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Advances and Toxicity to Immunotherapy for Endometrial Cancer

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Abstract

Endometrial cancer (EC) is the fifth most common cancer among women in the United States. Current therapy for EC involves a combination of surgery, chemotherapy, and/or radiation; however, these therapies have shown little efficacy in the treatment of advanced/recurrent EC. Immune checkpoint inhibitor (ICI) therapy is an emerging treatment modality that has demonstrated potential for the treatment of advanced/recurrent EC. Leading ICI therapies for EC include pembrolizumab and dostarlimab, which are monoclonal antibodies that modulate the programmed death receptor-1 (PD-1) pathway. This review examines current understanding of the efficacy and safety profiles for both pembrolizumab and dostarlimab ICI therapies in the treatment of advanced/recurrent EC.

Evidence regarding pembrolizumab and dostarlimab monotherapy has shown both efficacy and equivocal safety in the treatment of advanced/recurrent high microsatellite instability (MSI-H) and mismatch repair deficient (dMMR) endometrial cancer. However, there is less efficacy in the treatment of microsatellite stable (MSS) or mismatch repair proficient (pMMR) EC. Studies examining pembrolizumab or dostarlimab in combination with standard chemotherapy (paclitaxel-carboplatin) report a synergistic effect compared to chemotherapy alone for both dMMR/MSI-H and pMMR/MSS patient populations; however, ICI-chemotherapy combinations revealed a larger number of treatment-related adverse events. The KEYNOTE-146 and KEYNOTE-775 trials demonstrated the robust efficacy and manageable side effect profile of pembrolizumab in combination with lenvatinib for the treatment of both dMMR/MSI-H and pMMR/MSS advanced/recurrent EC.

Current research demonstrates that ICI therapies improve patient outcomes in advanced/recurrent EC, particularly in dMMR/MSI-H populations. Additional emerging and promising therapies for EC include chimeric antigen receptor (CAR)-T cell therapy. More research regarding best-practice treatment for advanced/recurrent EC is needed.

Keywords: Endometrial cancer; Chemotherapy; Efficacy; Safety; Pembrolizumab; Dostarlimab

Introduction

Endometrial cancer (EC) is a malignancy of the inner epithelial lining of the uterus. It is the most common gynecologic cancer in the United States and the fourth most common cancer in American females, serving as a major cause of both morbidity and mortality. The prevalence of EC in

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the United States is 25.7/100,000 women per year with a peak age of diagnosis between 55 and 64 years [1].

The natural history of endometrial endometrioid carcinoma begins with uncontrolled endometrial proliferation stimulated by estrogen (endogenous or exogenous) unopposed by progesterone or progestins. There is progression from endometrial hyperplasia to histologically atypical premalignant lesions known as endometrial intraepithelial neoplasia (EIN). EIN may transform into endometrioid carcinoma, characterized by endometrial stromal and/or myometrial invasion, often KRAS mutations, PTEN mutations, and microsatellite instability caused by mismatch repair defects [1].

The majority of endometrial cancers are pMMR (mismatch repair proficient) and microsatellite stable (MSS); however, nearly one-third of individuals diagnosed with EC display tumors characterized by elevated levels of high microsatellite instability (MSI-H) and deficiency in mismatch repair (dMMR). This deficiency can stem from either a sporadic methylation of the MLH1 promoter or as a hereditary mutation, notably in one of the mismatch repair (MMR) genes - MLH1, MSH2, MSH6, and PMS2 - known as Lynch syndrome. MMR gene defects hinder the correction of DNA replication errors, leading to the accumulation of point mutations within microsatellite regions and subsequent microsatellite instability [2].

Endometrial cancer is surgically staged, with grade of the lesion, histology type and lymphovascular space involvement recorded. The 2023 International Federation of Gynecology and Obstetrics (FIGO) classifies EC into three stages [3]. In Stage I, the lesion is confined to the uterine corpus and ovary. Stage II is characterized by invasion of cervical stroma without extrauterine extension or with substantial LVSI or aggressive histological types with myometrial invasion. Stage III involves local/regional spread of the tumor. Stage IV is characterized by spread to the bladder, intestinal mucosa and/or distance metastasis.

The mainstay for management of endometrial carcinoma is surgery with hysterectomy and salpingo-oophorectomy. The goal of surgery is to remove the primary tumor and identify prognostic factors that would indicate the need for adjuvant therapy. Pelvic and para-aortic lymph node dissection or sampling may also be performed to test for cancer spread. Depending on the stage of the endometrial carcinoma, other treatments including radiation and/or chemotherapy may be recommended. Radiation therapy for EC is commonly performed in two ways namely external beam pelvic radiation therapy, and vaginal brachytherapy which involves internal radiation therapy that targets the upper vagina in females who have had their uterus and cervix removed. Combination chemotherapy is often used for high-grade endometrial carcinomas. Common chemotherapy drugs used to treat EC include doxorubicin, cisplatin, and docetaxel. The most frequently used combination at present is paclitaxel and carboplatin. While paclitaxel-carboplatin is standard chemotherapy for the first-line treatment of primary advanced and recurrent EC, long-term outcomes remain poor with a median survival of 3 years [4]. Immunotherapy, such as Keytruda (Pembrolizumab) and Jemperli (Dostarlimab), is an emerging area of treatment for advanced/recurrent EC that has failed previous treatment.

Both Keytruda (pembrolizumab) and Jemperli (Dostarlimab) are IgG4 monoclonal antibodies that act on the human programmed death receptor-1 (PD-1) pathway. Cancers upregulate their expression of PD-1 and PD-2 ligands (PD-L1 and PD-L2) which in turn activate the PD-1 receptor on T cells, functioning as an immune checkpoint by inhibiting T-cell proliferation and cytokine production [5]. Keytruda and Jemperli bind to the PD-1 receptor on T-cells, preventing PD-L1 and PD-L2 ligands on tumor cells from binding to the PD-1 receptor and inactivating T-cells. This allows continued anti-tumor immune responses. Keytruda, as a single agent, has been approved by the FDA for advanced (unresectable or metastatic) or recurrent EC that is MSI-H or dMMR [6]. Jemperli, as a single agent, has been approved for advanced or recurrent dMMR EC that is experiencing disease progression despite being treated with platinum-containing chemotherapy.

Literature Review

A literature search utilizing the MEDLINE database was conducted to elicit all studies and/or trial updates published in the last 10 years up to 04/20/2024 that analyze the efficacy and/or safety of pembrolizumab and dostarlimab as immune checkpoint inhibitor therapies for the treatment of EC. Keywords for pembrolizumab studies included "pembrolizumab" AND "endometrial" AND "cancer OR carcinoma OR neoplasm". Similarly, keywords for dostarlimab included "dostarlimab" AND "endometrial" AND "cancer OR carcinoma OR neoplasm". The search for each pembrolizumab and dostarlimab was limited by: Last 10 years, Clinical Trials, and Randomized Clinical Trials. For pembrolizumab, 39 studies were identified and 31 were excluded due to irrelevance or the presence of a more updated version of results from the same trial; overall, 8 studies were analyzed for review (listed in Table 1). For dostarlimab, 7 studies were identified and 4 were excluded; overall, 3 studies were analyzed for review (listed in Table 2).

From each eligible article, the following data points were gathered (if present): authors, publication year, sample size/patient enrollment, efficacy data (progression free survival (PFS), objective response rate (ORR), overall survival (OS)), biomarker data (pMMR/MSS, dMMR/MSI-H), and data

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concerning treatment-related adverse events (TRAEs) and immune-related adverse events (irAEs). All patients involved in selected studies had confirmed EC and had undergone at least one prior systematic treatment and exhibited signs of disease advancement. Tumor response (complete response, partial response, progressive disease, and stable disease) to therapy was evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) criteria [7].

Intervention (pembrolizumab or dostarlimab) and placebo groups were often stratified into subgroups of analysis by biomarker status: pMMR, dMMR, MSS, and MSI-H. These biomarkers are commonly found in concordance and exist together as pMMR/MSS or dMMR/MSI-H.

Table 1: Keytruda (Pembrolizumab) Studies/Trials

	Study Title	Estimated Sample Size (n)*	Intervention (s)	Duration	EFFICACY: Progression-Free Survival (PFS) Objective Response Rate (ORR) Overall Survival (OS)	SAFETY: Treatment-Related Adverse Events (TRAE) Immune-Related Adverse Events (irAE)	Refere-nce
1	*Pembrolizumab in Patients With Microsatellite instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study*	90 (20 completed full treatment)	**Intervention Group:** Pembrolizumab monotherapy (No placebo) All patients were MSI-H/dMMR	Dose received every 3 weeks for 35 cycles	*In Intervention Patients:* *ORR:* *• 48% (95% CI, 37-60)* *Median PFS:* *• 13.1 months (95% CI, 4.3-34.4)* *Median OS:* *• NR (95% CI, 27.2 months- not reached)* *Median follow-up at 42.6 months*	**TRAE of any cause:** • 76% had ≥ 1 treatment-related AE **Grade 3 or 4 TRAE:** • Occurred in 12% of patients **irAE** • Occurred in 28% of patients	O'Malley et al (2022) (1)
2	*A Phase II Evaluation of Pembrolizumab for Recurrent Lynch-like versus Sporadic Endometrial Cancers with Microsatellite Instability*	25 (24 available for analysis)	**Intervention Group:** Pembrolizumab monotherapy (No placebo) All patients had confirmed MSI-H/ dMMR EC stratified by: • Lynch-like: n=6 • Sporadic: n=18	Pembrolizumab every 3 weeks for ≤ 2 years	*In Intervention Patients:* ***ORR*** *• Lynch-like: 100% (P=0.024)* *• Sporadic: 44% (P=0.024)* ***Median PFS:*** *• Lynch-like: 100% (P=0.017)* *• Sporadic: 30% (P=0.017)* ***Median OS:*** *• Lynch-like: 100% (P=0.043)* *• Sporadic: 43% (P=0.043)* *Median follow up at 25.8 months*	**TRAE of any cause:** • Occurred in 80% of patients **Grade 3 or 4 TRAE**: • Occurred in 12% of patients	Bellone et al (2021) (2)

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3	*Mismatch Repair Deficiency, Next-Generation Sequencing-based Microsatellite Instability, and Tumor Mutational Burden as Predictive Biomarkers for Immune Checkpoint Inhibitor Effectiveness in Frontline Treatment of Advanced Stage Endometrial Cancer*	371	**Intervention Group:** Immune checkpoint inhibitor monotherapy (Pembrolizumab, dostarlimab, nivolumab) (n=28) **Placebo Group:** Chemotherapy (n=343) (platinums) Stratification within treatment groups: • MSI-High cohort: o Interv.: n=15 o Placebo: n=66 • MSS cohort: o Interv.: n=13 o Placebo: n=277	Dosing & timetables were site-dependent and not explicitly indicated	**Median OS:** Intervention reduced risk of death compared to placebo by: • MSI-H: aHR = 0.29 (95% CI; 0.09-0.97); p= 0.036 • MSS: aHR = nonsignificant; p>0.05	N/A	Hill et al (2023) (3)
4	*Pembrolizumab plus Chemotherapy in Advanced Endometrial Carcinoma*	816 (588 for efficacy analysis)	**Intervention Group:** Combination Chemotherapy (carboplatin + paclitaxel) plus: Pembrolizumab (n=408) **Placebo Group:** Combination Chemotherapy (Paclitaxel-Carboplatin) plus: Placebo (n=408) Stratification within treatment groups: • pMMR cohort: o Interv.: n=276 o Placebo: n=274 • dMMR cohort: o Interv.: n=109 o Placebo: n=106	Dose received every 3 week for 6 cycles, followed by: up to 14 maintenance cycles every 3 weeks	**Median PFS:** Intervention reduced risk of progression compared to placebo by: • pMMR: HR = 0.54 (95% CI; 0.19-0.48) 1. Interv.: 13.1 months (95% CI; 0.10.5-18.8) 2. Placebo: 8.7 months (95% CI; 8.4-10.7) • dMMR: HR = 0.30 (95% CI; 0.41-0.71) 1. Interv.: NR (95% CI; 30.6-NR) 2. Placebo: 7.6 months (95% CI; 6.5-9.9) pMMR: median follow up at 12 months dMMR: median follow up at 7.9 months	**TRAE of any cause:** • pMMR: Pembro. (93.5%) vs. Placebo (93.4%) • dMMR: Pembro. (98.2%) vs. Placebo (99.1%) **Grade 3 or Higher TRAE:** • pMMR: Pembro. (55.1%) vs. Placebo (45.3%) • dMMR: Pembro. (66.3%) vs. Placebo (47.2%) **TRAE leading to death**: • pMMR: 8 total patients → Pembro. (75%) vs. Placebo (25%) • dMMR: 3 total patients → Pembro. (33.3%) vs. Placebo (66.6%)	Eskander et al (2023) (4)

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5	*Clinical and Biological Activity of Chemoimmunotherapy in Advanced Endometrial Adenocarcinoma: A Phase II Trial of the Big Ten Cancer Research Consortium*	46 (43 available for analysis)	**Intervention Group:** Combination Chemotherapy (carboplatin + paclitaxel) plus: Pembrolizumab (No placebo) Stratification within treatment groups: • pMMR and/or MSS cohort: n=31 • dMMR and/or MSI-H cohort: n=9 • No tumor status: n=3	Combination chemotherapy + pembrolizumab every 3 weeks for 6 cycles	*In Intervention Patients:* *ORR* *• 74.4% (P = 0.001)* *• pMMR/MSS: 71.4% (95% CI; 51.3-86.8)* *• dMMR/MSI-H: 88.9% (95% CI; 51.8-99.7)* *Median PFS:* *• 10.6 months (95% CI; 8.3-13.9)* *• pMMR/MSS: 8.8 months (95% CI; 1.5-16.2)* *• dMMR/MSI-H: not reached (p=0.07)*	**TRAE of any cause:** • Occurred in 100% of patients **Grade 3 or 4 TRAE:** • Occurred in 20.9% of patients	Barber et al (2022) (5)
6	*Pembrolizumab, Radiotherapy, and an Immunomodulatory Five-Drug Cocktail in Pretreated Patients with Persistent, Recurrent, or Metastatic Cervical or Endometrial Carcinoma: Results of the Phase II PRIMMO Study*	43	**Intervention Group: 5 Drug Immunomodulatory** Cocktail (cyclophosphamide, aspirin, lansoprazole, vitamin D, turmeric phytosome) AND radioimmunotherapy plus: Pembrolizumab (No placebo) Stratification by: • Endometrial cancer (n=25) • Cervical cancer (n=18)	2 weeks of daily 5 drug cocktail intake followed by radioimmunotherapy and IV pembrolizumab once every 3 weeks for 6 cycles	*In Intervention Patients:* *ORR* *• Endometrial: 12.0% (95% CI; 3.4-28.2)* *• Cervical: 11.0% (95% CI; 2.0-31.0)* *Median PFS:* *• Endometrial: 3.6 weeks (95% CI; 3.6-15.4)* *• Cervical: 4.1 weeks (95% CI; 4.1-25.7)* *Median OS:* *• Endometrial: 37.4 weeks (95% CI; 19.0-50.3)* *• Cervical: 39.6 weeks (95% CI; 15.0-67.0)* *Endometrial: median follow up at 34 weeks* *Cervical: median follow up at 36 weeks*	**TRAE of any cause:** • Endometrial: 80% • Cervical: 88.9% Grade 3 or Higher TRAE: • Endometrial: 36% • Cervical: 55.6%	

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7	*A Phase Ib/II Study of Lenvatinib and Pembrolizumab in Advanced Endometrial Carcinoma (Study 111/KEYNOTE-146): Long-Term Efficacy and Safety Update*	108	**Intervention Group:** Pembrolizumab plus lenvatinib Stratification by: • MSS/pMMR (n=94) • MSI-H/dMMR (n=11)	Pembrolizumab every 3 weeks	*In Intervention Patients:* ***ORR:** 39.8% (95% CI; 30.5-49.7)* *• MSS/pMMR: 38.3% (95% CI; 38.5-48.9)* *• MSI-H/dMMR 63.6% (95% CI; 30.8-89.1)* ***Median PFS:** 7.4 months (95% CI; 5.2-8.7)* *• MSS/pMMR: 7.4 months (95% CI; 4.4 to 7.6)* *• MSI-H/dMMR: 26.4 (4.0-NR)* ***Median OS:** 17.7 months (95% CI; 15.5-25.8)* *• MSS/pMMR: 17.2 months (95% CI; 15.0-25.8)* *• MSI-H/dMMR: NR (95% CI; 7.4-NR)* *Median follow up at 25.8 months*		Makker et al (2020) (3)
8	*Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/ KEYNOTE-775*	827	**Intervention Group:** Pembrolizumab + lenvatinib (n=411)\ **Placebo Group:** Chemotherapy of physician's choice (doxorubicin or paclitaxel) (n=416) Stratification within treatment groups: • pMMR cohort: o Interv.: n=346 o Placebo: n=351 • All-comers (includes dMMR) cohort: o Interv.: n=411 o Placebo: n=416	Dose received of either therapy every 3 weeks	**ORR:** Intervention vs. Placebo • pMMR: 32.4% vs. 15.1% • All-comers: 33.8% vs. 14.7 % **Median PFS:** Intervention reduced risk of progression compared to placebo by: • pMMR: HR = 0.60 (95% CI; 0.5-0.72) 1. Interv.: 6.7 months (95% CI; 5.6-7.4) 2. Placebo: 3.8 months (95% CI; 3.6-5.0) • All-comers: HR = 0.56 (95% CI; 0.48-0.66) 1. Interv.: 7.3 months (95% CI; 5.7-7.6) 2. Placebo: 3.8 months (95% CI; 3.6-4.2) **Median OS:** **Intervention** reduced risk of death compared to placebo by: • pMMR: HR = 0.70 (95% CI; 0.58-0.83) 1. Interv.: 18 months (95% CI; 14.9-20.5) 2. Placebo: 12.2 months (95% CI; 11.0-14.1) • All-comers: HR = 0.65 (95% CI; 0.55-0.77) 1. Interv.: 18.7 months (95% CI; 15.6-21.3) 2. Placebo: 11.9 months (95% CI; 10.7-13.3) Intervention: median follow up at 18.7 months Placebo: median follow up at 12.2 months	**TRAE of any cause:** • Intervention. (99.8%) vs. Placebo (99.5%) **Grade 3 or Higher TRAE:** • Intervention. (90.1%) vs. Placebo (73.7%)	Makker et al (2023) (2)

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Table 2: Jemperli (Dostarlimab) Trials

	Study Title	Sample Size (n)	Intervention(s)	Duration	EFFICACY: Progression-Free Survival (PFS) Objective Response Rate (ORR) Overall Survival (OS) Disease Control Rate (DCR)	SAFETY: Treatment-Related Adverse Events (TRAE) Immune-Related Adverse Events (irAE)	Refere-nce
1	*Safety and Antitumor Activity of Dostarlimab in Patients with Advanced or Recurrent DNA Mismatch Repair Deficient/ Microsatellite Instability-High (dMMR/MSI-H) or Proficient/ Stable (MMRp/ MSS) Endometrial Cancer: Interim Results from GARNET-a phase I, Single-Arm Study*	290	**Intervention Group:** Dostarlimab (No placebo) Stratification within treatment groups: • Cohort A1 (dMMR/ MSI-H): n=129 • Cohort A2 (pMMR/ MSS): n=161	Dostarlimab (500mg) IV every 3 weeks for 4 cycles Followed by: Dostarlimab (1000mg) IV every 6 weeks until disease progression	**ORR** • Cohort A1: 43.5% (95% CI; 34.0-53.4) • Cohort A2: 14.1% (95% CI; 9.1-20.6) **Immune-Related DCR** • Cohort A1: 55.6% (95% CI; 45.7-65.1) • Cohort A2: 34.6% (95% CI; 27.2-42.6) *Cohort A1: median follow up at 16.3 months* *Cohort A2: median follow up at 11.5 months*	**Grade 1-2 TRAE** -Overall Population: 75.5% **Grade 3 or Higher TRAE** -Overall Population: 16.6% **TRAE Leading to Discontinuation** -Overall Population: 5.5% **irAEs**	Oaknin et al (2022) (9)
2	*Antitumor Activity and Safety of Dostarlimab Monotherapy in Patients With Mismatch Repair Deficient Solid Tumors* *Interim Results from GARNET phase 1 trial*	347	**Intervention Group:** Dostarlimab (No placebo) Stratification within treatment groups: • dMMR EC (n=141) • dMMR non-EC (n=204)	Dostarlimab (500mg) IV every 3 weeks for 4 cycles Followed by: Dostarlimab (1000mg) IV every 6 weeks until disease progression, discontinuation, or withdrawal	**ORR** • **dMMR** EC: 45.5% (95% CI; 37.1-54.0) • dMMR non-EC: 43.1% (95% CI; 36.2-50.2) **Median PFS:** • dMMR EC: 6.0 months (95% CI; 4.1-18.0) • dMMR non-EC: 7.1 months (95% CI; 3.6-19.5) **Median OS:** • dMMR EC: NR (95% CI; 25.7-NR) • dMMR non-EC: NR (95% **CI; 31.5-NR)**	**Any TRAE** • Overall Population: 70.8% **Grade 3 or Higher TRAE** • Overall Population: 16.3% **TRAE Leading to Discontinuation** -Overall Population: 6.9% **irAEs** **-Overall** Population: 34.2%	Thierry et al (2023) (10)

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3	*Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer (RUBY Trial)*	494	**Intervention Group:** Combination Chemotherapy (Paclitaxel-Carboplatin)plus: Dostarlimab (n=245) **Placebo Group:** Combination Chemotherapy (Paclitaxel-Carboplatin) plus: Placebo (n=249) Stratification within treatment groups: • dMMR/MSI-H cohort (n=118) • Overall Population (including pMMR/MSS & dMMR/MSI-H) (n=494)	Dostarlimb (500mg) IV or placebo + chemotherapy (paclitaxel-carboplatin) every 3 weeks for 6 cycles Followed by: Dostarlimab (1000mg) or placebo every 6 weeks for up to 3 years	**2-Year PFS:** • Overall Population: 1. HR: 0.64 (95% CI; 0.51-0.80) • dMMR/MSI-H: 1. HR: 0.28 (95% CI; 0.16-0.50) **2-Year OS:** • Overall Population: 1. HR: 0.64 (95% CI; 0.46-0.87) • dMMR/MSI-H: 1. HR: 0.30 (95% CI; 0.13-0.70)	**Any TRAE:** **• Intervention Group:** 70.5% • Placebo: 59.8% **Serious TRAEs** • Intervention Group: 37.8% • Placebo: 27.6% **TRAE Leading to Discontinuation** • Intervention Group: 17.4% • Placebo: 9.3% **irAEs:** • Intervention Group: 38.2% • Placebo: 15.4%	Mirza et al. (2023) (11)

NR= Not Reached

Keytruda (Pembrolizumab)

Table 1 illustrates methodology and findings (efficacy and safety) from selected pembrolizumab studies. Three of the selected studies analyzed pembrolizumab monotherapy alone for the treatment of advanced/recurrent EC [8-10]. Two of the studies assessed pembrolizumab in combination with standard chemotherapy (carboplatin plus paclitaxel) [11,12]. Another assessed pembrolizumab in combination with a five-drug immunomodulatory cocktail, including cyclophosphamide, plus radiotherapy [13]. The final two studies evaluated tumor response to pembrolizumab in combination with lenvatinib [14,15]. Standard pembrolizumab dosing for all studies was 200 mg IV every 3 weeks for a variable number of cycles.

Efficacy

Pembrolizumab Monotherapy

In 2022, based on data from the KEYNOTE-158 study, pembrolizumab monotherapy was granted approval by the US Food and Drug Administration (FDA) for managing patients with a wide range of unresectable or metastatic MSI-H/dMMR cancers that have advanced after previous treatment and have exhausted other therapeutic avenues [6]. An article by O'Malley et al reported continued data from KEYNOTE-158, revealing strong and long-lasting antitumor efficacy with relatively mild toxicity of pembrolizumab monotherapy, specifically, for patients with advanced/recurrent MSI-H/dMMR endometrial cancer. This article endorsed the efficacy of pembrolizumab monotherapy for the treatment of advanced/recurrent MSI–H/dMMR EC as an ORR of 48% (95% CI, 37-60), a median PFS of 13.1 months (95% CI, 4.3-34.4), and a median OS that was not reached (95% CI, 27.2 months- not reached) [8]. A study conducted by Bellone et al analyzed advanced/recurrent MSI-H endometrial cancers further subcategorized into germline (Lynch Syndrome-like) or sporadic gene mutations. Although tumor mutational burden was higher in the Lynch-like cohort, the ORR, PFS, and OS in response to pembrolizumab therapy were all significantly more efficacious than that of the sporadic gene mutation population, suggesting prognostic significance of determining mutation-type during disease course [9].

Hill et al compared the efficacy of immune checkpoint inhibitor (ICI) monotherapy (pembrolizumab, dostarlimab, or nivolumab) to any standard platinum chemotherapy regimen for the treatment of advanced/recurrent EC. While this study did not speculate on the superiority of any one ICI monotherapy, it did show that ICI reduced the risk of death (OS) due to advanced EC by 70% in dMMR/MSI-H patients compared to standard chemotherapy ($p<0.05$). Notably, this study did not find that ICI led to any significant reduction in death compared to chemotherapy for patients with pMMR/MSS EC ($p>0.05$) [10].

Pembrolizumab plus Chemotherapy

In stage III, stage IV, and recurrent endometrial cancers, the objective response rate (ORR) to first-line chemotherapy (paclitaxel-carboplatin) alone varies between 38% and 52%, with median progression-free survival (PFS) ranging from 8 to 13 months and OS reported as a median of 37 months [16]. Two studies explored the synergistic effects of pembrolizumab in combination with first-line chemotherapy (paclitaxel-carboplatin) for the treatment of recurrent/advanced EC [11,12]. A study conducted by Eskander et al compared pembrolizumab plus chemotherapy to a standard

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chemotherapy placebo (paclitaxel-carboplatin) alone for the treatment of advanced/recurrent EC. While this study did not offer data on ORR, it reported a median PFS of 13.1 months (95% CI; 0.10.5-18.8) in the pMMR cohort and "not reached" (95% CI; 30.6-NR) in the dMMR cohort. Eskander et al found that the use of pembrolizumab in addition to combination chemotherapy significantly reduced the risk of EC progression (PFS) by 46% and 70% in both pMMR and dMMR patient populations, respectively, compared to placebo ($p<0.05$) [11].

Comparably, The Big Ten Research Consortium study reported the ORR for pembrolizumab plus chemotherapy to be 74.4%, far exceeding the ORR reported in previous studies for standard chemotherapy alone, while median PFS and OS appeared similar in efficacy (5,22). This study also stratified by pMMR and dMMR status, revealing an ORR 71.4% and 88.9%, respectively ($p<0.05$). While the difference between the pMMR and dMMR cohorts in terms of efficacy appears outstanding, there was not a large enough population size in this study to truly determine significance [12]. It is important to note that the study conducted by Eskander et al had a much larger population size (n=588) than that of the Big Ten Research Consortium (n=24) and had the advantage of being a double-armed study [11,12].

The Phase II PRIMMO study, analyzed the efficacy of pembrolizumab in combination with a five-drug immunomodulatory/chemotherapy cocktail (cyclophosphamide, aspirin, lansoprazole, vitamin D, turmeric phytosome) and radioimmunotherapy for the treatment of both advanced/recurrent endometrial and cervical cancers. While the population size for EC analysis was small (n=25), the PRIMMO study found the median PFS fell short at 3.6 weeks (95% CI; 3.6-15.4) and was similar in overall efficacy to pembrolizumab therapy alone [13].

Pembrolizumab plus Lenvatinib

Two trials, KEYNOTE-146 and KEYNOTE-775, analyzed the use of pembrolizumab in combination with lenvatinib, a multi-receptor tyrosine kinase inhibitor, for the treatment of advanced/recurrent EC [9,10]. Currently, pembrolizumab, as a single agent, is approved for use in advanced/recurrent EC that is MSI-H/dMMR only [6]. KEYNOTE-146 demonstrated robust efficacy (PFS and OS) for the use of pembrolizumab plus lenvatinib in advanced EC that is both dMMR/MSI-H and pMMR/MSS. In 2021, based on the findings of the KEYNOTE-146 study, the FDA granted approval for pembrolizumab plus lenvatinib to treat advanced non-MSI-H/dMMR EC that has progressed after previous systemic therapy and is ineligible for curative surgery or radiation [9]. The KEYNOTE-775 trial compared pembrolizumab plus lenvatinib to standard chemotherapy of physician's choice (doxorubicin or paclitaxel) for the treatment of advanced EC, regardless of biomarker status. The KEYNOTE-775 trial demonstrated similar improved efficacy of pembrolizumab plus lenvatinib in terms of OS, PFS, and ORR compared to standard chemotherapy. The KEYNOTE-775 trial determined a final analysis of OS as 35% and 30% reductions in risk of death from advanced EC for all-comer (including dMMR) and pMMR cohorts ($p<0.05$), respectively, and provided updated PFS and ORR results [10].

Safety

Amongst studies that investigated the safety of pembrolizumab as a monotherapy for the treatment of advanced/recurrent EC, the most common TRAEs of any grade were pruritus/skin disorders, fatigue, and diarrhea. Predominant grade 3 or greater TRAEs for both studies were fatigue, diarrhea, hyperglycemia, arthralgia, myalgia, and skin disorders; however, the two studies observed these grade 3 or higher adverse events in only 12% of patients overall. The most common irAEs reported were infusion reaction and hypothyroidism. Both studies reported manageable toxicity profiles, with adverse events being predominantly mild to moderate in severity [8,9].

The safety profile for pembrolizumab in combination with chemotherapy (carboplatin-paclitaxel) is comparable to that of chemotherapy alone, with the most common overall TRAEs being fatigue, peripheral sensory neuropathy, anemia, nausea, constipation, and diarrhea. The most commonly observed irAEs for pembrolizumab plus chemotherapy treatment, in descending order, were found to be anemia, thrombocytopenia, neutropenia, and lymphopenia [11,12]. Eskander et al reported that the occurrence of irAEs did not exceed that noted in prior investigations of pembrolizumab alone in individuals with advanced/recurrent EC [11].

Aside from its negligible findings regarding efficacy, the PRIMMO study also reported an increased toxicity profile for the use of pembrolizumab in combination with a 5-drug cocktail and radiotherapy compared to pembrolizumab monotherapy. The study reported grade ≥ 3 colitis affecting ~14% of patients, possibly due to aspirin- or radiotherapy-induced intestinal epithelial disruption. Additionally, grade ≥ 3 lymphopenia and anemia were observed to a greater degree than would be expected [13]. Similar AEs for pembrolizumab plus lenvatinib were observed in both the KEYNOTE-146 and KEYNOTE-775 trials, with the most common TRAEs being hypertension (33.3% vs. 65.0%, respectively) in both trials. Additional common TRAEs included hypothyroidism, gastrointestinal symptoms, elevated lipase, and fatigue. KEYNOTE-775 reported grade ≥ 3 TRAEs occurring in 90.1% of patients receiving lenvatinib plus pembrolizumab compared to 73.7% of patients receiving chemotherapy, however, endorsed an overall manageable safety profile for both groups [14,15].

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Jemperli (Dostarlimab):

Table 2 illustrates methodology and findings (efficacy and safety) from selected dostarlimab studies. Two of the selected studies were single-arm and analyzed dostarlimab monotherapy alone for the treatment of advanced/recurrent EC. The third study was double-armed and assessed dostarlimab in combination with standard chemotherapy (carboplatin plus paclitaxel) [4]. Standard dosing for dostarlimab in all studies was 500 mg IV every 3 weeks for 4-6 cycles followed by 1000 mg IV dostarlimab every 6 weeks until disease progression or drug discontinuation [17,18].

Efficacy

Dostarlimab Monotherapy

In 2023, based on the results of the GARNET trial, dostarlimab was FDA-approved as a monotherapy for the treatment of dMMR/MSI-H solid EC tumors that progressed despite prior systemic therapy and lacked alternative therapy options [17,18]. A 2022 study by Oaknin et al reported interim data from the GARNET trial, citing an ORR of 43.5% and 14.1% in dMMR and pMMR tumors, respectively ($p<0.05$). While ORR results for dMMR tumor types clearly supersedes that of pMMR tumor types, with an immune-related disease control rate of 34.6% in pMMR/MSS patients, dostarlimab was shown to hold a promising clinical benefit for these patients as well [17].

A second study from 2023 by André et al, also reporting interim data from the GARNET trial, investigated the use of dostarlimab in, specifically, dMMR/MSI-H solid tumors, including advanced EC. The ORR, PFS, and OS for dMMR EC tumors were reported as 45.5% (95% CI; 37.1-54.0), 6 months (95% CI; 4.1-18.0), and not reached (95% CI; 25.7-NR), respectively. Similar efficacy was reported for both EC and non-EC tumors in terms of ORR, PFS, and OS, which are promising results for the future use of dostarlimab in a wider range of dMMR/MSI-H solid tumors [18].

Dostarlimab plus Chemotherapy

Also in 2023, the RUBY trial, a double-blind placebo-controlled phase 3 trial, provided evidence for the FDA-approval of dostarlimab plus chemotherapy (carboplatin-paclitaxel) as a second-line treatment of dMMR/MSI-H advanced/recurrent EC. Dostarlimab plus chemotherapy reduced the risk of EC progression in dMMR and the overall patient population (including pMMR) by 72% and 36%, respectively, compared to standard chemotherapy placebo alone. While the overall benefit of the dostarlimab regimen is most apparent in the dMMR/MSI-H population, in those pMMR/MSS patients that did respond to the dostarlimab regimen, the response was durable [4].

Safety

Adverse events for dostarlimab as a monotherapy for advanced/recurrent EC in the GARNET trial were found to be similar between the two selected dostarlimab monotherapy studies. Most TRAEs were grade 1-2 (70-76%), among which, the most common across both studies were fatigue, diarrhea, and nausea. Grade ≥ 3 TRAEs occurred in 16-17% of all patients, of which anemia, increased alanine aminotransferase (ALT), fatigue, diarrhea, and increased amylase and lipase were the most common. TRAEs leading to dostarlimab discontinuation were 5.5% and 6.9% in each of the two studies, respectively, most frequently due to liver enzyme elevations. Immune-related adverse events were reported in around a third of patients in the overall population, with the most common being hypothyroidism, ALT increase, diarrhea, and arthralgia [17,18]. A recent report by Oaknin et al revealed no escalation in adverse effects when transitioning from a dostarlimab dosage of 500 mg every 3 weeks to a dosage of 1000 mg every 6 weeks [19].

In the RUBY trial, the dostarlimab-paclitaxel-carboplatin regimen resulted in higher frequency of overall adverse events and serious adverse events than the paclitaxel-carboplatin placebo alone by approximately 10 percentage points for each (Table 2). The most common TRAEs were nausea, alopecia, and fatigue. TRAEs leading to discontinuation occurred nearly two times more in the dostarlimab regimen group compared to chemotherapy alone. Reasons for discontinuation of the dostarlimab regimen were most frequently maculopapular rash and infusion reaction. Immune-related adverse events were reported in 38.2% of patients receiving the dostarlimab regimen which was more than double the rate that occurred in the placebo. The most common irAEs noted were hypothyroidism, rash, arthralgia, and elevated ALT [4].

Discussion

Although there are limited trials comparing the safety and efficacy of dostarlimab and pembrolizumab in treatment of endometrial cancer, the PERLA phase II trial investigated these outcomes for the treatment of metastatic non-squamous non-small cell lung cancer. 243 patients stratified by PD-L1 tumor proportion score and smoking status were randomized 1:1, receiving dostarlimab plus chemotherapy (DCT), or pembrolizumab plus chemotherapy (PCT) every three weeks. Dostarlimab demonstrated better clinical outcomes than pembrolizumab for the trial's endpoints including overall response rate (45% for DCT, 39% for PCT), median progression-free survival in months (8.8 for DCT, 6.7 for PCT), and median overall survival in months (19.4 for DCT, 15.9 for PCT). Safety profiles were similar between both groups [20]. Similar trials should be conducted for EC

treatment which may help further inform clinical use of these therapies.

Following the clinical efficacy and FDA approval of certain immune checkpoint inhibitor (ICI) therapies including pembrolizumab and dostarlimab, there has been further clinical research on treatment strategies for recurrent EC after ICI immunotherapy. Chimeric antigen receptor (CAR)-T cell therapy, a type of adoptive cellular therapy, is one of these promising new treatments. In CAR-T therapy, T cells are taken from the peripheral circulation and are genetically modified ex vivo before reinfusion. These CAR-T cells are genetically assembled MHC-complex independent molecules in which the effector site of the T cells recognize and interact with tumor-associated antigen (TAA)-expressing cells, inciting an antitumor response. This system bypasses the need for the immunologic activity of antigen presenting cells as a prerequisite for T cell activation. One of the potential molecular targets for CAR-T cells in endometrial immunotherapy is the tumor-suppressive protein phosphatase type II A (PP2A), as genetic mutations in PP2A have been noted in 40% of type II EC. Other targets include the human epidermal growth factor receptor 2 (HER-2) which is overexpressed in type II EC, and the androgen receptor which is overexpressed especially in metastatic EC. CAR-T cell therapy has shown promising results in the treatment of hematologic malignancies, and there are ongoing clinical trials analyzing the safety and efficacy in treating solid tumors, including EC [21].

Conclusion

Endometrial cancer is a common cancer diagnosis found in women in the United States. Endometrial cancer currently affects 25.7/100,000 women per year with an estimate that approximately 13,250 women will die from endometrial cancer in 2024. Current treatment modalities depend on cancer staging but include hysterectomy and salpingo-oophorectomy, radiation (external beam pelvic radiation therapy or vaginal brachytherapy) and/or chemotherapy typically with agents such as doxorubicin, cisplatin, and/or docetaxel). Immune checkpoint inhibitor therapies, such as pembrolizumab, dostarlimab, or nivolumab, are new treatment modalities that are currently being researched. The purpose of this report was to perform a review of research performed about ICI therapies.

There is currently limited data on patient outcomes with these therapies. Potential future areas of research include studying outcomes in ICI therapy with radiotherapy combination treatment. Additionally, a study assessing the difference in side effects and efficacy of monotherapy with pembrolizumab vs. dostarlimab vs. nivolumab for advanced/recurrent endometrial cancer would be beneficial in determining best therapy choice.

Disclosures:

All authors have no relevant conflicts of interest to declare.

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