XXII ASSEMBLEA MaNGO MILANO

STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
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MaNGO

New Endometrial Cancer Guidelines ESGO/ESTRO/ESP 2025: Medical perspective

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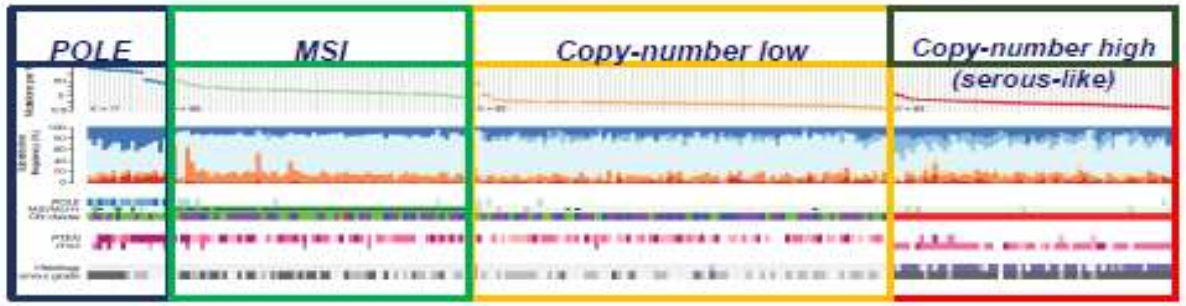
Oncologia Medica

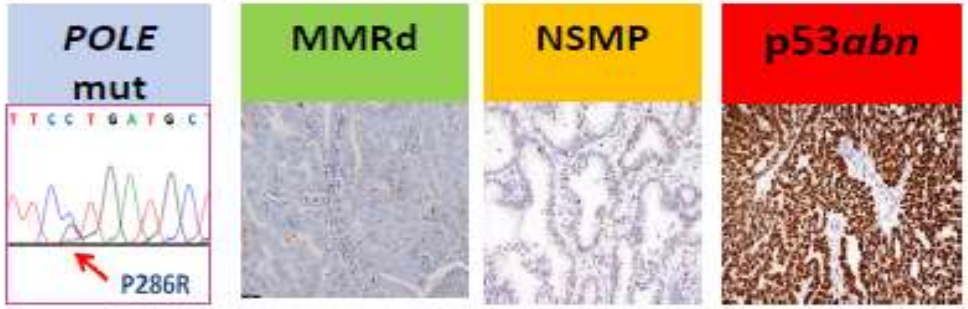
Disclosures

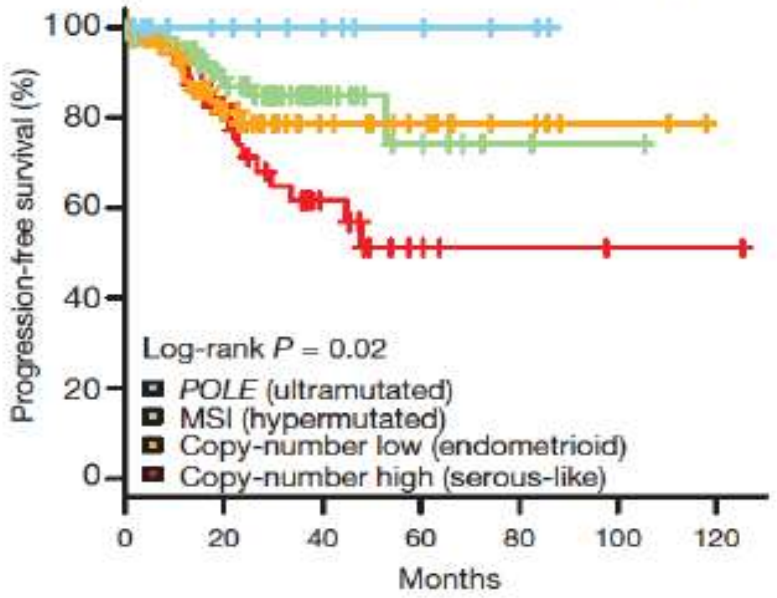
- Consulting/Advisory Board: AstraZeneca, Clovis Oncology, Eisai
- Lecture Fees: AstraZeneca, PharmaMar, GSK
- Travel Grants: AstraZeneca, GSK

What's new for Adjuvant Setting?

What The Cancer Genome Atlas (TCGA) has taught us……



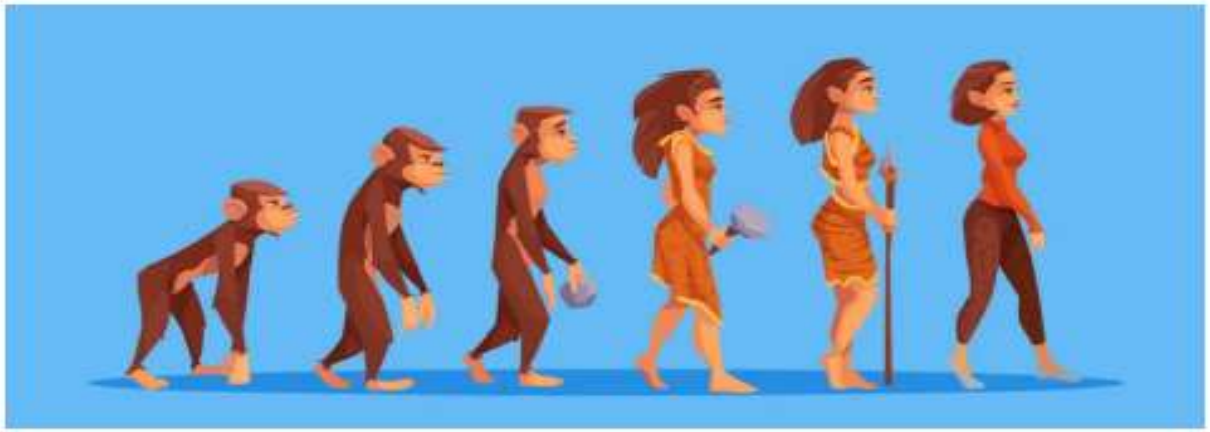




- **Immunohistochemistry** for **p53** & **mismatch repair proteins**
- **DNA sequencing** for ***POLE*** exonuclease domain mutations

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

Evolution of the Revolution …



Integration of
TUMOR BIOLOGY
into

FIGO staging system

2023 FIGO staging†			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			**	
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**			
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						
IVB/C1A		With synchronous disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Green denotes low risk for recurrence; yellow denotes intermediate risk; orange denotes high-intermediate risk and red denotes high risk; grey denotes uncertain risk classification because of lack of data.

† 2023 FIGO staging: when molecular classification is known, the FIGO stage should be reported with an annotation of m (for molecular) followed by the specific molecular subtype. There are two specific molecularly defined FIGO stages, namely stage IAm *POLE*mut (stages I and II disease with a pathogenic *POLE* mutation) and stage IICm p53abn (stages I and II disease with a p53 abnormality and myometrial invasion), these two molecularly defined FIGO stages are indicated in the table's cells)

*Details on determining the molecular classification, including allocation for double classifiers, are detailed in figure 2 and the webappendix, pp 18-20.

**The molecular subgroup NSMP high-grade/ERneg consists of either high-grade NSMP cases or ERneg NSMP cases. Thus, in FIGO stages referring to *low-grade* endometrioid carcinomas (i.e. IA1, IA2, IA3, IB, IIA and IIB) only to the ERneg cases of the molecular subgroup NSMP high-grade/ERneg apply.

***Substantial LVSI is defined according to WHO criteria by ≥4 vessels in at least one H&E slide (refer to appendix for information on LVSI, pp 18-20).

myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

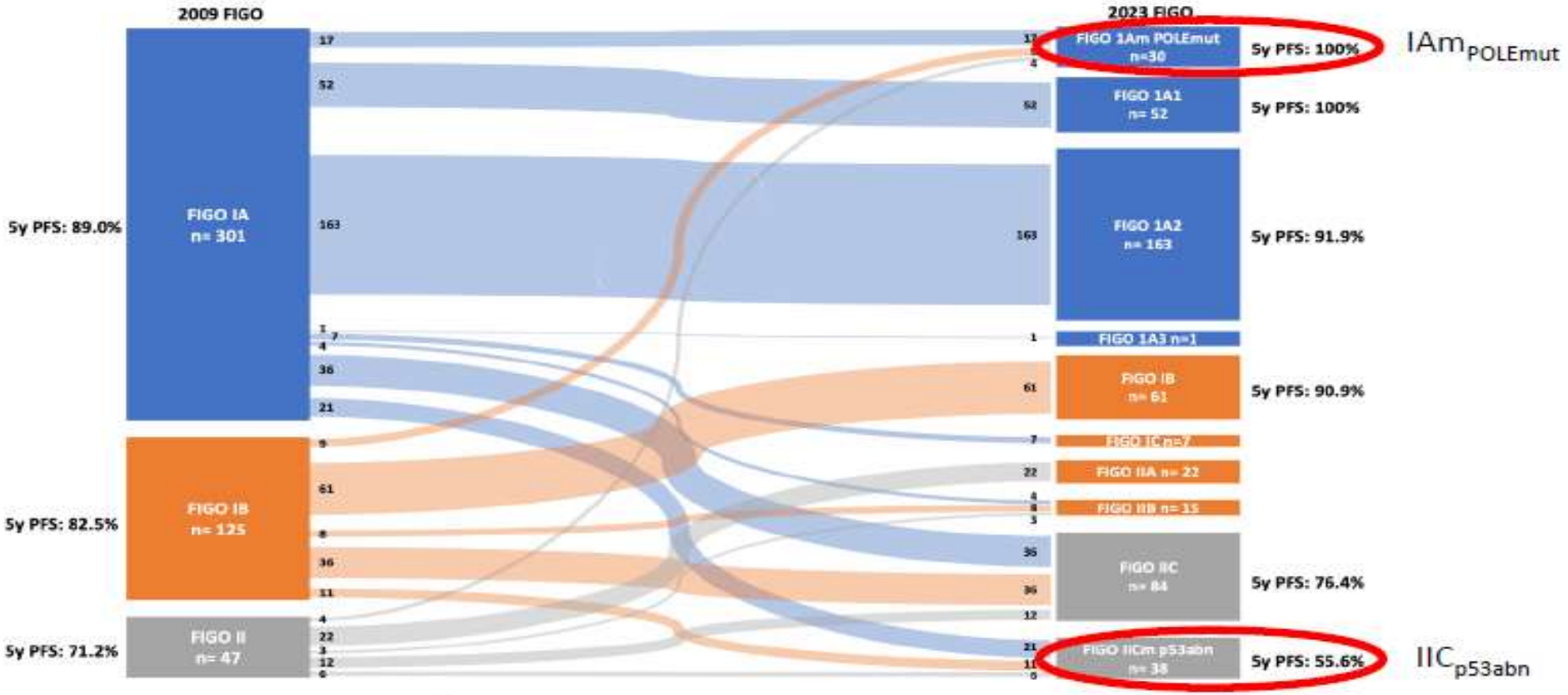
°High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous, clear cell carcinomas, carcinosarcomas, undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma.

Risk Groups

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

Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients – *an international pooled analysis of three ESGO accredited centers*

Stage shifts between 2009 and 2023 FIGO in **early stage endometrial carcinoma** (stages I/II N= 473)



$IAm_{POLEmut}$

IIC_{p53abn}

MEDICAL UNIVERSITY OF VIENNA

Gemelli

MEDIZINISCHE UNIVERSITÄT

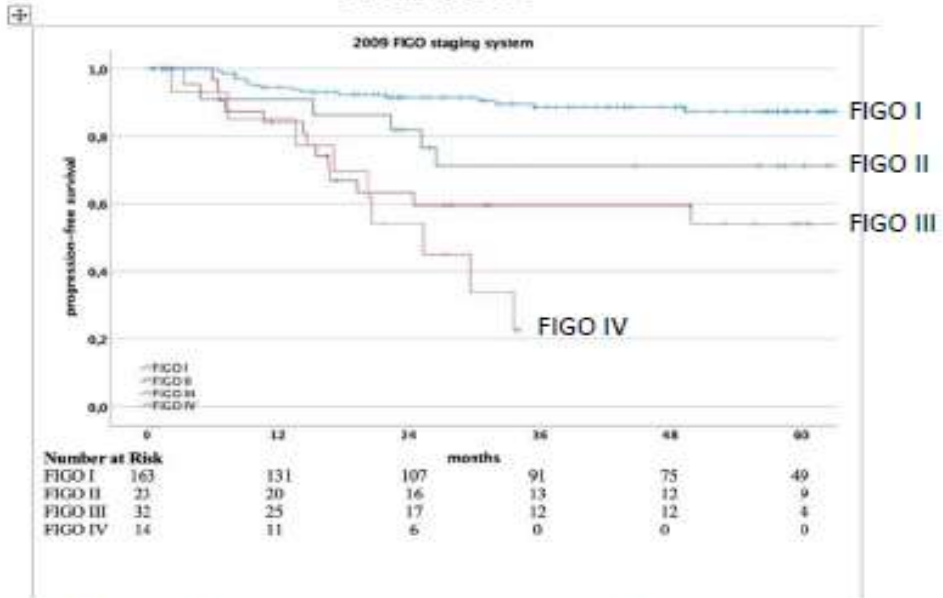
Schwameis R et al, Eur J Cancer 2023

presented: at ESGO congress Istanbul, best oral EC session 1 Oct 2023

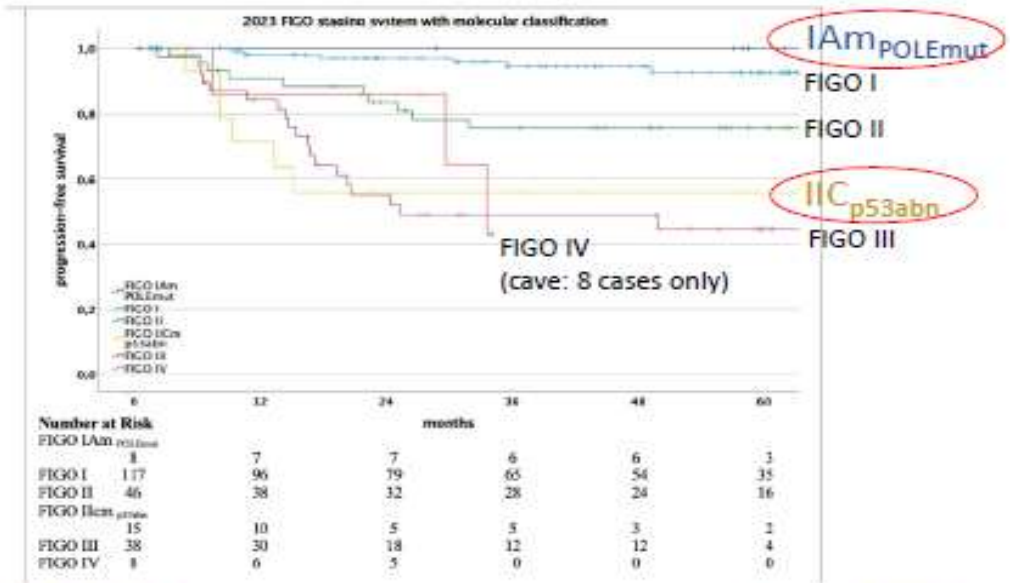
Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients –
an international pooled analysis of three ESGO accredited centers

Progression-free survival in a study cohort of 232 endometrial cancer patients *according to*

2009 FIGO



2023 FIGO



Statistical tests demonstrated superiority of 2023 FIGO staging system compared to 2009 to predict PFS and OS

Schwameis R et al, Eur J Cancer 2023
Editorial by Vergote I & Matias-Guiu X, Eur J Cancer 2023

new molecularly defined FIGO stages

$IAm_{POLEmut}$ & $IICm_{p53abn}$

immediate relevance for
treatment-decison making

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%;
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DEFINITION OF RISK GROUPS

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				
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#					
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI	IAm *POLE*mut				
IC		High-grade histologies^, limited to polyp/endometrium	IAm *POLE*mut				

Green denotes low risk for recurrence.

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myoinvasion <50% + no/focal LVSI + ovarian tumour pT1a

^High-grade histologies are the FIGO 2023 aggressive histotypes that include high-grade endometrioid (grade 3), serous, clear cell carcinomas, carcinosarcomas, undifferentiated, mixed, mesonephric-like, and gastrointestinal mucinous type carcinoma.

DEFINITION OF RISK GROUPS

2023 FIGO staging[π]			Molecular classification				
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II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm *POLE*mut				
IIB		Low-grade endometrioid, substantial LVSI**	IAm *POLE*mut				
IIC		High-grade histologies^, myoinvasion	IAm *POLE*mut				

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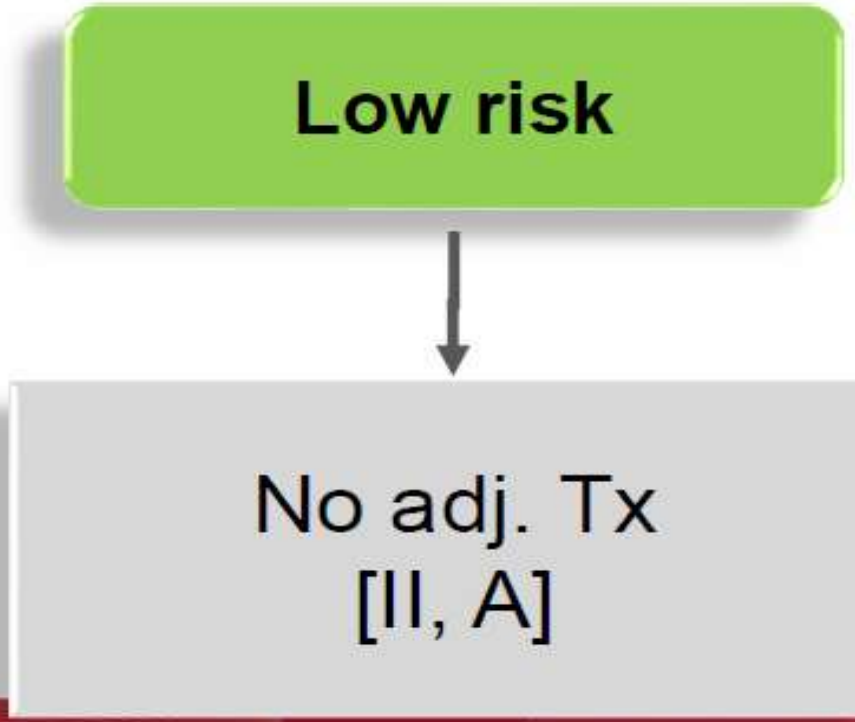
ADJUVANT THERAPY
LOW RISK

- For patients with low-risk EC: no adjuvant therapy is recommended [II, A].



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Concin N et al, accepted Lancet Oncology 2025

DEFINITION OF RISK GROUPS

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	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#				*	
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ADJUVANT THERAPY
FIGO 2023 IA1m NSMP high-grade/ERneg or p53abn & ICm NSMP high-grade/Erneg or p53abn

- There are limited data suggesting that the risk of recurrence is somewhat higher than for low-risk carcinomas. However, adjuvant therapy is generally not recommended [IV, C].

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Yellow denotes intermediate risk for recurrence.

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DEFINITION OF RISK GROUPS

ESTRO European Society of Pathology

ESGO European Society of Gynaecological Oncology

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IIC		High-grade histologies^, myoinvasion		Myoinvasion <50%, no/focal LVSI			
				Myoinvasion ≥50%, no/focal LVSI			

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ADJUVANT THERAPY
INTERMEDIATE RISK

- For patients with intermediate risk EC: adjuvant vaginal brachytherapy should be considered [I, A].
- No adjuvant therapy is an option [III, C], especially for patients under 60 years of age and/or low grade [II, A]

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Concin N et al, accepted Lancet Oncology 2025

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IIB		Low-grade endometrioid, substantial LVSI**					
IIC		High-grade histologies^, myoinvasion					
				Cervical stromal invasion, no/focal LVSI			
				Substantial LVSI*			

Orange denotes high-intermediate risk for recurrence.

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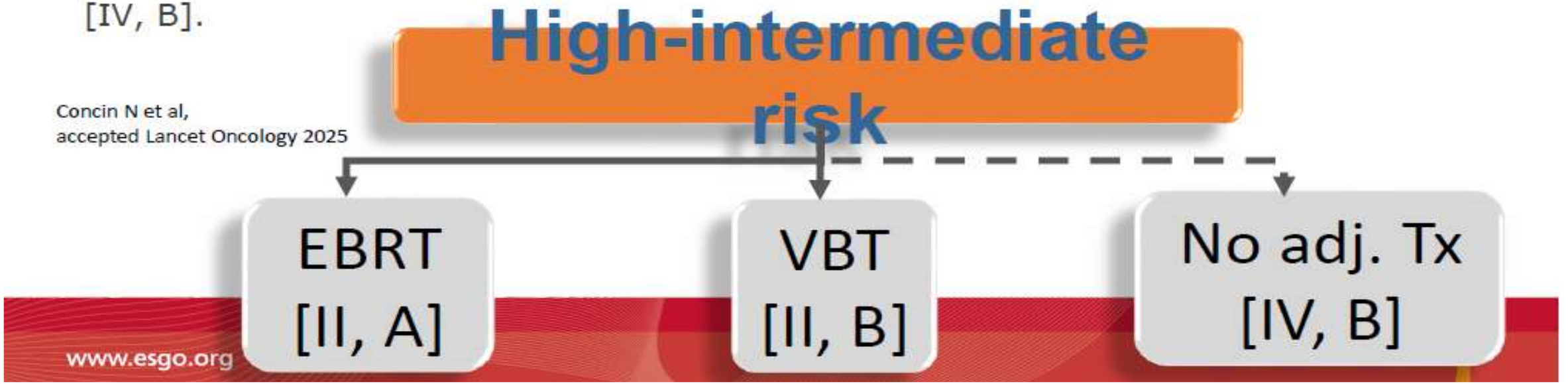
ADJUVANT THERAPY
HIGH-INTERMEDIATE RISK

- For patients with high-intermediate-risk EC: adjuvant EBRT is recommended for optimal pelvic control [II, A].
- Vaginal brachytherapy is an alternative option, especially for patients who underwent lymph node staging and are pN0 [II, B].
- No adjuvant therapy can be considered, especially for patients who underwent lymph node staging and are pN0, without substantial LVSI and low-grade disease [IV, B].



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	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary#				*	
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI				*	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium					

Red denotes high risk for recurrence.

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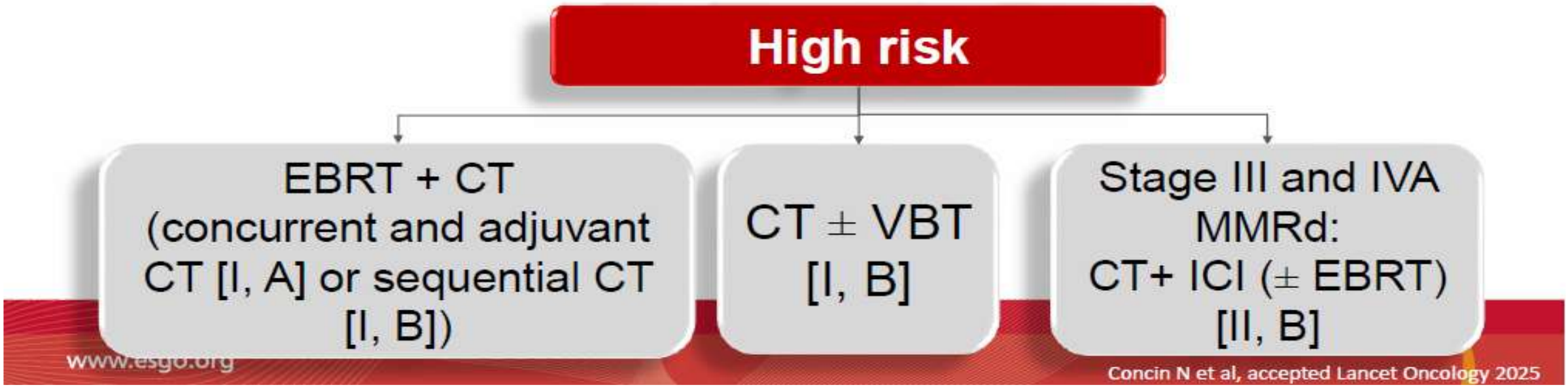
Low | Intermediate | High-Intermediate | High | Uncertain

		Molecular classification*				
		*POLE*mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
Local and/or regional spread beyond uterus						
	Spread to ovary or fallopian tube (except for #)	IIIA1	IIIA1	IIIA1	IIIA1	IIIA1
	Involvement of uterine subserosa or spread through the uterine serosa	IIIA2	IIIA2	IIIA2	IIIA2	IIIA2
	Metastasis or direct spread to the vagina and/or the parametrium	IIIB	IIIB	IIIB	IIIB	IIIB
	Metastasis to the pelvic peritoneum	IIIB2	IIIB2	IIIB2	IIIB2	IIIB2
	Metastasis to the pelvic lymph nodes	IIIC1	IIIC1	IIIC1	IIIC1	IIIC1
	Metastasis to the para-aortic lymph nodes	IIIC2	IIIC2	IIIC2	IIIC2	IIIC2
Locally advanced						
Invasion of bladder mucosa and/or intestinal mucosa		IVA	IVA	IVA	IVA	IVA
Low-grade endometrioid carcinoma of both the endometrium + ovary #						
Myoinvasive <50%, no/focal LVSI, ovarian tumour pT1a		IA3	IA3	IA3	IA3**	IA3

ADJUVANT THERAPY
HIGH RISK

- For patients with high risk EC: EBRT with concurrent and adjuvant chemotherapy [I, A].
- or alternatively sequential chemotherapy and radiotherapy are recommended [I, B].
- Chemotherapy ± brachytherapy is an alternative option [I, B].
- For patients with FIGO 2023 stage IIIm-IVAm MMRd EC, adjuvant chemotherapy combined with an ICI (± EBRT) should be considered [II, B].



ENGOT-EN11/GOG-3053/KEYNOTE-B21 Study Design

Key Eligibility Criteria

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

Stratification Factors

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

R 1:1
N=1095

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

Dual primary endpoints

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

[a]Chemotherapy was administered for 4 cycles in patients planned to receive chemoradiotherapy and 6 cycles for all other patients, including those planned for radiotherapy without radiosensitizing cisplatin. [b]Radiotherapy was optional at the discretion of the investigator, and cisplatin may have been given with EBRT as radiosensitizer; radiotherapy was started within 6 weeks after completion of carboplatin and paclitaxel (radiation may have been initiated during Stage 1 or Stage 2 depending on the number of cycles of chemotherapy that were administered).

T. Van Gorp et al. Annals of Oncology, 2024

ADJUVANT THERAPY
FIGO 2023 STAGES IIImPOLE$_{mut}$ and IVAm POLE$_{mut}$

- This part includes the following categories:
  - FIGO 2023 stages IIIm*POLE*mut
  - FIGO 2023 stage IVAm *POLE*mut

ADJUVANT THERAPY
FIGO 2023 STAGES IIImPOLE$_{mut}$ and IVAm POLE$_{mut}$

- For patients with FIGO 2023 stage IIIm *POLE*mut and IVAm *POLEmut* (prognostic risk group allocation is unclear) due to limited number of patients no firm treatment recommendations can be given, however, following a case-by-case multidisciplinary team discussion, de-escalation from high-risk treatment can be considered [IV, B].

KEY CHANGES

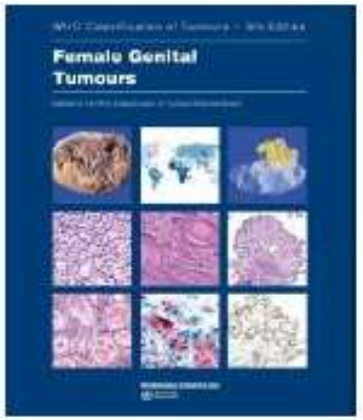
EARLY stage disease: stage I/II

- degree of **LVSI** (no/focal *vs* substantial)
- **histological subtypes and grading**
  (low-grade endometroid *vs* high-grade (aggressive) histological types)
- **Molecular classification**, *if available*

ADVANCED stage disease: stage I/II

- **Metastatic spread to the ovary**: Distinction of **low-grade endometrioid carcinoma involving the endometrium and the ovary**
- Refinement of of **lymph node metastasis** *(micro- vs macrometastasis)*
- New evaluation of **peritoneal carcinomatosis**

lymph vascular space invasion = LVSI



WHO definition

Extent of LVSI is important

- **Focal** LVSI is defined by the presence of a **single focus** around the tumor
- **Substantial** LVSI as **multifocal** *or* d**iffuse** arrangement of LVSI *or* the presence of tumor cells **≥ 5 lymphovascular spaces**.

ESGO-ESTRO-ECP consensus guideline on LVSI

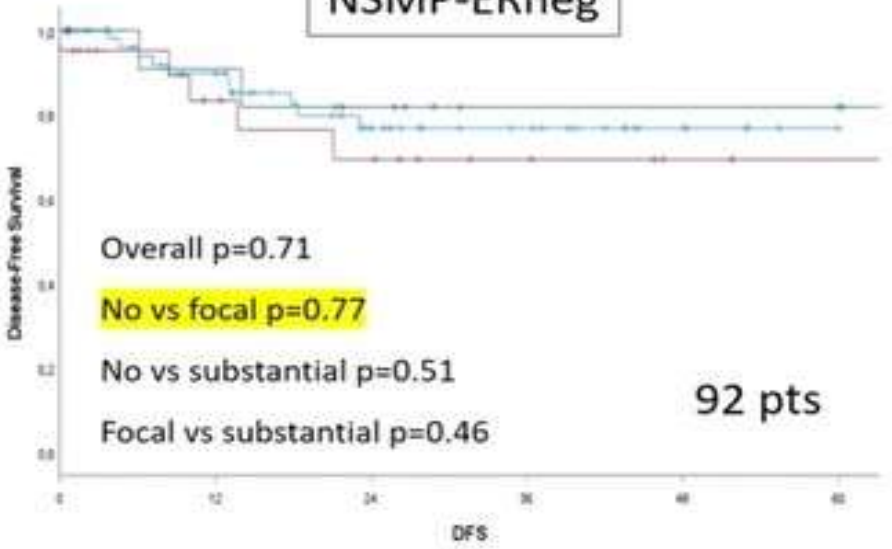
- Substantial LVSI is robust and shows **consistent prognostic results**, supporting the continues use as critical risk factor.

- Studying optimal threshold for altering clinical management remains complex, but **most current studies recommend 4 vessels**.

- Data on focal LVSI are not consistent (for understandable reasons). Present **data insufficient** to recommend differential treatment based on focal LVSI. <parallel with ITC discussion; report it, but don't act on>

- Prospective data on focal LVSI are eagerly awaited, ideally in the setting of molecularly classified stage I EC (**PORTEC4a**)

NSMP-ERneg



Overall p=0.71

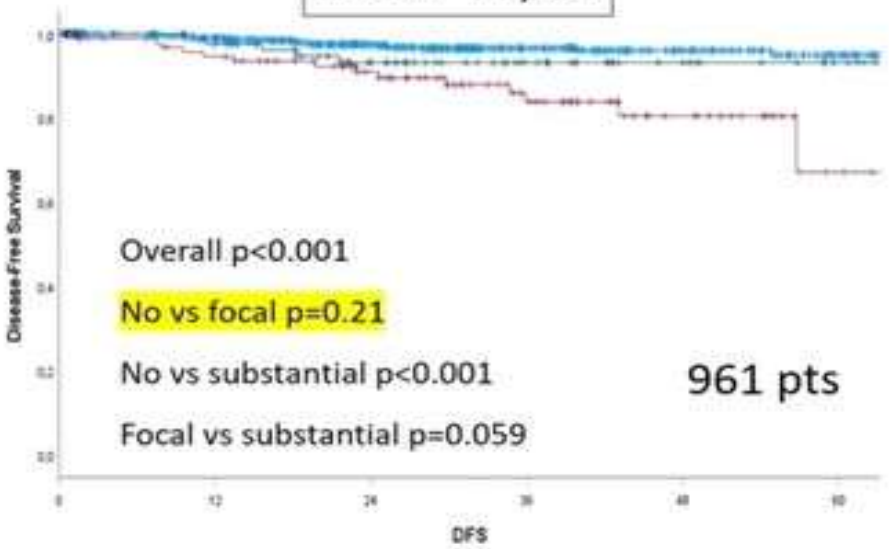
No vs focal p=0.77

No vs substantial p=0.51

Focal vs substantial p=0.46

92 pts

NSMP-ERpos



Overall p<0.001

No vs focal p=0.21

No vs substantial p<0.001

Focal vs substantial p=0.059

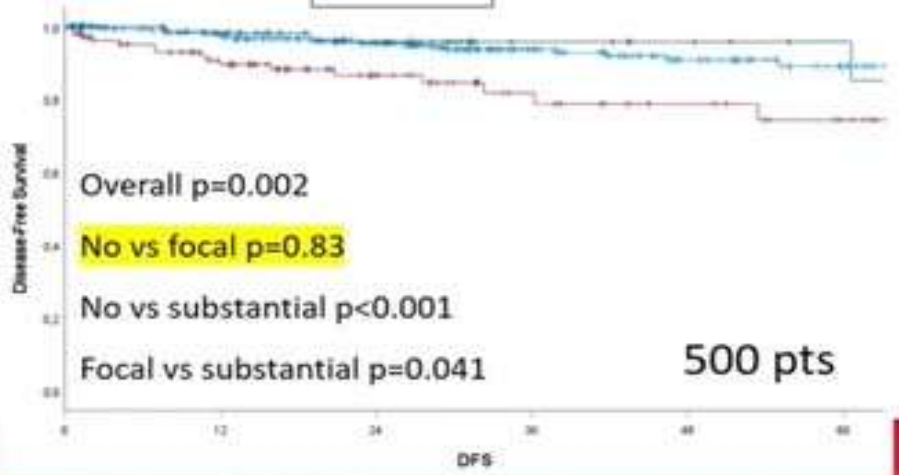
961 pts

LVSI negative

LVSI focal

LVSI substantial

MMRd



Overall p=0.002

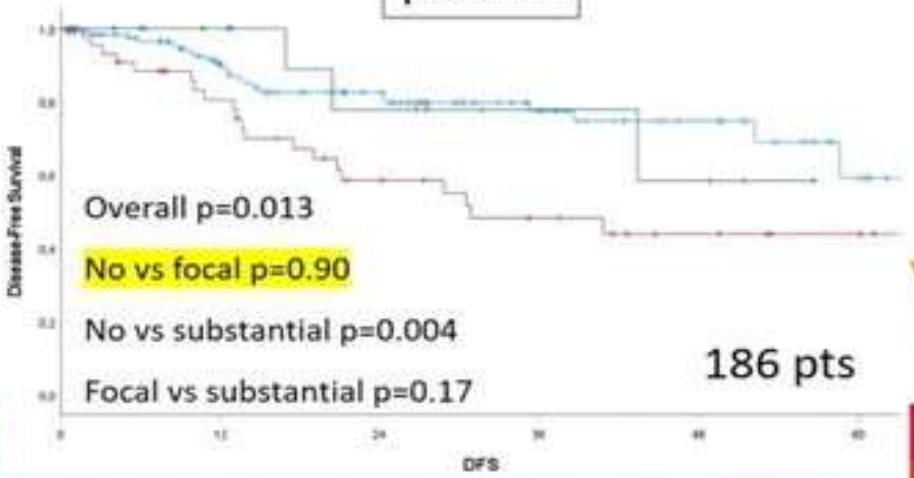
No vs focal p=0.83

No vs substantial p<0.001

Focal vs substantial p=0.041

500 pts

p53abn



Overall p=0.013

No vs focal p=0.90

No vs substantial p=0.004

Focal vs substantial p=0.17

186 pts

KEY CHANGES

EARLY stage disease: stage I/II

- degree of **LVSI** (no/focal *vs* substantial)
- **histological subtypes and grading**
  (low-grade endometroid *vs* aggressive histological types)
- **Molecular classification,** *if available*

ADVANCED stage disease

- **Metastatic spread to the ovary**: Distinction of **low-grade endometrioid carcinoma involving the endometrium and the ovary**
- Refinement of of **lymph node metastasis** *(micro- vs macrometastasis)*
- New evaluation of **peritoneal carcinomatosis**

low-grade endometrioid carcinoma involving the endometrium & the ovary (“synchronous tumors”)

molecular analysis: most of them are clonal (metastatic)

GOOD PROGNOSIS

✓ **When all the following criteria need to be met:**

according to WHO:

(1) no more than **superficial myometrial invasion** is present **(<50%)**

(2) the **absence of substantial LVSI**

(3) the absence of additional metastases

according to ESGO-ESTO-ESP Guidelines, in addition

(4) unilateral **ovarian tumors**, limited to the ovary, without capsule invasion/rupture (equivalent to **pT1a**)

KEY CHANGES

EARLY stage disease: stage I/II

- degree of **LVSI** (no/focal *vs* substantial)
- **histological subtypes and grading**
  (low-grade endometroid *vs* aggressive histological types)
- **Molecular classification,** *if available*

ADVANCED stage disease: stage I/II

- **Metastatic spred to the ovary**: Distinction of **low-grade endometrioid carcinoma involving the endometrium and the ovary**
- Refinement of of **lymph node metastasis** *(micro- vs macrometastasis)*
- New evaluation of **peritoneal carcinomatosis**

Application of FIGO 2023 staging criteria to patients with „previous FIGO 2009 IVB“ EC

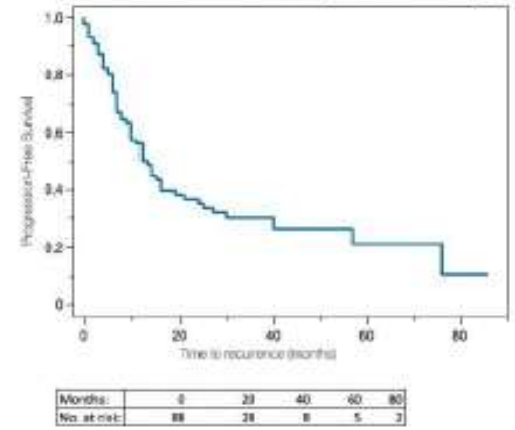
2009 FIGO IVB, n=88, Ohio State University Wexner Medical Center

Gynecologic Oncology

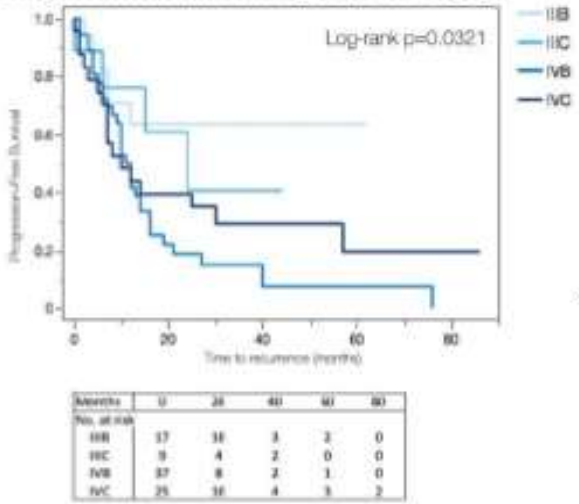
The right time for change: A report on the heterogeneity of IVB endometrial cancer and improved risk-stratification provided by new 2023 FIGO staging criteria

Paulina J. Haight *, Courtney J. Riedinger, Floor J. Backes, David M. O'Malley, Casey M. Cosgrove

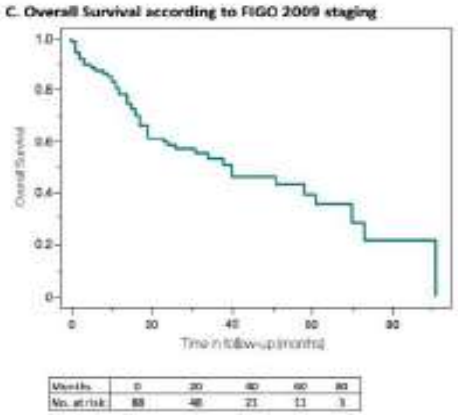
PFS stage IVB FIGO 2009



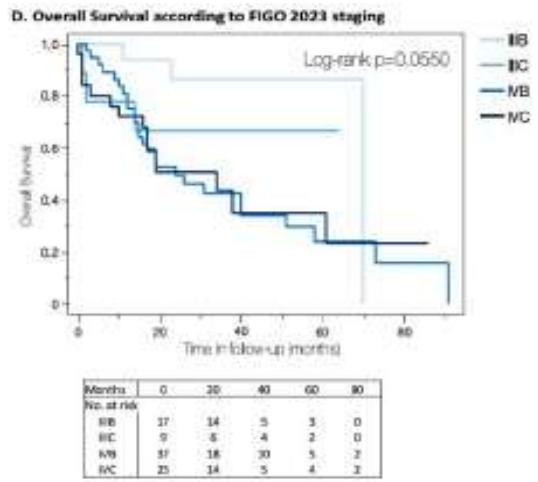
PFS same cohort FIGO 2023



OS stage IVB FIGO 2009



OS same cohort FIGO 2023

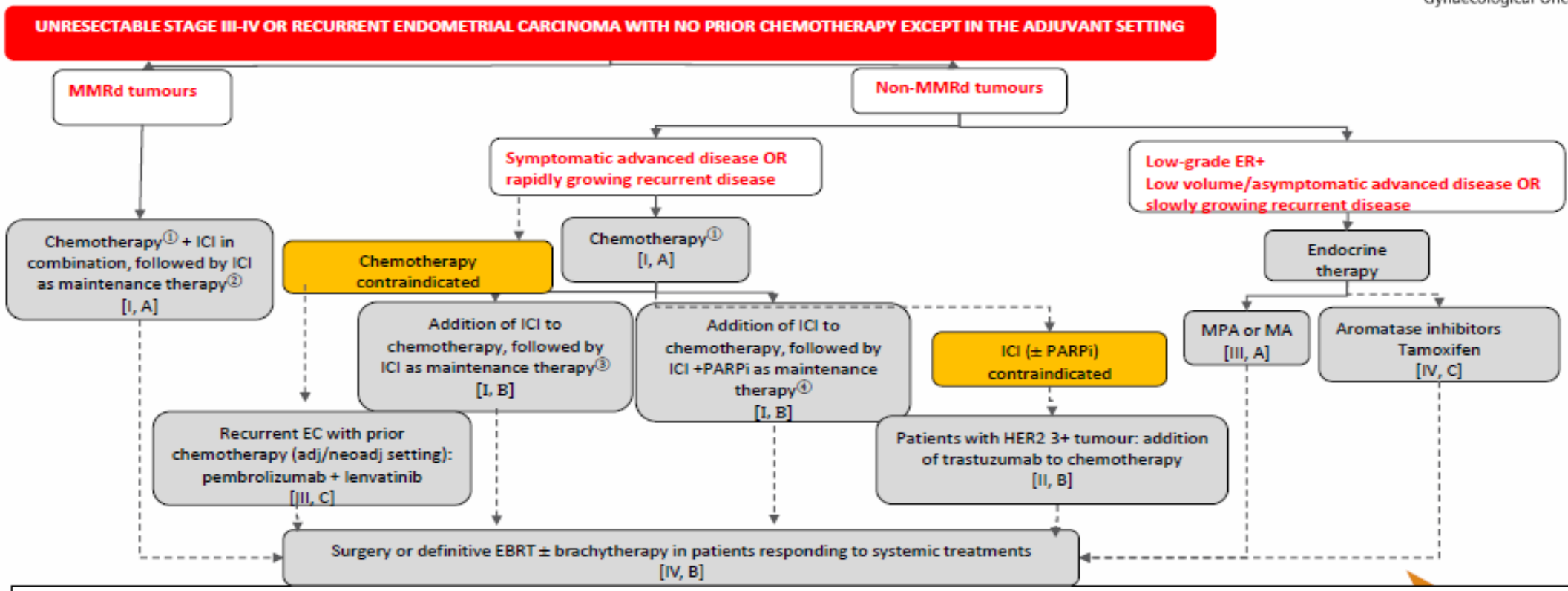


Conclusion: The 2023 FIGO staging criteria significantly improves our ability to risk-stratify patients.

Haight et al, Gynecol Oncol 2023 Sept

What's new for Advanced/Recurrent Setting?

First line systemic therapy in unresectable stage III-IV or recurrent endometrial carcinoma with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)



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.

SYSTEMIC THERAPY

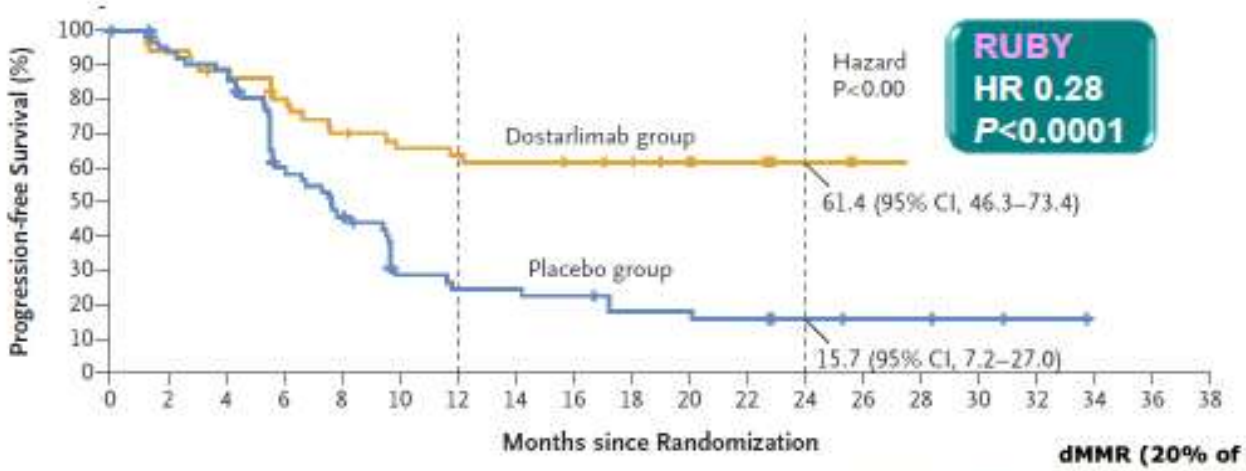
FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

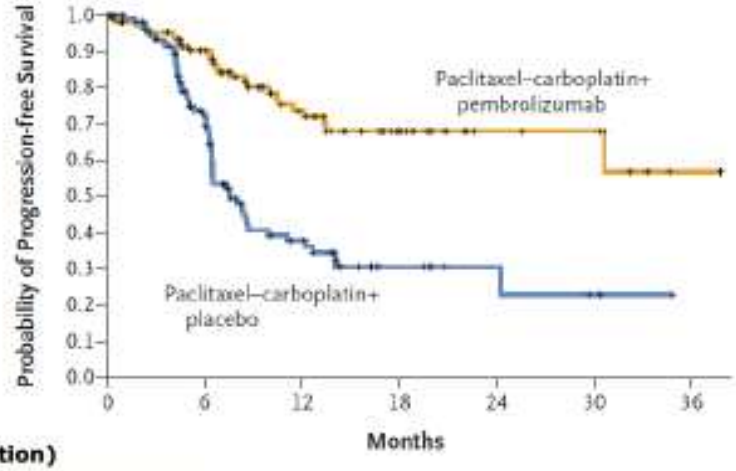
- The MMR status should be taken into consideration to determine the choice of first line therapy:
  - Patients with MMRd tumours should be offered an ICI e.g. dostarlimab or durvalumab or pembrolizumab (drugs mentioned in alphabetical order) in combination with carboplatin-paclitaxel chemotherapy followed by ICI as maintenance therapy [I, A].

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

ESGO European Society of Gynaecological Oncology

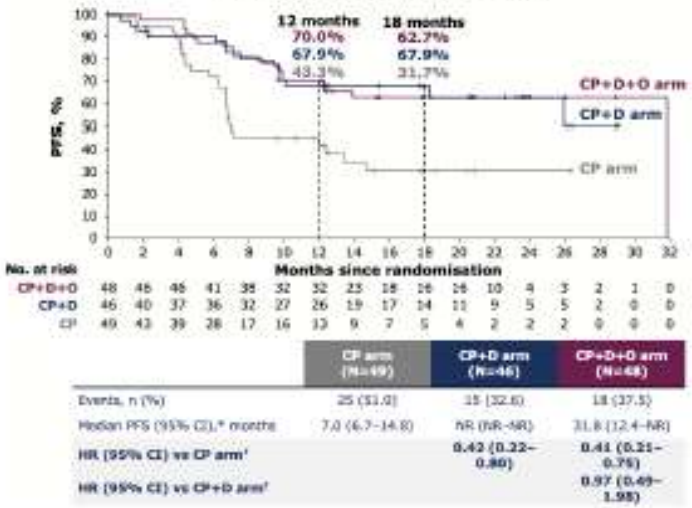


RUBY
HR 0.28
***P*<0.0001**



NRG-GY018
HR 0.30
***P*<0.0001**

dMMR (20% of population)



	CP arm (N=49)	CP+D arm (N=46)	CP+D+O arm (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 CP arm†		0.42 (0.22–0.80)	0.41 (0.21–0.75)
HR (95% CI) vs CP+D arm†			0.97 (0.49–1.98)

DUO-E
HR 0.42
(0.22–0.80)

Mansoor R. Mirza et al. NEJM August 2023,
Ramez N. Eskander et al. NEJM August 2023,
Westin SN *et al. J Clin Oncol* 2024;42:283–99N

SYSTEMIC THERAPY

FIRST LINE SYSTEMIC THERAPY

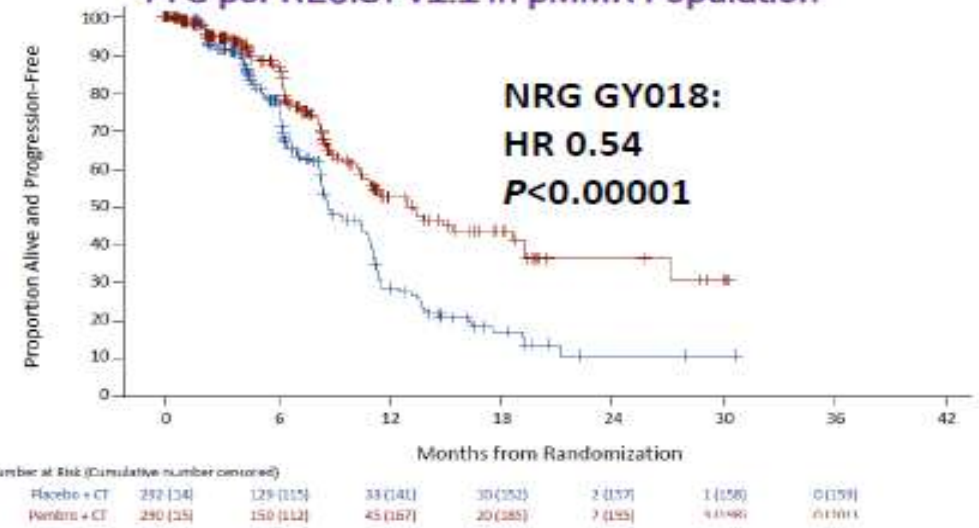
in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- Patients with non-MMRd tumours with rapidly growing/symptomatic disease should be offered carboplatin- paclitaxel chemotherapy [I, A]. The addition of ICI to chemotherapy followed by ICI as maintenance therapy, e.g. dostarlimab or pembrolizumab (drugs mentioned in alphabetical order), or the addition of ICI followed by a combination of ICI and PARPi as maintenance therapy, i.e. durvalumab and olaparib, can be considered [I, B].

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

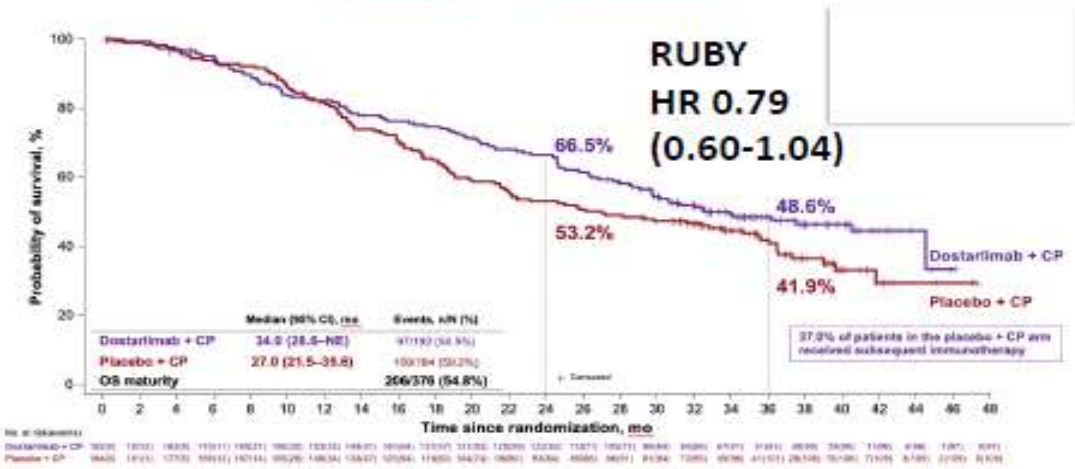
ESGO
European Society of Gynaecological Oncology

PFS per RECIST v1.1 in pMMR Population



ENGOT NSGO CTU GOG

MMRp/MSS Population[a]



pMMR (80% of population)

Eskander R, et al. N Eng J Med. March 2023
Powell, M.A. et al. Annals of Oncology, Volume 35, Issue 8, 726 – 738, 2024;
Westin SN *et al. J Clin Oncol* 2024;42:283–99
www.esgo.org

SYSTEMIC THERAPY

FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

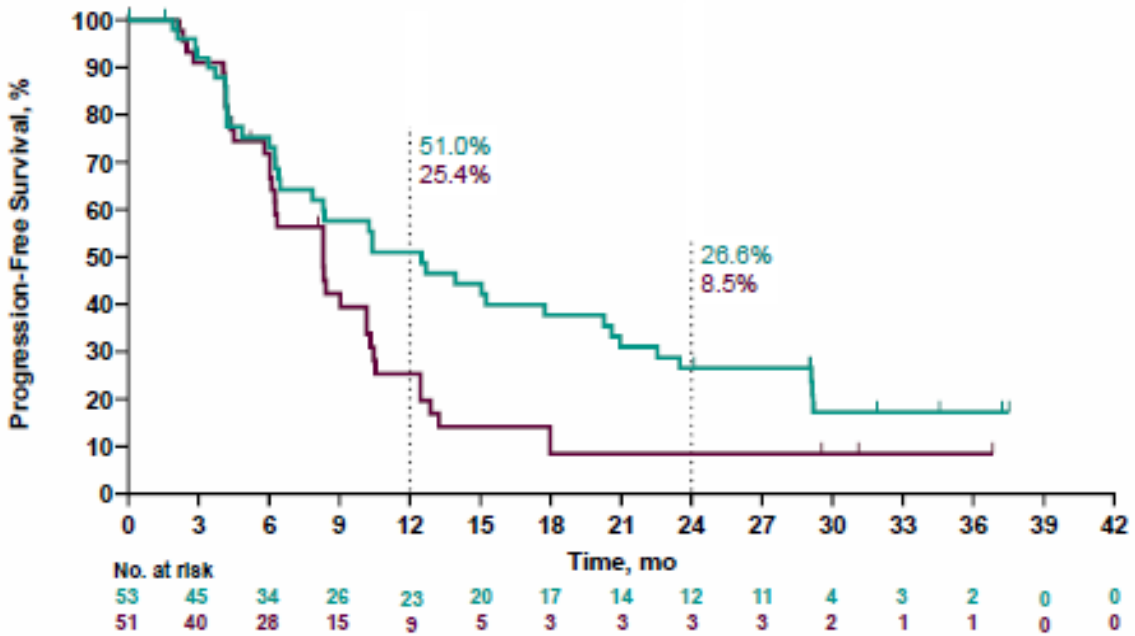
- If chemotherapy is contraindicated, in patients with non-MMRd relapsed disease and with prior chemotherapy in the adjuvant/neoadjuvant setting, a combination of pembrolizumab and the multi-tyrosine-kinase inhibitor lenvatinib may be considered [III, C].

ENGOT-en9/LEAP-001 Progression-Free Survival[a] Improved With LEN/PEMBRO vs TC in Prior Neoadjuvant/Adjuvant Chemotherapy Subgroup

ESGO European Society of Gynaecological Oncology

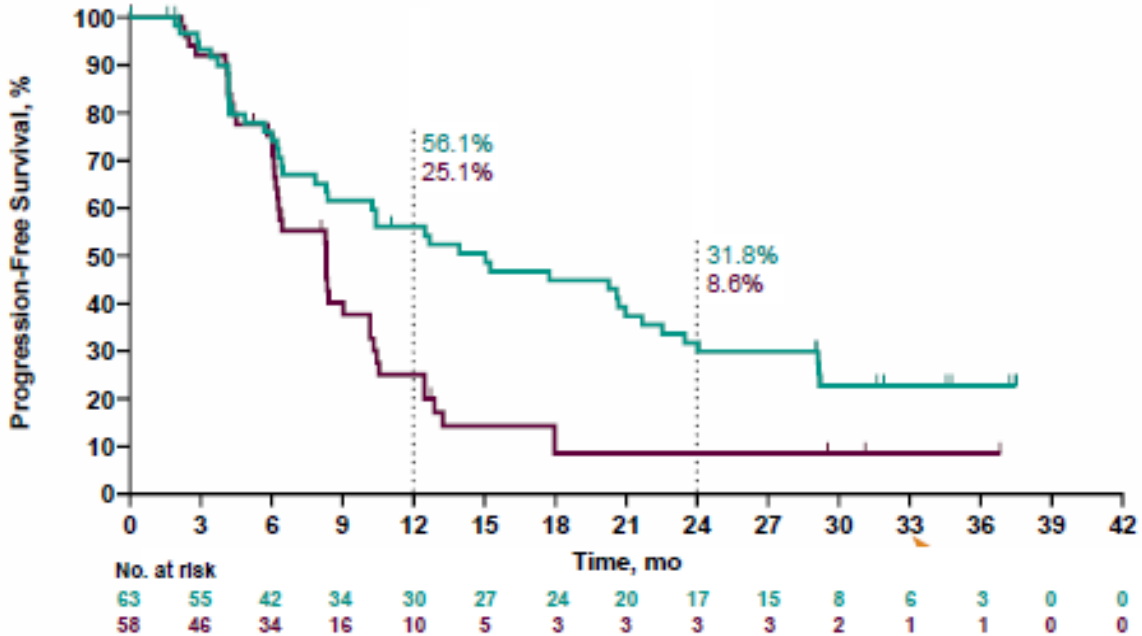
pMMR Population

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	37/53	12.5 (6.5–20.3)	0.60 (0.37–0.97)
TC	35/51	8.3 (6.1–10.2)	



All-comers

	Events, n/N	Median (95% CI), mo	HR (95% CI)
LEN/PEMBRO	42/63	15.0 (8.3–21.0)	0.52 (0.33–0.82)
TC	39/58	8.3 (6.2–10.2)	



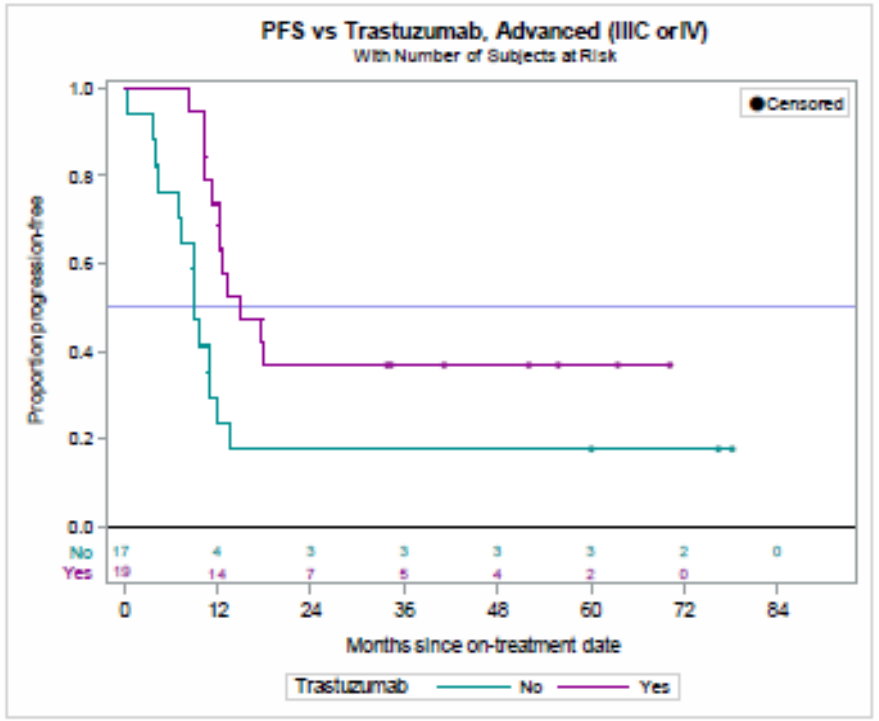
SYSTEMIC THERAPY

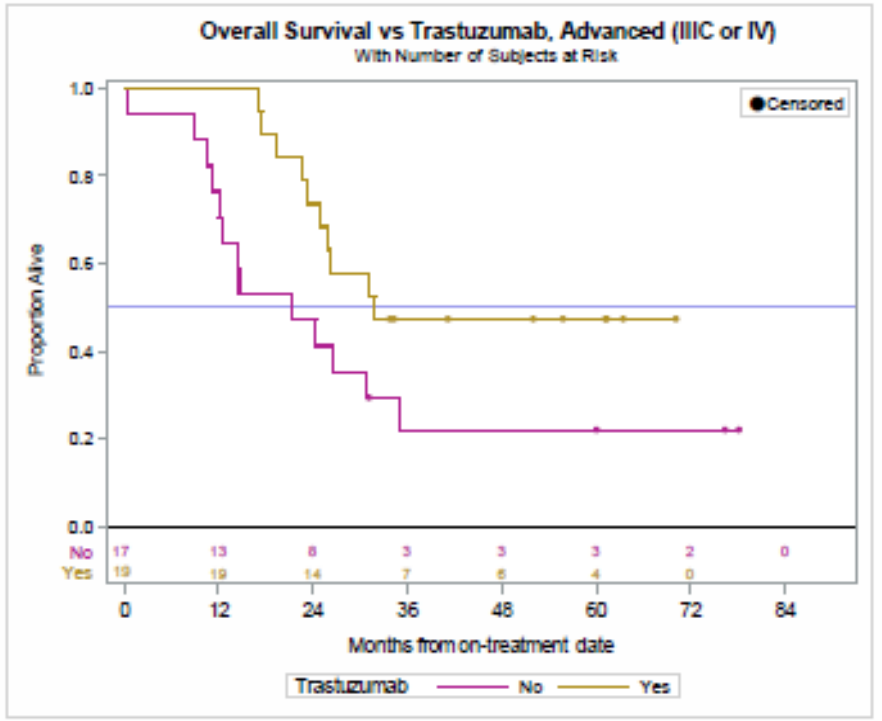
FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- If ICI (± PARPi) is contraindicated, for patients with a HER2 3+ tumour, a combination of carboplatin-paclitaxel plus trastuzumab may be considered [II, B].
- The standard chemotherapy regimen is 6 cycles of carboplatin-paclitaxel [I, A].

Carboplatin/paclitaxel+/-Trastuzumab (NCT01367002)
Updated Survival analysis stage III/IV





In a subset analysis of pts restricted to stage IIIC/IV disease, the addition of trastuzumab (n=17) continued to provide both (*left*) PFS benefit over control (n=19) and OS benefit over control (21.1 versus 31.9 months, HR 0.440 90% CI 0.219-0.882 p=0.0230).

SYSTEMIC THERAPY

FIRST LINE SYSTEMIC THERAPY

in unresectable stage III/IV or recurrent EC with no prior chemotherapy except in the adjuvant setting (including patients with residual disease after surgery)

- In low-grade ER-positive, low volume/asymptomatic advanced or slowly growing recurrent tumours, endocrine therapy is the preferred systemic therapy:
  - Progestins (medroxyprogesterone acetate or megestrol acetate) are recommended [III, A].
  - Alternative options include aromatases inhibitors, and tamoxifen [IV, C].

Open Questions…

- Are all POLE variants qualified as POLEmut EC?
- Which is the cut-off to define HR positive status in EC?
- Which is the prognostic role of focal LVSI? Which is the optimal clinical threshold?
- How to consider EC confined to polyp/endometrium with no myoinvasion?
- How to treat stage III/IVA POLEmut EC?
- Which is the best treatment option for advanced/recurrent non dMMR EC?

Take Home Messages

- New Endometrial Cancer FIGO staging system integrates tumor biology/molecular classification
- New FIGO staging system identifies treatment-relevant groups in order to customize the medical strategy for our patients
- There are still some ‘grey areas’ which need further investigation
- In advanced/recurrent setting immune-checkpoint inhibitors are paving the present and the future of EC

THE NEW FIGO CLASSIFICATION HAS COMPLETELY CHANGE THE MEDICAL PERSPECTIVE ON ENDOMETRIAL CANCER AND WE ARE STILL LEARNING..

Thank you!