Endometrial Cancer (EC): Novel therapies in the pipeline

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Disclosures

- **Employee**: University of Milan-Bicocca and European Institute of Oncology IRCCS, Milan
- **Consultant/Advisor**: AstraZeneca, Clovis Oncology, Eisai, GSK, Immunogen, Mersana, MSD/Merck, Nuvation Bio, Oncxerna, Pieris, Roche, Novocure; Gilead, Regeneron
- **Promotional Speaker**: AstraZeneca, Clovis, MSD/Merk, GlaxoSmithKline, Eisai
- **Investigator/Researcher**: AstraZeneca, GSK, Roche
- **Nonfinancial interests**: Steering Committee Member for ESMO Clinical Guidelines, Chair Scientific Committee ACTO onlus

Endometrial Cancer Post and beyond IO : New drugs and combinations?

New drugs and combinations

- IO rechallenge

✓ Pembrolizumab-Lenvatinib

- Looking for “druggable” targets (precision oncology)

✓ ER/CDK4-6
✓ **P53**
✓ BRCA , HRD
✓ **HER2**
✓ PIK3CA ?
✓ KRAS (?)

- Antibody drug conjugates

✓ Targeting TROP2
✓ Targeting HER2
✓ Targeting Fra

Table 1
Patient Tumor and Treatment Characteristics.

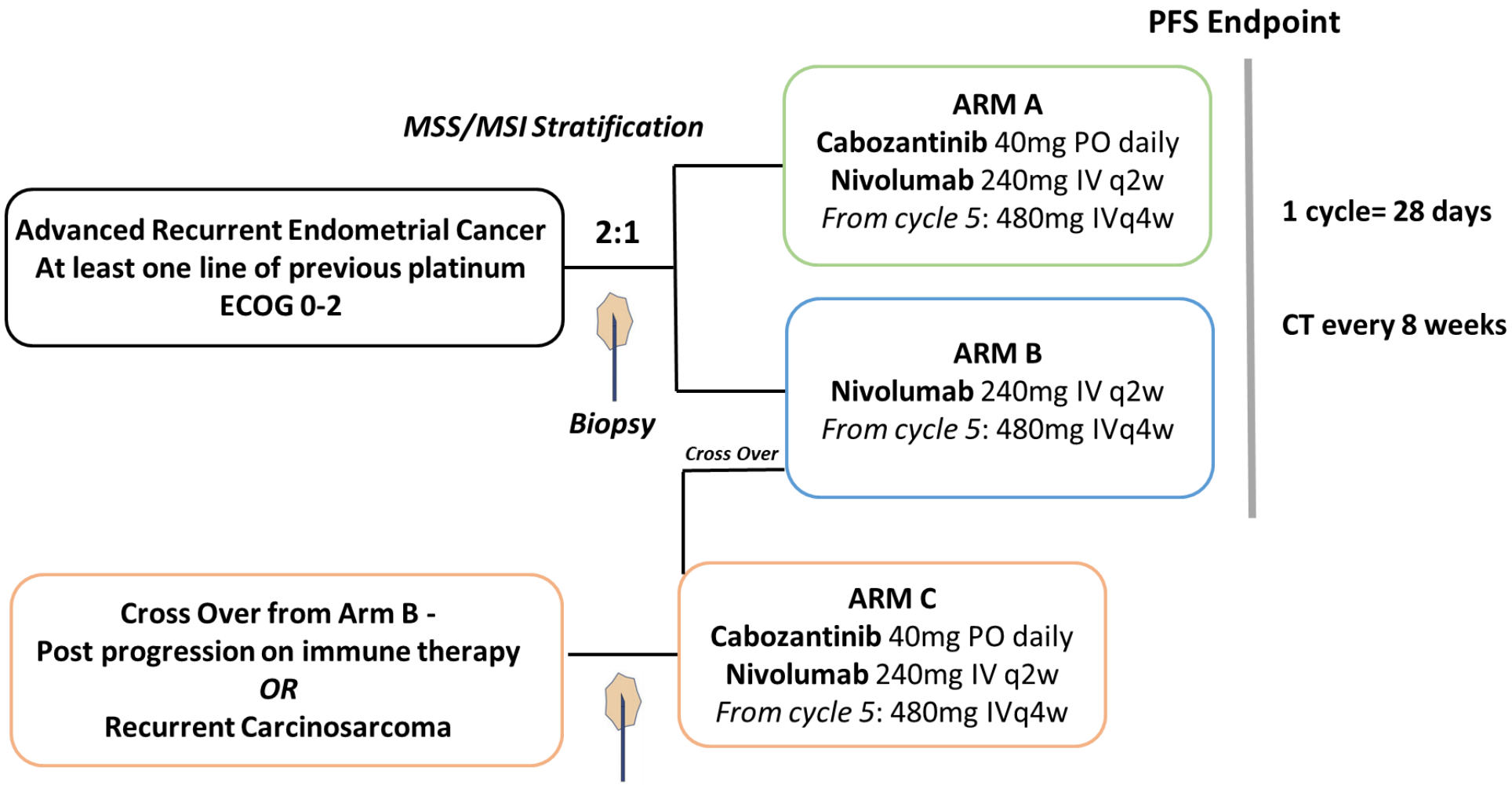
Patient number	MMRd	MLH 1 methyl	Age*	Stage FIGO 2009	Grade	Prior Systemic Therapy	Duration of Pembro	Response to Pembro	Duration of Pembro/ lenvima	Date initiated Lenvima Dose Starting/Final (# courses)	Response
1	MLH1/ PMS2	Present	54	IIIC1 Recurrent	FIGO 2	CP x 6	3 Cycles	Stable	25 cycles	7/1/2021 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	62	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 -	80	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: * Age when Pembo/lenvima started, A = Abraxane, B = Bevacizumab, C = Carboplatin, Cis = Cisplatin, Lenvima = Lenvatinib, Letro = Letrozole MLH1Methyl = MLH1 promoter hypermethylation, P = Paclitaxel, Pembro = Pembrolizumab, -=negative, + currently in active treatment.

- 6 of 8 had radiological response
- 2 with SD (1- Lynch, 1-pre treatment with 11 monotherapy cycles

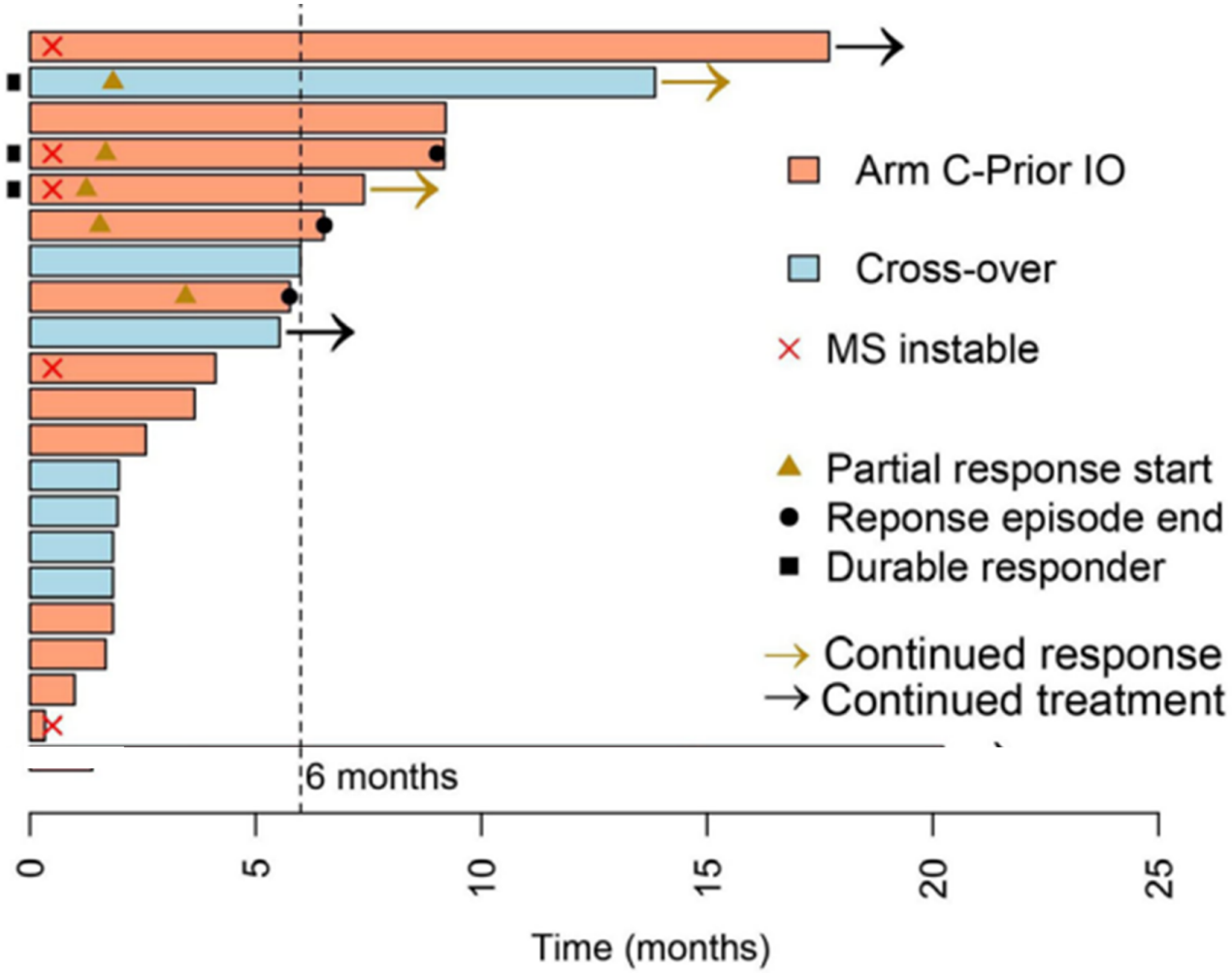
Rose PG et al: Gyn Oncol Rep. Nov 2023

IO after IO in Endometrial Cancer



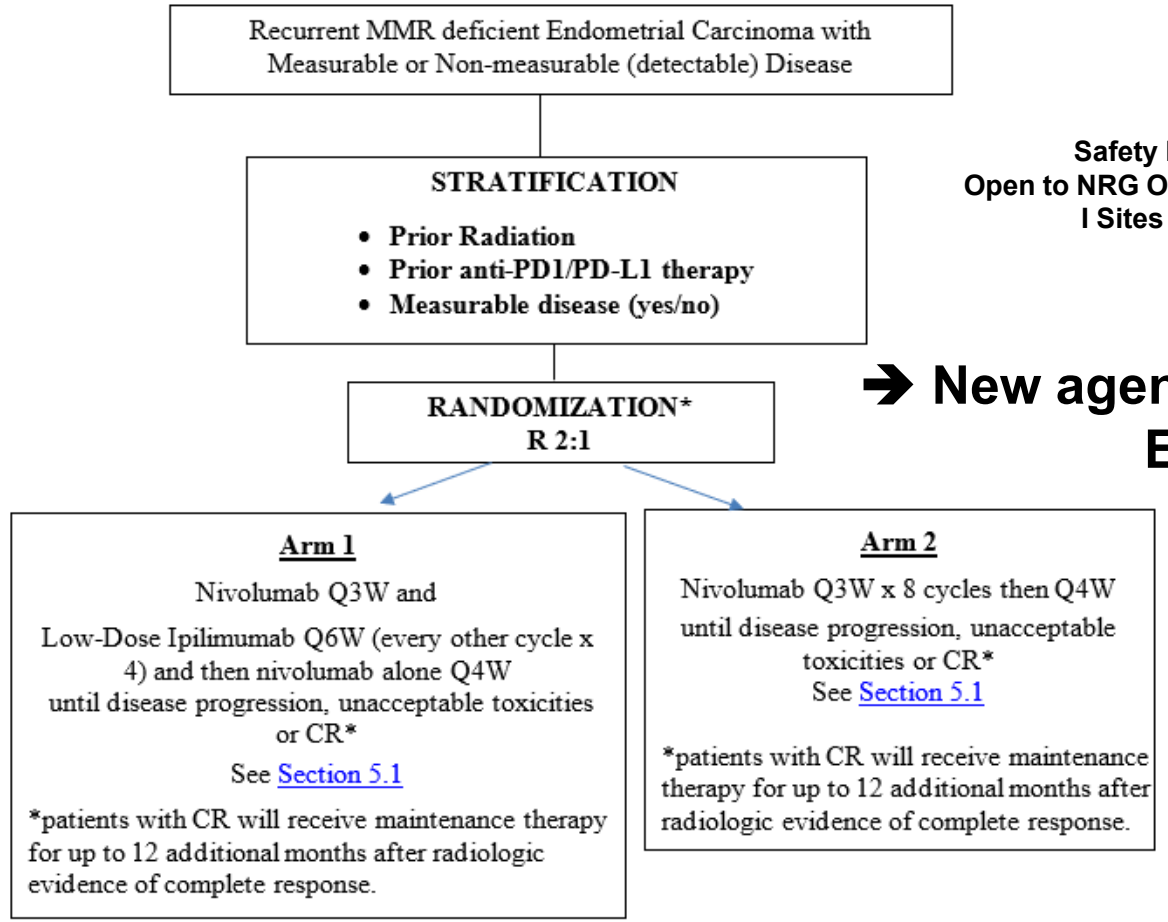
Lheureux S et al, JITC 2022

Exploratory Cohort: Post IO



Lheureux S et al, JITC 2022

Recurrent MMRd – NRG GY025



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

Safety lead-in
Open to NRG Oncology Phase I Sites ONLY

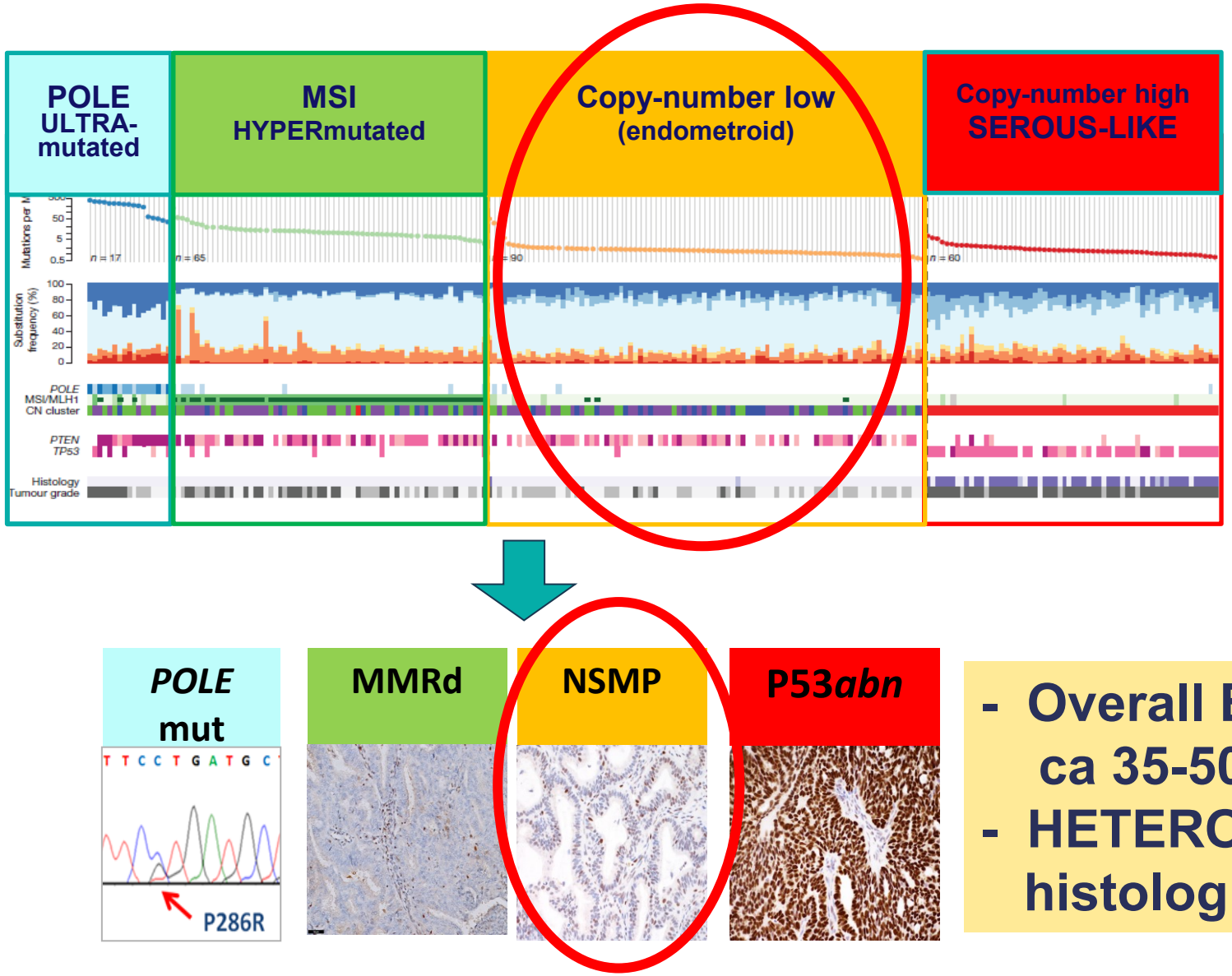
➔ **New agent combining dual checkpoint inhibitor**
Ex: PD1/CTLA4 – PD1/TIGIT

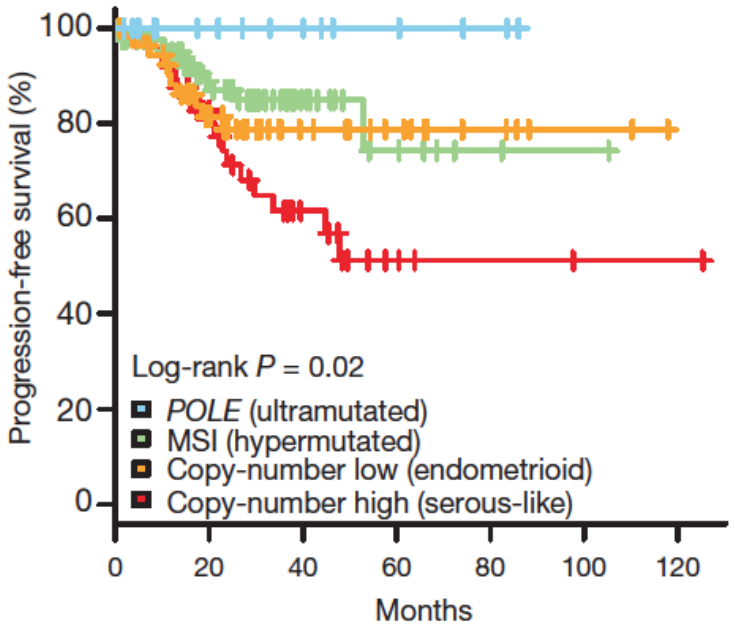
Study Chairs: Haider Mahdi, MD, MPH; K. Moore, MD; Matthew Powell, MD; Stephanie Gaillard, MD, PhD.

NCT05112601

Beyond IO
Which alternatives in p-MMR?

What the TCGA has taught us?





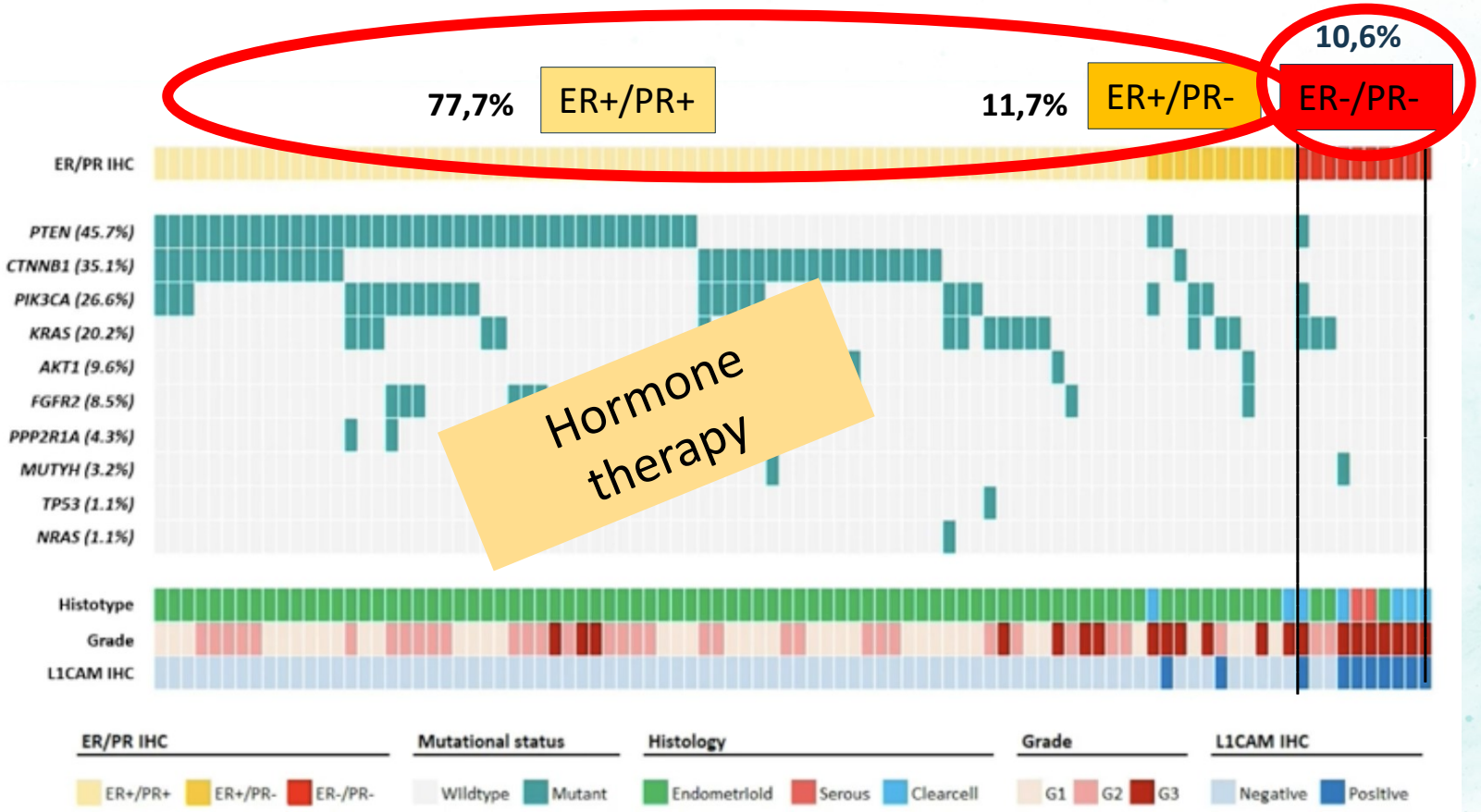
- **Overall EC: MAJORITY of ECs ca 35-50 %**
- **HETEROGENOUS group: histologically & molecularly & clinically**

Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

Molecular landscape of NSMP high risk EC

PORTEC-3 trial in high risk patients, n=122 NSMP cases with available FFPE material

IHC for ER/PR & L1CAM, NGS



Frequent mut in PTEN, CTNNB1, KRAS
Favourable characteristics: - low grade
- endometroid
- L1CAM neg

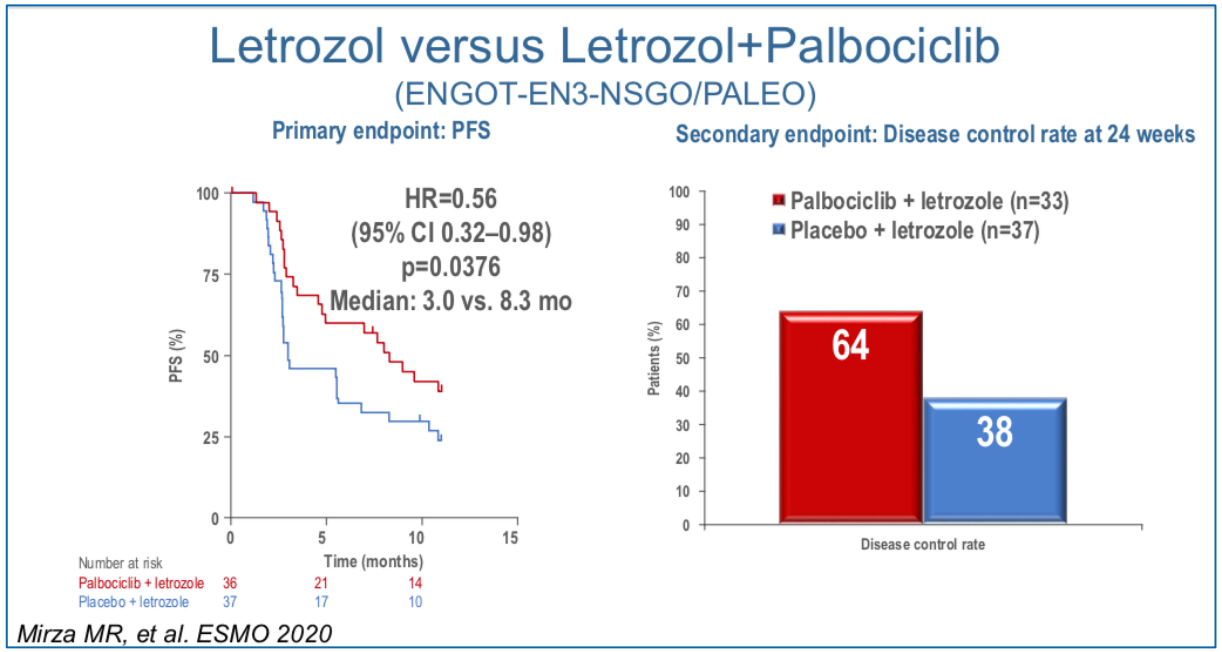
Mix of fav/ unfav charact.

Few somatic mutations
Unfavourable characteristics:
- **high grade**
- none-endometroid
- L1CAM pos

Lisa Vremij, ESGO congress Prague 2021
Vermij et al, British Journal of Cancer 2023

Aromatase inhibitors + CDK4/6 inhibitors in EC

- **AI + CDK4/6i; median PFS 8-9 months**

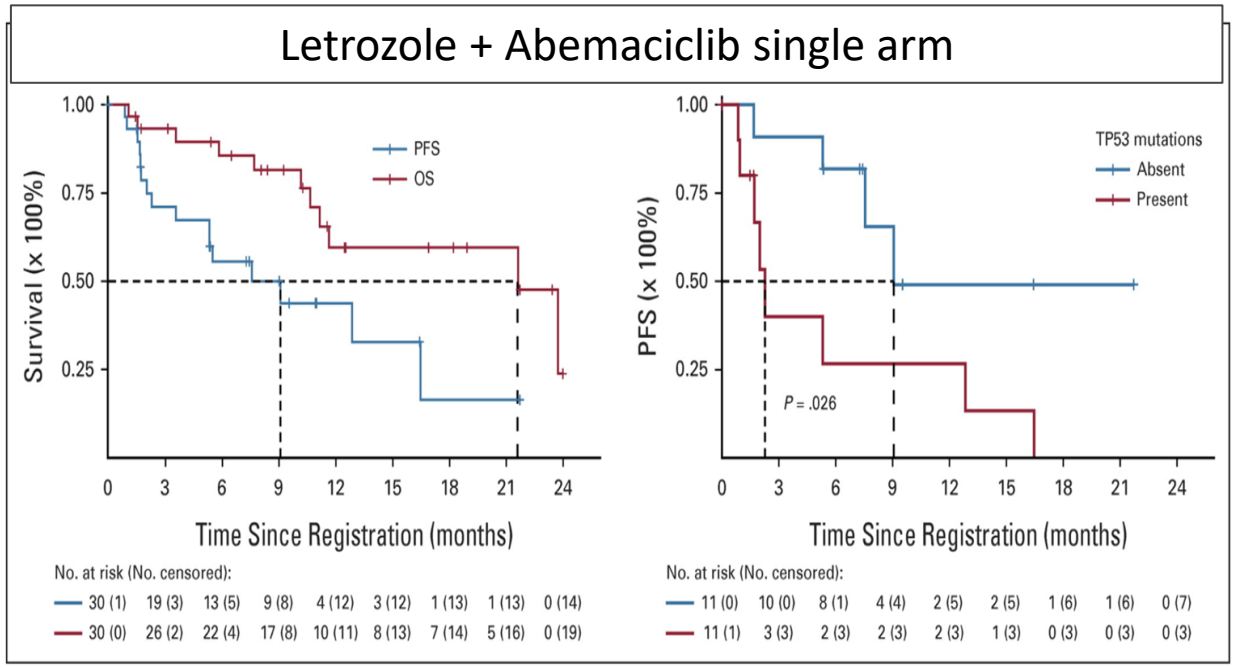


Mirza MR, et al. ESMO 2020

PALEO trial

- **N= 77, Stage 4 or relapsed ER-positive EC**
- **PFS = 8.3 vs 3 mths (p=0.0376)**
- **DCR = 63.6% vs 37.8%**

Randomized Phase III planned in ENGOT/GOG

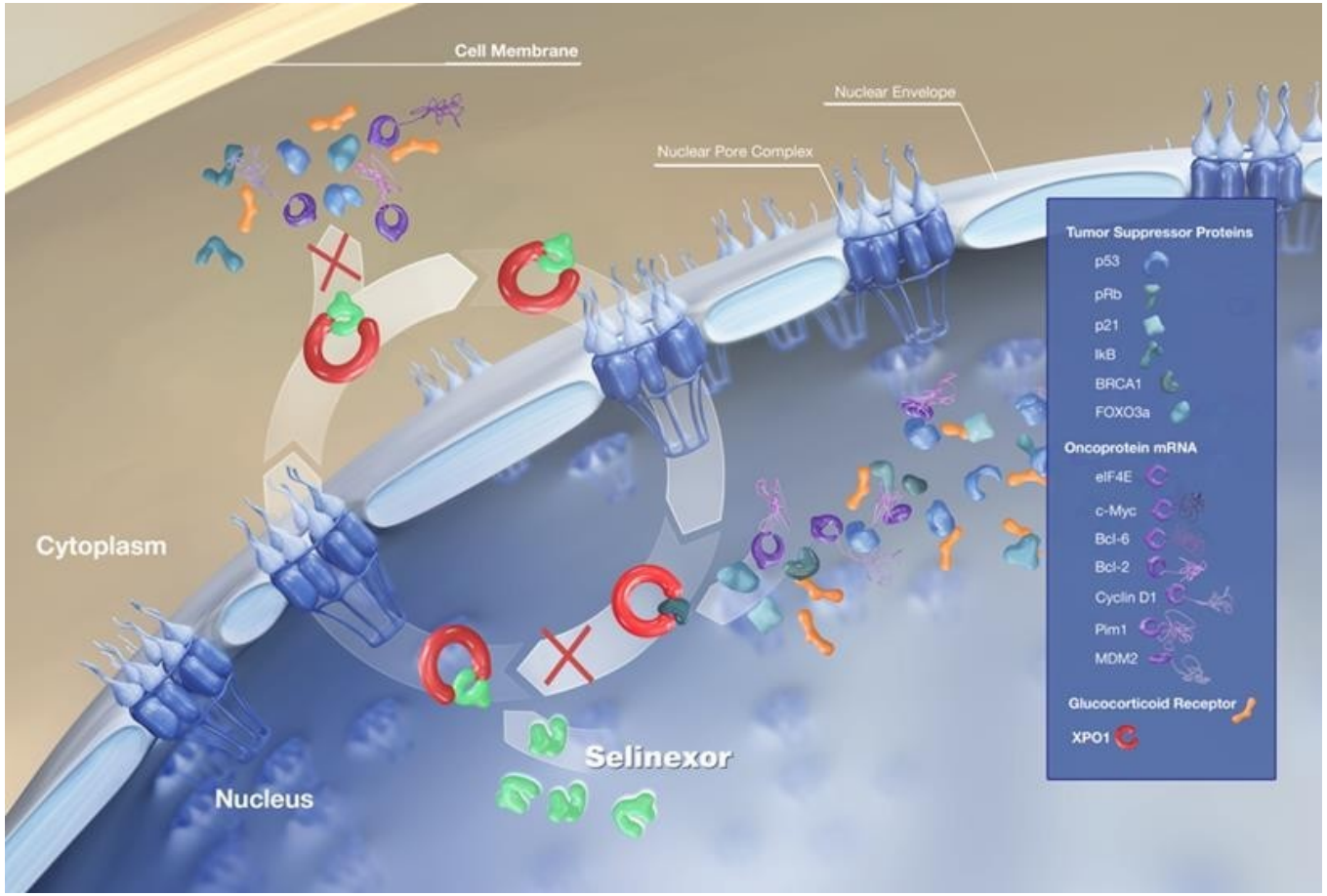


Konstantinopoulos JCO 2023

- **N= 30 (28 endometrioid EC)**
- **ORR 30%, all endometrioid**
- **Median PFS = 9.1 months**
- **Predictors of response: (*CTNNB1/KRAS/CDKN2A* mut)**
- **Predictors no response(*TP53mut*)**

NSMP EC
P53wt: the other face of the coin

Selinexor: XPO1 inhibition



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

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

Inhibition of XPO1 results in:[1]

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

Selinexor is an oral selective XPO1 inhibitor

Preclinical data for selinexor:[2]

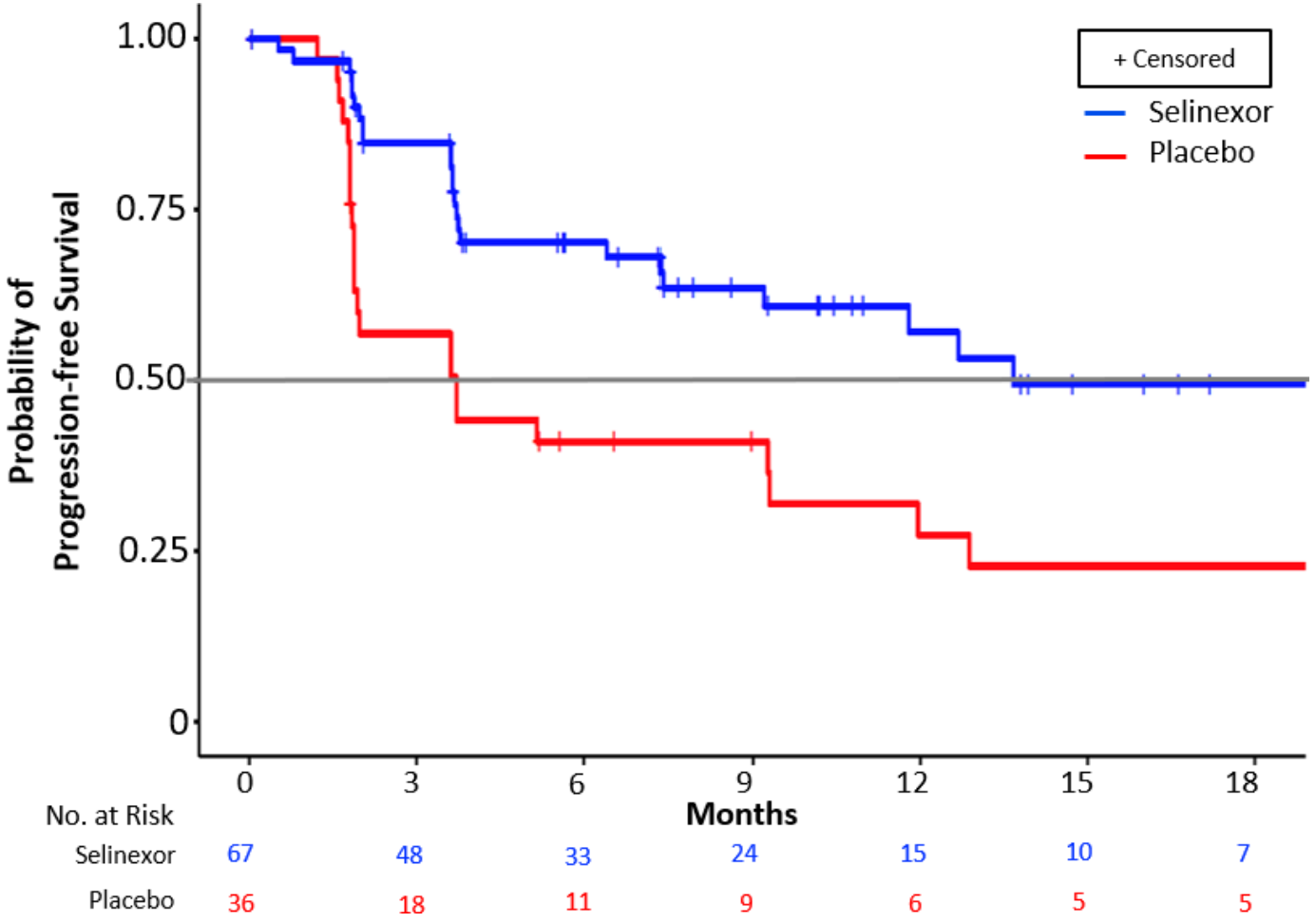
- Reactivates multiple TSPs, including p53 wild type, by preventing nuclear export

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

ENGOT-EN5/GOG-3055/SIENDO

SUBGROUP PFS: PATIENTS WITH WILD TYPE p53 EC

(BASED ON AUDITED STRATIFICATION FACTORS)



Median PFS

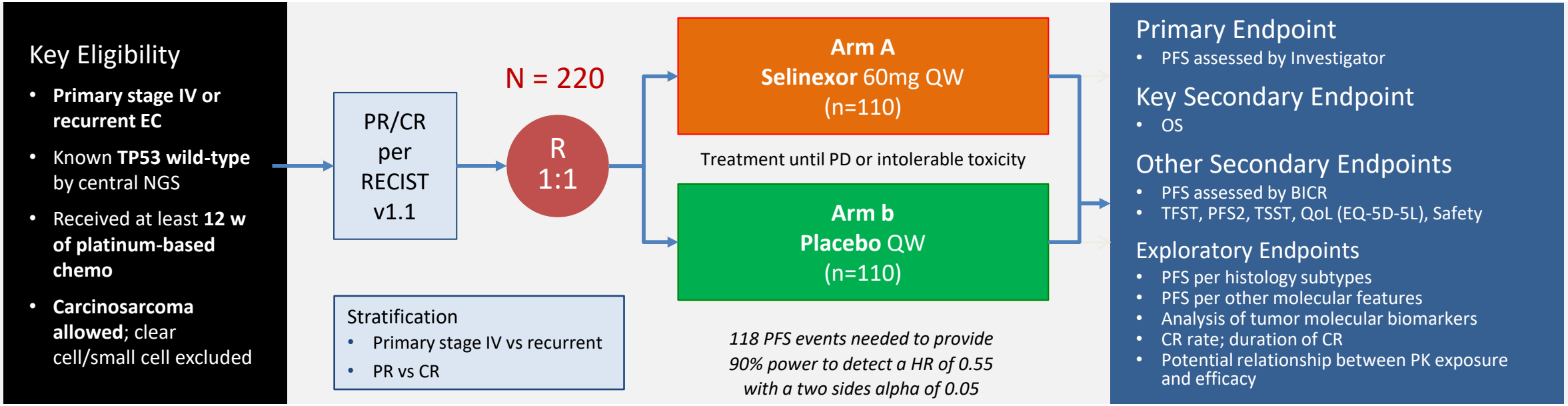
Selinexor (n=67): 13.7 mo (95% CI 9.20-NR)

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

HR (audited) = 0.375 (95% CI 0.210-0.670)

One-sided nominal P value = 0.0003

ENGOT-EN20/XPORT-EC-042: A phase 3, Randomized, placebo-controlled, double-blind, multicenter trial of selinexor in maintenance therapy after systemic therapy in patients with p53 wild-type, advanced or recurrent endometrial carcinoma



CHEMOTHERAPY

Identify potential patients as soon as possible during their treatment

Must receive at least 12 weeks of therapy

FOUNDATION MEDICINE TESTING

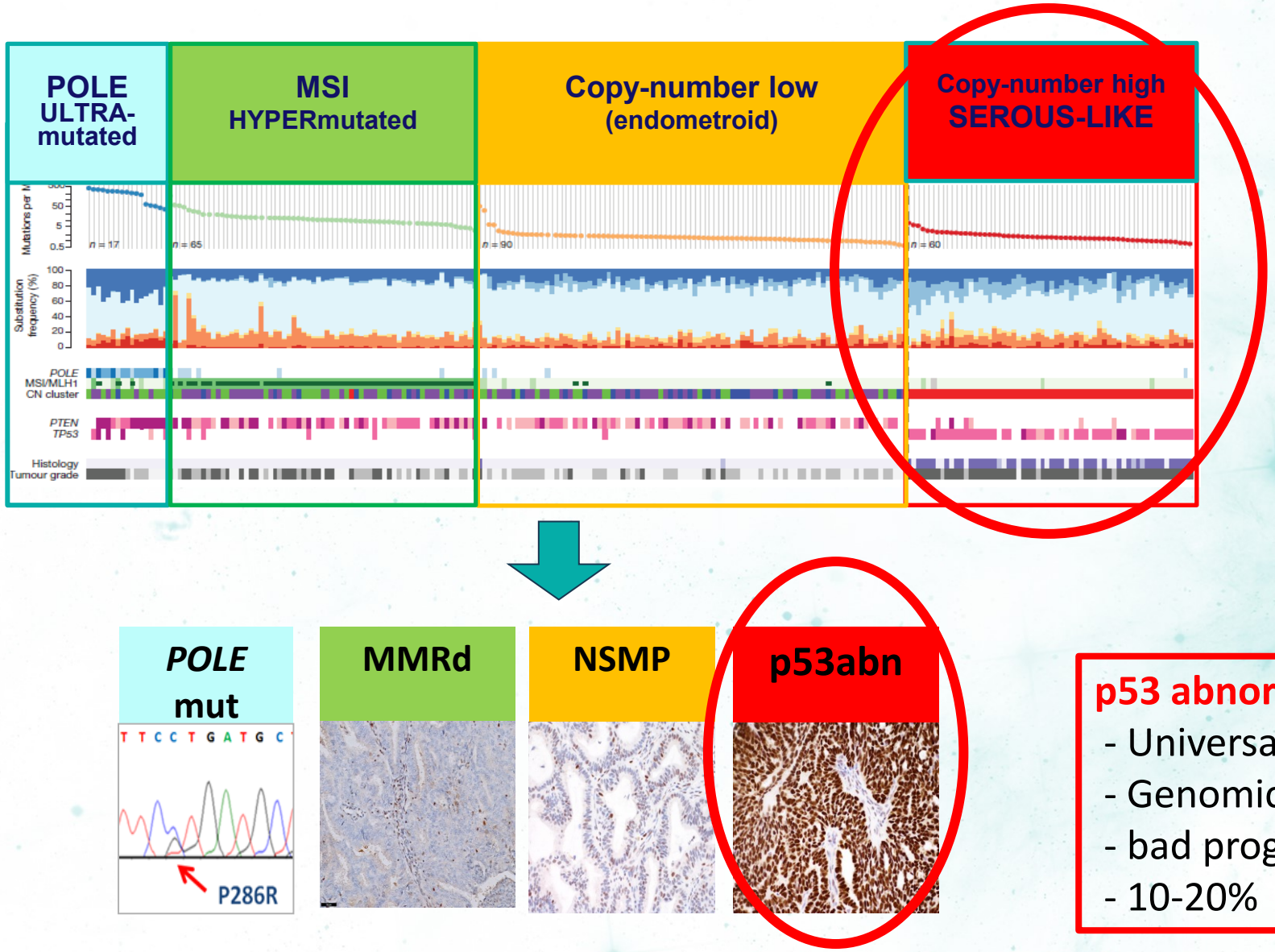
Complete FMI testing as soon as possible, ideally no later than the end of Cycle 5

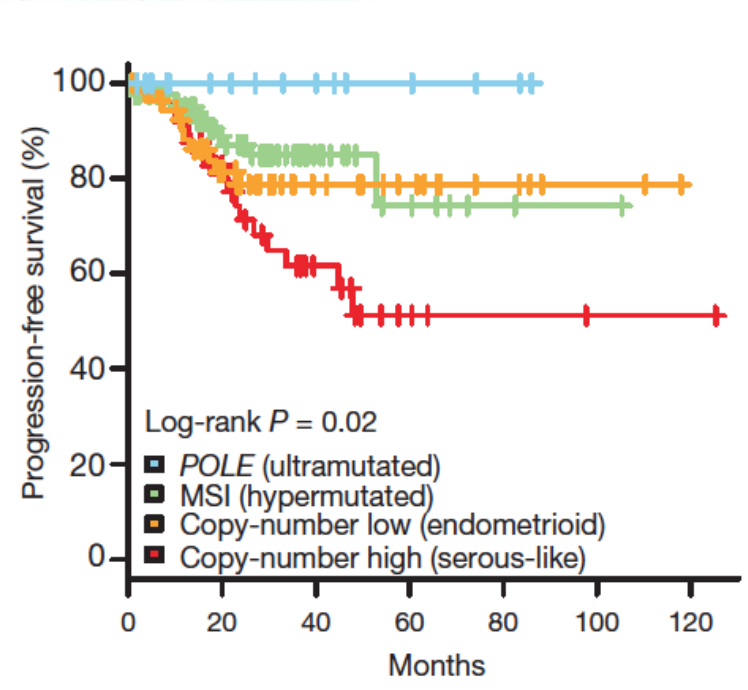
RANDOMIZATION

Patients must be randomized and start study treatment 3-8 weeks post chemotherapy

BGOG · ISGO · NOGGO e.V. · MITO Multicentre Italian Trials in Ovarian cancer · MaNGO · HeCOG Hellenic Cooperative Oncology Group · GEICO Grupo Español de Investigación en Cáncer ginecológico · CEEGOG Central and Eastern European Gynecologic Oncology Group · cancer trials ireland · ENGOT European Network of Gynaecological Oncological Trial groups

P53 abn





p53 abnormal
- Universal *TP53* mutations
- Genomic instability
- bad prognosis
- 10-20%

p53
BRCA, HRD
HER2

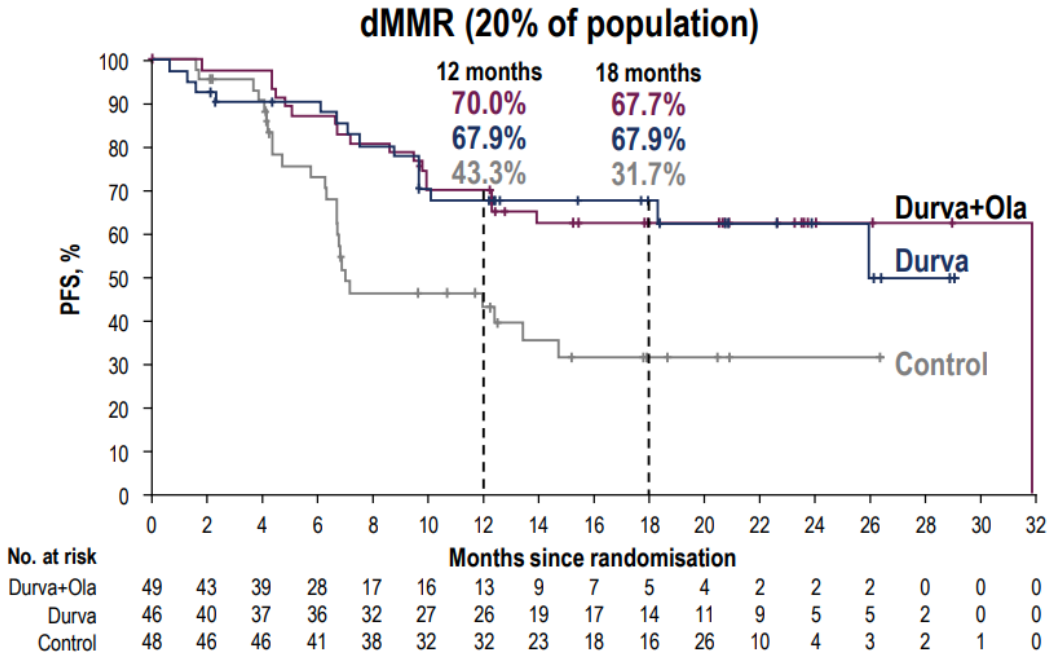
Kandoth et al, Nature 2013; Stelloo et al, Clin Cancer Research 2016 ; Talhouk et al, Cancer 2017

What about adding a PARPi to IO in first line? DUO-E

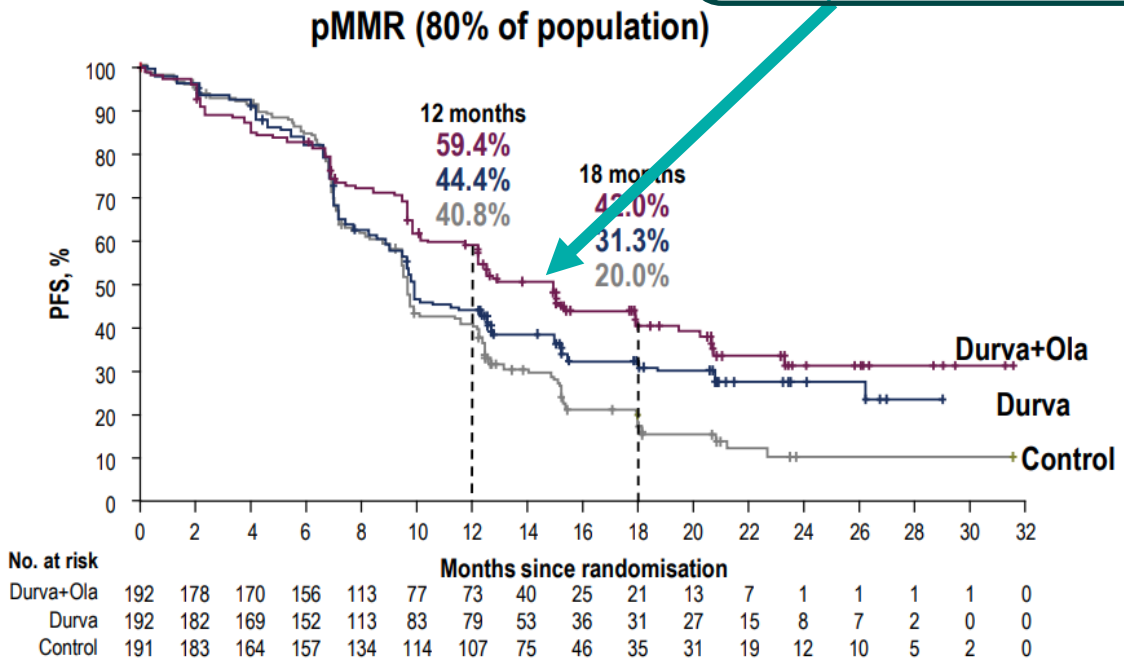
DUO-E study: PFS by MMR status

Prespecified exploratory analysis

How to identify these patients?



	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)**

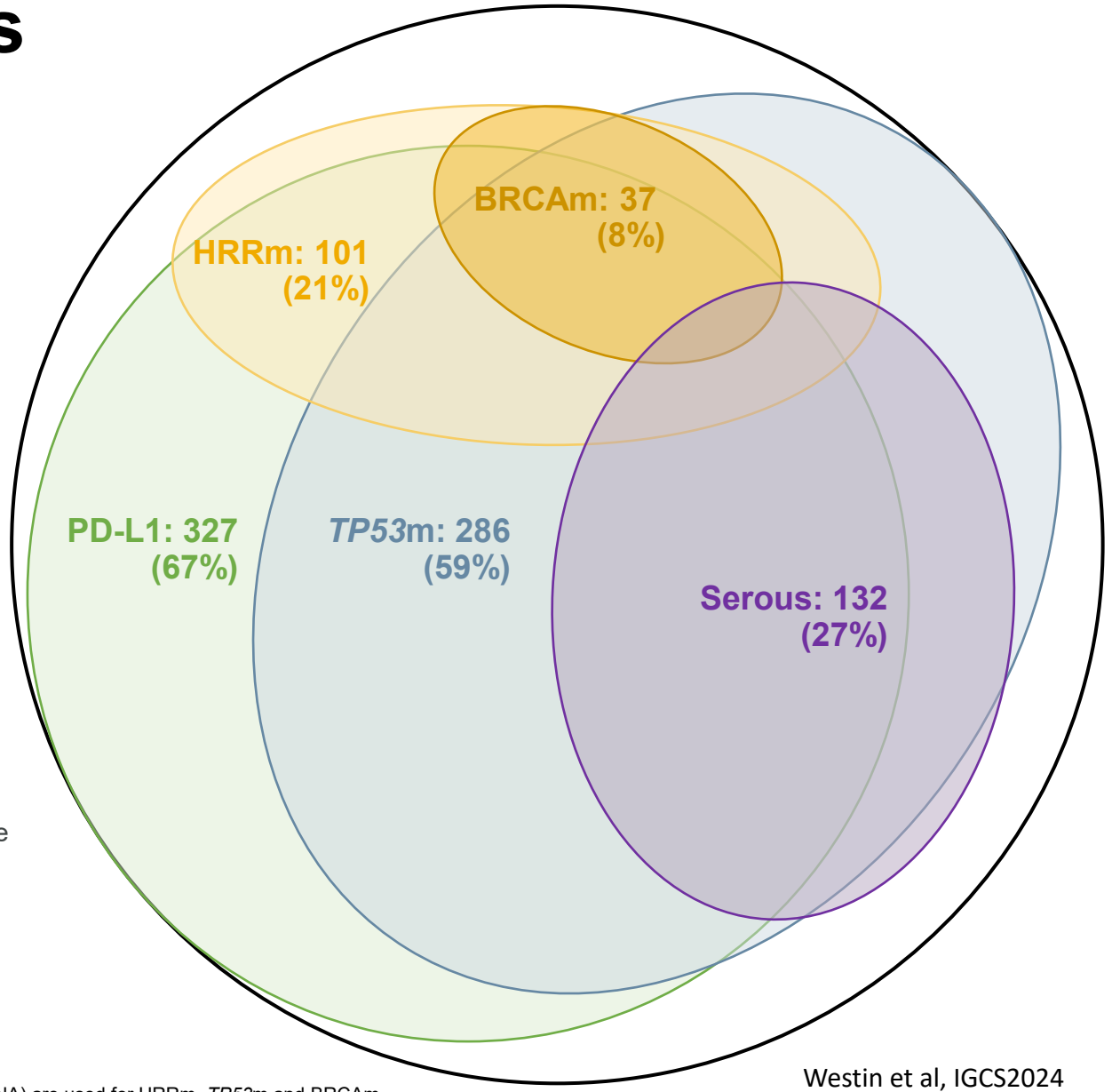
Westin SN et al. J Clin Oncol 2024;42:283–99

pMMR biomarker-known subpopulation: co-prevalence of biomarkers

The pMMR biomarker-known (n=486) subpopulation was heterogeneous, with a large overlap of biomarkers:

- 84% of patients were positive for one or more biomarkers
- PD-L1 positive and *TP53*m were the most prevalent biomarkers

	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%



Venn illustrates the overlap for key biomarker populations but does not show a complete set of all overlapping populations.
Venn includes 11 patients with a *POLE*m; biomarker overlap in this subgroup is not shown. Aggregate results (tissue + ctDNA) are used for HRRm, *TP53*m and BRCAm.

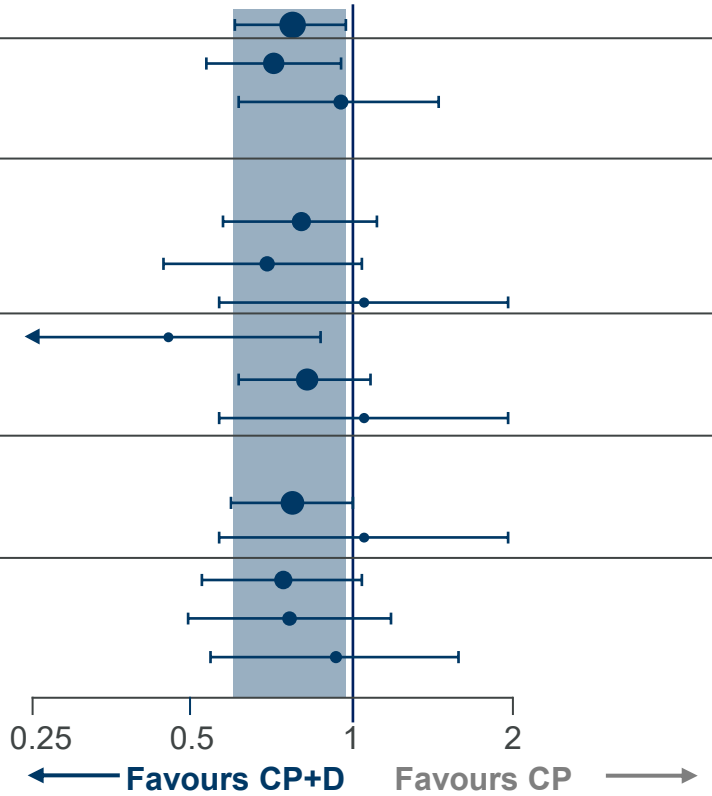
Westin et al, IGCS2024

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab versus 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 *TP53m* status**†,‡	*POLE*m	**NC (NC–NC)‖**
	*TP53*m	**0.80 (0.57–1.11)**
	TP53 wt	**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)**
Histology	Endometrioid	**0.74 (0.52–1.04)**
	Serous	**0.76 (0.49–1.18)**
	Other¶	**0.93 (0.54–1.58)**



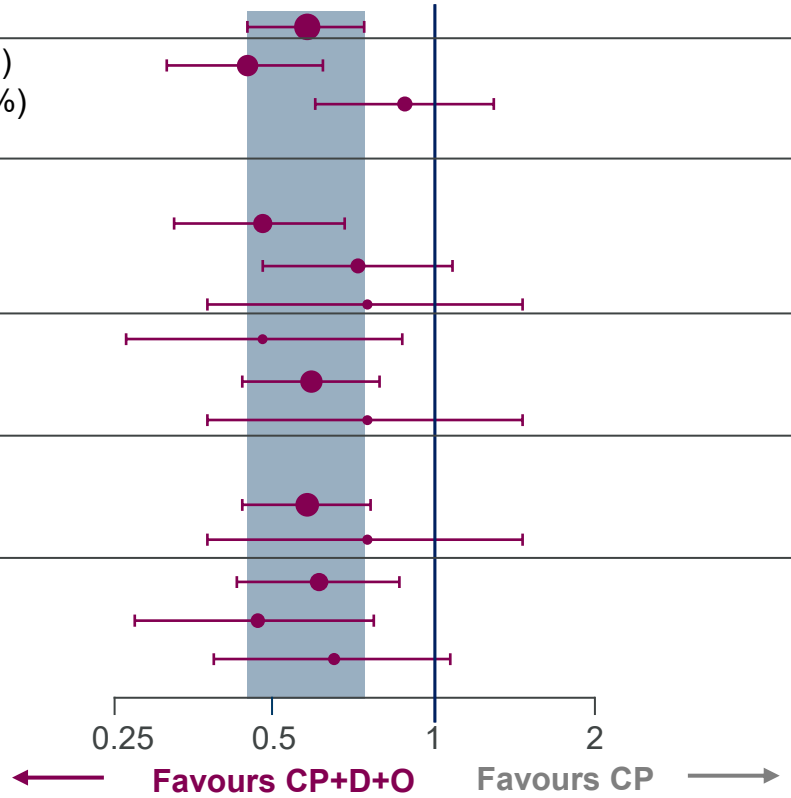
DCO: 12 April 2023. *PD-L1 expression was evaluated using the VENTANA PD-L1 (SP263) assay. PD-L1 positive defined as TAP ≥1%, PD-L1 negative defined as TAP <1%, and unknown included patients who withdrew consent or due to sample unavailability; †Status determined retrospectively in two ways: from tissue 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* wt 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*; and unknown *TP53*m status included patients recruited in China, where *TP53* and/or *POLE* testing was not performed, patients who withdrew consent and patients for whom no sample was available; §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; and unknown HRRm status included patients recruited in China, where HRR testing was not performed, patients who withdrew consent and patients for whom no sample was available; ‖Not calculated due to low event numbers; ¶'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other.
DCO, data cutoff; NC, not calculable.

Westin et al, IGCS2024

pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib versus CP

Post hoc exploratory analysis



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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 *TP53m* status** [†,‡]	*POLE*m	**NC (NC–NC)** [‖]
	*TP53*m	**0.47 (0.32–0.67)**
	TP53 wt	**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)**
Histology	Endometrioid	**0.60 (0.42–0.85)**
	Serous	**0.46 (0.27–0.76)**
	Other [¶]	**0.64 (0.38–1.06)**

DCO: 12 April 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%, and unknown included patients who withdrew consent or due to sample unavailability; †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* wt 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*; and unknown *TP53*m status included patients recruited in China, where *TP53* and/or *POLE* testing was not performed, patients who withdrew consent and patients for whom no sample was available; §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; and unknown HRRm status included patients recruited in China, where HRR testing was not performed, patients who withdrew consent and patients for whom no sample was available; ‖Not calculated due to low event numbers; ¶'Other' includes carcinosarcoma, mixed epithelial, clear cell, undifferentiated, mucinous, and other.
DCO, data cutoff; NC, not calculable.

Westin et al, IGCS2024

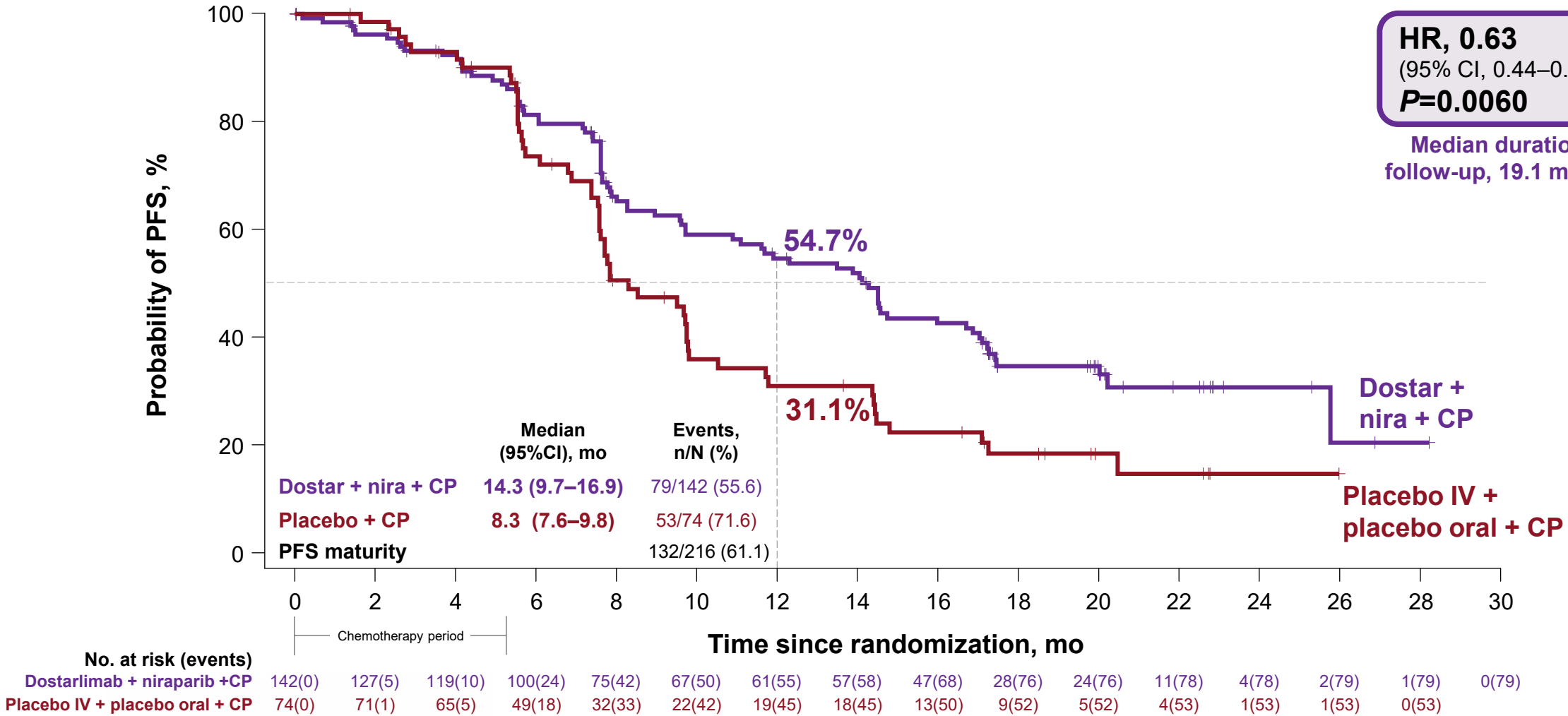
Conclusions

- DUO-E met both dual primary endpoints in the ITT population. The addition of olaparib maintenance to durvalumab further enhanced PFS benefit in the pMMR subpopulation[1]
- The pMMR subpopulation was highly heterogeneous with large overlap of biomarkers and histology; 84% of patients had one or more markers
- The PFS benefit provided by the addition of olaparib maintenance to durvalumab was observed across a range of biomarker and histological subgroups
- The safety profile of durvalumab plus olaparib in the pMMR subpopulation was generally consistent with the ITT population[1]

The pMMR subpopulation was highly heterogeneous, adding olaparib maintenance enhanced the PFS benefit observed across a range of biomarker and histological subgroups

1. Westin SN *et al. J Clin Oncol* 2024;42:283–99.

ENGOT-EN6-NSGO/GOG-3031/RUBY Part 2 (dostarlimab /niraparib) Statistically Significant PFS Benefit in MMRp/MSS Population

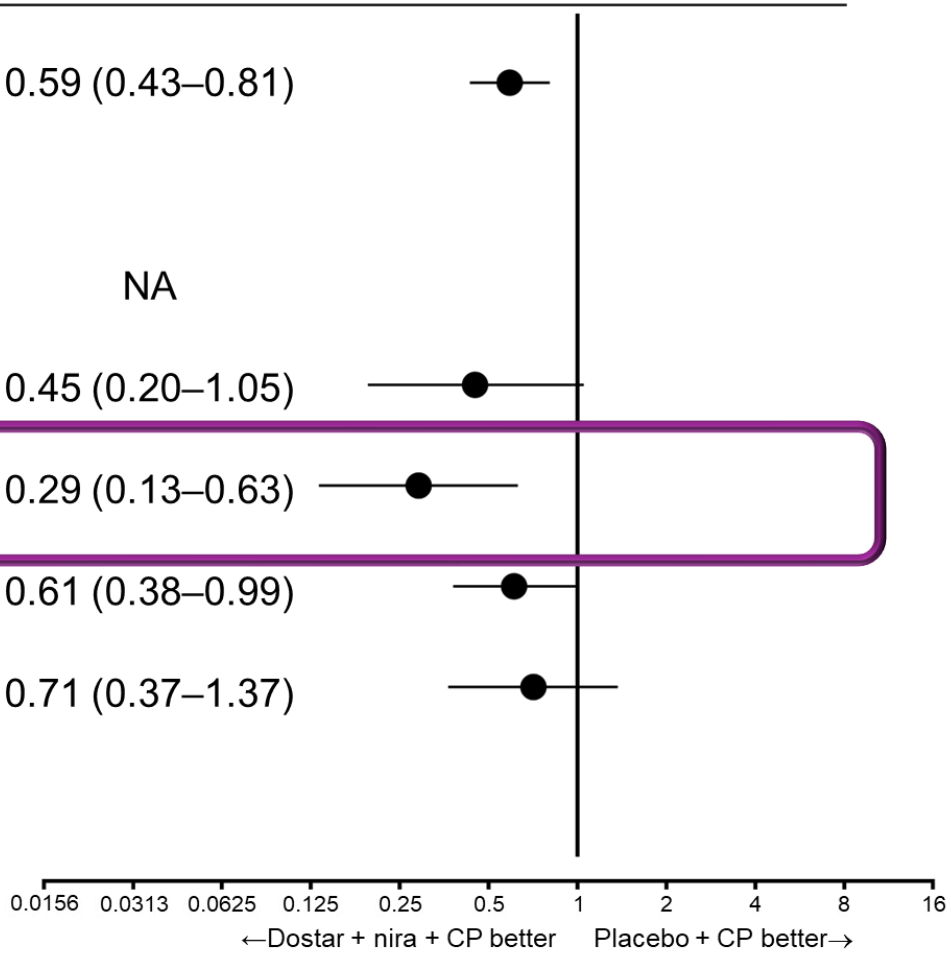


Mansoor Raza Mirza, SGO 2024

[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.

Exploratory PFS Molecular Subgroup Analyses in Overall Population

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



Results should be interpreted with caution as the study was not powered to detect a treatment difference in any subgroup, and there were small numbers and low data maturity in some subgroups. Where there were less than 20 events in the subgroup, the HR estimation and 95% CI were not analyzed as there were too few events ("not applicable").

[a]Based on available whole exome sequencing results. [b]Sample not available.

CP, carboplatin-paclitaxel; dMMR, mismatch repair deficient; dostar, dostarlimab; HR, hazard ratio; IHC, immunohistochemistry; IV, intravenous; MSI-H, microsatellite instability high; nira, niraparib; NSMP, no specific molecular profile; PFS, progression-free survival; POLE, polymerase epsilon.

Adavosertib (AZD1775) inhibits WEE1 and may be most active in p53-mutant background

Cell cycle checkpoints slow down the cell cycle

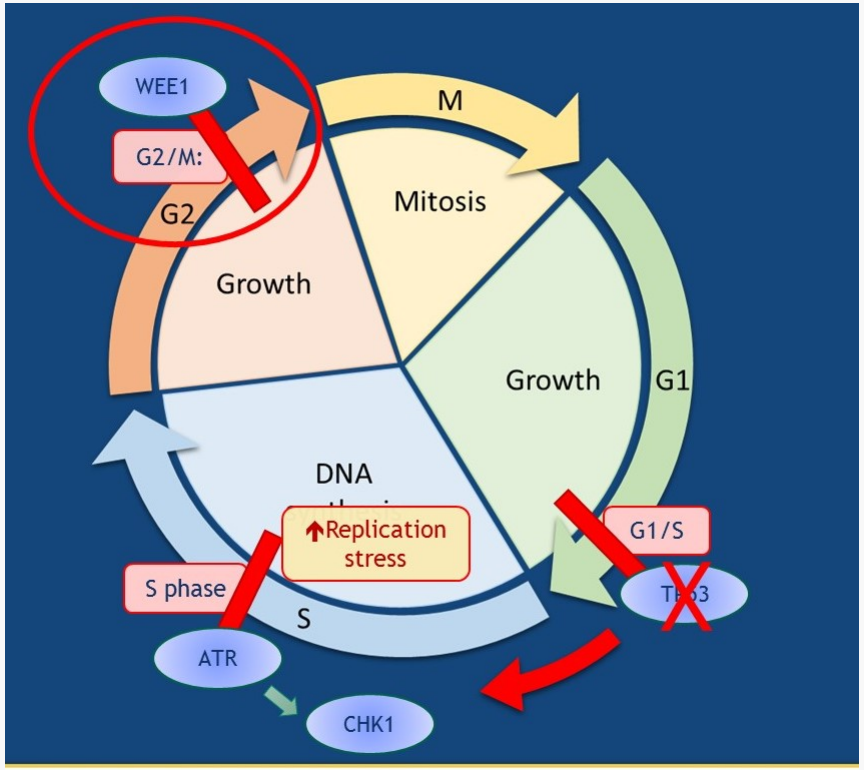
- Allow time for appropriate DNA replication
- Prevent progression to mitosis with DNA damage or underreplicated DNA

Cells with TP 53 mutation/loss lose their G1/S checkpoint

- Leads to early entry into S phase
- Increases replication stress
- Increases dependency on the G2/M checkpoint

WEE1 is a Key regulator of G2/M checkpoint

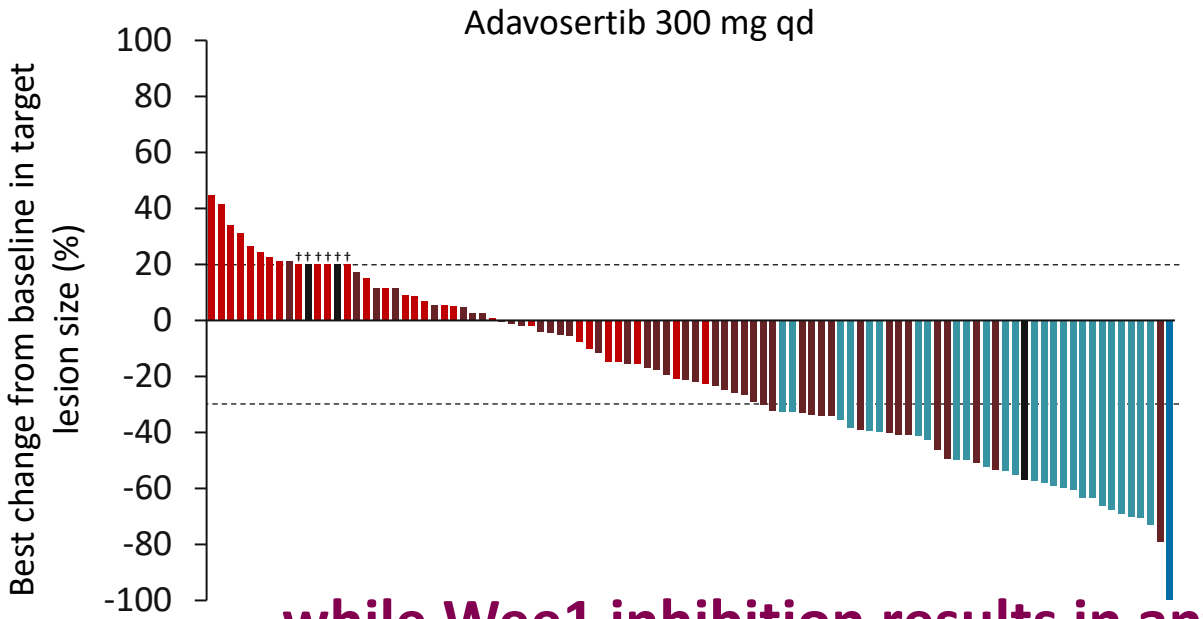
- WEE1 inhibition leads to disregulation of the G2/M checkpoint and to mitotic catastrophy



Adavosertib | C27H32N8O2 - PubChem (nih.gov)

ADAGIO: Deep and sustained responses were observed in some patients with adavosertib

Depth of response by BICR



ORR, n (%) [†] (95% CI)	**27 (26.0) (17.9–35.5)**
Disease control rate, n (%)[‡] (95% CI)	56 (51.4) (41.6–61.1)

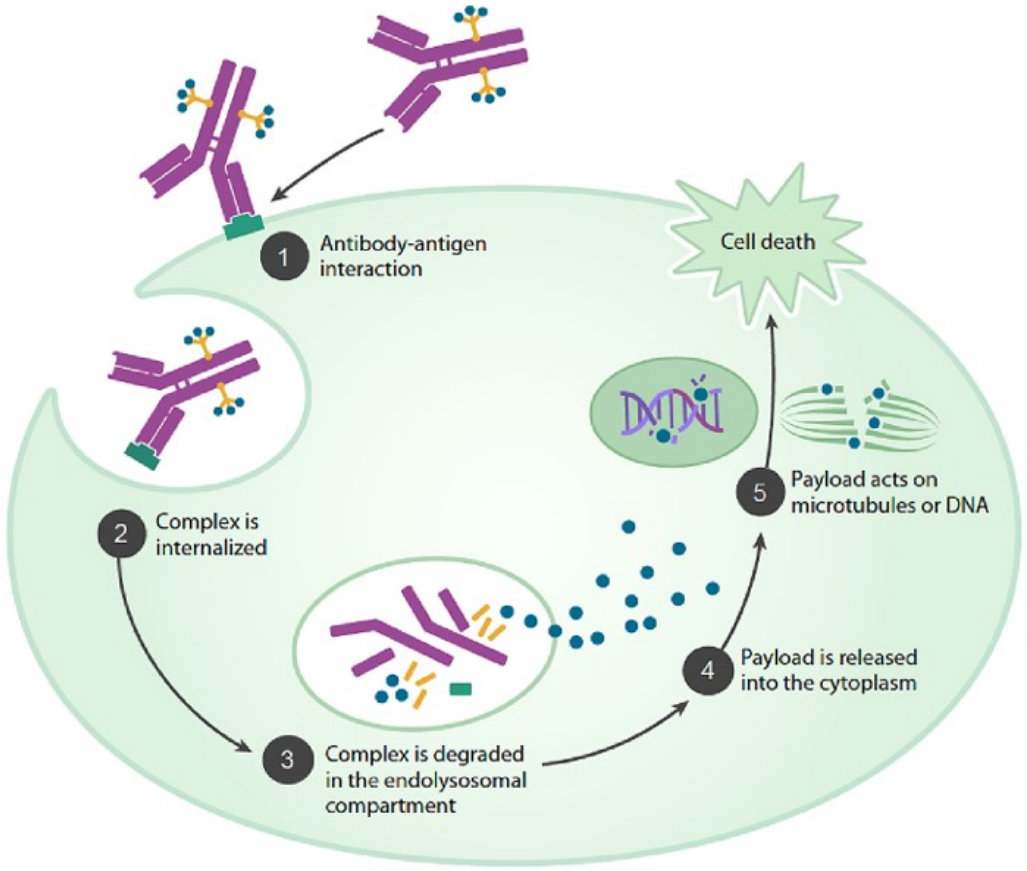
……while Wee1 inhibition results in antitumor activity and may remain a viable treatment target, the therapeutic window for adavosertib is narrow

BOR Complete response | Partial response | Stable disease | Progressive disease | Not evaluable

LIU et al, SGO 2023

[†]Indicates an imputed value; *Indicates progression due to non-target and/or new lesions
BICR, blinded independent central review; BOR, best overall response; qd, once daily

Antibody drug conjugates

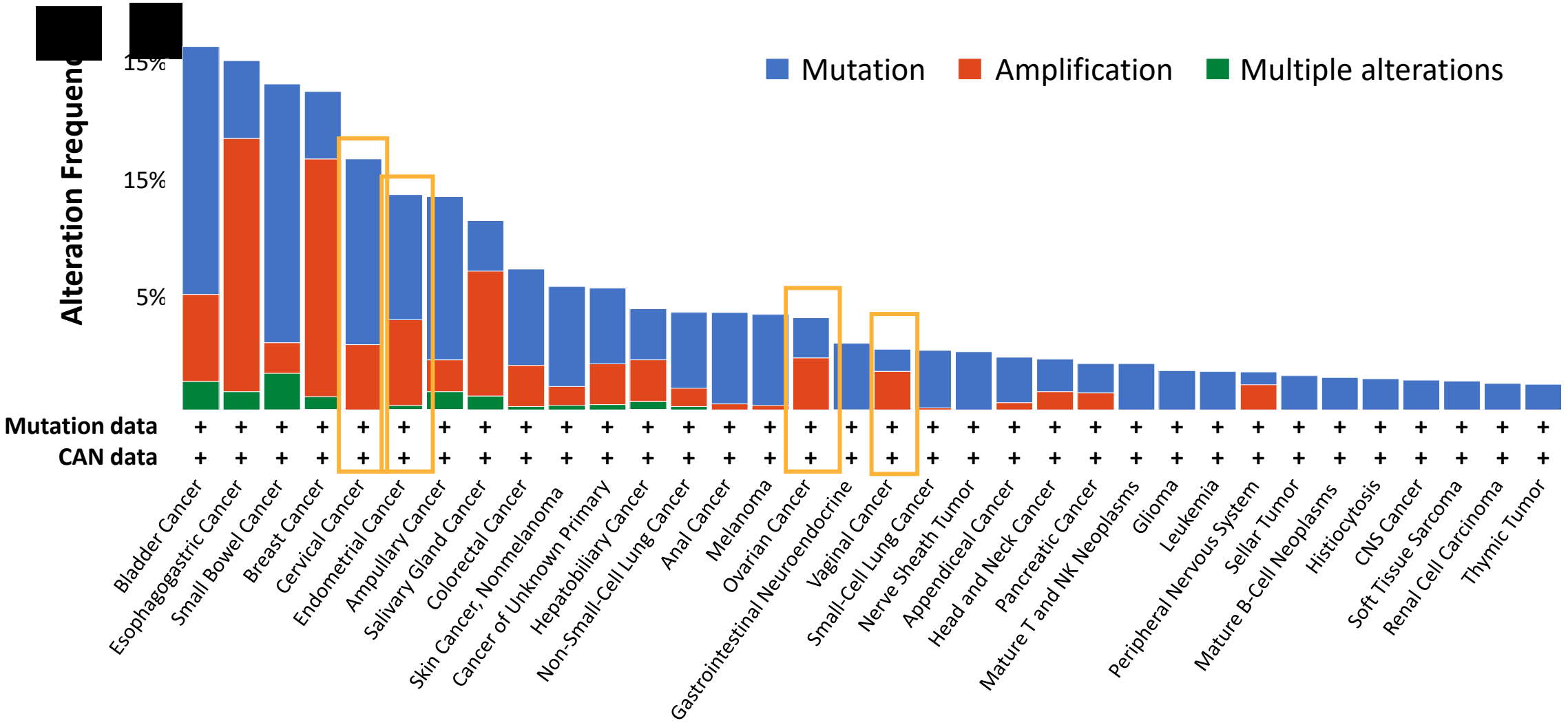


ADC	Target	Antibody	Linker	Payload
Mirvetuximab soravtansine	FRα	IgG1-kappa	Cleavable	DM4
MORAb-202	FRα	IgG1-kappa (farletuzumab)	Cleavable	Eribulin
Anetumab ravtansine	Mesothelin	IgG1-lambda	Cleavable	DM4
Tisotumab vedotin	Tissue factor	IgG1-kappa	Cleavable	MMAE
Lifastuzumab vedotin	NaPi2B	IgG1	Cleavable	MMAE
Trastuzumab emtansine (T-DM1)	HER2	IgG1	Non cleavable	DM1
Trastuzumab duocarmazine (SYD985)	HER2	IgG1	Cleavable	Duocarmicyn
Trastuzumab deruxtecan (T-DXd)	HER2	IgG1	Cleavable	Topoisomerase 1 inhibitor
Sacituzumab govitecan	Trop2	IgG1-kappa	Cleavable	SN38

Figure 2. Main ADCs under development in gynecological cancers and their structural composition. FRα: folate receptor alfa; NaPi2b: anti-sodium-dependent phosphate transport protein 2b; Trop2: human trophoblast cell-surface marker 2

Tolcher A et al: Can Treatment Rev 2023
Nerone M et al: Exploration target antitumor therapy 2022

Tumor Agnostic Prevalence of HER2 Alterations (Mutations and Amplifications)



Raghav. Clin Cancer Res. 2023;29:3251.

Endometrial cancer

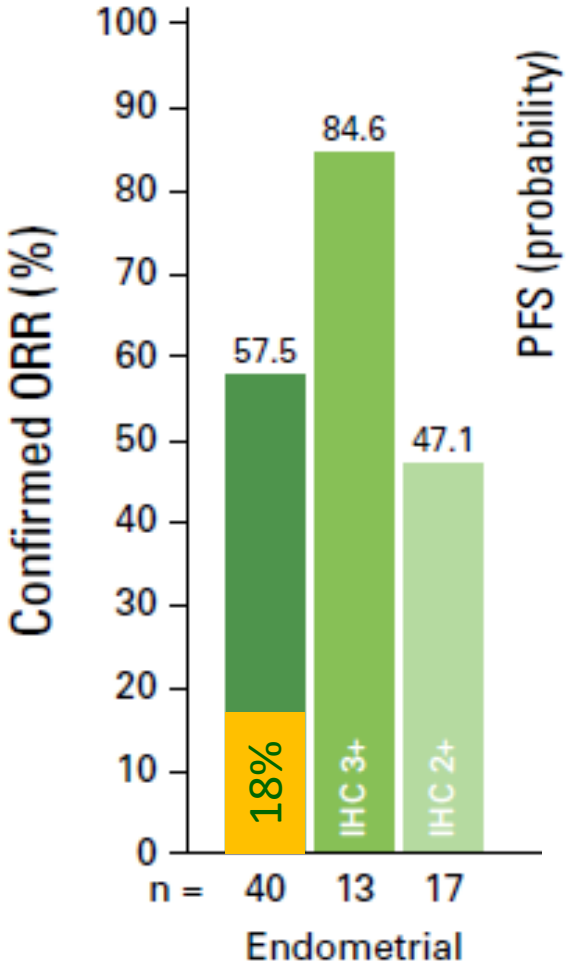
HER2

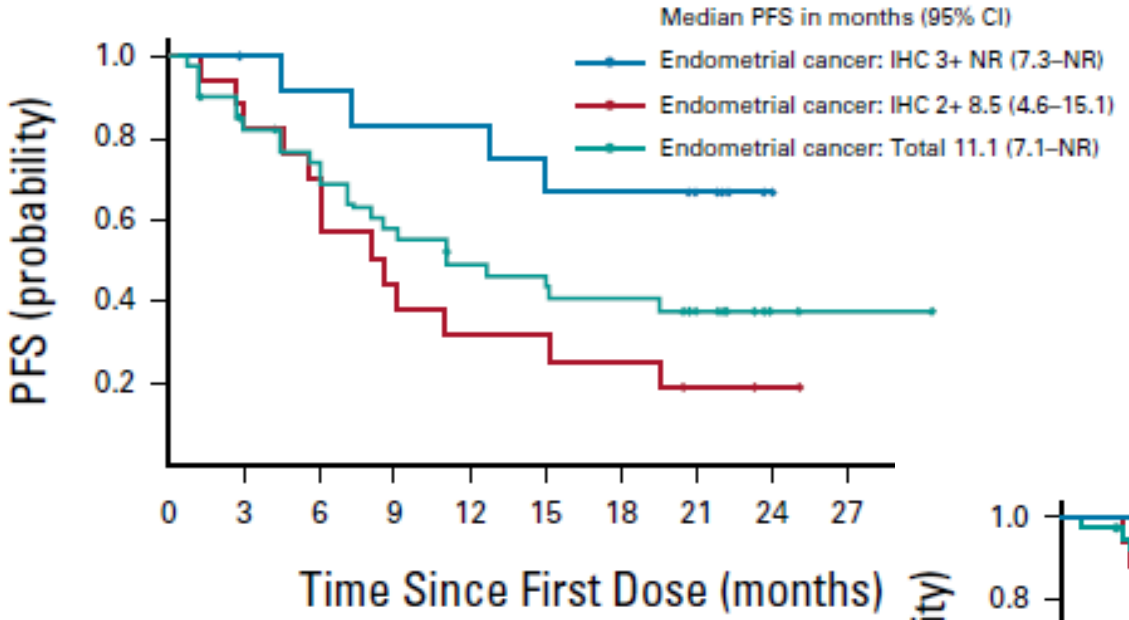
Trastuzumab deruxtecan
DB-1303/BNT323

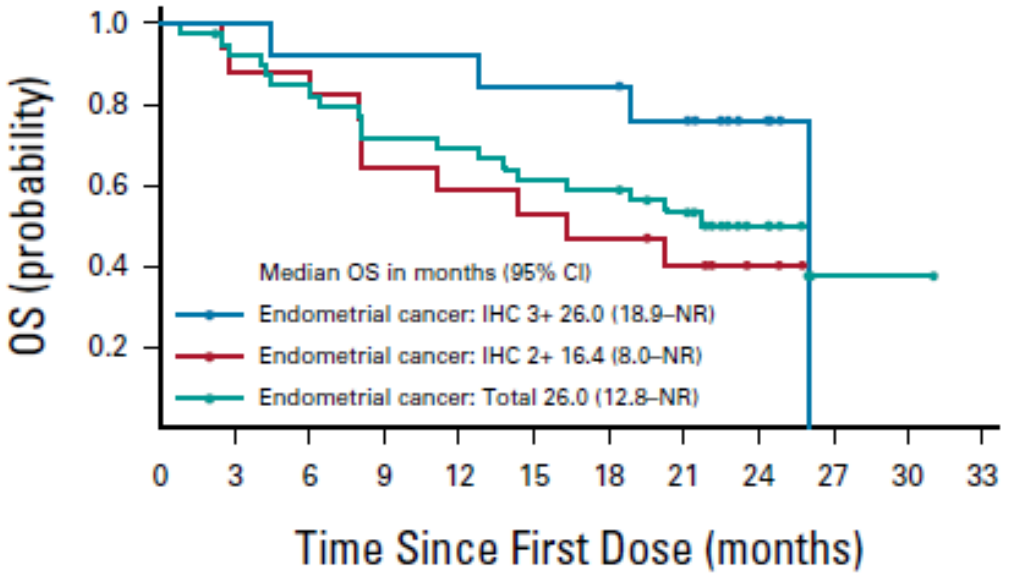
Histological type (n)		0	+	++	+++	++ / +++
All	**(530)**	**77**	**13**	**8**	**2**	
Endometrioid	(475)	81	13	4	0	4%
Serous	(33)	36	12	33	18	51%
Clear cell	(11)	27	27	36	9	45%
Mixed	(11)	36	18	27	18	45%

Nakajima et al. Hum Pathol. 2024;152:105649.

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial



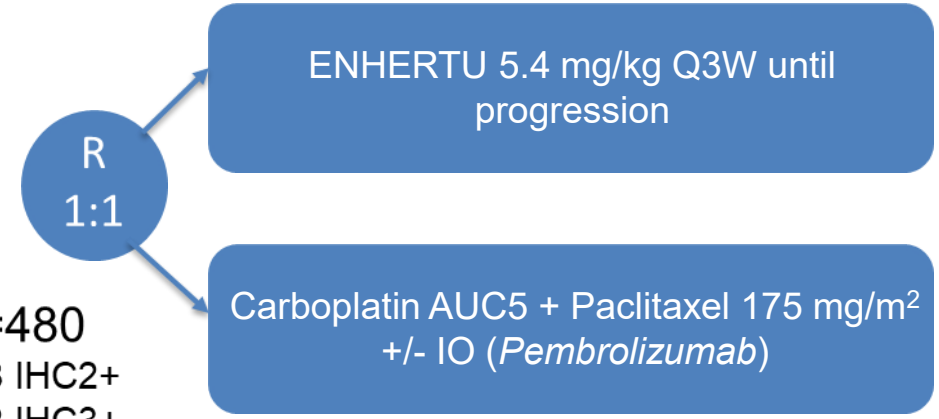




Funda Meric-Bernstam et al. JCO November 2023

ENGOT-EN24/NSGO-CTU/DESTINY-EC01

Study design



N=480
288 IHC2+
192 IHC3+

Stratification factors

- HER2 expression 3+ vs 2+
- Recurrent vs Primary Stage III vs Primary Stage IV

IO: *Pembrolizumab 200mg q3w x 6 cycles → Pembrolizumab 400 mg q6w x 14 cycles*

Endpoints

Primary:

- PFS BICR (IHC 3+/ 2+)

Secondary:

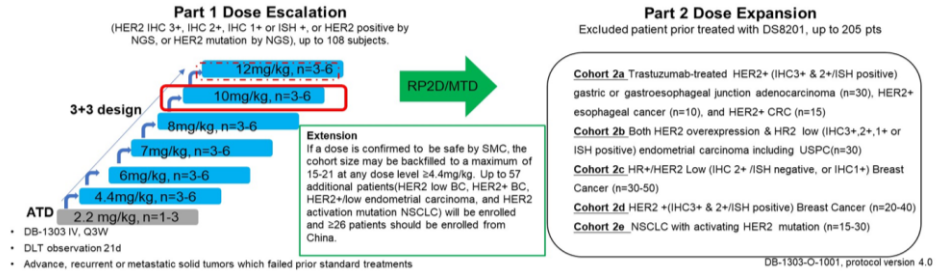
- PFS Investigator-assessed (IHC 3+/ 2+)
- OS (IHC 3+/ 2+)
- ORR and DoRin patients with measurable disease at baseline
- HRQoL

DB-1303/BNT323 in EC

DB-1303

- Monoclonal antibody directed to HER2
- Linker: cleavable maleimide tetrapeptide-based
- Payload: Topoisomerase I inhibitor (P1003)
- DAR=8
- Highest non-severely toxic dose: 80 mg/kg Q3W

Efficacy



32 patients with EC had received 7 or 8 mg/kg doses of DB-1303

A total of 17 patients were evaluable for response

PR: 58.8%

ORRs: 50.0% and 61.5%, for 7 and 8 mg/kg dose respectively

Overall DCR was 94.1%

Histologies: USPC 34.4%, adenocarcinoma 25.0%, UCS 18.8%

Median treatment duration: 2.6 (range, 0.7–10.4)

29 patients (90.6%) remained on treatment

Median number of prior regimens for metastatic disease: 2 (1–10)

Nineteen patients (59.4%) had prior immunotherapy (IO) therapy

Safety

TEAEs of **any grade** occurred in 30 patients (93.8%)

the most common (≥20%) were:

- nausea (50.0%)
- fatigue (31.2%)
- vomiting (28.1%)

Grade ≥ 3 occurred in 10 patients (31.2%)

the most common (≥5%) were:

- hypokalaemia (12.5%),
- anaemia (6.2%)
- syncope (6.2%).

No TEAEs led to drug discontinuation or death.

No interstitial lung disease occurred.

Moore K et al presented at ESGO 2023

FDA Grants Breakthrough Therapy Designation to BNT323/DB-1303 in Endometrial Cancer

Author(s): Ashling Wahner

The FDA has granted breakthrough therapy designation to the HER2-targeted antibody-drug conjugate BNT323/DB-1303 for use as a potential therapeutic option in patients with advanced endometrial cancer who have progressed on or after treatment with immune checkpoint inhibitors.

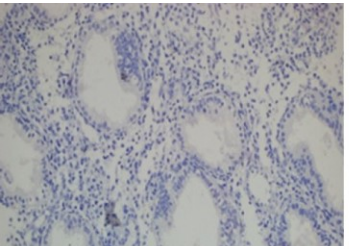
The FDA has granted breakthrough therapy designation to the HER2-targeted antibody-drug conjugate (ADC) BNT323/DB-1303 for use as a potential therapeutic option in patients with advanced endometrial cancer who have progressed on or after treatment with immune checkpoint inhibitors.[1]

ENGOT-en25/ GOG-3105 / BNT323-01:

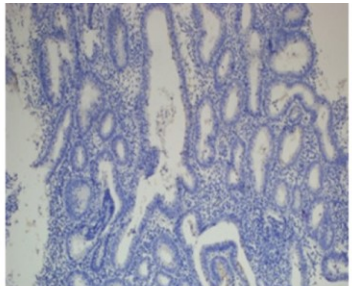
A Phase III, Randomized, Multi-site, Open-label Trial of BNT323/DB-1303 Versus Investigator's Choice of Chemotherapy in Previously Treated Patients With HER2- Expressing Recurrent Endometrial Cancer

Folate receptor α expression and significance in endometrioid endometrium carcinoma and endometrial hyperplasia

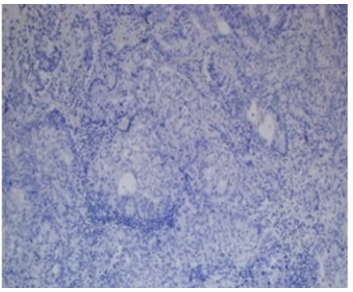
FRα immunreactivity



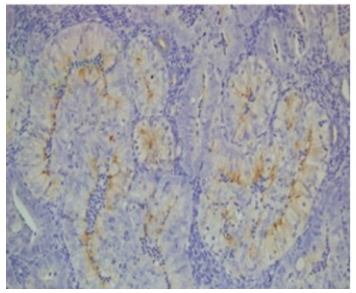
Negativity in secretory endometrium



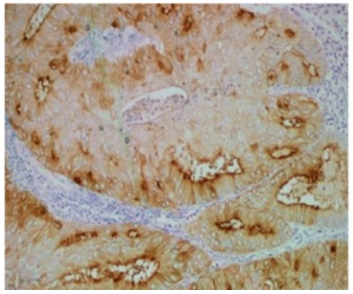
Negativity in simple EH



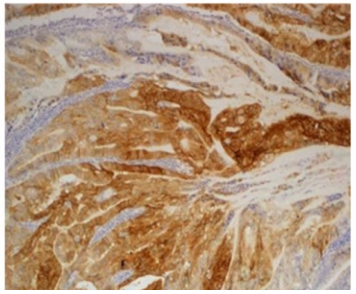
Negativity in EEC



+1/weak



2/moderate



+3/strong

Evaluation of folate receptor α (FRα) expression in endometrial carcinoma (EEC), atypical-complex endometrial hyperplasia (EH), simple endometrial hyperplasia, end normal endometrium

n (%)		EEC (n=95)	Atypical-Complex EH (n=61)	Simple w/o atipical EH (n=58)	Normal endometrium (n=30)	*P*
		n (%)	n (%)	n (%)	n (%)	
FRα	Negative	18 (18.9%)	37 (60.7%)	47 (81.0%)	30 (100.0%)	*0.001***
	+	29 (30.5%)	17 (27.9%)	10 (17.2%)	0 (0.0)	
	++	27 (28.4%)	7 (11.5%)	1 (1.7%)	0 (0.0%)	
	+++	21 (22.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
FRα	Low	47 (49.5%)	54 (88.5%)	57 (98.3%)	30 (100.0%)	*0.001***
	High	48 (50.5%)	7 (11.5%)	1 (1.7%)	0 (0.0%)	

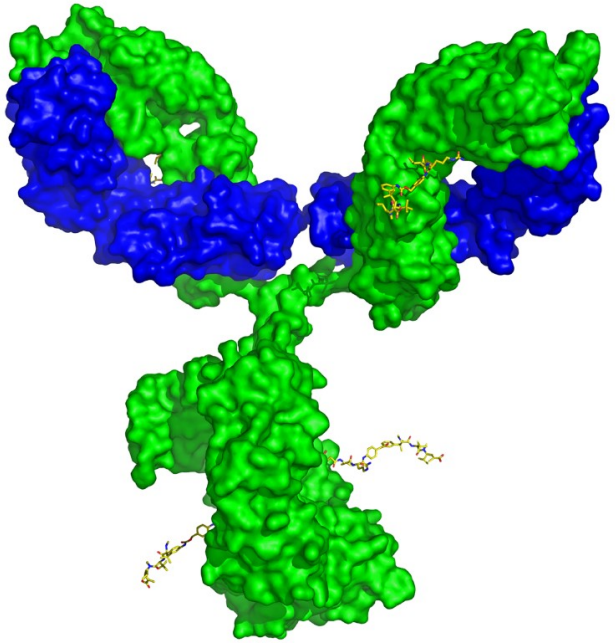
Fisher Freeman Halton Test, *p<0.05, **p<0.01.

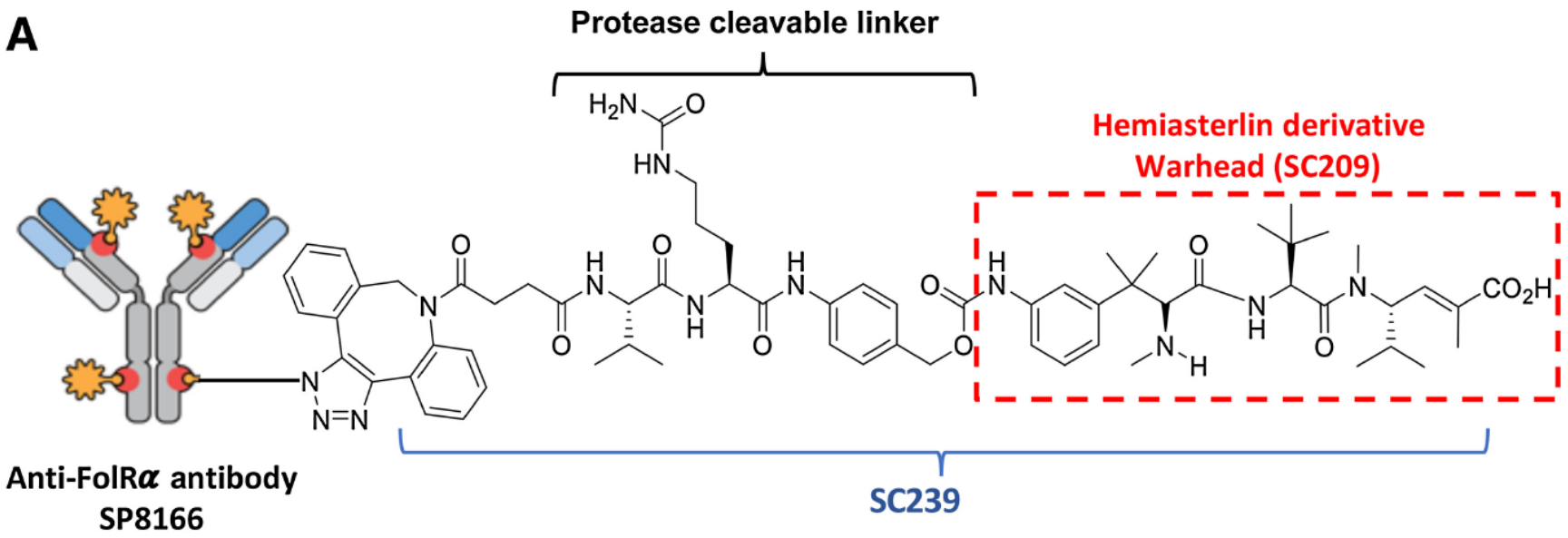
50.5%

0%

Serkan Senol, et al. Int J Clin Exp Pathol 2015

Discovery of STRO-002, a Novel Homogeneous ADC Targeting Folate Receptor Alpha, for the Treatment of Ovarian and Endometrial Cancers



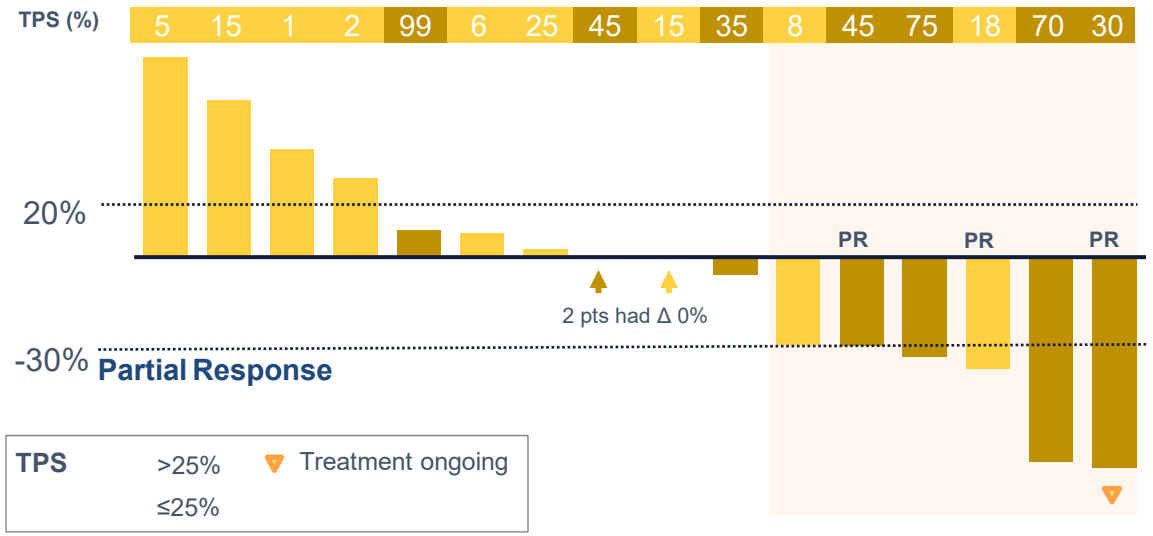


- STRO-002 lacks nonspecific cytotoxicity toward FolRα-negative cell lines
- Bystander killing of target negative cells when cocultured with target positive cells.
- STRO-002 is stable in circulation with no change in drug–antibody ratio for up to 21 days and has a half-life of 6.4 days in mice

Xiaofan Li, et al. Mol Cancer Ther; 22(2) February 2023

ADCs Emerging as Highly Active Therapeutics in EC- Folate Receptor α- STRO-002-GM1: Phase 1 Dose Expansion cohort of luveltamab tazevibulin in EC-NCT03748186

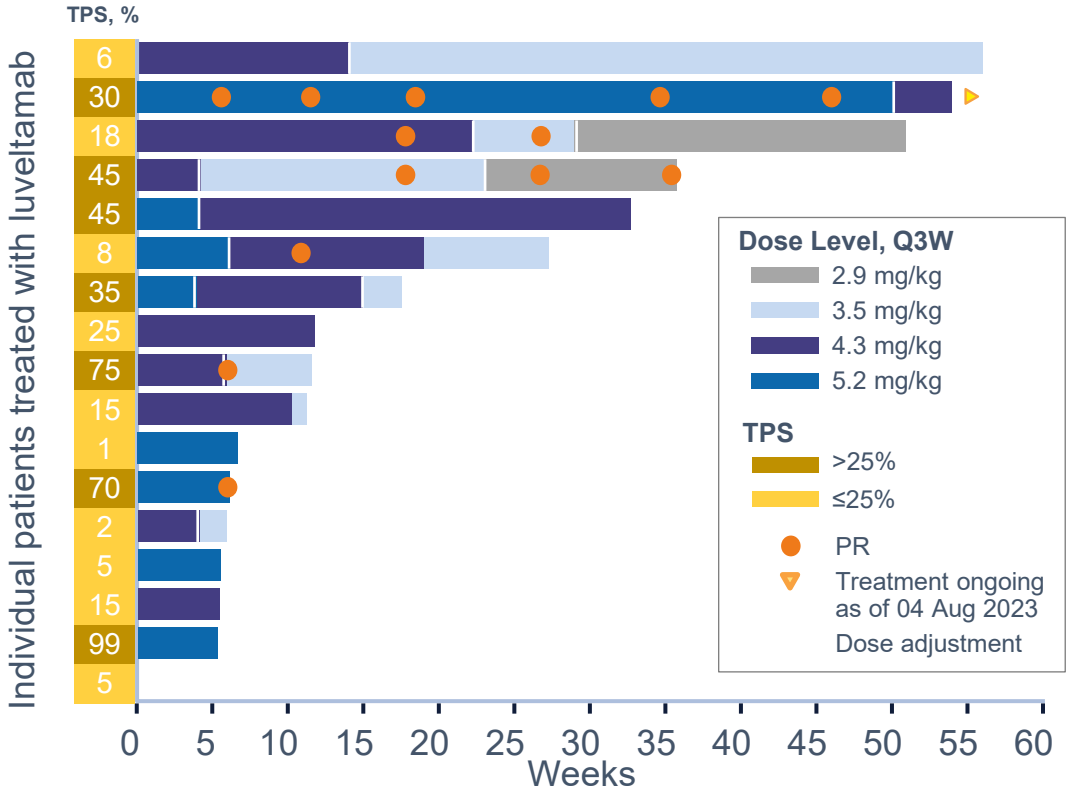
Maximum Reduction in Target Lesions*



Anti-tumor Activity*

n (%)	Overall FolRα ≥1% (n=16)	FolRα ≤25% (n=9)	FolRα >25% (N=7)
PR	3 (19)	1 (11)	2 (29)
SD†	8 (50)	4 (44)	4 (57)
PD	5 (31)	4 (44)	1 (14)
DCR	11 (69)	5 (56)	6 (86)

Treatment Duration and Dose Modifications



- Median exposure (range): 12 (3–53) weeks
- 5 of 17 (29%) patients received ≥5 cycles
- Median follow-up: 10.1 months

†3 unconfirmed PRs
Data cutoff: 04 August 2023. *n=16 response evaluable patients. DCR, disease control rate; EC, endometrial cancer; PR, partial response;

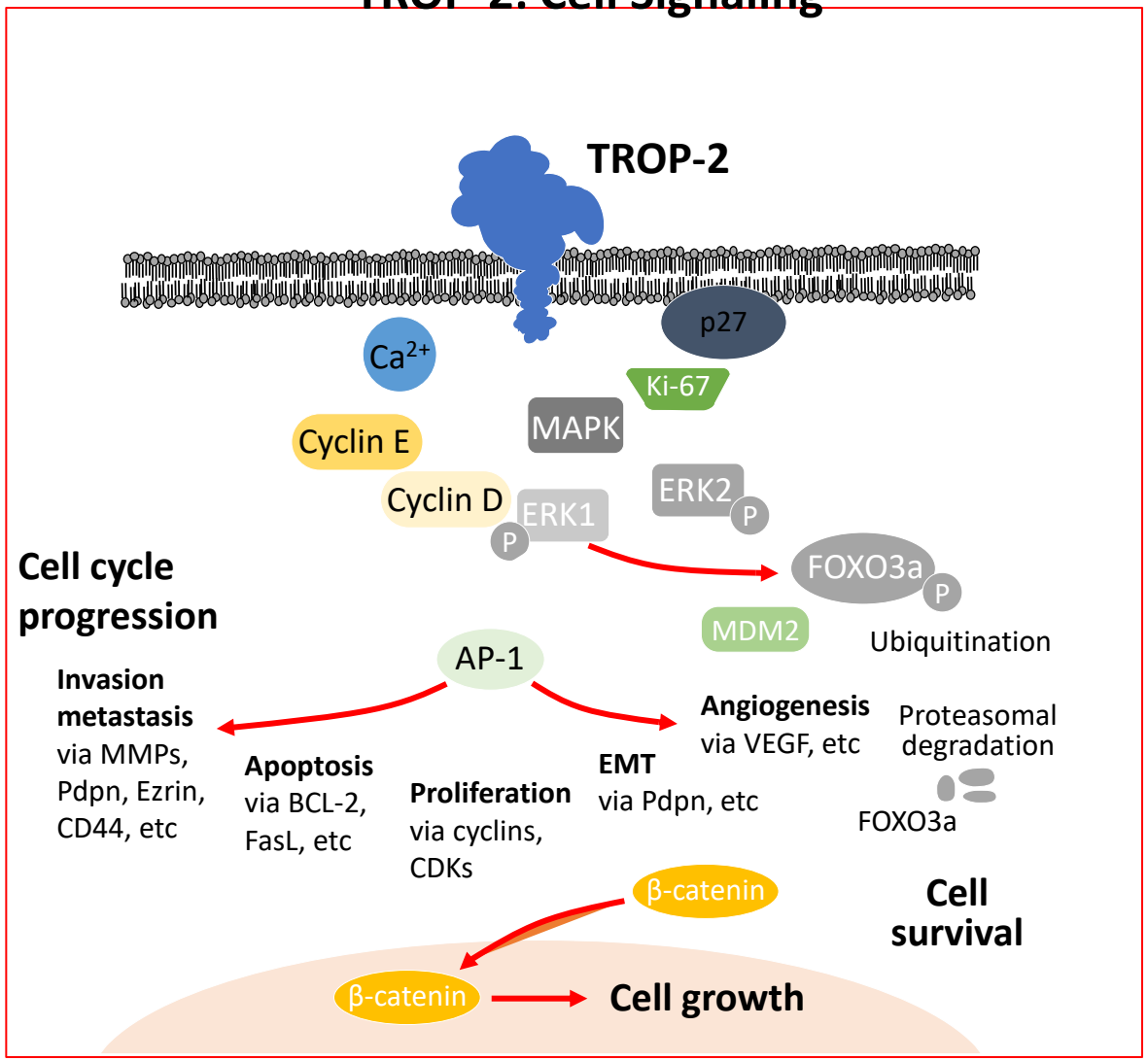
Q3W, every 3 weeks; TPS, tumor proportion score.

Pothuri B. et al. ESMO 2023

TROP-2 (trophoblast cell surface antigen 2) as a Therapeutic Target

- TROP-2 is a transmembrane glycoprotein overexpressed in solid tumors, including endometrial and cervical cancer
- TROP-2 is an epithelial adhesion molecule and regulates stem cell marker–associated cell regeneration

TROP-2: Cell Signaling

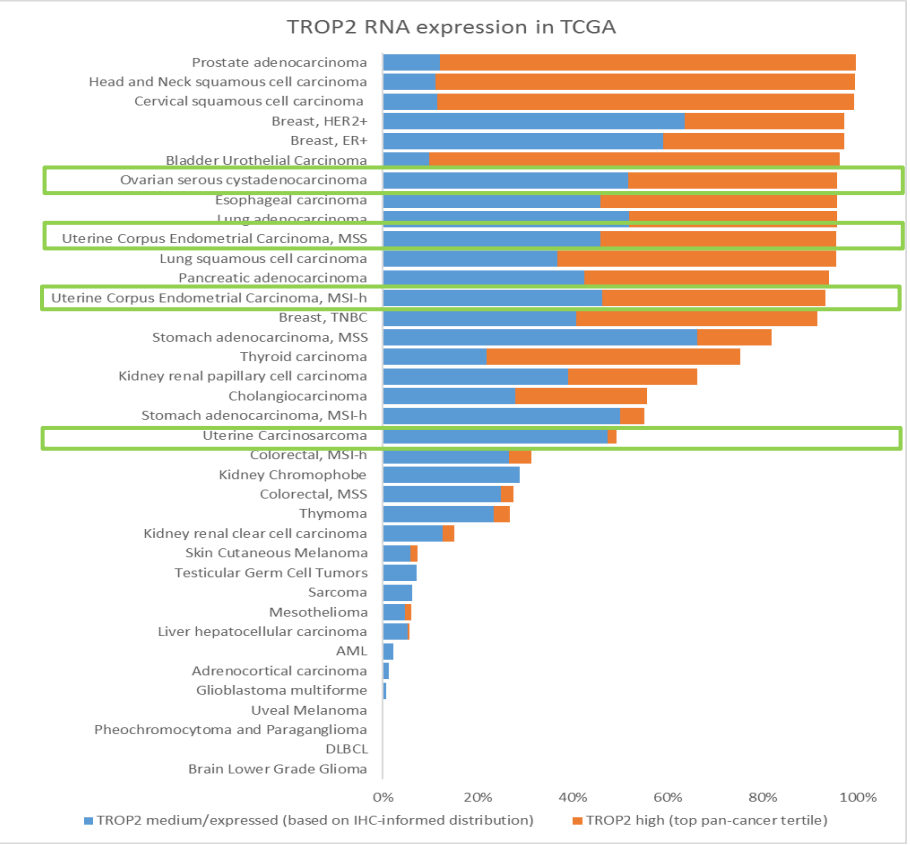


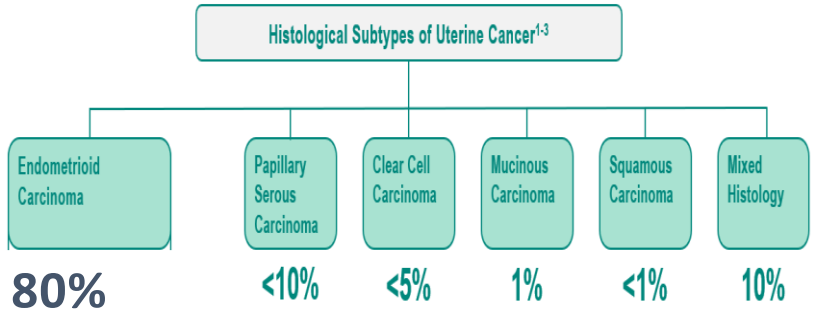
Jiang. Oncol Lett. 2013;6:375. Shvartsur. Genes Cancer. 2015;6:84.

Strong Scientific Rationale for Targeting TROP2 in EC

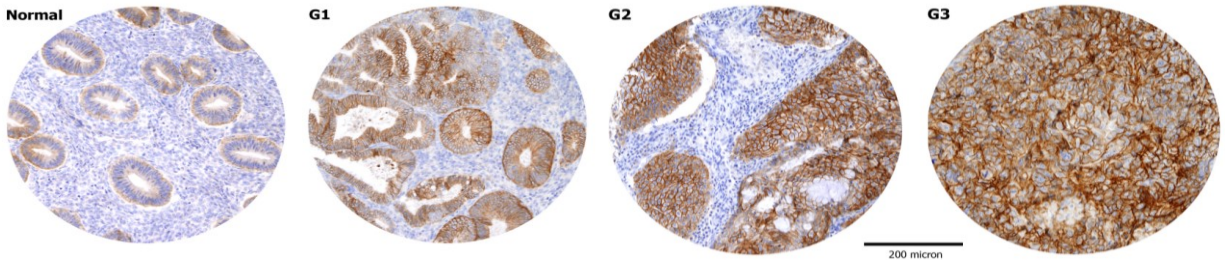
TROP2 is a transmembrane calcium signal transducer that is expressed in many normal tissues, but overexpressed in a variety of tumors

TROP2 mainly promotes tumor cell growth, proliferation, and metastasis by regulating the calcium ion signaling pathway and cyclin expression and reducing fibronectin adhesion





TROP2 Expression in Endometroid Histology is *inversely* correlated with differentiation.



Unlike other ADC targets, which may have variable expression across histological subtypes (ie Her2), TROP2 is broadly expressed across MMR status and EC histologies.

Morice, *Lancet*, 2016
Gordon, Global Library of Women's Medicine, 2008
Cerner Enviza, *CancerMPact, PatientMetrics*, Data Updated 25JAN2022.
Bardia, et al, Annals of Oncology, 2021,
Bignotti Int'L Gynecol Cancer Journal 2011

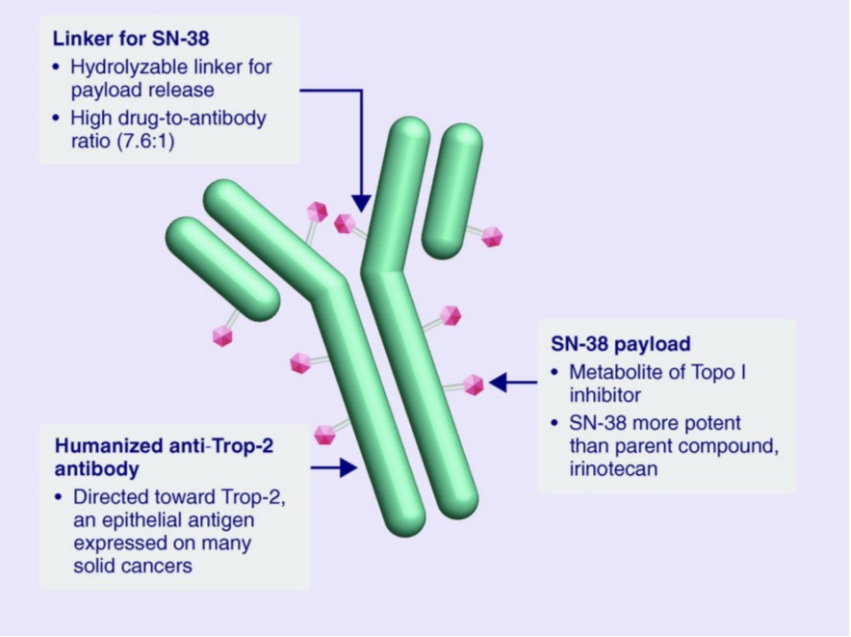
Anti–TROP-2 Antibody–Drug Conjugates

Characteristic	Dato-DXd	Sacituzumab Govitecan	Sacituzumab Tirumotecan
Antibody	Anti–TROP-2 IgG1	Anti–TROP-2 IgG1 kappa	Anti–TROP-2 IgG1
High affinity binding	+++	+++	+++
Linker	Cleavable	Cleavable	Cleavable
Payload	Deruxtecan derivative	SN-38	Belotecan derivative
DAR	4	7.6	7.4
Dose/schedule	6 mg/kg Q3W	10 mg/kg D1,8 Q3W	5 mg/kg Q2W

Okajima. Mol Can Ther. 2021;20(12):2329-2340. Sacituzumab govitecan PI. Xu. ASCO 2024 Annual Meeting. Abstr 880. NCT05347134.

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

ORR 33% in mEC



Sacituzumab govitecan ADC: anti–Trop-2 antibody linked to drug SN-38. Future Medicine. 2020 Mar. doi:10.2217/fon-2020-0163

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

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

*Out of 20 patients evaluable for durable disease control

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

Santin A et al ASCO 2023Abstract 5599. DOI: 10.1200/JCO.2023.41.16_suppl.5599

Sacituzumab govitecan in endometrial cancer

Poster!

733P - Efficacy and safety of sacituzumab govitecan (SG) in patients with advanced/metastatic endometrial cancer (EC): Updated results from TROPiCS-03

Presentation Number 733P
Speakers Bradley R. Corr (Aurora, United States of America)
Onsite Poster display date Saturday, 14 September 2024

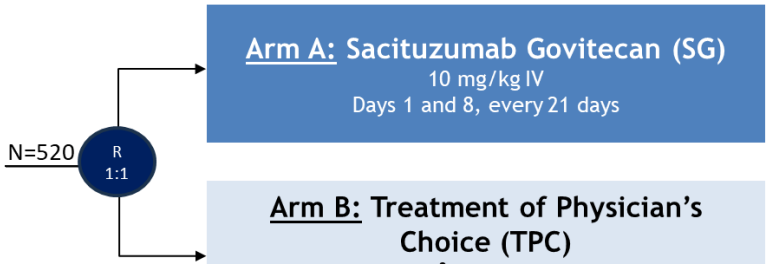
	All Patients (n = 41)
ORR (confirmed CR + PR), n (%) [95% CI]	11 (**27**) [14-43]
Clinical benefit rate (confirmed CR + PR + SD duration ≥ 6 months [b]), n (%) [95% CI]	17 (42) [26-58]
Median DOR [c] [95% CI], months	9.0 [2.8-NR]
Median PFS [95% CI], months	**5.0** [2.8-9.8]
Median OS [95% CI], months	**15.0** [5.9-NR]

Corr et al, ESMO 2024

A Randomized, Open-label, Phase 3 Study of Sacituzumab Govitecan Versus Treatment of Physician's Choice in Participants With Endometrial Cancer Who Have Received Prior Platinum-Based Chemotherapy and Anti-PD-1/PD-L1 Immunotherapy

Key Eligibility Criteria

- Recurrent endometrial carcinoma
- Histologically confirmed diagnosis of epithelial endometrial carcinoma, including carcinosarcoma
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy.
- Measurable or non-measurable disease



Stratification Factors

- # of Prior lines of systemic therapy in any setting (£2 vs 3)
- Prior Anti-PD-(L)1 therapy (yes vs no)
  Enrollment of participants who have not received prior anti-PD-1/PD-L1 therapy will be capped at approximately 10%.
- Geographic region (North America/Europe vs Asia/ROW)

Key Study Endpoints

Primary Endpoint:
- PFS by BICR
- OS

Key Secondary Endpoints:
- ORR by BICR
- Change from baseline and TTdD in Physical Function as assessed by EORTC-QLQ-C30

Secondary Endpoints:
- PFS by INV
- ORR by INV
- DOR, CBR by BICR and INV
- Safety
- Change from baseline in GHS/QoL as assessed by EORTC-QLQ-C30

Model C

ENGOT EN26/MaNGO

ENGOT PI: Nicoletta Colombo

GOG led study
Sponsor Gilead Sciences

MaNGO
Mario Negri Gynecologic Oncology

BARCELONA 2024 ESMO congress

Safety and Efficacy of Sacituzumab Tirumotecan (sac-TMT) in Patients with Previously Treated Advanced Endometrial and Ovarian Cancer from a Phase 2 Study

Presenter: Danbo Wang, MD, PhD

Liaoning Cancer Hospital, Shenyang, China

Danbo Wang, Ke Wang, Ruifang An, Guohua Yu, Keqiang Zhang, Dong Wang, Kui Jiang, Yunong Gao, Ying Cheng, Yunpeng Liu, Hui Qiu, Xiang Wang, Tianshu Liu, Omobolaji O. Akala, Elliot Chartash, Yaling Li, Xin Li, Xiaoping Jin, Junyou Ge, Jin Li

Sun, 15.09.2024, 14:50-14:55

715MO

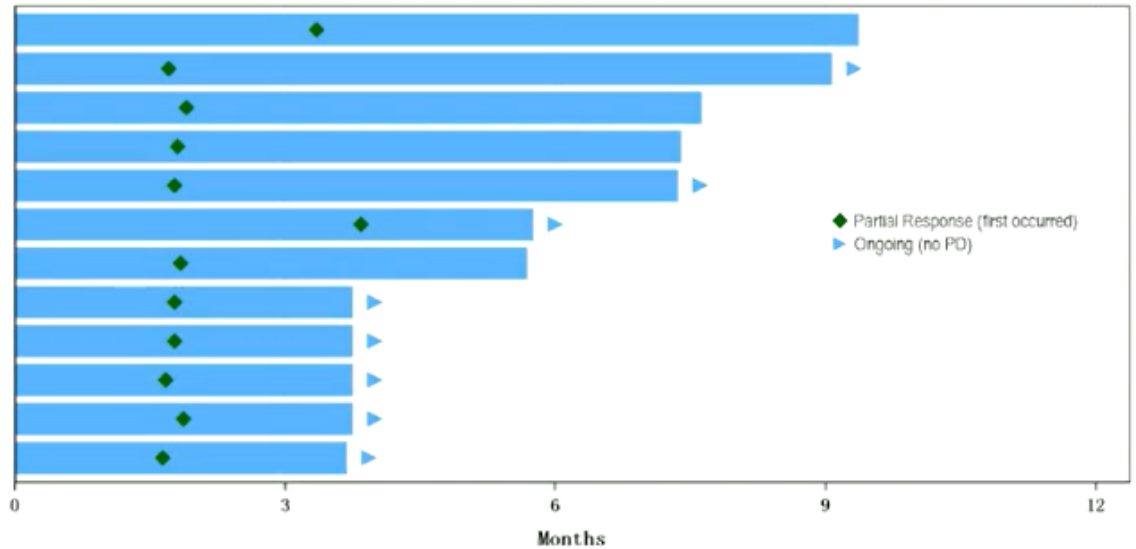
Preliminary Results: Efficacy in EC cohort

	EC (N = 44)[a]
ORR, % (n/N)	**34.1 (15/44)[b]**
Confirmed ORR	27.3 (12/44)
Subgroups	
TROP2 H-score >200	41.7 (5/12)
Prior IO	37.5 (6/16)
DCR, % (n/N)	**75.0 (33/44)**
PR	34.1 (15/44)
SD	40.9 (18/44)
DoR	
Median (range), months	5.7 (3.8, 7.4+)
PFS	
Median (95% CI), months	5.7 (3.7, 9.4)

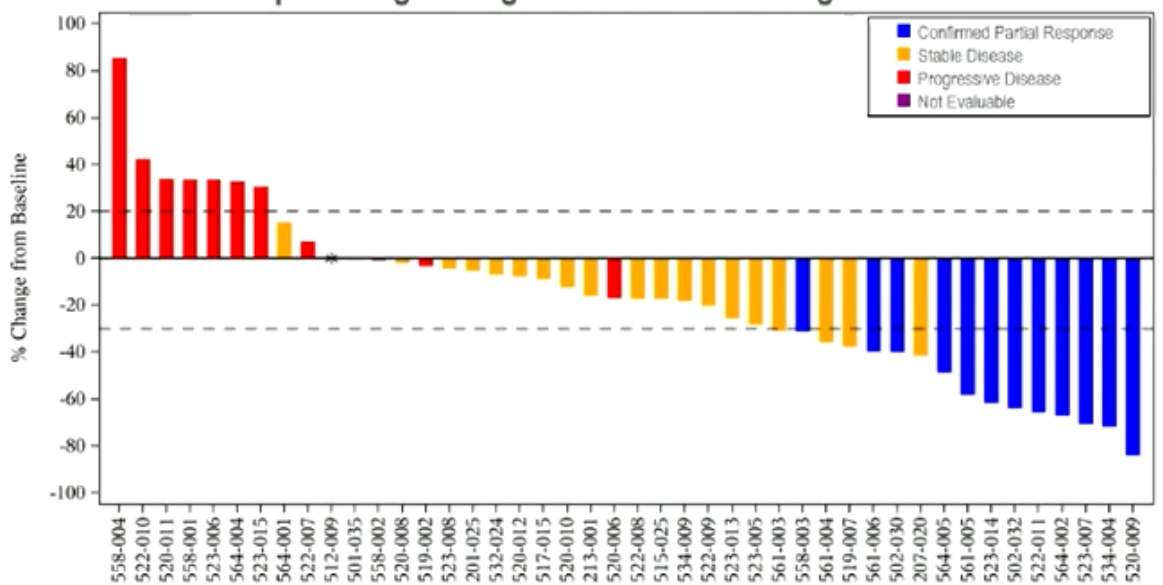
a. Responses assessed per RECIST v1.1 by investigator.
b. Two patients with unconfirmed response were still receiving treatment at the data cutoff date.

CI, confidential interval; DCR, disease control rate; DoR, duration of response; EC, endometrial cancer; IO, immunotherapy; ORR, objective response

Time to response and duration of treatment for confirmed responders



Best percentage change from baseline for target lesions



*: Percentage Change from Baseline for Target Lesions was 0%

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

Phase 3, randomized, active-controlled, open-label, multicenter study to compare the efficacy and safety of MK-2870 monotherapy versus treatment of physician's choice in participants with endometrial cancer who have received prior platinum-based chemotherapy and immunotherapy

Key Eligibility Criteria:

- ✓ Histologically-confirmed endometrial cancer
- ✓ Radiologically apparent measurable or non-measurable disease
- ✓ Prior platinum exposure AND prior anti-PD-1/PD-L1 exposure (given separately or in combination), in any setting

Randomization 1:1 N=710

- MK-2870 4 mg/kg IV Q2W → PD by BICR
- Treatment of Physician's Choice (TPC) Doxorubicin 60 mg/m^2 IV Q3W or Paclitaxel 80 mg/m^2 IV Q4W (3 weeks on, 1 week off) → PD by BICR

Dual Primary Endpoints

- PFS* (BICR)
- OS

Secondary Endpoints

- ORR
- DOR
- QoL
- Safety/Tolerability

Stratification:

- ❖ MMR (deficient MMR or proficient MMR)
- ❖ TROP2 expression (high or low/negative), per immunohistochemistry (IHC)
- ❖ Prior lines of therapy (≤ 2 or 3)
- ❖ Disease status at baseline per RECIST 1.1 as assessed by BICR (measurable vs nonmeasurable)

*Futility Analysis for PFS is planned to ensure a minimal threshold of efficacy is being met early in the conduct of the study

MK-2870 internal data: Protocol MK-2870-005. Merck 2023.
BICR, blinded independent central review; dMMR, mismatch repair deficient; DOR, duration of response; ECOG, eastern cooperative oncology group; MMR, mismatch repair; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death receptor-1; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; pMMR, mismatch repair proficient; QoL, quality of life; TROP2, transmembrane glycoprotein encoded by the Tacstd2 gene.

ENGOT
European Network of Gynaecological Oncological Trial groups

BARCELONA 2024 ESMO congress

Datopotamab deruxtecan (Dato-DXd) in patients with Ovarian or Endometrial Cancer: Results from the Phase 2 TROPION-PanTumor03 Study

Ana Oaknin,[1] Joo Ern Ang,[2] Sun Young Rha,[3] Kan Yonemori,[4] Rebecca Kristeleit,[5] Chia-Chi Lin,[6] Taroh Satoh,[7] Purificación Estévez-Garcia,[8] Mehmet Ali Nahit Şendur,[9] Laura Medina Rodriquez,[10] Antoine Italiano,[11] Iwona Lugowska,[12] Isabelle Ray-Cocquard,[13] Amit Oza,[14] Jimmy L. Zhao,[15] Srikanth Gajavelli,[15] Justyna Filant,[16] Shamim Gharagoozloo,[17] Yelena Janjigian,[18] Funda Meric-Bernstam[19]

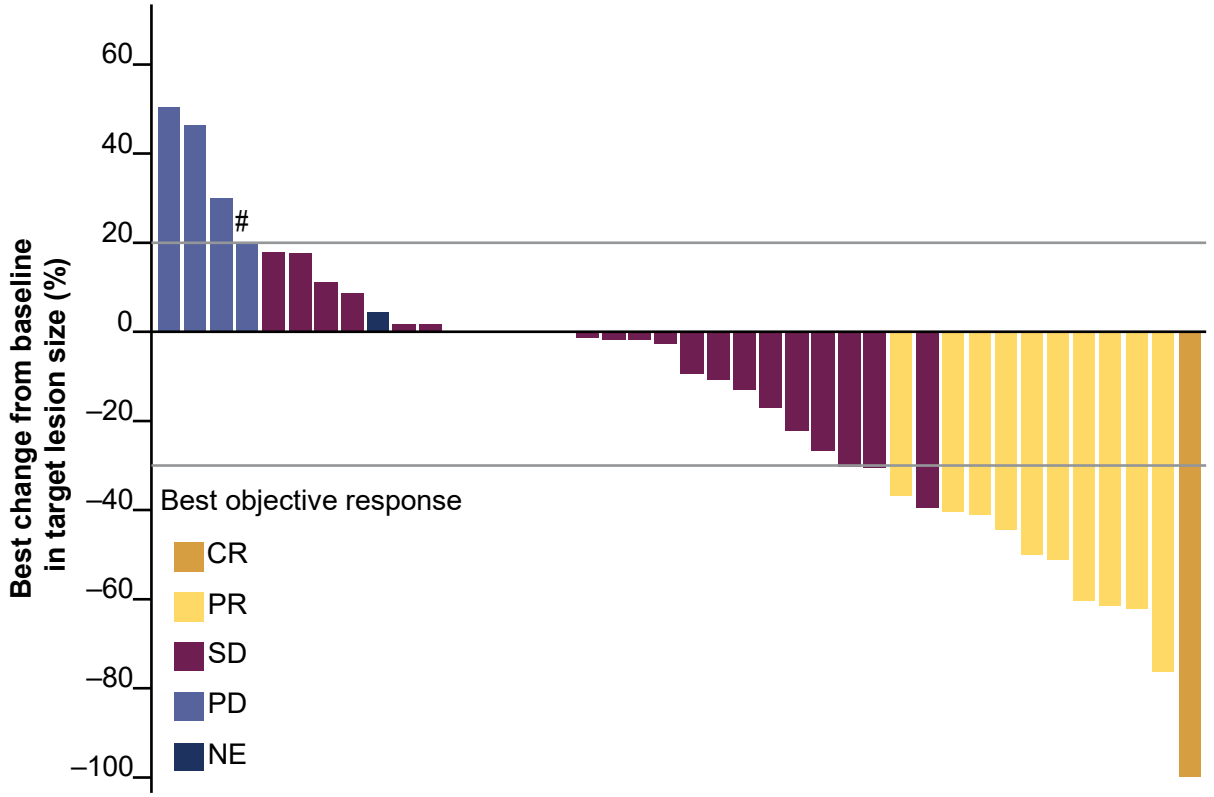
[1]Medical Oncology Service, Vall d'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]National Taiwan University Hospital, Taipei, Taiwan; [7]Osaka University Hospital, Suita, Japan; [8]Hospital Universitario Virgen del Rocio, Seville, Spain; [9]Ankara Yıldırım Beyazıt University Faculty of Medicine and Ankara Bilkent City Hospital, Ankara, Türkiye; [10]Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain; [11]Institut Bergonié, Bordeaux, France; [12]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [13]Centre Leon Bérard, Lyon, France; [14]Princess Margaret Cancer Centre, Toronto, Canada; [15]AstraZeneca, New York, NY, USA;[16]AstraZeneca, Warsaw, Poland; [17]Biostatistics, AstraZeneca, Cambridge, UK; [18]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [19]MD Anderson Cancer Center, University of Texas, Houston, TX, USA

Efficacy in Endometrial Cancer: Dato-DXd

As of June 14, 2024, median duration of follow-up* was 13.6 months (range 2.1–19.6) in the endometrial cohort

	Endometrial (N=40)
Confirmed ORR, % (95% CI)	27.5 (14.6–43.9)
Best overall response, n (%)	
CR	1 (2.5)
PR	10 (25.0)
SD†	23 (57.5)
PD‡	5 (12.5)
NE§	1 (2.5)
Median time to response, months (range)	2.8 (1.4–4.2)
Median DoR, months (95% CI)	16.4 (7.1–NC)
DCR at 12 weeks,‖ % (80% CI)	57.5 (46.1–68.3)
Median PFS, months (95% CI)	6.3 (2.8–NC)

Waterfall plot: best change from baseline in target lesion size¶



*Duration of follow-up calculated as the median time from randomisation to the date of censoring, in censored patients only; †Unconfirmed CR/PR, or SD ≥35 days; ‡RECIST progression or death ≤13 weeks; § SD <35 days, no valid baseline assessment or evaluable follow-up assessment; ‖Defined as the percentage of patients who achieved CR, PR or SD; ¶Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Lines at -30% and 20% indicate thresholds for PR and PD, respectively. If best percentage change cannot be calculated due to missing data, +20% will be imputed as the best percentage change in the following situations (otherwise left as missing): patient has no post-baseline assessment, has died, has new lesions or progression of lesions, or has withdrawn due to PD and has no evaluable target lesion data. Patients with imputed values marked with #.

Oaknin et al, ESMO 2024

Puxitatug samrotecan (P-Sam): A B7-H4 targeting topoisomerase I inhibitor (TOP1i) ADC

- **B7-H4 is a promising ADC target:**[1]
  - ✓ Highly expressed in several tumors including endometrial (EC), ovarian (OC), breast cancer (BC) and cholangiocarcinoma (CCA).
  - ✓ Limited normal tissue expression.
- **P-Sam is a B7-H4 TOP1i ADC (DAR8).**[1]
  - ✓ Novel, membrane-permeable "bystander-capable" TOP1i payload with a stable, cleavable linker.
  - ✓ Robust antitumor activity in PDX models, activity in PDX correlated with B7-H4 expression.
- **Here we present data from a Phase 1/2a study investigating P-Sam monotherapy in patients with advanced/metastatic EC, OC, BC or CCA.**

P-Sam robust activity in preclinical TNBC PDX models correlates with B7-H4 expression

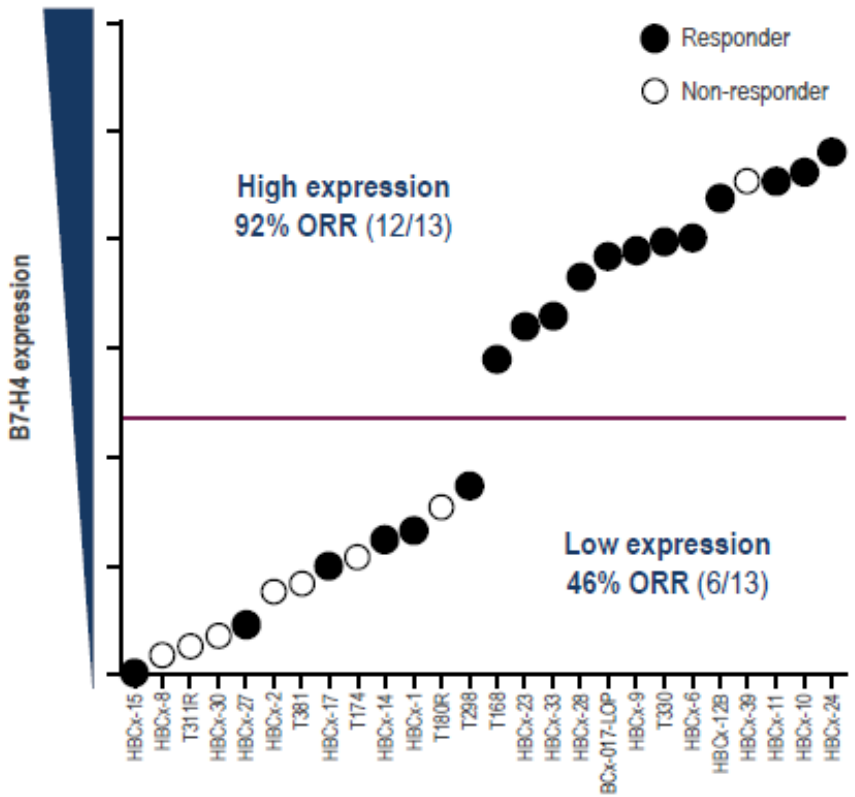


Figure reproduced with permission from Sapra P, et al. AACR 2023.

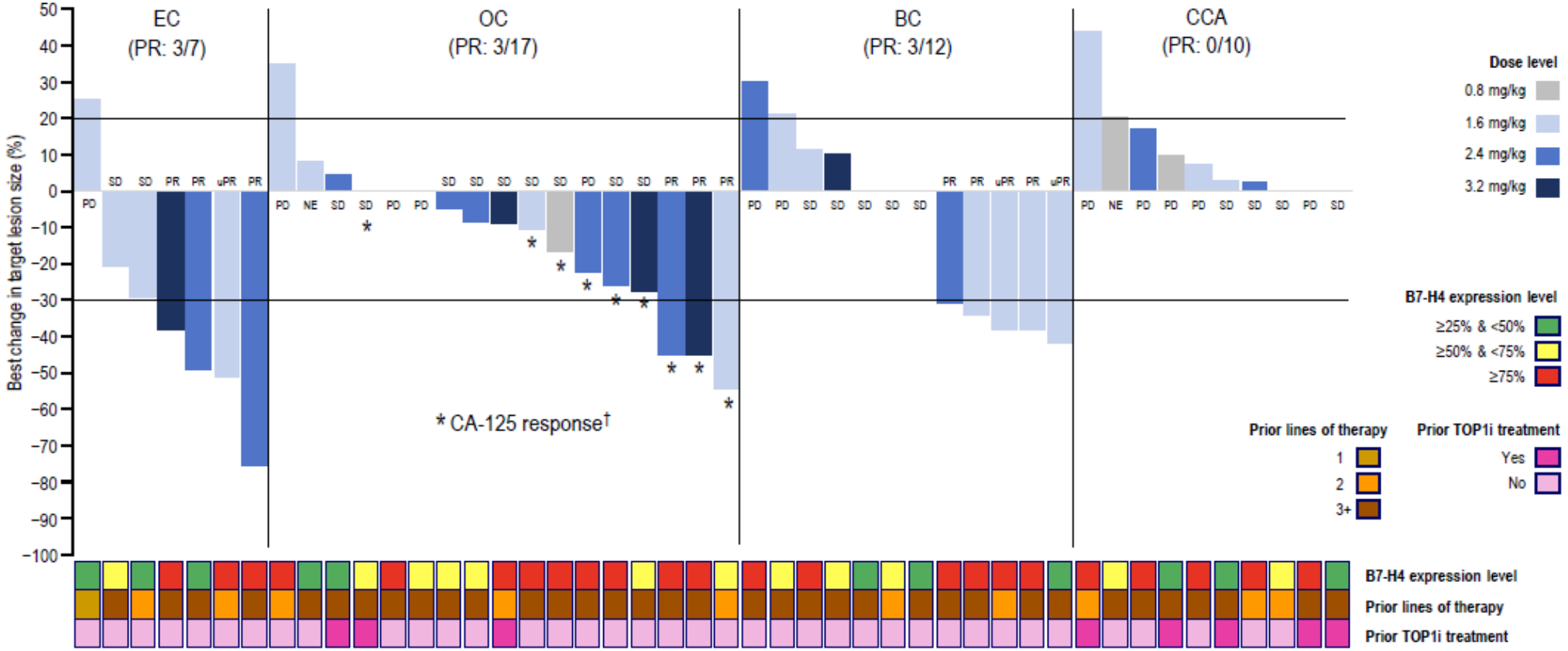
ADC, antibody drug conjugate; DAR, drug-to-antibody ratio; ORR, objective response rate; PDX, patient derived xenograft; TNBC, triple negative breast cancer

1. Kinneer, K, et al. *Clin Cancer Res* 2023;29:1086–101.

Meric-Bernstam F, ESMO 2024

Bluestar(NCT05123482): First-in-human, Phase 1/2° open label, multicenter study

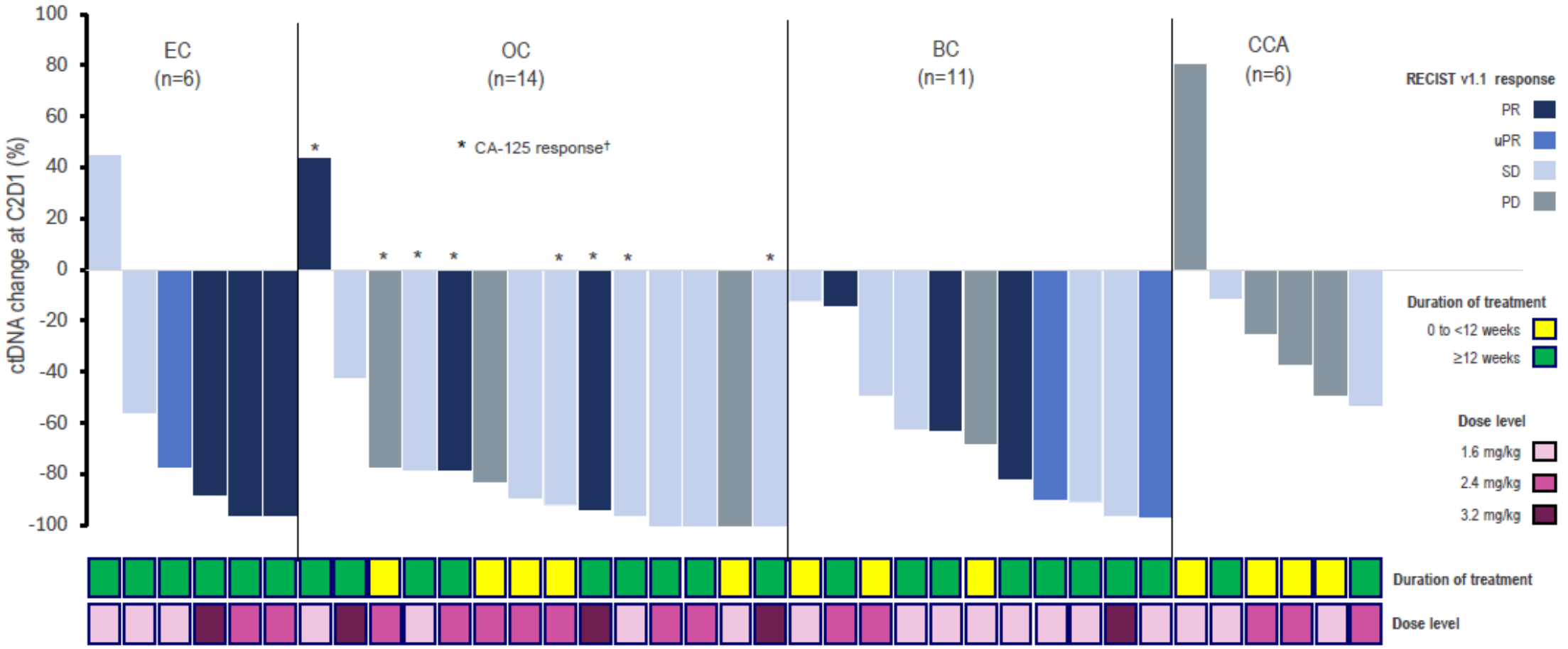
Nine responders in 44 patients treated with doses ≥1.6 mg/kg across B7-H4 expression levels



All doses are IV Q3W. Response evaluable set; data cut-off: July 3, 2024. Response based on RECIST v1.1 (response and progression defined as -30% and +20% change from baseline, respectively).
†Patients with baseline CA-125 value and ≥1 post-baseline CA-125 value were included. According to the GCIG criteria, patients can be evaluated for an investigator-assessed response based on RECIST v1.1 only if they have a baseline sample that is ≥2x the upper limit of normal, obtained within 2 weeks prior to starting treatment. CA-125 response is defined as a ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days.
BC, breast cancer (includes hormone receptor + and –); CCA, cholangiocarcinoma; EC, endometrial cancer; GCIG, Gynecological Cancer Intergroup; IV, intravenous; NE, not evaluable; OC, ovarian cancer; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uPR, unconfirmed PR; TOP1i, topoisomerase 1 inhibitor

Meric-Bernstam F, ESMO 2024

ctDNA reductions observed at cycle 2 day 1 across all indications in patients treated with doses ≥1.6 mg/kg



All doses are IV Q3W. Response evaluable set; data cut-off: July 3, 2024. Response based on RECIST v1.1. ctDNA samples analyzed at C2D1 vs C1D1 using GH360. †Patients with baseline CA-125 value and ≥1 post-baseline CA-125 value were included. According to the GCIG criteria, patients can be evaluated for an investigator-assessed response based on RECIST v1.1 only if they have a baseline sample that is ≥2x the upper limit of normal, obtained within 2 weeks prior to starting treatment. CA-125 response is defined as a ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days. BC, breast cancer (includes hormone receptor + and –); C, cycle; CCA, cholangiocarcinoma; ctDNA, circulating tumor DNA; D, day; EC, endometrial cancer; GCIG, Gynecological Cancer Intergroup; IV, intravenous; OC, ovarian cancer; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; uPR, unconfirmed PR

Meric-Bernstam F, ESMO 2024

ENDOMETRIAL CANCER: SUMMARY

- Treatment according to molecular profile is the way to move forward in advanced, and in the future, also adjuvant setting

- The majority of patients will receive immunotherapy with chemotherapy in the first line setting (or even adjuvant setting)

- Different strategies are currently under investigations in the post-IO scenarium taking into consideration the molecular characteristics of the tumor:

  - NSMP ER+: CDK4-6/AI
  - P53wt: Selinexor
  - P53 abn: DDR modulators
  - **HER2, FR alpha, TROP2, B7H4: ADC !!!**