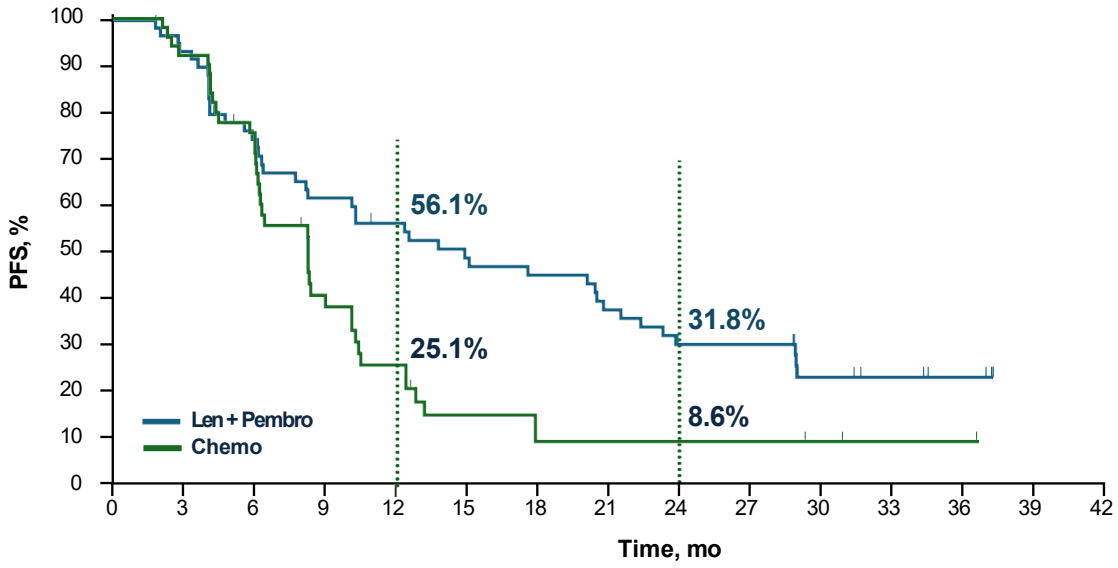
pMMR

Treatment Arm	Events, n/N	Median, mo (95% CI)	HR (95% CI)
Len + Pembro	37/53	12.5 (6.5-20.3)	**0.60** (0.37-0.97)
Chemo	35/51	8.3 (6.1-10.2)	



All-Comers

Treatment Arm	Events, n/N	Median, mo (95% CI)	HR (95% CI)
Len + Pembro	42/63	15.0 (8.3-21.0)	**0.52** (0.33-0.82)
Chemo	39/58	8.3 (6.2-10.2)	



Frontline Lenvatinib + pembrolizumab improved PFS vs chemotherapy in patients with prior neoadjuvant/adjuvant treatment.

IGCS 2025
Annual Global Meeting
CAPE TOWN
November 5 - 7

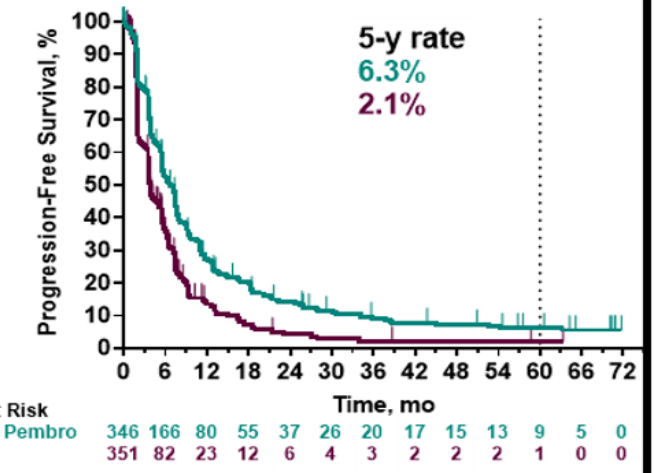
Vicky Makker
Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA

November 05, 2025

Lenvatinib Plus Pembrolizumab vs Treatment of Physician's Choice Chemotherapy in Participants With Advanced Endometrial Cancer: 5-Year Outcomes From Study 309/KEYNOTE-775

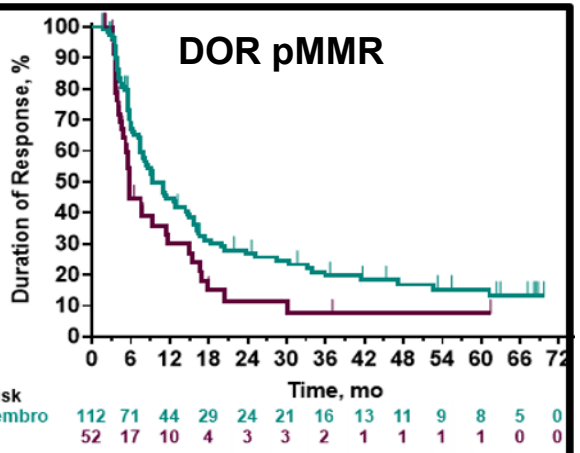
Vicky Makker, Nicoletta Colombo, Antonio Casado Herráez, Alessandro D. Santin, Emeline Colomba, David S. Miller, Keiichi Fujiwara, Sandro Pignata, Kan Yonemori, Yong Man Kim, Sally Baron-Hay, Isabelle Ray-Coquard, Ronnie Shapira-Frommer, Rebecca Kristeleit, Zhou Yu, Jodi McKenzie, Stephan Kruger, Robin Meng, Chinyere E. Okpara, Domenica Lorusso

PFS pMMR



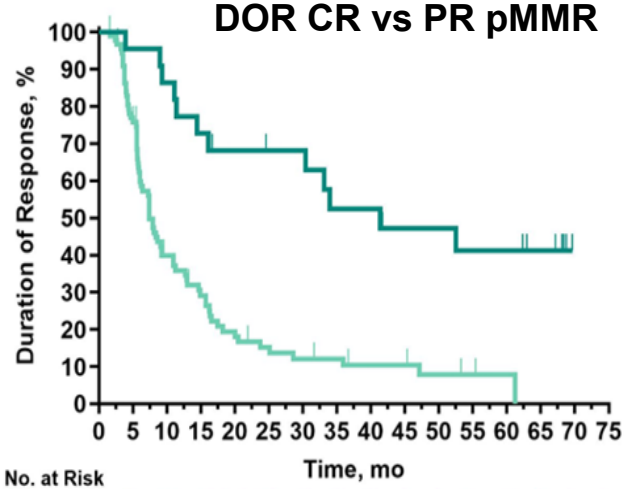
Median (95% CI),[b] mo	6.7 (5.6–7.4)	3.8 (3.6–5.0)
Events, n (%)	289 (83.5)	249 (70.9)
HR (95% CI)[c]	0.60 (0.51–0.72)	

DOR pMMR



ORR,[a] % (95% CI)	32.4 (27.5–37.6)	14.8 (11.3–19.0)
CR, %	6.4	2.6
PR, %	26.0	12.3
Median DOR[a] (95% CI),[b] mo	9.3 (7.4–14.4)	5.7 (4.7–11.4)
Participants with response ≥24 mo, n (%)[b]	24 (26.8)	3 (11.2)

DOR CR vs PR pMMR



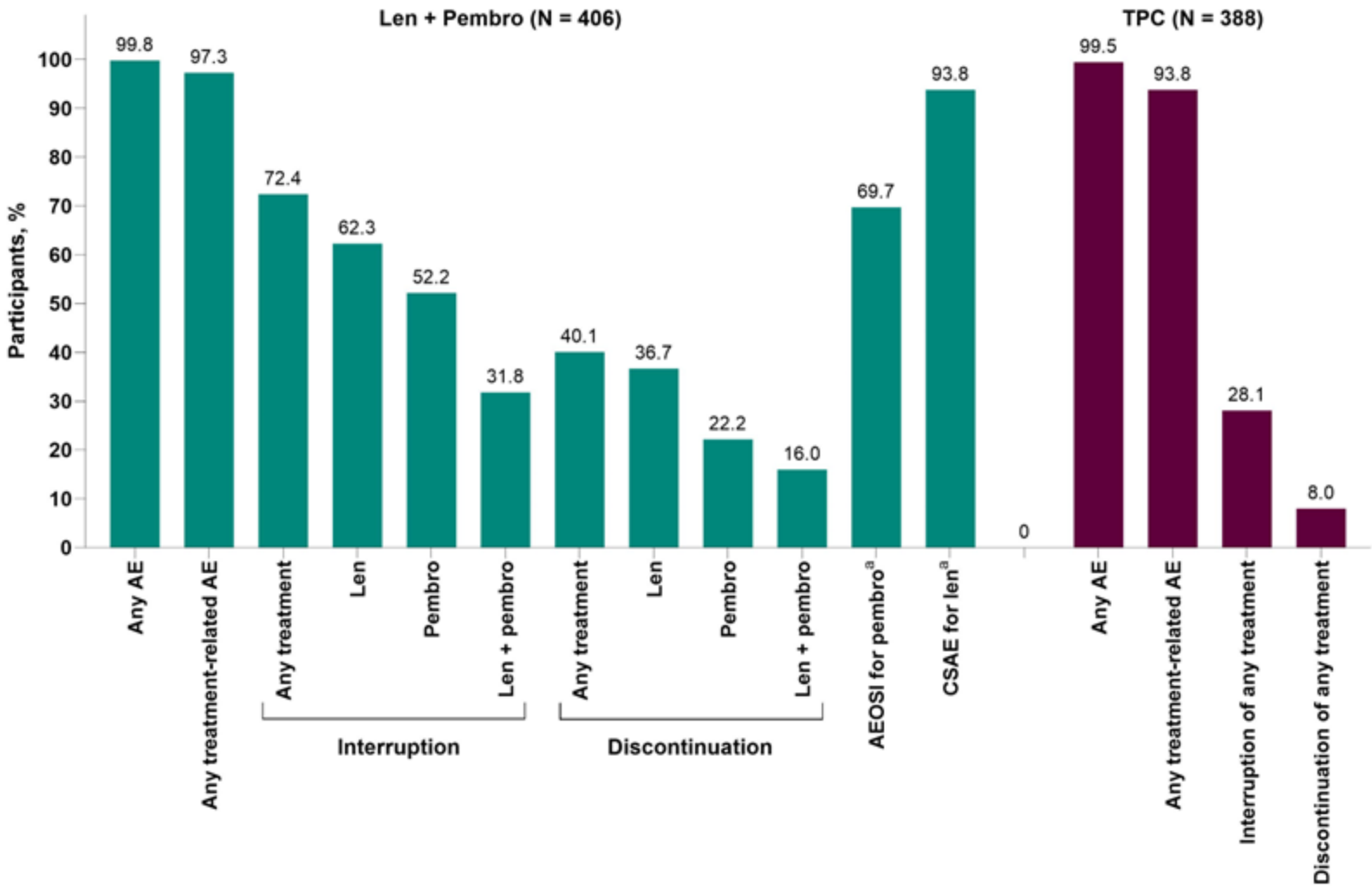
	Pts with CR[a]	Pts with PR[a]
Median DOR[a] (95% CI),[b] mo	41.4 (14.4–NR)	7.4 (6.0–10.9)
Participants with response ≥24 mo, n (%)[b]	14 (68.2)	10 (15.1)

Summary of Subsequent Systemic Therapy

	pMMR		dMMR		All-Comers	
	Len + Pembro n = 346	TPC n = 351	Len + Pembro n = 65	TPC n = 65	Len + Pembro N = 411	TPC N = 416
Any	171 (49.4)	185 (52.7)	13 (20.0)	28 (43.1)	184 (44.8)	213 (51.2)
Lines of subsequent therapy						
1	79 (22.8)	98 (27.9)	8 (12.3)	22 (33.8)	87 (21.2)	120 (28.8)
2	49 (14.2)	57 (16.2)	3 (4.6)	3 (4.6)	52 (12.7)	60 (14.4)
≥3	41 (11.8)	30 (8.5)	2 (3.1)	3 (4.6)	43 (10.5)	33 (7.9)
By class						
Chemotherapy	147 (42.5)	134 (38.2)	11 (16.9)	10 (15.4)	158 (38.4)	144 (34.6)
Hormonal	52 (15.0)	64 (18.2)	3 (4.6)	7 (10.8)	55 (13.4)	71 (17.1)
PD-1/PD-L1 based	18 (5.2)	54 (15.4)	2 (3.1)	15 (23.1)	20 (4.9)	69 (16.6)
Pembro based[a]	18 (5.2)	48 (13.7)	1 (1.5)	11 (16.9)	19 (4.6)	59 (14.2)
Len + Pembro	10 (2.9)	41 (11.7)	0	1 (1.5)	10 (2.4)	42 (10.1)
Pembro mono	7 (2.0)	4 (1.1)	1 (1.5)	10 (15.4)	8 (1.9)	14 (3.4)

Data cutoff: February 26, 2025. Data are n (%) of participants. [a]Including pembro monotherapy and pembro-based combination therapy.

Summary of AEs and Len Dose Reductions



	Len + Pembro (N = 406)
Len dose intensity, median (range), mg/d	13.4 (3–20)
Time to first len dose reduction, median (range), mo	2.0 (0.1–32.5)
Len dose reduction, %	
Any	72.2
1	23.4
2	24.4
3	15.5
4	8.9

Data cutoff: February 26, 2025. AE, adverse event; AEOSI, adverse event of special interest; CSAE, clinically significant adverse event. [a]AEs based on a list of terms specified by the sponsor and considered regardless of attribution by the investigators.

Gynecologic Oncology 194 (2025) 98–104

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

Platinum-free interval and response to platinum retreatment or lenvatinib/pembrolizumab in patients with recurrent endometrial cancer: A real-world endometrial cancer molecularly targeted therapy consortium cohort study

Paulina J. Haight [a,*], Marilyn Sanchez [b], Samantha M. Thomas [b], Carson Smitherman [c], Casey Cosgrove [a], Victoria Bae-Jump [d], Sarah Crafton [e], Kari Hacker [f], Emily Ko [g], Thomas Krivak [e], Olivia Lara [d], Kathleen Moore [h], Mary M. Mullen [i], Bhavana Pothuri [f], Premal H. Thaker [i], Christina Washington [h], Rebecca Arend [j], Bradley Corr [k], Linda Duska [l], Amanda Jackson [m], Gottfried E. Konecny [n], Jason Wright [o], Angeles Secord [c], Floor Backes [a]

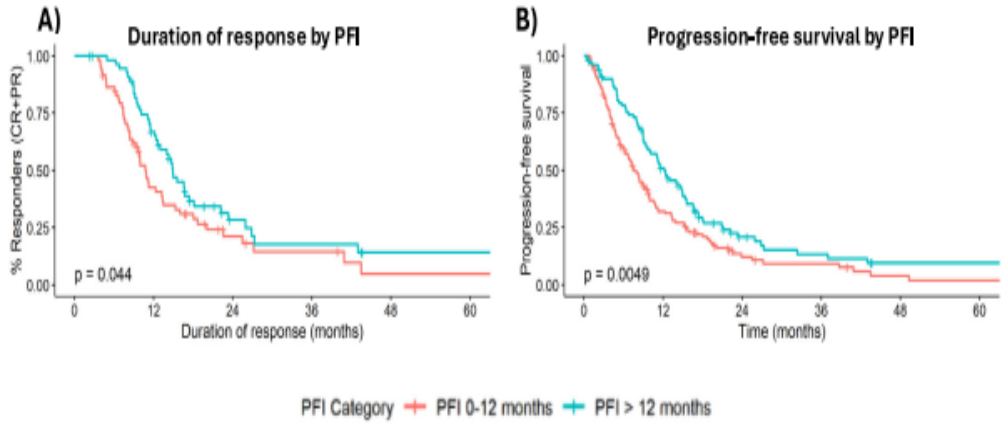


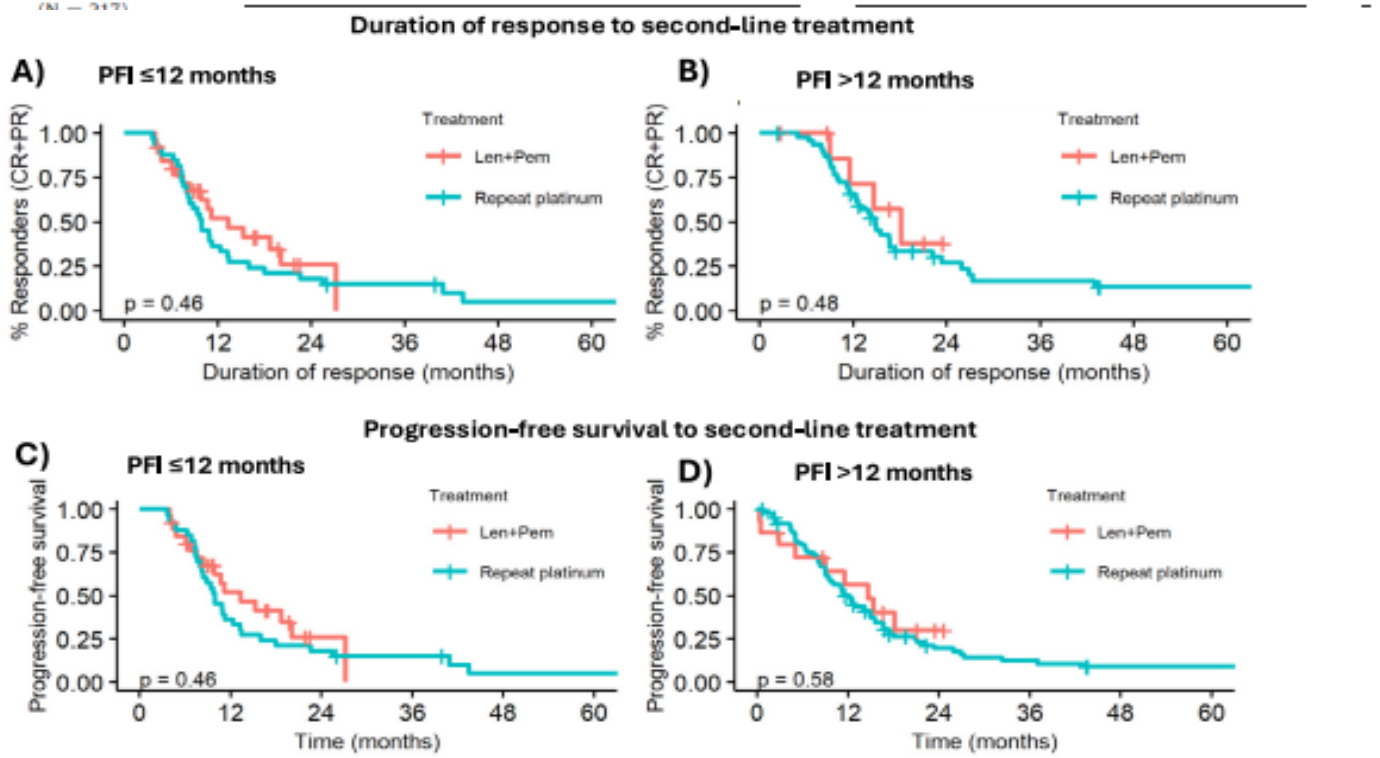
Table 2
Platinum-free interval and second-line treatment.

	Platinum-based chemotherapy (N = 140)	Lenvatinib/Pembrolizumab (N = 71)	Overall (N = 217)	P-Value
Platinum-free Interval (PFI)				<0.001
≤12 months	68 (53.5 %)	59 (46.5 %)	127	
>12 months	72 (85.7 %)	12 (14.3 %)	84	
Median PFI (months)				<0.001
Mean (SD	20.8 (24.9)	7.66 (9.24)	16.4 (21.8)	
Median [Min, Max]	12.9 [0.250, 142]	4.63 [0.700, 55.6]	8.07 [0.250, 142]	

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum.
Data presented as N (row %).

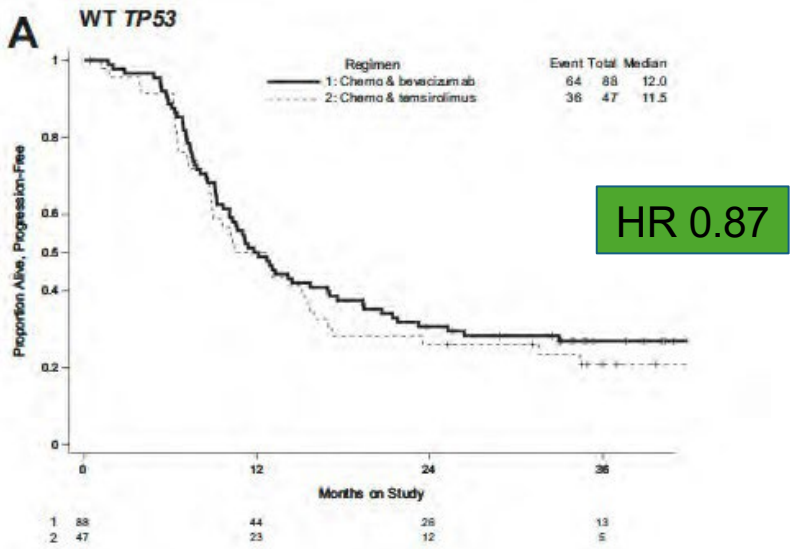
Table 3
Response to second-line treatment based on regimen or platinum-free interval.

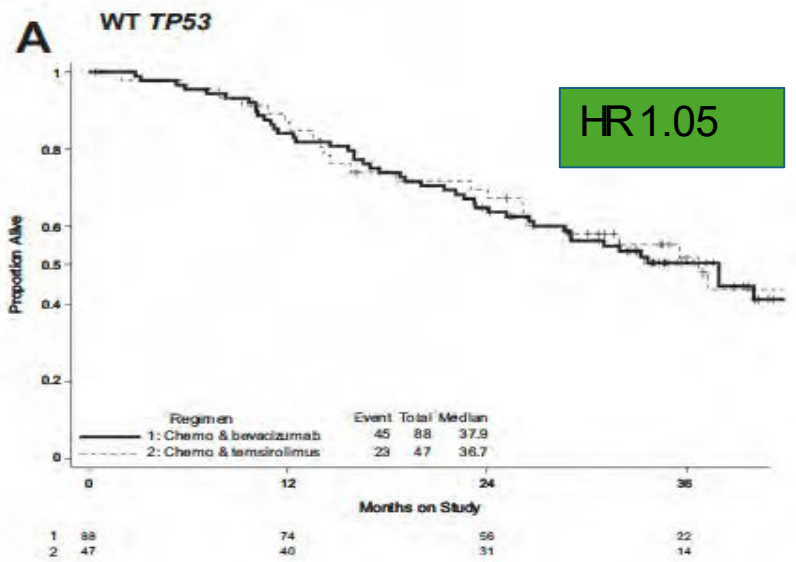
Overall	Second-line treatment	Platinum-free interval

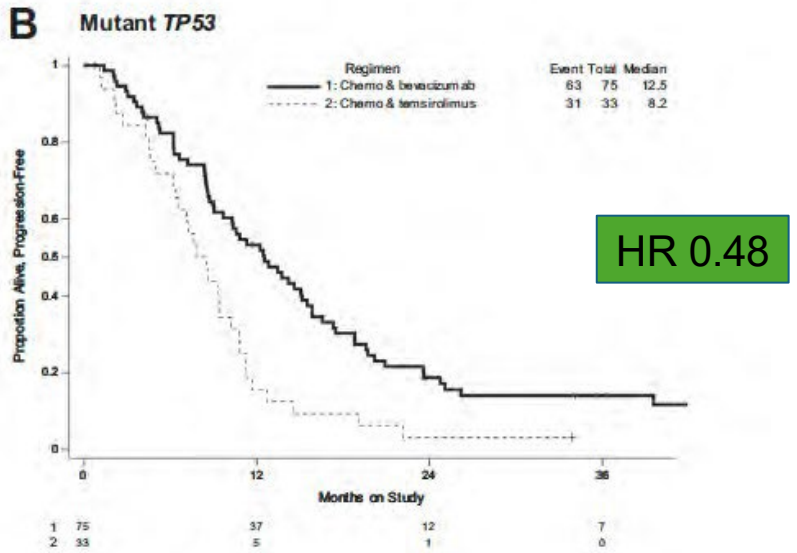


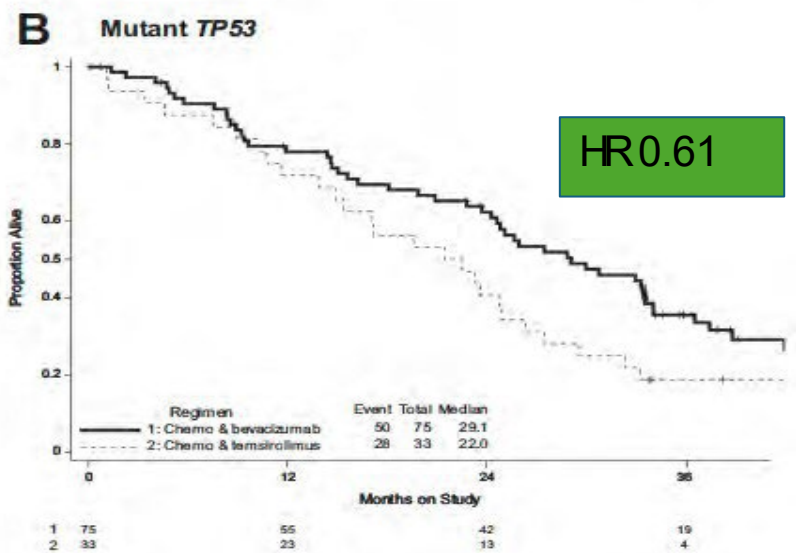
ig. 2. Duration of response and progression-free survival to second-line treatment. (A) Duration of response for all responders with PFI ≤12 months, stratified by second-line treatment egimen. (B) Duration of response for all responders with PFI >12 months, stratified by second-line treatment regimen. (C) Progression-free survival for all patients with PFI ≤12 months, tratified by second-line treatment regimen. (D) Progression-free survival for all patients with PFI >12 months, stratified by second-line treatment regimen.

TP53 mutation as a "biomarker" for response to Bevacizumab in Endometrial Cancer: Ancillary Investigation of GOG 86P









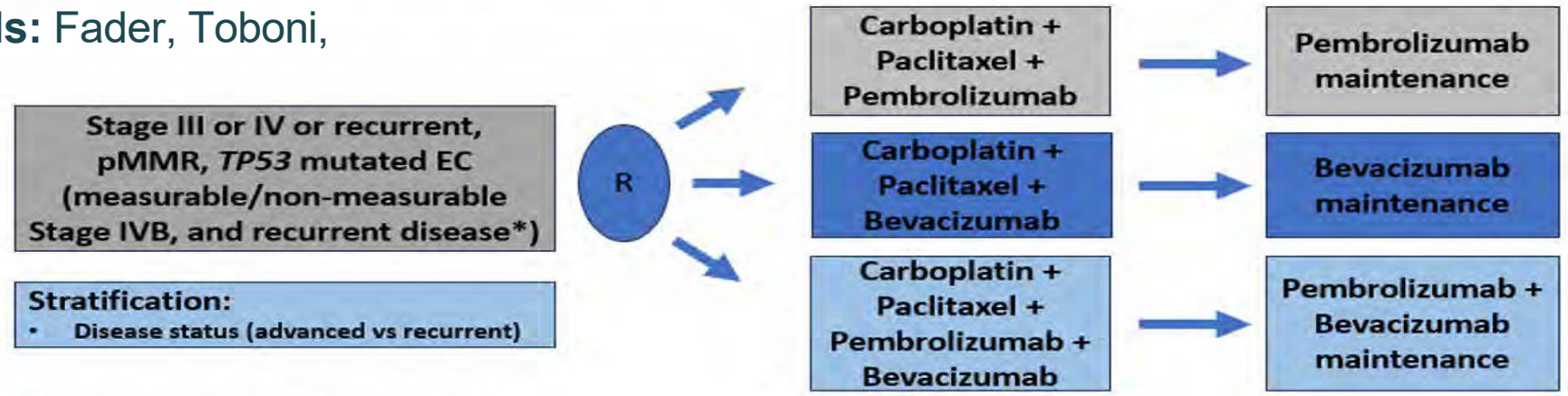
Leslie K. et al. Gyncol Oncol 2021

GY035 (UC2323)

Prelim trial design building on results of GY018 & GOG86P in TP53 mutated Endometrial cancer patients: approved by GCSC

Randomized Phase II/III Study of Carboplatin + Paclitaxel + Pembrolizumab vs. Carboplatin + Paclitaxel + Bevacizumab vs. Carboplatin + Paclitaxel + Pembrolizumab + Bevacizumab in Patients with Advanced or Recurrent, pMMR and *TP53* mutated Endometrial Cancer

PIs: Fader, Toboni,



*Primary Phase II endpoint: PFS by RECIST V1.1
*Primary Phase III endpoint: OS

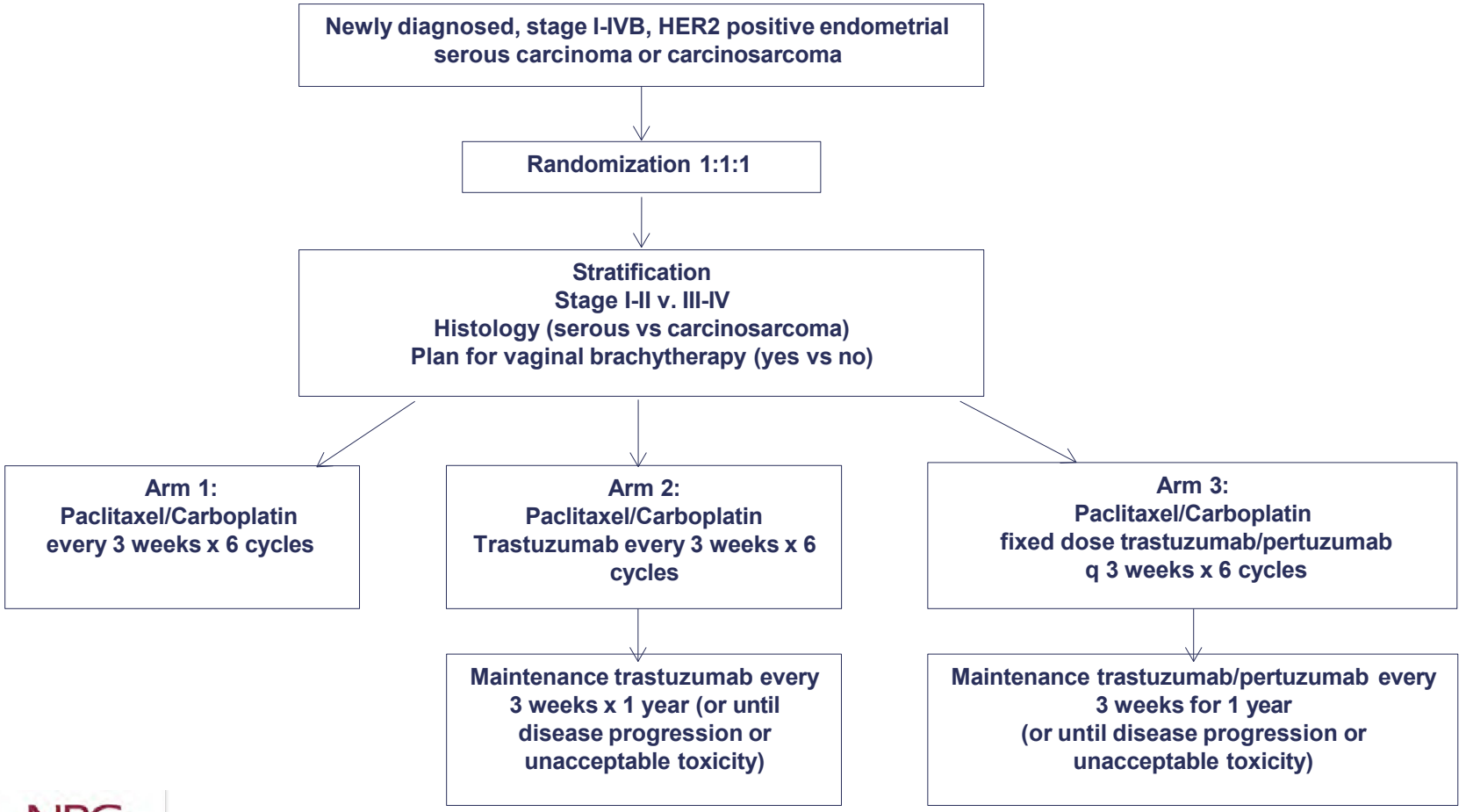
Treatment Plan:
Arm 1: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + IV pembrolizumab 200 mg on day 1 every 3 weeks x 6-10 cycles followed by 14 additional cycles of pembrolizumab 400 mg IV maintenance every 6 weeks.
Arm 2: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg on day 1 every 3 weeks x 6-10 cycles followed by 28 additional cycles of bevacizumab 15 mg/kg maintenance every 3 weeks.
Arm 3: IV carboplatin AUC 5 + IV paclitaxel 175 mg/m^2 + IV pembrolizumab 200 mg + bevacizumab 15 mg/kg on day 1 every 3 weeks x 6-10 cycles followed by 14 additional cycles of pembrolizumab 400 mg IV maintenance every 6 weeks and 28 additional cycles of bevacizumab 15 mg/kg IV maintenance every 3 weeks.
*Patients with recurrent disease who have received prior adjuvant therapy must have a platinum-free interval of >/=12 months.

Courtesy B. Monk

Targeting her2 in 1L: NRG-GY026

Phase II/III Study Of Paclitaxel/Carboplatin +/- Trastuzumab or Trastuzumab/ Pertuzumab in HER2 Positive, Stage I-IV Endometrial Serous Carcinoma or Carcinosarcoma

PI: Britt Erickson, MD | Co-PI: Amanda Nickles-Fader, MD



Key Inclusion

- Stage 1A-IVB (FIGO 2009) non-recurrent, chemo-naive, uterine serous or carcinosarcoma
- HER2 positive based in local testing (ASCO/CAP 2018 Breast guidelines recommended) or NGS
- OK for vaginal brachytherapy, pelvic radiotherapy not allowed.
- Patients must be within 8 weeks of primary surgery (or endometrial biopsy in patients who never undergo hysterectomy)

NRG ONCOLOGY
Advancing Research. Improving Lives.

NCT05256225

Targeting her2 1L adjuvant:
DESTINY-Endometrial02/ GOG-3122/ENGOT-en30

A Phase 3, Multicenter, Randomized, Open-label Trial of Trastuzumab Deruxtecan Versus Standard of Care Chemotherapy With or Without Radiotherapy as Adjuvant Treatment for HER2-Expressing (IHC 3+/2+) Endometrial Cancer

Tissue Screening

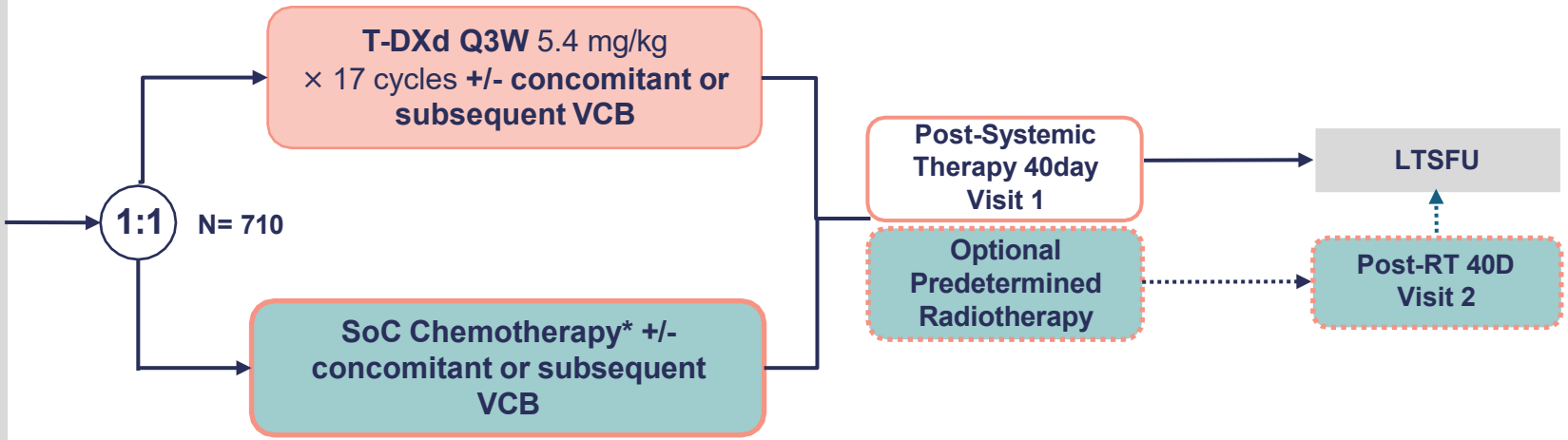
HER2 expression (IHC 3+/2+) per 2016 ASCO CAP gastric cancer IHC scoring guidelines by central confirmation

Main Screening

Key Patient Population

- Histologically confirmed diagnosis of endometrial cancer
- FIGO2023 Stage IIC or III
- NO evidence of disease post-surgery as per investigator and confirmed by BICR
- Treatment naïve (systemic therapy) in any setting including the neoadjuvant setting for endometrial cancer

Treatment



Follow-up

*SoC Chemotherapy +/- EBRT Options

- 6 cycles of carboplatin AUC 5 or 6 and paclitaxel 175 mg/m2 Q3W followed by EBRT
- 4 cycles carboplatin AUC 5 or 6 and paclitaxel 175 mg/m2 Q3W followed by chemoradiotherapy (EBRT plus cisplatin 50 mg/m2 on days 1 and 29
- 6 cycles of carboplatin AUC 5 or 6 and paclitaxel 175 mg/m2 Q3W

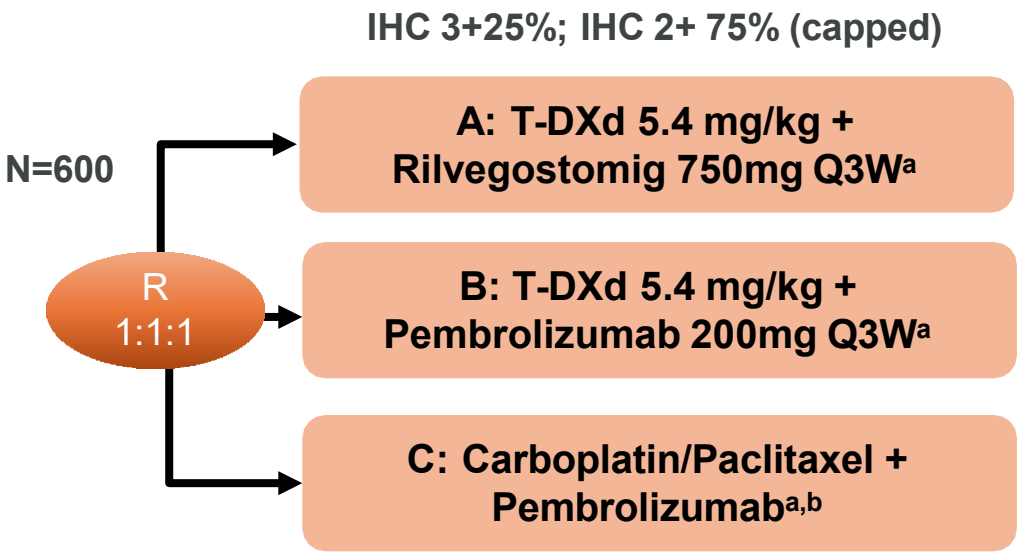
NCT07022483

Targeting her2 1L advanced/recurrent: DESTINY-Endometrial01/ GOG-3098/ ENGOT-EN24

A Phase III Study of Trastuzumab Deruxtecan Plus Rilvegostomig or Pembrolizumab as First-Line Treatment of HER2-Expressing (IHC 3+/2+), Mismatch Repair Proficient (pMMR) Endometrial Cancer

Patient Population

- HER2 expressing (IHC 3+/2+) EC by central test
- pMMR EC by central test
- Stage III, Stage IV, or recurrent, histologically-confirmed endometrial cancer
- Stage III must have measurable disease
- Any histological subtype except for sarcomas
- May have received 1 prior line of adjuvant/ neoadjuvant chemotherapy (chemotherapy and/ or chemoradiation) if recurrence ≥ 6 months after last dose of chemo
- No prior exposure to ADCs or ICIs
- ECOG PS 0 or 1



Stratification factors:
- HER2 IHC 3+ vs 2+
- PD-L1 TAP ≥1% vs TAP <1%
- Asia vs Non-Asia

Endpoints

Primary:
- PFS (BICR) in ITT

Secondary:
- OS (key secondary endpoint)
- PFS (Investigator)
- ORR
- PFS2
- HRQoL

[a] *Treatment will continue until objective disease progression according to RECIST v1.1 as assessed by the Investigator and confirmed by BICR or until other discontinuation criteria is met, whichever occurs first.*

[b] *Carboplatin AUC5, paclitaxel 175 mg/m2, and pembrolizumab 200 mg IV once Q3W x 6 cycles*, followed by maintenance with pembrolizumab 400 mg IV Q6W. Treatment with pembrolizumab will continue for up to 20 total cycles (approximately 24 months, accounting for combination and maintenance phases) or until other discontinuation criteria is met, whichever occurs first.*

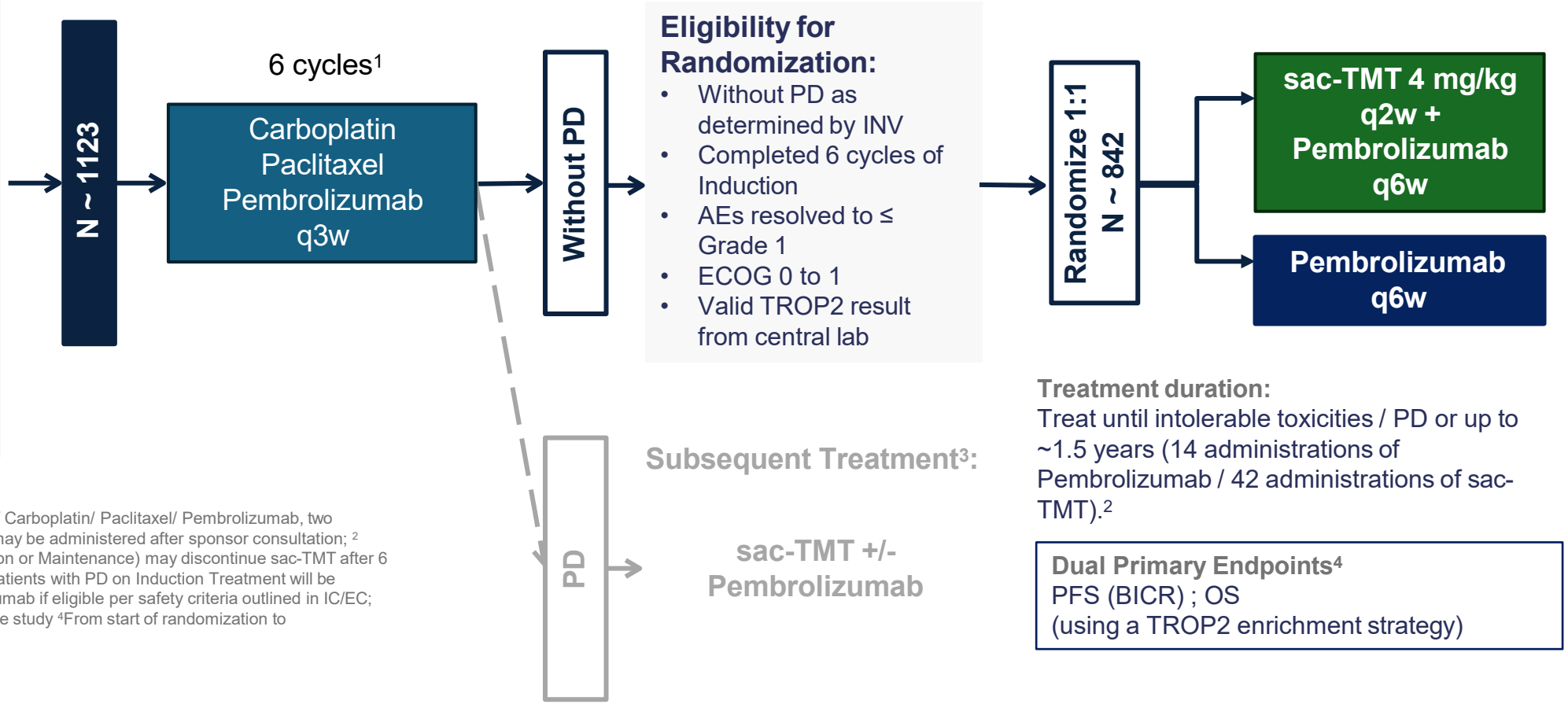
** At the discretion of the treating Investigator, participants may continue to receive carboplatin, paclitaxel and pembrolizumab Q3W for up to 10 cycles.*

Targeting Trop2 1L advanced/recurrent: MK-2870-033/TroFuse-033/GOG-3119/ENGOT-en29

A Phase 3 Study to Compare Sacituzumab Tirumotecan in Combination With Pembrolizumab Vs Pembrolizumab Alone as Treatment in Participants With MMR-P Endometrial Cancer (TroFuse-033)

Key Eligibility Criteria

- Primary advanced/recurrent endometrial carcinoma
- pMMR
- No prior systemic therapy OR recurred after adjuvant (no PFI required)
- No prior anti-PD-1/PD-L1
- Radiologically apparent disease (measurable for St. III, measurable or non-measurable for St. IV & recurrent disease)
- Available tissue to test for TROP2 / MMR / p53
- ECOG 0 to 1



Treatment duration:
Treat until intolerable toxicities / PD or up to ~1.5 years (14 administrations of Pembrolizumab / 42 administrations of sac-TMT).[2]

Dual Primary Endpoints[4]
PFS (BICR) ; OS
(using a TROP2 enrichment strategy)

[1] If pt. needs more time to recover after 6 cycles of Carboplatin/ Paclitaxel/ Pembrolizumab, two additional cycles of pembrolizumab (cycle 7 + 8) may be administered after sponsor consultation; [2] Pts. with confirmed CR by BICR (following Induction or Maintenance) may discontinue sac-TMT after 6 months of sac-TMT after sponsor consultation; [3]Patients with PD on Induction Treatment will be randomized to sac-TMT vs. sac-TMT + pembrolizumab if eligible per safety criteria outlined in IC/EC; Subsequent Treatment is an exploratory part of the study [4]From start of randomization to Maintenance;

Targeting Trop2 2L: ASCENT-GYN-01/GOG-3104/ENGOT-en26

A Phase 3 Study of SG vs TPC in Patients With Endometrial Cancer Who Have Received Prior Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy

Key Eligibility Criteria

- Recurrent or persistent endometrial cancer (endometrial carcinoma or carcinosarcoma)
- Up to 3 prior lines of systemic therapy for endometrial cancer, including systemic platinum-based chemotherapy and anti-PD-1/PD-L1 therapy, either in combination or separately
- Radiologically evaluable disease (either measurable or nonmeasurable) per RECIST v1.1
- ECOG Performance Status of 0-1

N=520

R
1:1

Sacituzumab Govitecan (SG)
10 mg/kg on D1 and 8 of a 21-day cycle

Treatment of Physician's Choice (TPC)
Doxorubicin 60 mg/m^2 on D1 of a 21-day cycle, or
Paclitaxel 80 mg/m^2 on D1, 8, and 15 of a 28-day cycle

Treat until disease progression or unacceptable toxicity

Key Endpoints

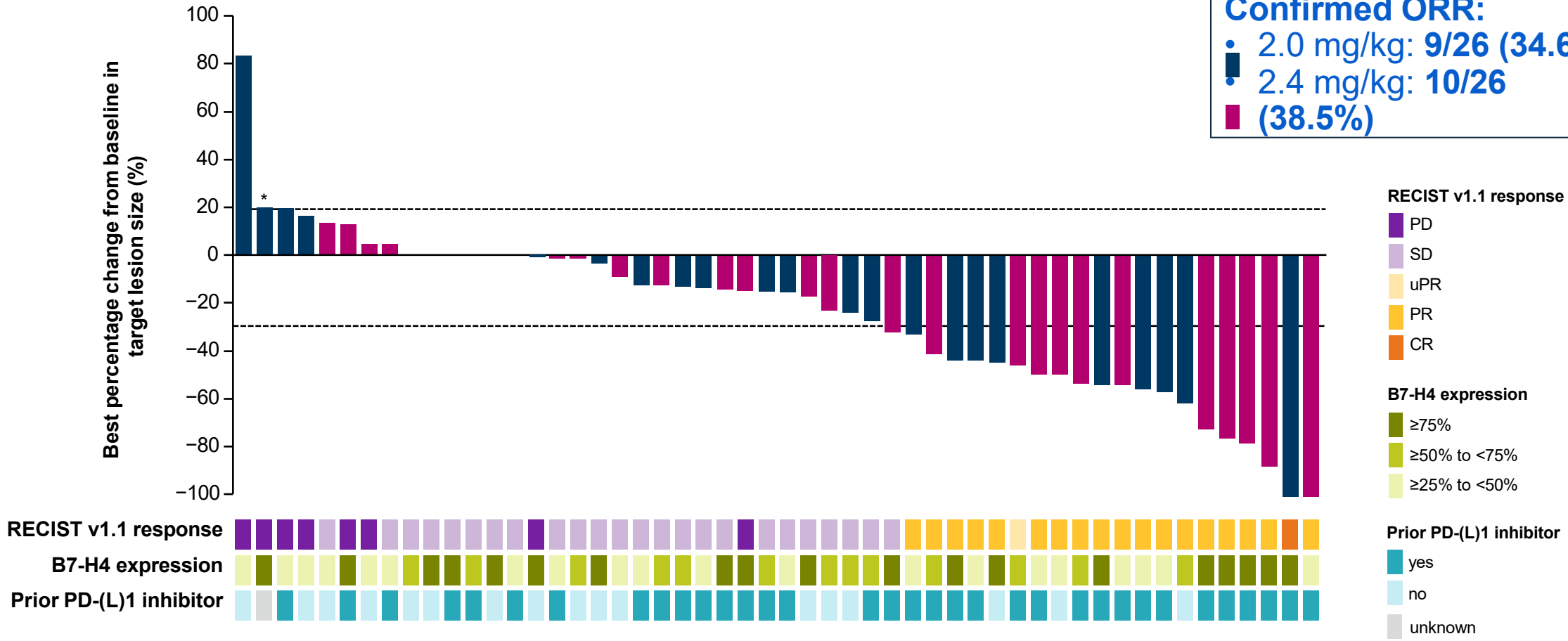
Primary Endpoints
- PFS by BICR
- OS

Secondary Endpoints
- ORR, DOR, CBR
- PFS by INV
- Safety
- QOL

ClinicalTrials.gov ID: NCT06486441

Targeting B7-H4 2L+:Puxitatug samrotecan (Puxi-Sam):TOPO-1 ADC Efficacy observed in EC across B7-H4 expression

Confirmed ORR:
- 2.0 mg/kg: **9/26 (34.6%)**
- 2.4 mg/kg: **10/26 (38.5%)**



Includes patients who had the opportunity for ≥13 weeks of follow-up at data cut-off: January 30, 2025
*Patient was discontinued prior to first evaluation scan
CR, complete response; ORR, objective response rate; PD, progressive disease; PD-(L)1, programmed cell death (ligand) 1; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uPR, unconfirmed partial response

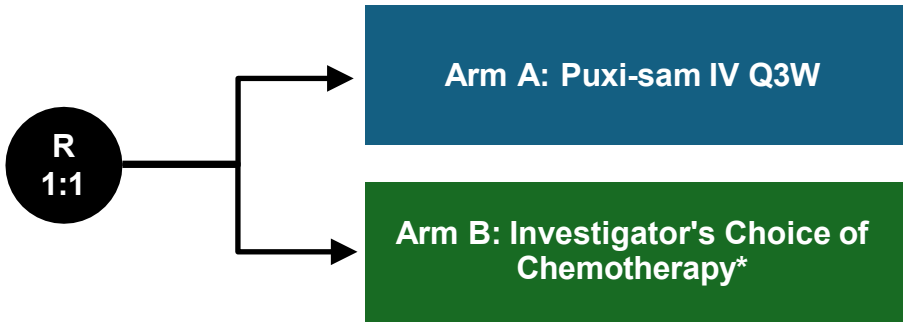
Presented at SGO Annual Meeting, 2025, Seattle, WA

Targeting B7-H4 2/3L: Bluestar-Endometrial01/GOG 3110/ENGOT-en28

Puxitatug Samrotecan (Puxi-sam) Monotherapy vs Chemotherapy in B7-H4 Selected Advanced/Metastatic Endometrial Cancer Who Progressed On or After Platinum Based Chemotherapy and Anti-PD-1/Anti-PD-L1 Therapy

Key Eligibility Criteria

- Histologically confirmed endometrial cancer (EC) or carcinosarcoma
- Advanced or recurrent/metastatic EC
- B7-H4 expression
- Prior platinum-based chemotherapy and anti-PD-1/anti-PD-L1 therapy, either separately or in combination
- Has received no more than 2 prior lines of therapy in advanced/metastatic setting
- Neoadjuvant ± adjuvant platinum-based chemotherapy would count as 1 line of therapy if the recurrence occurred within 12 months after the date of the last platinum dose.
- WHO/ECOG 0 or 1
- At least 1 measurable lesion per RECIST 1.1
- No prior TOP1 inhibitors or B7-H4 agents



*Doxorubicin 60 mg/m² IV Q3W
or
Paclitaxel 80 mg/m² IV on Days 1, 8, and 15 in a Q4W cycle

Dual primary endpoints

PFS, OS

Secondary endpoints

ORR, DoR, PFS2, TFST, TSST, TDT, Time to worsening, Safety

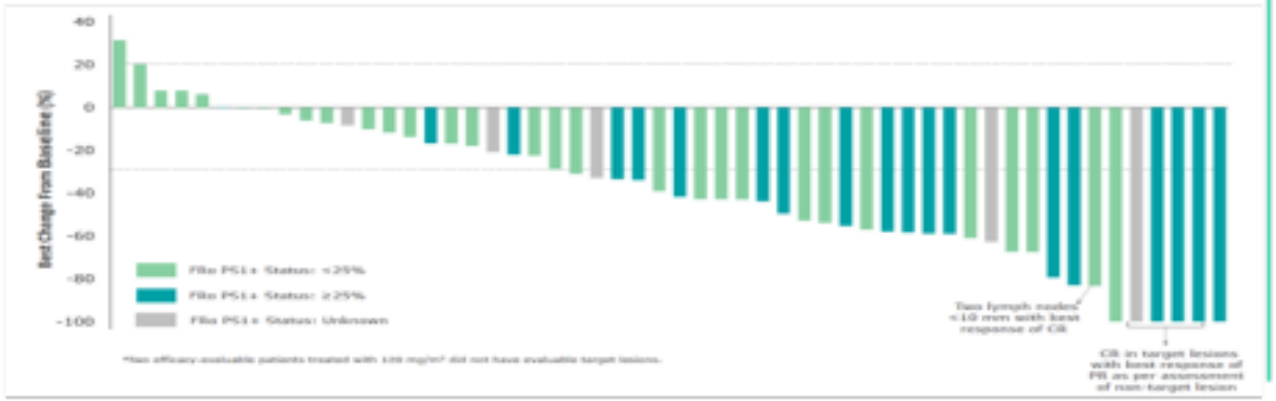
PFS, Progression Free Survival; OS, Overall Survival; ORR, Overall Response Rate; DoR, Duration of Response; TFST, Time until first subsequent anticancer therapy; TSST, Time until second subsequent anticancer therapy; TDT, Time until discontinuation of treatment; IV, intravenous

Targeting FRa 2L+: Rina-S for patients with advanced stage/recurrent EC: RAINFOL-01

ESMO 2025: Endometrial Cancer

Responses by FRα Expression

- Responses with Rina-S® 100 mg/m² and 120 mg/m² are shown pooled by FRα status <25% and ≥25%, exploratory cutoffs that may be indicative of low and high FRα-expression in EC, respectively, similar to published literature
- Confirmed radiological responses were observed regardless of FRα expression levels (0-100%)



Overall Safety

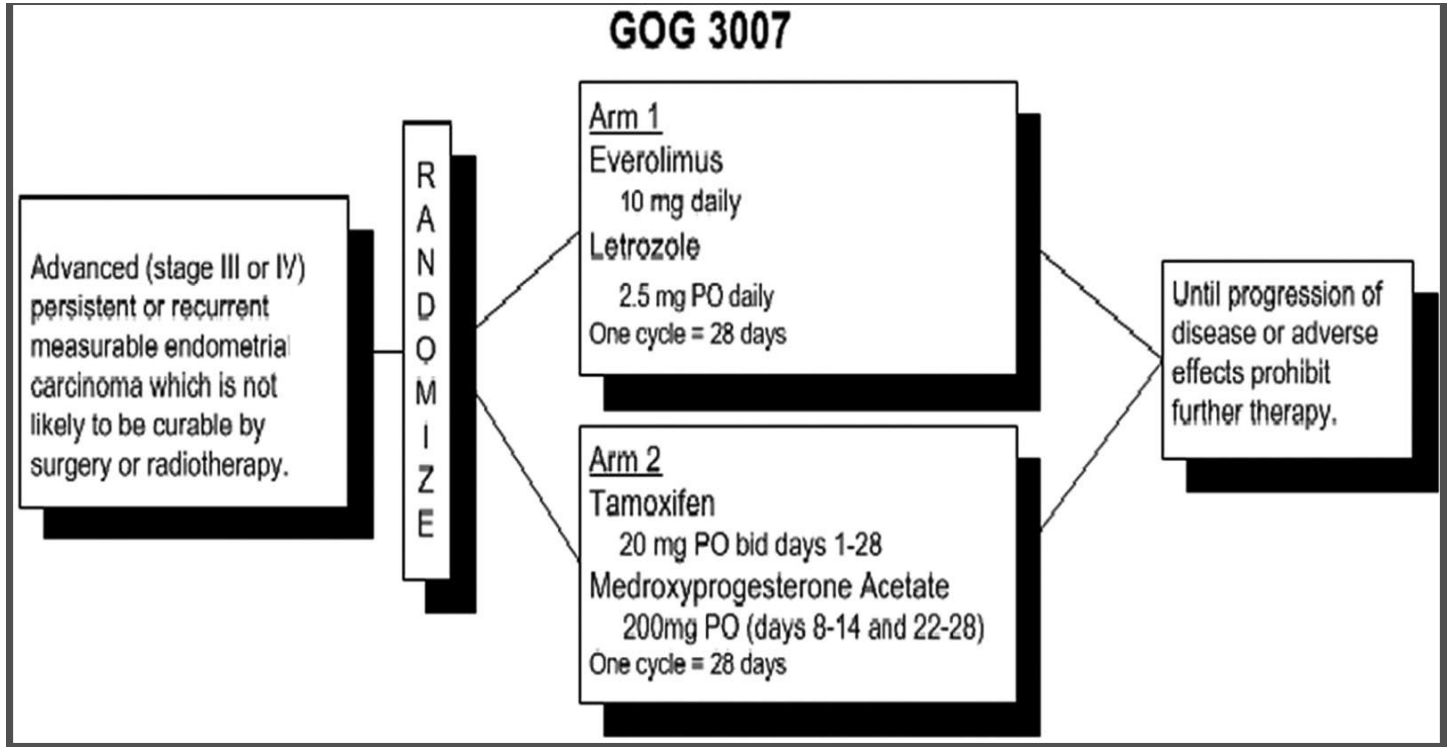
- Rina-S® TEAEs consisted primarily of cytopenias and low-grade gastrointestinal events
- No signals of ocular toxicity, neuropathy, or interstitial lung disease were observed, consistent with prior reports

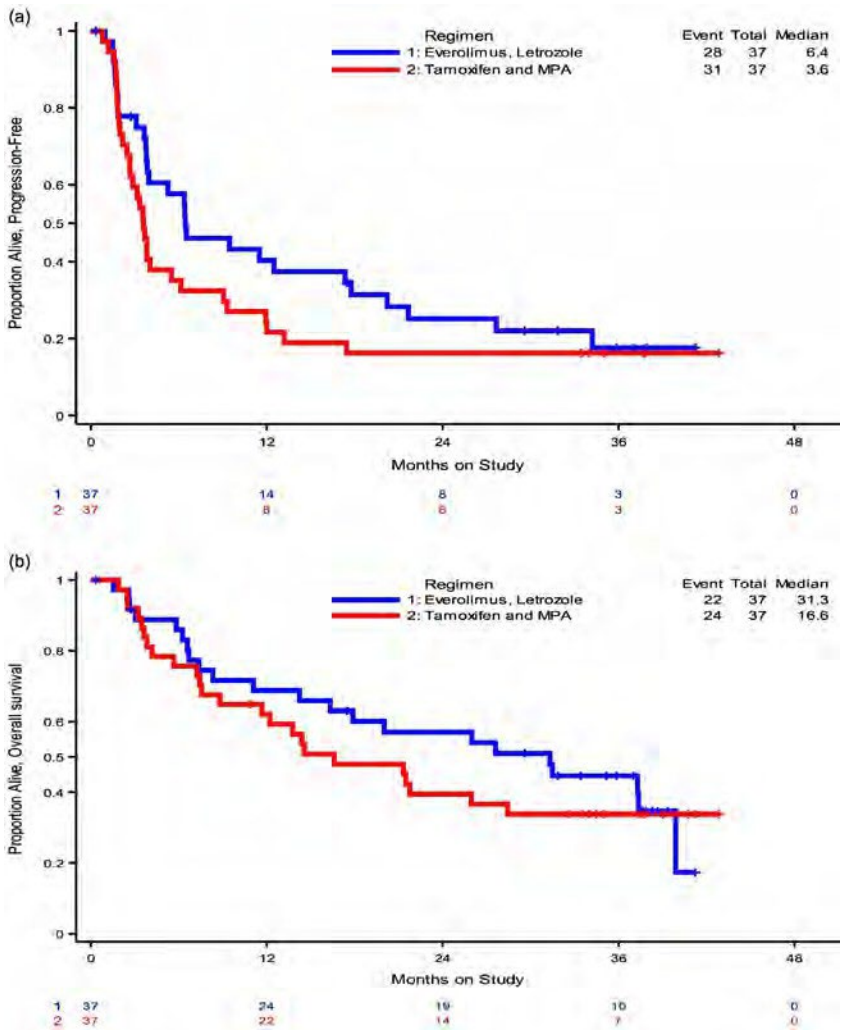
	100 mg/m² (n=22)	120 mg/m² (n=42)
Any grade TEAE, n (%)	22 (100)	42 (100)
Grade ≥3 TEAEs, n (%)	17 (77.3)	35 (83.3)
Serious TEAEs, n (%)	8 (36.4)	22 (52.4)
Fatal TEAEs, n (%)	0	2 (4.8)[a]
TEAE leading to dose reduction, n (%)	4 (18.2)	8 (19.0)
TEAE leading to discontinuation, n (%)	0	4 (9.5)[b]

[a]One grade 5 TEAE of acute kidney injury (unrelated to Rina-S per investigator) and one grade 5 TEAE of septic shock (related to Rina-S per investigator; confounded by comorbidities).
[b]TEAEs leading to discontinuations were not related to Rina-S per investigator except for one event of *Citrobacter* sepsis with 120 mg/m².

Cloven et al ESMO 2025

GOG 3007: Everolimus/Letrozole





Slomovitz et al. Gynecol Oncol 164 (3): 481-91

Non- ADCs in Development in EC

Sponsor	Agent	Target/MOA	clinicaltrials.gov
Zentalis	Azenosertib	WEE1 inhibitor	NCT04814108
Acrivon	ACR-368 (Prexasertib)	CHK1 and CHK2 inhibitor	NCT0554829*
Faeth	Serabelisib + Sapanisertib	PI3K/AKT/mT OR inhibitor	NCT06463028*
Repare	Camonsertib + Lunresertib	ATR/PKMYT1	NCT0485565*

* Biomarker informed populations

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

PI: Shannon Westin

Key Eligibility: Recurrent or persistent USC; ≥1 prior platinum-based chemotherapy regimen; Prior HER-2 directed therapy for known HER2+ (if indicated); Prior anti-PD(L)1 (if indicated); Measurable disease per RECIST; ECOG PS 0-1

All Comers Enrollment

Part 1b: N = 80

Dose 1:
N = 40*
Azenosertib 400 mg QD 5:2

Dose 2:
N = 40
TBD based on study ZN-c3-001

*** 14 slots available as of 16Dec24**

All Comers Enrollment

Part 2: N = 60 (Total N at the target dose = 100)

TBD based on Part 1b and Study ZN-c3-001

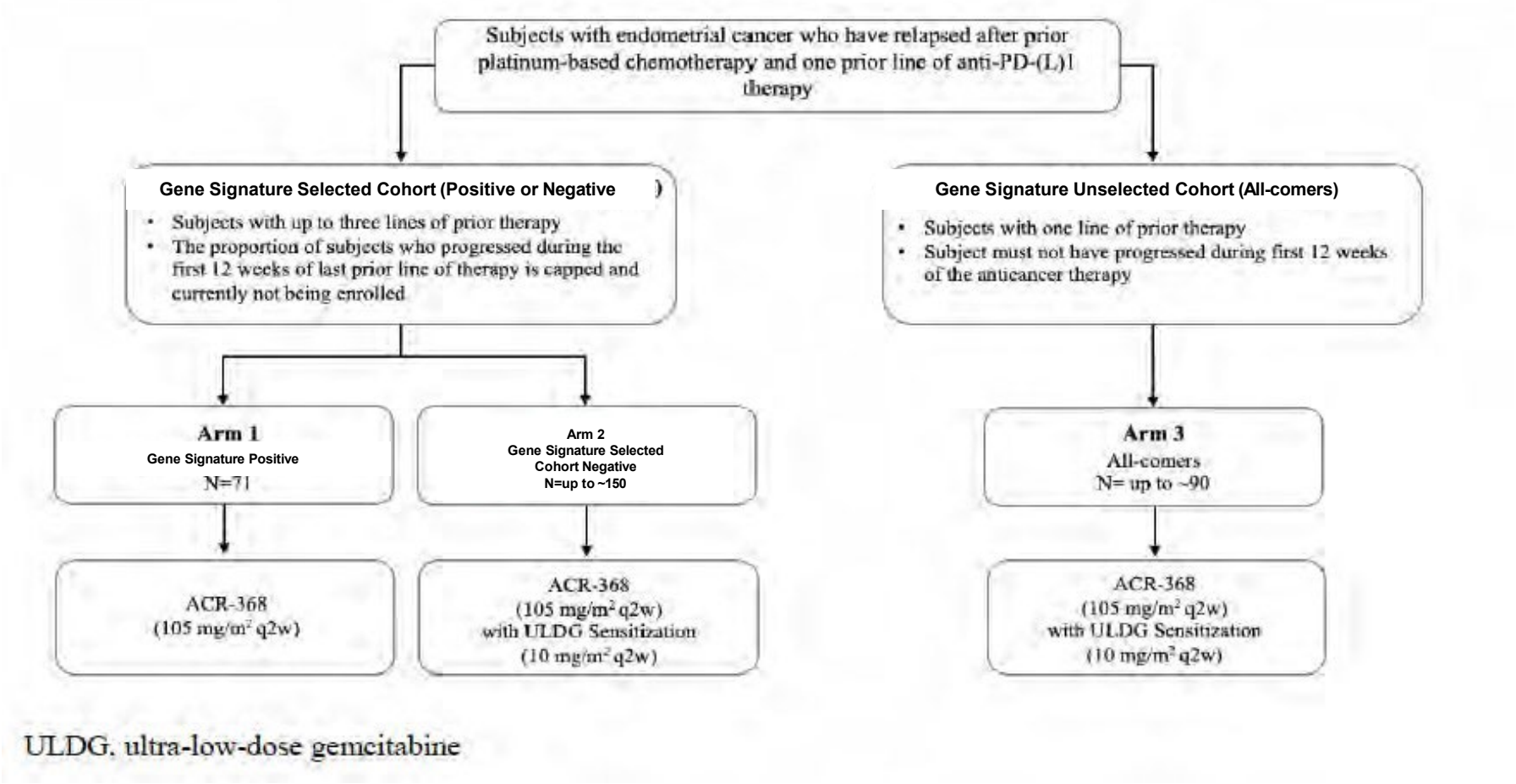
Endpoints (ICR)

ORR
DOR

NCT04814108

GOG-3082 / ACR-368-201

A PHASE 1B/2 BASKET STUDY OF ACR-368 AS MONOTHERAPY AND IN COMBINATION WITH GEMCITABINE IN ADULT SUBJECTS WITH PLATINUM-RESISTANT OVARIAN CARCINOMA, ENDOMETRIAL ADENOCARCINOMA, AND UROTHELIAL CARCINOMA BASED ON ACRIVON GENE SIGNATURE STATUS



ULDG, ultra-low-dose gemcitabine

GOG-3069

A Phase 2 Study of Alpelisib and Fulvestrant for PIK3CA-mutated Estrogen Receptor (ER)-positive Endometrioid Endometrial Cancers

(PI: Stéphanie Gaillard, MD PhD)

BACKGROUND

- The PI3K/PTEN/PIK3CA pathway is altered in 93% of endometrioid endometrial cancer with PIK3CA activating mutations in 53%[1]
- Recent data have shown promising responses in patients with ER positive endometrial cancer treated with endocrine therapy plus mTOR inhibitors or CDK4/6 inhibitors[2-5].
- The combination of alpelisib and fulvestrant was FDA approved for treatment of ER+ PIK3CA-mutated Breast Cancer on May 24, 2019, based on the SOLAR-1 study[6].
- GOG3069 is evaluating the efficacy of alpelisib and fulvestrant for the treatment of ER+ PIK3CA-mutated Endometrioid Endometrial Cancer

METHODS

- Conditional stratified Phase 2 study
- Stratified by prior chemotherapy exposure
- Target accrual 50 patients

Screening/Registration

⬇

TREATMENT
Alpelisib 300mg orally daily
+
Fulvestrant 500mg IM Day 1 and Day 15 of Cycle 1, then Day 1 each 28-day cycle

⬇

Disease evaluations every 8 weeks for the first 3 evaluations then every 12 weeks until PD

Primary Outcome:
ORR
Secondary Outcomes:
safety/toxicity, PFS, OS, DoR

Eligibility

- Advanced, persistent, recurrent endometrial cancer
- Endometrioid histology
- PIK3CAmutated (CLIA-certified testing)
- ER+ (≥ 1% of tumor cells)
- Measurable disease by RECISTv1.1
- Prior endocrine therapy allowed
- No prior mTOR, PIK3CA, PI3K, or AKT inhibitors allowed

NCT05154487

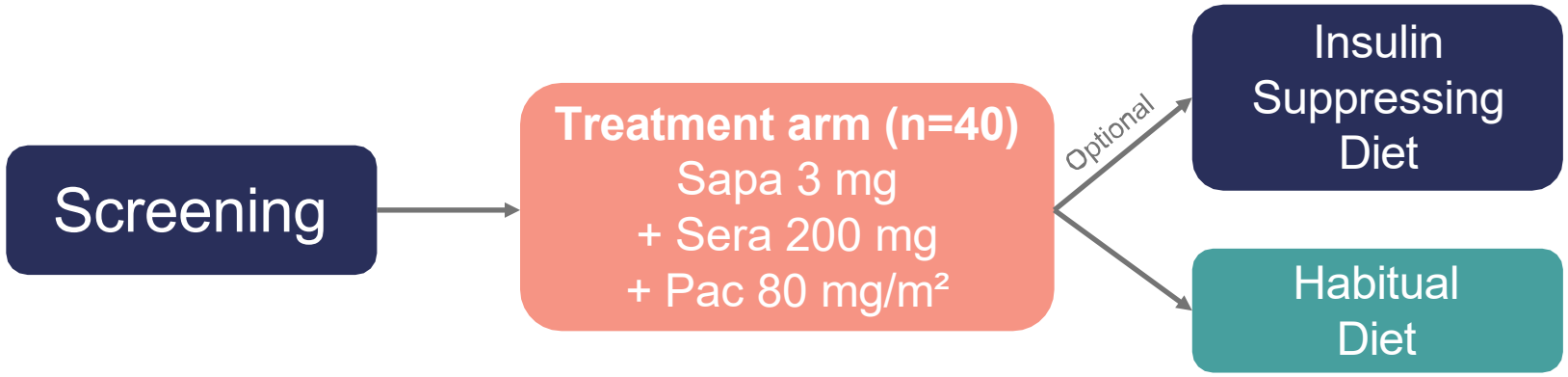
GOG-3111

Sapanisertib and Serabelisib (PIKTOR) With Paclitaxel and a Substudy With Diet in Patients With Advanced/Recurrent Endometrial Cancer

Background
- PIKTOR is a multi-node PI3K-pathway inhibitor targeting mTORC1, mTORC2, and PI3K.
- Investigated in combination with **Paclitaxel** ± a dietary intervention.

Phase 1b Results
- 47% overall response rate (ORR) in all-comers
- In the endometrioid EC subset (n=5): 80% ORR (3 complete responses [CRs], 1 partial response [PR])

Eligibility
- Endometrial-endometrioid cancer
- 2nd line or later
- Post Pembrolizumab
- Must have PI3K pathway mutation



NCT06463028

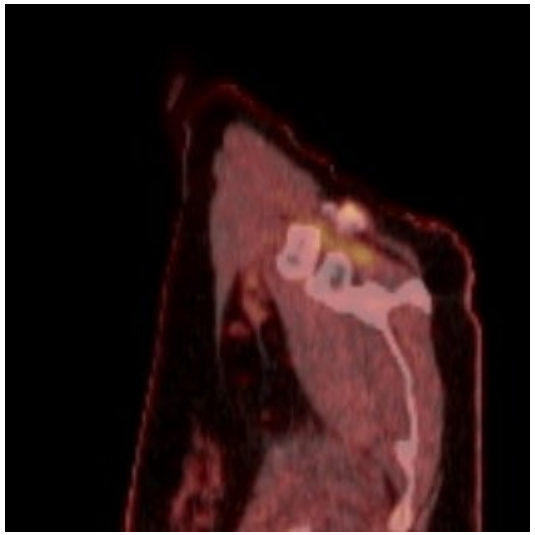
What are the options again?

- Add to single agent IO
  - Anti-VEGF
    - Lenvatinib/pembrolizumab
    - Bevacizumab/pembrolizumab
  - IO/PARPi
    - Olaparib/durvalumab
    - Niraparib/dostarlimab
  - IO/ADC
    - Trop2
    - Her2
- Non-IO, ADC
- Non-IO, Non-ADC

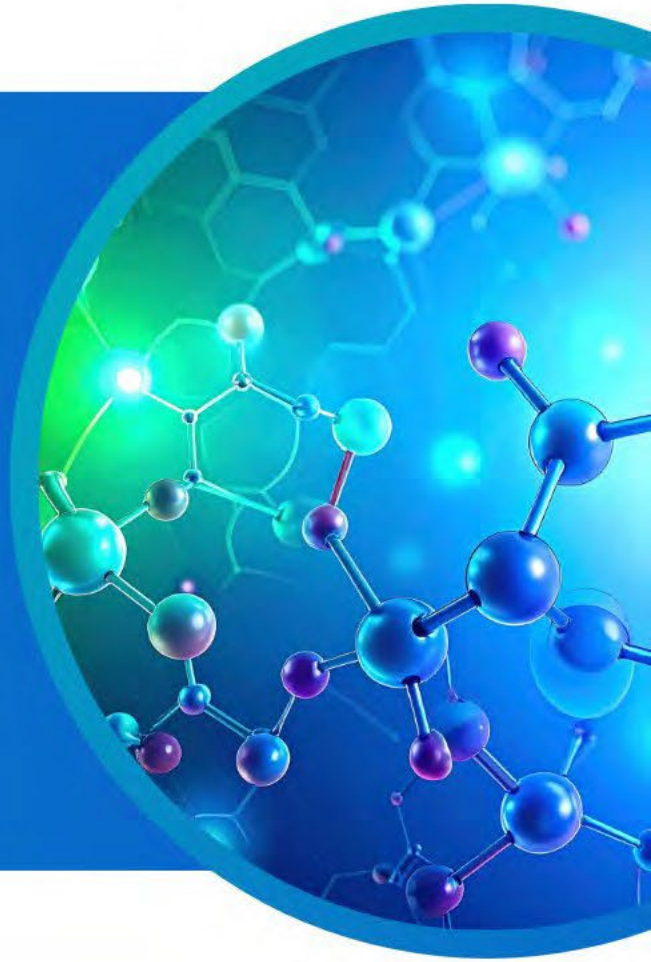
Recurrent, metastatic endometrial cancer continued…

- 7/2025 PET/CT with new axillary nodal and pre-trapezial avid masses
- Perc biopsy trapezius mass confimrd metastatic high-grade endometrial carcinoma.
- NGS testing was same as at diagnosis: p53 mut, PIK3R1, pMMR
- What did we give her???

- Lenvatinib/pembrolizumab
- BLUESTAR or Rina-S trial (if screen fail, await commercial trop2 ADC-sac TMT or saci-govi)
- ACR-368



Panel Discussion



All Faculty

Closing & Key Takeaways

Christian Marth, MD, PhD
Innsbruck Medical University
Innsbruck, Austria

Thank You

View this symposium as part of the IGCS on-demand program following the meeting