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REVIEW ARTICLE

Molecular Subtypes of Endometrial Cancer and Their Therapeutic Implications

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ABSTRACT

Endometrial cancer (EC) is a complex disease with various subtypes. Although it is considered a treatable disease due to early diagnosis and symptoms, the advanced stage, which represents approximately 8% of cases, is associated with poor outcomes, reflecting the absence of efficient systemic therapy. There are various molecular classifications available and many pathways involved in EC pathogenesis. Advances in understanding its biology have led to the development of a classification system to help tailor treatment strategies depending on both patients and disease features. Currently, immunotherapy and targeted therapies are key treatments for EC, whether recurrent or advanced. In this review, we aim to summarize the molecular classification of EC briefly and its impact on treatment strategies, as well as the proposed targeted therapy. The data collection is based on searches on scientific websites, clinical trials (ClinicalTrials.gov), and international guidelines from Europe's leading medical oncology society (ESMO) and the National Comprehensive Cancer Network (NCCN).

Keywords: Endometrial Cancer, Molecular Classifications, Target therapy.

INTRODUCTION

Endometrial cancer (EC) is the most common cancer of the female genital tract, ranking fourth worldwide. In 2022, there were 65,950 new cases and 12,550 disease related deaths [1].

While most oncologists view EC as a treatable disease, with up to 67% of cases being diagnosed at early stages due to early symptoms, approximately 8% are detected at an advanced stage with a poor survival outcome, resulting in a 5-year survival rate of 17%, proving that there is no efficient systemic treatment [2].

To enhance survival rates, it is crucial to tailor treatment plans according to individual patient and disease characteristics.The standard management of EC involved a multidisciplinary team (MDT) comprising a gynecological surgeon, oncologist, radiotherapist, and palliative care specialist [3].

Immune checkpoint inhibitors (ICIs) are used in the treatment of advanced or recurrent EC either as a single agent or in combination with chemotherapy (CTH) or tyrosine kinase inhibitors (TKI), resulting in varying responses [3].Assessing genomicfeatures, involving actionable mutations, is crucial to expand treatment options and improve overall survival (OS) in advanced EC patients [4].This review will highlight the molecular classifications of EC and their implications for management.

Histological Classification

For years, EC was classified into two groups based on the Bokhman system: type I for the

endometrioid subtype and type II for other subtypes. Tumors were graded as low-grade (G1 & G2) or high-grade (G3) [5].Progesterone Receptor (PR) and Estrogen Receptor (ER) status is typically evaluated in EC. Type I EC is often low grade, localized to the uterus, and has a favorable prognosis with treatment (5-year OS of 86%). In contrast, Type II EC is linked to a worse prognosis (5-year OS of 59%) [6].

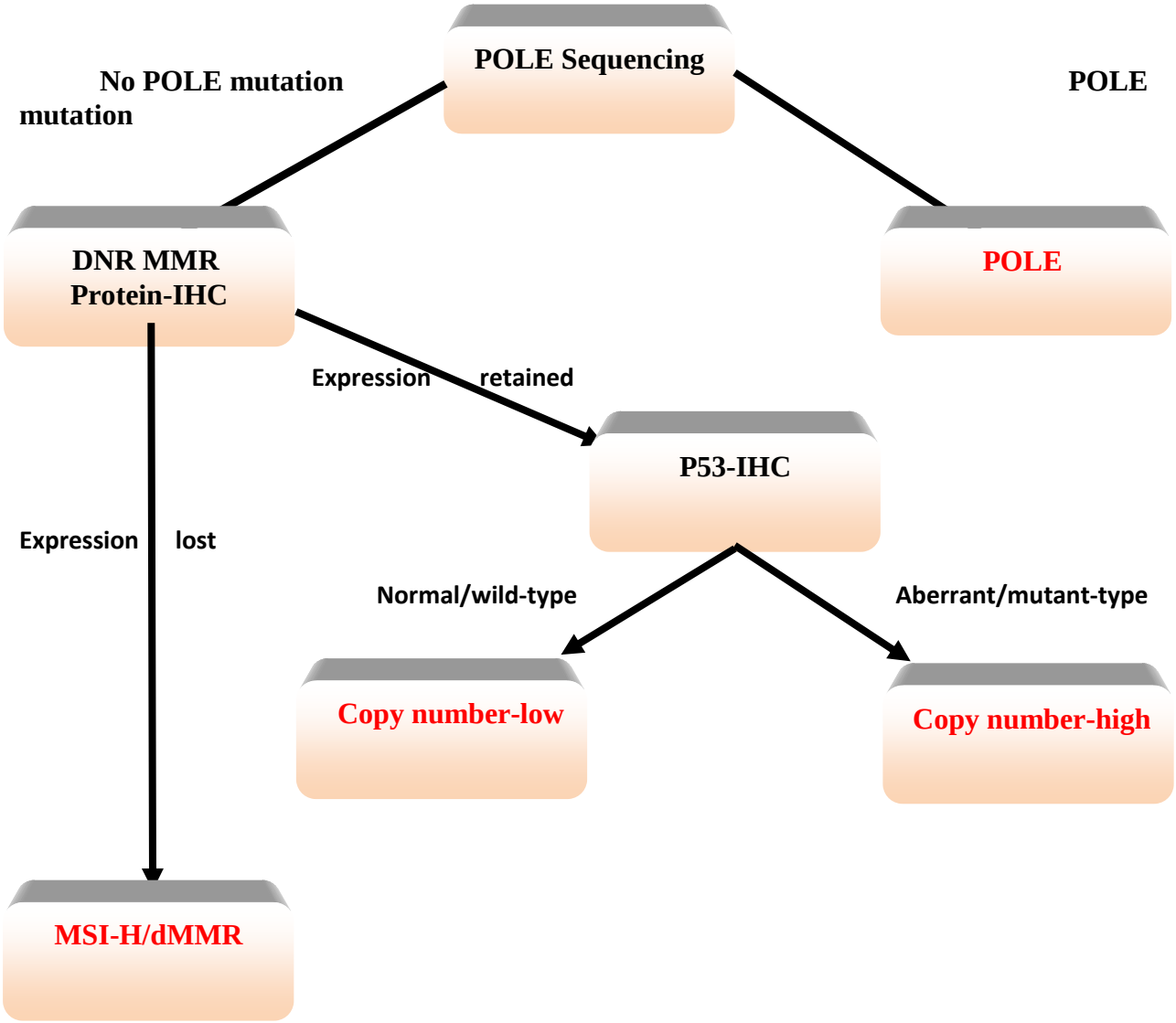
Histological factors such as lymphovascular space invasion (LVSI) have been linked to a high risk of recurrent disease, complicating local disease management. Substantial LVSI, characterized by extensive tumor emboli invasion into vascular spaces, is a significant poor prognostic factor. It is defined as the presence of four or more LVSI-positive vessels per slide. Tumors with LVSI may indicate the need for adjuvant therapy in stage II EC. Accurately describing histology can be challenging for pathologists due to the lack of reproducibility in morphologic classification. Due to the incomplete characterization of tumor biology, type I and type II groups exhibit significant heterogeneity and diversity. As a result, choosing a targeted therapy for EC has always been difficult [7, 8].

Molecular classification and genetic determinants

Approximately 95% of EC cases are initiated by sporadic mutations, while only 5% are attributed to genetic mutations that may occur up to 20 years prior to the sporadic cases. Given the growing similarity in histopathological characteristics of these tumors, utilizing molecular analysis and classification is essential for guiding treatment decisions [9].Based on genomic abnormalities of 373 patients with EC, including endometrioid type (either low or high grade) and serous type, The Cancer Genome Atlas (TCGA) identified four prognostic subtypes of EC in 2013. A molecular classification using immunohistochemistry (IHC) was later developed for clinical use [10].The molecular subtypes illustrated in **figure 1**and included POLE-mutant, MSI-H, copy number low, and copy number high.The European societies; Pathology, Gynecological Oncology, Radiotherapy, and Oncology categorize risk groups and determine treatment based on these molecular classification [11].

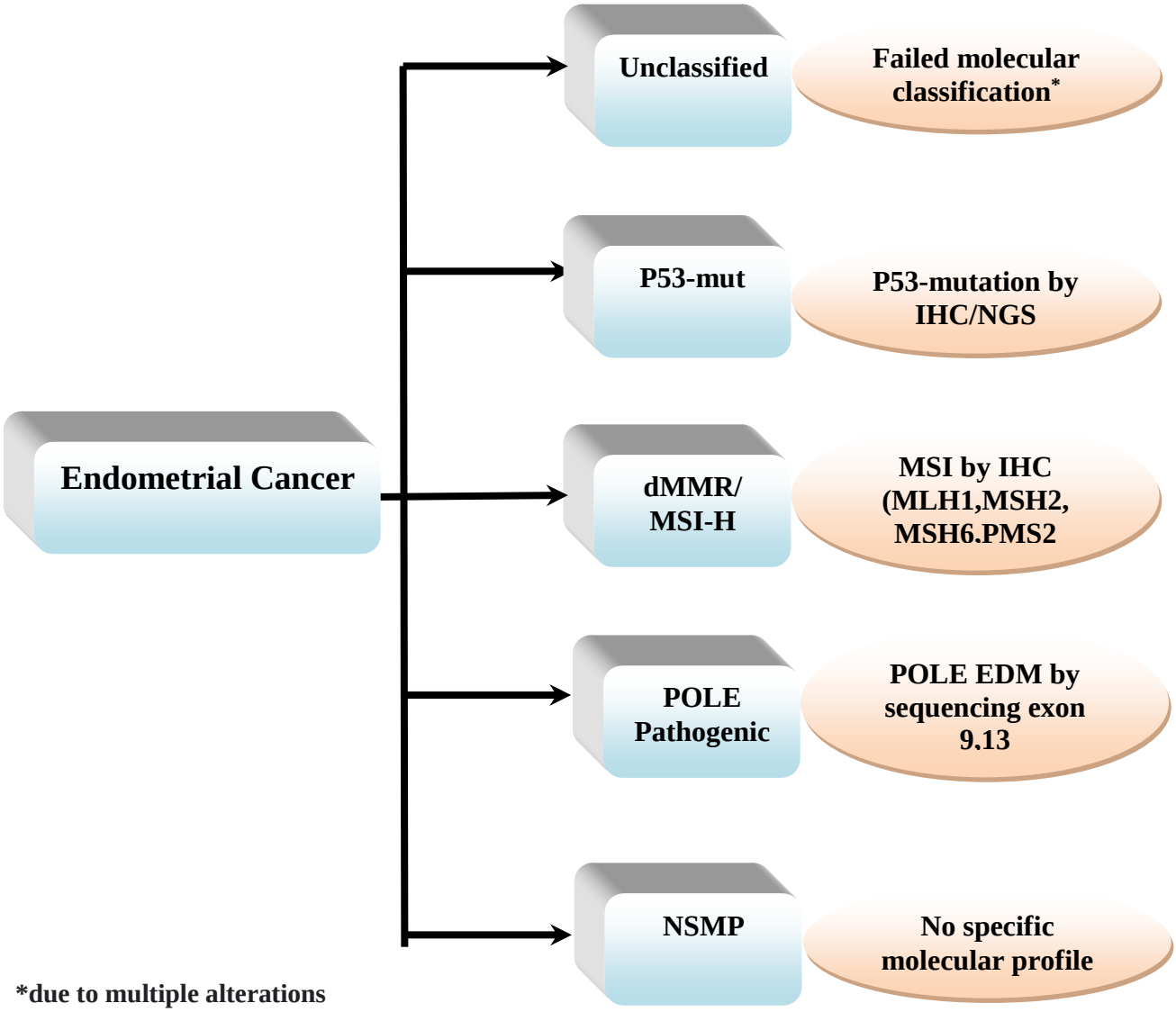
Two main classifiers have been utilized in recent years to classify EC based on TCGA research. The ProMisE classifier categorizes tumors into stages,**(figure1)**while the Leiden classifier excludes cases with multiple molecular alterations**(figure2)**. Both classifiers may identify the opportunity of treatment failure, aiding in treatment decisions for early-stage EC. These classifiers have been validated in large studies and show promise in reducing over and under-treatment in future trials [12, 13].

Figure 1: Molecular classification of endometrial cancer using the ProMisE molecular classifier developed by Kommos et al.



IHC, Immunohistochemistry; MMR, mismatch repair; MSI-H,microsatellite instability high; dMMR, mismatch repair deficient; ProMISE, proactive molecular risk classifier; POLE, polymerase epsilon. Adapted from Kommoss et al (12)

Figure 2: Molecular classification of endometrial cancer by Leiden classifier.



***due to multiple alterations**

IHC, Immunohistochemistry; NGS, next generation sequencing; MMR, mismatch repair; MSI-H, microsatellite instability high; dMMR, mismatch repair deficient; POLE EDM, POLE exonuclease domain mutation; POLE, polymerase epsilon. Adapted from Stelloo E et al (13)

POLE mut

This group represents a small percentage (10-15%) of EC patients with exonuclease mutations domain of POLE. These mutations, such as V411L and P286R, are associated with high-fidelity replication. Patients typically have a low body mass index (BMI), early stage at diagnosis, high grade endometrioid subtype,high tumor infiltrating lymphocytes (TILs), frequent mutations in PTEN, PIK3R1, PIK3CA, ARID1A, KRAS, and TP53.Tumors in this group show an enhanced cytotoxic T-cell response and high neoantigen loads, making them potential candidates for ICTs. With a better prognosis and high response rates, targeted therapy may be considered as a new treatment option for these subtypes of patients [14].

Mismatch Repair Deficient Tumors (dMMR) or Microsatellite Instability-High (MSI-H)

They account for 25% to 30%. Similar to the POLEmut group, they exhibit high level of TILs and high-grade endometrioid. The BMI is higher compared to the POLEmut cases. Patients with Lynch syndrome are diagnosed if they have a germline mutation in the MMR items (MLH1, MSH6, MSH2, or PMS2). It is

advised in such circumstances to screen for additional frequency cancers, involving those in families. The prognosis for these patients is intermediate, and they show significant benefits from ICI treatment. IHC for MMR is a straightforward and effective method for screening patients. dMMR EC is indicated by the total lack of expression of >=one MMR proteins through IHC [15]. Apart from IHC, NGS can be used to evaluate MMR system.These patients are believed to have a high number of somatic mutations, resulting in elevated neoantigen loads and increased of CD8+ T lymphocytes infiltration, making them promising candidates for ICIs as evidenced in clinical studies [16].

Copy number low

It accounts for 39% of cases and lacks a unique molecular feature (NSMP). It characterized by poorer prognosis and lower mutational burden compared to POLE-mutant and dMMR tumors. Mutations primarily involve CTTNB1, PIK3, and PTEN, with TP53 mutations being rare. Most tumors are low-grade with higher ER and PR expression, potentially responsive to hormonal therapy. Increased RAD50 expression, linked to DNA repair, has been observed. This heterogeneous group may benefit from targeted therapies such as mTOR inhibitors, endocrine therapy, and WNT/beta-catenin pathway inhibition. Further characterization and specific targeted therapies are needed for this group [17].

Copy number high

Approximately one quarter of EC patients belong to a high-risk group, which includes non-endometrioid types (such as serous) and G 3 endometrioid . These patients exhibit more copy number changes, mutations in PPP2R1A, PIK3, and FBXW7 and minimal DNA methylation alterations. TP53 mutation is almost always present in this group (>90%) and may necessitate more aggressive treatment for better outcomes. About 50-60% of these patients show abnormalities in the PI3K/AKT/mTOR pathway, while 25% have ERBB2 alterations, making them potential targets for novel combination therapies [18].

Other EC Characterization

New biomarkers like ER/PR, HER2 status, and CCNE1 amplification are being identified in evolving data for EC characterization. Efforts are also underway to explore potential targets rather than tumor tissue, with ctDNA emerging as a valuable tool for timely target identification. A study analyzing the mutational status of primary EC and circulating tumor cell (ctDNA) levels in 38 patients found that 92% of primary mutations of tumor were identified in ctDNA at presentation. Detection of ctDNA varies between cohorts, with longitudinal samples showing predictive value for clinical benefit in patients on immunotherapy. CtDNA monitoring has shown potential for early detection of progression and recurrence, with the ability to reflect treatment response and identify genetic changes under treatment pressure. CtDNA holds promise as a tool for guiding treatment decisions in EC, with ongoing studies to further evaluate its utility [19].

Current Guidelines for Front-Line Treatment of Advanced EC

Conventional CTH is the primary treatment for metastatic/ recurrentEC. Combination therapy is recommended for majority of patients. Frontline therapy with carboplatin and paclitaxel for six cycles has a PFS and OS of 14 and 32 months, respectively. In the GOG0209 study, this regimen was found to be non-inferior to a more dense therapy involving triplet CTH; paclitaxel- cisplatin - doxorubicin, with accepted tolerance and better quality of life [20].Hormonal therapy is an option for treating low-grade endometrioid tumors, particularly when the tumors are positive for ER and PR. It has shown a RR of 10-20% with a survival rate < 1 year. A recent meta-analysis found an ORR of 21%, which increased to 26% when ER was positive and 35% when PR was positive. In the second-line therapy, the RR was 18.5%. Hormonal therapy typically involves progestins like megestrol acetate, aromatase inhibitors (AIs), fulvestrant, or t amoxifen. It is recommended for low-grade endometrioid tumors and elderly patients who are not suitable for CTH. If hormonal treatment is not suitable, frontline chemotherapy with a combination of paclitaxel and carboplatin should be considered [21].The NCCN guidelines recommend total abdominal hysterectomy

(TAH) for EC with distant metastasis with systemic therapy. Most studies, though retrospective and referred to CTH of carboplatin and paclitaxel, show promising results. In another retrospective study of over 3000 patients with stage IVB, the TAH plus CTH had a significantly longer median OS compared to the CTH alone (11 vs. 19.8 months, HR=0.59). This survival advantage was consistent regardless of whether CTH was administered before or after TAH, and was further enhanced when combined with locoregional radiation therapy. While there may be a selection bias favoring younger and healthier patients in this study, other studies and meta-analyses support the use of locoregional approach as a viable option, pending further prospective results [22].

Second-line and subsequent therapy

Many oncologists follow the concept of platinum sensitivity for re-introduce with platinum-based regimens. If disease progression happens > 6 months after initial platinum treatment, reintroducing platinum is considered acceptable. Retrospective cohort studies have shown that longer platinum-free intervals lead to better response rates (RR). For instance, Nagao et al. demonstrated that a platinum-free interval < 6 months resulted in a 25% RR, while an interval > 24 months led to a 65% RR. When platinum-based treatments are no longer effective, other CTH options such as taxanes or doxorubicin are used as monotherapy in the palliative setting. Prior to the introduction of immunotherapy, organizations like ESMO or NCCN did not establish a specific protocol for systemic therapy in advanced EC post first-line treatment [23].

Highlight on a significant biomarkers

PD-L1 status has been extensively studied as a predictive biomarker. EC exhibits one of the highest rates of PD-L1 positivity through gynecological malignant tumors, with approximately 50% positivity. Through a meta-analysis involving over 1500 patients, PD-L1 expression was not found to be correlated with OS or PFS but was linked to advanced stage and grade. Data on PD-1 and its relevance for ICI response are conflicting. The KEYNOTE-028 trial, which focused on pembrolizumab in PD-L1 positive EC, reported an objective ORR of 26% in the PD-1 positive subgroup without a power correlation [24].

Tumor mutational burden (TMB) is a key biomarker studied in cancer research. In the KEYNOTE158 trial, 805 patients were evaluated for TMB, with 13% having TMB-high with a higher ORR of 20% compared to 6% in other patients. TMB is correlated with dMMR, POLE mutations, and MSI-H. TMB assessment is important in identifying potential responders to ICT. A study of 60 EC patients, those with MSS and high TMB treated by pembrolizumab had better PFS than those with low TMB. The definition of low and high TMB varies, with further research needed to clarify its predictive role, especially in EC not classified as dMMR or POLE-mutated [25].The microenvironment composition, including TIL infiltration rate, is a prognostic factor. ARID1A alterations affect TIL infiltration and PD-L1 expression, making them possible predictive biomarkers for ICI therapy in various cancers, including EC. Further research is needed in EC specifically.Prognosis under ICIs differs between hereditary Lynch syndrome and sporadic MMR pathway alterations in MSI-H patients [26-29].

ICI is a game changer in the field of EC; Implication on therapy.

Current data augments the use of ICI in patients with advanced/recurrent EC who have MSI-H or dMMR after first-line CTH failure and have not received ICIs treatment before, based on the following trials; KEYNOTE-158, GARNET, and nonrandomized phase II clinical trial of pembrolizumab, dostarlimab, and durvalumab, respectively [16, 30,31].In MSS EC, single-agent ICI after platinum-based CTH have shown limited RR. However, MSS EC is a diverse group with specific genetic characteristics and accounts for the majority of cases (75%). Combination therapies involving ICIs with antiangiogenic agents, PARPi, and CTH have been explored to enhance the immune response by cell populations and modulating tumoral microenvironment. Antiangiogenesis reduce T cell- regulatory activity, counteract the immunosuppression of VEGF, and enhance

T-cell infiltration, potentially improving treatment outcomes [32].

Pembrolizumab and lenvatinib combination therapy has shown promising results in treating MMRp EC patients who have progressed on platinum-based CTH. Initial phase 2 trial with 94 patients demonstrated a 37% ORR and 7.4 months median PFS. A phase 3 trial with 827 recurrent EC patients confirmed significant benefits in PFS and OS for MMRp patients. Another study with cabozantinib and nivolumab in recurrent EC showed improved ORR with the combination. Atezolizumab and bevacizumab combination also yielded durable responses in recurrent EC patients, especially those with pMMR tumors [33].

PARPi have shown promise in combination with ICT for treating EC. Patients with homologous recombination repair pathway alterations had better PFS compared to those without these alterations. Another trial, the DOMEC trial, investigated the combination of durvalumab and olaparib in recurrent EC patients, with an overall response rate of 16%. However, this result was not statistically significant, and there was no difference in PFS based on molecular classification [34, 35].

A non-randomized phase 2 study (NEC trial) in 22 recurrent EC patients found modest activity with the combination of dostarlimab and niraparib (ORR 14%). To enhance outcomes, additional agents have been explored. A recent report demonstrated improved ORR 39% with manageable toxicity by combining bevacizumab, atezolizumab, and rucaparib in 30 patients. The DUO-E trial (n = 718) investigated upfront durvalumab ±platinum-based CTH, followed by maintenance therapy with durvalumab plus olaparib or durvalumab alone or placebo in advanced or recurrent EC. The durvalumab + olaparib arm showed an improved PFS (P<0.0001) vs control. Exploratory analysis in 97 patients with HRR mutations showed a positive signal in PFS with olaparib and durvalumab (HR 0.30; 0.15 to 0.58) compared to non-HRRm, warranting further data [36].

Recent phase 3 studies have explored the combination of ICI with platinum-based CTH in patients with advanced or recurrent EC. The RUBY study included 494 patients who were randomly received dostarlimab or placebo in combination with paclitaxel and carboplatin . In the dMMR population, dostarlimab showed a significant improvement in PFS compared to placebo. Another trial, NRG-GY018, demonstrated a persistent benefit in PFS with the compination of pembrolizumab to CTH in both dMMR and pMMR cohorts. Preliminary results from the Attend/ENGOT-EN7 trial with atezolizumab also showed an improvement in PFS. Molecular analyses from the RUBY study revealed better PFS in dMMR and TP53 mutated subtypes with dostarlimab and CTH[37].**Table 1** exhibits in brief some of target therapies with ICTs in EC either advanced or recurrent

Table 1 Targeted and immunotherapy for advanced/ recurrent endometrial cancer in practice.

Therapy	Class	Indication	Markers
Pembrolizumab	ICTs	▪ Post or progression of CTH.	▪ dMMR ▪ dMMR ▪ TMB-H
Dostarlimab	ICTs	▪ Combined with CTH, followed by single agent dostarlimab	▪ dMMR ▪ MSI-H
Lenvatinib	TKI	▪ Combined with pembrolizumab.	▪ Absence of MSI-H or dMMR
Larotrectinib	KI	▪ After failure of other line of treatment	▪ Positive NTRK

ICTs; Immune checkpoint therapy, TKI; Tyrosine Kinase Inhibitors; KI; Kinase Inhibitors; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient. TMB-H; Tumor Mutational Burden

Targeted Therapy Perspectives

Understanding biological processes could lead to new therapeutic approaches, but not all identified targets may be effective in treating cancer. Functional evaluation is crucial to ensure that the target is druggable and can be applied into clinical action to control tumor progression. Effective drug development for EC requires knowledge of the genomics and biology of the disease, identification of druggable targets, and precise drug delivery systems. Resistance mechanisms must also be understood to optimize personalized therapy.Combination therapy is often used to maximize treatment effectiveness, and patient-reported outcomes should be considered to improve quality of life. The optimal treatment sequence for EC, including the use of ICTs, remains unclear and requires long-term evaluation [38, 39].**Table 2** summarizes the most targeted therapies on progress.

Table 2 Targeted Therapy Perspectives

- ***Antibody-drug conjugates (ADCs) [40-44, 49];***
  1. Tisotumab
  2. Mirvetuximab soravtansin
  3. Luveltamab tazevibulin
  4. Sacituzumab govitecan
  5. T-DM1 and T-Dxd
- ***Epidermal growth factor receptor (EGFR) [45,46];***
  1. Selumetinib
  2. Selinexor
- ***The PI3K/AKT signaling [47,48];***
  1. Metformin
  2. GLP-1R agonists and SGLT2 inhibitors
- ***Anti-Her-2 [49];***
  1. Trastuzumab
  2. Trastuzumab and Pertuzumab
- ***Anti-angiogenic therapy [50];***
  1. Bevacizumab
- ***Cyclin-dependent kinase (CDK) 4/6 inhibition [51]***
  1. Ribociclib
  2. Abemaciclib
  3. Palbociclib

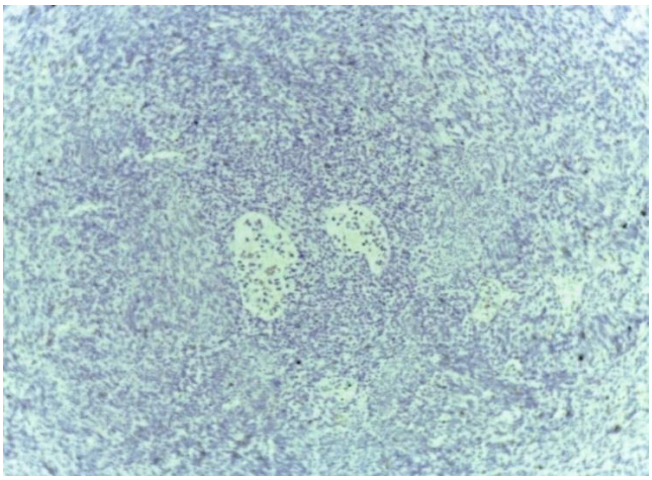


Figure 3:section revealed loss of MLH1 immunohistochemistry in endometrial carcinoma (IHC x100)

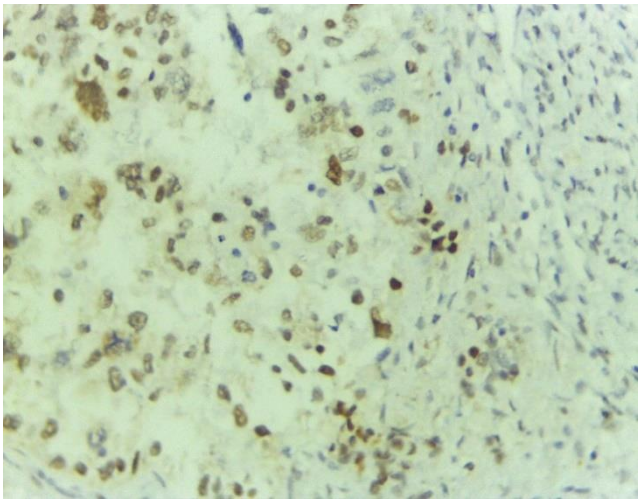


Figure 4: section revealed preserved MSH2 immunostain in endometrial carcinoma (IHC x 400)

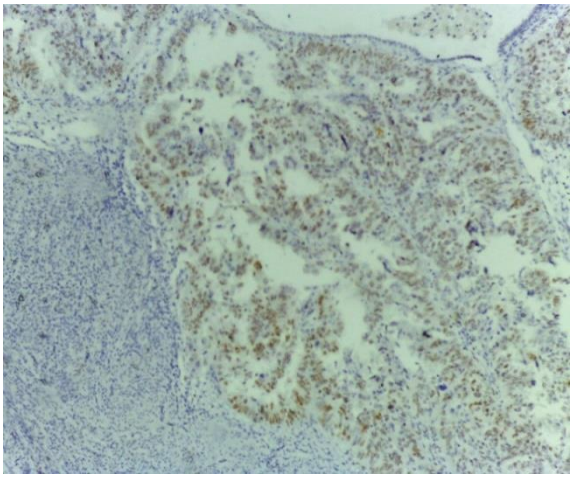


Figure 5:section revealed preserved MSH6 immunostain in endometrial carcinoma (IHC x 400)

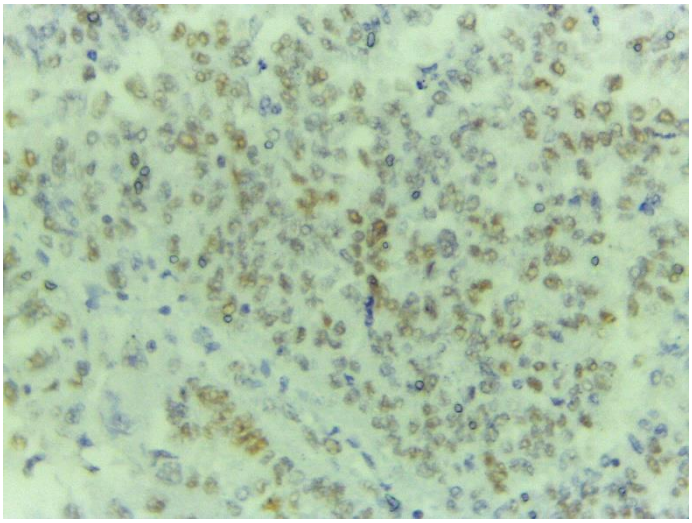


Figure 6:section revealed preserved PMS2 immunostain in endometrial carcinoma (IHC x 400)

CONCLUSION

This molecular characterization has shifted focus towards targeted therapies, moving away from standard CTH. Personalized oncology offers new treatment options for EC, with potential benefits from novel drugs targeting specific molecular alterations. Identifying therapeutic targets is crucial for improving cases selection and advancing drug evolutions**.** Moreover, further research into resistance mechanisms and the tumor microenvironment is needed to develop robust biomarkers for aiding in individualized therapy.

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