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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda) in Combination With Lenvatinib (Lenvima)

Indication: For the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high or mismatch repair deficient, who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda in Combination With Lenvima?

CADTH recommends that Keytruda in combination with Lenvima (Keytruda-Lenvima) should be reimbursed by public drug plans for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda-Lenvima should only be covered in patients with endometrial cancer that has spread to the pelvis or other body parts, that is classified as proficient mismatch repair (pMMR), and has further spread after 1 prior systemic, platinum-based chemotherapy.

What Are the Conditions for Reimbursement?

Keytruda-Lenvima should only be reimbursed if prescribed in an outpatient oncology clinic or institution with expertise in delivering systemic therapy, when administered in combination, and if the cost is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Keytruda-Lenvima experienced tumour shrinkage, delay in the spread of cancer, and a longer life. Keytruda-Lenvima meets patient needs of delaying disease progression and prolonging survival and was unlikely to worsen health-related quality of life (HRQoL). Keytruda-Lenvima is not considered cost-effective when compared to physician's choice of chemotherapy.
- Economic evidence suggests that even at a 100% price reduction in the cost of Keytruda, Keytruda-Lenvima would not be cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) in the indicated population. Based on public list prices, Keytruda-Lenvima will cost the public drug plans $106,543,234 over 3 years.

Additional Information

What Is Endometrial Cancer?

Endometrial cancer begins in the uterus Advanced or metastatic endometrial cancer has spread to the pelvis or to other body parts, such as lung or liver.

Unmet Needs in Endometrial Cancer

Patients with advanced endometrial cancer are in need of treatment options with a different or better toxicity profile and improved health benefits. There is currently no established standard of care second-line treatment option.

How Much Does Keytruda Cost?

Treatment with Keytruda-Lenvima is expected to cost approximately $15,949 per 28-day cycle.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab combined with lenvatinib (PEN-LEN) be reimbursed for the treatment of adult patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, randomized, open-label phase III trial (KEYNOTE-775; N = 697 for patients with pMMR disease) demonstrated that treatment with PEM-LEN resulted in added clinical benefit when compared with treatment of physicians' choice (TPC) (doxorubicin or paclitaxel), in adult patients with advanced pMMR (i.e., not MSI-H and not dMMR) endometrial carcinoma, who had disease progression following prior platinum-based systemic therapy, and were not candidates for curative surgery or radiation.

The KEYNOTE-775 trial showed that, compared with TPC, PEM-LEN was associated with statistically significant and clinically meaningful improvements in overall survival (OS) (hazard ratio [HR] = 0.68; 95% confidence interval [CI], 0.56 to 0.84; P < 0.0001) and progression-free survival (PFS) (HR = 0.60; 95% CI, 0.50 to 0.72; P < 0.0001). Treatment with PEM-LEN also showed a statistically significant and clinically meaningful improvement in objective response rate (ORR) (ORR = 30.3% and 15.1% with PEM-LEN and TPC, respectively). While measures of HRQoL and symptom severity appeared similar between study groups, pERC was unable to draw definitive conclusions due to noninferential analyses of patient-reported outcomes and the open-label design of the KEYNOTE-775 trial. pERC considered the safety profile of PEM-LEN to be manageable with dose modifications and best supportive care. Supportive evidence was available from a single-arm phase II trial (KEYNOTE-146, N = 94), in which patients treated with PEM-LEN achieved an ORR of 38.3% (95% CI, 28.5 to 48.9).

Patients identified a need for treatments that improve disease symptoms, achieve disease control, have fewer side effects with good quality of life (QoL), and extend survival. pERC concluded that PEM-LEN meets some of the patients' needs as it prolongs survival, delays disease progression, and likely does not have detrimental effects on HRQoL when compared with TPC.

Using the sponsor-submitted price for pembrolizumab (PEM) and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for PEM-LEN was $366,399 per QALY compared with TPC. PEM-LEN is not cost-effective at a $50,000 per QALY willingness-to-pay threshold for the indicated population. Even with a 100% price reduction for PEM, PEM-LEN would not be cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with PEM-LEN should be initiated in patients who have all of the following: 1.1. advanced, recurrent, or metastatic endometrial carcinoma 1.2. radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen 1.3. have received up to 2 regimens of platinum-based chemotherapy in total, as long as 1 was given in the neoadjuvant or adjuvant treatment setting.	Evidence from the KEYNOTE-775 trial demonstrated a statistically significant clinical benefit in patients who fulfilled these characteristics.	pERC agreed with the clinical experts consulted by CADTH that the results of the KEYNOTE-775 trial could be generalized to patients with multiple prior lines of chemotherapy who otherwise met the trial's eligibility criteria.
2. Patient must not have either of the following: 2.1. MSI-H 2.2. dMMR disease.	The Health Canada indication specifies that PEM-LEN be used in patients with advanced endometrial carcinoma that is not MSI-H or dMMR.	MSI or MMR status must be determined before initiating treatment to ensure patients do not have MSI-H or dMMR disease (i.e., pMMR or MSS).
3. Patients must not have any of the following: 3.1. unstable CNS metastases 3.2. carcinosarcoma and sarcomas 3.3. active autoimmune disease.	The KEYNOTE-775 trial excluded patients with active CNS metastases; carcinosarcoma (malignant mixed Műllerian tumour), endometrial leiomyosarcoma, and endometrial stromal sarcomas; and with active autoimmune disease (except psoriasis). There is no evidence to suggest these patients will benefit from treatment with PEM-LEN.	Patients with treated or stable CNS metastases should be eligible for treatment. Patients with carcinosarcoma who otherwise met the trial's eligibility criteria may receive treatment at the discretion of the treating physician. Treatment of patients with autoimmune disease may be at the discretion of the treating physician.
4. Patients should have good performance status	Patients with an ECOG PS of 0 or 1 were included in the KEYNOTE-775 trial.	Patients with an EGOC PS of 2 may be treated at the discretion of the treating clinician.
Discontinuation		
5. Discontinuation should be based on a combination of clinical and radiological progression or significant adverse events potentially related to PEM-LEN.	Consistent with clinical practice, patients from the KEYNOTE-775 trial discontinued treatment upon progression or unacceptable toxicity.	—

Reimbursement condition	Reason	Implementation guidance
6. PEM should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks), 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer. LEN can be continued beyond this time.	Patients in the KEYNOTE-775 trial were treated with PEM for a maximum of 35 cycles. In the presence of clinical benefit, patients who completed 35 cycles of treatment with PEM (approximately 2 years) could continue LEN alone beyond this time point.	It would be reasonable to re-administer PEM at the time of relapse (up to 17 additional every 3-week doses or up to 1 year), with or without lenvatinib, at the discretion of the treating physician for patients who have discontinued PEM before any disease progression or disease progression occurred during a treatment break.
Prescribing		
7. PEM-LEN should be prescribed in an outpatient oncology clinic; treatment should be supervised and/or delivered in institutions with expertise in systemic therapy delivery.	To ensure that PEM-LEN is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	PEM may be given at a dose of 400 mg IV every 6 weeks instead of 200 mg IV every 3 weeks. It can be given based on weight at 2 mg/kg up to 200 mg every 3 weeks or 4 mg/kg up to 400 mg every 6 weeks.
8. PEM-LEN should only be reimbursed when administered in combination.	There is no data supporting the efficacy and safety of PEM-LEN when used in combination with additional anticancer drugs, or when either component is initially used as monotherapy.	LEN can continue as monotherapy after 35 cycles of PEM.
Pricing		
9. A reduction in price	The ICER for PEM-LEN is $366,399 per QALY when compared with physician's choice chemotherapy. Even with a 100% price reduction for PEM, PEM-LEN would not be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY, due to the cost of lenvatinib.	—
Feasibility of adoption		
10. The feasibility of adoption of PEM-LEN must be addressed.	At the submitted price, the budget impact of PEM-LEN is expected to be greater than $40 million in year 2 and year 3.	—

CNS = central nervous system; dMMR = deficient mismatch repair; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental-cost-effectiveness ratio; LEN = lenvatinib; MMR = mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability high; MSS = microsatellite stable; PEM = pembrolizumab; PEM-LEN = pembrolizumab combined with lenvatinib; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; pMMR = proficient mismatch repair; QALY = quality-adjusted life-year; TPC = treatment of physician's choice.

Discussion Points

- Input from patient groups and clinicians highlighted that advanced endometrial carcinoma is an aggressive disease and patients who relapse on first-line platinum-based chemotherapy have a poor prognosis and currently have no established standard second-line treatment option. pERC agreed with the clinical experts consulted by CADTH that there is an unmet need for effective and safe therapy options in the present target setting.

- pERC discussed the results of the KEYNOTE-775 trial and noted that OS, PFS, and ORR were identified as clinically relevant outcomes by patients and clinicians and were statistically significant in favour of PEM-LEN. Given that the prognosis of patients with recurrent endometrial cancer is poor, with a median survival of about 12 months, the benefits observed with PEM-LEN over TPC were considered clinically meaningful in a setting with no standard treatment option.
- pERC noted that the comparator in the KEYNOTE-775 trial (i.e., TPC [doxorubicin or paclitaxel]), was appropriate in the target setting. pERC acknowledged input from the clinical experts consulted by CADTH that to avoid toxicity from doxorubicin, some patients may be re-treated with platinum-based combination chemotherapy after first-line platinum-based chemotherapy and a treatment-free interval of 6 months or more.
- pERC noted that the safety profile of PEM-LEN was mainly driven by higher rates of hypertension, hypothyroidism, and diarrhea in the PEM-LEN group, which could be adequately managed in clinical practice. pERC agreed with the clinical experts consulted by CADTH that most adverse events (AEs) associated with PEM-LEN could be managed with dose modifications and best supportive care and that no unexpected safety concerns were observed with PEM-LEN.
- The sponsor's submitted pharmacoeconomic analysis did not consider the possibility that some patients may be re-treated with platinum-based chemotherapy if a sufficient treatment-free period is reached. Due to this limitation within the evidence, the cost-effectiveness of PEM-LEN compared to platinum re-treatment is unknown.

Background

Endometrial cancer is the most common gynecological cancer in Canada. Molecular testing of cancer biomarkers during endometrial biopsy assists in identifying treatment options and risk stratification. Two molecular cancer biomarkers commonly assessed are MSI and MMR protein expression. Based on biomarkers testing, endometrial cancer can be classified into MSI-H (or dMMR), and not MSI-H (or pMMR). In clinical practice and in clinical trials, the terms non-MSI-H and pMMR, as well as dMMR and MSI-H, are often used interchangeably. For patients with advanced or recurrent endometrial cancer who have progressed on or after platinum-based chemotherapy, there is currently no established standard effective or curative second-line therapy.

The PEM-LEN combination has a Health Canada indication for the treatment of adult patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation. PEM is an inhibitor of programmed cell death receptor 1 (PD-1). It is available as powder for solution for infusion 50 mg and solution for infusion 100 mg per 4 mL vial. The recommended dose for PEM is 200 mg every 3 weeks or 400 mg every 6 weeks administered as an IV infusion until disease progression, unacceptable toxicity, or up to 24 months.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 pivotal phase III randomized controlled trial (KN-775) and 1 relevant single-arm study (KN-146) for the treatment of adult patients with pMMR advanced endometrial carcinoma, who have disease progression following prior platinum-based systemic therapy in any setting and are not candidates for curative surgery or radiation
- patients' perspectives gathered by a joint input from the Colorectal Cancer Resource & Action Network (CCRAN), in collaboration with the Canadian Cancer Society (CCS) and the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with endometrial cancer
- input from 1 clinician group, Ontario Health (Cancer Care Ontario) Gynecology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups.

The input from patient advocacy groups for PEM-LEN for the treatment of advanced endometrial cancer was provided by CCRAN, in collaboration with CCS and CCSN. CCRAN is a Canadian not-for-profit patient advocacy group that focuses on patients with colorectal cancer, with an extended mandate to support other cancer populations, either those who lack capacity or representative patient groups.

The information provided by the CCS was collected through an online survey that was conducted between October 22 and November 3, 2021, with 22 responses from people in Canada (20 patients and 2 caregivers). CCSN conducted an outreach survey on December 5, 2021, and provided feedback from 1 patient with endometrial cancer who lives in Canada. CCRAN provided additional feedback from 1 caregiver and 3 patients with advanced endometrial cancer via telephone interviews that took place from December 1 to December 14, 2021, in Canada.

The 3 patient groups reported that individuals with endometrial cancer experience physical symptoms (e.g., vaginal bleeding, pelvic pain, diarrhea, nausea, fatigue) and psychological symptoms (feeling isolated and lonely). Some of the patients expressed substantial frustration related to their long diagnostic journey, noting that it might have contributed to their advanced-stage diagnosis and disease progression. Endometrial cancer negatively influences the QoL of patients and their families. Many patients report issues with work, daily chores, and socialization. Caregivers and family members have to take on additional responsibilities and deal with emotional tolls such as stress and anxiety.

Regarding current treatment, patients reported a variety of options, including surgery, chemotherapy, and hormonal therapy. The CCSN survey and CCRAN interviews captured a general lack of efficacy with, as well as debilitating side effects from, standard of care treatments indicated for the management of patients with advanced endometrial cancer.

Three patients in Canada had experience with the PEM-LEN combination through a clinical trial or a private pay plan. Two of these patients, one after 26 months of therapy and the other after 4 months of therapy, reported complete amelioration of cancer-induced symptoms, disease regression, and superior QoL. These patients reported being able to function at an almost normal level and resume daily activities. Treatment-induced side effects were reported by 2 patients and included diarrhea, fatigue, and urinary tract infection. One patient experienced dose adjustment of lenvatinib (LEN) (14 mg per day to 10mg per day) due to a headache at the beginning of the treatment. Patients also appreciated having access to an oral treatment (lenvatinib) as well as short infusion time of PEM (30 to 45 minutes every 3 weeks).

Key outcomes identified by the patient advocacy groups as important to patients with endometrial cancer included improved symptoms, cancer control, fewer side effects, good QoL, and extension of survival.

Overall, the CCRAN patient group indicated that there is an urgent, unmet need for the treatment of patients with advanced endometrial cancer. The group emphasized that patients need access to treatments with fewer side effects that would extend and improve the quality of their lives. CCRAN strongly supported the use of the PEM-LEN combination therapy as a second-line treatment option for patients with MSS or pMMR whose tumours are inoperable, metastatic, or recurrent.

Clinician Input

Input the From Clinical Experts Consulted by CADTH

The clinical experts consulted for this review indicated, there is currently a lack of treatment options and no standard second-line therapy for individuals with metastatic or recurrent endometrial carcinoma. Both clinical experts noted that most patients undergoing current therapies show low response rates, short duration of response (DOR), and progression. This represents a critical unmet need in this patient population.

The clinical experts consulted for this review indicated that patients with endometrial carcinoma who have progressed on platinum chemotherapy currently receive cytotoxic treatments such as carboplatin and paclitaxel, doxorubicin, or pegylated liposomal doxorubicin. Additional chemotherapy drugs that can be taken into consideration include topotecan, gemcitabine, pemetrexed ifosfamide, and hormonal treatments (e.g., megestrol acetate, tamoxifen). The described treatments are not considered curative and have low expected response rates and short durations.

Both clinical experts indicated that the PEM-LEN combination would become standard second-line therapy for patients with endometrial carcinoma after recurrence or failure of typical platinum-based regimens. This treatment combination would address the underlying disease process. The clinical experts felt it would be preferable to initiate treatment with the drug under review before other therapies.

The clinical experts indicated that, in the case of relapse, there is currently no evidence to support re-treatment with the same drugs.

Clinical experts agreed that all patients with endometrial carcinoma who experience recurrent or progressive disease following platinum-containing chemotherapy and have good performance status would benefit most from the PEM-LEN combination (i.e., Eastern Cooperative Oncology Group Performance Status [ECOG PS] of 0 or 1). Although not supported by clinical trial evidence, the experts also indicated that the treatment might be extended to patients with an ECOG PS of 2 if the patient is appropriately informed and motivated. The experts noted that there is currently a lack of data on treatment response among patients with other histologic types of endometrial carcinoma (e.g., carcinosarcoma, endometrial leiomyosarcoma, and endometrial stromal sarcomas). One expert indicated that presence of unstable central nervous system metastases should be treated with neurosurgical resection and postoperative cranial irradiation before considering treatment with the PEM-LEN combination.

Regarding the identification of patients, 1 clinical expert mentioned that standard practice includes a clinical examination by an oncologist, diagnostic imaging, and biopsies. The other expert noted that biomarker testing for MMR status via immunohistochemistry staining is applied across many centres in Canada.

The clinical experts reported that treatment with the PEM-LEN combination would be least suitable in patients with poor performance status (i.e., ECOG PS of 3 or 4). One expert also noted that patients with multiple lines of chemotherapy, and patients with an intolerance or contraindications to PEM, would be least suited to receive the drug under review.

According to the clinical experts, evaluation of treatment response in clinical practice is performed through an assessment of clinical symptoms, imaging (e.g., CT, MRI), and physical exam findings. One expert noted that treatment benefit for most biologics would include absence of progression and good tolerance to treatment.

Both experts agreed that improved PFS and OS, maintained or improved QoL, and symptoms control can be considered clinically meaningful responses for the treatment under review. Assessment of treatment response should be conducted every 12 to 16 weeks (3 to 4 months).

According to the clinical experts, treatment with the PEM-LEN combination should be discontinued in case of disease progression (confirmed clinically or on imaging), appearance of serious immune AEs, or intolerable treatment toxicities.

Both experts noted that, if toxicity or tolerability issues are related to LEN, it would be reasonable to continue treatment with PEM alone in case that the patient is benefiting from the therapy.

Clinical experts consulted by CADTH indicated that treatment administration and monitoring of patients with endometrial cancer should be undertaken by a specialist, namely a gynecologist oncologist or medical oncologist. Treatment monitoring can potentially be conducted by a GP oncologist, but under the overview of 1 of the specialists.

The experts recommend that PEM-LEN be administered in an infusion setting, either hospital or oncology centre clinics with appropriate monitoring capabilities. In terms of companion

diagnostics, 1 expert noted that detection of MMR status through immunohistochemistry staining would be required.

The clinical experts consulted by CADTH noted that fixed dosing would be applied for PEM and anticipated that dose modifications of LEN would be common in clinical practice. One clinical expert indicated that less frequent administrations (i.e., over 6-week periods) would be better for patients, clinicians, and health centres.

One clinical expert expressed concerns with the high costs of the treatment under review and indicated that the costs might improve with increased availability of other programmed death-ligand 1 (PD-L1) inhibitors on the market.

Clinician Group Input

One joint clinician input was provided by 7 physicians on behalf of the Ontario Health (Cancer Care Ontario) Gynecology Cancer Drug Advisory Committee. The clinician group noted the absence of currently available therapies for patients with recurrent or progressive endometrial cancer. The group recognized the unmet needs of this patient population, indicating that most patients remain unresponsive to available treatments and highlighting a need for better-tolerated treatment options. The clinician group stated that the PEM-LEN combination could be used in the second line as a preferred option for all patients with endometrial cancer who recur or progress after platinum-based chemotherapy. Prolonged life, delayed disease progression, symptomatic relief, partial response, full response, and improved HRQoL were identified as the most important treatment goals. In terms of assessing response to treatment, the clinician group stated that imaging, clinical exam, and symptomatic improvement should be assessed in clinical practice. The clinician group also advised that the PEM-LEN combination should be discontinued if a patient experiences disease progression or intolerable side effects related to the treatment. Lastly, outpatient hospital settings were noted as appropriate treatment settings for these patients.

Of note, 5 out of 7 physicians provided CADTH with a conflict of interest declaration within the clinician group input.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
What is the guidance on the maximum number of prior lines of platinum therapy to be eligible for PEM-LEN combination treatment?	According to the KEYNOTE-775 eligibility criteria, patients had to have progressive disease after 1 prior systemic, platinum-based chemotherapy regimen. Patients were excluded if they had received more than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant therapy). In the PEM-LEN group, 77.7%, 21.7%, and 0.3% of patients had received 1, 2, and 3 or more lines of prior platinum-based chemotherapy, respectively. In the TPC group, 64.4%, 32.5%, and 3.1% of patients had received 1, 2, and 3 or more lines of prior platinum--

Drug program implementation questions	Clinical expert response
	based chemotherapy, respectively. pERC agreed with the clinical experts consulted by CADTH that the results of the KEYNOTE-775 trial could be generalized to patients with multiple prior lines of platinum- and non–platinum-based chemotherapy who otherwise met the trial's eligibility criteria. pERC acknowledged input from the clinical experts that most patients would not have received more than 3 lines of platinum-based chemotherapy in clinical practice, given the toxicity concerns with repeated chemotherapy treatments.
What is the guidance on re-treatment?	In the KEYNOTE-775 trial, PEM treatment was given for a maximum of 35 cycles (i.e., for up to 24 months). Patients who discontinued treatment with PEM-LEN and had stable disease or better were allowed to receive an additional year of treatment (17 cycles) with PEM with or without LEN if they progressed after stopping study treatment during the initial treatment period. If LEN was discontinued due to toxicity during the initial treatment period, only PEM was allowed to be administered during the second course; otherwise, LEN was permitted to be administered with PEM during the second course. Subsequent PEM-LEN was received by 3 patients in the PEM-LEN study group of the KEYNOTE-775 trial. pERC agreed with the clinical experts consulted by CADTH that re-treatment per the previously outlined KEYNOTE-775 criteria would be reasonable and consistent with pERC guidance on PEM for other indications.
Considerations for prescribing of therapy	
Jurisdictions may implement weight-based dosing up to a maximum dose for PEM (i.e., 2 mg/kg up to a maximum of 200 mg IV every 3 weeks). Should PEM 4 mg/kg up to a maximum of 400 mg IV every 6 weeks be an option?	Patients in the KEYNOTE-775 trial received a PEM dose of 200 mg IV infusion over 30 minutes every 3 weeks for up to 35 cycles or for a total duration of 24 months. pERC agreed with the clinical experts that generalizing the trial results to an alternative PEM dosing schedule of 400 mg IV every 6 weeks seemed reasonable. pERC also agreed that a weight-based dosing up to a cap (i.e., 2 mg/kg up to a maximum of 200 mg IV every 3 weeks or 4 mg/kg up to a maximum of 400 mg IV every 6 weeks) would be a reasonable alternative to flat dosing and would be consistent with pERC guidance on PEM for other indications.
For patients receiving PEM-LEN — if one of the drugs has to be discontinued due to toxicity, can the other drug be continued? LEN is not publicly funded for endometrial cancer.	pERC agreed with the clinical experts that at the discretion of the treating physician, patients could continue with 1 drug if the other drug in the treatment combination is not well tolerated or was discontinued.
Due to the high frequency of dose modifications of LEN reported on the KEYNOTE-775 study (66.5% of patients required LEN dose modifications) are "dose modifications for LEN" in clinical practice anticipated to be common?	pERC acknowledged input from the clinical experts indicating that dose modifications of LEN are common in Canadian clinical practice settings. The frequency of the dose modification of LEN would be the same or higher than 66.5%, as reported in the KEYNOTE-775 trial.

Drug program implementation questions	Clinical expert response
Generalizability	
Can the PEM-LEN combination therapy be extended to patients with an ECOG PS > 1?	The KEYNOTE-775 trial included patients with an ECOG PS of 0 to 1 (61.3% and 59.0% of patients in the PEM-LEN and TPC study groups, respectively, had an ECOG PS of 0). pERC agreed with the clinical experts that it would be reasonable to generalize the KEYNOTE-775 trial results to patients with an ECOG PS of up to 2 at the discretion of the treating physician.
Study KN775 excluded patients with carcinosarcoma and sarcoma (i.e., leiomyosarcoma and stromal sarcomas). Can the PEM-LEN combination therapy be extended to patients with carcinosarcoma or sarcomas?	pERC agreed with the clinical experts that it would be reasonable to generalize the KEYNOTE-775 trial results to patients with carcinosarcomas. pERC noted that it is unlikely that there will be trials specifically designed for this small group of patients and there is no biological rationale to assume that outcomes of PEM-LEN therapy would be different for these patients given that carcinosarcomas share similar histology, epidemiology, and risk factors with endometrial carcinomas. pERC agreed with the clinical experts that testing for the MSI or MMR status is required before considering PEM-LEN combination therapy in these patients. pERC noted that there is insufficient evidence to extend the results to patients with sarcomas given the difference in histologies between sarcomas and endometrial carcinomas.
Study KN775 excluded patients with unstable CNS metastases. Can the PEM-LEN combination therapy be extended to patients with unstable CNS metastases?	pERC agreed with the clinical experts that patients with stable or treated brain metastases should be eligible for PEM-LEN. However, patients with new or unstable CNS metastases should not be eligible to receive therapy with PEM-LEN before receiving treatment for the CNS metastases.
Can pERC clarify when time-limited funding would be applicable?	pERC agreed that switching should be allowed for toxicity reasons if the patient has not progressed on the previous treatment or if the patient cannot tolerate an adequate dose of a regimen. Clinician judgment should be exercised.
Care provision issues	
LEN is available as 4 mg and 10 mg capsules. The variety of potential daily doses are available from the manufacturer, packaged in blister cards of 5-day increments. This packaging provides flexibility for dispensing different durations of therapy, though it may require pharmacies to carry multiple different strengths of blister cards to anticipate the multiple doses that may be clinically indicated. Dose modifications for LEN in clinical practice are anticipated to be common, due to the high frequency of dose modifications reported on the KN775 study (66.5% of patients required LEN dose modifications). In addition, if dose reductions are required between prescription fills of LEN (e.g., midcycle), drug wastage would occur for any previously dispensed supply of LEN as these cannot be re-dispensed.	pERC acknowledged the issues of drug packaging and wastage. pERC suggested that the pricing of the various sizes should be clarified with the manufacturer. pERC noted that patient education and counselling will be necessary to avoid over- or underdosing with LEN.

Drug program implementation questions	Clinical expert response
MSI or MMR testing is needed to confirm eligibility for PEM-LEN combination therapy. Is there a standardized test to determine a patient does not have MSI-H or pMMR status to guide implementation of eligibility criteria?	pERC acknowledged input from the clinical experts, who indicated that in Canadian clinical practice, MMR testing is usually based on IHC staining of the tumour as a screening test and MSI status is determined based on PCR testing.
When should testing for MSI/MMR status take place in patients with endometrial cancer?	pERC agreed with the clinical experts that testing for the MSI/MMR status is required before considering PEM-LEN combination therapy.

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IHC = immunohistochemistry; LEN = lenvatinib; MSI = microsatellite instability; MSI-H = microsatellite instability high; PCR = polymerase chain reaction; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PEM = pembrolizumab; PEM-LEN = pembrolizumab combined with lenvatinib; pMMR = proficient mismatch repair; TPC = treatment of physician's choice.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Keynote-775 is an ongoing phase III, multicentre, randomized, open-label, active-controlled superiority study comparing PEM-LEN to TPC for the treatment of adult patients 18 years of age or older with advanced endometrial carcinoma, who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation. The Keynote-775 trial included a total of 827 patients (697 with pMMR disease and 130 with dMMR disease). This review focused on patients with pMMR disease only. A total of 697 patients with pMMR disease were randomized in a 1:1 ratio to receive PEM-LEN (n = 346) or TPC (n = 351). The primary outcomes were PFS and OS. The secondary outcomes included ORR and HRQoL (measured with the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire core [QLQ-C30] global health status/overall quality of life [GHS/QoL] scale). The exploratory outcomes included DOR and other HRQoL measurements (i.e., EORTC QLQ-C30, EORTC QLQ-Endometrial Cancer Module [EN24] urological symptoms score, and EQ-5D 5-Levels).

Efficacy Results

Based on the data cut-off date of October 26, 2020, and a median follow-up time of 12.2 months, PEM-LEN combination therapy demonstrated a statistically significant and clinical meaningful improvement in OS compared to TPC (HR = 0.68; 95%CI, 0.56 to 0.84; P = 0.0001). Such improvements were also reported in subgroup analyses of those with ECOG PS of 0 (HR = 0.56; 95%CI, 0.42 to 0.75), patients without endometrioid tumours (HR = 0.56; 95%CI, 0.42 to 0.74), and patients with 1 prior line of systemic therapy (HR = 0.61; 95%CI, 0.47 to 0.78).

Similarly, PEM-LEN combination therapy also showed a statistically significant and clinical meaningful improvement in PFS compared to TPC (HR = 0.60; 95% CI, 0.50 to 0.72; P = 0.0001). Subgroup analyses of OS were consistent with the primary analysis (i.e., HR < 1) in those with ECOG PS of 0 (HR = 0.57; 95% CI, 0.45 to 0.72) and ECOG PS of 1 (HR = 0.65; 95% CI, 0.49 to 0.86), patients with endometrioid tumours (HR = 0.59; 95% CI; 0.46 to 0.76), those without endometrioid tumours (HR = 0.56; 95% CI, 0.43 to 0.73), and patients with 1

prior line of systemic therapy (HR = 0.52; 95% CI, 0.42 to 0.65). [redacted]

ORR was statistically significantly higher in those receiving PEM-LEN combination therapy than that those receiving TPC. The between group difference (PEM-LEN minus TPC) was 15.2% (95% CI, 9.1 to 21.4; P < 0.0001). [redacted] The results for ORR are in line with the survival benefit seen for OS and PFS.

Overall, no obvious between group difference of change from baseline were observed in the patient-reported and HRQoL outcomes.

Harms Results

Based on the data cut-off date of October 26, 2020, the proportion of patients with at least 1 treatment-emergent adverse event (TEAE) appeared similar in the PEM-LEN and TPC groups (99.7% in both groups). The frequency of serious adverse events (SAEs) was higher for PEM-LEN than for the TPC group. However, when adjusted for exposure, the incidences of SAEs appeared similar between the 2 treatment groups; that is, the number of SAEs per 100 person months were 9.83 versus 9.40 in PEM-LEN and TPC groups, respectively. More patients discontinued the study medication due to AEs with PEM-LEN than with TPC (PEM-LEN versus TPC = 31.0% versus 8.3%). The notable AEs (i.e., the AEs of the special interest for this review) were higher in the PEM-LEN group than the TPC group. The higher incidence of notable harms in the PEM-LEN group was primarily driven by hypothyroidism, hyperthyroidism, and hypertension. Overall, the clinical experts consulted by CADTH for this review agreed that the safety profile of PEM-LEN observed in this study appeared consistent with the known safety profile of each individual drug (PEM or LEN) and no additional safety signals were identified. Additionally, the clinical experts indicated that the AEs observed in the study were generally manageable with dose interruption or discontinuation of either PEM or LEN or both, or with a LEN dose reduction, with or without concomitant steroid therapy.

Critical Appraisal

The Keynote-775 study was an open-label trial and the study investigators and patients were aware of their treatment status, which increases the risk of detection and performance biases, which have the potential to influence subjective outcome reporting (i.e., safety and HRQoL). The direction of anticipated bias related to these outcomes is unclear.

Forty-seven (13.7%) patients in PEM-LEN group and 37 (11.4%) patients in TPC group received antineoplastic agents as concomitant medications. The impact of those concomitant anticancer drugs on the comparative efficacy assessment between the 2 treatment groups remains unknown. Nevertheless, due to the very small number of patients using those individual drugs (e.g., carboplatin, cisplatin, doxorubicin, paclitaxel, LEN, and PEM), the clinical experts CADTH consulted for this review considered the unknown potential impact on the comparative efficacy assessment (PEM-LEN versus TPC) to be negligible.

The patient-reported and HRQoL outcome — EORTC QLQ-C30 GHS — was assessed as a secondary outcome. However, it was not controlled for type I error. The other patient-reported outcomes (EORTC QLQ-C30-Physical Functioning, EORTC QLQ-EN24 Urological Symptoms Score, and EQ VAS score) were assessed as exploratory outcomes. There is a potential risk of bias due to a large number of patients not having complete measures, substantial missing data, and the open-label nature of the trial design. Overall, the magnitude and direction of the

biases on the patient-reported outcomes are unknown, and the findings of HRQoL should be viewed as supportive evidence only.

The primary analysis of PFS, OS, and ORR were based on the intention-to-treat analysis. In the pMMR, important protocol deviations were reported for 17 patients, 9 (2.6%) patients in the PEM-LEN group and 8 (2.3%) patients in the TPC group. No per-protocol analysis was conducted to assess whether the per-protocol analyses were consistent with the intention-to-treat analysis. However, given that the proportion of patients with important deviations was relatively low and also balanced in both groups, its impact on comparative efficacy findings (PEM-LEN versus TPC) was expected to be negligible.

Furthermore, the median follow-up duration for pMMR was 12.2 months, which is relatively short and may mean that survival data (e.g., OS) are evolving. Although the protocol-specified criteria were met for the efficacy analyses, safety and efficacy monitoring is ongoing. [redacted]

This study was a multinational, multicentre trial. Among 67 sites that participated in 21 countries, a total of 58 patients living in Canada participated in 11 sites in the country. According to the clinical experts CADTH consulted for this review, the Keynote-775 study population is considered reflective of the requested target population, and there is no concern on generalizing the findings from the pivotal study to Canadian clinical settings.

Indirect Comparisons

No indirect comparison evidence was identified.

Other Relevant Evidence

An additional relevant study (Keynote-146) included in the sponsor's submission to CADTH was considered to provide additional longer-term evidence for this review.

Description of Studies

Keynote-146 is an ongoing multinational, open-label, single-arm phase Ib/II study of PEM-LEN in patients with selected solid tumours, including endometrial carcinoma. This review only reports on the cohort of patients with advanced non-MSI-H or non-pMMR endometrial carcinoma.

Included patients were adults (≥ 18 years old) with histologically and/or cytologically confirmed advanced pMMR endometrial carcinoma, with up to 2 prior lines of systemic therapy, ECOG PS of 0 or 1, and life expectancy of 12 or more weeks.

Patients (N = 94) received the PEM-LEN combination treatment, which consisted of PEM 200 mg IV once every 3 weeks (maximum of 35 PEM treatments) and LEN 20 mg once daily orally. The primary efficacy outcome was ORR at week 24. Key secondary outcomes were ORR, DOR, PFS, and OS.

At the time of data cut-off (January 10, 2019), the median duration of treatment with PEM-LEN was 7.38 months. Overall, the median follow-up time was 18.7 months. At an updated data cut-off date (August 18, 2020), the median follow-up time was 35.8 months.

Efficacy Results

Overall Survival

At the January 10, 2019, data cut-off date, the median OS was 16.4 months (95% CI, 13.5 to 25.9). The survival probabilities of patients at 12, 18, and 24 weeks were 69.5% (95% CI, 58.6 to 78.1%), 43.8% (95% CI, 31.2 to 55.7%), and 39.2% (95% CI, 26.7 to 51.5%), respectively. At the updated analysis (August 18, 2020), the median OS was 17.2 months (95% CI, 15.0 to 25.8).

Progression-Free Survival

At the January 10, 2019, data cut-off date, the median PFS was 5.4 (95% CI, 4.4 to 7.6) months. PFS rates at 6, 12, and 18 months were 49.4%, 33.2%, and 33.2.0%, respectively. At the updated analysis (August 18, 2020), the median PFS was 7.4 months (95% CI, 4.4 to 7.6).

Objective Response Rate

At the January 10, 2019, data cut-off date, in patients who had been enrolled at least 26 weeks before the data cut-off date, 36 out of 94 patients achieved an objective response, resulting in an ORR of 38.3% (95% CI, 28.5 to 48.9). The results at the updated analysis (August 18, 2020) were consistent with those at the January 10, 2019, data cut-off date.

Duration of Response

Based on the product-limit method (Kaplan-Meier) for censored data, the median DOR was not reached (95% CI, 6.3 to not reached).

Harms Results

At the January 10, 2019, data cut-off date, patients had experienced at least 1 TEAE (N = 94, 100%). The most common TEAEs (occurring in ≥ 50% patients) were hypertension (63.8%), diarrhea (62.8%), fatigue (54.3%), and decreased appetite (51.1%). The proportion of patients reporting an SAE was 52.1%. The most frequent SAEs (> 5%) were hypertension and abdominal pain, each reported in 7.4% and 5.3% of patients, respectively. The proportion of patients with an AE leading to discontinuation from the treatment was 25.5%. The most common events leading to discontinuation from the treatment were muscular weakness and pancreatitis, each reported in 2.1% of patients. Three patients (3.2%) died due to AEs. Overall, the safety profile of PEM-LEN was generally consistent with the known safety profiles of each drug when used as monotherapy, with no new safety signals identified for the combination.

Critical Appraisal

The main limitation of the Keynote-146 study was the single-arm study design, which does not include a comparator arm. Such a design, in addition to a lack of consideration of confounding variables, precludes causal inferences (i.e., the outcomes cannot be directly attributed to PEM). Without an active comparator, nor any statistical hypothesis testing, it is not possible to assess the relative therapeutic benefit or safety of PEM against other available treatments (such as chemotherapy in this population). [redacted]

Overall, no apparent generalizability issue was identified.

Conclusion

One sponsor-submitted, phase III, multinational, open-label, randomized, active-controlled trial (Keynote-775) was included in this review. Compared with TPC, PEM-LEN combination therapy showed a statistically significant and clinically meaningful benefit in terms of OS, PFS, and ORR in the treatment of adult patients with advanced pMMR (i.e., not MSI-H or dMMR) endometrial carcinoma, who had disease progression following prior platinum-based systemic therapy and were not candidates for curative surgery or radiation. The clinical experts CADTH consulted for this review indicated that the safety profile of PEM-LEN observed in this study appeared consistent with the known safety profile of each individual drug (i.e., PEM or LEN) and no additional safety signals were identified. AEs observed in the study were generally manageable with dose interruption, dose discontinuation, or LEN dose reduction, with or without concomitant steroid therapy.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Second-line treatment of adult patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior platinum-based systemic therapy and are not candidates for curative surgery or radiation
Treatment	PEM-LEN
Submitted price	PEM, 100 mg, solution: $4,400.00 per 100 mg/4 mL vial
Dosing	PEM: 200 mg every 3 weeks or 400 mg every 6 weeks LEN: 20 mg orally, once daily
Treatment cost	$15,949 per 28 days
Comparator	Physician's choice of chemotherapy (doxorubicin or paclitaxel)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	KEYNOTE-775, a multicentre, open-label, randomized, phase III trial
Key limitations	• The long-term extrapolations of OS and PFS data were likely overestimated, resulting in clinically implausible estimates of the proportion alive at various time points. • The sponsor's use of a partitioned survival model results in a post-progression survival bias in favour of PEM, the magnitude of which is uncertain based on the trial data. • The sponsor's model did not consider patients re-treated with platinum therapy; as a result, cost-effectiveness compared to platinum-containing therapies is unknown. • The price used for LEN in the analysis is not reflective of pan-Canadian pricing. Moreover, the formulas used to calculate the cost of LEN per administration were uncertain in that package sizes did not align

Component	Description
	with the product monograph. • The pricing for doxorubicin did not reflect the lowest publicly available price and the sponsor's calculation of wastage was uncertain.
CADTH reanalysis results	• The CADTH reanalysis addressed the previously noted limitations by choosing alternate survival extrapolations and updating the costs of lenvatinib, doxorubicin, and paclitaxel based on publicly available sources. • The CADTH reanalysis resulted in an ICER for PEM-LEN of $366,399 per QALY (incremental costs = $150,222; incremental QALYs = 0.41) compared with physician's choice of chemotherapy, with a 0% probability of being cost-effective at a $50,000 per QALY threshold. CADTH reanalyses suggest that even with a 100% price reduction for PEM, the PEM-LEN combination would not be cost-effective at this threshold. Cost-effectiveness of PEM-LEN compared to rechallenge with platinum-based therapy is unknown.

dMMR = mismatch repair deficient; ICER = incremental cost-effectiveness ratio; LEN = lenvatinib; LY = life-year; MSI-H = microsatellite instability high; OS = overall survival; PEM = pembrolizumab; PEM-LEN = pembrolizumab combined with lenvatinib; PFS = progression-free survival; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the costs of paclitaxel and doxorubicin are outdated, and the cost of LEN did not reflect prices paid by public drug plans; the proportion of advanced or metastatic endometrial cancer is uncertain; and there is uncertainty in the market share of comparators as well as the market uptake of PEM-LEN combination therapy.

CADTH reanalysis included updating lenvatinib, paclitaxel, and doxorubicin costs; revising the market share of comparators based on clinical experts; excluding clinical trial data from the market mix; and excluding dMMR or MSI-H testing costs.

Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing PEM-LEV combination therapy for patients with pMMR or MSS endometrial cancer in second- or subsequent lines of therapy is expected to be $106,543,254 (year 1 = $9,469,160; year 2 = $40,112,025; year 3 = $56,962,069). The estimated budget impact is highly sensitive to the proportion of patients with endometrial cancer who are considered to have advanced disease.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: July 13, 2022

Regrets: Two of the expert committee members did not attend.

Conflicts of interest: None