Changing treatments paradigms and role of immunotherapy in recurrent endometrial cancer

Anca Chelariu-Raicu[a], *Haider Mahdi*[b], *and Brian M. Slomovitz*[c]

Purpose of review
Over the past decade, the treatment of patients diagnosed with endometrial cancer (EC) shifted away from the use of chemotherapy to more novel targeted therapy and immunotherapy approaches.

Recent findings
The Cancer Genome Atlas data demonstrated different subgroups within ECs, more specifically, it facilitated the identification of predictive biomarkers. In particular, immunotherapies (immuno-oncology (IO)) are active either as monotherapy or in combination with other agents, depending on the biomarker profile of the tumor.

Summary
In May 2017, pembrolizumab was approved for patients with microsatellite instability high (MSI-H) EC. More recently, this approval was extended for patients harvesting tumors with a high tumor mutational burden status. Furthermore, in July 2021, the combination of pembrolizumab and lenvatinib was approved for patients who do not exhibit MSI-H disease. Given the wealth of targets in EC and different targetable mutations, the challenge will be to choose the proper treatment and the proper sequencing to derive the best outcome in the first-line setting and improve outcomes in subsequent settings. This review summarizes the current indications of immunotherapy for the treatment of advanced and recurrent EC. We outline the role of testing for uterine cancer and its implication in therapy management. Finally, we address new concepts for immunotherapy combinations with other therapies.

Keywords
endometrial cancer, immunotherapy, mismatch repair system, molecular biomarkers

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological cancer and mainly affects postmenopausal women. In the United States, there will be approximately 66,570 new cases of uterine cancer and 12,940 uterine cancer-related deaths in 2021 [1]. The 5-year survival rates for tumor limited to the uterus, tumor with regional spread, and distant metastasis is 95%, 69%, and 17%, respectively [2].

Given the fact that 70% of women are diagnosed at the stage of localized disease, staging surgery, including total hysterectomy and the evaluation of pelvic and para-aortic lymph nodes, represents the gold standard for first-line therapy. Factors such as advanced age, deep invasion, grade 3 tumor, and lymph-vascular space invasion have become evidence-based parameters assessing the risk of recurrence and help guide the adjuvant treatment of high-risk patients [3]. However, a systematic review reported an overall recurrence risk of 13% for all patients and 3% for patients at low risk [4].

Especially in the low-risk cases, there has been increased interest in identifying the molecular patterns of tumors that predict disease recurrence. Previous studies investigated different molecular biomarkers, such as estrogen regulation genes, DNA ploidy, mismatch repair deficiency (MMR), and homologous recombination deficiency [5–7]. None of these markers have been adopted into clinical practice. Therefore, the identification of

[a]Department of Obstetrics and Gynecology, Breast Cancer, Gynecologic Oncology Center and CCC Munich, LMU University Hospital, Munich, Germany, [b]Division of Gynecologic Oncology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania and [c]Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, Florida, USA

Correspondence to Brian M. Slomovitz, MD, MS, Division of Gynecologic Oncology, Mount Sinai Medical Center, Miami Beach, Florida, USA. E-mail: bslomovitz@gog.org

Curr Opin Obstet Gynecol 2022, 34:28–35
DOI:10.1097/GCO.0000000000000768

KEY POINTS

- Pembrolizumab and lenvatinib were approved for patients who do not exhibit MSI-H disease, extending the indication for immunotherapy in recurrent endometrial cancer.
- Several trials are investigating the efficacy of immunotherapy combined with chemotherapy in frontline settings.
- Future challenges for both frontline and recurrent endometrial cancer will be to choose the proper sequencing of chemotherapy, immunotherapy and other targeted agents.

predictive markers for recurrent low-risk EC patients remains an unmet need.

Recently, the therapeutic landscape of recurrent EC expanded from a combination of platinum- and taxane-based chemotherapy to immune checkpoints inhibitors in second line and subsequent settings (Fig. 1) [8▪▪,9▪,10]. This was based on distinctive genomic features, which involves defects in mismatch repair genes, leading to microsatellite instability (MSI) as well as frequent mutations in *PTEN, CTNNB1, PIK3CA, ARID1A*, and *KRAS* [11].

TEXT OF THE REVIEW

The immune landscape of endometrial cancer

During replication, DNA damage can be induced by both exogenous or endogenous factors, which will lead to the accumulation of either single-strand or double-strand breaks. These events will subsequently activate several DNA repair pathways throughout the cell-cycle [12]. The MMR pathway is activated during the S/G2 phase and is responsible for repairing single-strand breaks (SSB) using key proteins such as MSH2, MLH1, PMS2 or MSH6 [13]. Repairs occur in two steps, one involving MSH2/MSH6 heterodimers that bind to the initial DNA mismatched base errors followed by the excision and synthesis of corrected DNA chains at the mismatch site performed by MLH1/PMS2 heterodimers [14].

Based on the expression levels and functions of these proteins, a normal status refers to proficient MMR (pMMR), whereas decreased expression or dysfunctionality, including epigenetic silencing of *MHL-1*, results in deficient MMR (dMMR). Inactivation of any one of the *MMR* genes may result in DNA errors, such as base-base mismatches, insertions and deletions in repeated sequences, which may generate MSI [11]. Historically, even though the MSI

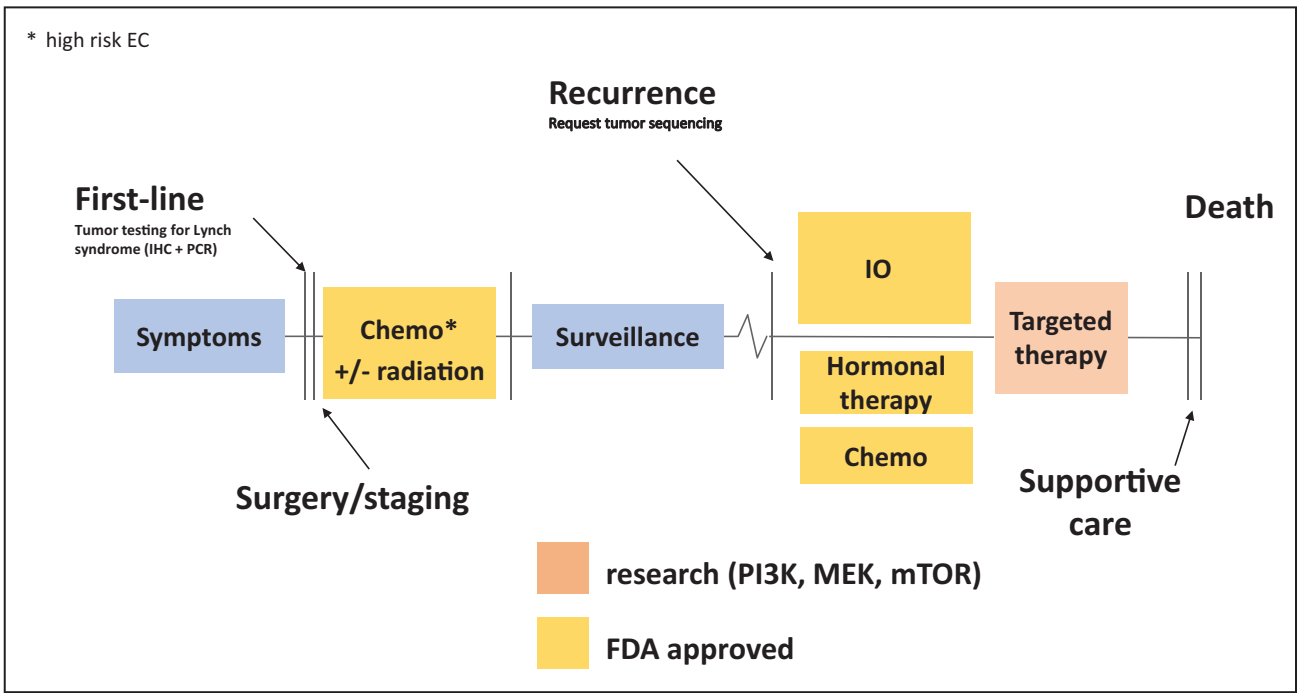

FIGURE 1. Treatment landscape in EC. *High risk EC. EC, endometrial cancer.

phenotype was recognized in EC cases, its value gained traction during the past 7 years following publications presenting the genomic characterization of EC [11,15]. In this analysis of 373 tumors using genomic, transcriptomic and proteomic studies, EC was classified into four molecular distinct entities, including ultra-mutated, hypermutated, copy-number low and copy number high. Interestingly, sequencing of the hypermutated group of tumors demonstrated decreased *MLH1* mRNA expression due to promoter methylation, therefore showing a high frequency of MSI in this group. The other groups of ultra-mutated and copy-number low groups, were generally classified as microsatellite instability stable (MSS) tumors.

A subgroup of MSI phenotype tumors consists of patients with Lynch syndrome, an autosomal dominant inherited tumor predisposition. This is characterized by a germline mutation in the MMR genes, accounting for a 2–5% frequency among EC patients [16]. Previous studies suggest that a significant percentage of women diagnosed with Lynch syndrome will present with EC as their initial cancer diagnosis [17]. Considering the high lifetime risk of developing other cancers, such as colorectal, ovarian, pancreatic and ureteral for women diagnosed with Lynch syndrome, regular testing for dMMR is indicated in EC patients as suggested by current guidelines [18,19]. Furthermore, these patients are given the opportunity for prevention through prophylactic salpingo-oophorectomy or screening for other cancers [20,21].

Beyond the dMMR/MSI signature, the biology of EC is characterized by a high mutational burden (Table 1). Using exome sequence analysis, The Cancer Genome Atlas (TCGA) identified a different tumor mutation burden (TMB) in the 4 molecular subtypes, including 232 $\times 10^{-6}$ mutations per Megabase (Mb) in the ultra-mutated group, 18 $\times$ 10^{-6} mutations per Mb in the hypermutated group, 2.9 $\times$ 10^{-6} mutations per Mb in the copy number low group and 2.3 $\times$ 10^{-6} mutations per Mb in the copy number high group. The high mutational load will generate changes in proteins and build neoantigens [22].

Altogether, the addition of the molecular characterization of EC using dMMR/MSI/TMB status to the histologic subtypes-based approach led to a better understanding of clinical outcomes based on the biology of EC and demonstrated that EC is a highly immunogenic tumor type. Considering these findings, several Food and Drug Administration (FDA) biomarker driven approvals for immunotherapy for the treatment of advanced and recurrent EC occurred over the last 4 years.

Table 1. A list of molecular alterations and their frequencies for endometrial cancers types [11]

Gene alteration	Prevalence in type I (%)***	Prevalence in type II (%)
PTEN	77.7	N/A
PIK3CA	53.1	41.9
PIK3R1	37.1	N/A
CTNNB1*	36.6	N/A
ARID1A	35.4	7
KRAS	24.6	N/A
CTCF	20.6	N/A
RPL22	12.6	N/A
TP53**	11.4	90.7
FGFR2	10.9	7
ARID5B	10.9	N/A
ATR	6.9	N/A
CCND1	5.7	N/A
MML4	9.1	N/A
BCOR	8	N/A
SPOP	5.7	7
SIN3A	5.7	N/A
MKI67	5.7	N/A
FBXW7	5.1	30.2
FOXA2	5.1	N/A
NRAS	2.9	N/A
PPP2R1A	N/A	27.9
CH4	N/A	16.3
CSMD3	N/A	11.6
COL11A1	N/A	11.6
PRPF18	N/A	7
CDH19	N/A	7
FOXA2	N/A	4.6
USP36	N/A	4.6

Molecular testing: deficient mismatch repair/microsatellite instability signature and beyond

In contrast to *BRCA1/2* testing in patients with ovarian cancer where the testing in performed in front-line setting for both germline and somatic mutations, the evaluation of *MMR* genes in newly diagnosed EC patients is performed regularly using tumor tissues, therefore assessing the exclusively of somatic mutations in the *MSH2, MLH1, PMS2* or *MSH6* genes. An absence of any proteins involved in the MMR pathway, as determined by immunohistochemistry, will further offer support for genetic counseling and germline testing to confirm or exclude the diagnosis of Lynch syndrome. Considering that MLH1 protein loss commonly occurs due

to *MLH-1* hypermethylation, immunohistochemistry is usually followed by the assessment of MLH-1 promoter methylation before initiating germline testing [23].

Although information on protein expression obtained from the immunohistochemistry assays can indirectly facilitate the assessment of a MSI-H score, that is defined by the loss of two MMR proteins, additional molecular biology techniques, such as the polymerase chain reaction (PCR), are routinely employed for the direct assessment of MSI through the evaluation of five independent primary microsatellite loci, including Bat-25, Bat-26, D2S123, D5S346 and D17S250 [24]. Tumors are defined as MSI-H when at least two of the five microsatellite loci are abnormal [25]. Previous studies investigating the detection rate of MSI compared immunohistochemistry or PCR alone vs performing both techniques together to reveal a 100% detection rate when both assays were used [26].

Furthermore, two different studies demonstrated the accuracy of detecting the MSI phenotype using a sequencing panel based on mutational phenotype [27,28]. Another advantage of tumor sequencing is the evaluation of TMB. This is especially important since TMB itself has been recently approved as predictive biomarker for selecting patients for immunotherapy [9▪]. Given the complete molecular profile of the tumor provided by sequencing, including predictive biomarkers such as dMMR/MSI and TMB for therapy guidance, this single test demonstrates several clinical advantages. However, few, newly diagnosed EC patients will be provided with such an extensive molecular diagnosis, especially given the costs of sequencing. Therefore, immunohistochemistry and PCR remain reliable gold standard assays currently used in front-line setting, whereas tumor sequencing is performed in advanced or recurrent setting. A summary of the testing techniques along with their limitations is summarized in Table 2.

Table 2. Summary of assessments for molecular biomarkers in EC

Biomarker	Tumor material	Assay
MMR	Protein	Immunohistochemistry on FFPE
MSH2		
MLH1		
PMS2		
MSH6		
MSI	DNA	1. Immunohistochemistry on FFPE
MLH1 methylation		2. PCR
TMB	DNA	Targeted DNA sequencing panel

EC, endometrial cancer; FFPE, Formalin-Fixed Paraffin-Embedded; MMR, mismatch repair; MSI, microsatellite instability ; PCR, polymerase chain reaction; TMB, tumor mutational burden.

Clinical development of IO in microsatellite instability-high cancers

Since the dramatic increase in both PFS and overall survival (OS) after immune checkpoints inhibitors in melanoma and nonsmall lung cell cancer, clinical research in the field of immunotherapy experienced exponential growth. However, the immunogenic potential across different cancer subtypes is driven by several mechanisms, such as mutations, mismatches and viral infections, which are all distinguished based on the level of neoantigen load necessary for activating the immune response. Besides a consistent response to therapy for melanoma and lung cancer due to their high mutation rate secondary to ultraviolet (UV) light and tobacco smoke exposure, the dMMR signature showed a significant correlation with PD-1 blockade response and subsequently led to several FDA approvals for cancers with dMMR (Fig. 2) [29–31].

Keynote-016, a phase 2 trial that investigated pembrolizumab in the treatment of tumors with dMMR or pMMR, was the first clinical study testing the hypothesis that dMMR tumors present higher susceptibility to PD-1 blockade than the proficient group [32]. Despite the small sample size of patients ($n = 16$) enrolled in this study, the immune-related objective response rate (ORR) of 40% vs 0% and the immune-related PFS of 78% vs 11% was impressive when comparing the dMMR vs the pMMR cohorts. The observations of KEYNOTE-016 led to an extended assessment of MMR deficiency as a predictive biomarker in a larger cohort of patients across 12 different tumor types. Interestingly, in this study, colorectal cancer MSI-H patients demonstrated a similar ORR as noncolorectal patients with MSI-H as shown by 52% (95% CI, 36–68%) and 54% (95% CI, 39–69%), respectively [31].

In light of these findings as well as clinical results from 149 patients diagnosed with MSI-H cancer enrolled in five uncontrolled, multicohort, multicenter, single-arm clinical trials, in 2017, the FDA granted the first accelerated approval of pembrolizumab for the treatment of different cancers, including EC [8▪▪,33–35]. Preliminary data in the 2017 FDA approval included an open-label, phase II KEYNOTE-158 multicohort study of pembrolizumab. This trial was performed in 233 patients who had previously treated, advanced noncolorectal MSI-H tumors, totaling 27 different histologies, was reported in its final form in 2019 [9▪]. Key

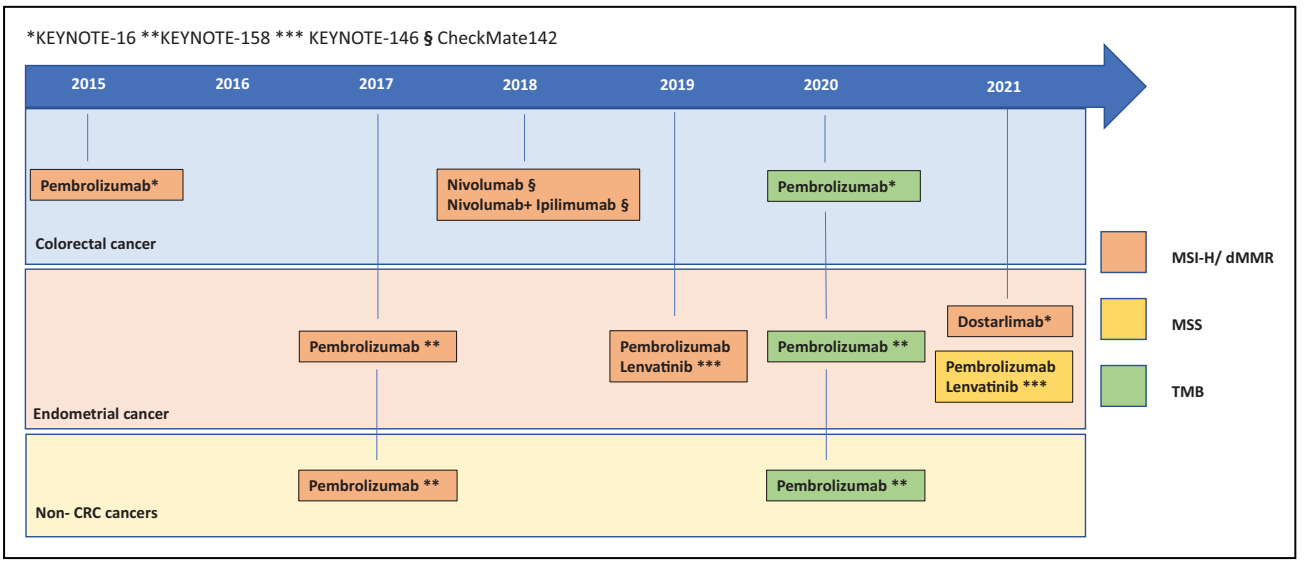

FIGURE 2. FDA approvals summary for IO based on MSI and TMB status in solid tumors. *KEYNOTE-16; **KEYNOTE-158; *** KEYNOTE-146; § CheckMate142. EC, endometrial cancer; MSI, microsatellite instability; TMB, tumor mutational burden.

findings of this trial included an overall response rate (ORR) of 34.3%, with approximately one-third of patients demonstrating a complete response. Furthermore, the median duration of the response was not reached when the manuscript was published, but the extent of response anticipated by the authors was a PFS exceeding 24 months. Interestingly in the subset of 49 patients with MSI-H EC, the ORR was 57% and median PFS was 24.7 months. These data are impressive with durable efficacy that support testing immunotherapy alone in the first-line setting in MSI-H subset. Further, another immune checkpoint inhibitor, anti-PD1 dostarlimab was investigated in 104 MSI-H recurrent EC, the ORR was 42%. The responses were durable [36▪]. These data led to FDA approval of dostarlimab in MSI-H EC in April 22, 2021.

In addition, a second analysis of the trial was to explore the association of TMB with clinical outcomes of patients receiving pembrolizumab monotherapy. These results revealed an ORR of 30.3% (95% CI, 21.5–40.4) in the tTMB-high group ($n = 99$), an ORR of 27.1% (95% CI, 18.0–37.8) in the tTMB-high group excluding MSI-H ($n = 85$) and an ORR of 6.7% (95% CI, 4.9–9.0) in the tTMB-low ($n = 652$) [9▪]. However, results on PFS and OS in the TMB-high and TMB-low groups were difficult to interpret due to numerous baseline variables influencing long-term prognosis, including prior therapy and prevalence of tumor types. Surprisingly, when limiting the analysis to the TMB high, non MSI-H patient cohort, the response rate was still 4-fold more than the response rate observed for the tTMB-low group, (27.1% vs 6.7%, respectively).

Furthermore, this observation supports prior knowledge that less than 20% of cases with high TMB are MSI-H, supporting the value of TMB as a predictive biomarker [22]. In April 2020, the FDA extended the approval of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors and tumors with high mutational burden (TMB-H; $\geq$10 mutations/Mb). In contrast to the 2017 FDA approval of pembrolizumab in MSI-H tumors with no approved companion test for MSI testing, the recent FDA approval added the FoundationOneCDx assay as a companion diagnostic for pembrolizumab to identify patients with TMB high solid tumors who may benefit from immunotherapy.

Clinical development of IO in microsatellite instability stable endometrial cancer cancers

Despite 30% of EC cases presenting the MSI-H phenotype, which represents the highest frequency among all cancer subtypes, the other 70% of EC are microsatellite-stable and have limited treatment options in the recurrent setting [37]. More specifically, the ORR reported by previous clinical studies evaluating the treatment with antiangiogenic agents or palliative chemotherapy in advanced and recurrent EC accounts for only 14–16% of patients [38]. Taken together, this led to the initiation of a phase 2 KEYNOTE-146 multicenter, open-label, single-arm study that investigated the combination of pembrolizumab with lenvatinib, a multikinase inhibitor against VEGFR1, VEGFR2 and VEGFR3 in patients with advanced EC, irrespective

Table 3. FDA approvals for IO treatment in patients with recurrent endometrial cancer

Drug	Indication	Year
Pembrolizumab plus lenvatinib	Treatment of adult patients with advanced endometrial cancer who have disease progression following prior systemic therapy who are not candidates for curative surgery or radiation and who have disease that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).	July 21, 2021
Dostarlimab	Treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following a prior platinum-containing regimen.	April 22, 2021
Pembrolizumab	Treatment of adult and pediatric patients with unresectable or metastatic solid tumors with tissue tumor mutational burden-high (TMB-H) who have progressed following prior treatment and who have no satisfactory alternative treatment options.	April 7, 2020
Pembrolizumab plus lenvatinib	Pembrolizumab plus lenvatinib - Treatment of adult patients with advanced endometrial cancer who have disease progression following prior systemic therapy who are not candidates for curative surgery or radiation and who have disease that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).	Sep 17, 2019
Pembrolizumab	Treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have progressed following prior treatment and who have no satisfactory alternative treatment options- multiple studies	May 23, 2017

of MSI status [39]. Preliminary ORR analysis of 54 patients after a median follow-up of 13.3 months demonstrated an HR of 39.6% (95% CI, 26.5–54.0). These findings supported a third FDA approval of IO in combination with lenvatinib, which is the only approval specific for EC besides the FDA approvals for pembrolizumab in patients with advanced EC tumors harboring MSI-H and TMB (Table 3). Recently, a confirmatory phase III of the KEYNOTE-775 trial was reported at the annual SGO 2021 meeting. The study included 827 patients with advanced metastatic or recurrent EC after progression on one prior platinum-based regimen. The study showed that pembrolizumab/lenvatinib significantly improved OS, PFS and objective response compared to single-agent chemotherapy (physician choice of Adriamycin or weekly paclitaxel). Median PFS was 7.2 months vs 3.8 months (HR 0.56, $P < 0.0001$) and median OS was 18.3 vs 11.4 months (HR 0.63, $P < 0.0001$). The ORR was 31.9% with pembrolizumab/lenvatinib compared to 14.7% with physician choice chemotherapy. Based on these data, in July 21, 2021 the FDA granted regular approval for pembrolizumab in combination with lenvatinib for patients with advanced endometrial carcinoma that is not MSI-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Clinical data from two different trials investigating avelumab and durvalumab in recurrent EC setting for all comers were reported over the last 2 years (Table 4). Konstantinopoulos *et al.* evaluated the PD-L1 inhibitor, avelumab, in 33 patients irrespective of MSI status [40]. Overall, there were five confirmed responders, four in the dMMR group and only one in the pMMR group, who were still receiving therapy at the cutoff date. However, despite showing antitumor efficacy, the insufficient clinical benefit among the pMMR cohort does not support additional evaluation. Lastly, preliminary results from the PHAEDRA study evaluated the activity of durvalumab in a single-arm phase II trial using a cohort of recurrent EC. The ORR was 40% in the dMMR population, showing 4 CR and 10 PR, whereas only one patient showed a response in the pMMR population, with an ORR of 3% [41].

Novel combination immunotherapy approaches

Given MSI-H EC is highly immunogenic tumor, further efforts are warranted to investigate the role and clinical efficacy of other immune checkpoint inhibitors along with anti-PD1/PDL1. Common targets to be tested in combination with anti-PD1/PDL1 therapy are anti-CTL4 and anti-LAG3 therapies. Utilizing TCGA data of EC, patients with EC with POLE mutated or MMRd tumors are

Table 4. Immunotherapy trials Phase I/II in recurrent endometrial cancer

Study	MSI status	Prior therapy	Experim arm	ORR ITT	ORR MSI_H	ORR MSS
GARNET I/II *Oaknin et al.*	All comers	≤2 prior lines	Dostarlimab	29.6% (21.8%–38.4%)	48.8% (32.9% to 64.9%)	20.3% (12.0%–30.8%)
KEYNOTE-146 Ib/II *Makker et al.*	All comers	≤2 prior lines	Pembrolizumab Lenvatinib	38% (28.8%–47.8%)	63.6% (30.8%–89.1%)	36.2% (26.5%–46.7%)
KEYNOTE-158 II *Marabelle et al.*	MSI-H	No limit	Pembrolizumab	N/A	57.1% (42.2%–71.2%)	
Phase II Konstantinopoulos *et al.*	All comers	No limit	Avelumab	N/A	27% (7.8%– 55.1%)	6% (0.16% to 30.2%)
PHAEDRA II Mirelli *et al.*	All comers	≤3 prior lines	Durvalumab	N/A	43% (26%–56%)	3% (1%–14%)

MSI-H, microsatellite instability high; ORR, objective response rate.

Table 5. Immunotherapy trials in first line metastatic or recurrent endometrial cancer

Study	Design/Description
GOG-3031/RUBY NCT03981796	A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) Plus Carboplatin-paclitaxel vs Placebo Plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer
GOG-3041/DUO-E NCT04269200	A Randomized, Multicenter, Double-blind, Placebo-controlled, Phase III Study of First-line Carboplatin and Paclitaxel in Combination With Durvalumab, Followed by Maintenance Durvalumab With or Without Olaparib in Patients With Newly Diagnosed Advanced or Recurrent Endometrial Cancer
LEAP -001 NCT04865289	Pembrolizumab (MK-3475) Plus Lenvatinib (E7080/MK-7902) vs Chemotherapy for Endometrial Carcinoma (ENGOT-en9/MK-7902-001)
Attend NCT03603184	Phase III Double-blind Randomized Placebo Controlled Trial of Atezolizumab in Combination With Paclitaxel and Carboplatin in Women With Advanced/Recurrent Endometrial Cancer
NRG-GY-018 NCT03914612	Testing the Addition of the Immunotherapy Drug Pembrolizumab to the Usual Chemotherapy Treatment (Paclitaxel and Carboplatin) in Stages III–IV or Recurrent Endometrial Cancer

characterized by up-regulation of PD1 and CTLA4 compared to patients with proficient MMR. Similar findings were noted for LAG3 [42].

Combination of immunotherapy with chemotherapy in first-line setting

Given the encouraging activity of immunotherapy-based therapies in second-line settings, currently there are several phase III trials investigating the efficacy of immunotherapy combined with chemotherapy or pembrolizumab/lenvatinib compared to chemotherapy alone in first line advanced stage metastatic or recurrent EC (Table 5). The results of these trials will be important to direct future care of patients with EC both in first line and second-line settings.

CONCLUSION

These data support the role of immunotherapy in EC. Future trials are warranted to test the efficacy of immunotherapy alone in first line MSI-H EC as well as combination immunotherapy. Further, studies to understand mechanism of resistance and approaches to overcome resistance to immunotherapy in these cancers.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. NCI, Cancer Stat Facts: Uterine Cancer. 2021. https://seer.cancer.gov/statfacts/html/corp.html.
2. Society, A.C., Cancer Facts & Figures 2021. 2021. https://www.cancer.org/latest-news/facts-and-figures-2021.html.
3. Creutzberg CL, Lu KH, Fleming GF. Uterine cancer: adjuvant therapy and management of metastatic disease. J Clin Oncol 2019; 37:2490–2500.
4. Fung-Kee-Fung M, Dodge J, Elit L, *et al.* Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol 2006; 101:520–529.
5. Westin SN, Broaddus RR, Deng L, *et al.* Molecular clustering of endometrial carcinoma based on estrogen-induced gene expression. Cancer Biol Ther 2009; 8:2126–2135.
6. Susini T, Amunni G, Molino C, *et al.* Ten-year results of a prospective study on the prognostic role of ploidy in endometrial carcinoma: dNA aneuploidy identifies high-risk cases among the so-called 'low-risk' patients with well and moderately differentiated tumors. Cancer 2007; 109:882–890.
7. McMeekin DS, Tritchler DL, Cohn DE, *et al.* Clinicopathologic significance of mismatch repair defects in endometrial cancer: An NRG oncology/gynecologic oncology group study. J Clin Oncol 2016; 34:3062–3068.
8. ■■ Makker V, Taylor MH, Aghajanian C, *et al.* Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol 2020; 38:2981–2992.

This trial demonstrated that the combination of lenvatinib plus pembrolizumab is effective for the treatment of patients with advanced endometrial cancer that is not microsatellite instability-high or mismatch deficient. This granted FDA regular approval for pembrolizumab in combination with lenvatinib for this group of patients.

9. ■ Marabelle A, Le DT, Ascierto PA, *et al.* Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the Phase II KEYNOTE-158 Study. J Clin Oncol 2020; 38:1–10.

This multicohort study of pembrolizumab was performed in 233 patients with recurrent noncolorectal MSI-H tumors, totaling 27 histologies. The results indicated that approximately one third of patients demonstrated a complete response, being the first study which included noncolorectal histologies.

10. Colombo N, Lorusso D, Casado Herráez A, *et al.* Outcomes by histology and prior therapy with lenvatinib plus pembrolizumab vs treatment of physician's choice in patients with advances endometrial cancer (Study 309/KEYNOTE-775). Ann Oncol 2021; 32:S729–S730.
11. Cancer Genome Atlas Research Network. Kandoth C, Schultz N, Cherniack AD, *et al.* Integrated genomic characterization of endometrial carcinoma. Nature 2013; 497:67–73.
12. Lheureux S, Mirza M, Coleman R. The DNA repair pathway as a target for novel drugs in gynecologic cancers. J Clin Oncol 2019; 37:2449–2459.
13. Germano G, Amirouchene-Angelozzi N, Rospo G, *et al.* The clinical impact of the genomic landscape of mismatch repair-deficient cancers. Cancer Discov 2018; 8:1518–1528.
14. Zhao P, Li L, Jiang X, *et al.* Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. J Hematol Oncol 2019; 12:54.
15. Basil JB, Goodfellow PJ, Rader JS, *et al.* Clinical significance of microsatellite instability in endometrial carcinoma. Cancer 2000; 89:1758–1764.
16. Lynch HT, Snyder CL, Shaw TG, *et al.* Milestones of Lynch syndrome: 1895-2015. Nat Rev Cancer 2015; 15:181–194.
17. Lu KH, Dinh M, Kohlmann W, *et al.* Gynecologic cancer as a 'sentinel cancer' for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol 2005; 105:569–574.
18. Concin N, Matias-Guiu X, Vergote I, *et al.* ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2020; 31:.
19. NCCN, Endometrial Carcinoma and Uterine Sarcoma Guidelines. 2021.
20. Schmeler KM, Sun CC, Bodurka DC, *et al.* Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. Obstet Gynecol 2006; 108(3 Pt 1):515–520.
21. Jenkins MA, Dowty JG, Ait Ouakrim D, *et al.* Short-term risk of colorectal cancer in individuals with lynch syndrome: a meta-analysis. J Clin Oncol 2015; 33:326–331.
22. Ros J, Baraibar I, Vivancos A, *et al.* Review of Immunogenomics and the Role of Tumor Mutational Burden as a Biomarker for Immunotherapy Response. J Immunother Precis Oncol 2019; 2:.
23. Esteller M, Levine R, Baylin SB, *et al.* MLH1 promoter hypermethylation is associated with the microsatellite instability phenotype in sporadic endometrial carcinomas. Oncogene 1998; 17:2413–2417.
24. Berg KD, Glaser CL, Thompson RE, *et al.* Detection of microsatellite instability by fluorescence multiplex polymerase chain reaction. J Mol Diagn 2000; 2:20–28.
25. Umar A, Boland CR, Terdiman JP, *et al.* Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004; 96:261–268.
26. Funkhouser WK Jr, Lubin IM, Monzon FA, *et al.* Relevance, pathogenesis, and testing algorithm for mismatch repair-defective colorectal carcinomas: a report of the association for molecular pathology. J Mol Diagn 2012; 14:91–103.
27. Nowak JA, Yurgelun MB, Bruce JL, *et al.* Detection of mismatch repair deficiency and microsatellite instability in colorectal adenocarcinoma by targeted next-generation sequencing. J Mol Diagn 2017; 19:84–91.
28. Stadler ZK, Battaglin F, Middha S, *et al.* Reliable detection of mismatch repair deficiency in colorectal cancers using mutational load in next-generation sequencing panels. J Clin Oncol 2016; 34:2141–2147.
29. Berger MF, Hodis E, Heffernan TP, *et al.* Melanoma genome sequencing reveals frequent PREX2 mutations. Nature 2012; 485:502–506.
30. Lee W, Jiang Z, Liu J, *et al.* The mutation spectrum revealed by paired genome sequences from a lung cancer patient. Nature 2010; 465:473–477.
31. Le DT, Durham JN, Smith KN, *et al.* Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 2017; 357:409–413.
32. Le DT, *et al.* PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372:2509–2520.
33. O'Neil BH, Wallmark JM, Lorente D, *et al.* Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. PLoS One 2017; 12:e0189848.
34. Chow LQM, Haddad R, Gupta S, *et al.* Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the Phase Ib KEYNOTE-012 Expansion Cohort. J Clin Oncol 2016; 34:3838–3845.
35. FDA, Prescribing information pembrolizumab injection for intravenous use. 2021.
36. ■ Oaknin A, Tinker AV, Gilbert L, *et al.* Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a non-randomized Phase 1 Clinical Trial. JAMA Oncol 2020; 6:1766–1772.

This trial demonstrated durable efficacy of anti-PD1, dostarlimab, which was investigated in 104 MSI-H recurrent endometrial cancer. This led to FDA approval of dostarlimab for recurrent endometrial cancer in April 2021.

37. Hause RJ, Pritchard CC, Shendure J, *et al.* Classification and characterization of microsatellite instability across 18 cancer types. Nat Med 2016; 22:1342–1350.
38. Makker V, Green AK, Wenham RM, *et al.* New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract 2017; 4:19.
39. Makker V, Rasco D, Vogelzang NJ, *et al.* Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2019; 20:711–718.
40. Konstantinopoulos PA, Luo W, Liu JF, *et al.* Phase II Study of avelumab in patients with mismatch repair deficient and mismatch repair proficient recurrent/persistent endometrial cancer. J Clin Oncol 2019; 37:2786–2794.
41. Diver E, Dorigo O, Berek J. ASCO 2019 meeting review. J Gynecol Oncol 2019; 30:e107.
42. van Gool IC, Eggink FA, Freeman-Mills L, *et al.* POLE proofreading mutations elicit an antitumor immune response in endometrial cancer. Clin Cancer Res 2015; 21:3347–3355.