What Clinicians Want to Know: Addressing Community Oncologists' Questions About the Current and Future Management of Endometrial Cancer

Sunday, May 31, 2026
7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)

Faculty

Floor J Backes, MD
Brian M Slomovitz, MD

Moderator

Shannon N Westin, MD, MPH, FASCO, FACOG

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Dr Backes — Disclosures
Faculty

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Contracted Research	ImmunoGen Inc, Merck, Natera Inc
Data and Safety Monitoring Boards/Committees	MacroGenics Inc

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Dr Slomovitz — Disclosures
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Consulting Agreements	Aadi Bioscience, AstraZeneca Pharmaceuticals LP, Genmab US Inc, GSK, Karyopharm Therapeutics, Seagen Inc
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Dr Westin — Disclosures
Moderator

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Contracted Research	AstraZeneca Pharmaceuticals LP, Avenge Bio, Bayer HealthCare Pharmaceuticals, Bio-Path Holdings Inc, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Genmab US Inc, GSK, Jazz Pharmaceuticals Inc, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Mereo BioPharma, Novartis, Nuvectis Pharma Inc, Pfizer Inc, pharmaand GmbH, Verastem Inc, Zentalis Pharmaceuticals

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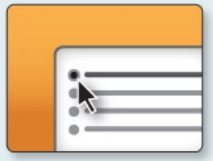
Clinicians in the Meeting Room

Networked iPads are available.

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



Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

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

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

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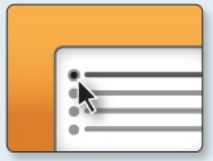
Clinicians Attending via Zoom

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



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

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

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

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About the Enduring Program

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

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Friday May 29	**Gastroesophageal Cancers** 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	**Ovarian Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	**Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	**ADCs for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	**Myelofibrosis (Webinar)**

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What Clinicians Want to Know: Addressing Community Oncologists' Questions About the Current and Future Management of Endometrial Cancer

Survey of US-Based General Medical Oncologists and Gynecologic Oncologists
May 13-26, 2026

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Agenda

Module 1: Current Up-Front Chemoimmunotherapeutic Approaches for Advanced Endometrial Cancer (EC) — Dr Backes

Module 2: Current and Future Role of Anti-PD-1/PD-L1 Antibodies in Combination with Systemic Therapies Beyond Chemotherapy for Advanced EC — Dr Westin

Module 3: Promising Agents Under Investigation for EC — Dr Slomovitz

Agenda

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Module 3: Promising Agents Under Investigation for EC — Dr Slomovitz

Biology of Advanced Endometrial Cancer

Current Up-Front Chemoimmunotherapeutic Approaches for Advanced Endometrial Cancer (EC)

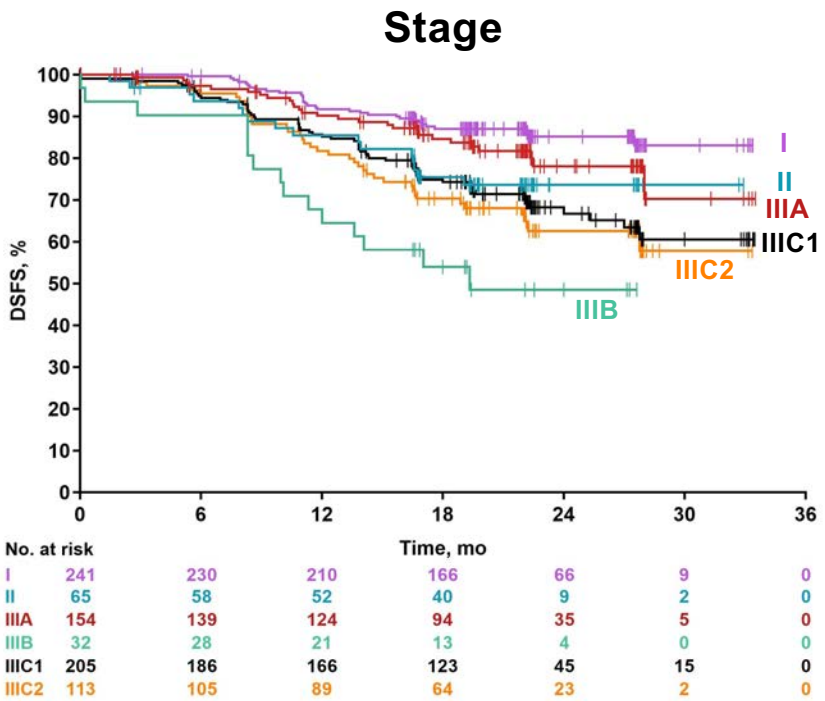
Floor Backes, MD
Professor
Division of Gynecologic Oncology
The Ohio State University
Columbus, OH, USA

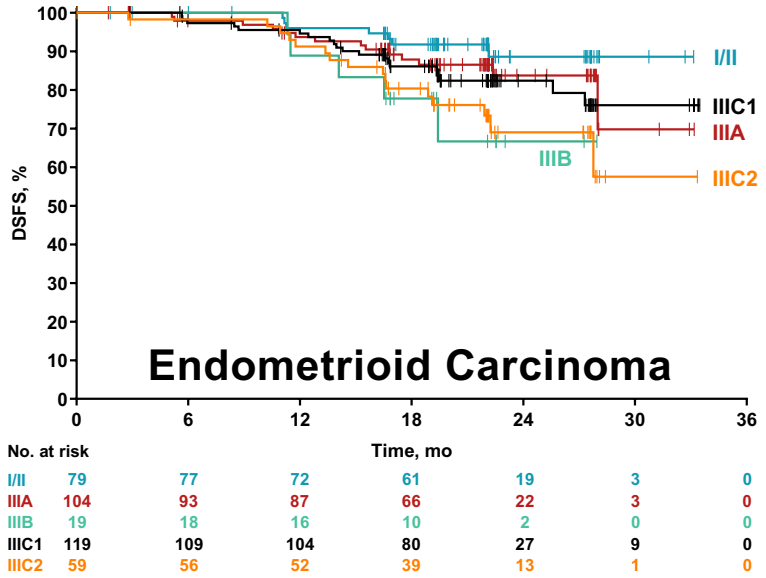
The James
THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

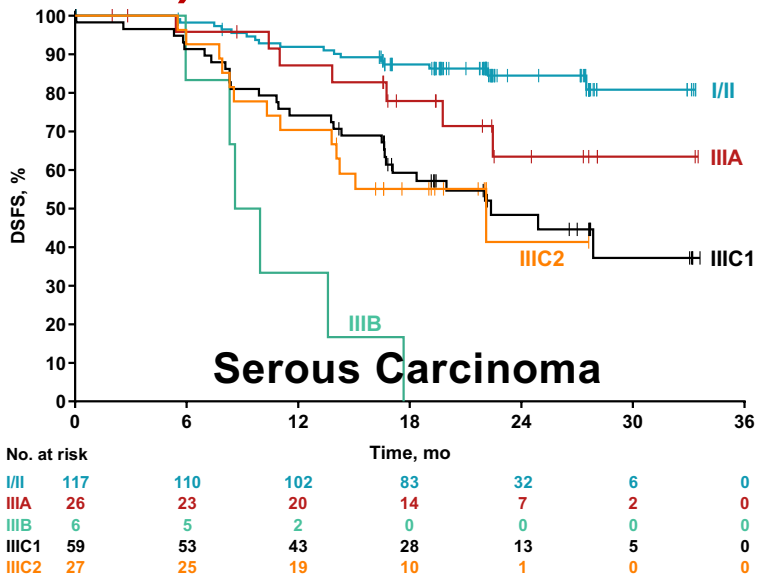
Objectives

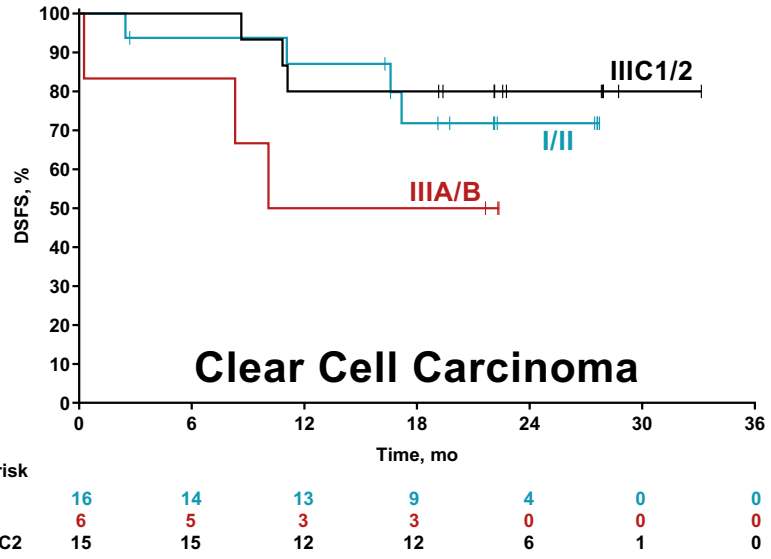
- Discuss endometrial cancer molecular subtypes
- Review implications for prognosis and therapeutic decision-making
- First-line treatment for advanced or recurrent endometrial cancer
  - Potential biomarkers of response to immune checkpoint inhibition
- Ongoing first-line studies in dMMR endometrial cancer

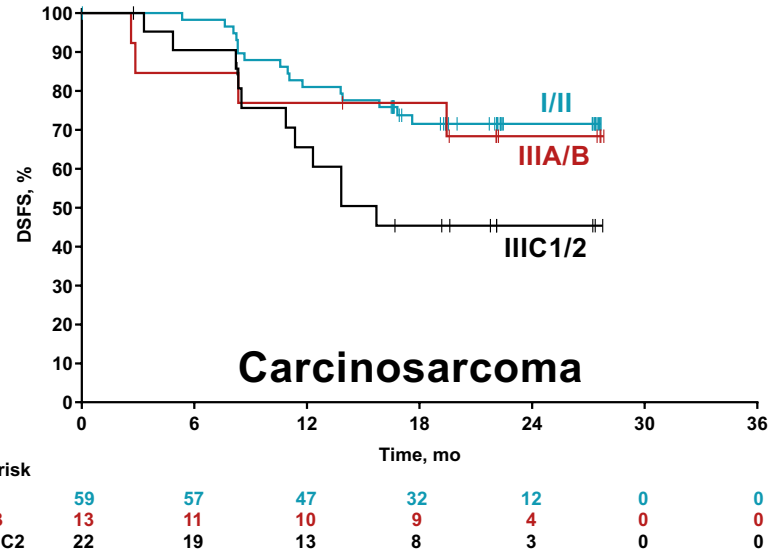
Prognosis by Stage (FIGO 2009) and Histology in pMMR EC (Keynote-B21 Treatment Arms Combined)





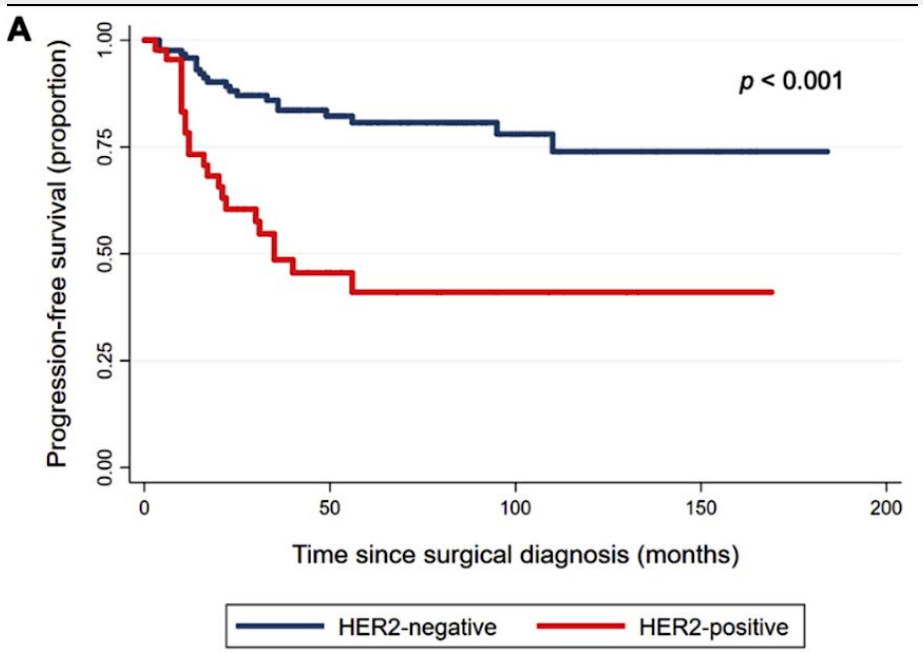






Halaskala, ESGO 2024

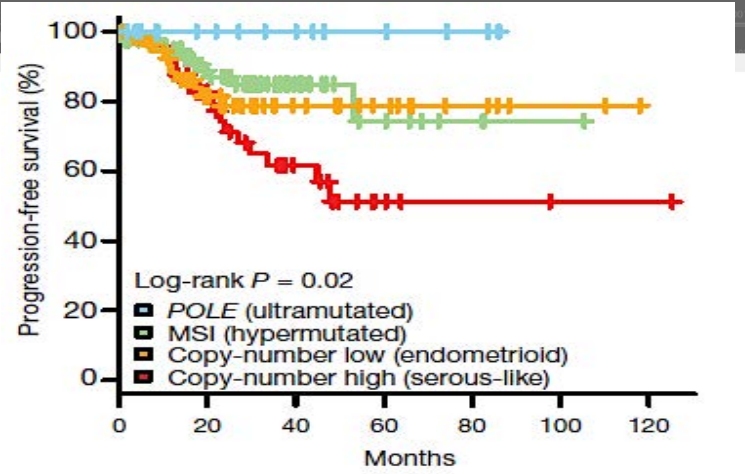
Uterine Serous Carcinoma

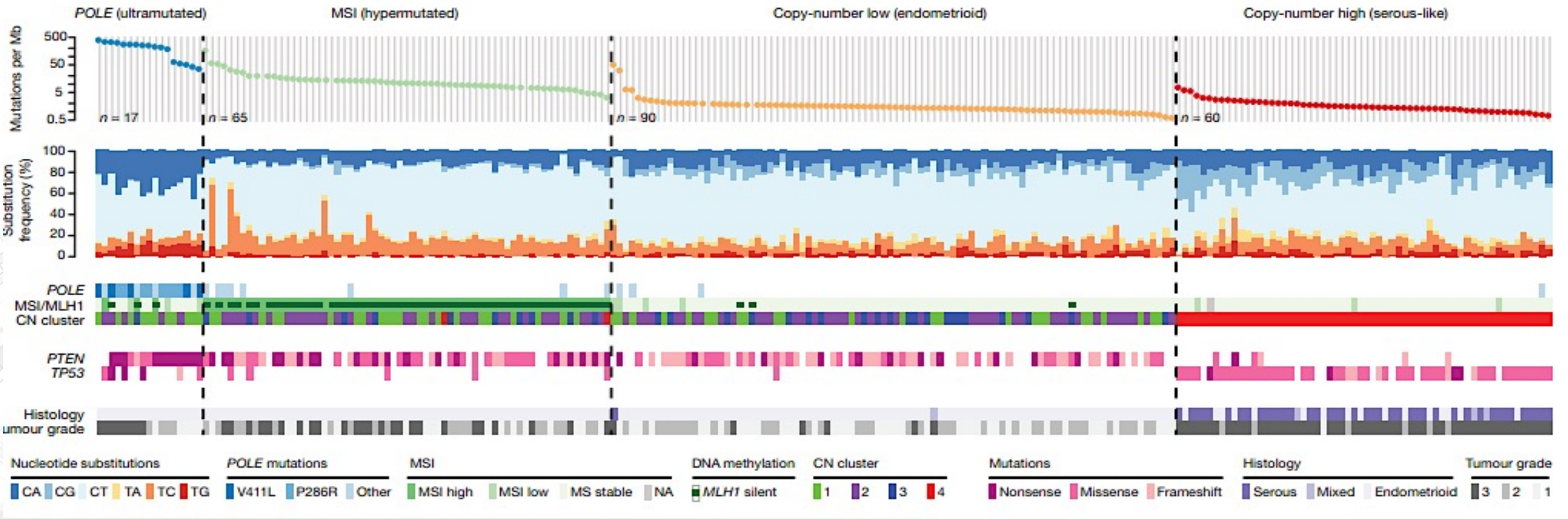


- 10% of all endometrial cancers, but 40% of deaths
- 75% have TP53 alteration
- HER2 overexpression and/or amplification ERBB2
  - 18-42%
- Stage I uterine serous uterine cancer:
  - 26% were HER2 positive (by IHC and/or FISH).
  - Recurrence for HER2 positive 50.0% vs 16.8%, p<0.001 (despite 70% of patients receiving chemotherapy)
- HER2 associated with worse PFS and OS
- Trastuzumab and Pertuzumab are humanized monoclonal antibodies against HER2
- Trastuzumab-Deruxtecan and Trastuzumab-Pamirtecan are HER2 targeting ADCs

Erickson, Gynecol Oncol 2020; Curr Opin Obstet Gynecol 2020

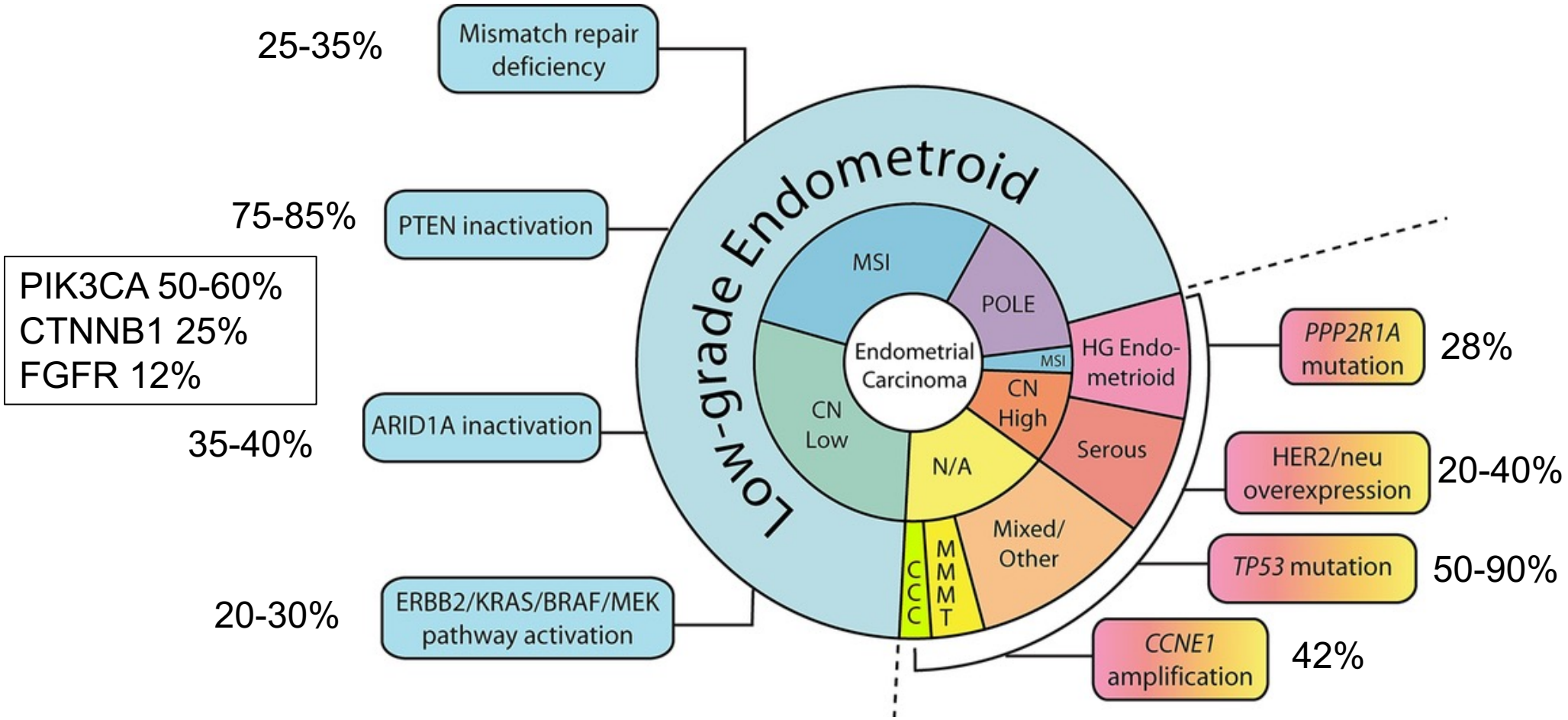
Molecular Profiling





Cancer Genome Atlas Research Network., Kandoth C, Nature 2013

Changing Molecular Landscape



Other Factors
p53
PD-L1
HER2 IHC/FISH
TROP2 (>90%)
FRα (64%)
B7H4 (80%)
HRD/HRR (22%)

Yen TT, et al. *Int J Gynecol Pathol*. 2020;39(1):26-35.

The James

The Ohio State University
Comprehensive Cancer Center

Molecular subgroups and treatment decision making

PORTEC-3: TCGA Subgroups

TCGA group	n	Treatment	5-yr RFS	HR (95% CI)	5-year OS	HR (95% CI)
p53abn	93 (23%)	EBRT versus CisRT + chemo	36.2% 58.6%	1 0.52 (0.30-0.91)	41.8% 64.9%	1 0.55 (0.30-1.00)
POLEmut	51 (12%)	EBRT versus CisRT + chemo	96.6% 100%	1 0.02 (<0.01->10^5)	96.6% 100%	1 0.02 (<0.01->10^5)
MMRd	137 (33%)	EBRT versus CisRT + chemo	75.5% 68%	1 1.29 (0.68-2.45)	84% 78.6%	1 1.33 (0.64-2.75)
NSMP	129 (32%)	EBRT versus CisRT + chemo	67.7% 79.7%	1 0.68 (0.36-1.3)	87.6% 89.3%	1 0.68 (0.26-1.77)

- TCGA = The Cancer Genome Atlas; NSMP = no specific molecular profile; EBRT = external beam radiation; CisRT = cisplatin/radiotherapy.
- Leon-Castillo, 2020.

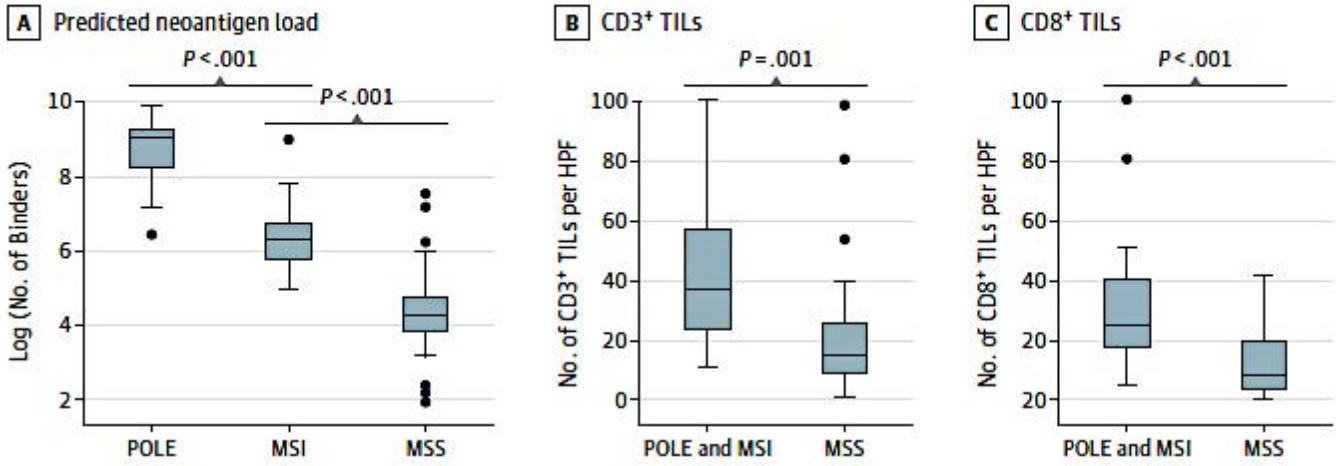
Hyper-mutated/Microsatellite Instable Group: Responses to IO in the 2nd Line Setting as compared to MSS/MMRp

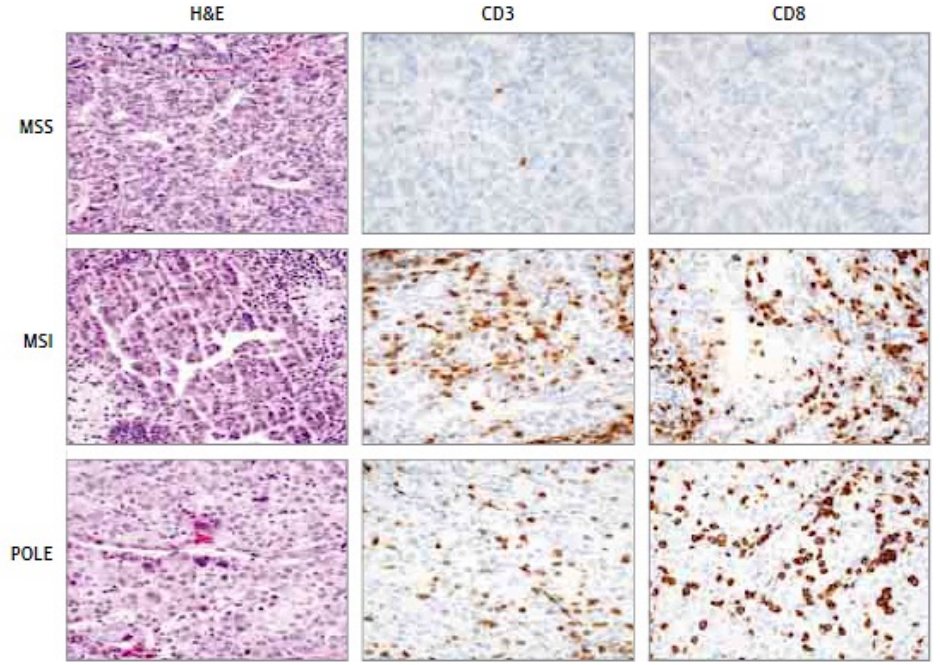
	Keynote-158[1]	GARNET[2]	KEYNOTE-028[3]	NCT01375842[3]	GARNET[2]
Phase / type	2	2	1b	1a	2
Population	Previously treated MSI-H	Previously treated MSI-H/dMMR	Previously treated PD-L1+ MSS/pMMR	Recurrent EC MSS/pMMR	Recurrent MSS/pMMR
Patients, n	90	108	24	15	156
Treatment	Pembrolizumab	Dostarlimab	Pembrolizumab	Atezolizumab	Dostarlimab
Prior lines	0 - >5	1-3			1-3
ORR, %	48%*	43.5%	13%	13	14.1%
DCR, %	66%	56%	26%	27%	35%
DOR	NR (3-50+)	NR	—	—	NR
mPFS	13.1 mo	Immature	1.8 mo	1.7 mo	
mOS	12-mo OS= 69%	NR	NR	9.6 mo	
Safety summary (TRAE grade ≥3)	12%	13%	16.7%	Any TRAE: 47%	19%

1. O'Malley D et al. JCO 2022 ; *in efficacy population n=79 (patients who received 1 or more doses of pembro and were enrolled >26 weeks before data cut off. 2.. Oaknin A et al. J Immunother 2022; 3. Ott PA et al. *J Clin Oncol*. 2017;35(22):2535-2341; 4. Fleming GF et al. 2017 ASCO Annual Meeting. Abstract 5585;

Tumor Microenvironment in Endometrial Cancer

Figure 1. Neoantigen load and CD3⁺ and CD8⁺ Tumor-Infiltrating Lymphocytes (TILs) in Polymerase e (POLE), Microsatellite-Instable (MSI), and Microsatellite-Stable (MSS) Tumors



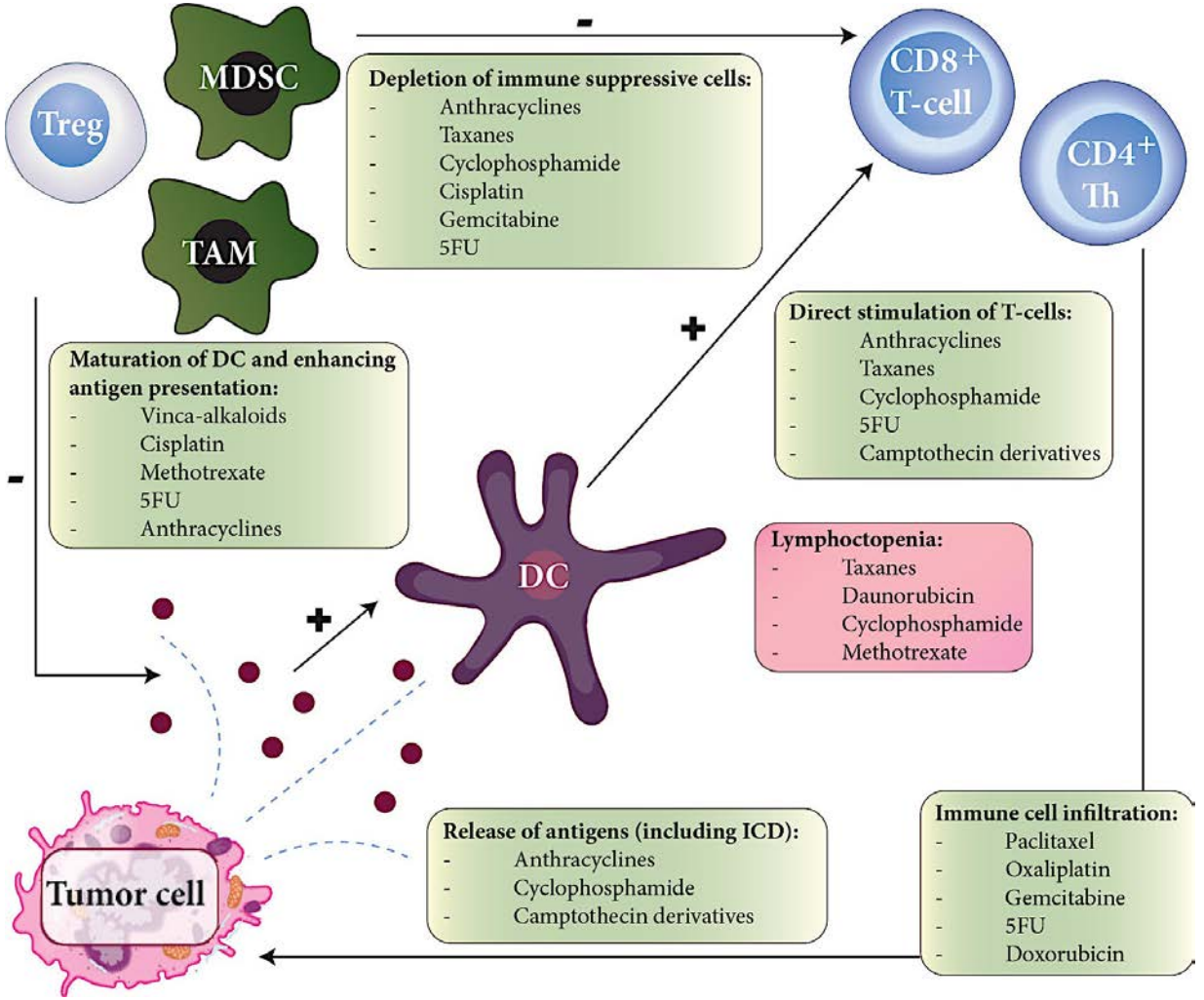


- CD = cluster of differentiation; PD-1 = programmed cell death protein 1; TILs = tumor-infiltrating lymphocytes; MSS = microsatellite stable.
- Howitt et al, 2015.

- Both POLE and MSI are associated with significantly increased predicted neoepitopes and numbers of CD3-positive and CD8-positive TILs compared with MSS tumors
- In addition, hypermutated tumors harbor higher neoantigen loads and are associated with increased tumor infiltration by cytotoxic T lymphocytes
- POLE and MSI tumors are excellent candidates for immunotherapies targeting the PD-1 pathway

Rationale for Combining Chemo and IO

- ↓ Myeloid-derived suppressor cells
- ↑ Antigen cross-presentation after immunogenic cell death
- ↑ Dendritic cell activity through STAT6 pathway inhibition
- ↑ Ratio of cytotoxic lymphocytes to regulatory T cells.
- ↑ Antigenic diversity in tumors by causing DNA damage and releasing tumor-associated antigens



Heinhuis, Ann Oncol 2019

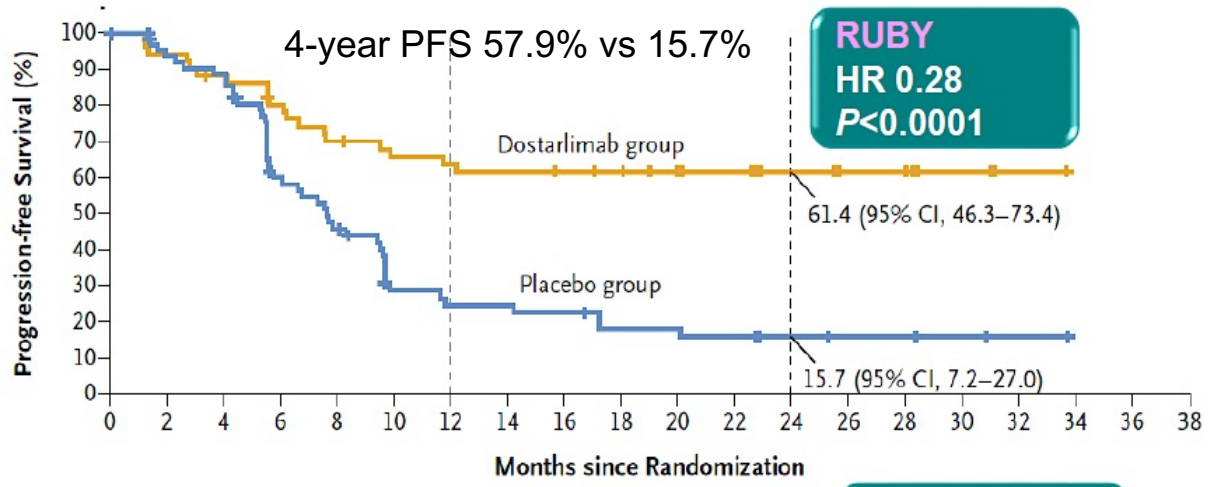
Summary of Study Designs across Key Chemo/IO Trials

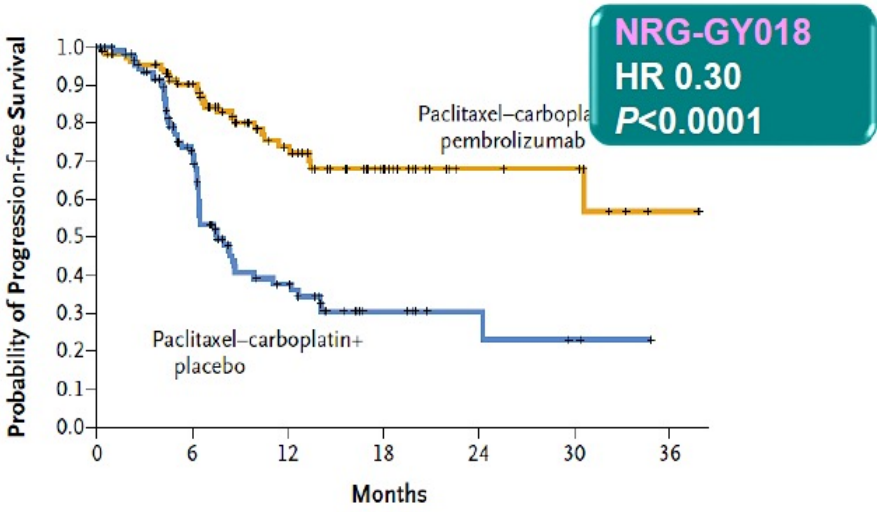
	GY018/KN-868 Pembrolizumab	RUBY-I Dostarlimab	RUBY-II Dostarlimab + Niraparib	DUO-E Durvalumab ± Olaparib	AtTEnd Atezolizumab

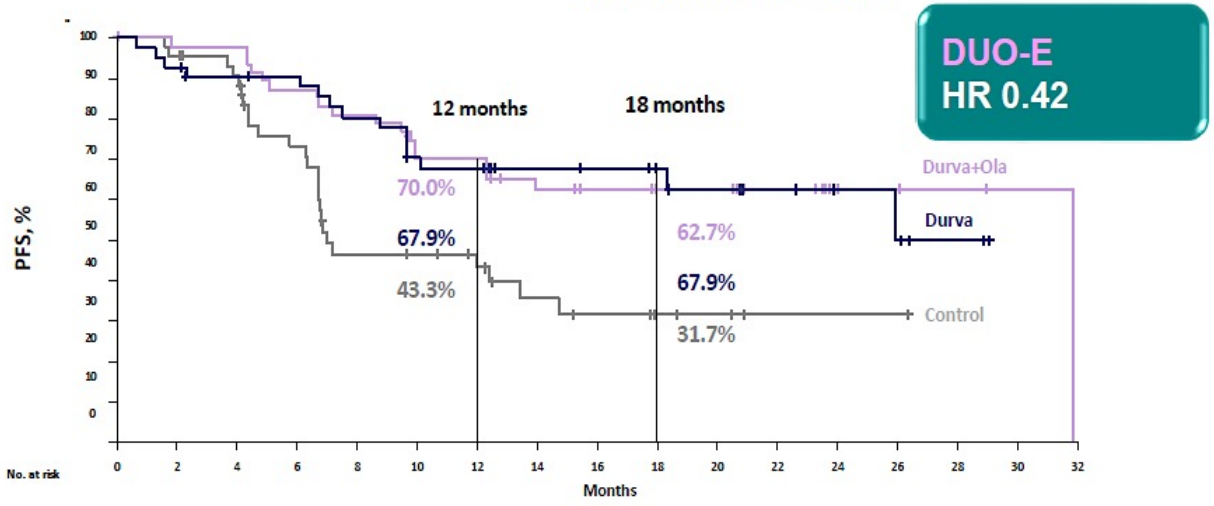
Patient Population	• Stage III/IVA, measurable, or (non)measurable stage IVB or recurrent EC
	• No prior chemo except if completed ≥12 mo before study
		• Stage III, IV or recurrent
		  • Stage IIIA–IIIC1: Evaluable or measurable disease
		  • Stage IIIC2–IV: Measurable or nonmeasurable
		• Adj/neoadj chemo allowed if recurrence ≥6 mo
				• Measurable stage III or (non)measurable stage IV or recurrent endometrial cancer
				• No prior systemic therapy except if adjuvant chemo completed ≥ 12 mo
					• Newly diagnosed advanced stage (III/IV) endometrial cancer measurable or evaluable
					• Adj/neoadj chemo allowed if recurrence ≥6 mo

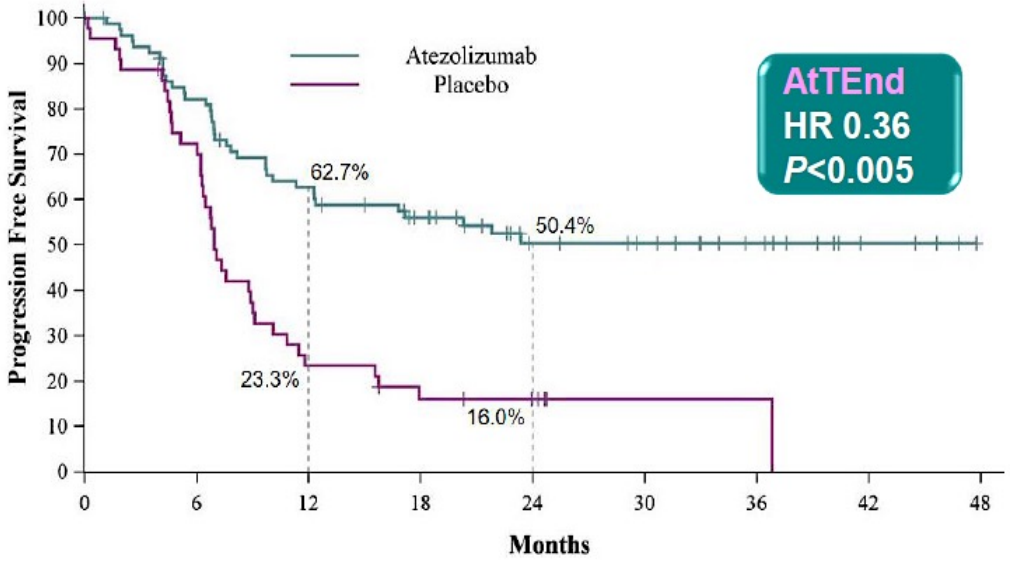
Study Design	Pembro + CP → Pembro vs CP	CP + Dost → Dost vs CP	CP + Dost → Dost + Nira vs CP	Durva+ CP → Durva ± Ola vs CP	CP + Atezo → Atezo vs CP
N	**810**	**494**	**291**	**718**	**539**
Duration of Maintenance	**Up to 2 years**	**Up to 3 years**	**Up to 3 years**	**Until progression**	**Until progression**
Primary Endpoints	PFS (inv. and RECIST)	PFS (inv.) OS	PFS (inv.) OS	PFS (OS analytical secondary end point)	PFS OS
Statistical Design	Separate dMMR & pMMR	dMMR followed by ITT	dMMR followed by ITT	ITT	dMMR followed by ITT
Key Study Locations	US, Canada, Japan, South Korea	US, EU, UK	US, EU, UK	US, EU, Asia, Japan	Australia, EU, UK, Japan

Recurrent dMMR Endometrial Cancer: Carboplatin/paclitaxel + Immunotherapy





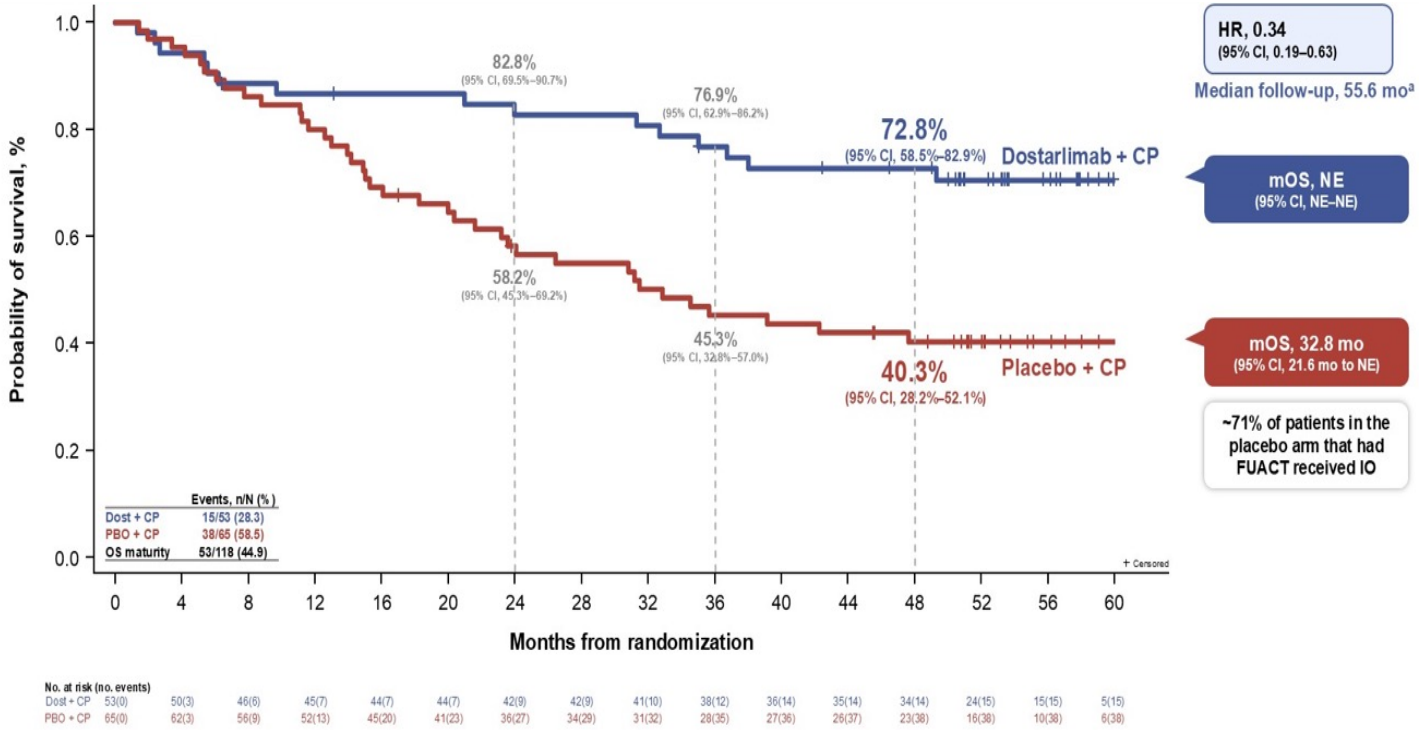




Mansoor R. Mirza et al. NEJM August 2023, Ramez N. Eskander et al. NEJM August 2023, Westin SN, et al. J Clin Oncol 2024, Nicoletta Colombo et al., Lancet Oncol 2024

Sustained Overall Survival Benefit at 4 years in dMMR

RUBY



HR, 0.34
(95% CI, 0.19–0.63)

Median follow-up, 55.6 mo[a]

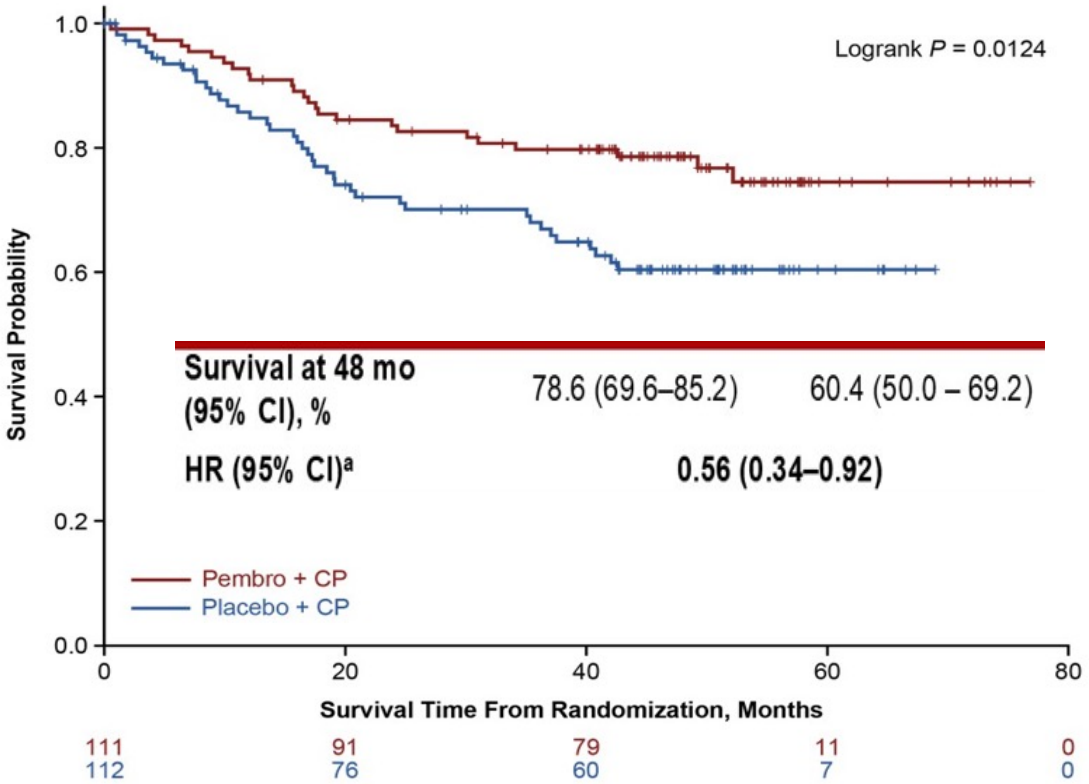
mOS, NE
(95% CI, NE–NE)

mOS, 32.8 mo
(95% CI, 21.6 mo to NE)

~71% of patients in the placebo arm that had FUACT received IO

55% crossover
Median follow up 5 months

GY018



55% crossover
Median follow up 49 months
Information fraction 43%

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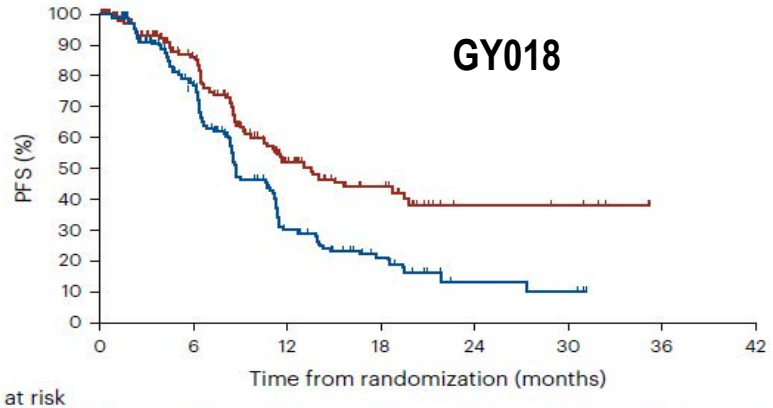
Powell, ASCO 2026; Eskander, ASCO 2026

Chemo/IO in pMMR: PFS

a

	Events, n/N	Median PFS (95% CI), months	HR (95% CI)[a], P value[b]
Pembrolizumab + CT	95/294	13.1 (10.6–19.5)	0.57 (0.44–0.74)
Placebo + CT	138/294	8.7 (8.4–11.0)	P < 0.0001

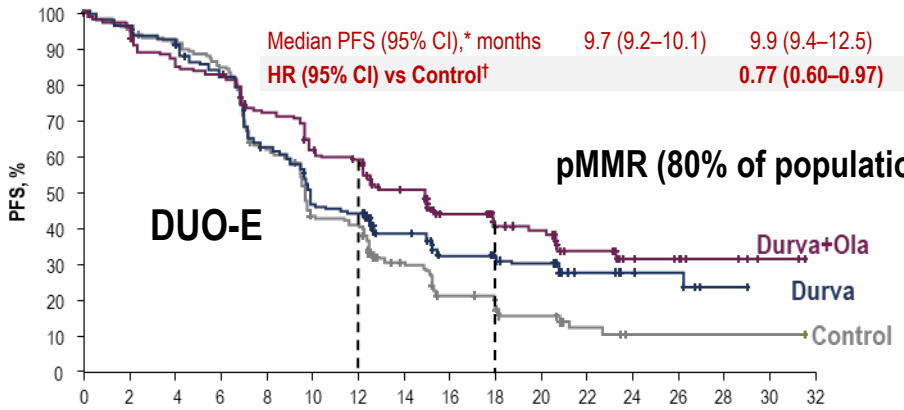
GY018



Number at risk								
Pembrolizumab + CT	294	162	57	29	7	6	0	0
Placebo + CT	294	144	36	15	4	3	0	0

DUO-E

pMMR (80% of population)

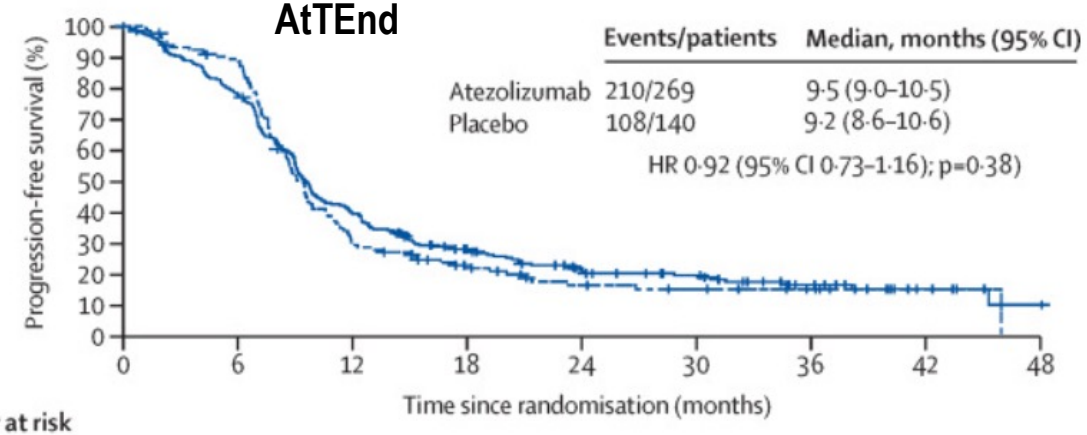


	Durva+Ola	Durva	Control
Median PFS (95% CI),* months	9.7 (9.2–10.1)	9.9 (9.4–12.5)	15.0 (12.4–18.0)
HR (95% CI) vs Control†		0.77 (0.60–0.97)	0.57 (0.44–0.73)

No. at risk																	
Durva+Ola	192	178	170	156	113	77	73	40	25	21	13	7	1	1	1	1	0
Durva	192	182	169	152	113	83	79	53	36	31	27	15	8	7	2	0	0
Control	191	183	164	157	134	114	107	75	46	35	31	19	12	10	5	2	0

C

AtTEnd



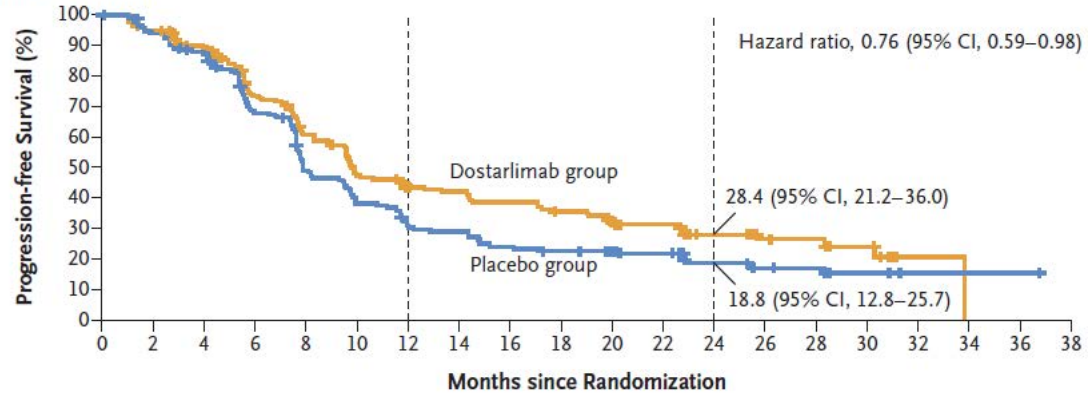
	Events/patients	Median, months (95% CI)
Atezolizumab	210/269	9·5 (9·0–10·5)
Placebo	108/140	9·2 (8·6–10·6)

HR 0·92 (95% CI 0·73–1·16); p=0·38)

Number at risk (number censored)									
Atezolizumab	269 (0)	205 (7)	103 (8)	62 (20)	40 (28)	31 (34)	16 (45)	5 (55)	2 (57)
Placebo	140 (0)	117 (9)	39 (10)	24 (16)	14 (20)	11 (22)	7 (26)	3 (30)	0 (32)

RUBY

C pMMR–MSS Population

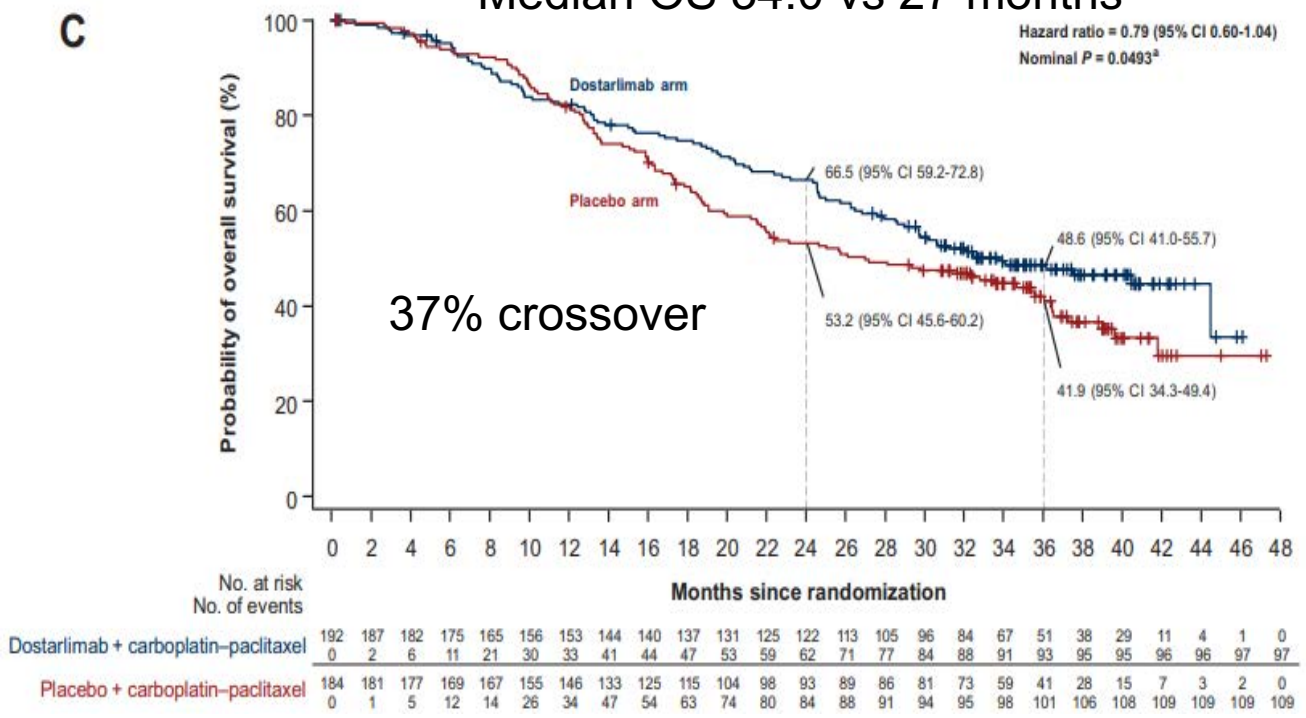


No. at Risk																			
Dostarlimab group	192	172	153	118	96	74	64	61	56	51	41	33	21	14	13	8	1	0	
Placebo group	184	162	146	110	77	60	47	45	37	34	31	25	16	11	10	3	1	1	1	0
No. of Events																			
Dostarlimab group	0	9	19	45	65	86	92	94	99	103	108	109	112	113	113	114	115	116	
Placebo group	0	10	22	53	83	100	112	114	122	124	124	125	128	129	129	130	130	130	130	130

Overall Survival in Recurrent pMMR Endometrial Cancer

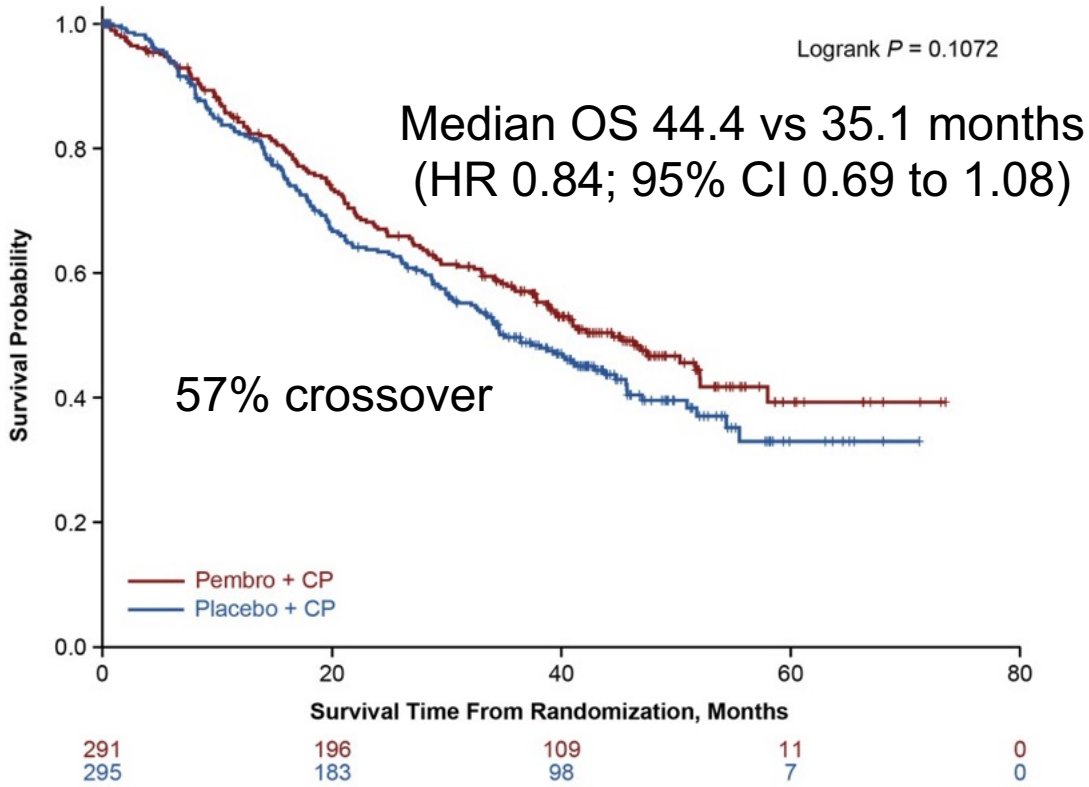
RUBY

Median OS 34.0 vs 27 months



55% information fraction

GY018



82% information fraction

- Powell, Ann Oncol 2024; Eskander ASCO 2026

Chemotherapy +/- IO: PFS

Study	Chemotherapy + Drug	Hazard ratio dMMR (vs chemo alone)	Hazard ratio pMMR (vs chemo alone)
GY018	Pembrolizumab	0.30	0.57
RUBY	Dostarlimab	0.28	0.76
AtTEnd	Atezolizumab	0.36	0.92
MITO END-3	Avelumab	0.46	1.17
DUO-E	Durvalumab +olaparib	0.42 0.41	0.77 0.57
RUBY Part 2	Dostarlimab +Niraparib	0.48	0.63

Different responses across trials?

- Different populations?
- 20% Asian in AtTEnd, 28% in DUO-E, 5.3% in GY018, none in RUBY
- Subgroup analysis with *negative predictive* effect of Asian race for IO except for MMRd/MSI-H
- Lower clinical efficacy of drugs across populations?
- Does gut microbiome play a role?
- PD-1 vs PD-L1 inhibitors?
- What was the molecular breakdown?

DUO-E

		Durvalumab Arm n/N (%)	Control Arm n/N (%)	HR (95% CI)
All Patients		139/238 (58.4)	173/241 (71.8)	0.68 (0.55 to 0.86)
Disease status[a]	Newly diagnosed	67/113 (59.3)	81/115 (70.4)	0.59 (0.42 to 0.82)
	Recurrent disease	72/125 (57.6)	92/126 (73.0)	0.79 (0.58 to 1.07)
MMR status[a]	Proficient tumors	124/192 (64.6)	148/192 (77.1)	0.77 (0.60 to 0.97)
	Deficient tumors	15/46 (32.6)	25/49 (51.0)	0.42 (0.22 to 0.80)
Region[a]	Asia	44/68 (64.7)	45/68 (66.2)	0.98 (0.65 to 1.49)
	Non-Asia	95/170 (55.9)	128/173 (74.0)	0.59 (0.45 to 0.78)
Age group, years	<65	66/122 (54.1)	90/124 (72.6)	0.63 (0.46 to 0.87)
	≥65	73/116 (62.9)	83/117 (70.9)	0.73 (0.53 to 1.00)
Race	White	72/136 (52.9)	102/143 (71.3)	0.59 (0.43 to 0.79)
	Black or African American[b]	11/11 (100.0)	8/10 (80.0)	NC (NC to NC)
	Asian	47/72 (65.3)	50/73 (68.5)	0.96 (0.65 to 1.44)
	Other[c]	9/19 (47.4)	13/15 (86.7)	0.38 (0.15 to 0.88)
HRRm status	HRRm	12/26 (46.2)	23/32 (71.9)	0.57 (0.27 to 1.13)
	Non-HRRm	85/138 (61.6)	96/132 (72.7)	0.72 (0.54 to 0.97)
	Unknown	42/74 (56.8)	54/77 (70.1)	0.65 (0.43 to 0.97)
PD-L1 expression	Positive	97/170 (57.1)	114/163 (69.9)	0.63 (0.48 to 0.83)
	Negative	38/61 (62.3)	57/75 (76.0)	0.89 (0.59 to 1.34)
	Unknown	4/7 (57.1)	2/3 (66.7)	NC (NC to NC)
Histology[d]	Endometrioid	71/141 (50.4)	92/139 (66.2)	0.65 (0.47 to 0.88)
	Serous	41/58 (70.7)	43/54 (79.6)	0.71 (0.46 to 1.11)
	Other	27/39 (69.2)	38/48 (79.2)	0.76 (0.46 to 1.25)

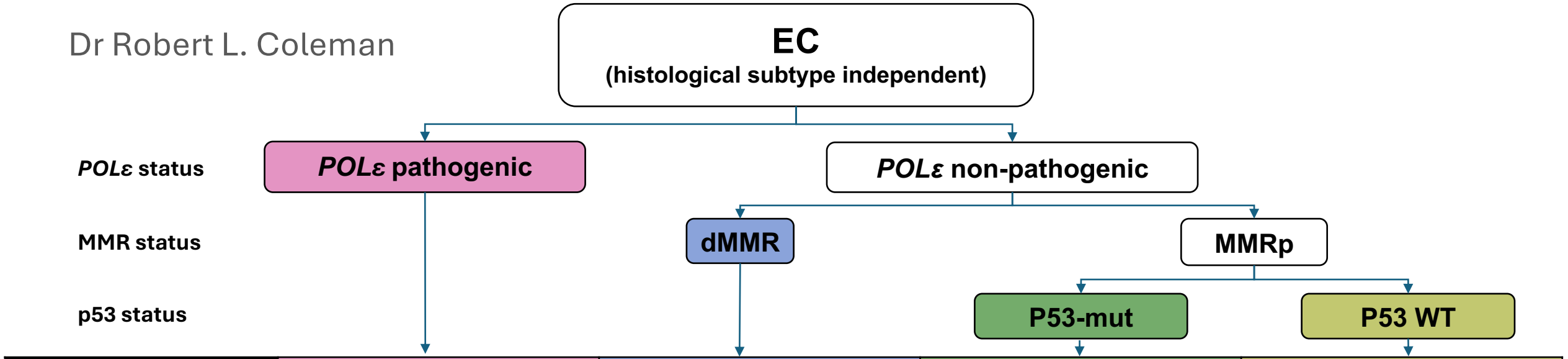
AtTEnd

Race				0·028
Non-Asian	209/291 (72%)	125/146 (86%)	0·65 (0·52–0·81)	
Asian	44/69 (64%)	23/43 (53%)	1·17 (0·71–1·94)	
Status of disease*				0·33
Newly diagnosed, stage III	13/21 (62%)	5/10 (50%)	1·37 (0·49–3·87)	
Newly diagnosed, stage IV	72/96 (75%)	39/52 (75%)	0·88 (0·60–1·31)	
Recurrent	168/243 (69%)	103/126 (82%)	0·68 (0·53–0·87)	
Histological type				0·74
Carcinosarcoma	30/35 (86%)	12/15 (80%)	0·88 (0·45–1·73)	
Endometrioid	150/227 (66%)	99/125 (79%)	0·68 (0·53–0·88)	
Papillary serous	47/59 (80%)	23/29 (79%)	0·87 (0·52–1·45)	
Other	26/39 (67%)	14/20 (70%)	0·86 (0·45–1·66)	
Previous chemotherapy				0·66
No	172/253 (68%)	100/129 (78%)	0·77 (0·60–0·99)	
Yes	81/107 (76%)	48/60 (80%)	0·68 (0·47–0·97)	
Mismatch repair status				0·0001
dMMR	37/81 (46%)	37/44 (84%)	0·36 (0·23–0·57)	
pMMR	210/269 (78%)	108/140 (77%)	0·92 (0·73–1·16)	
Not evaluable	6/10 (60%)	3/5 (60%)	1·13 (0·28–4·54)	

RUBY MOLECULAR CLASSIFICATION ALGORITHM

In RUBY Part 1, molecular classification was performed for all participants with WES results – 400 of 494 patients

Dr Robert L. Coleman

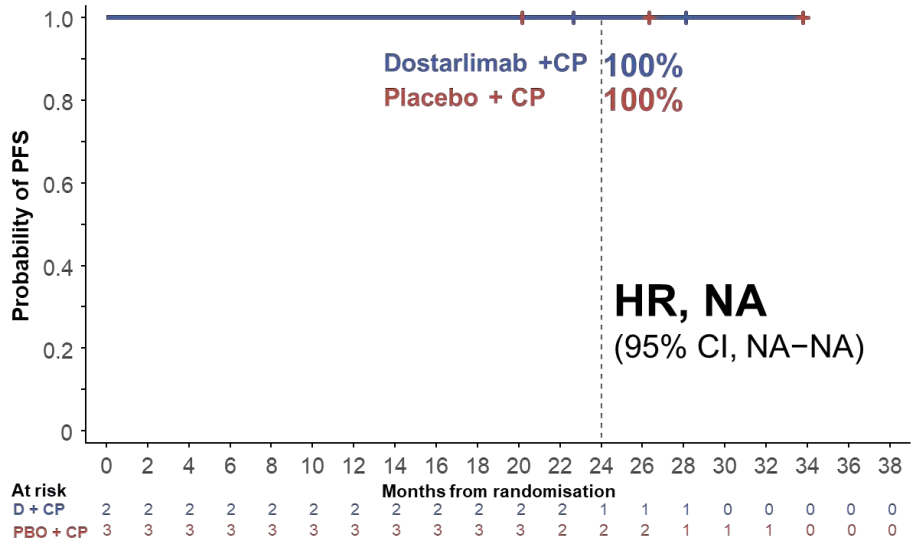


Integrated diagnosis	*POLε*mut (EDM)	dMMR (or MSI-H)	TP53 aberrant[a]	NSMP
Prevalence in RUBY, % (n/N)	**1.25%** (5/400)	**22.75%** (91/400)	**22%** (88/400)	**54%** (216/400)
Diagnostic test	WES	Results of local (IHC, NGS, PCR) or central test (IHC) provided for RUBY at randomization	WES	—

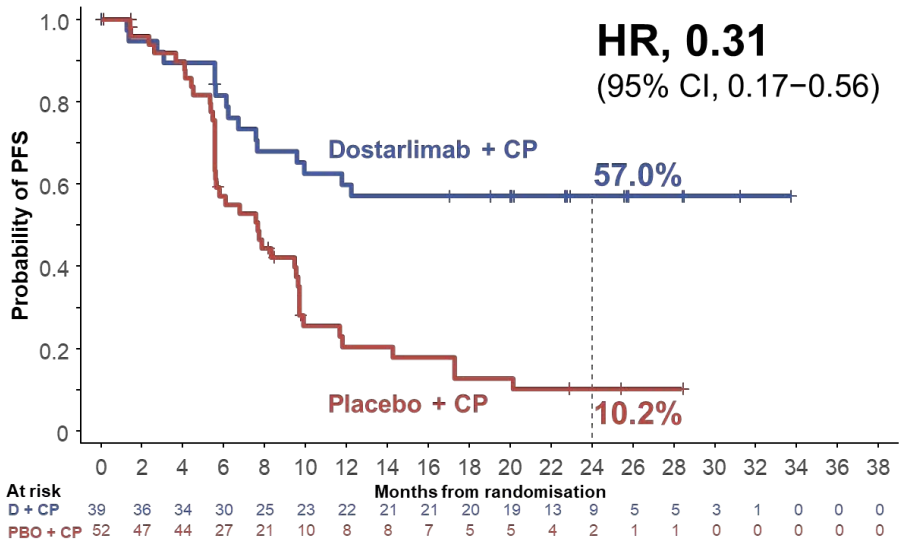
R. Coleman, ESMO GYN 2024. Mirza, ESMO 2023

RUBY: PFS According to Molecular Subgroup

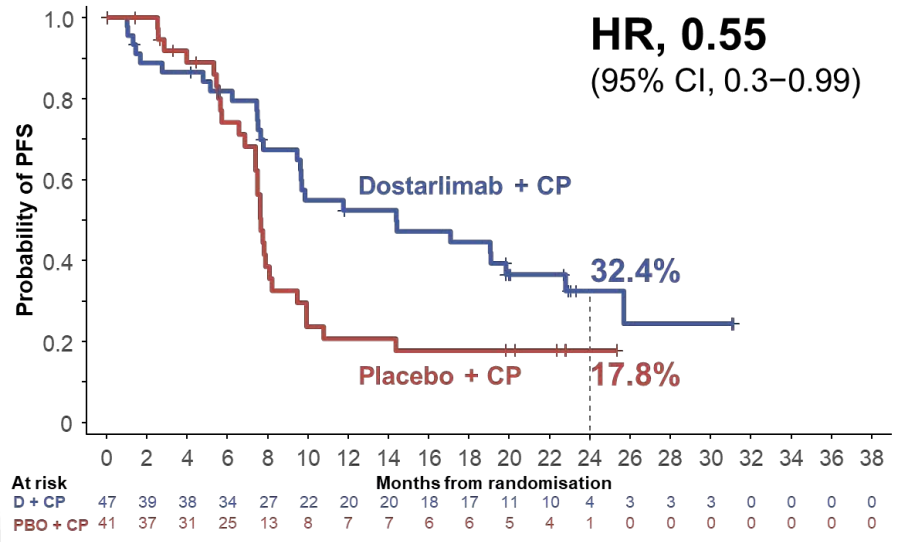
POLε mut



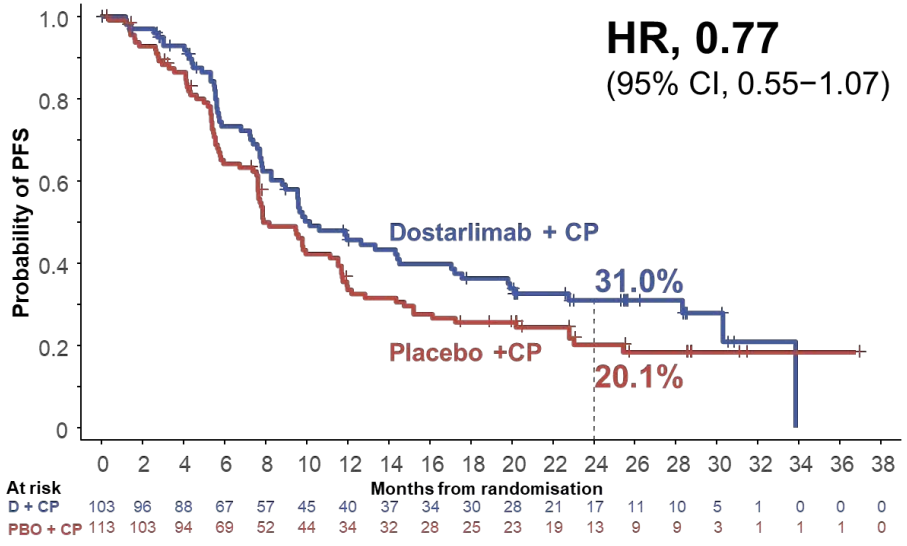
dMMR/MSI-H



TP53 mut



NSMP



mes

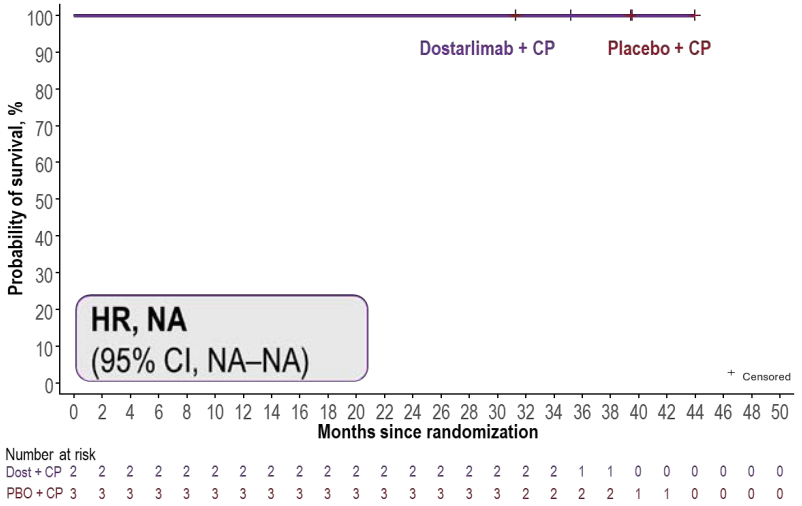
- Dr Mansoor Raza Mirza, ESMO 2023

Data based on exploratory analysis based on 400 patients from the RUBY trial with known molecular classification with whole exome sequencing. CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability–high; mut, mutated; NR, not reached; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; POLε , polymerase epsilon; TP53, tumor protein 53.

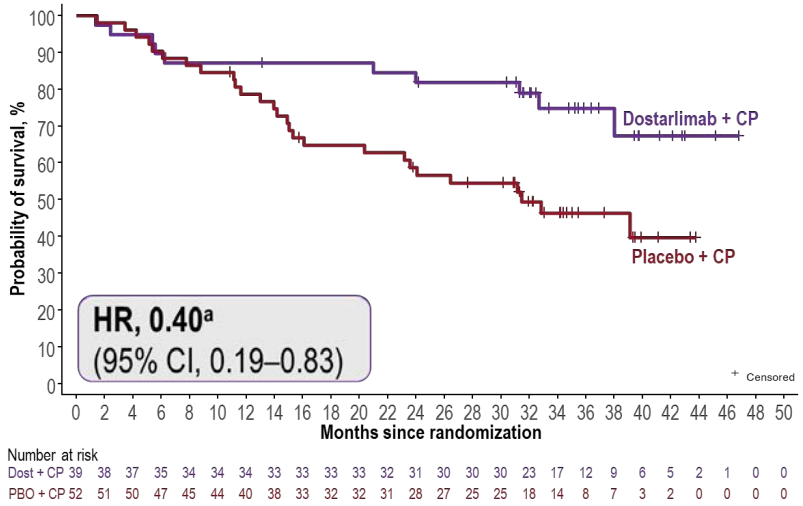
Exploratory analysis of OS per molecular subgroup

- Based on 400/494 patients with known molecular classification per WES

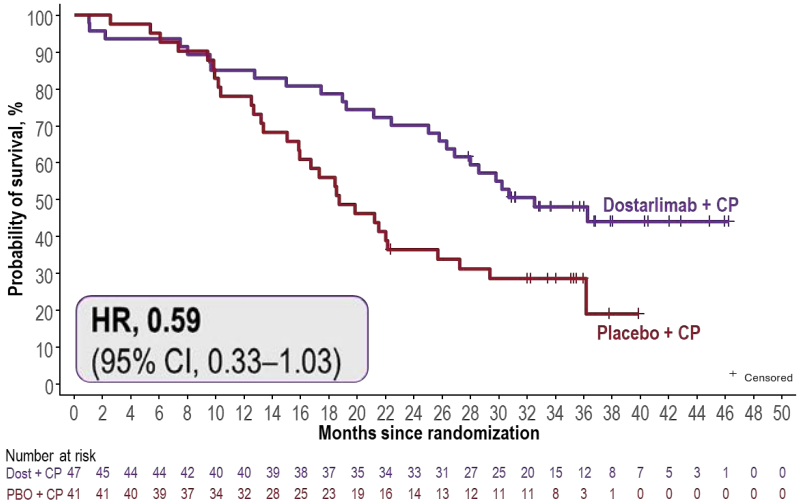
POL□mut



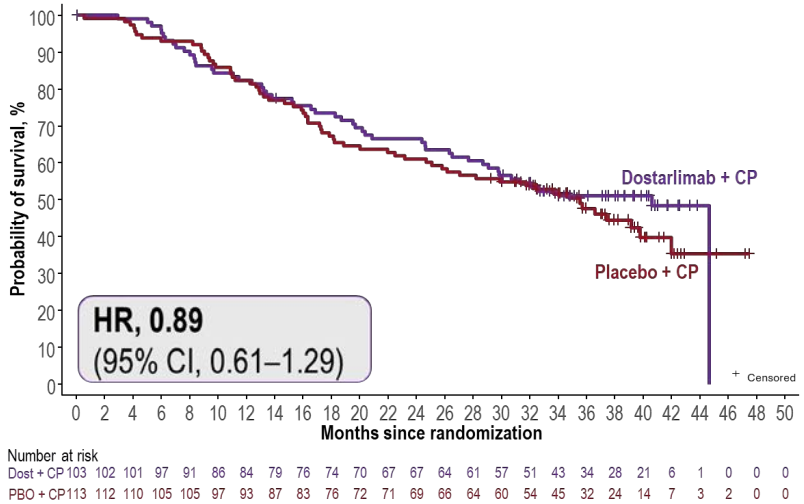
dMMR/MSI-H



TP53mut



NSMP

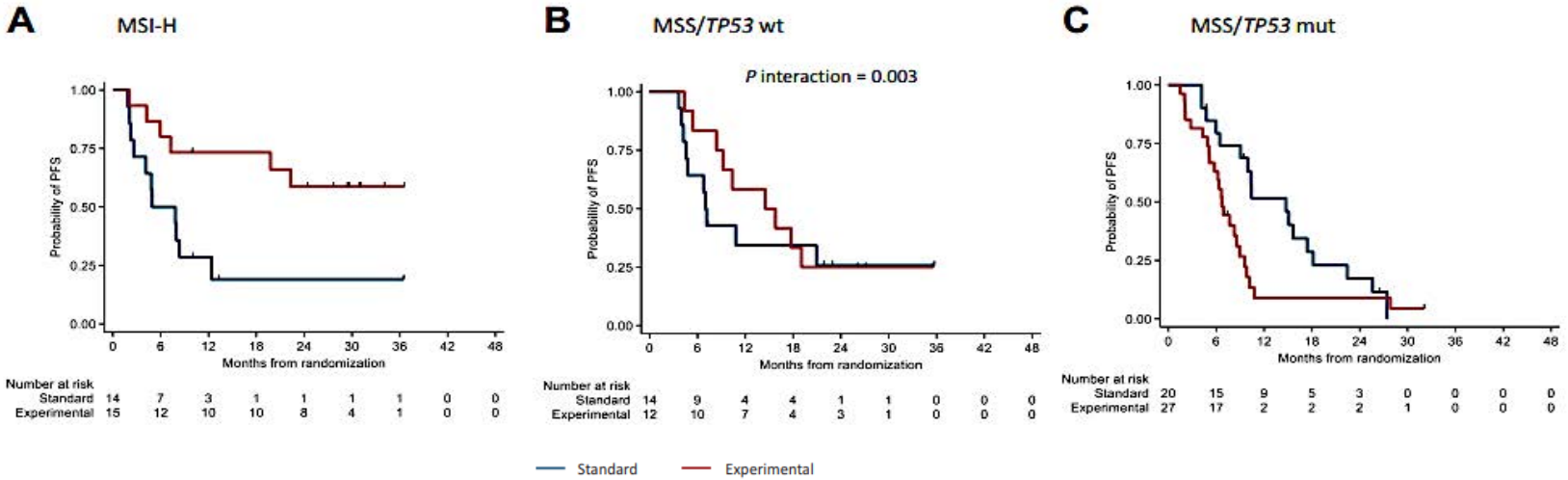


Median expected duration of follow-up in the overall population: 37.2 months (range, 31.0–49.5 months).

[a]Analysis shown on this slide is post hoc exploratory analysis of 91 patients with dMMR/MSI-H EC and WES results. In the prespecified OS analysis of the own earlier, HR was 0.32. CP, carboplatin-paclitaxel; Dost, dostarlimab; dMMR, mismatch repair deficient; HR, hazard -high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; OS, overall survival; PBO, placebo; mor protein 53; WES, whole-exome sequencing.

Are all pMMR/MSS/p53mut the same?

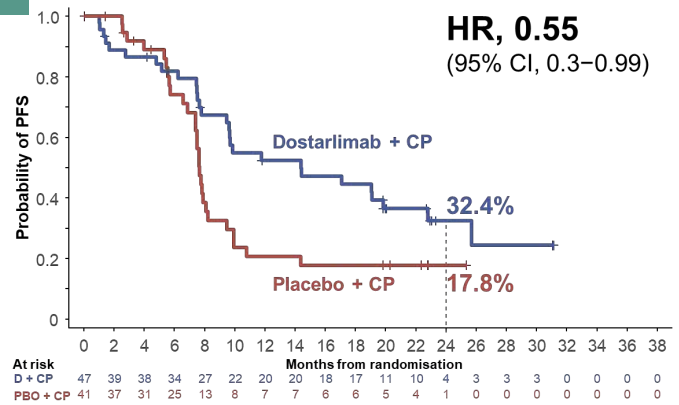
MITO END-3 (Avelumab)



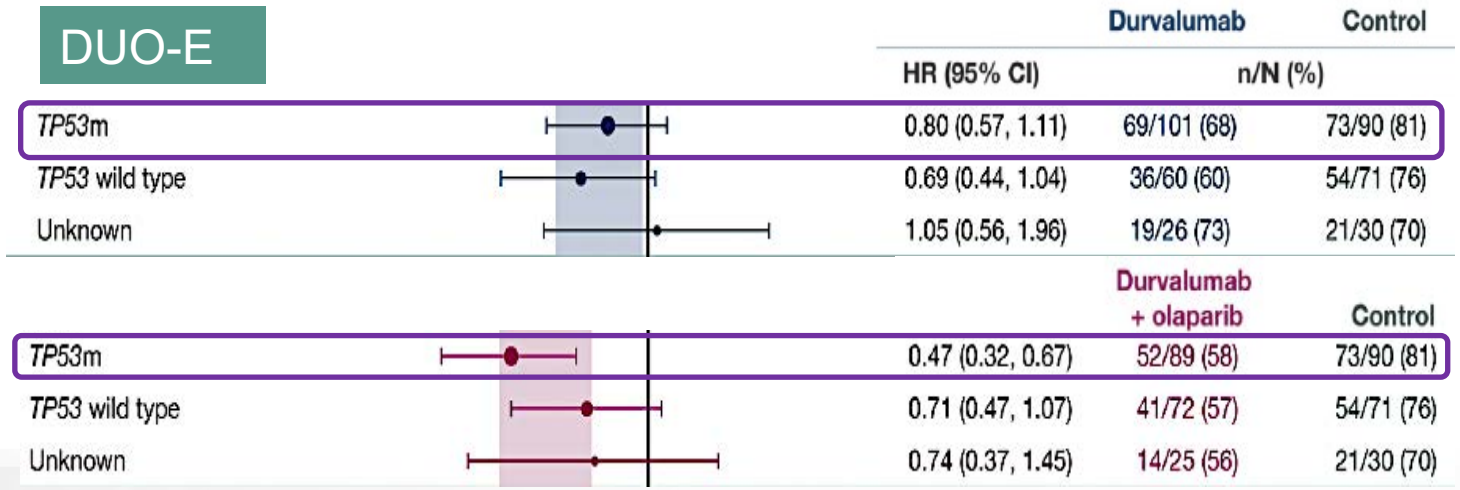
TP53 mutation is associated with a poor effect of avelumab, while mutations of PTEN and ARID1A are related to a positive effect of the drug in patients with advanced EC.

RUBY

TP53 mut



DUO-E

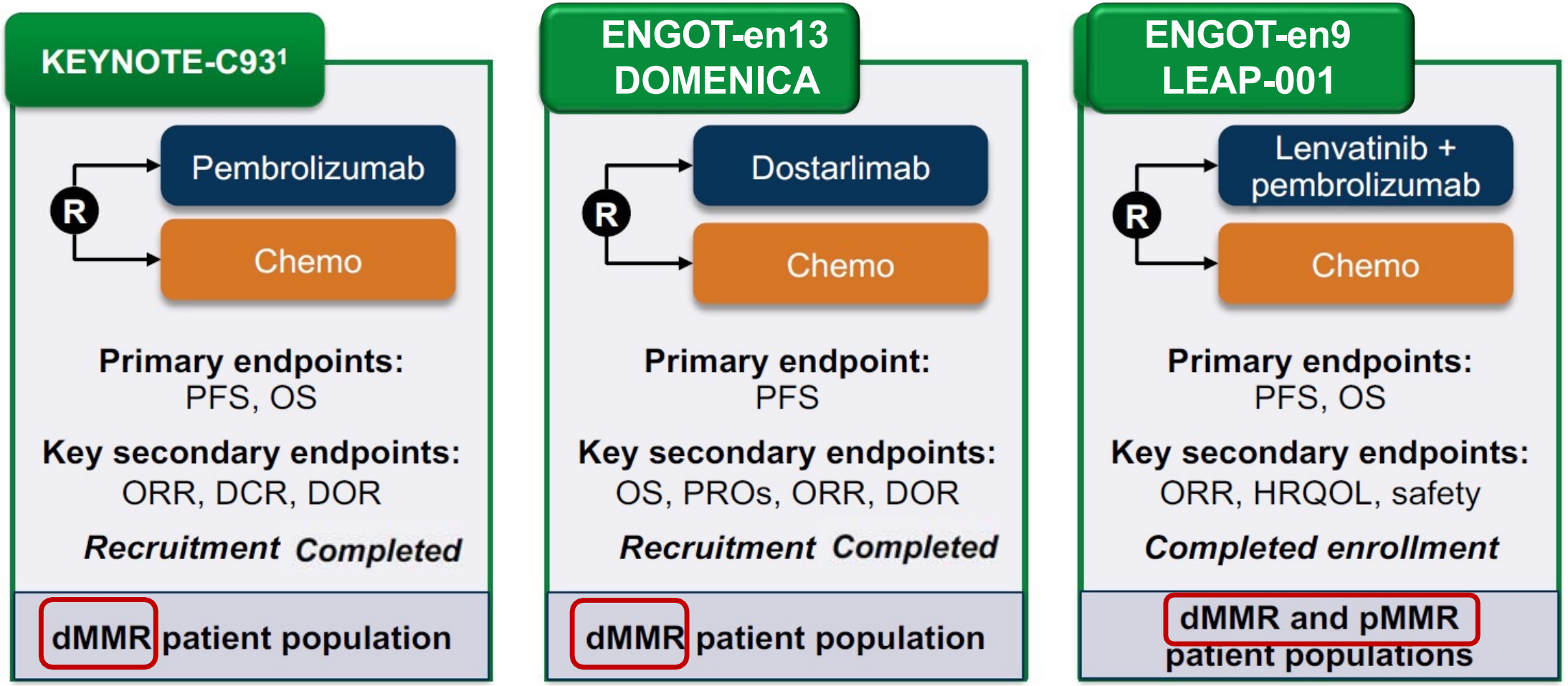


MADRID 2023 ESMO congress

THE OHIO STATE UNIVERSITY COMPREHENSIVE CANCER CENTER

Pignata, Ann Oncol 2024; Mirza, ESMO 2023; Westin Gynecol Oncol 2026

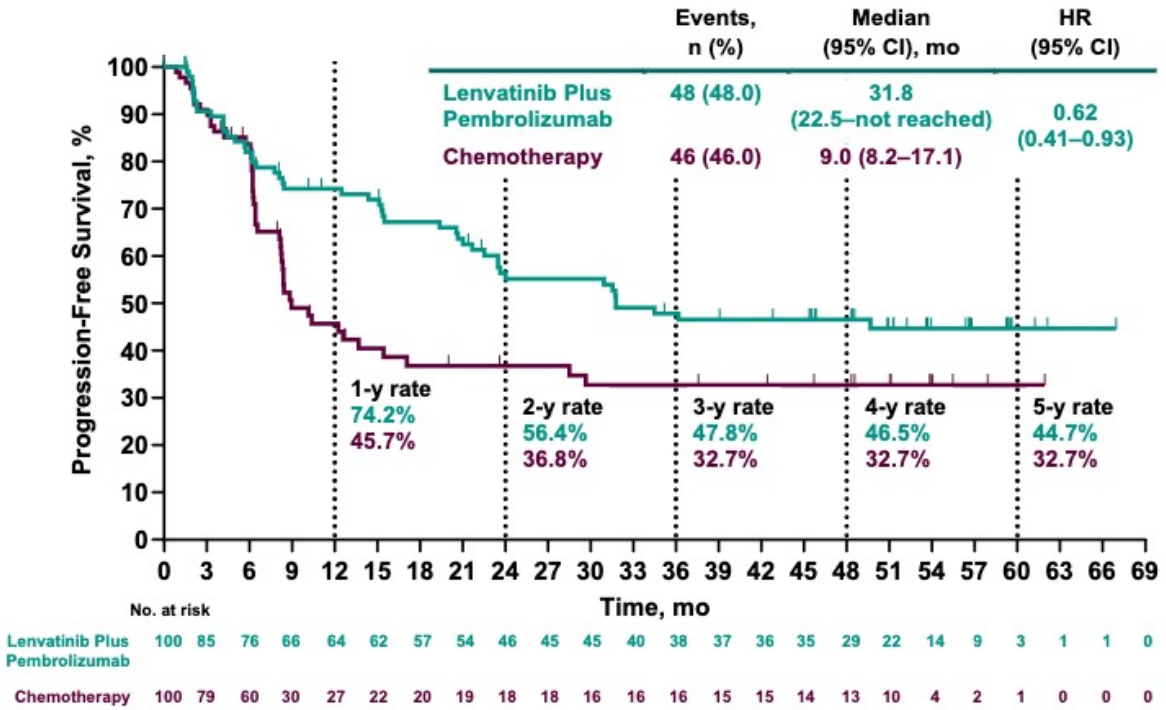
Do patients with dMMR recurrent endometrial cancer need chemotherapy?



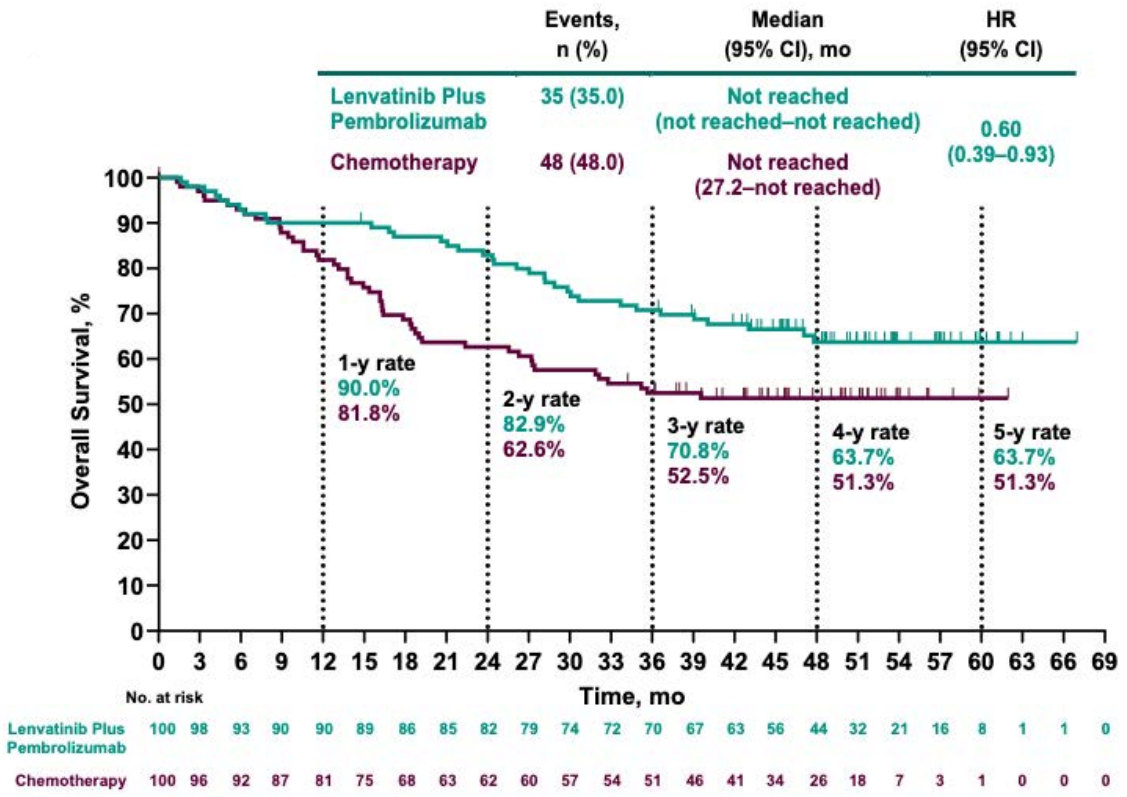
NCT05173987; NCT05201547; NCT03884101

LEAP001: Chemotherapy versus IO combination in dMMR

PFS in dMMR population



OS in dMMR population



- Marth, C. *Intl J Gynecol Cancer* 2026;36(1):102795

The James

The Ohio State University Comprehensive Cancer Center

Conclusions

- Molecular profiling has prognostic and predictive implications
- Across most subsets there is a benefit of IO in addition to chemotherapy
- Lack of strong predictive biomarker, other than MMR/MSI status
- Awaiting results whether first-line chemotherapy remains necessary in dMMR population

Discussion Questions

42-year-old woman with metastatic endometrial cancer, MMR-proficient, started on carboplatin/paclitaxel and dostarlimab with complete radiographic response.

Which biomarker assays do the faculty recommend for newly diagnosed endometrial cancer? Are you generally attempting to determine molecular subtype? If so, what do you do with that information?

How do you decide on first-line treatment? For patients with dMMR EC, how do the experts choose among the approved checkpoint inhibitors in the first line? What about patients with pMMR EC?

How long do you continue IO in the maintenance setting if a patient is in a complete radiographic response?

Discussion Questions

48-yr-old woman w/ pMMR metastatic EC w/ malignant ascites and peritoneal mets.
Carboplatin/paclitaxel/bevacizumab followed by lenalidomide/pembrolizumab upon progression.

For patients with pMMR EC with ascites, would you administer chemo/bevacizumab first line or chemo/IO? Can bev be combined with up-front chemo/IO regimens for patients like this who could clearly benefit?

Discussion Questions

62-year-old woman with recurrent endometrial cancer that is dMMR is started on single-agent pembrolizumab. After 4 cycles, she reports new-onset diarrhea (4-5 loose stools per day), fatigue and a mild rash on her trunk. Her thyroid function tests show an elevated TSH.

How should these likely immune-related adverse events be managed?

What symptoms would prompt immediate withholding of immunotherapy and initiation of corticosteroids?

In which situations, if any, do you save IO for the second line?

Which patients with preexisting autoimmune disease lead you to hold off on first-line IO? What about patients with prior transplants?

RTP
RESEARCH
TO PRACTICE

Discussion Questions

52 yo patient with de novo MSI-H metastatic endometrial cancer initially treated with carboplatin/paclitaxel/pembrolizumab. Progressive disease 9 months into maintenance pembrolizumab.

Do you have any theories as to why some MSI-H tumors do not respond to IO?

What would you recommend in the second-line setting? Is there any role for ipilimumab/nivolumab?

Discussion Questions

79 yo woman, locally advanced uterine serous carcinoma (3-cm cervical mass with bilateral parametrial involvement, fixed in the pelvis).
p53-mutated, dMMR, PD-L1-negative, HER2-negative.
CAD s/p CABG and stent (2018), PVD s/p bypass x 2 (2024), COPD and CKD.
Treated with neoadjuvant carboplatin, paclitaxel and pembrolizumab with the hope of turning resectable.

In patients with locally advanced endometrial cancer that is initially unresectable, NCCN suggests either neoadjuvant radiation or neoadjuvant chemotherapy. How do you decide which approach to take? Do molecular factors play a role?

If her disease were to recur in the future, what would you consider as first-line therapy given that she has already received pembrolizumab?

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TO PRACTICE

Agenda

Module 1: Current Up-Front Chemoimmunotherapeutic Approaches for Advanced Endometrial Cancer (EC) — Dr Backes

Module 2: Current and Future Role of Anti-PD-1/PD-L1 Antibodies in Combination with Systemic Therapies Beyond Chemotherapy for Advanced EC — Dr Westin

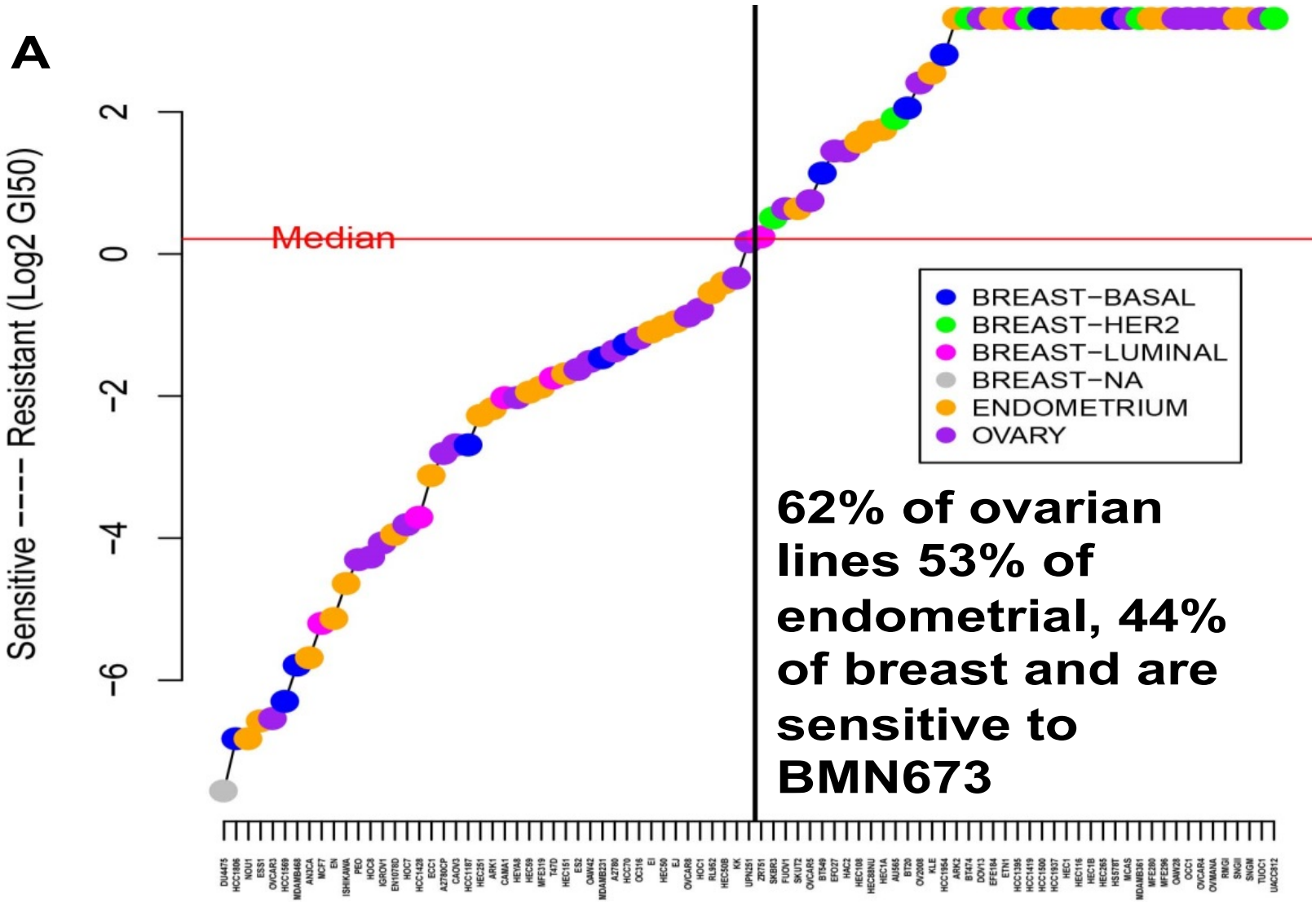
Module 3: Promising Agents Under Investigation for EC — Dr Slomovitz

Current and Future Role of Anti-PD-1/PD-L1 Antibodies in Combination with Systemic Therapies Beyond Chemotherapy in Advanced Endometrial Cancer

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

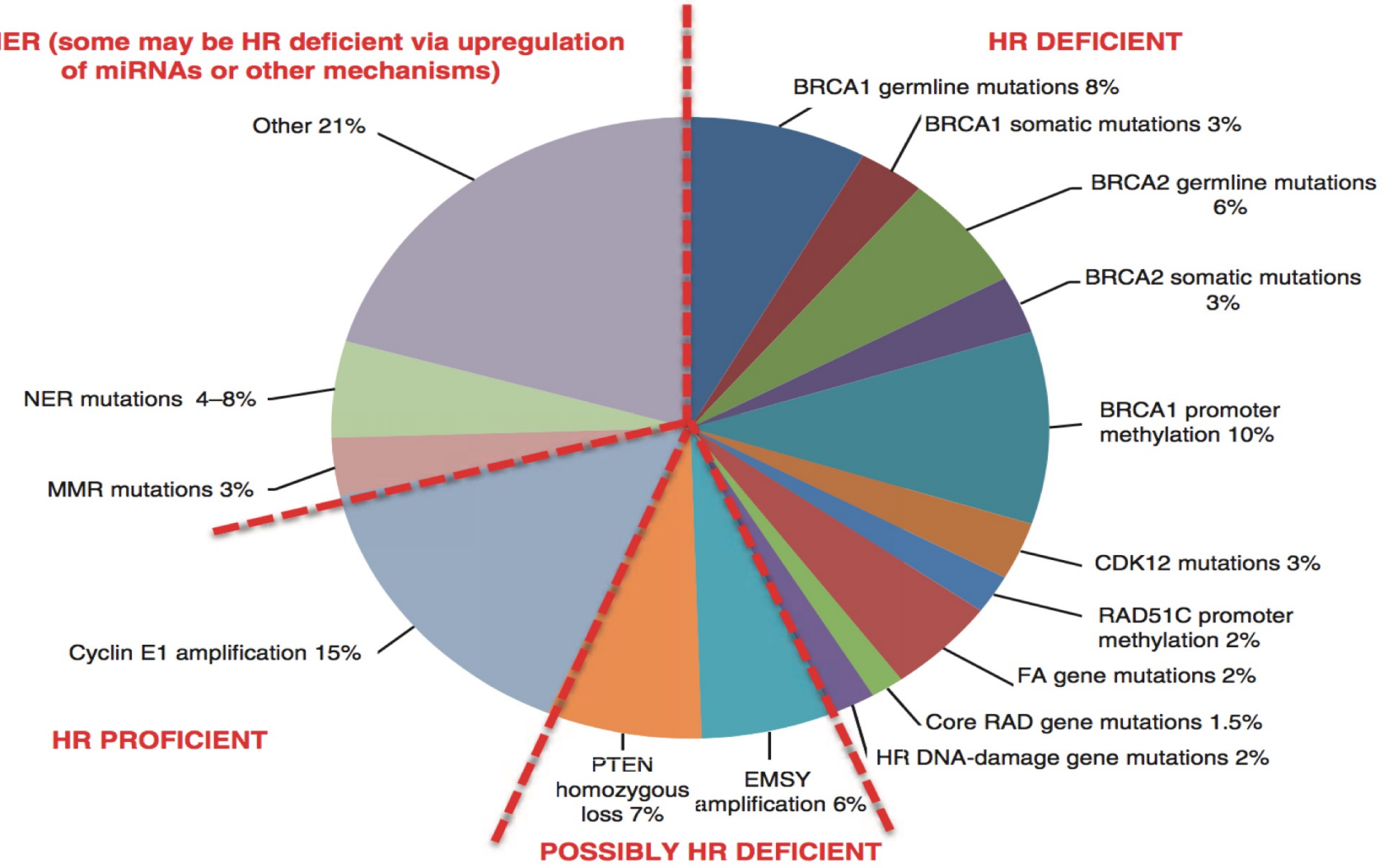
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

PARPi activity across cell lines



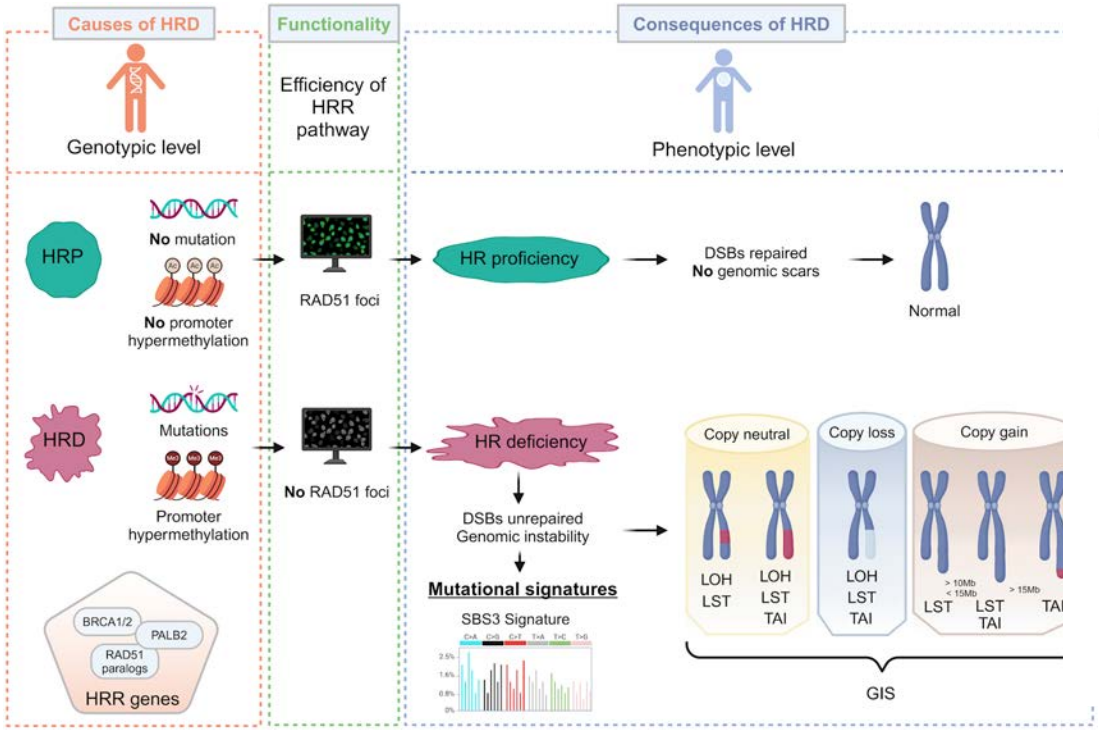
Ovarian, endometrial, and breast cancer cell lines were cultured for 5 days with BMN673 and plotted based on log 2 G150.

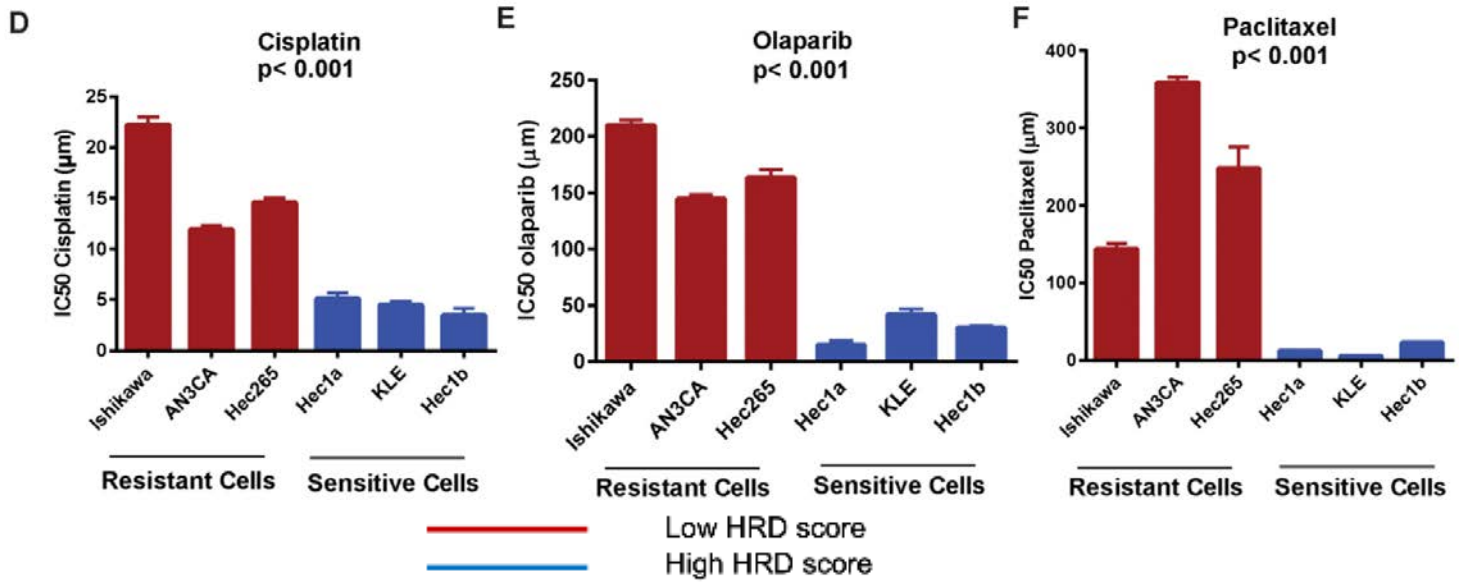
Opportunity for PARP in Endometrial Cancer? Beyond *BRCA* - Mechanisms of HRD



Konstantinopoulos Cancer Discovery 2015

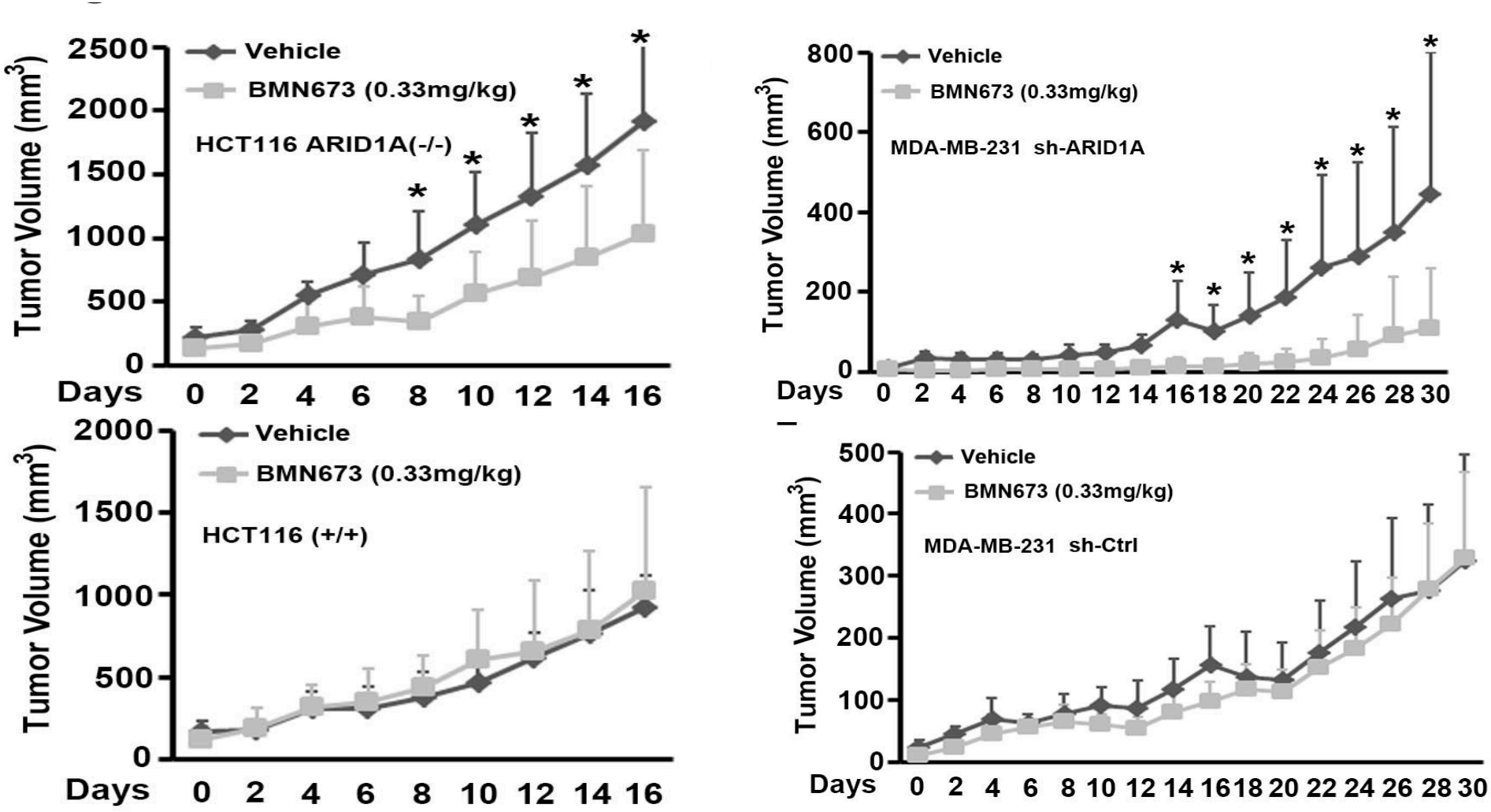
HRD Score in Endometrial Cancer





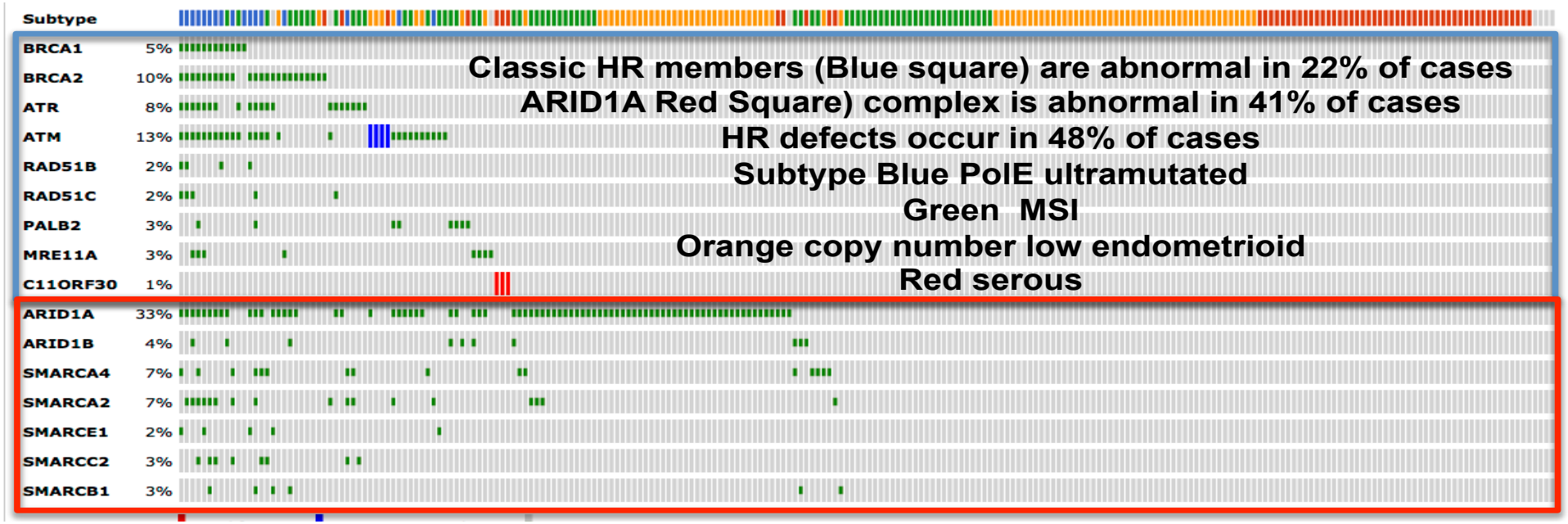
Witz et al, *Biomarker Research*, 2025, **Siedel, et al. Gynecol Oncol 2021**

ARID1A sensitizes to PARPi in EC



Shen Cancer Discov 2015

Homologous Recombination Defects in Endometrial Cancer

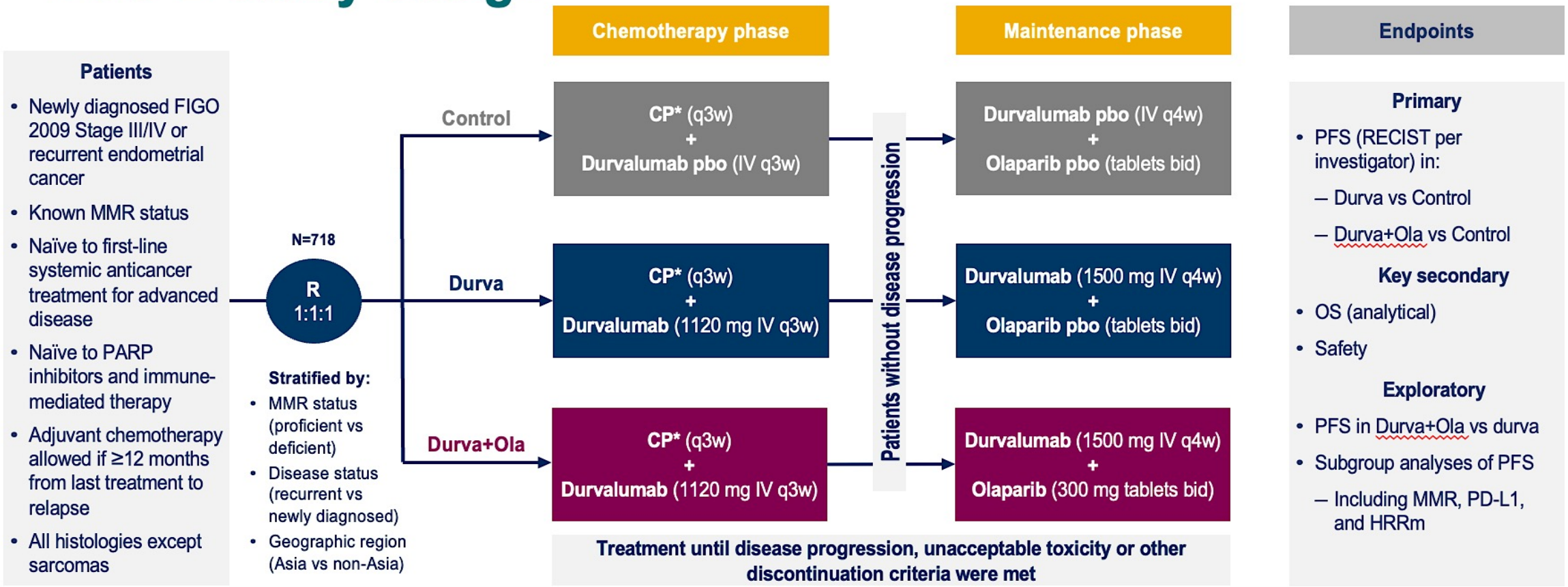


- Classic HRD members: 22%
- ARID1A: 41%
- HRD + ARID1A: 48%
- HRD, ARID1A, PTEN: 77%

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

DUO E: Combination of Durvalumab and Olaparib

DUO-E study design



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

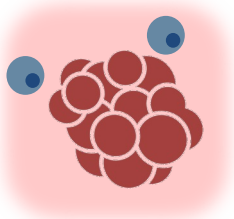
MADRID 2023 ESMO congress

Shannon N. Westin

Westin JCO 2023

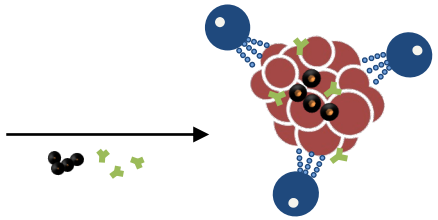
Addition of Olaparib to Durvalumab Further Enhanced PFS Benefit in pMMR Subpopulation

pMMR endometrial cancer



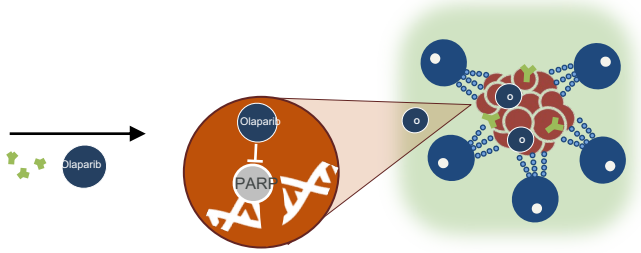
Biologically heterogeneous population – diverse genomic drivers and variable immune priming[2-4]

INDUCTION: CP + durvalumab

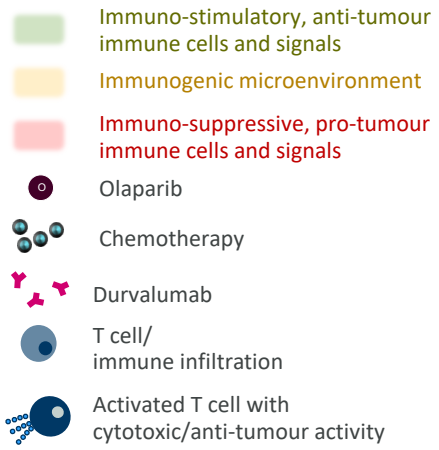


CP + durvalumab drives direct tumour killing, which may promote immune priming[3-8]

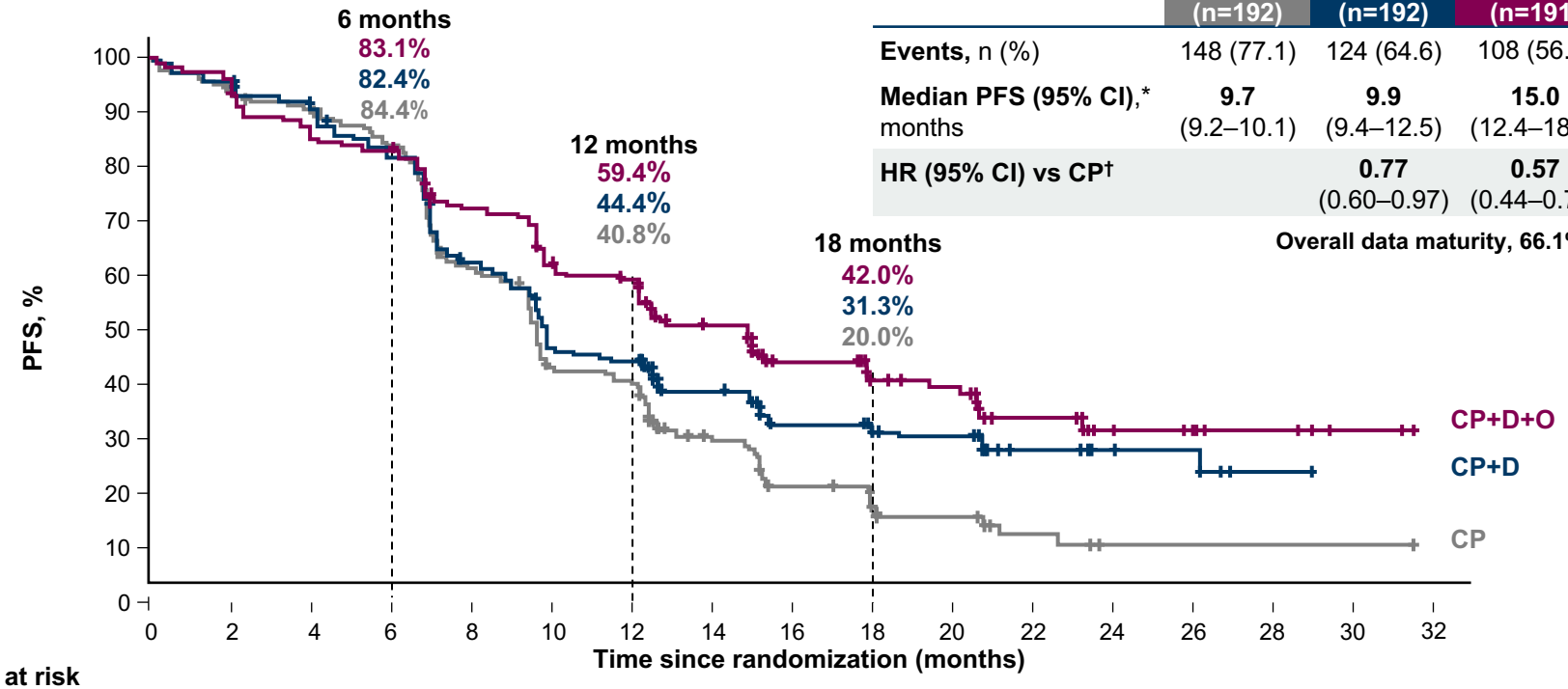
MAINTENANCE: durvalumab + olaparib



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



prespecified exploratory analysis – PFS in pMMR[1]



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

Overall data maturity, 66.1%

*CI for median PFS is derived based on the Brookmeyer–Crowley method; †The HR and CI were estimated from a Cox proportional-hazards model stratified by MMR and disease status.

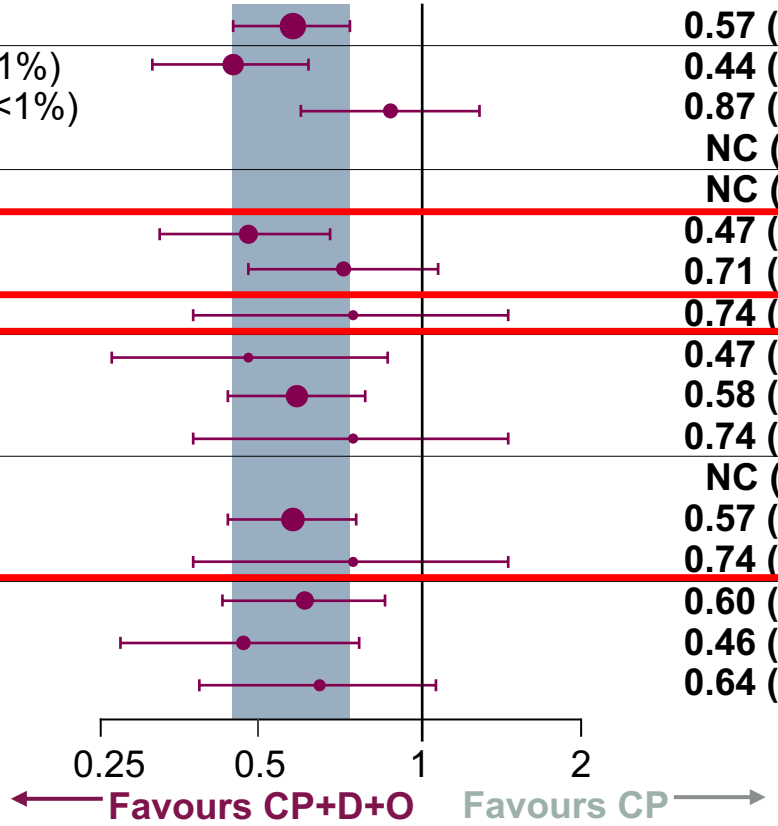
1. Westin SN, et al. *J Clin Oncol.* 2024;42:283–99; 2. Rizzo A, et al. *J Clin Med.* 2022;11:3912; 3. Yang Y, et al. *Int J Gynaecol Obstet.* 2024;164:436–459; 4. Antill Y, et al. *Cancer.* 2022;128 1157–1161; 5. Corr B, et al. *BMJ Med.* 2022;1:e000152; 6. Eskander RN & Powell MA. *Ther Adv Med Oncol.* 2021;13:1–9; 7. Liu T-Y, et al. *Theranostics.* 2021;11:5365–5386; 8. El-ghazzi N, et al. *Onco Targets Ther.* 2023;16:359–369; 9. Stewart RA, et al. *Cancer Res.* 2018;78:6717–6725; 10. Musacchio L, et al. *Cancer Manag Res.* 2020;12:6123-6135; 11. Post CCB, et al. *Crit Rev Oncol Hematol.* 2020;152:102973.

pMMR Subpopulation: PFS by Biomarker Subgroup

CP + Durvalumab + Olaparib vs CP

***Post hoc* exploratory analysis**

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



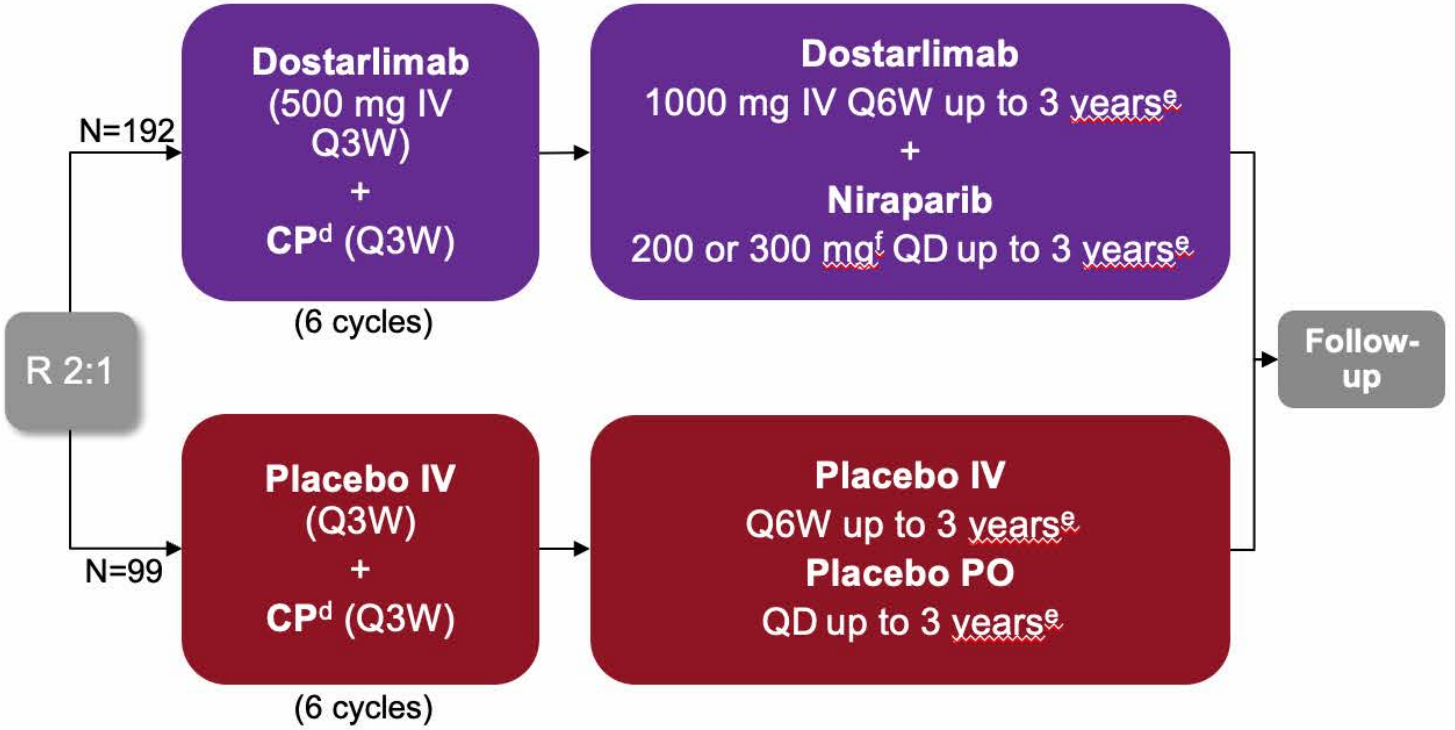
RUBY Part 2 : Dostarlimab + Niraparib in Endometrial Cancer

Eligible patients

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

Stratification

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



Primary endpoint

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

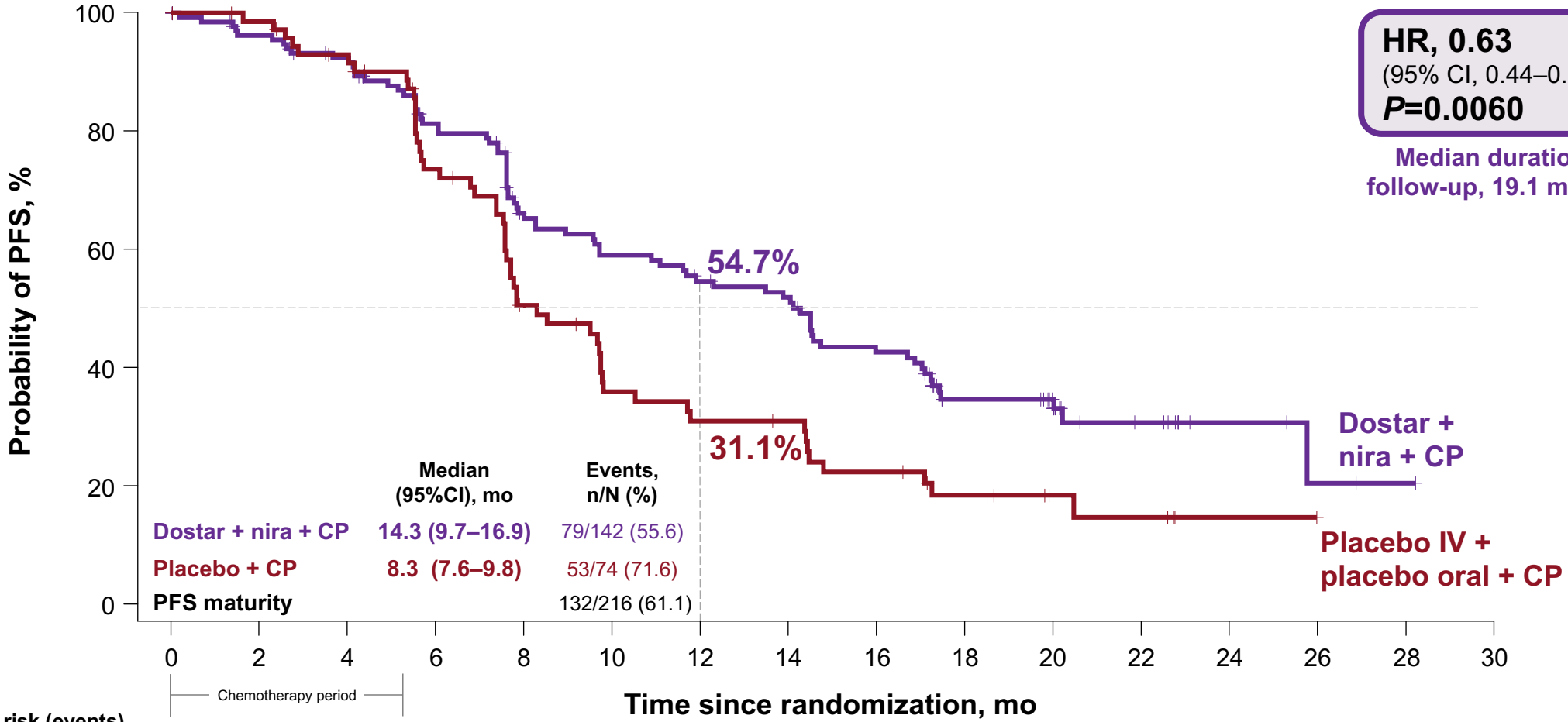
Secondary endpoints

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

Mirza. SGO 2024.

Statistically Significant PFS Benefit in MMRp/MSS Population

Primary endpoint

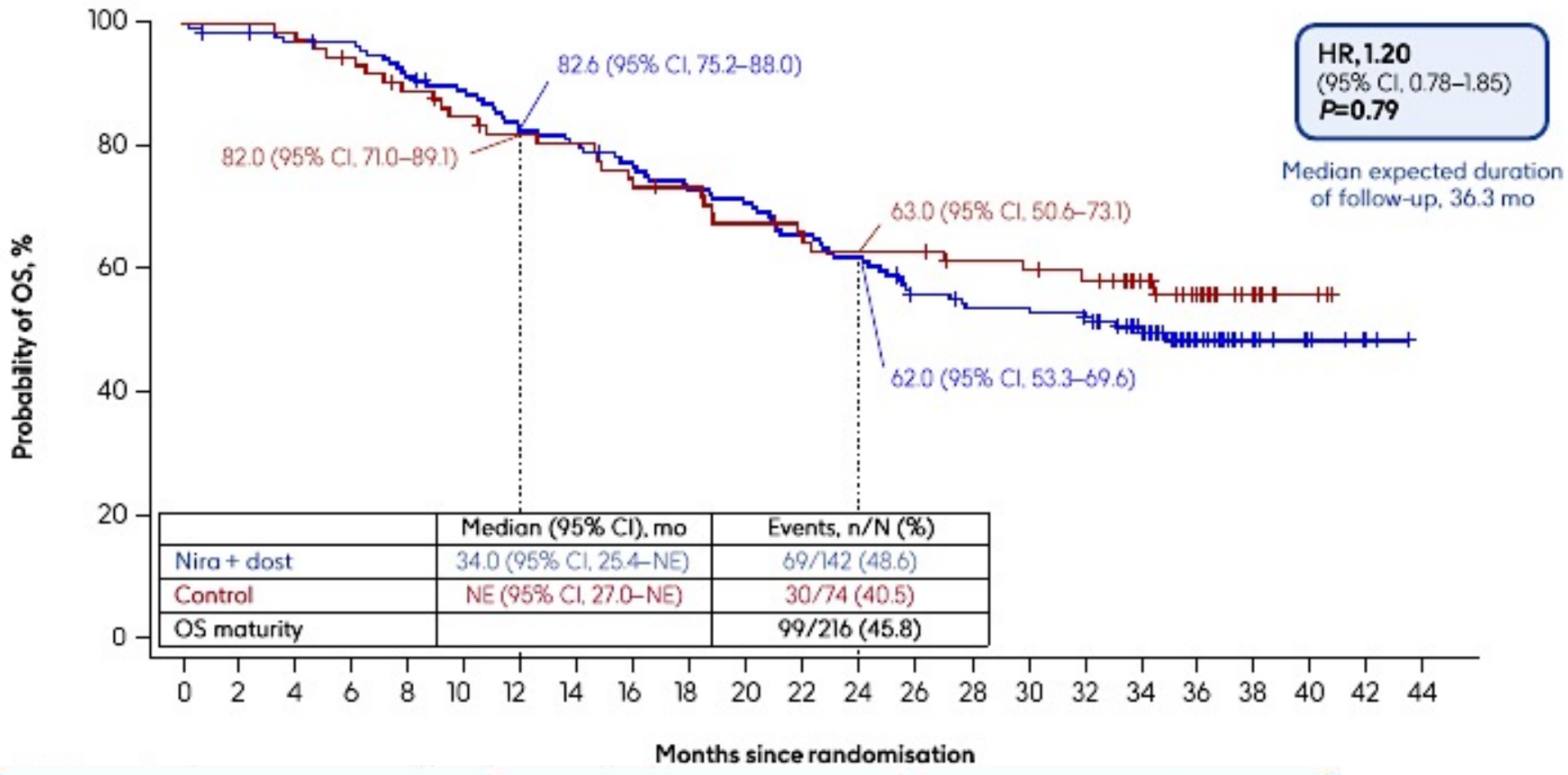


No. at risk (events)															
Dostarlimab + niraparib +CP	142(0)	127(5)	119(10)	100(24)	75(42)	67(50)	61(55)	57(58)	47(68)	28(76)	24(76)	11(78)	4(78)	2(79)	1(79)	0(79)
Placebo IV + placebo oral + CP	74(0)	71(1)	65(5)	49(18)	32(33)	22(42)	19(45)	18(45)	13(50)	9(52)	5(52)	4(53)	1(53)	1(53)	0(53)	

Mirza. SGO 2024.

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

No Overall Survival Benefit in MMRp/MSS Population



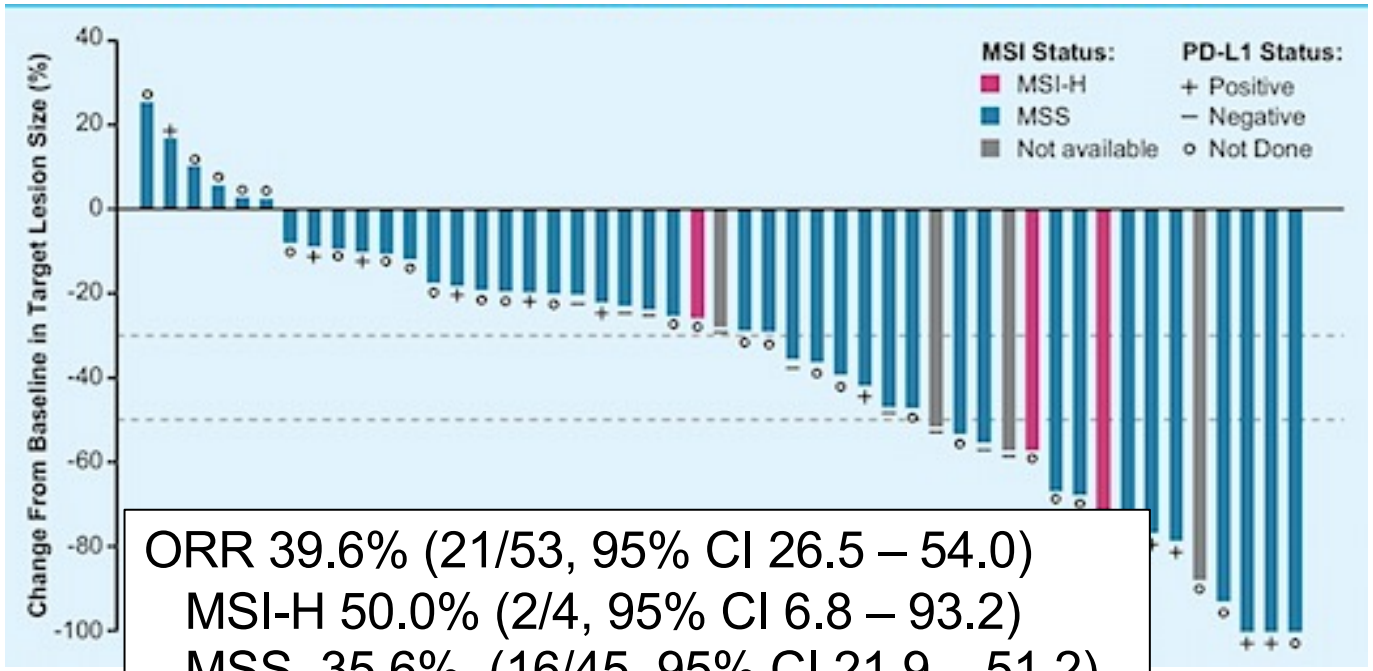
	Median (95% CI), mo	Events, n/N (%)
Nira + dost	34.0 (95% CI, 25.4–NE)	69/142 (48.6)
Control	NE (95% CI, 27.0–NE)	30/74 (40.5)
OS maturity		99/216 (45.8)

	Overall population		MMRp/MSS population	
	Nira + dost (n=192)	Control (n=99)	Nira + dost (n=142)	Control (n=74)
Any follow-up anticancer therapy	47.4 (91)	63.6 (63)	55.6 (79)	63.5 (47)
Patients receiving follow-up anticancer therapy[a]	N=91	N=63	N=79	N=47
Chemotherapy	52.7 (48)	28.6 (18)	53.2 (42)	36.2 (17)
Immunotherapy	28.6 (26)	69.8 (44)	29.1 (23)	63.8 (30)

Powell, ESGO 2026

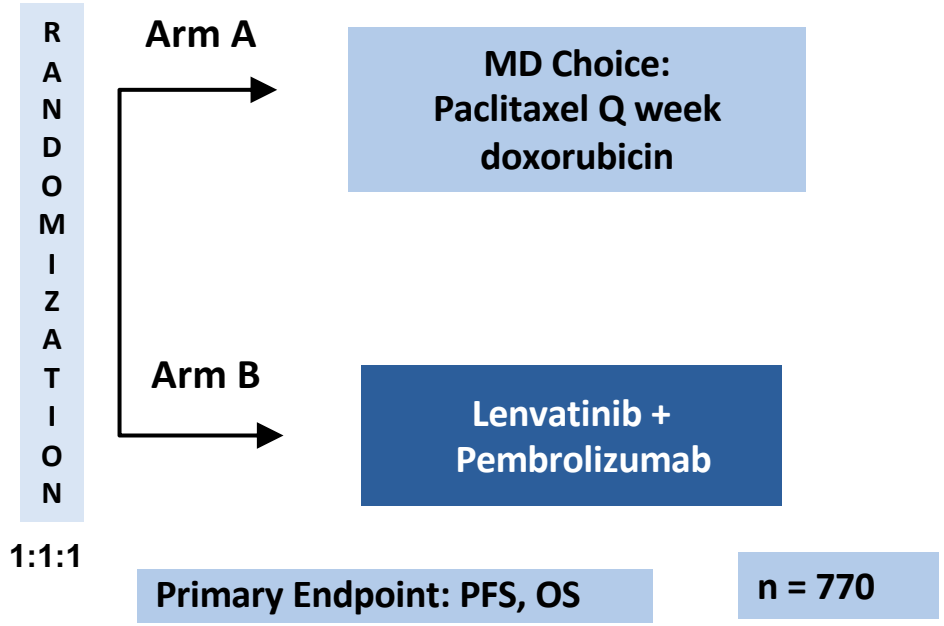
Lenvatinib and Pembrolizumab

KEYNOTE-146: A basket study of lenvatinib + pembrolizumab: Results in patients with advanced platinum resistant ovarian cancer NCT02501096



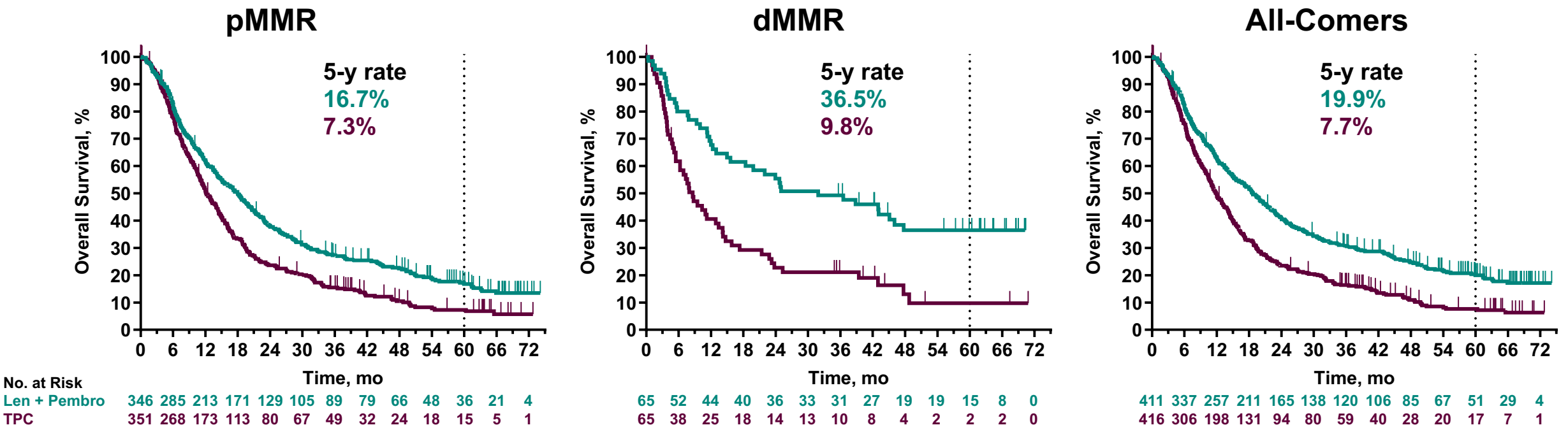
ORR 39.6% (21/53, 95% CI 26.5 – 54.0)
MSI-H 50.0% (2/4, 95% CI 6.8 – 93.2)
MSS 35.6% (16/45, 95% CI 21.9 – 51.2)

KEYNOTE-775: Randomized phase II trial of lenvatinib + pembrolizumab vs. MD choice chemotherapy in recurrent endometrial cancer NCT03517449



Makker ASCO 2017, Makker ASCO 2018

At 5 Years, Len + Pembro OS Benefit Continues to be Consistent With the Primary Analysis



Median (95% CI),[a] mo	18.0 (14.9–20.5)	12.2 (11.0–14.1)
Events, n (%)	285 (82.4)	310 (88.3)
HR (95% CI)[b]	0.70 (0.60–0.83)	

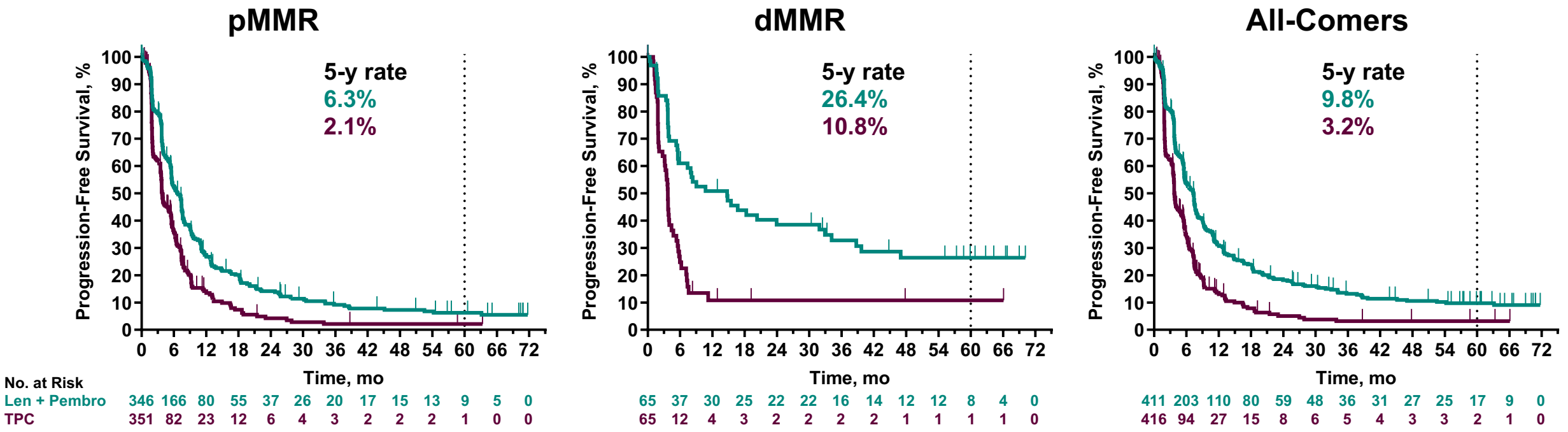
Median (95% CI),[a] mo	31.9 (15.6–47.7)	8.6 (5.5–13.4)
Events, n (%)	40 (61.5)	53 (81.5)
HR (95% CI)[b]	0.44 (0.29–0.67)	

Median (95% CI),[a] mo	18.7 (15.6–21.3)	11.9 (10.6–13.3)
Events, n (%)	325 (79.1)	363 (87.3)
HR (95% CI)[b]	0.66 (0.57–0.77)	

Data cutoff: February 26, 2025. The tick marks indicate censored data. [a]Based on Kaplan-Meier method for censored data. [b]Based on Cox regression model with the Efron method of tie handling and treatment as a covariate; analyses were stratified for the pMMR population and all-comers.

Makker, IGCS 2025

At 5 Years, Len + Pembro PFS[a] Benefit Continues to be Consistent With the Primary Analysis



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)	

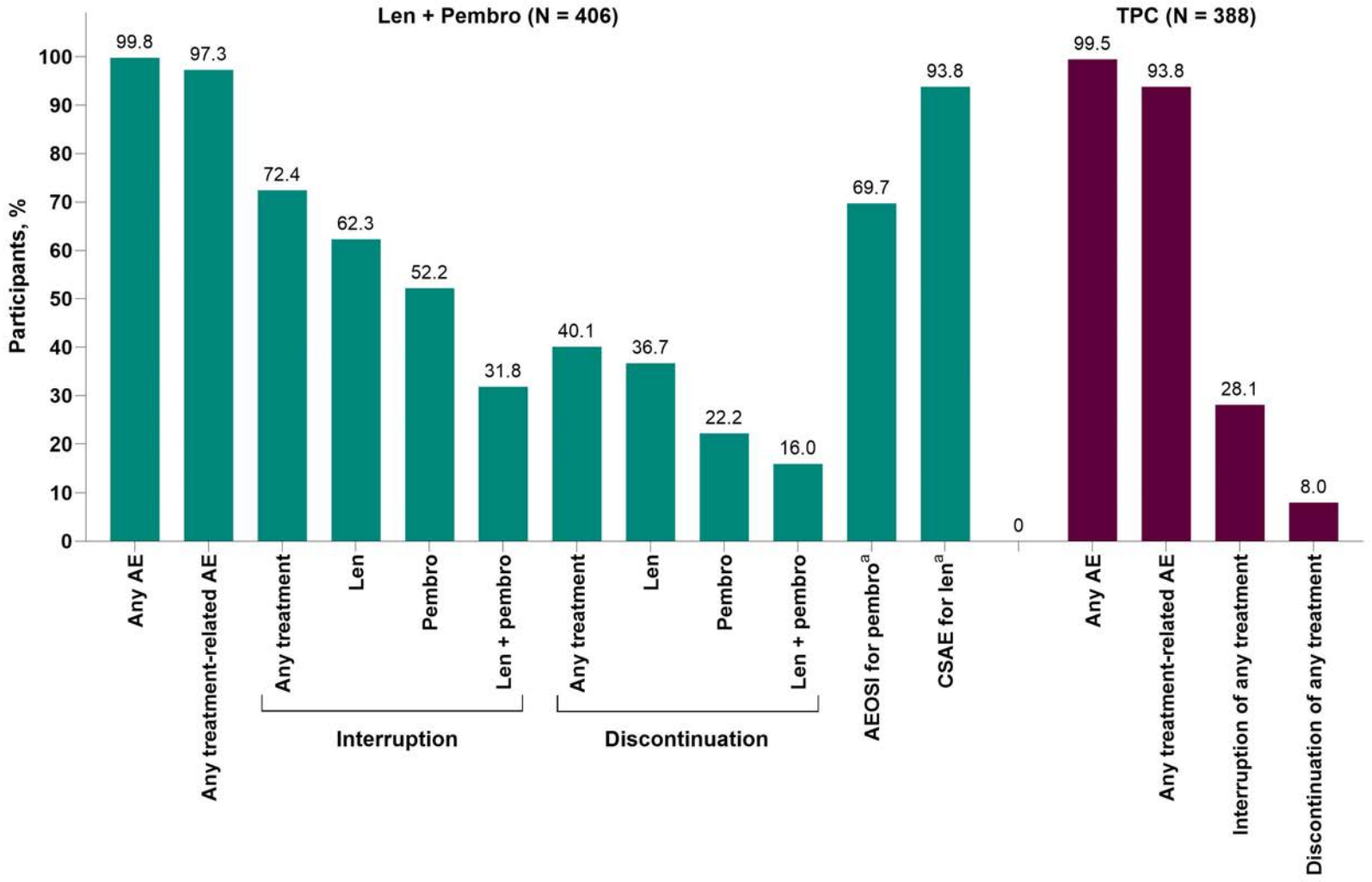
Median (95% CI),[b] mo	14.8 (5.6–31.9)	3.7 (3.1–4.4)
Events, n (%)	43 (66.2)	49 (75.4)
HR (95% CI)[c]	0.39 (0.25–0.60)	

Median (95% CI),[b] mo	7.3 (5.7–7.6)	3.8 (3.6–4.2)
Events, n (%)	322 (80.8)	298 (71.6)
HR (95% CI)[c]	0.56 (0.48–0.66)	

Data cutoff: February 26, 2025. The tick marks indicate censored data. [a]Per RECIST version 1.1 by BICR. [b]Based on Kaplan-Meier method for censored data. [c]Based on Cox regression model with the Efron method of tie handling and treatment as a covariate; analyses were stratified for the pMMR population and all-comers.

Makker, IGCS 2025

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.

ENGOT-en9/LEAP-001 Study Design

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 up to 7 cycles[c]

Endpoints

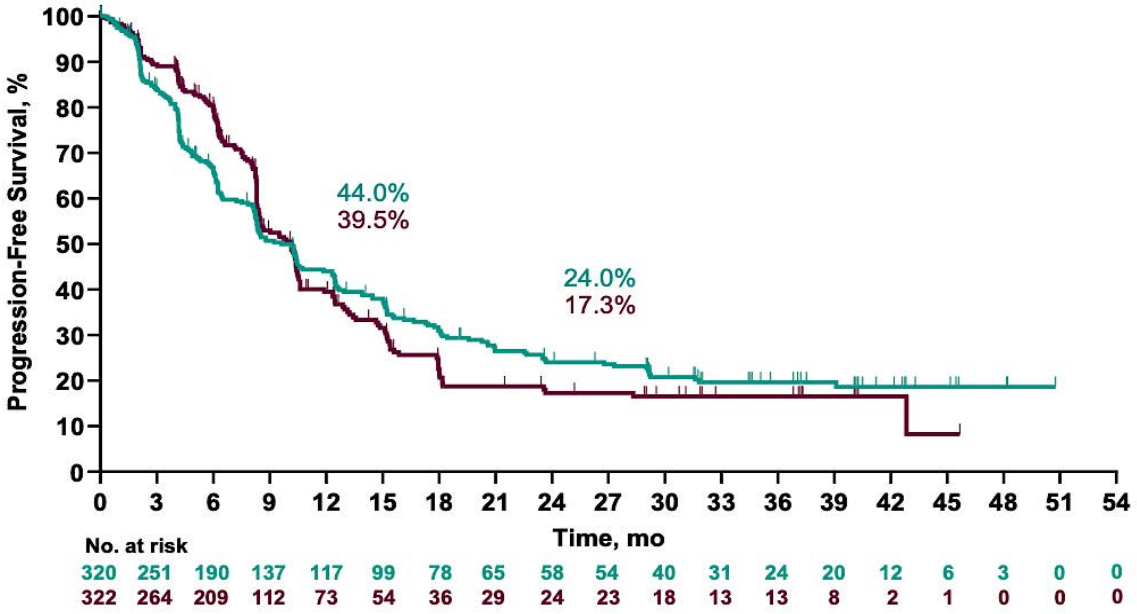
- **Dual primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR per RECIST v1.1 by BICR, safety, and HRQoL
- **Exploratory:** Included DOR per RECIST v1.1 by BICR

Marth ESGO 2024, SGO 2024

No Difference in PFS and OS LEN/PEM and TC in pMMR

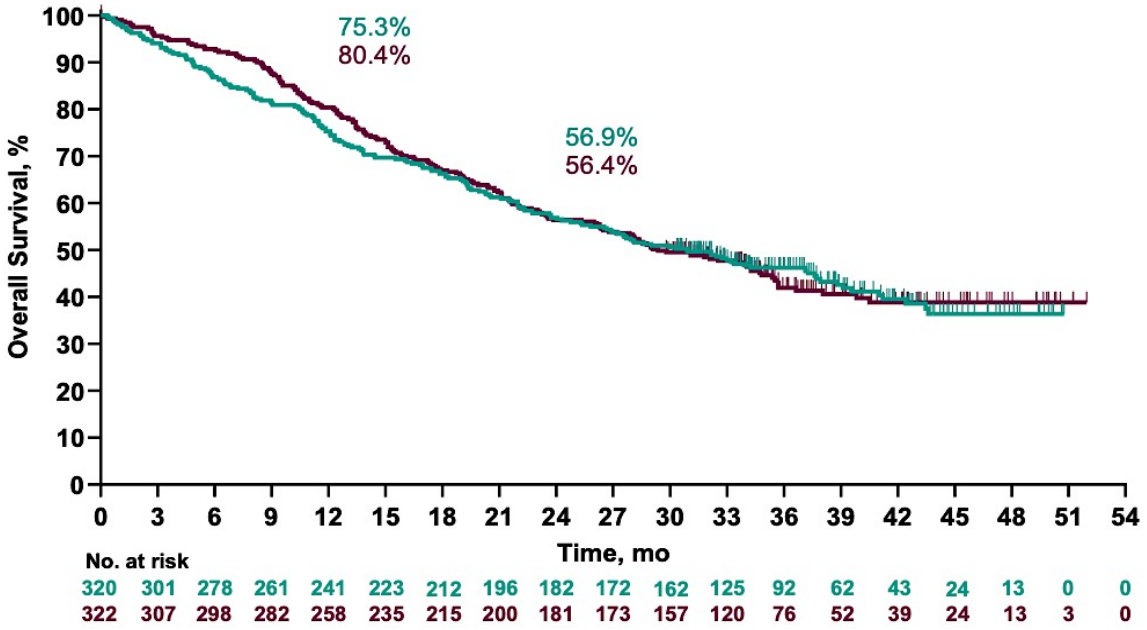
pMMR Population

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	224/320	9.6 (8.2–11.9)	0.99 (0.82–1.21)
TC	187/322	10.2 (8.4–10.5)	



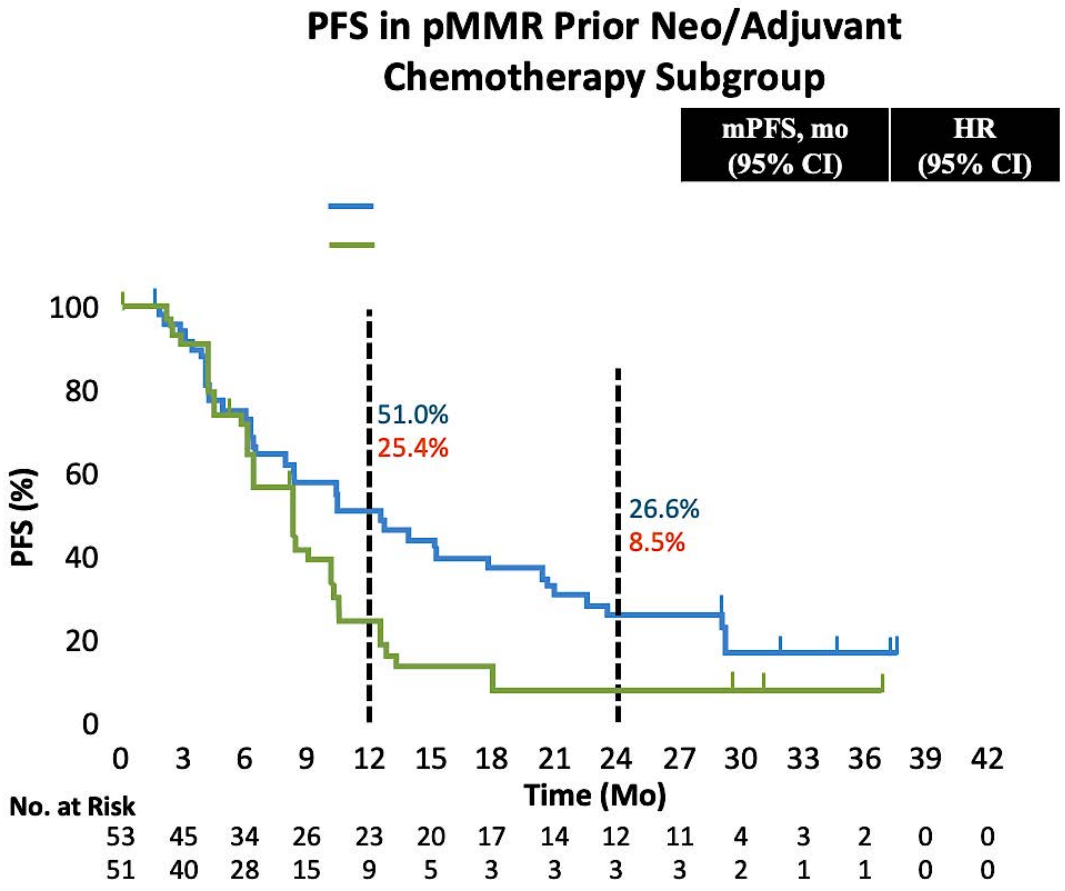
pMMR Population

	Events, n/N	Median (95% CI), mo	HR (95% CI)	p-Value
LEN/PEMBRO	183/320	30.9 (25.4–37.7)	1.02 (0.83–1.26)	0.246[a]
TC	183/322	29.4 (26.2–35.4)		

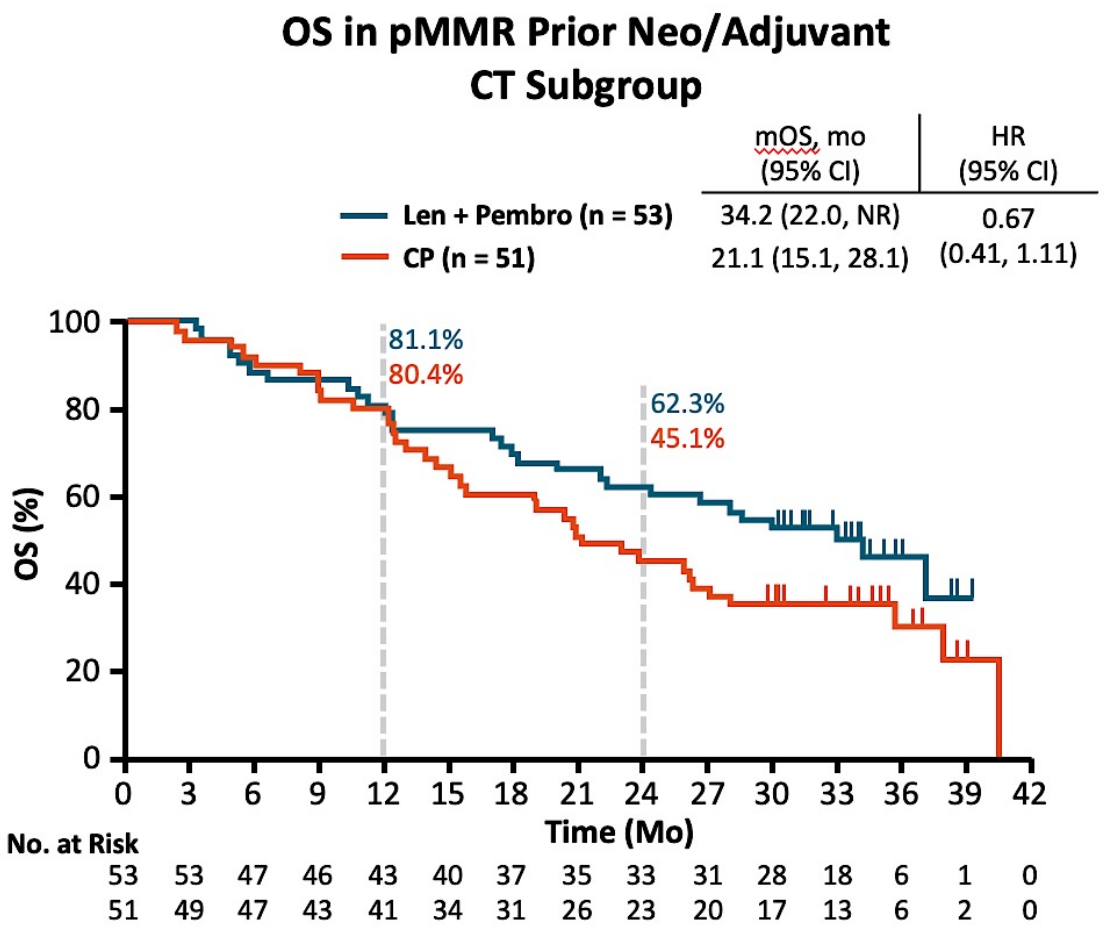


Marth ESGO 2024, SGO 2024

LEAP-001: PFS and OS in Prior Neo/Adjuvant CT Subgroup

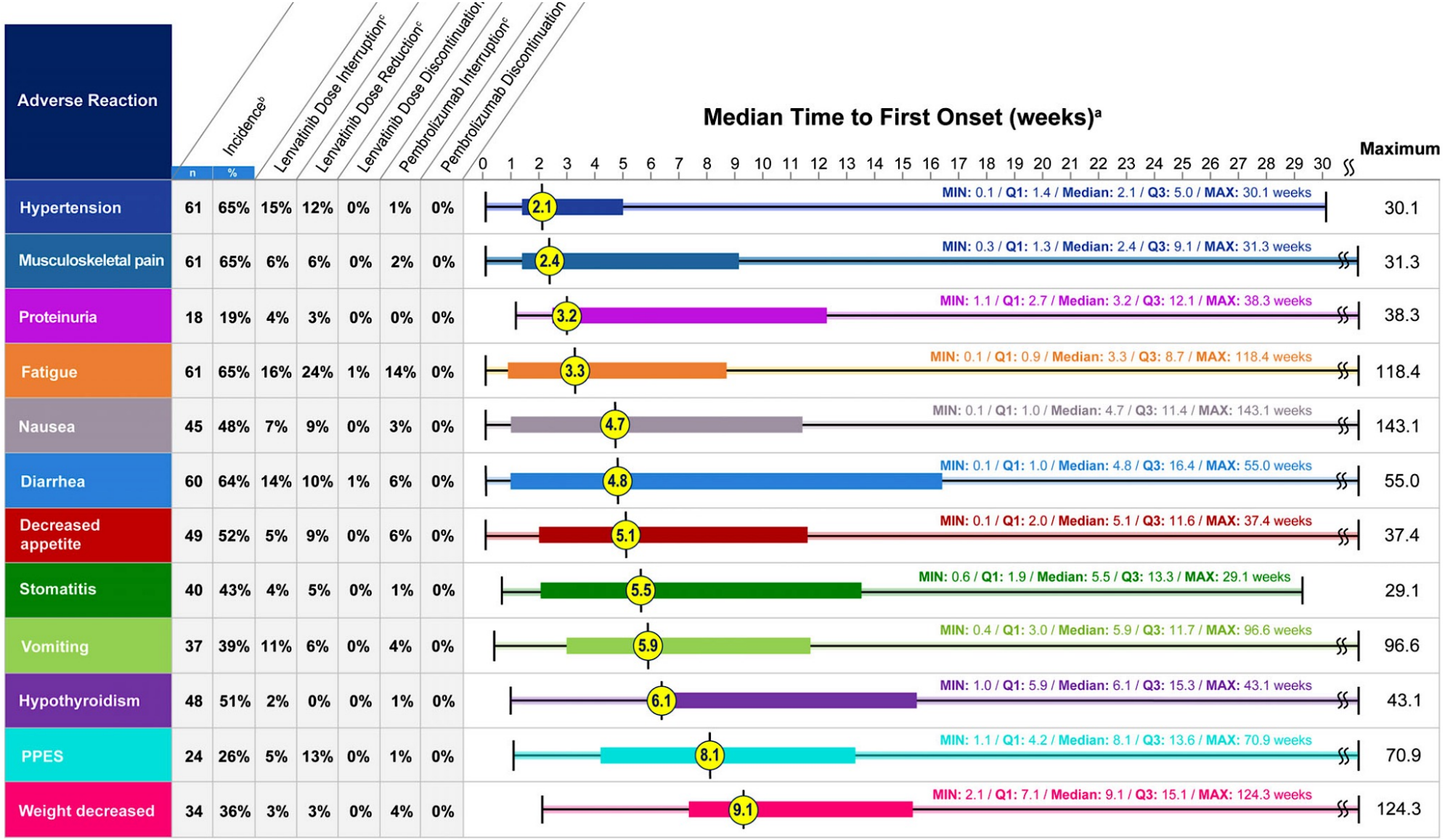


NCT03884101. Marth. SGO 2024.



Marth ESGO 2024, SGO 2024

Len/Pem Toxicity Timing



Makker et al. Oncologist 2021

Specific Guidelines for Toxicity Management for Len/Pem

Hypertension

- Daily monitoring
- Consideration of antihypertensive Rx

Diarrhea

- Reporting
- Antimotility agents
- Consider the timeline
- Dose interruption

Fatigue

- Rule out other causes
- Exercise
- Dose interruption/reduction

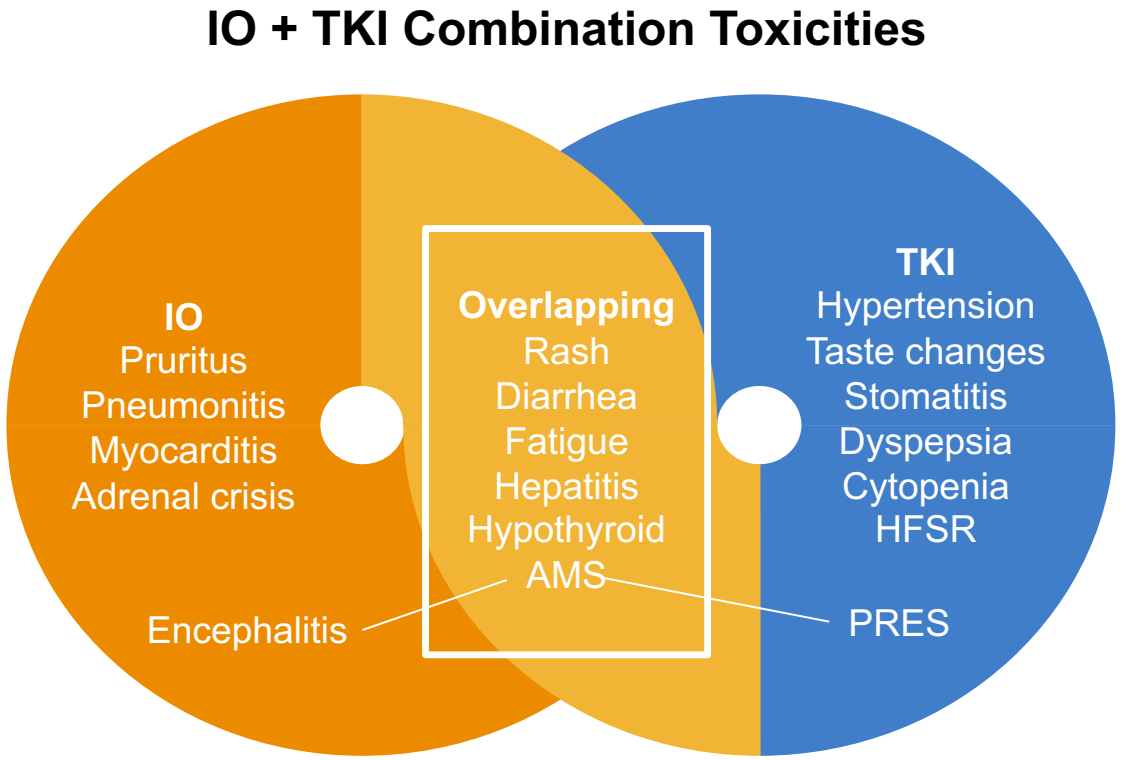
Nausea

- Prophylactic antiemetics
- High fat foods
- Small frequent meals

Makker. Oncologist 2021

Management of AEs in IO Plus TKI Therapy

- Two mechanisms of action result in two sets of AE profiles that are not mutually exclusive
- It is important to determine which therapy is causing the AE in order to plan a management strategy



Makker V et al. *Oncologist*. 2021;26:e1599-e1608.
How JA et al. *Gynecol Oncol*. 2021;162:24-31.

Prevention/Management AEs

- Lower starting dose
- Early recognition
- Clarification of cause
  - Hold TKI
- Outpatient vs. inpatient
- Initiation of corticosteroid therapy (grade ≥ 2)
  - 1-2 mg/kg/day methylprednisolone
  - Slow steroid taper over 4-6 weeks
  - Prevention of adverse events
- Consultation

Discussion Questions

67 yo woman
Stage IVB pMMR endometrioid endometrial carcinoma (lung and omental metastases).
BMI 38, type 2 diabetes, hypertension.
First-line carboplatin/paclitaxel/pembrolizumab → partial response but disease progression at 14 months (new liver metastases). Second-line lenvatinib + pembrolizumab → grade 3 hypertension, grade 2 proteinuria, lenvatinib dose reduction to 14 mg, then 10 mg.

I'd like to learn how the investigators titrate the lenvatinib dose — do you start at the recommended dose and reduce as needed or start low and escalate?

Discussion Questions (Continued)

67 yo woman
Stage IVB pMMR endometrioid endometrial carcinoma (lung and omental metastases).
BMI 38, type 2 diabetes, hypertension.
First-line carboplatin/paclitaxel/pembrolizumab → partial response but disease progression at 14 months (new liver metastases). Second-line lenvatinib + pembrolizumab → grade 3 hypertension, grade 2 proteinuria, lenvatinib dose reduction to 14 mg, then 10 mg.

Beyond dose modification, what strategies for side-effect prevention and management do the experts recommend to safely and effectively employ pembrolizumab/lenvatinib?

Discussion Questions (Continued)

67 yo woman
Stage IVB pMMR endometrioid endometrial carcinoma (lung and omental metastases).
BMI 38, type 2 diabetes, hypertension.
First-line carboplatin/paclitaxel/pembrolizumab → partial response but disease progression at 14 months (new liver metastases). Second-line lenvatinib + pembrolizumab → grade 3 hypertension, grade 2 proteinuria, lenvatinib dose reduction to 14 mg, then 10 mg.

What would you use in the second line if a pMMR patient is progressing on chemo-IO? Do you consider IO rechallenge with lenvatinib/pembrolizumab in this setting?

What would you offer third line? Any ADC trials of interest?

Discussion Questions

67 yo woman, metastatic endometrial cancer, pMMR, declines chemotherapy.
Treated with 1L lenvatinib + pembrolizumab. Now with stable disease.

Do you agree with first-line lenvatinib/pembrolizumab in this situation given the patient's refusal of chemotherapy?

If this had been MSI-high disease, would we need chemo versus single-agent IO? What about for POLE-mutant tumors?

Discussion Questions

58 yo woman
Stage IIIC2 serous endometrial carcinoma (para-aortic nodal metastases), pMMR, TP53-abnormal, BRCA1 somatic mutation.
Debulking surgery → first-line carboplatin/paclitaxel + dostarlimab → complete response after 6 cycles. Started maintenance with dostarlimab + niraparib. Tolerated well for 10 months, then developed recurrent disease (peritoneal carcinomatosis).

How would you have provided care for this patient, and what would you do now?

Discussion Questions (Continued)

58 yo woman
Stage IIIC2 serous endometrial carcinoma (para-aortic nodal metastases), pMMR, TP53-abnormal, BRCA1 somatic mutation.
Debulking surgery → first-line carboplatin/paclitaxel + dostarlimab → complete response after 6 cycles. Started maintenance with dostarlimab + niraparib. Tolerated well for 10 months, then developed recurrent disease (peritoneal carcinomatosis).

What is the current role of PARP inhibition in BRCA-mutated endometrial cancer? What about pMMR tumors more broadly, given that they don't benefit as much from chemo-IO alone?

Could we use ctDNA to identify candidates who might benefit from PARP in the maintenance setting?

RTP RESEARCH TO PRACTICE

Discussion Questions

55-year-old woman with advanced pMMR endometrial cancer with a somatic BRCA2 mutation. Completes 6 cycles of carboplatin/paclitaxel and is started on maintenance olaparib. On cycle 3, she develops grade 2 anemia (hemoglobin 8.2 g/dL), nausea and moderate fatigue.

Do you support this approach, or is IO absolutely necessary?

What are the expected toxicities requiring dose modification or supportive care with PARP inhibitor maintenance in EC, and how frequently should hematologic parameters be monitored during maintenance therapy?

What is the ideal dosage with olaparib in this situation?

RTP
RESEARCH
TO PRACTICE

Discussion Questions (Continued)

55-year-old woman with advanced pMMR endometrial cancer with a somatic BRCA2 mutation. Completes 6 cycles of carboplatin/paclitaxel and is started on maintenance olaparib. On cycle 3, she develops grade 2 anemia (hemoglobin 8.2 g/dL), nausea and moderate fatigue.

Are there data to support PARP inhibitor rechallenge after treatment interruption?

Would you consider switching to an alternative PARP inhibitor? For a patient with controlled disease but worsening fatigue and cytopenias, what supportive care interventions have been most helpful in maintaining treatment tolerance?

Agenda

Module 1: Current Up-Front Chemoimmunotherapeutic Approaches for Advanced Endometrial Cancer (EC) — Dr Backes

Module 2: Current and Future Role of Anti-PD-1/PD-L1 Antibodies in Combination with Systemic Therapies Beyond Chemotherapy for Advanced EC — Dr Westin

Module 3: Promising Agents Under Investigation for EC — Dr Slomovitz

PROMISING AGENTS UNDER INVESTIGATION FOR THE MANAGEMENT OF PATIENTS WITH ENDOMETRIAL CANCER

Brian M. Slomovitz, MD, FACOG

Director, Gynecologic Oncology, Mount Sinai Medical Center

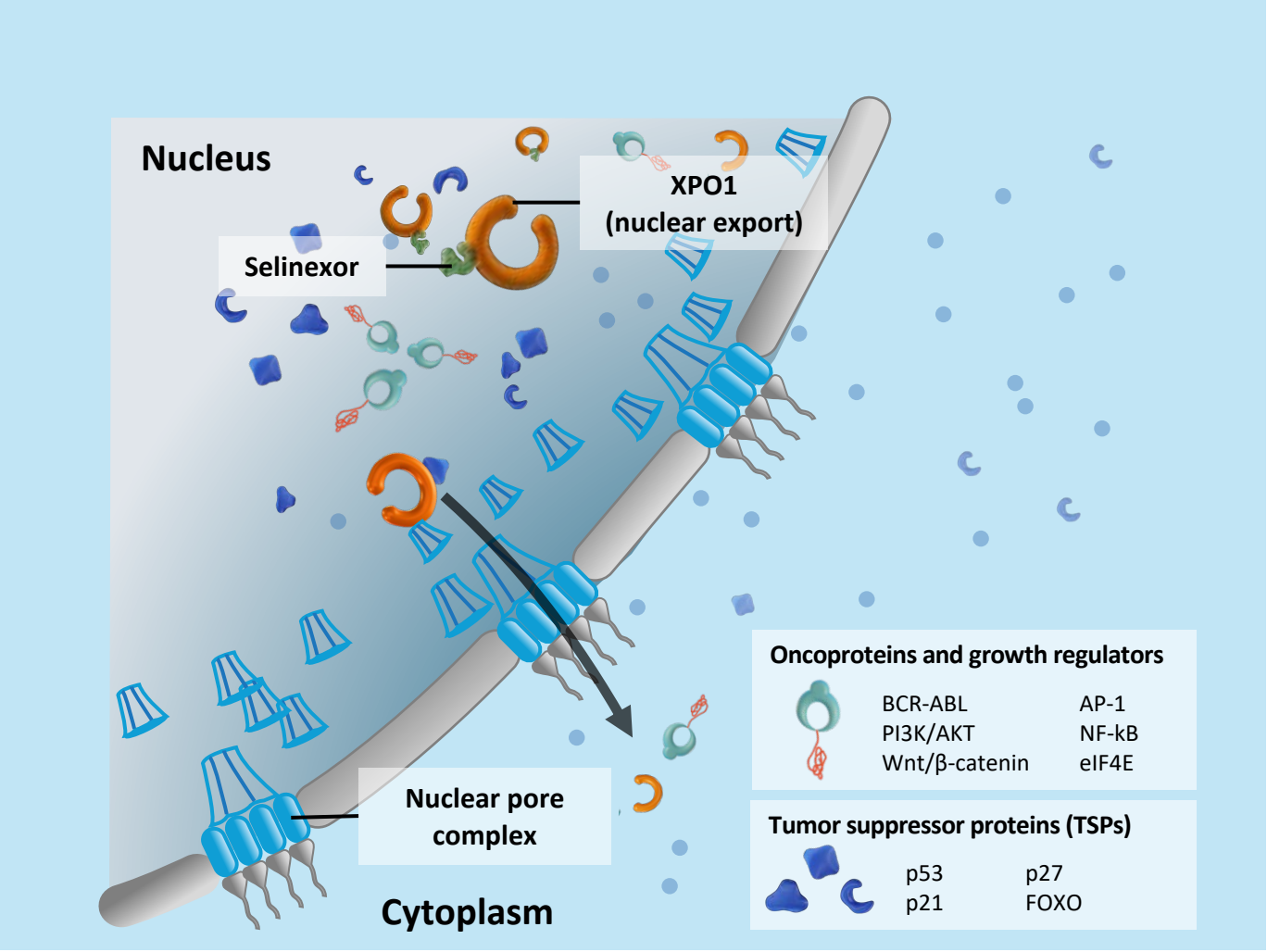
Professor, Obstetrics and Gynecology, Florida International University

Member, Board of Directors, GOG Foundation

Uterine Cancer Clinical Trial Lead, GOG Partners

Miami Beach, FL

Selinexor Is a Targeted Oral XPO1 Inhibitor

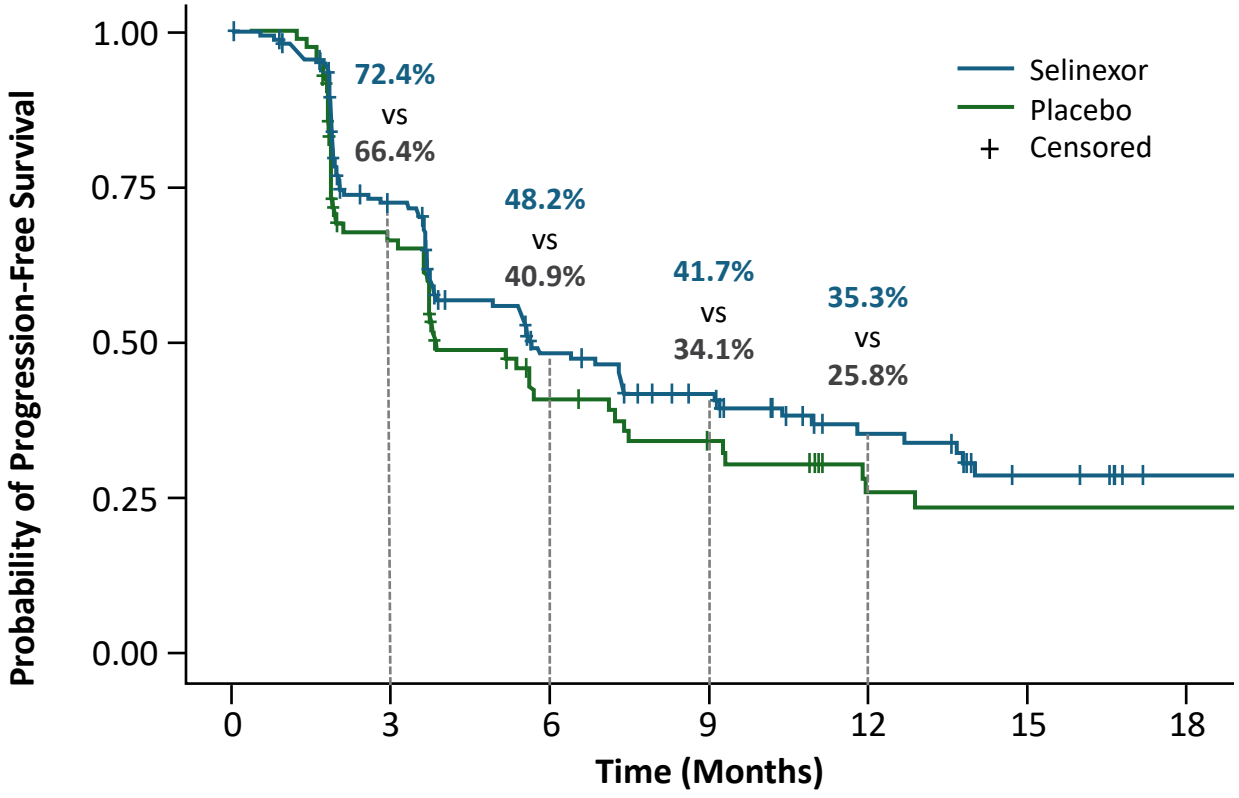


XPO1 inhibition by Selinexor results in:

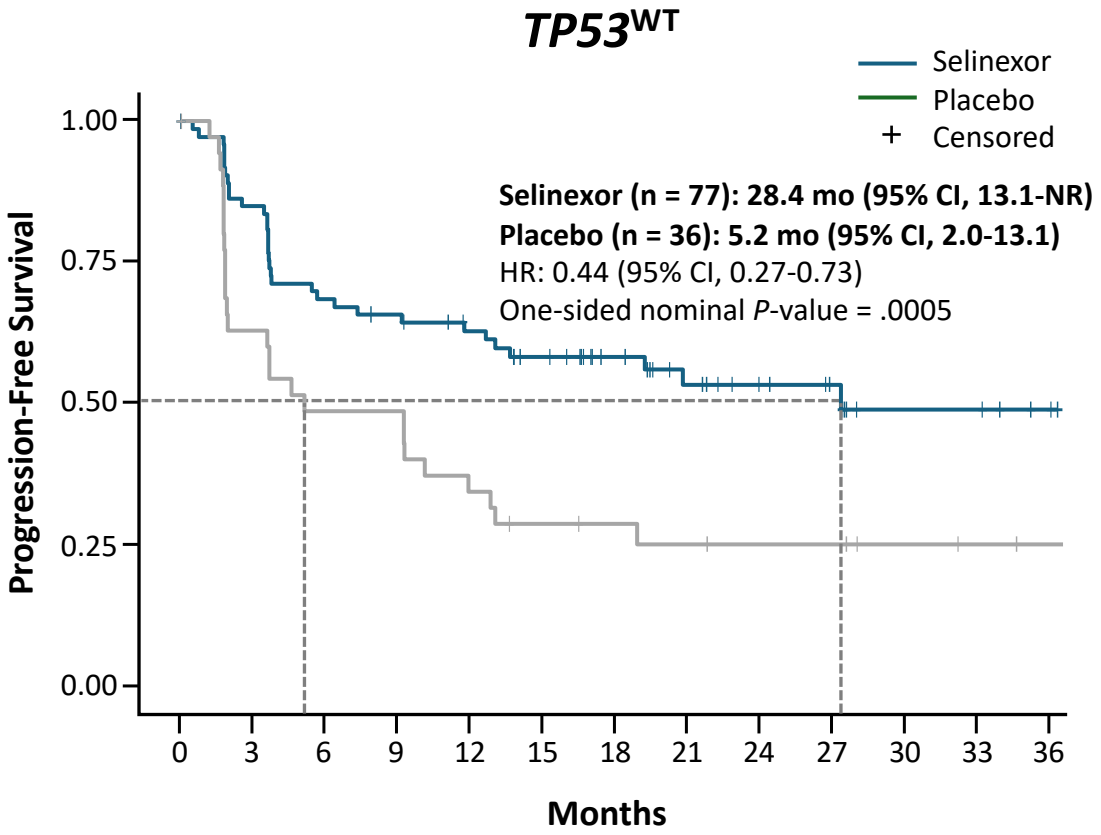
- Nuclear retention and functional reactivation of TSPs (eg, p53), which selectively kill cancer cells and largely spare normal cells
- Inhibition of mRNA export of select oncogenes, thus decreasing subsequent translation and synthesis of oncoproteins
- Simultaneous targeting of several oncogenic pathways involved in cancer development, maintenance, and progression

Tai Y-T, et al. *Leukemia*. 2014; Gandhi UH, et al. *Clin Lymphoma Myeloma Leuk*. 2018; Sun Q, et al. *Signal Transduct Target Ther*. 2016.

ENGOT-EN5/GOG-3055/SIENDO: PFS in ITT and TP53 WT Population



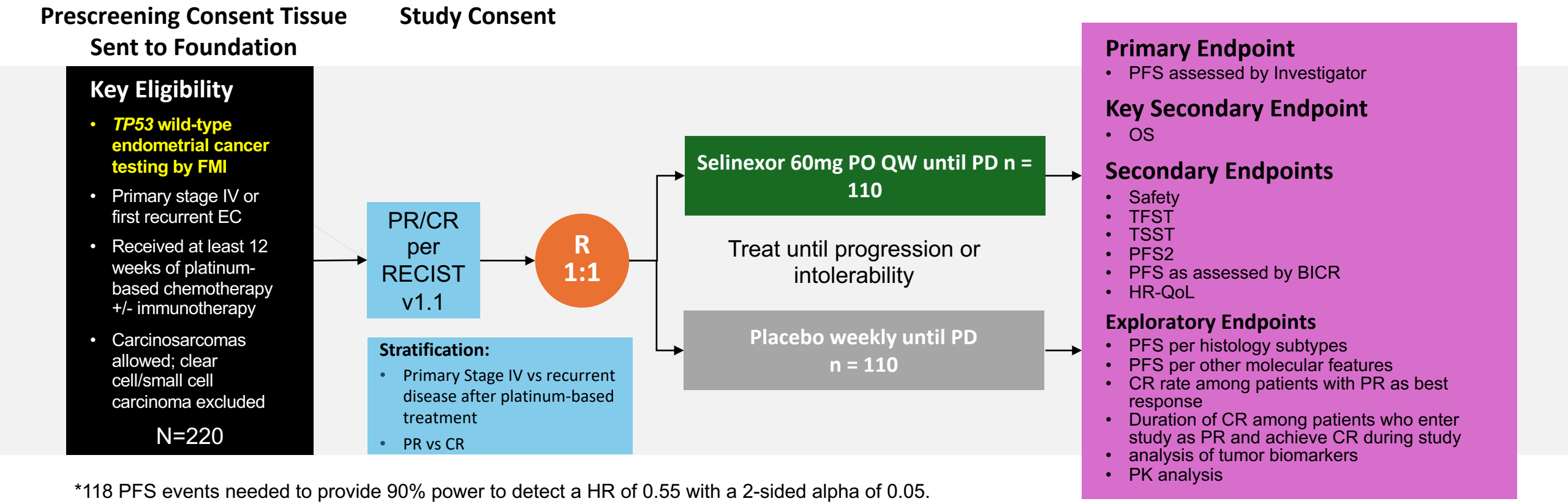
Median follow-up: 10.2 months (95% CI 8.97, 13.57)



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

XPORT-EC-042: A Phase 3 of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With *TP53* Wild-type, Advanced, or Recurrent EC



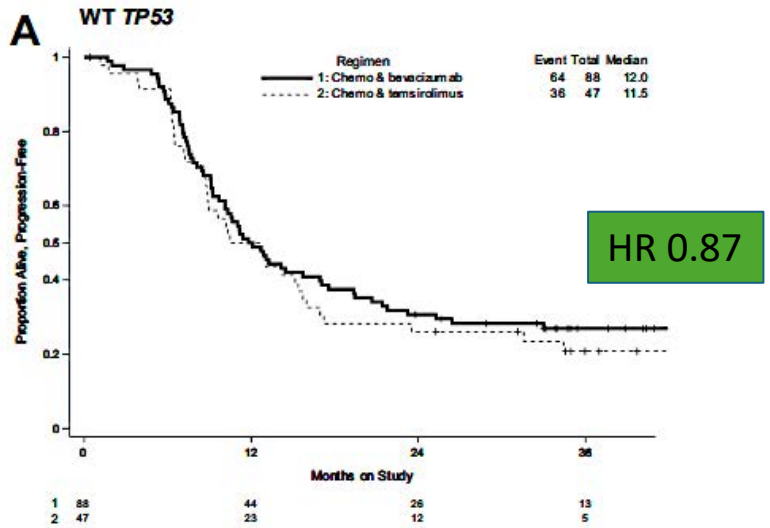
*118 PFS events needed to provide 90% power to detect a HR of 0.55 with a 2-sided alpha of 0.05.

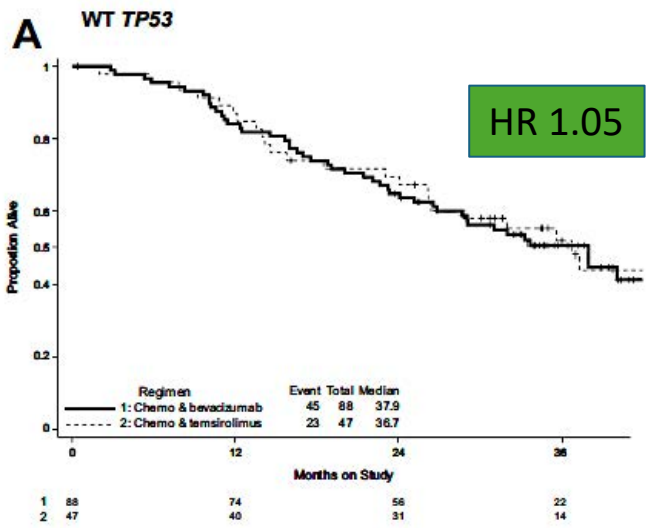
GOG FOUNDATION Transforming the standard of care

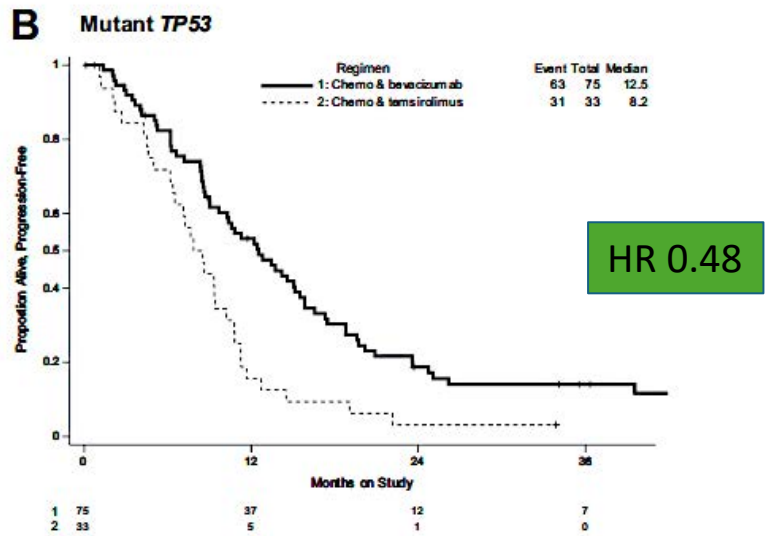
ENGOT European Network of Gynaecological Oncological Trial groups

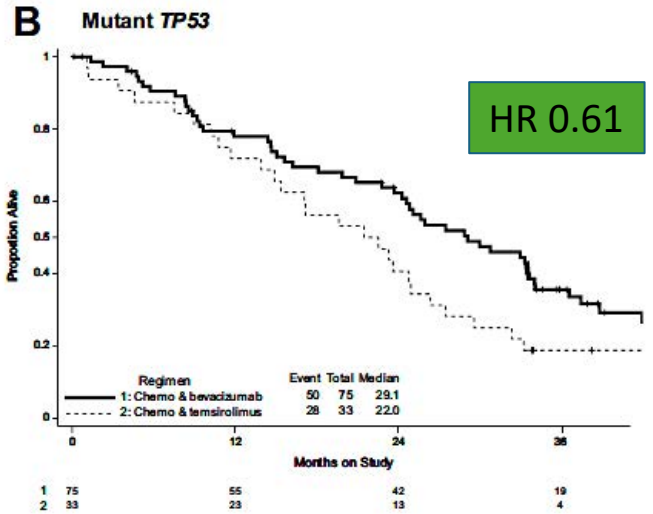
CT.gov:NCT05611931

P53 mutation as a “biomarker” for response to Bevacizumab in Endometrial Cancer: Ancillary Investigation of GOG 86P









Leslie K. et al. Gyncol Oncol 2021

NRG-GY035 A Randomized Phase III Trial of Carboplatin, Paclitaxel, Pembrolizumab Versus Carboplatin, Paclitaxel, Bevacizumab Versus Carboplatin, Paclitaxel, Pembrolizumab, Bevacizumab in the Treatment of pMMR, *TP53* Mutated Advanced or Recurrent Endometrial Cancer

NRG-GY035
SCHEMA

1. pMMR, *TP53* mutated endometrial cancer
2. Stage III and Stage IVA RECIST-evaluable disease; Stage IVB (with or without measurable disease), or recurrent (with or without measurable disease).

Stratification:
- Disease Status (newly diagnosed versus recurrent)
- Prior chemotherapy (yes/no)

RANDOMIZE*
*Randomization is 1:1:1

Arm 1
Paclitaxel + Carboplatin + Pembrolizumab every 3 weeks for 6-10 cycles
Pembrolizumab maintenance every 6 weeks for 14 additional cycles

Arm 2
Paclitaxel + Carboplatin + Bevacizumab (or anti-VEGF antibody biosimilar) every 3 weeks for 6-10 cycles
Bevacizumab maintenance every 3 weeks for 28 additional doses

Arm 3
Paclitaxel + Carboplatin + Pembrolizumab + Bevacizumab (or anti-VEGF antibody biosimilar) every 3 weeks for 6-10 cycles
Pembrolizumab maintenance every 6 weeks for 14 additional cycles and
Bevacizumab maintenance every 3 weeks for 28 additional doses

Reassessment imaging for all patients every 9 weeks for the full first year and then every 12 weeks thereafter.

Interim Futility Analysis

Primary endpoint is PFS. **PFS will not be reported until all accrual is completed.**

PI: Amanda Nickles Fader
Co-PI: Michael D. Toboni

SYMBIOTIC-GYN-18 (GOG-3145/ENGOT-EN37/APGOT-EN6/LACOG 0426-EVA): Phase 3 Randomized Open Label Study in Advanced or Recurrent Endometrial Cancer Patients with Proficient MMR Status (NCT07578649)

- pMMR only
- Measurable stage III*
- Stage IV* (with or without measurable disease) or
- Recurrent (with or without measurable disease) disease where the potential for cure by surgery alone or in combination with other modalities is poor
- No prior systemic therapy except for adjuvant chemotherapy for recurrent disease
- Time from prior adjuvant chemotherapy to relapse > 6 months
- Carcinosarcoma is allowed
- ECOG 0 or 1

*FIGO 2023 classification

1:1
N=600

Carboplatin and Paclitaxel Q3W for 6 cycles
+
PF-08634404 10 mg/kg QW3, followed by PF-08634404 maintenance 10mg/kg Q3W (for 2 years/total 35 cycles)

Carboplatin and Paclitaxel Q3W for 6 cycles
+
Pembrolizumab 200mg Q3W, followed by pembrolizumab maintenance 400mg Q6W (for 2 years/total 20 cycles)

Primary endpoints:
- Progression Free Survival (BICR)

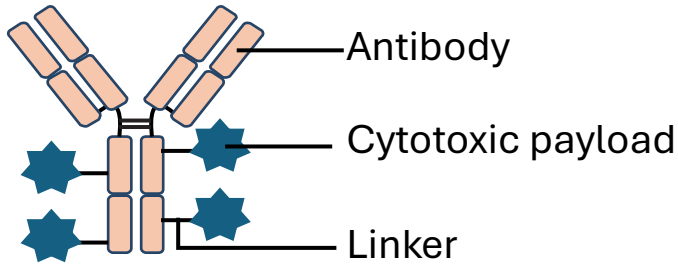
Key Secondary Endpoint:
- Overall Survival

Secondary Endpoints:
- ORR
- DOR
- Safety
- PK
- Other: Biomarkers, PROs

PI: Katy Moore

ADCs in Endometrial Cancer

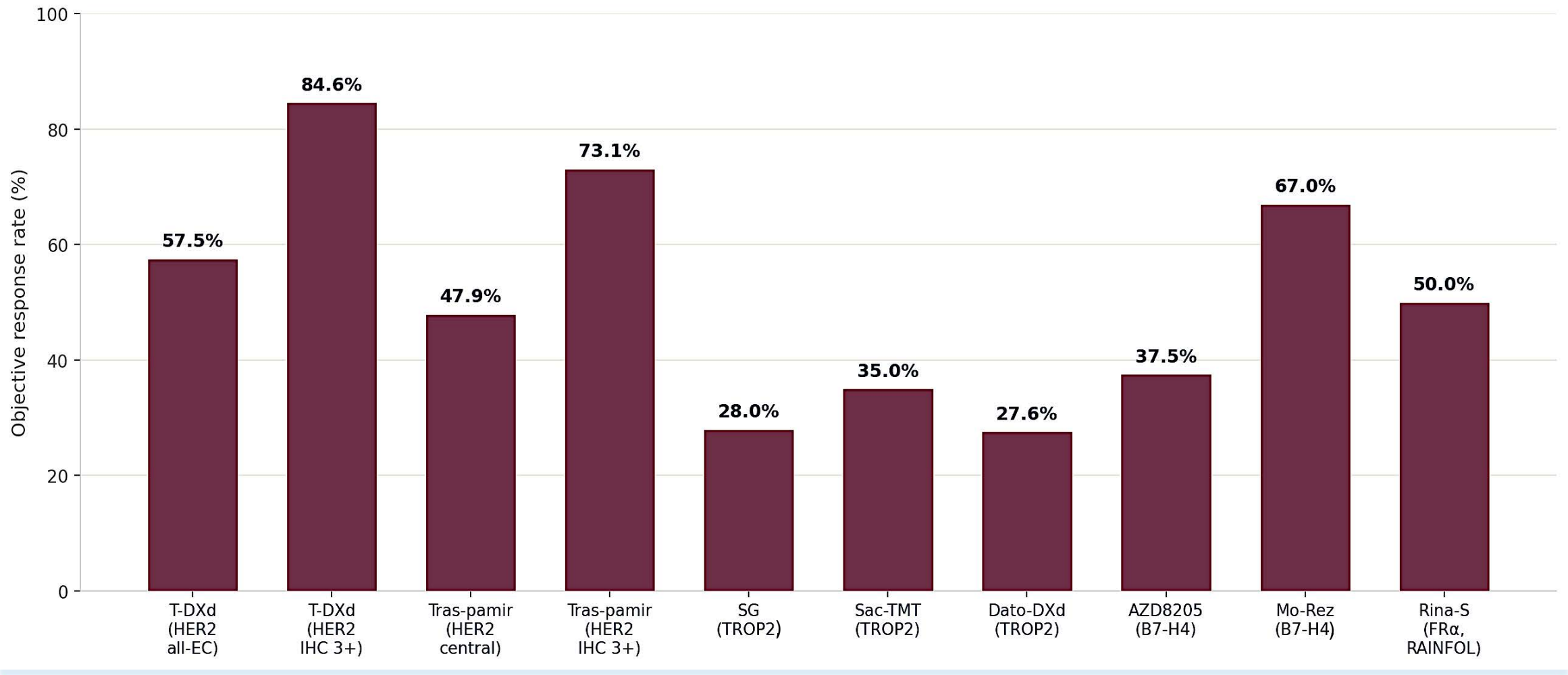
- **Trop 2**
  - Sacituzumab govitecan
  - Sacituzumab tirumotecan
  - Datopotamab deruxtecan
- **HER 2**
  - Trastuzumab deruxtecan
- **B7H4**
  - Mocertatug rezetecan
  - Puxitatug samrotecan (P-Sam)
- **Alpha Folate Receptor**
  - Mirvetuximab
  - Rinatabart sesutecan



ADC Components

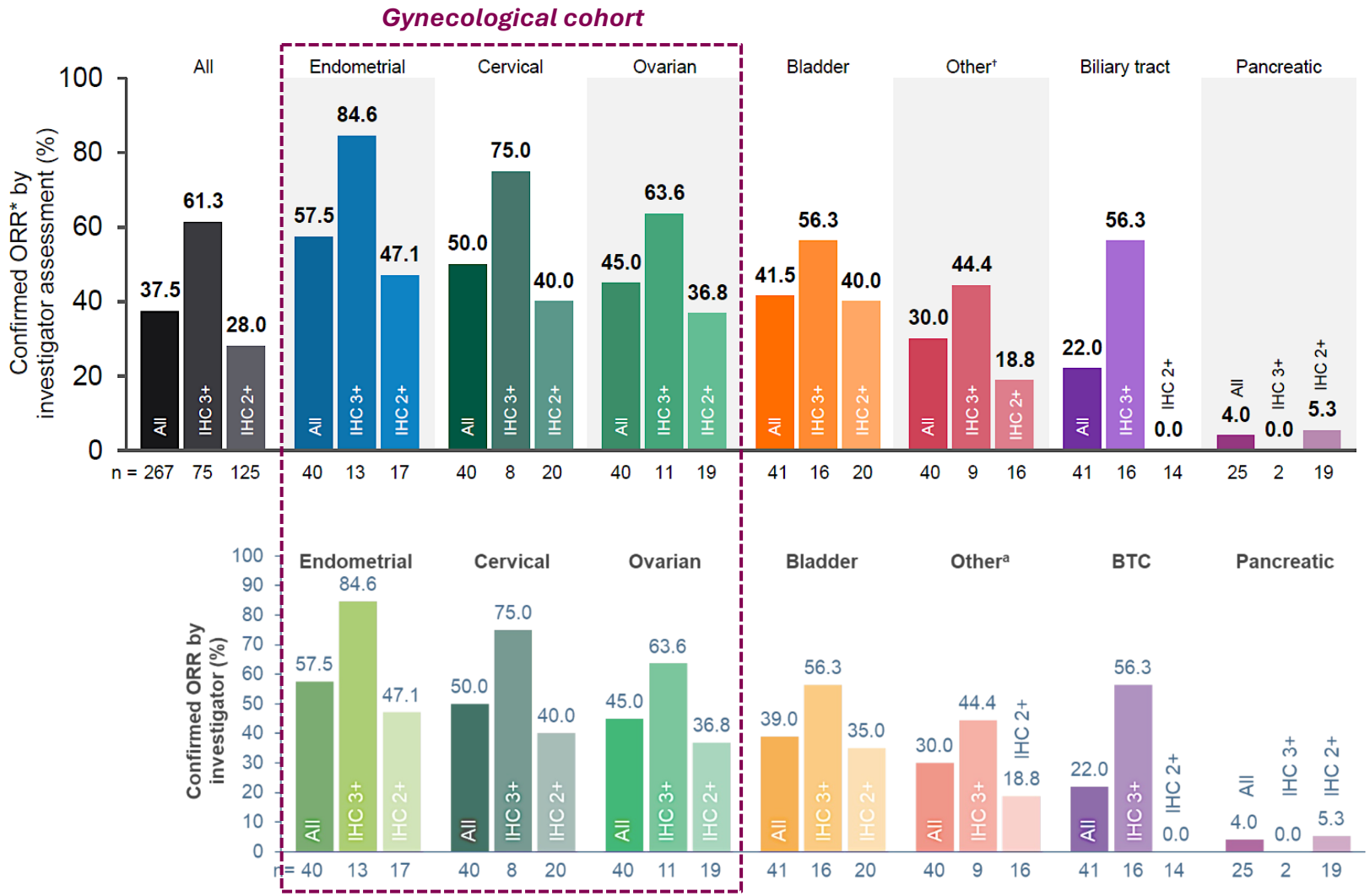
- **Antibody** specific for target antigen on cancer cells
- High potency **cytotoxic payload**
- Cleavable or non-cleavable **linker** between antibody and payload

Comparative ORR across ADC targets in EC



Cross-trial comparisons are illustrative only; populations, prior therapy, and assays differ.

DESTINY-PanTumor02 – Final Analysis (confirmed ORR)



FINAL ANALYSIS

Median (range) follow up (all cohorts) – 12.98 (0.4–47.4) months

PRIMARY ANALYSIS

Median (range) follow up (all cohorts) – 12.75 (0.4–31.6) months

FDA granted accelerated approval to trastuzumab deruxtecan for unresectable or metastatic HER2-positive solid tumors in April 2024.

Phase III DESTINY-Endometrial01 Study

Patient population (N≈600)

- Primary advanced or first recurrent histologically confirmed endometrial cancer
- HER2 expression (IHC 3+/2+) and pMMR by central IHC testing
- Naïve to first-line systemic anticancer therapy
- One prior line of (neo)adjuvant chemotherapy if recurrence / disease progression occurred ≥6 months after prior chemotherapy
- No prior exposure to ADCs or ICIs
- ECOG performance status 0 or 1

Stratification factors

- HER2 expression: IHC 3+ versus 2+
- PD-L1 status: tumor area positivity ≥1% versus <1%
- Geographical region: Asia versus non-Asia

Randomization

1:1:1

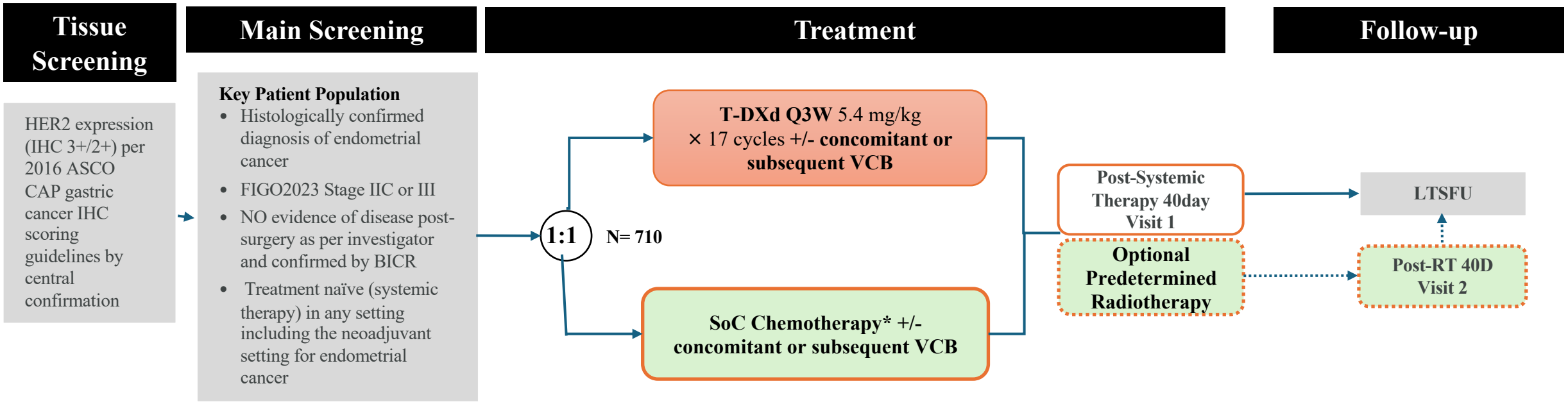
Arm A (n≈200): T-DXd + rilvegostomig*†

Arm B (n≈200): T-DXd + pembrolizumab*†

Arm C (n≈200): carboplatin/paclitaxel + pembrolizumab‡

Slomovitz B et al. ESMO 2025

ADJUVANT:
DESTINY-Endometrial02/ GOG-3122/ENGOT-en30/GINECO : 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



***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

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ENGOT European Network of Gynaecological Oncological Trial groups

NCT07022483

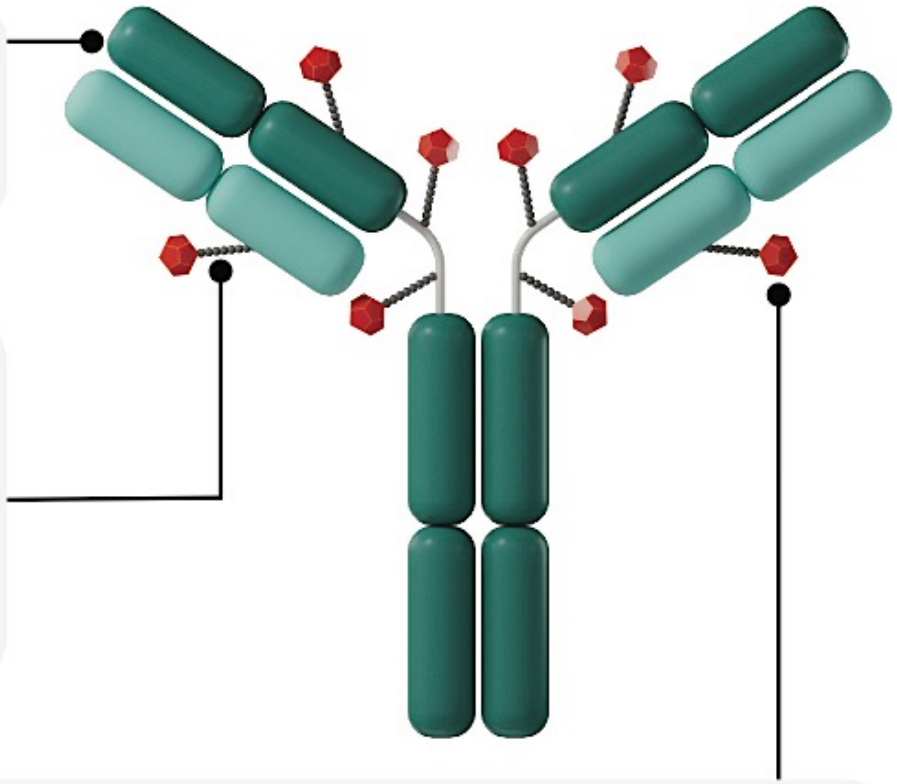
Phase I/II Trial Sacituzumab Tirumotecan (Sac-TMT) in Advanced/Metastatic Endometrial Carcinoma

Monoclonal antibody

- Sacituzumab, a humanized anti-TROP2 antibody with high affinity for TROP2

Unique, bifunctional linker

- Maximizes payload delivery to tumor cells
- Irreversible connection with the antibody ensures minimal payload loss in the circulation
- pH-sensitive cleavage from the payload in the lysosome ensures payload release in the tumor cell

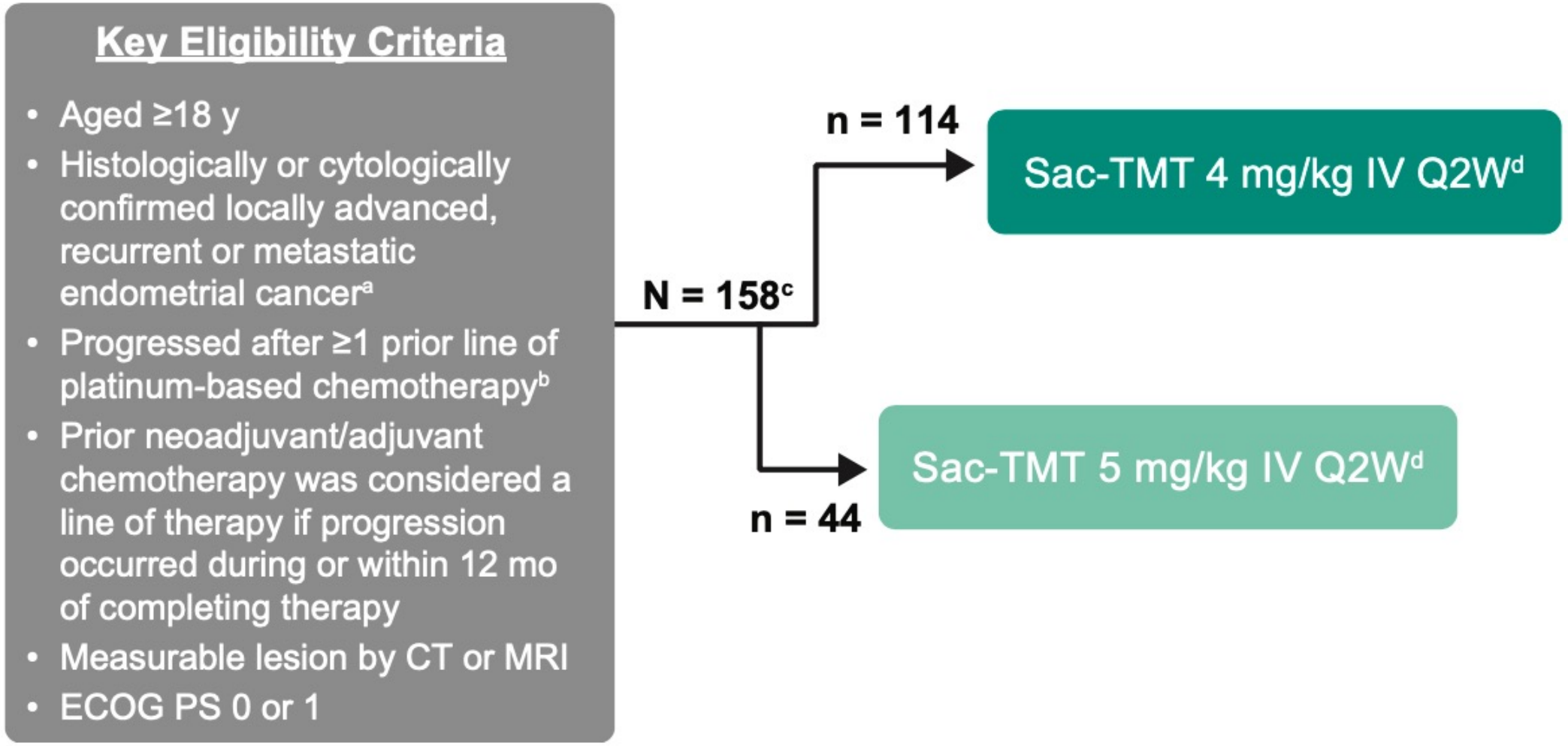


Cytotoxic payload

- Novel, belotecan-derived topoisomerase I inhibitor payload
- Average DAR of 7.4 (range, 7–8)
- Membrane permeability elicits a bystander effect in nearby tumor cells

Wang, et al 111P, ESMO 2025

Phase I/II Trial Sacituzumab Tirumotecan (Sac-TMT) in Advanced/Metastatic Endometrial Carcinoma



Wang, et al 111P, ESMO 2025

Phase I/II Trial Sacituzumab Tirumotecan (Sac-TMT) in Advanced/Metastatic Endometrial Carcinoma

	Sac-TMT 4 mg/kg n = 114	Sac-TMT 5 mg/kg n = 44	Total N = 158
ORR (95% CI), %			
Confirmed ORR	30.7 (22.4–40.0)	34.1 (20.5–49.9)	31.6 (24.5–39.5)
Unconfirmed ORR	35.1 (26.4–44.6)	36.4 (22.4–52.2)	35.4 (28.0–43.4)
DCR (95% CI), %	74.6 (65.6–82.3)	75.0 (59.7–86.8)	74.7 (67.2–81.3)
Best overall response, n (%)			
PR	35 (30.7)	15 (34.1)	50 (31.6)
SD	50 (43.9)	18 (40.9)	68 (43.0)
PD	22 (19.3)	10 (22.7)	32 (20.3)
NE	7 (6.1)	1 (2.3)	8 (5.1)
DOR, median (95% CI), mo	9.3 (2.1+ to 12.0+)	8.7 (3.8 to 17.7)	9.3 (2.1+ to 17.7)

DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
"+" indicates a censored observation.

Wang, et al 111P, ESMO 2025

Phase I/II Trial Sacituzumab Tirumotecan (Sac-TMT) in Advanced/Metastatic Endometrial Carcinoma

	Sac-TMT 4 mg/kg n = 114	Sac-TMT 5 mg/kg n = 44	Total N = 158
Any treatment-related AE[a]	113 (99.1)	44 (100)	157 (99.4)
Grade ≥3	59 (51.8)	34 (77.3)	93 (58.9)
Led to treatment discontinuation	2 (1.8)	1 (2.3)	3 (1.9)
Led to any dose reduction	28 (24.6)	19 (43.2)	47 (29.7)
Serious	13 (11.4)	9 (20.5)	22 (13.9)
Led to death[b]	1 (0.9)	0	1 (0.6)

Wang, et al 111P, ESMO 2025

NEWS RELEASE

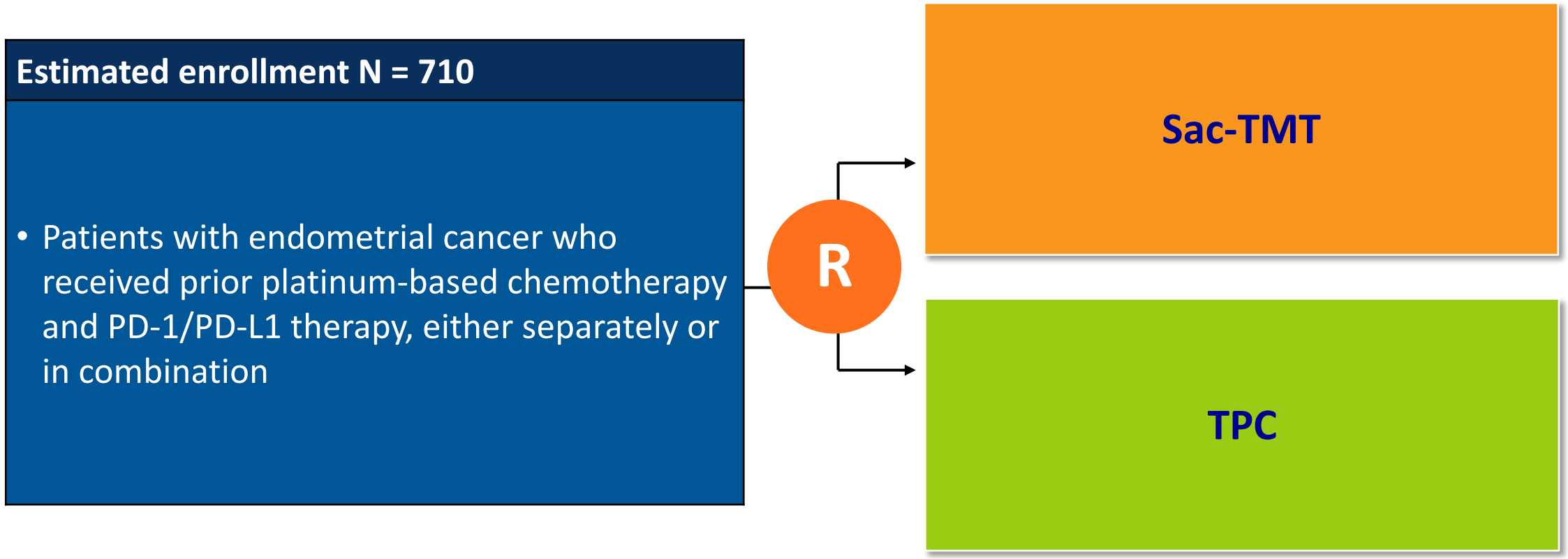
[The Manufacturer] Announces TroFuse-005 Trial Evaluating Sacituzumab Tirumotecan (Sac-TMT) Met Primary Endpoints of Overall Survival (OS) and Progression-Free Survival (PFS) in Certain Patients with Advanced or Recurrent Endometrial Cancer

2026-05-18

Sac-TMT is the first TROP2 ADC to improve OS and PFS compared to chemotherapy in patients with advanced or recurrent endometrial cancer who have progressed after platinum-based chemotherapy and anti-PD-1/L1 immunotherapy in a global Phase 3 study

RAHWAY, N.J.--(BUSINESS WIRE)-- [The manufacturer] today announced the pivotal Phase 3 TroFuse-005 trial evaluating sacituzumab tirumotecan (sac-TMT), an investigational TROP2-directed antibody-drug conjugate (ADC) [...] met its primary endpoints of overall survival (OS) and progression-free survival (PFS) in certain patients with

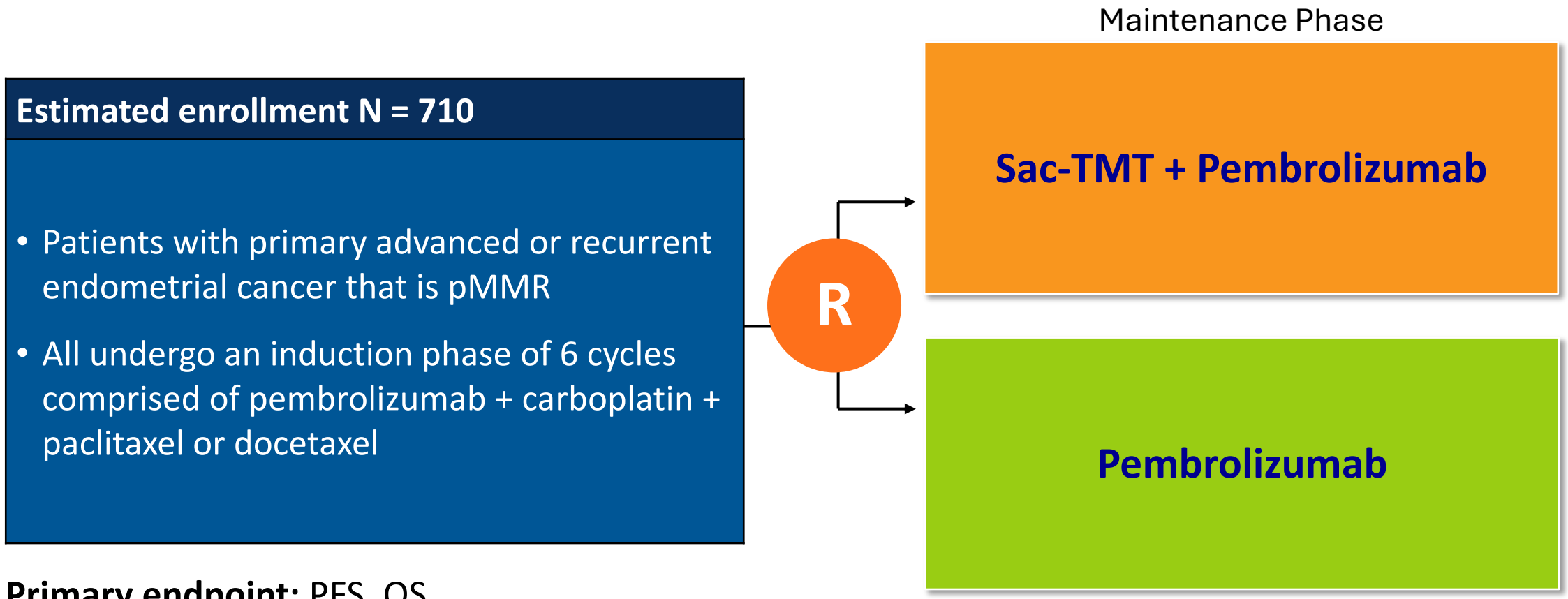
TroFuse-005 Phase III Trial Design



Primary endpoint: PFS, OS

https://clinicaltrials.gov/study/NCT06132958. Accessed May 2026.

TroFuse-033 Phase III Trial Design



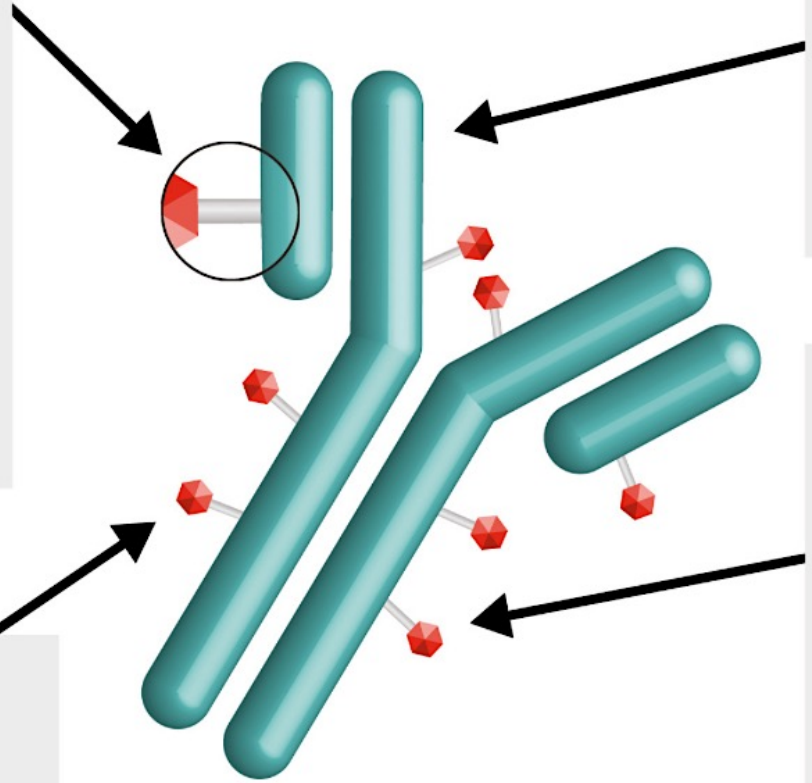
Primary endpoint: PFS, OS

https://clinicaltrials.gov/study/NCT06952504. Accessed May 2026.

Efficacy and Safety of Sacituzumab Govitecan in Patients With Advanced Solid Tumors (TROPiCS-03): Analysis in Patients With Advanced Endometrial Cancer

Linker for SN-38

- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)



Humanized anti–Trop-2 antibody

- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

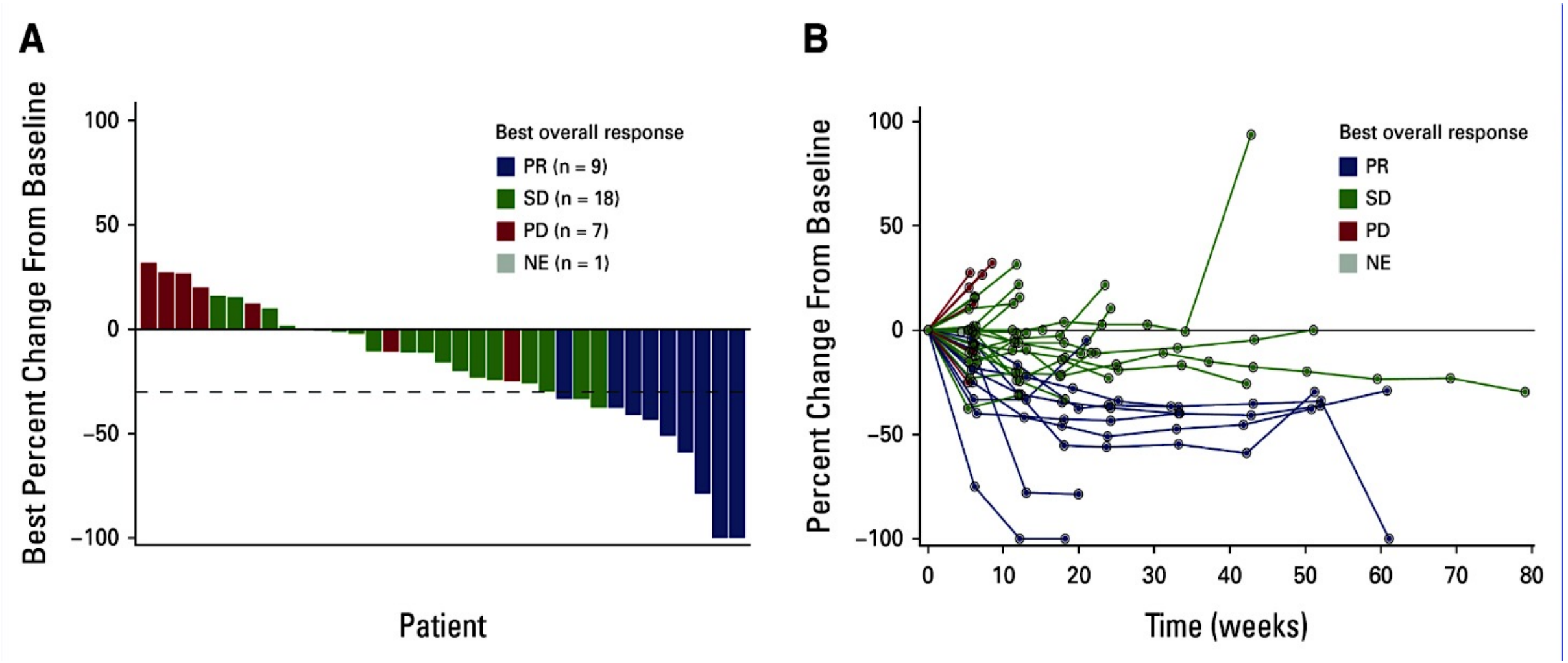
SN-38 payload

- SN-38 is more potent than parent compound, irinotecan (topoisomerase I inhibitor)
- SN-38 was chosen for its moderate cytotoxicity (with IC_{50} in the nanomolar range), permitting delivery in high quantity to the tumor

Internalization and enzymatic cleavage by tumor cell not required for SN-38 liberation from antibody

Santin AD, Corr BR, J Clin Oncol. 2024 Oct 10;42(29):3421-3429

Efficacy and Safety of Sacituzumab Govitecan in Patients With Advanced Solid Tumors (TROPiCS-03): Analysis in Patients With Advanced Endometrial Cancer



Santin AD, Corr BR, J Clin Oncol. 2024 Oct 10;42(29):3421-3429

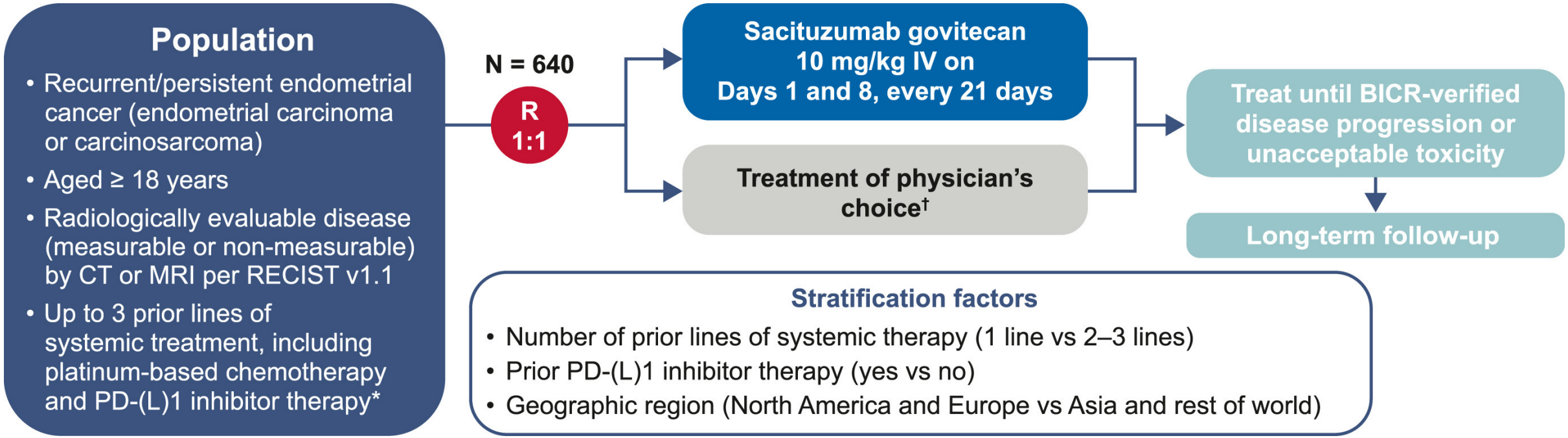
Efficacy and Safety of Sacituzumab Govitecan in Patients With Advanced Solid Tumors (TROPiCS-03): Analysis in Patients With Advanced Endometrial Cancer

Summary of Responses

Variable	All Patients (N = 41)
ORR (confirmed CR + PR), No. (%)	9 (22)
95% CI	11 to 38
Best overall response, No. (%)	
Confirmed CR	0
Confirmed PR	9 (22)
SD	18 (44)
PD	8 (20)
NE	2 (5)
Not assessed[a]	4 (10)
Clinical benefit rate (confirmed CR + PR + SD ≥6 months), No. (%)	13 (32)
95% CI	18-48
Time to response, months[b,c]	
Median (range)	2.8 (1.4-5.8)
DOR, months[b,d]	
Median (95% CI)	8.8 (2.8 to NE)

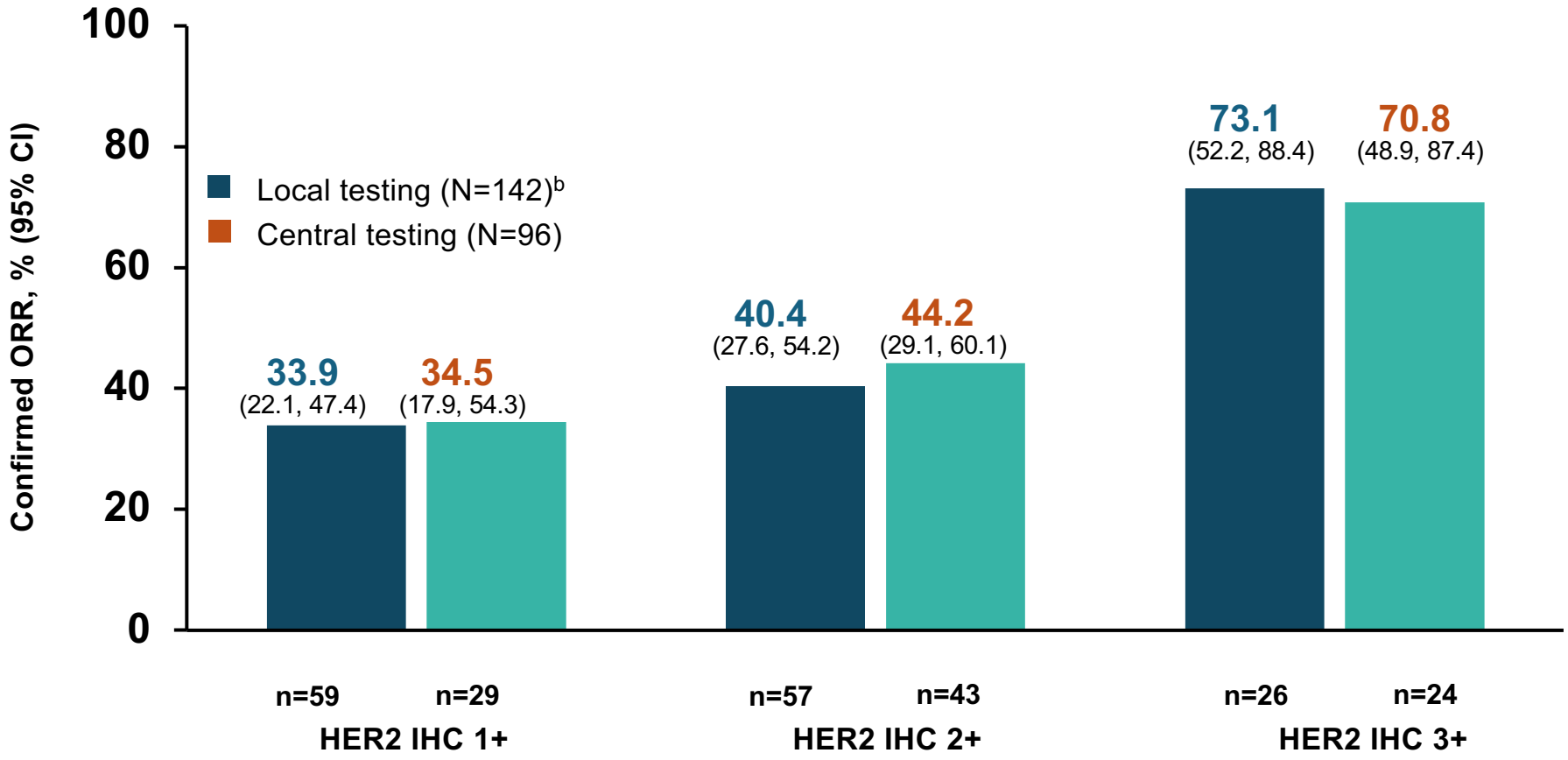
Santin AD, Corr BR, J Clin Oncol. 2024 Oct 10;42(29):3421-3429

Phase III ASCENT-GYN-01 Study



Eskander RN et al. IJGC 2025

T-pamirtecan (DB-1303/BNT323) in HER2-expressing, recurrent endometrial cancer

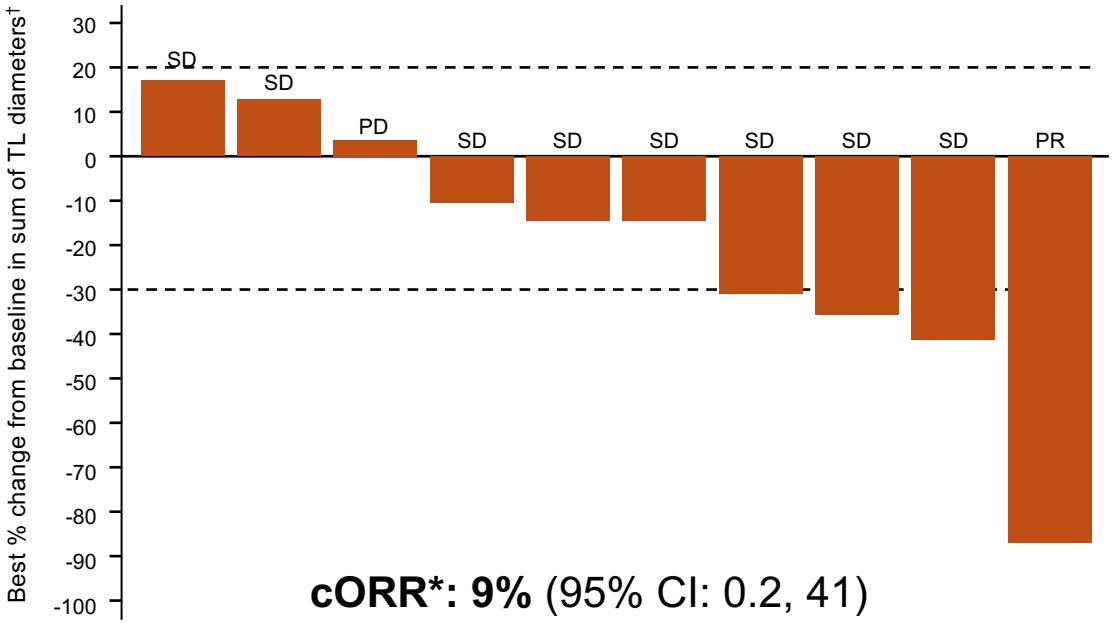


[a]By IRC in the modified FAS, which includes patients who received ≥1 dose of trastuzumab pamirtecan and had at least one measurable lesion as assessed by IRC at baseline according to RECIST v1.1; [b]IHC score was not available for one patient; patient tested positive by ISH.

Mocertatug Rezetecan (GSK5733584), a B7-H4 Targeted Antibody-Drug Conjugate in EC: First Results from the Global BEHOLD-1 Study

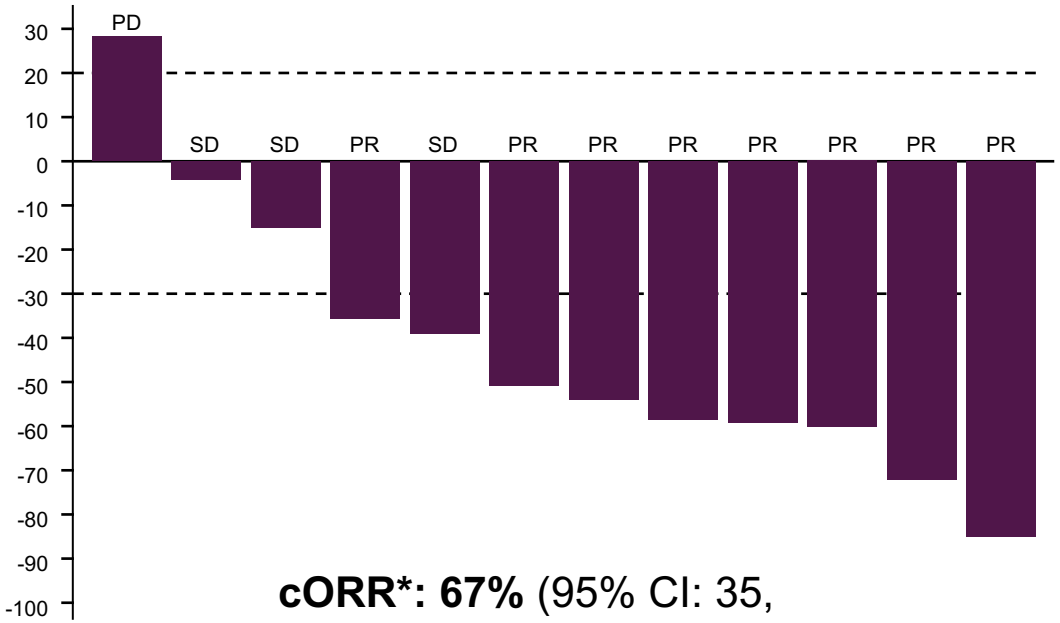
Confirmed ORR was 67% (n=8/12) in patients with EC at the 4.8 mg/kg Q3W dose

Mo-Rez 2.8 mg/kg (N=11)



cORR*: 9% (95% CI: 0.2, 41)

Mo-Rez 4.8 mg/kg (N=12)

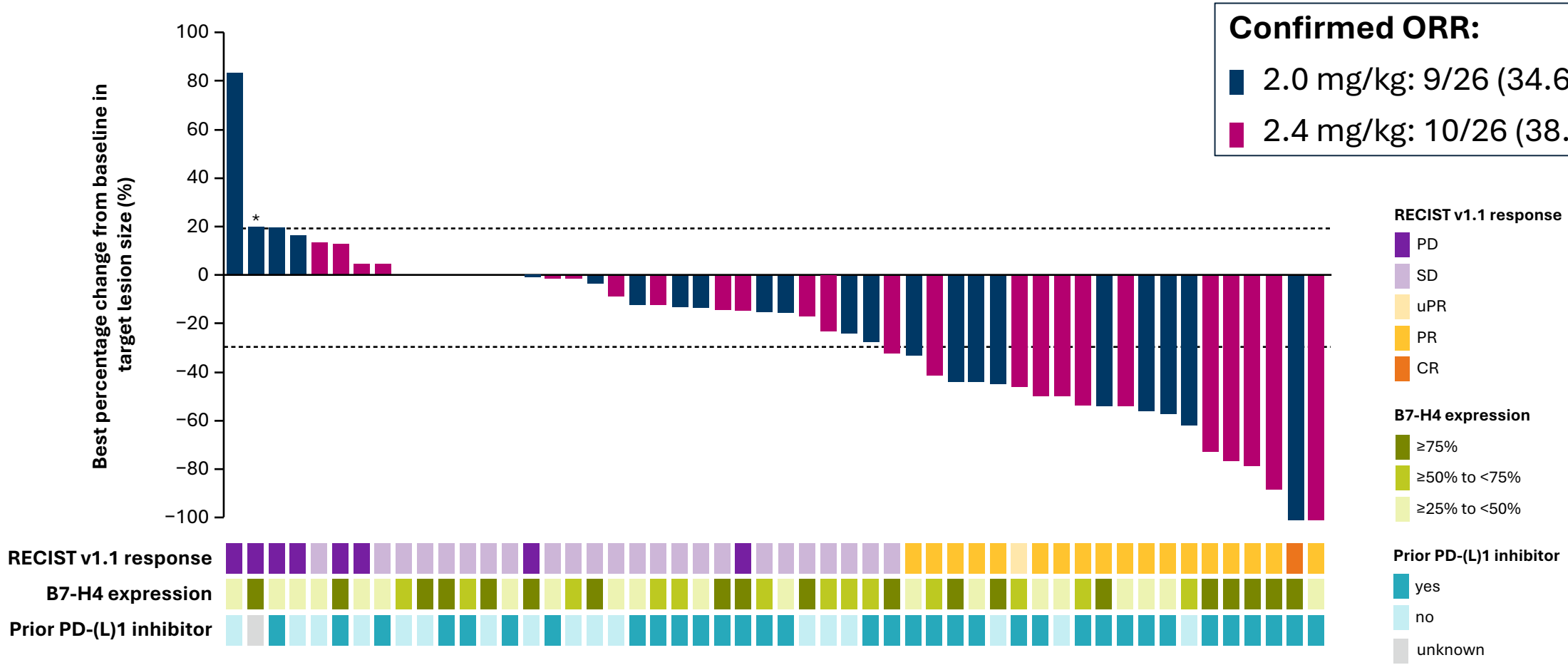


cORR*: 67% (95% CI: 35, 90)

Responses were observed across a range of B7-H4 expression levels

Median (IQR) follow-up was 4.0 (1.7, 5.8) months for the overall cohort (N=49)

Puxitatug samrotecan (P-Sam): a B7-H4–targeting TOP1i ADC Efficacy was observed in patients with EC across B7-H4 expression



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

Rinatabart sesutecan (Rina-S®) for patients with advanced or recurrent endometrial cancer (a/r EC): Update from dose expansion cohort B2 of RAINFOL™-01

Antitumor Activity

	100 mg/m^2 (n=22)	120 mg/m^2 (n=34)[a]
Median on-study follow-up[b], months (95% CI)	11.7 (11.3-12.4)	13.8 (11.5-16.5)
Confirmed ORR[c], % (95% CI)	50.0 (28.2-71.8)	44.1 (27.2-62.1)
Confirmed response, n (%)		
CR	2 (9.1)	1 (2.9)
PR	9 (40.9)	14 (41.2)
SD	11 (50.0)	13 (38.2)
NE	0	1 (2.9)
DCR, % (95% CI)	100 (84.6-100.0)	82.4 (65.5-93.2)

[a]Response-evaluable population (includes patients with ≥1 post-baseline scan). [b]Median on-study follow-up is the median time from first dose to censoring for all patients at data cutoff. [c]Based on investigator assessment.

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease

Pivotal Phase 3 trials in post-platinum / post-IO recurrent EC

Trial / ID	Agent	Target & selection	Sponsor / Status
GOG-3095: TroFuse-005 NCT06132958	Sacituzumab tirumotecan (sac-TMT)	TROP2	
GOG-3104: ASCENT-GYN-01 NCT06486441	Sacituzumab govitecan (SG)	TROP2	
GOG 3105: Fern-EC-01 NCT06340568	Trastuzumab pamirtecan	HER2 IHC 1+, 2+, 3+ (central)	
GOG 3110: Bluestar-01 NCT07044336	Puxitatug samrotecan (Puxi-Sam)	B7H4	
GOG-3128 / RAINFOL-03 NCT07166094	Rinatabart sesutecan (Rina-S)	FRα	
GOG-3031/BEHOLD-Endometrial 01	Mocertatug Rezetecan (Mo Rez)	B7H4	
BEHOLD-Endometrial 02 NCT06796907	Mocertatug rezetecan (Mo Rez)	B7H4	

References: ClinicalTrials.gov accessed May 2026: NCT06132958, NCT06865677, NCT06340568, NCT07166094. Merck press release May 18, 2026; Genmab press release Oct 2025; BioN[illegible]

Discussion Questions

58-year-old woman with advanced MSS endometrial cancer, TP53 wild type

Do the faculty test for aberrant TP53 expression in all of their patients at initial diagnosis? Or only certain ones, like those with MSS/pMMR disease?

When is the Phase III trial of selinexor in TP53 wild-type disease expected to be reported?

Given that selinexor is already accessible in other tumor types, should we be trying to access it for our patients with TP53 wild-type disease, particularly those with pMMR?

If selinexor were available for TP53 wild-type advanced EC, would you employ it together with an anti-PD-1/PD-L1 antibody in the maintenance setting for a patient who received up-front chemoimmunotherapy?

If approved, what tolerability issues are likely with selinexor, and how will these be prevented and managed?

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Discussion Questions

58-year-old with Stage III serous endometrial cancer, p53-mutant, MMR-proficient. Received carboplatin/paclitaxel first line, progressed at 10 months. Started lenvatinib/pembrolizumab second line with further progression.

What is the next option? Given the recent press release, do you think sac-TMT will soon be an option for patients like this?

What is known about other TROP2 ADCs in EC? Have any of the faculty members seen meaningful responses with sacituzumab govitecan? Are there any circumstances in which you would attempt to access off-label sacituzumab govitecan, given its availability in other tumor types and the indications of efficacy with TROP2-targeted agents in EC?

Discussion Questions (Continued)

58-year-old with Stage III serous endometrial cancer, p53-mutant, MMR-proficient. Received carboplatin/paclitaxel first line, progressed at 10 months. Started lenvatinib/pembrolizumab second line with further progression.

If TROP2 ADCs reach the clinic in EC, how, when and for whom do you envision we'll be using them? For a patient progressing on first-line chemoimmunotherapy, would a TROP2 ADC be preferable to lenvatinib/pembrolizumab given its alternative mechanism of action?

How likely is it that TROP2 ADCs will eventually move forward in the treatment sequence?

What are the most common toxicities of sac-TMT? Are they identical to sacituzumab govitecan, or are there considerable differences?

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Discussion Questions

63-year-old woman s/p multiple treatments for metastatic pMMR EC. HER2 IHC 2+. T-DXd resulted in a meaningful clinical response with improvement in symptoms, reduction in tumor burden and radiographic partial response, which was sustained.

For a patient with pMMR, HER2-positive EC, would the faculty favor carbo/paclitaxel with IO or with trastuzumab as frontline therapy? Is there any way of predicting which of these will benefit these patients most? Would you ever use both?

How should we sequence pembro/lenvatinib relative to HER2-directed therapy for patients with R/R disease who are eligible for both?

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Discussion Questions (Continued)

63-year-old woman s/p multiple treatments for metastatic pMMR EC. HER2 IHC 2+. T-DXd resulted in a meaningful clinical response with improvement in symptoms, reduction in tumor burden and radiographic partial response, which was sustained.

Any tips on managing nausea/asthenia in patients receiving T-DXd? What is the optimal approach to screening for ILD?

What is the next step in this patient's treatment? Could we try off-label use of a HER2-targeted drug that has proven effective in other tumor types, like zanidatamab?

Would a TROP2 ADC be a reasonable option for this patient? Given both T-DXd and the various TROP2 ADCs have topoisomerase I payloads, would you be comfortable sequencing them?

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What Clinicians Want to Know: Addressing Community Oncologists' Questions About the Current and Future Role of Antibody-Drug Conjugates in the Management of Breast Cancer

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Monday, June 1, 2026

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

Faculty

Professor Giuseppe Curigliano, MD, PhD

Rebecca A Dent, MD, MSc

Erika Hamilton, MD

Nadia Harbeck, MD, PhD

Moderator

Hope S Rugo, MD

RTP RESEARCH TO PRACTICE

Second Opinion: Investigators Provide Perspectives on the Current and Future Use of Novel Therapies for Non-Hodgkin Lymphoma

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Monday, June 1, 2026

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

Faculty

Christopher Flowers, MD, MS, FASCO

Matthew Lunning, DO

Sonali M Smith, MD

Moderator

Brad S Kahl, MD

RTP RESEARCH TO PRACTICE

Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Relapsed/Refractory Multiple Myeloma

A CME Symposium Held Adjunct with the 2026 ASCO® Annual Meeting

Monday, June 1, 2026

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

Faculty

Melissa Alsina, MD

Hans Lee, MD

Paul G Richardson, MD

Moderator

Sagar Lonial, MD, FACP, FASCO

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