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Molecular characterization as new driver in prognostic signatures and therapeutic strategies for endometrial cancer

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ABSTRACT

Endometrial cancer (EC) incidence and mortality rates have been increasing, particularly among young females. Although more than 90% of ECs are sporadic, 5–10% are hereditary, a majority of which occurs within Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC) or Lynch syndrome. The traditional histopathological classification differentiates EC between two main groups: type I (or endometrioid) and type II (including all other histopathological subtypes). However, this classification lacks reproducibility and does not account for the emerging molecular heterogeneity. In 2013, The Cancer Genome Atlas (TCGA) project proposed EC molecular classification defining four groups with different prognostic and predictive values and the current international guidelines are progressively establishing EC risk stratification and treatment based on both histopathological and molecular criteria. Our manuscript aims to summarize the current state of EC molecular characterizations, including germline alterations at the basis of hereditary EC predisposition, to discuss their clinical utility as prognostic and predictive markers.

Introduction

Endometrial Cancer (EC) is the most commonly diagnosed gynecological cancer in the USA [1]. Worldwide, it is in seventh place among female cancers and the most common gynecological malignancy in high/intermediate developed countries, with a majority of cases occurring post menopause [2,3]. African american patients are more likely to present with high-risk EC and more likely to die from the disease, regardless of stage or histology at the time of diagnosis [4]. Even though the majority of cases are diagnosed as an early-stage disease and tend to have good prognosis (5-year survival 95 %), those with metastatic or recurrent disease have lower response to therapy and poor survival (5-year survival 16 %) [5].

EC incidence is continuously rising and mortality rates have been increasing by 1.9 % per year on average [6,7], particularly among young females [8]. These trends can be explained by increasing rates of obesity, the main risk factor for EC, particularly related to the endometrioid subtypes [9,10]. Besides obesity, other risk factors also include high body mass index, hypertension, hyperinsulinemia and prolonged exposure to unopposed estrogen (a majority of cases related to nulliparity, polycystic ovary syndrome or tamoxifen use) [11,12]. On the other hand, factors that provide protection against EC include parity and oral contraceptive use, which reduce risk by 30 % to 40 % [13]. Although more than 90 % of ECs are sporadic, 5 %-10 % are hereditary, a majority of which are hereditary non-polyposis colorectal cancer syndrome (HNPCC) or Lynch syndrome.

The traditional histopathological classification differentiates between two main groups: type I (or endometrioid) EC and type II (including all other histopathological subtypes) [14]. However, this classification lacks reproducibility and produces heterogenous molecular groups [15,16] (Fig. 1). On the other hand, The Cancer Genome Atlas (TCGA) project proposed a new EC classification. This combines somatic mutational burden and somatic copy number alterations helping to identify prognostic and predictive factors, to consequently offer the most appropriate therapy. More precisely, the classification proposes a molecular stratification of ECs into four distinct molecular groups: polymerase epsilon (POLE)-mutated EC (5–15 %), microsatellite unstable/mismatch repair deficient (MSI/dMMR) EC (25–30 %), copy number-

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high EC (5–15 %) and copy number-low EC (30–40 %) [17].

Our manuscript aims to summarize the current state on EC molecular characterizations, including germline alterations at the basis of hereditary EC predisposition, to discuss their clinical validity for prognosis and therapeutic targeting.

Somatic alterations in molecular subtypes in EC

Traditionally, EC risk stratification has been based on histopathological and clinical characteristics [14,18,19]. In the last ten years, with the increasing implementation of precision medicine, molecular factors have been considered to optimize risk classification and its clinical implications (Fig. 1). The Cancer Genome Atlas (TCGA) (2013) [17] and subsequent studies [20–22] described the prognostic value of four distinct EC molecular subtypes: ultramutated, that is associated to *POLE* pathogenic/likely pathogenic variants (PV/LPVs); hypermutated, characterized by microsatellite instability; somatic copy number-high, with frequent *TP53* abnormalities; and somatic copy number-low, which is not characterized by specific molecular alterations despite its usual correlation with PV/LPVs in PI3K and WNT pathways.

The Ultramutated EC. The ultramutated subtype (>100 mutations per megabase) is characterized by somatic PV/LPVs in the exonuclease domain of *POLE*, a gene codifying for DNA polymerase epsilon involved in DNA replication and repair [17]. Notwithstanding the aggressiveness in some of their features, *POLE*-mutated ECs show the best outcome compared with other molecular subtypes. In several studies, the *POLE*-mutated phenotype has been described in younger, often nulliparous women with a current or prior smoking history, mostly affected by endometrioid EC in early FIGO stages I-II with myometrial invasion < 50 %, a prominent lymphocytic infiltrate with a high tumor grade and LVSI [17,23–26].

About 5–15 % of ECs exhibit somatic *POLE* exonuclease domain mutations, among which P286R and V411L represent the most common pathogenic ones followed by S297F, A456P and S459F [27]. Additionally, a recent study has identified two new hotspot *POLE* mutations, R375Q and P452L, in patients with aggressive endometrial cancer subtypes but with favorable prognosis [28]. In fact, ultramutated patients usually show improved prognosis in terms of overall survival (OS) and progression free survival (PFS), even in the presence of poor clinical-pathological factors [17,23–26,29,20]. Therefore, *POLE*-mutated status can be considered as an independent favorable prognostic value, which may correlate with an enhanced antitumor immune response induced by high neoantigen expression and elevated tumor-infiltrating lymphocyte count [30,31].

The Hypermutated EC. The hypermutated molecular subtype (10–100 mut/Mb) shows microsatellite instability. This status is defined by a loss of mismatch repair (MMR) proteins – PMS2, MLH1, MSH6 and MSH2 – whose normal function is to monitor and repair error incorporation in microsatellites. MMR deficiency (MMRd) and its consequent microsatellite instability-high (MSI-H) phenotype can originate through three pathways: germline MMR gene mutations (Lynch Syndrome), somatic MMR gene mutations (labelled as Lynch-like), and homozygous methylation of the MLH1 gene promoter (named sporadic) [32].

About 25–30 % of ECs, generally with endometrioid hystotype, present MMRd [17] and tend to be associated with adverse clinical-pathologic features (LSVI, higher tumor grade, later FIGO stages III-IV) and with good/intermediate prognosis [17,33,20]. Interestingly, it has been histologically confirmed that MSI-H tumors exhibit higher infiltration of both T cells (CD8 + and CD3 +) and CD20 + B cells compared to MSS tumors [29,34,35], possibly because of high neoantigen expression.

The Copy Number-High EC. The copy number-high (CN-H) molecular subtype lacks both microsatellite instability and *POLE* PV/LPVs. Nonetheless, it correlates with an alteration of several cell cycle regulators and primarily with *TP53* mutations [17]. *TP53* codifies for the transcription factor p53, which has been singled out as "genome guardian" in light of its key role in preserving DNA stability.

Approximately 5–15 % of ECs display abnormal p53 (p53abn). These usually affect older as well as lower-BMI patients and occur at advanced FIGO III-IV stages [22]. Histologically, CN-H tumors are mainly

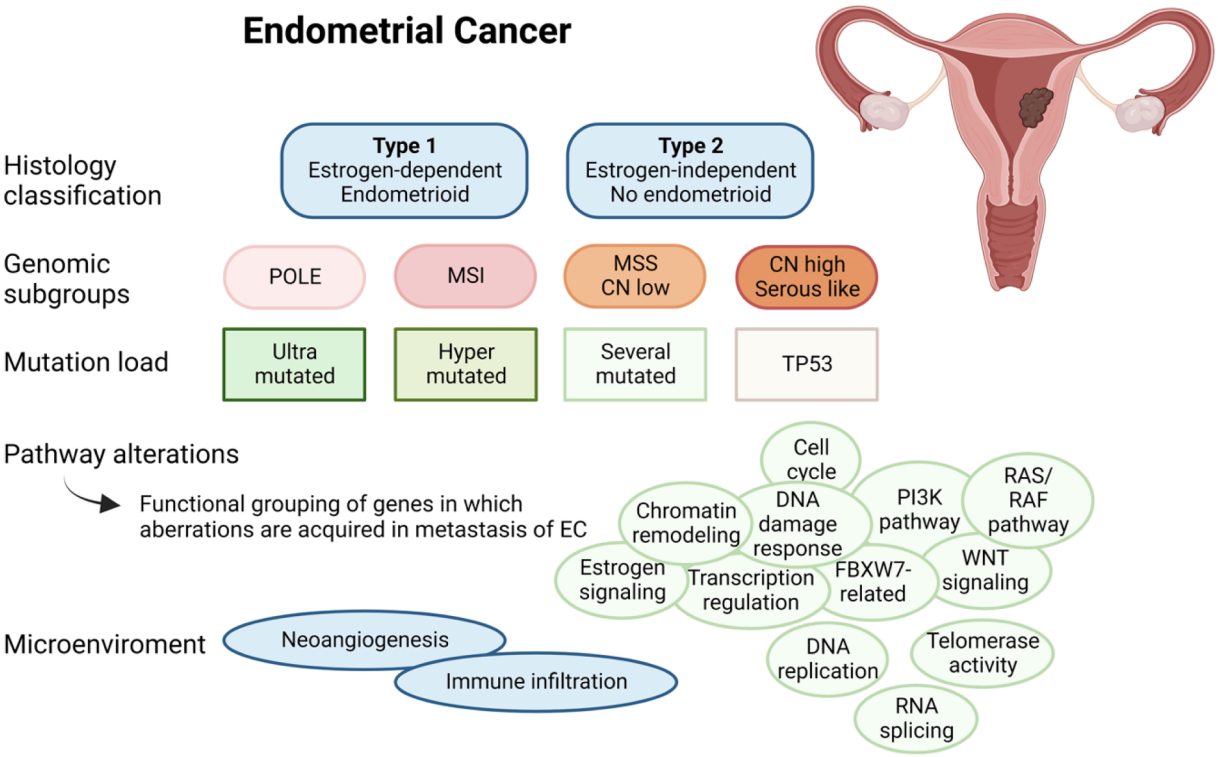

Fig. 1. Traditional classification vs TGCA molecular subtypes of endometrial cancer. MSI, microsatellite instability; MSS, microsatellite stability; CN, copy number; EC, endometrial cancer.

identified in serous EC, but also in other unfavorable histological subgroups such as carcinosarcoma, clear cell EC and G3 endometrioid EC [36]. Regardless of the histotype, *TP53*-mutated patients typically show worse prognosis – even reaching 50–70 % EC mortality rate [17,22,35,37,38] – compared to other molecular subtypes.

The Copy Number-Low EC. The fourth molecular subgroup in the TCGA classification includes copy number-low (CN-L) ECs with a non-specific molecular profile (NSMP) as lacking *POLE* PV/LPVs, microsatellite instability and p53 abnormalities [17]. This category accounts for 30–40 % of ECs (mainly endometroid) being characterized by a heterogeneous genomic landscape that results in both indolent and aggressive biological behaviors. In these tumors, prognosis is generally intermediate between *POLE* and *TP53*-mutated groups [17,39]. Frequent alterations involve the PI3K/Akt/mTOR pathway, *CTNNB1* (beta catenin 1) and *L1CAM* (L1 cell adhesion molecule) usually associated with poorer outcomes. *CTNNB1* mutation correlates with increased distant recurrence and reduced recurrence-free survival (RFS) [40,41]. Likewise, *L1CAM* predicts low survival and tends to be connected with other adverse clinical-pathological factors including > 50 % myometrial invasion, lymph node positivity and LVSI [42–44]. Another biomarker that seems to be correlated with higher recurrence risk is *ARID1A* mutation [45]. In CN-L ECs, recurrent estrogen and progesterone receptor positivity (ER+, PR +) is otherwise a strong favorable prognostic value in terms of PFS and RFS [41,46].

Germline Alterations: Hereditary EC

In 90 % of cases, ECs occur in the sporadic form, while a familial association can be observed in about 5–10 % of cases. These inherited forms mostly occur within the Lynch syndrome-associated tumor spectrum (about 5 % of ECs) linked to the presence of PV/LPVs in the MMR genes [47].

Although less frequent and less studied, other PV/LPVs within familial syndromes may lead to increased susceptibility in the development of EC. Some of these better-known genes include BRCA1/2, PTEN, STK11 and POLE/POLD-1 (Fig. 2).

Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC) or Lynch Syndrome. Lynch syndrome (LS), also known as Hereditary Non-Polyposis Colorectal Cancer syndrome (HNPCC), is an autosomal dominant inherited cancer susceptibility disorder. It is caused by germline PV/LPVs in the DNA MMR genes (*MLH1*, *MSH2*, *MSH6* or *PMS2*) or epithelial cell adhesion molecule (*EPCAM*, which causes epigenetic silencing of *MSH2*) [48]. MMR maintains genomic stability repairing mismatches resulting from DNA replication, the malfunction of which can lead to changes in DNA microsatellite length known as microsatellite instability (MSI), a condition of genetic hypermutation that increases susceptibility to cancer [49].

LS is associated with a lifetime risk of developing several types of cancers, which are classically grouped into Lynch type 1 and Lynch type 2 (extracolonic cancers), summarized in Table 1 [50].

LS-associated EC (LS-EC) is the most common extra-intestinal sentinel tumor of LS. It often occurs before the onset of colorectal cancer, which requires early screening and preventive strategies to reduce

Table 1
Summary of tumor sites associated with Lynch syndrome.

Lynch type 1	Lynch type 2
Colorectal (30–73 %)	Endometrial (30–51 %) Ovarian Urinary tract GastricSmall intestine PancreaticBiliary tract Brain Skin (sebaceous cancers) Breast Prostate

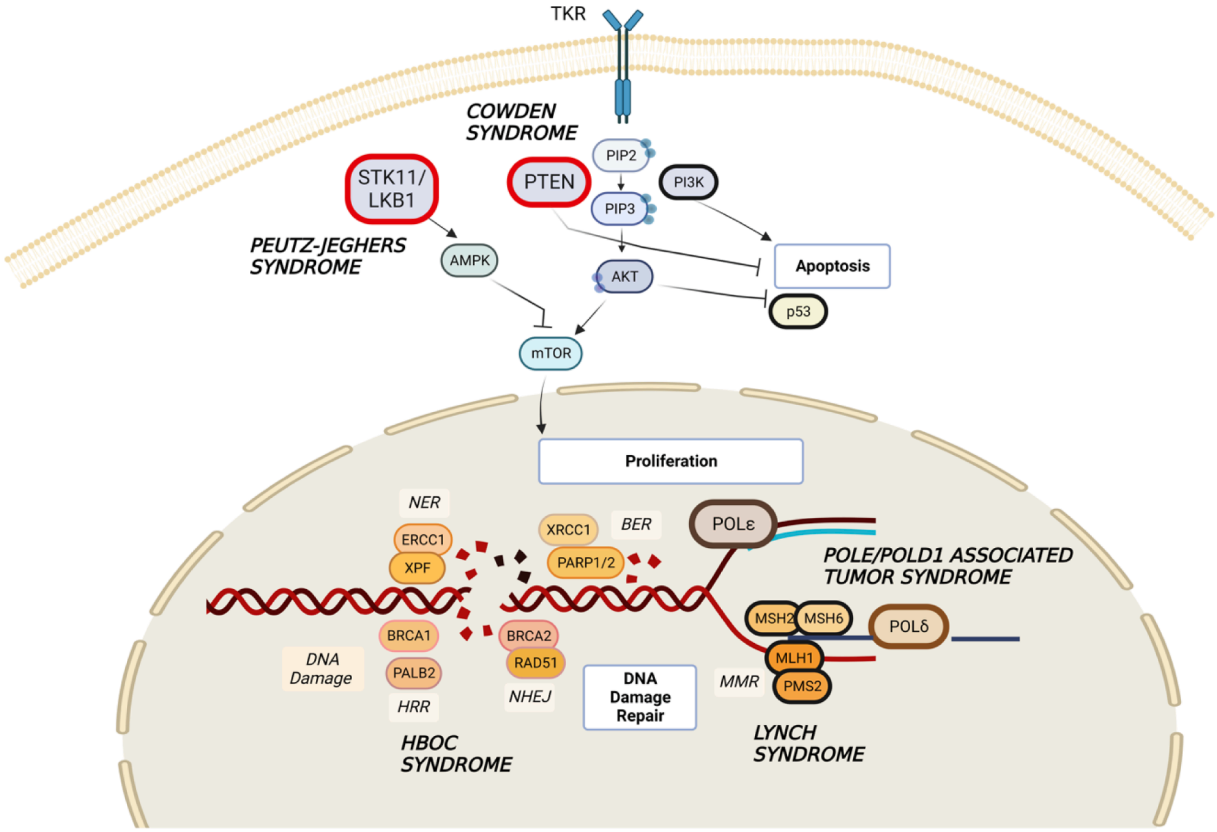

Fig. 2. Germline alterations and associated signaling pathways in endometrial cancer.

cancer-related morbidity and mortality [51].

Among all MMR mutated genes characterizing LS, *MSH2* is the most commonly associated to extra-colonic cancers [52]. Accordingly, the cumulative EC risk in 75-year-old women was about 48.9 % in *MSH2* gPV/LPV carriers. On the other hand, cumulative EC risk amounted to 41.1 %, 37 % and 12.8 % for *MSH6, MLH1* and *PMS2* gPV/LPV carriers, respectively [53].

Age at diagnosis is earlier for LS-EC than sporadic EC, while different genetic alterations result in different onset ages. The study reported in Ryan et al. demonstrated that patients carrying *MSH6* gPV/LPV develop EC later than *MSH2* or *MLH1* gPV/LPV carriers. More specifically, onset age in the latter carriers was 39–49.5 years, whereas patients with *MSH6* gPV/LPV were older (50.6–59.5 years) [54]. In contrast to sporadic EC, LS-EC has a greater tendency to occur in the lower uterine segment (LUS), as shown by Masuda et al. [55] and Westin et al. [56]. Such localization can be identified as a risk factor for lymph node metastases [57], which have a negative impact on prognosis [54]. Moreover, endometrioid carcinomas are a predominant feature of LS-EC histology. Non-endometrioid types are observed in the remaining cases, particularly in *MSH2* gPV/LPV carriers, resulting in a more variable histological spectrum for LS-EC [58,59].

LS-EC stage and grade based on the International Federation of Gynecology and Obstetrics (FIGO) remain controversial. The reason for this is that some studies suggest an intermediate/high development stage for LS-EC [60,61], while other studies show that, compared to sporadic EC, LS-EC occurs in a low-grade [62] and early-stage form [57]. Considering also the clinical phenotype of LS-EC women, it seems that women with *MSH6* and *PMS2* gPV/LPV have a milder clinical phenotype compared to women with *MLH1* and *MSH2* gPV/LPV [63,64].

Regarding outcomes, favorable prognosis may be related to a stronger presence of tumor-infiltrating lymphocytes (TILs) due to the increased number of neoantigens resulting from the high mutational load typical of MMRd and/or MSI-H tumors [65].

In the light of similar Lynch-syndrome rates in EC and CRC and the potential to reduce mortality through colorectal surveillance and cascade testing of relatives, the Consensus Group strongly recommends that women with EC should be screened for Lynch syndrome as well [66].

Hereditary Breast and Ovarian Cancer (HBOC) Syndrome. gPV/LPVs in the *BRCA1* or *BRCA2* genes are the most frequent causes of hereditary breast and ovarian cancer (HBOC) syndrome, an autosomal dominant inherited disorder in which the risk of breast cancer (BC) and tubo-ovarian cancer (OC) is higher than normal. It is characterized by young onset age, more than one synchronous or metachronous tumor, increased risk of other neoplasms including prostate cancer, pancreatic cancer and gastric cancer, especially in individuals with *BRCA2* gPV/LPVs [67].

The *BRCA1/BRCA2* genes encode for tumor suppressor proteins that participate in homologous recombination repair (HRR). In case of HRR deficiency (HRD), repair mechanisms such as error-prone non-homologous end-joining (NHEJ) or microhomology-mediated end-joining pathways (MMEJ) are activated, inducing complex genomic rearrangements and apoptosis. On the other hand, the enzyme Poly-(ADP-ribose) polymerase (PARP) binds DNA single-strand breaks (SSBs) and then performs their repair by synthesizing PAR chains on target proteins (the so-called PARylation). The use of and response to platinum derivatives and PARP inhibitors (PARPi) is based on these alterations and repair mechanisms [68].

Whether EC should be considered part of HBOC syndrome is still under debate. Several studies have examined the question, but to date none of them seems to support the presence of substantial EC risk resulting from *BRCA1/2* PV/LPVs [69]. In some cases, the greatest risk was restricted to a rare but aggressive subgroup of serous-like EC, such as uterine serous carcinomas and carcinosarcomas [17,70,71], as reported by Shu et al. In two further studies, a statistically significant increase of serous-like histology was reported for EC, apparently restricted to *BRCA1* [72,73]. In the multicenter cohort study by de Jonge et al., it was found that *BRCA1* and *BRCA2* carriers show a two- to threefold increased EC risk, with the highest increased risks for the subgroups of serous-like histology and p53-abnormal EC. Moreover, de Jonge et al. showed that increased EC risk cannot be fully explained by previous use of hormone therapy and is therefore most likely associated with *BRCA1/2* gPV/LPVs [74]. Several other studies have highlighted that the p53-abnormal EC molecular subgroup is the most commonly associated with *BRCA 1/2* gPV/LPVs [17,36,75], although EC risk in this molecular subgroup has not yet been calculated. Indeed, two previous studies had already highlighted that ECs in *BRCA1/2* carriers are significantly enriched for tumors of the p53-abnormal molecular subgroup. In these studies, it was also argued that these tumors demonstrate loss of heterozygosity (LOH) of the BRCA wild-type allele [76], while ECs from this subgroup are frequently HRD or show genomic scars associated with HRD [74].

Cowden Syndrome. Cowden syndrome (CS) is a rare autosomal dominant condition characterized by hamartomatous tumors in multiple organs. CS has been linked to increased cumulative lifetime risk of BC (77–85 %), thyroid (35–38 %), renal (34 %) and endometrial (28 %) carcinomas, along with other features [77,78]. *PTEN* gPV/LPVs have been reported in 77–81 % of classic CS cases [79]. *PTEN* is one of the most commonly altered genes in EC [80] but gPV/LPVs are rare.

Lifetime EC risk in *PTEN* gPV/LPV carriers ranges from 10 % to 28 % [77,81]. Endometrioid EC is the most prevalent histologic type in the general population. Data from the International Multi-Center Prospective Study by Madhi et al. confirm that endometrioid histology is also the most prevalent histologic type in CS patients with EC. This study also highlights that EC occurs earlier (mean age 44) in *PTEN* gPV/LPVs [82]. In the light of an increased risk of other CS-related cancers, it would be important to identify those ECs associated with *PTEN* gPV/LPVs, in order to recommend prevention programs to patients and their families and take the opportunity of personalized therapies.

Pole/Pold1-Associated Tumor Syndrome. *POLE/POLD1*-associated tumor syndrome is a dominant inherited clinical condition with high penetrance characterized by a broad tumor spectrum due to *POLE/POLD1* gPV/LPVs. In 2013, Palles et al. [83] showed that specific heterozygous germline variants in proofreading exonuclease coding and splicing sequences of DNA polymerase ε (POLE) and δ (POLD1) were associated with multiple adenoma and/or CRC cases.

POLE and POLD1 form the major catalytic subunits of the Pol ε and Pol δ enzyme complexes that respectively synthesize the leading and lagging strands during DNA replication [27,84]. *POLE/POLD1* PV/LPVs map within the proofreading exonuclease domain (ED) of the respective enzymes. This may lead to an impairment of the normal DNA replication system with a potential increase in base substitutions, or cause the replication fork to collapse, resulting in DNA double-strand breaks and thus initiating tumorigenesis [85].

Germline mutations of *POLE* and *POLD1* may, even less frequently, predispose to other cancers than CRC, such as EC and BC [82]. *POLE* gPV/LPVs are rare and reported in 0.25–4 % of EC cases [86]. In the study by Siraj et al., for instance, four germline PV/LPVs (0.93 %) were identified in *POLE* and *POLD1* proofreading domains [87] in a cohort of 432 EC women from Saudi Arabia. Of the 47 EC patients in another study from South-East Asia, 4.3 % showed germline *POLD1* PV/LPVs and 29.7 % harbored germline or somatic *POLE* PV/LPVs [88].

STK11 – Peutz-Jeghers Syndrome (PJS). Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant syndrome characterized by multiple hamartomatous gastrointestinal polyps, mucocutaneous melanin spots in the oral mucosa, lips, wings of the nose, fingers and toes, and an increased risk of gastrointestinal and extra-intestinal cancers [89,90]. PJS is a disorder most often due to germline PV/LPVs in the tumor suppressor gene *STK11/LKB1* [91].

PJS is complicated by benign and malignant tumors of various organs. Among non-gastrointestinal clinical manifestations are testicular, ovarian, endocervix, breast and thyroid papillary malignancies, with a

different lifetime risk for each. In particular, the risk of developing gynecological cancers is high in PJS women, with an EC lifetime risk reported to be 9 % [92]. EC surveillance in patients with PJS is not recommended, unlike for ovarian, cervical and breast cancer [93].

Impact of EC molecular alterations in clinical practice

In the last years, the traditional pathological classification of EC has been integrated with a molecular system introduced by The Cancer Genome Atlas (TCGA) and analyzed in several subsequent studies. These revealed the strong prognostic and/or predictive value of each molecular subtype. Therefore, in order to optimize the decision-making process in relation to treatment, especially in adjuvant settings, the European guidelines, including those by the European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), European Society of Pathology (ESP) [65] and European Society of Medical Oncology (ESMO) [46], highlight the clinical relevance of combining molecular and pathological factors into risk stratification assessment (Table 2). In this scenario, the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial carcinoma was updated in June 2023 [94]. Compared to the previous version, FIGO 2023 staging includes non-anatomic parameters (such as tumor type, tumor grade, lymphovascular space invasion, and molecular alterations), offering a more detailed and evidence-based stratification of stages and, emphasizing the need to account for the complex heterogeneity of EC in the diagnostic-therapeutic process.

Table 2
Adjuvant therapy recommendations and risk stratification assessment according to both molecular and pathological criteria (ESMO Guidelines 2022) [47].

RISK GROUP	DESCRIPTION	RECOMMENDATION
LOW RISK	• Stage IA G1-G2 with endometrioid type, no or focal LVSI, dMMR or NSMP. • Stage I and II POLEmut cancer.	Adjuvant therapy is not recommended.
INTERMEDIATE RISK	• Stage IA non-endometrioid type, without myometrial invasion and no or focal LVSI and/or p53-abn cancers.	Adjuvant therapy is not recommended.
	• Stage IA G3 with endometrioid type, no or focal LVSI, dMMR or NSMP. • Stage IB G1-G2 with endometrioid type, no or focal LVSI, dMMR or NSMP. • Stage II G1 endometrioid type, no or focal LVSI, dMMR or NSMP.	Adjuvant therapy is recommended.
HIGH-INTERMEDIATE RISK	• Stage I with endometrioid type, any grade, any depth of invasion, with substantial LVSI, dMMR or NSMP. • Stage IB G3 with endometrioid type, regardless of LVSI, dMMR or NSMP. • Stage II G1 endometrioid type, with substantial LVSI, dMMR or NSMP. • Stage II G2-G3 endometrioid type, dMMR or NSMP.	Adjuvant therapy is recommended.
HIGH RISK	• All stages and all histologies with p53-abn and myometrial invasion. • All stages with serous or undifferentiated carcinoma including carcinosarcoma with myometrial invasion. • All stage III and IVA with no residual tumor, regardless of histology and regardless of molecular subtype.	Adjuvant therapy is recommended.

dMMR, mismatch repair deficient; G1-G3, grade 1–3; LVSI, lymphovascular space invasion; NSMP, no specific molecular profile; p53-abn, p53-abnormal; POLEmut, polymerase epsilon-ultramutated.

According to international guidelines, concerning the molecular classification, it is sound clinical practice to define *POLE* mutational status in the first place, then MMR expression in *POLE* wildtype ECs and finally p53 alteration in MMRp tumors (Fig. 3).

In everyday practice, surrogate markers are currently available to investigate MMR proteins and p53 status using immunohistochemistry (IHC). This has shown high concordance with microsatellite instability analysis [95,96] and *TP53* sequencing, respectively [97,98]. In contrast, current resources might not allow to detect *POLE* somatic pathogenic variants through DNA sequencing on all ECs: cheaper and more rapid testing techniques are needed.

Prospective studies are currently ongoing, such as the blue trial in the Refining Adjuvant treatment IN endometrial cancer Based On molecular features (RAINBO) [99], the phase III clinical trial PORTEC4a [100], the Tailored Adjuvant therapy in *POLE*-mutated and p53 wildtype early-stage Endometrial cancer (TAPER) [101] and CANSTAMP (NCT04159155), to name a few. Their aim is to improve risk evaluation and therapeutic patient care according to both molecular and clinical-pathological criteria.

The Ultramutated EC. In this subgroup, an excellent impact on recurrence rate and OS has been widely observed. In a recent *meta*-analysis, *POLE*-mutated women experienced almost no recurrences or cancer-related deaths, even in the presence of unfavorable features and regardless of adjuvant treatment [102]. Likewise, the phase III trial PORTEC3, carried out on patients with high-risk ECs, showed that ultramutated ECs had a good outcome in both adjuvant arms, resulting in 5-year Relapse free survival (RFS) and OS of 100 % with combined adjuvant chemotherapy and radiotherapy (CRT), as opposed to 96.6 % with radiotherapy alone (RT) [36]. In the light of this evidence, guidelines suggest classifying all stage I-II *POLE*-mutated ECs as low-risk tumors and de-escalating their adjuvant management. Regarding stage III *POLE*-mutated ECs, adequate de-escalation still needs to be further defined. In case of treatment, immune checkpoint inhibitors (ICIs) seem to be a potentially appropriate therapeutic resource, due to the high-density immune infiltrate that usually populates this subtype [30,103].

The Hypermutated EC. Assessing MMR status in ECs is recommended by guidelines for three main purposes: 1) identifying Lynch Syndrome cases; 2) obtaining prognostic information and 3) detecting patients who might benefit from immune-oncology (IO) treatment.

In the last few years, ample evidence has encouraged ICI use in monotherapy or in combination with other medications in advanced or recurrent ECs after progression to the first-line treatment. Following results from the GARNET study [104], the FDA and EMA have recently approved Dostarlimab (anti-PD1) for the treatment of recurrent or advanced MMRd ECs that failed on prior platinum-based therapy. Pembrolizumab alone also received FDA approval for previously-treated advanced MMRd ECs with high tumor mutational burden (defined as > 10 mut/Mb), according to outcomes in the KEYNOTE-158 trial [105]. Avelumab [106] and Durvalumab [107] are other ICIs for which promising findings were published in relation to MMRd ECs.

In contrast, IO in monotherapy does not appear efficient enough for MMRp ECs. Excellent outcomes were recorded with Pembrolizumab plus Lenvatinib administered as a second-line treatment in EC patients independent of MMR status [108], so that this IO-TKI combination was approved by the FDA and EMA.

More, encouraging and revolutionary results were very recently published about the therapeutic potential of ICI-chemotherapy combination, which might become a new standard in first-line treatment of recurrent/advanced ECs. The phase III RUBY study [109] documented a noteworthy advantage in terms of PFS in recurrent or primary advanced ECs treated with Dostarlimab plus Carboplatin-Paclitaxel, especially in MMRd group. Similarly, the NRG-GY018 trial [110] showed that the

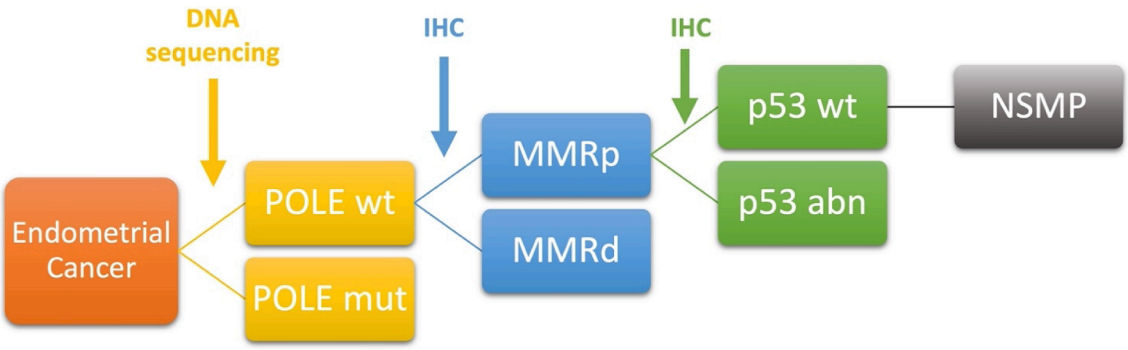

Fig. 3. Diagnostic algorithm to define molecular classification in endometrial cancer. POLE wt, POLE wild-type; POLE mut, POLE mutated; MMRd, mismatch repair deficient; MMRp, mismatch repair proficient; p53 wt, p53 wild-type; p53 abn, p53 abnormal; NSMP, no specific molecular profile; IHC, immunohistochemistry.

addition of Pembrolizumab to standard chemotherapy resulted in significantly longer PFS than with chemotherapy alone in both MMRd and MMRp populations.

In adjuvant setting, hypermutated ECs seem to be more susceptible to radiotherapy [111,112], but prospective studies are needed to confirm this. An ongoing phase III randomized trial (NRG-GY020) is evaluating whether the addition of Pembrolizumab to radiation therapy is more effective in stage I-II MMRd ECs. In the same way, the MMRd-GREEN trial included in the RAINBO program is estimating the outcome in early hypermutated ECs treated with adjuvant pelvic external beam radiotherapy combined with and followed by Durvalumab for one year [98].

Recurrent MMRd endometrial cancers are currently treated as one entity, but their susceptibility to ICIs tends to vary. A phase II clinical trial [113] showed a better outcome for Pembrolizumab in patients with mutational MMRd tumors than those with epigenetic MMRd tumors, consistent with previous evidence [114–116].

The Copy Number-High EC. According to current guidelines, stage IA non-endometrioid CN-H ECs without myometrial invasion and no or focal LVSI are classified as at intermediate risk of recurrence. However, this does not make them strong candidates for adjuvant treatment because of a lack of data clearly supporting benefits in terms of RFS. It is therefore recommended that every case be discussed by a multidisciplinary team [46]. On the other hand, all stages and all hystotypes with both *TP53* PV/LPVs and myometrial invasion are considered high-risk. As such, they should be treated with adjuvant chemotherapy added to radiotherapy (CRT) in a concomitant or sequential regimen [36,46].

Some trials are ongoing to improve therapeutic outcomes in CN-H ECs. Since a high genomic instability suggestive of homologous recombination deficiency (HRD) was revealed in CN-H ECs [75,117], the ongoing RAINBO program has been studying invasive stage I–III CN-H ECs treated with adjuvant CRT followed by two years of maintenance with Olaparib [98]. Likewise, the ongoing phase II/III CAN-STAMP trial (NCT04159155) aims to determine if the maintenance with niraparib could improve PFS in advanced CN-H ECs.

In the metastatic setting, interesting results were recently observed in the RUBY trial [109]. In this phase 3 study, dostarlimab plus carboplatin–paclitaxel significantly showed to increase PFS among patients with primary advanced or recurrent EC, with a substantial benefit in the dMMR–MSI-H population. Surprisingly, dostarlimab was also associated with improved PFS (HR, 0.55; 95 %CI, 0.3–0.99) and OS (HR, 0.41; 95 % CI, 0.2–0.82) in the TP53 subgroup [118]. Similarly, a NRG Oncology/Gynecologic Oncology Group (GOG) Study proved a PFS and OS advantage in patients treated chemotherapy plus bevacizumab [119,120].

Another potential targetable marker in CN-H ECs seems to be the human epidermal growth factor receptor 2 (HER2), which is overexpressed in 20–25 % cases [121]. Indeed, guidelines recommend carrying out IHC Her2Neu testing for patients with stage III or IV serous ECs. A randomized phase II trial in advanced or recurrent uterine serous HER2-positive carcinomas proved increased PFS and OS with carboplatin–paclitaxel–trastuzumab, compared to carboplatin–paclitaxel [122]. These results could be confirmed in the phase II/III NRG-GYO26 with trastuzumab and/or pertuzumab. In the recent phase II STATICE Trial, finally, trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate targeting HER2 with a topoisomerase I inhibitor payload, showed great efficacy and manageable toxicity in advanced or recurrent uterine carcinosarcomas pre-treated with chemotherapy, regardless of HER2 grade [123].

The BRCA-Associated EC. Nowadays, no specific therapeutic implications arise from the finding of *BRCA1/2* PV/LPVs in ECs. However, since some authors highlight a possible similarity between ovarian and uterine serous carcinomas, the need to associate hysterectomy with salpingo-oophorectomy (SO) in a risk-reducing treatment for *BRCA1/2* mutated women is a matter of debate [124]. A multicenter prospective cohort study of 1083 *BRCA 1/2* mutated women showed that, while the overall risk for uterine cancer after risk-reducing SO was not increased, the risk for uterine serous cancer was higher, suggesting that hysterectomy might be beneficial [71]. Conversely, the combined procedure of hysterectomy and SO amplifies costs, surgical complexity and potential complications (such as bleeding, infection, vaginal cuff dehiscence). For this reason, more evidence is still needed to justify routine prophylactic hysterectomy at the time of SO.

To date, PARPi have been approved for *BRCA* ovarian, breast, pancreatic and prostatic cancer, but not for uterine tumors. However, some cases of tumor remission with the use of PARPi in *BRCA*-mutated ECs are reported in the literature [125,126].

The PTEN-Associated EC. Currently, there is no approved and validated specific therapy for *PTEN* mutated EC. Studies to identify therapeutic targets for patients with *PTEN*-mutated EC have focused on the PI3K/AKT/mTOR pathway [127,128].

Several mTOR inhibitors have been studied in the context of *PTEN* mutated tumors, without confirming their preferential response in clinical trials. Among these, everolimus [129], temsirolimus [130] and ridaforolimus [131] have shown limited single-agent activity in phase II studies. It is noteworthy that everolimus, when combined with letrozole, achieved a 32 % ORR in recurrent EC, demonstrating particular effectiveness in cases with endometrioid histology [132]. In a randomized phase II study (GOG 248), temsirolimus showed modest activity (ORR 22 %), but the combination with megestrol acetate and tamoxifen was halted prematurely due to an increased risk of venous thrombosis [133]. In phase II studies, ridaforolimus showed moderate effectiveness in women with recurrent or metastatic EC [134], also when compared with progestin or investigator choice chemotherapy, even if associated with notable toxicity [131].

In this vein, recent studies have explored therapies targeting different components of the PI3K/AKT/mTOR pathway, such as PI3K, AKT and dual inhibitors. However, these treatments have shown limited

activity in their effectiveness [135] and many of them were limited by significant toxicity [136,137]. In addition, ECs are linked to obesity and there is a growing recognition of the impact of the PI3K pathway in promoting insulin resistance and cancer growth. As a result, there is rising interest in the study of metabolic therapies for EC [138]. In this way, preclinical investigations have demonstrated encouraging efficacy of metformin (via activation of the AMPK pathway) in EC cell lines [139], but no additional benefit was observed adding metformin to paclitaxel/carboplatin in the GOG 286 trial [140].

Among dual PI3K/mTOR inhibitors, a recent study on samotolisib (LY3023414) showed an 16 % ORR with a manageable safety profile in a population selected for PI3K pathway mutations, including *PTEN* [141]. Finally, studies involving AKT inhibitors have been constrained by toxicity issues and have reported minimal activity [142,143].

It should also be considered that *PTEN*, frequently mutated in EC, is indirectly involved in the homologous DNA recombination pathway through the upregulation of *RAD51* expression levels. The loss of *RAD51* function causes HRD [144]. The novel drug classes PARPi in HRD cancer cells have been shown to cause huge DNA damage with the accumulation of double-strand breaks, blocking DNA single-strand break repair via BER and trapping PARP enzymes. This therapeutic strategy exploits the phenomenon of synthetic lethality [145]. Several in vivo and in vitro studies have explored PARPi effectiveness in endometrioid EC lacking *PTEN* expression. Based on in vitro studies, Dedes et al. and Dinkic et al. have demonstrated that *PTEN* deficiency in EC cells provided significant sensitivity to PARPi [135], while the addition of the PARPi Olaparib sensitized EC cells to paclitaxel-induced apoptosis when exposed to the carboplatin/paclitaxel doublet [146]. In the context of the alteration of the PI3K/mTOR pathway, the use of PARPi in combination with PI3K inhibitors in EC cells showed good results [147,148]. Moreover, different in vivo studies conducted in breast cancer cell lines and in ovarian cancer patients showed that PARPi increased PD-L1 expression, while combining PARPi with anti-PD-L1 agents increased therapeutic efficacy [149].

Current PARPi trials in EC. Based on preclinical, clinical and translational data, several trials are ongoing to evaluate the strategic role of PARPi in metastatic, advanced and recurrent EC, alone or in combination with other drugs.

Among the completed studies, the Clovis-001 phase II trial showed that the combination of bevacizumab with rucaparib didn't induce any benefit in terms of PFS in patients with recurrent EC [150]. Otherwise, the phase II EndoBARR trial suggested a significantly improved response in patients with metastatic/recurrent EC, although long term survival data are still awaited [151]. Moreover, the ENDOLA phase Ib/II trial showed that the combination of olaparib 300 mg BID plus metformin 1500 mg/day and metronomic cyclophosphamide 50 mg/day is safe with a 61.5 % non-progression rate at 10 weeks [152]. The other main ongoing studies are summarized in Table 3.

Conclusions

Our knowledge on EC has been revolutionized in the last decade. Traditionally, prognosis and therapeutic decisions were based on histopathological and clinical factors. However, since TCGA project, the molecular alterations have been increasingly revealed and incorporated into risk stratification for EC. Thus, EC treatments shall be established in clinical practice according to both clinical-pathological and molecular criteria, mainly defining *POLE* mutational status, MMR expression and p53 alterations. At the same time, somatic and germline molecular EC characterizations have not yet been completed, and we expect that each molecular subtype will be further stratified to be managed accounting distinct therapeutical strategies focusing on different molecular EC subtypes to ultimately optimize clinical outcome.

Funding

Table 3
Summary of the main PARPi clinical trials in EC patients, available on clinicaltrials.gov.

NCT id	Drugs	Setting	Phase	Status	Primary EP
NCT04269200	Durvalumab ± Olaparib (DUO-E)	Advanced/Recurrent	III	Active, not recruiting	PFS
NCT03682289	Ceralasertib ± Olaparib or Durvalumab	Advanced/Metastatic	II	Recruiting	ORR
NCT03016338	Niraparib + Dostarlimab	Recurrent	II	Active, Not recruiting	antitumor activity
NCT05870761	Niraparib + Dostarlimab	Recurrent/Persistent	II	Recruiting	ORR
NCT03476798	Rucaparib + Bevacizumab (Clovis-001)	Recurrent	II	Completed	PFS
NCT03745950	Olaparib (UTOLA)	Advanced/Metastatic	II	Active, Not Recruiting	PFS
NCT05156268	Olaparib + Pembrolizumab	Persistent/Recurrent	II	Recruiting	ORR
NCT03617679	Rucaparib	Mestastatic/Recurrent maintenance	II	Active, Not Recruiting	PFS
NCT04080284	Niraparib	Advanced	II	Recruiting	PFS
NCT02912572	Talazoparib ± Avelumab/Axitinib	Recurrent/Persistent	II	Active, Not Recruiting	PFS
NCT03694262	Rucaparib + Atezolizumab + Bevacizumab (EndoBARR)	Recurrent/Persistent	II	Completed	ORR
NCT03660826	Olaparib ± Durvalumab/Cediranib/Capivasertib or Cediranib ± Durvalumab (NRG-GY012)	Recurrent/Refractory	II	Active, Not Recruiting	PFS
NCT05554328	Selumetinib ± olaparib (ComboMATCH)	Recurrent/Persistent	II	Recruiting	PFS
NCT02755844	Olaparib + Cyclophosphamide + Metformin (ENDOLA)	Recurrent	I/II	Completed	RP2D
NCT02208375	Olaparib + Vistusertib or Capivasertib	Advanced/Recurrent	Ib/II	Active, not recruiting	MTD
NCT04644068	AZD5305 ± other anticancer agents (PETRA)	Advanced	I /IIa	Recruiting	AEsDLT
NCT03586661	Niraparib + Copansilib	Recurrent	Ib	Active, not recruiting	MTD
NCT03552471	Rucaparib + Mirvetuximab Sorvtansine	Recurrent	I	Active, Not recruiting	RP2D
NCT04585958	Trastuzumab deruxtecan + Olaparib	Metastatic/Inoperable	I	Recruiting	MTD
NCT01366144	Veliparib + Paclitaxel + Carboplatin	Metastatic/Inoperable	I (early)	Active, Not recruiting	MTD
NCT03968406	Talazoparib + Radiotherapy	Advanced/Recurrent	I	Recruiting	MTDDLT
NCT04586335	Olaparib + CYH33 (PI3Kα inhibitor)	Advanced	Ib	Recruiting	DLTORR

PFS, progression free survival; MTD, maximally tolerated dose; RP2D, recommended phase 2 trial dose; DLT, dose limiting toxicity; ORR, overall response rate; AEs, adverse events.

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Elisa D'Agostino: Conceptualization, Methodology, Writing – original draft, Project administration. **Luciana Mastrodomenico:** Writing – original draft. **Ornella Ponzoni:** Writing – original draft. **Cinzia Baldessari:** Writing – review & editing. **Claudia Piombino:** Writing - Review & Editing. **Stefania Pipitone:** Writing – review & editing. **Maria Giuseppa Vitale:** Writing – review & editing. **Roberto Sabbatini:** Validation, Writing – review & editing. **Massimo Dominici:** Supervision. **Angela Toss:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision, Project administration, Funding acquisition. All authors have read and agreed to the published version of the manuscript.

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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