Update on gynecologic pathology

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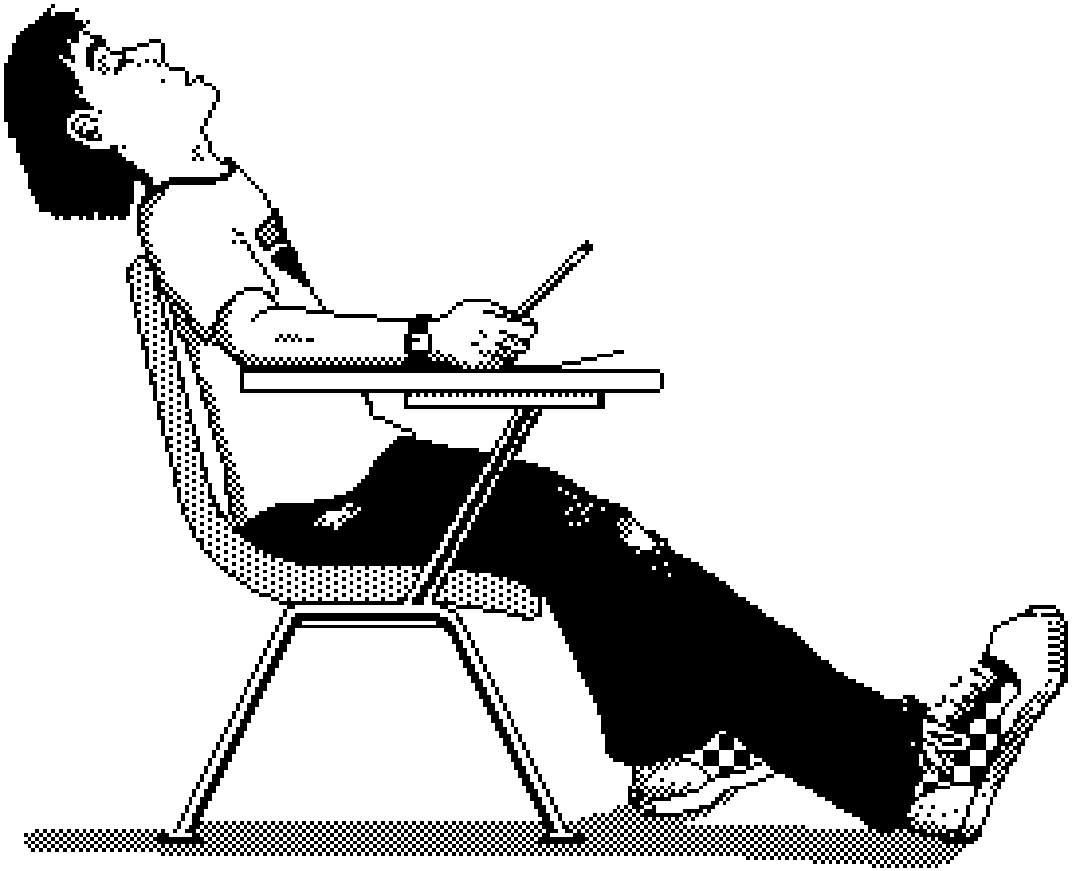
Disclosure

- Consultant and/or lecturer for MSD, Astra-Zeneca and Roche/Ventana

Disclosure - Gyn pathologists



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Topics

- Vulvar carcinoma and precursor lesions
- Cervical carcinoma
- Female genital sarcomas
- Endometrial carcinoma
- Tubo-ovarian tumors

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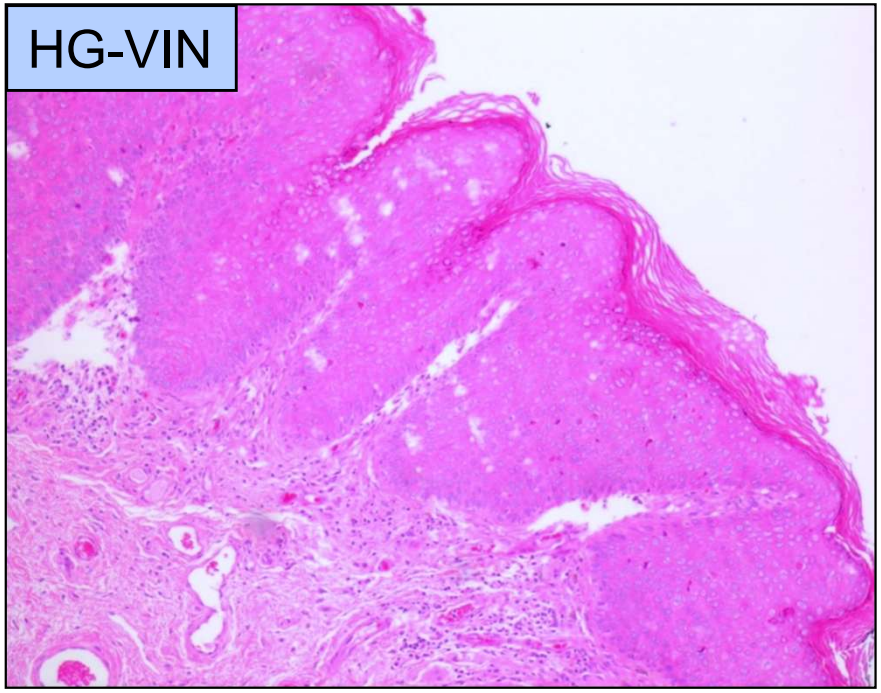
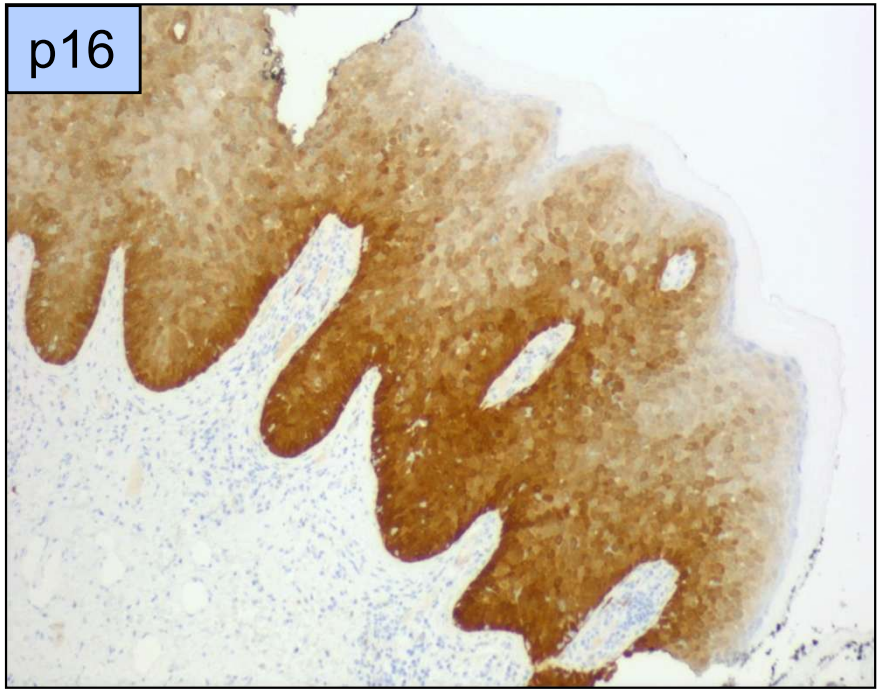
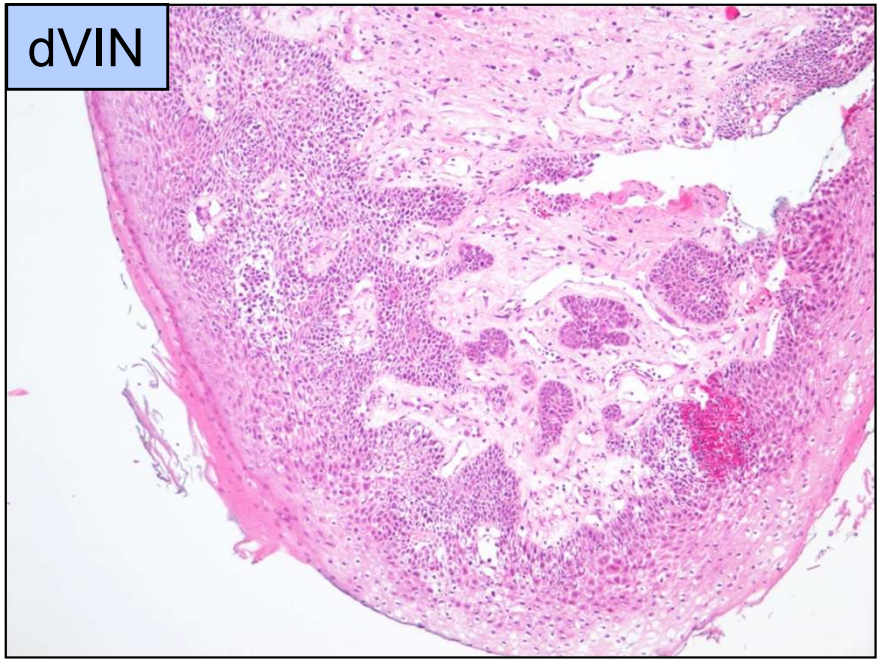
HG-VIN or dVIN vs. reactive







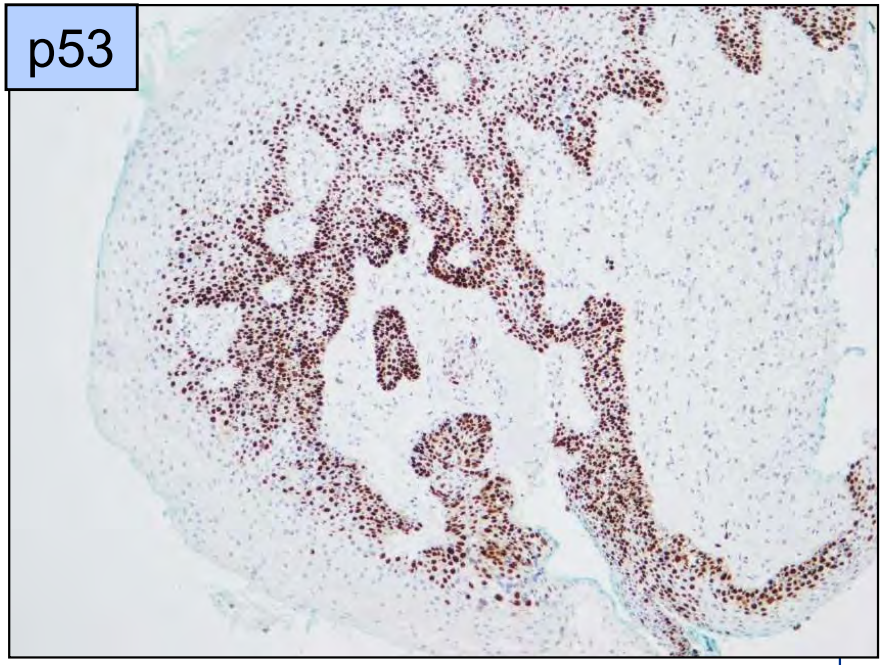
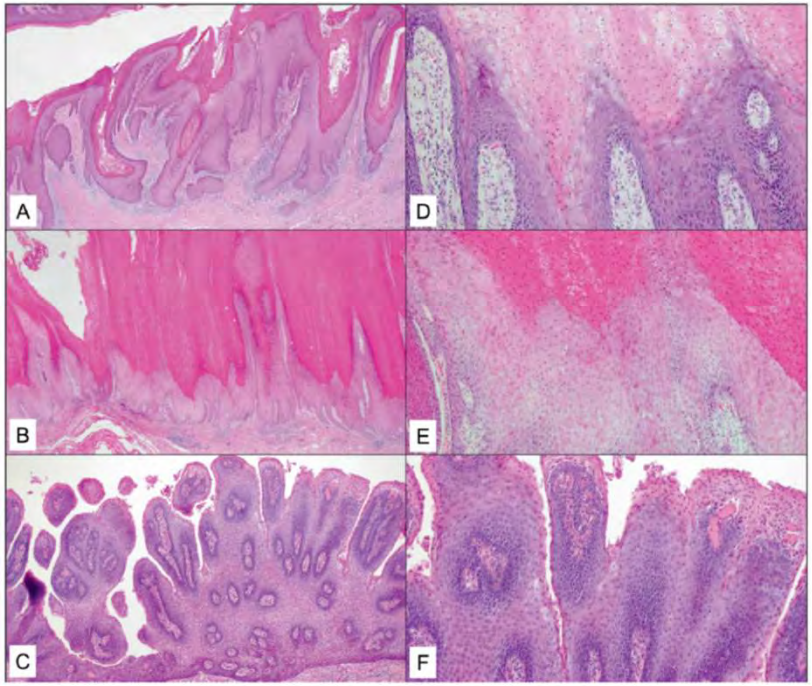
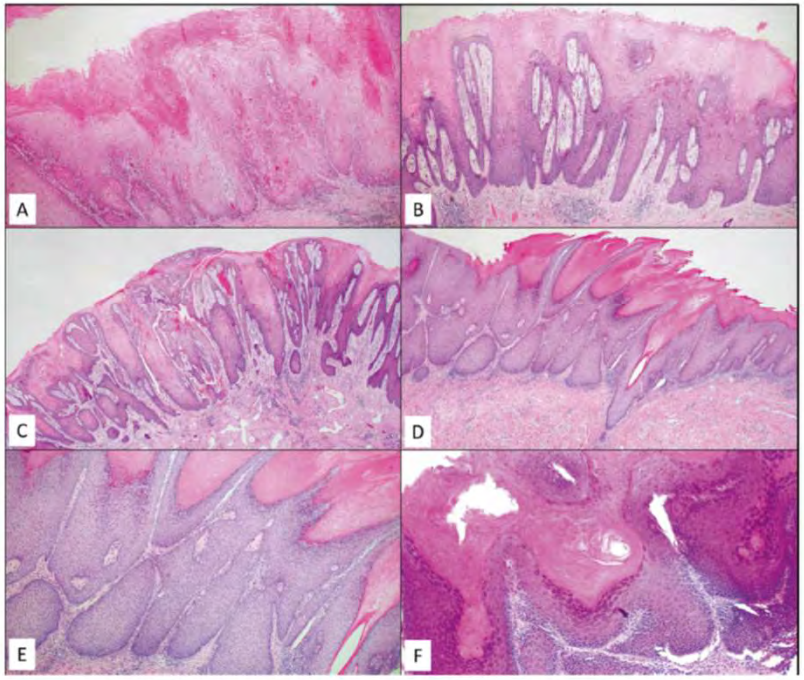


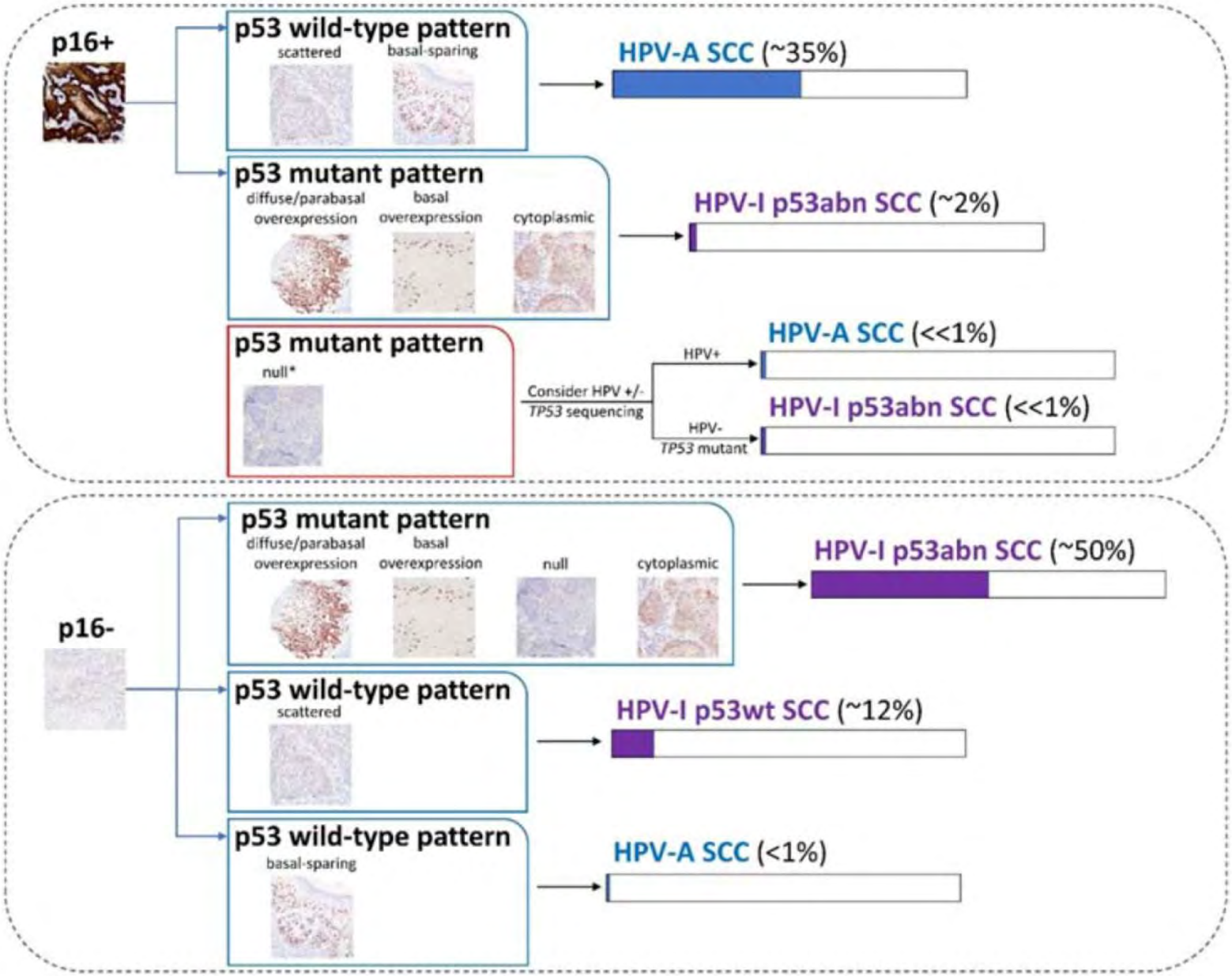
Table 2. Modern classification of vulvar intraepithelial neoplasia including the recommended terminology and diagnostic criteria for each lesion type.

VULVAR SQUAMOUS INTRAEPITHELIAL NEOPLASIA		
HPV-ASSOCIATED VULVAR INTRAEPITHELIAL NEOPLASIA High Grade Squamous Intraepithelial Lesion (HSIL)	**HPV-INDEPENDENT p53 MUT VULVAR INTRAEPITHELIAL NEOPLASIA Differentiated VIN (dVIN)**	**HPV-INDEPENDENT p53 WT VULVAR INTRAEPITHELIAL NEOPLASIA Verruciform/Acanthotic VIN (vaVIN)**
● Atypia extending to upper layers ● Large hyperchromatic nuclei ● Loss of polarity and organization ● Loss of maturation with basaloid appearance & brisk mitotic activity with extension beyond basal layers	● Atypia often confined to the basal layer ● Large nuclei with open chromatin ● Prominent nucleoli ● Retained but abnormal maturation with elongated and/or fused rete ridges, acantholysis & dyskeratotic cells	● No cytologic atypia ● Verruciform acanthosis with flat (VAAD) or exophytic growth pattern (DEVIL) ● Retained but altered maturation with hypogranulosis & cytoplasmic pallor (VAAD/DEVIL) or hypergranulosis (vLSC)
p16 = Overexpressed * p53 = Wild type (mid-epithelial) **	p16 = Negative or patchy p53 = Mutant pattern **	p16 = Negative or patchy p53 = Wild type (scattered) **





Parra-Herran et al., Mod Pathol 2022;35:1317-26



Alfaraidi et al., Adv Anat Pathol 2025;32:20-29

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TABLE 1. Clinicopathological Features of VSCC Subtypes

	HPV-asociated VSCC	HPV-independent (p53 wild-type) VSCC	HPV-independent (p53 abnormal) VSCC
Percentage (approximate), %[32–34]	17-18	10-19	66-72
Median age, y[31,33]	59-62	68-73	74-75
Precursor lesion	High-grade squamous intraepithelial lesion (HSIL)	HPV-I (p53wt) VIN	HPV-I (p53abn) VIN (differentiated VIN)
Histologic appearance	Warty or basaloid	Verrucous (well-differentiated)[35]	Keratinizing
p16 IHC	Positive	Negative	Negative
p53 IHC	Reduced staining (null-like) Mid-epithelial staining (basal sparing, classic or central patterns)	Scattered	Basal overexpression Parabasal/diffuse overexpression Absent cytoplasmic
Local recurrence, %[31]	5.3	16.3	22.6
Prognosis[36]	Good	Intermediate	Poor

LVSI and p16 in vulvar SqCC

Table 2 Survival analysis – OS (126 patients)

Parameter	Distribution	Univariate	Multivariate
Age		$p=0.234$	NE
≤60	82		
>60	44		
Tumor diameter		**$p=0.013$**	p=0.545
≤4 cm	102		
>4 cm	24		
Lymphovascular invasion[a]		**$p<0.001$**	**$p=0.001$**
Yes	17		
No	108		
Lichen sclerosus [b]		**$p=0.019$**	$p=0.286$
Yes	37		
No	87		
Pathological tumor-free margin [c]		$p=0.534$	NE
Yes	108		
No	9		
Lymph node metastasis (yes vs. no)[d]		**$p<0.001$**	$p=0.469$
Yes	30		
No	84		
Lymph node metastasis (number) [d]		**$p<0.001$**	$p=0.166$
>1	10		
1	20		
0	84		
p16 [e]		**$p=0.007$**	**$p=0.02$**
Positive	49		
Patchy/negative	63		
p53 [f]		**$p=0.012$**	$p=0.987$
Aberrant	61		
Wild-type	55		
HPV status [g]		**$p=0.021$**	$p=0.197$
Positive	66		
Negative	49		
Post-operative radiation		**$p<0.001$**	$p=0.985$
Yes	29		
No	97		

Values in bold are statistically significant ($p<0.05$)

Abbreviations: *NE* not entered

[a] Available for 125 patients

[b] Available for 124 patients

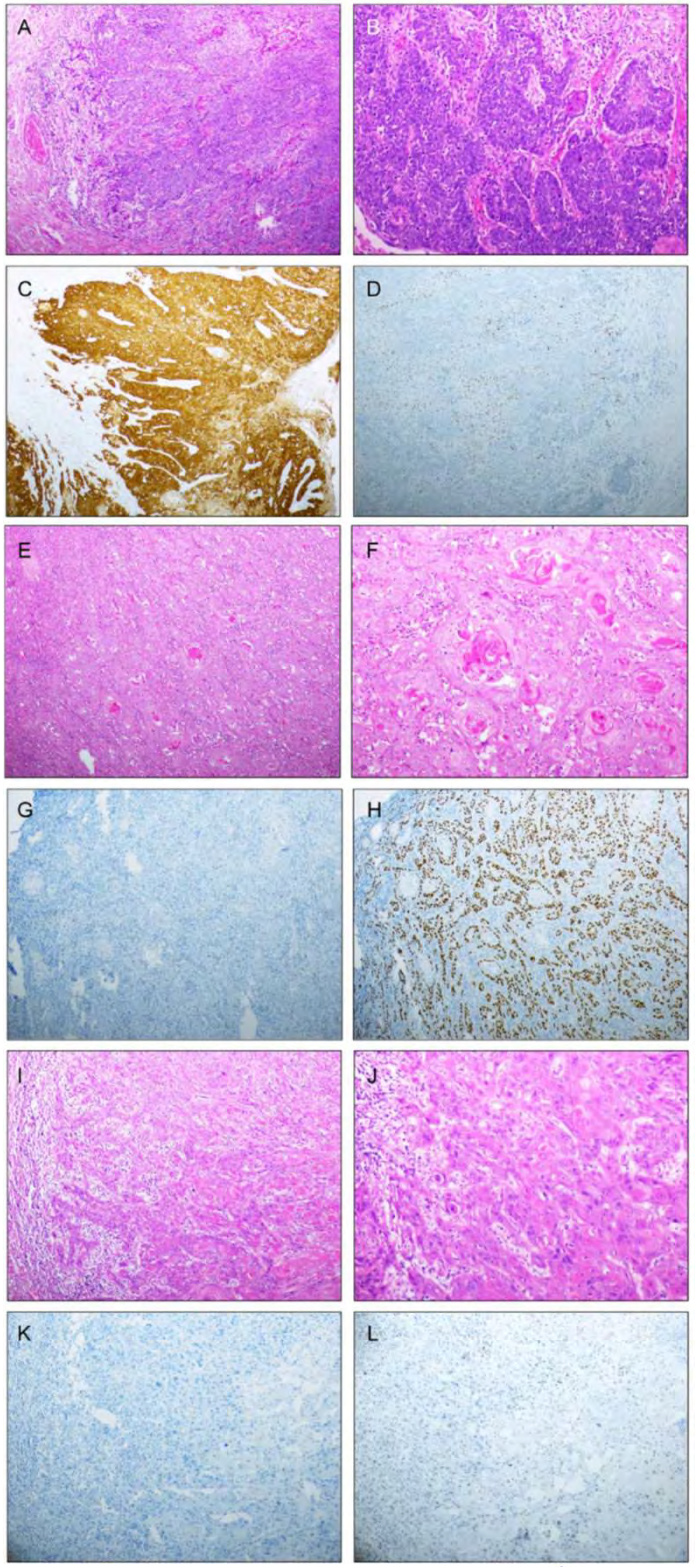
[c] By carcinoma; Available for 117 patients; remaining cases operated at other hospitals and specimens were inconclusive with respect to margin

[d] Available for 114 patients

[e] Data for 112 patients; remaining cases operated at other hospitals with block unavailable ($n=10$) or stained with inconclusive result ($n=4$)

[f] Data for 116 patients; remaining cases operated at other hospitals with block unavailable ($n=10$)

[g] Data for 115 patients; remaining cases operated at other hospitals with block unavailable ($n=10$) and 1 failed test



Davidson et al., Virchows Arch 2024;484:951-63

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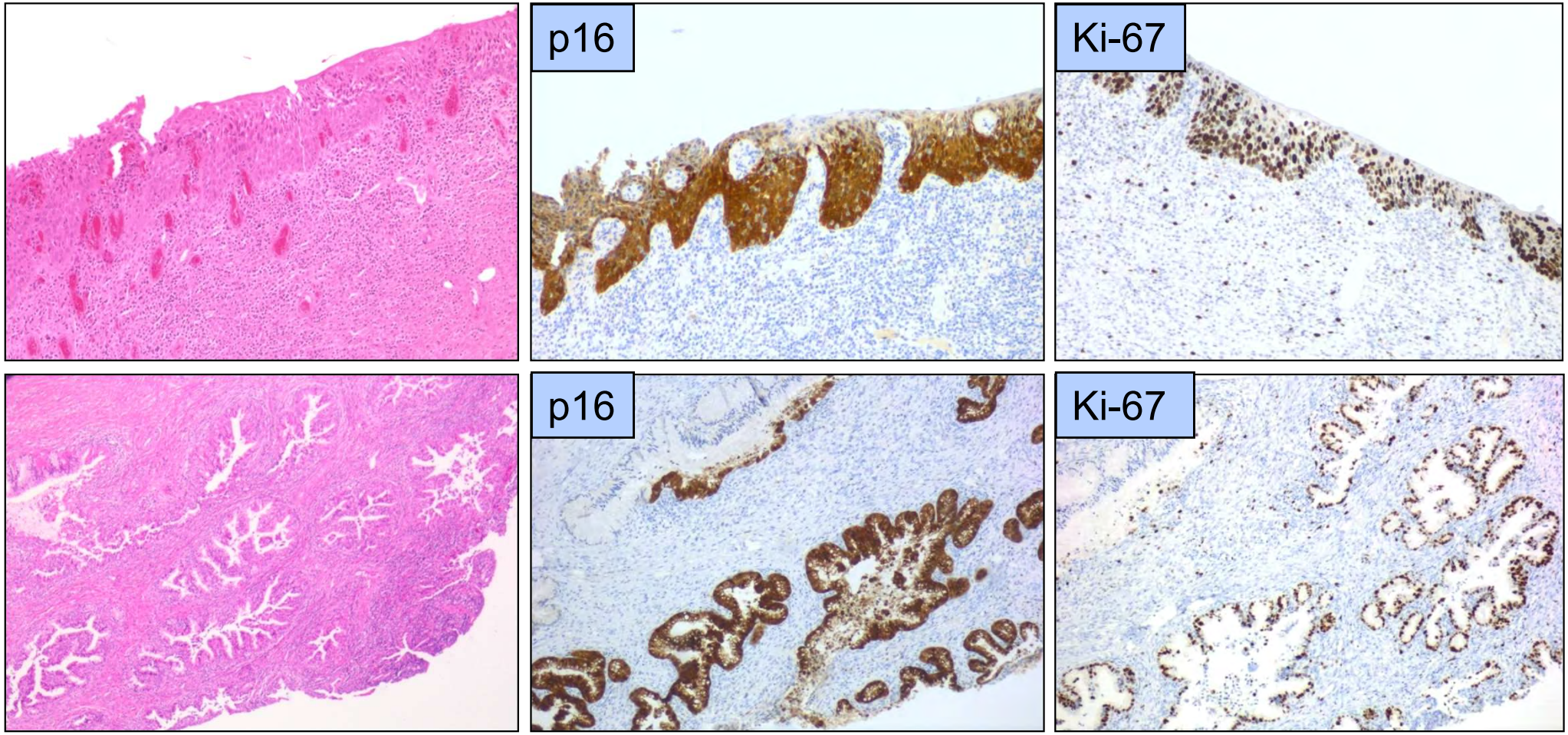
- Female genital sarcomas
- Endometrial carcinoma
- Tubo-ovarian tumors

HSIL/AIS vs. reactive



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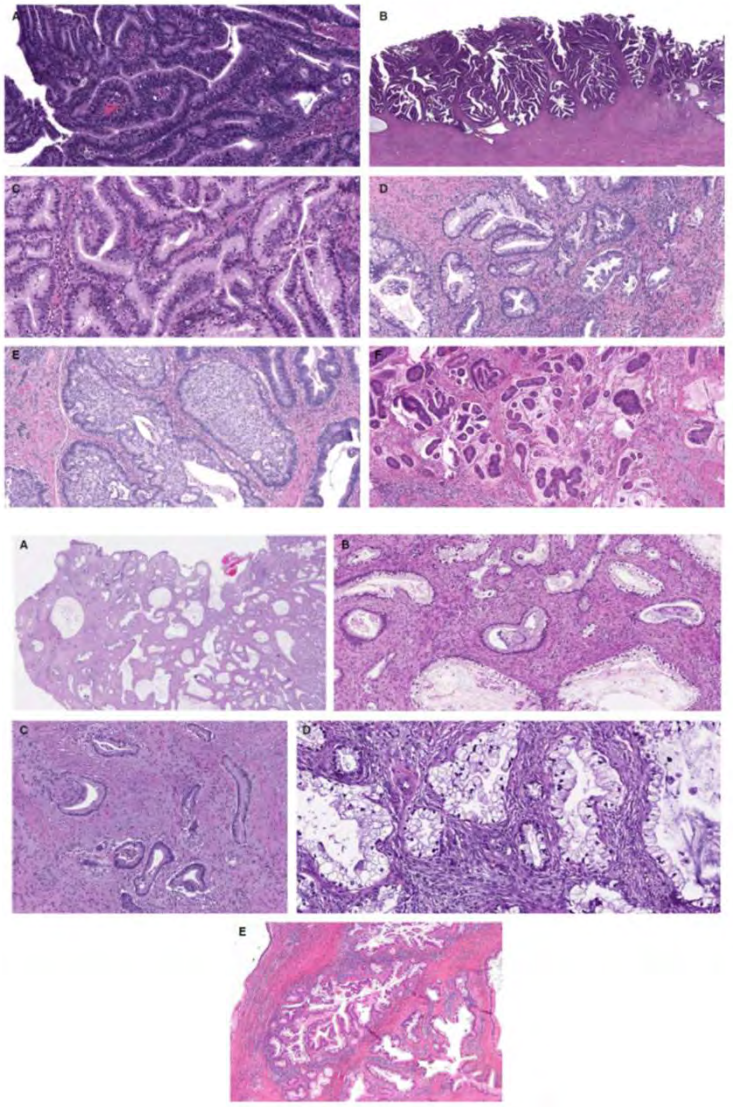
Cervix – HPV-based classification

Table 1. Endocervical adenocarcinoma classification by World Health Organisation 2014 compared to International Endocervical Criteria and Classification (IECC)

WHO 2014	IECC 2018	
Usual type	HPV-associated (HPVA)	Non-HPV-associated (NHPVA)
Mucinous carcinoma, NOS	Usual type	Gastric type
Gastric type	Villoglandular	Clear cell
Intestinal type	Mucinous, NOS	Mesonephric
Signet ring cell	Mucinous, intestinal	Endometrioid
Villoglandular	Invasive stratified mucin-producing	
Endometrioid	Micropapillary	
Clear cell	'Serous'-like	
Serous		
Mesonephric		

HPV, Human papillomavirus; NOS, Not otherwise specified.



Park KJ, Histopathology 2020;76:112-27

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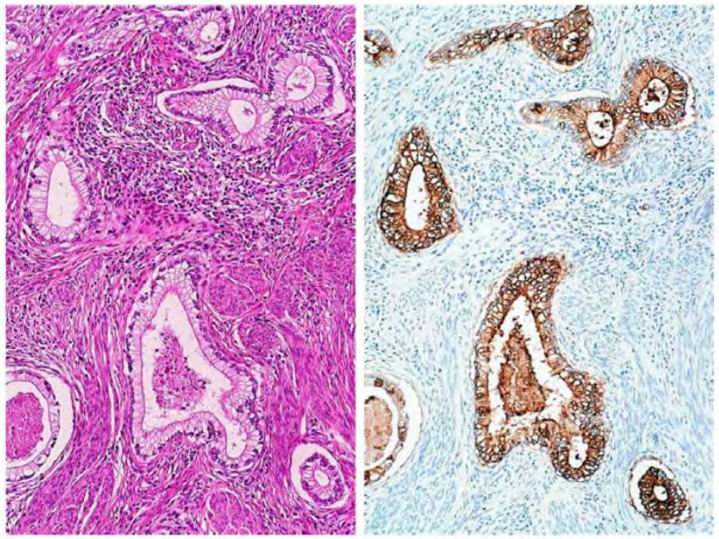
HPV-independent adenocarcinoma – gastric type



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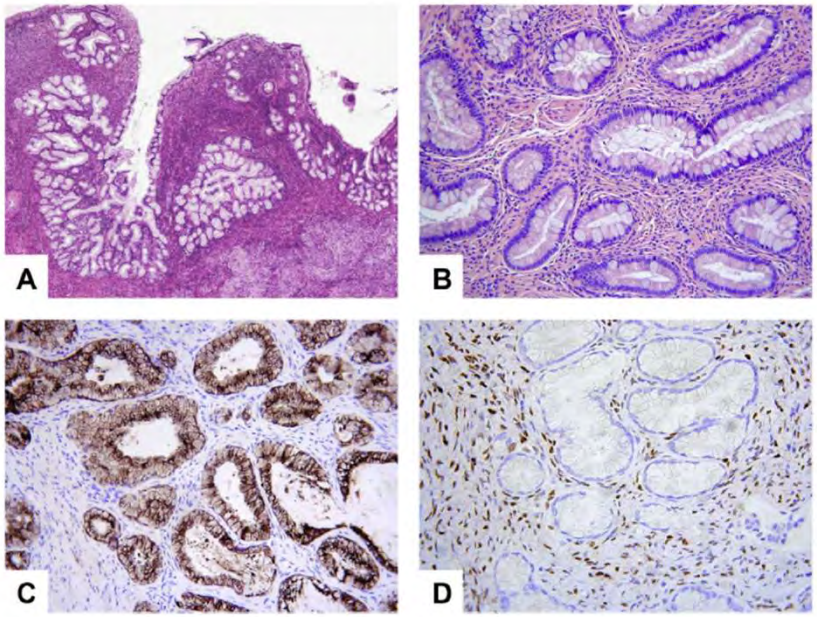
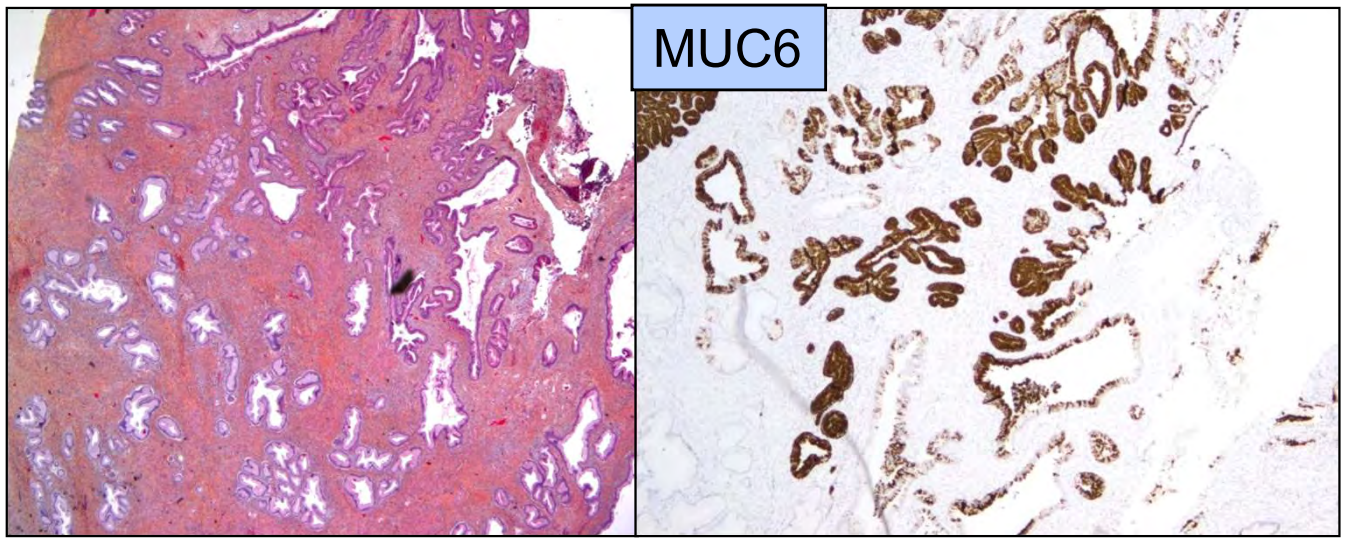


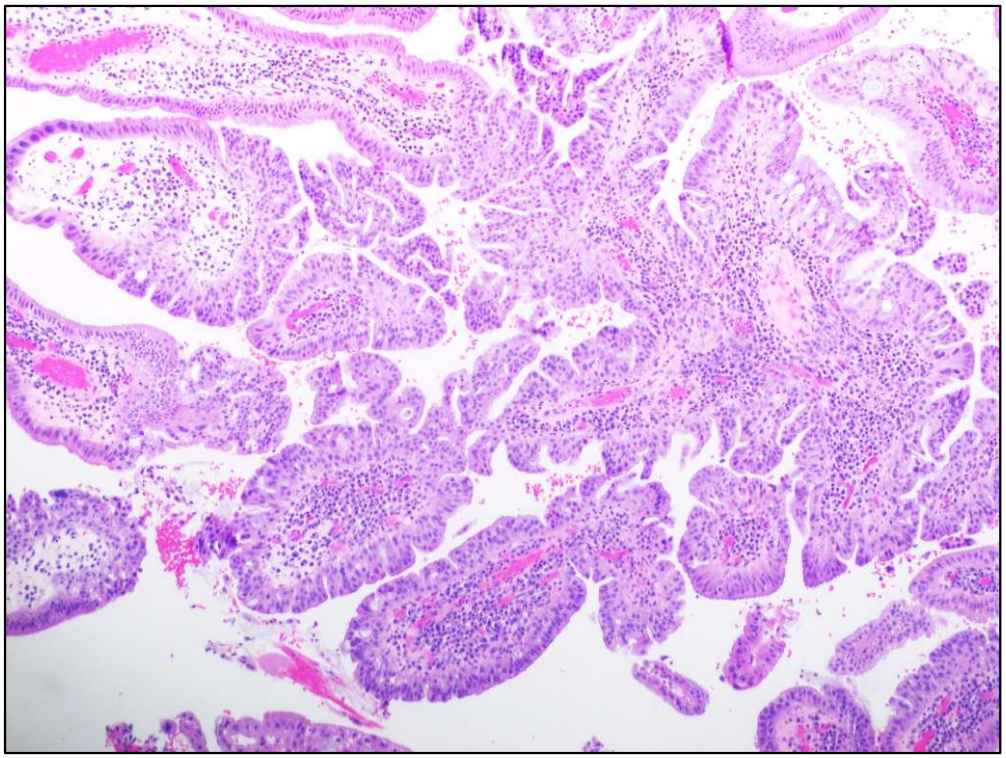
Fig. 2 LEGH. (A) Lobular aggregates of glands surrounding a dilated duct, (B) LEGH with goblet cells, (C) positive MUC6, and (D) negative ER staining in LEGH.

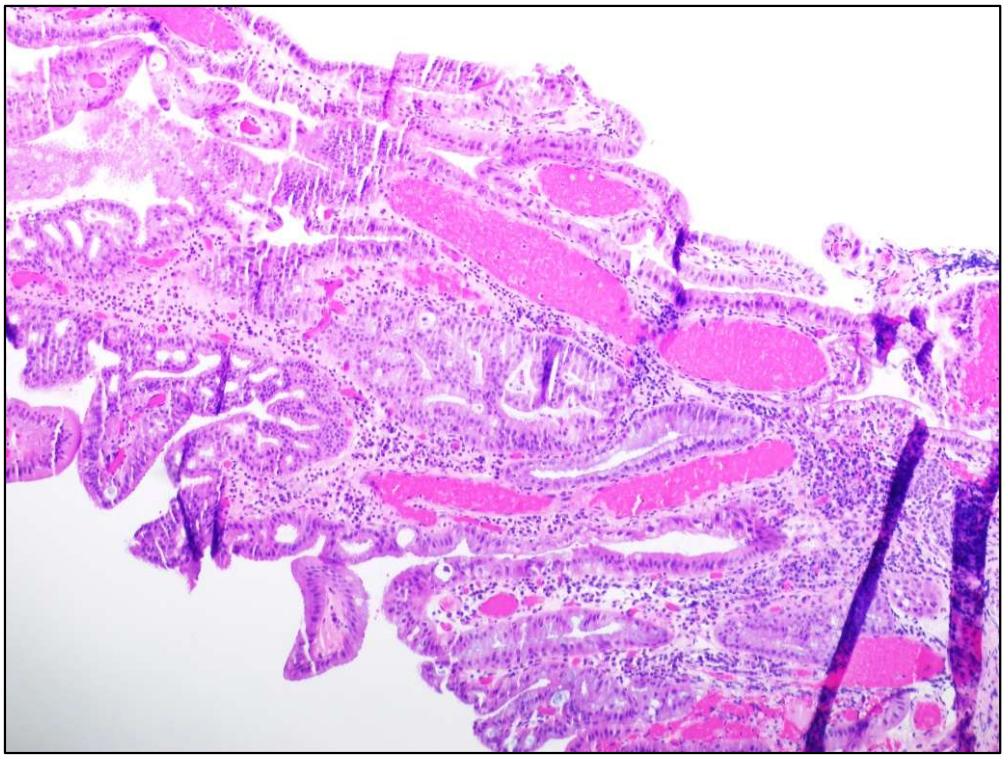
Often:
CEA-positive
Aberrant p53
p16 patchy/negative
ER/PR-negative
MUC5AC and MUC6-positive

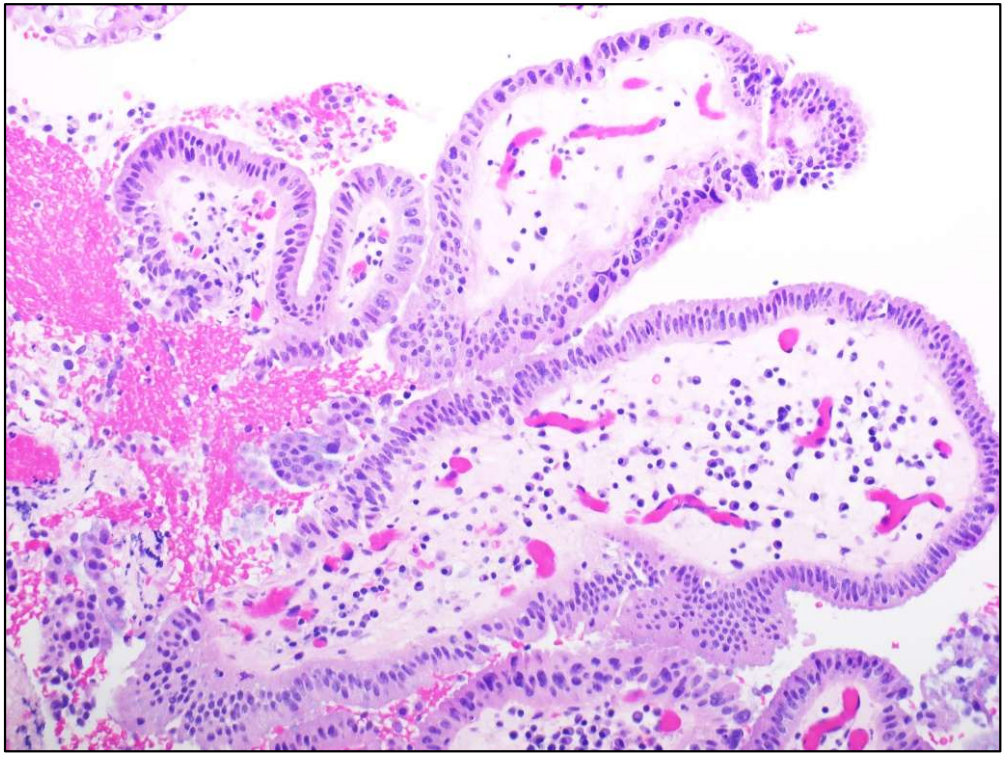


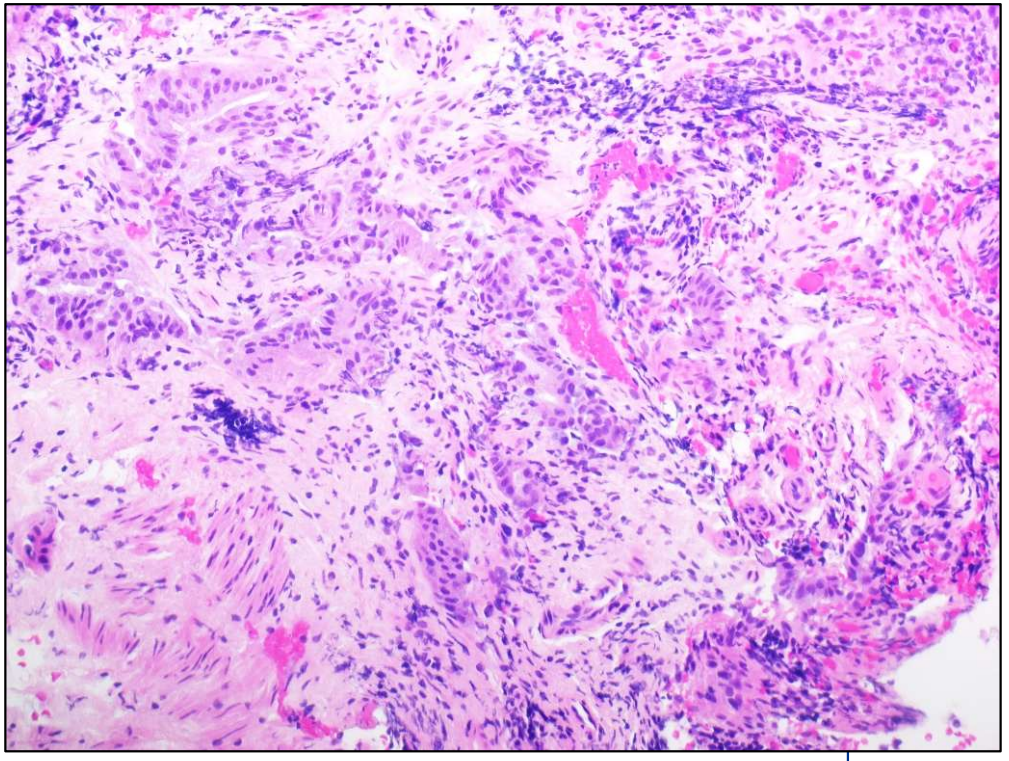
DD: GI metastasis

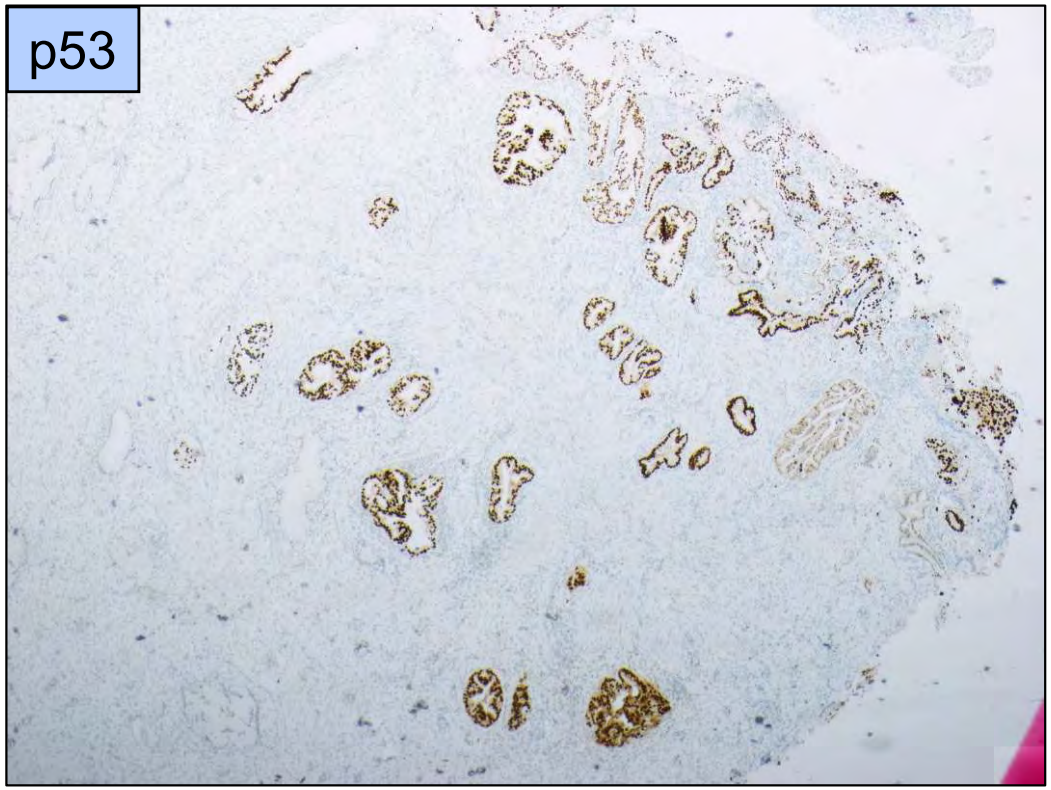
Mikami Y, Histopathology 2020;76:102-111
Talia and McCluggage, Pathology 2018;50:122-33

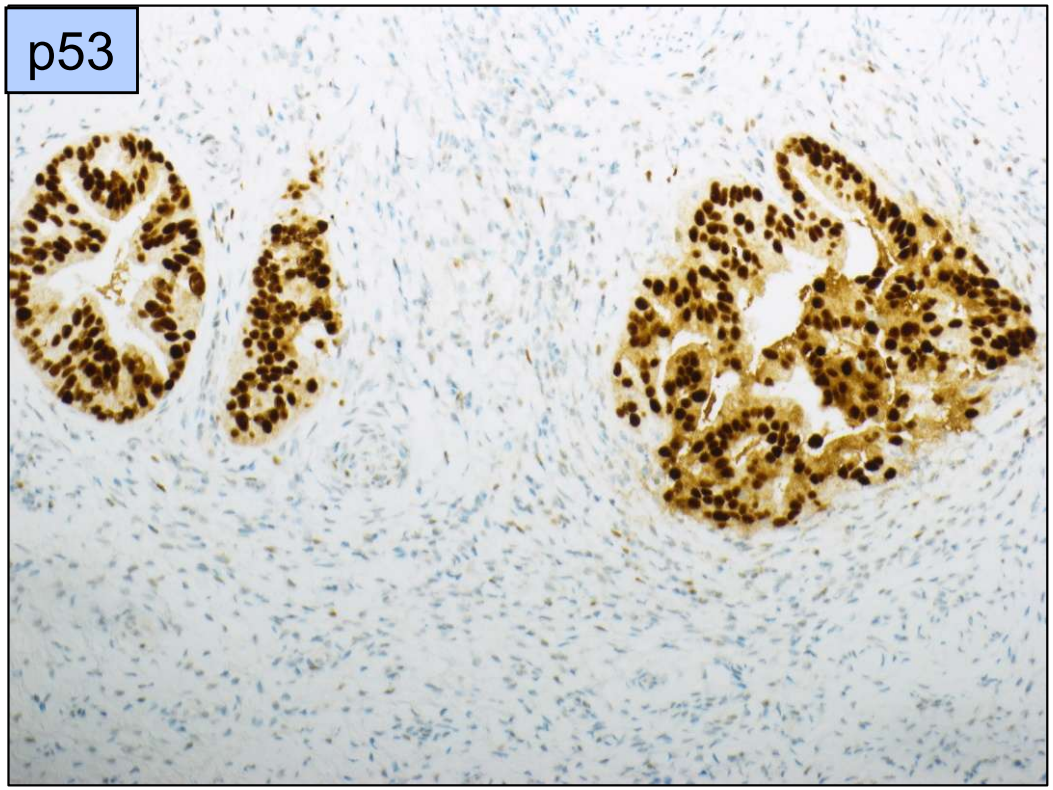












Molecular analysis: 3 pathogenic *TP53* mutations
Surgery: HPV-independent AC

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HPV status in cervical SqCC

Table 1:

Comparison of clinical and pathologic features of HPV-associated and HPV-independent invasive squamous cell carcinoma.

	HPV-associated invasive squamous cell carcinoma	HPV-independent invasive squamous cell carcinoma
Etiology/pathogenesis	HR-HPV and LR-HPV	No HR-HPV and LR-HPV
Clinical features	Small or large tumors	Large tumors
Mean age	51 years	>60 years
Location	Transformation/junctional zone	Transformation/junctional zone
Microscopic features	Any growth pattern	Any growth pattern
p16 expression/HPV testing	Block-type positive for p16/ HR-HPV and LR-HPV ISH positive	Negative for p16/ HR-HPV and LR-HPV ISH negative
Treatment	Surgery and oncologic treatment	Surgery and oncologic treatment
Prognosis	Usually good	Worse

HPV = human papillomavirus; HR = high risk; LR = low risk; ISH = in situ hybridization

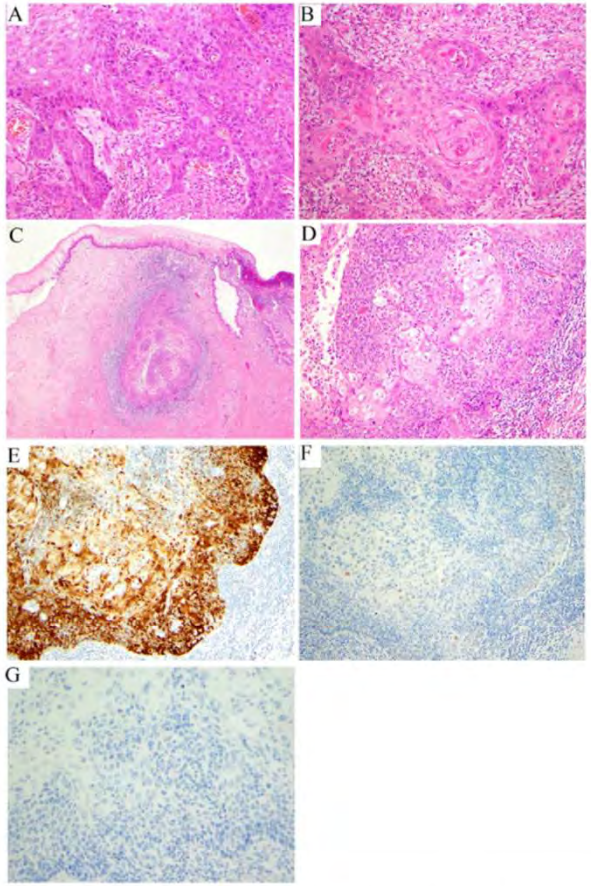

Figure 8: Human papillomavirus-independent (HPVI) precursor and infiltrating squamous cell carcinoma (SCC):

HPVI constitute 5-7% of cervical SqCC
May harbor *TP53* mutations

Stolnicu et al., Adv Anat Pathol 2024;31:1-14

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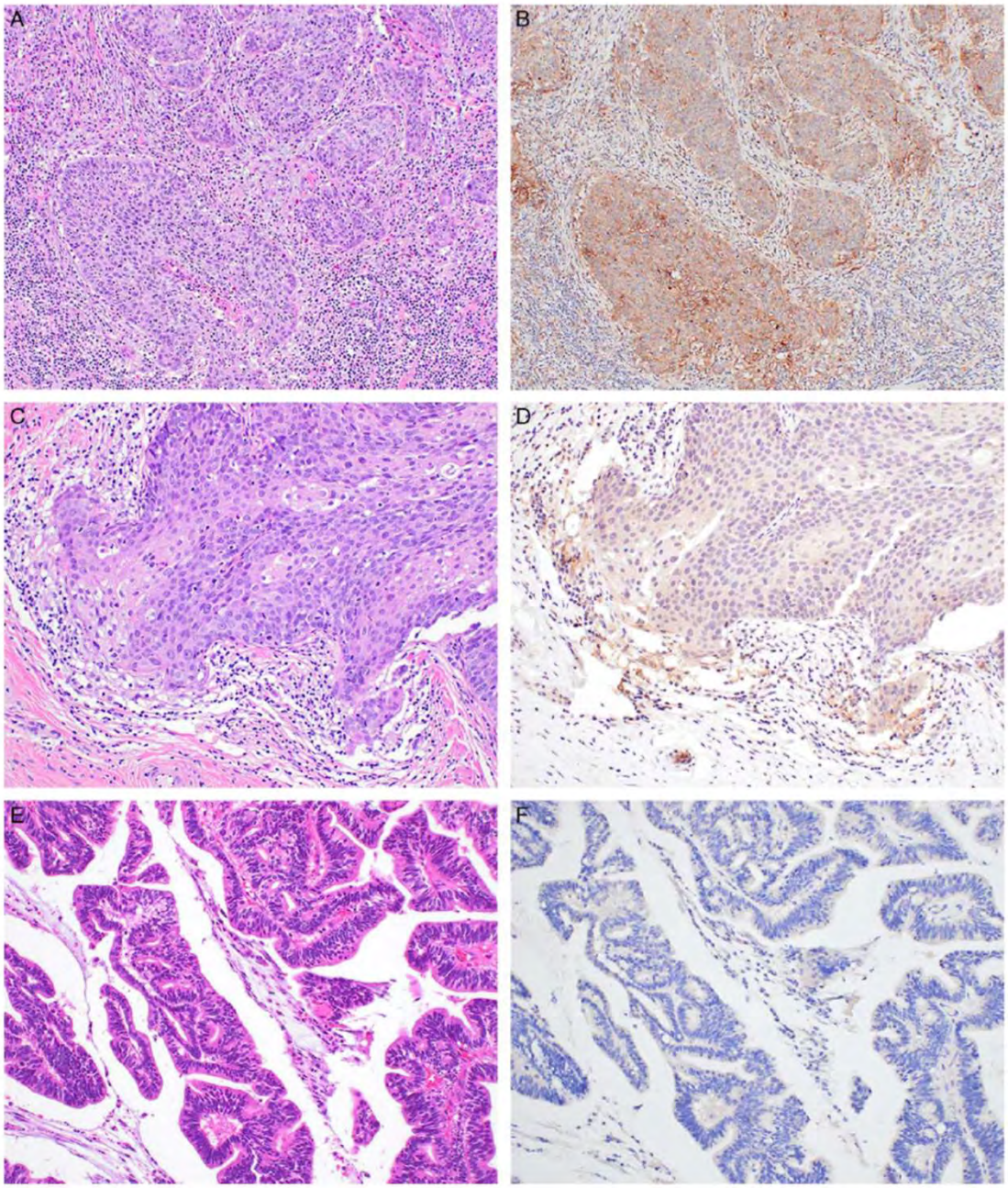

Candidates for Pembrolizumab tx
Cervical + other carcinomas
22C3 Dako/Agilent test
CPS >1

Mills and Pinto, Adv Anat Pathol 2024;31:1-14

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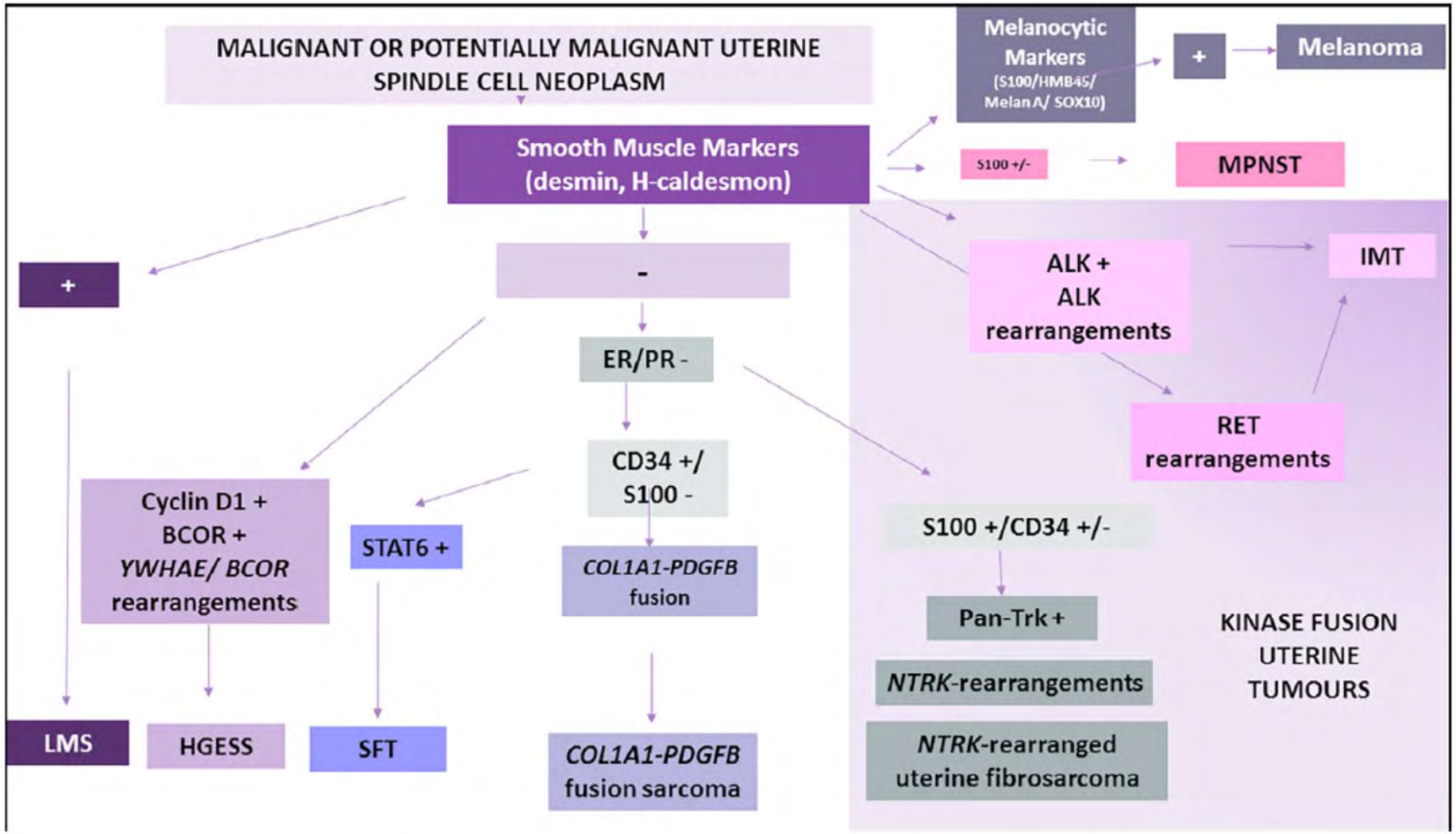

FIGURE 6 Diagnostic algorithm when dealing with a malignant or potentially malignant uterine spindle cell neoplasm

Croce et al., Genes Chromosomes Cancer 2021;60:147-59

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Table 3. Summary of the potential therapeutic targets that arise due to genetic aberrations frequently occurring in uLMS.

Aberration	Frequency	Therapeutic Target	Potential Drugs
TP53	26–92%	Mutant p53 [90]	APR-246 [91]
		WEE-1 [95]	AZD1775/MK-1775 [103,107]
RB1	27–88%	AURKA [109,110]	MLN8237/Alisertib [113,114,117]
		E2F [108]	HLM006474 [118,119]
ATRX	24–34%	ATR	VE-821 [141], VX-970, AZD6738
		EZH2 [139,148,149]	Tazemetostat, GSK-126
		BLM	ML216 [142]
		PCNA	T2AA [143]
		PARP	PJ34 [147]
		WEE-1	AZD1775 [144,145]

Aberration	Frequency	Therapeutic Target	Potential Drugs
PTEN	19–75%	PI3K [163,164]	AZD6482 [162], Buparlisib
		AKT [163,164]	MK-2206 [162], AZD5363
		mTORC1 [163,164]	Temsirolimus [162,166], Everolimus, Ridaforolimus [165]
		SRC	Dasatinib [172]
		FAK	VS-4718, VS-6063, PF-573228, PF-562271, GSK2256098 [168]
		PARP	KU0058948 [174], Olaparib [175]
MED12	12–21%	TGF-βR	LY2157299 [185]
		BET [193]	JQI
HRD	7–60%	PARP [78,81,202]	Olaparib [59,60]

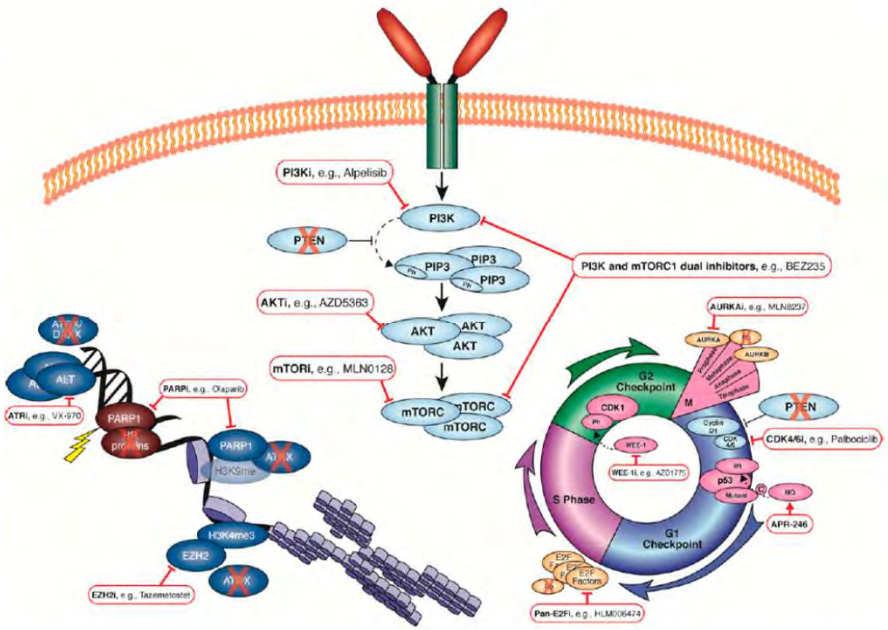


Figure 1. Summary of the common genetic aberrations in uLMS and their potential therapeutic targets.

TABLE 1. Clinicopathologic Characteristics

	PLAG1 Fusion Status (n)	
	Positive (4 [27%])	Negative (11 [73%])
Age (y)		
Median	49	51
Range	28-74	44-65
Stage		
I	2	1
II	1	1
III	0	2
IV	0	1
Unknown	1	6
Tumor size (cm)		
Median	17	15
Range	15-24	10-20
Unknown	1	5
Tumor necrosis		
Absent	2	7
Present	2	4
Nuclear atypia		
Mild	0	3
Moderate	4	4
Severe	0	4
Mitotic index (#/10 HPF)		
<2	1	4
2-10	2	5
>10	1	2
Vascular invasion		
Absent	4	11
Present	0	0

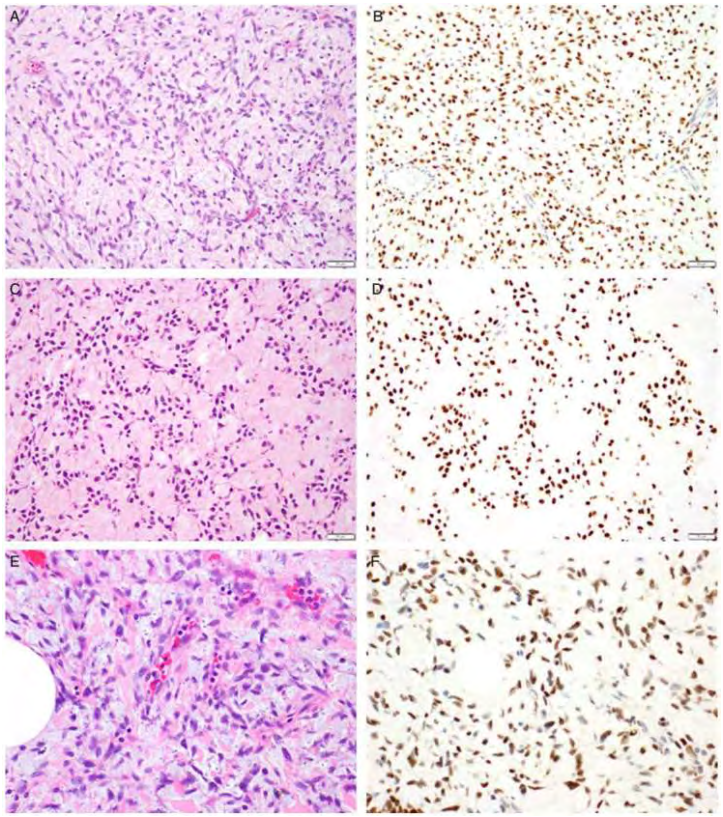


TABLE 2. Immunohistochemical and Molecular Characteristics

	Immunohistochemistry				Fluorescence In Situ Hybridization					
Case	PLAG1	ALK	BCOR	MSK-Solid Fusion Assay	*PLAG1*	*HMGA2*	*BCOR*	*BCORL1*	*ALK*	Revised Diagnosis
1	+ (S >95%)	NP	NP	*TRPS1-PLAG1*	NP	NP	NP	NP	NP	mLMS with *PLAG1* fusion
2	+ (S >95%)	NP	NP	*TRPS1-PLAG1*	NP	NP	NP	NP	NP	mLMS with *PLAG1* fusion
3	NP	NP	NP	*TRPS1-PLAG1*	NP	NP	NP	NP	NP	mLMS with *PLAG1* fusion
4	+ (S >95%)	–	–	*RAD51B-PLAG1*	NP	NP	NP	NP	NP	mLMS with *PLAG1* fusion
5	+ (M >95%)	–	+ (W <5%)	–	–	–	–	–	–	mLMS
6	+ (S >95%)	–	+ (W <5%)	–	–	–	–	–	–	mLMS
7	NP	–	+ (W 30%)	–	-	–	–	–	–	mLMS
8	+ (W <5%)	–	+ (M 50%)	–	–	–	–	–	–	mLMS
9	+ (W <5%)	–	–	F	–	–	–	–	–	mLMS
10	–	–	–	F	–	–	–	–	–	mLMS
11	–	–	–	F	–	–	–	–	–	mLMS
12	+ (W <5%)	–	–	F	–	–	–	–	–	mLMS
13	+ (S >95%)	–	–	NP	–	–	–	–	–	mLMS
14	+ (W <5%)	–	–	NP	–	–	–	–	–	mLMS
15	+ (W 50%)	–	+ (M 50%)	NP	–	–	–	–	–	mLMS

F indicates failed; M, moderate; mLMS, myxoid leiomyosarcoma; NP, not performed; S, strong; W, weak.

Arias-Stella et al, Am J Surg Pathol 2019;43:832-8

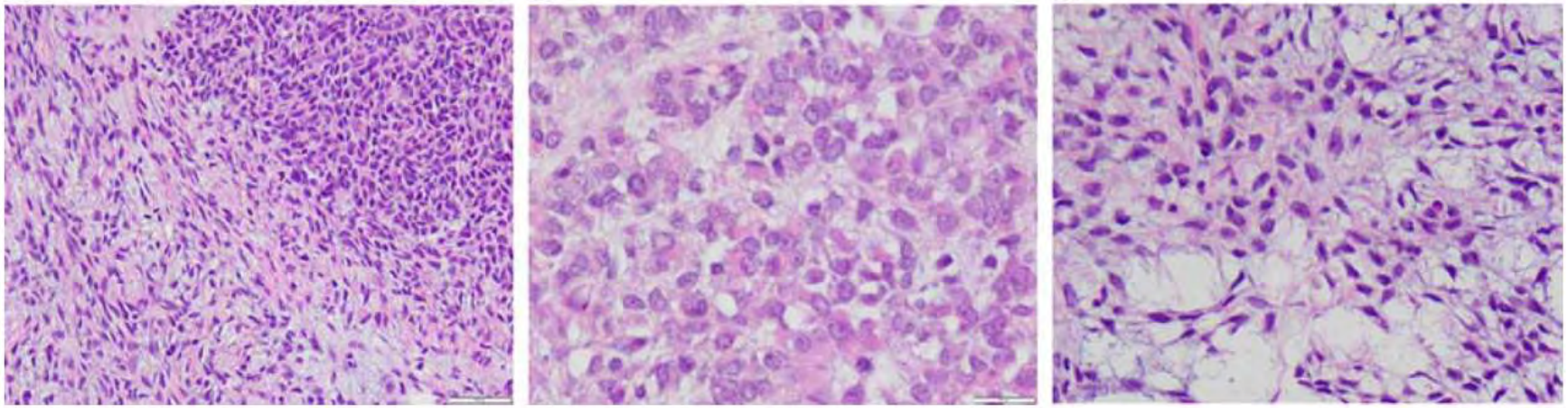
TABLE 1. Summary of Study Cohort

Tumor Type	n	*PGR* Rearrangement (n)	*NR4A3* Rearrangement (n)
Epithelioid leiomyosarcoma	17	6	4
Endometrial stromal tumor	6	0	0
Low-grade endometrial stromal sarcoma	1	0	0
High-grade endometrial stromal sarcoma	4	0	0
Endometrial stromal nodule	1	0	0
Perivascular epithelioid cell tumor	3	0	0

TABLE 3. Pathologic Features of *PGR* Fusion-positive Uterine Sarcomas

		Morphology						Immunohistochemical Profile					
Case	Size (cm)	Spindled	Rhabdoid	Myxoid	MI	LVI	Necrosis	CD10	Desmin	ER	PR	HMB45	Fusion Status
1*	5	+	+	+	19	−	−	0	4	4	4	0	*NR4A3-PGR*
2	12	+	+	+	9	−	−	0	2	4	4	NP	*NR4A3-PGR*
3	3	+	+	+	4	−	−	0	4	4	4	0	*NR4A3-PGR*
4	15	−	+	−	12	+	−	0	3	3	4	0	*PGR* rearrangement only
5	4	+	+	−	10	+	−	0	3	4	4	NP	*NR4A3-PGR*
6	27	+	+	−	10	−	+	NP	3	4	4	0	*PGR* rearrangement only

*Index case subjected to RNA sequencing.
LVI indicates lymphovascular invasion; MI, mitotic index (#/10 HPF); NP, not performed.



Chiang et al, Am J Surg Pathol 2019;43:810-8

TABLE 4. Differential Diagnosis Of Spindle Cell Leiomyosarcoma

Diagnosis	Distinctive morphologic features	Helpful Immunohistochemistry	Pitfalls	General points
LMBN	Karyorrhectic nuclei mimicking atypical mitoses in the absence of brisk mitotic index Lack of tumor necrosis Absence of cytologic atypia in background/ interspersed nonbizarre cells	None	Positivity for p16 (common) and aberrant p53 (occasionally)	Adequate sampling is recommended
STUMP	Criteria for LMS is not fulfilled	None	Heterogeneous group of tumors Interobservervariability in assessing tumor necrosis Metastasis/extrauterine spread is not a definitive criteria for LMS	Judicious sampling is recommended
PEComa	Often with two patterns (epithelioid and spindled) More delicate vessels Granular cytoplasm of cells Melanin pigment (rare) Multinucleated giant cells and 'spider" cells (rare)	Melanocytic markers: Melan-A, HBM45, PRAME, PNL2 Myogenic markers: SMA, Desmin, H-Caldesmon Cathepsin-K TFE3	Significant morphologic overlap in some cases LMS may express Cathepsin-K in ~50%, and melanocytic markers in a subset	Molecular testing may help in select cases (*TSC 1/2* alterations, *TFE3* rearrangement, *RAD51* mutations)
UUS	Diffuse sheets and fascicles of undifferentiated, highly malignant cells with necrosis	Absent staining for myogenic or any lineage-specific markers	Rare cells may, however, stain with Desmin or SMA; "allowable" extent of positivity is somewhat arbitrary	Diagnosis of exclusion No specific molecular alterations
Carcinosarcoma	High-grade epithelial component is present (even if in very small quantity) Sarcoma component is heterogeneous and often has heterologous differentiation (rhabdomyosarcomatous, chondrosarcomatous, and osteosarcomatous)	Variable; carcinoma component stains for epithelial markers (Keratins, EMA) while sarcoma component stains for mesenchymal markers (dependent of the type of differentiation)	LMS can show positivity for keratin in a subset of cases; a morphologic correlate (carcinoma) must be present Entrapped benign endometrial glands in LMS	Tumors arise from the endometrium Correlation with patient's endometrial samples to ensure that no high-grade carcinoma was priorly diagnosed
Mullerian adenosarcoma	Bland epithelial component is present (even if in very small quantity) Phyllodiform architecture Rigid cysts Sarcoma component is usually long, nonintersecting fascicles with peri-glandular accentuation	Variable; sarcoma component may stain for CD10, ER and show myogenic differentiation	A subset shows MDM2 overexpression and aberrant p53 (usually high-grade tumors), both of which can be seen in LMS	Tumors arise from the endometrium and are often exophytic
Rhabdomyosarcoma	Rhabdomyoblasts Cross striations Marked cell pleomorphism in PRMS Cambium layer, occasional cartilage in ERMS	Myogenin Myo-D1	Also positive for Desmin and SMA Rare cases of LMS with "rhabdomyosarcomatous differentiation" have been described	Rare No specific molecular alterations (other than PAX3 or PAX7 /FOXO1 fusion in ARMS) All RMS types have been described in the uterus

Table 1. The Spectrum of Aberrations Occurring in Low-Grade Endometrial Sarcoma, High-Grade Endometrial Sarcoma, and Tumors With Mixed Low-Grade and High-Grade Features

General Category[a]	Aberration	Diagnosis						
		No. of Cases	ESN	LG-ESS	ESS (NOS)	HG-ESS	LG/HG ESS	Sarcoma NS and Other Diagnoses
LG-ESS/ESN	*JAZF1* rearrangement	32	6	25	1			
LG-ESS/ESN	*JAZF1*::SUZ12	97	18	66		3	6	4[b]
LG-ESS	*JAZF1*::*PHF1*	16		10	2		4	
LG-ESS	*PHF1* rearrangement	12		7	5			
LG-ESS	*CDKN1A*::*JAZF1*	1		1				
LG-ESS	*SYNGAP1*::*JAZF1*	1			1			
LG-ESS	*PHF1*::*BRD8*	4		2		1	1	
LG-ESS	*EPC1*::*PHF1*	10		5	3		2	
LG-ESS	*EPC2*::*PHF1*	2		1	1			
LG-ESS	*ING3*::*PHF1*	1					1	
LG-ESS	*MEAF6*::*PHF1*	7		5	2			
LG-ESS	*MBTD1*::*PHF1*	1		1				
LG-ESS	*MBTD1*::*CXorf67*	2		2				
LG-ESS	*MEAF6*::*SUZ12*	1		1				
HG-ESS	*EPC1*::*SUZ12*	1				1		
LG-HG	*EPC1*::*EED*	3					3	
LG-HG	*EPC1*::*EZH2*	1					1	
HG-ESS *BCOR*	*BCOR* rearrangement	2				2		
HG-ESS *BCOR*	*ZC3H7B*::*BCOR*	61		1	2	58		
HG-ESS *BCOR*	*EPC1*::*BCOR*	1				1		
HG-ESS *BCOR*	*BCOR*::*EP300*	2				2		
HG-ESS *BCOR*	*BCOR*::*LPP*	1				1		
HG-ESS *BCOR*	*BCOR*::*NUTM2G*	1				1		
HG-ESS *BCOR*	*BCOR*::*MAP7D2*	1				1		
HG-ESS *BCOR*	*BCOR*::*RALGPS1*	1				1		
HG-ESS *BCOR*	*BCOR*::*RGAG1*	1				1		
HG-ESS *BCOR*	*BCOR*::*ING3* and *NUGGC*	1				1		
HG-ESS *BCOR*	*BCOR*::*KMTD2*	1				1		
HG-ESS *BCOR*	*BCOR*::*MAP7D2*	1				1		
HG-ESS *BCOR*	*CREBP*::*BCOR*	2			1	1		
HG-ESS *BCORL1*	*JAZF1*::*BCORL1*	10		1		7		2[c]
HG-ESS *BCORL1*	*EPC1*::*BCORL1*	1				1		
HG-ESS *BCORL1*	*EP300*::*BCORL1*	1				1		
HG-ESS *YWHAE*	*YWHAE* rearrangement	13		1		11		1[d]
HG-ESS *YWHAE*	*YWHAE*::*NUTM2*	63				58		5[e]
HG-ESS *YWHAE*	*YWHAE*::*NUTM2A*/B	20			1	19		
HG-ESS *YWHAE*	*YWHAE*::*NUTM2E*	4			4			
KAT6A/B	*KAT6B*::*KANSL1*	24			1			23[f]
KAT6A/B	*KAT6A*::*KANSL1*	2						2

Dundr et al, Arch Pathol Lab Med 2025;149:90-102

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Table 2. The Spectrum of Aberrations Occurring in Tumors With Tyrosine Kinase Fusions

General Category[a]	Aberration	Diagnosis				
		No. of Cases	Kinase Fusion/Fibrosarcoma-like	IMT	ESS NOS	HG Sarcoma
NTRK rearranged	*NTRK3* rearrangement	2	2			
NTRK rearranged	*NTRK1*::*TPM3*	23	23			
NTRK rearranged	*SPECC1L*::*NTRK3*	3	3			
NTRK rearranged	*EML4*::*NTRK3*	4	4			
NTRK rearranged	*C16orf12*::*NTRK1*	2	2			
NTRK rearranged	*C16orf12*::*NTRK1*	7	7			
NTRK rearranged	*TFG*::*NTRK3*	1	1			
NTRK rearranged	*IRF2BP2*::*NTRK1*	2	2			
NTRK rearranged	*STRN*::*NTRK3*	1	1			
NTRK rearranged	*ETV6*::*NTRK3*	1	1			
NTRK rearranged	*LMNA*::*NTRK1*	2	1		1	
NTRK rearranged	*RBPMS*::*NTRK3*	1	1			
IMT with *ALK* fusion	*DCTN1*::*ALK*	2		2		
IMT with *ALK* fusion	*SEC31*::*ALK*	1		1		
IMT with *ALK* fusion	*DES*::*ALK*	3		3		
IMT with *ALK* fusion	*TPM3*::*ALK*	1		1		
IMT with *ALK* fusion	*TIMP3*::*ALK*	14		14		
IMT with *ALK* fusion	*THBS1*::*ALK*	11		11		
IMT with *ALK* fusion	*FN1*::*ALK*	6		6		
IMT with *ALK* fusion	*NRP2*::*ALK*	2		2		
IMT with *ALK* fusion	*TNC*::*ALK*	1		1		
IMT with *ALK* fusion	*TNS1*::*ALK*	7		7		
IMT with *ALK* fusion	*LBH*::*ALK*	1		1		
IMT with *ALK* fusion	*ACTG2*::*ALK*	1		1		
IMT with *ALK* fusion	*CASC15*::*ALK*	1		1		
IMT with *ALK* fusion	*IGFB5*::*ALK*	17		17		
IMT with *ALK* fusion	*RANBP2*::*ALK*	1		1		
IMT with *ALK* fusion	*PPP1CB*::*ALK*	1		1		
IMT with other fusion	*FN1*::*ROS1*	1		1		
IMT with other fusion	*THBS1*::*INSR*	1		1		
IMT with other fusion	*TFG*::*ROS1*	1		1		
IMT with other fusion	*TIM3*::*RET*	1		1		
IMT with other fusion	*IGFB5*::*PDGFRB*	1		1		
IMT with other fusion	*NUDCD3*::*ROS1*	1		1		
IMT with other fusion	*TIMP3*::*RET*	1		1		
IMT with other fusion	*SORB51*::*RET*	1		1		
Other fibrosarcoma-like	*FGFR1*::*TACC1*	2	1		1	
Other fibrosarcoma-like	*RET*::*SPECC1L*	1	1			
Other fibrosarcoma-like	*COL1A1*::*PDGFRB*	9	8			1

Dundr et al, Arch Pathol Lab Med 2025;149:90-102

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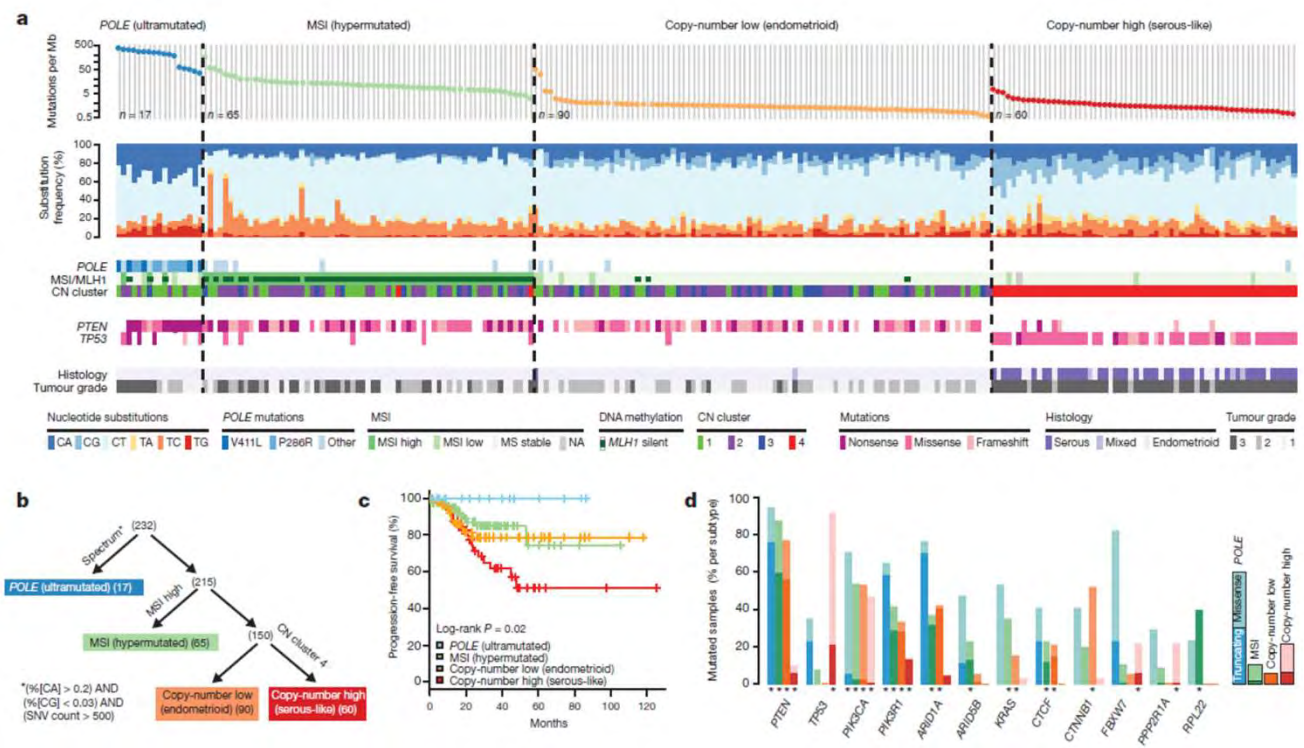
Table 3. The Spectrum of Aberrations Occurring in Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT), Perivascular Epithelioid Cell Tumor (PEComa), Alveolar Soft Part Sarcoma (ASPS), and Soft Tissue–Type Tumors With Known Recurrent Aberrations

			Diagnosis											
General Category[a]	Aberration	No. of Cases	UTROSCT	LG Sarcoma	ESS NOS	HG Sarcoma	Sarcoma NS	SRBCT	PNET	DSRCT	Epithelioid Sclerosing Fibrosarcoma	Synovial Sarcoma	PEComa	ASPS
UTROSCT	*ESR1*::*NCOA2*	10	10											
UTROSCT	*ESR1*::*NCOA3*	19	18		1									
UTROSCT	*GREB1*::*NCOA1*	10	10											
UTROSCT	*GTF2A1*::*NCOA2*	2	2											
UTROSCT	*GREB1*::*NCOA2*	15	13		1	1								
UTROSCT	*NCOA2* rearrangement	3	3											
UTROSCT	*NCOA1* rearrangement	7	7											
UTROSCT	*NCOA3* rearrangement	9	9											
PEComa	*TFE3* rearrangement	8											8	
PEComa	*TFE3*::SFPQ	2											2	
PEComa	*RADB1B* rearrangement	1											1	
PEComa	*RAD51B*::*RRAGB/OPHN1*	2											2	
PEComa	*RAD51B*::*OPHN1*	1											1	
ASPS	*ASPSCR1*::*TFE3*	11												11
UTROSCT	*GREB1*::*NR4A3*	1	1											
UTROSCT	*GREB1*::*SS18*	1	1											
UTROSCT	*GREB1*::*CTNNB1*	1	1											
Other sarcomas	*MEIS1*::*NCOA2*	5		3		2								
PNET	*EWRS1*::*ERG*	1							1					
PNET	*EWSR1* rearrangement	14							14					
PNET	*EWSR1*::*FLI1*	7							7					
Sclerosing epithelioid fibrosarcoma	*EWSR1*::*CREB3L2*	1									1			
Synovial sarcoma	*(SS18)SYT*::*SSX1*	2										2		
Synovial sarcoma	*(SS18)SYT* rearrangement	1										1		
GLI1 altered	*ACTB*::*GLI1*	1			1									
GLI1 altered	*PTCH1*::*GLI1*	1			1									
GLI1 altered	*PAMR1*::*GLI1*	1				1								
DSRCT, sarcoma NS	*EWSR1*::*WT1*	4					2			2				
CIC-rearranged sarcoma	*CIC*::*DUX4*	1						1						
CIC-rearranged sarcoma	*CIC* rearrangement	1						1						

Dundr et al, Arch Pathol Lab Med 2025;149:90-102

Topics

- Vulvar carcinoma and precursor lesions
- Cervical carcinoma
- Female genital sarcomas
- Endometrial carcinoma
- Tubo-ovarian tumors



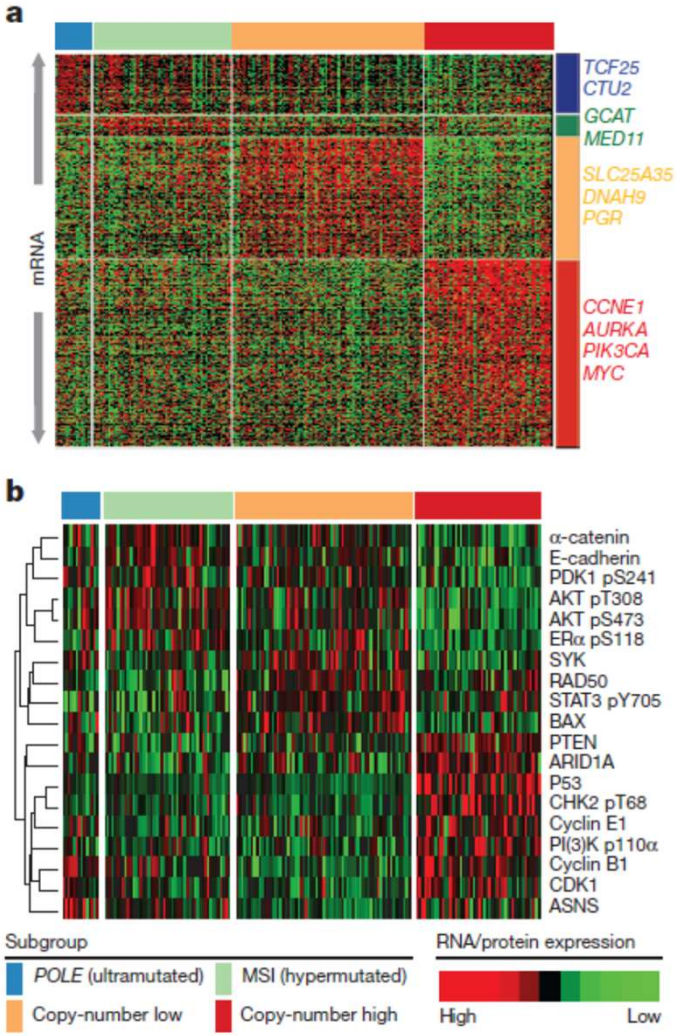


TABLE 3. *The 4 molecular subtypes of endometrial carcinoma*

Mutation profile	Surrogate marker (genetic)	Surrogate marker (IHC)
Ultramutated	*POLE* mutation	None available
Hypermutated	MSI-H	MMR-D
Copy number high	*TP53* mutation	p53 abn
Copy number low	Absence of other markers	Absence of other markers (p53 wt)

abn indicates abnormal; IHC, immunohistochemistry; MMR-D, mismatch repair deficient; MSI-H, microsatellite instability-high; POLE, polymerase E; wt, wild-type.

N=373; 307 EEC, 53 SC, 13 mixed

Cancer Genome Atlas Research Network, Nature 2013;497:67-73

Soslow et al., Int J Gynecol Pathol 2019;38:S64-S74

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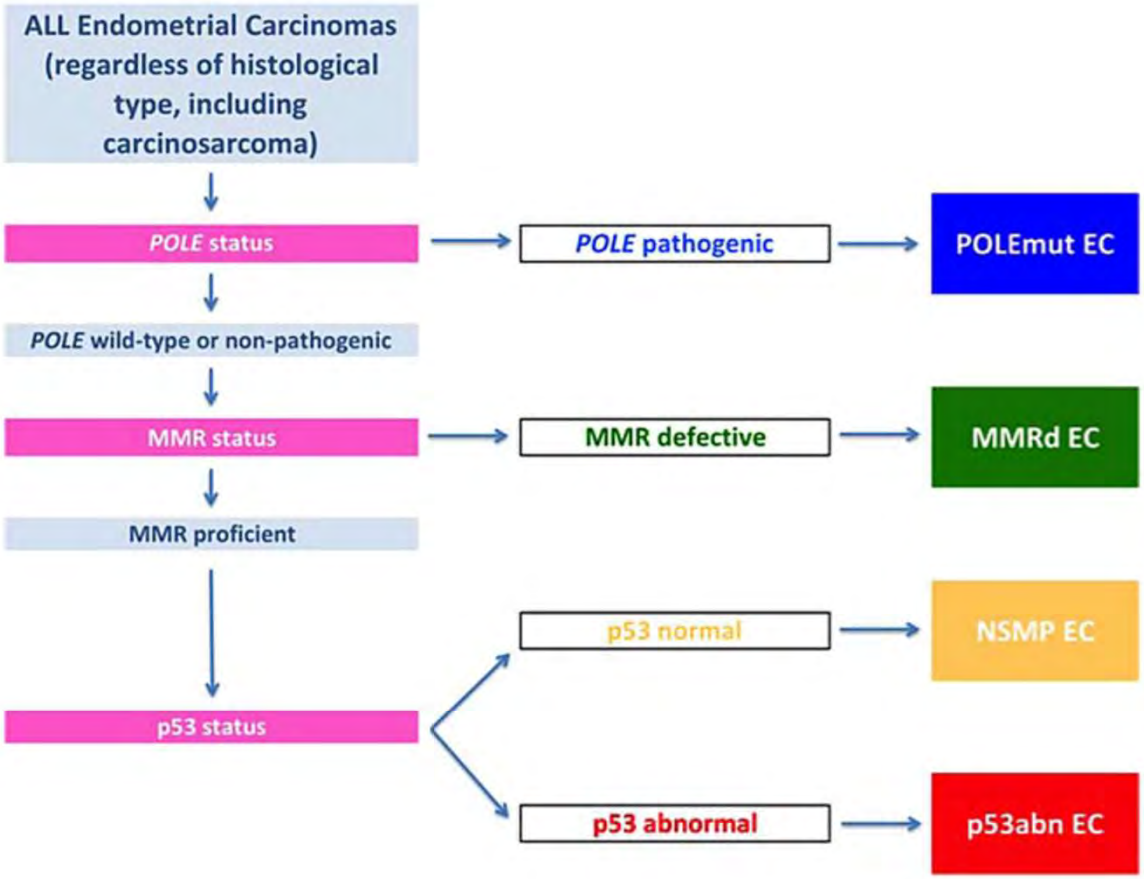

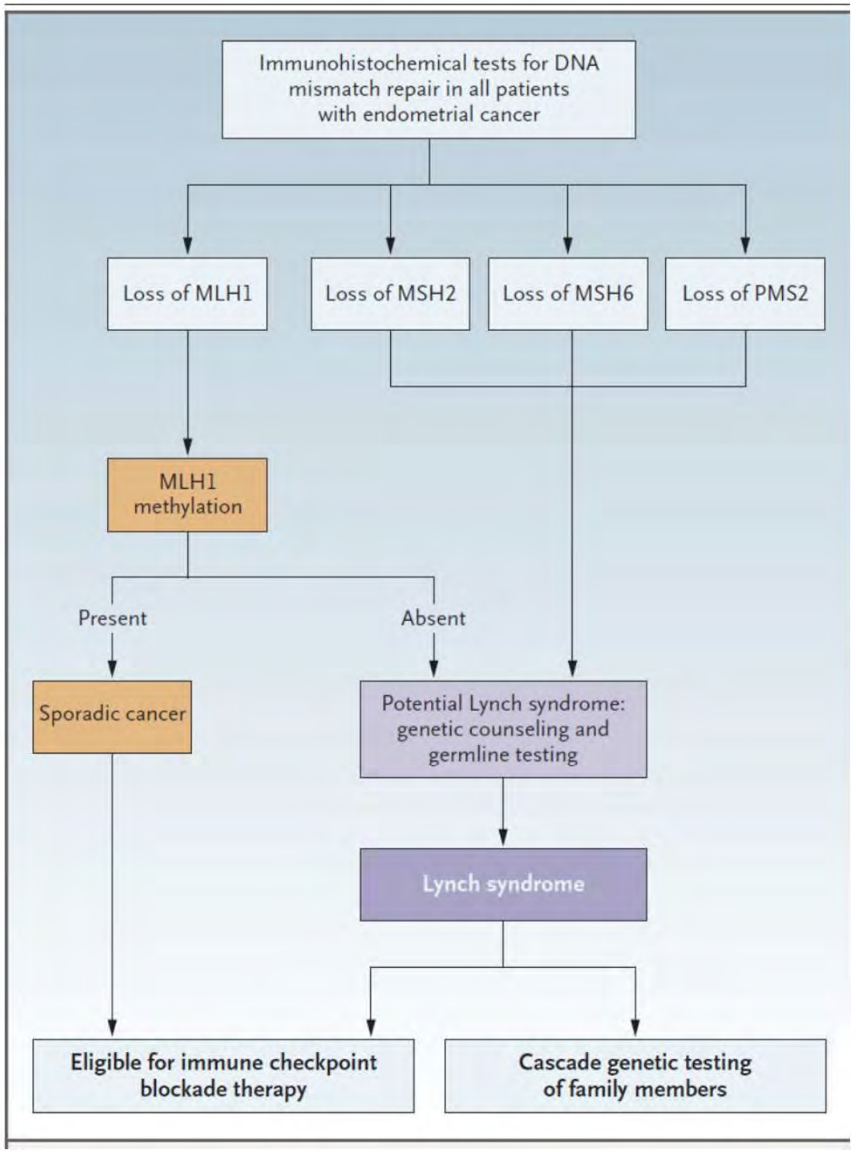

Casey and Singh, Int J Gynecol Pathol 2020;40:5-16

Lu and Broaddus, N Engl J Med 2020;383:2053-64

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Table 3. Pathogenic *POLE* EDM based on POLE-score

Protein change	Nucleotide substitution
P286R	c.857C>G
V411L	c.1231G>T/C
S297F	c.890C>T
S459F	c.1376C>T
A456P	c.1366G>C
F367S	c.1100T>C
L424I	c.1270C>A
M295R	c.884T>G
P436R	c.1307C>G
M444K	c.1331T>A
D368Y	c.1102G>T

Leon et al., J Pathol 2020;250:323-35

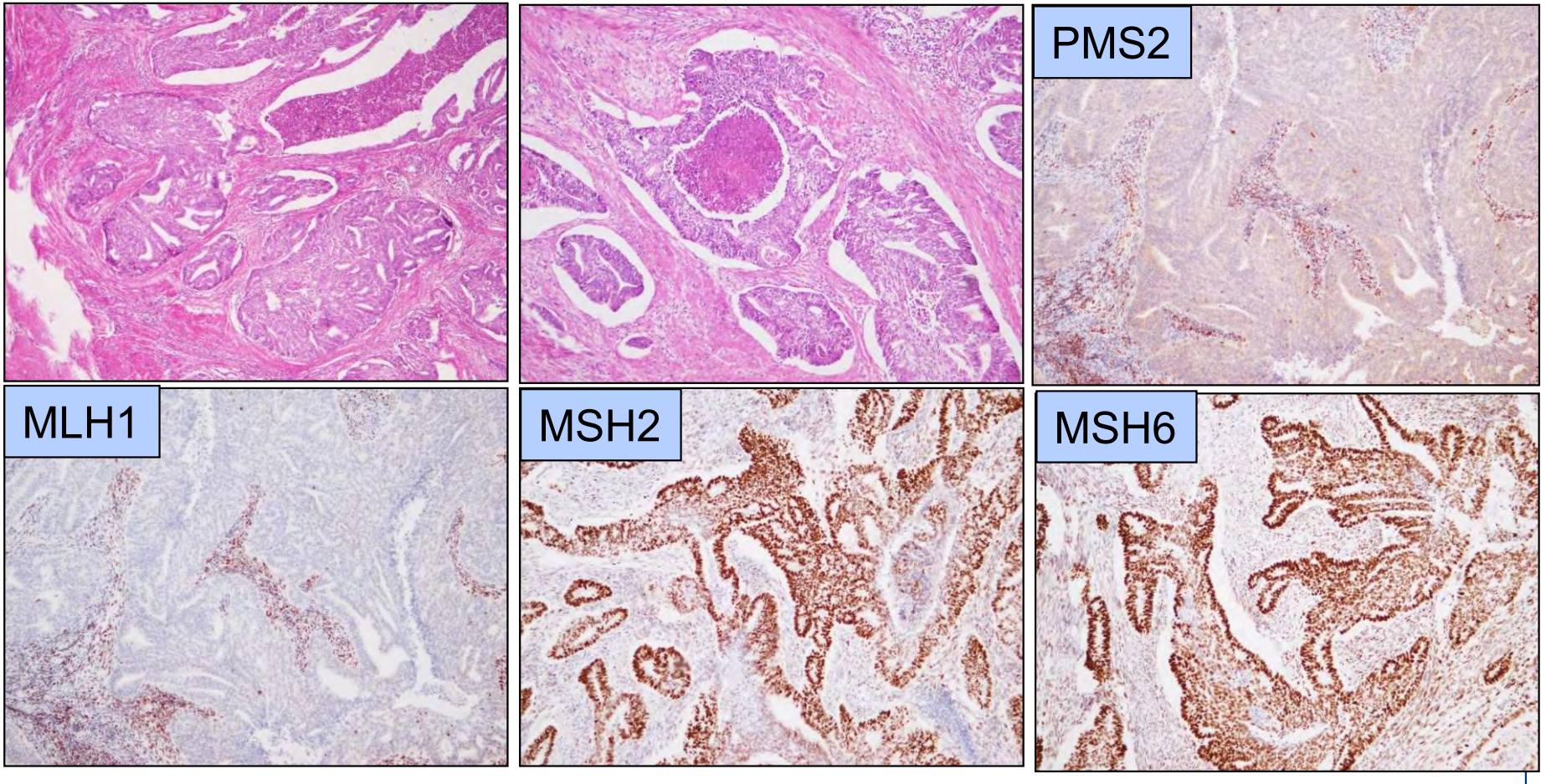

Table 3. Multivariable analysis of recurrence-free survival including clinicopathological and molecular features for MMRd, p53abn and NSMP endometrial cancers.

	MMRd EC ($n = 206$, 58 events)			p53abn EC ($n = 164$, 85 events)			NSMP EC ($n = 202$, 60 events)		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age									
≤60 years	1			NP			NP		
>60 years	1.55	0.88–2.74	0.13						
Stage									
I–II	1			1			1		
III	2.33	1.36–3.98	0.002	3.66	2.34–5.72	<.001	2.18	1.27–3.75	0.005
Histology and grade									
Endometrioid, low-grade							1		
Endometrioid, high-grade	NP			NP			2.39	1.16–4.94	0.018
Non-endometrioid							1.54	0.63–3.81	0.35
Treatment received									
RT (VBT or EBRT)	NP			1			1		
RT (VBT or EBRT) + CT				0.56	0.33–0.93	0.025	0.44	0.22–0.88	0.020
ER IHC									
Negative (<10%)	NP			NP			1		
Positive (≥10%)							0.33	0.15–0.75	0.008

Model fit multivariable models: MMRd (AIC 510.85, C-index 0.63), p53abn (AIC 652.18, C-index 0.67), NSMP (AIC 499.16, C-index 0.70). Bootstrap resampling model validation: MMRd (C-index re-estimation 0.64), p53abn (C-index re-estimation 0.68), NSMP (C-index re-estimation 0.70).
MMRd mismatch repair-deficient, *EC* endometrial cancer, *p53abn* p53-abnormal, *NSMP* no specific molecular profile, *HR* hazard ratio, *CI* confidence interval, *NP* not performed, *LVSI* lymphovascular space invasion, *RT* radiotherapy, *VBT* vaginal brachytherapy, *EBRT* external beam radiotherapy, *CT* chemotherapy.

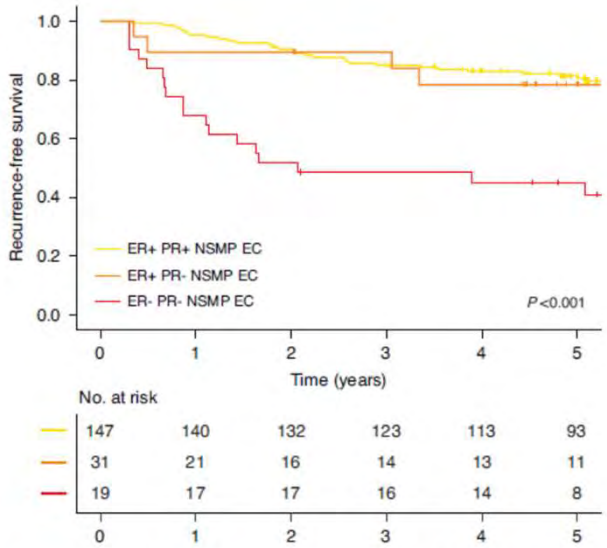

Fig. 1 Recurrence-free survival for patients with NSMP high-risk endometrial cancer by ER and PR expression. Kaplan–Meier survival curves of patients with NSMP high-risk endometrial cancer for recurrence-free survival by ER and PR expression.

Vermij et al., Br J Cancer 2023;128:1360-8

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FIGO 2009

	FIGO stage	UICC TNM stage (TNM categories)	5-year survival (95% CI)
Tumour confined to the corpus uteri	Stage I	I (T1 N0 M0)	92% (91·3–93·0)
Tumour limited to endometrium or invading less than one half of myometrium	Stage IA	IA (T1a N0 M0)	..
Tumour invades one half or more of myometrium	Stage IB	IB (T1b N0 M0)	..
Tumour invades cervical stroma, but does not invade beyond uterine corpus	Stage II	II (T2 N0 M0)	74% (74·9–77·5)
Local or regional spread	Stage III	III (T1–T3b N1 M0 or T3a–3b N0 M0)	48% (45·4–50·3)
Tumour invades the serosa of the corps uteri or adnexae (direct extension or metastasis)	Stage IIIA	IIIA (T3a N0 M0)	..
Vaginal or parametrial involvement (direct extension or metastasis)	Stage IIIB	IIIB (T3b N0 M0)	..
Metastasis to pelvic or para-aortic lymph nodes	Stage IIIC	IIIC (T1–3 N1 M0)	..
Metastasis to pelvic lymph nodes	Stage IIIC1	IIIC1 (T1–3 N1 M0)	..
Metastasis to para-aortic lymph nodes with or without pelvic lymph node metastasis	Stage IIIC2	IIIC2 (T1–3 N2 M0)	..
Tumour invades bladder or bowel mucosa, or distant metastases, or any combination thereof	Stage IV	IV (T4 N_{any} M0 or T_{any} N_{any} M1)	15% (13·2–17·3)
Tumour invades bladder or bowel mucosa, or both	Stage IVA	IVA (T4 N_{any} M0)	..
Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa) including intra-abdominal metastases, inguinal nodes, or intra-abdominal nodes other than pelvic or para-aortic nodes, or any combination thereof	Stage IVB	IVB (T_{any} N_{any} M1*)	

FIGO=International Federation of Gynecology and Obstetrics. FIGO does not include stage 0. UICC=Union for International Cancer Control. TNM classification: N0 (no regional lymph node metastasis), M0 (no distant metastasis), N1–N3 (increasing involvement of regional lymph nodes), M1 (distant metastasis). *Microscopically confirmed distant metastasis.

Table 1: **FIGO and TNM classification of endometrial cancer defined by surgical and histological characteristics, and 5-year overall survival by stage[49–51]**

Crosbie et al., Lancet 2022;399:1412-28

FIGO 2023

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 endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) 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 LVSI
	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 LVSI[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 LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[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 IIICii 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

Berek et al., Int J Gynecol Obstet 2023;162:383-94

FIGO 2023 endometrial cancer staging: too much, too soon?

W Glenn McCluggage [1], Tjalling Bosse,[2] C Blake Gilks [3], Brooke E Howitt,[4] Jessica N McAlpine,[5] Marisa R Nucci,[6] Joseph T Rabban,[7] Naveena Singh,[8] Karen L Talia,[9] Carlos Parra-Herran[10]

Int J Gynecol Cancer. 2024 Jan 5;34(1):138-143.

European Journal of Cancer 213 (2024) 115115

Contents lists available at ScienceDirect

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journal homepage: www.ejcancer.com

FIGO 2023 staging for endometrial cancer, when, if it is not now?

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Endometrial carcinoma: 10 years of TCGA (the cancer genome atlas): A critical reappraisal with comments on FIGO 2023 staging

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HIGHLIGHTS

- The Cancer Genome Atlas Research Network described 4 molecular subgroups of endometrial carcinomas with different outcome
- High-grade, early-stage EECs with *POLE* mutations are uncommon. These patients could benefit from a de-escalating treatment
- Conventional histopathologic classification should be complemented with, but not replaced by, TCGA classification
- Molecular data should not be integrated into the staging, but rather should be collected as complementary information
- The 2023 FIGO staging is a complicated and non-intuitive classification that makes its clinical application difficult

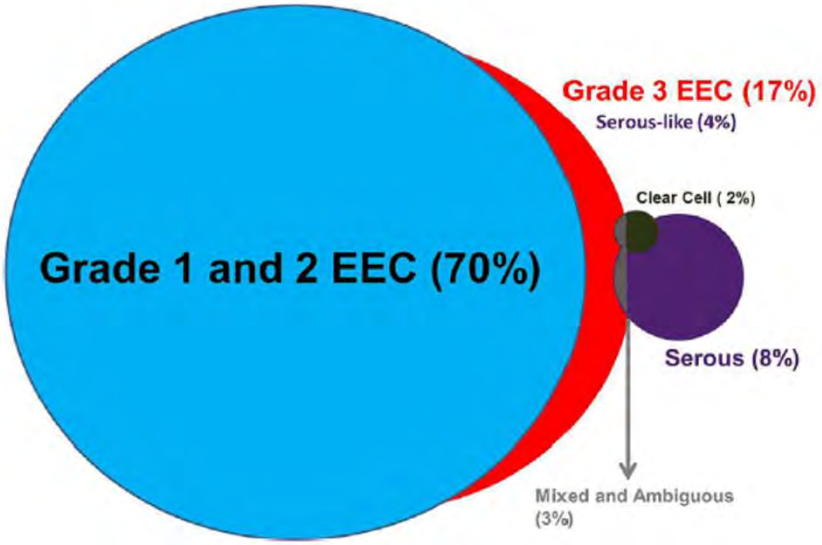


Fig. 1. Low-grade (G1–G2) and high-grade (G3) endometrioid carcinomas. There is a small "gray" zone between G3 endometrioid and type 2 (mostly serous) tumors with sharing features.

Endometrial Carcinomas (WHO 2020)

- Endometrioid Carcinoma 85%
- Serous carcinoma <10%
- Clear cell carcinoma 2%
- Mixed carcinoma (EEC+SC) 3%
- Undifferentiated – dedifferentiated ca 2%
- Carcinosarcoma <2%
- Other carcinomas -

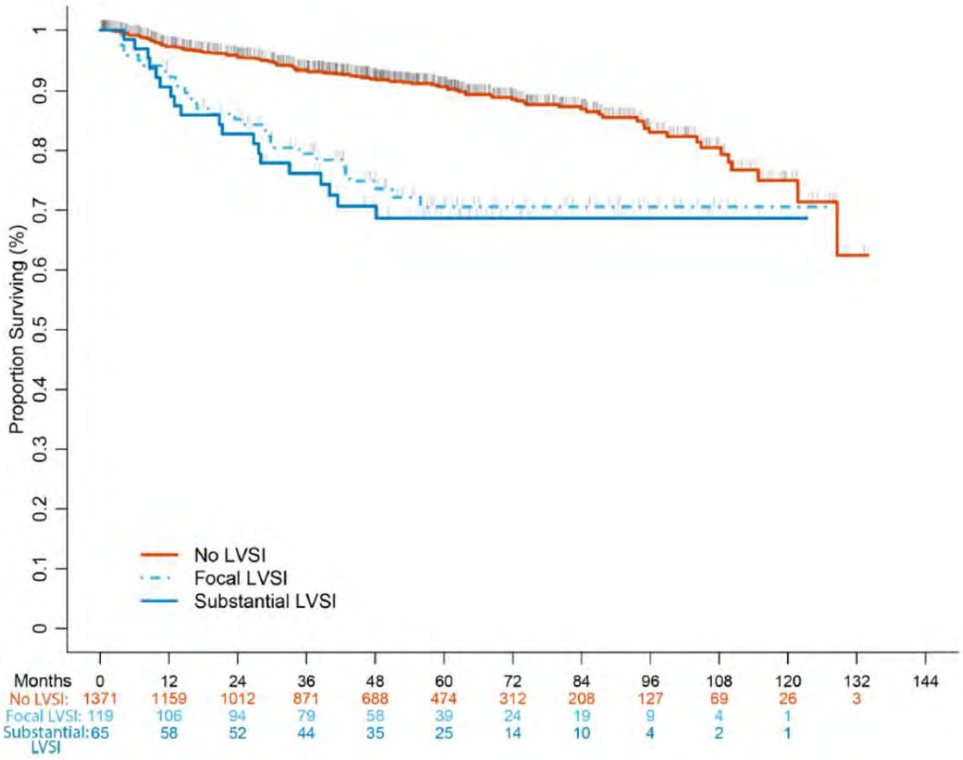
- Mesonephric adenocarcinoma/Mesonephric-like adenocarcinoma/Squamous carcinoma/Gastric (gastrointestinal)-type mucinous carcinoma

LVSI

Table 2 Univariate and multivariate analyses of progression-free survival for patients with FIGO 2009 stage I endometrioid endometrial cancer treated surgically with pathology-proven negative nodes (n=1555)

Characteristics	N (event)	5-year PFS rate (95% CI)	Univariate HR (95% CI)	Multivariate aHR (95% CI); Cox Pv
Cohort	1555 (174)	87.9% (85.8% to 89.7%)	–	–
Extent of LVSI				
No LVSI	1371 (125)	90.7% (88.6% to 92.3%)	Reference	Reference
Focal LVSI	119 (30)	70.5% (60.3% to 78.6%)	2.80 (2.39 to 3.27)	1.84 (1.73–1.96); <0.001
Substantial LVSI	65 (19)	68.7% (55.2% to 78.8%)	3.13 (2.58 to 3.79)	2.17 (1.96–2.39); <0.001
Age at surgery (1-year increment)		–	1.09 (1.08 to 1.1)	1.08 (1.07–1.09); <0.001
BMI category*				
BMI <30 kg/m^2	747 (85)	88.8% (85.9% to 91.2%)	Reference	–
BMI ≥30 kg/m^2	804 (88)	87% (83.9% to 89.6%)	1.14 (0.76 to 1.7)	
Self-reported race				
White	1296 (152)	87.7% (85.5% to 89.6%)	Reference	–
Black	66 (10)	76.1% (57.6% to 87.4%)	1.47 (0.88 to 2.45)	
Asian	107 (5)	95.4% (88.2% to 98.3%)	0.47 (0.4 to 0.56)	
Other	86 (7)	89% (76.4% to 95.1%)	0.86 (0.49 to 1.51)	
Surgical approach				
MIS	1361 (128)	89.7% (87.5% to 90.8%)	Reference	Reference
Laparotomy	194 (39)	82% (75.2% to 87.1%)	1.58 (1.43 to 1.75)	1.18 (1.05–1.33); 0.006
FIGO 2009 stage				
IA	1361 (128)	89.7% (87.6% to 91.5%)	Reference	–
IB	194 (46)	77.8% (70.9% to 83.3%)	2.22 (1.75 to 2.82)	
FIGO grade				
G1	1083 (80)	91.5% (89.1% to 93.3%)	Reference	Reference
G2	336 (60)	82.2% (77.2% to 86.2%)	2.22 (1.99 to 2.47)	1.37 (1.11–1.68); 0.003
G3	136 (34)	76.9% (68.7% to 83.2%)	2.75 (1.89 to 4.01)	1.55 (0.94–2.59); 0.089
Depth of myometrial invasion				
None	842 (41)	95% (92.9% to 96.5%)	Reference	Reference
<50%	519 (87)	83% (79% to 86.3%)	3.06 (2.64 to 3.54)	1.75 (1.47–2.08); <0.001
≥50%	194 (46)	78% (71.3% to 83.4%)	4.13 (3.82 to 4.46)	1.34 (1.08–1.66); 0.008
Landmark analysis				
No adjuvant treatment	1173 (121)	89% (86.6% to 91%)	Reference	–
Adjuvant treatment	320 (50)	82.5% (76.5% to 86.2%)	1.39 (0.53 to 3.59)	

Cox Pv: p value obtained using the multivariate Cox proportional hazards regression analysis.
*BMI information was missing for four patients.
aHR, adjusted HR; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; G, grade; LVSI, lymphovascular space invasion; MIS, minimally invasive surgery; N, number; PFS, progression-free survival.



Dagher et al, Int J Gynecol Cancer 2024;34:1485-92

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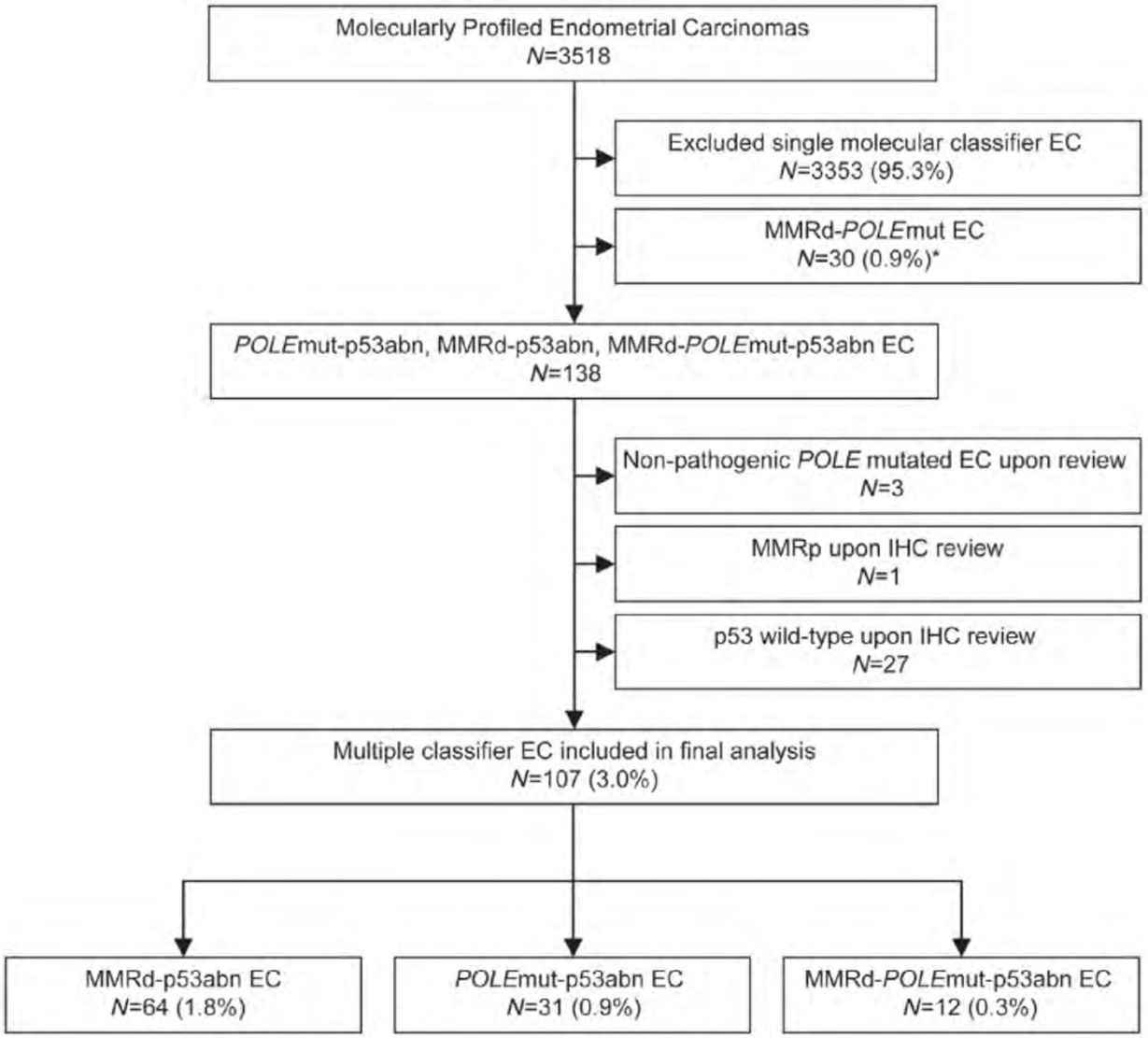
Multiple-classifier carcinomas



Leon-Castillo et al., J Pathol 2020;250:312-322

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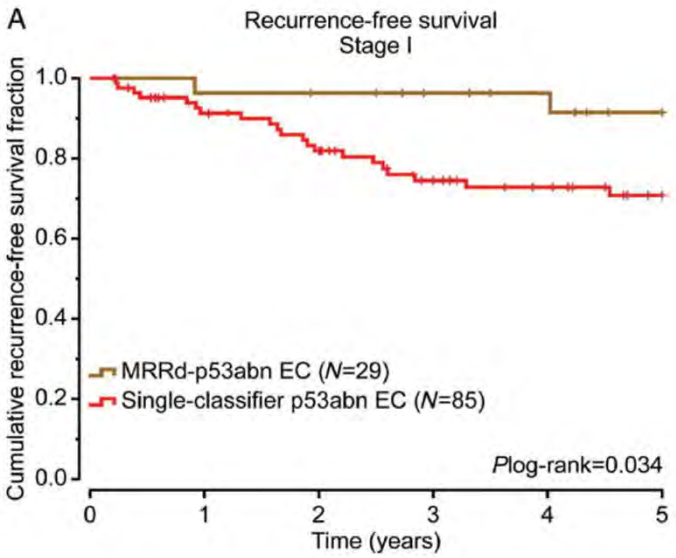
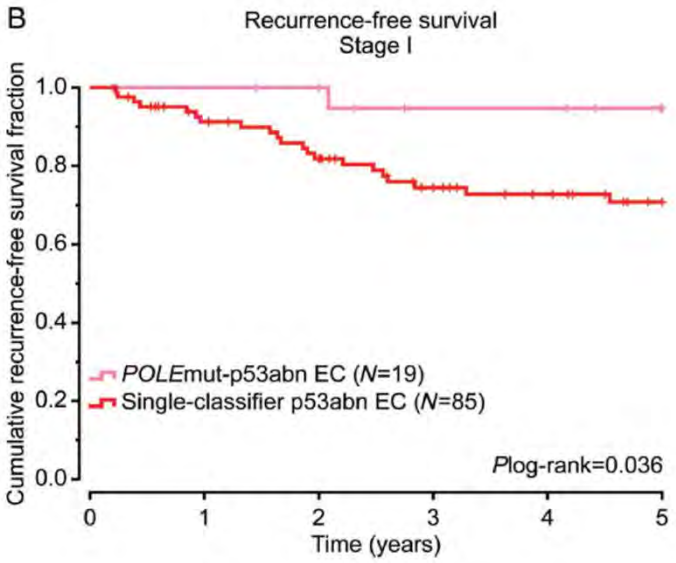
Table 1. Clinicopathological characteristics of multiple-classifier EC with abnormal p53

	Total $n = 107$ (%)	MMRd–p53abn EC $n = 64$ (%)	*POLE*mut–p53abn EC $n = 31$ (%)	MMRd–*POLE*mut–p53abn EC $n = 12$ (%)
Age, years				
Mean [range]	61.6 [35–87]	61.7 [35–87]	62.1 [50–83]	59.9 [47–74]
< 60	51 (47.7)	28 (43.8)	16 (51.6)	7 (58.3)
60–70	33 (30.8)	22 (34.4)	8 (25.8)	3 (25.0)
> 70	22 (20.6)	14 (21.9)	6 (19.4)	2 (16.7)
Missing	1 (0.9)	0 (0)	1 (3.2)	0 (0)
Stage				
IA	41 (38.3)	25 (39.1)	9 (29)	7 (58.3)
IB	41 (38.3)	22 (34.4)	15 (48.4)	4 (33.3)
II	3 (2.8)	2 (3.1)	1 (3.2)	0 (0)
III	16 (15)	11 (17.2)	4 (12.9)	1 (8.3)
IV	6 (5.6)	4 (6.3)	2 (6.5)	0 (0)
Histology				
Endometrioid	77 (72)	46 (71.9)	22 (71)	9 (75.0)
Serous	9 (8.4)	6 (9.4)	2 (6.5)	1 (8.3)
Mixed	16 (15)	8 (12.5)	6 (19.4)	2 (16.7)
Clear cell	3 (2.8)	2 (3.1)	1 (3.2)	0 (0)
Undifferentiated	2 (1.9)	2 (3.1)	0 (0)	0 (0)
Grade				
1–2	25 (23.4)	16 (25)	7 (22.6)	2 (16.7)
3	82 (76.6)	48 (75)	24 (77.4)	10 (83.3)
Myometrium invasion				
Intramucosal	4 (3.7)	2 (3.1)	0 (0)	2 (16.7)
< 50%	45 (42.1)	28 (43.8)	11 (35.5)	6 (50.0)
> 50%	53 (49.5)	31 (48.4)	19 (61.3)	4 (33.3)
Missing	5 (4.7)	3 (4.7)	1 (3.2)	0 (0)
LVSI				
Absent	44 (41.1)	22 (34.4)	15 (48.4)	7 (58.3)
Present	32 (29.9)	23 (35.9)	5 (16.1)	4 (33.3)
Missing	31 (29.0)	19 (29.7)	11 (35.5)	1 (8.3)
Treatment				
Radiotherapy	18 (16.8)	12 (18.8)	5 (16.1)	1 (8.3)
Chemotherapy	9 (8.4)	4 (6.3)	4 (12.9)	1 (8.3)
Radiochemotherapy	10 (9.3)	7 (10.9)	3 (9.7)	0 (0)
None	15 (14.0)	9 (14.1)	4 (12.9)	2 (16.7)
Missing	55 (51.4)	32 (50)	15 (48.4)	8 (66.7)
Risk classification (ESMO clinical practice guidelines, 2013 [27])				
Low risk	9 (8.4)	6 (9.4)	3 (9.7)	0 (0)
Intermediate risk	31 (29.0)	16 (25)	8 (25.8)	7 (58.3)
High risk	51 (47.7)	30 (46.9)	17 (54.8)	4 (33.3)
Advanced stage I	13 (12.1)	10 (15.6)	2 (6.5)	1 (8.3)
Metastatic	3 (2.8)	2 (3.1)	1 (3.2)	0 (0)
Risk classification (ESMO–ESTRO–ESGO clinical practice guidelines, 2016 [28])				
Low risk	4 (3.7)	2 (3.1)	2 (6.5)	1 (8.3)
Intermediate	11 (10.3)	7 (10.9)	3 (9.7)	0 (0)
High–intermediate	22 (20.6)	11 (17.2)	5 (16.1)	6 (50)
High	59 (55.1)	37 (57.8)	17 (54.8)	5 (41.7)
Advanced or metastatic	6 (5.6)	4 (6.3)	2 (6.5)	0 (0)
Not assessable	5 (4.7)	3 (4.7)	2 (6.5)	0 (0)





Leon-Castillo et al., J Pathol 2020;250:312-322

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Table 4 Features of "multiple classifier" endometrial carcinomas

	Molecular subtype	*POLE* mutation	Histological type of ca, grade	MMR status	p53 IHC expression	*TP53* mutation	Stage	Follow-up	*FU* lenght —months	*LVI*	Lymph node (LN) metastasis	Administered treatment
1	Type 1 — *POLE*mut	c.1231G > T, p.(Val411Leu)	Endometroid, 3	p	Null pattern	c.637C > T, p.(Arg 213Ter)	min cT1 N0	AWD	27	Absent	No	No surgery — inoperable (obesity and comorbidities), adjuvant RT
2	Type 1 — *POLE*mut	c.1231G > T, p.(Val411Leu)	Endometroid, 2	p	Overexpression	c.587G > A p.(Arg196Gln)	pT2 N0	NED	21	Present (focal)	No	No adjuvant therapy
3	Type 1 — *POLE*mut	c.1376C > T, p.(Ser459Phe)	Endometroid, 3	d (MLH1, PMS2)	Normal pattern	Wild type	pT4 cN2	AWD, locally aggressive EC	34	Present (focal)	Yes (in LN of mesenterium, retroperitoneum)	Paliative CHT
4	Type 1 — *POLE*mut	p.(Val411Leu), p.(Ala426Val)	Endometroid, 2	p	Overexpression	c.722C > T,p.(Ser241Phe); c.869G > A,p.(Arg290His) c. 644G > A,p.(Ser215Asn)	min.T3b N2	DOD (22 months after dg)	22	Not detected (in curetage)	Yes (paraaortal LN)	No surgery, no adjuvant therapy (age, advanced disease)
5	Type 2 — Hypermutated	Wild type	Endometroid, 1	d (MLH1, PMS2)	Normal pattern	c.1146del p.(Lys382 AsnfsTer40)	pT4	AWD – infiltration of small bowel (at the time of dg)	1	Not detected	Not detected	Not known (consult case)
6	Type 2 — Hypermutated	Wld type	Endometroid, 1	d (MLH1, PMS2)	NA	c.817C > T p.(Arg273Cys)	pT1a	NA	NA	Not detected	Not detected	Not known (consult case)
7	Type 2 — Hypermutated	Wild type	Endometroid, 2	d (MLH1, PMS2)	Subclonal pattern	c.733G > A, p.(Gly245Ser)	pT3a N0	NED	26	Present (focal)	No	Adjuvant CHT and RT
8	Type 2 — Hypermutated*	Wild type	Endometroid, 3	d (MLH1, PMS2)	Subclonal pattern	c.652_654del, p.(Val218del)	pT1a N0	NED	21	Absent	No	Adjuvant CHT and RT
9	Type 2 — Hypermutated*	Wild type	Endometroid, 1	d (MLH1, PMS2)	Normal pattern	c.328C > T, p.(Arg110Cys)	M1	DOD (1 month after dg)	1	Absent	Yes (inguinal LN)	No adjuvant therapy (age, advanced disease)
10	Type 2 — Hypermutated*	Wild type	Endometroid, 3	d (MLH1, PMS2)	NA	c.481G > A,p.(Ala161Thr) c.902del p.(Pro301 GlnfsTer44)	M1	AWD — generalized disease with distant metastases	24	Absent	No	Surgery, palliative CHT
11	Type 2 — Hypermutated*	Wild type	Endometroid, 3	d (MSH6)	Subclonal pattern	c.734G > A p.(Gly245Asp)	NA	NA	NA	Absent	No	Not known (consult case)
12	Type 2 — Hypermutated*	Wild type	Endometroid, 3	d (MSH6, MSH2)	NA	c.743G > A p.(Arg248Gln)	pT1a	NA	NA	Absent	No	Not known (consult case)

Table 4 (continued)

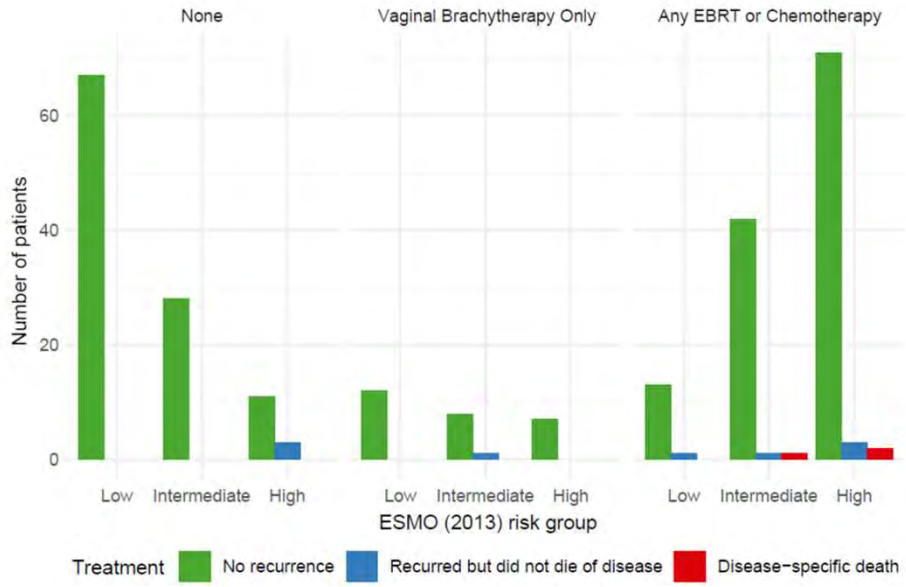
Michalova et al., Virchows Arch 2024 Dec 15 Epub

TABLE 3. Any Disease-Related Adverse Survival Events and Adjuvant Treatments Received With No Differences Noted

		Adverse Events (PFS and/or DSS) and Adjuvant Treatment Received			
Variable	Level	Censored	Event	Total	P
Treatment, No. (%)	None	106 (97)	3 (3)	109 (100)	.6
	Vaginal brachytherapy only	27 (96)	1 (4)	28 (100)	
	EBRT without chemotherapy	81 (94)	5 (6)	86 (100)	
	Any chemotherapy	45 (94)	3 (6)	48 (100)	
Total, No. (%)[a]		259 (96)	12 (4)	271 (100)	

		Adverse Events (PFS and/or DSS) and Adjuvant Treatment Received (None vs Any)			
Variable	Level	Censored	Event	Total	P
Treatment, No. (%)	None	106 (97)	3 (3)	109 (100)	.42
	Any[b]	153 (94)	9 (6)	162 (100)	
Total, No. (%)[a]		259 (96)	12 (4)	271 (100)	

Abbreviations: DSS, disease-specific survival; EBRT, external-beam radiotherapy; PFS, progression-free survival.
[a]Row-wise percentages were computed.
[b]*Any* encompasses any form of adjuvant radiation (EBRT and/or vaginal brachytherapy) or chemotherapy.



- No association with traditional cliniocopathologic parameters
- No benefit in additional treatment

Berek et al., Int J Gynecol Obstet 2023;162:383-94

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Endometrial ca. with ambiguous histology

Case	Age	BMI	FIGO stage[a]	LVSI	LN resected	Omentum resection	Recurrence	TTR	OS	Status
1	56	29.8	II	Yes	Pelvic	Yes	Lung	9	25	DOD
2	76	25.8	II	Yes	Pelvic + aortic	No	Lung + vagina	28	63	DOD
3	48	30.5	IA	No	Pelvic + aortic	No	No	-	169	NED
4	70	23.6	IB	Yes	Pelvic + aortic	Yes	Vagina	21	45	DOD
5	77	23.8	IA	No	Pelvic + aortic	Yes	Multiple	46	59	DOD
6	74	26	IB	No	Pelvic	No	Lung	30	51	DOD
7	79	29.3	IB	No	Pelvic + aortic	No	No	-	69	DOC
8	66	41	IA	No	Pelvic + aortic	Yes	No	-	99	NED
9	74	50.9	IA	No	SLN	No	No	-	74	NED
10	60	38.1	IA	No	SLN	No	No	-	55	NED
11	70	37.3	II	Yes	Pelvic + aortic	No	No	-	143	NED
12	69	22.5	IVB	No	Pelvic	Yes	Multiple	12	72	AWD
13	60	34.1	IA	No	Pelvic	Yes	Pelvis	23	86	NED
14	74	16.4	IA	No	Pelvic + aortic	Biopsy	No	-	85	NED
15	83	28.2	IIIC1	Yes	Pelvic	No	Multiple	19	46	DOD
16	79	26.1	IA	No	Pelvic	Yes	No	-	88	NED
17	65	36.6	IA	No	Pelvic	Yes	Pelvis + lung	29	79	DOD
18	68	29.3	IIIC2	Yes	Pelvic + aortic	Yes	Multiple	8	58	DOD

Abbreviations: *BMI*, body mass index; *LVSI*, lymphovascular space invasion; *LN*, lymph nodes; *TTR*, time to recurrence; OS, overall survival; *NA*, not available; *NED*, no evidence of disease; *AWD*, alive with disease; *DOD*, dead of disease; *DOC*, dead of other cause; *SLN*, sentinel lymph node

[a] 2009 staging

Davidson et al., Virchows Arch 2025;486:697-705

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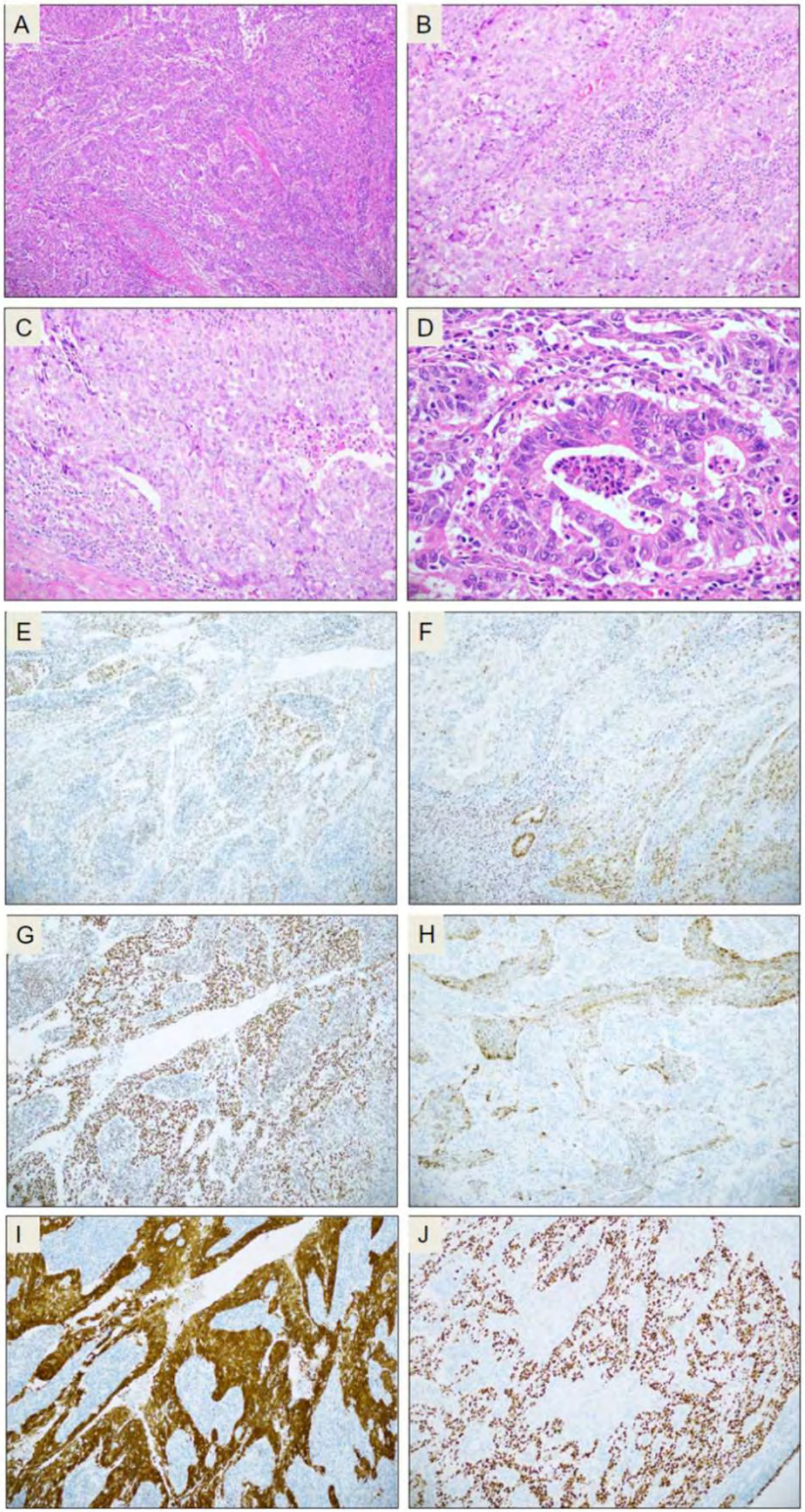
Fig. 1 Case # 8. **A–D** Morphology, H&E staining: invasive adenocarcinoma with high-grade nuclear features growing predominantly with a solid pattern, with a minor component showing glandular/acinar pattern. The tumor is infiltrated by a large number of mature lymphocytes. **E–J** Immunostaining. The tumor is only focally positive for ER (**E**) and PR (**F**). ARID1A is retained (**G**), PTEN is lost (**H**). p16 stains with block-positivity (**I**), p53 is aberrant/mutation-type (diffusely positive; **J**)



Davidson et al., Virchows Arch 2025;486:697-705

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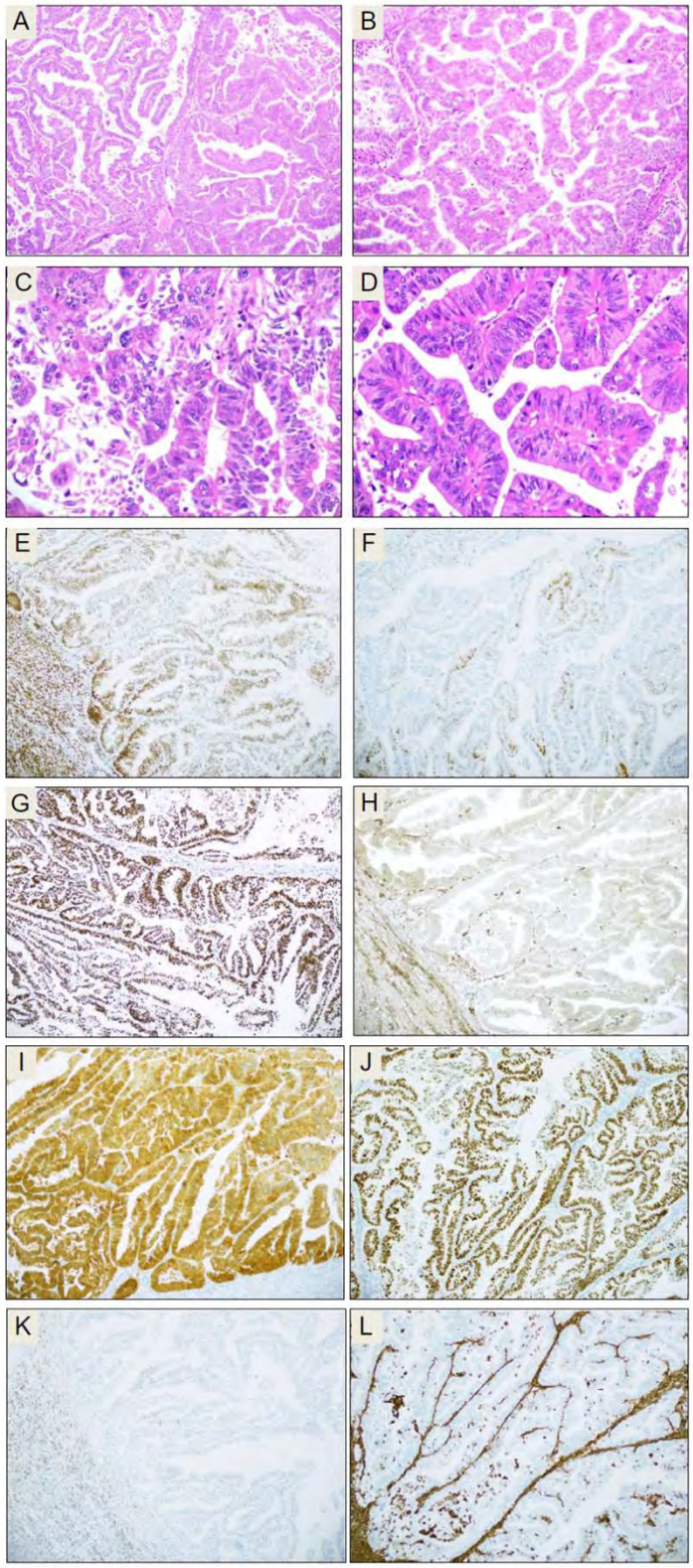
Fig. 2 Case # 16. **A–D** Morphology, H&E staining: invasive adenocarcinoma growing with confluent glandular/acinar and trabecular pattern. The tumor consists of high columnar cells with high-grade nuclear features and strongly eosinophilic cytoplasm, with brisk mitotic activity. The tumor is infiltrated by some mature lymphocytes, though less densely than the case in Fig. 1. **E–L** Immunostaining. The tumor is partly positive for ER (**E**), but only focally positive for PR (**F**). ARID1A is retained (**G**), PTEN is lost (**H**). p16 stains with block-positivity (**I**), p53 is aberrant/mutation-type (diffusely positive; **J**). The tumor is negative for WT1 (**K**) and vimentin (**L**)



Davidson et al., Virchows Arch 2025;486:697-705

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Table 3 p53, MMR, and MS status

Case	p53	MSH6	PMS2	MS status
1	Aberrant	Lost	Retained	MSI high
2	Aberrant	Retained	Retained	MSI high
3	Wild type	Lost	Retained	MSI high
4	Aberrant	Retained	Retained	MSS
5	Aberrant	Retained	Retained	MSS
6	Wild type	Retained	Retained	MSS
7	Wild type	Retained	Lost	MSI high
8	Aberrant	Retained	Retained	MSS
9	Aberrant	Retained	Retained	MSS
10	Aberrant	Retained	Retained	MSS
11	Aberrant	Retained	Retained	MSS
12	Aberrant	Retained	Retained	MSS
13	Aberrant	Retained	Retained	MSS
14	Aberrant	Retained	Retained	MSS
15	Aberrant	Retained	Retained	MSS
16	Aberrant	Retained	Retained	MSI high
17	Aberrant	Retained	Retained	MSS
18	Wild type	Retained	Lost	MSI high

Abbreviations: *MMR*, mismatch repair; *MSI*, microsatellite unstable; *MSS*, microsatellite stable

[a]All aberrant p53 with the diffusely positive pattern

In exome sequencing, none of the tumors had pathogenic *POLE* mutation. Fourteen tumors (78%) harbored *TP53* mutations, and 2 (11%) had mutations in MMR genes. Eleven carcinomas (61%) were classified as copy number high and 7 (39%) as MSI-hypermutated.

Other mutations that were found in > 1 tumor affected *MUC16* (7 tumors), *PIK3CA* (6 tumors), *PPP2R1A* (6 tumors), *ARID1A* (5 tumors), *PTEN* (5 tumors), *FAT1* (4 tumors), *FAT4* (3 tumors), *BRCA2* (2 tumors), *ERBB2* (2 tumors), *FBXW7* (2 tumors), *MET* (2 tumors), *MTOR* (2 tumors), *JAK1* (2 tumors), and *CSMD3* (2 tumors). Data are summarized in Supplementary Table 1.

Table 2. Comparisons of four phase III randomized trials evaluating the efficacy of front-line immune checkpoint inhibitors in advanced or recurrent endometrial cancer

Trials	RUBY part 1	NRG-GY018	AtTEnd	DUO-E
Patients	494	816	551	718
Drug	Dostarlimab	Pembrolizumab	Atezolizumab	Durvalumab + olaparib
Treatment duration	About 3 yr	About 2 yr	Until progression	Until progression
Permitted treatment interval from previous chemotherapy	≥6 mo	≥12 mo	≥6 mo	≥12 mo
Carcinosarcoma	Included	Excluded	Included	Included
Primary outcomes	PFS, OS	PFS in dMMR and pMMR	PFS, OS	PFS
PFS in ITT population	mPFS: 11.8 vs. 7.9 mo HR=0.64; 95% CI=0.51–0.80; p<0.001	Not available	mPFS: 10.1 vs. 8.9 mo HR=0.74; 95% CI=0.61–0.91; p=0.0022	mPFS, 15.1 vs. 10.2 vs. 9.6 mo Durva + ola arm vs. control, HR=0.55; 95% CI=0.43–0.69; p<0.0001 Durva arm vs. control, HR=0.71; 95% CI=0.57–0.89; p=0.003
PFS in dMMR	mPFS: NR vs. 7.7 mo HR=0.28; 95% CI=0.16–0.50; p<0.001	mPFS: NR vs. 7.6 mo HR=0.30; 0.19–0.48; p<0.001	mPFS: NE vs. 6.9 mo HR=0.36; 95% CI=0.23–0.57; p=0.0005	mPFS: 31.8 vs. NR vs. 7.0 mo Durva + ola arm vs. control, HR=0.41; 95% CI=0.21–0.75 Durva arm vs. control, HR=0.42; 95% CI=0.22–0.80
PFS in pMMR	mPFS, 9.9 vs. 7.9 mo HR=0.76; 95% CI=0.59–0.98	mPFS, 13.1 vs. 8.7 mo HR=0.54; 95% CI=0.41–0.71; p<0.001	mPFS, 9.5 vs. 9.2 mo HR=0.92; 95% CI=0.73–1.16; p=0.38	mPFS, 15.0 vs. 9.9 vs. 9.7 mo Durva + ola arm vs. control, HR=0.57; 95% CI=0.44–0.73 Durva arm vs. control, HR=0.77; 95% CI=0.60–0.97
OS in ITT population	mOS, 44.6 vs. 28.2 mo HR=0.69; 95% CI=0.54–0.89; p=0.002	Not available	mOS, 38.7 vs. 30.2 mo HR=0.82; 95% CI=0.63–1.07; p=0.048	mOS, NR vs. NR vs. 25.9 mo Durva + ola arm vs. control, HR=0.59; 95% CI=0.42–0.83; p<0.003 Durva arm vs. control, HR=0.77; 95% CI=0.56–1.07; p=0.120
OS in dMMR	mOS, NR vs. 31.4 mo HR=0.32; 95% CI=0.17–0.63; p=0.0002	mOS, NR vs. NR HR=0.55; 95% CI=0.25–1.19; p=0.0617	mOS, NE vs. 25.7 mo HR=0.41; 95% CI=0.22–0.76; p=0.0026	Not available
OS in pMMR	mOS, 34.0 vs. 27.0 mo HR=0.79; 95% CI=0.60–1.04; p=0.0493	mOS, 28.0 vs. 27.4 mo HR=0.79; 95% CI=0.53–1.17; p=0.1157	mOS, 31.5 vs. 28.6 mo HR=1.00; 95% CI=0.74–1.35; p=0.54	Not available
Any grade ≥3 AE	72.2% vs. 60.2%	75.3% vs. 45.8%	66.9% vs. 63.8%	67.2% vs. 54.9% vs. 56.4%

AE, adverse event; CI, confidence interval; dMMR, deficient mismatch repair; HR, hazard ratio; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; pMMR, proficient mismatch repair.

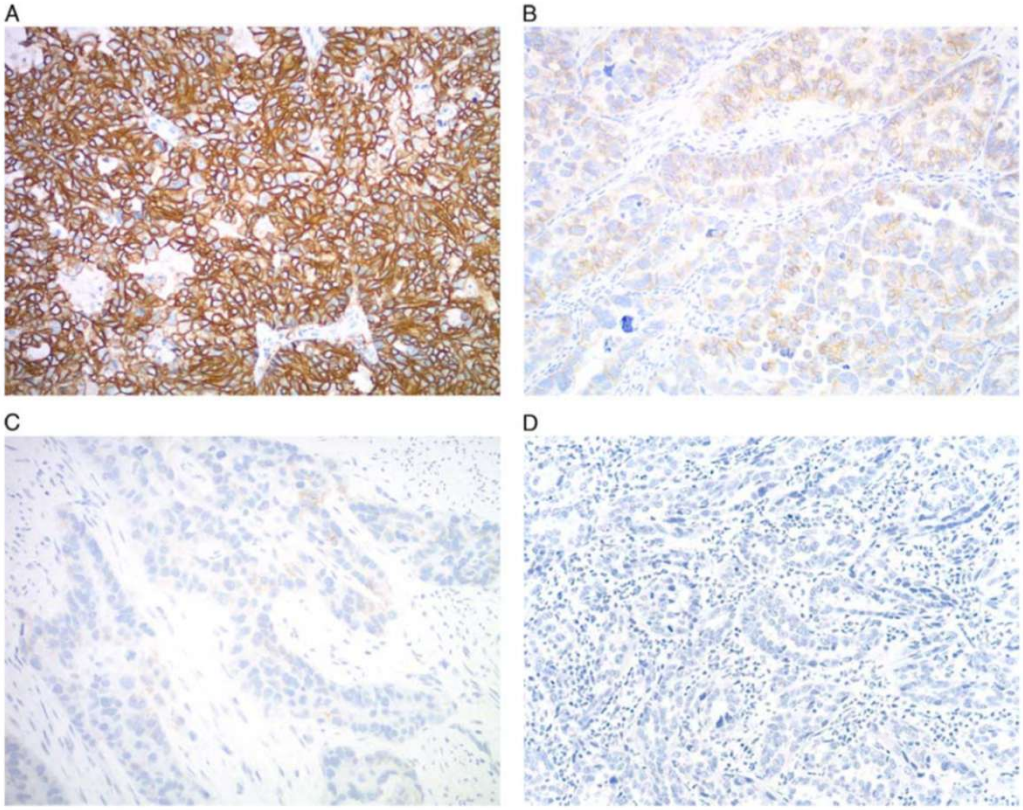
Lee et al., J Gynecol Oncol 2025;36:e72

HER2 in serous carcinoma

TABLE 1. *Criteria for HER2 positivity by immunohistochemistry and FISH in different tumor types*

	Breast (ASCO/CAP 2007) (27)	Breast (ASCO/CAP 2013) (28)	Breast (ASCO/CAP 2018) (29)	Gastric (ASCO/CAP 2016) (30)	Colorectal (HERACLES trial) (31)	Endometrial serous (Fader et al clinical trial) (24,25)
HER2 IHC 3+	> 30% strong, uniform, complete	> 10% circumferential, strong, complete	> 10% circumferential, strong, complete	≥ 10%, strong complete, or basolateral/lateral	≥ 50% strong complete, or basolateral/ lateral	> 30% strong complete, or basolateral/ lateral
HER2 FISH amplification	*HER2*/CEP17 ratio > 2.2 patients with *HER2*/CEP17 ratio between 2.0 and 2.2 also eligible for treatment)	*HER2*/CEP17 ratio ≥ 2.0 OR ratio < 2.0 and HER2 signal ≥ 6.0/nucleus	*HER2*/CEP17 ratio ≥ 2.0 and HER2 signal ≥ 4.0/nucleus OR ratio < 2.0 and HER2 signal ≥ 6.0/nucleus (if IHC score 2+ or 3+)	*HER2*/CEP17 ratio ≥ 2.0 OR ratio < 2.0 and HER2 signal > 6.0 /nucleus	*HER2*/CEP17 ratio ≥ 2.0 in ≥ 50% of cells	*HER2*/CEP17 ratio ≥ 2.0

FISH indicates fluorescent in situ hybridization; IHC, immunohistochemistry.



Buza N, Int J Gynecol Pathol 2020;40:17-23

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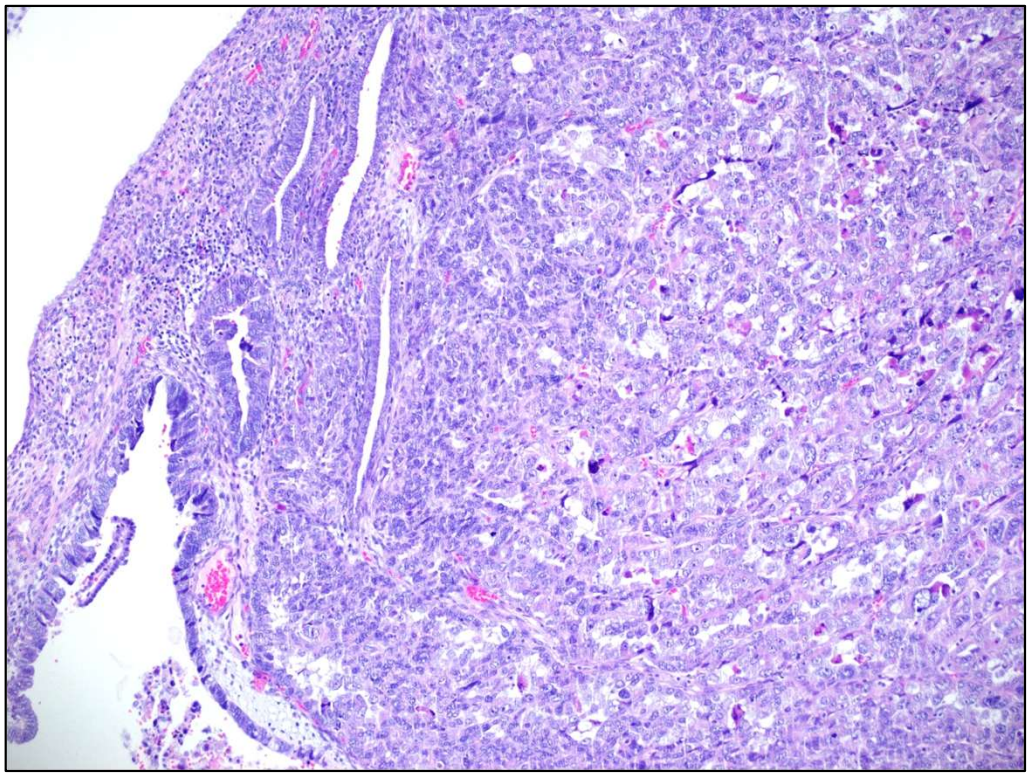

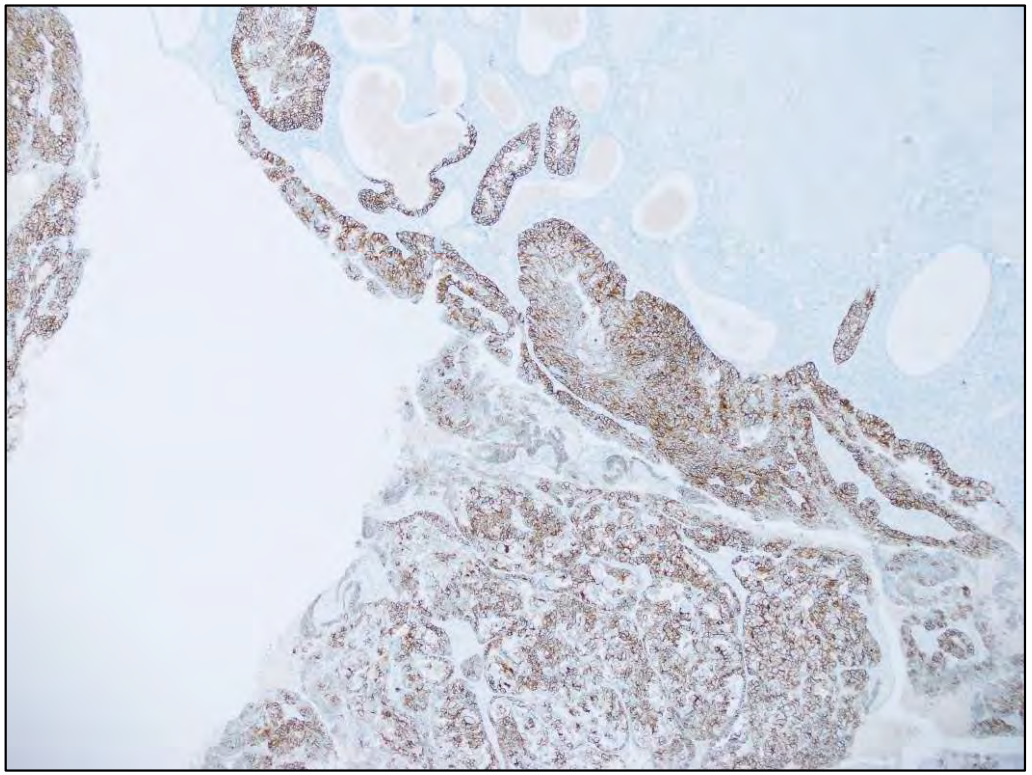

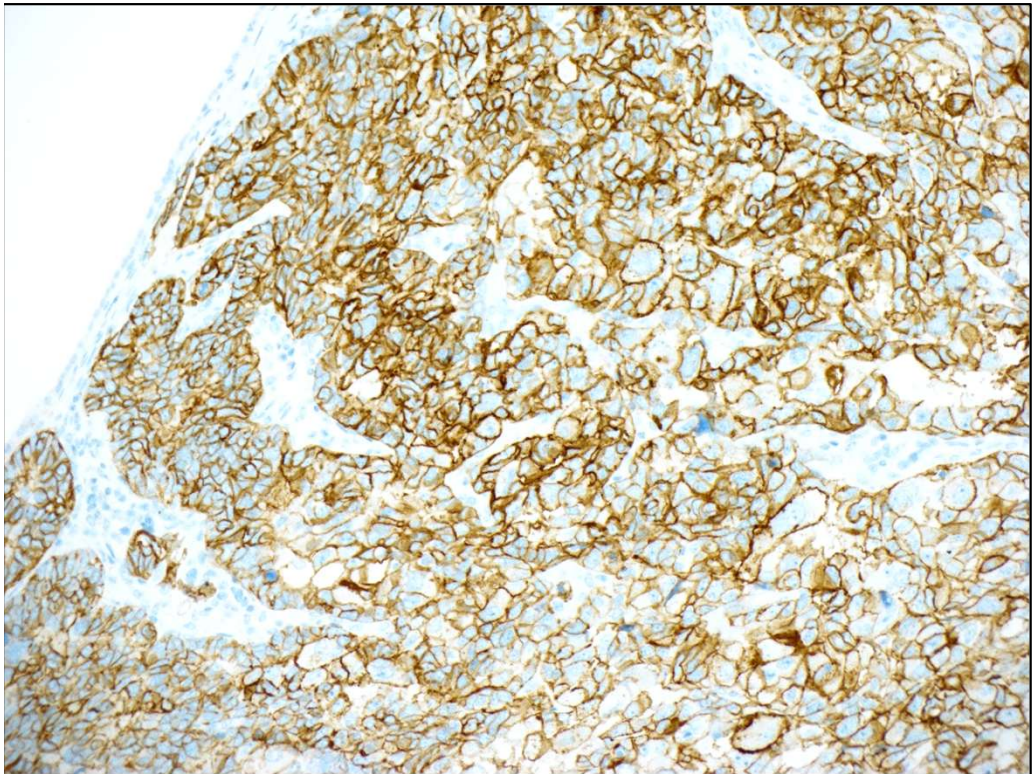

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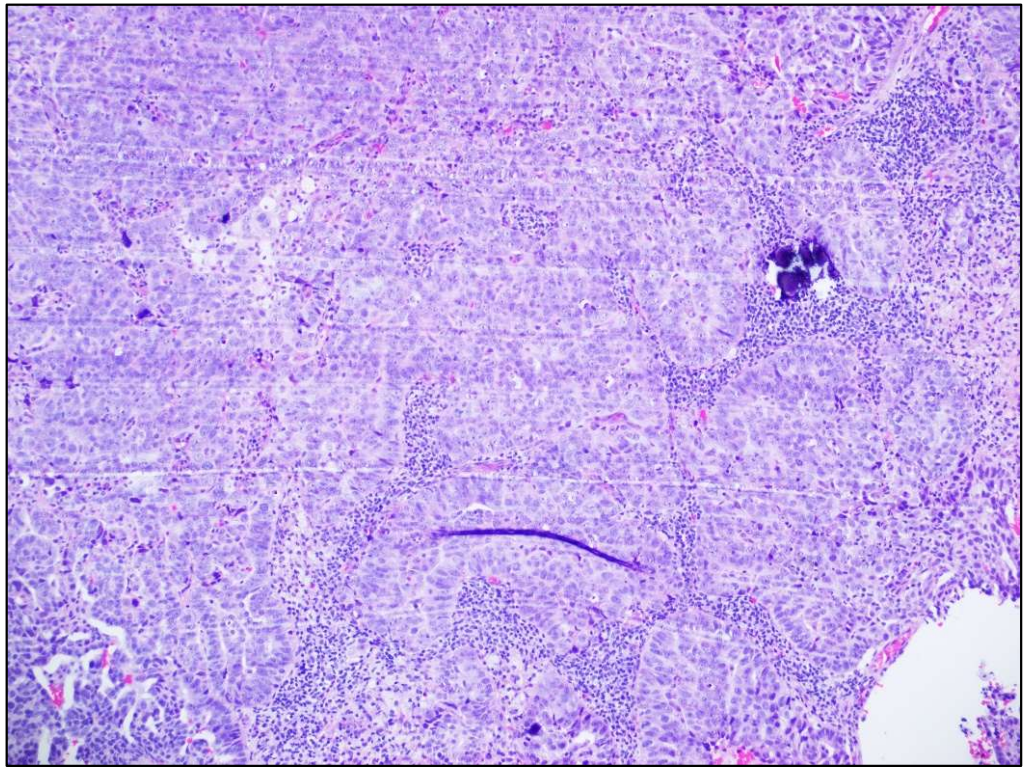
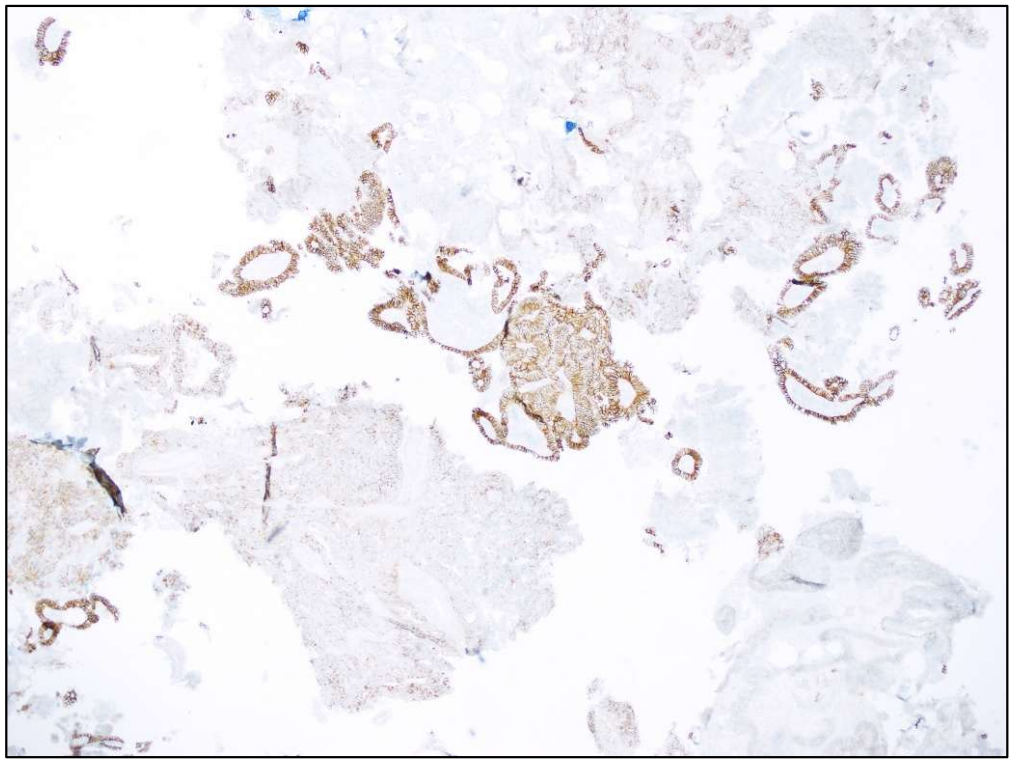
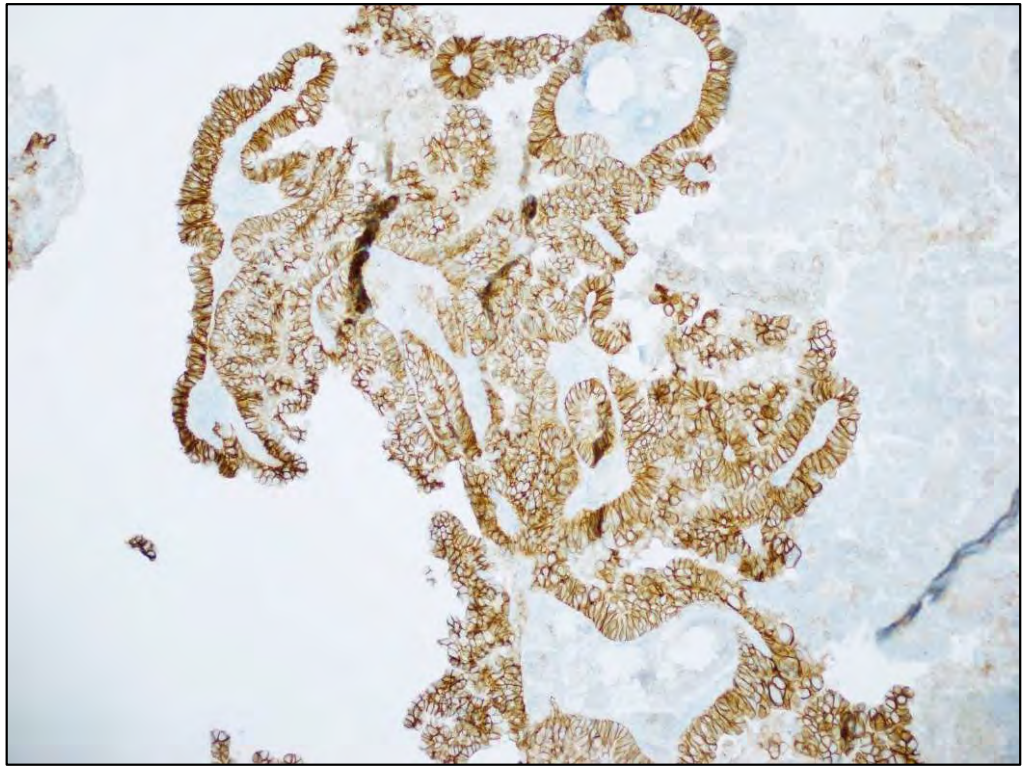
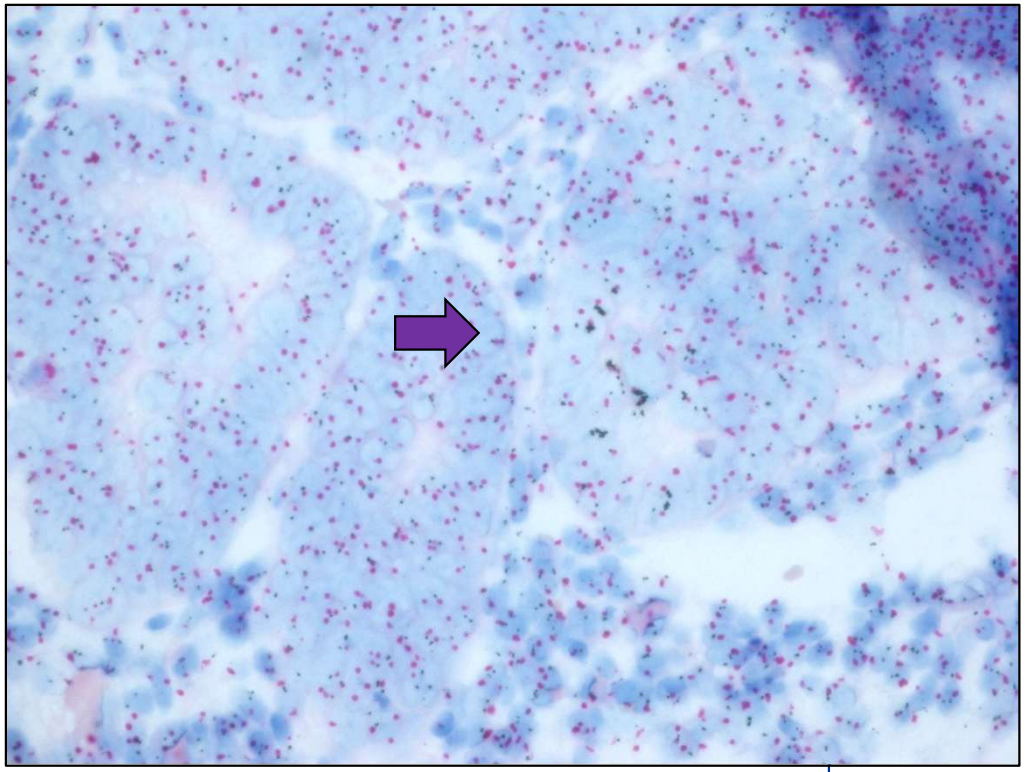




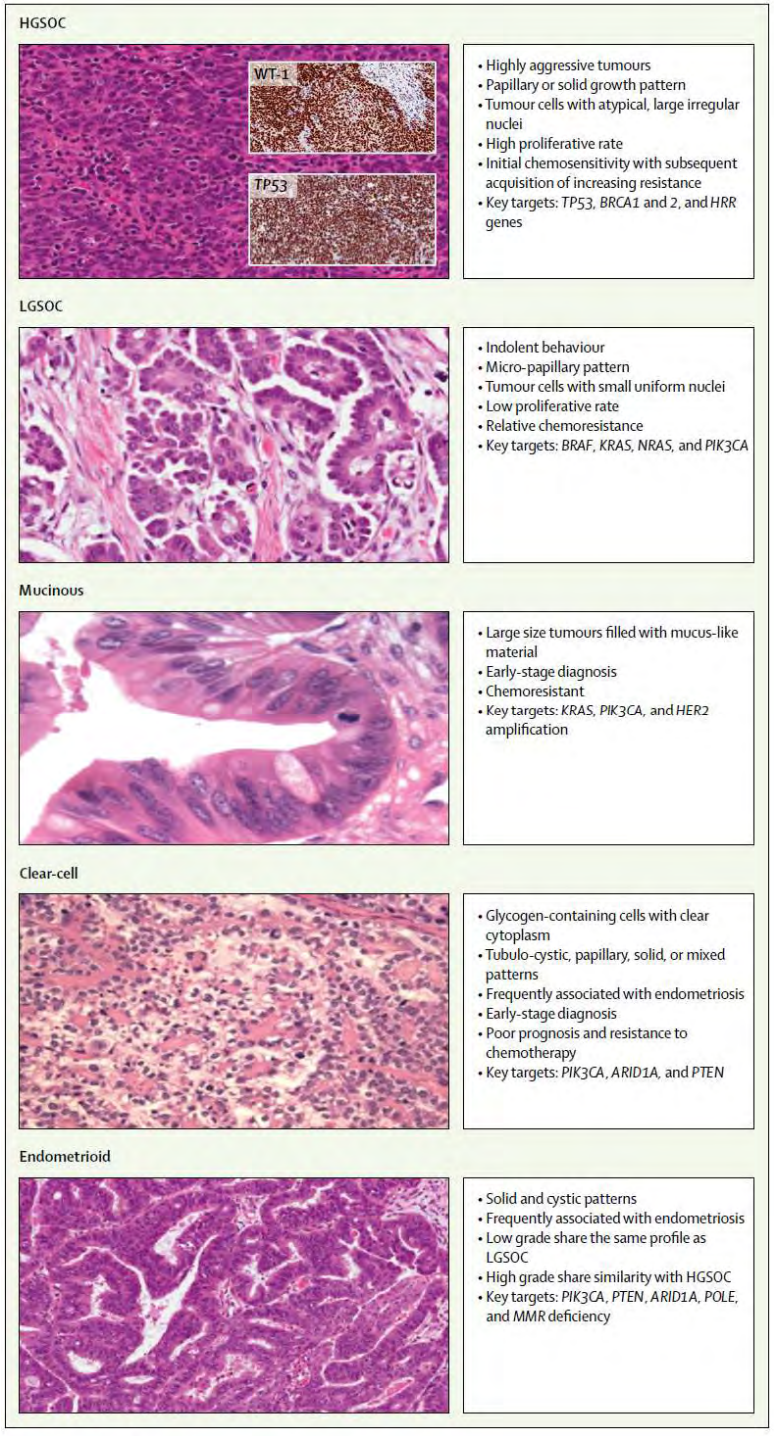


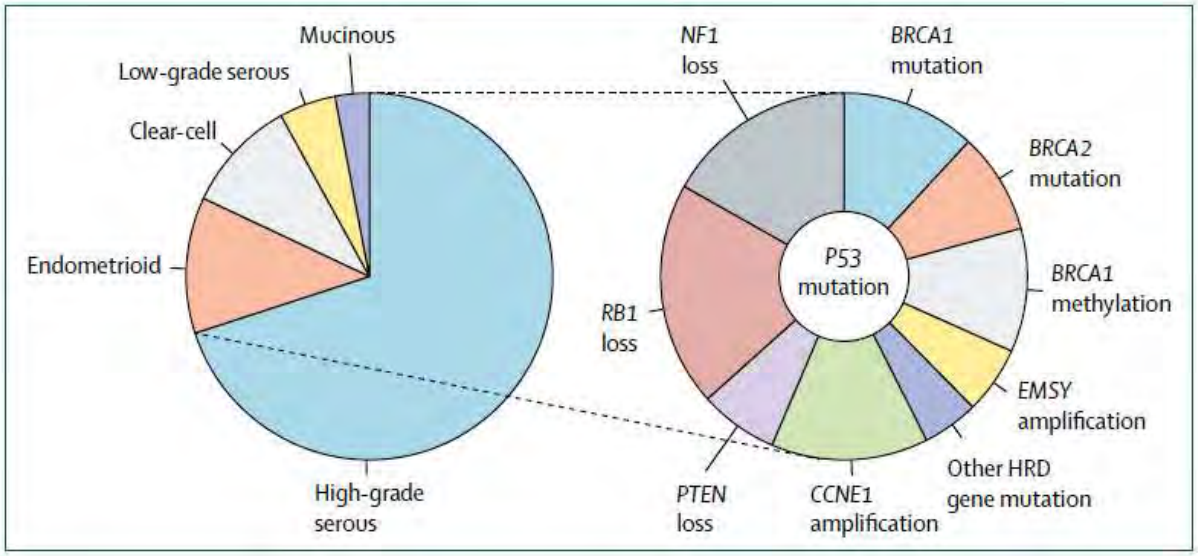


Topics

- Vulvar carcinoma and precursor lesions
- Cervical carcinoma
- Female genital sarcomas
- Endometrial carcinoma
- Tubo-ovarian tumors

Tubo-ovarian carcinoma





Lheureux et al., Lancet 2019;393:1240-53

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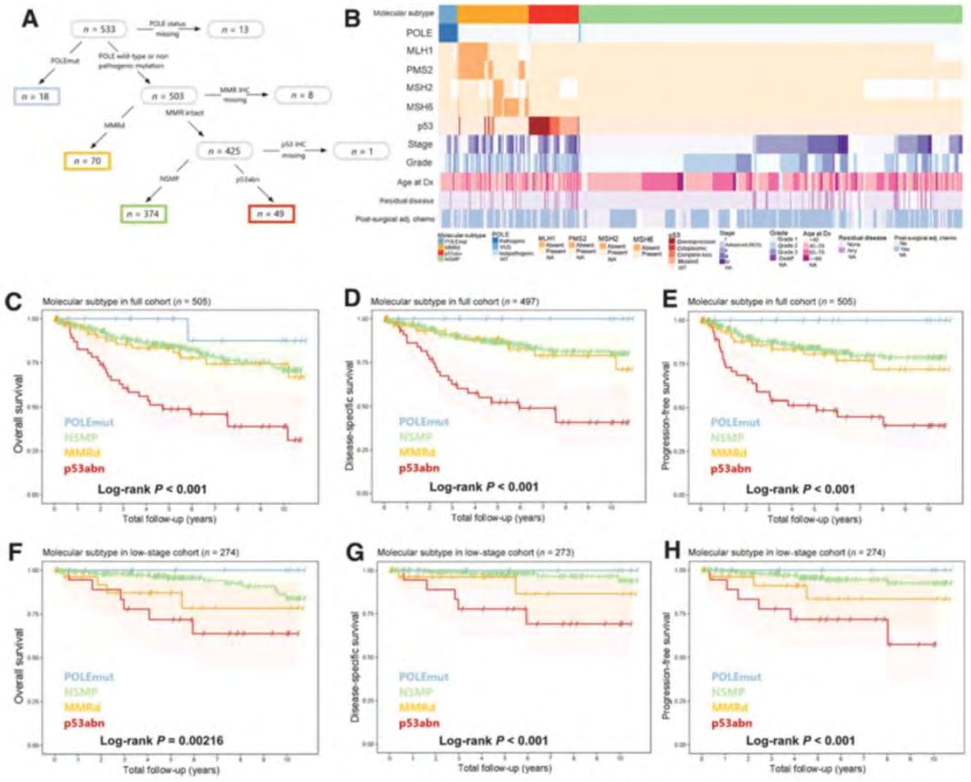
TCGA-based classification of EC



1. A total of 511 tumors, of which 3.5% were POLEmut, 13.7% MMRd, 9.6% p53abn, and 73.2% NSMP

2. Significant association with survival – Median OS was 18.1 years in NSMP, 12.3 years in MMRd, 4.7 years in p53abn, and not reached for POLEmut cases (p<0.001). Similar association with DSS and PFS.

3. Molecular subtype independently prognostic of OS, DSS and PFS in multivariate analysis including age, stage, grade, residual disease and postsurgical chemotherapy.

Krämer P, et al. Clin Cancer Res 2020;26:5400-10

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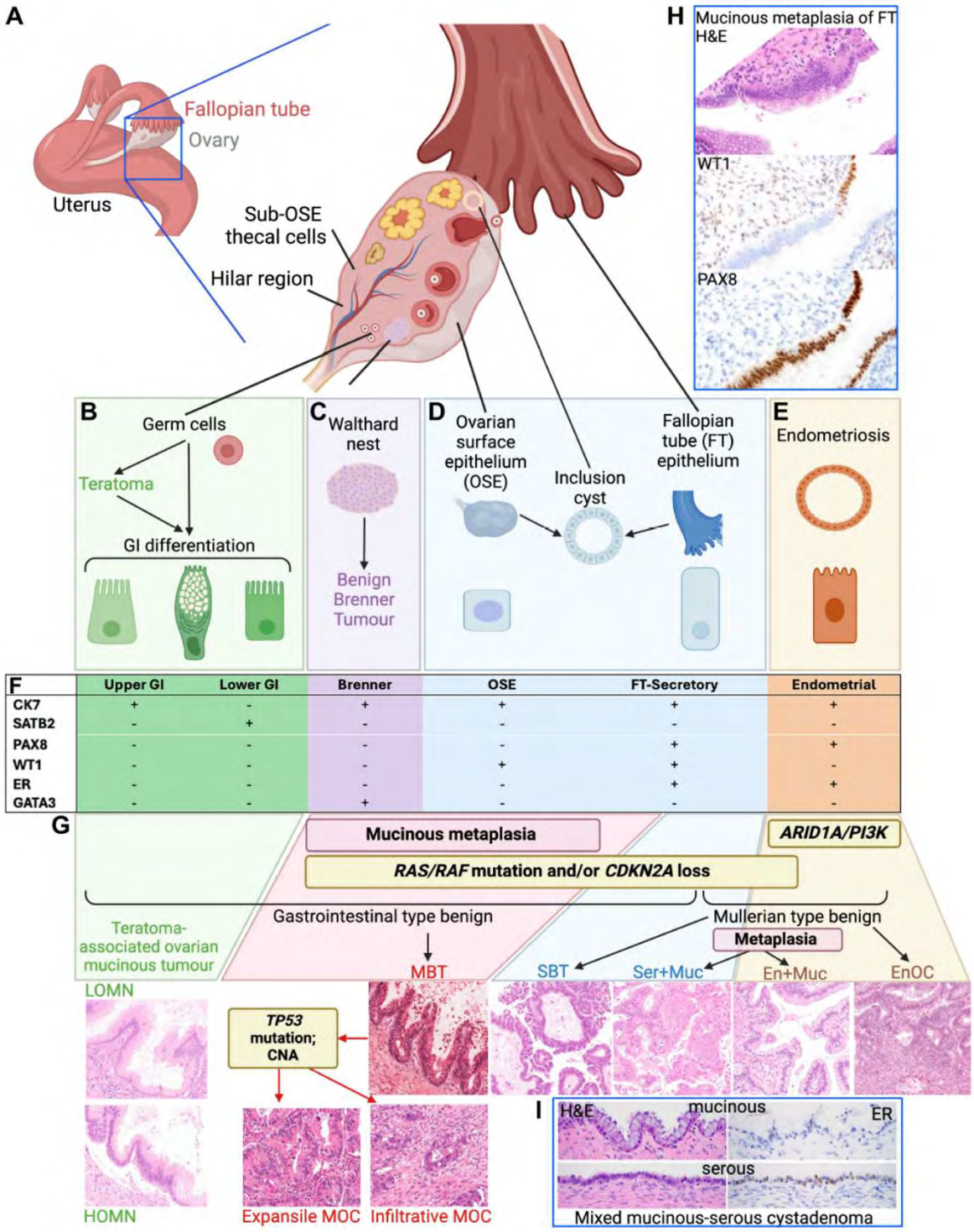

Meagher et al., J Pathol 2025 Mar 3, Epub

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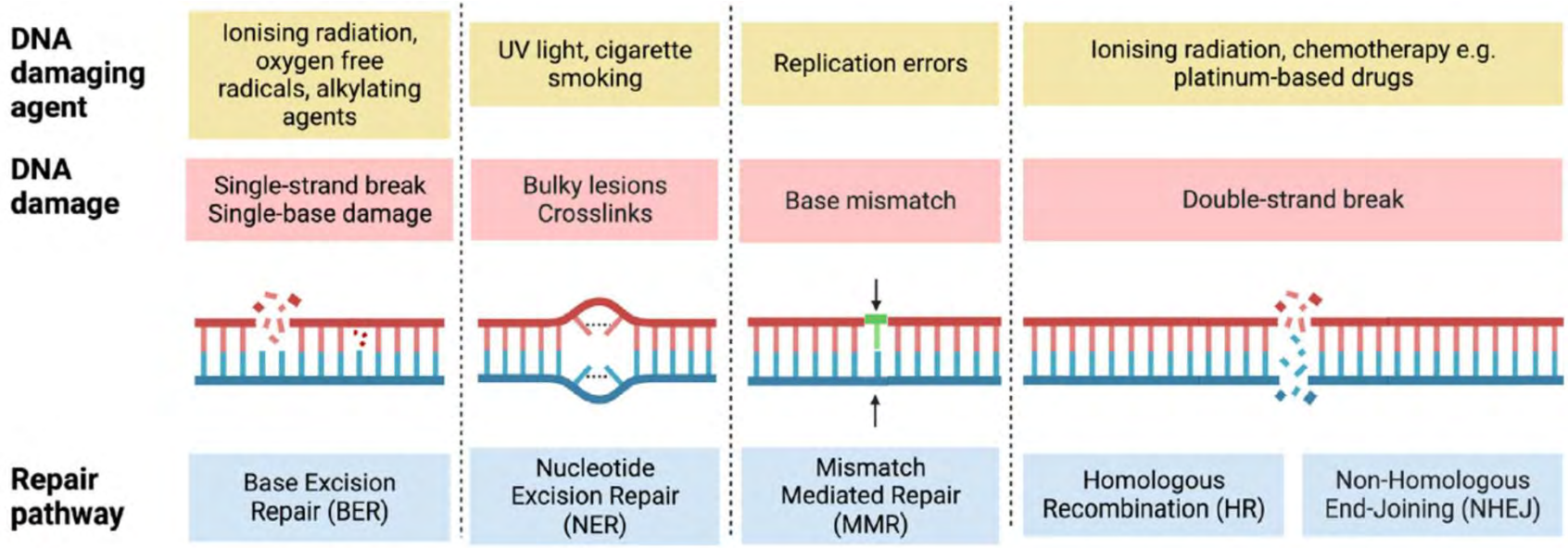

Figure 1.
Mechanisms of DNA damage, their causes, and their repair pathways.

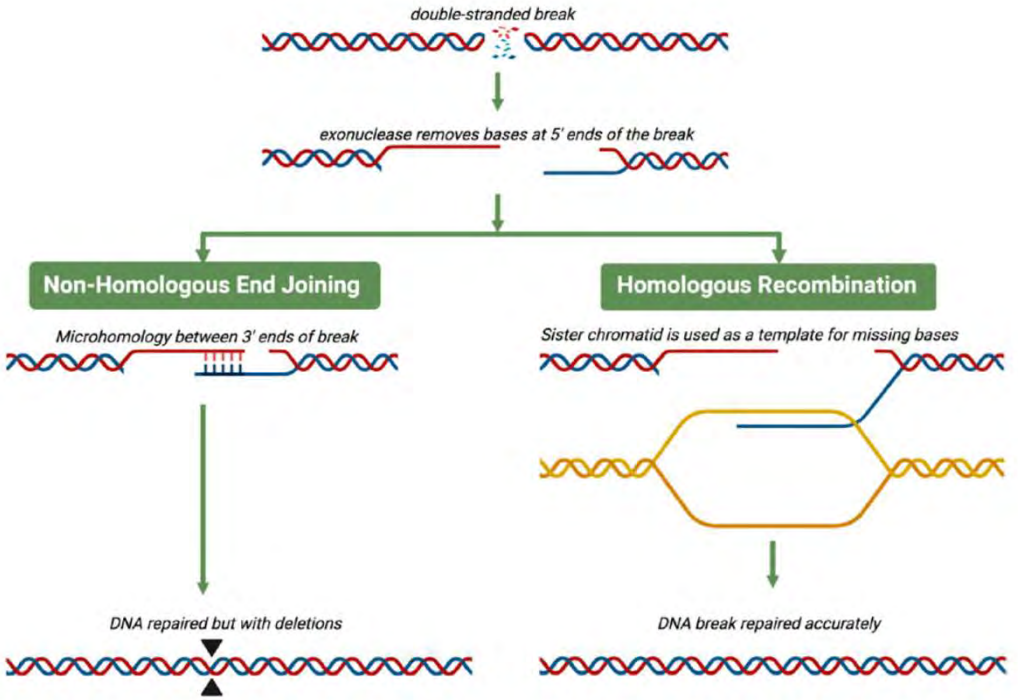

Figure 3.
DNA double-stranded break repair mechanisms. Nonhomologous end joining leaves evidence of its activity on the genome in the form of deletions flanked with a small number of homologous bases (microhomology). By contrast, no traces are left by the homologous recombination repair pathway.

Doig KD, et al.,
Mod Pathol 2023;163:427-32

Table 2
HRD assays described in the text are summarized with their biomarkers.

	Company or patent holder	Myriad Genetics	Foundation Medicine	SOPHiA Genetics	AmoyDx	Nik-Zainal and colleagues	Utrecht University Medical Centre	Harvard Medical School
	Name	myCHOICE CDx Plus	Foundation Focus CDx BRCA	Homologous Recombination Solution	HRD Focus Panel	HRDetect	CHORD	SigMA
Assays	Clinical Indication	Breast, Ovarian	Ovarian	Ovarian	Breast, Ovarian	Breast, Ovarian, Pancreatic	Pan-cancer	Pan-cancer
	Specimen	FFPE	FFPE	FFPE	FFPE	Fresh/frozen	FFPE	FFPE
	Regulatory Status	CDx	CDx	RUO	IVD	LDT	LDT	LDT
Biomarkers	Genomic scarring	LOH[a]	LOH[b]	—	LOH[c]	Flanking micro-homology	Flanking micro-homology	—
	Copy number analysis	—	—	lpWGS	—	WGS	WGS	—
	HRR gene mutations	*BRCA1*/2 + 13 genes	*BRCA1*/2	*BRCA1*/2 + 26 genes	*BRCA1*/2	Whole genome	Whole genome	≥300 gene panel
	Base substitution signatures	—	—	—	—	Sig 3, Sig 8	—	Sig 3
	Rearrangement signatures	—	—	—	—	Sig 3, Sig 5	Sig 3, Sig 5	—

FFPE, formalin-fixed paraffin-embedded; HRD, homologous recombination deficiency; IVD, in-vitro diagnostic; LOH ,loss of heterozygosity; LDT, laboratory developed test; RUO, research use only; WGS, whole genome sequencing.
Available assays may use a variable, weighted, and often proprietary combination of multiple genomic parameters to improve the accuracy of HRD prediction.
[a] 54,000 SNP backbone and a combined weighted score of LOH, TAI, and LST (see text).
[b] SNP resolution not published; percentage of LOH across genome, ignoring arm scale LOH.
[c] 24,000 SNP backbone; machine learning model incorporating LOH segment length, telomere/centromere proximity, and allelic association.

Doig KD, et al., Mod Pathol 2023;163:427-32

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TABLE 1. Molecular Events in Ovarian Sex Cord-Stromal Tumors

Tumor	Recurrent molecular events (useful in diagnosis)	Other molecular events (may be useful in prognostication)	Tumor syndrome
AGCT	*FOXL2* (somatic missense C134W mutation)	*TP53, TERT, CDKN2A, KMT2D, MED12*	None
JGCT	None	*TERT, AKTC, GNAS, KMT2C*	Olliers disease and Maffucci syndrome
Steroid cell tumor	None	Genomic instability in malignant tumors	None
SCTAT	*STK11* mutations in Peutz-Jeghers-associated cases		Peutz-Jeghers syndrome
SLCT	*DICER1* variants (except well-differentiated SLCT). *FOXL2* variants in some tumors in older patients		DICER1 syndrome
Sclerosing stromal tumor	*FHL2 : GLI2* fusion		None
MST	*CTNNB1* and *APC* mutations		Familial adenomatous polyposis

AGCT indicates adult granulosa cell tumor; JGCT, juvenile granulosa cell tumor; MST, microcystic stromal tumor; SCTAT, sex cord tumor with annular tumors; SLCT, Sertoli Leydig cell tumor.

Rabban and McCluggage, Adv Anat Pathol 2025;32:70-84

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Table 2. Indications for germline *DICER1* testing.

Category	Indication
Genetic	• Known familial *DICER1* variant • *DICER1* variant(s) on tumor sequencing
Thoracic	• PPB (all types) • Thoracic ERMS • Pulmonary blastoma • Well-differentiated fetal lung adenocarcinoma • Lung cyst(s) in childhood, especially if multiseptated, multiple and/or bilateral, and/or unexplained by other risk factors such as infection, prematurity, or mechanical ventilation in infancy • Lung cyst(s) in adulthood[a]
Female reproductive tract	• Ovarian SLCT (including gynandroblastoma) • Ovarian JGCT (especially if anaplasia and/or high mitotic index) • Ovarian sarcoma (all types) • Uterine, cervical, and vaginal ERMS • Gynecologic neuroendocrine tumors
Renal	• Cystic nephroma • Anaplastic sarcoma of the kidney • Wilms tumor[a,b] • Renal cysts[a,b]
CNS	• Pineoblastoma • Pituitary blastoma • Primary intracranial sarcoma, *DICER1*-mutant • ETMR-like tumor without C19MC alteration
Thyroid	• Multinodular goiter[b] • DTC[b] • PDTC in childhood/early adulthood • Thyroblastoma
Other neoplasms	• Ciliary body medulloepithelioma • Nasal chondromesenchymal hamartoma • Peritoneal PPB–like sarcoma
Other	• Macrocephaly[a,b] • Juvenile hamartomatous intestinal polyps[a,b] • Mesenchymal hamartoma of the liver[a,b] • Childhood nonparasitic liver cysts[a,b]

Abbreviations: ERMS, embryonal rhabdomyosarcoma; ETMR, embryonal tumor with multilayered rosettes; JGCT, juvenile granulosa cell tumor.
[a]Especially if other individual or family history to suggest *DICER1*-related tumor predisposition.
[b]Multinodular goiter, differentiated thyroid cancer (papillary or follicular carcinomas), sarcomas, Wilms tumor, neuroendocrine tumors, renal cysts, and macrocephaly may also be associated with other genetic predisposition syndromes. Consider testing for additional hereditary cancer predispositions and/or a next-generation sequencing panel that includes deletion/duplication of *DICER1* and/or other genes indicated by clinical and family history.

Schultz et al, Clin Cancer Res 2024;30:5681-92

Table 3. Suggested signs and symptoms and imaging surveillance by system for individuals with *DICER1* pathogenic variants. Adapted from 2018 surveillance guidelines (15).

System	Condition	Signs/symptoms	Surveillance recommendation	Additional considerations
Pulmonary	• PPB • Lung cysts • Pulmonary blastoma	Tachypnea, cough, fever, chest pain, and pneumothorax	Chest X-ray at birth and then **every 6 months** until 8 years of age and every year until 12 years of age. Chest CT at 3 months of age and 2.5 years of age	Consider third-trimester ultrasound
Renal	• Cystic nephroma • Anaplastic sarcoma of the kidney • Wilms tumor	Abdominal and/or flank pain and hematuria	Abdominal ultrasound every 6 months until 8 years of age and every year until 12 years of age	Some anaplastic sarcomas of the kidney have been diagnosed after 12 years of age. Consider extending these evaluations pending evolving data. Consider baseline ultrasound if diagnosed at >12 years of age
Female reproductive tract	• SLCT • Cervical ERMS • *DICER1*-associated ovarian sarcoma	Virilization, abdominal and/or pelvic pain, abdominal distension, and amenorrhea	**Pelvic ultrasound[a] every 6 months beginning at detection of a *DICER1* variant**	Most *DICER1*-related ovarian tumors are diagnosed prior to 40 years of age. Shared decision-making about risks/benefits of cessation of surveillance after 40 years of age is recommended
CNS	• Pineoblastoma • Pituitary blastoma • ETMR-like tumors • Primary intracranial sarcoma, *DICER1*-mutant	Headache, emesis, diplopia, decreased ability for upward gaze, and altered gait (pineoblastoma); precocious puberty and Cushing syndrome (pituitary blastoma)	Monitor for signs and symptoms	Shared decision-making about the role of surveillance MRI in late adolescence and adulthood. For all: urgent brain MRI recommended for any signs or symptoms of concern
Thyroid	• Multinodular goiter • DTC • Poorly differentiated carcinoma in adolescence/early adulthood	Visible or palpable thyroid nodule(s), persistent cervical lymphadenopathy, hoarseness, dysphagia, neck pain, and cough	**Thyroid ultrasound every 3 years starting at 8 years of age[b]**	If nodules are identified, advise further evaluation based on age-appropriate ATA guidelines
Ophthalmologic	• Ciliary body medulloepithelioma	Decreased visual acuity and leukocoria	Consider annual eye exam from 3 to 10 years of age	None
ENT	• Nasal chondromesenchymal hamartoma	Nasal obstruction	Monitor for signs and symptoms	None
Gastrointestinal	• Small intestine polyps	Signs of intestinal obstruction	Monitor for signs and symptoms	None

Bold: updates to surveillance guidelines compared with 2018 guidelines.
Abbreviations: ENT, ear, nose, and throat; ERMS, embryonal rhabdomyosarcoma; ETMR, embryonal tumor with multilayered rosettes.
[a]Pelvic ultrasounds in children and adolescents are generally performed via a transabdominal approach and via a transvaginal approach for women.
[b]Also consider annual surveillance for 5 years following end of therapy for individuals who have received chemotherapy.

Schultz et al, Clin Cancer Res 2024;30:5681-92

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Future directions

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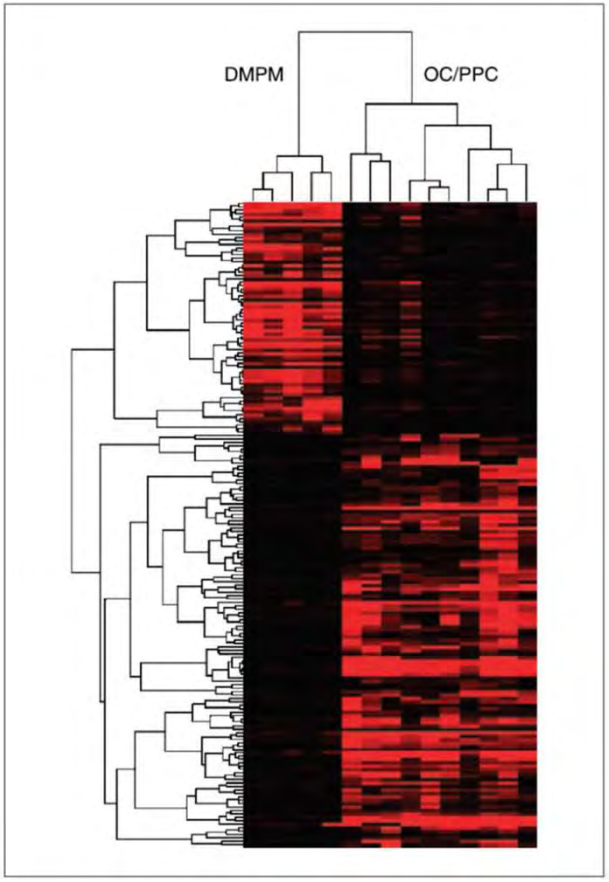
Biomarker evolution

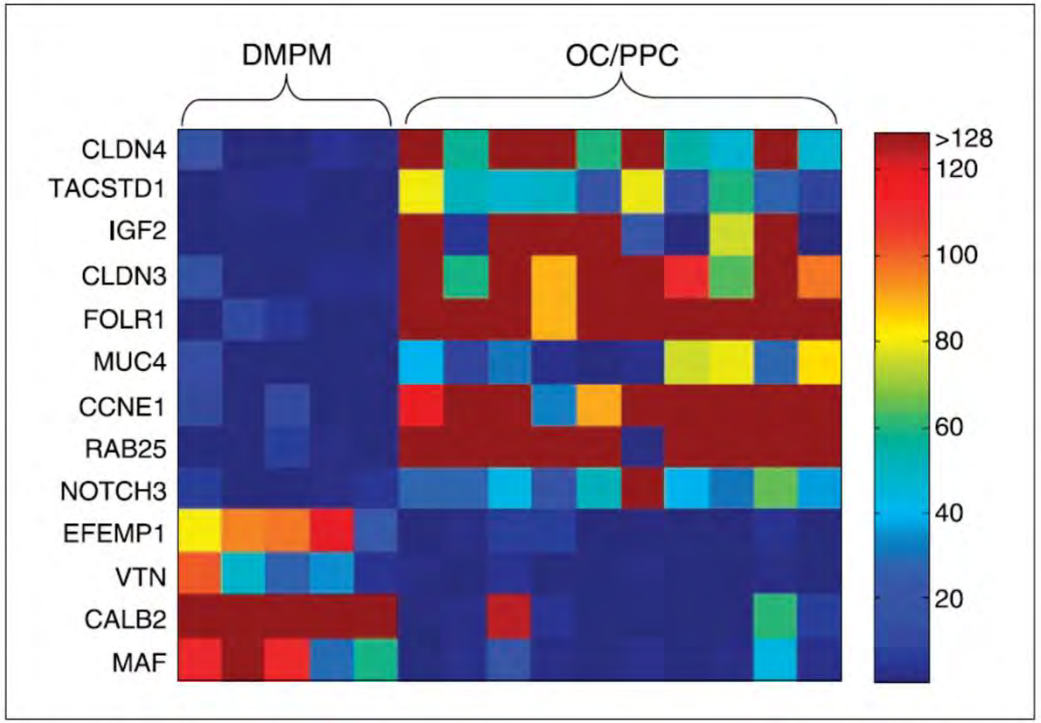
Human Cancer Biology

Gene Expression Signatures Differentiate Ovarian/Peritoneal Serous Carcinoma from Diffuse Malignant Peritoneal Mesothelioma

Ben Davidson,[1] Zhen Zhang,[2] Lilach Kleinberg,[1] Mei Li,[3] Vivi Ann Flørenes,[1] Tian-Li Wang,[3] and Ie-Ming Shih[2,3]

Clin Cancer Res 2006;12(20) October 15, 2006





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Human Pathology (2009) 40, 1453–1460

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Original contribution

Expression of the folate receptor genes *FOLR1* and *FOLR3* differentiates ovarian carcinoma from breast carcinoma and malignant mesothelioma in serous effusions☆

Yuan Yuan MD[a,b], Dag André Nymoen MSc[b], Hiep Phuc Dong MSc[b], Ola Bjørang MSc[b], Ie-Ming Shih MD, PhD[c], Philip S. Low PhD[d], Claes G. Trope' MD, PhD[e,f], Ben Davidson MD, PhD[b,f,*]

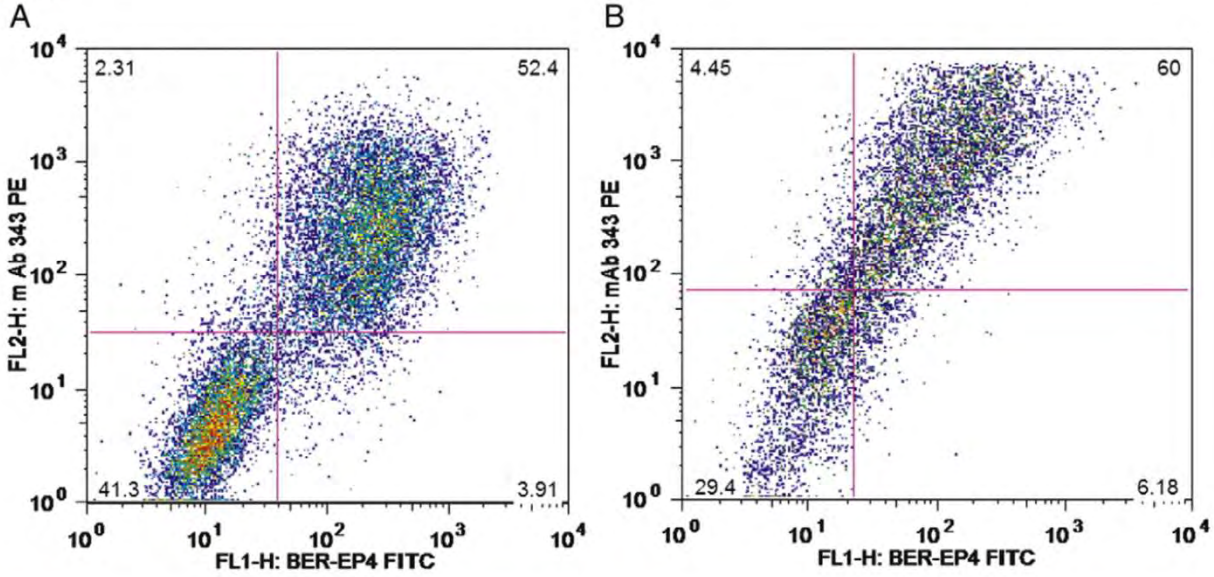

Table 2 Cancer cell FR expression in effusions[a]

Molecule/Tumor	FOLR1 (mRNA)	FOLR3 (mRNA)	FR-α (protein)
	No. of positive cases (%); [expression range; median][b]		
OC	71/71 (100) [5.77-17821.71; 1158.4]	71/71 (100) [0.04-141.61; 5.89]	40/40 (100) [1-88; 52]
Breast carcinoma	9/10 (90) [0.06-744.1; 59.12]	10/10 (100) [0.10-499.7; 0.74]	7/10 (70) [1-65; 3]
Mesothelioma	8/10 (80) [0.01-762.77; 0.03]	10/10 (100) [0.04-5.52; 0.52]	3/9 (33) [2-15; 0]

[a] Ninety-two and 59 effusions analyzed for mRNA and protein expression, respectively.
[b] $P < .001$ for all comparative analyses.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

The efficacy and safety of mirvetuximab soravtansine in FRα-positive, third-line and later, recurrent platinum-sensitive ovarian cancer: the single-arm phase II PICCOLO trial

A. Alvarez Secord[1*], S. N. Lewin[2], C. G. Murphy[3,4], S. C. Cecere[5,6], A. Barquín[7], F. Gálvez-Montosa[8], C. A. Mathews[9], G. E. Konecny[10], I. Ray-Coquard[11,12], A. Oaknin[13], M. J. Rubio Pérez[14,15], A. Bonaventura[16], E. J. Diver[17], S.-M. Ayuk[17], Y. Wang[17], B. R. Corr[18] & V. Salutari[19]

Volume 36 ■ Issue 3 ■ 2025

International Journal of *Molecular Sciences*

MDPI

Article

Deciphering Folate Receptor alphaGene Expression and mRNA Signatures in Ovarian Cancer: Implications for Precision Therapies

Maria Kfoury [1,*], Pascal Finetti [2], Emilie Mamessier [2], François Bertucci [1,2] and Renaud Sabatier [1,2]

Int. J. Mol. Sci. **2024**, *25*, 11953.

Development of an FRα Companion Diagnostic Immunohistochemical Assay for Mirvetuximab Soravtansine

Racheal L. James, BS; Taryn Sisserson, MS; Zhuangyu Cai, PhD; Megan E. Dumas, PhD; Landon J. Inge, PhD; James Ranger-Moore, PhD; Albert Mason, MD; Callum M. Sloss, PhD; Katherine McArthur, MS

Arch Pathol Lab Med. 2024;148:1226–1233;

Gynecologic Oncology 192 (2025) 102–110

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Analysis of real world FRα testing in ovarian, fallopian tube, and primary peritoneal cancers

Rebecca A. Previs [a,b,*], Kyle C. Strickland [a,c], Zachary Wallen [a], Heidi Ko [a], Michelle Green [a], Maureen Cooper [a], Elizabeth Lyon [e], Michael Biorn [e], Jennifer Armetta [e], Rennie Quarles [e], Catherine H. Watson [f], Kari Ring [g], Jonathan L. Klein [a], Brian Caveney [e], Eric A. Severson [a], Shakti Ramkissoon [a,d]

Folate Receptor Immunohistochemical Staining and Gynecologic Tumors: Initial Experience With 216 Cases

Barrett C. Lawson, MD, Mario L. Marques-Piubelli, MD,† Shannon N. Westin, MD,‡ and Anais Malpica, MD**

Int J Gynecol Pathol 2025;44:167–173

Antibody-Drug Conjugates in Gynecologic Cancers

Mary Katherine Anastasio, MD[1,*]
Stephanie Shuey, PharmD[2]
Brittany A. Davidson, MD[1]

Current Treatment Options in Oncology (2024) 25:1–19

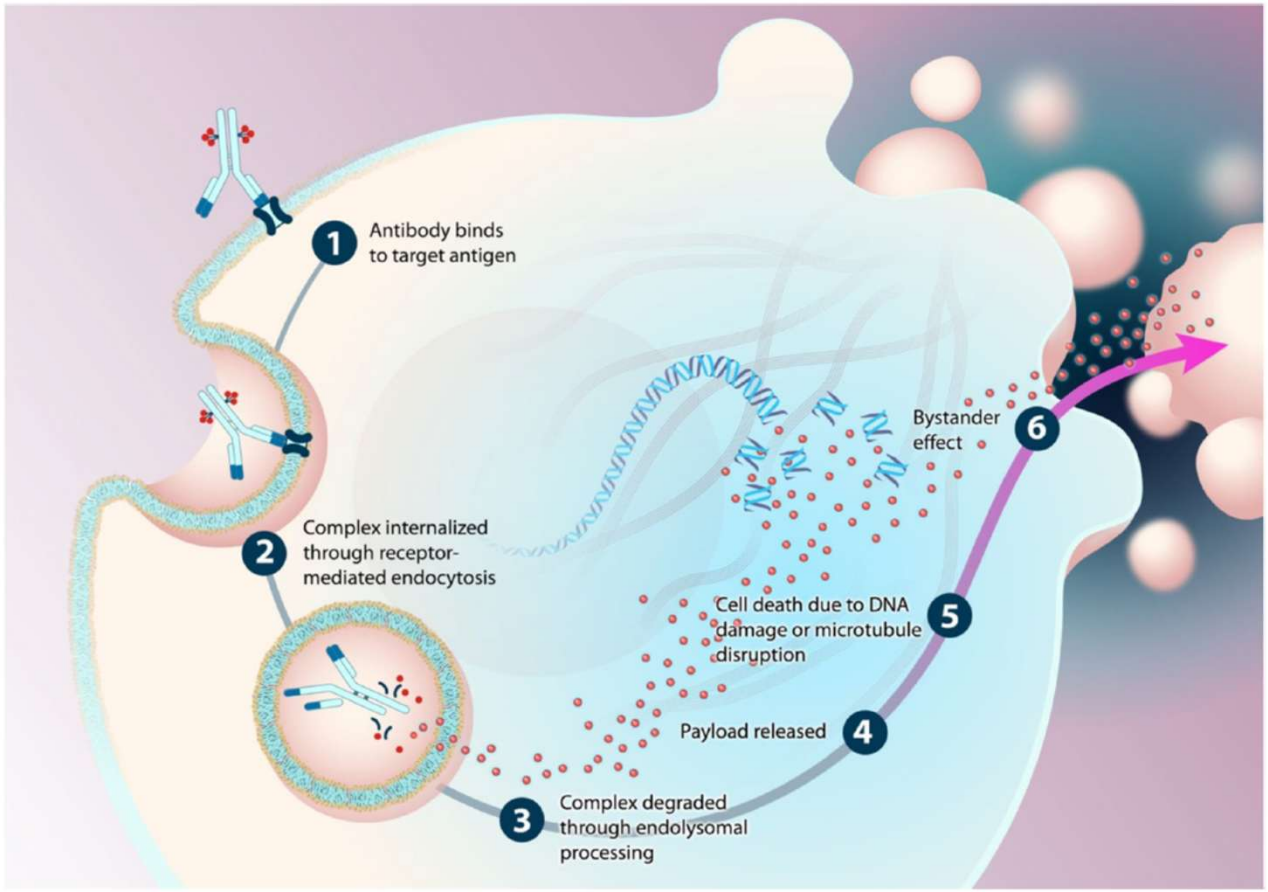

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Table 1. ADCs with FDA accelerated approval in gynecologic cancer

ADC	Mirvetuximab soravtansine	Tisotumab vedotin
Setting	FRα-high platinum-resistant, epithelial ovarian cancer	Recurrent or metastatic cervical cancer
Target antigen	FRα	Tissue factor
Linker	Sulfo-SPDB disulfide linker	Protease-labile Val-Cit-PABA linker
Cytotoxic payload	DM4	MMAE
Trial identifiers	SORAYA (NCT04296890)	InnovaTV 204/GOG 3023/ENGOT-cx6 (NCT03438396)
Trial primary endpoint	Objective response rate	Objective response rate
Common adverse events	Blurred vision, keratopathy, nausea	Neutropenia, fatigue, ulcerative keratitis, peripheral neuropathy

Table 2. Select ADCs under investigation in gynecologic cancer

ADC	Target antigen	Linker	Cytotoxic payload	Clinical trial identifier	Setting	Regimen	Primary outcomes	Phase
Anetumab ravtansine	Mesothelin	Sulfo-PDB	DM4	NCT03587311	Platinum-resistant or platinum refractory	Bevacizumab + weekly anetumab ravtansine vs bevacizumab + weekly paclitaxel	PFS	II
Endometrial								
Trastuzumab deruxtecan	HER2	Cleavable tetrapeptide linker	Topoisomerase I inhibitor	DESTINY-PanTumor02 (NCT04482309)	HER-2 expression, locally advanced or metastatic endometrial	Trastuzumab deruxtecan	ORR	II
				NCT04585958	HER-2 expressing serous endometrial	Trastuzumab deruxtecan + olaparib	Maximum tolerated dose Adverse events	I
DB-1303	HER2	Cleavable peptide linker	Topoisomerase I inhibitor	NCT05150691	Advanced, metastatic endometrial	DB-1303 dose escalation and expansion	Maximum tolerated dose Adverse events	I/IIa

Targeted therapy - AC

- HRD testing for HGSC and HG-EC
- MMR, p53 and *POLE* for EC
- Hormone receptor status for EC and LGSC
- HER2 for MC
- *KRAS*/*BRAF*/*NRAS* for LGSC and MC
- FRα targeting in SC and CS

Thank you for your attention

São Miguel, Azores