

Post
ESTRO
2025
AFRIQUE DU NORD



Société Marocaine de **Cancérologie**
الجمعية المغربية لداء السرطان



الجمعية التونسية للأمراض الورميه والمعالج بالاشعاع
Société Tunisienne d'Oncologie Radiothérapie

BY SMC/STOR
LE 28 MAI 2025 À 18H00 (GMT+1)
Evenement VIRTUEL

Dr Ghaiet EL Fida **Noubbigh**
Pr Ag en radiothérapie
HMPIT, Tunis

ESGO-ESTRO-ESP Guidelines on the management of patients with endometrial carcinoma - Update 2025

Nicole Concin, Xavier Matias-Guiu, David Cibula, Nicoletta Colombo, Carien L. Creutzberg, Jonathan Ledermann, Mansoor Raza Mirza, Ignace Vergote, Nadeem R. Abu-Rustum, Tjalling Bosse, Cyrus Chargari, Sophie Espenel, Anna Fagotti, Christina Fotopoulou, Sonia Gatus, Antonio González-Martin, Sigurd Lax, Bar Levy, Domenica Lorusso, Gabriella Macchia, Christian Marth, Philippe Morice, Ana Oaknin, Maria Rosaria Raspollini, Richard Schwameis, Jalid Sehouli, Alina Sturdza, Alexandra Taylor, Anneke Westermann, Pauline Wimberger, François Planchamp, Remi A. Nout

**Lancet Oncology, 2025
in press**



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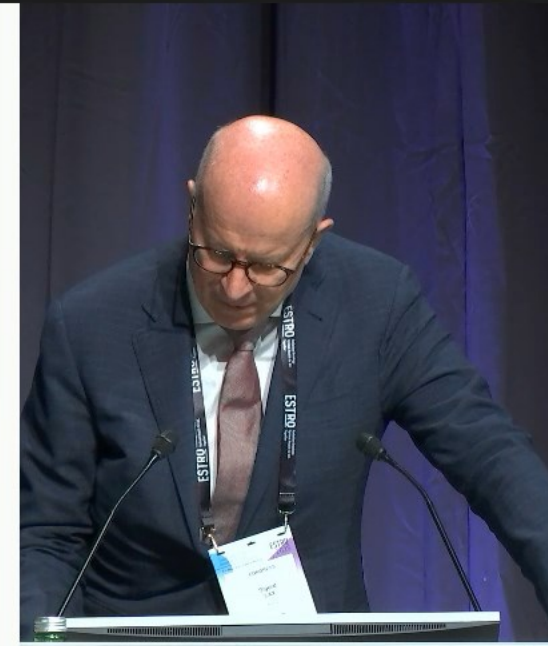
**ESTRO**
2025**2-6 May 2025****Vienna, Austria**

Background of Molecular Classification and Highlights from Pathology

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**LKH Graz II**

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Classification of endometrial carcinoma

Conventional

- Tumor type
- Histopathological grade
- Stage (clinical, surgical, pathological)
- Lymphovascular space invasion (LVSI)

Molecular

- P53 immunoreactivity/ TP53 mutations
- MMR deficiency/ microsatellite instability (MSI)
- Pathogenic POLE mutations



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Histopathological types and behavior

Non-aggressive

- Low grade endometrioid

Aggressive

- High grade endometrioid
- Serous
- Clear cell
- Undifferentiated
- Carcinosarcoma
- Mixed
- Others (mesonephric-like, intestinal mucinous, neuroendocrine)

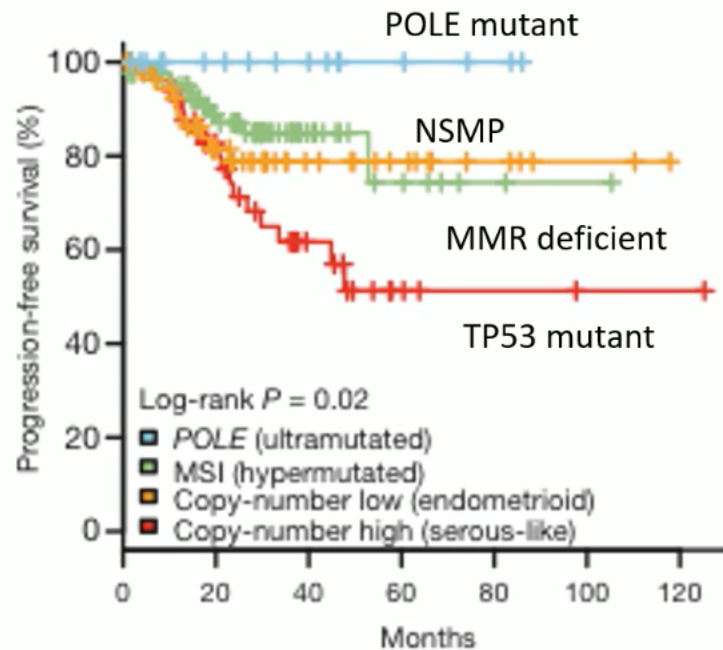
According to WHO 2020, ESGO guidelines, FIGO staging 2023



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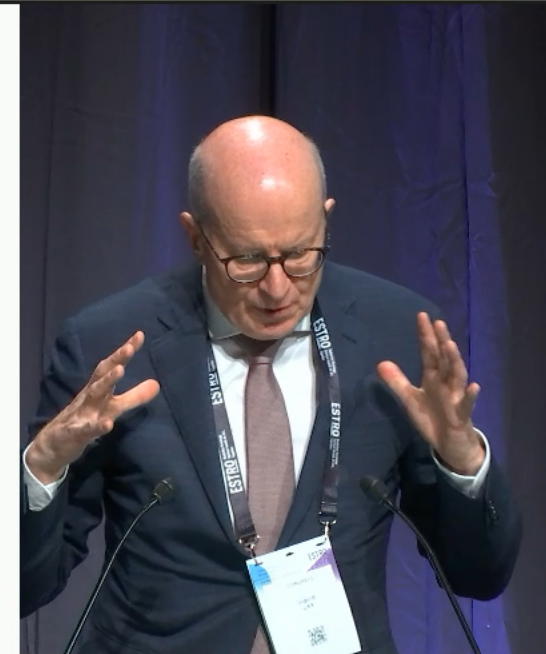
Molecular subtypes of endometrial carcinoma



The TCGA Research Network, Nature 2013

Molecular subtype	Definition
POLE mutant	High mutation rates (ultramutated) due to pathogenic POLE mutations
MMR deficient	Microsatellite instable /MSI, mostly due to MLH1 promoter methylation
NSMP: No special molecular profile	MSS; POLE, TP53 wild type, frequent CTNNB mutations; low copy number abn
TP53 mutant/p53 abnormal	High-copy number abnormalities

WHO Classification of tumors, 5th edition 2020



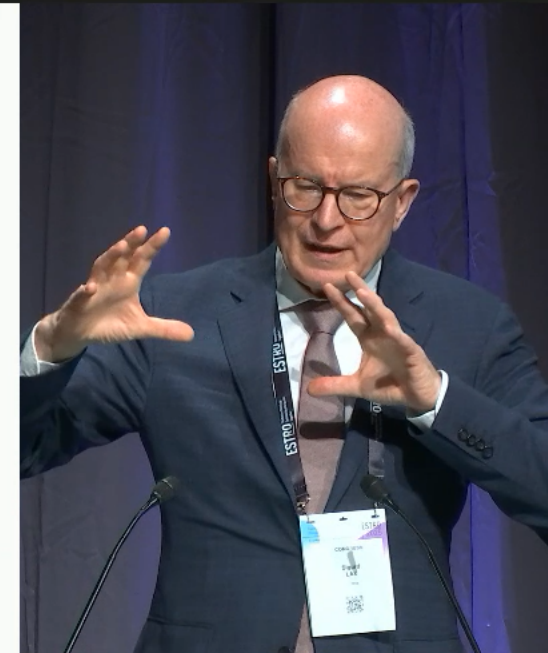
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Molecular subtype and prognosis

- TP53mut worst prognosis
- NSMP and MMRd intermediate prognosis without statistical significance for total collective but varies for subgroups
- Differences also between overall and recurrence-free survival
- TP53mut, NSMP and MMRd affected by adverse clinicopathological factors (stage, grade, LVSI)
- POLEmut best prognosis, not affected by adverse clinicopathological factors

Kommoss et al., Ann Oncol 2018; Raffone et al., Gynecol Oncol 2019



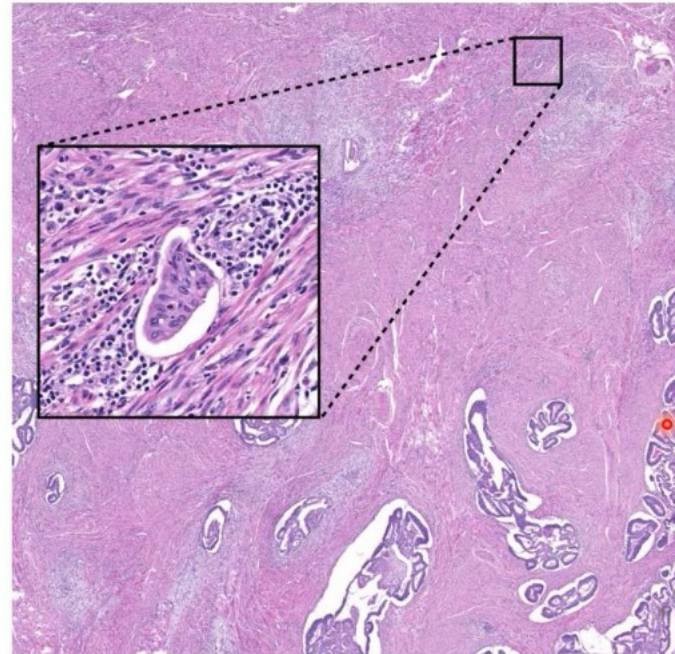
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Lymphovascular space invasion (LVSI)

- Also: lymphovascular invasion (LVI)
- Tumor cells within endothelial-lined spaces (lymphatics, blood vessels)
- Mimics/lookalikes: MELF, retraction
- No, focal, substantial (extensive)
- Cut-off varies between ESGO (≥ 4 within one slide), WHO (≥ 5), IJGP (≥ 3) and published studies
- Only few cases between 3 and 5 and numbers usually not reported

Hachisuga et al., Cancer 1999; Peters et al., Histopathology 2019



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≥ 5



Testing Strategy Recommendation

- “One stop shop” testing on biopsy/ curettage; repetition on surgical specimen only for selected cases
- Most accepted strategy:
 - Immunohistochemistry for MMR proteins (2 antibody approach), ER, p53 on all cases; on biopsy/curettage
 - POLEmut analysis: desirable on all cases; at least on high grade, low stage carcinomas or if adjuvant chemotherapy/ radiation planned; for 2023 FIGO staging required
 - Molecular analysis for p53 (NGS) and MSI if IHC is equivocal
 - HER2 testing for all p53abn/*TP53*mut carcinomas



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Multiple classifier

- Rare (about 3.5 % of endometrial carcinomas)
- 3 subtypes:
 - MMRd/p53abn (60%)
 - POLEmut/p53abn (29%)
 - POLEmut/MMRd/p53abn (11%)
- Prognosis significantly better than for p53abn tumors
- TP53 mutations seem to be passengers without impact
- POLEmut/MMRd are considered POLEmut

Leon-Castillo et al., J Pathol 2020

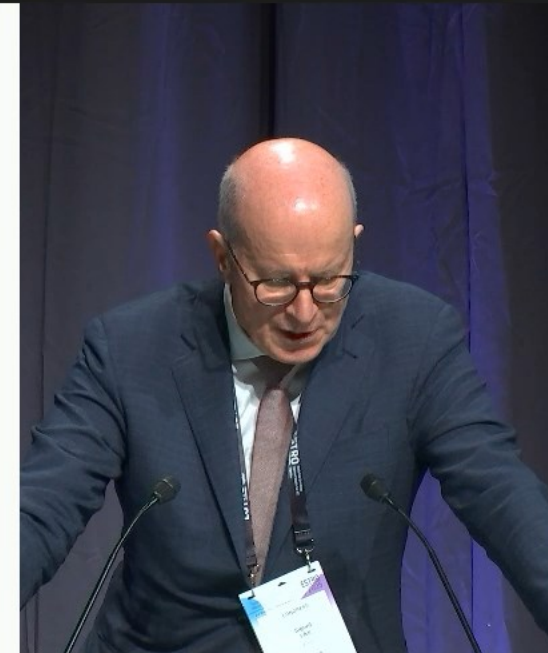


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Summary

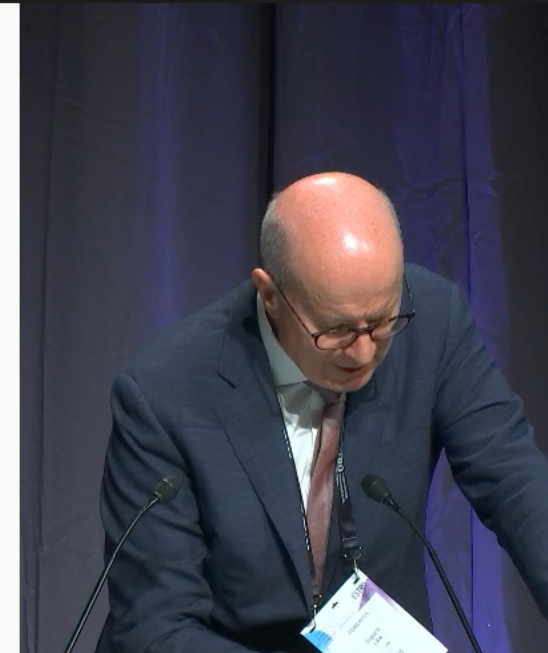
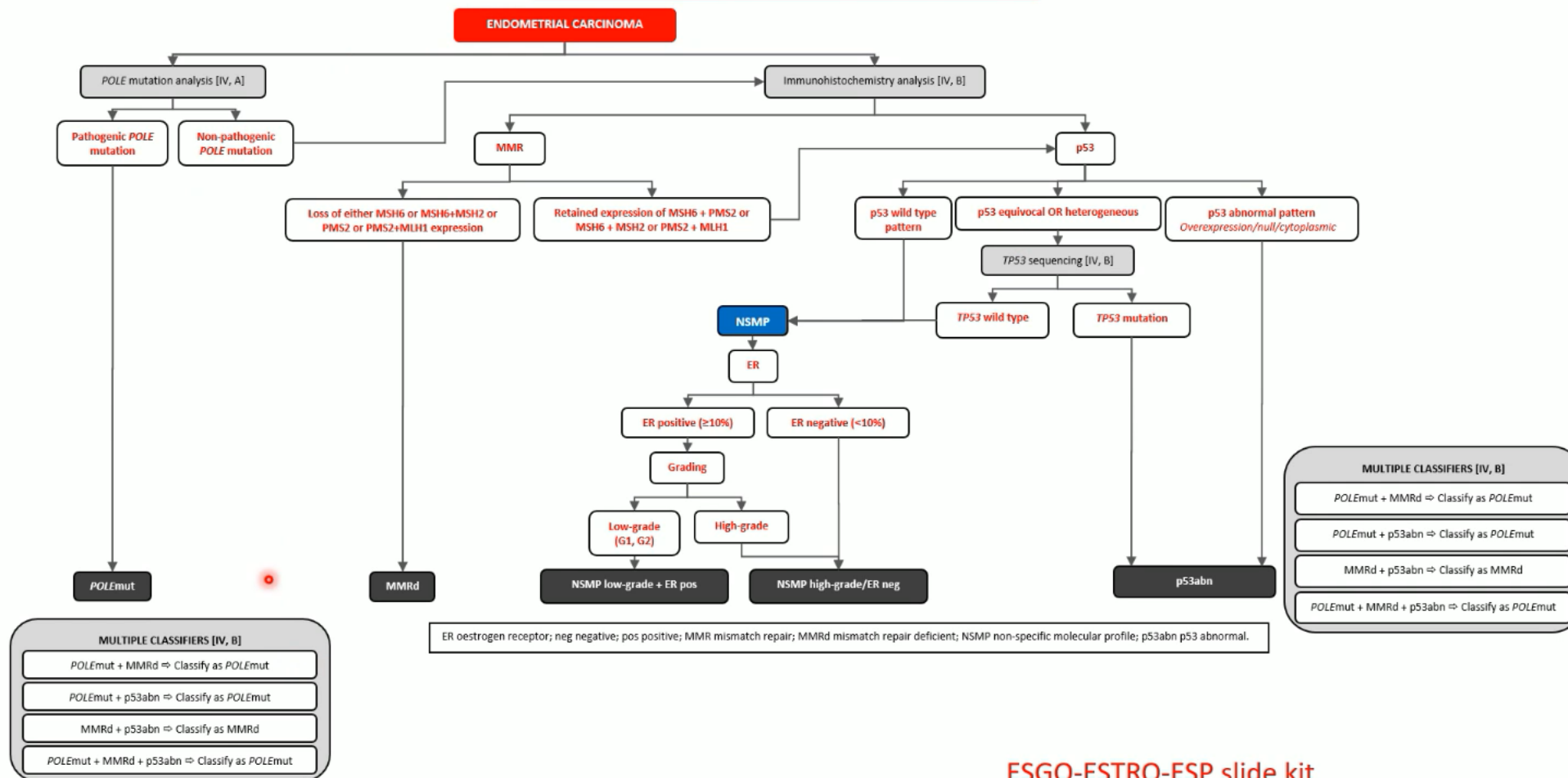
- Molecular classification of endometrial carcinoma is standard: evidence-based, prognostic and increasing therapeutic impact
- Integrated into the WHO classification, 2023 FIGO staging and multidisciplinary guidelines by ESGO-ESTRO-ESP.
- Molecular classification on all EC, preferred on curettage/bx
- MMR proteins, ER, p53 IHC and POLE status on all cases
- POLE status required for FIGO staging and adjuvant therapy
- HER2 IHC for all p53abn/TP53mut cases



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Assessment of molecular classification



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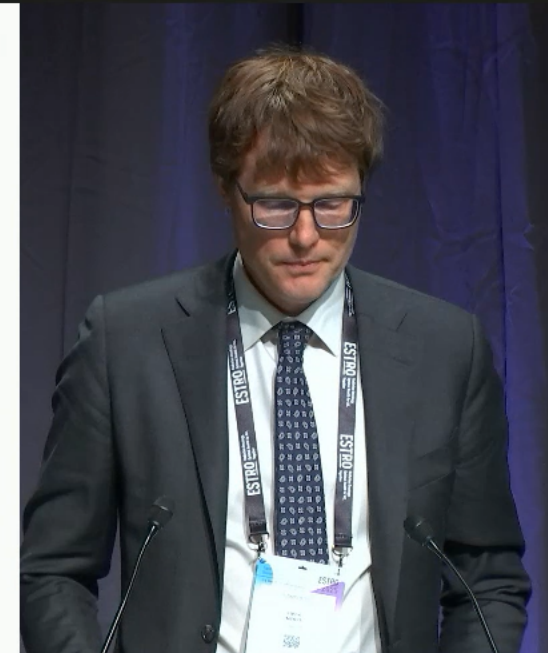
ESGO-ESTRO-ESP slide kit



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Erasmus MC
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ESGO-ESTRO-ESP Endometrial Cancer Guideline update

*Implications for adjuvant therapy and
radiotherapy highlights*



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2023 FIGO staging of cancer of the endometrium

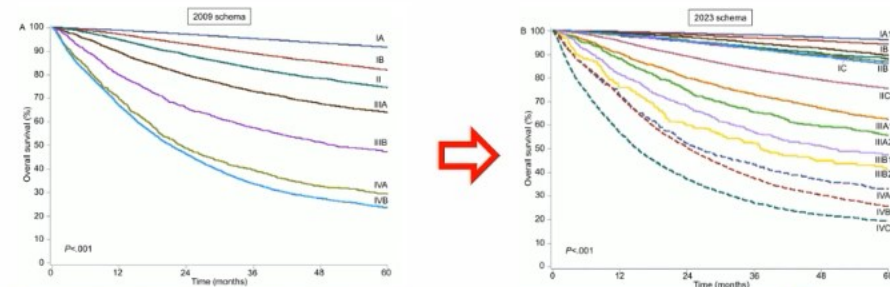
TABLE 1 2023 FIGO staging of cancer of the endometrium.^{a,b}

Stage	Description
Stage I	Confined to the uterine corpus and ovary ^c
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometrioid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVS) OR good prognosis disease IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVS IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary ^c
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVS ^d
IC	Aggressive histological types ^e limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVS OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVS ^d of non-aggressive histological types
IIC	Aggressive histological types ^e with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria) ^c IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both ^f IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIIC1ii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
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
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

TABLE 2 FIGO endometrial cancer stage with molecular classification.^a

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage IAm ^{POLEmut}	POLEmut endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVS or histological type
Stage IIcM ^{p53abn}	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVS or histological type

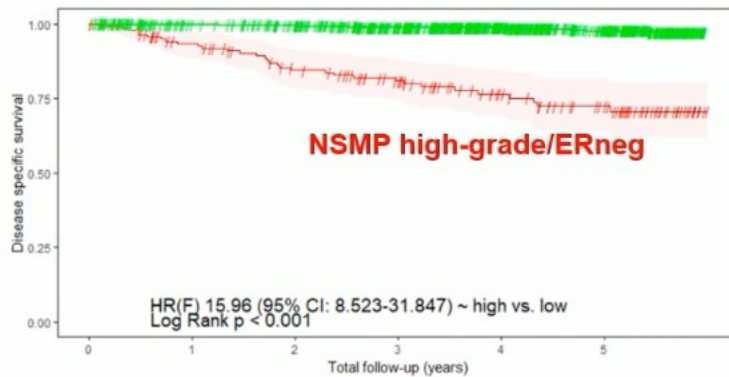
Molecular integrated

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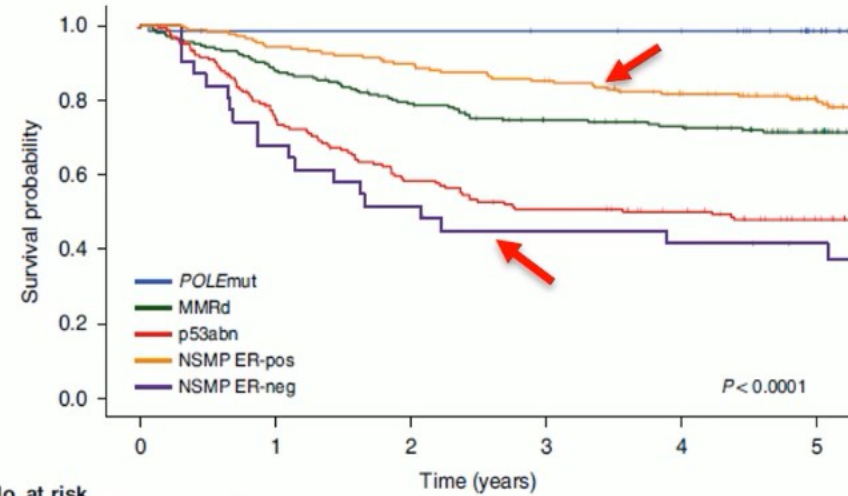
NSMP role of ER-status

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

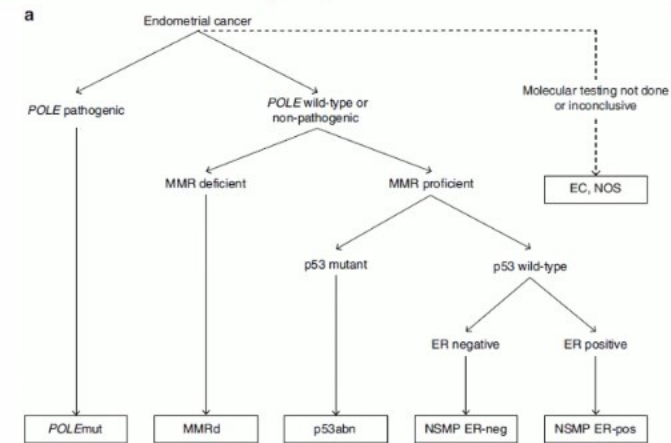
B DSS all stages NSMP low-grade+ERpos



Jamieson et al. Modern Pathology 2023



No. at risk



Vermij et al. BJC 2023



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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:

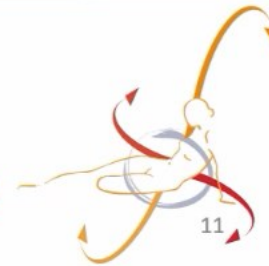
risk higher than 25%.



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The European Voice of Gynaecological Oncology

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Question

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LOW RISK

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)	1Am POLEmut				
	IA2	Low-grade endometrioid, myoinvasion <50%, no focal LVSI	1Am POLEmut				
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary ^{††}					
	IB	Low-grade endometrioid, myoinvasion >50%, no focal LVSI	1Am POLEmut				
	IC	High-grade histologies [‡] , limited to polyp/endometrium	1Am POLEmut				
II	Confined to the uterus						
	IIA	Low-grade endometrioid, invasion of the cervical stroma	1Am POLEmut				
	IIB	Low-grade endometrioid, substantial LVSI ^{**}	1Am POLEmut				
	IIC	High-grade histologies [‡] , myoinvasion	1Am POLEmut				
			1Am POLEmut				
			1Am POLEmut				
III	Local and/or regional spread						
	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)					
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa					
	IIIB1	Metastasis or direct spread to the vagina and/or the parametria					
	IIIB2	Metastasis to the pelvic peritoneum					
	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 myometrium					
	Metastatic disease or residual disease after primary treatment						
	II-IVA	With residual disease					
	IVB	Peritoneal metastasis beyond the pelvic cavity					
	IVC	Distant metastasis					

ADJUVANT THERAPY LOW RISK

- This includes the following categories:
 - FIGO 2023 stage IA1m-IA2-IA3m *POLEmut*, MMRd, NSMP low-grade+ERpos
 - FIGO 2023 stage IBm *POLEmut*
 - FIGO 2023 stage ICm *POLEmut*, MMRd
 - FIGO 2023 stage IIm (IIA, IIB, IIC) *POLEmut*

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data

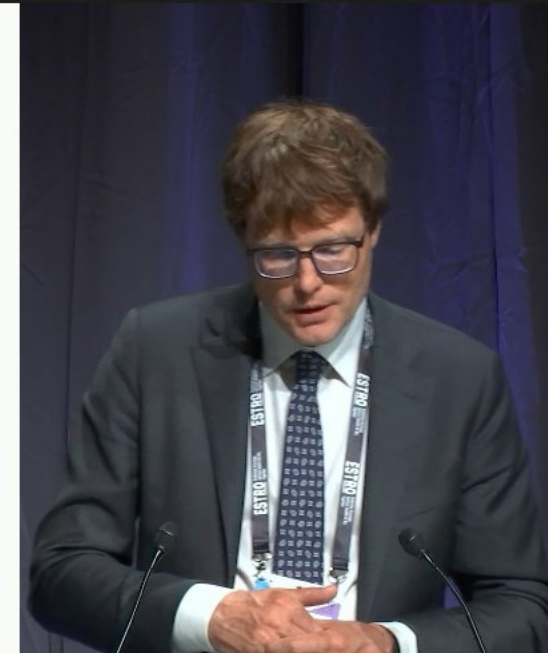


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ADJUVANT THERAPY LOW RISK

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

- No benefit of EBRT in absence of risk factors PORTEC-1 (Creutzberg et al. Lancet 2000), GOG#99 (Keys et al. Gyn Onc 2004)
- No benefit of VBT in low risk (Sorbe et al. Int J Gyn Cancer 2009)
- PORTEC-1 & 2 molecular groups and radiotherapy response (Stello et al CCR 216; Horeweg et al. JCO 2023)



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ADJUVANT THERAPY



Uncertain, lack
of data

1^{ère} Grey ZONE

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)				*	
	IA2	Low-grade endometrioid, myoinvasion <50%, no focal LVSI					
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary ^{††}					
	IB	Low-grade endometrioid, myoinvasion >50%, no focal LVSI					
	IC	High-grade histologies [‡] , limited to polyp/endometrium					
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma					
IIIB		Low-grade endometrioid, substantial LVSI ^{‡‡}					
IIIC		High-grade histologies [‡] , myoinvasion					
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						
II-IVA		With residual disease					
IVB		Peritoneal metastasis					
IVC		Distant metastasis					

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data



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FIGO 2023 IA1m NSMP high-grade/ERneg or p53abn & ICm NSMP high-grade/ERneg or p53abn

- This part includes the following categories:

- FIGO 2023 IA1m NSMP high-grade/ERneg or p53abn
- FIGO 2023 stage ICm NSMP high-grade/ERneg or p53abn

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].
- NCDB analysis suggest benefit systemic therapy, however good results without adjuvant therapy (Barney et al. IJROBP 2013; Mysona et al/ Gyn Onc 2020)



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ADJUVANT THERAPY
INTERMEDIATE RISK

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)					
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI					
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary [‡]					
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI					
IC		High-grade histologies [§] , limited to polyp/endometrium					
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma					
IIIB		Low-grade endometrioid, substantial LVSI**					
IIC		High-grade histologies [§] , myoinvasion	Myoinvasion <50%, no/focal LVSI				
			Myoinvasion ≥50%, no/focal 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							
II-IVA		With residual disease					
IVB		Peritoneal metastasis					
IVC		Distant metastasis					

This includes the following categories:

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data



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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

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].
- VBT effective PORTEC-2 (Nout et al. Lancet 2010), Swedish trial (Sorbe et al. IJROBP 2012)
- PORTEC-2 outcomes in molecular groups and risk factors (Wortman et al. BJC 2018)
- PORTEC-1 & 2 molecular groups and radiotherapy response (Stello et al CCR 216; Horeweg et al. JCO 2023)



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ADJUVANT THERAPY
HIGH-INTERMEDIATE RISK

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)					
	IA2	Low-grade endometrioid, myoinvasion <50%, no focal LVSI					
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary ^{††}					
IB		Low-grade endometrioid, myoinvasion >50%, no focal LVSI					
IC		High-grade histologies [‡] , limited to polyp/endometrium					
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma					
IIIB		Low-grade endometrioid, substantial LVSI ^{**}					
IIC		High-grade histologies [‡] , myoinvasion					
				Cervical stromal invasion, no focal LVSI			
				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					
IIC	IIC1	Pelvic lymph node metastasis					
	IIC1i	Micrometastasis					
	IIC1ii	Macrometastasis					
	IIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIC2i	Micrometastasis					
	IIC2ii	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						
II-IVA							
IVB							
IVC							

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data



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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

ADJUVANT THERAPY
HIGH-INTERMEDIATE RISK

ESTRO European Society of Pathology
ESGO European Society of Gynaecological Oncology

- 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].
 - GOG#249 EBRT compared to VBT+chemo (Randall et al. IJROBP 2017)
 - PORTEC-2 outcomes in molecular groups and risk factors (Wortman et al. BJC 2018), substantial LVSI (Bosse et al. EJC 2015)
 - PORTEC-1 & 2 molecular groups and radiotherapy response (Stello et al CCR 216; Horeweg et al. JCO 2023)
 - PORTEC-3 CCRT versus EBRT (de Boer et al. Lancet Oncol 2019); Molecular groups (Leon-Castillo et al. JCO 2020)



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ADJUVANT THERAPY
HIGH RISK

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)					
	IA2	Low-grade endometrioid, myoinvasion <50%, no focal LVSI				*	IICm p53abn
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary ^{††}				*	IICm p53abn
IB		Low-grade endometrioid, myoinvasion >50%, no focal LVSI				*	IICm p53abn
IC		High-grade histologies [‡] , limited to polyp/endometrium					
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma				*	IICm p53abn
IIIB		Low-grade endometrioid, substantial LVSI ^{††}				*	IICm p53abn
IIC		High-grade histologies [‡] , myoinvasion					IICm 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						
II-IVA							
IVB							
IVC							

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data



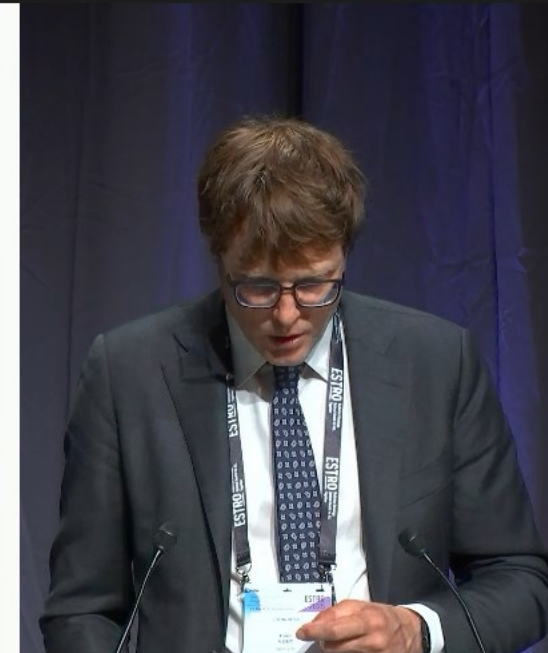
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This includes the following categories:

- 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

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 $\pm$ brachytherapy is an alternative option [I, B].
- For patients with FIGO 2023 stage IIIm-IVAm MMRd EC, adjuvant chemotherapy combined with and ICI ($\pm$ EBRT) should be considered [II, B].
- PORTEC-3 CCRT versus EBRT (de Boer et al. Lancet Oncol 2019); Molecular groups (Leon-Castillo et al. JCO 2020)
- GOG#258 CT vs CCRT (Matei et al. NEJM 2019)
- Keynote-B21 Immune Checkpoint Inhibition (van Gorp et al, Ann Oncol 2024)



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ADJUVANT THERAPY



Uncertain, lack
of data

2^{ème} Grey ZONE

2023 FIGO staging [†]			Molecular classification				
			POLEmut	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)					
	IA2	Low-grade endometrioid, myoinvasion <50%, no focal LVSI					
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary†					
IB		Low-grade endometrioid, myoinvasion >50%, no focal LVSI					
IC		High-grade histologies*, limited to polyp/endometrium					
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma					
IIIB		Low-grade endometrioid, substantial LVSI**					
IIC		High-grade histologies*, myoinvasion					
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					
IIC	IIC1	Pelvic lymph node metastasis					
	IIC1i	Micrometastasis					
	IIC1ii	Macrometastasis					
	IIC2	Para-aortic lymph node metastasis (up to renal vessels)					
	IIC2i	Micrometastasis					
	IIC2ii	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						
II-IVA		With residual disease					
IVB		Peritoneal disease					
IVC		Distant metastasis					

Definition of risk groups based on FIGO2023 staging and molecular classification

	Low
	Intermediate
	High-intermediate
	High
	Uncertain, lack of data



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ADJUVANT THERAPY

FIGO 2023 STAGES IIIImPOLE_{mut} and IVAm POLE_{mut}

- This part includes the following categories:

- FIGO 2023 stages IIIImPOLE_{mut}
- FIGO 2023 stage IVAm POLE_{mut}

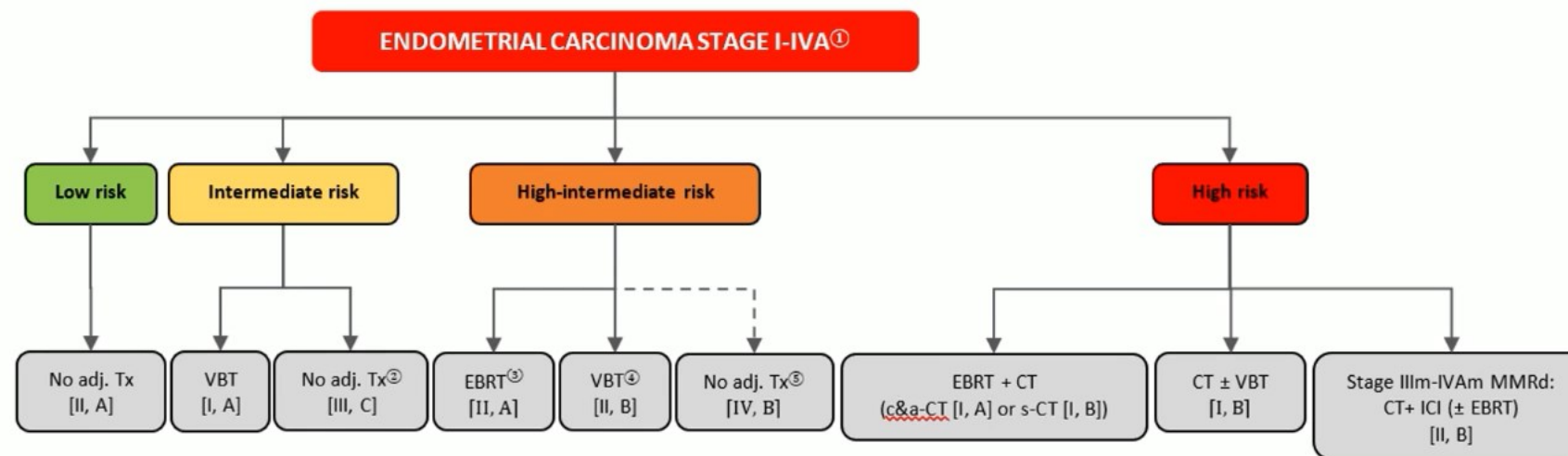
ADJUVANT THERAPY**FIGO 2023 STAGES IIImPOLE_{mut} and IVAm POLE_{mut}**

- For patients with FIGO 2023 stage IIIm *POLE*_{mut} and IVAm *POLE*_{mut} (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].

- Good outcomes POLE in PORTEC-3 molecular groups (Leon-Castillo et al. JCO 2020)
- Good outcomes in surgery alone Danish high-grade cohort (Leon-Castillo et al. Gyn Onc 2022)



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^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 IIIIm *POLE*mut & IVAm *POLE*mut, no firm recommendation can be given, however de-escalation from high-risk treatment can be considered.

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

^③ EBRT is recommended for optimal pelvic control.

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

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

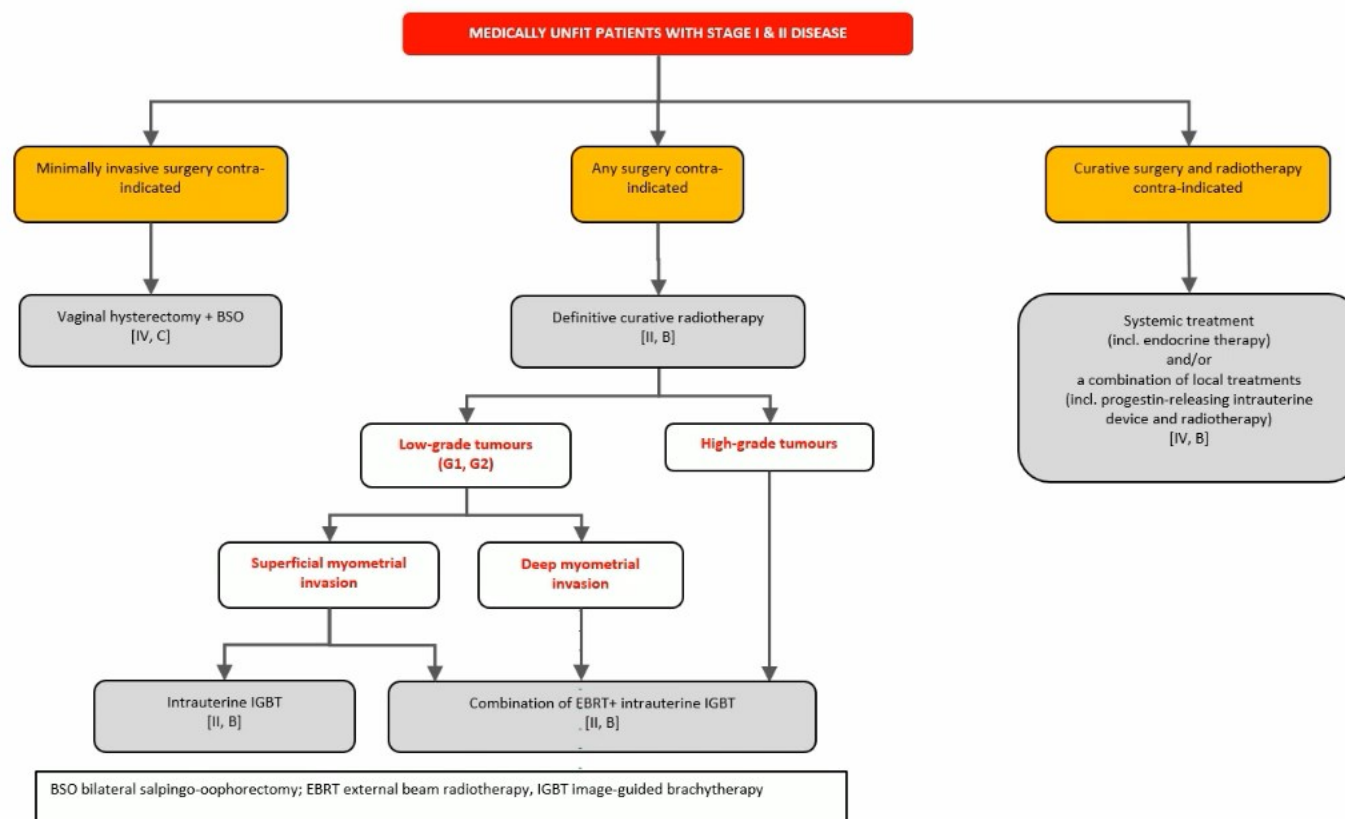
Adj. Tx adjuvant therapy; c&a-CT concurrent and adjuvant chemotherapy; CT chemotherapy; EBRT external beam radiotherapy; ICI immune checkpoint inhibitor; s-CT sequential chemotherapy; VBT vaginal brachytherapy.

Adjuvant therapy in endometrial carcinoma stage I-IVA

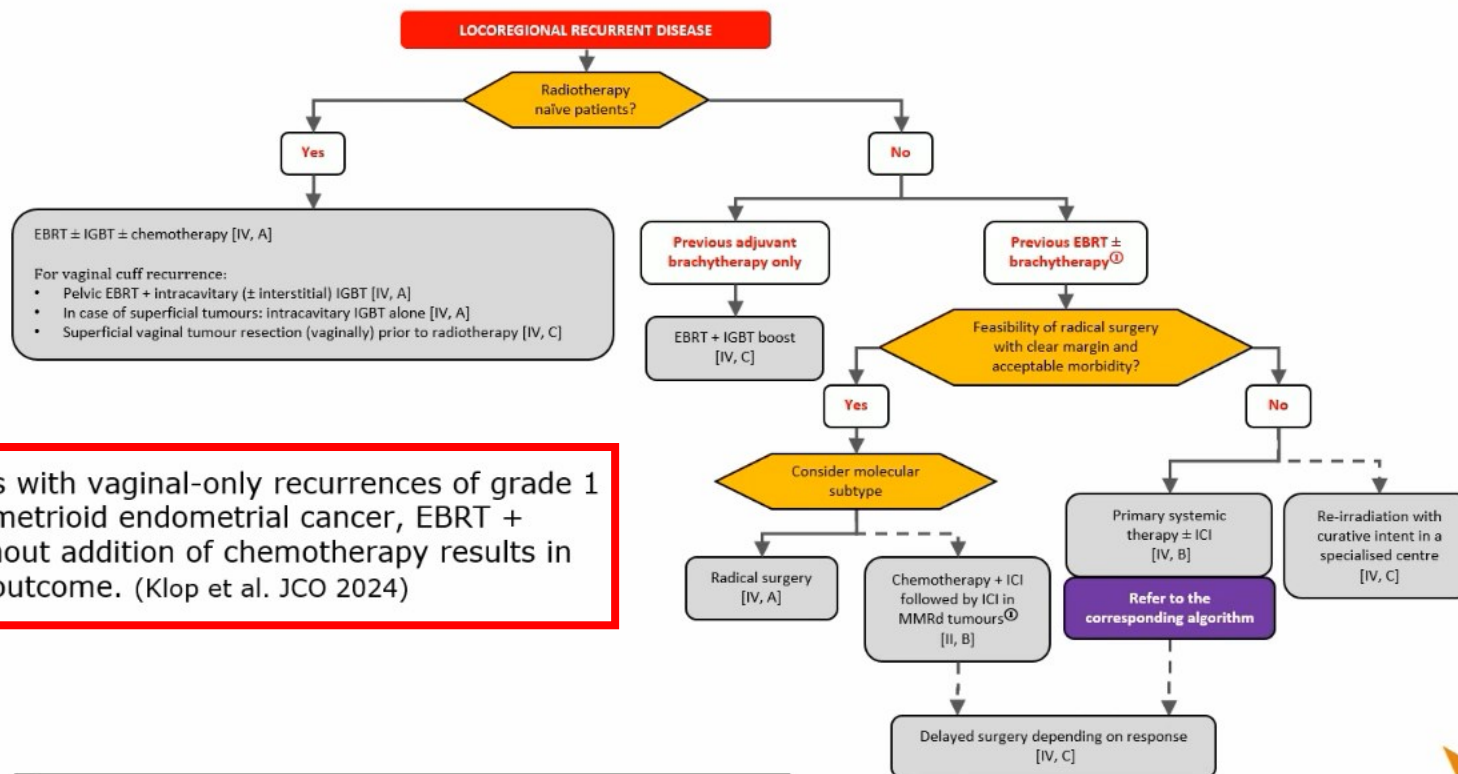


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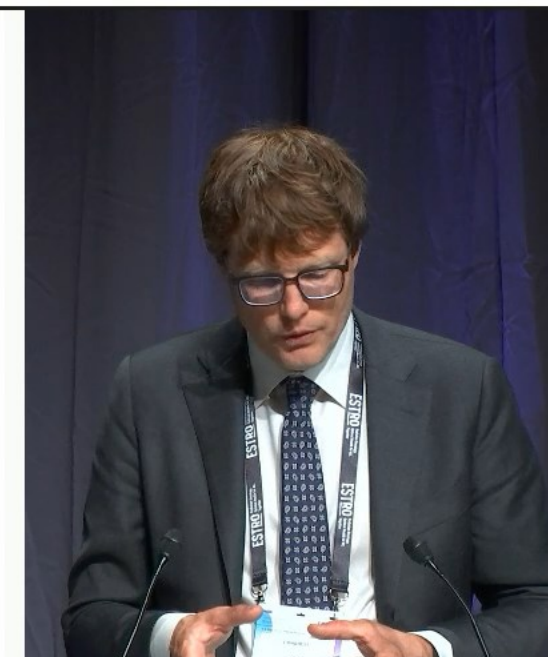
Cas particuliers

Medically unfit patients with stage I & II disease**Remi Nout**
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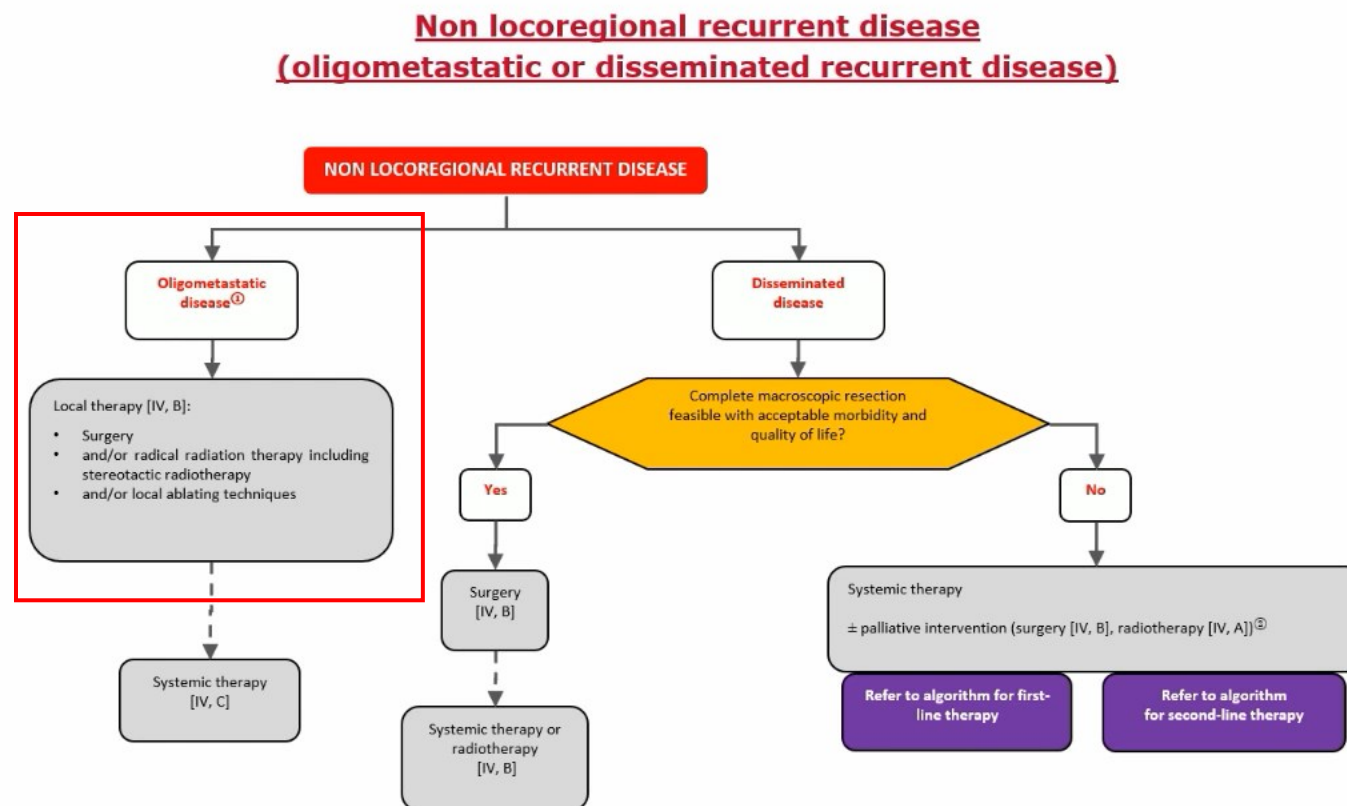
Locoregional recurrent disease



- In patients with vaginal-only recurrences of grade 1 or 2 endometrioid endometrial cancer, EBRT + IGBT, without addition of chemotherapy results in excellent outcome. (Klop et al. JCO 2024)

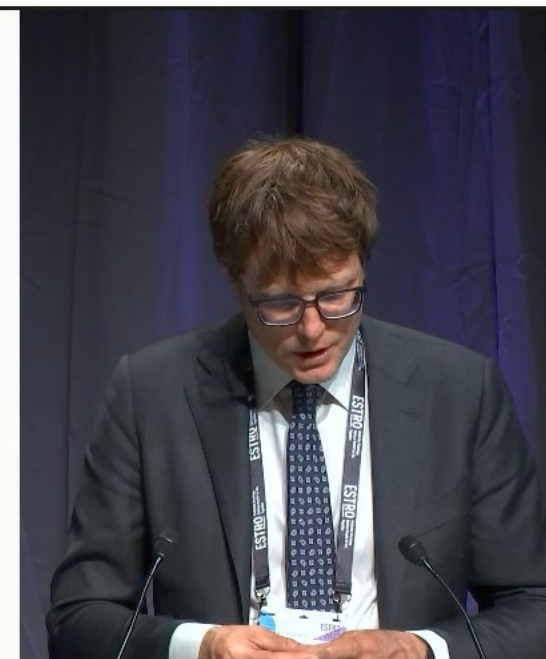


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① 1-5 metastases/up to 3 regions.

② Palliative surgery can be performed in selected cases to alleviate symptoms (e.g. bleeding, fistula, bowel obstruction). Palliative radiotherapy is indicated for symptoms related to pelvic or systemic disease.



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PORTEC 4a

Hypothesis and aims of the PORTEC-4a trial

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



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

Hypothesis and aims of the PORTEC-4a trial

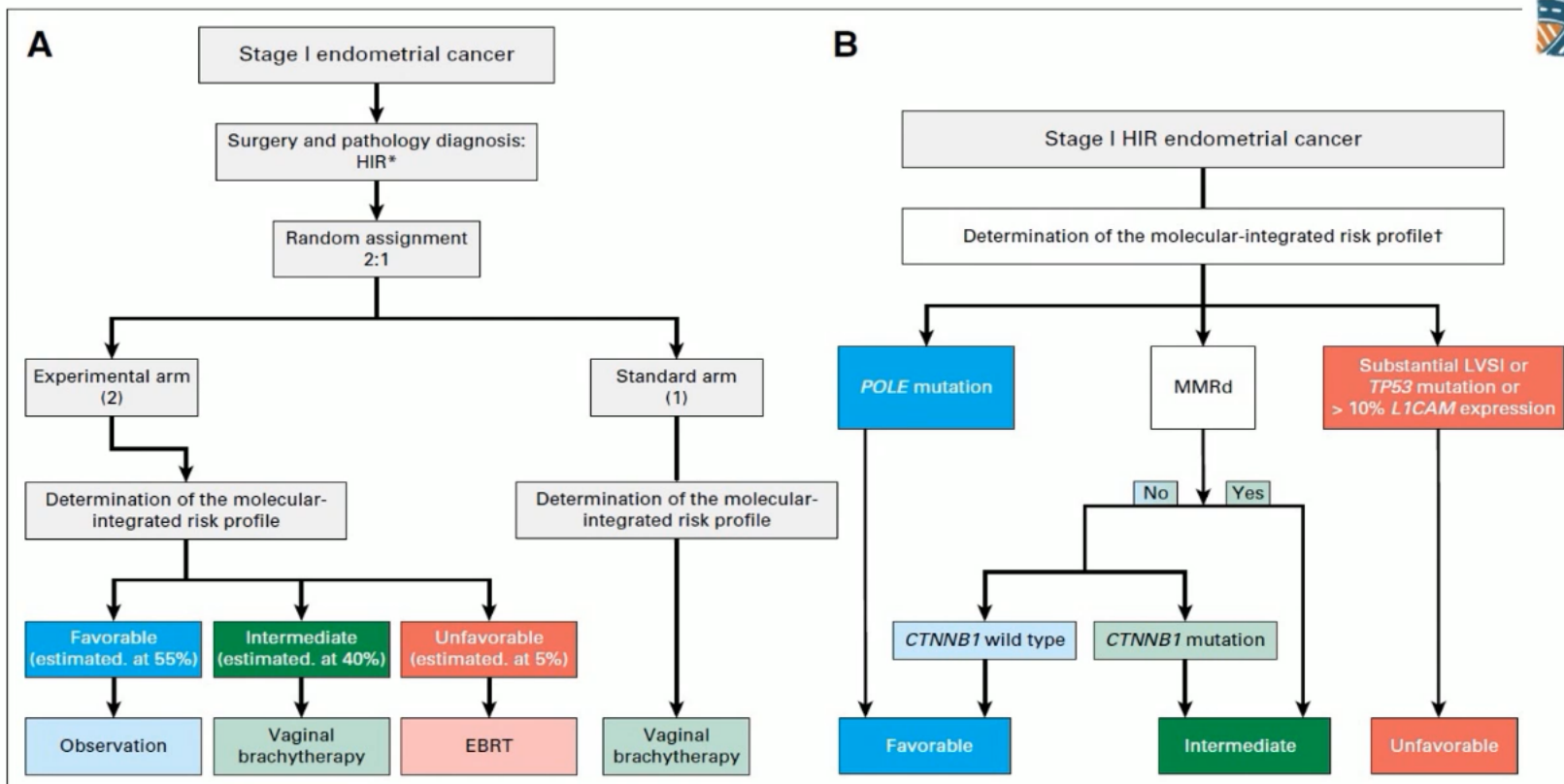
- Molecular-integrated profile-based individualised adjuvant treatment reduces over- and undertreatment in patients with HIR-EC
- Primary endpoint
 - 5-year cumulative incidence of vaginal recurrence
- Secondary endpoints
 - Recurrence-free and overall survival
 - Vaginal tumour control
 - Pelvic, locoregional and distant recurrence
 - Adverse events and Quality of life
 - EC related healthcare costs



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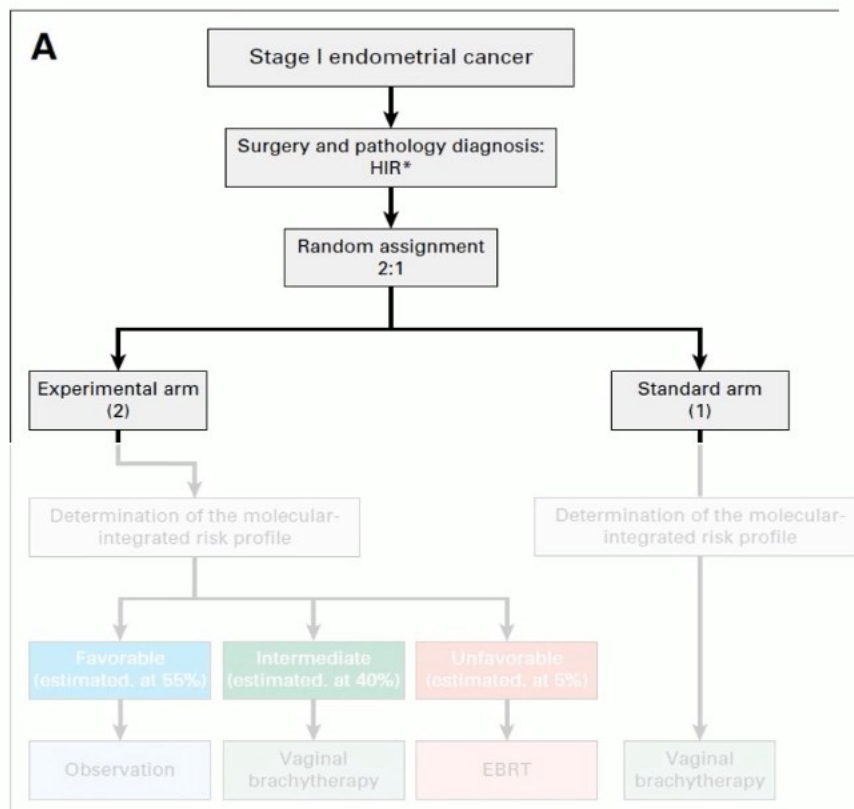
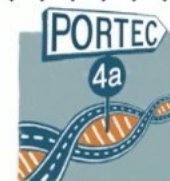
Design PORTEC-4a trial 2016 - 2021



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

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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



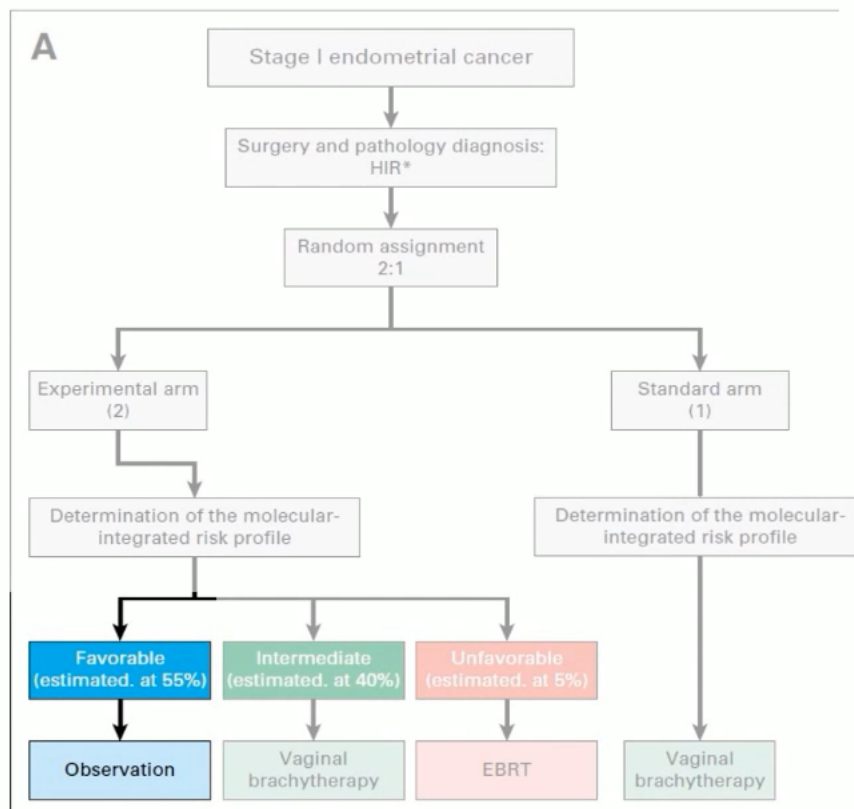
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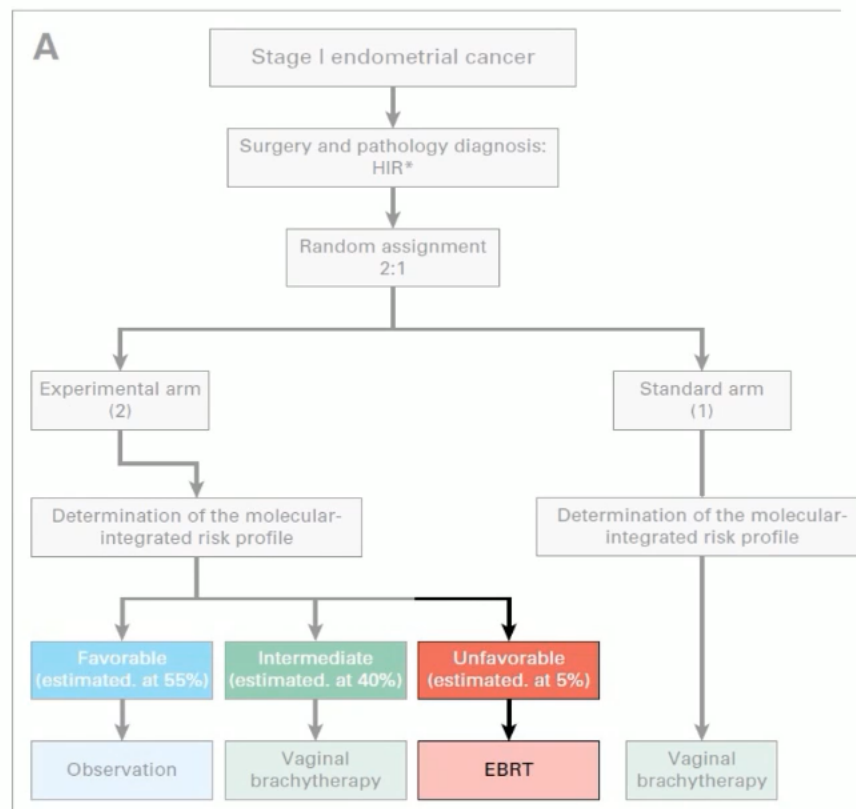


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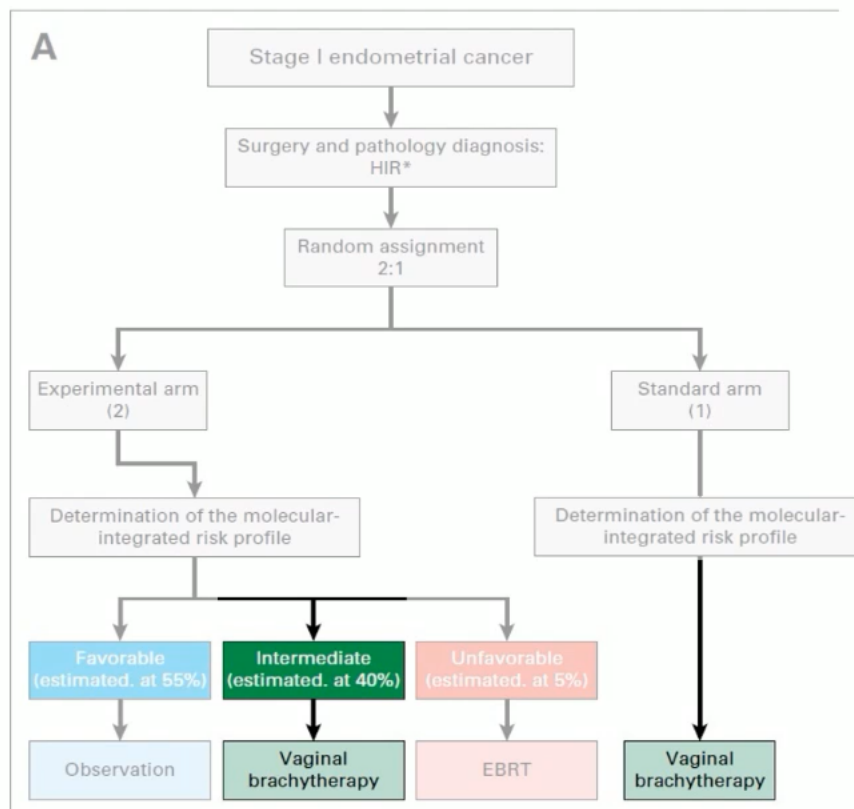


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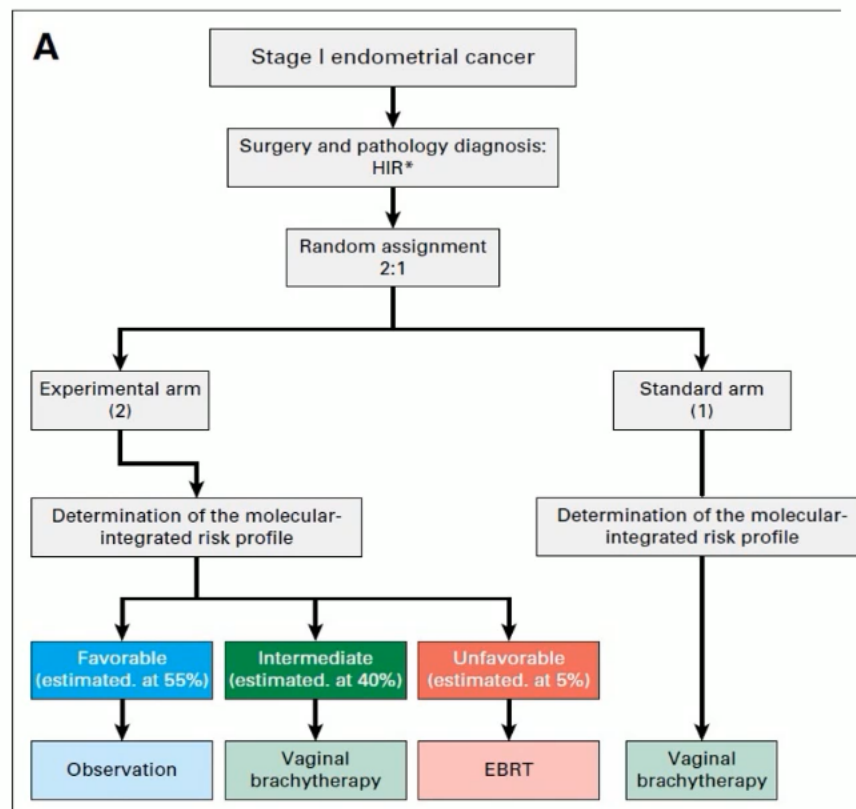


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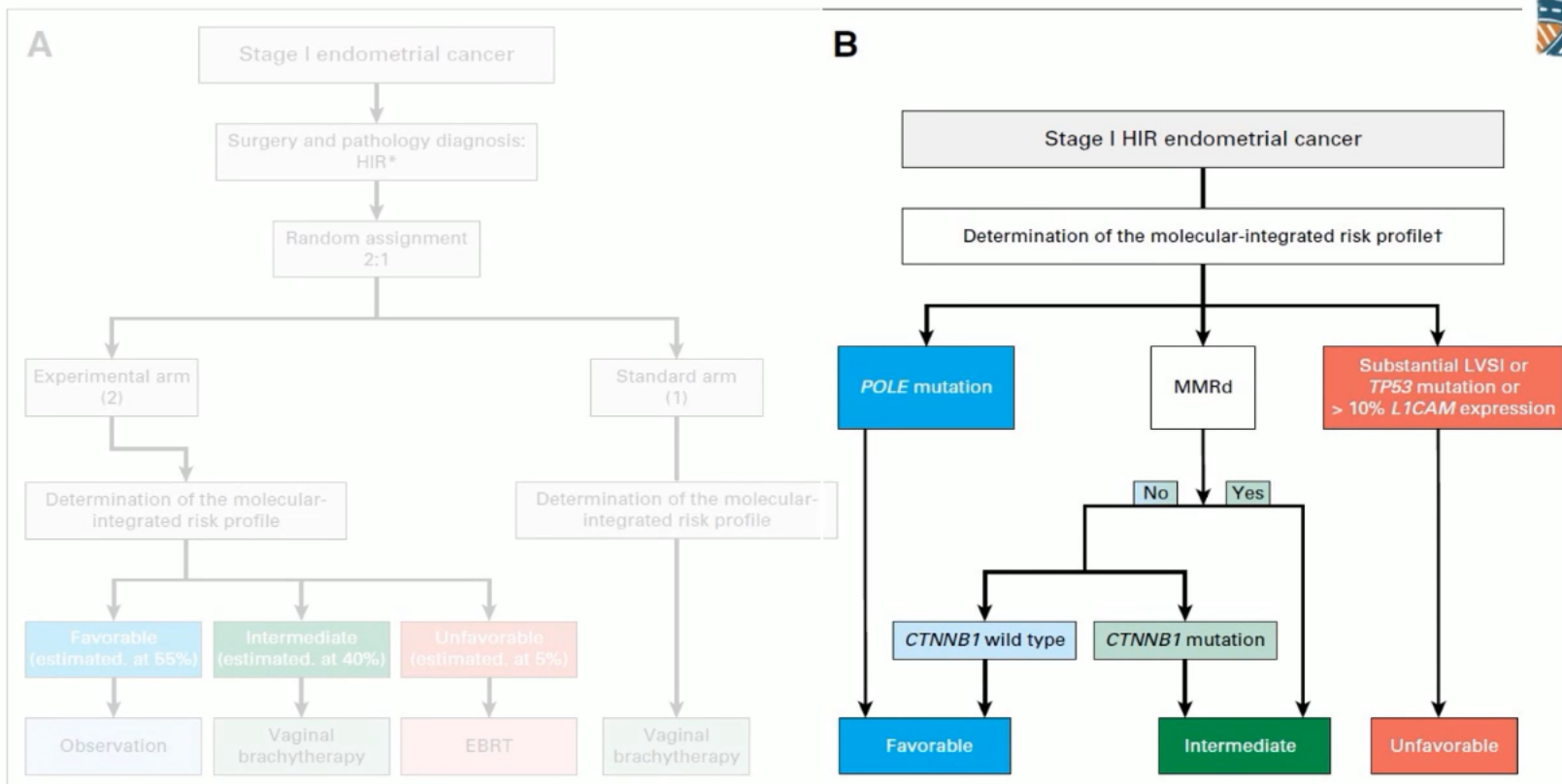
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- Results of the molecular risk profile were shared with treating physicians in the molecular-profile arm (< 2 weeks)

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

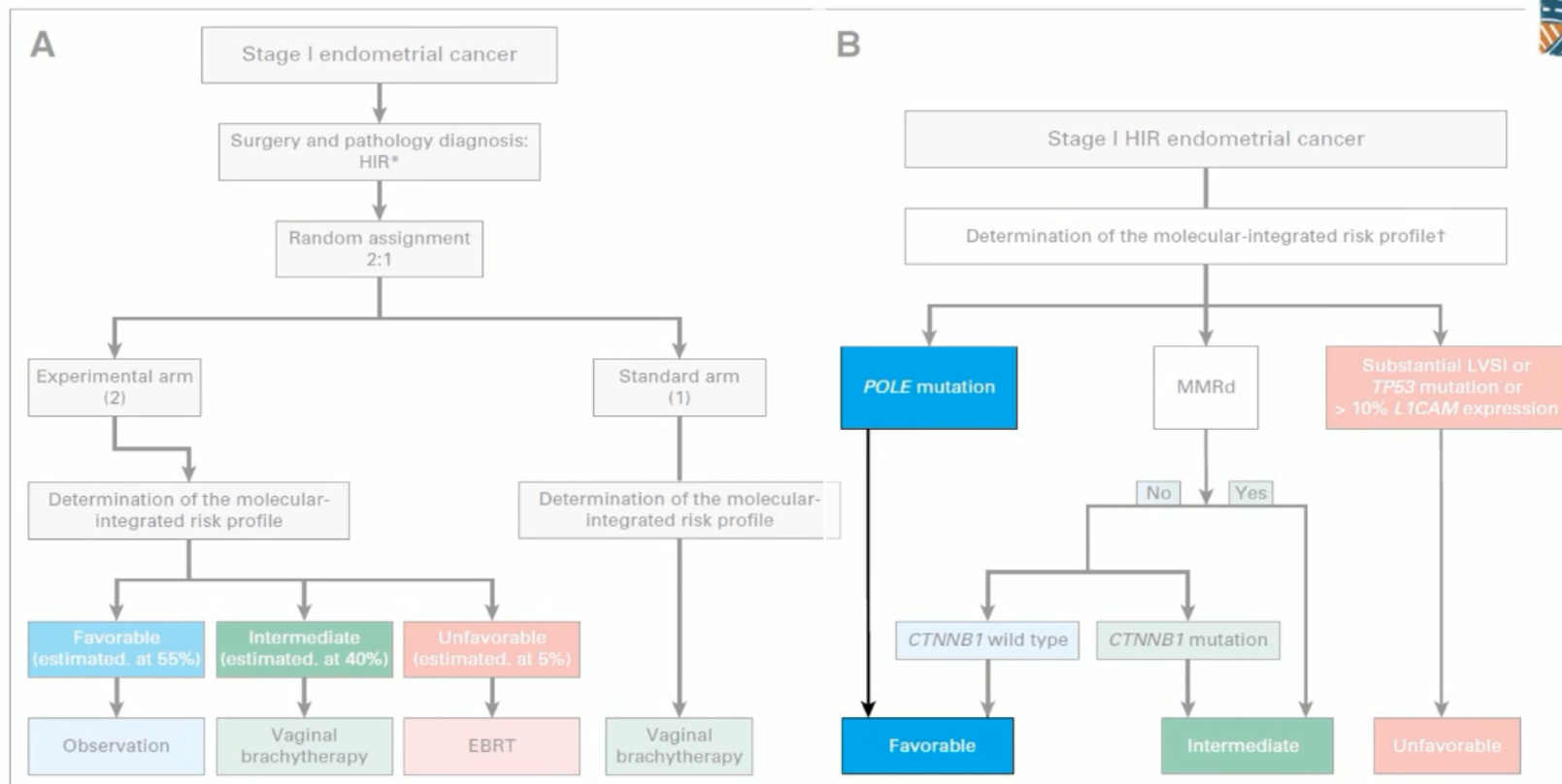
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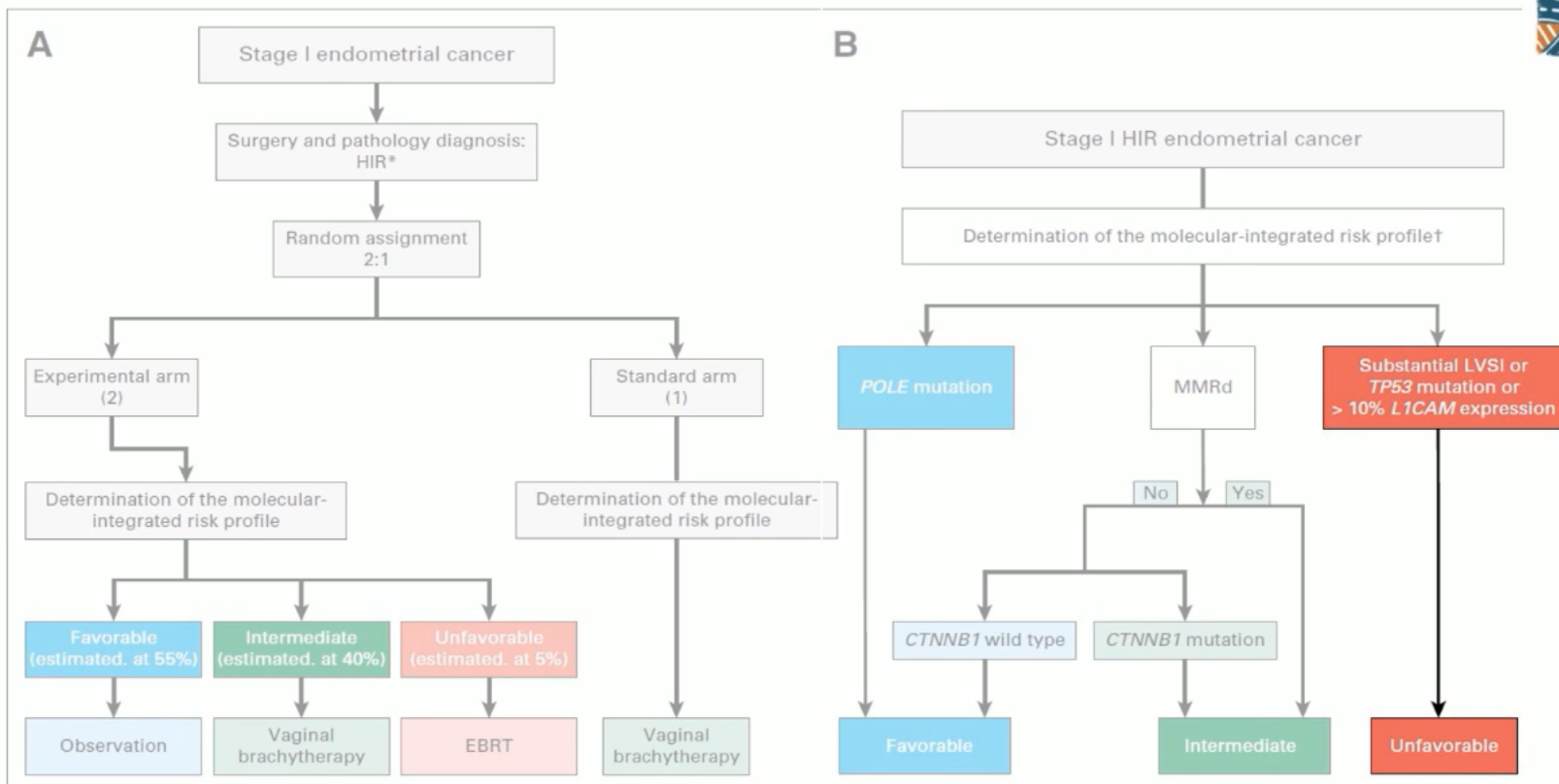
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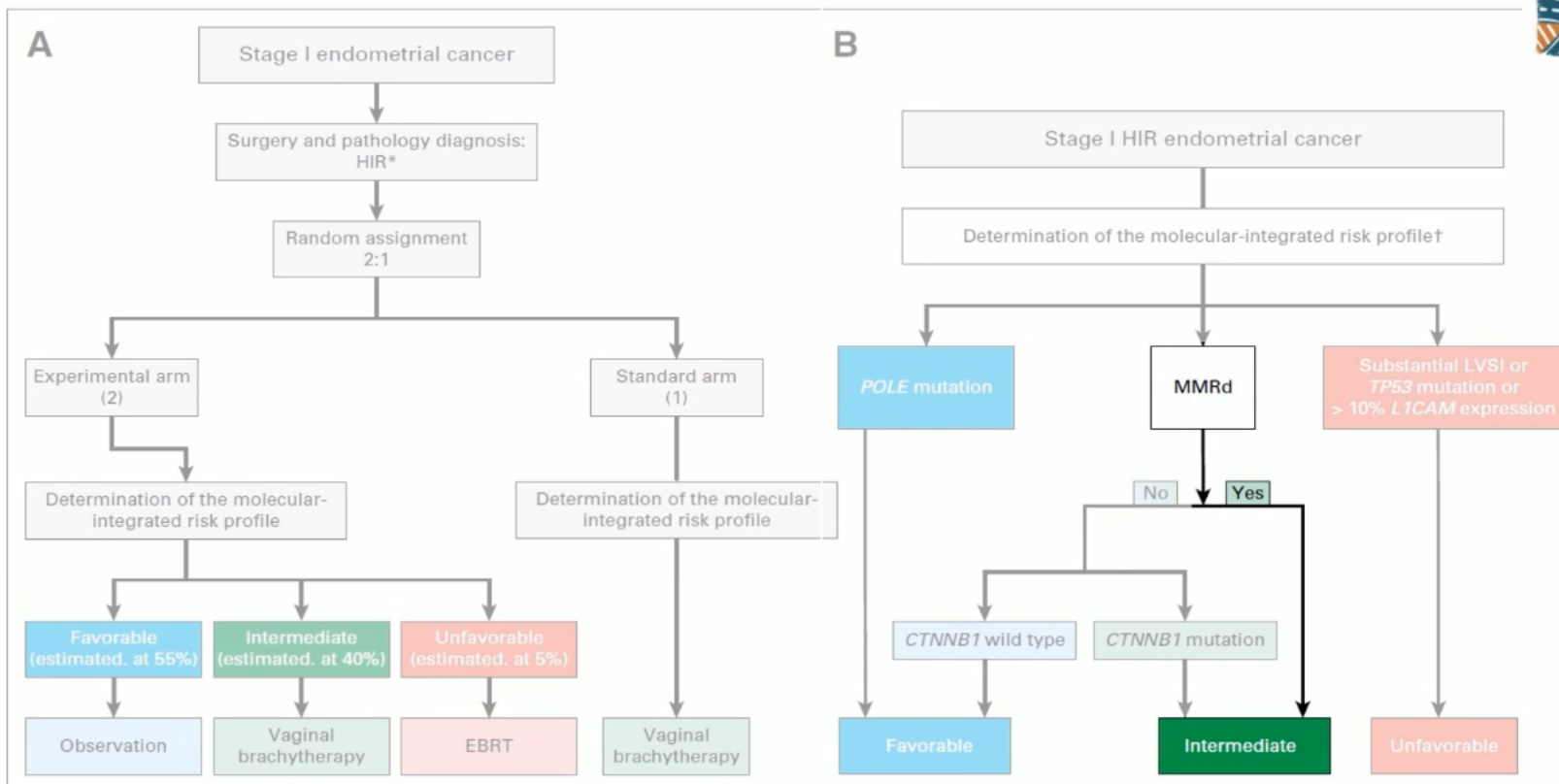
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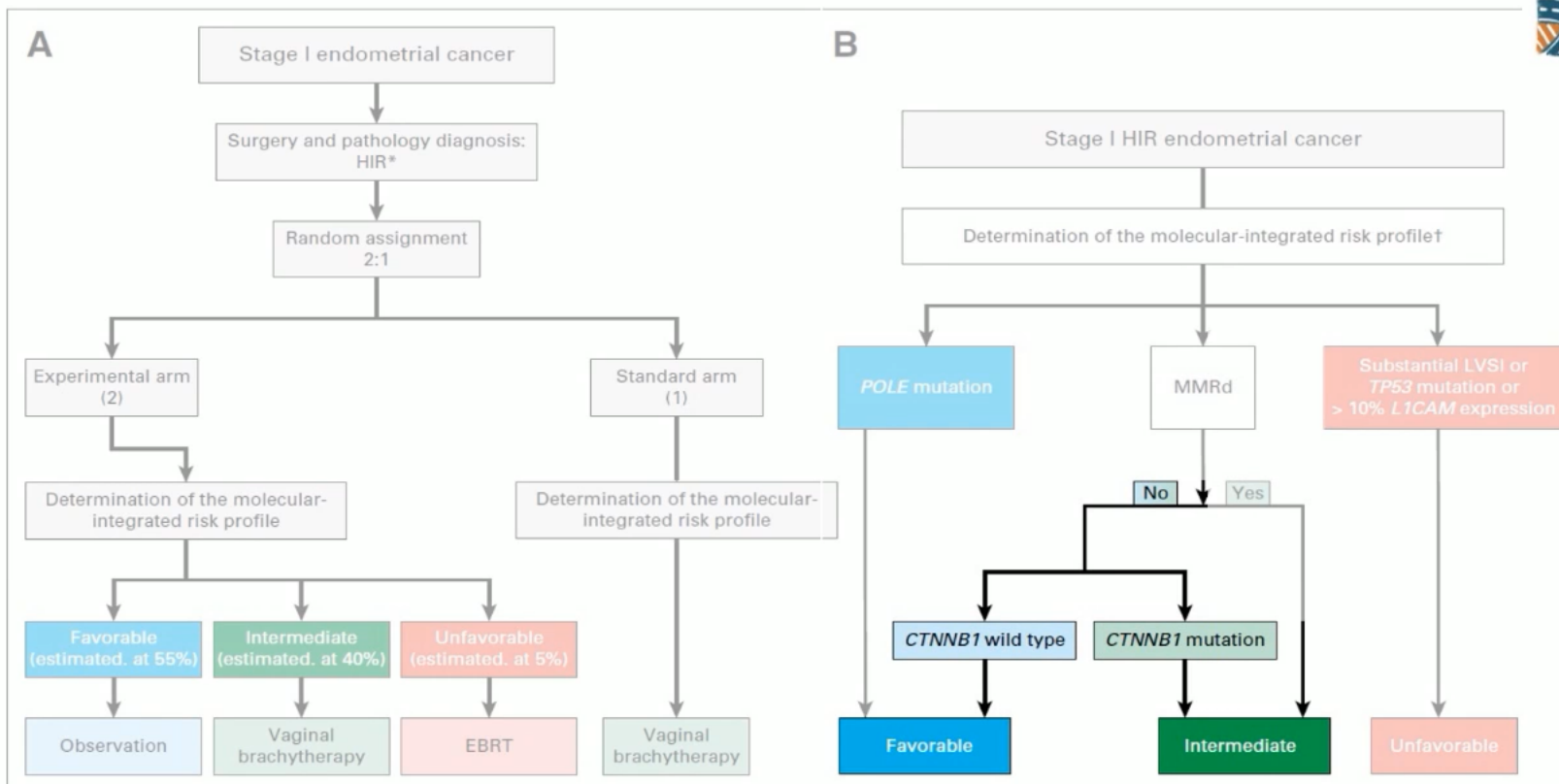
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Statistical analysis

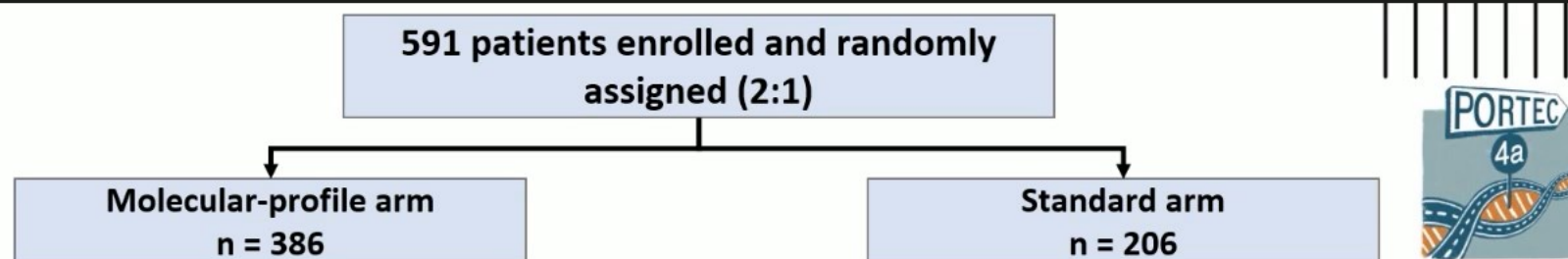


- Non-inferiority design
 - To exclude a clinically relevant difference in cumulative incidence of vaginal recurrence
 - With an equivalence margin of 7% in the **whole PORTEC-4a population**
 - With an equivalence margin of 8.5% in **those with a favourable profile**
 - Descriptive comparison of outcomes in patients with unfavourable profile
- Analysis of endpoints
 - Log-rank, Kaplan Meier and Cox regression
 - Competing risk analysis for vaginal, pelvic, locoregional and distant recurrence

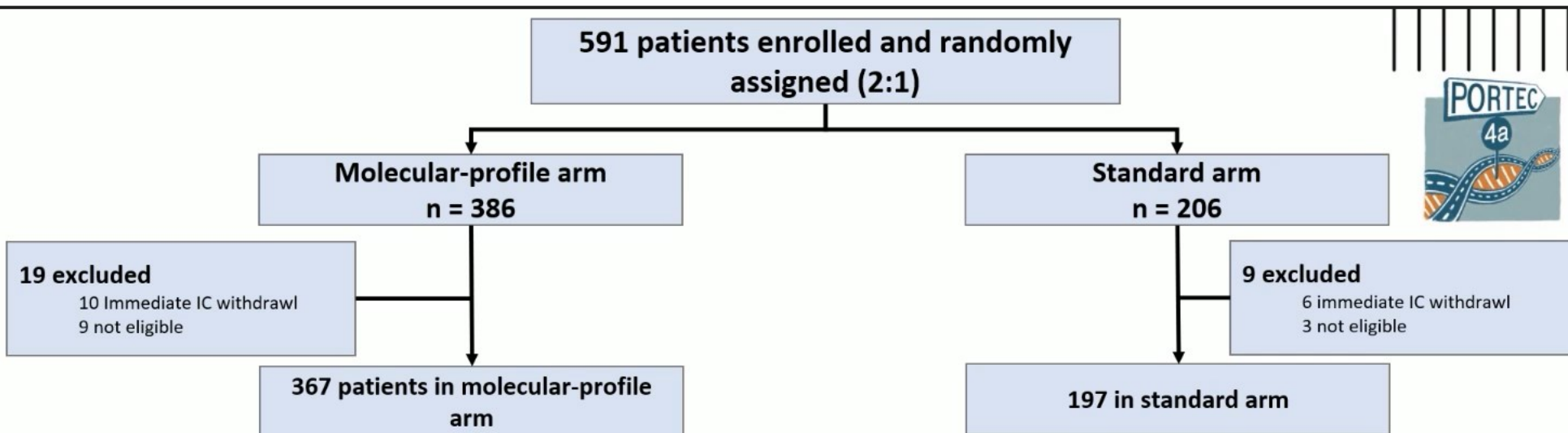


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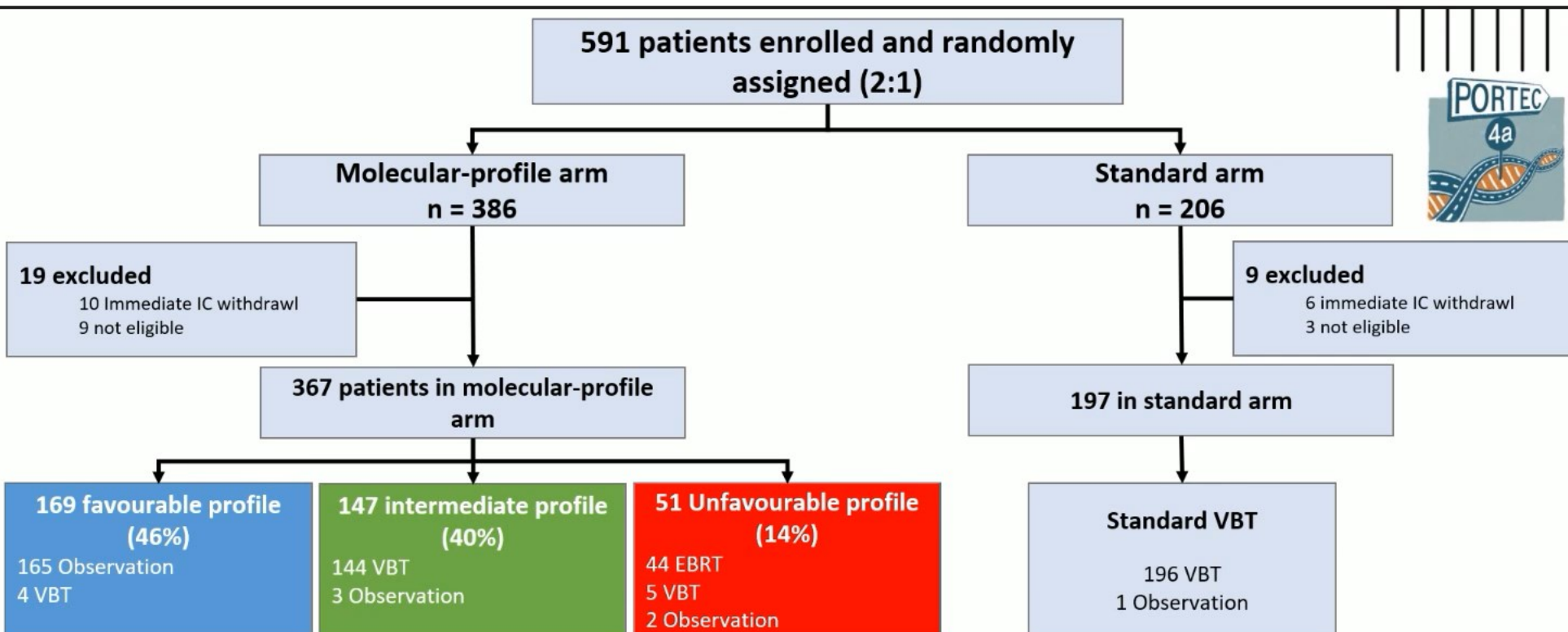
Van den Heerik et al, IJGC, 2020; Putter et al, Stat Med, 2009



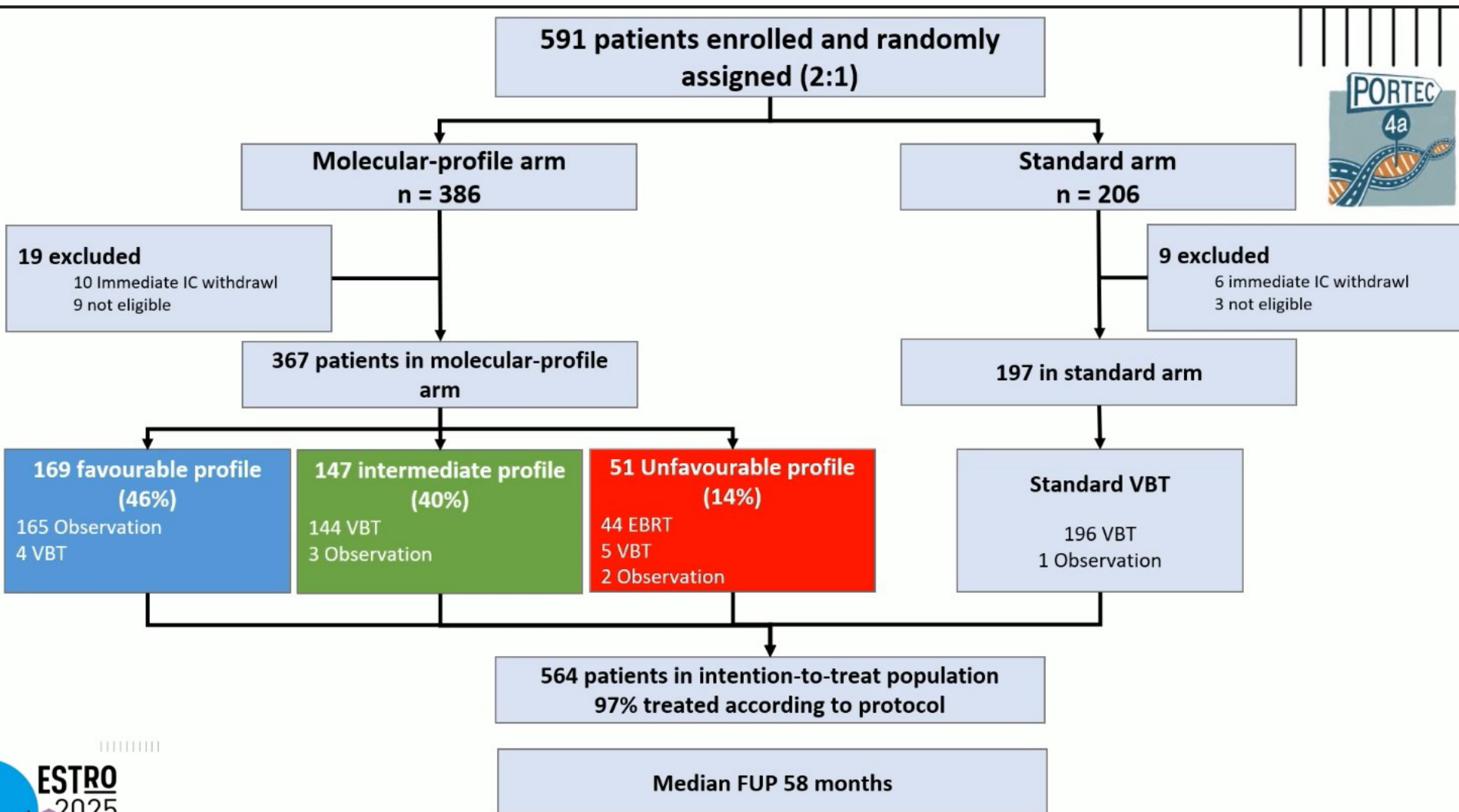
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Patient characteristics



		Molecular-profile arm n = 367	Standard VBT arm n = 197
Age	Median (IQ Range)	69 (41 - 89)	69 (36-90)
WHO status	0	75%	69%
	1	23%	30%
	2	2%	2%
Type of surgery	TAH-BSO	11%	15%
	TAH-BSO and lymphadenectomy	12%	11%
	Laparoscopy	64%	61%
	Laparoscopy and lymphadenectomy	13%	13%



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Tumour characteristics



		Molecular-profile arm n = 367	Standard VBT arm n = 197
FIGO stage (2009)	IA	13%	13%
	IB	82%	83%
	II	5%	5%
Grade	grade 1-2	85%	84%
	grade 3	16%	16%
LVSI	None/focal	91%	92%
	Substantial	9%	8%
Molecular class	<i>POLE</i>	9%	9%
	MMRd	31%	24%
	NSMP	57%	63%
	p53-abnormal	3%	4%
L1CAM	<10% expression	91%	94%
	>10% overexpression	9%	6%



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Tumour characteristics

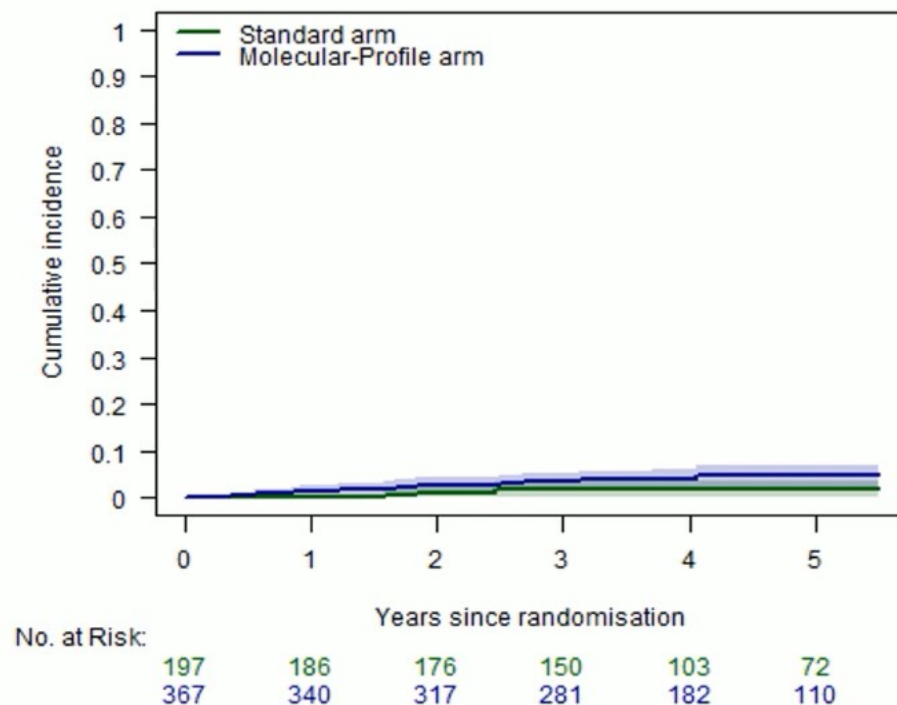
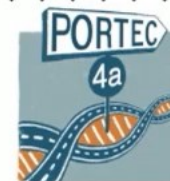


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Vaginal recurrence



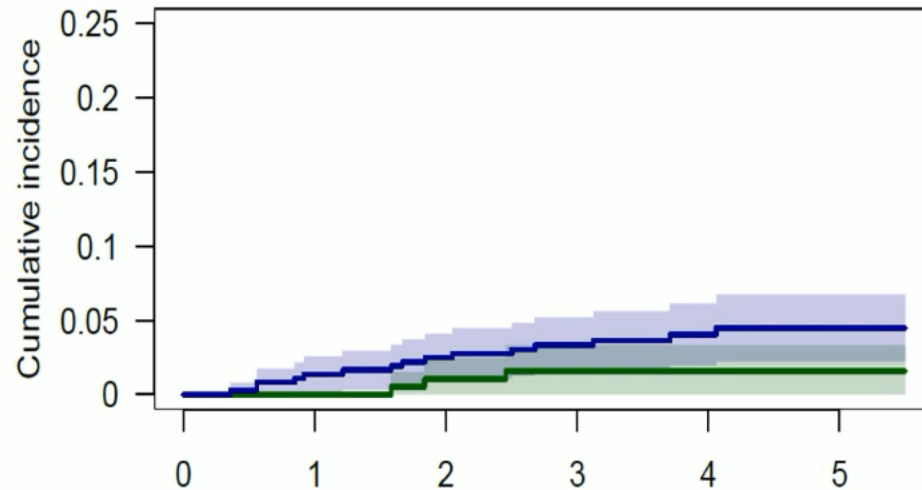
Only 23 vaginal recurrences

- 8 isolated, of which 4 in distal vagina



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Vaginal recurrence



4.5% vs 1.6% at 5 years

HR 2.71 (95% CI 0.79 - 9.34)

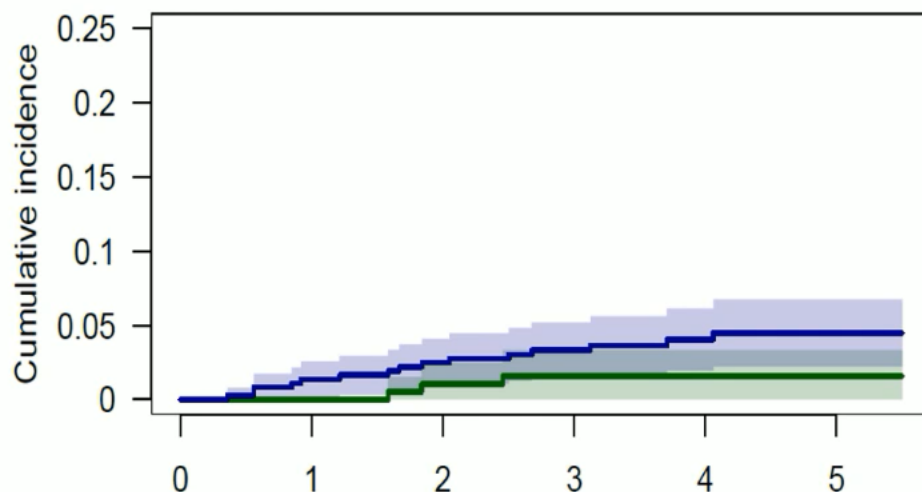
No. at Risk:

Years since randomisation					
0	1	2	3	4	5
197	186	176	150	103	72
367	340	317	281	182	110



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Vaginal recurrence



4.5% vs 1.6% at 5 years

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One-sided equivalence margin of 5.3%

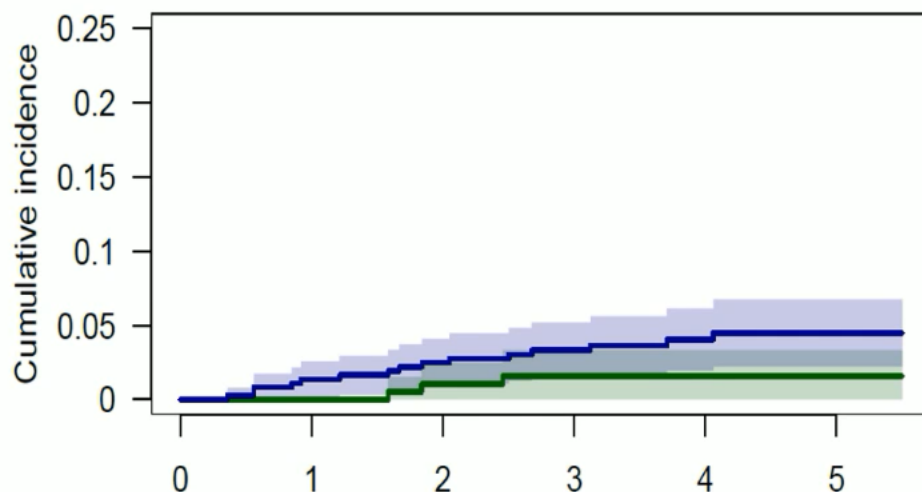
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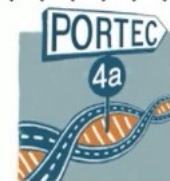
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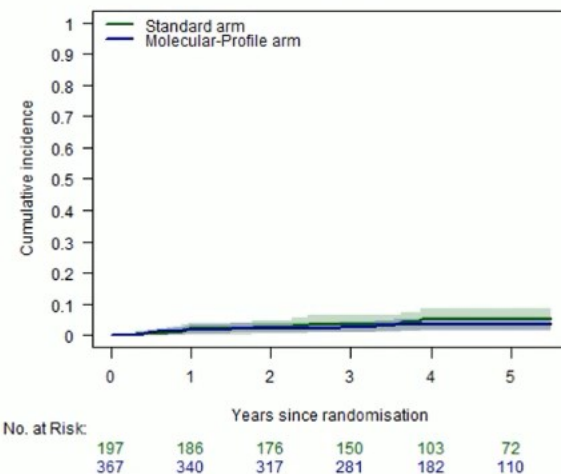
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Molecular-profile based treatment is non-inferior to standard VBT

Pelvic and combined vaginal/pelvic (locoregional) recurrence Distant metastasis

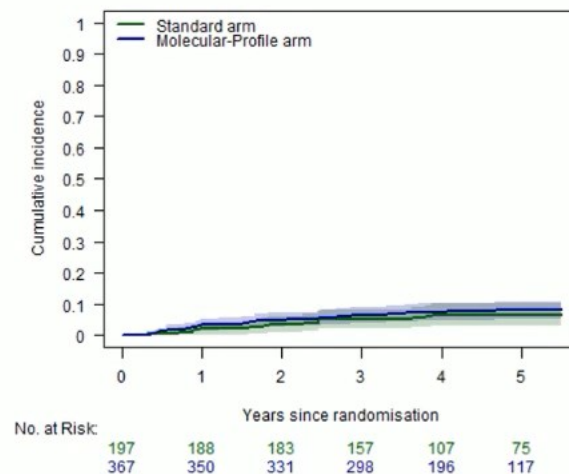


Pelvic recurrence



3.2% vs 5.2% ($p=0.32$)

Locoregional recurrence

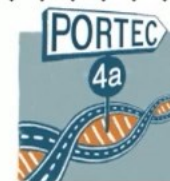


8.8% vs 7.5% ($p=0.62$)

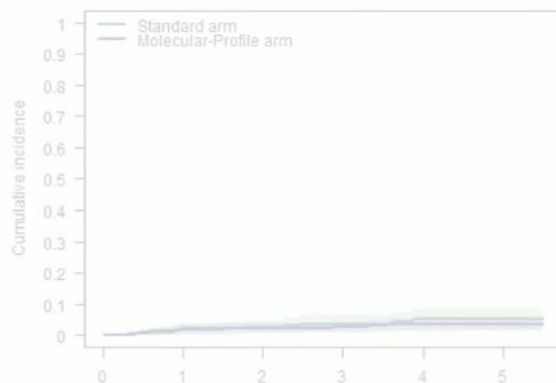


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Pelvic and combined vaginal/pelvic (locoregional) recurrence Distant metastasis

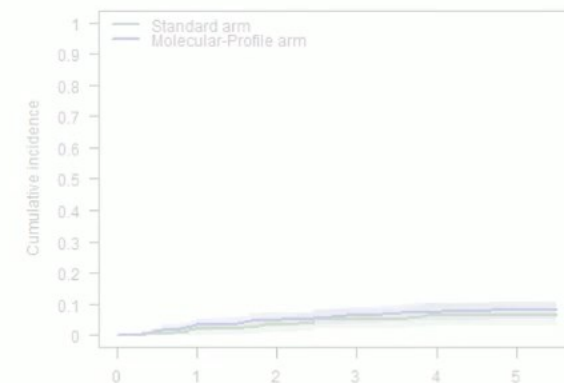


Pelvic recurrence



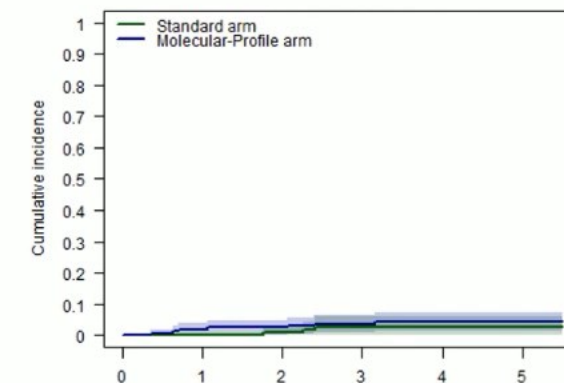
3.2% vs 5.2% ($p=0.32$)

Locoregional recurrence



8.8% vs 7.5% ($p=0.62$)

Distant recurrence

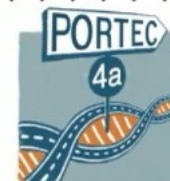


10.4% vs 10.5% ($p=0.99$)

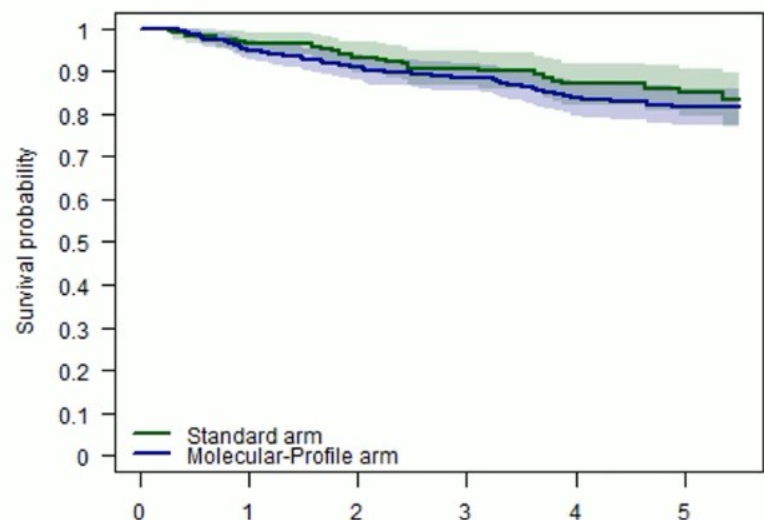


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Recurrence-free and overall survival



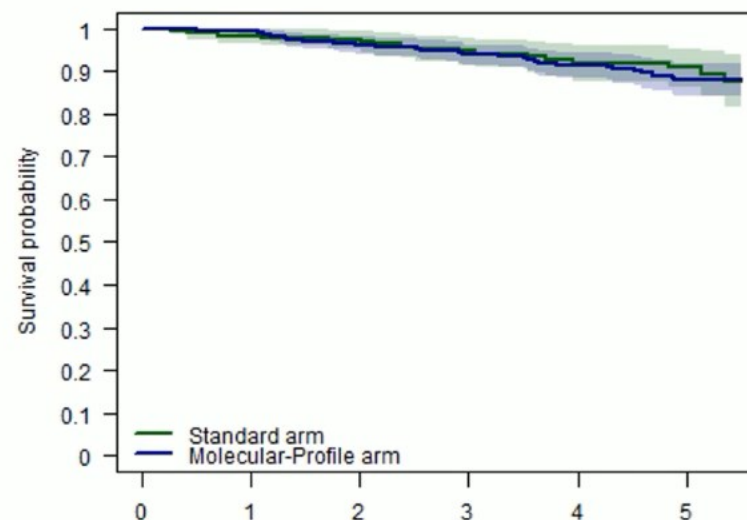
Recurrence-free survival



No. at Risk:						
0	1	2	3	4	5	
197	188	180	155	107	74	
367	345	324	292	189	115	

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

Overall survival



No. at Risk:						
0	1	2	3	4	5	
197	192	188	163	111	78	
367	361	343	310	210	125	

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

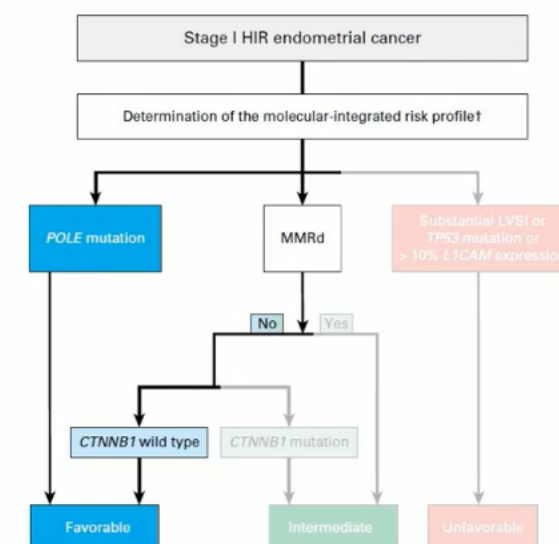
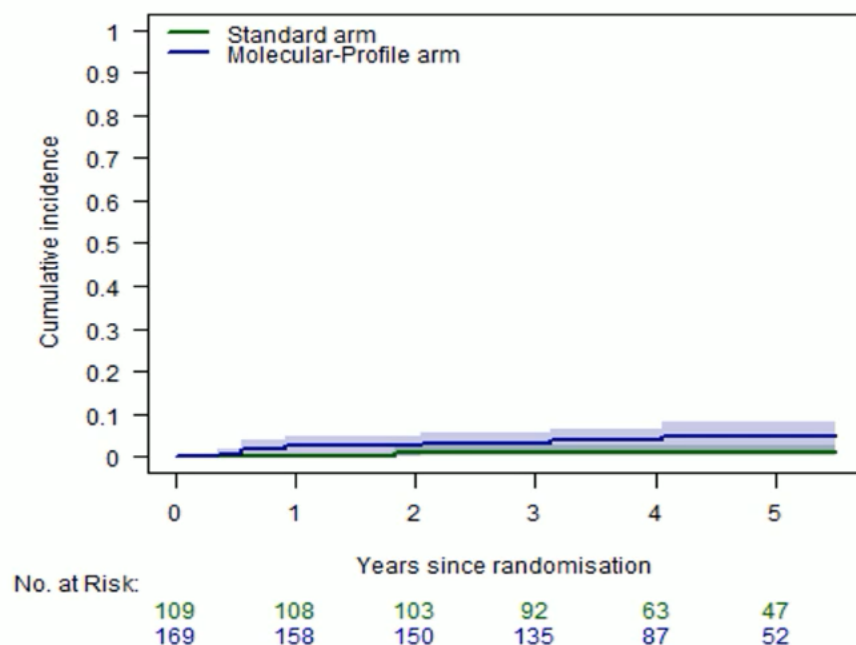


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Netherlands

Vaginal recurrence - Favourable profile



Vaginal recurrence, favourable subgroup

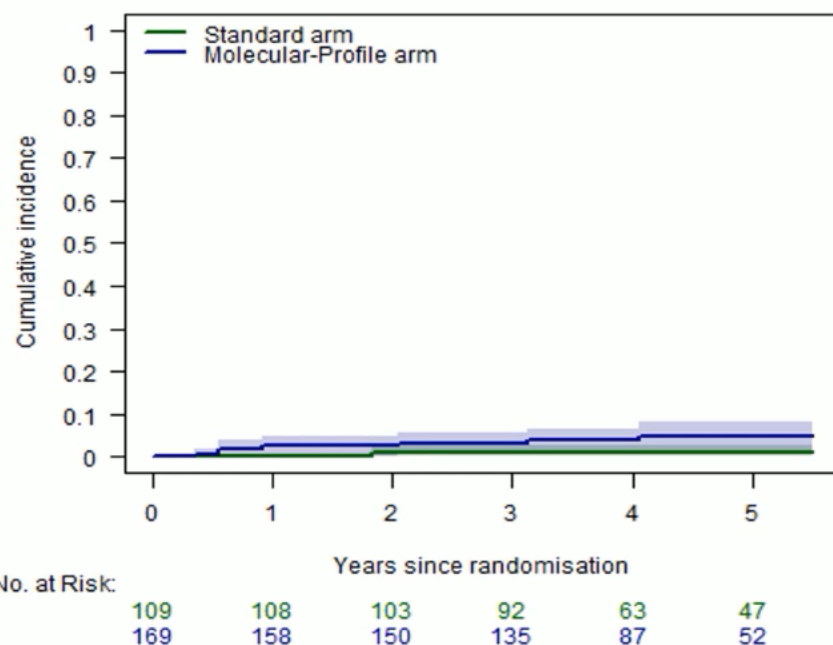


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Vaginal recurrence - Favourable profile



Vaginal recurrence, favourable subgroup



4.7% vs 0.9% (HR 4.61, $p=0.09$)

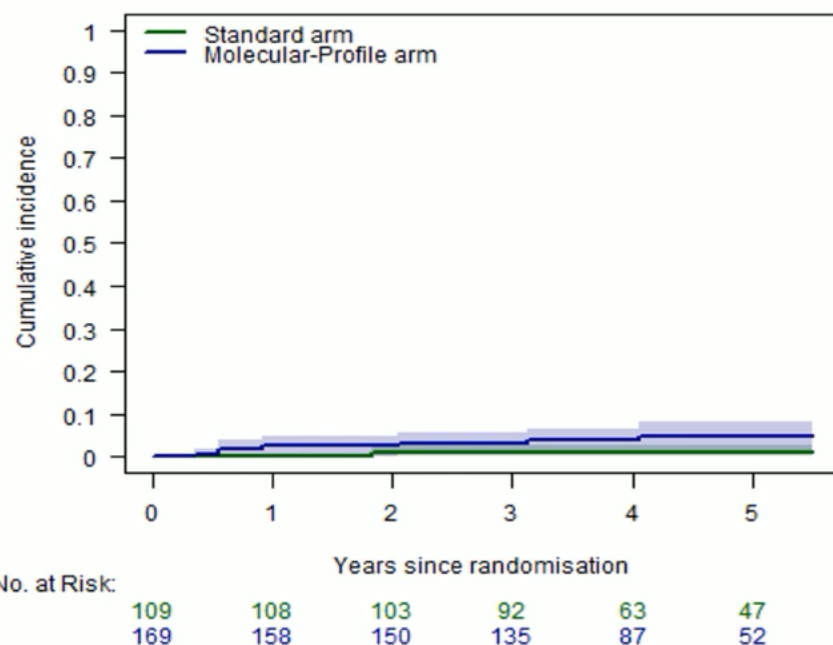


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Vaginal recurrence - Favourable profile



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4.7% vs 0.9% (HR 4.61, $p=0.09$)

One-sided equivalence margin of 7.0%

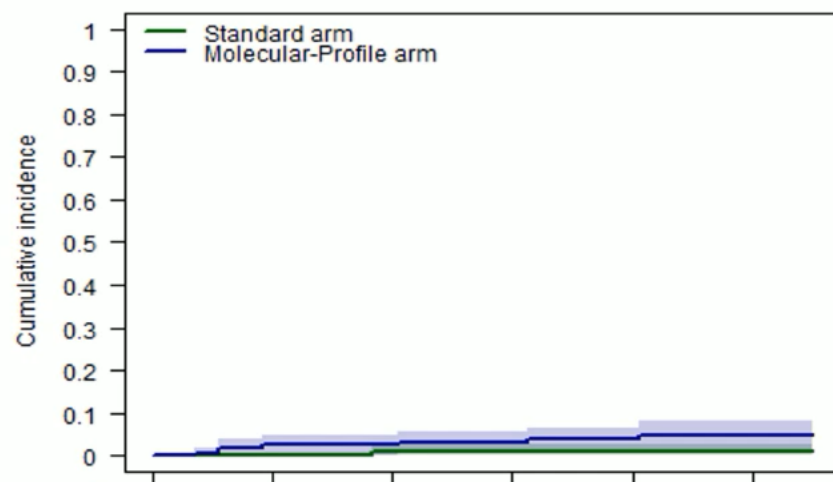


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Vaginal recurrence - Favourable profile



Vaginal recurrence, favourable subgroup



4.7% vs 0.9% (HR 4.61, $p=0.09$)

One-sided equivalence margin of 7.0%

Omission of adjuvant treatment in patients with a favourable profile is non-inferior to standard VBT

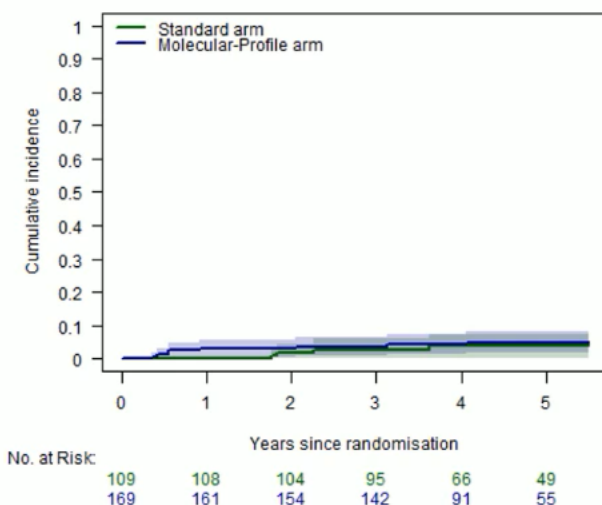


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Locoregional recurrence in the three molecular profiles

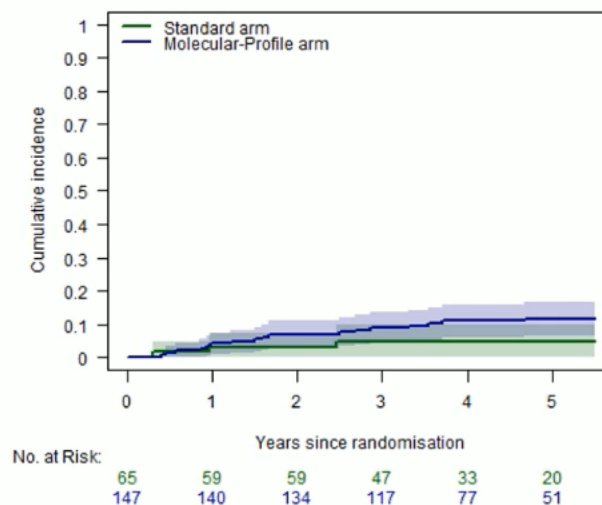


Favourable profile



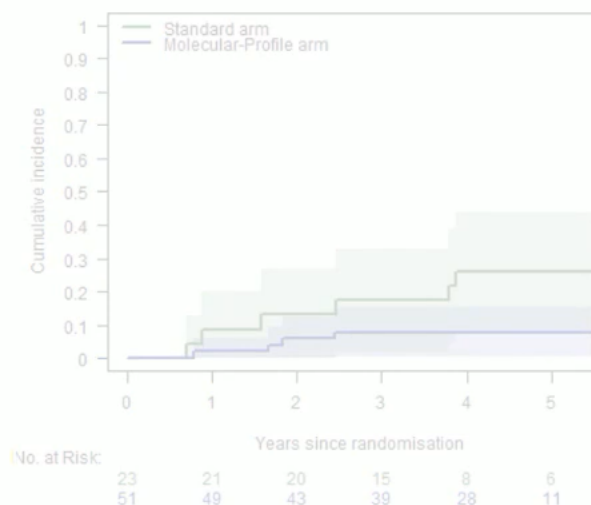
5.2% vs 4.1%
($p=0.60$)

Intermediate profile



13.0% vs 4.7%
($p=0.21$)

Unfavourable profile

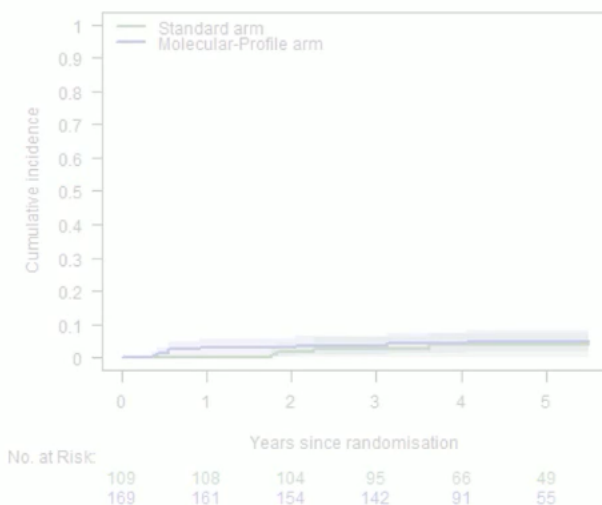


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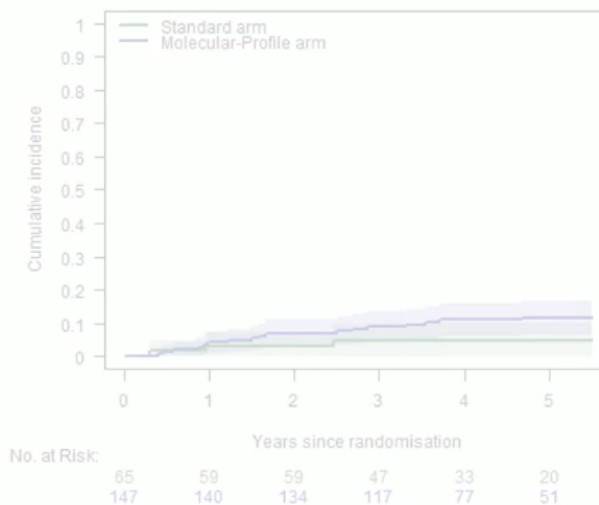
Locoregional recurrence in the three molecular profiles



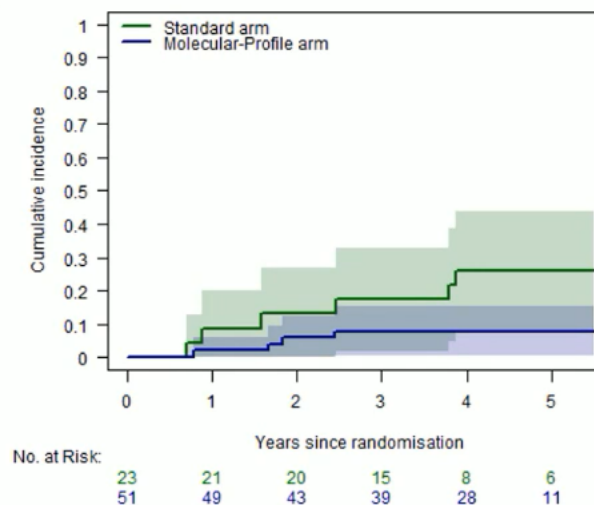
Favourable profile



Intermediate profile



Unfavourable profile



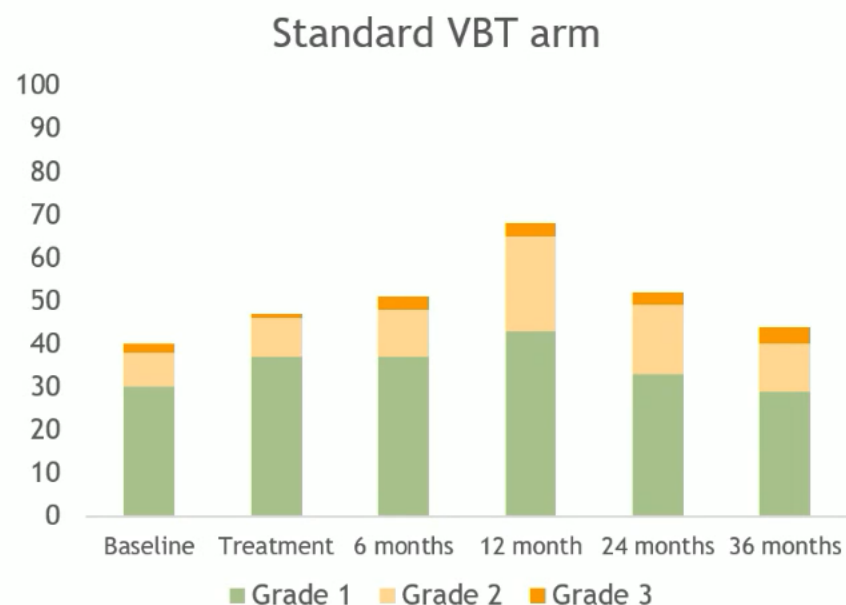
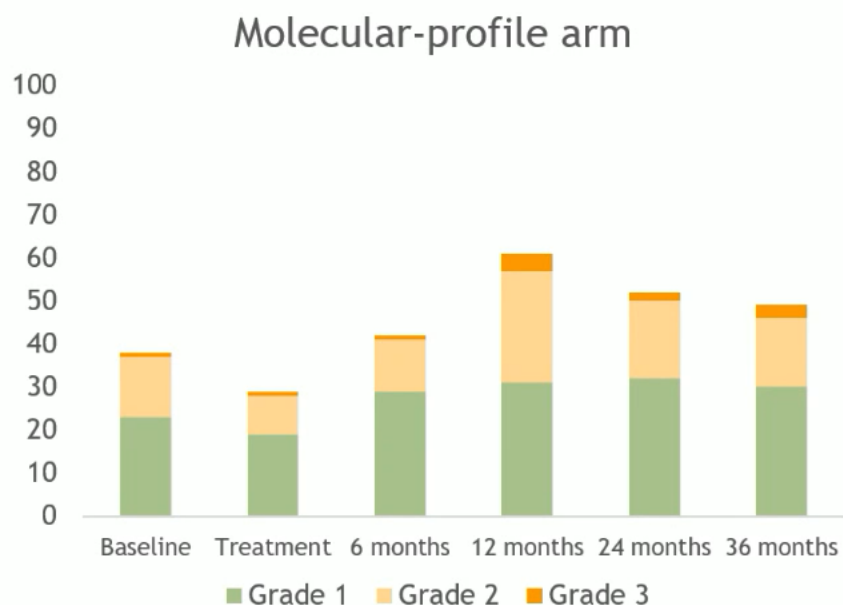
8.4% vs 30.5%
(HR 0.28, $p=0.05$)



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Adverse events (CTCAE v4.0) - All events

- Only 5 Serious Adverse Events, of which 1 possibly related

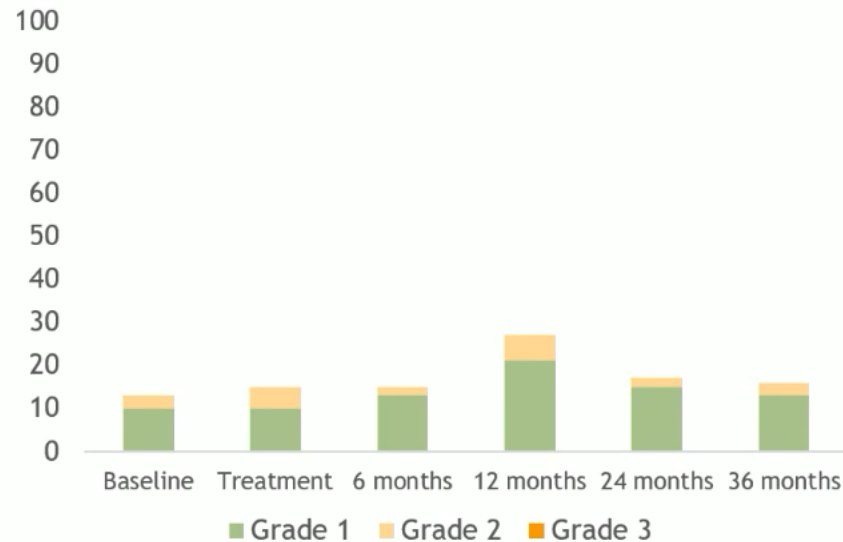


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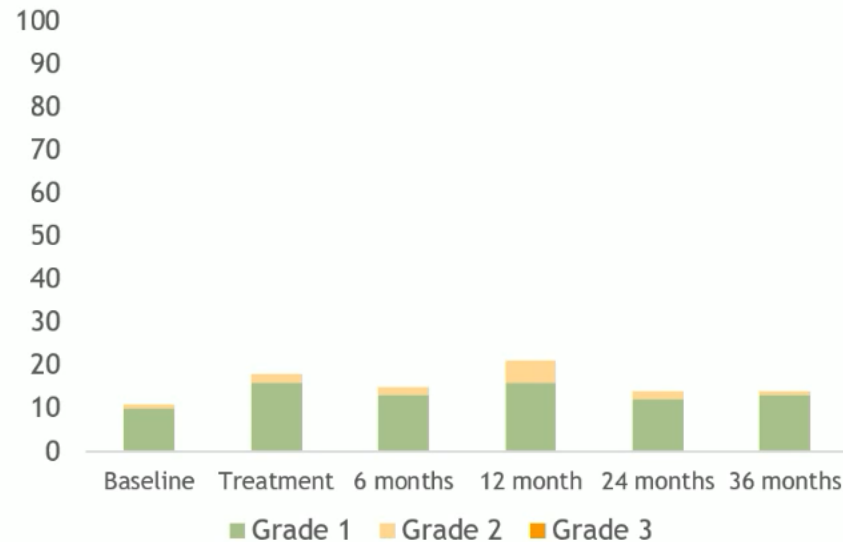
Adverse events (CTCAE v4.0) - gastro-intestinal toxicity



Molecular-profile arm



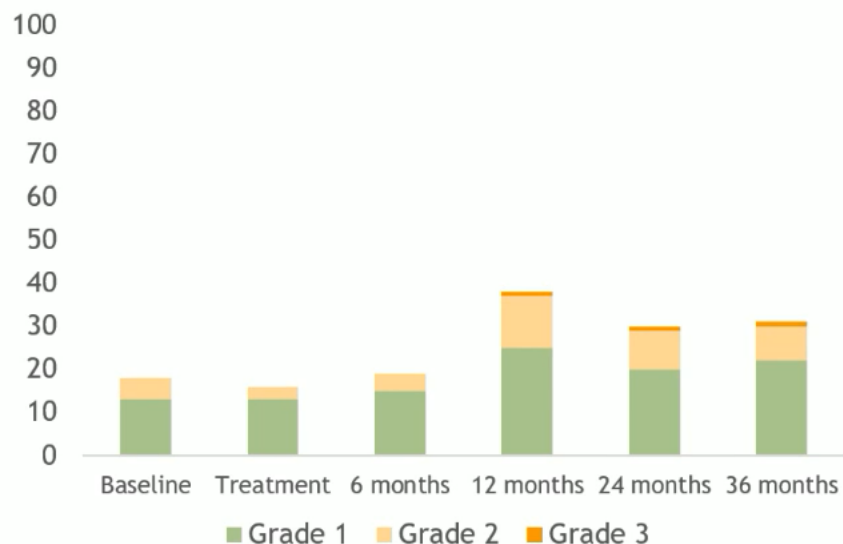
Standard VBT arm

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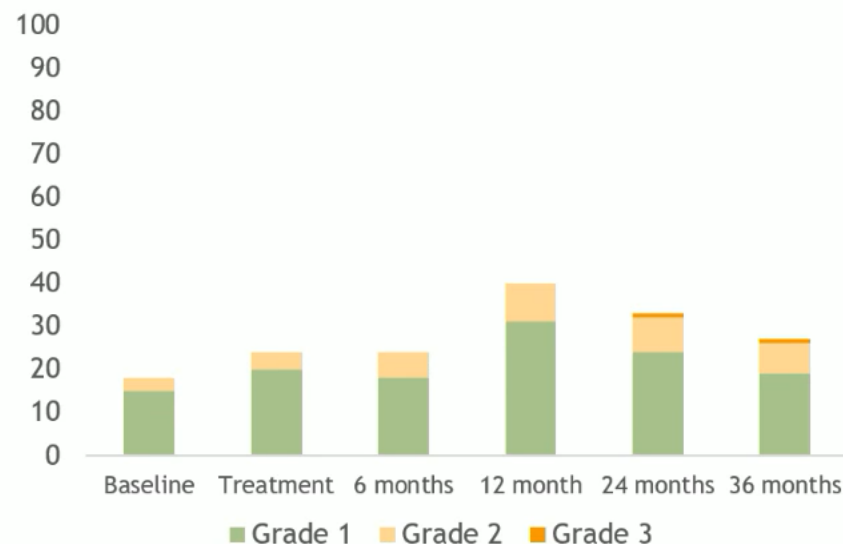
Adverse events (CTCAE v4.0) - urinary toxicity



Molecular-profile arm



Standard VBT arm



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Conclusions of the PORTEC-4a trial

- 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



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Conclusions of the PORTEC-4a trial



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- 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

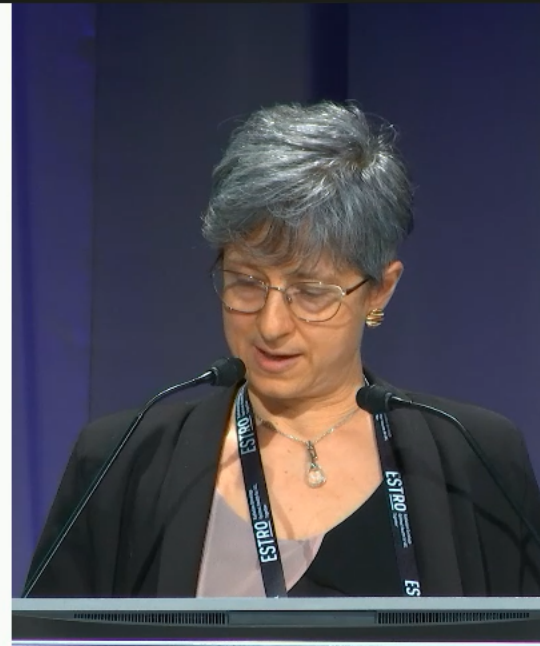


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PORTEC-4a: Beyond the Data - A Critical and Clinical Perspective

Gabriella Macchia
Radiation Oncology Unit
Campobasso, Italy



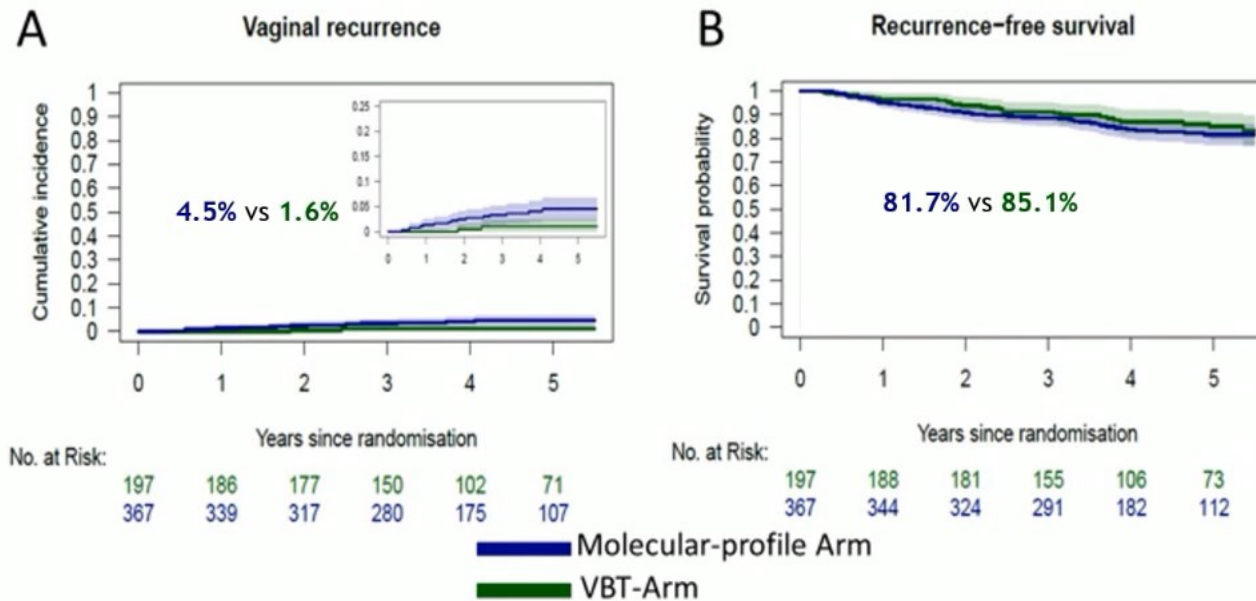
Gabriella Macchia
Italy



Take-home Messages

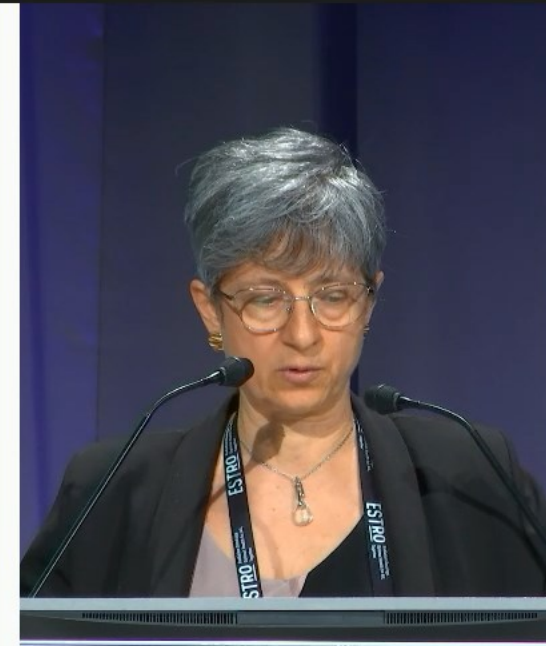
First Phase III Evidence for Molecularly Guided Adjuvant Treatment in Endometrial Cancer

Significant Reduction in Overtreatment Without Compromising Oncologic Safety



A – 5-year cumulative incidence of vaginal recurrence between the two treatment arms, without adjuvant treatment in 46% of patients in the molecular-profile arm

B – Recurrence free survival



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Italy



Statistical considerations



Randomized design
minimizes biases



Well-defined hypothesis
and primary endpoint



Non-inferiority trial
adequately powered



Secondary endpoints support
robustness of results

....even if in **Immune Checkpoint Inhibitor** era is **easier** to interpretate the **PFS** than OS



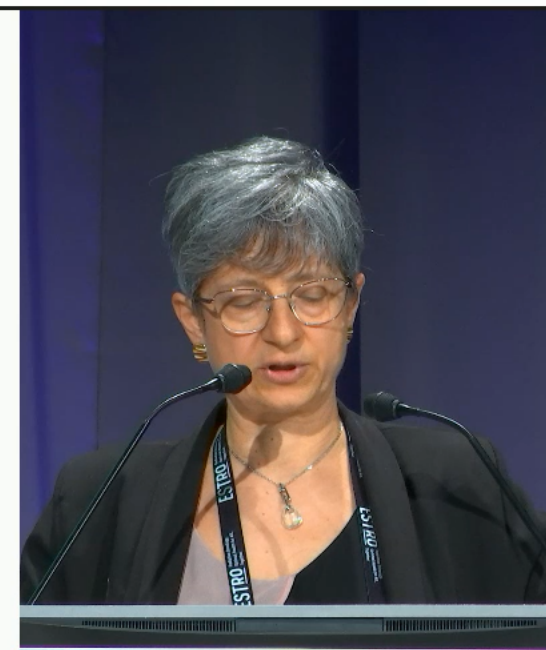
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Potential Impact on Existing Clinical Guidelines



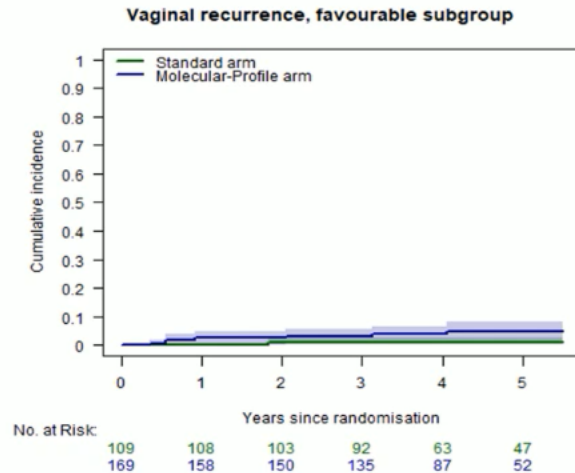
molecular profiling
reduce overtreatment
enhancing quality of life



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Vaginal recurrence - Favorable profile



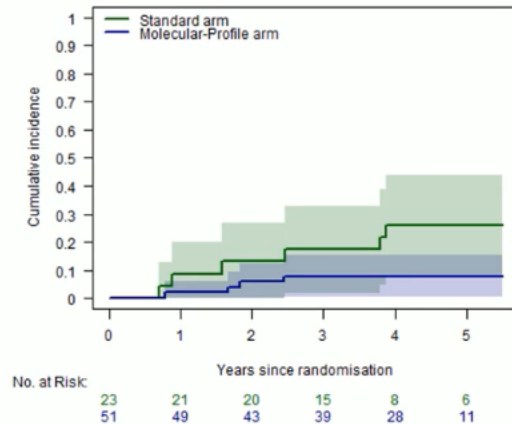
Subgroup analysis:

favourable profile patients showed 5-year cumulative incidence of **VR of 4.7% vs. 0.9%, $p=0.09$, below the predefined equivalence margin**

Data Supports:

- De-escalation strategy (favourable profile), reducing unnecessary exposure to RT and its long-term side effects
- Intensification in Unfavorable Molecular Subgroups

Locoregional recurrence - Unfavourable profile



Exploratory analysis:

unfavorable profiles had a substantially **lower locoregional recurrence rate** (8.4% vs. 30.5%, $p=0.05$) and **Distant Metastases** (22.3% vs 41.8%)

Data aligns with and Anticipates New Guidelines



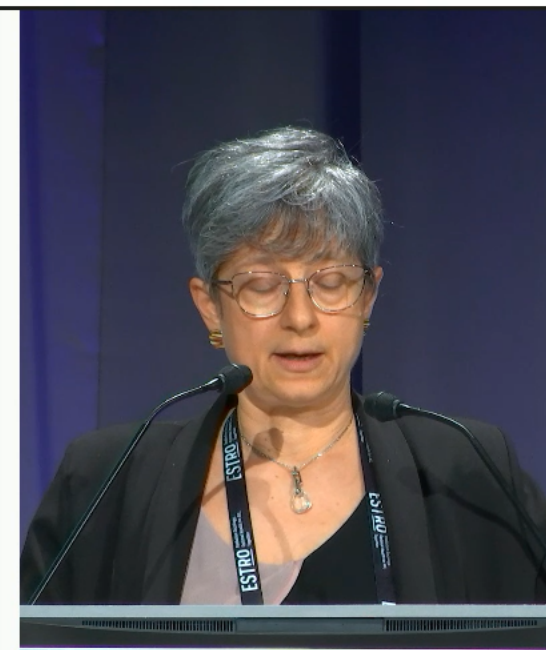
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HIR Stage IA (with invasion), grade 3 (any age, with or without
FIGO lymph-vascular space invasion)
2009 Stage IB, grade 3 without lymph-vascular space invasion



IIC FIGO 2023



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HIR Stage IA (with invasion), grade 3 (any age, with or without lymph-vascular space invasion)

FIGO 2009 Stage IB, grade 3 without lymph-vascular space invasion

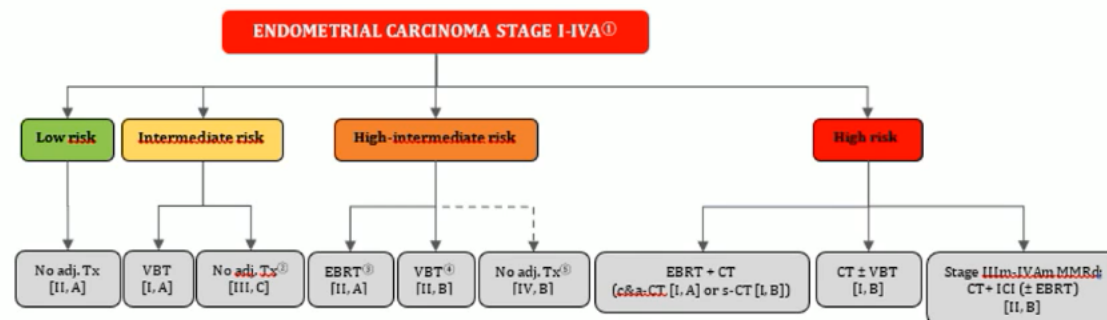


IIC FIGO 2023

Risk groups:

- Low
- Intermediate
- High-Intermediate
- High
- Uncertain

2023 FIGO staging ^{II}			Molecular classification*				
			<i>POLE</i> mut	MMRd	NSMP low-grade+ERpos	NSMP high-grade/ERneg**	p53abn
II	Confined to the uterus						
IIA		Low-grade endometrioid, invasion of the cervical stroma	IAm <i>POLE</i> mut			**	IICm p53abn
IIB		Low-grade endometrioid, substantial LVSI***	IAm <i>POLE</i> mut			**	IICm p53abn
IIC		High-grade histologies [^] , myoinvasion	IAm <i>POLE</i> mut	Myoinvasion <50%, no/focal LVSI	n.a.		IICm p53abn
			IAm <i>POLE</i> mut	Myoinvasion ≥50%, no/focal LVSI			
			IAm <i>POLE</i> mut	Cervical stromal invasion, no/focal LVSI			
			IAm <i>POLE</i> mut	Substantial LVSI**			



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HIR
FIGO 2009 Stage IB, grade 1 or 2 with documented lymph-vascular space invasion

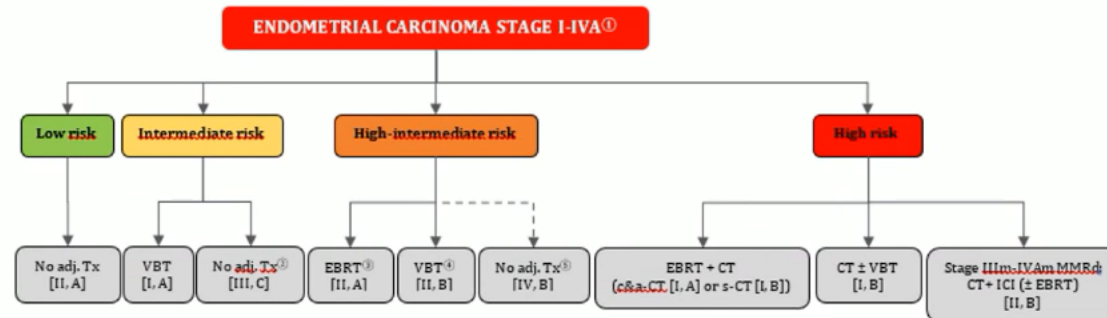


IIB FIGO 2023

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- Low
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2023 FIGO staging ^{II}			Molecular classification*				
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PAS DE CURIETHERAPIE seule!!



Question

Potential Impact on Existing Clinical Guidelines

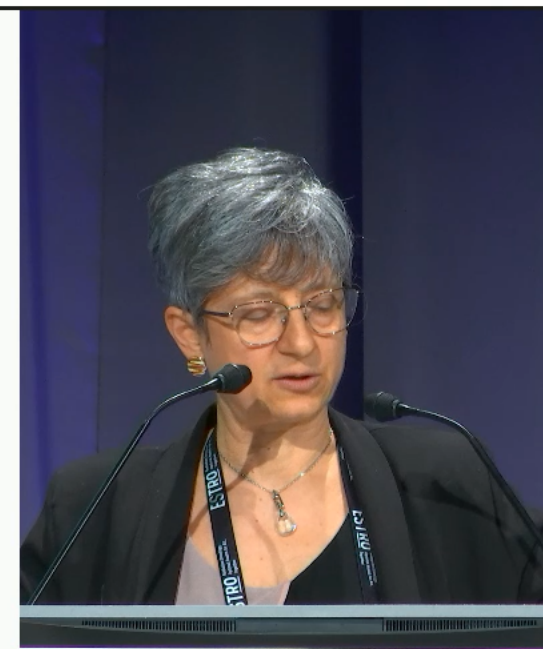


molecular profiling
reduce overtreatment
enhancing quality of life



Incredibly impactful for

Elderly patients or
those with multiple
comorbidities



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Will this study change clinical practice tomorrow?

Role of age

Age not considered in the new GL



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Potential Impact on Existing Clinical Guidelines



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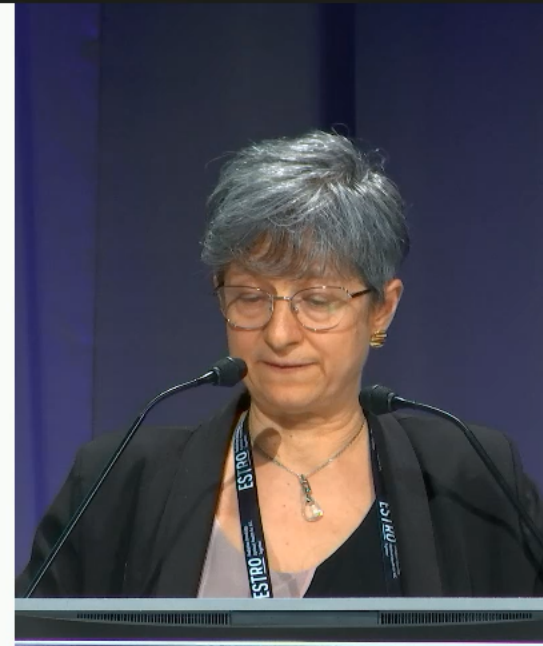


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Remaining Evidence Gaps

The findings are most applicable to patients
with high-intermediate risk endometrial
cancer (2016 Guidelines)



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Question

Potential Impact on Existing Clinical Guidelines



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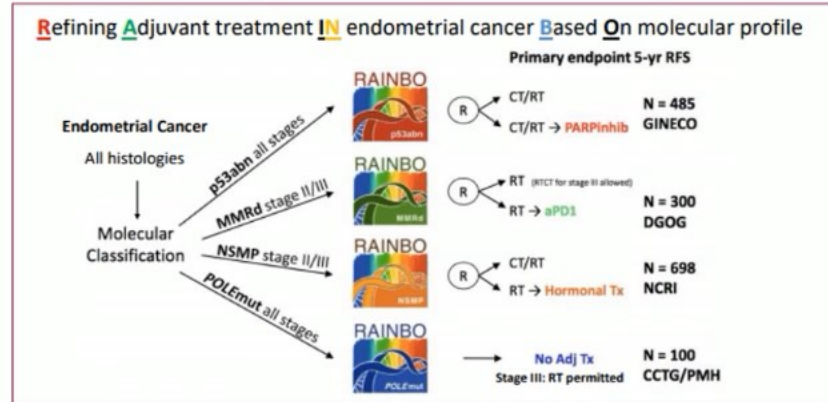


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Potential Impact on Existing Clinical Guidelines



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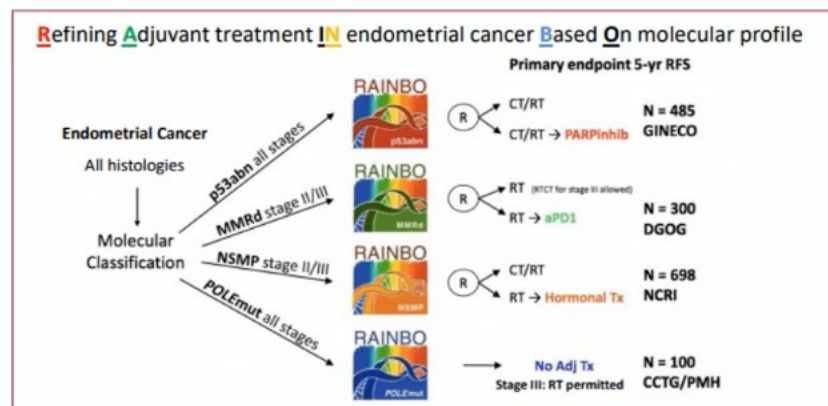


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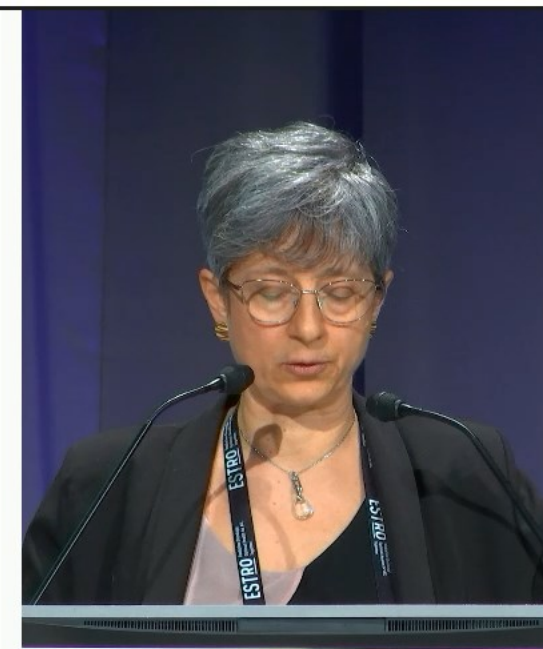
Elderly patients or
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Remaining Evidence Gaps

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**Economic impact on a large
scale is a critical factor in its
widespread adoption**



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Italy

Will this study change clinical practice tomorrow?

Role of age

Age not considered in the new GL

Feasibility and Resources (global scale and LMIC)

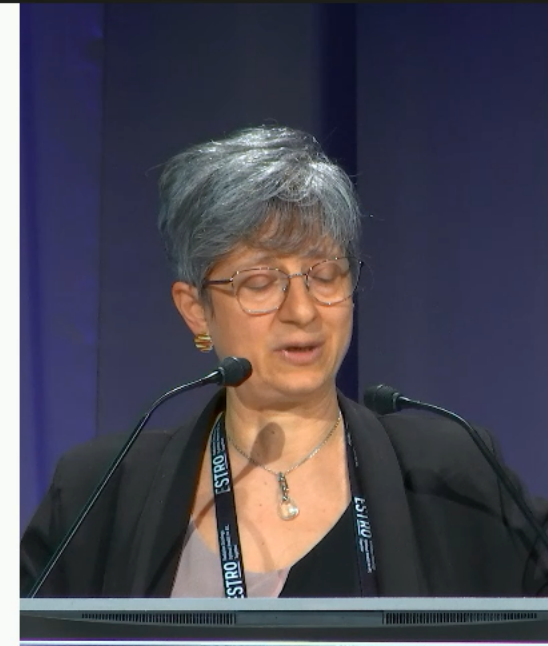
Is the 14-day timeframe suggested for molecular classification **reliable everywhere?**

2023 FIGO staging is **difficult** to apply on a global scale and **unfeasible** in resource-poor settings

Legal and ethical challenges

Post-treatment genetic findings
Rising patient expectations
Overtreatment consequences
Delays in molecular data
Equity and cost

- **Further analyses of secondary endpoints, including quality of life and cost-utility evaluations, to confirm the clinical value and potential impact of this approach in the treatment of endometrial cancer.**

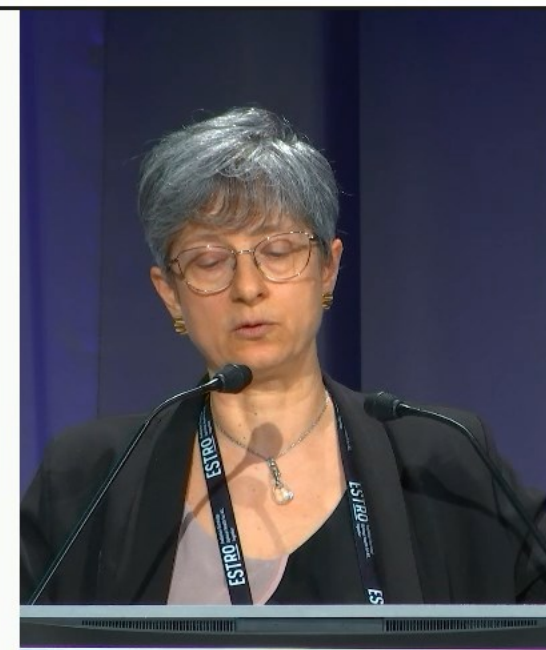


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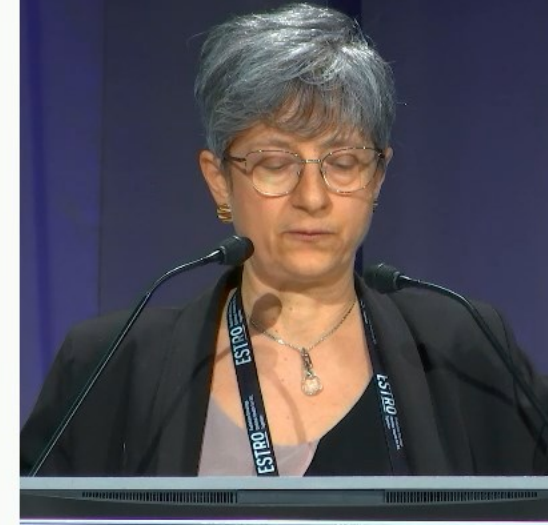
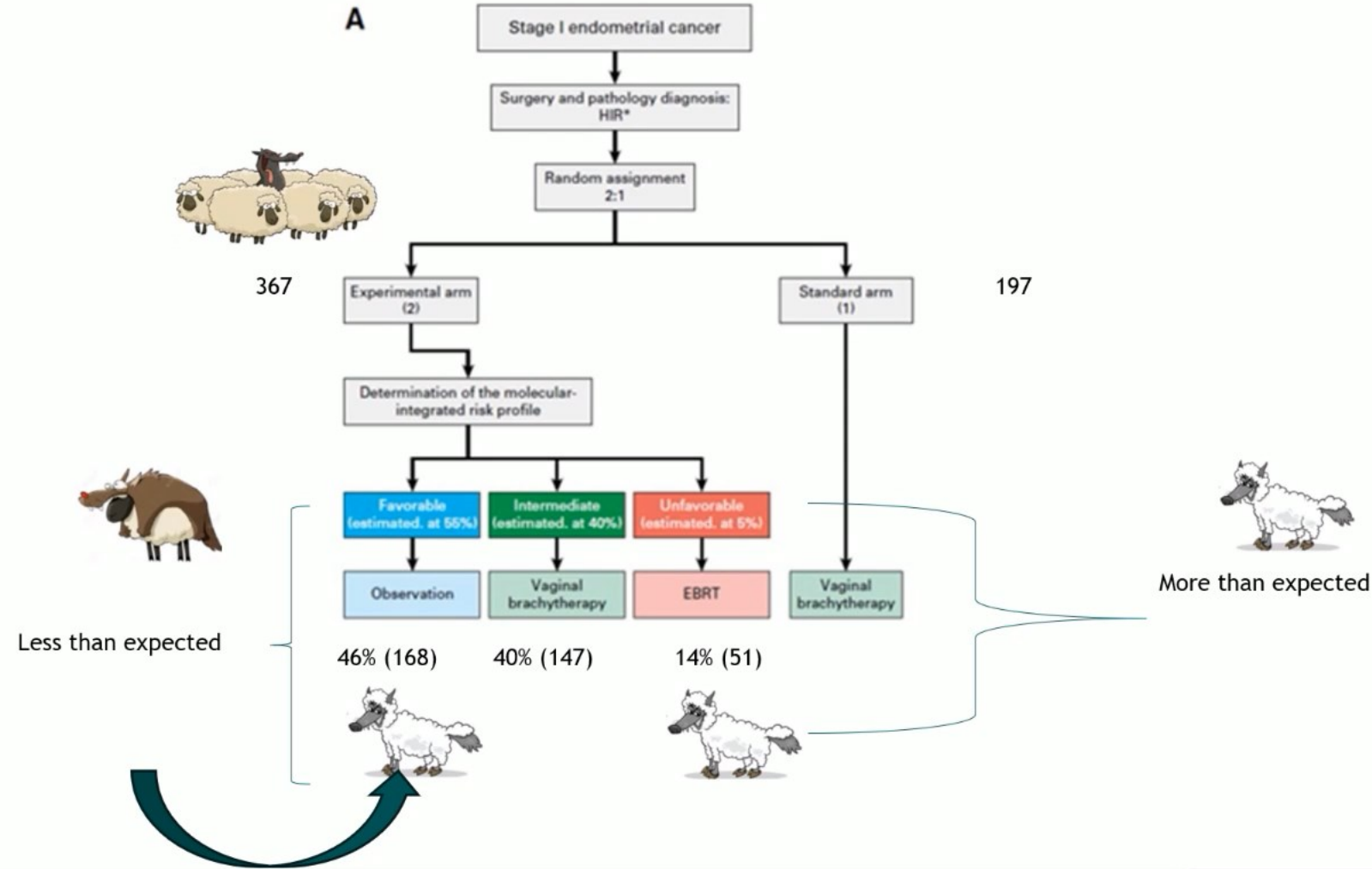
- **Reclassify the favorable cases** according to the new FIGO 2023 staging (who are the wolves in sheep's clothing among the favorable cases?)
- **Investigate vaginal recurrence cases** within the favourable-risk population (which molecular or histological factors may have influenced recurrence? Grading? Estrogen receptor expression?)



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Consideration: higher-than-anticipated proportion of “wolves in sheep’s clothing”

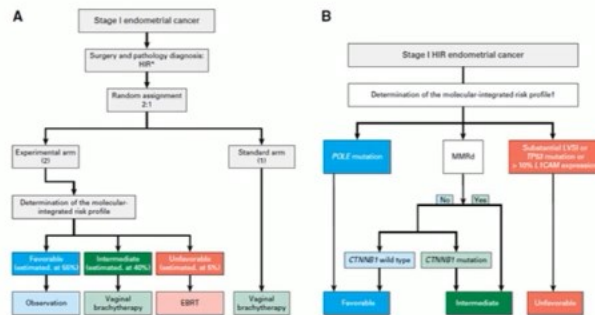


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Summary

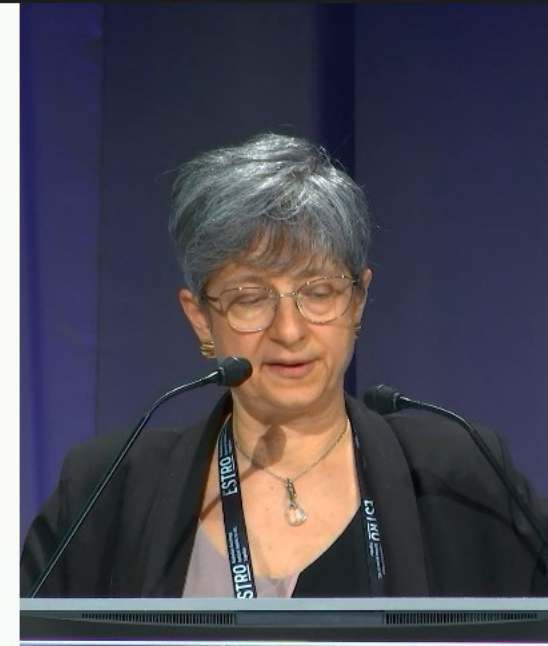
First phase I-level evidence supporting the use of molecular profiling to modulate treatment

Although designed before the 2023 FIGO classification and the updated 2025 guidelines, the PORTEC-4a trial **aligns closely with their direction**, reinforcing the shift toward molecularly guided, risk-adapted management.



INTEGRATION OF MOLECULAR CLASSIFICATION AND OTHER BIOMARKERS

- Molecular classification (*POLE*mut, *MMR*d, non-specific molecular profile (NSMP), p53abn) should be performed on all ECs and requires 3 basic analyses to determine the *POLE* mutational, *MMR* and p53 status (2020 WHO tumour classification) [IV, A].
- Molecular classification is particularly relevant in high-grade carcinomas [IV, B].



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**MERCI POUR VOTRE
ATTENTION**