

Supplementary Table S 4. Molecular and clinicopathological features of endometrial cancer molecular subgroups¹

	POLEmut (i.e. <i>POLE</i> EDM)	dMMR (i.e. MSI)	NSMP (i.e. p53 wt)	p53aberrant (i.e. p53abn, p53mut)
Prevalence in TCGA cohort	5%-15%	25%-30%	30%-40%	5%-15%
Associated molecular features	>100 mut/Mb, SCNA-very low, MSS	10-100 mut/Mb, SCNA-low, MSI	<10mut/Mb, SCNA-low, MSS	<10mut/Mb, ScNA-high, MSS
Associated histological features	Endometrioid	Endometrioid	Mostly low grade	All histological subtypes
	Often high grade	Often high grade	Notable absence of TILS	Mostly high grade
	Ambiguous morphology	LVSI substantial	Squamous differentiation	High cytonuclear atypia
	Prominent TILS and TLS	Prominent TILS MELF-type invasion	ER/PR diffuse	Low level of TILS
Associated clinical features	Lower BMI	Higher BMI	Higher BMI	Lower BMI
	Early stage (IA-IB)	Lynch syndrome		Advanced stage
	Early onset			Late onset
Diagnostic test	NGS/Sanger/Hotspot: P286R, V411L, S297F, A456P, S459F	MMR-IHC: MLH1, MSH2, MSH6, PMS2 MSI assay		p53-IHC Mutant-like/abnormal staining
Prognosis	Excellent	Intermediate	Intermediate Stage-dependent	Poor

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BMI, body mass index; dMMR, mismatch repair deficient; EDM, exonuclease domain mutation; ER, (o)estrogen receptor; IHC, immunohistochemistry; LVSI, lymphovascular space invasion; MELF, microcystic elongated and fragmented type of invasion; MMR-IHC, mismatch repair immunohistochemistry; MSI, microsatellite instability; MSS, microsatellite stable; mut/Mb, mutations/megabase; NGS, next-generation sequencing; NSMP, no specific molecular profile; p53abn, p53 abnormal; p53mut, p53 mutant; p53-wt, p53-wild type; PgR, progesterone receptor; *POLE*, polymerase epsilon; *POLE*mut, polymerase epsilon-ultramutated; SCNA, somatic copy number alteration; TCGA, The Cancer Genome Atlas; TIL, tumour infiltrating lymphocyte; TLS, tertiary lymphoid structure.

References

- 1 Oaknin A, Bosse TJ, Creutzberg CL et al. Endometrial cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022.
- 2 McAlpine J, Leon-Castillo A, Bosse T. The rise of a novel classification system for endometrial carcinoma; integration of molecular subclasses. *J Pathol* 2018; 244 (5): 538-549.