CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Pembrolizumab (Keytruda) in combination with Lenvatinib (Lenvima)

Indication: 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

Sponsor: Merck Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: August 2022
Report Length: 17 Pages

Single Technology

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab combined with lenvatinib be reimbursed 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 only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicenter, randomized, open-label phase III trial (KEYNOTE-775; N = 697 for patients with proficient mismatch repair [pMMR] disease) demonstrated that treatment with pembrolizumab in combination with lenvatinib (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; 30.3% and 15.1% with PEM+LEN and TPC, respectively). While measures of health-related quality of life (HRQoL) and symptom severity appeared similar between study groups, pERC was unable to draw definitive conclusions due to non-inferential 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 (BSC). 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, and extend survival. pERC concluded that PEM+LEN met some of the patients' needs as it prolongs survival, delays disease progression and likely does not have detrimental effects on HRQoL versus TPC.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for PEM+LEN was $366,399 per quality-adjusted life-year (QALY) compared with physician's choice of chemotherapy (PCC). PEM+LEN is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for the indicated population. Even with a 100% price reduction for pembrolizumab, 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 Received up to 2 regimens of platinum-based chemotherapy in total, as long as one 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.	—
2. Patient must not have either of the following: a. MSI-H b. dMMR disease	The Health Canada indication specifies that PEM+LEN be used in patients with advanced endometrial carcinoma that is not MSI-H or not dMMR.	MSI/MMR status must be determined prior to 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 tumor), 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 ECOG performance status of 0 or 1 were included in the KEYNOTE-775 trial.	Patients with EGOC performance status of 2 may be treated at the discretion of the treating clinician.
Discontinuation		
5. Discontinuation should be based on a combination of clinical/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.	—
6. Pembrolizumab should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks) or 18 cycles (400 mg every 6 weeks) or 2 years, whichever is	Patients in the KEYNOTE-775 trial were treated with pembrolizumab for a maximum of 35 cycles. In the presence of clinical benefit, patients who completed 35 cycles of treatment with pembrolizumab	It would be reasonable to re-administer pembrolizumab (up to 17 additional administrations of 200 mg), with or without lenvatinib, at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of

Reimbursement Condition	Reason	Implementation Guidance
longer. Lenvatinib can be continued beyond this time.	(approximately 2 years) could continue lenvatinib alone beyond this time-point.	relapse, only if the treatment was discontinued before 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.	Pembrolizumab 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.	Lenvatinib can continue as monotherapy after 35 cycles of pembrolizumab.
Pricing		
9. A reduction in price	The ICER for PEM+LEN is $366,399 per QALY when compared with Physicians Choice Chemotherapy. Even with a 100% price reduction for pembrolizumab, 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 = Eastern Cooperative Oncology Group; ICER = incremental-cost-effectiveness ratio; IV = intravenous; LEN = lenvatinib; MSI-H = microsatellite instability high; MSS = microsatellite stable; PEM = pembrolizumab; pMMR = proficient mismatch repair; QALY = quality adjusted live year; TPC = treatment of physician's choice.

Discussion Points

- Patient groups and clinician input to CADTH 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 options. 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 in order 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.

- 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 BSC 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 retreatment 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 the 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. Pembrolizumab 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/4 mL vial. The recommended dose for pembrolizumab is 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion until disease progression, unacceptable toxicity, or up to 24 months.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of one pivotal phase III RCT (KN-775) and one 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 of 3 patient groups: Colorectal Cancer Resource & Action Network (CCRAN), in collaboration with Canadian Cancer Society (CCS) and Canadian Cancer Survivor Network (CCSN).
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Input from two clinical specialists with expertise diagnosing and treating patients with endometrial cancer
- Input from one 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 pembrolizumab in combination with lenvatinib 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 focusing on colorectal cancer patients, 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, conducted between October 22 and November 3, 2021, with 22 responses from Canada (20 patients and 2 caregivers). CCSN conducted an outreach survey on December 5, 2021 and provided feedback from one Canadian endometrial cancer patient. CCRAN provided additional feedback from 1 caregiver and 3 advanced EC patients 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 quality of life 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. CCSN survey and CCRAN interviews captured a general lack of efficacy and debilitating side effects of standard of care treatments indicated for the management of advanced endometrial cancer.

Three Canadian patients had experience with the PME+LEN combination, through a clinical trial or a private pay plan. Two patients, after 26 and 4 months of therapy, reported complete amelioration of cancer induced symptoms, disease regression, and superior quality of life. Patients reported being able to function at an almost normal level and resume daily activities. Treatment-induced side effects were reported by two patients and included diarrhea, fatigue, and urinary tract infection. One patient experienced dose adjustment of lenvatinib (14mg to 10mg/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 pembrolizumab (30-45 minutes every 3 weeks).

Key outcomes identified by the patient advocacy groups as important to endometrial cancer patients included the following: improved symptoms, cancer control, fewer side effects, good quality of life 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 life. CCRAN strongly supported the use of the PEM+LEN combination therapy as a second line treatment option for MSS/pMMR patients whose tumor is inoperable or metastatic/recurrent.

Clinician input

Input from clinical experts consulted by CADTH

The clinical experts consulted for this review indicated, currently, there is 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 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 chemotherapeutic agents that can be taken in consideration occasionally include topotecan, gemcitibine, pemetrexed ifosfamide, and hormonal treatments (megesterol 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 EC after recurrence/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 prior to other therapies.

Clinical experts indicated that there is currently no evidence to support re-treatment with the same agents in the case of relapse.

Clinical experts agreed that all patients with endometrial carcinoma who experience recurrent/progressive disease following platinum containing chemotherapy and have good performance status would benefit most from the PEM+LEN combination (i.e., ECOG performance status of 0 or 1). Although not supported by clinical trial evidence, the experts also indicated that the treatment might be extended to patients with ECOG performance status of 2 if the patient is appropriately informed and motivated. The experts noted that there is currently a lack of data on the treatment response among patients with other histologic types of EC (carcinosarcoma, endometrial leiomyosarcoma and endometrial stromal sarcomas). One expert indicated that presence of unstable CNS metastases should be first treated with neurosurgical resection and post-operative cranial irradiation, before considering treatment with pembrolizumab/lenvatinib combination.

Regarding the identification of patients, one 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 (IHC) staining is applied across many centers in Canada.

The clinical experts reported that treatment with the PEM+LEN combination would be least suitable in patients with poor performance status (ECOG 3, 4). In addition, one expert also added that patients with multiple lines of chemotherapy, and patients with an intolerance or contraindications to pembrolizumab 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 to treatment under review. Assessment of treatment response should be conducted each 12-16 weeks (3-4 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 adverse events or intolerable treatment toxicities.

Both experts noted that, if the toxicity/tolerability issues are related to lenvatinib, it would be reasonable to continue treatment with pembrolizumab 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 (EC) 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 one of the specialists.

The experts recommend that PEM+LEN be administered in an infusion setting, either hospital or oncology center clinics with appropriate monitoring capabilities. In terms of companion diagnostics, one expert noted that detection of MMR status through IHC staining would be required.

In reference to dosing, clinical experts consulted by CADTH noted that fixed dosing would be applied for pembrolizumab and anticipated that dose modifications of lenvatinib 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 centers.

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 PLD1 inhibitors on the market.

Clinician group input

One joint clinician input was provided by seven 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 recurrent/progressive EC patients. The group recognized the unmet needs of this patient population, indicating 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 second line as a preferred option for all EC patients who recurred or progressed after platinum-based chemotherapy. Prolonged life, delayed disease progression, symptomatic relief, partial response, full response, and improved health-related quality or life 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 in order 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-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-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 treatment.
What is the guidance on retreatment?	In the KEYNOTE-775 trial pembrolizumab treatment was given for a maximum of 35 cycles (i.e., for up to 24 months). Patients who discontinued treatment with pembrolizumab plus lenvatinib with stable disease or better were allowed to receive an additional year of treatment (17 cycles) with pembrolizumab +/- lenvatinib if they progressed after stopping study treatment during the initial treatment period. If lenvatinib was discontinued due to toxicity during the initial treatment period, only pembrolizumab was allowed to be administered during the second course, otherwise lenvatinib was permitted to be administered with pembrolizumab 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 retreatment as per the KEYNOTE-775 criteria outlined above would be reasonable and consistent with pERC guidance on pembrolizumab for other indications.
CONSIDERATIONS FOR PRESCRIBING OF THERAPY	
Jurisdictions may implement weight-based dosing up to a maximum dose for pembrolizumab (i.e., 2 mg/kg up to a maximum of 200 mg IV every 3 weeks). Should pembrolizumab 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 pembrolizumab dose of 200 mg intravenous 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 pembrolizumab 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 pembrolizumab for other indications.
For patients on PEM+LEN – if one of the agents has to be discontinued due to toxicity, can the other agent be continued?	pERC agreed with the clinical experts that at the discretion of the treating physician, patients could continue with one drug if the other drug in the treatment combination is not well tolerated or discontinued.

Drug Program Implementation Questions	Clinical Expert Response
Lenvatinib is not publicly funded for endometrial cancer.	
Due to the high frequency of dose modifications of Lenvatinib reported on the KEYNOTE-775 study (66.5% of patients required lenvatinib dose modifications) are "dose modifications for Lenvatinib" in clinical practice anticipated to be common?	pERC acknowledged input from the clinical experts indicating that dose modifications of lenvatinib are common in Canadian clinical practice settings. The frequency of the dose modification of lenvatinib would be the same or higher than 66.5% as reported in the KEYNOTE-775 trial.
GENERALIZABILITY	
Can the PEM+LEN combination therapy be extended to patients with ECOG>1?	The KEYNOTE-775 trial included patients with ECOG performance status of 0 to 1 (61.3% and 59.0% of patients in the PEM+LEN and TPC study groups, respectively, had ECOG performance status of 0). pERC agreed with the clinical experts that it would be reasonable to generalize the KEYNOTE-775 trial results to patients with ECOG performance status 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 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 since carcinosarcomas share similar histology, epidemiology, and risk factors as endometrial carcinomas. pERC agreed with the clinical experts that testing for the MSI/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 different histology.
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 prior to receiving treatment for the CNS metastases.
Can pERC clarify the instances wherein time-limited funding would be applicable?	pERC agreed with the clinical experts 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 judgement should be exercised.
CARE PROVISION ISSUES	
Lenvatinib capsules are 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 lenvatinib 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 lenvatinib dose modifications).	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 in order to avoid over- or under-dosing with lenvatinib.

Drug Program Implementation Questions	Clinical Expert Response
In addition, if dose reductions are required in-between prescription fills of lenvatinib (e.g., mid-cycle), drug wastage would occur for any previously dispensed supply of lenvatinib as these cannot be re-dispensed.	
MSI/MMR testing is needed to confirm eligibility for PEM+LEN combination therapy. Is there a standardized test to determine not MSI-H/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; dMMR = deficient mismatch repair; ECOG = Eastern Cooperative Oncology Group; LEN = lenvatinib; MSI-H = microsatellite instability high; PEM = pembrolizumab; 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, multi-centre, 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 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. 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 EORTC QLQ-C30 GHS/QoL scale). The exploratory outcomes included duration of response (DOR) and other HRQOL measurements (i.e., EORTC QLQ-30, EORTC QLQ-EN24 urological symptoms score and EQ-5D-5L)

Efficacy Results

Based on the data cut-off date of Oct 26, 2020, and a median follow-up time of 12.2 months, the 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 ECOG PS of 0 (HR: 0.56, 95%CI, 0.42 to 0.75), non-endometrioid patients (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). [redacted]

Similarly, the 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 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); endometrioid patients (HR: 0.59, 95%CI, 0.46 to 0.76) and non-endometrioid patients (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 PEM+LEN combination therapy than that in TPC. The between group difference (PEM+LEN – 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 Oct 26, 2020, the proportion of patients with at least one 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 arm. However, when adjusted for exposure, the incidences of SAEs appeared similar between the two treatment groups, that is the number of SAEs per 100 person months were 9.83 vs. 9.40 in PEM+LEN and TPC groups respectively. More patients discontinued the study medication due to adverse events with PEM+LEN than with TPC (PEM+LEN vs. TPC: 31.0% vs. 8.3 %). The notable adverse events (i.e., the adverse events of the special interest for this review) were higher in the PEM+LEN group versus TPC. The higher incidence of notable harms in 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 agent (pembrolizumab or lenvatinib) and no additional safety signals were identified. Additionally, the clinical experts indicated that the adverse events observed in the study were generally manageable with dose interruption or discontinuation of either pembrolizumab or lenvatinib or both, or with lenvatinib dose reduction, with or without concomitant steroid therapy.

Critical Appraisal

Study Keynote-775 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 two treatment groups remains unknown. Nevertheless, due to the very small number of patients using those individual drug (e.g., carboplatin, cisplatin, doxorubicin, paclitaxel, lenvatinib as well as pembrolizumab), the clinical experts CADTH consulted for this review, considered the unknown potential impact on the comparative efficacy assessment (PEM+LEN vs. 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 1 error. The other patient reported outcomes (EORTC QLQ-C30- Physical Functioning, EORTC QLQ-EN24 Urological Symptoms Score and EQ-5D 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. The findings of HRQoL should be viewed as supportive evidence only.

The primary analysis of PFS, OS and ORR were based on ITT analysis. In the pMMR, important protocol deviations were reported for 17 patients, 9 (2.6%) patients in the PEM+LEN and 8 (2.3%) patients in the TPC groups, respectively. No per protocol analysis was conducted to assess whether the per protocol analyses were consistent with the ITT analysis. However, since the proportion of patients with important deviations was relatively low and also balanced in both groups, its impact on comparative efficacy findings (PEM+LEN vs. 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, multicenter trial. Among 67 sites in 21 countries that participated, a total of 58 Canadian patients participated in the trial in 11 sites in Canada. According to the clinical experts CADTH consulted for this review, the Keynote-775 study population is considered reflective of the requested target population. 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 tumors including endometrial carcinoma. This review only reports the cohort of patients with advanced non-MSI-H/pMMR EC.

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

Patients (N=94) received the PEM + LEN combination treatment. Pembrolizumab 200 mg intravenously once every 3 weeks (maximum of 35 pembrolizumab treatments) and lenvatinib 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, 24 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 (Kaplan-Meier) method 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 one TEAE (N=94, 100%). The most common TEAEs (occurred in ≥50% patients) were hypertension (63.8%), diarrhea (62.8%), fatigue (54.3%) and decreased appetite (51.1%). The proportion of patients reporting a SAE was 52.1%. The most frequent SAEs (>5%) were hypertension and abdominal, each reported

in 7.4% and 5.3% 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% 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 Study Keynote-146 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 pembrolizumab). Without an active comparator, nor any statistical hypothesis testing, it is not possible to assess the relative therapeutic benefit or safety of pembrolizumab 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 and 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 agent (pembrolizumab or lenvatinib) and no additional safety signals were identified. Adverse events observed in the study were generally manageable with dose interruption, dose discontinuation or lenvatinib dose reduction, with or without concomitant steroid therapy.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Second-line 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.
Treatment	Pembrolizumab in combination with lenvatinib
Submitted price	Pembrolizumab, 100 mg, solution: $4,400.00 per 100 mg/4 mL vial
Treatment Cost	$15,949 per 28 days
Comparator	Physician's choice of chemotherapy (PCC; doxorubicin or paclitaxel)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	KEYNOTE-775, a multicenter, 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 favor of pembrolizumab, 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.

Component	Description
	• The price used for lenvatinib in the analysis is not reflective of pan-Canadian pricing. Moreover, the formulae used to calculate the cost of lenvatinib per administration were uncertain in that package sizes did not align 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 above 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 pembrolizumab-lenvatinib of $366,399 per QALY (inc. costs: $150,222; inc. QALYs: 0.41) compared with PCC, 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 pembrolizumab, the pembrolizumab-lenvatinib combination would not be cost-effective at this threshold. Cost-effectiveness of PEM+LEN compared to re-challenge with platinum-based therapy is unknown.

ICER = incremental cost-effectiveness ratio; LY = life-year; PCC = physician's choice of chemotherapy; PSM = partitioned survival model; 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 lenvatinib 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 market share of comparators based on clinical experts, excluding clinical trial from the market mix, and excluding dMMR/MSI-H testing costs.

Based on the CADTH reanalysis, the three-year budget impact to the public drug plans of introducing pembrolizumab-lenvatinib combination therapy for patients with pMMR/MSS endometrial cancer in second- or subsequent-line 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 endometrial cancer patients that are considered to have advanced disease.

pCODR Expert Review Committee (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