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Molecular Profiling in Endometrial Cancer: Pay More Now, Save More Later?

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GART
Advanced Radiation Therapy

ENDOMETRIAL CANCER TIMELINE

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2025 **New ESGO guidelines**

TGCA and Surogate Markers in Endometrial Cancer

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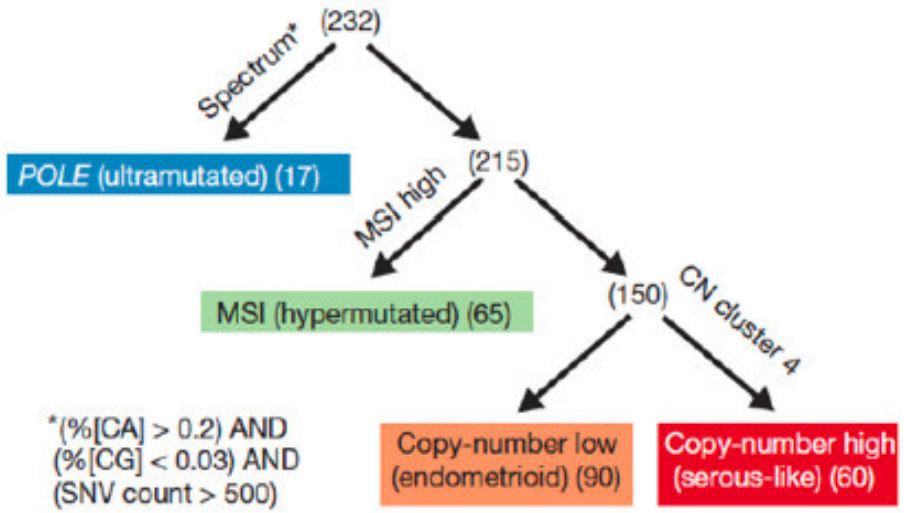
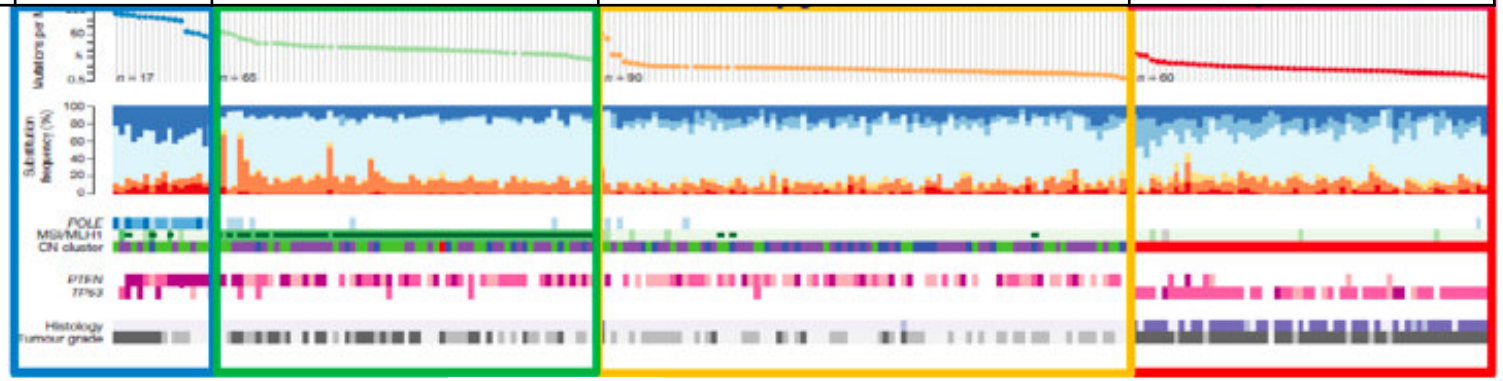
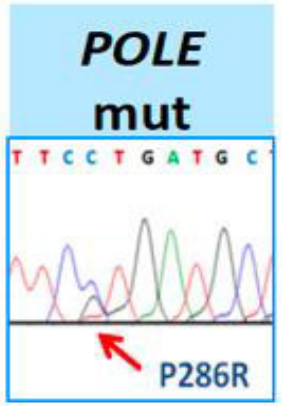
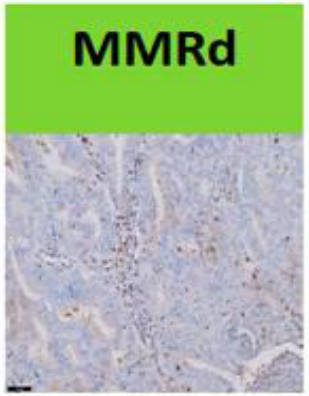
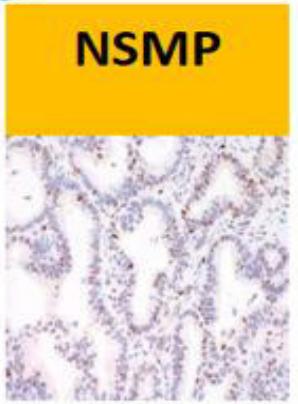
	POLE	dMMR	NSMP	P53mutant
Estimated prevalence	5-15%	25-30%	30-40%	5-15%











1. **Immunohistochemistry** for p53 and mismatch repair proteins
2. **DNA sequencing** for POLE exonuclease domain mutations

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

COST OF MOLECULAR CLASSIFICATION

Testing strategy	Components	Estimated cost (USD / EUR)*
IHC only	MMR / p53 / ER / PR	~$200–400
IHC + NGS panel	MMR + p53 + NGS for POLE, TP53, etc.	~$800–1500
IHC + FPG500	MMR + p53 + FPG500 (XCLARINS)	~$2500–4000

IN ITALY	Components*
IHC only	200 €
IHC + NGS panel	2.000-4.000 €
IHC + FPG500 (XCLARINS)	>1.500 €

**Estimates based on published cost-effectiveness literature; actual costs vary by region/institution*

How the new molecular classification guides treatment decisions in clinical practice

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To define risk classes → **Tailoring adjuvant of treatment (according to 2025 guidelines)**

To guide treatment tailoring for advanced / first-line / recurrent disease (since 2022)

How the new molecular classification guides treatment decisions in clinical practice

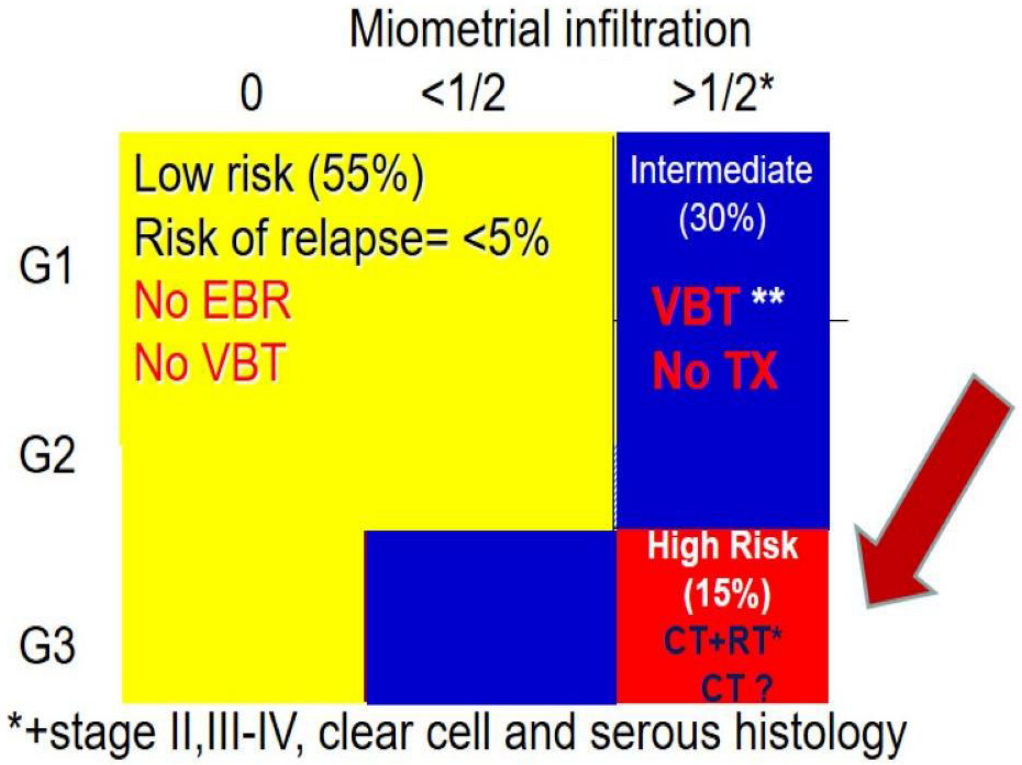
To define risk classes → Tailoring of adjuvant treatment (according to 2025 guidelines)

To guide treatment tailoring for advanced / first-line / recurrent disease (since 2022)

Risk factors and Adjuvant treatment in EC (ESGO-ESMO-ESTRO 2016)

Low	• Stage I Endometrioid + gr 1-2 + <50% myometrial invasion + LVSI neg	
Low Inter	• Stage I Endometrioid + gr 1-2 + ≥50% myometrial invasion + LVSI neg	
High Inter Risk	• Stage I Endometrioid + gr 3 + <50% myometrial invasion, regardless of LVSI status • Stage I Endometrioid + gr 1-2 + LVSI unequivocal positive, regardless of depth of invasion	I II
High Risk	• Stage I Endometrioid + gr 3 + ≥50% myometrial invasion, regardless of LVSI status • Stage II & stage III no residual disease • Non endometrioid (serous or clear cell or undifferentiated carcinoma, carcinosarcoma)	I I I
Adv M+	• Stage III residual disease & IVa • Stage IVB	I I

FIGO 2009 staging used
Molecular factors were considered but not included
Tumor size was considered but not included
Nodal status may be considered for treatment recommendations



**Considered EBRT if G3 or LVI + and no nodal staging

ESGO-ESTRO-ESP GUIDELINES 2021

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Risk Group	Molecular Classification Unknown	Molecular Classification Known[Δ,*]
Low	• Stage IA endometrioid + low-grade** + LVSI negative or focal	• Stage I-II ***POLE*mut** endometrial carcinoma, no residual disease • Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal
Intermediate	• Stage IB endometrioid + low-grade** + LVSI negative or focal • Stage IA endometrioid + high-grade** + LVSI negative or focal • Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	• Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade** + LVSI negative or focal • Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade** + LVSI negative or focal • Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High-intermediate	• Stage I endometrioid + substantial LVSI, regardless of grade and depth of invasion • Stage IB endometrioid high-grade**, regardless of LVSI status • Stage II	• Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI, regardless of grade and depth of invasion • Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade**, regardless of LVSI status • Stage II **MMRd/NSMP** endometrioid carcinoma
High	• Stage III-IVA with no residual disease • Stage I-IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	• Stage III-IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease • Stage I-IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease • Stage I-IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced Metastatic	• Stage III-IVA with residual disease • Stage IVB	• Stage III-IVA with residual disease of any molecular type • Stage IVB of any molecular type

Less data in the ADVANCED stage for POLE; unable to advice; clincial trial or data collection when possible.

First integration of histopathological and molecular features in risk groups:

- POLE good
- MMRd & NSMP intermediate
- P53 poor

Shifts in historical risk groups:

Shift from high to high-intermediate
- Endometrioid stage I grd3 & II; substantial LVSI

Shift from high-intermediate to intermediate
- Endometrioid low-grade IB and high-grade IA Shift from intermediate to low

Concin N, et al. Int J Gynecol Cancer. 2021;31(1):12-39; Oaknin A, et al. Ann Oncol. 2022;33(9):860-877.

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ENDOMETRIAL CANCER TIMELINE

2020

Risk Stratification (**molecular**)

+

FIGO 2009

I	The tumor is confined to the corpus uteri
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invades the cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA	Tumor invades serosa of the corpus uteri and/or adnexae
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastasis to pelvic or para-aortic lymph nodes
IIIC1	Pelvic lymph node involvement
IIIC2	Para-aortic lymph node involvement, with or without pelvic node involvement
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion bladder mucosa and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

=

FIGO 2023

	FIGO 2023[3]
Stage I	Tumor confined to the uterine corpus and ovary
Stage IA	Confined to the endometrium OR non-aggressive histological type with MI < 50% with no substantial LVSI OR good prognosis disease
Stage IA1	Non-aggressive histological type confined to the endometrium or limited to a polyp
Stage IA2	Non-aggressive histological type with MI < 50% with no substantial LVSI
Stage IA3	Low-grade endometrioid EC limited to the uterine corpus and ovary
Stage IAm $_{POLE\ MUT}$	POLE mut EC, confined to the uterus, regardless histology and degree of LVSI
Stage IB	Non-aggressive histological type with MI ≥ 50%, with no extensive LVSI
Stage IC	Aggressive histological type confined to the endometrium or limited to a polyp
Stage II	Non-aggressive histological type with substantial LVSI
Stage IIA	Non-aggressive histological type with cervical stromal involvement
Stage IIB	Non-aggressive histological type with substantial LVSI
Stage IIC	Aggressive histological type with any myometrial involvement
Stage IICm p53 $_{abn}$	p53 abn EC, confined to the uterus, regardless of histology and degree of LVSI
Stage III	Local/regional spread
Stage IIIA	Serous of the corpus uteri and/or adnexa
Stage IIIA1	Adnexal involvement (except when meeting stage IA3 criteria)
Stage IIIA2	Subserosa or serosal involvement
Stage IIIB	Vaginal and/or parametrial and/or pelvic peritoneum involvement
Stage IIIB1	Vaginal and/or parametrial involvement
Stage IIIB2	Pelvic peritoneum involvement
Stage IIIC	Positive pelvic and/or para-aortic nodes
Stage IIIC1	Positive pelvic nodes
Stage IIIC1i	Positive pelvic nodes (micrometastasis)
Stage IIIC1ii	Positive pelvic nodes (macrometastases)
Stage IIIC2	Positive para-aortic nodes (up to the renal vessels)
Stage IIIC2i	Positive para-aortic nodes (micrometastasis)
Stage IIIC2ii	Positive para-aortic nodes (macrometastases)
Stage IV	Tumor invades bladder and/or bowel mucosa and/or distant metastases
Stage IVA	Tumor invades bladder and/or bowel mucosa
Stage IVB	Abdominal peritoneal (extra-pelvic) metastases
Stage IVC	Distant metastasis, including extra- and intra-abdominal nodes above the renal vessels, lungs, liver, and other organs

Stage shifts according to the 2009 and 2023 FIGO staging system

519 patients
123 (23.7%) Upstage
20 (3.9%) Downstage

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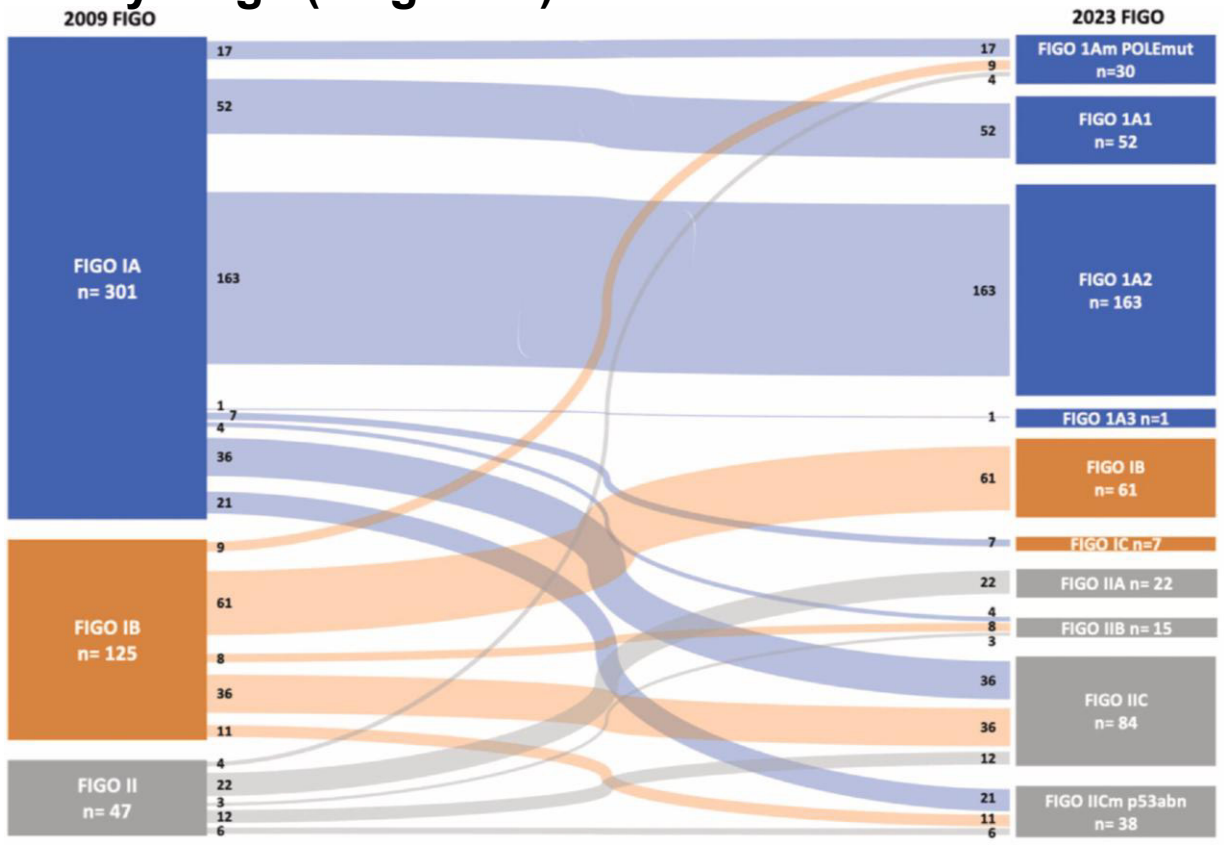
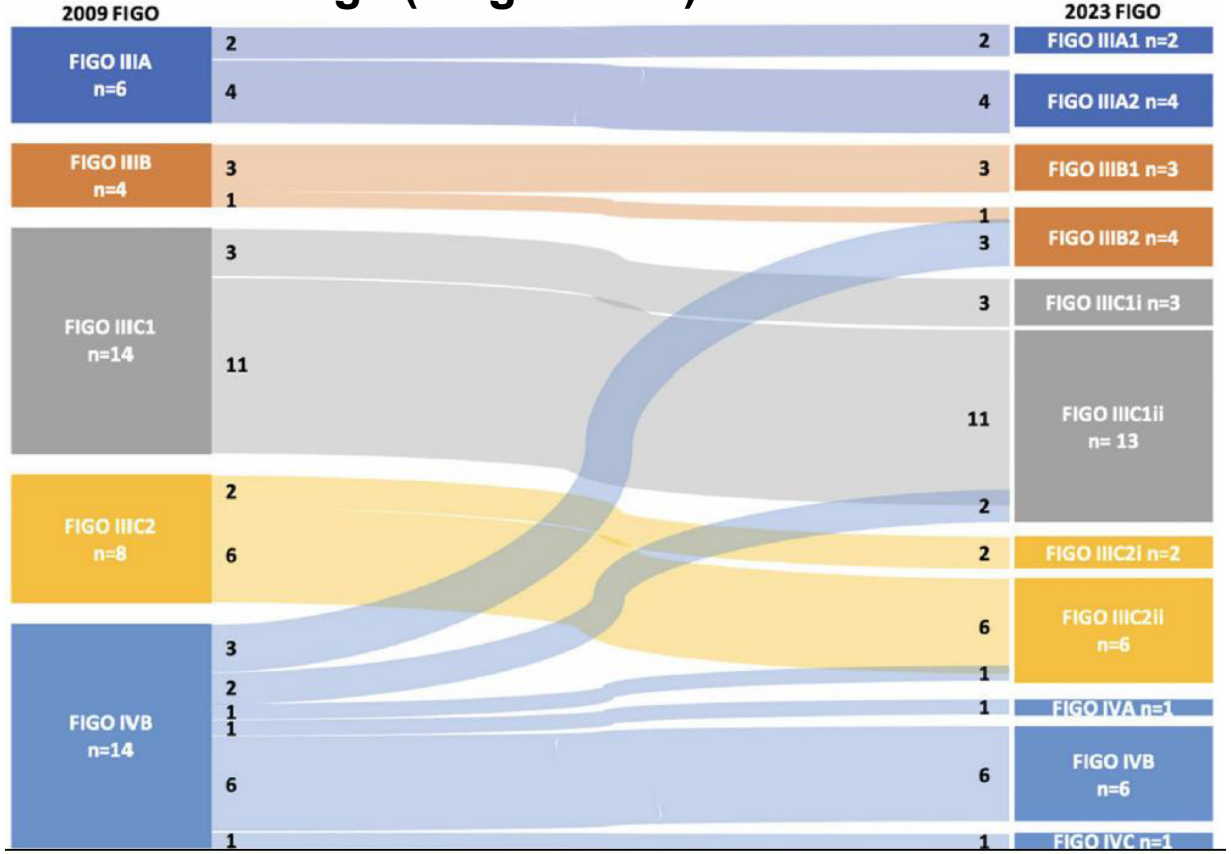
Early stage (stages I/II)



	All patients	All shift	Upstage shift	Downstage shift
Early-Stage EC	473	136 (28.8%)	123 (26.0%)	13 (2.7%)

Advanced stage (stages III/IV)



	All patients	All shift	Upstage shift	Downstage shift
Advanced-Stage EC	46	7 (15.2%)	0	7 (15.2%)

Schwameis R. et al. EJC 2023

2023 FIGO staging[π]			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						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Risk Groups

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

2023 FIGO stage IIC carcinomas other than p53 abnormal are not depicted in this table.

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).

*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 *low-grade* endometrioid carcinomas of both the endometrium + ovary, only 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

Remi Nout, ESGO 2025

Definition of RISK GROUPS

FIGO Staging 2023

Molecular Classification & ER

	Overall 5-Year Risk of Recurrence
Low Risk	< 8%
Intermediate Risk	8-15%
High-intermediate Risk	15-25%
High Risk	> 25%

Unpublished data from patients included in all PORTEC studies

LOW RISK endometrial cancer

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			**	
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						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

This includes the following categories:

- **IA1m NSMP high-grade/ER-neg or p53abn**
- **ICm NSMP high-grade/ER-neg or p53abn**

Uncertain risk

Limited data suggesting that the risk of recurrence is higher than for low-risk carcinomas.

Adjuvant therapy is generally not recommended [IV, C]

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INTERMEDIATE RISK endometrial cancer

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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			**	
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				
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						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

Intermediate Risk

Vaginal brachytherapy [I, A]

No adjuvant treatment [III, C] especially for patients **under 60 years of age** and/or **low grade** [II, A]

This includes the following categories:

- **FIGO 2023 stage IBm MMRd, NSMP: low-grade +ERpos**
- **FIGO 2023 stage IIAm NSMP: low-grade+ERpos**
- **FIGO 2023 IICm MMRd, with myoinvasion (regardless of depth of myometrial invasion), without cervical stromal invasion and without substantial LVSI**

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HIGH-INTERMEDIATE RISK endometrial cancer

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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			**	
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			**	
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				
			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					
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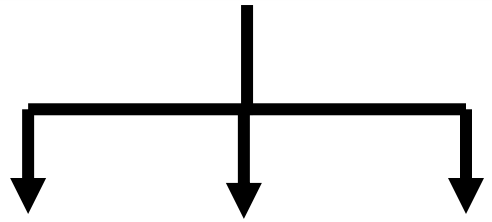
IV	**Locally advanced and/or metastatic disease**						
IVA		Invasion of the mucosa and/or the intestinal mucosa					
	Metastatic disease or residual disease after surgery						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					

High-Intermediate Risk



EBRT	Vaginal BRT*	No ADJ**
[II, A]	[II, B]	[IV, B]

*especially for **pN0**
[II, B]

especially for **pN0, **without substantial LVSI and low-grade disease**
[IV, B]

This includes the following categories:

- **FIGO 2023 stage IIAm MMRd**
- **FIGO 2023 stage IIBm MMRd, NSMP low-grade+ERpos**
- **FIGO 2023 stage IICm MMRd with cervical invasion (independent of LVSI) or with substantial LVSI**

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Journal of Clinical Oncology®

Molecular Classification Predicts Response to Radiotherapy in the Randomized PORTEC-1 and PORTEC-2 Trials for Early-Stage Endometrioid Endometrial Cancer

Nanda Horeweg, MD, PhD[1]; Remi A. Nout, MD, PhD[1,2]; Ina M. Jürgenliemk-Schulz, MD, PhD[3]; Ludy C.H.W. Lutgens, MD, PhD[4]; Jan J. Jobsen, MD, PhD[5]; Marie A.D. Haverkort, MD[6]; Jan Willem M. Mens, MD[2]; Annerie Slot, MD[7]; Bastiaan G. Wortman, MD, PhD[1,8]; Stephanie M. de Boer, MD, PhD[1]; Ellen Stelloo, PhD, MSc[9]; Karen W. Verhoeven-Adema, PhD[10]; Hein Putter, PhD[11]; Vincent T.H.B.M. Smit, MD, PhD[9]; Tjalling Bosse, MD, PhD[9]; and Carien L. Creutzberg, MD, PhD[1]; for the PORTEC Study Group

Large, randomized radiotherapy trials in women with early- stage endometrioid EC.

PORTEC-1

- Total: 484 patients included
- Compared **pelvic EBRT with no adjuvant therapy** in early-stage intermediate-risk EC
-No Brachytherapy

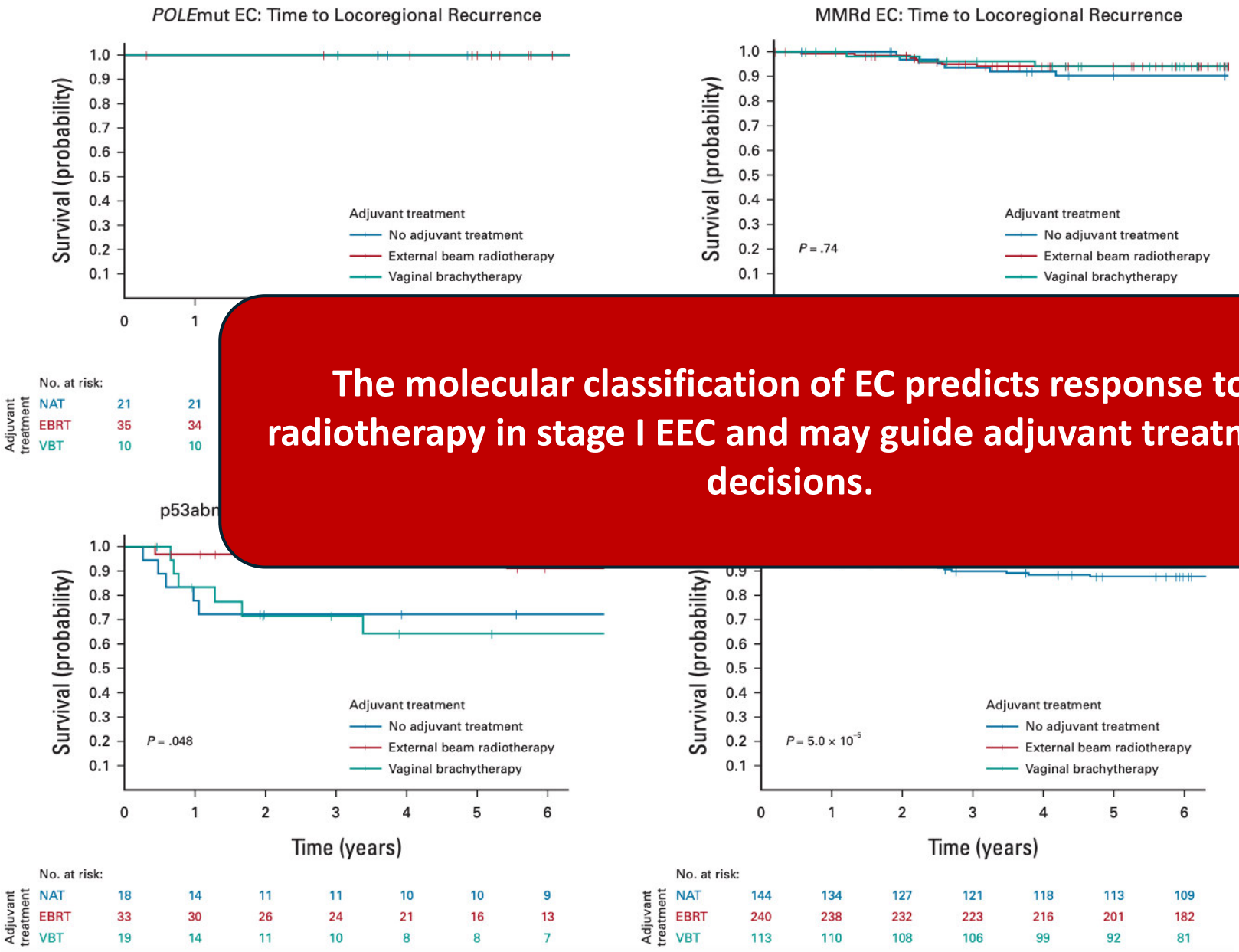
Creutzberg et al, I. J. Radiation Oncology, 2009

PORTEC-2

- Total: 396 patients included
- Compared **vaginal brachytherapy versus pelvic external beam radiotherapy** in early-stage high-intermediate-risk EC

Nout et al, Lancet 2010

	*POLE*mut EC	MMRd EC	p53abn EC	NSMP EC	Total
PORTEC-1 and PORTEC-2: locoregional recurrence-free survival					
EBRT (n = 434)	No events	94.2 (90.1 to 98.5)	96.9 (91.0 to 100)	98.3 (96.6 to 100)	97.1 (95.5 to 98.7)
VBT (n = 197)	No events	94.2 (87.9 to 100)	64.3 (44.8 to 92.3)	96.2 (92.7 to 99.9)	93.0 (89.4 to 96.7)
NAT (n = 249)	No events	90.3 (83.2 to 98.0)	72.2 (54.2 to 96.2)	87.7 (82.4 to 93.4)	88.3 (84.3 to 92.5)
All (N = 880)	No events	93.1 (89.9 to 96.4)	81.6 (72.6 to 91.6)	94.8 (92.8 to 96.8)	93.7 (92.1 to 95.4)
P	—	.74	.048	5.0×10^{-5}	.0001



The molecular classification of EC predicts response to radiotherapy in stage I EEC and may guide adjuvant treatment decisions.

POLEmut EC:

- At 5 years, no locoregional recurrences were observed.
- **Omitting radiotherapy seems to be safe in POLEmut EC**.

MMRd EC:

EBRT and VBT yielded a small, non significant benefit compared with no adjuvant therapy.

p53abn EC:

- High risk of recurrence
- **EBRT is recommended**

NSMP EC:

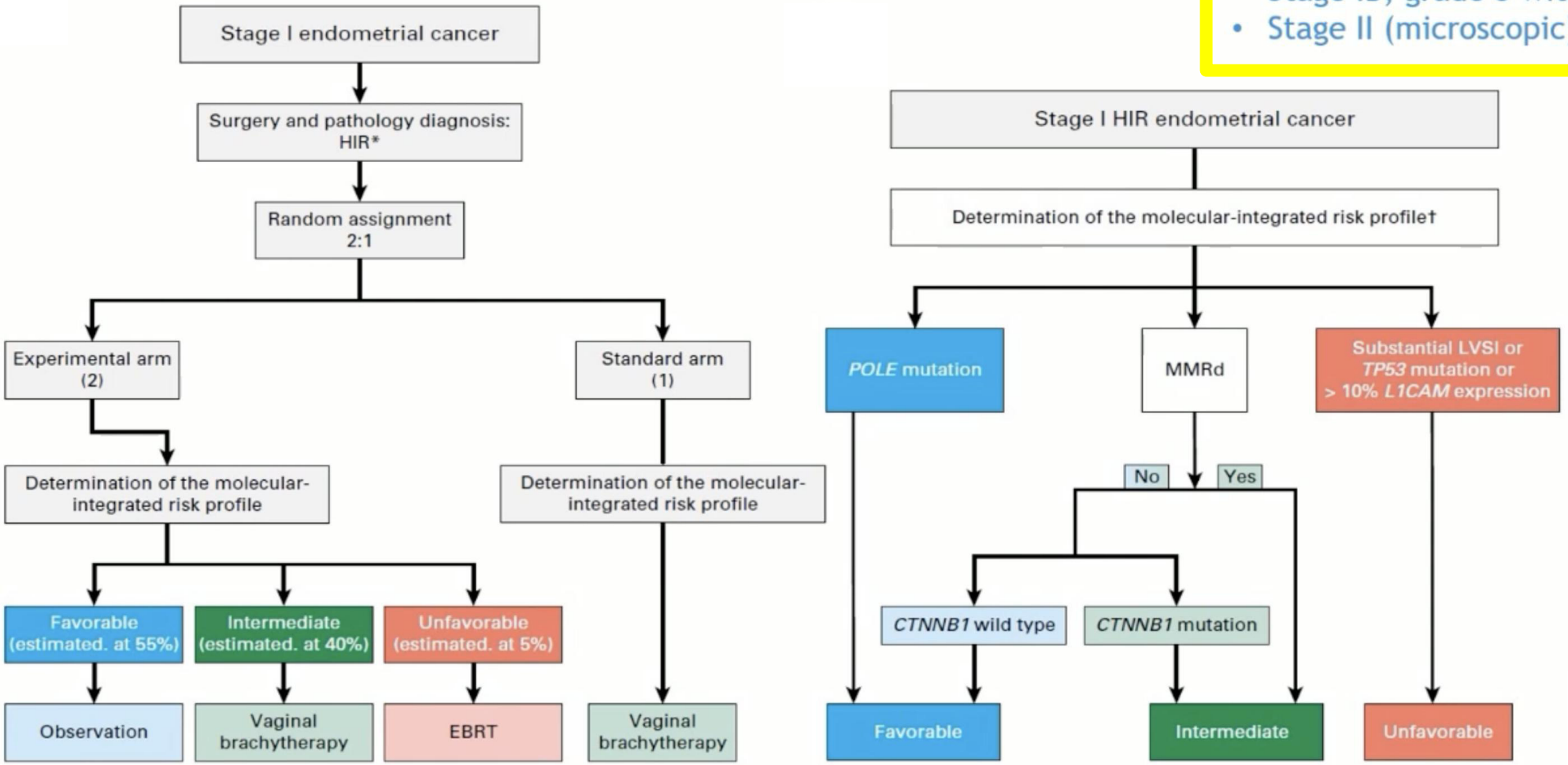
- Significant benefit from adjuvant radiotherapy
- **VBT is the treatment of choice** as it is as effective as EBRT but has a much milder toxicity profile.

PORTEC-4a: an international randomised trial

Design PORTEC-4a trial 2016-2021

(High)intermediate risk (FIGO 2009 stage):

- Stage IA (with invasion), grade 3 (any age, irrespective of LVSI
- Stage IB, grade 1-2 and age ≥60 years
- Stage IB, grade 1-2 with LVSI
- Stage IB, grade 3 without LVSI
- Stage II (microscopic), grade 1



Wortman et al, Gyn Onc, 2018; Van den Heerik et al, UGC, 2020

PORTEC-4a: an international randomised trial

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MODERN RADIATION ONCOLOGY
35° RESIDENTIAL COURSE

Hypothesis and aims

Molecular-integrated profile-based individualised adjuvant treatment reduces over- and undertreatment in patients with HIR-EC

Primary endpoint

- 5-year cumulative incidence of vaginal recurrence

Secondary endpoints

- Recurrence-free and overall survival
- Vaginal tumour control
- Pelvic, locoregional and distant recurrence
- Adverse events. and Quality.of.life
- EC related healthcare costs

Wortman et al, Gyn Onc, 2018; Van den Heerik et al, UGC, 2020

PORTEC-4a: Recurrence Rate

Standard Arm *vs* Molecular-profile Arm

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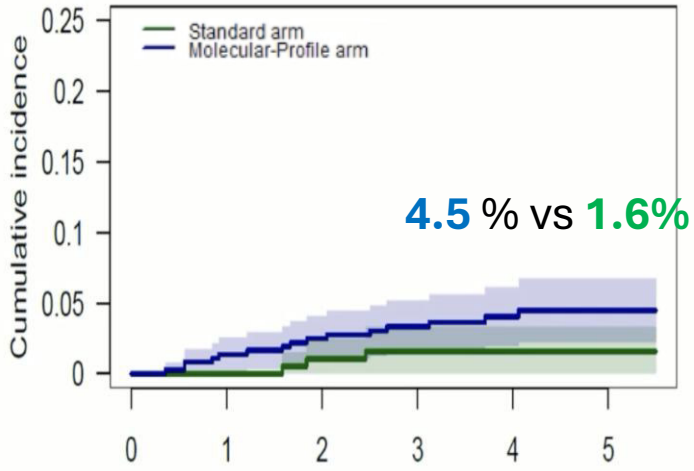
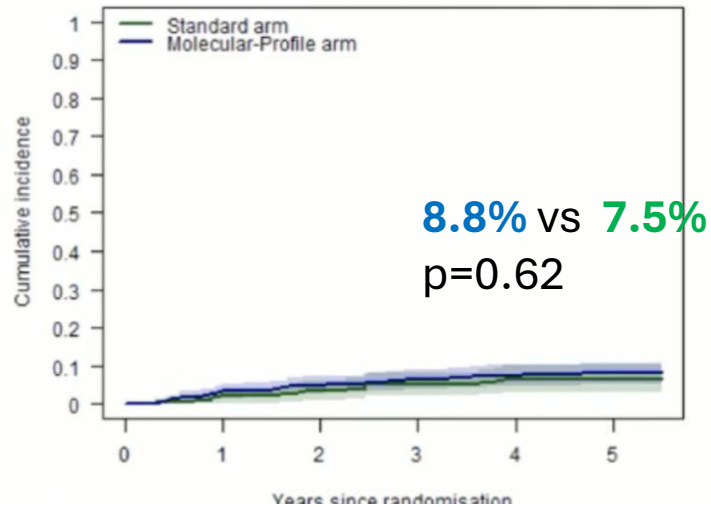
Vaginal recurrence



4.5 % vs **1.6%**

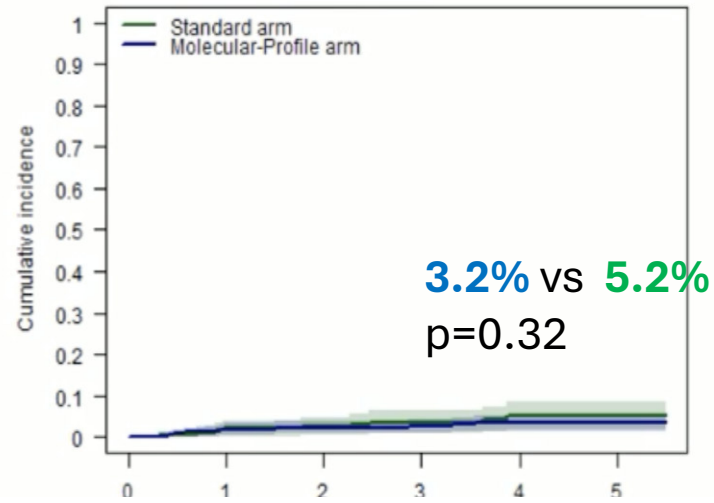
- **No difference in vaginal and locoregional tumour control**
- **Molecular-profile based treatment is non-inferior to standard VBT**

Locoregional recurrence



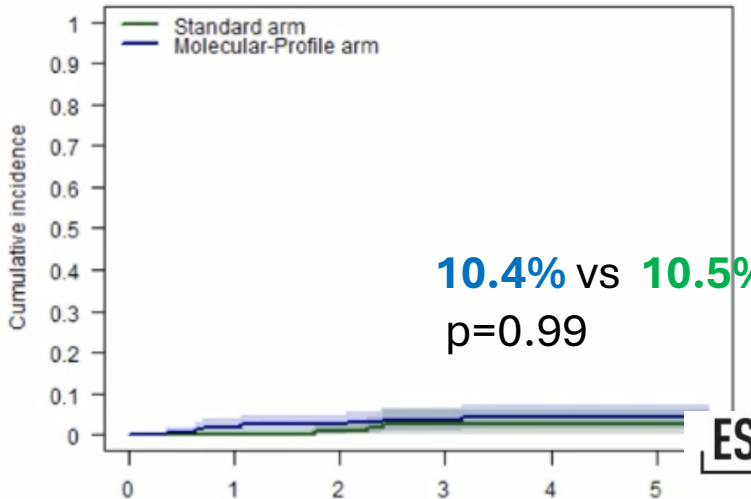
8.8% vs **7.5%**
p=0.62

Pelvic recurrence



3.2% vs **5.2%**
p=0.32

Distant recurrence



10.4% vs **10.5%**
p=0.99

ESTRO 2025

PORTEC-4a: Recurrence-free and overall survival

Standard Arm *vs* Molecular-profile Arm

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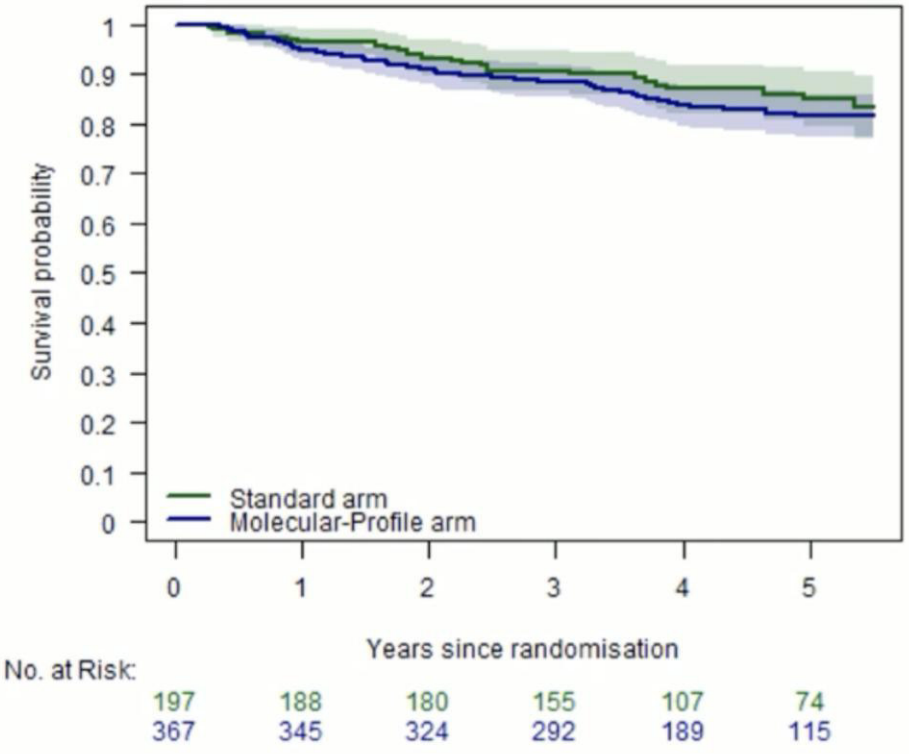
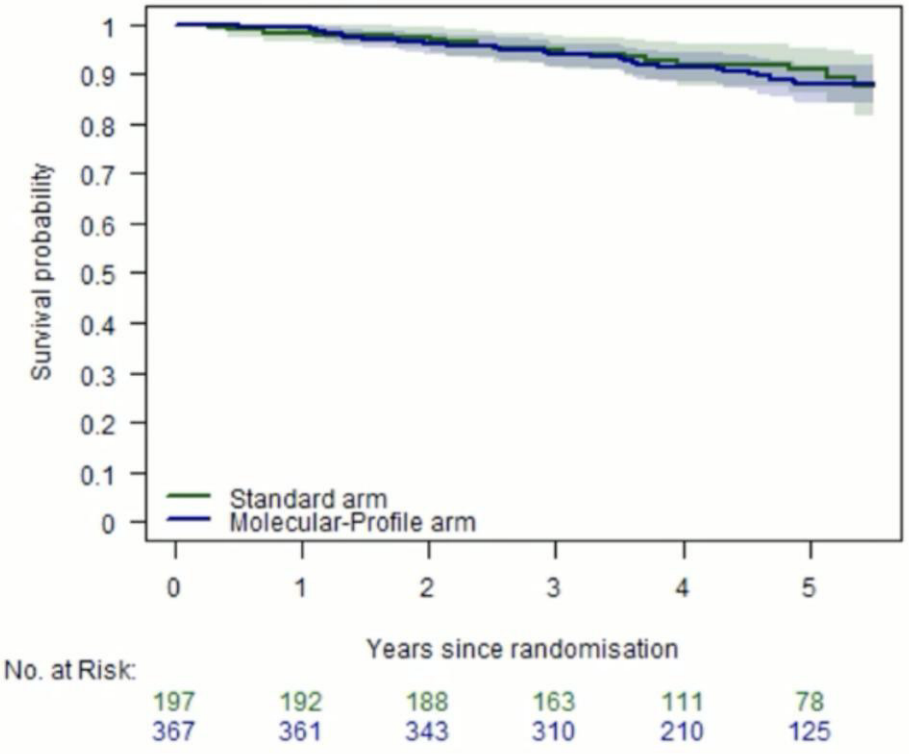
Recurrence-free survival



81.7% vs 85.1% (*p*=0.36)

Overall survival



88.0% vs 90.9% (*p*=0.34)

ESTRO 2025

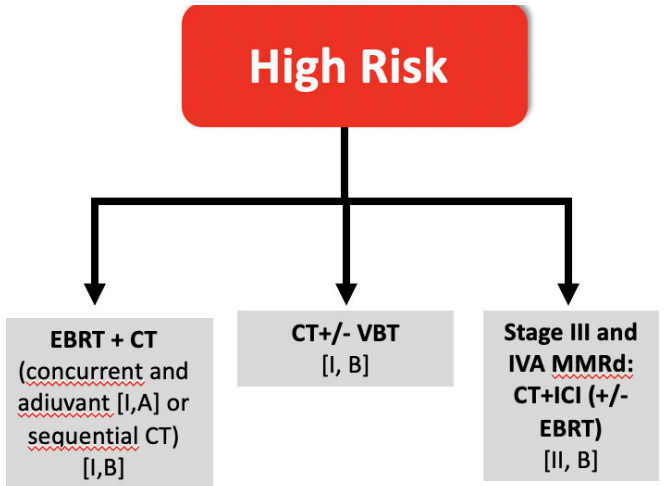
PORTEC-4a trial

Conclusions

- First trial to provide prospective evidence on a molecular-profile based adjuvant treatment for women with HIR-EC
- Individualised adjuvant treatment is non-inferior to standard VBT
  - **No difference in vaginal and locoregional tumour control and survival**
  - **Toxicity was low in both arms**
- Omitting adjuvant treatment is safe for patients with a favourable profile
  - **Almost half of HIR-EC patients can be spared the burden of adjuvant treatment**
- Molecular profile based EBRT improves locoregional control for the patients with an unfavourable profile

HIGH RISK endometrial cancer

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	IBm *POLE*mut			**	IICm p53abn
IC		High-grade histologies^, limited to polyp/endometrium	ICm *POLE*mut				
II	**Confined to the uterus**						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IIAm *POLE*mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IIBm *POLE*mut			**	IICm p53abn
IIC		High-grade histologies^, myoinvasion	IICm *POLE*mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IICm *POLE*mut	Myoinvasion ≥50%, no/focal LVSI			
			IICm *POLE*mut	Cervical stromal invasion, no/focal LVSI			
			IICm *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						
III/IVA		With residual disease					
IVB		Peritoneal metastasis beyond the pelvis					
IVC		Distant metastasis					



This includes the following categories:

- **FIGO 2023 stages IA2, IA3, IBm NSMP high-grade/ERneg, p53abn**
- **FIGO 2023 stages IIm (IIA, IIB, IIC) NSMP high-grade/ERneg, p53abn**
- **FIGO 2023 stage IIIm (IIIA, IIIB, IIIC) MMRd, NSMP low-grade+ERpos, NSMP high-grade/ERneg, p53abn**
- **FIGO 2023 stage IVAm MMRd, NSMP low-grade+ERpos, NSMP high-grade/ERneg, p53abn**

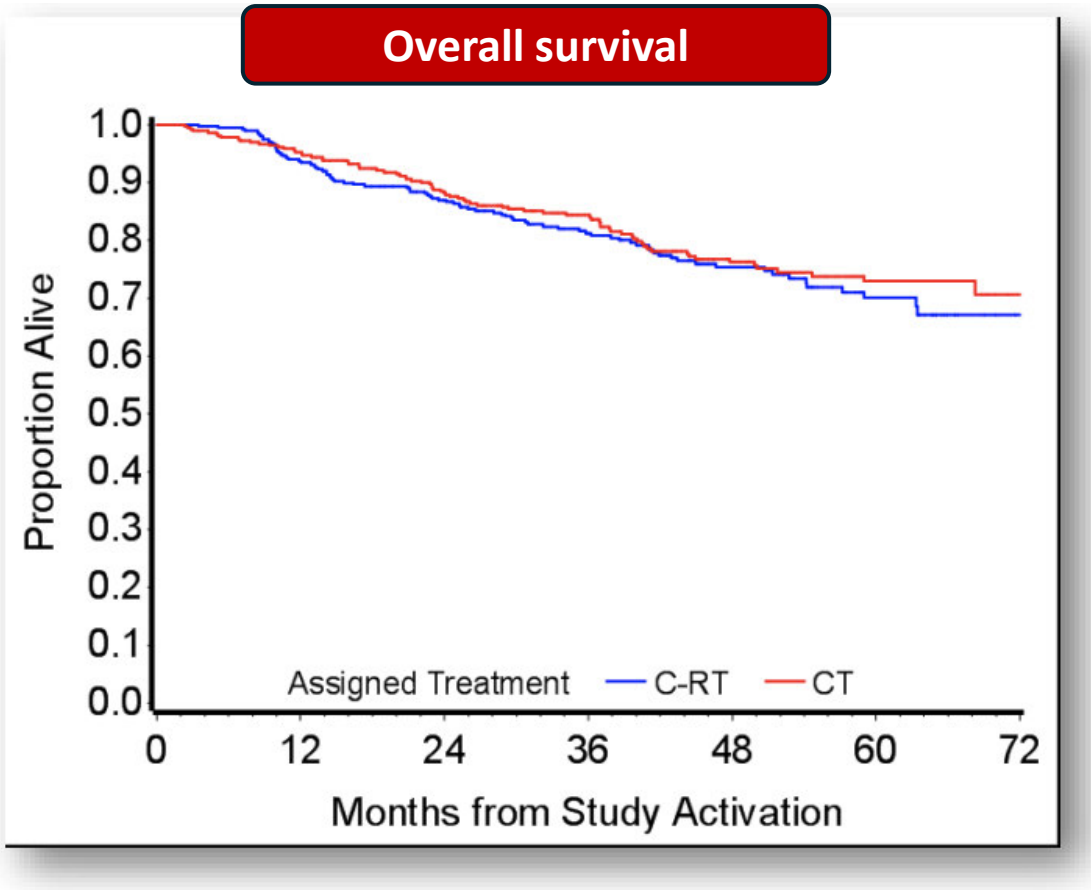
Antonio González-Martín, ESGO 2025

Do we need radiotherapy at all?

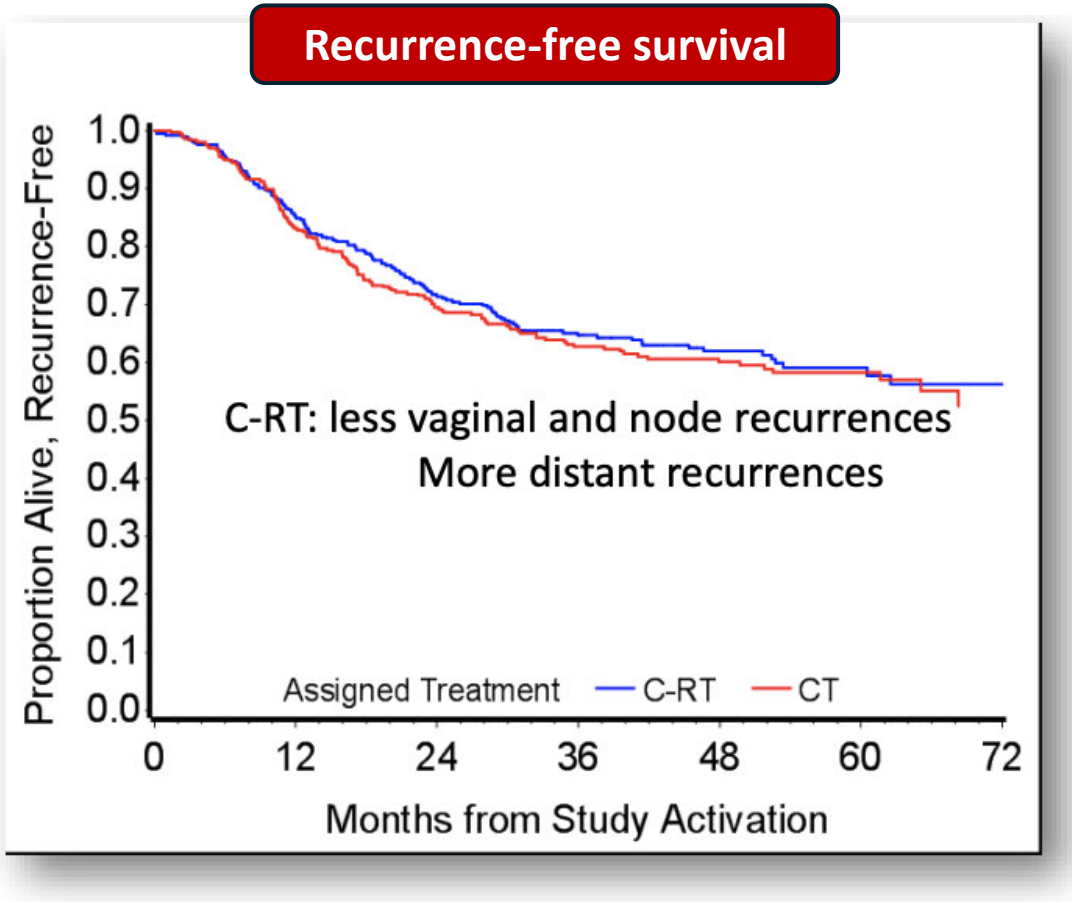
GOG 258: C-RT vs CT

Stage III or IV A (IIIC 75%)
or
Stage I-II Clear/UPSC

Overall survival



Recurrence-free survival



Matei D. et al., N Engl J Med, 2019

ENGOT-en11/GOG-3053/KEYNOTE-B21 Study Design

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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)

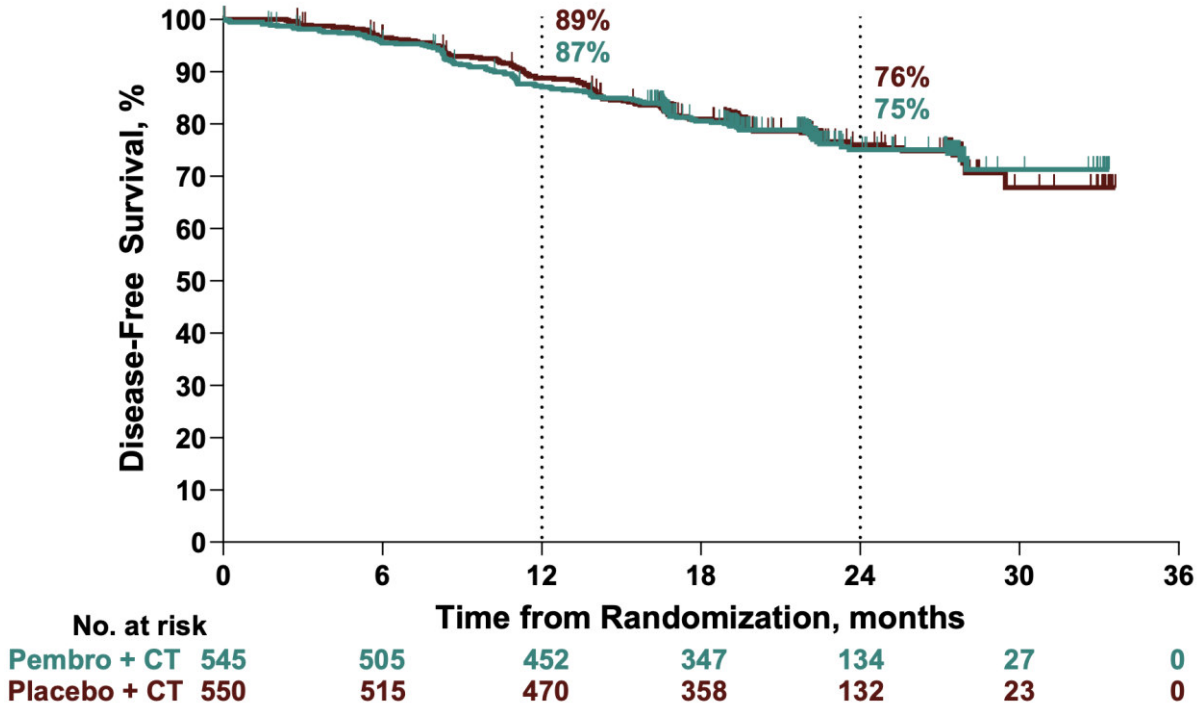
Dual primary endpoints

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

T Van Gorp et al., Ann Oncol., 2024

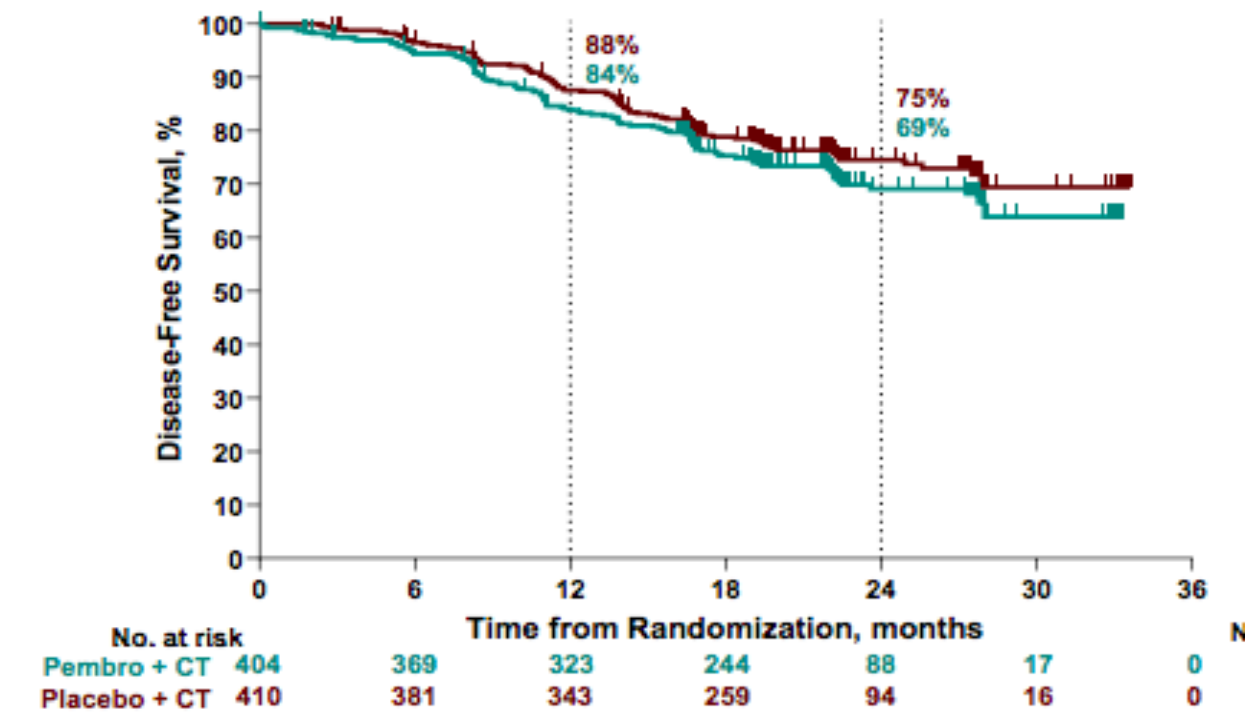
Pembrolizumab plus Chemotherapy and DFS

ITT Population



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

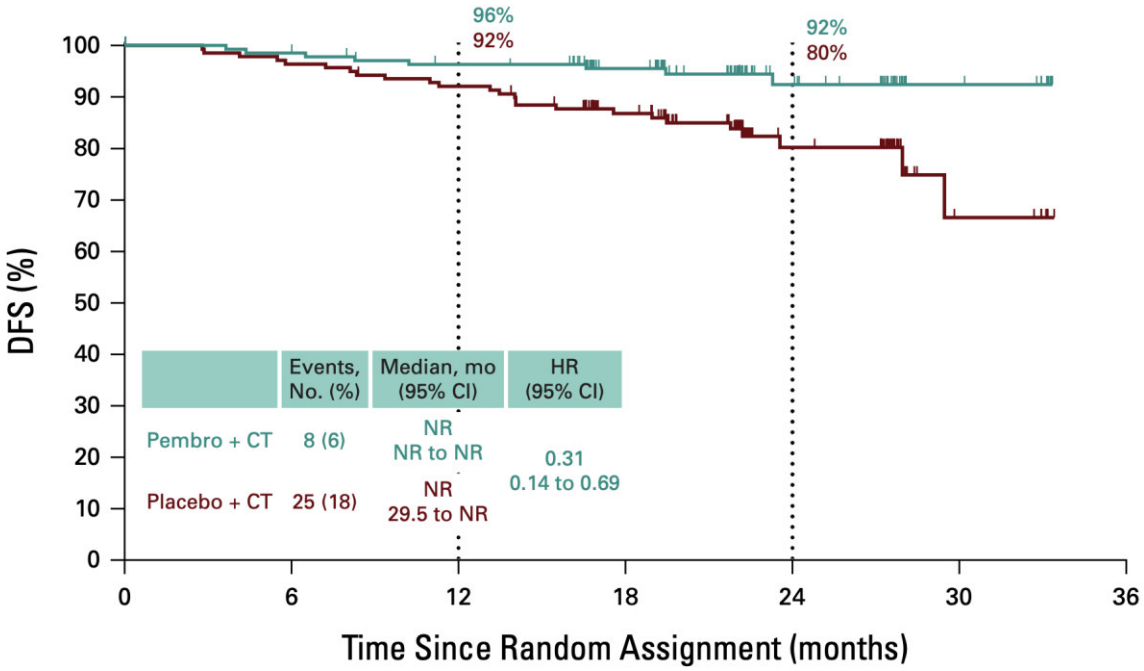
pMMR Population

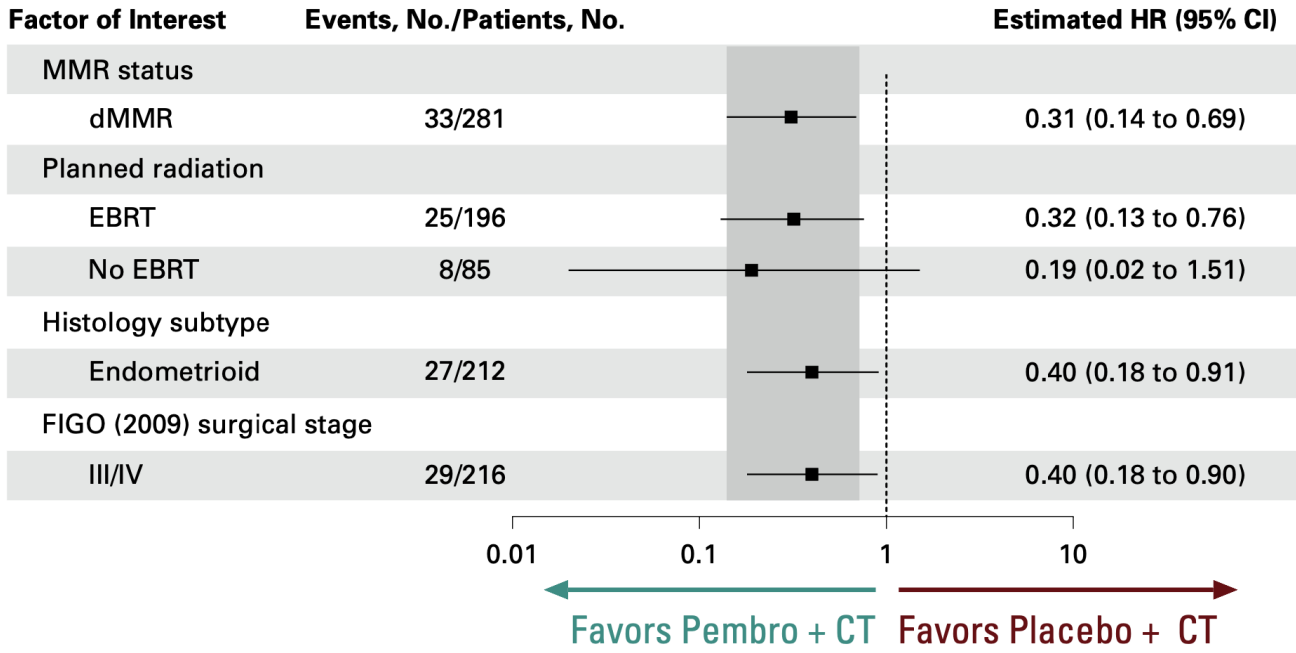


	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembro + CT	111 (27)	NR (NR–NR)	1.20 (0.91–1.57)
Placebo + CT	96 (23)	NR (NR–NR)	

T Van Gorp et al., Ann Oncol., 2024

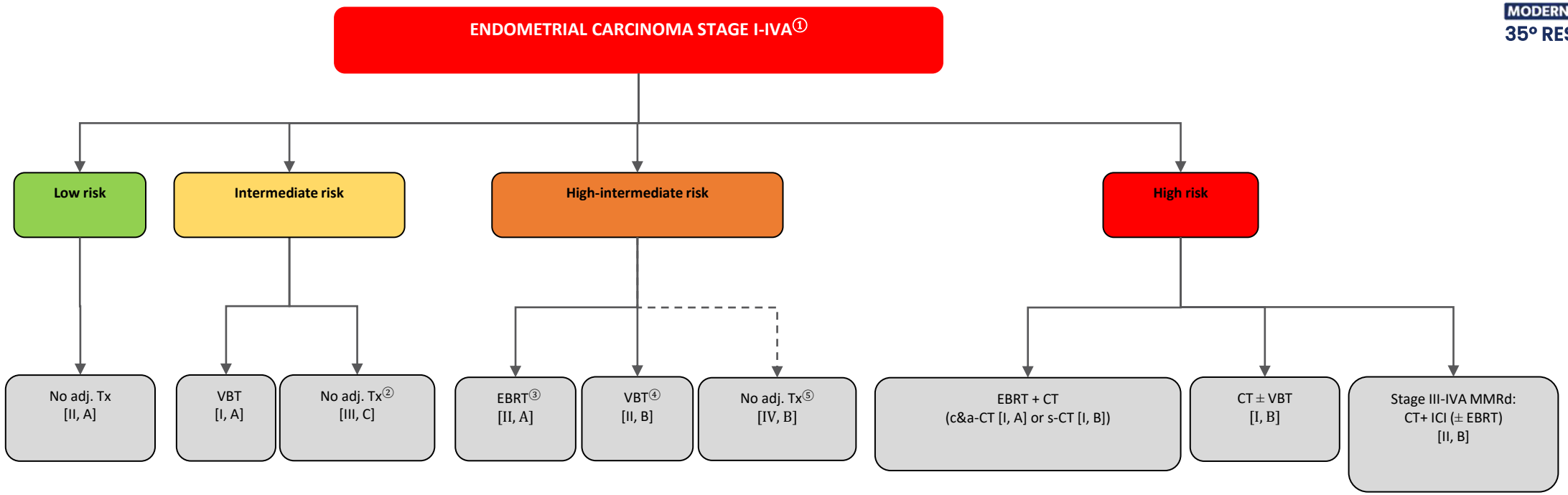
Pembrolizumab Plus Chemotherapy Improved DFS per Investigator in dMMR Subgroup





Slomovitz, J Clin Oncol, 2024

Adjuvant therapy in endometrial carcinoma stage I-IVA



①for patients with FIGO 2023 stage IIIm *POLE*mut and IVAm *POLE*mut, no firm recommendation can be given, however de-descalation 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.

Antonio González-Martín et al., ESGO, 2025

Changes in Endometrial Cancer Treatment Based on FIGO 2023 Molecular Staging.

The adoption of the FIGO 2023 staging system, leading to both upstaging and downstaging in selected cases, has resulted in clinically meaningful changes in therapeutic management.

Oaknin, Ann Oncol, 2021;
Concin, Lancet, 2025

			FIGO 2009 + risk classification 2021
STAGE I		**Confined to the uterine corpus and ovary**	
IA	IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium	FUP
	IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI	FUP
	IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary	EBRT+ChT
IB		Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI	VBT
IC		Aggressive histological types limited to a polyp or confined to the endometrium	FUP
STAGE II		**Invasion of cervical stroma without extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion**	
IIA		Invasion of the cervical stroma of non-aggressive histological types	EBRT
IIB		Substantial LVSI of non-aggressive histological types	EBRT+/-ChT
IIC		Aggressive histological types with any myometrial involvement	EBRT+ChT
STAGE III		**Local and/or regional spread of the tumor of any histological subtype**	
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)	EBRT+ChT
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa	EBRT+ChT
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria	EBRT+ChT
	IIIB2	Metastasis to the pelvic peritoneum	ChT
IIIC	IIIC1i	Metastasis to the pelvic lymph nodes - Micrometastasis	EBRT+ChT
	IIIC1ii	Metastasis to the pelvic lymph nodes - Macrometastasis	EBRT+ChT
	IIIC2i	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes- Micrometastasis	EBRT+ChT
	IIIC2ii	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes-Macrometastasis	EBRT+ChT
STAGE IV		**Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis**	
IVA		Invasion of the bladder mucosa and/or the intestinal/bowel mucosa	ChT
IVB		Abdominal peritoneal metastasis beyond the pelvis	ChT
IVC		Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone	EBRT+ChT / ChT

Cost-effectiveness analysis of tumor molecular classification in high-risk early-stage endometrial cancer

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)
No molecular testing	32,875		4.675		
Tumor molecular classification	34,655	1,780	4.744	0.070	25,578

Tumor molecular classification slightly increased costs but improved quality-adjusted survival because it helps tailor adjuvant therapy—avoiding overtreatment in low-risk POLE-mutated tumors and identifying p53-abnormal cases that may benefit from intensified therapy.

Orellana et al., Gynecologic Oncology, 2022

Cost-effectiveness analysis of tumor molecular testing in stage III endometrial cancer

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER ($/QALY)	Result
TMT	82,299		4.322			Favored
No TMT	88,384	6,085	4.322	0.000	159,023,526.8	
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TMT	126,029		4.339			Dominant
No TMT	141,675	15,647	4.333	-0.006		
MMR IHC	122,608		4.324			Favored
TMT	126,029	3,421	4.339	0.015	226,558.62	

Molecular testing in stage III endometrial cancer is a cost saving strategy when compared to no molecular testing. However, when compared to MMR IHC testing, tumor molecular testing was no longer cost-effective

First line setting:
TMT vs No TMT: TMT **cost-effective**
TMT vs MMR IHC alone: TMT cost ***not*** clearly cost-effective
TMT vs MMR IHC +p53: TMT **cost effective**

Immunotherapy for 1st relapse setting:
TMT vs No TMT: TMT **cost-effective**
TMT vs MMR IHC alone: TMT cost ***not*** clearly cost-effective

Orellana et al., Gynecologic Oncology, 2023

How the new molecular classification guides treatment decisions in clinical practice

To define risk classes → **Tailoring of adjuvant treatment (according to 2025 guidelines)**

To guide treatment tailoring for advanced / first-line / recurrent disease (since 2022)

Single agent IO efficacy in non-biomarker selected and biomarker selected in Endometrial Cancer

pMMR

Study	Drug	N	Patient Selection	ORR (%)
Keynote 28:	Pembrolizumab	24	Advanced/metastatic PDL1+	13%
Garnet	Dostarlimab	156	Previously treated recurrent/advanced p-MMR	15.4%
PHAEDRA	Durvalumab	36	Advanced/metastatic p-MMR	3%
NCT02912572	Avelumab	16	Advanced/metastatic p-MMR	6%

dMMR

Study	Drug	N	Patient Selection	ORR (%)
KEYNOTE-158	Pembrolizumab	49	Advanced/metastatic dMMR	57%
GARNET	Dostarlimab	103	Previously treated recurrent/advanced dMMR	45%
PHAEDRA	Durvalumab	35	Advanced/metastatic dMMR	43%
NCT02912572	Avelumab	15	Advanced/persistent dMMR	27%

Ott et al., JCO, 2017; Oaknin, ASCO, 2022; Antill, ASCO, 2019, Konstantinopoulos, ASCO, 2019; Mirabelle et al., J Clin Oncol, 2020; Bonneville et al., JCO Precis Oncol, 2017; Oaknin et al., ESMO 2020; Antill et al., J Clin Oncol, 2019; Konstantinopoulos et al, J Clin Oncol, 2019;

1L IO studies in EC: key differences in study design and eligibility criteria

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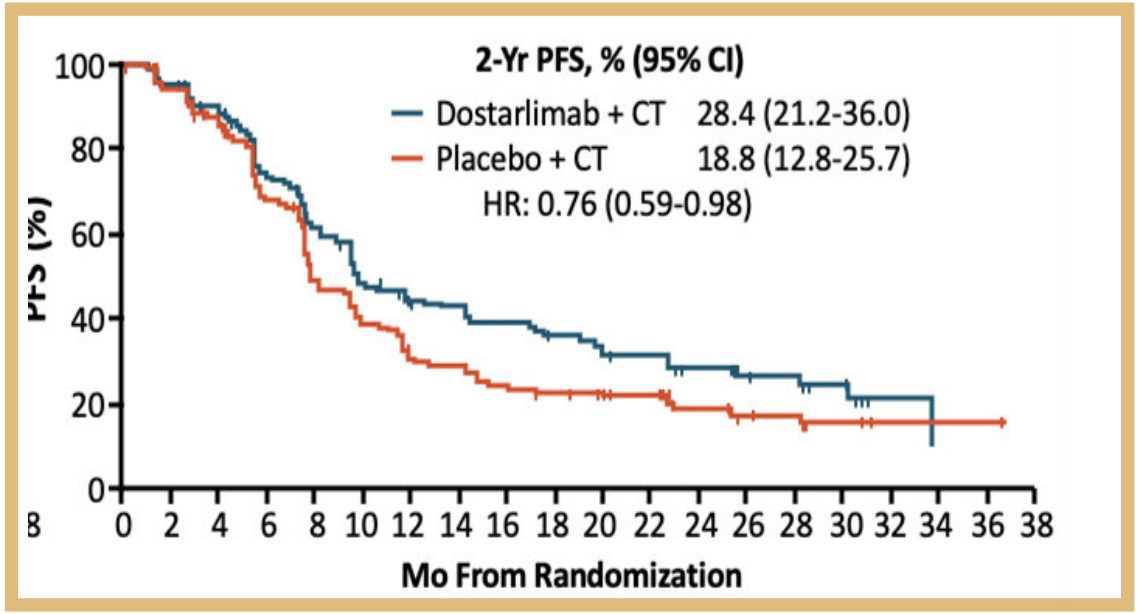
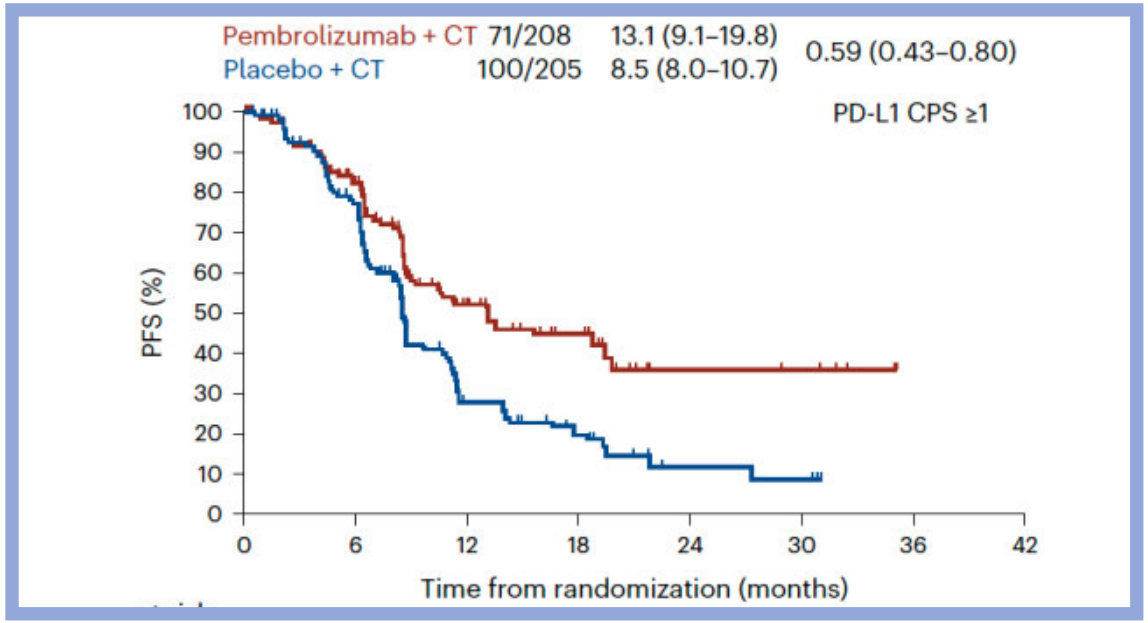
	RUBY[1–4]	GY018[5,6]	DUO-E[7,8]	AtTEnd[9,10]
Investigational agent (target)	**Dostarlimab** (PD-1)	**Pembrolizumab** (PD-1)	**Durvalumab** (PD-L1) olaparib (PARPi)	**Atezolizumab** (PD-L1)
If prior CT	**≥6 months** prior	**≥12 months** prior	**≥12 months** prior	**≥6 months** prior
Participating regions	North America, Eastern and Western Europe	North America, Japan, South Korea	Australia, Europe, Asia, South America, North America	Europe, Australia, New Zealand, and Asia
Measurable disease required, except	**High-risk stage IIIC1**, stage IIIC2, and stage IV	**Stage IVB**	**Stage IV**	Inoperable **stage III–IV**
Histology criteria	**Allows** carcinosarcoma	**Does not allow** carcinosarcoma	**Allows** carcinosarcoma	**Allows** carcinosarcoma
Primary endpoint(s)	PFS **(overall and dMMR)** OS **(overall population)**	PFS **(dMMR, MMRp populations)**	PFS **(overall population)**	PFS **(overall and dMMR)** OS **(overall population)**
Stratification	MMR/MSI status, prior RT, disease status	MMR status, ECOG PS, previous CT	MMR status, disease status, geographic region	MMR status, disease status, histological subtype, country
Median follow-up	**37** months	**~10** months	**~15** months	**28** months

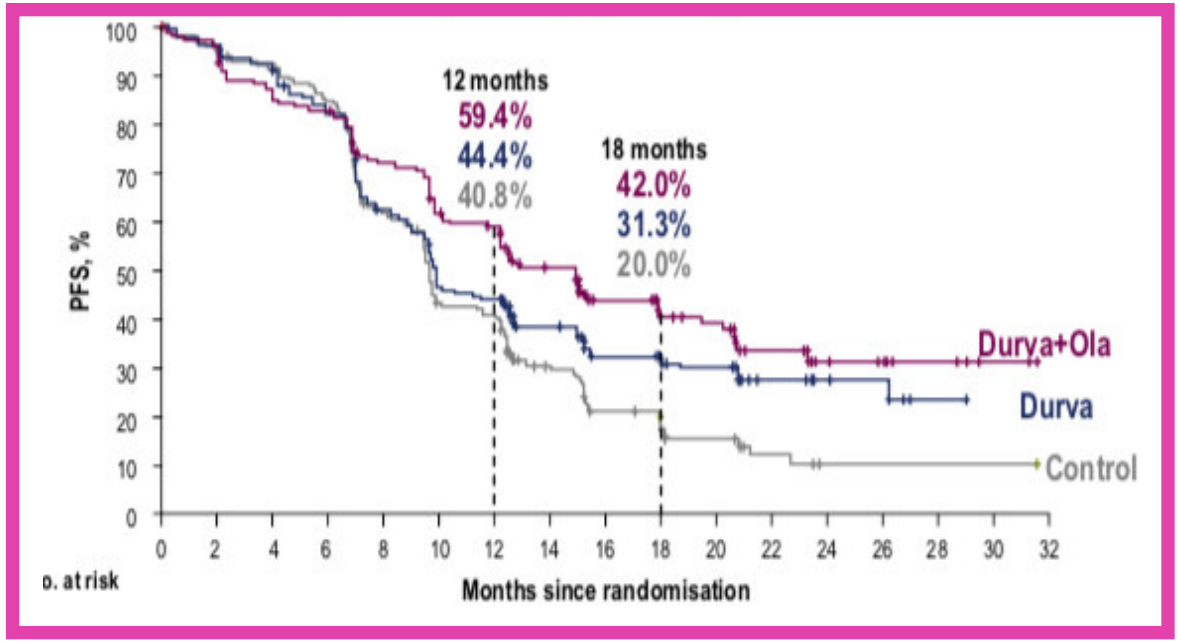
Mirza MR et al., NEJM, 2023; Mirza MR et al., Ann. Oncol., 2023; Eskander RN et al., NEJM, 2023; Eskander RN et al., SGO, 2023; Arend RC, SGO, 2023; Colombo N et al., ESMO, 2023; Westin SN et al., JCO, 2023; Powell MA et al., SGO, 2024; Eskander RN et al., SGO, 2024; Colombo N et al., ESMO, 2023; Baurain JF, SGO, 2024

Tailoring First Line Therapy: Adding IO in pMMR/MSS

Impact on PFS





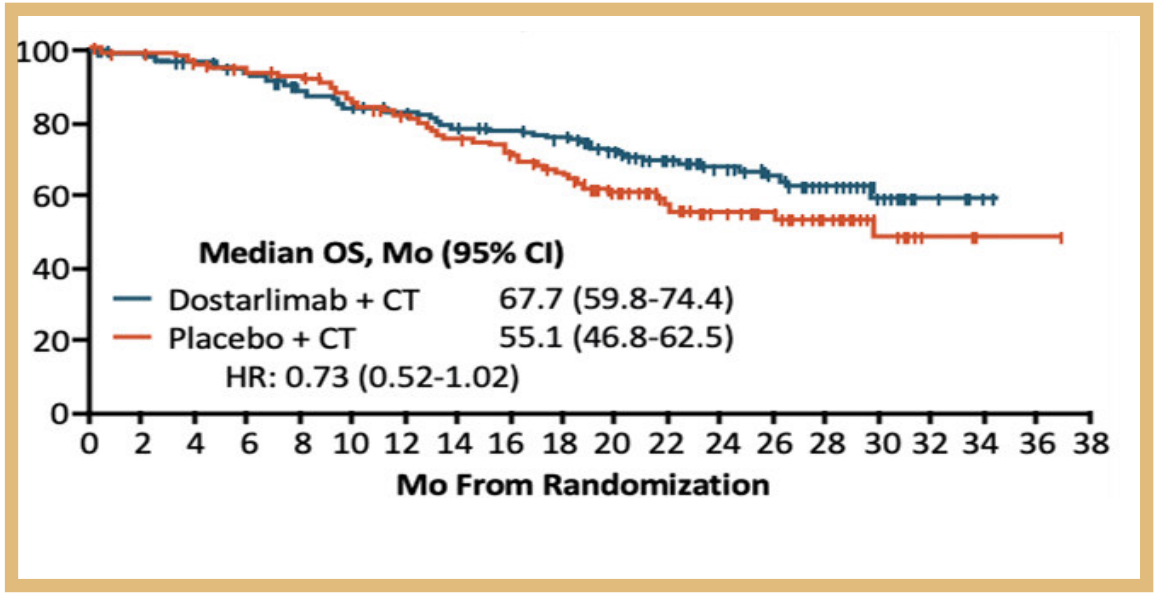


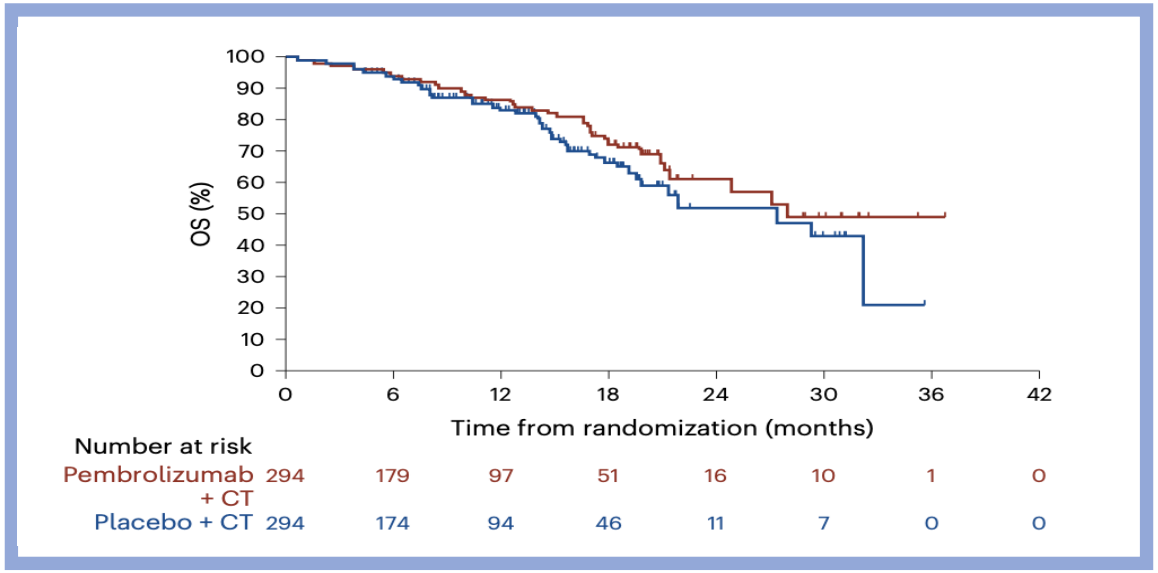
RUBY-Part 1	Dostarlimab	**0.76** (95% CI 0.59-0.98)
NRG-GY018	Pembrolizumab	**0.59** (95% CI 0.43-0.80)
DUO-E Arm 1	Durvalumab	**0.77** (95% CI 0.60-0.97)
DUO-E Arm 2	Durvalumab + Olaparib	**0.57** (95% CI 0.44-0.73)

Mirza et al., NEJM, 2023; Eskander et al., Nat Med, 2025; Westin et al., ESGO, 2023

Tailoring First Line Therapy: Adding IO in pMMR/MSS

Impact on OS



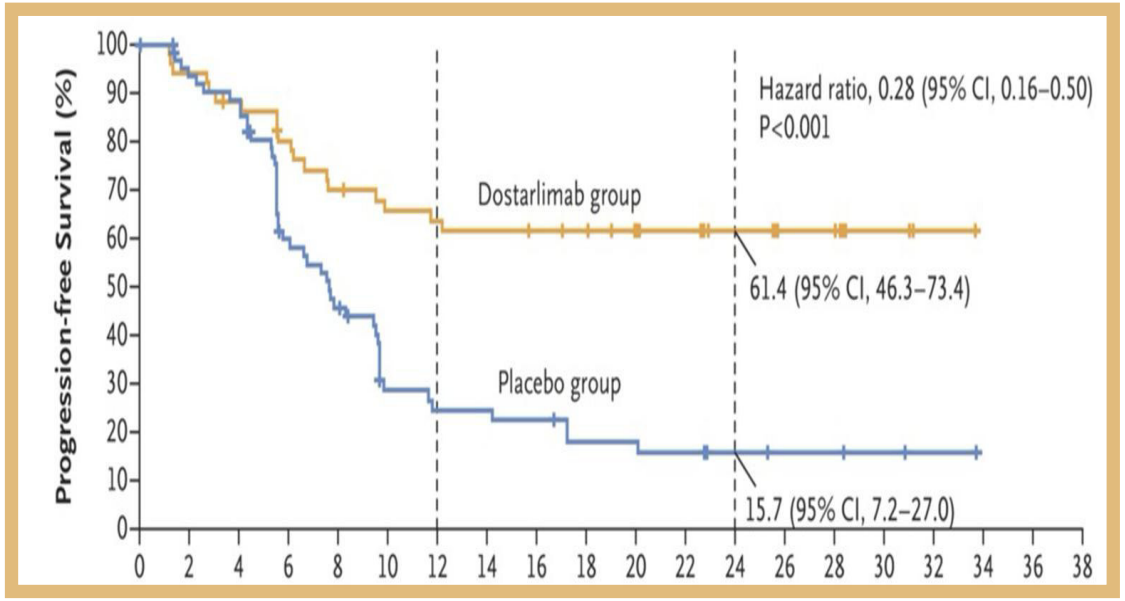


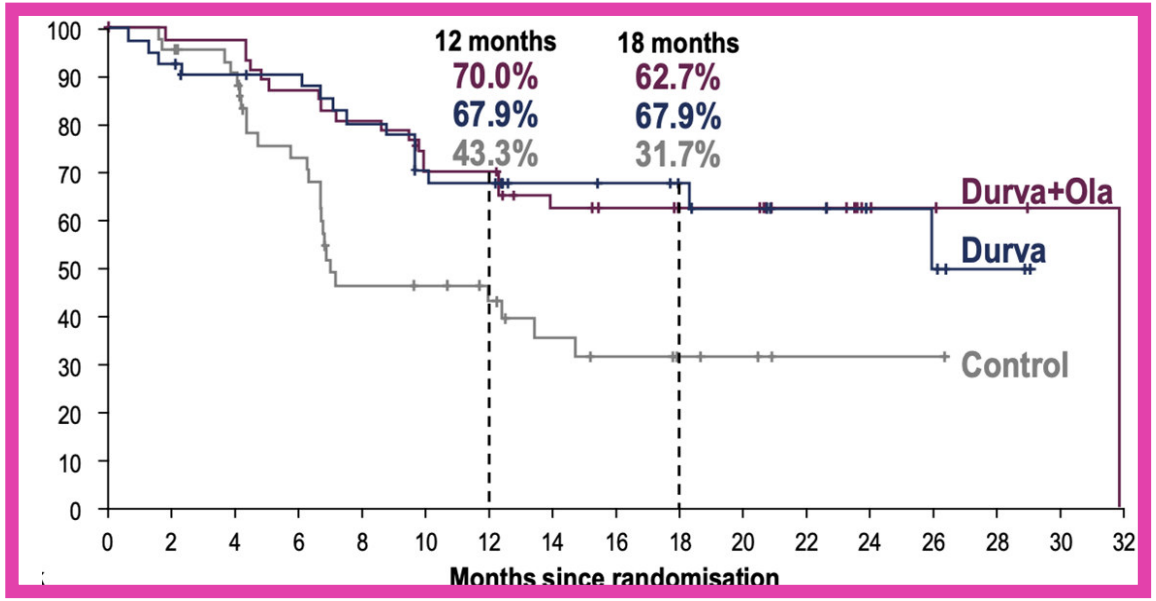
TRIAL	ICI	HR PFS
RUBY-Part 1	Dostarlimab	**0.79** (95% CI 0.60-1.04)
NRG-GY018	Pembrolizumab	**0.79** (95% CI 0.53-1.17)
DUO-E Arm 1	Durvalumab	**NOT AVAILABLE**
DUO-E Arm 2	Durvalumab + Olaparib	**NOT AVAILABLE**

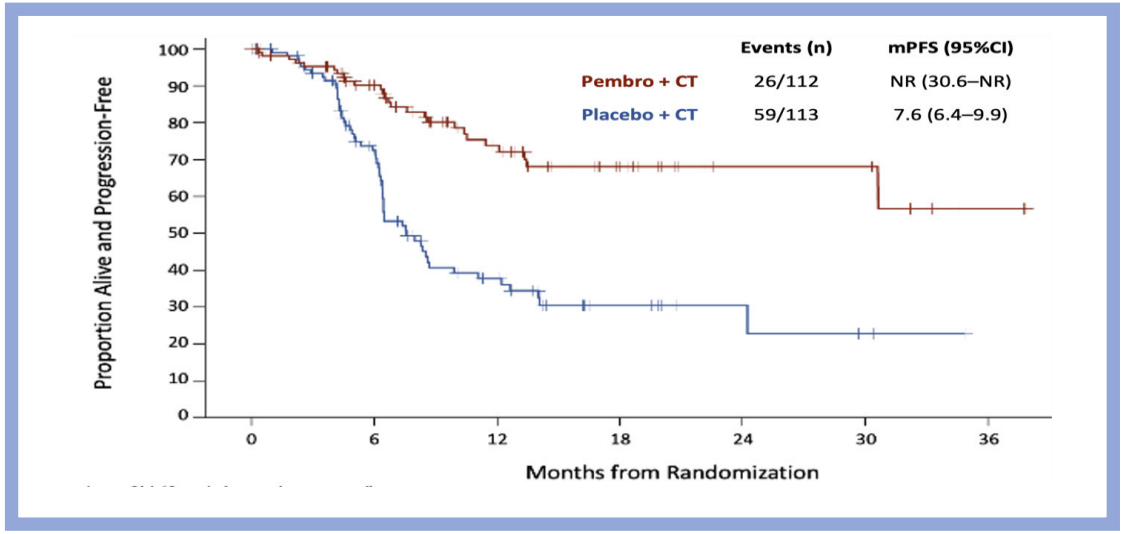
Mirza et al., NEJM, 2023; Eskander et al., Nat Med, 2025; Westin et al., ESGO, 2023

Tailoring First Line Therapy: Adding IO in dMMR

Impact on PFS





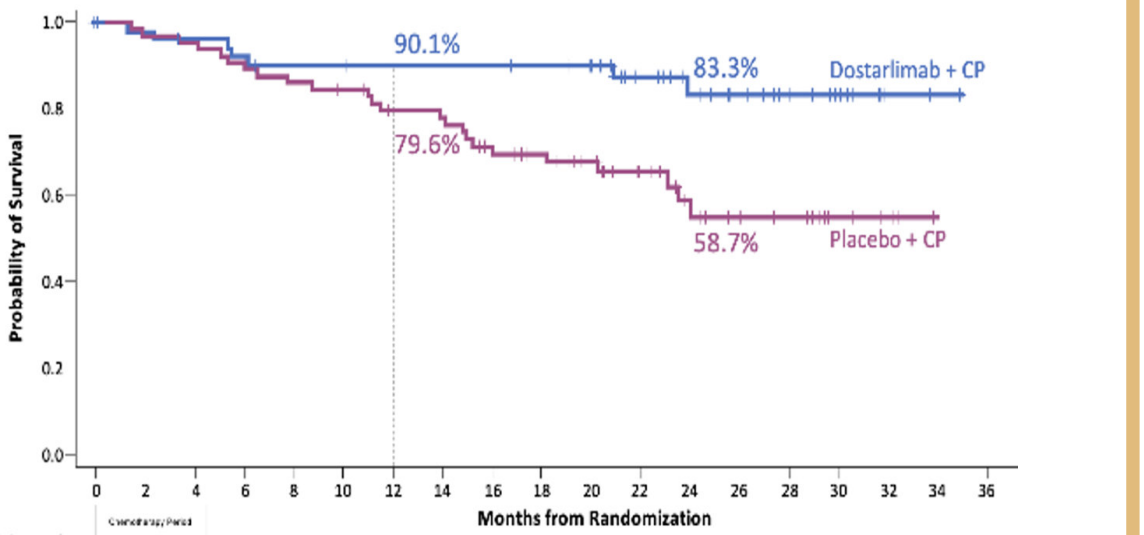


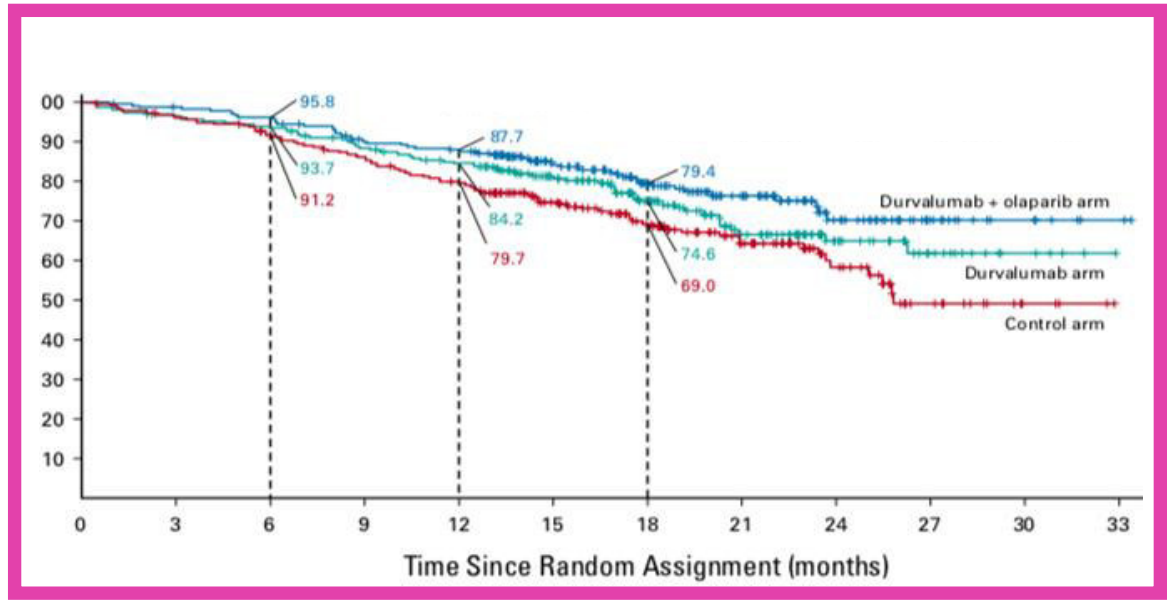
TRIAL	ICI	HR PFS
RUBY-Part 1	Dostarlimab	**0.28** (95% CI 0.16-0.49)
NRG-GY018	Pembrolizumab	**0.30** (95% CI 0.19-0.48)
DUO-E Arm 1	Durvalumab	**0.42** (95% CI 0.22-0.80)
DUO-E Arm 2	Durvalumab + Olaparib	**0.41** (95% CI 0.21-0.75)

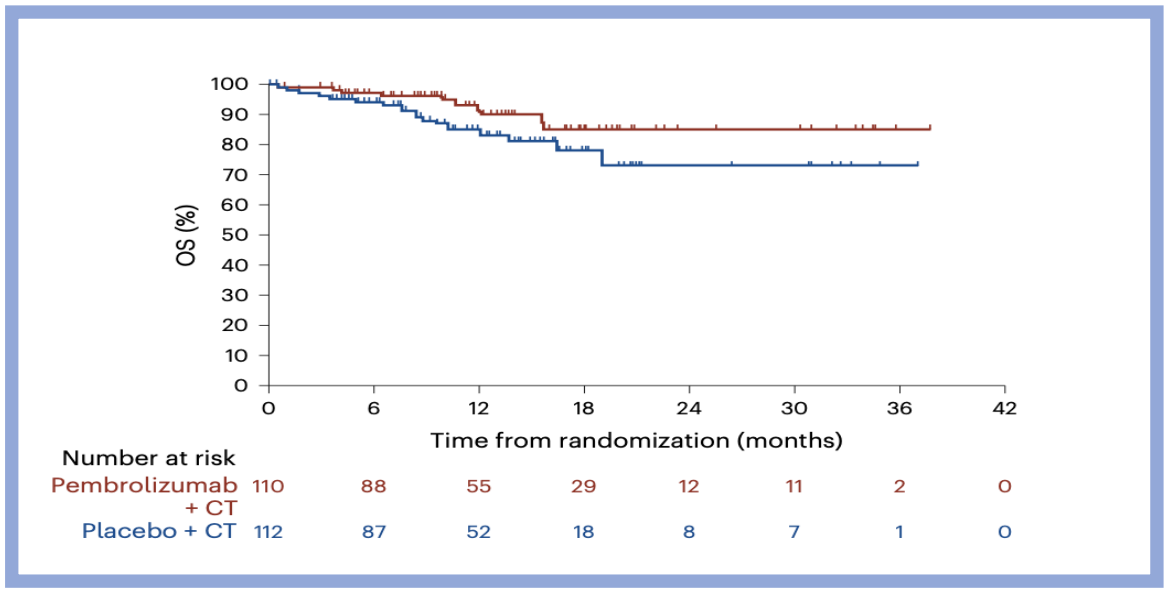
Mirza et al., NEJM, 2023; Eskander et al., NEJM, 2023; Westin et al., JCO, 2024

Tailoring First Line Therapy: Adding IO in dMMR/ MSI-H

Impact on OS







TRIAL	ICI	HR PFS
RUBY-Part 1	Dostarlimab	**0.32** (95% CI 0.17-0.63)
NRG-GY018	Pembrolizumab	**0.35** (95% CI 0.19-0.48)
DUO-E Arm 1	Durvalumab	**0.77** (95% CI 0.56-1.07)
DUO-E Arm 2	Durvalumab + Olaparib	**0.59** (95% CI 0.42-0.83)

*ITT population (dMMR 20%)

Mirza et al., NEJM, 2023; Eskander et al., Nat Med, 2025; Westin et al., ESGO, 2023

Cost-effectiveness of Immunotherapy in Advanced Endometrial Cancer

Do the gains in survival and quality of life provided by these treatments justify their incremental costs relative to standard chemotherapy?

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Study (Year)	Population / Setting	Treatment comparison	ICER (cost/QALY)	WTP threshold	Conclusion on cost-effectiveness
Ackroyd et al, 2021	First-line advanced/recurrent EC; MSS and MSI-H cohorts analyzed separately	Pembro + lenvatinib vs carboplatin/paclitaxel (chemo)	MSS: Dominated; MSI-H: $2,849,882/QALY	$150,000/QALY (USA)	Not cost-effective (MSS: inferior to chemo; MSI-H: high ICER, ~85% price reduction needed)
Kim et al, 2023	First-line primary advanced dMMR EC	Chemo (TC) vs TC + pembrolizumab vs TC + dostarlimab	Pembrolizumab: $377,718/QALY; Dostarlimab: Dominated (~$401 k/QALY)	$100,000/QALY (USA)	Not cost-effective; pembrolizumab needs ~61% cost reduction to meet $100 k/QALY
Huo et al, 2024	First-line advanced/recurrent EC; dMMR and pMMR cohorts	Chemo vs chemo + pembrolizumab	dMMR: $41,305/QALY; pMMR: $90,285/QALY	$150,000/QALY (USA)	Cost-effective in both (high value in dMMR, borderline in pMMR)
Huo et al, 2024	First-line primary advanced EC; dMMR and pMMR	Chemo vs chemo + pembrolizumab	dMMR: $60,349/QALY; pMMR: $175,788/QALY	$150,000/QALY (USA)	Cost-effective in dMMR; not in pMMR (~15% price cut needed)
Liu et al, 2025	First-line advanced/metastatic EC (~74% pMMR)	Pembro vs chemo + pembrolizumab vs chemo +	pMMR: Pembro $974 k/QALY, Dostarlimab $234 k/QALY;	$150,000/QALY (USA)	Dostarlimab preferred for dMMR; neither cost-effective for pMMR
Zhang et al, 2025					CERs exceed
Diggs et al., 2023					drug price
Sun et al., 2022					e price cut
Dioun et al., 2023		pembrolizumab	Pembro: dominated		% price cut needed

In the dMMR subgroup immunotherapy is actually cost-effective, often falling within or close to the accepted willingness-to-pay thresholds.

In contrast, for pMMR or unselected patients, the cost remains high and large price reductions would be needed.

Inami K. et al., Gyn Oncol Rep, 2025

Conclusions

Molecular Profiling in Endometrial Cancer: Pay More Now, Save More Later?

YES

- Molecular classification has revolutionized endometrial cancer management, redefining risk assessment and treatment decisions.
- Integration of FIGO 2023 and ESGO 2025 guidelines enables a more precise, biology-driven approach to patient care.
- POLE, MMR, and p53 profiling allow a refined stratification that reduces both over- and undertreatment (see PROTC4a).
- The PORTEC-4a trial confirmed the clinical safety and efficacy of molecular-guided adjuvant therapy de-escalation.
- For advanced disease, immunotherapy has become a paradigm-shifting option, particularly in the dMMR/MSI-H population.
- However, cost-effectiveness remains a critical consideration, especially for pMMR and MSS subgroups.
- Investing in molecular profiling today will ultimately yield greater clinical and economic value for patients and healthcare systems tomorrow.

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Thank you

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