



Review

A Narrative Approach to Mismatch Repair-Deficient Endometrial Cancer

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Abstract

Endometrial cancer (EC) is the sixth most common cancer in women. Its overall incidence has increased by 132% over the past 30 years, reflecting an increase in the prevalence of risk factors. The mortality rate decreased by 15% in the last 30 years, despite the high number of endometrial cancer-related deaths occurring world-wide. An inverse relationship has been observed between the incidence of EC, mortality and socio-economic status: more patients living in low-income countries die from EC because they do not have access to timely and effective treatment. About 80% of EC cases are diagnosed in an early stage and have a good prognosis. However, about 20% of cases present in advanced stages and are characterized by a poor prognosis. The molecular classification proposed by The Cancer Genome Atlas (TCGA) and its surrogate for clinical use allowed the adoption of personalized treatments. The assessment of the status of the MMR has revolutionized the treatment of advanced ECs, leading to significant results both in terms of PFS and OS. In this review we will focus on MMR deficiency (dMMR)/microsatellite instability-hypermutated (MSI-H) tumors, which globally account for 20–30% of ECs. The dMMR group encompasses multiple etiologies, including sporadic defects in MMR genes, germline mutations, and hypermethylation of the MLH1 promoter. Currently, the combination of immunotherapy (I-O) with standard chemotherapy has become the new standard first-line treatment for dMMR advanced or recurrent ECs. Although the main clinical trials involving patients with MMRd/MSI-H ECs treated with I-O and chemotherapy have demonstrated efficacy and long-term control of the disease, a significant number of patients do not respond to treatment (intrinsic or primary resistance) and others develop progression during treatment (acquired or secondary resistance). In this narrative approach the biological and molecular bases of these tumors have been integrated with recent advances involving diagnostic techniques, therapeutic opportunities and the genomic and phenotypical alterations underpinning the mechanisms of resistance. Special attention was given to the need for robust, clinically affordable biomarkers to promptly identify responders and non-responders to the current treatment regimens.

Keywords: endometrial cancer; dMMR; MSI-high; immunotherapy



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1. Introduction

Globally, endometrial cancer (EC) is the sixth most common cancer in women, with 417,000 new diagnoses made in 2020 [1]. In a 2021 study, Gu et al. reported that the overall incidence has increased by 132% over the past 30 years, and that this reflected an increase in the prevalence of risk factors [2]. The risk of EC increases with age and with

Body Mass Index (BMI); among the most common solid tumors, EC has the strongest link with obesity [3]. Hyperestrogenism, hypertension and type 2 diabetes are other important risk factors [4]. Lynch syndrome-associated EC is the most common extraintestinal cancer of this medical condition. The probability of developing EC as the first malignancy is approximately 40–60% in women with Lynch syndrome (LS) [5].

Paradoxically the mortality rates decreased by 15% in the last 30 years [2], despite the high number of endometrial cancer-related deaths. Therefore, an inverse relationship has been observed between the incidence of EC, mortality and socio-economic status: more patients living in low-income countries die from EC because they do not have access to timely and effective treatment [4].

However, several advances have produced benefits in the quality of care in many patients. Among these, the adoption of the sentinel lymph node mapping technique in low-volume disease [6], the molecular classification proposed by The Cancer Genome Atlas (TCGA) [7], its surrogate for clinical use [8] and finally the revisiting of the staging system [9] have improved prognostic accuracy and allowed the adoption of personalized treatments.

The molecular classification divides endometrial cancer into four groups according to the molecular profile: POLE-mutated, mismatch repair-deficient (dMMR), No Specific Molecular Profile (NSMP), or p53-abnormal (p53abn) [8].

Each group is included in a specific risk stratification model and this allows a better prognostic prediction [8]. In fact, each group has a biological profile that cannot be superimposed on the classic clinical–pathological parameters such as histotype and grade. The great advantage of molecular classification is its reproducibility between different laboratories and between biopsy and surgical samples [8,10].

Molecular classification is based on simple assays available in most laboratories: mismatch repair proteins and p53 protein are evaluated with immunohistochemical staining while POLE gene status is evaluated by sequencing.

Since about 5% of cases (so-called multiple classifiers) are positive for more than one assay [11], their interpretation must follow an algorithm proposed by the WHO [12].

It is preferable to perform the tests on endometrial biopsies as the tissue is generally better preserved and can be immediately fixed in formalin. However, the test may be repeated when the biopsy sample is insufficient or the results are ambiguous, or the hysterectomy sample reveals a tumor component that was not previously detected on the biopsy [13].

The clinical impact of molecular classification is significant. It allows a considerable number of cases to be reallocated into different risk classes. More than a third of patients with POLE mutation could have been overtreated and, conversely, almost 40% of patients with abnormal p53 would have been undertreated and would not have benefited from any adjuvant therapy [14]. It is important to note that POLE-mutated tumors share biological characteristics with dMMR ones. The mutations localized in the proofreading domain of the gene impact DNA replication, leading to proofreading defects and resulting in an ultramutated tumor with over 100 mutations per Mb and a favorable prognosis [15].

The number of tumor neoantigens produced by POLE-mutated ECs is 15-fold higher than that of dMMR/MSI-high and more than 100-fold higher than that of pMMR/MSS [16].

The high TMB and the immunogenic profile are pivotal parameters for I-O benefit [17].

This ultra-high mutation rate is usually associated with MSS. However, there are rare examples of POLE-mutated ECs with concomitant dMMR, a more aggressive molecular subtype with a high TMB and frequent relapses [18].

About 80% of EC cases are diagnosed in an early stage and have a good prognosis. More than 85% of these patients experience 5 years of OS.

However, about 20% of cases present in advanced stages and are characterized by a poor prognosis, with a 5-year OS rate of less than 25% for patients treated with carboplatin and paclitaxel [19,20].

The assessment of the status of the MMR has revolutionized the treatment of advanced ECs, leading to significant results both in terms of PFS and OS.

In this review we will focus on MMR deficiency (dMMR)/microsatellite instability-hypermutated (MSI-H) tumors, which globally account for 20–30% of ECs. The adoption of immunotherapy (I-O) combined with standard chemotherapy significantly improved progression-free survival and overall survival compared to chemotherapy alone, with the greatest benefit observed in this dMMR subgroup [21,22].

2. The MMR System

The DNA MMR system recognizes and corrects insertions, deletions and base pair mismatches that occur during DNA replication.

In humans, there are at least seven proteins involved in MMR, four of which have the greatest clinical relevance in cancer biology [17]. The system involves two key heterodimers: MutL α , composed of MutL homolog 1 (MLH1) and post-meiotic segregation increased 2 (PMS2), and MutS α , consisting of MutS homolog 2 (MSH2) and MutS homolog 6 (MSH6). The MLH1/PMS2 pairing recognizes mismatched nucleotide base pairs and initiates repair, while the MSH2/MSH6 pairing acts as an endonuclease [18] cutting phosphodiester bonds within a DNA or RNA strand and creating breaks internally.

MMR deficiency can be caused by germline or somatic mutations, or by hypermethylation of the promoter of MMR genes; these events induce the destabilization of the heterodimers of the MMR system and cause the loss of nuclear protein expression [23,24].

Lynch syndrome (LS) was first described by the American physician Henry T Lynch in 1966. It is a familial tumor condition that is almost always associated with the presence of a mono-allelic germline mutation in an MMR gene. Affected patients are at increased risk of developing cancer, mainly colorectal and endometrial.

The complete inactivation of the tumor suppressor genes of MMR machinery can be reached by loss of heterozygosity (LOH) (i.e., loss of function of both the alleles). dMMR can arise when one of the genes has one inherited or somatic pathogenic variant (first hit), and a second hit on the wild-type allele. In Lynch syndrome-associated tumors, LOH affecting the wild-type allele of an MMR gene is a mechanism that can convert a heterozygous germline mutation into full functional loss and results in an MSI-high/dMMR phenotype [25].

A subset of women, estimated at 2–5%, develop LS-associated EC [20]. As we reported in the Introduction, the probability of developing EC as the first malignancy is approximately 40–60% in women with LS [5].

When a patient with LS has been diagnosed, her relatives can be offered genetic counseling, proper testing and intensified surveillance.

However, the vast majority of cases of EC with dMMR are due to a somatic inactivation of MLH1 sustained by the hypermethylation of its promoter [26,27].

Mutations in the EPCAM gene are a rare cause of Lynch syndrome; in particular EPCAM deletions can cause the silencing of the adjacent MSH2 gene [28].

Another rare cause of dMMR can be a double somatic MMR gene pathogenic variant in the tumor. For example, the absence of MLH1 and PMS2 without methylation of MLH1 could be due to double somatic mismatch repair mutations [29].

2.1. The Identification of Tumors with dMMR: Pro and Cons

Pathologists are more familiar with immunohistochemistry to evaluate the expression of MMR proteins in tumor cell nuclei. In view of the heterodimerism of the proteins,

the model of their loss of expression provides useful clues to the most likely genetic or epigenetic defects which cause dMMR (Table 1).

Table 1. Immunohistochemistry: patterns of MMR protein loss.

Protein Loss	Potential Clinical Implication
MLH1 and PMS2	MLH1 promoter methylation
	MLH1 mutation
	Double somatic mutation
MSH2 and MSH6	MSH2 mutation
	EPCAM mutation
MSH6	MSH6 mutation
	MSH2 mutation (MSH2 forms heterodimers with proteins other than MSH6)
PMS2	PMS2 mutation
	MLH1 mutation
MLH1	MLH1 promoter methylation
	MLH1 mutation

It should be remembered that in some cases heterogeneity of protein expression can be observed. It manifests itself as a focal loss of coloration of the nuclei in a diffusely positive context. After ruling out any technical problems, a clonal somatic gene mutation or localized methylation can be hypothesized. Although this pattern was not thought to imply a germline mutation [30], a recent study has shown that a heterogeneous staining for even one protein can identify a dMMR phenotype and that heterogeneous immunostaining is not equivalent to a positive and widespread immunostaining [31].

2.2. Microsatellite Instability—Hypermutated (MSI-H)

Microsatellites are short tandem repeats occurring through the genome which can be altered during DNA replication by misalignment, and corrected by MMR. Therefore, in cases of dMMR, microsatellite instability occurs.

IHC and assays for the study of MSI are considered interchangeable in the clinical routine. However, in EC the evaluation of this parameter is more complex than in other cancers. This is because EC has in 30% of cases a “mild” instability, characterized by minimal microsatellite shift (defined as a one- to three-nucleotide repeat shift at an involved locus) observed at least at one locus [32]. The combined assessment of IHC and MSI could overcome this limitation. In addition, a mutation that alters the function of a protein may be present at the immunohistochemical level. A missense mutation causing a single amino acid change in the protein can alter its function without preventing it from being detected by IHC [33].

On 23 May 2017, the FDA approved Pembrolizumab, an anti PD-1 inhibitor, to treat adult and pediatric patients with unresectable or metastatic solid tumors identified as having a biomarker known as MSI-H or dMMR [34]. For the first time a cancer treatment based on a common biomarker, rather than the location in the body where the tumor originated, was approved.

Since then, a plethora of different assays to evaluate the MSI status have become commercially available. In particular PCR-based panels such as the pentaplex and hexaplex panels became widely applied. They surpassed in precision the classic Bethesda panel [35].

Recently a comparison study among four different platforms to evaluate critical aspects of microsatellite instability testing in EC suggested that the test should rely on

fluorescent capillary electrophoresis because its resolution was able to identify a non-negligible proportion of critical cases that could be misdiagnosed with other strategies [36].

Next-Generation Sequencing (NGS) allows one to obtain a complete evaluation of genetic alterations and MSI status in a single assay and with high concordance with IHC and PCR-based techniques [37,38].

However, if the concordance among different tests is high, a clinically meaningful percentage of cases shows discordant results with obvious implications on the therapeutic options. The molecular mechanisms involved in discordance are mainly due to MSH6 mutations with functional compensation by MSH3, and MLH1 loss predominantly driven by promoter methylation [39]. MSI status can be impacted by factors that fall outside the protein expression, mainly by POLE alterations and/or by the detection thresholds that may limit the identification of faint MMR alterations.

The comprehensive profile offered by NGS represents an invaluable tool in result interpretation and consequently in diagnostic accuracy. The most advanced NGS assays eliminate the limit of PCR-based techniques: the low number of evaluated loci. NGS-based MSI can simultaneously detect hundreds to thousands of microsatellite loci, limiting some drawbacks such as ethnicity-associated variations or variations related to tumor type [40]. But these high-performing assays need bioinformatic algorithms to detect the percentage of instable loci and specialized personnel. As reported by Swaerts et al. [41], MSI evaluation can be performed in different ways: (A) by comparing indel distributions of microsatellites in paired tumor–normal samples, on exome data with computational tools (MSIsensor, MANTIS, MSIseq) or targeted gene panels (USCI-msi), (B) by comparing indel distributions in a tumor sample versus a fixed reference set on targeted gene panels (mSINGS, MSIFinder), or (C) by analyzing the number of single-nucleotide variants and indels throughout the genome to detect the hypermutated status as consequence of dMRR (MSIseq).

Recently, circulating tumor DNA (ctDNA)-based NGS testing showed that the MSI status could be evaluated in different cancer types [42].

The validation of MSI detection using a Comprehensive Plasma-Based Genotyping Panel (Guardant 360) on 28,459 advanced cancer samples (ECs included) demonstrated a robust analytic performance for MSI detection on a cfDNA panel previously validated for detection of the other four variant types (SNV, indels, copy number variations, fusions) [42].

Artificial Intelligence (AI) technology has been used to forecast MSI/dMMR status on hematoxylin–eosin-stained slides. AI algorithms performed very well in colorectal cancer, but not so well for EC [43].

In colorectal cancers, BRAF p.V600E mutation helps to exclude LS in patients with MSI-high tumors, allowing those who are BRAF wild-type to proceed with further LS screening. In EC the rare BRAF mutations (mainly p.V600E) are not considered efficient biomarkers to distinguish LS from sporadic MSI; currently these alterations are not validated in clinical use for predicting MMR-negative mutation status [44,45].

2.3. MMRd/MSI-H: A Rationale for Immunotherapy

MSI-H/dMMR status is today a histology-independent predictive biomarker of the clinical benefit of immune checkpoint inhibitors (ICIs). In fact, the introduction of ICIs in the treatment of advanced MSI-H/dMMR solid tumors has revolutionized the therapy of patients with these tumors [34]. In the near future, the foreseeable efficacy of ICIs in patients with early-stage MSI-H/dMMR tumors will also change the standard of care.

MMR deficiency is caused by loss-of-function mutations or epigenetic silencing of genes encoding key proteins in the MMR system. LS is generated by germline mutations in these genes or by deletions in the terminus 3' of EPCAM with consequent silencing of the

MSH2 gene, located only 15 kb downstream [28]. However, most ECs with MSI-H/dMMR are sporadic and sustained by somatic alterations in each allele in an MMR gene [46].

MSI-H ECs are characterized by a variation in DNA length in microsatellite loci, i.e., segments that include from one to ten mono-/di-/tri- or tetra-nucleotides repeated even several times [47]. In healthy cells, these abnormal nucleotide segments are recognized and eliminated by the MMR system, but in MSI-H tumors, they remain unrepaired. Some of them are located in coding regions, where their destabilization can cause frameshift mutations that shift an open read frame, thus providing a significant source of tumor-specific neoantigens [48].

These neoantigens confer a high mutational load in microsatellite regions which show a typical pattern of alterations represented by insertion or deletion of nucleotides. When the indels pinpoint codifying genes, frameshift peptides are produced and bounded to a class 1 major histocompatibility complex molecule recognized by T-cells [49].

The production of aberrant peptides is recognized by the immune system as non-self and is able to induce an immune response. However, cancer cells can evade immune surveillance through increased expression of immune checkpoint proteins such as PD-1 and PD-L1. In fact, the interaction between PD-1 and its ligands, in particular PD-L1, on both tumor cells and T cells allows the tumor to evade immunosurveillance mechanisms. It is precisely the possibility of overcoming immune evasion through the use of checkpoint inhibitors that represents the rationale for the use of I-O [50].

Current evidence agrees that ECs with dMMR/MSI-H demonstrate marked sensitivity to chemotherapy-associated or non-associated ICIs [51–53].

However, there are no studies showing that specific EC histotypes have a different impact on response to therapy. In particular, it has not been demonstrated that endometrioid carcinomas respond differently from serous, clear cell, undifferentiated/dedifferentiated carcinomas. Excluding mutated POLEs, any differences are likely to be of little significance compared to the dominant effect of dMMR/MSI-H [51–54]. Moreover, non-endometrioid dMMR MSI-H subtypes are rare; therefore, the available cohorts are underpowered for histotype-stratified efficacy analyses.

2.4. Immunotherapy as a Key to Success in Advanced/Recurrent EC with MMRd/MSI-H

The first steps of ICIs in the treatment of ECs have not been encouraging. In 2017, the KEYNOTE-28 study evaluated the use of pembrolizumab monotherapy in a series of different solid tumors that also included a cohort of advanced ECs, characterized by high PD-L1 expression, progressing after standard chemotherapy.

The overall response rate (ORR) was 13% and the median progression-free survival (mPFS) was only 1.8 months [55].

The reason for the failure was clear: the molecular classification of EC had not yet been used. In fact, in the subsequent KEYNOTE-158 trial, a cohort of recurrent EC with dMMR/MSI-H showed an ORR of 48% with an mPFS of 13.1 months and an OS not reached [52]. The trial showed the critical importance of biomarker-guided therapy. The use of biomarkers increases the quality of diagnosis, indicates a therapeutic strategy and provides predictive elements of response to ICIs. The histological and molecular interpretation of biomarkers and their reporting must be matched by the understanding of biological mechanisms at the clinical level to optimize therapeutic options. Pathology Departments must in turn use standardized and controlled protocols to achieve robustness and reproducibility of the assays used to identify dMMR tumors.

Different phase 3 placebo-controlled randomized trials have confirmed that adding an ICI to first-line chemotherapy improves outcomes for patients with dMMR EC (Table 2).

Table 2. Main characteristics of phase 3 placebo-controlled and randomized clinical trials in dMMR cohort.

Name of the Study, Year (Reference)	Experimental Arm	Control Arm	Characteristics of the Pts	mPFS (Months) Experimental Arm vs. Control Arm HR (CI 95%, <i>p</i>)	mOS (Months) Experimental Arm vs. Control Arm HR (CI 95%, <i>p</i> Value)
Ruby, 2023 [56] 2024 [57]	Dostarlimab + carboplatinum and paclitaxel	Placebo + carboplatinum and paclitaxel	Pts with primary advanced or recurrent EC dMMR/MSI-HIGH: 23.9% pMMR/MSS: 76.1%	NR vs. 7.7 HR = 0.28 (CI: 0.16–0.5, <i>p</i> < 0.001)	NR vs. NR
NRG-GY018 2023 [53] 2025 [58]	Pembrolizumab + carboplatinum and paclitaxel	Placebo + carboplatinum and paclitaxel	Pts with primary advanced or recurrent EC dMMR/MSI-HIGH: 27.6% pMMR/MSS: 72.4%	NR vs. 7.6 HR = 0.3 (CI: 0.19–0.48; <i>p</i> < 0.001)	NR vs. NR HR = 0.55 (CI: 0.25–1.19, <i>p</i> : not significant)
AfTEnd 2024 [59]	Atezolizumab + carboplatinum and paclitaxel	Placebo + carboplatinum and paclitaxel	Pts with primary advanced or recurrent EC dMMR/MSI-HIGH: 26% pMMR/MSS: 74%	NR vs. 6.9 HR = 0.36 (CI: 0.23–0.57; <i>p</i> = 0.0005)	NR vs. 25.7 HR = 0.41 (CI: 0.22–0.76; <i>p</i> = 0.0026)
DUO-E 2023 [60]	Durvalumab + carboplatinum and paclitaxel	Placebo + carboplatinum and paclitaxel	Pts with primary advanced or recurrent EC dMMR/MSI-HIGH: 20% pMMR/MSS: 80%	NR vs. 9.9 HR = 0.42 (CI: 0.22 to 0.88; <i>p</i> significant)	Not assessed

Legend: mPFS: median progression-free survival; mOS: median overall survival; HR: Hazard Ratio; NR: not reached. CI: confidence interval; *p* = *p* value. *p* < 0.05 corresponds to statistical significance.

These studies have conclusively supported the use of a combination of anti-PD1 and anti-PD-L1 in first-line chemotherapy [53,56–60].

2.5. Are All dMMR Endometrial Cancers Created Equal?

This is the provocative title of a study proposed by Capasso et al. [61]. The authors evaluated the potential differences in prognostic terms between two variants of dMMR EC: the one associated with LS and the other sustained by MLH1 hypermethylation. They demonstrated that MLH1-hypermethylated dMMR ECs were associated with unfavorable clinicopathologic features (larger tumor size, deeper myometrial invasion, lymphovascular invasion, lower frequency of early-stage and low-risk disease). However, no significant differences in prognosis were detected among the dMMR subtypes. In a previous study [62], patients with LS-associated ECs showed a trend towards better recurrence-free survival and higher risk for second cancers compared with patients with MLH1 hypermethylation. Mannin-Geist et al. reported that patients with MLH1 promoter hypermethylation were older and more obese and had more advanced disease at diagnosis. These ECs exhibited lower Tumor Mutational Burden (TMB) and Tumor-Infiltrating Lymphocyte (TIL) scores compared with endometrial cancers harboring germline or somatic MMR mutations [63]. Differences in the immunologic profiles were also described: T-cell counts (CD3+, CD8+, FoxP3+) were significantly higher in LS-associated tumors [64]. These findings indicate that MLH1-hypermethylated tumors may represent a biologically distinct subgroup of dMMR endometrial cancers with specific epidemiologic and immunophenotypic characteristics.

Taken together, these observations suggest that ECs with MLH1 promoter hypermethylation may have a relatively lower level of immunogenicity compared with mutation-driven dMMR tumors. However, available studies have not consistently demonstrated significant prognostic differences between hypermethylated and mutation-associated dMMR endometrial cancers [65].

A phase 2 trial comparing the outcomes of patients with mutated and hypermethylated EC receiving pembrolizumab showed that hypermethylated tumors had worse PFS and

OS [54], but two phase III trials that evaluated chemotherapy with or without anti-PD-1 antibodies in patients with advanced/metastatic EC have not demonstrated significant differences in PFS according to the process that generates dMMR [66,67]. However, a lower response to ICIs in hypermethylated MLH1 tumors compared to mutated MLH1 has been reported [63,64], but a clinical significance was not achieved in view of the relatively small proportion of MLH1-mutated tumors within the general dMMR population. Despite these biological differences, current evidence from randomized trials does not support the use of the specific mechanism of MMR loss (methylation versus mutation) to guide treatment selection in the first-line setting. The clinically relevant biomarker for chemo-immunotherapy remains the presence of dMMR/MSI-high status itself. However, it is desirable to prospectively evaluate these different biological mechanisms in clinical trials, through which it will be possible to define when ICI therapy alone is usable or when combination therapy is more appropriate. Overall, while biological heterogeneity exists within the dMMR subgroup, this variability has not yet translated into clinically actionable differences in therapeutic management.

In conclusion, despite differences in patient selection in major trials, such as statistical design, histological subtypes considered, and duration of immunotherapy, the data are consistent in finding that dMMR is a strong biomarker predictive of response for the combination of chemotherapy with ICIs, regardless of the mechanism of MMR loss, mutation or epigenetic alteration [65].

It should be considered that potential differences in terms of benefit may be due to the different ICIs used (anti-PD-1 vs. anti-PD-L1 antibodies). Mechanistic differences between PD-1 and PD-L1 inhibitors could affect their efficacy. PD-1 inhibitors such as dostarlimab and pembrolizumab work by inhibiting PD-1 binding to both PD-L1 and PD-L2, while PD-L1 inhibitors such as atezolizumab and durvalumab block PD-L1 only, sparing PD-L2-mediated signaling and attenuating immune activation [68]. Moreover, the frequent lack of individual patient data precluded specific analyses on other parameters such as the representation of racial and ethnic minorities, the histologic subtypes and molecular aberrations.

2.6. The Problem of Resistance to ICIs and Chemotherapy in MMRd-ECs

Although the main clinical trials involving patients with MMRd/MSI-H ECs treated with ICI and chemotherapy have demonstrated efficacy and long-term control of the disease, some patients do not respond to treatment (intrinsic or primary resistance) and others develop progression during treatment (acquired or secondary resistance). In these studies the ORR in the dMMR subgroup was approximately 60–70%, indicating that a relevant proportion of patients (about 30–40%) do not achieve a durable response. The percentage of non-responders in patients with dMMR ECs enrolled in RUBY, NRG-GY018, DUO-E, and AtTend trials ranged from 22.4 to 35% [57–59]. Currently, the updated analyses of these trials do not report the percentage of patients who develop secondary resistance [57–59]. All available data are limited to aggregate ORR and PFS/OS in dMMR and pMMR subgroups and do not allow a clear distinction between primary and acquired resistance. To obtain these data a dedicated IPD-level (Individual Participant Data) meta-analysis of the pivotal randomized clinical trials would be required.

The percentage of non-responders to immunotherapy alone in dMMR advanced endometrial cancer was reported in the phase-II KEYNOTE-158 study, which evaluated pembrolizumab monotherapy. In this subgroup the ORR was 48% and more than 50% of the patients were non-responders [52,69,70]. However, it should be considered that most of the currently described molecular mechanisms of resistance to ICIs derive from studies of immunotherapy monotherapy in later-line settings, and their applicability to the first-line chemo-immunotherapy combination remains under investigation.

To define the determinants of resistance, a translational approach encompassing different biomarkers represents an ideal tool. The study of the tumor itself and its microenvironment (TME) could offer a privileged point of view. In conclusion the identification of predictive biomarkers able to recognize the subset of resistant tumors represents an unmet clinical need and is currently addressed by active research (Table 3).

Table 3. Mechanisms of resistance and associated biomarkers.

Resistance Mechanisms	Biomarkers	References
Impairment of Ag presentation	B2M mutations Jak1 mutations	[70–81]
TMB	>10 mutations/megabase (TMB high)	[51,82,83]
Tumor and TME features	<PD-L1 (low) <CD8+ cells (low) <Tertiary lymphoid structures (low) <Dendritic cells (low) >Tim-3, Lag-3, IDO1 (high) <TAM (low)	[81–91]
Gene signatures	CD8, stromal CD8, PD-L1, and HLA-I H-score; Simultaneous co-expression: CD8+PD-1+TOX+; >Expression of fibroblast and endothelial cell genes	[69,91–96]

Legend: TMB: Tumor Mutational Burden; TME: tumor microenvironment.

2.7. Potential Biomarkers of Resistance

(a) Impairment of antigen presentation.

The stability and expression of the HLA system on the cell surface are closely related to their interaction with B2M (Beta 2 Microglobulin).

B2M is the light chain of major histocompatibility complex (MHC) class I, and plays a role in tumor antigen presentation to cytotoxic T lymphocytes. The impairment of antigen presentation is one of the most important mechanisms of resistance to immunotherapy related to B2M [71,72]. Alterations of the B2M gene degrade assembly and transport of MHC-I molecules to the cell surface. Consequently, CD8+ T cells do not recognize the epitopes present on the surface of tumor cells, evading immunosurveillance and their elimination [73]. Gulhan et al. analyzed somatic sequencing from patients treated with avelumab in monotherapy (dMMR cohort) and identified B2M mutations and a higher indel burden in non-responder ECs in a retrospective cohort of patients treated with ICIs only [70]. However, benefit has been demonstrated in patients with colorectal cancers with dMMR and B2M alterations treated with ICIs [74]. It is assumed that in the presence of B2M alterations, not only immunoeffector cells such as CD8+ can play a role. ICIs can increase the number of $\gamma\delta$ T cells and stimulate the expression of PD-1 and cytotoxic molecules. In murine models, B2M inactivation has not decreased the efficacy of ICIs in dMMR, tumors where an important role for CD4+ T cells in tumor rejection was identified [75,76]. In EC, B2M mutations are a biologically important mechanism of resistance to checkpoint inhibitors, but B2M loss explains not all the non-responders and future studies need to clarify the role of $\gamma\delta$ T cells in EC.

Interferon γ (IFN γ) stimulates immune responses against tumor progression, activating cytotoxic T lymphocytes and natural killer cells and inducing the differentiation of macrophages to an M1 phenotype. However, IFN γ can paradoxically induce the expression of PD-L1, IDO1 and epithelial–mesenchymal transition (EMT) to immune resistance [77].

IFN γ activates the JAK-STAT pathway by means the phosphorylation of the transcription factor STAT1. JAK1-mutant gynecological cancer cell lines defective in STAT1 phosphorylation can inhibit the antigen-processing machinery components such as LMP2 and TAP1. The high rate of JAK1 mutations in MSI endometrial cancer is suggestive of an adaptation favoring tumor survival by blocking the JAK/STAT pathway activity, and impeding an adequate immune response [78,79]. In conclusion, in ECs JAK1 mutations are frequently associated with tumor immune evasion.

But that is not entirely true: a non-negligible portion of dMMR ECs with JAK1 mutations respond to CPIs. The response to this observation can be due to the zygosity or clonality of the JAK1 mutation. Carballo et al. [80] recently showed that JAK1 mutation in heterozygosis responds to ICIs, while mutations in homozygosis do not.

(b) Tumor Mutational Burden.

MMR protein status and high Tumor Mutational Burden (TMB) (more than 10 mutations per megabase) are considered predictive biomarkers of response to ICIs. These ECs frequently exhibit high levels of lymphocyte infiltration and strong expression of immunological checkpoint-related proteins (PD1, PD-L1, lymphocyte-activation gene 3 (LAG3), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Indoleamine 2,3-dioxygenase 1 (IDO1)) [81]. However, only half of these patients receive a significant clinical benefit from I-O. In the GARNETT trial, a subset of dMMR/MSI-H tumors (13.5%) expressed a low TMB and showed an objective response rate of 21% [43]. TMB probably provides limited predictive value within a dMMR/MSI-H EC population because a clonal and not a subclonal neoantigen presentation could induce response to ICIs in these tumors [82].

(c) Tumor microenvironment and its features.

To improve the reliability of predictive biomarkers, the research moved from tumor-intrinsic features to TME features using spatial immune profiles.

Grau Bejar et al. [69] compared the TME features of dMMR responders and non-responders to ICIs using this technique and unsupervised hierarchical clustering analysis. The tumors of non-responders exhibited few CD8 $^{+}$ cells, absent terminally differentiated T cells, lack of mature tertiary lymphoid structures and dendritic cells, and a loss of Human Leukocyte Antigen class I. In this study up to 30% of dMMR ECs were classified as “desert” tumors, with a non-immune-infiltrated TME, with seven of the nine non-responders included in this cluster. PD-L1 negativity was common among non-responders, while alternative checkpoints (TIM-3, LAG-3, IDO1) were present in a substantial subset, suggesting new opportunities for combinatorial blockade.

In the future, an in-depth study of the TME will be feasible thanks to the advancements in single-cell technologies such as single-cell RNA sequencing. A systematic evaluation of the TME will provide insights into the functional diversities of tumor-infiltrating immune cells [83].

Tumor and peritumoral infiltration of inflammatory cells, both in quantitative and qualitative terms, is a fundamental parameter of response to immunotherapy in many solid tumors [83].

In situ multispectral immunofluorescence tumor tissue staining and digital image analysis offer a useful tool in understanding the dynamic interactions among the intra-tumoral immune infiltrate, the presence of lymphoid aggregates and/or tertiary lymphoid follicles, and tumor-associated macrophages (TAM). Recently Les Saux et al. showed that dMMRd had more immune structures, such as lymphoid aggregates and tertiary lymphoid structures, compared to pMMR ECs. Moreover, they observed that a significantly lower number of TAMs, which are related to the inhibition of immune response, was linked to a favorable response to ICIs [84]. Among TAMs, M2 macrophages secrete tissue-remodeling and pro-angiogenic factors (such as matrix metalloproteinases and VEGF) associated with

tumor progression [85]. These cells are localized around the tumor margins and enhance invasiveness and tumor growth [86].

Other cells playing a pivotal role in the mechanism of resistance to ICIs are the dendritic cells (DCs). DCs are specialized to capture and process antigens, converting proteins to peptides that are presented on major histocompatibility complex (MHC) molecules, recognized in turn by T cells. Then DCs interact with natural killer cells (NK) and B cells to create a link between adaptive and innate immune systems [87]. Solid tumors including ECs secrete soluble factors such as IL-10 and TGF- β to inhibit the differentiation of DCs and to suppress their ability to activate immune response [88,89].

To overcome the potential loss of function of DCs and the consequent resistance to I-O in advanced EC, a combination of a peptide-loaded DC vaccine with carboplatin-paclitaxel chemotherapy has been recently proposed in a single-arm phase I/II study [90].

(d) Gene signatures of resistance to I-O.

At the moment, no single immune feature can be considered a reliable and robust predictive biomarker; as a result there is a clinical need to identify patients with dMMR ECs who do not respond to I-O combined with chemotherapy or I-O alone. Predictive models based on genomic and transcriptomic signatures were therefore born. Spatial multiomics combines protein cell phenotyping with gene expression profiling, providing precise information on cellular functions and disease mechanisms within the tumor and its TME. This combined approach makes it possible to identify biomarkers in specific tissue compartments.

Grau Bejar et al. identified a simple signature based on four key immune parameters: intra-epithelial CD8, stromal CD8, PD-L1, and HLA-I H-score [69]. This model recapitulates two key immunological parameters: the antigen presentation and the presence of exhausted cytotoxic T cells. Their logistic regression model distinguished between responders and non-responders to I-O with a discriminative power of 92%.

Another signature described in patients with dMMR uterine and ovarian cancer treated with nivolumab regards the presence of dysfunctional CD8+ cells (CD8 cells with upregulation of TOX that can impair antitumor function) and simultaneous co-expression of PD-1 (CD8+PD-1+TOX+) and CD8+ cells that can downregulate the adaptive immune response [91,92].

Fibroblasts and endothelial cells express specific genes that define their identity and function. MSI-H ECs treated with pembrolizumab showed a significant increase in fibroblast and endothelial cell transcriptomic signatures in non-responders compared to responders. In non-responders the expression of TAGLN (fibroblast gene) and endothelial cell genes (EMCN, KDR, MMRN1, MYCT1, PEAR1, PTPRB and TEK) was reportedly more elevated [93–95].

3. Future Perspectives and Emerging Biomarkers

dMMR-MSI-H ECs are a heterogeneous group of entities predominantly characterized by a high tumor antigen burden and by an inflamed TME that sustain the response to I-O and/or I-O combined with chemotherapy. However, a non-negligible percentage of patients do not respond to treatment, demonstrating primary or secondary resistance to therapy.

Different clinical approaches have been proposed to overcome resistance: dual checkpoint blockade (pairing PD-1/PD-L1 inhibitors with CTLA-4 inhibitors [96]), the association of I-O with anti-angiogenic drugs like Lenvatinib [97] or with PARP inhibitors [60], and the emergence of cell therapies (CAR-T [98] and TCR-T cells [99]).

Combination strategies with neoantigen vaccines combined with PD-1 blockade improved progression-free survival in a phase 1–2 clinical trial [90].

There is an unmet need to detect non-responders with robust biomarkers to avoid inappropriate treatments for patients, but rather to refer them to clinical trials and innovative strategies.

Only a multi-dimensional approach could lead to efficient and robust predictive criteria of response to ICIs in monotherapy or in combination with chemotherapy for patients with dMMR/MSI-high ECS.

The knowledge integration of different biological phenomena, such as the causes of the non-functioning pathway of MMR, the evaluation of the immunogenicity of the neoantigens produced by the mutational burden, and the awareness of the integrity of the mechanisms of antigen presentation will bring this contribution. In addition, it will be necessary to acquire the ability of dynamically observing how the tumor itself, the TME and the systemic immune response will evolve under therapeutic pressure.

Recent developments in single-cell RNA sequencing improved our understanding of TME function at a cellular level. Unlike bulk RNA sequencing, this technique provides information on the mechanisms of gene expression in the various cell subpopulations.

Guan et al. used public bulk and single-cell RNA-seq, mutation/CNV data, and the Tumor Immune Dysfunction and Exclusion (TIDE) algorithm to bioinformatically deconvolute the TME in ECs featured in the Cancer Genome Atlas Uterine Corpus Endometrial Carcinoma database (TCGAUCEC) [100]. They observed a prevalence of M2-like tumor-associated macrophages (TAMs) within the TME of patients in the non-responder group. However, this is an example of a retrospective and computational study which should be confirmed in perspective analyses performed on clinical trials.

Another technique that could offer important information is liquid biopsy. Liquid biopsy refers to any type of non-invasive test that uses human body fluids, primarily blood, to detect tumor biomarkers such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), soluble proteins, and exosomes. It has been demonstrated that the detection of EC-specific gene alterations, TMB and microsatellite instability is feasible with ctDNA in a non-invasive way [101,102]. Liquid biopsy could be used for screening in patients with inadequate biopsies, to monitor the evolution of the tumor and to obtain predictive parameters for ICI therapy.

We have learnt from the lesson of Non-Small Cell Lung Cancer (NSCLC) that Whole-Exome Sequencing for determination of TMB in liquid biopsy from patients with advanced NSCLC suggests that liquid biopsy-derived TMB may be used as a useful biomarker for predicting the ICI response [103].

Recently it has been shown with different techniques, such as bidirectional pyrophosphorolysis-activated polymerization PCR (Bi-PAP), droplet-digital PCR and NGS, that the concentration of ctDNA strongly correlates with ICI therapy response [104] in patients with solid tumors. In conclusion, the use of liquid biopsy-based strategies to detect mechanisms of primary or secondary resistance to I-O are under investigation. However specific information regarding immune evasion mechanisms has been obtained in a non-invasive way: mutations in β 2-microglobulin or JAK1 and 2, changes in HLA expression and defects in interferon signaling have already been detected in this non-invasive way [105,106].

The final (but by no means least important) topic in this review is the microbiome-based approach to cancer: a cutting-edge innovation to augment standard-of-care therapeutics. The dynamic ecosystem of bacteria plays a role in maintaining immune homeostasis, and its imbalance, called dysbiosis, is considered linked to carcinogenesis [107,108].

The impact of the gut microbiota on ICI therapy responses was investigated in the phase II PRIMMO clinical trial, which evaluated a pembrolizumab-based regimen in patients with recurrent and/or metastatic cervical or endometrial carcinoma who had at least one prior line of systemic therapy [109]. The authors reported that the *Blautia* genus was associated with favorable efficacy, whereas the *Enterobacteriaceae* family presented poor efficacy. In the study, seven patients with MSI-high EC were included, but differences in gut microbiome and in response to pembrolizumab were not reported for this small

series. Deciphering the interplay between microbiome and ICIs is challenging because the interaction can be bi-directional: some bacterial strains enhance immunity while others decrease it, mainly in the context of TME [110]. Detection of bacteria associated with tumor response is yet a difficult task. There are differences in the studied populations, in life styles, in sample collections, in sequencing and in data analysis [110].

Recently, serious methodological errors were found in a large collection of DNA and RNA sequencing samples taken from 33 different human cancers and from matched normal tissues, showing the lack of robustness and reliability of the analytical tools [111].

In conclusion, these studies suggest that there are associations between gut microbiome profiling and outcomes in patients with advanced ECs treated with ICIs, but these findings are preliminary and require replication in larger cohorts. Certainly, microbiota testing is a promising predictive assay in tumors qualifying for I-O, but in EC it remains a research tool waiting for clinical validation.

4. Conclusions

dMMR EC is an example of a biomarker-driven clinical entity, linking molecular pathology with therapeutic decision-making. Routine identification of MMR deficiency is now central to patient management, informing prognosis, Lynch syndrome screening, and eligibility for immunotherapy. However, significant heterogeneity exists within dMMR tumors, and not all patients derive durable benefits from immunotherapy. Future efforts should focus on refining predictive biomarkers, elucidating mechanisms of primary and acquired resistance, and optimizing combination strategies.

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