XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI

MaNGO

Improving outcomes in non-MMRd disease

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Disclosure

Tipo di affiliazione o supporto finanziario	Sponsor
Partecipazione ad eventi scientifici	MSD / Astra Zeneca
Partecipazione ad eventi scientifici	GSK

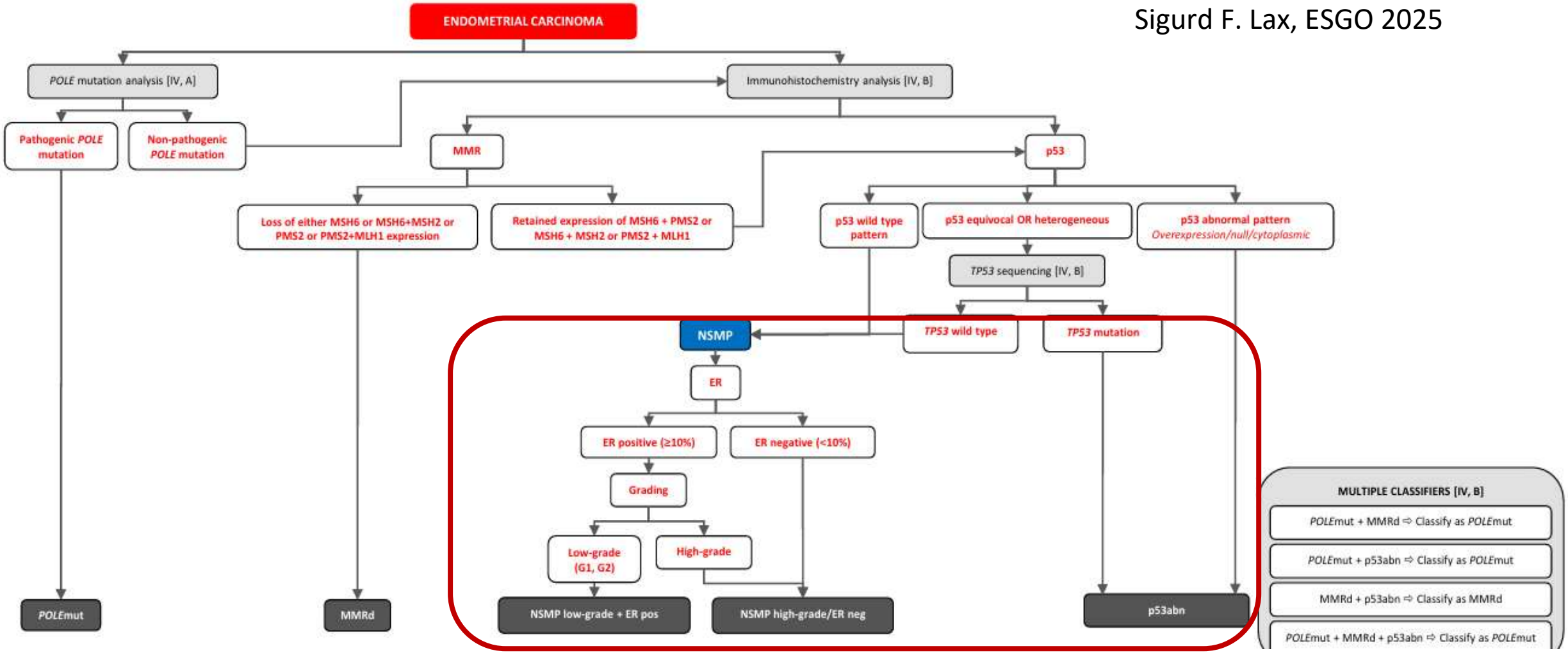
Molecular types of endometrial carcinoma

	Mismatch Repair (MMR) deficient	P53 mutant	POLE mutant	No special molecular profile (NSMP)
Molecular characteristics	MMR deficient/MSI, POLE & p53 wild type	P53 mutations, POLE mostly wild type, MMR proficient/MSS	Pathogenic POLE mutation, p53 wt, MMR proficient/MSS	MMR proficient/MSS, p53 and POLE wild type
Multiple classifier	Yes (p53 mut)	No	Yes (p53mut/MMRd)	No
Histological types (most frequent)	Endometrioid, undifferentiated	Serous, carcinosarcoma	Endometrioid, undifferentiated	Endometrioid, clear cell
Grade endometrioid	Low > high	Low << high	Low > high	Low >> high
Stage (frequent)	Stage I	Stage >I	Stage I	Stage I
Prognosis	Good/intermediate	Poor	Very good	Good/intermediate
% of all endometrial carcinoma	25-30%	15-20%	5-10%	45-50%

Huvila et al. 2021; Lax Onko News Austria 2022

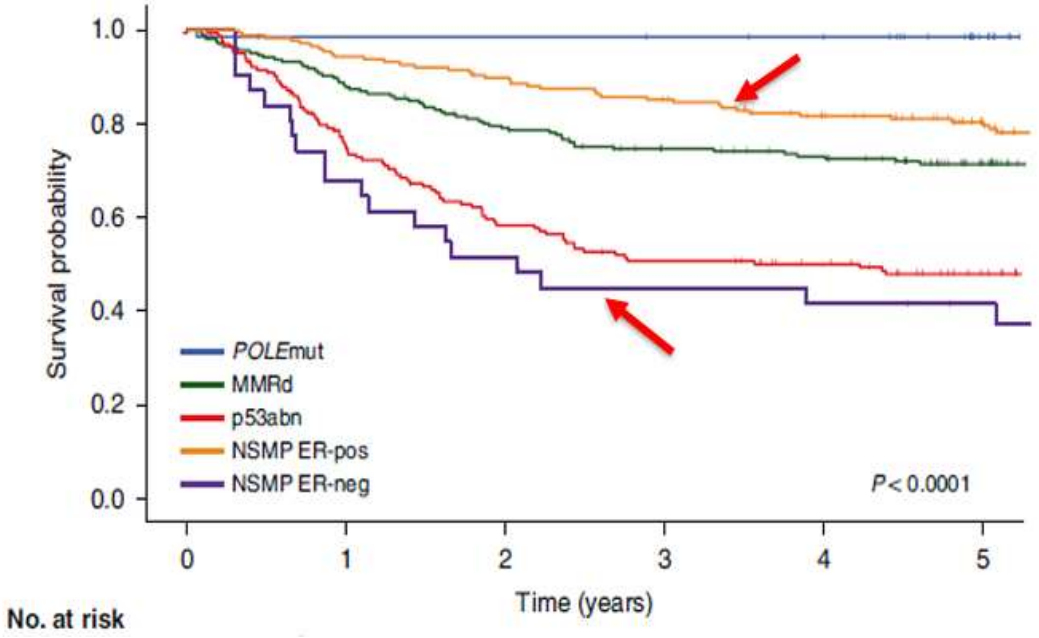
Assessment of molecular classification

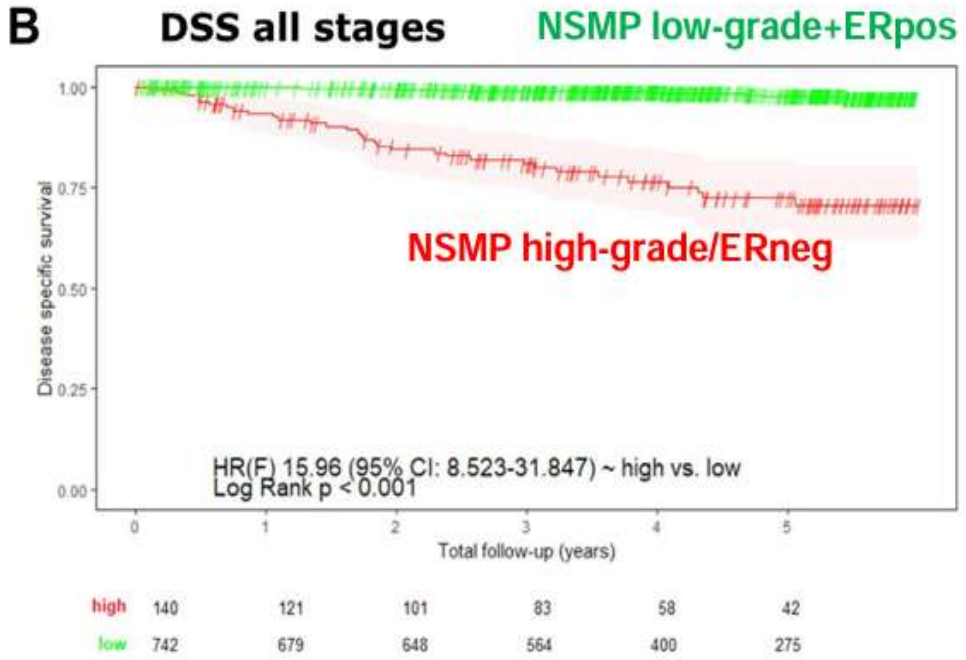
Sigurd F. Lax, ESGO 2025



Role of ER-status in NSMP

- Prognosis of NSMP ER-neg similar to p53abn
- Stongest model within NSMP: combination ER-neg OR grade 3 versus ER-pos AND endometrioid grade 1/2





Jamieson et al., Moderm Pathology 2023; Vermij et al., BJC 2023

non-MMRd disease

Paziente

non-MMR

ER positive (Low grade)

BASSO RISCHIO

POLEmut

ER negative (High grade)

ALTO RISCHIO

P53 abn

p53wt

Definition of risk groups

Prognostic risks in the respective groups are defined as estimated overall 5-year risk of recurrence:

- **low risk group**: risk less than 8%;
- **intermediate risk group**: risk between 8 and 15%;
- **high-intermediate risk group**: risk between 15 and 25%;
- **high risk group**: risk higher than 25%.

Remi Nout, ESGO 2025

Definition of risk groups based on 2023 FIGO staging and molecular classification

Remi Nout, ESGO 2025

Low risk
Intermediate risk
High-intermediate risk
High risk
Uncertain, lack of data

2023 FIGO staging[T]			Molecular classification*				
			*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
I	**Confined to the uterine corpus**						
IA	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)	IAm *POLE*mut			**	
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#	IAm *POLE*mut			**	IICm p53abn
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut		n.a.		
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IAm *POLE*mut	Substantial LVSI**			

Definition of risk groups based on 2023 FIGO staging and molecular classification

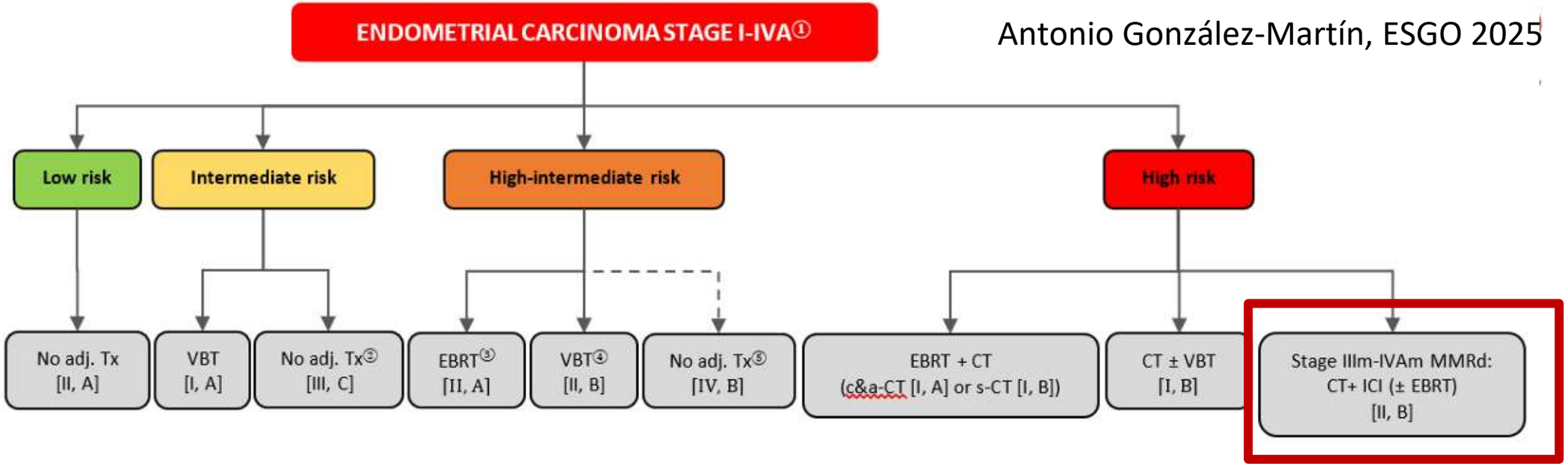
Remi Nout, ESGO 2025

Low risk
Intermediate risk
High-intermediate risk
High risk
Uncertain, lack of data

2023 FIGO staging[T]			Molecular classification*				
			*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
III	**Local and/or regional spread**						
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria					
	IIIB2	Metastasis to the pelvic peritoneum					
IIIC	IIIC1	Pelvic lymph node metastasis					
	IIIC1i	Micrometastasis					
	IIIC1ii	Macrometastasis					
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIIC2i	Micrometastasis					
	IIIC2ii	Macrometastasis					
IV	**Locally advanced and/or metastatic disease**						
IVA		Invasion of the mucosa and/or the intestinal mucosa					
	Metastatic disease or residual disease after surgery						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Adjuvant therapy in endometrial carcinoma stage I-IVa

Antonio González-Martín, ESGO 2025



① For patients with FIGO 2023 stages IA1m NSMP high-grade/ERneg or p53abn & ICm NSMP high-grade/ERneg or p53abn, there are limited data and adjuvant therapy is generally not recommended.
For patients with FIGO 2023 stages IIIm *POLE*mut & IVAm *POLE*mut, no firm recommendation can be given, however de-escalation from high-risk treatment can be considered.

②Especially for patients under 60 years of age and/or low-grade [II, A].

③EBRT is recommended for optimal pelvic control.

④VBT is an alternative option, especially for patients who underwent lymph node staging and are pN0.

⑤No adjuvant therapy can be considered, especially for patients who underwent lymph node staging and are pN0, without substantial LVSI and low-grade.

Adj. Tx adjuvant therapy; c&a-CT concurrent and adjuvant chemotherapy; CT chemotherapy; EBRT external beam radiotherapy; ICI immune checkpoint inhibitor; s-CT sequential chemotherapy; VBT vaginal brachytherapy.

ENGOT-en11/GOG-3053/KEYNOTE-B21

Key Eligibility Criteria

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

R 1:1
N=1095

	Stage 1	Stage 2
Carboplatin + paclitaxel	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m² (Q3W, 4 or 6 cycles)[a]	± RT ± cisplatin[b]
Pembrolizumab	Pembrolizumab 200 mg Q3W (6 cycles)	Pembrolizumab 400 mg Q6W (6 cycles)
Carboplatin + paclitaxel	Carboplatin (AUC 5 or 6) + paclitaxel 175 mg/m² (Q3W, 4 or 6 cycles)[a]	± RT ± cisplatin[b]
Placebo	Placebo Q3W (6 cycles)	Placebo Q6W (6 cycles)

Stratification Factors

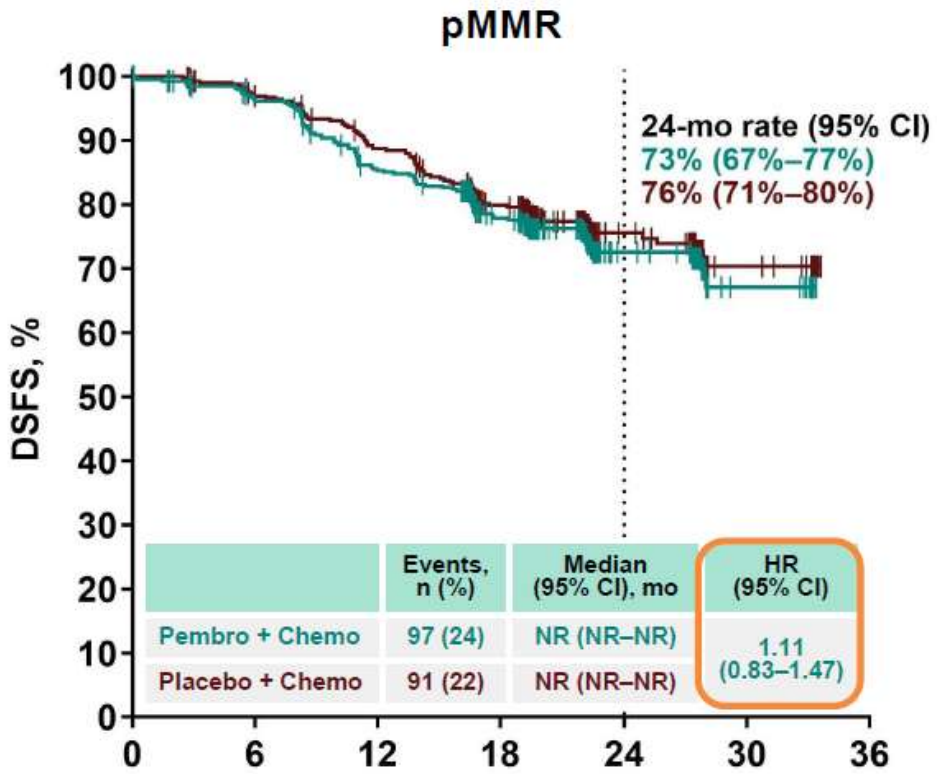
- **MMR status (pMMR vs dMMR)**, and within pMMR stratum:
  - Planned RT (chemo-EBRT vs EBRT vs no EBRT)
  - Histology (endometrioid vs non-endometrioid)
  - FIGO (2009) surgical stage (I/II vs III/IVA)

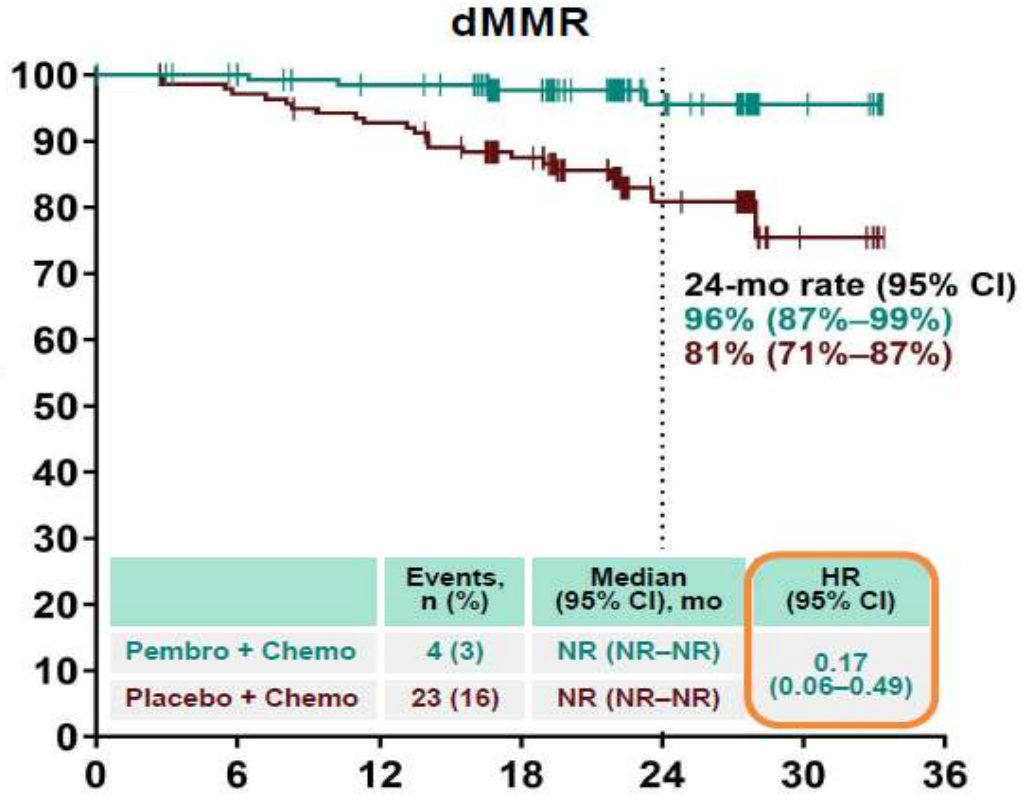
Dual primary endpoints: DFS and OS

Exploratory endpoint: DSFS by TMB, PD-L1, histology, and stage

Van Gorp T, ESMO 2024; Van Gorp T, ESGO 2025

ENGOT-en11/GOG-3053/KEYNOTE-B21





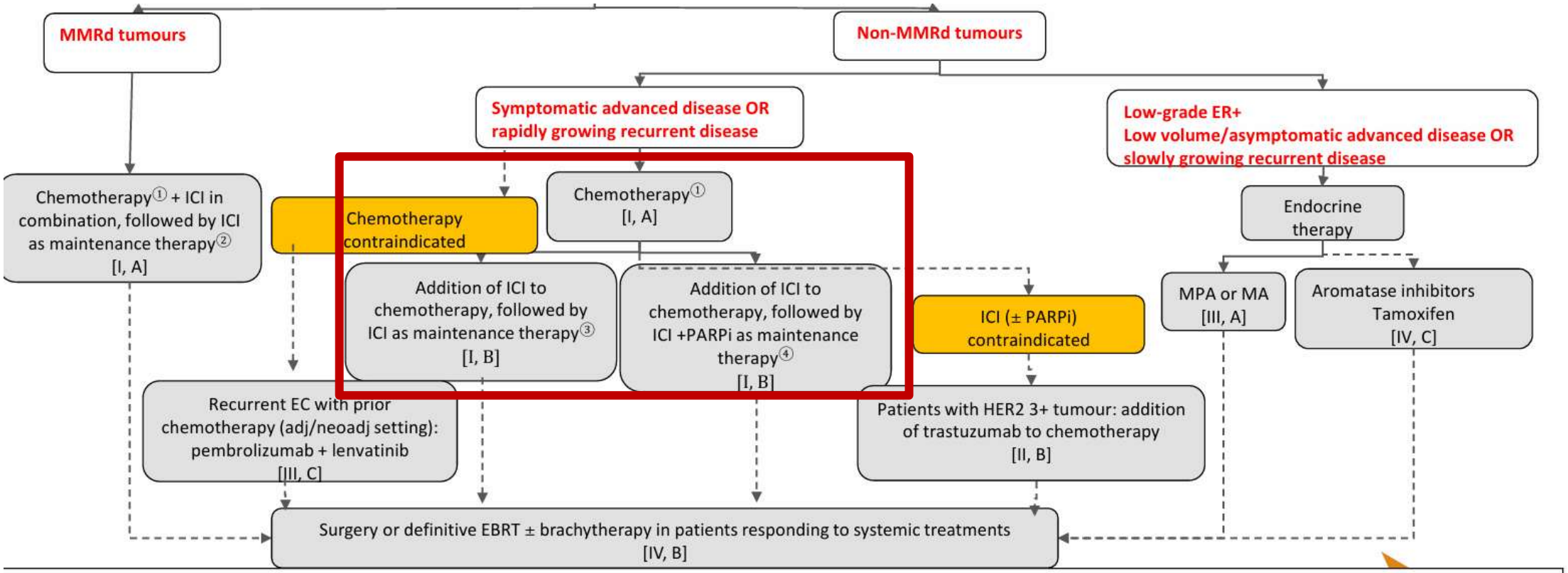
In dMMR EC, DSFS improved with the addition of pembrolizumab regardless of PD-L1 expression or TMB. Of note, there were only few events in PD-L1 CPS <1 and TMB-low tumors

In pMMR EC, DSFS did not improve with the addition of pembrolizumab regardless of PD-L1 or TMB status

Van Gorp T, ESMO 2024;
Van Gorp T , ESGO 2025

Unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting

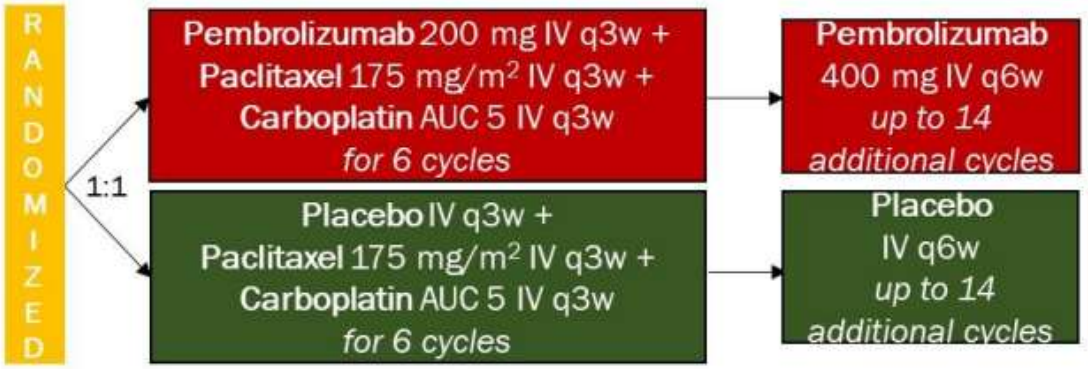
Colombo N and Ledermann J, ESGO 2025



①The standard chemotherapy regimen is carboplatin + paclitaxel.
②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).
③ICI: dostarlimab or pembrolizumab.
④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.
Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP non-specific molecular profile.

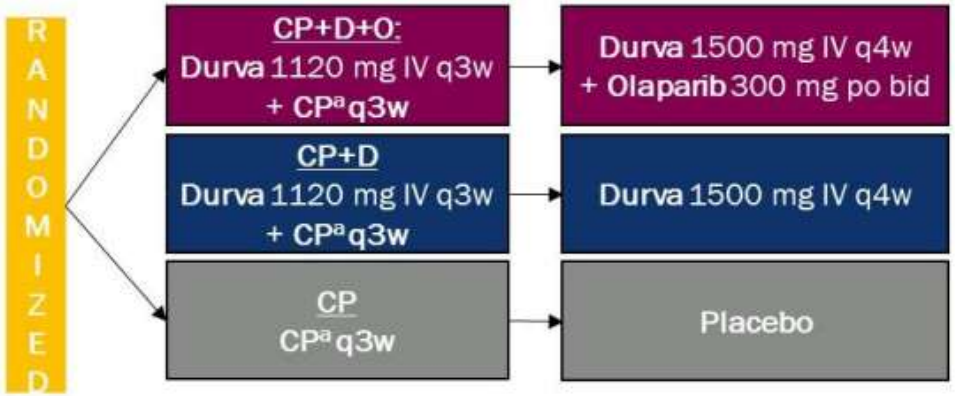
Transformative Clinical Trials in the Advanced Stage / Recurrent Setting

NRG GY018



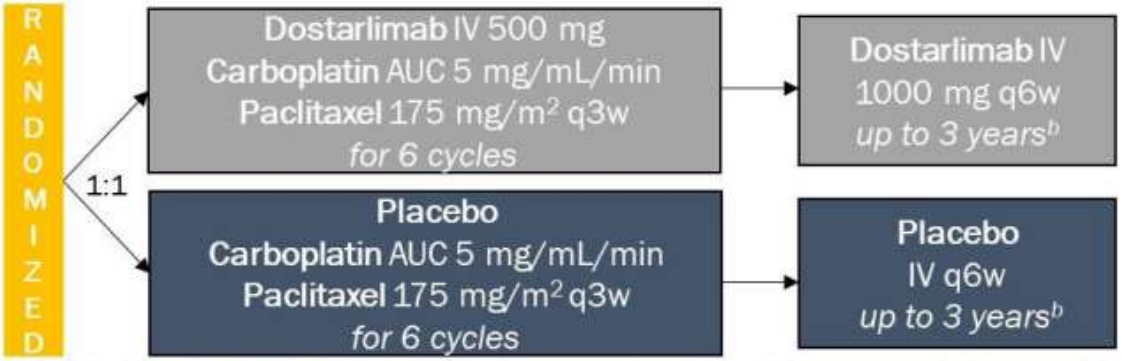
Stratified by MMR status (pMMR vs dMMR), ECOG status, and prior adjuvant Chemo

DUO-E/GOG 3041



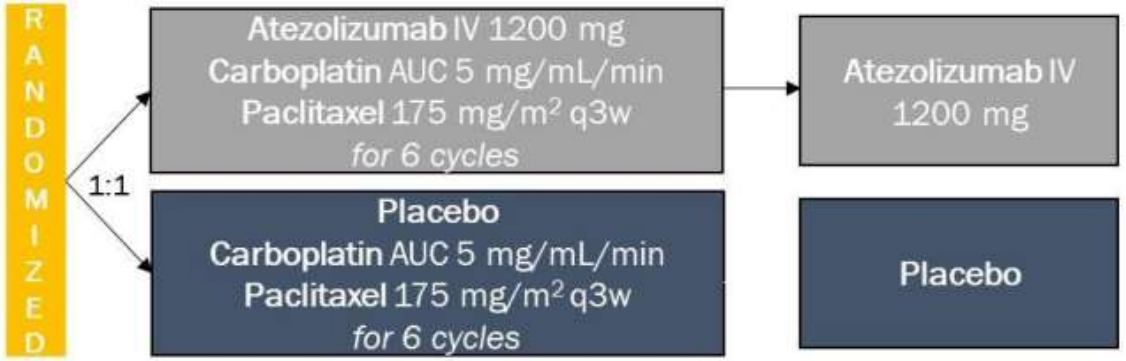
Stratified by MMR status, Disease status, Region of world

GOG 3031/RUBY



Stratified by MMR/MSI status,[c] prior external pelvic radiotherapy, and disease status

AtTEnd



Eskander R, et al. SGO 2023. Abstract 264. N Eng J Med March 2023; Mirza MR, et al. SGO 2023. Abstract 265. N Eng J Med March 2023; Westin, S et al. ESMO 2023 and J Clin Oncol Jan 2024; Colombo et al. ESMO 2023

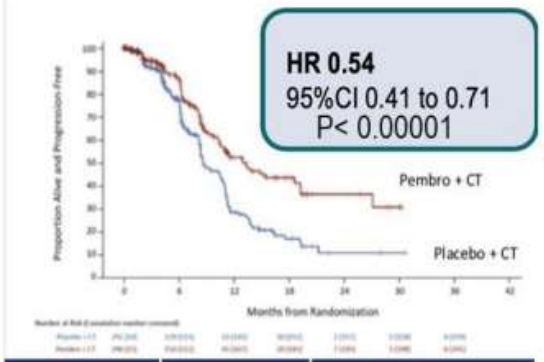
Brian Slomovitz, ASCO 2024

Transformative Clinical Trials in the Advanced Stage / Recurrent Setting

Benefit of IO + Chemo in the pMMR EC population: PFS

Brian Slomovitz, ASCO 2024

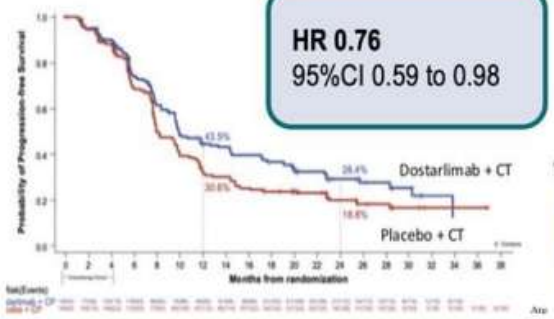
GY018



	No with events%	Median
Pembro + CT	30.6	13.1 (10.5-18.8)
Placebo + CT	45.5	8.7 (8.4-10.7)
Maturity	38.1%	

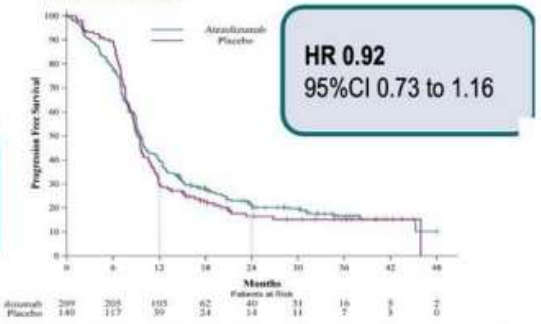
Only trial with prespecified alpha allocated analysis in pMMR EC cohort as primary endpoint

RUBY



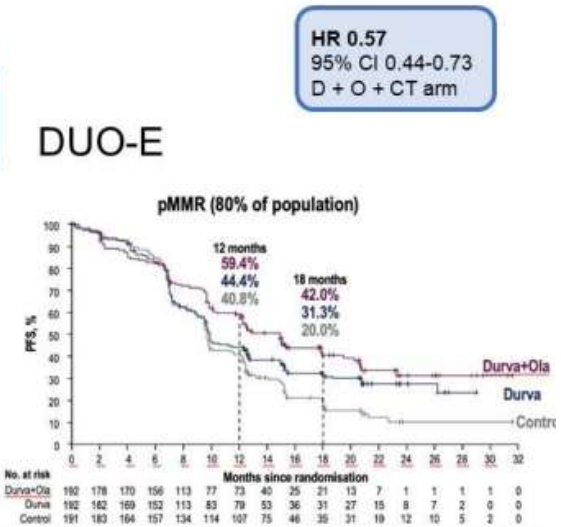
	No with events%	Median
Dorsta + CT	60.4	9.9 (9.0-13.3)
Placebo + CT	70.7	7.9 (7.6-9.8)
Maturity	65.4%	

AtTEnd



	No with events%	Median
Atezo + CT	78	9.5 (9.0-10.4)
Placebo + CT	77	9.2 (8.5-9.9)
Maturity	78%	

DUO-E



	No with events %	Median
Durva + CT	64.6	9.9 (9.4-12.5)
Durva + O + CT	56.5	15 (12.4-18)
Placebo + CT	77.1	9.7 (9.2-10.1)

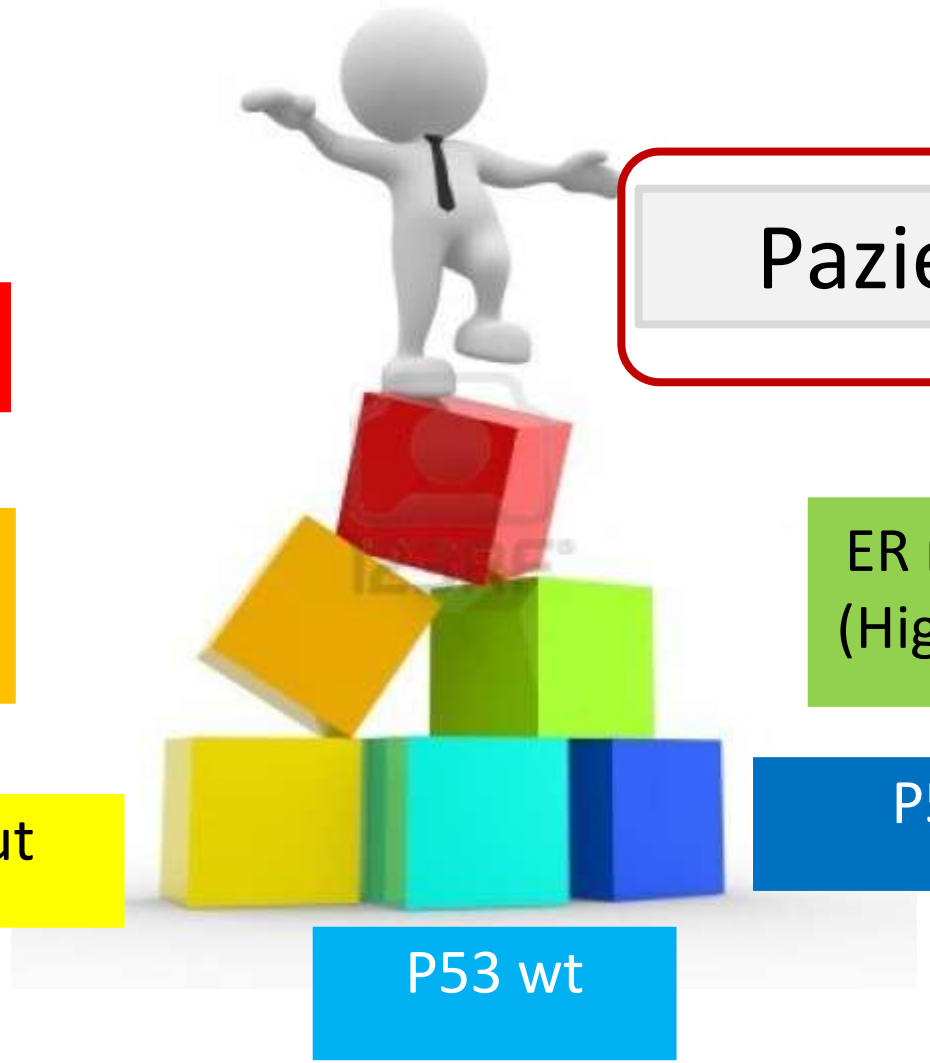
non-MMR disease

ICI

non-MMR

ER positive
(Low grade)

POLEmut



Paziente

ER negative
(High grade)

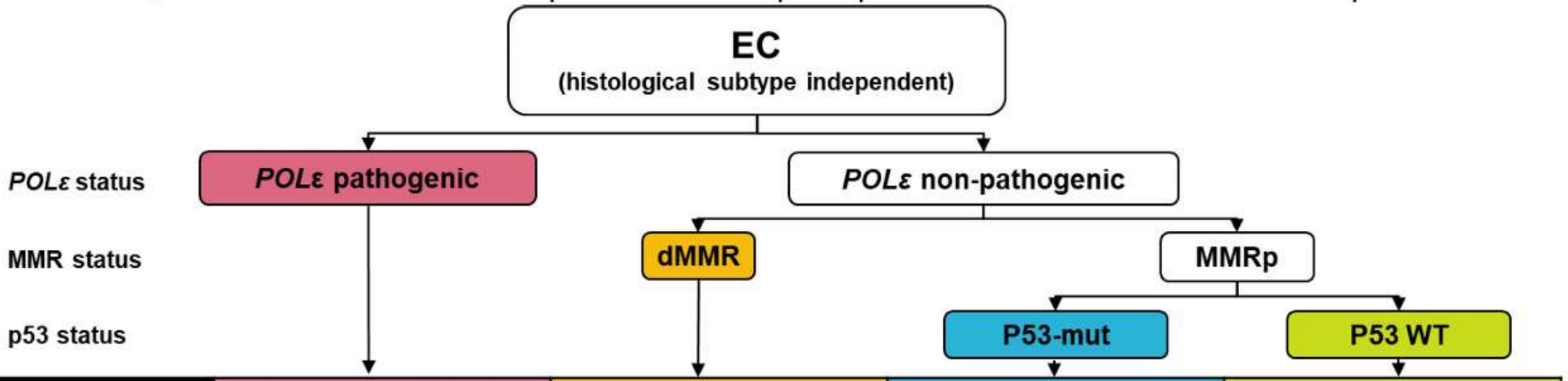
P53 abn

P53 wt

RUBY Molecular Classification Algorithm

Scan for slides

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



Integrated diagnosis	POLεmut (EDM)	dMMR (or MSI-H)	TP53 aberrant	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	

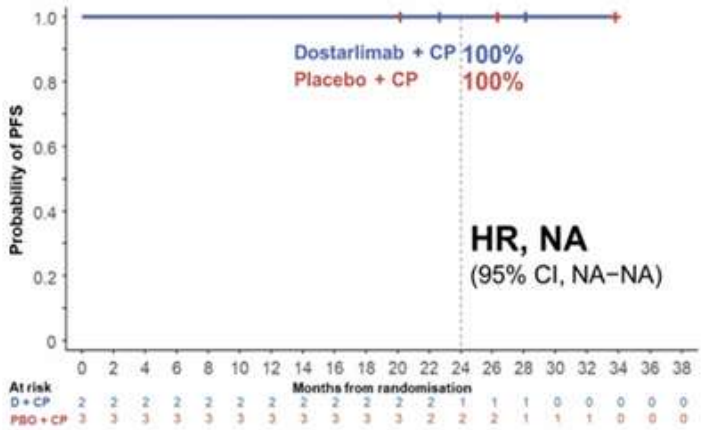
Efficacy per molecular classification was an exploratory analysis.
dMMR, mismatch repair deficient; EC, endometrial cancer; EDM, exonuclease domain; IHC, immunohistochemistry; MMRp, mismatch repair proficient; MSI-H, microsatellite instability high; mut, mutated; NGS, next-generation sequencing; NSMP, no specific molecular profile; PCR, polymerase chain reaction; POLε, polymerase epsilon; TP53, tumour protein 53; WES, whole-exome DNA sequencing; WT, wild type.

Exploratory Analysis of PFS According to Molecular Subgroup

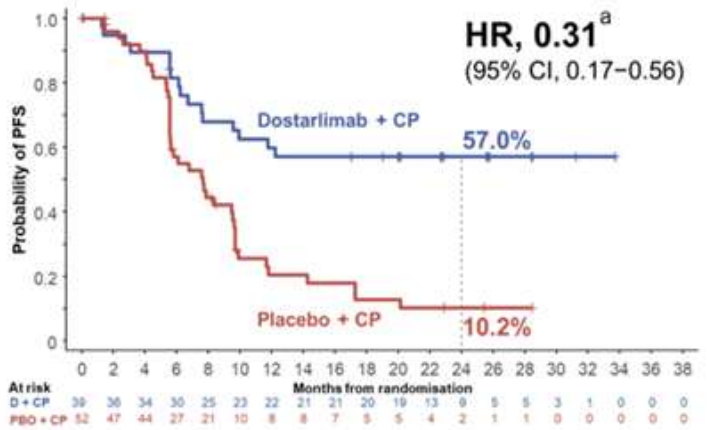
Based on 400/494 patients with known molecular classification per whole-exome sequencing

Scan for slides

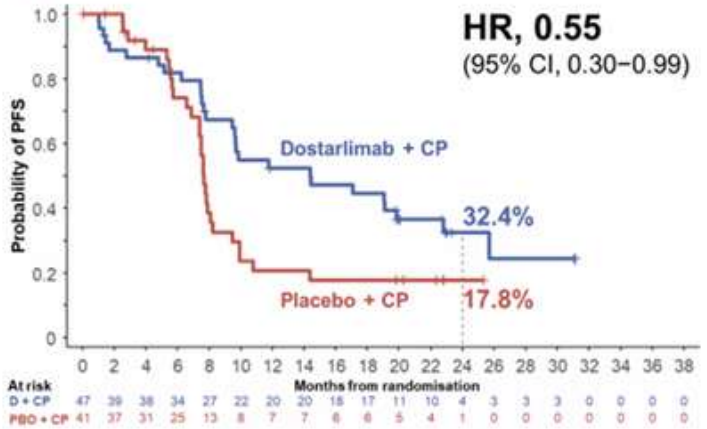
POLε mut



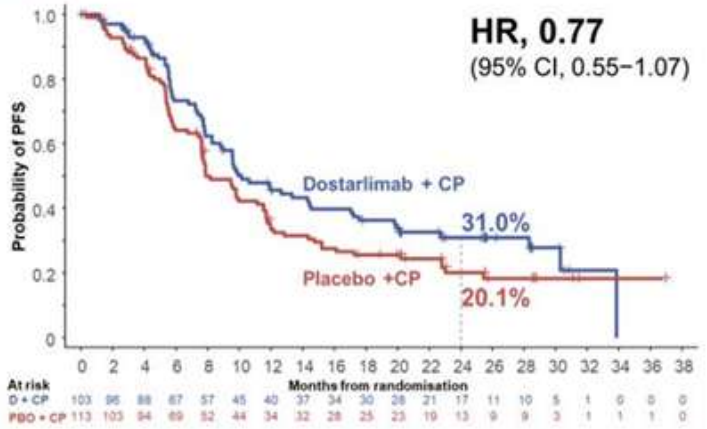
dMMR/MSI-H



TP53 mut



NSMP



Mirza M R et al

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

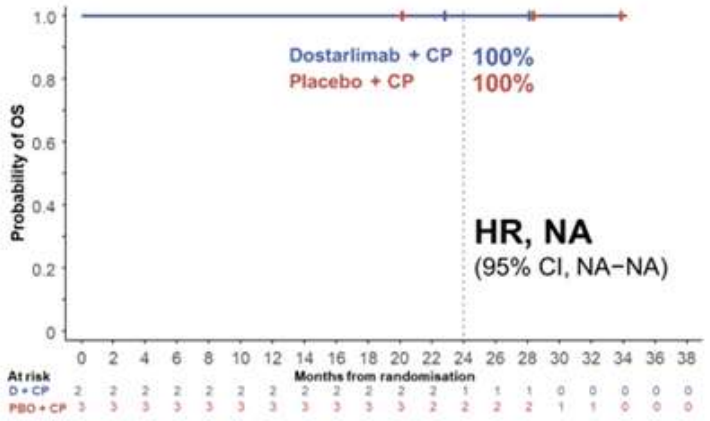
Data cutoff date: September 28, 2022. CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; PBO, placebo; PFS, progression-free survival; POLε , polymerase epsilon; TP53, tumour protein 53.

Exploratory Analysis of OS According to Molecular Subgroup

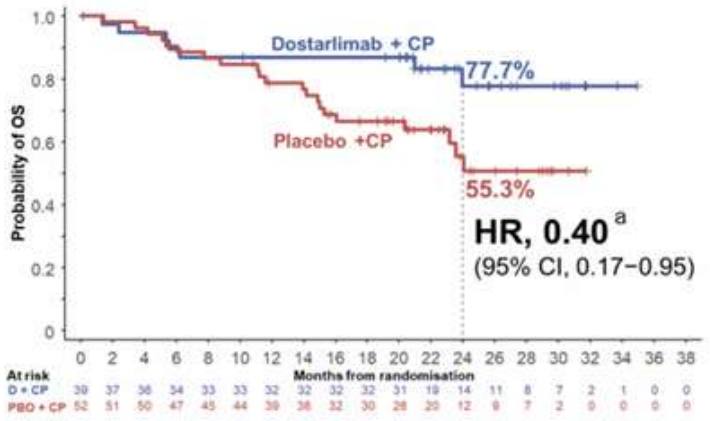
Based on 400/494 patients with known molecular classification per whole-exome sequencing

Scan for slides

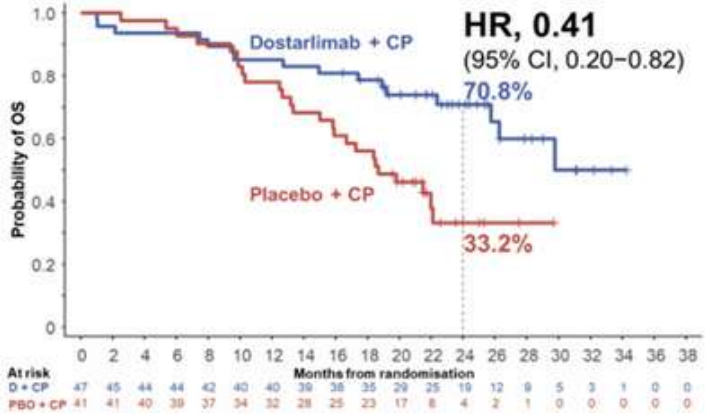
POLε mut



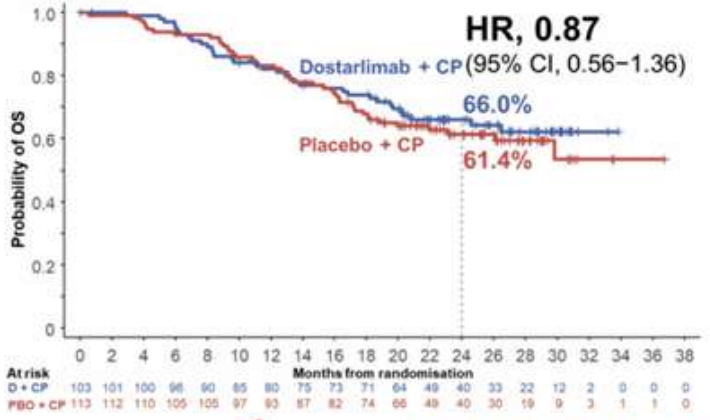
dMMR/MSI-H



TP53 mut



NSMP



Mirza MR et al

[a]Prespecified OS analysis in dMMR/MSI-H patients (n=118) showed HR, 0.30.
Data cutoff date: September 28, 2022. CP, carboplatin-paclitaxel; D, dostarlimab; dMMR, mismatch repair deficient; HR, hazard ratio; MSI-H, microsatellite instability high; mut, mutated; NA, not applicable; NSMP, no specific molecular profile; PBO, placebo; PFS, progression-free survival; POLε , polymerase epsilon; TP53, tumour protein 53.

3rd debate:

TP53m pMMR impact on treatment decisions?

Discussants:

Pro: Alexandra Leary, France

Con: Annamaria Ferrero, Italy

RUBY part 1

Mirza M R et al, ESMO 2023

	D+CP	PBO+CP
Overall, n	245	249
PFS by INV, HR (95% CI)	0.64 (0.507–0.800)	
OS, HR (95% CI)	0.64 (0.464–0.870)	
Patients with both MMR/MSI status and mutational data, n	191	209
POLεmut, n	2	3
PFS by INV, HR (95% CI)	NA[a]	
OS, HR (95% CI)	NA[a]	
dMMR/MSI-H, n	39	52
PFS by INV, HR (95% CI)	0.31 (0.17–0.56)	
OS, HR (95% CI)	0.4 (0.17–0.95)	
TP53mut, n	47	41
PFS by INV, HR (95% CI)	0.55 (0.3–0.99)	
OS, HR (95% CI)	0.41 (0.2–0.82)	
NSMP, n	103	113
PFS by INV, HR (95% CI)	0.77 (0.55–1.07)	
OS, HR (95% CI)	0.87 (0.56–1.36)	

dMMR, MSI-h

TP53mut

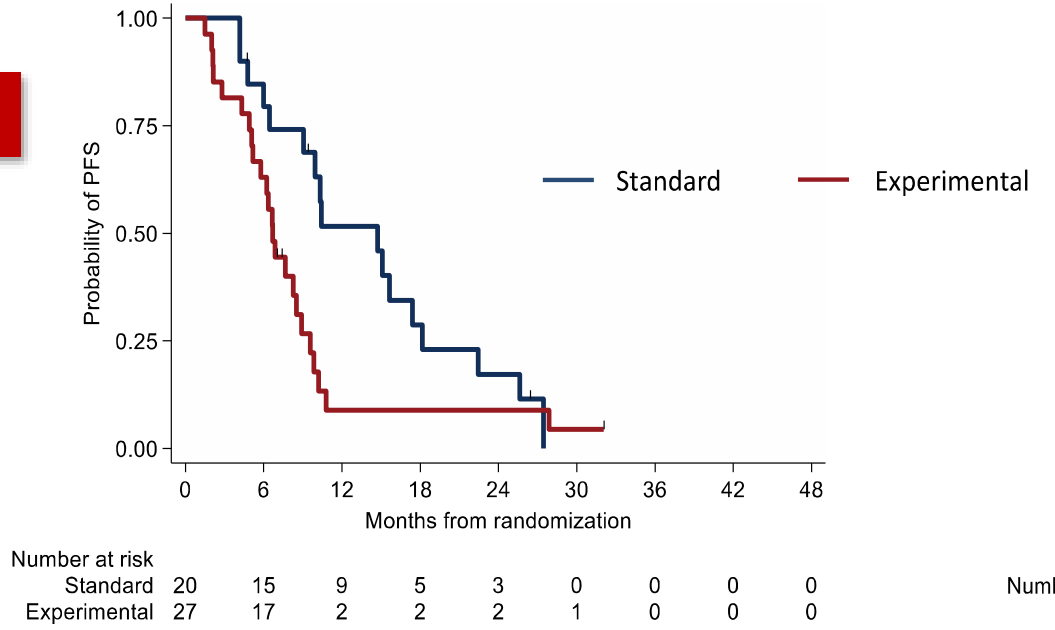
NSMP

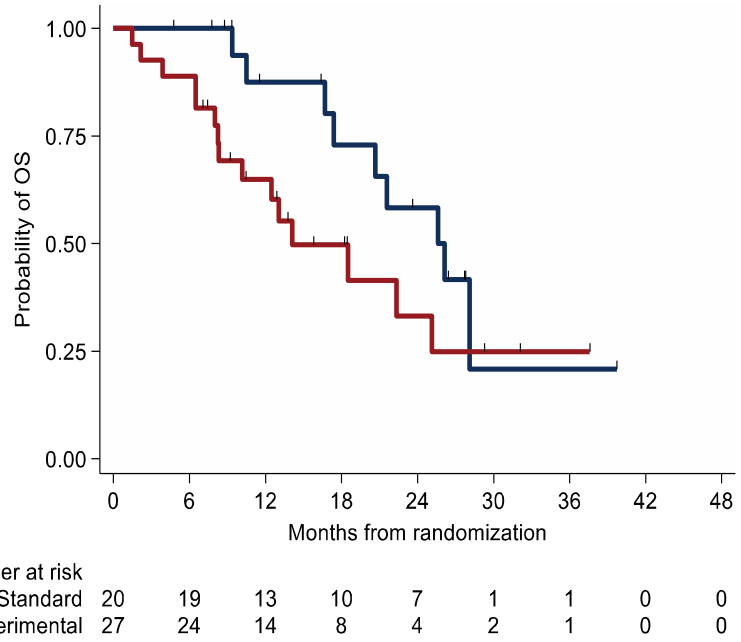
MITO END-3 trial

Pignata S. et al, Annals of Oncology 2024

- Phase II randomized trial, translational analysis
- Avelumab plus carboplatin/paclitaxel versus carboplatin/paclitaxel as first–line treatment
- 109 analyzed NGS patients, 47 MSS/TP53 mutated

MSS/TP53mut





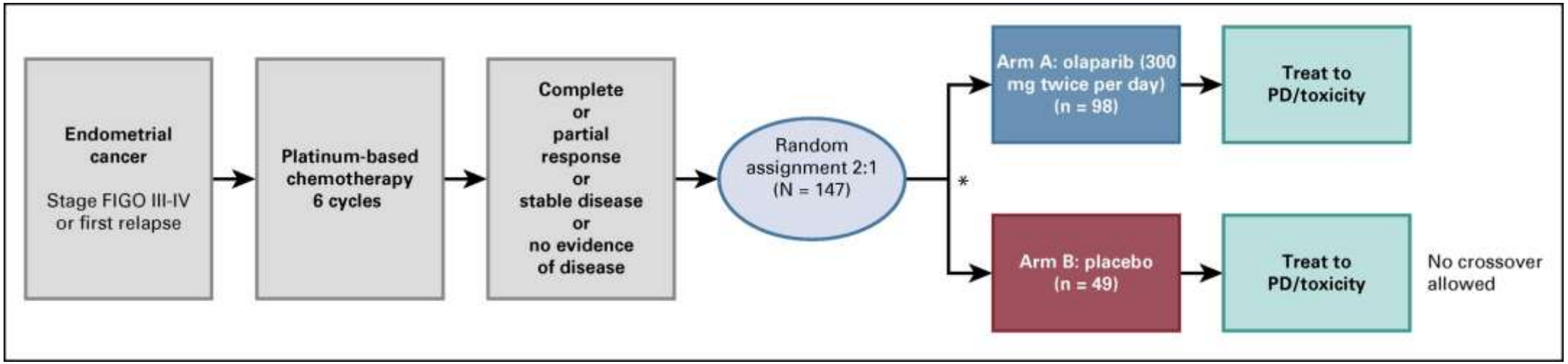
MITO END-3 trial

Pignata S. et al, Annals of Oncology 2024

	n	Progression-free survival	HR	(95% CI)	*P* value	Overall survival	HR	(95% CI)	*P* value
Whole population	109		0.78	(0.50-1.24)			1.03	(0.55-1.94)	
TCGA[a]					0.003				0.069
MSI-H	29		0.30	(0.10-0.87)			0.33	(0.08-1.29)	
MSS/*TP53* wt	26		0.68	(0.27-1.72)			1.40	(0.19-10.4)	
MSS/*TP53* mut	47		2.24	(1.06-4.72)			2.08	(0.82-5.26)	
TP53					0.009				0.131
Wild type	55		0.47	(0.23-0.97)			0.52	(0.17-1.61)	
Mutated	54		1.71	(0.89-3.28)			1.57	(0.71-3.49)	
PIK3CA					0.102				0.329
Wild type	50		1.37	(0.68-2.75)			1.52	(0.53-4.37)	
Mutated	59		0.50	(0.26-0.98)			0.66	(0.26-1.66)	
ARID1A					0.010				0.562
Wild type	59		1.66	(0.86-3.19)			1.24	(0.49-3.10)	
Mutated	50		0.48	(0.22-1.01)			0.82	(0.32-2.10)	
PTEN					0.002				0.026
Wild type	58		1.58	(0.86-2.90)			2.07	(0.83-5.13)	
Mutated	51		0.36	(0.17-0.76)			0.39	(0.13-1.20)	
TMB					0.001				0.018
<10	68		1.50	(0.86-2.63)			1.99	(0.88-4.49)	
≥10	35		0.26	(0.10-0.70)			0.31	(0.08-1.23)	

UTOLA trial

F Joly Lobbedez et al



Phase IIb trial

Primary endpoint: PFS in the ITT population

Main secondary endpoints:

- **PFS according to P53 status** and to CT response
- OS
- safety

UTOLA trial

147 randomized patients (98 to Olaparib, 49 to placebo)

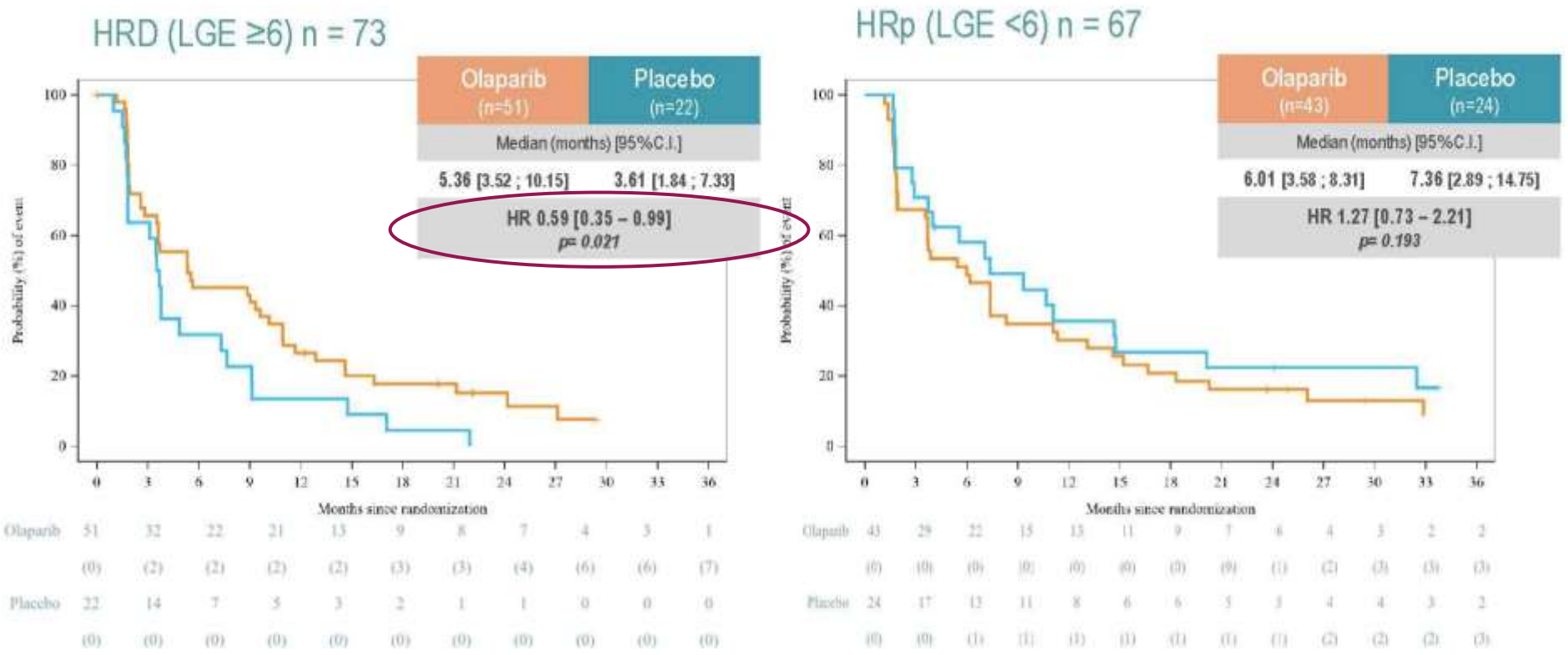
F Joly Lobbedez et al

Population	mPFS olaparib (months)	mPFS placebo (months)	
ITT	5.6	4.0	HR:0.94, p=0.29
P53 mut	5.6	3.6	HR:0.75, p=0.12
P53 wt	6.1	7.7	HR:1.13, p=0.3
HRD pos	5.4	3.6	HR:0.59, p=0.02

52% (73) were HRD positive:

- 79% in P53mut
- 23% in P53WT

UTOLA trial



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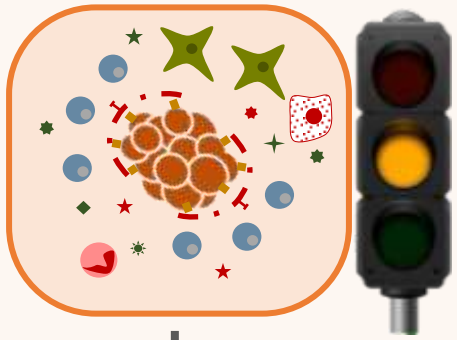
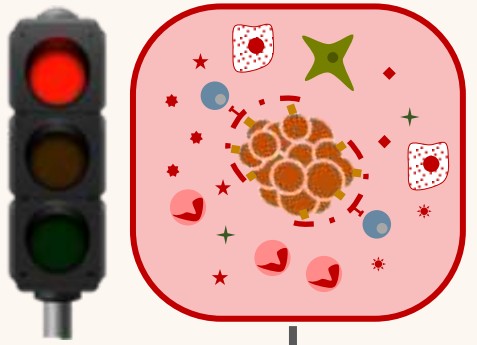
PFS was statistically higher with olaparib in HRD tumors, **regardless of P53 status**

1 ***Induction phase***
Platinum chemotherapy (SoC) + durvalumab

dMMR

Pre-existing immune response held in check by PD-L1 inhibition of T cells





pMMR

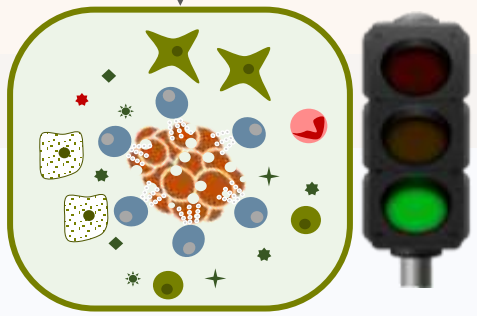
Biologically heterogeneous population – diverse genomic drivers and variable immune priming

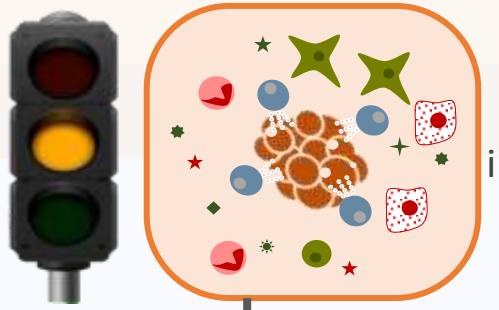
Immuno-suppressive, pro-tumour immune cells and signals

Immuno-stimulatory, anti-tumour immune cells and signals

Cytotoxic T cell

Chemotherapy + durvalumab drives direct tumour cell killing and an enhanced immune response through blockade of PD-L1





Blockade of PD-L1 leads to more limited anti-tumour immunity in pMMR tumours

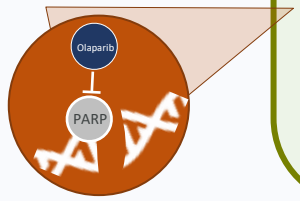
2 ***Maintenance phase***
Durvalumab
Durvalumab + olaparib

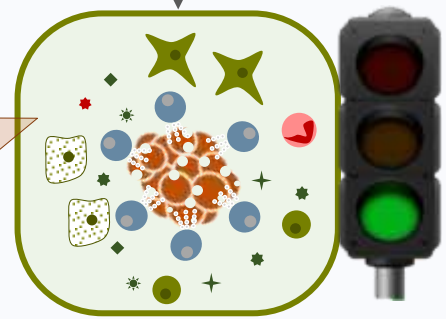
Tumour Microenvironments

Immuno-suppressive

Active anti-tumour immune response

Blockade of PD-L1 with **durvalumab** drives prolonged anti-tumour immunity and durable clinical activity in dMMR tumours, with limited potential for further enhancement





Olaparib induced DNA damage leads to tumour cell death and further immune priming promoting a more robust anti-tumour immunity and more durable benefit for the **durvalumab + olaparib** combination

IGCS 2024 Annual Global Meeting DUBLIN

DUO-E trial

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Patients

- Newly diagnosed Stage III/IV or recurrent endometrial cancer
- Known MMR status
- Naïve to first-line systemic anticancer treatment
- Naïve to PARP inhibitors and immune-mediated therapy
- All histologies except sarcomas

N=718

R 1:1:1

Stratified by:

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

	Chemotherapy phase (six cycles)	Maintenance phase*
CP	CP†	Placebos
CP+D	CP† + durvalumab‡	Durvalumab§
CP+D+O	CP† + durvalumab‡	Durvalumab§ + olaparib‖

Patients without disease progression

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

Endpoints

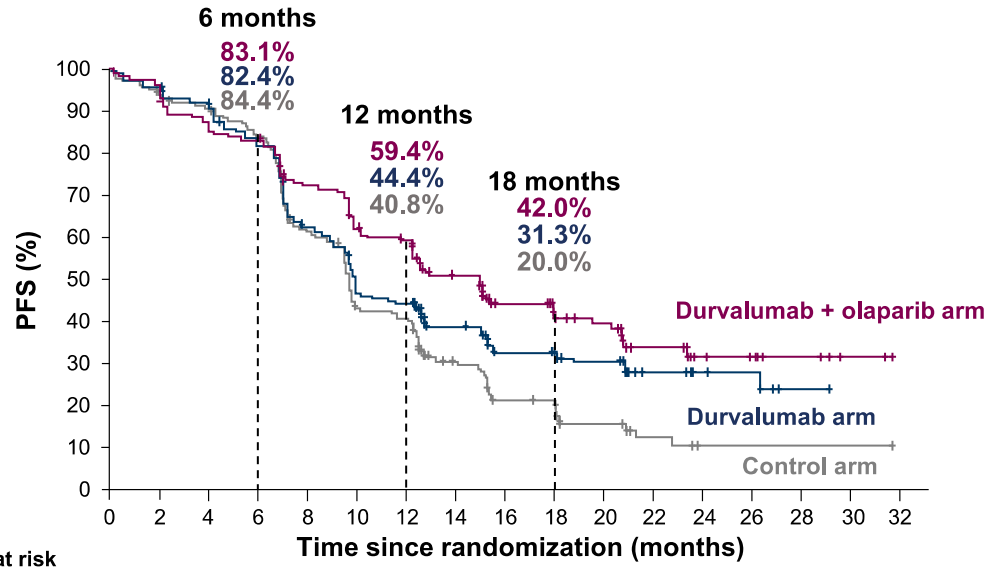
Primary (ITT): PFS (RECIST per investigator) in CP+D versus CP and CP+D+O versus CP

Secondary (ITT): OS (key secondary) and safety

Prespecified exploratory analyses: Subpopulation analyses of PFS by MMR status

***Post hoc* exploratory analyses:** PFS by molecular subgroup in the pMMR subpopulation

pMMR subpopulation: PFS – prespecified exploratory analysis[1]



No. at risk

Durvalumab + olaparib arm	191	185	183	168	164	159	157	141	134	132	114	109	107	77	75	72	46	46	35	32	31	20	19	19	12	11	10	5	5	4	2	2	0
Durvalumab arm	192	186	182	174	169	159	152	128	113	107	83	81	79	53	53	50	36	36	31	27	27	17	15	15	8	7	7	3	2	2	0	0	0
Control arm	192	184	178	172	170	163	156	126	113	108	77	76	73	44	40	37	25	25	21	13	13	8	7	6	1	1	1	1	1	1	1	1	0

	Control arm (n=192)	Durvalumab arm (n=192)	Durvalumab + olaparib arm (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)

pMMR biomarker-known subpopulation

Exploratory subgroup analyses

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In the pMMR subpopulation (n=575), biomarker status was known in:

575 patients (100%)	for histology at diagnosis
562 patients (98%)	for PD-L1* status
494 patients (86%)	for *POLE*m and *TP53*m†,‡ status
494 patients (86%)	for HRRm†,§ status
494 patients (86%)	for BRCAm† status

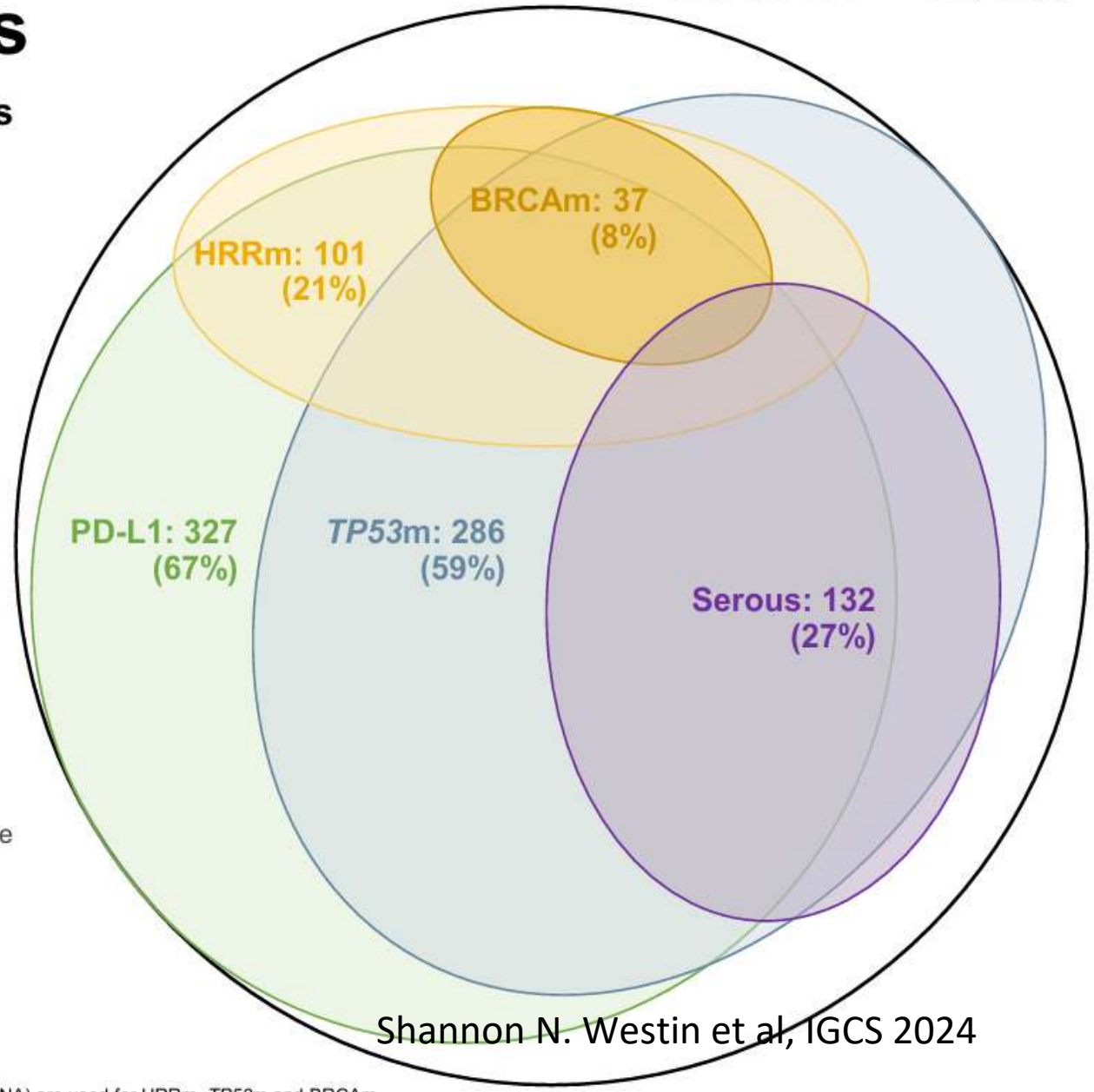
Biomarker-known population:
486 patients
(85% of pMMR subpopulation)
had known status for all
biomarkers of interest

pMMR biomarker-known subpopulation: co-prevalence of biomarkers

The pMMR biomarker-known (n=486) subpopulation was heterogeneous, with a frequent 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%



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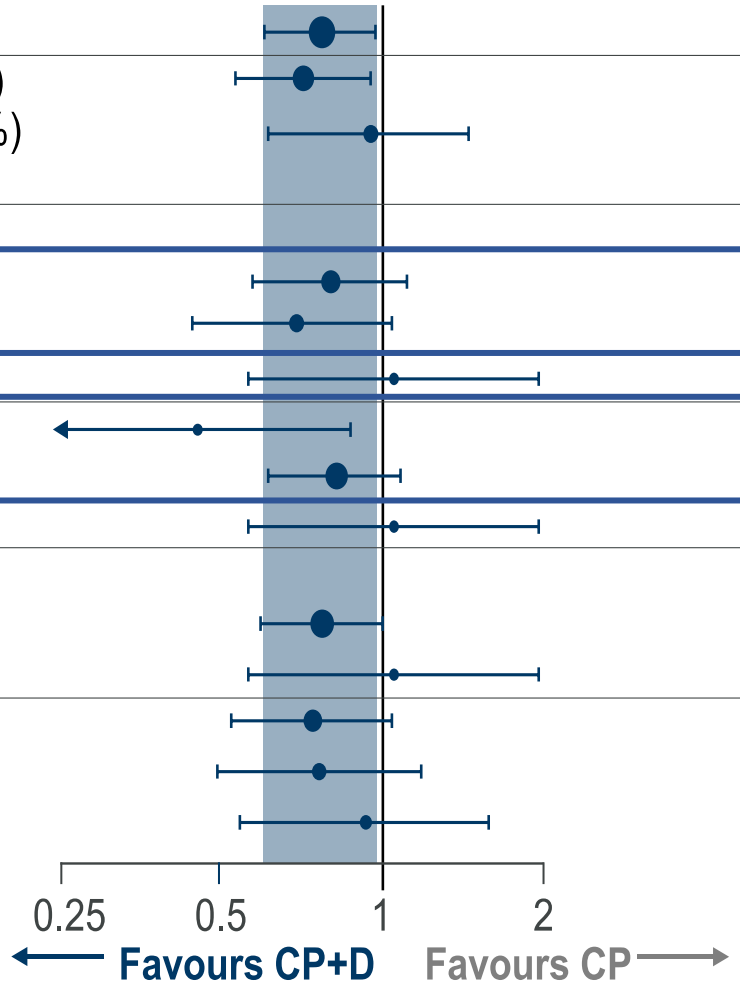
Venn illustrates the overlap for key biomarker populations but does not show a complete set of all overlapping populations.
Venn includes 11 patients with a *POLE*m; biomarker overlap in this subgroup is not shown. Aggregate results (tissue + ctDNA) are used for HRRm, *TP53*m and BRCAm.

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 *TP53*m status†,‡**	*POLE*m	**NC (NC–NC)‖**
	*TP53*m	**0.80 (0.57–1.11)**
	TP53 wild-type	**0.69 (0.44–1.04)**
	Unknown	**1.05 (0.56–1.96)**
HRRm status†,§	HRRm	**0.45 (0.23–0.87)**
	Non-HRRm	**0.82 (0.61–1.08)**
	Unknown	**1.05 (0.56–1.96)**
BRCAm status†	BRCAm	**NC (NC–NC)‖**
	Non-BRCAm	**0.77 (0.59–1.00)**
	Unknown	**1.05 (0.56–1.96)**
Histology	Endometrioid	**0.74 (0.52–1.04)**
	Serous	**0.76 (0.49–1.18)**
	Other¶	**0.93 (0.54–1.58)**

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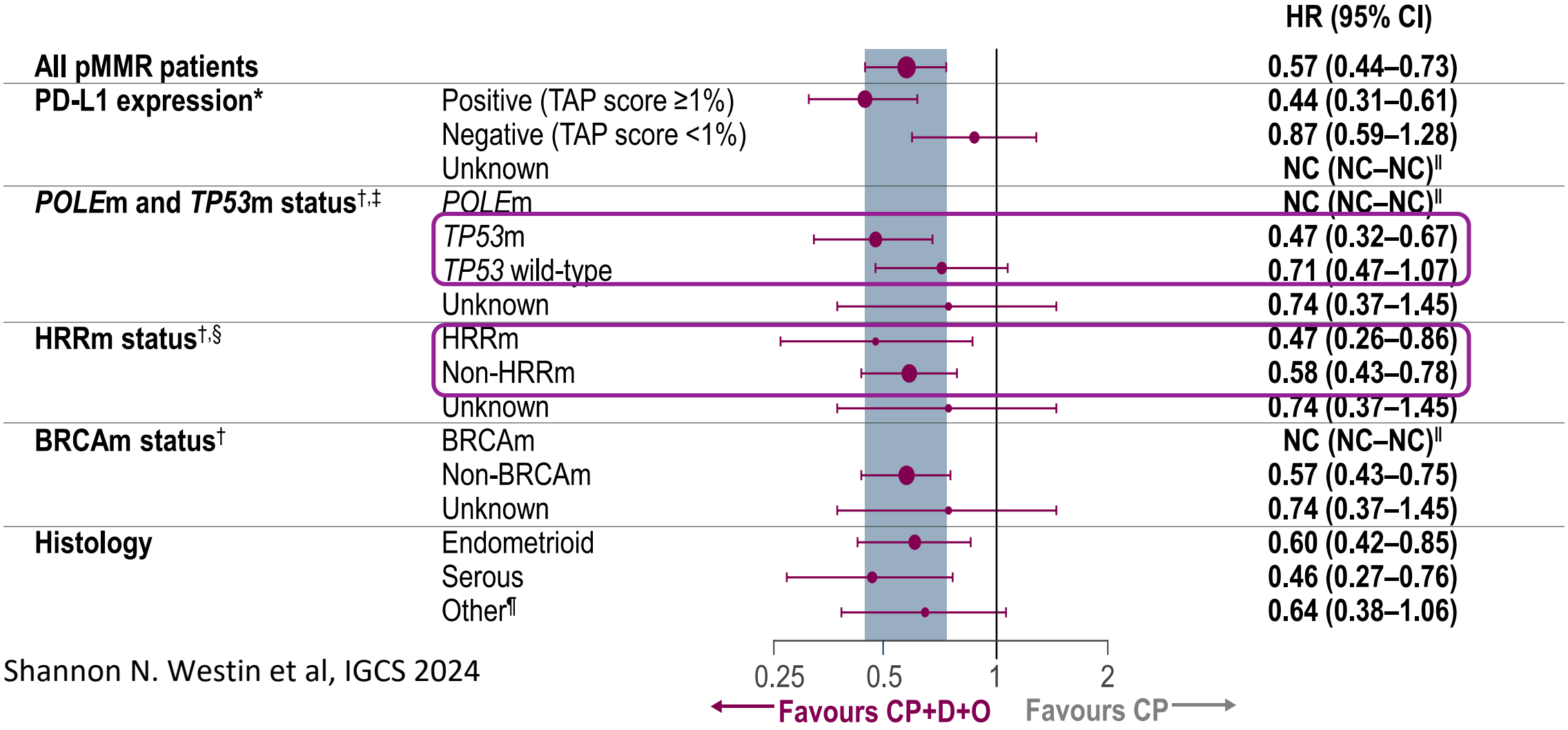
pMMR subpopulation: PFS by biomarker subgroup

CP + durvalumab + olaparib versus CP

Post hoc exploratory analysis



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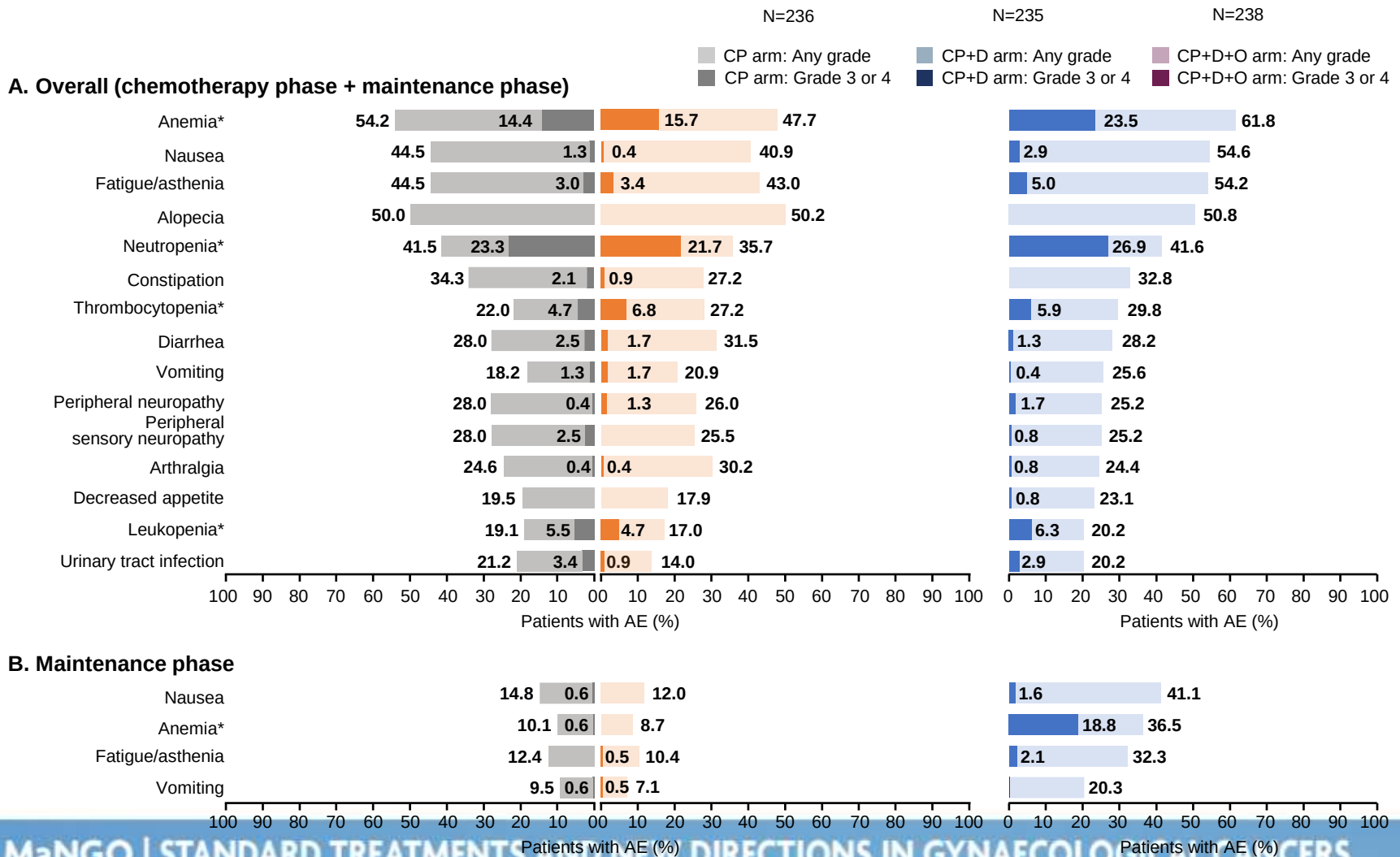
Most common events that occurred in the overall phase in ≥20% of patients were mostly low grade, and were expected



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

Mirza M R et al

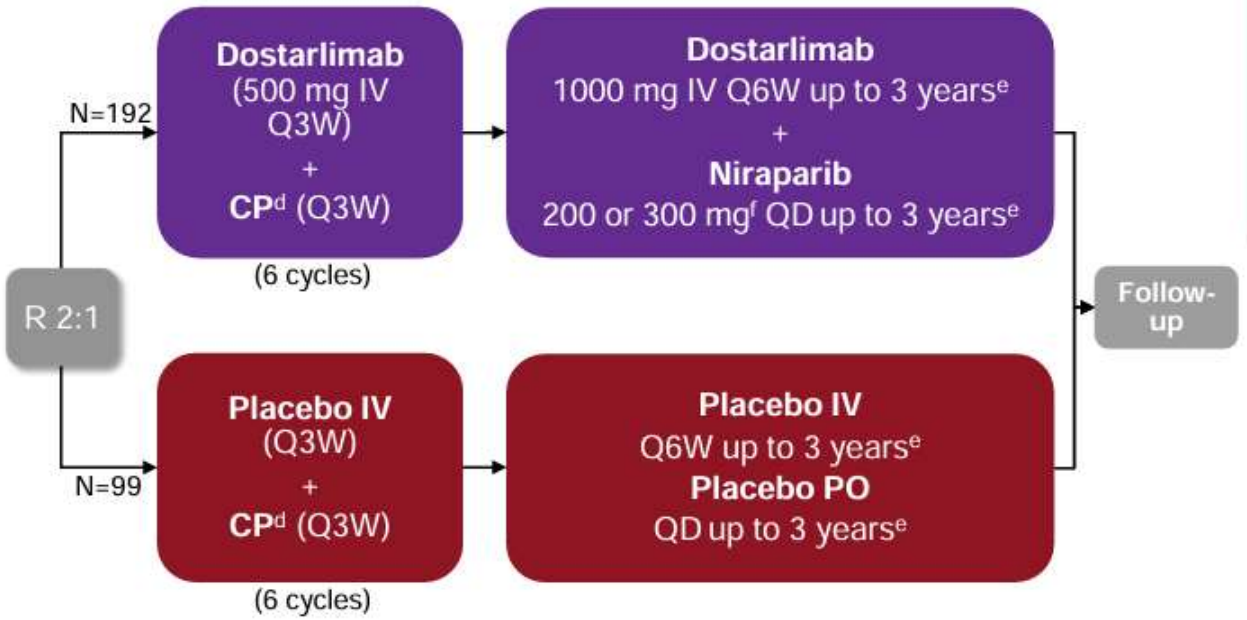
Scan for slides

Eligible patients

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

Stratification

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



Primary endpoint

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

Secondary endpoints

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

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

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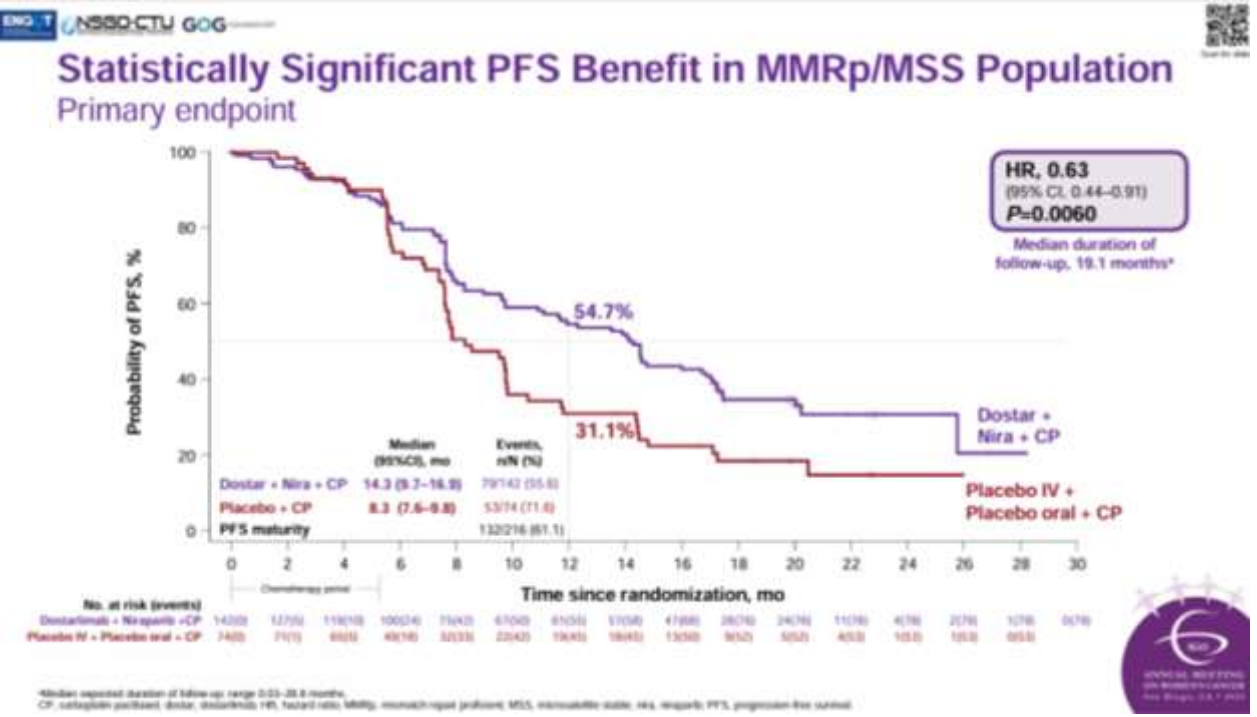

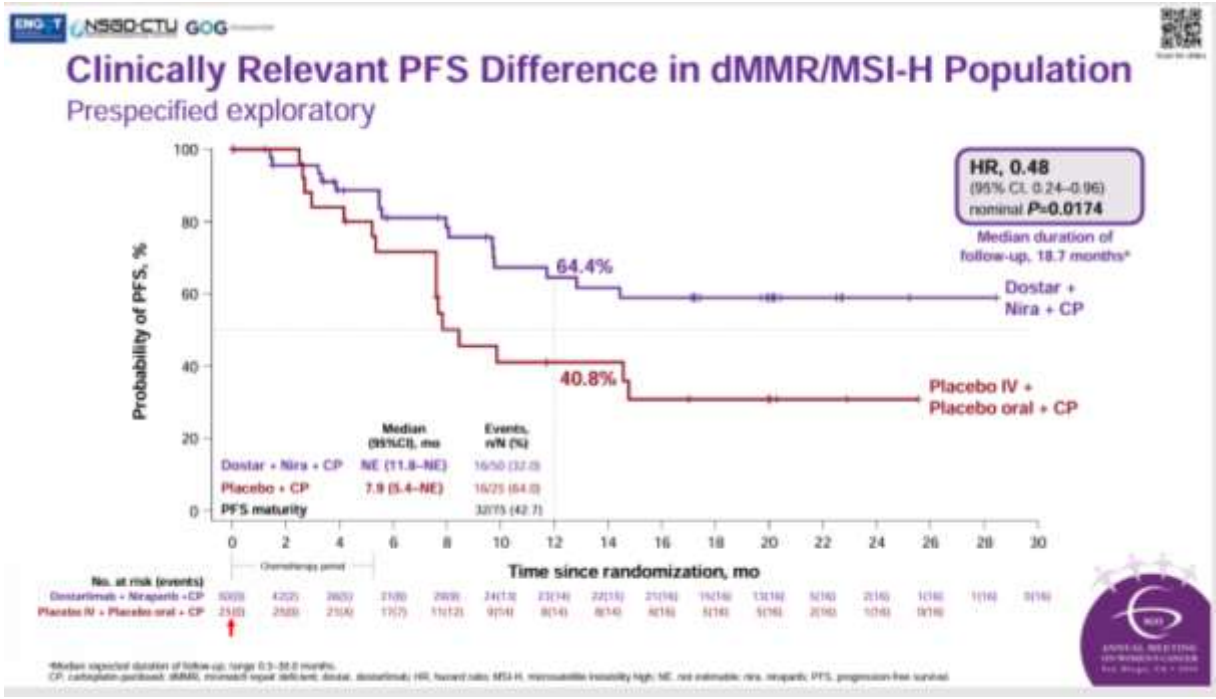

- RUBY Part 2 met its primary endpoint, showing significant and clinically meaningful improvement in PFS for dostarlimab + chemotherapy followed by dostarlimab + niraparib in the overall and MMRp/MSS populations
  - The trial is ongoing for OS follow-up
- The safety profile observed was generally consistent with the known safety profiles of the individual agents

Mirza M R et al

- These outcomes demonstrate a potential role for PARP inhibitor maintenance in patients receiving dostarlimab plus chemotherapy, in particular for MMRp/MSS disease

Exploratory PFS Molecular Subgroup Analyses in Overall Population

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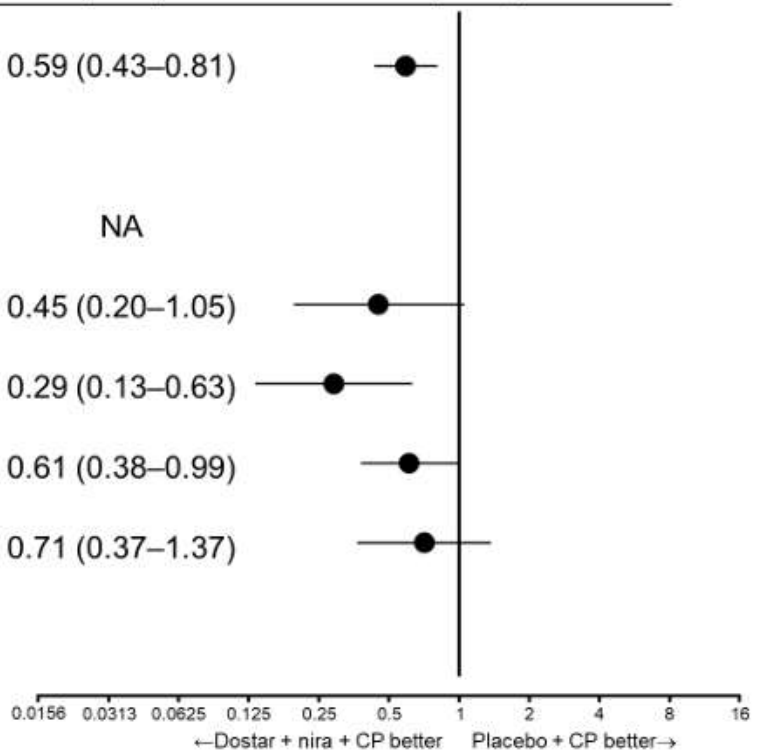
	Dostarlimab + Niraparib + CP N=192	Placebo IV + Placebo oral + CP N=99	HR (95%CI)
	No. of patients with events/No. of patients		
All patients	95/192	69/99	0.59 (0.43–0.81)
Molecular subgroup[a]			
POLEmut	0/3	1/2	NA
dMMR/MSI-H	12/37	10/17	0.45 (0.20–1.05)
TP53mut	27/39	10/10	0.29 (0.13–0.63)
NSMP	37/75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



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Transforming Gynecologic Cancer Care

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.

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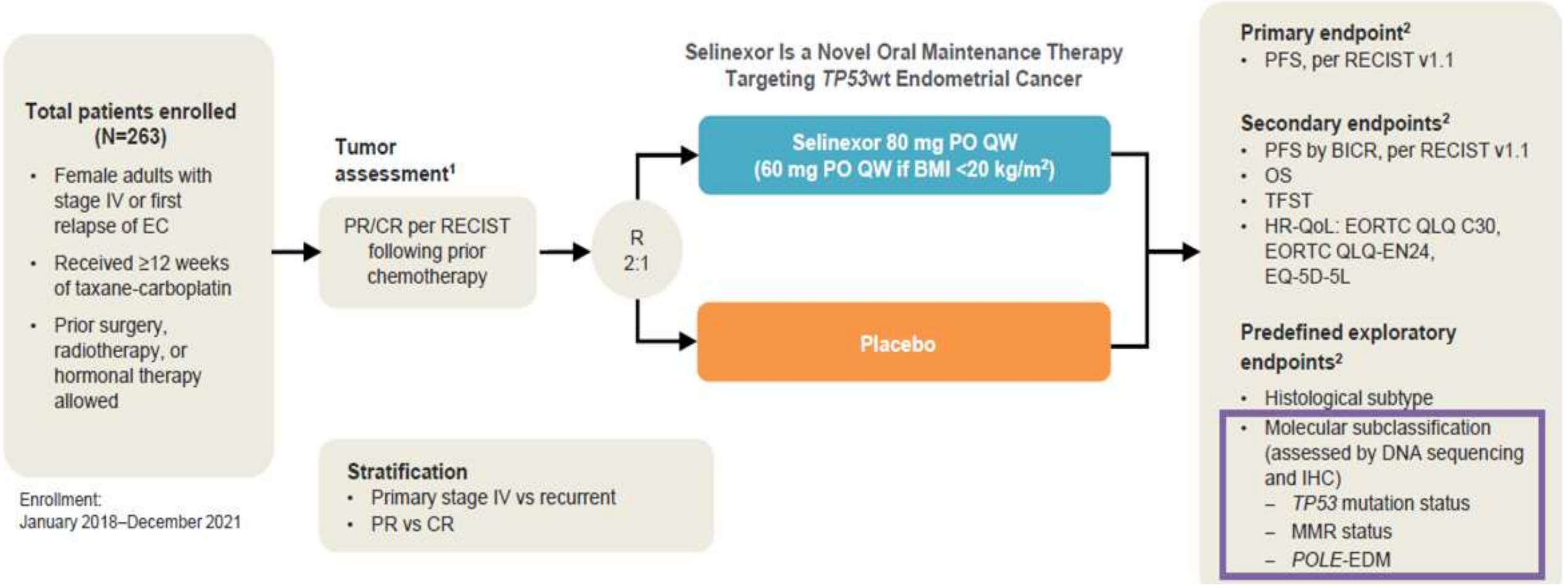
ENGOT-EN5/GOG-3055/SIENDO



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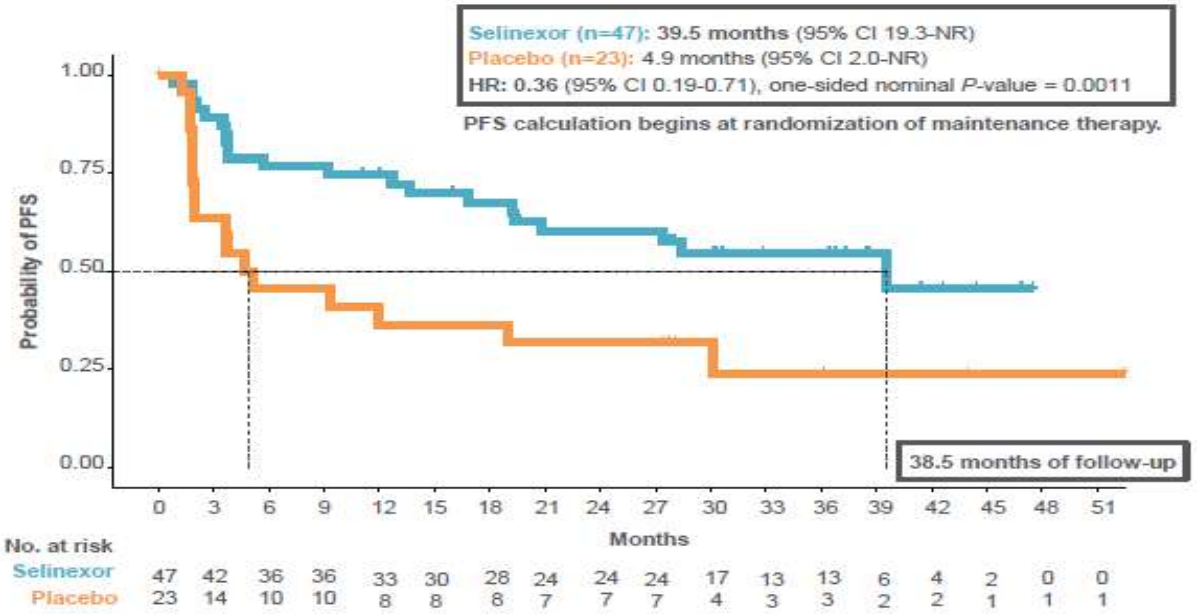
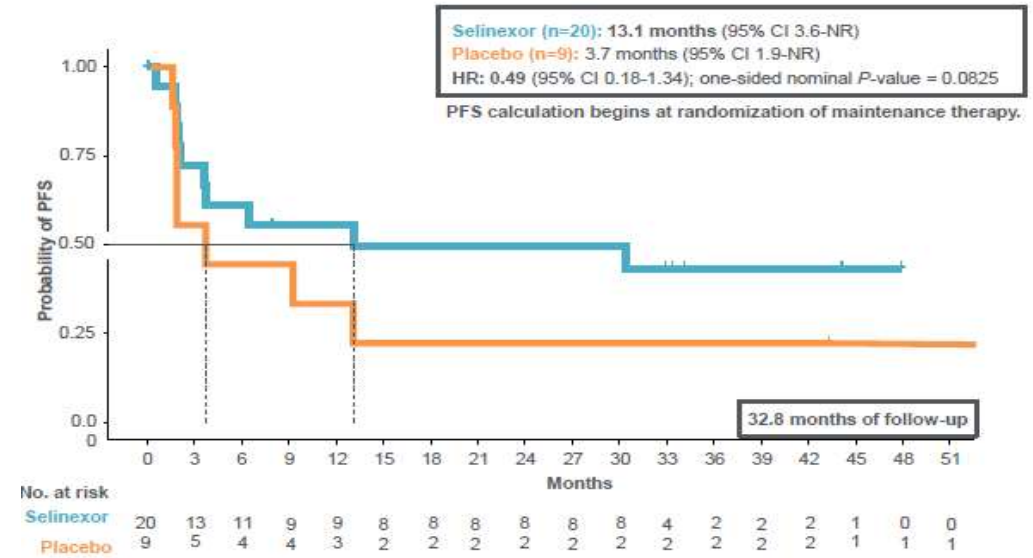
ENGOT-EN5/GOG-3055/SIENDO

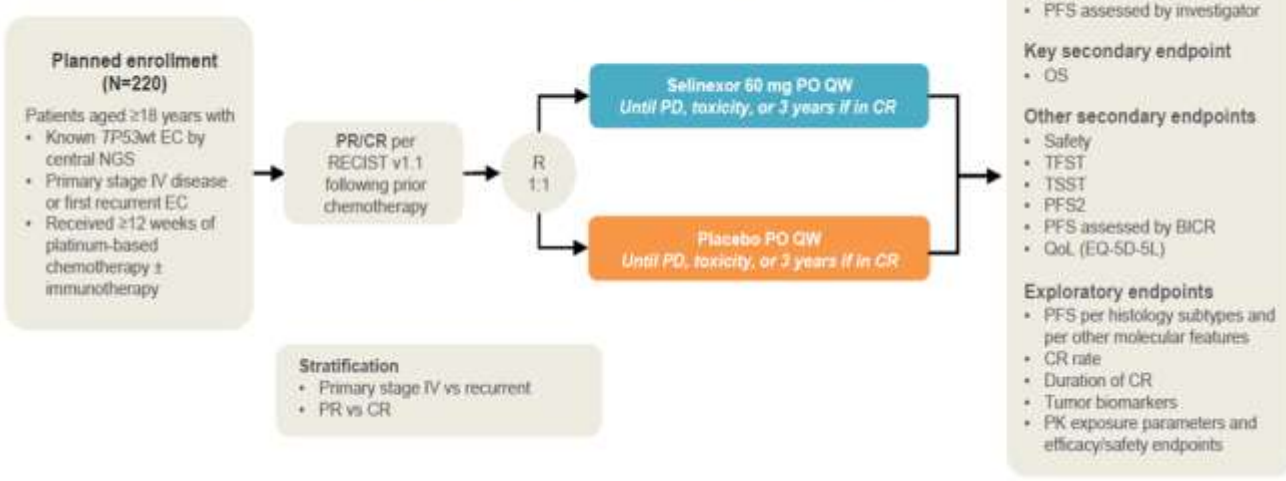
*TP53*wt/pMMR



*TP53*wt/dMMR



Study is ongoing and actively enrolling



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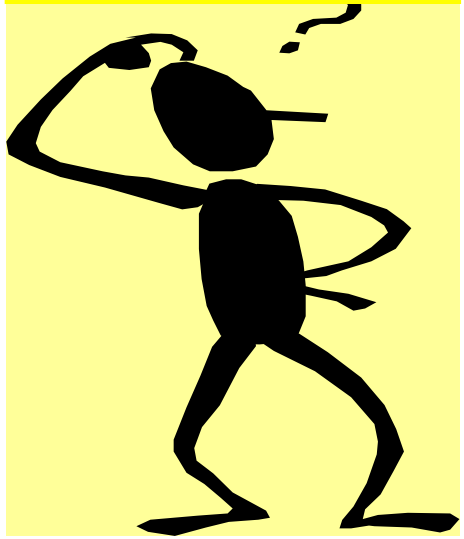
non-MMR disease

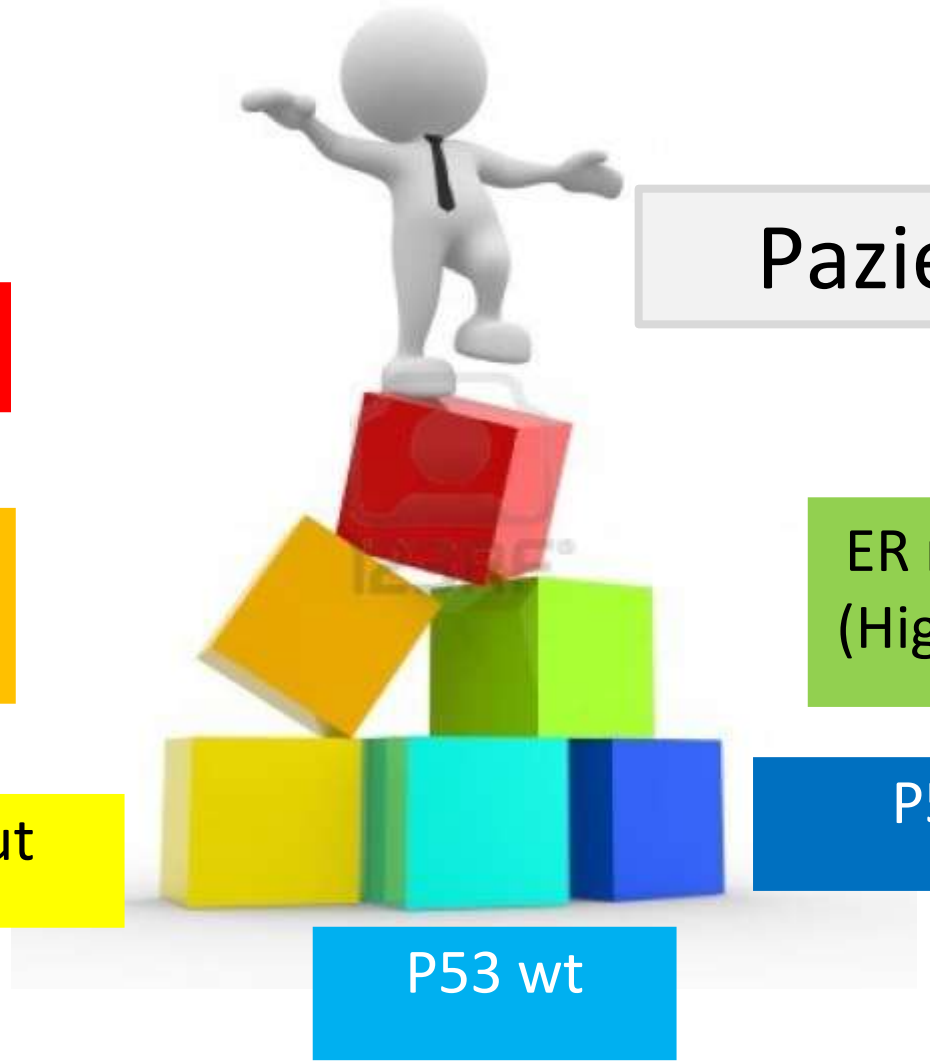
ICI or
ICI + PARPi



non-MMR

ER positive
(Low grade)

POLEmut



Paziente

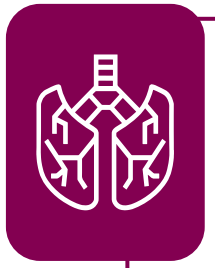
ER negative
(High grade)

P53 abn

P53 wt

DUO-E EAP: riassunto dei criteri di eligibilità dei pazienti

La popolazione interessata è composta da adulti con carcinoma endometriale epiteliale confermato da analisi istologica, recentemente diagnosticati con stadio III/IV, o recidivo di EC.

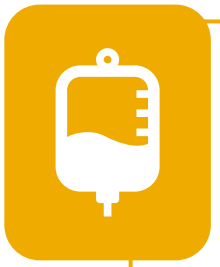


Caratteristiche malattia / paziente (pz)

- Tutte le istologie sono consentite, incluso il carcinosarcoma, ed eccezione dei sarcomi.
- Pz. recentemente diagnosticati con stadio III e con malattia misurabile dopo chirurgia
- Pz. recentemente diagnosticati con stadio IV con o senza malattia misurabile dopo chirurgia
- Pz. recidivi, con malattia misurabile o non, nei quali la possibilità di cura con la sola chirurgia risulta poco probabile

Campione del tumore

- Stato MMR conosciuto



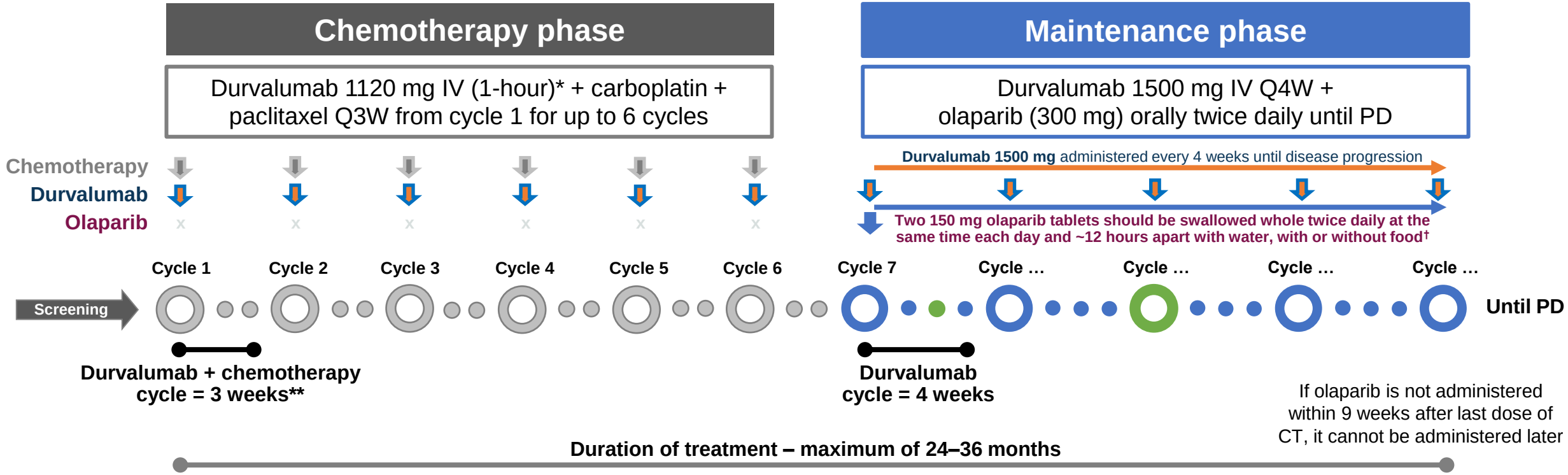
In relazione con la terapia

- Naïve alla prima-linea di trattamento antitumorale sistemico
- Chemioterapia adiuvante ± radioterapia è consentita solo se trascorsi almeno 6 mesi dall' ultima dose alla ricaduta

Criteri di esclusione

- Ogni effetto avverso irrisolto di grado ≥2 dalla precedente terapia antitumorale
- Attivi o precedentemente documentati disordini autoimmuni o infiammatori
- MDS/AML presunto o tale
- Pz. che hanno partecipato ad uno studio clinico con un IMP somministrato all' interno degli ultimi 12 mesi
- Precedente immuno-terapia mediata (es. anti-PD-1, anti-PD-L, anti-CTLA-4 or anti programmed cell death ligand 2 antibodies)

Dosing treatment sequence for patients with pMMR a/r EC



Treatment with olaparib will commence a between **3–9 weeks** after the last day of chemotherapy infusion#

Key differences between DUO-E clinical trial and EAP protocols

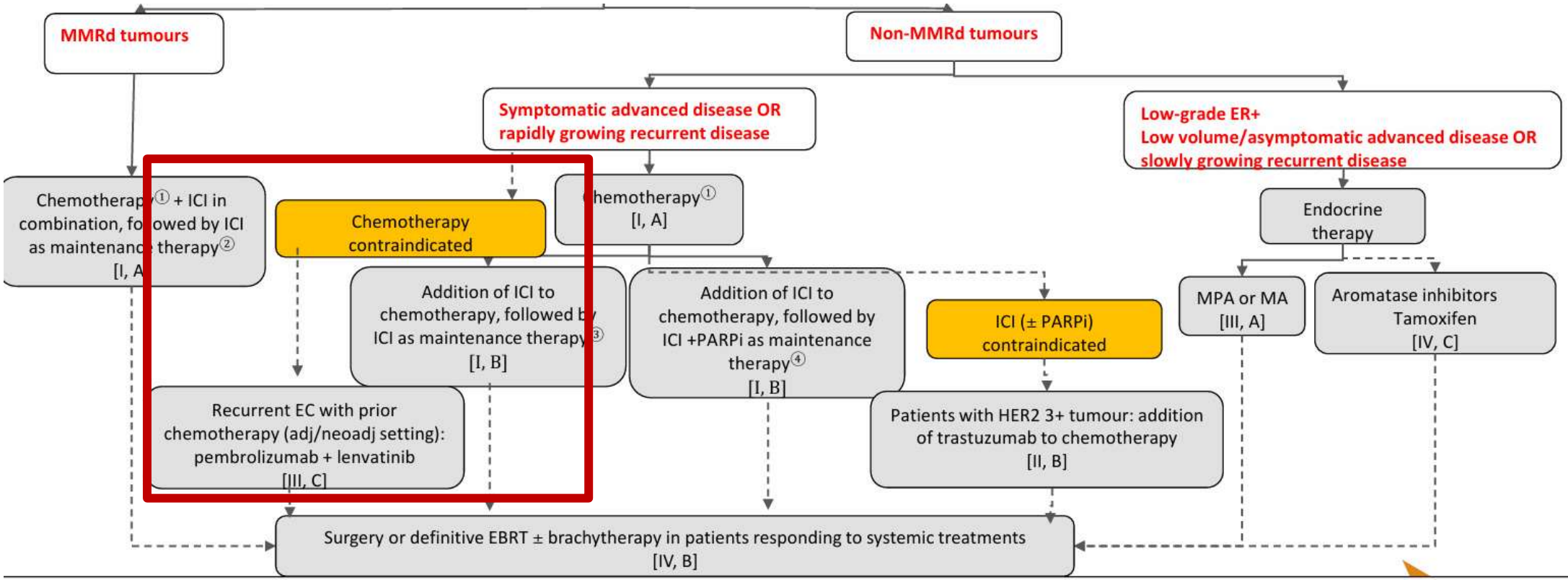
1. Olaparib is provided only to patients with confirmed pMMR disease
2. Time since previous adjuvant systemic therapy is now 6 months (vs 12 months in DUO-E clinical trial protocol)
3. The DUO-E clinical trial protocol specifies carboplatin/paclitaxel while the DUO-E EAP encompass any platinum-based chemotherapy regimen
4. Minimum 4 cycles of platinum chemotherapy requirement removed from EAP protocol
5. Brain metastases or spinal cord compression do not exclude a patient from inclusion within the EAP
6. ECOG requirements removed in EAP

DOSTARLIMAB EAP

- Carcinoma dell’endometrio avanzato o recidivante
- Senza deficit MMR (pMMR) / con stabilità dei microsatelliti (MSS)
- Trattamento di prima linea
- Non disponibili alternative terapeutiche autorizzate

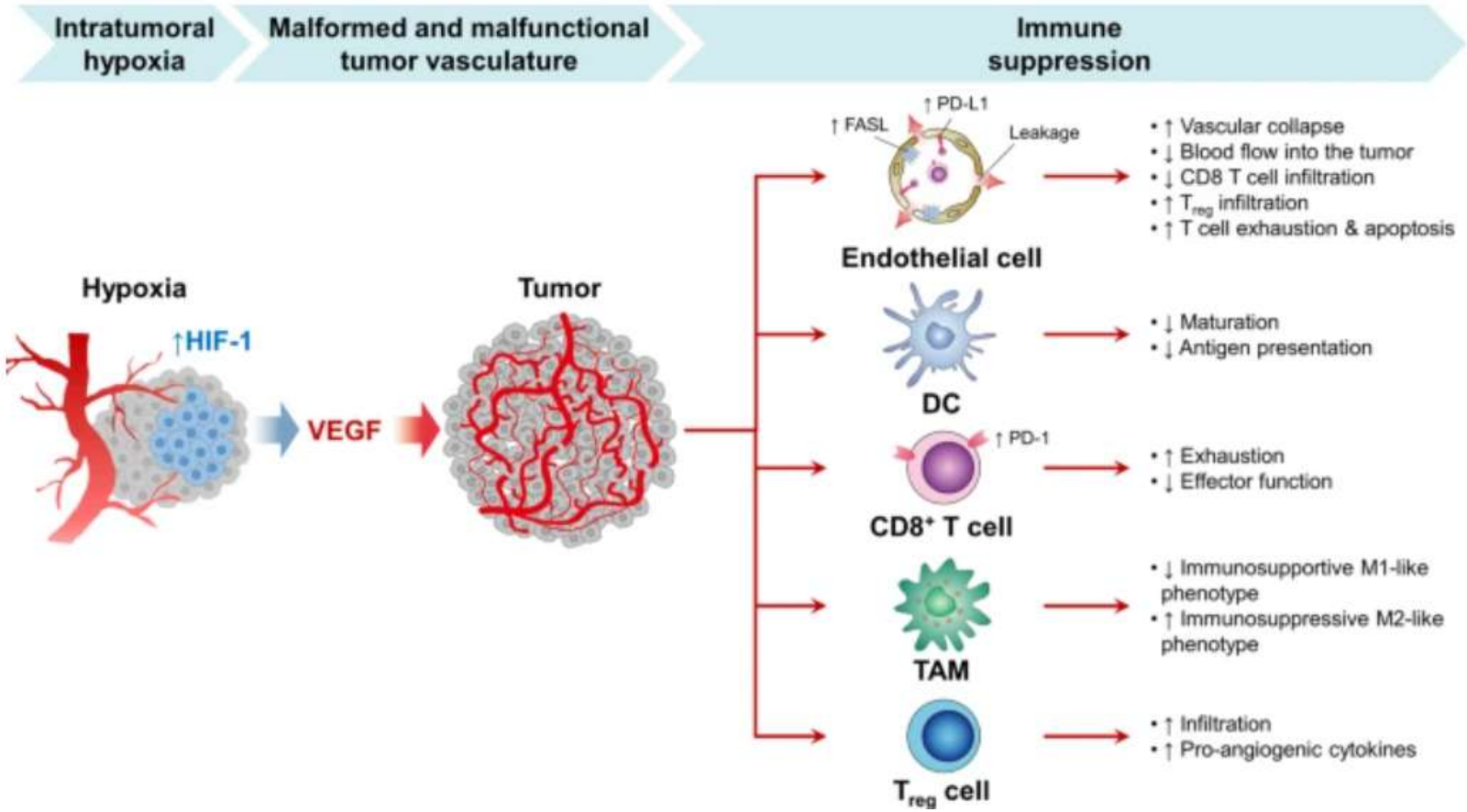
Unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting

Colombo N and Ledermann J, ESGO 2025



①The standard chemotherapy regimen is carboplatin + paclitaxel.
②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).
③ICI: dostarlimab or pembrolizumab.
④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.
Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP non-specific molecular profile.

Abnormal tumor vasculature and immune-suppression in the tumor microenvironment



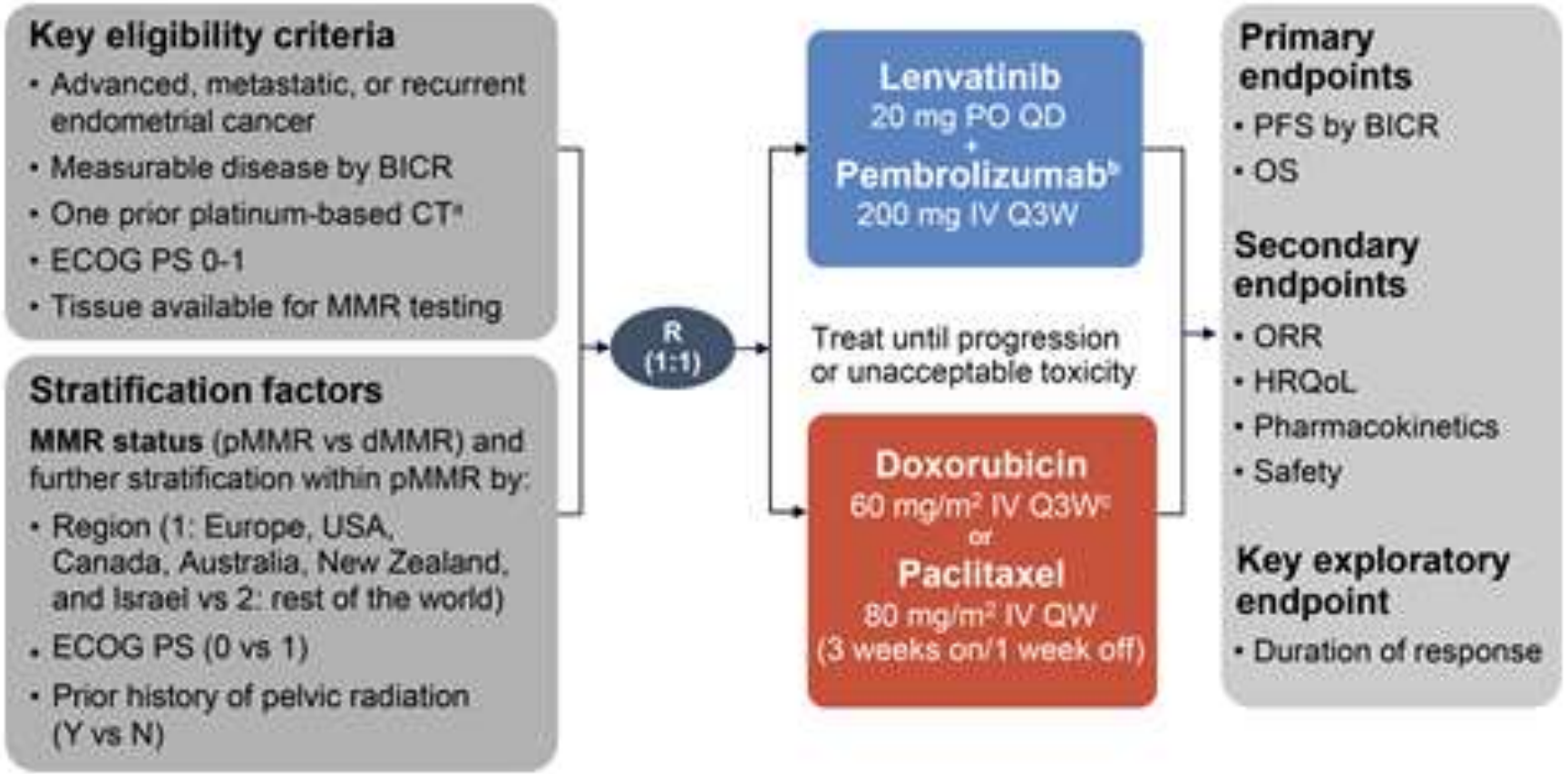
Combination of:

- anti-angiogenic therapy
- immune checkpoint blockade

normalizes vascular-immune crosstalk to potentiate cancer immunity

Lee WS et al, Experimental & Molecular Medicine2020

STUDY 309 / KEYNOTE-775: updated efficacy and safety

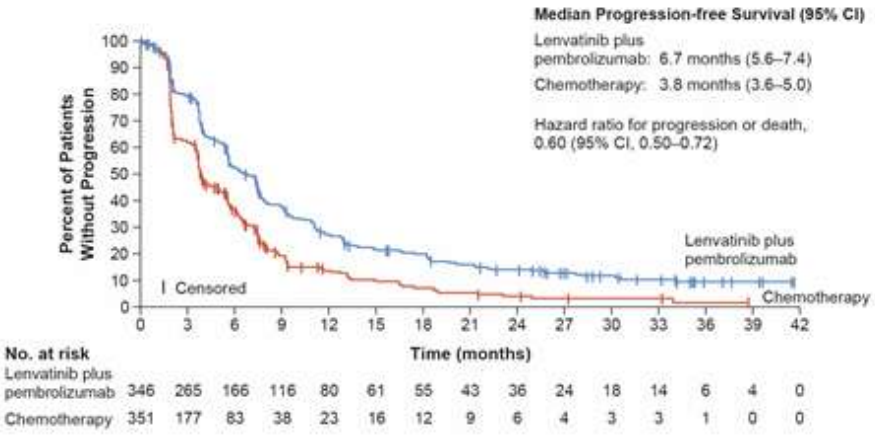


Makker V, ESMO 2022

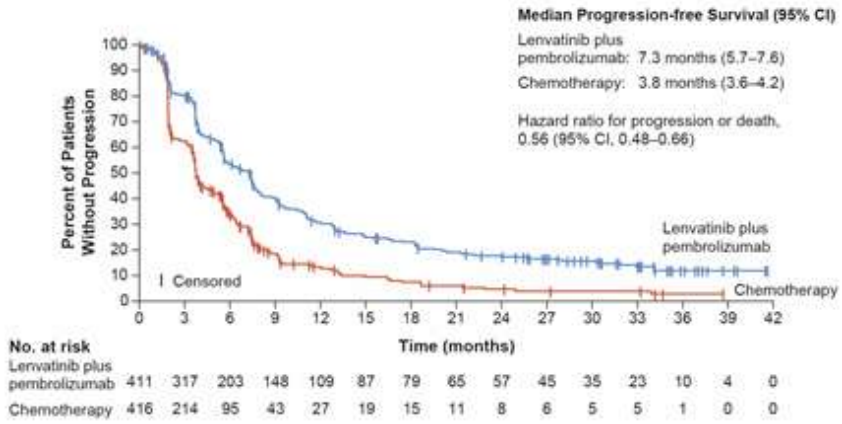
[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 was given in the neoadjuvant or adjuvant treatment setting; [b]maximum of 35 doses; [c]maximum cumulative dose of 500 mg/m².

STUDY 309 / KEYNOTE-775: updated efficacy and safety

pMMR Population



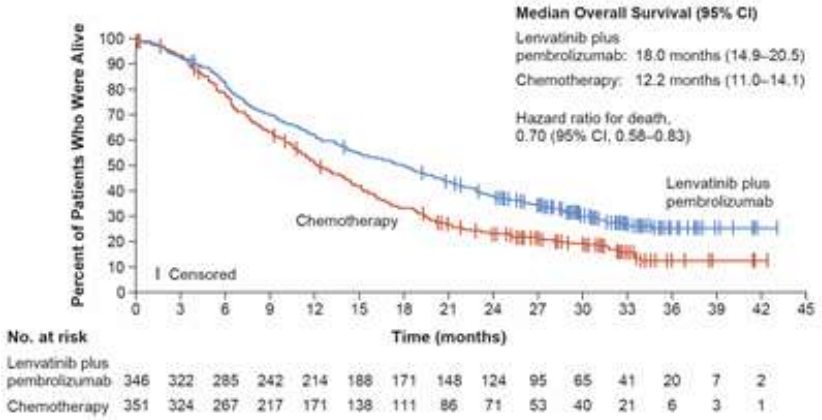
All-Comer Population



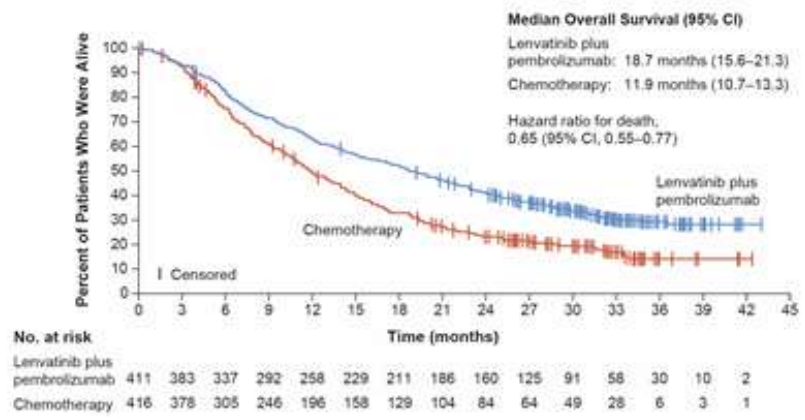
PFS

OS

pMMR Population



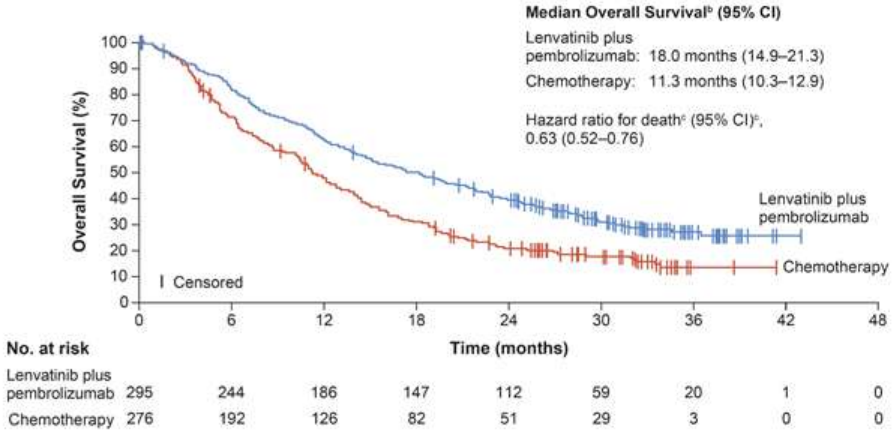
All-Comer Population



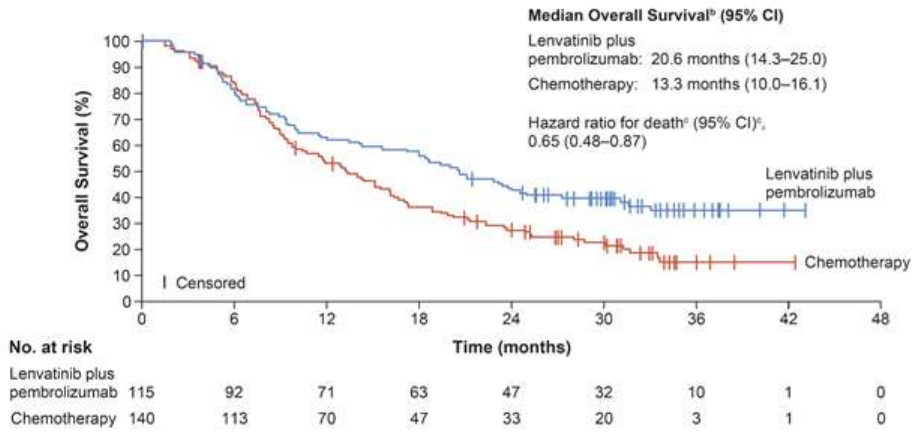
Makker V, ESMO 2022

STUDY 309 / KEYNOTE-775: updated efficacy and safety

All-comer patients with 1 prior systemic therapy[a]



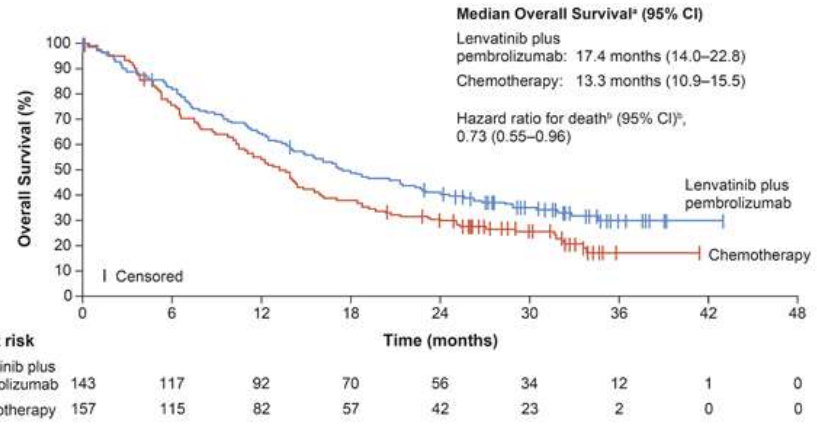
All-comer patients with ≥ 2 prior systemic therapies[a]



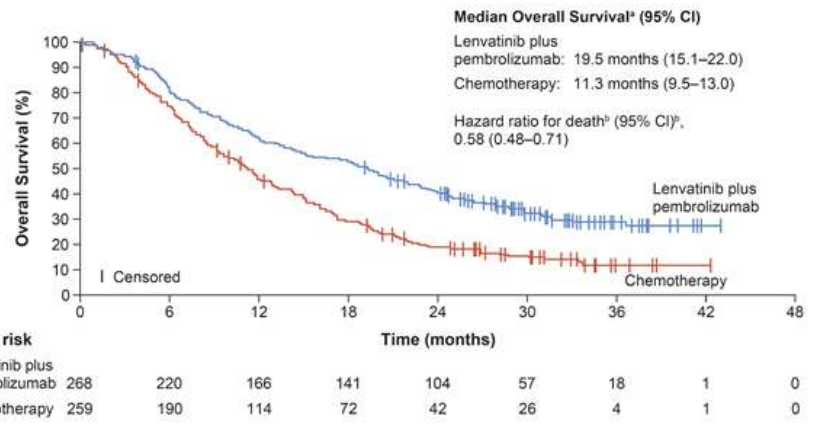
OS

OS

All-comer patients previously treated only in a neo-adjuvant/adjuvant setting



All-comer patients previously treated in any other setting



Lorusso D, ESGO 2022

Phase 3 ENGOT-En9/LEAP-001 Study

Marth C, ESGO 2024; Pignata S, ESMO GYN 2024

Background

- Phase 3 KEYNOTE-775/Study 309: established lenvatinib plus pembrolizumab (LEN/PEMBRO) as standard of care option in advanced endometrial cancer (aEC) following prior systemic therapy[1]
  - Treatment benefit of LEN/PEMBRO was observed regardless of histology[1]
- LEN/PEMBRO is therefore a standard of care for patients with advanced or recurrent endometrial cancer following progression on prior systemic therapy in any setting including prior neoadjuvant or adjuvant therapy[2,3]
- In the **ENGOT-en9/LEAP-001** phase 3, randomized, open-label study, we compared the efficacy and safety of LEN/PEMBRO vs paclitaxel and carboplatin (TC) as first-line therapy for aEC

ENGOT-en9/LEAP-001 Study Design (NCT03884101)

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/m² 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

Exploratory analysis

- PFS per RECIST v1.1 by BICR and OS analyzed by tumor histology

Makker V, et al. *N Engl J Med.* 2022;368:437-448. 2. NCCN. Uterine Neoplasms (v1 2024), https://www.nccn.org/. 3. Makker V, et al. *J Clin Oncol.* 2023;41(5):974-979.
UC, area under the concentration-time curve; BICR, blinded independent central review; DOR, duration of response; HRQoL, health-related quality of life.
Carcinosarcoma (malignant mixed Müllerian tumor), endometrial leiomyosarcoma or other high-grade sarcomas, or endometrial stromal sarcomas excluded.
l prior line of neoadjuvant and/or adjuvant chemotherapy in the setting of curative-intent resection was permitted if recurrence occurred ≥6 months after last dose; prior radiotherapy with or without chemotherapy, or prior hormonal therapy were also permitted.
Patients with ongoing clinical benefit could continue chemotherapy beyond 7 cycles if approved by sponsor.

Phase 3 ENGOT-En9/LEAP-001 Study

Marth C, ESGO 2024; Pignata S, ESMO GYN 2024

Summary of Efficacy Outcomes[a]

Efficacy Outcome	pMMR Population		All-Comers[b]	
	LEN/PEMBRO n = 320	TC n = 322	LEN/PEMBRO n = 420	TC n = 422
PFS				
Median (95% CI), mo	9.6 (8.2–11.9)	10.2 (8.4–10.5)	12.5 (10.3–15.1)	10.2 (8.4–10.4)
HR (95% CI)	0.99 (0.82–1.21)		0.91 (0.76–1.09)	
Subgroups, HR (95% CI)				
Endometrioid histology	0.96 (0.75–1.24)		0.78 (0.62–0.97)	
Non-endometrioid/other histology[c]	1.06 (0.77–1.44)		1.12 (0.83–1.50)	
Prior neo/adjuvant chemotherapy	0.60 (0.37–0.97)		0.52 (0.33–0.82)	
OS				
Median (95% CI), mo	30.9 (25.4–37.7)	29.4 (26.2–35.4)	37.7 (32.2–43.6)	32.1 (27.2–35.7)
HR (95% CI)	1.02 (0.83–1.26)[d]		0.93 (0.77–1.12)	
Subgroups, HR (95% CI)				
Endometrioid histology	0.93 (0.71–1.22)		0.80 (0.63–1.01)	
Non-endometrioid/other histology[c]	1.16 (0.85–1.58)		1.14 (0.84–1.54)	
Prior neo/adjuvant chemotherapy	0.67 (0.41–1.11)		0.64 (0.40–1.03)	
ORR (95% CI), %	50.6 (45.0–56.2)	54.7 (49.0–60.2)	55.7 (50.8–60.5)	55.5 (50.6–60.3)
Median DOR (range), mo	16.1 (1.0+ to 48.7+)	10.6 (1.1+ to 43.8+)	23.2 (1.0+ to 49.0+)	10.9 (1.1+ to 46.9+)

"+" indicates no progressive disease at the time of last disease assessment. DCR, disease control rate (CR + PR + SD ≥7 weeks).

[a]Tumor response assessed per RECIST v1.1 by blinded independent central review. [b]Median follow-up duration defined as time from randomization to data cutoff date: 38.4 (range, 30.3–52.9) months. [c]Includes non-endometrioid, adenocarcinoma with no further information (17 patients in the pMMR population; 22 patients among all-comers) and other (2 patients in the pMMR population; 3 patients among all-comers). [d]1-sided noninferiority $P = 0.246$ based on log-rank test stratified by ECOG performance status and prior chemotherapy and/or chemoradiation was nonsignificant, not crossing the prespecified OS noninferiority boundary of $P = 0.0158890$. Because the prespecified statistical criterion for OS noninferiority was not met at final analysis, no further statistical testing of efficacy endpoints was performed. Data cutoff date: October 2, 2023.

non-MMRd disease

Paziente

non-MMR

ER positive (Low grade)

BASSO RISCHIO

POLEmut

ER negative (High grade)

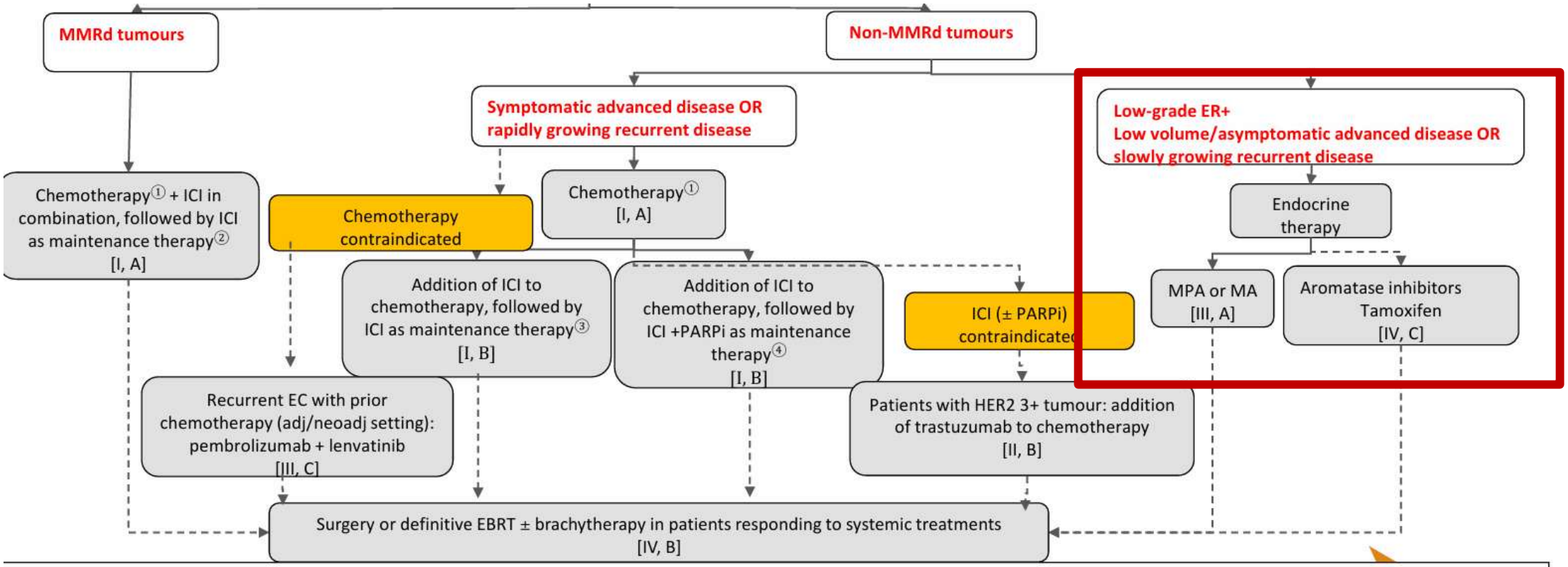
ALTO RISCHIO

P53 abn

p53wt

Unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting

Colombo N and Ledermann J, ESGO 2025



①The standard chemotherapy regimen is carboplatin + paclitaxel.
②Immune checkpoint inhibitor (ICI): dostarlimab or durvalumab or pembrolizumab (drugs in alphabetical order).
③ICI: dostarlimab or pembrolizumab.
④ICI + poly(ADP-ribose) polymerase inhibitor (PARPi): durvalumab + olaparib.
Adj/neoadj adjuvant/neoadjuvant; EBRT external beam radiotherapy; ER+ estrogen receptor positive; MA megestrol acetate; MMRd mismatch repair deficiency, MPA medroxyprogesterone acetate; non-MMRd non-mismatch repair deficiency; NSMP non-specific molecular profile.

ER positive population

2025 ASCO ANNUAL MEETING

Phase 2 study of letrozole, abemaciclib and metformin in estrogen receptor (ER) positive, recurrent endometrial cancer (EC)

Panagiotis A. Konstantinopoulos, Ningxuan Zhou, Richard T. Penson, Susana Campos, Carolyn Krasner, Alexi A. Wright, Rebecca Porter, Neil Horowitz, Sara Bouberhan, Hannah Sawyer, Lani Koppermann, Martin Hayes, Madeline Polak, Meghan Shea, Page Widick, Su-Chun Cheng, Cesar Castro, Ursula A. Matulonis, Elizabeth K. Lee

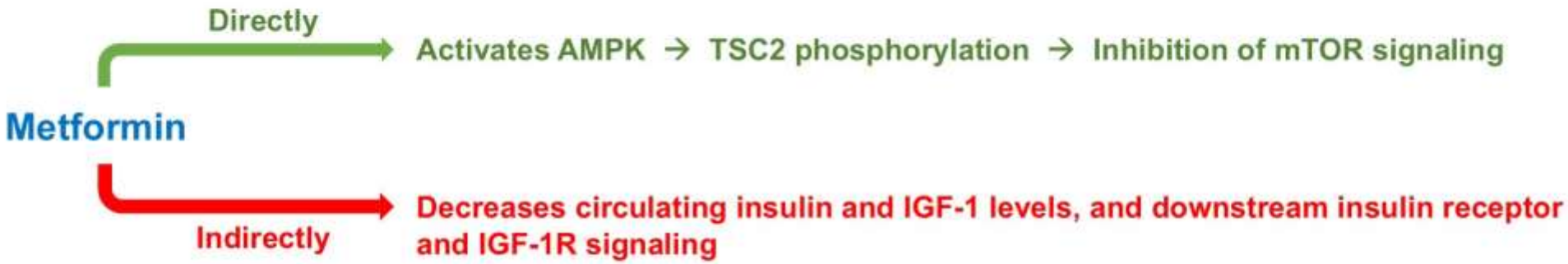
Rationale for combined ER, CDK4/6 and PI3K inhibition in EC

- Previous studies have demonstrated promising activity of combined hormonal therapy and CDK4/6 inhibition in ER positive endometrioid EC*
- ctDNA sequencing at the time of progression through letrozole/abemaciclib demonstrated frequent acquired PI3K pathway alterations suggesting that there is a **strong selective pressure to activate the PI3K pathway upon exposure to combined aromatase and CDK4/6 inhibition** in EC**
- Preclinical studies have demonstrated **significant synergism with simultaneous inhibition** of the ER, CDK4/6 and PI3K pathways***

2025 ASCO ANNUAL MEETING #ASCO25

** Konstantinopoulos et al. JCO 2023, Green et al. Clin Can Res 2024, Mirza et al. Gyn Onc 2025*
*** Konstantinopoulos et al. JCO Precision Oncology 2025 *** Vora et al. Cancer Cell 2014, Herrera-Abreu et al. Cancer Res 2016*

Metformin inhibits PI3K pathway signaling



- Window of opportunity (WOO) studies in endometrial cancer have demonstrated that metformin **at a dose of 850mg orally daily** decreases phospho-AKT and phospho-S6rp in endometrial cancer tissue samples as well as **decreases circulating insulin and IGF-1 levels***

- Based on these considerations, **we hypothesized that PI3K inhibition using metformin may further enhance the activity of letrozole/abemaciclib in endometrial cancer**

PRESENTED BY: Panagiotis A. Konstantinopoulos

* *Schuler et al. Cancer Med 2015, Soliman et al. Gyn Onc 2016*

Eligibility and Endpoints

Key Eligibility Criteria

- Recurrent **ER+** EC defined as **≥1% of nuclei** by immunohistochemistry (IHC)
- **Endometrioid** Histology
- **No limit** of prior therapies
- **Any Prior Hormonal Therapy Allowed**
- **Measurable** disease by RECIST 1.1
- **No prior CDK4/6** inhibitors
- **No current metformin** use

Primary Endpoints

- **Objective response (OR) rate (ORR)**
- **Progression-free survival ≥6 months (PFS6)**

Secondary Endpoints

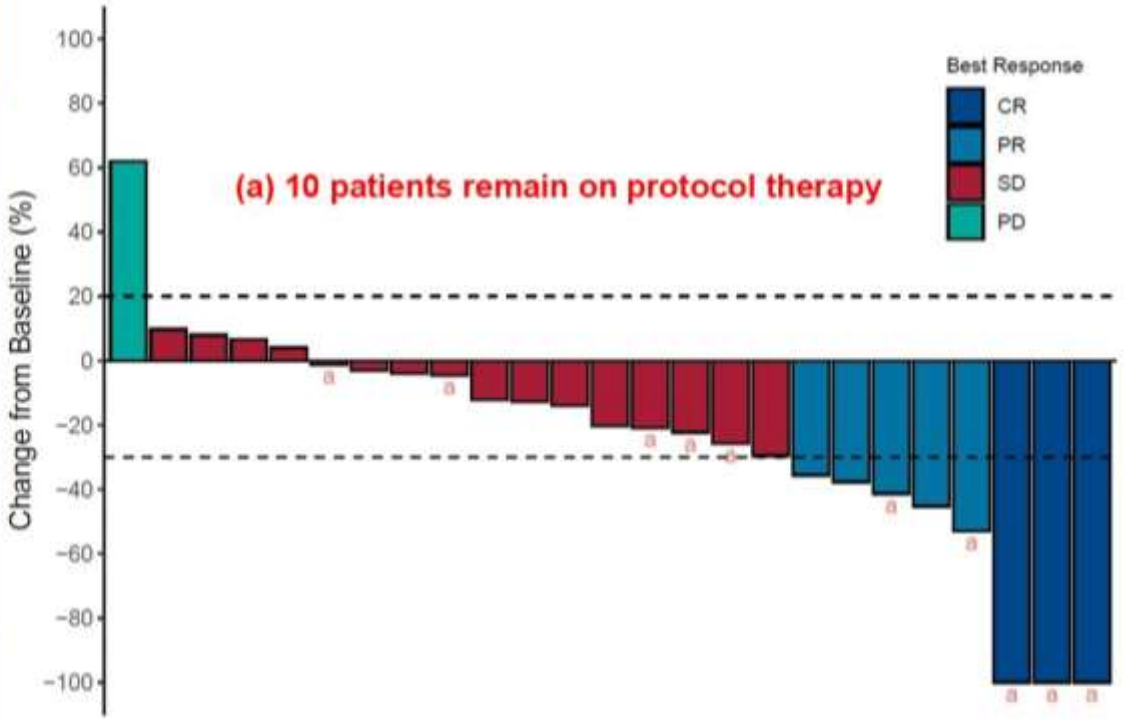
- **PFS and Overall Survival (OS)**
- **Toxicity**

Correlative Studies

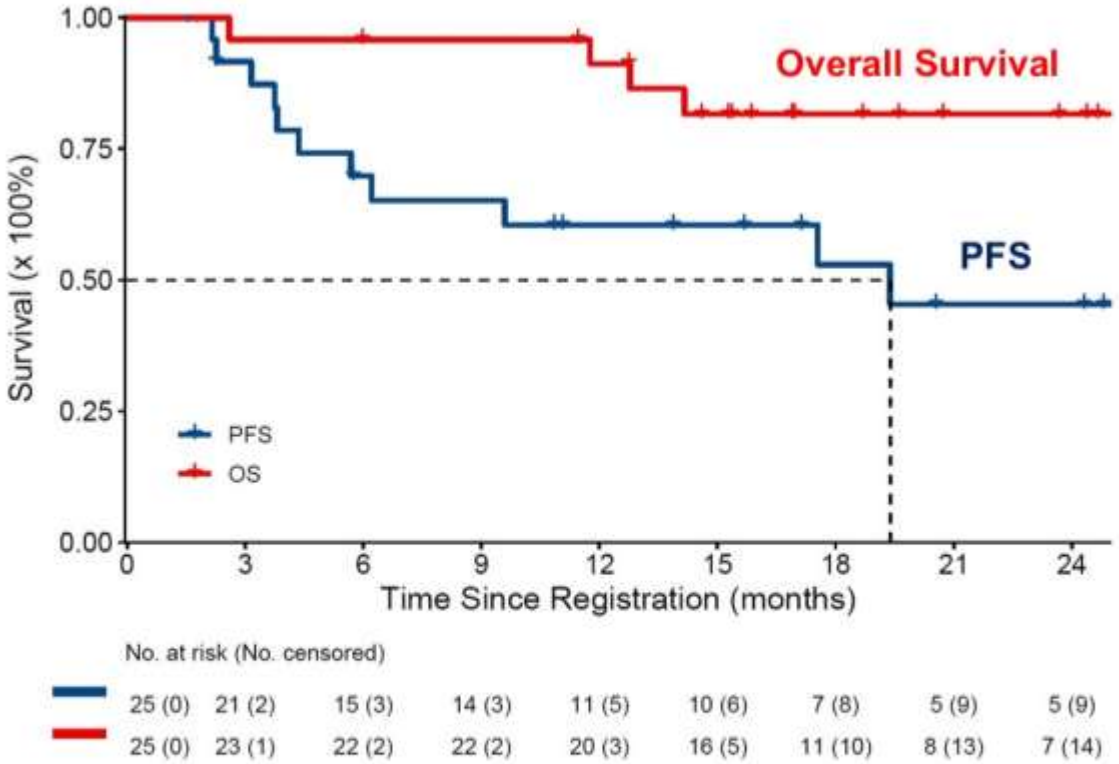
- **Pharmacokinetic (PK) analyses of metformin**
- **Molecular profiling via Oncopanel targeted NGS assay**
- **Progesterone receptor (PrgR) expression (IHC)**

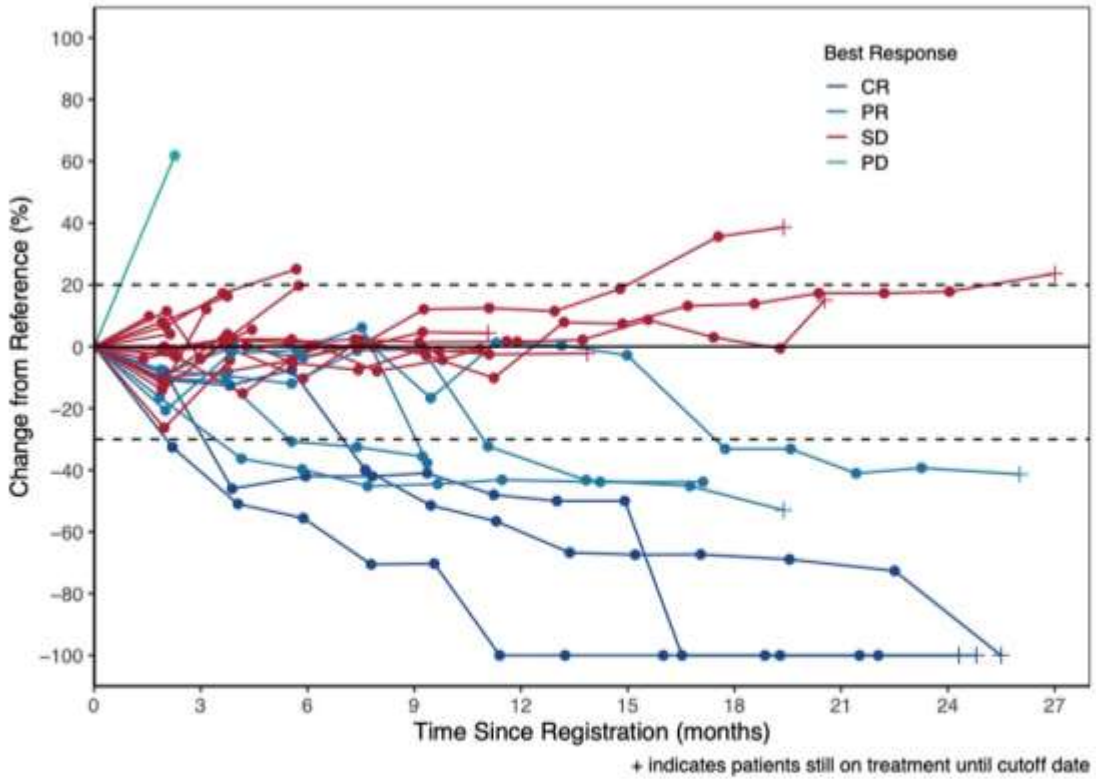
Objective Response Rate (ORR)

RESPONSE	Overall (N=25) n (%)
Complete Response (CR)	3 (12%) (1 unconfirmed CR but confirmed PR)
Partial Response (PR)	5 (20%) (1 unconfirmed)
Stable Disease (SD) ≥ 6 months	7 (28%)
SD < 6 months	9 (36%)
Progressive Disease	1 (4%)
ORR	**8 (32%)**



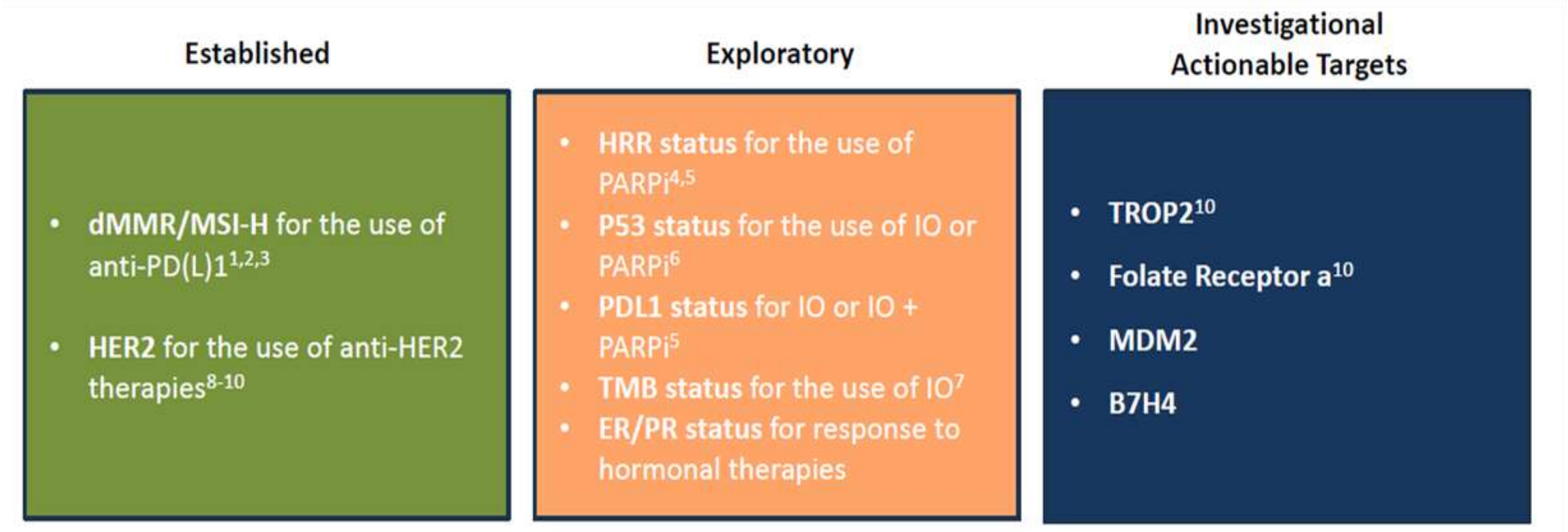
Progression Free Survival (PFS)





Median PFS 19.4 months (median follow-up time 18.7 months)
Kaplan Meier estimate of PFS6: 69.8% (95% CI: 46.9% to 84.3%)

Predictive biomarkers in endometrial cancer



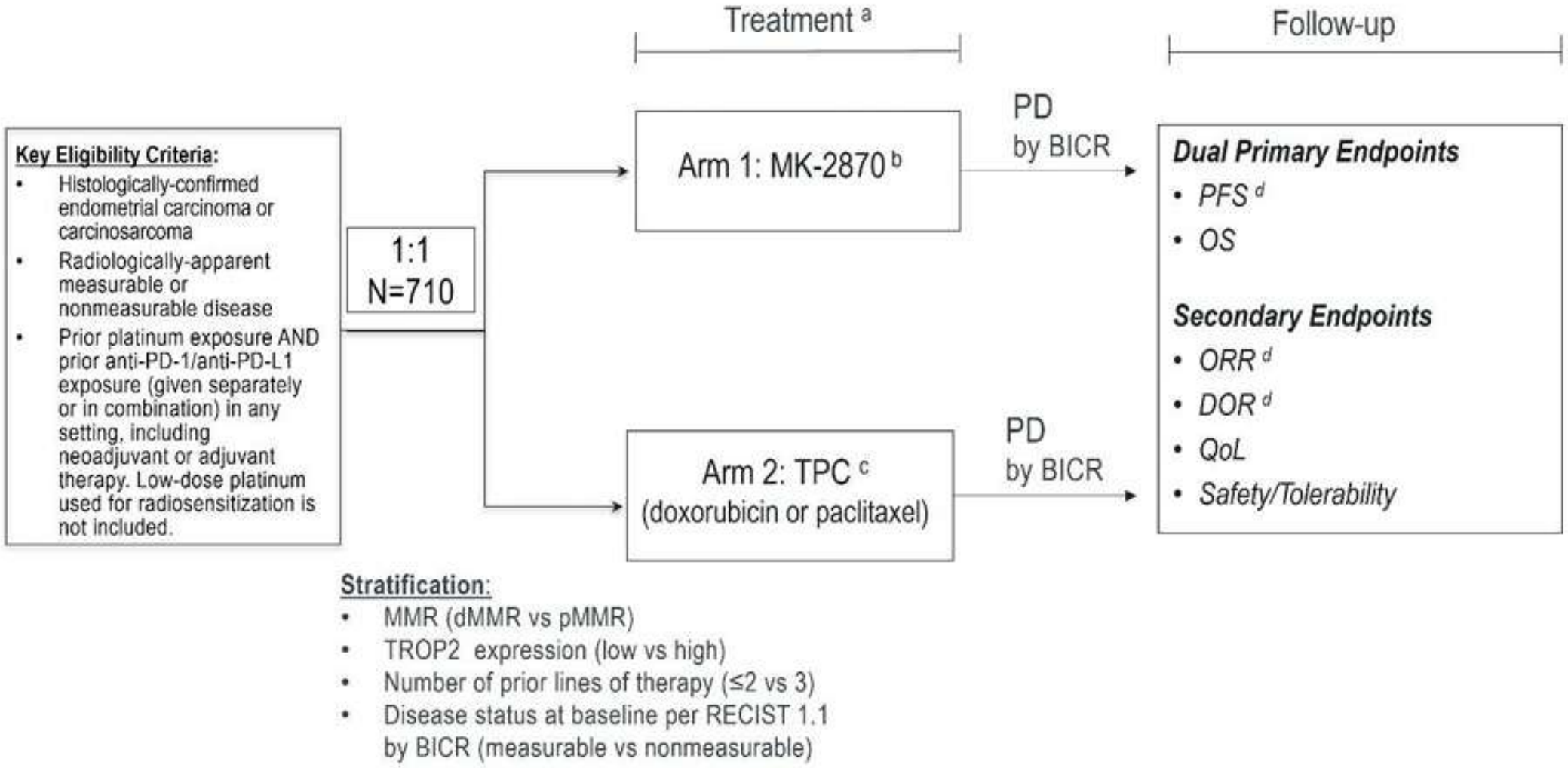
ESGO 2025

ADC in clinical development in endometrial cancer

ESGO 2025

Target	Drug	Linker	DAR	Payload	Development Stage
FRα	**Luveltamab tazevibulin (STRO-002)**	Valine-citrulline (cleavable)	4	SC239 (hemiasterlin)	Phase 1
	Farletuzumab ecteribulin (MORAb-202)	Val-Cit	4	Eribulin mesylate	Phase 1/2
B7-H4	**XMT-1660**	Polymer scaffold (cleavable)	6	AF-HPA/AF	Phase 1b
	SGN-B7H4V	Protease-cleavable mc-vc linker	4	MMAE	Phase 1
	AZD8205	Val-ala peptide linker with a PEG8 spacer	8	Topoisomerase I inhibitor	Phase 1/2
Trop-2	**Sacituzumab govitecan**	Hydrolyzable linker	7.5	Topoisomerase I inhibitor (SN-38)	Phase 2
	Datopotomab deruxtecan (Dato-DXd)	Cleavable tetrapeptide-based linker	~4	Topoisomerase I inhibitor (Dxd)	Phase 2
	MK-2870 (SKB264)	sulfonyl pyrimidine-CL2A-carbonate	7.4	Belotecan-derived topoisomerase I inhibitor	Phase 3
HER2	**Trastuzumab duocarmazine (SYD985)**	Mb-Val-Cit-PABC	2.7	Duocarmycin	Phase 2
	Trastuzumab deruxtecan (T-DXd)	Peptide-based	7-8	Topoisomerase I inhibitor (Dxd)	Phase 2
	DB-1303/BNT323	Maleimide tetrapeptide-based	~8	Topoisomerase I inhibitor (P1003)	Phase 1/2a

MK 2870-005 /ENGOT-en23 /GOG3095



DESTINY-Endometrial01/GOG-3098/ENGOT-EN24

Patient Population

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

IHC 3+25%; IHC 2+ 75% (capped)

N=600

R 1:1:1

- **A: Enhertu 5.4 mg/kg + Rilvegostomig 750mg Q3W[a]**
- **B: Enhertu 5.4 mg/kg + Pembrolizumab 200mg Q3W[a]**
- **C: Carboplatin/Paclitaxel + Pembrolizumab[b]**

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

Endpoints

Primary:
- PFS (BICR) in ITT

Secondary:
- OS
- PFS (Investigator)
- ORR
- PFS2
- HRQoL

Futility analysis at 40% IF

TRASTUZUMAB-DERUXTECAN

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

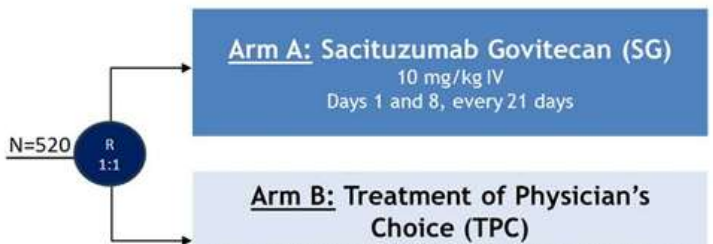
b. Carboplatin AUC5, paclitaxel 175 mg/m2, and pembrolizumab 200 mg IV once Q3W x 6 cycles*, followed by maintenance with pembrolizumab 400 mg IV Q6 eat ith pembrolizumab will continue for up to 20 total cycles (approximately 24 months, accounting for combination and maintenance phases) or until other discontinua ter et, whichever occurs first.

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

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

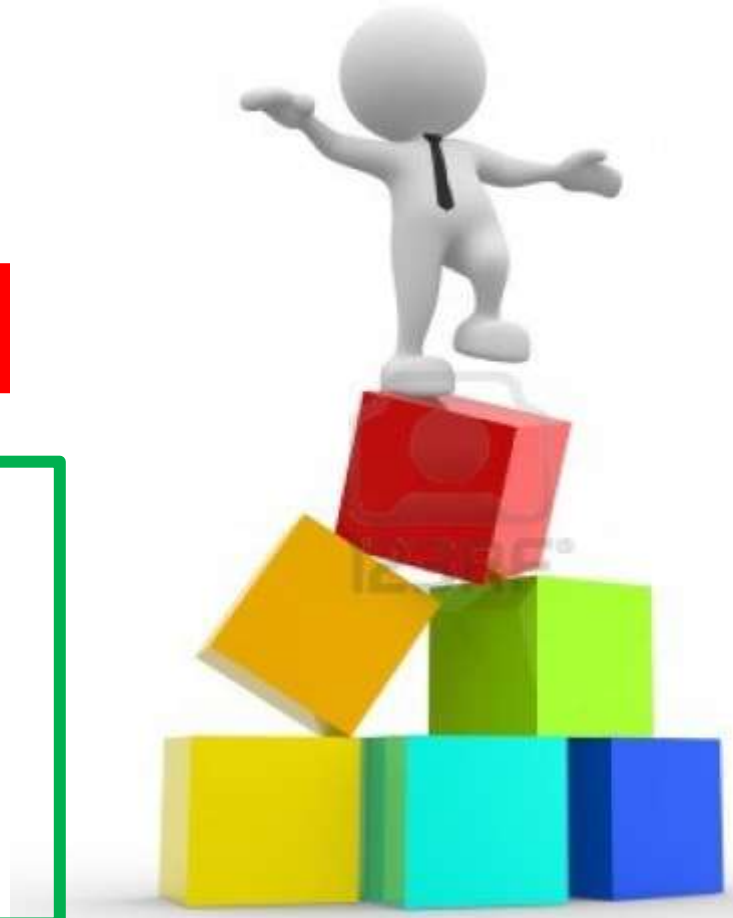
ENGOT PI: Nicoletta Colombo

GOG led study
Sponsor Gilead Sciences

MaNGO
Manes Negri Gynecologic Oncology

ENGOT
European Network of Gynaecological Oncological Trial groups

non-MMRd disease



Paziente

non-MMR

BASSO RISCHIO

ER positive (Low grade)

POLEmut

P53 wt

ER negative (High grade)

ALTO RISCHIO

P53 abn

ICI / PARPi

Grazie per l'attenzione!