European Journal of Surgical Oncology 52 (2026) 111453

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Review Article

Integrating molecular classification into endometrial cancer management☆

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ARTICLE INFO

Keywords:
Endometrial cancer
Molecular classification
POLE mutation
MMR deficiency/MSI-H
Precision medicine

ABSTRACT

Endometrial carcinoma is biologically heterogeneous. Molecular classification derived from The Cancer Genome Atlas (TCGA) identifies clinically relevant molecular subtypes, each with distinct prognostic and therapeutic implications. FIGO 2023 recognizes tumor biology in staging, and the new 2025 ESGO guidelines incorporate molecular data into risk-stratified management. This is a position paper on the incorporation of molecular classification in endometrial cancer. We focused on molecular taxonomy, diagnostic surrogates, prognostic validation, and therapeutic implications of immune and targeted agents. The five molecular subtypes (*POLE*mut; MMRd/MSI-H; p53abn; NSMP ER-positive; NSMP ER-negative) provide stronger prognostic discrimination than grade or histotype alone. We recommend that molecular subtype should guide adjuvant treatment de-escalation or intensification, inform the use of immunotherapy and targeted agents, and refine risk stratification beyond conventional parameters. We also discussed implementation challenges, including test standardization, reporting, equity of access, and areas of ongoing uncertainty. This position paper aims to support consistent, equitable, and biologically informed management of endometrial carcinoma in contemporary practice.

1. Introduction

Endometrial cancer is an increasingly prevalent malignancy among women worldwide [1]. Traditionally, risk assessment has relied on anatomical stage, histologic subtype and grade, and more recently pathologic features such as lymphovascular space invasion (LVSI) [2]. However, prognostic accuracy and concordance using these clinicopathologic variables alone remain limited, often resulting in over- or under-treatment [3].

The Cancer Genome Atlas (TCGA) integrative genomic analysis identified four molecularly distinct subtypes that capture the clinical heterogeneity and provide a biological framework for risk stratification [4]. These molecular classes include: DNA Polymerase Epsilon (*POLE)* ultramutated, microsatellite instability hypermutated, copy-number high, and copy-number low [4]. Subsequent studies from ProMisE and PORTEC, using pragmatic surrogate methods, demonstrated that immunohistochemistry (IHC) (for mismatch repair (MMR) and p53 proteins) and targeted molecular sequencing (for pathogenic *POLE*mutations (*POLE*mut)) are both feasible and clinically informative [5,6]. These efforts led to inclusion in WHO 2020 and ESGO 2021 guidelines [2,7] with the four 'new' molecular subtypes maintaining prognostic discernment of endometrial cancers and named for their defining features; *POLE*mut, MMRd, p53abn (p53 abnormal), and NSMP (no specific molecular profile).

Modern clinical classification now further stratifies NSMP by estrogen receptor (ER) status: about 85 % NSMP ER-positive and about 15 % NSMP ER-negative tumors [8,9], the latter being formally recognized as a high-risk entity in the 2025 ESGO/ESTRO/ESP guidelines [10]. Incorporating molecular classification has proven to refine prognostic estimates and better guide adjuvant therapy decisions, especially in

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https://doi.org/10.1016/j.ejso.2026.111453
Received 18 December 2025; Received in revised form 20 January 2026; Accepted 27 January 2026
Available online 29 January 2026

patients with early-stage disease or ambiguous histopathologic features (e.g., endometrioid grade 3 endometrial cancer) [11,12].

The 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system formally recognized tumor biology as a key determinant in staging, thus providing a paradigm shift of a pure anatomical stage [13]. Building on this foundation, the 2025 European Society of Gynaecological Oncology (ESGO), European SocieTy for Radiotherapy and Oncology (ESTRO), and European Society of Pathology (ESP) (ESGO/ESTRO/ESP) guidelines move from conventional clinicopathologic assessment toward a biology-driven approach to risk stratification, testing, and clinical management [10]. By integrating molecular data into diagnostic and treatment pathways, these guidelines aim to improve individualized patient care, reduce both over- and under-treatment, and harmonize management across centers. This position paper synthesizes the most recent evidence and provides practical recommendations for molecular testing, reporting, and therapeutic decision-making in the context of this paradigm shift, highlighting the evolving role of tumor biology in shaping modern endometrial cancer care.

2. Position statements

This position paper reflects the shared perspective of a multicenter group of gynecologic oncologists with extensive clinical and research experience in molecular classification of endometrial cancer. The following position statements summarize the authors' interpretative and practice-oriented stance on the role of molecular classification in endometrial cancer.

Position Statement 1: Molecular classification should be performed in all newly diagnosed endometrial cancer, irrespective of stage, histotype, or grade**.**

Rationale. Validated surrogate assays (MMR immunohistochemistry, p53 immunohistochemistry, and *POLE* sequencing) provide prognostic and therapeutic information that exceeds conventional clinicopathologic parameters and are now central to contemporary staging and risk stratification frameworks.

Position Statement 2: Pathogenic *POLE* exonuclease-domain mutations should drive adjuvant treatment de-escalation in early-stage endometrial cancer.

Rationale. When *POLE* pathogenicity is confirmed, tumor biology supersedes traditional risk factors such as grade and depth of invasion, supporting omission of adjuvant radiotherapy and systemic therapy in stage I–II disease within guideline-defined criteria.

Position Statement 3: MMRd endometrial carcinomas should be systematically identified at diagnosis for both prognostic and predictive purposes.

Rationale. Beyond Lynch syndrome screening, MMR status has direct implications for systemic treatment selection, particularly in advanced or recurrent settings where immunotherapy-based strategies represent standard of care.

Position Statement 4: p53abn endometrial cancer should be regarded as biologically high-risk tumors, even at early anatomical stages.

Rationale. The aggressive molecular profile of p53abn disease justifies treatment intensification strategies, including multimodal therapy and HER2-targeted approaches when indicated, independent of stage alone.

Position Statement 5: NSMP endometrial cancer should not be managed as a single clinical entity, and estrogen receptor status must be incorporated into risk stratification**.**

Rationale. ER expression provides clinically meaningful prognostic refinement within NSMP tumors, identifying ER-negative disease as a higher-risk subgroup distinct from ER-positive tumors, which generally exhibit more indolent behavior.

Position Statement 6: In tumors with multiple molecular classifiers, subtype assignment should strictly follow the established hierarchical algorithm.

Rationale. Adherence to the hierarchy (*POLE*mut → MMRd → p53abn → NSMP) ensures consistency in staging, risk stratification, and treatment planning, avoiding misclassification driven by secondary molecular alterations.

Position Statement 7: Standardization of molecular testing, reporting, and multidisciplinary interpretation is essential for equitable clinical implementation.

Rationale. Harmonized diagnostic pathways and structured reporting are required to prevent variability in interpretation and access, particularly across institutions with differing resources and expertise.

3. Methods

This manuscript was developed as a position paper and narrative synthesis aimed at interpreting and contextualizing the role of molecular classification in contemporary endometrial cancer management. The objective was not to conduct a systematic review or meta-analysis, but to formulate an evidence-informed, practice-oriented position aligned with recent international staging systems and guideline updates. Evidence was assembled through targeted searches of the biomedical literature, using key terms related to endometrial cancer and molecular classification such as TCGA, ProMisE, *POLE*, MMR/MSI, p53, NSMP, estrogen receptor, FIGO 2023, and ESGO 2025. We screened reference of landmark articles. In parallel, we reviewed major international guideline and staging documents relevant to molecular classification and its clinical implementation. To support this position, we drew on landmark genomic studies, validated molecular classification frameworks, major clinical trials, and international guidelines addressing the prognostic and therapeutic implications of molecular subtypes in endometrial cancer [14–18]. Evidence was selected based on clinical relevance, reproducibility, and direct applicability to patient management, with particular attention to areas where molecular classification informs treatment de-escalation, escalation, or systemic therapy selection. Evidence was synthesized qualitatively according to molecular subtype and clinical context, emphasizing consistency across cohorts and alignment with current guideline recommendations. Draft position statements were developed through iterative expert discussion among the authors, integrating clinical and translational perspectives. The final manuscript reflects a consensus-based interpretation of the available evidence rather than a formal guideline or systematic literature review, with the aim of providing a pragmatic framework for clinical decision-making.

3.1. The molecular taxonomy of endometrial carcinoma

This section provides the biological and clinical rationale supporting Position Statements 1 and 2. The molecular landscape of endometrial cancer is a clear example of how genomic profiling has transformed a histology-based classification into a biology-driven one. Although TCGA originally defined four genomic clusters, contemporary clinical practice now uses five operational molecular subtypes (with NSMP ER-negative added as a distinct high-risk group) [10]. These subtypes have become key to modern diagnostic, prognostic, and therapeutic strategies [4–6, 10]. Modern molecular subtyping therefore builds on, but is not equivalent to, the original TCGA genomic groups; contemporary clinical subtypes are defined using validated surrogate assays rather than whole-genome platforms [4,10].

The 2025 ESGO/ESTRO/ESP recommendations reaffirm the central role of this classification and advocate for universal molecular testing in all newly diagnosed endometrial cancers, irrespective of histotype or stage. This shift reflects the recognition that conventional pathological parameters, such as grade and histotype lack reproducibility and are insufficient to capture the biological diversity of the disease. Molecular profiling, by contrast, provides objective, highly reproducible biomarkers that directly inform risk stratification and guide individualized

treatment decisions [10].

The *POLE*mut subtype is defined by the presence of one of the eleven pathogenic exonuclease-domain mutations in the *POLE* gene. These alterations generate an "ultramutated" phenotype (analogous to, but not identical with, the TCGA ultramutated class) characterized by extremely high tumor mutational burden and a prominent immune infiltrate [4].

Accumulating data demonstrate that, despite their frequent high-grade morphology and deep myometrial invasion, patients with *POLE*mut endometrial cancers consistently experience excellent outcomes, with virtually absent disease-specific mortality across multiple independent cohorts [10,11,19–21]. Importantly, it is these reproducible clinical data (not the high mutational burden *per se*) that underpin ongoing investigations into adjuvant treatment de-escalation [12]. Only the eleven pathogenic variants defined by León-Castillo et al. should be considered actionable; variants of uncertain significance should not guide de-escalation decisions [21]. The list of pathogenic variants is provided in Supplemental Material 1.

The MMRd subtype, defined by IHC loss of one or more mismatch repair proteins (MLH1, PMS2, MSH2, MSH6) or by microsatellite instability assays revealing MSI-H profile, displays an intermediate prognosis and marked sensitivity to immune checkpoint blockade. In fact, in advanced/metastatic setting (chemo)immunotherapy has become the gold standard [15–18]. MLH1-hypermethylated tumors (about 90 % of MLH1 loss) may show lower immune infiltration and worse outcomes than Lynch-associated MMRd [22].

The p53abn molecular subtype is defined by overexpression or complete loss of p53 expression on IHC, or identified *TP53* mutation on next generation sequencing. p53abn corresponds to TCGA copy-number high tumors and encompasses most serous and some high-grade endometrioid carcinomas [25–57]. These tumors exhibit poor prognosis and are frequently associated with genomic instability and HER2 amplification [11,14,23–25]. 2025 ESGO/ESTRO/ESP guidelines endorse intensified multimodal treatment for this group, aligning with FIGO 2023 recognition of biologically defined substages (e.g., IICm-p53abn) [10,13]. The NSMP group, derived from TCGA copy-number low, includes tumors lacking *POLE*mut, MMRd, or p53abn. It represents the most heterogeneous class, accounting for nearly half of endometrial cancer. Recent studies indicate that within NSMP, ER expression provides further prognostic refinement, distinguishing favorable ER-positive tumors from higher-risk ER-negative subsets [8,9,26–28]. ER-positive tumors behave indolently. NSMP ER-negative tumors are now recognized as high-risk, with recurrence patterns approaching those of p53abn endometrial carcinomas. The data summarized here form the basis of Position Statement 5 regarding ER-based risk refinement within NSMP tumors. Of note, most studies use an IHC percentage threshold (commonly $\geq$10 % positive nuclei) to define ER positivity, but the optimal cut-off (e.g., 10 % vs 50 % vs 80 %) and whether ER should be treated as a continuous variable remain uncertain.

A minority of endometrial cancers (approximately 3–7 %) show more than one defining molecular feature and are therefore classified as "multiple classifiers." Examples include *POLE*mut tumors with an additional p53 abnormality, *POLE*mut with MMRd, MMRd with p53abn, or, rarely, tumors exhibiting all three features.

Diagnostic assignment in these cases follows the established hierarchical algorithm (pathogenic *POLE*mut → MMRd → p53abn → NSMP), which ensures consistent classification and avoids misinterpretation of secondary molecular alterations [29]. The 2025 ESGO/ESTRO/ESP guidelines highlighted the importance of this hierarchy and explicitly recommend applying it to all multiple-classifier tumors to support uniform staging, risk stratification, and treatment planning (Position Statement 6) [10]. Taken together, molecular testing is recommended for all newly diagnosed endometrial carcinomas by the 2025 ESGO/ESTRO/ESP guidelines. This standardized, stepwise approach (MMR IHC, p53 IHC, and *POLE* sequencing) provides a globally applicable diagnostic strategy and forms the basis of the biology-driven staging framework introduced in FIGO 2023 [10,13].

Implications for clinical practice: Molecular classification should be routinely incorporated into the diagnostic workup of all endometrial carcinomas using a standardized, stepwise testing approach, as histotype and grade alone are no longer sufficient for risk assessment or treatment planning (see Table 1).

3.2. Integration of molecular data into staging and risk models

The 2023 FIGO staging system for endometrial cancer represented an important step toward a biologically based classification. For the first time, FIGO included molecular features as stage modifiers, recognizing that prognosis and treatment decisions depend not only on the tumor's anatomical extent but also on its molecular profile. This change has been further applied in the 2025 ESGO/ESTRO/ESP guidelines, which incorporate molecular classification into all stages of patient management, from diagnosis to adjuvant therapy [10]. These developments directly support Position Statement 4, reinforcing the primacy of tumor biology over anatomical stage alone. Table 2 reports the main findings related to the integration of molecular classification into ESGO 2025 risk stratification [10].

Historically, prognostic assessment in endometrial cancer relied on surgical-pathologic variables such as depth of myometrial invasion, cervical involvement, histologic grade, LVSI, and nodal status. Although clinically useful, these parameters often suffer from interobserver

Table 1
Key innovations in the 2025 ESGO-ESTRO-ESP guidelines for endometrial cancer.

Domain	Innovations	Rationale
Risk Stratification	Integration of molecular subtypes (*POLE*mut, MMRd, p53abn, NSMP) into risk classification.	Molecular classification allows precise prognosis estimation and personalized treatment selection, refining previous histology-based approaches.
Staging	Adoption of FIGO 2023 staging system, incorporating molecular and anatomical factors.	Combines tumor biology with anatomical spread to improve prognostic accuracy and guide treatment planning.
Adjuvant Therapy	Recommendations for selective use of radiotherapy (external beam or vaginal brachytherapy) and addition of chemotherapy for high-risk disease.	Tailored adjuvant therapy reduces overtreatment in low-risk patients while ensuring aggressive management for high-risk groups.
Immunotherapy	Consideration of immunotherapy in MMRd advanced or recurrent cases, alone or with chemotherapy.	Reflects evidence that MMRd tumors are more responsive to immunotherapy, improving outcomes in select patients.
Surgical Approach in Advanced Disease	Emphasis on complete macroscopic resection; avoidance of routine systematic lymphadenectomy in favor of targeted node resection.	Minimizes surgical morbidity while maintaining oncologic outcomes; aligns surgery with tumor biology and patient-specific risk.
Follow-up	Individualized follow-up schedules focusing on quality of life, sexual health, menopause management, and treatment side effects.	Evidence suggests routine intensive follow-up does not improve overall survival; holistic patient-centered care is prioritized.
Patient-Centered Care	Active inclusion of patient representatives in guideline development; dedicated sections on survivorship, psychosocial support, and education.	Integrates patient voice into clinical practice, addressing unmet needs in survivorship, education, and psycho-oncology.

Abbreviation: POLE, DNA Polymerase Epsilon (*POLE*); MMRd, Mismatch repair deficient; p53abn, p53 abnormal); and NSMP, no specific molecular profile.

Table 2
Integration of molecular classification into risk stratification.

Molecular Subtype	FIGO Stage	Risk Group	Adjuvant Recommendation	Consideration on adjuvant therapy
*POLE*mut	I-II	Low	None	Adjuvant de-escalation supported by PORTEC4a and the ongoing RAINBO – BLUE trial [14,30,31]
MMRd	I-II	Intermediate	Consider brachytherapy or limited EBRT	Immunotherapy in recurrent/advanced disease supported by published randomized controlled trials [17,18,31,32]
NSMP (ER+)	I-II	Low–Intermediate	Surgery ± adjuvant therapy	Hormonal therapy may be considered (tested in the RAINBO-ORANGE arm) [14]
NSMP (ER-)	I-II	High-Intermediate	Surgery + tailored adjuvant therapy	Higher recurrence risk [8,9]
p53abn	Any stage	High	Multimodal therapy + HER2-targeted therapy if applicable	Aggressive biology dictates treatment escalation, chemoradiation plus consideration of trial or targeted therapy (e.g. HER2 targeted, RAINBO p53abn-RED trial evaluating the addition of PARP inhibitors) [14]

Abbreviation: *POLE*, DNA Polymerase Epsilon; MMRd, Mismatch repair deficient; p53abn, p53 abnormal); and NSMP, no specific molecular profile.

variability and limited reproducibility. Numerous studies have demonstrated that tumors with identical morphologic features may exhibit dramatically different outcomes depending on their molecular classes [5–8]. Consequently, the 2025 ESGO/ESTRO/ESP guidelines framework prioritizes molecular classification as the primary determinant of risk, to be interpreted in conjunction with, but not subordinate to, traditional histopathology [10]. Importantly, the guidelines formally recognize five clinically relevant molecular subtypes (*POLE*mut, MMRd, p53abn, NSMP ER-positive, NSMP ER-negative). NSMP ER-negative tumors, newly assigned to the high-risk category, have prognostic patterns that approach those of p53abn cancers, whereas NSMP ER-positive tumors behave much more indolently [8,9,33,34]. This represents a substantial evolution beyond the original four TCGA classes.

The updated FIGO staging includes molecularly annotated substages (e.g., IAm for *POLE*mut, IICm for p53abn), reflecting their distinct prognostic trajectories. Then, the 2025 ESGO/ESTRO/ESP guidelines defined five composite risk groups (i.e., low, intermediate, high-intermediate, high, and advanced/metastatic), integrating both clinicopathologic and genomic parameters. Indeed, stage I and II, *POLE*mut tumors, regardless of grade or invasion depth, are classified as low risk, given their negligible recurrence potential [10]. Conversely, p53abn carcinomas are categorized as high risk, even in early stages, due to their aggressive molecular profile and poor survival outcomes [33,34]. MMRd tumors have an intermediate position [4,22]. The incorporation of ER status is essential for NSMP tumors, distinguishing NSMP ER-positive (low–intermediate risk) from NSMP ER-negative (high--intermediate or high risk) [10,26–28]. This framework aligns with emerging evidence but also introduces new complexity for clinicians [10].

This molecularly integrated risk model has several clinical implications. It supports the potential adjuvant therapy de-escalation in low-risk *POLE*mut tumors and treatment intensification for high-risk p53abn cases, moving toward a precision-based allocation of therapy. Importantly, it also harmonizes with the ongoing RAINBO trial platform, which prospectively aims to validate these risk–treatment alignments across the four molecular classes [14].

The 2025 ESGO/ESTRO/ESP guidelines recommend that pathology reports explicitly document molecular subtype together with conventional histological parameters (stage, grade, LVSI, and nodal involvement) using the ICCR dataset format [10,19]. The guidelines also encourage multidisciplinary discussion of molecular findings before adjuvant treatment decisions, reflecting the principle that "biology supersedes morphology" in the modern management of endometrial cancer.

Implications for clinical practice: Risk stratification and adjuvant treatment decisions should be primarily guided by molecular subtype, with anatomical stage and conventional pathologic features interpreted within a biology-driven framework as outlined in FIGO 2023 and ESGO/ESTRO/ESP 2025.

3.3. Prognostic and therapeutic implications for clinical management

The use of molecular classification in endometrial cancer has improved our understanding of prognosis and treatment response. Among all molecular subtypes, stage I-II *POLE*mut carcinomas demonstrate the most favorable outcome. Despite frequently high-grade histology and deep myometrial invasion, these tumors are characterized by an "ultramutated" genotype, exceptionally high tumor mutational burden, and dense lymphocytic infiltration. Multiple independent cohorts, including the PORTEC and ProMisE analyses, have shown near-zero recurrence rates following surgery alone [5,6]. A meta-analysis of 294 *POLE*mut patients showed that progression and cancer-specific mortality were low at 4.1 % and 1 % of patients, respectively [20]. 2025 ESGO/ESTRO/ESP guidelines formally endorse de-escalation of adjuvant therapy for patients with early stage (I-II) *POLE*mut tumors: omission of external-beam radiotherapy and systemic therapy even with high-grade morphology, provided that *POLE* pathogenicity is confirmed by sequencing. This represents a paradigm shift to biology-driven precision management, enabling patients to avoid toxic therapies unlikely to provide survival benefit, aligning with FIGO 2023 substage IAm (*POLE*mut) [13]. The PORTEC-4a trial provides the first prospective validation of molecularly guided adjuvant de-escalation in early-stage endometrial cancer. The PORTEC-4a trial assigned patients with high intermediate risk endometrial carcinoma who had pathogenic *POLE* mutations to the 'favorable' risk group and directed them to observation/no treatment. Their data demonstrate molecular stratification can spare a large portion of patients treatment without inferior outcomes [30,31]. Ongoing EN.10/RAINBO-BLUE is also prospectively directing de-escalation in carefully defined subsets of early stage *POLE*mut cancers (Arm A.1; n = 120). Although there is also an opportunity in the trial to assess subsets of patients with *POLE*mut tumors considered to be at higher risk e.g., up to stage III disease (Arm A.2), it will likely be underpowered to provide definitive answers for the 'best' treatment for advanced stage *POLE*mut. This also reflected in the ESGO/ESTRO/ESP 2025 guidelines to guide treatment and perhaps that international practice ranges from immunotherapy, to de-escalation with salvage therapy if recurrence [10,20]. Currently, there is insufficient evidence to guide management of advanced/metastatic *POLE*mut disease and it is recommended these patients are discussed at multidisciplinary tumor board and clinical trial participation should be considered.

MMRd tumors have an intermediate prognosis. The approval of anti-PD-1 agents (i.e., dostarlimab and pembrolizumab) for MMRd or MSI-high endometrial carcinoma has revolutionized the treatment landscape for recurrent and advanced disease [15–18]. Table 3 shows the details of four randomized controlled trials testing the role of chemotherapy plus immunotherapy vs. chemotherapy alone in advanced/recurrent endometrial carcinoma [17,18,32,35]. The 2025 ESGO/ESTRO/ESP guidelines recommends molecular screening for MMR deficiency in all patients at diagnosis for treatment purpose but also for identify patients harboring Lynch syndrome (approximately 3 %

Table 3
Main RCTs focusing on first-line chemo-immunotherapy.

Study	No. of Patients	Treatment Arms	Primary Endpoint	Median PFS (months)	Hazard Ratio (PFS)	Median OS (months)	Hazard Ratio (OS)	Follow-up Duration	Key Findings
RUBY [17] NCT03981796	494	Dostarlimab + carboplatin/ paclitaxel → dostarlimab vs placebo + carboplatin/ paclitaxel → placebo	PFS, OS	10.1 (dostarlimab) vs 8.9 (placebo)	HR 0.76 (95 % CI, 0.59–0.98)	Not reached (dostarlimab) vs 29.8 (placebo)	HR 0.73 (95 % CI, 0.52–1.02)	37.2 months	Significant improvement in PFS and OS with dostarlimab in dMMR/MSI-H patients.
NRG-GY018 [18] NCT03914612	549	Pembrolizumab + carboplatin/ paclitaxel → pembrolizumab vs placebo + carboplatin/ paclitaxel → placebo	PFS, OS in MMRd and MMRp	Not specified	HR 0.65 (95 % CI, 0.51–0.83)	Not specified	Not specified	Not specified	Pembrolizumab added to chemotherapy improved PFS in dMMR/MSI-H patients.
AtTEnd [32] NCT03603184	551	Atezolizumab + carboplatin/ paclitaxel → atezolizumab vs placebo + carboplatin/ paclitaxel → placebo	PFS, OS	10.1 (atezolizumab) vs 8.9 (placebo)	HR 0.74 (95 % CI, 0.61–0.91)	38.7 (atezolizumab) vs 30.2 (placebo)	HR 0.82 (95 % CI, 0.63–1.07)	28.3 months	Atezolizumab improved PFS and OS in dMMR/MSI-H patients.
DUO-E [35] NCT04269200	718	Durvalumab + carboplatin/ paclitaxel → durvalumab vs placebo + carboplatin/ paclitaxel → placebo	PFS	20.8 (combination) vs 9.5 (control)	HR 0.55 (95 % CI, 0.43–0.69)	Not specified	Not specified	Not specified	Durvalumab improved PFS in both dMMR/MSI-H and pMMR patients.

Abbreviations PFS, progression-free survival; OS, overall survival; HR, Hazard ratio; CI, confidence interval.

of all endometrial carcinomas and about 10 % of MMRd/MSI-H endometrial cancer) [10,22]. Adjuvant management follows risk-based principles; however, in advanced, metastatic or recurrent settings, immunotherapy (with or without chemotherapy) is now considered the preferred systemic option for eligible MMRd/MSI-H patients [15–18,32,35]. Combination strategies pairing chemotherapy, immunotherapy, and PARP inhibitors are under investigation in ongoing trials (including RUBY part 2), aiming to extend durable benefit to MMRp carcinomas [15,35]. Further studies (including the NRG-GY020) are focusing on early-stage disease [36]. These data support the Position Statement 3.

The p53-abnormal subtype has the poorest prognosis and is marked by high genomic instability and frequent ERBB2 (HER2) amplification [35,36]. These tumors are predominantly serous or high-grade endometrioid and exhibit aggressive clinical behavior with early systemic dissemination. The new 2025 ESGO/ESTRO/ESP guidelines classifies p53abn disease as high risk even in early stages and recommends treatment intensification through multimodal therapy (comprising surgery, adjuvant chemotherapy, and external-beam radiotherapy) [10]. Chemotherapy has been shown to be especially important for patients with p53abn subtype, with chemoradiation benefiting patients over radiation alone [11,26]. For HER2-positive p53abn carcinomas, the addition of trastuzumab to platinum-based chemotherapy is endorsed, based on improved progression-free survival observed in randomized data [35,36]. Moreover, the intensification with novel targeted agents (such as trastuzumab-deruxtecan and PARP inhibitors) is under investigation in this subtype [14,37–39].

The NSMP subtype remains the most heterogeneous and clinically challenging. These tumors, lacking *POLE*, MMR, or p53 alterations, account for nearly half of all endometrial cancer and encompass both low-grade and high-grade endometrioid histologies as well as a panoply of less common histotypes including clear cell carcinomas (~50 % are NSMP), dedifferentiated, mesonephric-like, gastric type, etc. The 2025 ESGO/ESTRO/ESP guidelines highlight the prognostic heterogeneity within NSMP and the emerging role of ER expression as an additional discriminator [10]. ER-positive NSMP tumors tend to behave indolently and may benefit from hormonal therapy, whereas ER-negative NSMP cancers exhibit increased recurrence risk, approaching that of p53abn disease [10]. The incorporation of ER status into the 2025 risk model refines adjuvant decision-making, guiding clinicians toward individualized therapy intensity [10,26–28].

Translating these molecular insights into clinical management, the 2025 ESGO/ESTRO/ESP guidelines propose a molecularly integrated therapeutic framework that redefines both adjuvant and systemic treatment recommendations. For low-risk disease, represented primarily by *POLE*mut and ER-positive NSMP, surgery alone is adequate; adjuvant therapy can be safely omitted. Intermediate- and high-intermediate-risk groups, often comprising MMRd or selected NSMP tumors, may receive vaginal brachytherapy or limited external-beam irradiation, balancing local control with quality of life. High-risk disease, particularly p53abn carcinomas, mandates combined modality treatment, including chemotherapy and pelvic irradiation. The integration of HER2 testing ensures the identification of candidates for trastuzumab-based therapy [36]. Finally, management of advanced or metastatic tumors now requires molecularly stratified systemic approaches including chemotherapy plus immunotherapy in first line and immunotherapy with or without Tyrosine Kinase Inhibitor (TKI) in second line (for patients who are immunotherapy naïve) [15]. Interestingly, a retrospective analysis of the RUBY trial suggested that MMRd/MSI-H and p53 abnormal groups are more likely to experience benefit from the combination between chemotherapy and immunotherapy rather than chemotherapy alone; while the addition of immunotherapy does not provide benefit in NSMP and *POLE*mut patients. This latter group (5 patients) did not experience recurrence after chemotherapy (n = 3) and chemotherapy plus immunotherapy (n = 2) [17].

Those data supported de-escalation for indolent types spares patients unnecessary toxicity, while escalation for aggressive molecular profiles improves therapeutic efficacy [30,38,40,41]. Importantly, the integration of predictive biomarkers also redefines recurrence management [39–43]. Ongoing trials are testing innovative treatments in managing advanced and recurrent endometrial cancer (Table 4).

Table 4
Ongoing trials testing new approaches in advanced/recurrent endometrial cancer.

Therapy/Agent	Target/Mechanism	Clinical Trial	Phase	Population/Line of Therapy	Key Findings/Notes
Selinexor	XPO1 inhibitor; induces nuclear localization of tumor suppressor proteins (including p53)	ENGOT-EN5/GOG-3055/SIENDO	Phase III	263 patients; platinum-based chemotherapy; intention-to-treat and TP53 wild-type subgroups	No PFS benefit in overall population; exploratory TP53 wild-type subgroup showed improved PFS. Ongoing XPORT-EC trials further investigate *TP53* wild-type patients [42].
Mirvetuximab soravtansine-gynx	Antibody-drug conjugate (ADC) targeting folate receptor α (FRα) with DM4 payload	Ongoing studies	Phase II/III	Second line or beyond; FRα-high endometrial or ovarian cancer	Significant antitumor activity in FRα-high ovarian cancer; being tested alone or in combination with immunotherapy, PARP inhibitors, bevacizumab [43].
Trastuzumab deruxtecan (T-DXd, DS-8201)	HER2-targeted ADC	DESTINY-PanTumor02 (NCT04482309)	Phase II	Endometrial cancer with measurable disease progressing after prior therapy	Overall response rate 57.5 %; response influenced by HER2 IHC: IHC3+ 84.6 % [39]
CDK4/6 inhibitors	Cyclin-dependent kinase 4/6 inhibitors	Multiple ongoing trials	Phase II/III	Second line or beyond; hormone-sensitive/NSMP endometrial cancer	Well tolerated and effective in combination with hormonal therapy.
Small molecule inhibitors (e.g., WEE1, ATR, PIK3CA inhibitors)	Various molecular targets	Multiple ongoing studies	Early phase	Second line or beyond	Actively being investigated

Abbreviations: PFS, progression-free survival; IHC, immunohistochemistry; ADC, antibody-drug conjugate; ATR, Ataxia Telangiectasia and Rad3-related; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PARP, Poly (ADP-ribose) polymerase.

Implications for clinical practice: Adjuvant and systemic therapies should be tailored to molecular subtype, enabling treatment de-escalation in early-stage *POLE*mut endometrial cancer and intensification in p53-abnormal tumors.

3.4. Implementation challenges, equity considerations, and future perspectives

Bringing molecularly guided management from academic centers into everyday clinical practice is both the main achievement and the main challenge of the 2025 ESGO/ESTRO/ESP guidelines. Despite representing an important scientific advancement, both FIGO 2023 and the 2025 ESGO/ESTRO/ESP guidelines introduce several practical challenges that may limit their usability in everyday clinical practice [10,13]. First, the overall framework is complex: clinicians must navigate numerous algorithms, tables, footnotes, and conditional pathways, creating a steep learning curve and making real-time application difficult. In addition, the integration of anatomical staging with molecular classification into single composite risk groups may blur clinically meaningful distinctions. For example, NSMP ER-negative tumors and p53abn carcinomas are both categorized as "high-risk," yet they differ considerably in terms of underlying biology, chemo-sensitivity, and expected response to immunotherapy [10]. This can also lead to therapeutic non-equivalence: an early-stage p53abn carcinoma and an advanced-stage NSMP ER-positive tumor may fall into the same risk group despite requiring very different treatment strategies. Another important limitation relates to adaptability. Since guideline revisions typically occur every few years, the system risks lagging behind fast-evolving biomarkers, such as refinements in *POLE* pathogenicity, emerging HRD markers, or the increasingly relevant ER stratification within NSMP tumors. For these reasons, an alternative conceptual framework that separates anatomical stage from molecular subtype, rather than merging them into unified categories, might offer greater clarity, facilitate more flexible updates, and better reflect the biological diversity of endometrial cancers [40,41]. A key concern highlighted by experts is that guidelines updated only every several years may struggle to remain nimble enough to incorporate rapidly emerging biomarkers such as refined *POLE* pathogenicity, ER stratification, or HRD signatures.

Further gaps emerge when considering the practical applicability of these guidelines across diverse healthcare settings. The documents provide limited guidance for clinicians working in resource-constrained environments where sentinel lymph-node mapping, universal molecular testing, or *POLE* sequencing are not readily available. Similarly, the absence of a section dedicated to fertility-sparing management is notable and remains unexplained, despite its clinical relevance. Fertility preservation is an increasingly relevant clinical issue, and molecular profiling may be useful in improving the process of patients' selection. However, data are still scarce. *POLE*mut and NSMP ER-positive tumors seems represent distinct subgroups in which tailored counseling and data collection should be prioritized [44]. The recommendations regarding ovarian preservation also appear to miss an opportunity to address the importance of molecular context in coexistent endometrioid carcinomas (formerly termed "synchronous"), particularly in patients with p53abn or NSMP ER-negative disease, where ovarian management may have important prognostic implications. Finally, the assignment of Stage IA p53abn carcinomas without myometrial invasion to the low-risk category conflicts with several retrospective studies reporting recurrence rates well above the ≤5 % threshold typically expected for this group. These inconsistencies highlight areas where future guideline updates may need to provide greater nuance and alignment with emerging evidence.

A broader implementation challenge concerns equity: universal molecular testing requires appropriate laboratory infrastructure, workforce training, and sustainable reimbursement models. Without coordinated investments and harmonized reporting systems, molecularly guided care risks being accessible only to high-resource centers, thereby widening global disparities [38]. These challenges highlight the practical relevance of Position Statement 7. Future research priorities include refining the NSMP subtype through transcriptomic and immunogenomic profiling, exploring mechanisms of immune resistance in MMRd and *POLE*mut tumors, and validating adaptive clinical-trial platforms such as RAINBO. As new biomarkers emerge, ranging from ER stratification to HRD signatures, the ability to incorporate these rapidly into clinical algorithms will be essential.

Implications for clinical practice: Effective translation of molecular classification into routine care requires standardized testing, structured reporting, and equitable access to diagnostics, with multidisciplinary interpretation and clinical trial enrollment encouraged where uncertainty persists.

4. Conclusions

Molecular classification has fundamentally reshaped the management of endometrial carcinoma, offering a biologically grounded framework that improves risk stratification and informs therapeutic decision-making. Modern clinical practice now relies on five molecular subtypes (*POLE*mut, MMRd, p53abn, NSMP ER-positive, and NSMP ER-negative) each associated with distinct prognostic trajectories and

patterns of treatment sensitivity. Patients with *POLE*mut endometrial cancer experience excellent outcomes, supporting the rationale for adjuvant de-escalation when pathogenic mutations are confirmed. Patients with p53abn endometrial cancer face a substantially higher risk of recurrence. MMRd tumors highlight the predictive value of subtyping for immunotherapy and the importance of identifying Lynch syndrome, whereas NSMP cancers remain the most heterogeneous group. Within NSMP, ER expression provides crucial refinement, identifying NSMP ER-negative disease as a high-risk entity that behaves more aggressively and may require tailored treatment strategies.

The 2025 ESGO/ESTRO/ESP guidelines reflect this paradigm shift by integrating molecular data into staging, risk assessment, and therapeutic pathways [10]. However, their complexity, limited adaptability to rapidly emerging biomarkers, and the challenges associated with implementation across diverse healthcare settings underscore the need for future refinement. Ensuring equitable access to molecular testing, adopting reporting standards that facilitate consistency across centers, and maintaining flexibility to incorporate new biomarkers will be essential for translating molecular classification into global clinical practice. Further research is required to clarify optimal management for NSMP ER-negative tumors, stage IA p53abn carcinomas without myometrial invasion, and multiple-classifier cases, as well as to better understand mechanisms of immune resistance in MMRd and *POLE*mut cancers. Finally, integrating molecular classification into routine care represents a major step toward personalized and biologically informed management of endometrial cancer, with the potential to improve outcomes while minimizing unnecessary treatment for patients worldwide.

Authors contribution

Conceptualization: GB, JNM; Methodology: All authors.; Data extraction: All authors; Project administration: GB, JNM; Supervision: JNM; writing – original draft: All authors; writing – review & editing: All authors.

Funding

None.

Conflict of interest statement

GB participated in advisory board of Astellas, Corcept Th, and GSK. Given his role as members of the editorial board of EJSO, GB had no involvement in the peer review of this article and has no access to information regarding its peer review. He did not participate in the editorial evaluation of the paper. JNM has received honorariums from GSK. The other authors declare no funding or conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2026.111453.

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