



Molecular characterization of NSMP endometrial cancer and its relevance for treatment

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HIGHLIGHTS

- NSMP endometrial cancers are the most prevalent molecular subtype of the disease.
- NSMP tumors show substantial histologic and immunogenomic heterogeneity.
- Hormonal therapies show activity in NSMP tumors, which frequently express ER and PR.
- Targeted therapies, immunotherapies, and antibody-drug conjugates are currently being explored in NSMP tumors.
- New trials should incorporate molecular stratification and prioritize response biomarker development.

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ABSTRACT

Endometrial cancers classified as having no specific molecular profile (NSMP) represent the most prevalent molecular subtype of the disease. In this review, we summarize the immunogenomic landscape and phenotypic features of NSMP endometrial cancer and discuss current and emerging therapeutic strategies, including endocrine therapies, targeted agents, immunotherapies, and antibody-drug conjugates. We further highlight the need for future clinical trials to incorporate molecular stratification and prioritize the development of predictive biomarkers and rational combination approaches to improve outcomes for patients with NSMP endometrial cancer.

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1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, and its mortality rate continues to increase, rising by 1.3% annually from 2016 to 2023 [1]. Molecular classification has transformed the management of endometrial cancer by providing biologically meaningful subgroups that complement traditional clinicopathologic factors [2,3]. The Cancer Genome Atlas (TCGA) identified 4 distinct molecular subgroups: DNA polymerase epsilon (POLE)-mutated, mismatch repair-deficient (dMMR), copy-number low, and copy-number high [4]. The ProMisE algorithm was subsequently developed to integrate TCGA categorization into clinical practice [5]. This algorithm uses a stepwise classification process. First, immunohistochemistry (IHC) is performed to assess mismatch repair (MMR) protein expression; loss of expression indicates a dMMR tumor. Then, cancers with intact MMR expression (pMMR) undergo sequencing for POLE exonuclease domain mutations. If no POLE mutation is detected, IHC for p53 is then performed. Cancers with normal p53 expression are classified as having no specific molecular profile (NSMP) [5].

NSMP tumors constitute the largest and most heterogeneous category, representing approximately 40% to 50% of all endometrial carcinomas and nearly one-third of advanced or recurrent cases [5–8]. NSMP cancers carry an intermediate prognosis relative to other molecular subtypes [5,9,10], with recurrence and cancer specific death rates of 17.1% (14.7%–19.7%) and 11.0% (9.0%–13.2%), respectively across all stages [10]. However, these cancers exhibit a spectrum of clinical behavior, ranging from indolent [11] to aggressive disease [12] suggesting that biologically distinct entities exist within this molecular subgroup [13]. This variability also reflects the histologic heterogeneity within the NSMP group; while most NSMP tumors are endometrioid carcinomas, this group also includes high-risk histologic subtypes, including clear cell, mesonephric-like, carcinosarcoma, and undifferentiated/dedifferentiated endometrial carcinomas [11].

The need for improved characterization of NSMP disease has become increasingly relevant in the era of precision oncology. Recent phase III trials have demonstrated substantial benefit from the addition of immune checkpoint inhibitors to chemotherapy in patients with advanced or recurrent endometrial cancer, with the greatest efficacy observed in POLE-mutated [13] and dMMR cancers [14,15]. In contrast, pMMR tumors derive comparatively more modest clinical benefit from these approaches [14–17]. Nearly 70% of pMMR endometrial cancers are classified as NSMP, with the remaining tumors comprising the POLE-mutated and p53-abnormal molecular subtypes [5,18]. Consequently, efficacy data reported for pMMR populations may not accurately reflect outcomes specific to NSMP cancers. Similarly, the benefit of other treatment modalities, including radiation therapy, also varies according to molecular subtype, underscoring the need for a more refined, molecularly informed treatment approach [19,20].

In this review, we summarize current approaches to refine prognostic and therapeutic stratification within NSMP endometrial cancers, focusing on hormone receptor expression, genomic alteration profiles, and the tumor immune microenvironment. Because the majority of NSMP tumors are endometrioid carcinomas [11], the evidence discussed primarily reflects this histologic subtype. We also review emerging biomarker-informed therapeutic strategies and highlight opportunities to advance precision medicine approaches for patients with NSMP endometrial cancer.

2. Immunogenomic biomarkers that refine prognosis in NSMP cancers

NSMP cancers confer an intermediate prognosis in progression free survival (PFS), disease specific survival (DSS) and overall survival (OS) compared to the other molecular subtypes [5,21,22]. However NSMP cancers have a variable prognosis [5,11,23–25]. In this section, we examine how hormone receptor status, genomic alteration profiles, and immunophenotypic features can further stratify this subtype.

2.1. Hormone receptor expression in NSMP cancers

Hormone receptor (ER/PR) positivity correlates with improved clinical outcomes in patients with NSMP cancers [11,12,26–29]. ER expression of $\geq 1\%$ has been linked to improved OS, particularly among low tumor grade (1–2) tumors [11] and in patients with low-grade endometrioid carcinomas [12,26]. In a multivariable analysis adjusting for histology and grade, Lam et al. demonstrated that ER positivity remained independently associated with improved OS in NSMP tumors [12].

Higher combined ER and PR expression is associated with improved outcomes in NSMP cancers. In a study by Verde et al., 5-year disease DSS rates were 43% for low ($<10\%$), 84% for intermediate (20–80%), and 98% for high ($>90\%$) combined ER/PR expression [28]. Similarly, Vermij et al. reported that ER and PR expression levels $\geq 10\%$ were independently associated with improved recurrence-free survival (ER: HR 0.274, PR: HR 0.395) [29]. ER and PR positivity of $\geq 1\%$ were associated with improved OS (HR 0.22 and 0.26, respectively) according to a meta-analysis of 14 retrospective studies [30]. Collectively, these findings support ER and PR expression as independent prognostic markers in NSMP endometrial carcinomas, with higher expression linked to improved clinical outcomes. Whether ER/PR expression in NSMP cancers is purely prognostic, reflecting less-aggressive tumor biology, or also predictive of endocrine therapy benefit remains an important clinical question. The emergence of *ESR1* mutations following aromatase inhibitor treatment provides indirect evidence of functional ER pathway dependence, suggesting a potential predictive role [31]. Direct clinical evidence addressing this question is reviewed in Section 3.

The optimal threshold for ER expression to guide hormonal therapy in endometrial cancer remains undefined [32]. The College of American Pathologists recommends using the same ER scoring system as in breast carcinoma, classifying cancers with $\geq 1\%$ ER staining as positive to identify patients likely to benefit from hormonal therapy [32]. Previous studies correlating ER/PR status with response to endocrine therapy have retrospectively employed various methods to quantify ER/PR positivity, including cytosolic receptor concentrations [33], nuclear and cytosolic IHC staining [34] and, more recently, mRNA expression levels of ER-specific target genes [35]. These studies demonstrate that higher expression of ER/PR or their transcriptional targets is associated with improved clinical outcomes [33–35]. However, future prospective studies stratified by receptor expression, receptor activity, and molecular subgroup could better define the patients most likely to benefit from endocrine therapy.

2.2. Genomic alterations in NSMP cancers

Distinct genomic alterations in NSMP cancers are associated with differences in clinical outcomes [4,23,36–40]. Large-scale genomic

studies have demonstrated that the PI3K/AKT and Wnt/ β -catenin pathways are frequently mutated in NSMP cancers [39,40]. In a retrospective single institution study, NSMP cancers harboring *PTEN/PIK3R1* mutations had more favorable overall survival than those with *PTEN/PIK3CA* mutations, whereas high-level chromosome 1q gain in the absence of *PTEN* alterations was associated with the poorest outcomes [39]. However, a subsequent meta-analysis did not identify a significant association between *PIK3CA/PTEN* mutations and survival in endometrial cancer overall, although NSMP-specific analyses were not performed [25].

Copy number alterations, including those affecting *MDM4*, may also be prognostic in NSMP cancers [41,42]. Amplification of chromosome 1q32.1, which contains *MDM4*, was associated with inferior relapse-free survival and an increased risk of distant recurrence in an exploratory biomarker analysis of the PORTEC-1 and PORTEC-2 trials [42]. *MDM4* represses p53 transcriptional activity through interaction with p53's transactivation domain, potentially resulting in a p53-abnormal-like tumor phenotype. This mechanism may underlie the association between 1q32.1 amplification and more aggressive disease [43]. Additionally, NSMP cancers with copy number changes and/or harboring *CTNNB1* or *AKT1* mutations may have an increased propensity for metastasis [41]. Supporting this observation, metastatic endometrioid NSMP tumors demonstrate higher frequencies of *CTNNB1* and *AKT1* mutations than primary NSMP tumors, although the retrospective design and use of unmatched cohorts limit definitive conclusions [41]. Notably, mutations in *CTNNB1*, *KRAS* and *SOX17* that lead to alterations in the Wnt/ β -catenin pathway are reported to be mutually exclusive [4].

Collectively, these studies demonstrate that the genomic landscape of NSMP endometrial cancer is characterized by alterations in the PI3K-AKT and Wnt/ β -catenin pathways. Integration of these biomarkers may improve prognostic stratification within the NSMP molecular subtype. At present, PI3K/AKT pathway alterations, chromosome 1q32.1/*MDM4* amplification, *CTNNB1* mutations, and copy-number alterations are primarily of prognostic significance, as they may be associated with differences in survival, recurrence risk, and metastatic potential [39,41,42]. However, most available data are derived from retrospective cohort studies [39,41] or exploratory post hoc biomarker analyses [42], and are therefore susceptible to confounding and selection bias.

Beyond their prognostic relevance, several of these alterations may be therapeutically actionable. The PI3K/AKT pathway represents a therapeutic target in endometrial cancer [44], while targeting of the Wnt/ β -catenin pathway remains largely investigational [45,46]. Notably, 92% of NSMP cancers harbor at least one molecular alteration classified within tiers I–III of the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT), underscoring the potential for biomarker-directed therapeutic strategies [40]. Therapeutic strategies targeting these molecular alterations in NSMP cancers are discussed in Section 3.

2.3. Immune microenvironment in NSMP cancers

NSMP cancers generally exhibit lower levels of immune cell infiltration than other molecular subtypes, and the degree of immune depletion appears to correlate with clinical outcomes [47–49]. In the PORTEC-1 and -2 cohorts, NSMP tumors had the highest proportion of immune-depleted cancers among stage I endometrioid endometrial carcinomas [49]. Consistent with this finding, immune profiling of 213 NSMP tumors identified three distinct immune phenotypes: immune-desert (absence of lymphocytic infiltration), immune-excluded (lymphocytes confined to the invasive margin), and immune-inflamed (intratumoral lymphocytic infiltration), which accounted for 41.8%, 12.7%, and 45.3% of cases, respectively [48]. Clinical outcomes varied substantially across these groups, with 2-year disease-free survival rates of 96.2% in immune-inflamed tumors, compared with 83.2% and 40.5% in immune-desert and immune-excluded tumors, respectively [48].

Differences in the composition of tumor-infiltrating lymphocyte (TIL) populations have been observed across molecular subsets of endometrial cancer [47,50]. Compared with other molecular classes, NSMP tumors demonstrate the lowest densities of epithelial and stromal PD-1+CD8– (putative CD4+) and PD-1+CD8+ T cells [50]. Higher CD8+ cell density was associated with reduced recurrence among 374 NSMP tumors on univariate analysis (HR 0.88, $p = 0.048$), but narrowly missed significance on multivariate analysis (HR 0.88, $p = 0.055$) [49]. Collectively, these studies indicate that most NSMP cancers show limited immune infiltration, particularly of cytotoxic CD8+ T cells, whereas immune-inflamed tumors are associated with more favorable clinical outcomes.

These immune microenvironment features may partly explain the comparatively reduced efficacy of immune checkpoint inhibitors in pMMR/NSMP endometrial cancers relative to dMMR tumors [51–53]. dMMR endometrial cancers demonstrate significantly higher CD8+ T-cell, PD-1+, and PD-L1+ immune cell infiltration compared to pMMR tumors reflecting a more immunoreactive tumor microenvironment [54,55]. The predominance of immune-desert and immune-excluded phenotypes in NSMP cancers aligns with the reduced responsiveness of non-immunoreactive (“cold”) tumors across multiple solid cancers [56,57]. In contrast, the immune-inflamed subset of NSMP cancers (~45%) shows more favorable disease-free survival [48] and may represent a population more likely to benefit from immunotherapy, although this hypothesis requires prospective validation. Supporting this, higher intratumoral CD8+ T-cell infiltration has been associated with improved responses to PD-1/PD-L1 blockade across solid cancers [58], suggesting CD8+ density as a potential biomarker of immunotherapy sensitivity in NSMP disease. Nevertheless, immune phenotyping in NSMP endometrial cancer remains investigational and has not yet been incorporated into clinical treatment algorithms for immunotherapy selection.

2.4. Integrated risk prognostic groups for NSMP cancers

Emerging data suggests that NSMP cancers can be stratified into low- and high-risk tumors [11,12,26,30]. Low-risk tumors are typically estrogen receptor positive, low grade, and endometrioid in histology [26,59], whereas high-risk tumors are more often ER-negative and high-grade. Across all stages, the 5-year disease-specific death rate is less than 2% for low-risk NSMP cancers, compared with more than 20% for high-risk (grade 3, ER-negative) tumors [11]. The poor prognosis of ER-negative tumors likely reflects their frequent association with high-risk histologies, including clear cell, mesonephric-like, carcinosarcoma, and undifferentiated/dedifferentiated endometrial carcinomas [11,60]. As the biologic complexity of NSMP tumors becomes increasingly recognized, integrating hormone receptor status, genomic alterations, and features of the tumor immune microenvironment may enable more refined prognostic stratification. The clinical relevance of such stratification was recently demonstrated in the PORTEC-4a trial in which observation was non-inferior to vaginal brachytherapy in high-intermediate-risk early-stage NSMP cancers lacking *CTNNB1* mutations, supporting the use of molecular biomarkers to personalize treatment decisions [19].

3. Therapeutic strategies for NSMP cancers

NSMP cancers harbor a range of oncogenic alterations and signaling pathways that are actively being explored as therapeutic targets [44,61]. (Fig. 1) However, because most clinical trials have been designed around individual molecular alterations rather than the NSMP subtype itself, the applicability of their findings to the broader NSMP population remains uncertain. In this section we review therapeutic strategies pertinent to NSMP cancers, including hormonal therapies, inhibitors of the PI3K/AKT, ATR, and XPO1 pathways, and antibody-drug conjugates, highlighting NSMP-specific evidence whenever available.

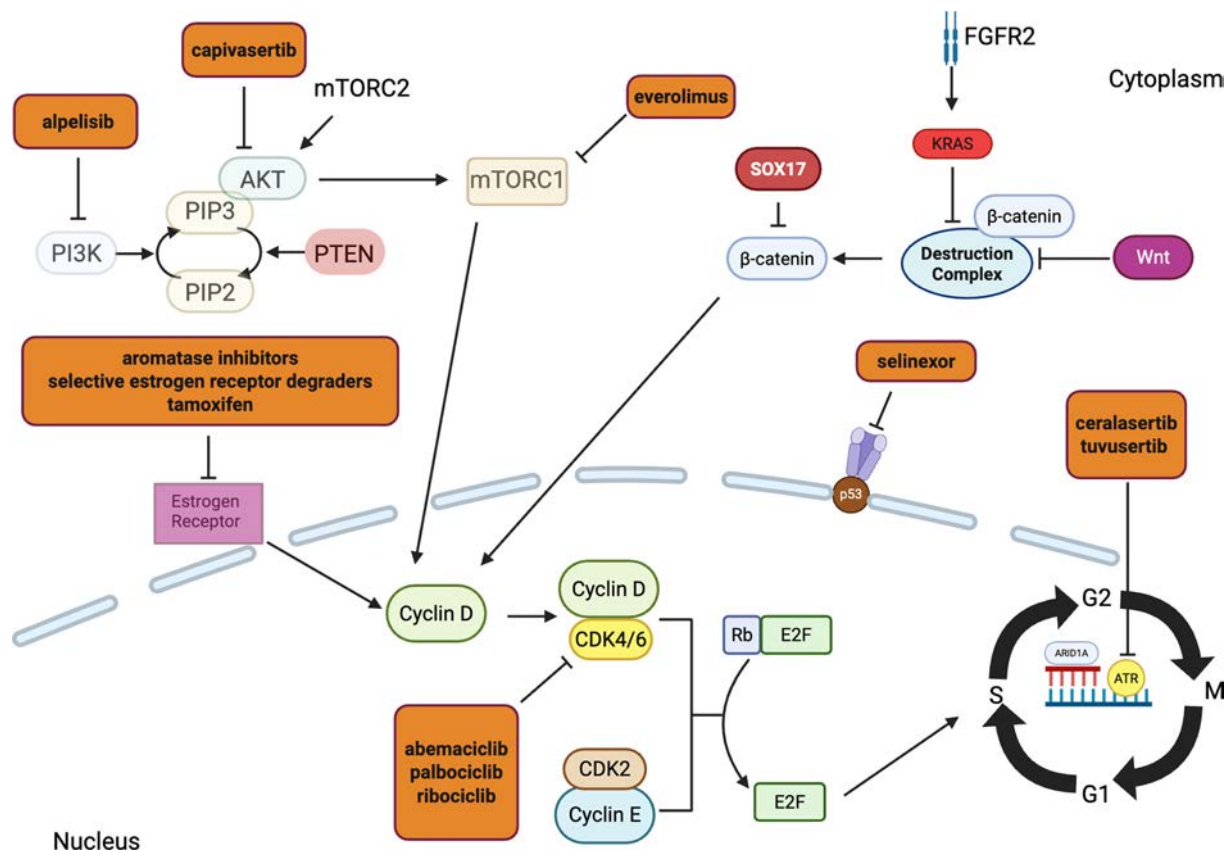


Fig. 1. Schematic representation of key molecular pathways and targeted therapies in NSMP endometrial cancer. The PI3K/AKT/mTOR signaling cascade, regulated by PTEN, is targeted by inhibitors of PI3K (alpelisib), AKT (capivasertib), and mTOR (everolimus). The Wnt/β-catenin pathway can be oncogenic through mutually exclusive mutations in CTNNB1, KRAS and SOX17. Cell cycle progression through G₁/S transition is regulated by cyclins (D and E) and CDKs (4/6 and 2). CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) block the G₁/S transition. DNA damage response via ATR and ARID1A is inhibited by ceralasertib. Selinexor targets nuclear export protein XPO1, causing p53 nuclear retention. Estrogen receptor signaling promotes Cyclin D expression, linking hormonal pathways to cell cycle control. Therapeutic agents are highlighted in orange boxes [140].

3.1. Hormonal therapy for NSMP cancers

In the current treatment landscape, hormonal therapy is generally reserved for patients with hormone receptor-positive recurrent endometrial cancer who have low-grade disease, low-volume tumor burden, or are poor candidates for cytotoxic chemotherapy [62,63]. The majority of NSMP endometrial cancers express >1% ER positivity, making it an attractive target for endocrine therapy [11,64]. Endocrine monotherapies [65–67] and combination regimens [68–70] have demonstrated efficacy in hormone-sensitive endometrial cancers. However, earlier clinical trials evaluating these therapies predated molecular stratification, limiting assessment of efficacy in NSMP cancers. Notably, in a phase II study of everolimus plus letrozole, clinical benefit was observed exclusively in patients with endometrioid tumors, including several harboring *CTNNB1* mutations, whereas no responses were reported among serous carcinomas [70]. These findings suggest that molecular features underlying distinct histologic subtypes may influence sensitivity to hormonal therapy.

With respect to NSMP cancers, combination therapy involving CDK4/6 inhibitors and endocrine agents has been investigated [20,71]. (Table 1) The combination of letrozole and abemaciclib demonstrated an objective response rate (ORR) of 50% among 8 NSMP patients in a phase II trial of recurrent ER-positive (≥1%) endometrial cancer [71]. Notably, 3 NSMP patients with *CTNNB1* mutations achieved an objective response, and 2 additional patients with *KRAS* mutations experienced clinical benefit, defined as PFS of at least 6 months. The responses seen in the NSMP patients with *CTNNB1* mutations are likely due to beta-catenin upregulation of cyclin-D expression [72,73]. In contrast,

among ER-positive cases, those with *TP53* mutations showed almost no responses to letrozole/abemaciclib and derived less clinical benefit compared to patients with *TP53* wildtype cancers [71]. Similarly, in a phase II study, the combination of fulvestrant and abemaciclib demonstrated clinical benefit, with an ORR seen in 10 of 17 NSMP tumors (59%) and a median PFS of 9.0 months (90% CI; 1.8–20.4). Again, *TP53*-mutant cancers failed to respond, whereas the only partial responses among patients with *KRAS* hotspot mutations occurred in those with NSMP tumors [20].

A separate study tested the addition of metformin to letrozole and abemaciclib [74]. Metformin was used as it can inhibit PI3K-AKT signaling [75], which is thought to be a resistance mechanism to CDK4/6 inhibition [76]. The combination demonstrated an ORR of 50% and Kaplan Meier estimate of PFS6 of 87.5%, among patients with NSMP cancer lacking *RB1* and *CCNE1* alterations [74]. In contrast, no responses were observed in NSMP patients who harbored *RB1* or *CCNE1* alterations, or in cancers with *TP53* mutations [77]. Although these findings require prospective validation, they suggest that genomic alterations beyond ER expression may substantially influence sensitivity to hormonal therapies in endometrial cancer.

Evidence supporting CDK4/6 inhibition in endometrial cancer also comes from the randomized ENGOT-EN3/PALEO trial, in which palbociclib plus letrozole improved median PFS compared with placebo plus letrozole in patients with ER-positive (≥10%) endometrioid endometrial cancer (8.3 vs 3.1 months). However, this trial did not stratify by molecular subtype and interestingly the PFS benefit for the combination did not translate into an OS benefit [78]. Differences in subsequent therapies, including greater use of immunotherapy in the placebo arm,

Table 1
Clinical trials reporting outcomes in NSMP tumors.

Target	Therapy	NCT #	Phase of Study	Clinical Status	Prior # Treatment	Numbers of Patients	Results
CDK4/6	abemaciclib/ letrozole	NCT04393285	II	recurrent	1–8	30	ORR: 30% (95% CI, 14.7–49.4), 27% confirmed mPFS: 9.1 months (95% CI, 3.5 to 16.5) ORR 50%
	fulvestrant/ abemaciclib	NCT03643510	II	advanced/ recurrent	1 (48.1%) 2 (51.9%)	NSMP 8 (26.6% of patients) 27	ORR: 44% (90% CI; 27.0%–62.1%), mPFS 9.0 months (90% CI; 1.8–20.4) ORR 59%
	abemaciclib/ letrozole/ metformin	NCT03675893	II	recurrent	0–8	NSMP 18 (66.7% of patients) 25	ORR: 32% (95% CI; 14.9–53.5), 28% confirmed mPFS: 19.4 months (95% CI; 5.7–NE) ORR 38.1%
XPO-1	selinexor	NCT03555422	II	advanced/recurrent	Maintenance	263	mPFS: 5.7 months (95% CI; 3.81 to 9.20) vs 3.8 months (95% CI; 3.68 to 7.39) mPFS 39.5 months (95% CI; 19.3–NR) vs 4.9 months (95% CI; 2–NR)
Angiogenesis/PD-1	lenvatinib/ pembrolizumab	NCT02501096	II	advanced/recurrent	1 (51.9%) ≥ 2 (48.1%)	NSMP 70 (26.6% of patients) 108	ORR: 39.8% (95% CI; 30.5–49.7) mPFS: 7.4 months (95% CI; 5.2 to 8.7) ORR 40%
						NSMP 20 (18.5% of patients) 35	ORR: 25.7% (95% CI; 12.5–43.3%) PFS: 7 months (95% CI; 3.9 to 7.5) ORR 28.6%
Angiogenesis/ PD-(L)1	axitinib/ avelumab	NCT02912572	II	advanced/recurrent	1–4	NSMP 7 (21.9% of patients) NSMP 216	Exploratory Subgroup PFS HR 0.77, 95% CI 0.55–1.07)
Chemotherapy/ PD-1	carboplatin/ paclitaxel/ dostarlimab	NCT03981796	III	advanced/recurrent	Firstline	NSMP 26	Exploratory Subgroup PFS HR of 0.68 (95% CI 0.27–1.72)
Chemotherapy/ PD(L)1	carboplatin/ paclitaxel/ avelumab	NCT03503786	III	advanced/recurrent	Firstline		

may have contributed to this result [78]. It is also possible that an imbalance of molecular subgroups may have influenced response in the two arms as well as subsequent responses to immunotherapy leading to the OS result. Furthermore, inclusion of cancers with *TP53*, *RB1*, or *CCNE1* mutations may have tempered responses compared to those in the aforementioned CDK4/6 inhibitor trials.

Although carboplatin/paclitaxel combined with an immune checkpoint inhibitor remains the preferred first-line treatment for recurrent disease and lenvatinib plus pembrolizumab is an established option for patients with pMMR tumors that progress after platinum-based therapy [79], hormonal therapies continue to attract interest because of their favorable toxicity profile [59,80,81]. NSMP tumors may also be less chemosensitive than p53-abnormal cancers, as suggested by the relatively smaller benefit of adding chemotherapy to radiotherapy in advanced-stage NSMP disease seen in the PORTEC-3 trial [82]. Taken together, endocrine-based combinations, particularly CDK4/6 inhibitors plus aromatase inhibitors, represent a promising strategy for NSMP endometrial cancer. Importantly, ER expression alone may be insufficient to predict response, whereas additional genomic alterations appear to influence treatment sensitivity, with *TP53*, *RB1*, and *CCNE1* alterations associated with reduced benefit and *CTNNB1* mutations associated with enhanced sensitivity to CDK4/6 inhibitor-based therapy [71,77]. Although these observations are derived from phase II studies and require prospective validation, collectively, these findings raise the possibility that ER+, *CTNNB1*-mutated NSMP tumors represent a subgroup likely to benefit from endocrine-based treatment strategies. Notably, many patients enrolled in CDK4/6 inhibitor–aromatase inhibitor trials had received prior systemic therapy, demonstrating that hormonal strategies can retain activity in pretreated populations [20,71,78].

Clinical trials of non-inferiority or randomized phase II comparisons that evaluate endocrine based therapy in earlier lines against standard therapy may be possible for molecularly selected NSMP populations. This approach is further supported by GOG 3007, in which chemotherapy-naïve patients treated with letrozole plus everolimus achieved a median PFS of 28 months compared with 4 months among patients who had previously received chemotherapy [69]. Collectively, these findings support further investigation of endocrine-based strategies as lower-toxicity alternatives for selected patients with ER-positive NSMP endometrial cancer, although their optimal integration with chemotherapy, immunotherapy, and other targeted therapies remains to be defined.

3.2. Targeted therapy for NSMP cancers

Targeted therapeutic strategies under investigation in NSMP tumors include PI3K/AKT pathway inhibition [44], ATR inhibition [83], and XPO1 blockade [84]. Clinical experience with PI3K-AKT pathway inhibitors in endometrial cancer has been comprehensively reviewed elsewhere [44,85,86]. Monotherapy targeting individual components of the PI3K–AKT–mTORC1 pathway generally achieves modest ORR (0–14%) although stable disease is frequently observed [87–91]. The limited efficacy of single-node PI3K pathway inhibition likely reflects resistance by pathway feedback reactivation and co-occurring mutations affecting multiple pathway components, both of which are common in endometrial cancer [92]. Simultaneous inhibition of multiple nodes within the pathway may therefore overcome the adaptive resistance that limits monotherapy. Supporting this approach, the combination of serabelisib (a PI3K α inhibitor), sapanisertib (an

mTORC1 inhibitor), and paclitaxel demonstrated encouraging activity, with three complete responses and one partial response among five patients with endometrioid endometrial cancer [93], the predominant histologic subtype of NSMP tumors [94]. Although derived from a small cohort, these findings provide proof-of-concept for multi-node PI3K pathway inhibition, and a phase II study is currently ongoing [95].

Data specifically evaluating PI3K/AKT pathway inhibition in NSMP tumors remain limited. 5 of 8 NSMP patients (62.5%) achieved a partial response following treatment with a PI3K inhibitor or an AKT inhibitor combined with carboplatin/paclitaxel in a small retrospective study of 12 patients with mixed molecular subtypes [96]. Next-generation sequencing was performed in 7 of 12 patients and identified *PIK3CA* and *PTEN* mutations in 4 patients each, although their distribution among NSMP responders was not reported. Given the high prevalence of PI3K pathway alterations in NSMP tumors [39] these findings support further investigation of PI3K/AKT pathway inhibition in this subtype, with prospective studies needed to determine whether *PIK3CA* or *PTEN* alterations predict treatment response.

ATR inhibition represents another promising strategy, particularly in the context of frequent *ARID1A* loss-of-function alterations in NSMP endometrial cancer [39,40,97]. *ARID1A* mutations occur in approximately 50% of NSMP tumors, with most resulting in loss of protein expression or function [98,99]. Notably, discordance between *ARID1A* mutation status and protein expression has been reported in endometrial cancers, suggesting that genomic sequencing alone may fail to identify all tumors with functional *ARID1A* deficiency [100]. Loss of *ARID1A* increases reliance on ATR-mediated cell-cycle checkpoint control; ATR inhibition induces premature mitotic entry, genomic instability, and apoptosis [101,102]. In a study of *ARID1A*-deficient tumors identified by immunohistochemistry, the ATR inhibitor ceralasertib produced a complete response in 1 of 3 patients with NSMP endometrial cancer, while the remaining 2 patients achieved stable disease. Notably, all patients with dMMR endometrial cancer experienced disease progression [103]. Although the numbers are small, these differences raise the possibility that *ARID1A*-deficient NSMP tumors are particularly responsive to ATR inhibition compared to other molecular subtypes. Combination studies incorporating ATR inhibitors are ongoing, [104,105] and may further define the role of ATR inhibition in NSMP cancers.

XPO1 is an attractive target for NSMP cancer which are p53 wildtype [106]. Selinexor, which is FDA approved in multiple myeloma [107] blocks XPO1-dependent nuclear export thereby increasing the nuclear retention of p53 and other major tumor suppressor proteins, reactivating their tumor suppressor function and leading to cell cycle arrest, senescence, and/or apoptosis [108]. In a pre-specified subgroup analysis of the ENGOT-EN5/GOG-3055/SIENDO trial, patients with NSMP tumors who received maintenance selinexor experienced substantially prolonged progression-free survival compared with placebo (median PFS 39.5 months versus 4.9 months.) [84] However, it remains unclear whether selinexor's benefit is consistent across NSMP cancers with different molecular characteristics including ER status, PI3K pathway alterations, *ARID1A* mutations, or other co-existing features. The ongoing confirmatory XPORT-EC-042 trial, which incorporates comprehensive genomic profiling, may address this question [109]. Overall, these studies support further investigation of PI3K/AKT, ATR, and XPO1 targeted therapies in NSMP endometrial cancer. The diversity of actionable alterations within NSMP tumors underscores the limitations of treating NSMP as a single biological entity and highlights the need for biomarker-directed therapeutic development. Future trials should incorporate comprehensive molecular profiling and pre-specified biomarker-stratified analyses to identify the patients most likely to benefit from targeted therapies.

3.3. Immunotherapy for NSMP cancers

The addition of immune checkpoint inhibitors to chemotherapy has demonstrated clinically meaningful activity in pMMR endometrial

cancer [14,15]. Pembrolizumab plus chemotherapy significantly improved PFS in the overall pMMR population (HR 0.57 95% CI; 0.44–0.74) with benefit observed across histologic subgroups, including grade 1/2 and endometrioid tumors (which are enriched for the NSMP molecular profile) in NRG-GY018 [110]. Molecular translational analyses from this trial are awaited and may provide further insight into outcomes within the NSMP subgroup. Although overall survival did not reach statistical significance in the pMMR cohort (HR, 0.84; 95% CI, 0.69–1.08),^[111] this was a secondary endpoint for which the study was not independently powered [15], and interpretation is further limited by data immaturity and subsequent immunotherapy-based treatment in 81.1% of patients in the pMMR control arm [111]. Notably, in the dMMR cohort, the OS HR was 0.56 (95% CI, 0.34–0.92), despite 93.2% of patients in the control arm receiving post-study immunotherapy [111].

Within pMMR tumors, several exploratory analyses have suggested that NSMP tumors may derive less benefit from chemoimmunotherapy than *TP53* mutated tumors, although these findings remain inconclusive. In RUBY, exploratory analysis found that the PFS HR for addition of dostarlimab to chemotherapy in NSMP tumors was 0.77 (95% CI, 0.55–1.07) compared with 0.55 (95% CI, 0.30–0.99) for *TP53*-mutant tumors [13]. Conversely, in MITO END-3, the PFS HR for addition of PD-L1 antibody avelumab to chemotherapy in NSMP tumors was 0.68 (95% CI, 0.27–1.72), while the PFS HR for *TP53*-mutated tumors was 2.24 (95% CI, 1.06–4.72) suggesting detrimental effect of avelumab in *TP53*-mutated tumors but not in NSMP tumors. However, this analysis included only 26 patients with NSMP tumors and only 47 patients with *TP53* mutated tumors [53]. In DUO-E, the PFS HR for chemoimmunotherapy versus chemotherapy alone among NSMP tumors was HR 0.69 (95% CI 0.44–1.04). The addition of maintenance olaparib yielded a HR 0.71, (95% CI 0.47–1.07), suggesting that, unlike *TP53* mutated tumors, there is limited benefit with addition of olaparib among NSMP tumors [112]. KEYNOTE-B21, which evaluated adjuvant pembrolizumab plus chemotherapy in patients with no measurable disease following primary surgery, did not demonstrate a disease-free survival benefit in the overall pMMR population (HR, 1.20; 95% CI, 0.91–1.57)) [52] Molecular subgroup analyses from the pMMR cohort of KEYNOTE-B21 have not yet been reported, and the specific impact of immunotherapy in NSMP tumors therefore remains uncertain. Importantly, despite the absence of statistically significant findings within NSMP subgroups, most studies reported hazard ratios favoring the immunotherapy-containing arms, suggesting that clinically meaningful benefit cannot be excluded and may simply have been undetectable because of limited statistical power.

As discussed previously, the tumor immune microenvironment is heterogeneous among NSMP endometrial cancers [48] In particular, NSMP cancers characterized by higher CD8+ T-cell infiltration may be more likely to benefit from immunotherapy-based approaches, whereas immune-excluded cancers may represent a less responsive subgroup [113] The potential role of immunotherapy in NSMP endometrial cancer is further supported by clinical trials evaluating combinations of immune checkpoint inhibitors with targeted therapies, including lenvatinib plus pembrolizumab [114,115] and axitinib plus avelumab [116]. NSMP cancers demonstrated response rates of 40% [117] and 28.6% [116] to these tyrosine kinase inhibitor (TKI)-immunotherapy combinations, respectively. Prospective incorporation of immune biomarkers into future clinical trials may help identify subsets of NSMP tumors most likely to benefit from the addition of immunotherapy to chemotherapy or from immunotherapy-targeted therapy combinations.

Notably, in the TKI-immunotherapy studies discussed above, patients had received at least one prior line of therapy. By contrast, frontline treatment with lenvatinib plus pembrolizumab versus chemotherapy in the ENGOT-en9/LEAP-001 trial did not demonstrate a statistically significant improvement in clinical outcomes for the overall pMMR population. Exploratory analyses, however, suggested improved

outcomes with lenvatinib plus pembrolizumab in patients who had previously received neoadjuvant or adjuvant chemotherapy [118]. Furthermore, a substantial proportion of pMMR patients assigned to chemotherapy alone in NRG-GY018 subsequently received lenvatinib plus pembrolizumab, which may have attenuated OS differences between the treatment arms [111]. Collectively, these observations raise the possibility that, in an unselected pMMR or NSMP population, part of the benefit associated with immunotherapy-based treatment may be achievable through a sequential treatment strategy employing TKI-immunotherapy in the recurrent setting rather than through universal frontline administration. Importantly, the molecular subgroup analyses discussed above should be interpreted with considerable caution. Whether pre-specified or post hoc, subgroup analyses are inherently susceptible to both false-positive and false-negative findings [119]. Furthermore, when multiple subgroups are tested without adjustment for multiplicity, the probability of a false-positive finding increases substantially [119]. In trials demonstrating an overall treatment benefit, an apparent lack of benefit within an individual subgroup should generally not be considered reliable unless supported by a statistically significant treatment-by-subgroup interaction [120]. Therefore, the molecular subgroup findings discussed here should be regarded as hypothesis-generating rather than practice-changing, and these findings do not support withholding immunotherapy-based treatment strategies from patients with NSMP endometrial cancer who otherwise meet established treatment criteria.

3.4. Antibody drug conjugates for NSMP cancers

The therapeutic potential of antibody–drug conjugates (ADCs) in gynecologic malignancies, including endometrial cancer has been comprehensively reviewed elsewhere [121–123]. Several ADC targets are relevant to NSMP cancers based on their expression, including B7-H4, FGFR2, TROP2, folate receptor alpha (FR α), and HER2. B7-H4 expression was identified in 78.9% of NSMP cancers in a study by Zong et al. [124]. Similarly, Sengal et al. reported FGFR2a/c expression in 45% of NSMP tumors [125]. TROP2 expression appears consistent across all molecular subtypes [126]. FR α expression, defined as moderate or strong staining in $\geq 25\%$ of tumor cells, was observed in 14.3% and 50% of NSMP tumors in two independent cohorts analyzed by Xiao et al. [127]. HER2 overexpression (IHC 2+/3+) has been reported in 2.5–18.6% of NSMP tumors [128,129]. Several ADCs targeting these antigens are currently approved or undergoing clinical development for endometrial cancer [123,130,131]. However, although the expression of some ADC targets varies across molecular subtypes [128], no endometrial cancer ADC trial has yet reported efficacy outcomes stratified by TCGA molecular subtype. Consequently, the extent to which NSMP status influences ADC responsiveness remains unknown.

Notably, emerging evidence suggests that RNA expression of ADC targets may have prognostic relevance within NSMP tumors. In ER– NSMP cancers, top-quartile expression of B7-H4, ERBB3, ERBB2, and Nectin4 was associated with improved OS (HR 0.62–0.74, $p < 0.05$), while top-quartile B7-H3 and Nectin1 expression was associated with worse OS (HR 1.40, $p = 0.01$). Similarly, in ER+ NSMP cancers, top-quartile TROP2 and Tissue Factor expression was associated with improved OS (HR 0.73–0.82, $p < 0.05$), whereas top-quartile ERBB2 and CDH6 expression was associated with worse OS (HR 1.24–1.29, $p < 0.05$) [132].

At present, patient selection for ADC therapy is based primarily on target expression, typically assessed by immunohistochemistry, rather than molecular subtype, reflecting the antigen-dependent mechanism of ADC activity [133,134]. Nevertheless, the relationship between target expression and clinical efficacy may not be straightforward, as demonstrated by the limited association between TROP2 expression and response to Sacituzumab-govitecan [135]. Consequently, although molecular subtype may help identify ADC targets that are more frequently expressed in NSMP tumors, it remains unclear whether target

expression alone is sufficient to predict benefit. Future ADC trials incorporating molecular subtype analyses may clarify whether NSMP-specific biology contributes to treatment response beyond antigen expression.

3.5. Future directions

The 2025 ESGO-ESTRO-ESP guidelines have incorporated estrogen receptor (ER) assessment into the NSMP category, expanding the molecular classification to five subtypes: POLEmut, MMRd, p53abn, NSMP ER-positive, and NSMP ER-negative [136]. This evolution reflects a broader shift toward prospective molecular stratification in clinical trial design, moving beyond retrospective and exploratory subgroup analyses. The PORTEC-4a trial and the ongoing RAINBO platform trial exemplify this molecularly driven approach [19,137].

RAINBO is a platform trial comprising four parallel studies tailored to molecular subgroups. Within this platform, the NSMP-ORANGE arm evaluates whether adjuvant progestin therapy can replace chemotherapy in ER-positive NSMP cancers [137]. If successful, this study would provide the first randomized evidence supporting hormonal therapy in a prospectively defined molecular subgroup of endometrial cancer. Trials such as NSMP-ORANGE, along with emerging data on CDK4/6 inhibitor–hormonal combinations showing preferential activity in NSMP tumors [20,71], may help establish a biomarker-driven framework for the incorporation of endocrine strategies into routine clinical practice.

Despite these advances, NSMP cancers constitute a molecularly heterogeneous group, and further subclassification beyond ER status will likely be required to optimize treatment selection. Patients with NSMP tumors remain eligible for frontline chemoimmunotherapy, as current evidence does not support withholding immunotherapy based on exploratory subgroup analyses suggesting attenuated benefit. Concurrently, a growing number of novel therapeutic approaches including new antibody–drug conjugates (e.g., targeting B7-H4 [138] or TROP2 [139]), hormonal therapies [71], and targeted therapies [95] are being evaluated in endometrial cancer and may have particular relevance for biologically defined subsets of NSMP tumors.

The integration of translational biomarkers into prospective clinical trial design will be essential to advance the field. Candidate biomarkers emerging from translational studies – including *CTNNB1* mutations [41], PI3K-AKT pathway alterations [39], and *MDM4* copy number changes [42] – should ideally be incorporated prospectively as stratification factors to move beyond their current role as retrospective correlates. Future clinical trials should move beyond treating NSMP as a single entity and instead prospectively enrich for biologically defined subgroups based on ER status, genomic alterations, ADC target expression, and immune microenvironment features such as CD8+ T-cell infiltration. Such an approach has the potential to improve trial efficiency, enhance predictive biomarker discovery, and accelerate the development of more effective and individualized therapies for patients with NSMP endometrial cancer.

4. Conclusions

The NSMP subgroup is the largest molecular subtype of endometrial cancer, and it is characterized by substantial prognostic heterogeneity. Integration of genomic alterations, hormone receptor status, and features of the immune microenvironment, has the potential to improve risk stratification and refine prognostic assessment within this diverse group. From a therapeutic perspective, endocrine-based treatment may be particularly effective in NSMP cancers due to its frequent expression of estrogen and progesterone receptors. In addition, comprehensive molecular profiling may identify opportunities for targeted treatment approaches, including therapies directed against the PI3K-AKT pathway, ATR, and XPO1. Future clinical studies of NSMP cancers should ideally incorporate genomic, hormonal, and immunologic

biomarkers to enable more precise patient selection and optimize therapeutic strategies. Furthermore, clinical trials in endometrial cancer, should routinely report outcomes according to molecular subtype, including NSMP disease, to better define the activity of emerging therapies and inform future drug development. Collectively, these approaches may facilitate a more personalized and effective management paradigm for patients with NSMP endometrial cancer.

Disclosures

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CRedit authorship contribution statement

Tarik Silk: Writing – review & editing, Writing – original draft. **Ursula A. Matulonis:** Writing – review & editing, Writing – original draft, Conceptualization. **Panagiotis A. Konstantinopoulos:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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