Emerging Treatment Options for Advanced or Recurrent Endometrial Cancer

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Abstract

Endometrial cancer is the most common cancer of the female reproductive organs. The American Cancer Society estimates that there will be over 65,950 new cases diagnosed in 2022. According to the National Comprehensive Cancer Network (NCCN) Guidelines, response rates in the front-line setting are approximately 40% to 62%. Prior to the recent U.S. Food and Drug Administration (FDA) approvals of immunotherapy, there had been no standard of care for women after failing front-line carboplatin and paclitaxel. In May 2017, the FDA approved single-agent pembrolizumab in microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) endometrial cancer patients following failure of systemic therapy. Then, in September 2019, the FDA approved pembrolizumab and lenvatinib for women who are not MSI-H or are MMR-proficient. This approval was based on KEYNOTE-146 and Study 111. Among 94 non–MSI-H women, 80% of those treated with pembrolizumab and lenvatinib had tumor shrinkage, and 38.3% had objective response by RECIST 1.1 as assessed by an independent radiology committee. The median duration of response was not reached, with 69% being progression free at 6 months. Grade 3/4 treatment-related adverse events (AEs) occurring in > 20%, including fatigue, hypertension, and gastrointestinal AEs. With supportive care, early identification, and intervention, the side effect profile was manageable, with only 21% discontinuing treatment due to AEs.

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, with an estimated 65,950 new cases and 12,550 deaths in 2022 (American Cancer Society, 2022). Over the past decade, the incidence has increased by about 1% per year, which is thought to be related to longer life expectancy and higher obesity rates (American Cancer Society, 2022; Levine & The Cancer Genome Atlas Research, 2013; National Comprehensive Cancer Network [NCCN], 2022). Most women are diagnosed at an early stage and have a

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good prognosis with treatment; 5-year survival is 95% with local disease and 69% with regional disease (American Cancer Society, 2021). However, about 8% are diagnosed at a later stage or with recurrent disease; these women have a 5-year overall survival (OS) rate of 17%, in part related to the lack of effective systemic treatment options (American Cancer Society, 2021; Makker et al., 2017).

Although EC is a disease usually associated with older age, it can present in women at any age. Approximately 70% of the disease can be attributed to excess body weight and insufficient physical activity, most likely due to an increase in circulating estrogen associated with obesity (American Cancer Society, 2022). A BMI in excess of 30 kg/m^2 is associated with up to 81% of diagnosed EC (Moore & Brewer, 2017). Risk factors for EC include increased estrogen exposure—early menarche, late menopause, nulliparity, hormone replacement therapy, or tamoxifen—and genetic mutations such as Lynch syndrome (American Cancer Society, 2022; Di Tucci et al., 2019; Makker et al., 2017). Most EC results from a spontaneous mutation, but up to 5% of cases are associated with germline mutations in mismatch repair (MMR) genes (Di Tucci et al., 2019). Endometrial cancer associated with germline mutations tends to develop in younger women, making screening for Lynch syndrome a particularly important recommendation for patients < 50 years of age presenting with EC (NCCN, 2022).

ENDOMETRIAL CANCER CLASSIFICATIONS

Based on a system developed in the 1980s, EC has been classified as type 1 (60%–70% of cases) or type 2 (~30% of cases; Bokhman, 1983; Giannone et al., 2019; Le Gallo & Bell, 2014; Makker et al., 2017). Type 1 EC is characterized by endometrioid histology, endometrial hyperplasia, expression of estrogen receptors (ER) and progesterone (PR) receptors, and frequently MMR deficiency (dMMR)/microsatellite instability (MSI). The typical type 1 EC patient is younger, obese or overweight, and nulliparous. Type 1 EC is generally low grade and confined to the uterus; it has a good prognosis with treatment, as the 5-year OS rate is 86% (Giannone et al., 2019; Makker et al., 2017).

Type 2 EC is characterized by nonendometrioid histology, usually serous or clear cell carcinoma or high-grade adenocarcinoma, and is not dependent on estrogen for proliferation. The cancer tends to have little or no ER/PR expression but may be human epidermal growth factor receptor 2 (HER2)–positive and show aneuploidy. Typically, the patient with type 2 EC is older, often a woman of color, a smoker, and less likely to be obese or nulliparous. Type 2 EC is associated with a poorer prognosis, with a 5-year OS rate of 59% (Giannone et al., 2019; Makker et al., 2017).

Multiple genetic pathways have been implicated in the development and proliferation of type 2 EC, including the *PI3K*/AKT/mammalian target of rapamycin complex 1 (mTOR) pathway in type 1 EC, and *TP53* mutation, *PIK3CA* mutation, and HER2 amplification, but there may be overlap of these pathways (Giannone et al., 2019; Le Gallo & Bell, 2014). The *PI3K* pathway is often altered in EC, with downstream effects on insulin-like growth factor (which is upregulated in obesity and EC), mTOR, and AKT (Makker et al., 2017). Although this pathway offers potential targets for treatment, to date, only mTOR inhibitors have shown promising activity in EC in combination with endocrine therapy (Slomovitz et al., 2015, 2018).

MOLECULAR PROFILING

There are several challenges associated with using histologic type and ER/PR expression to classify EC. For instance, it is often difficult to classify tumors histologically, and many have overlapping clinical characteristics or genetic mutations. Another issue is that morphologic classification is generally not reproducible and presents an imperfect characterization of tumor biology (Giannone et al., 2019; Le Gallo & Bell, 2014; Liu, 2007; Makker et al., 2017; Suarez et al., 2017).

A more accurate way to classify EC tumors is by genomic subgroups focused on reproducible profiles; mutational burden; MSI/dMMR; presence of specific *TP53*, *POLE*, and *PTEN* mutations; and histology (Levine & The Cancer Genome Atlas Research Network, 2013; Suarez et al., 2017; Talhouk et al., 2017). The Cancer Genome Atlas Research Network has identified four distinct subgroups of EC using tumor samples and germline DNA from 373 women with EC (Levine & The Cancer Genome Atlas Research Network, 2013; NCCN, 2022).

POLE Ultra-Mutated

These represent 17.4% of high-grade endometrioid tumors and carry a high mutational burden but are associated with good prognosis and the longest progression-free survival (PFS) times. POLE tumors rarely recur after front-line treatment, but metastatic recurrences have been reported (Giannone et al., 2019; NCCN, 2022; Stasenko et al., 2020).

Microsatellite Instability-High

These represent 28.6% of low-grade and 54.3% of high-grade endometrioid tumors. An analysis of MSI-H prevalence in 39 cancer types found a rate of 31.4% overall in EC, which was the highest rate among solid tumors that were analyzed. MSI-H EC has a high mutation rate related to the MMR system (i.e., dMMR; Bonneville et al., 2017; Giannone et al., 2019).

Copy Number Low

These are low-grade endometrioid tumors with a low mutation rate, characterized by microsatellite stable (MSS) and high ER/PR expression. Approximately 77% of copy number low EC have *PTEN* and 90% have *PI3K* mutations (Giannone et al., 2019).

Copy Number High Serous-Like Tumors

These tumors have serous or mixed histology with low mutation rates but a high percentage of *TP53* mutation. This type of EC is characterized by HER2 amplification, cell cycle deregulation, and a poor prognosis with the shortest PFS times (Giannone et al., 2019; Levine & The Cancer Genome Atlas Research Network, 2013).

Testing

As knowledge and treatment options advance, management becomes more complex. Because of the implications for treatment and prognosis, the NCCN recommends universal MMR and MSI testing for all patients with endometrial carcinomas. Identification of *MLH1* loss requires further evaluation for promoter methylation to determine whether an epigenetic or germline mutation is present. For all other MMR abnormalities, and for patients who are dMMR-negative or unscreened with a strong family history of endometrial or colorectal cancer, referral for genetic counseling and testing (e.g., for Lynch syndrome) is recommended. The NCCN further recommends that ER testing be done in advanced or recurrent disease, and that HER2 status be determined for possible treatment of advanced or recurrent serous EC (NCCN, 2022).

FRONT-LINE TREATMENT OF ADVANCED ENDOMETRIAL CANCER

Front-line treatment for women with advanced EC is firmly established as platinum-based chemotherapy plus a taxane (Concin et al., 2020; NCCN, 2022). Recommendations from the NCCN give preference to carboplatin (target AUC 5–6) plus paclitaxel (175 mg/m^2) on a 21-day cycle (Concin et al., 2020). This combination is used with or without trastuzumab (Herceptin) depending on the patient's HER2 status. Other possible regimens include carboplatin and paclitaxel with bevacizumab, carboplatin and docetaxel, cisplatin and doxorubicin, or various recommended agents used as monotherapy based on individual patient factors (NCCN, 2022).

Multiagent regimens are considered for most women. Response rates with carboplatin plus paclitaxel range from 40% to 62%, with median OS times of 13 to 29 months. Response rates with other options as front-line treatment range from 31% to 81%, but the duration of response tends to be shorter. In a Gynecologic Oncology Group analysis of women with advanced or recurrent EC, median OS was < 12 months, and median PFS ranged from 3 to 6 months with these options, depending on tumor histology (Makker et al., 2017; McMeekin et al., 2007).

All of these front-line treatment options are associated with significant toxicity; thus, a discussion about patient preferences and quality of life should be a part of shared decision-making (Makker et al., 2017). Common side effects of carboplatin include nausea and vomiting. Neutropenia and peripheral neuropathy can occur with paclitaxel. Hematologic effects are common with the carboplatin/paclitaxel combination, and patients may require dose modifications if neutropenia or other cytopenias develop (Michener et al., 2005). Patients should be monitored for hematologic toxicity with regular blood counts.

Hormone treatment is another front-line option for some women. It can be considered for women with low-grade endometrioid tumors and smaller tumor volume or slow tumor growth (Concin et al., 2020; NCCN, 2022). The preferred options are progestins (megestrol 160 mg or medroxyprogesterone 200–300 mg). Other options include aromatase inhibitors, fulvestrant, and tamoxifen (Concin et al., 2020; NCCN, 2022). To date, these have been studied only in patients with endometrioid histology, and not one of these approaches has been shown to be superior to the others. Prognostic factors for response to hormonal therapy are well-differentiated, ER/PR-positive tumor, a long disease-free interval in recurrent disease, and the location or extent of metastases (NCCN, 2022).

In a phase II trial, everolimus (10 mg) plus letrozole (2.5 mg) was compared with a recommended progestin (medroxyprogesterone acetate 200 mg) and tamoxifen (20 mg twice daily) combination in 74 women with metastatic EC, most of whom had endometrioid histology (Slomovitz et al., 2018). Response rates were similar (24% vs. 22%) and highest among patients without prior chemotherapy exposure. Progression-free survival (6.4 vs. 3.8 months) and OS (20.0 vs. 16.6 months) were longer with the everolimus and letrozole combination. This investigational approach may benefit some patients with endometrioid histology who cannot tolerate chemotherapy (NCCN, 2022).

Clinicians should note that at present, the only hormonal therapy approved by the U.S. Food and Drug Administration (FDA) for treatment of EC is megestrol. Chemotherapy regimens that are used, including carboplatin and paclitaxel, are FDA-approved for other cancer types.

NEW OPTIONS FOR SUBSEQUENT LINES OF TREATMENT

Clinicians caring for patients with recurrent or metastatic EC are faced with a quandary, as the "best" treatment approach in this setting remains undefined. The European Society for Medical Oncology stated in 2016 that most patients with recurrent or advanced EC are candidates for systemic palliative therapy, with the choice between hormonal or chemotherapy regimens as front-line options and "no standard of care for second-line" treatment (Colombo et al., 2016). Although patients may receive additional chemotherapy, development of chemoresistance is common, results are poor, and toxicity is substantial considering the limited survival times gained (Guo et al., 2018). Chemoresistance in EC often involves DNA repair pathways, including MMR, which allow tumors to evade platinum-mediated apoptosis and continue to proliferate.

In 2020, pembrolizumab (Keytruda) as monotherapy received accelerated FDA approval for the treatment of adult and pediatric patients with unresectable or metastatic TMB-high (TMB-H) solid tumors (defined as ≥ 10 mutations per megabase), which have progressed following prior treatment and where there are no alternative treatment options. Well-defined second-line treatments for advanced EC include immunotherapy with pembrolizumab, which has demonstrated efficacy in a number of solid tumor types, including melanoma, non–small cell lung cancer, and others, and a combination of lenvatinib (Lenvima) and pembrolizumab. Programmed cell death protein 1 (PD-1), a receptor found on T cells that is upregulated in some tumors, plays a role in T-cell proliferation and cytokine response that is crucial to the immune response (du Rusquec et al., 2019, NCCN, 2022). This response is inhibited when PD-1 binds to its ligands, PD-L1 and PD-L2. By preventing PD-1 interaction with PD-L1/2, pembrolizumab potentiates the immune response.

Other drugs in this class include nivolumab (Opdivo) and the immune checkpoint inhibitor dostarlimab (Jemperli), which received accelerated FDA approval in 2021 for recurrent or advanced endometrial cancer that is mismatch-repair deficient (dMMR) and has progressed on or after a platinum-containing regimen. Nivolumab and dostarlimab, like pembrolizumab, target PD-1, and several immune checkpoint inhibitors directly target PD-L1 (e.g., atezolizumab [Tecentriq], durvalumab [Imfinzi], avelumab [Bavencio]).

Many advanced or metastatic EC tumors are PD-L1–positive and show response to pembrolizumab. However, it should be noted that while PD-L1 expression is important to pembrolizumab's effect, it is not clear how this may influence response to treatment (du Rusquec et al., 2019).

The KEYNOTE-028 study enrolled cohorts of patients with different types of solid tumors that shared the characteristic of PD-L1 overexpression (Ott et al., 2017). The EC cohort enrolled adult women with confirmed, metastatic disease that was measurable by the Response Evaluation Criteria in Solid Tumors (RECIST) methodology who had progressed after standard therapy or for whom no therapy was available. Among 73 patients evaluable for PD-L1, 36 (48%) were PD-L1 positive and 24 received treatment with pembrolizumab 10 mg/kg IV every 2 weeks for up to 24 months. Median patient age was 67 years, 70% had endometrioid adenocarcinoma, and 83% had been previously treated with a platinum and taxane combination.

The objective response rate (ORR) by RECIST criteria was 13%, consisting of three partial responses among patients with endometrioid disease (Table 1; Mehnert et al., 2016; Merck & Co., 2020; Ott et al., 2017). At the data cutoff, 6- and 12-month PFS were 19.0% and 14.3%, respectively, and OS rates were 67.0% and 51.0%, respectively. Patients with partial response (PR) had durable responses of approximately 64 weeks at the time of data cutoff, and the median duration of stable disease with treatment was approximately 25 weeks (Ott et al., 2017).

Additionally, approximately 30% of EC fall into the MSI-H subgroup, a type of tumor for which pembrolizumab also has demonstrated efficacy. It is currently the treatment approved for treatment of solid tumors that exhibit MSI-H or dMMR, regardless of the cancer type (du Rusquec et al., 2019; Merck & Co., 2020).

COMBINED IMMUNOTHERAPY AND VEGF INHIBITION

For patients without MSI-H/dMMR tumors, the options are generally chemotherapy regimens or hormonal therapy, and alternative options are needed. A combination of pembrolizumab and lenvatinib (Lenvima) has emerged as a potential option for patients with MSS tumor types (Makker et al., 2019). Lenvatinib is an oral multikinase inhibitor that targets several vascular endothelial growth factor (VEGF) receptors (VEGF1, VEGF2, VEGF3), as well as several other receptors involved in angiogenesis and tumor growth. In EC, it is indicated in combination with pembrolizumab for patients with MSS disease that has progressed after prior therapy based on results of KEYNOTE-146/Study 111. Results of this study have also led to inclusion of this indication in pembrolizumab prescribing information (Eisai, 2020; Merck & Co., 2020).

Final results of this phase II study showed that, with a median 18.7 months of follow-up, combination therapy with pembrolizumab (200 mg IV

Table 1. Pembrolizumab Monotherapy for PD-L1+ Advanced EC: Outcomes of KEYNOTE-028

Outcomes	No.	Percent (95% CI)
Objective response rate[a]		13.0 (2.8–33.6)
Complete response	0	0
Partial response[b]	3	13.0 (2.8–33.6)
Stable disease	3	13.0 (2.8–33.6)
Progressive disease[c]	13	56.5 (34.5–76.8)
No assessment[d]	3	13.0 (2.8–33.6)
Not evaluable[e]	1	4.3 (0.1–21.9)
Median PFS	1.8 mo (95% CI = 1.6–2.7)	
Overall survival	Not reached at time of publication	

Note. Information from Ott et al. (2017).
[a]There were no complete responses.
[b]Patients with partial response had endometrioid disease.
[c]One patient had MSI-H and best objective response was progressive disease.
[d]Three patients had no post-baseline imaging assessments: one had clinical progression and two withdrew consent.
[e]Not evaluable because of poor image quality.

Table 2. Pembrolizumab + Lenvatinib for Advanced EC

At Week 24	MSS/pMMR (n = 94)	MSI-H/dMMR (n = 11)	Total (N = 108)
Objective response	37.2% (27.5–47.9)	63.6% (30.8–89.1)	38.0% (21.8–47.8)
Best objective response:			
Complete response	2.1%	9.1%	2.8%
Partial response	34.0%	54.5%	35.2%
Stable disease	47.9%	27.3%	46.3%
Progressive disease	10.6%	9.1%	11.1%
Not evaluable	5.3%	0	4.6%

Note. Information from Makker et al. (2020). dMMR = mismatch repair deficient; MSS = microsatellite stable; MSI-H = microsatellite instability high; pMMR = mismatch repair proficient.

every 3 weeks) and lenvatinib (20 mg once daily) achieved an ORR at week 24 of 38% among 108 patients (Table 2; Makker et al., 2020).

This was a multicenter, open-label study of adult women with metastatic EC without regard to MSI status or PD-L1 expression, with measurable disease by immune-related RECIST, and life expectancy > 12 weeks. Only 49.1% of patients were PD-L1 positive; 39.8% were PD-L1 negative, and 11.1% had unknown PD-L1 status. Most patients had MSS tumors (n = 94); only 11 patients (8%) had MSI-H disease. Patients had received one (52.8%), two (37.0%), or three or more (10.2%) prior therapies and had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Ninety-eight percent had previously received a platinum doublet chemotherapy regimen. Enrolled patients had to have controlled blood pressure—with or without drugs—and adequate renal, cardiac, liver, and bone marrow function (Makker et al., 2020).

The primary endpoint was the proportion of patients with an objective response, which included patients with complete response (CR) or PR at week 24. Objective response rate at 24 weeks was higher among the patients with MSI-H disease (63.6%) than MSS disease (36.2%). Median PFS was 7.4 months, and median OS was 17.7 months. Median duration of response, regardless of MSI status, was 21.2 months. Median time to response was 2.7 months. Among patients with objective response, 83% had a response of ≥ 6 months, and 64.5% had a response of ≥ 12 months' duration (Makker et al., 2020). A post hoc analysis of this study looked at patients with MSS disease

Table 3. Proactive Management of Potential Toxicity With Pembrolizumab/Lenvatinib

Prior to initializing treatment	On treatment
Evaluate: • Liver function • Renal function/proteinuria • Thyroid function Evaluate and control blood pressure Evaluate and correct electrolyte abnormalities	Monitor: • Blood pressure: after 1 week, then every 2 weeks for first 2 months; then monthly • Liver function: every 2 weeks for first 2 months, then monthly • Blood calcium: monthly • Proteinuria: at regular intervals • Thyroid function: at regular intervals • Blood glucose: at each visit • ECG in patients with comorbid disease or treatment-related QT prolongation risk Assess for: • Signs of cardiac dysfunction, colitis, dehydration, impaired wound healing, potential hemorrhagic events, renal impairment

Note. Information from Eisai (2020); Merck (2020).

who had one prior line of therapy in the adjuvant or metastatic setting (n = 63). Objective response rate of 41.3% (12.7% CR) was achieved with pembrolizumab/lenvatinib therapy. In a subgroup of those who received adjuvant therapy for locoregional disease and had received only cytotoxic chemotherapy (n = 21), ORR was 57.1% (23.8%). Treatment-related toxicity led to lenvatinib dose reductions in 42 patients, and overall, 12 patients discontinued one or both treatments. Serious treatment-related adverse events (TRAEs) were reported in 18 patients (Makker et al., 2020). Figure 1 summarizes an approach to advanced or metastatic EC based on tumor characteristics.

MANAGEMENT OF TREATMENT TOXICITIES

Recommended pretreatment evaluation and on-treatment monitoring are summarized in Table 3. Recommended dose modifications for TRAEs are summarized in Tables 4 and 5.

Hypertension

Hypertension is a frequent complication associated with VEGF inhibition that may also represent a biomarker for treatment efficacy. In addition to significant increases in blood pressure, treatment-related hypertension may include serious acute complications such as malignant hypertension (Hamnvik et al., 2015). An analysis of 1,120 patients with solid and other tumors who were treated with anti-VEGF tyrosine kinase inhibitors—primarily sunitinib and sorafenib—found that almost 50% of patients developed treatment-related hypertension, with mean maximum increases of 21 mm Hg and 15 mm Hg in systolic and diastolic blood pressure. The median time to developing a treatment-related response was 29 days, but blood pressure increases could be noted within the first 2 weeks of anti-VEGF therapy. In most patients, treatment-related hypertension was managed by intensifying existing or initiating new blood pressure medications. Risk factors for development of hypertension with anti-VEGF inhibitors include preexisting hypertension, older age, and BMI of 25 kg/m^2 or greater.

Any-grade hypertension associated with lenvatinib monotherapy is a frequent complication, occurring in more than 30% of patients. In combination with pembrolizumab for treatment of EC, any-grade hypertension was reported in 65% of patients and grade 3 or 4 hypertension was reported in 38% (Eisai, 2020). Given the typical profile of patients with advanced EC, anti-VEGF–associated hypertension can be expected.

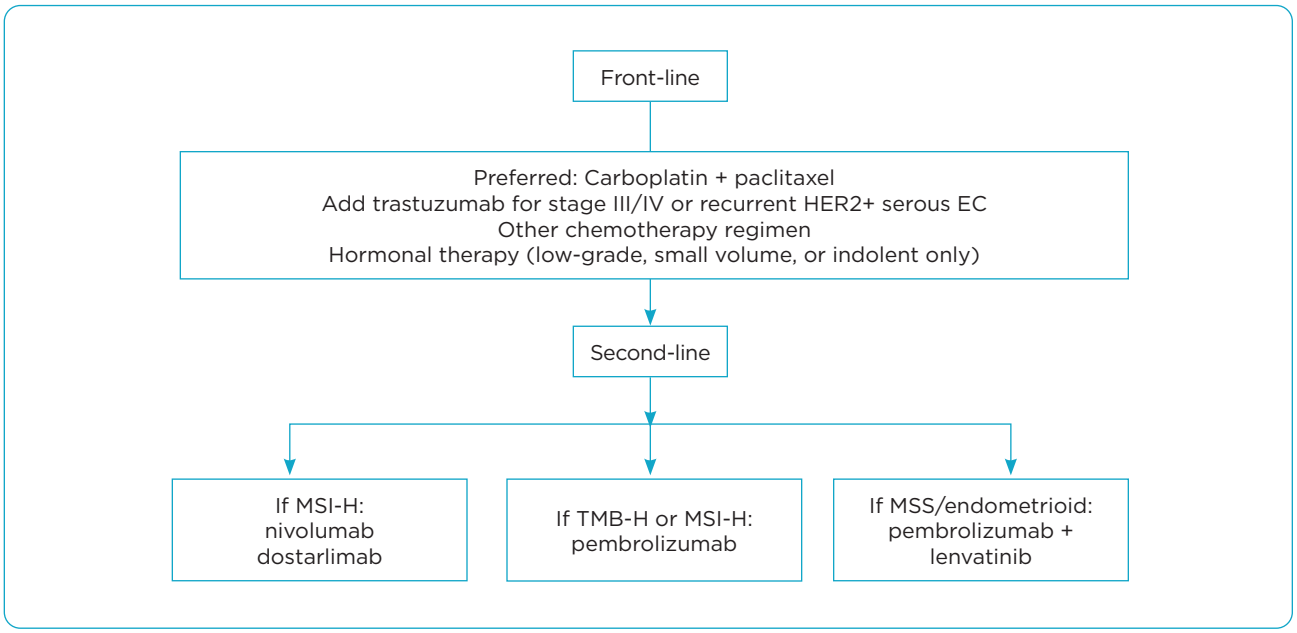

Figure 1. Algorithm for advanced/metastatic endometrial cancer based on tumor characteristics. EC = endometrial cancer; MSI-H = microsatellite instability high; MSS = microsatellite stable; TMB-H = tumor mutational burden high. Information from NCCN (2022).

Table 4. Dose Modifications for Adverse Events With Lenvatinib

Treatment-emergent adverse events	Severity/Action
Hypertension	Grade 3: If persists despite BP medication, withhold and resume at reduced dose when resolves to grade ≤ 2 Grade 4: Permanently discontinue
Diarrhea	Initiate diarrhea management Grade 3: Withhold until resolves to grade ≤ 1, resume at reduced dose Grade 4: Permanently discontinue
Hemorrhagic events	Grade 3: Withhold until resolves to grade ≤ 1, resume at reduced dose Grade 4: Permanently discontinue
Hepatotoxicity/renal failure or impairment	Grade 3 or 4: Withhold until resolves to grade ≤ 1, then resume at reduced dose or permanently discontinue
Proteinuria	Withhold treatment for proteinuria ≥ 2 g/24 hours; resume at lower dose when < 2 g/24 hours Permanently discontinue treatment for nephrotic syndrome

Note. Information from Eisai (2020); Merck (2020).

Lenvatinib should not be initiated until a patient's blood pressure is controlled for their age and coexisting conditions (Table 4). If hypertension develops, standard antihypertensive agents can be used (Cabanillas & Takahashi, 2019). Use of angiotensin-converting enzyme (ACE) inhibitors is recommended and can also help mitigate treatment-related proteinuria (Zhang et al., 2018). If hypertension occurs or is worsened by VEGF treatment to the point of requiring treatment interruption or discontinuation, monitoring should be continued until blood pressure normalizes to pretreatment levels (Table 4).

Because of the risk of developing or worsening hypertension, patients should take and record their blood pressure every morning to identify any treatment-related elevations early on and allow prompt management. Patients should bring their home blood pressure monitor to their next appointment so the clinician can evaluate their competency in checking this value. Patients should be educated on proper technique, including taking blood pressure at the same time each day, sitting properly with feet on the floor, and resting and avoiding caffeine for 30 minutes prior to measurement. They should be instructed to take two or three measurements each time, with 1-minute intervals between each. Clinicians also should ensure that patients know which levels of systolic and diastolic blood pressure are concerning (for example, > 140 mm Hg/> 90 mm Hg) and which constitute an emergency that requires immediate attention (hypertensive crisis: > 180 mm Hg/ > 120 mm Hg; American Heart Association, 2017) Of course, such thresholds must be customized to individual patient factors.

GI AEs With Lenvatinib

Gastrointestinal side effects are frequent with lenvatinib, whether used alone or combined with pembrolizumab (Eisai, 2020). When used in combination with pembrolizumab in KEYNOTE-146/Study 111, 52.8% of patients reported any-grade diarrhea and 6.5% reported grade 3 or 4 diarrhea. Nausea and vomiting are also common with lenvatinib monotherapy, although few grade ≥ 3 events have been reported (Eisai, 2020). In combination with pembrolizumab, 39.8% reported any-grade nausea (2.8% grade 3 or 4) and 26.9% reported any-grade vomiting (no grade 3 or 4; Makker et al., 2020).

Proactive management of gastrointestinal side effects includes patient and caregiver education on recognition and management of symptoms, diet modification, and dehydration management (Cabanillas & Takahashi, 2019). Prophylactic use of antidiarrheal medication (e.g., loperamide 2 mg) may be a useful mitigation strategy. Clinicians should instruct patients to let their provider

know if diarrhea occurs, especially if more severe, as dose modification may be necessary (Table 4). Less severe diarrhea can be managed with over-the-counter antidiarrheal medications, hydration, and electrolyte replacement. Management of persistent or more severe diarrhea should include consultation with a gastroenterologist and evaluation for colitis when lenvatinib is used in combination with pembrolizumab (Castellano et al., 2018).

Other AEs Associated With VEGF Inhibition

Proteinuria may occur related to hypertension in patients treated with VEGF inhibitors, and patients should be monitored prior to starting and periodically during treatment (Eisai, 2020). In combination with pembrolizumab for treatment of EC, 22.2% of patients developed any-grade proteinuria (3.7% grade 3 or 4; Makker et al., 2020). Treatment should be withheld if protein levels exceed 2 g per 24 hours and discontinued if nephrotic syndrome develops (Eisai, 2020; Zhang et al., 2018).

Other frequent TRAEs of any grade occurring with the lenvatinib/pembrolizumab combination were fatigue (17% grade 3 or 4), hemorrhagic events (4% grade 3 or 4), decreased appetite (no grade 3), and palmar-plantar erythrodysesthesia syndrome (3% grade 3; Eisai, 2020; Makker et al., 2020).

AEs Associated With Pembrolizumab and Dostarlimab

Pembrolizumab is better tolerated than cytotoxic chemotherapy and associated with lower rates of typical chemotherapy side effects such as mucosal inflammation, stomatitis, and alopecia (Nishijima et al., 2017; Wang et al., 2019; Yang et al., 2019). The most common adverse reactions with dostarlimab were fatigue/asthenia, nausea, diarrhea, anemia, and constipation (GlaxoSmithKline, 2021).

Fatigue is the most frequently reported any-grade TRAE associated with dostarlimab or pembrolizumab treatment alone or in combination with lenvatinib (Merck & Co., 2020; GlaxoSmithKline, 2021). Among EC patients included in KEYNOTE-028, any-grade fatigue was reported in 20.8%; no grade 3 or 4 fatigue was reported (Ott et al., 2017). According to the Oncology Nursing Society, fatigue is a multicomponent symptom present in many patients with cancer; however, in patients treated with anti–PD-1 immunotherapy, it may be a symptom of a treatment-related pituitary or thyroid disorder (Oncology Nursing Society, n.d.). After ruling out and correcting any treatment-related endocrine disorder, fatigue can be mitigated through physical activity or exercise. Other interventions that may help include yoga, cognitive behavioral therapy, energy conservation management, and massage. Multicomponent approaches may be more effective, especially for patients for whom exercise is not easily achievable.

Other frequent any-grade TRAEs with pembrolizumab monotherapy in KEYNOTE-028 were pyrexia (12.5%) and decreased appetite (12.5%). Grade 3 TRAEs occurred in four (16.7%) patients who reported eight different TRAEs: one had asthenia and back pain; one had anemia, hyperglycemia, and hyponatremia; one had chills and pyrexia; and one had diarrhea. No grade 4 TRAEs were reported (Ott et al., 2017).

Like other immunotherapy agents, pembrolizumab and dostarlimab are associated with specific immune-related adverse events (irAE); the exact mechanism of these irAEs remains unknown. They can affect almost any body system but are most often reported in the skin, gastrointestinal tract, and lungs (Brahmer et al., 2018). Those most frequently encountered in the early treatment period are related to immune-related epithelial inflammation and present as rash, colitis, or pneumonitis (NCCN, 2021). Because of the variety of irAEs and overlap with some other treatment and disease side effects, the true incidence of irAEs is still being revealed as clinical experience accumulates. Immune-related AEs commonly present as inflammatory autoimmune reactions and may be managed with supportive care, immune modulation, or corticosteroid treatment, depending on severity (Castellano et al., 2018, GlaxoSmithKline, 2021).

Because of their similar etiology (if different presentation), management of irAEs is similar independent of where they manifest. According to guidelines from the American Society of Clinical Oncology (ASCO), grade 1 irAEs can usually be managed with symptomatic relief. For grade 2, clinicians should consider holding immunotherapy and initiating a low-dose steroid (e.g., prednisone 0.5 or 1 mg/kg/day) until resolution. For grade 3 irAEs, immunotherapy should

be held and a high-dose steroid (e.g., prednisone 1–2 mg/kg/day) initiated and tapered over 4 to 6 weeks; treatment may be restarted at resolution, but if the reaction recurs, should be permanently discontinued. Any grade 4 or otherwise very serious irAE (e.g., grade 3 Stevens-Johnson syndrome) warrants immediate and permanent discontinuation of immunotherapy (Brahmer et al., 2018). As these ASCO recommendations are generalized for all immunotherapy and tumor types, clinicians should also consult prescribing information for more specific details (Table 5; Merck & Co., 2020).

Cutaneous reactions, usually rash, are frequently encountered; 16.7% of patients treated with pembrolizumab in KEYNOTE-028 reported grade 1 or 2 pruritus (Ott et al., 2017), and in combination with lenvatinib, 26.9% reported rash, including 4.6% grade 3 or 4 rash (Makker et al., 2020). Grade 1 rash can generally be managed with supportive treatment such as topical steroids or antipruritic medication to relieve symptoms. Severe reactions, including Stevens-Johnson syndrome, can occur, and after treatment discontinuation dermatology consultation is recommended if a grade ≥ 3 cutaneous immune-related TRAE is suspected (Castellano et al., 2018).

Gastrointestinal events occur frequently and tend to develop from 6 to 7 weeks after treatment initiation. Diarrhea and/or colitis may occur, but absolute rates are difficult to know because these often are related to other treatment. Coadministration with lenvatinib complicates assessment when diarrhea occurs, and clinicians must ascertain whether persistent diarrhea is related to VEGF inhibition or a result of immune-related colitis. If grade ≥ 2 colitis is suspected, workup includes complete laboratory evaluation and stool culture to rule out *Clostridium difficile* or other viral or bacterial causes. Imaging for ulceration may be necessary with colonoscopy if colitis is suspected and does not resolve with pembrolizumab withholding (Brahmer et al., 2018). In combination with lenvatinib, colitis led to discontinuation of pembrolizumab in 2% of patients (Merck & Co., 2020). In that study, any-grade colitis occurred in 3.7% of patients and grade 3 or 4 colitis in 1.9% (Makker et al., 2020). Severe hepatotoxicity is rare (Castellano et al., 2018).

Pembrolizumab and dostarlimab can cause immune-related endocrine disorders, including type 1 diabetes, and patients should be assessed for development of hyperglycemia or other symp-

Table 5. Dose Modifications for Adverse Events With Pembrolizumab

Immune-mediated TRAEs	Severity/Action
Pneumonitis	Grade 2: Withhold treatment; discontinue if not at least partially resolved after 12 weeks on corticosteroid Grade 3 or 4: Permanently discontinue
Colitis	Grade 2/3: Withhold treatment; discontinue if not at least partially resolved after 12 weeks on corticosteroid Grade 4: Permanently discontinue
Endocrinopathy	Grade 3 or 4: Withhold treatment until stable
Nephritis	Grade 2: Withhold treatment: discontinue if not at least partially resolved after 12 weeks on corticosteroid Grade 3 or 4: Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS: Withhold; discontinue if not at least partially resolved after 12 weeks on corticosteroid Confirmed SJS, TEN, or DRESS: Permanently discontinue
Other	
Infusion-related reactions	Grade 1 or 2: Interrupt or slow infusion rate Grade 3 or 4: Permanently discontinue

Note. TRAEs = treatment-related adverse events; DRESS = drug rash with eosinophilia and systemic symptoms; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis. Information from Merck (2020).

toms (Castellano et al., 2018; GlaxoSmithKline, 2021; Merck & Co., 2020).

A rare but serious irAE with pembrolizumab and dostarlimab is pneumonitis, which has been reported in about 2.7% of patients treated with anti–PD-1 agents (Brahmer et al., 2018; GlaxoSmithKline, 2021). Patients presenting with suspected pneumonitis should have chest imaging and treatment withheld if evidence of progression is seen. Treatment can be restarted with evidence of improvement. Grade 2 pneumonitis should be treated with prednisone (1–2 mg/kg/day) tapered down over 4 to 6 weeks and may require empiric antibiotics or bronchoscopy. For grade 3 or 4, pembrolizumab should be discontinued (Brahmer et al., 2018; Merck & Co., 2020).

Another rare (< 1%) but potentially serious irAE with pembrolizumab and dostarlimab is development of myocarditis that can increase risk for cardiovascular death or another major cardiovascular event (GlaxoSmithKline, 2021; Mahmood et al., 2018). In a multicenter registry of cancer patients treated with immune checkpoint inhibitors (46% with pembrolizumab), the median time to presentation was 34 days, and myocarditis was the first and only irAE experienced by 54% of cases (Mahmood et al., 2018). Clinical presentation included troponin elevation in 94% and abnormal ECG in 89%. Ventricular function was normal in 51% of cases. Risk factors for myocarditis development included preexisting diabetes, overweight/obesity, and use of combined anti–CTLA-4/anti–PD-1/L1 therapy. If new or acute cardiovascular symptoms occur, pembrolizumab should be stopped and patients referred to a cardiologist for additional evaluation and management.

To facilitate shared decision-making, it is important for clinicians to inform and educate patients and caregivers about differences in mechanism of action and efficacy, as well as the expected TRAEs between treatments and the irAEs associated with pembrolizumab (Brahmer et al., 2018). Clinicians and patients should be aware that irAEs can occur at any time during treatment, and that these therapies may continue to influence the immune system after discontinuation. Patients must be educated to inform all of their health-care providers about their use of immunotherapy, as this may affect other disease treatment and management decisions.

Most irAEs can be managed with supportive care and treatment interruption or dose modification, and if more severe should involve a multidisciplinary team with specialists knowledgeable about the specific reaction or symptom (e.g., dermatologists or gastroenterologists). In their irAE management practice guideline, ASCO recommends use of standard assessment forms for recognizing irAEs and suggests using a wallet card to indicate immunotherapy use and the specific type of treatment; a printable card can be obtained from the Oncology Nursing Society (Brahmer et al., 2018).

EMERGING AGENTS AND CLINICAL TRIALS

The limited options for second-line therapy of advanced EC have led to intense research using agents of proven benefit in other cancer types, as well as development of new agents. Many targeted therapies found to be beneficial in hormone-driven cancers are being studied, for the most part, in early phase I or II trials. Several are summarized in this section.

Much of the research has focused on the potential for PD-L1 inhibition in the treatment of recurrent or advanced EC. Existing PD-L1 inhibitors currently in phase II trials include atezolizumab, avelumab, and durvalumab (Antill et al., 2019; Colombo et al., 2019; Konstantinopoulos et al., 2019). In early results of a phase II study, treatment with avelumab produced an ORR of 26.7% (4/15) in patients with previously treated MSI-H/POLE EC; no responses were seen in patients with MSS disease (Konstantinopoulos et al., 2019).

Durvalumab is also being studied in combination with the CTLA-4 inhibitor tremelimumab (Rubinstein et al., 2019). CTLA-4 is an immune regulator expressed on regulatory T cells that prevents binding of CD28 and inhibits activation of cytotoxic T cells, which offers a second pathway to activate immune response to tumor cells (Di Tucci et al., 2019). At a planned interim analysis, durvalumab alone and combined with tremelimumab produced modest responses (ORR 14.8% and 11.1%, respectively) in MSS and MSI-H patients (Rubinstein et al., 2019). Phase III trials are summarized in Table 6 (ClinicalTrials.gov).

Data for the PD-1 inhibitor dostarlimab indicated for the treatment of dMMR recurrent or

advanced EC have been published (Oaknin et al., 2020). The phase I GARNET trial enrolled 25 patients with MSI-H advanced or recurrent EC previously treated with platinum-based chemotherapy. Patients received dostarlimab 500 mg IV every 3 weeks for 4 cycles, and then 1,000 mg IV every 6 weeks thereafter. Of 71 evaluable patients at a median follow-up of 11.2 months, 42.3% (n = 30) had a confirmed ORR, including 12.7% (n = 9) with a CR. The disease control rate was 57.7%, and median duration of response had not been reached. Frequent TRAEs were asthenia, diarrhea, fatigue, and nausea; anemia was the most frequently reported grade 3 side effect at 2.9%. Immune-related AEs were reported in 23.1%, of which diarrhea and hypothyroidism were the most frequent. A phase III trial is planned with dostarlimab plus carboplatin/paclitaxel as front-line therapy (Table 6). Early phase studies with nivolumab in various combinations and the investigational agent MGA012 are ongoing (ClinicalTrials.gov, 2022; Mehnert et al., 2018).

Based on their efficacy in breast cancer, CDK4/6 inhibitors are of interest for potentially overcoming resistance to hormone therapies. A focus in phase II studies has been combined CDK4/6 inhibition and aromatase inhibitor therapy (Giannone et al., 2019). Among 20 patients with relapsed, ER-positive EC who received combined ribociclib (Kisqali) and letrozole (Femara) treatment in a phase II trial presented in 2019, 11 were alive and progression free at 12 weeks (PFS12,

Table 6. Novel Agents in Phase III Clinical Trials

Drug(s)	Treatment arms	Setting/Primary outcome(s)	Eligibility (NCT identifier)
Pembrolizumab Lenvatinib	Pembrolizumab/lenvatinib vs. physician's choice (paclitaxel or doxorubicin)	2nd line PFS, OS	Active, not recruiting: Histologically confirmed EC progressed after 1 prior platinum-based CT; prior PD-1, PD-L1, VEGF therapy excluded, prior immunotherapy excluded if grade ≥ 3 irAE
Pembrolizumab Lenvatinib	Pembrolizumab/lenvatinib vs. CT	Front-line PFS, OS	Active, not recruiting: Advanced/recurrent EC w/o prior CT (prior chemoradiation OK), immunotherapy, or VEGF therapy; significant CV disease, CNS metastases, certain GI conditions excluded (NCT 03884101)
Dostarlimab	Dostarlimab + CT vs. placebo + CT	Front-line PFS	Recruiting: Primary advanced or recurrent EC (Identifier: ENGOT-EN6/NSGO-RUBY; NCT 03981796)
Durvalumab Tremelimumab[a]	Durvalumab vs. durvalumab/tremelimumab	≥ 2nd line ORR	Active, not recruiting: Advanced/recurrent EC; ≥ 1 prior CT regimens; prior grade ≥ 3/unresolved irAE excluded (NCT 03015129)
Atezolizumab	Atezolizumab + CT vs. placebo + CT	Front-line OS, PFS	Recruiting: Newly diagnosed, residual or inoperable advanced disease with no prior front-line CT or no prior tx for recurrent disease (NCT 03603184)

Note. Information from ClinicalTrials.gov. Accessed January 14, 2022. GI = gastrointestinal; CNS = central nervous system; CT = carboplatin/paclitaxel; CV = cardiovascular
[a]Phase II trial.

55%), which compared favorably with historical data for letrozole monotherapy (PFS12, 45%). Grade 3 or greater hematologic TRAEs and fatigue occurred in 13% to 18% of patients (Colon-Otero et al., 2019).

Other strategies in early trials are a dual PI3K inhibitor/mTOR inhibitor, PARP inhibition with olaparib (Lynparza) or rucaparib (Rubraca; based on shared molecular characteristics between serous ovarian carcinoma and serous EC), and combinations with metformin (based on theorized EC tumor inhibition through AMP kinase activation and mTOR inhibition, as well as reductions in circulating insulin; Alter et al., 2019; Bendell et al., 2018; Di Tucci et al., 2019; Mackay et al., 2019; Soliman et al., 2016).

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

With the recent rapid advances in EC treatment, it is sometimes difficult to stay up to date on new therapeutic strategies, their optimal use, and their associated toxicities. This is important because advanced practitioners must understand how these immune checkpoint inhibitors and novel targeted therapies work to make effective treatment decisions and educate patients and their caregivers. A current knowledge of molecular and biomarker testing and the implications for treatment selection helps guide treatment decisions. As combination strategies emerge for EC, advanced practitioners must be up to date on their optimal use.

Advanced practitioners play a major role in the management of AEs, so it is critical that they be familiar not only with new therapies, but also with their associated toxicities. An advanced practitioner is often the first person that a patient contacts when AEs develop, and they must therefore have a thorough understanding of the identification and management of these agents, particularly regarding the AEs of immune checkpoint inhibitors, which are unique from those associated with chemotherapy or targeted therapy. Advanced practitioners play a critical role in educating patients and caregivers about how to recognize AEs, and when and how to seek help (including, for instance, providing patients with emergency contact numbers for the oncology care team and clear instructions about how to describe the type of therapy they are on, such as immunotherapy vs. chemotherapy). However, because of recent advances in the treatment of EC, advanced practitioners may not yet be familiar with toxicities of novel agents.

CONCLUSION

Patients with advanced EC who progress after front-line chemotherapy have limited options and a poor prognosis. Recent advances in immunotherapy have demonstrated a survival benefit with pembrolizumab treatment for women with MSI-H/dMMR tumors, with tolerable side effects. For women with MSS tumors, combined treatment with pembrolizumab and lenvatinib is a promising option, with ORR of 38% and median PFS of 7.4 months, and median OS of 16.7 months (Makker et al., 2020). Although immunotherapy is associated with specific irAEs, most side effects of these treatments are mild, and patients and their caregivers should be educated about them. Hypertension is a frequent complication of lenvatinib and other VEGF inhibitors. Clinicians should work with a well-coordinated multidisciplinary team to ensure optimal care of their patients with advanced EC.

Disclosure

The author has no conflicts of interest to disclose.

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