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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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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.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda monotherapy be reimbursed by public drug plans for the treatment of adults with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer that cannot be treated with surgery or has spread to other body parts, and whose tumours have progressed following prior therapy and who have no alternative treatment options, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat adults with unresectable or metastatic MSI-H or dMMR endometrial cancer who are in relatively good health (i.e., have good performance status [PS] as determined by a specialist). Keytruda also should only be covered for patients who have not been treated previously with a programmed cell death 1 protein (PD-1) or programmed cell death 1 ligand 1 (PD-L1) inhibitor, and do not have active central nervous system (CNS) metastases or active autoimmune disease.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if it is prescribed in an outpatient oncology clinic where treatment is supervised and delivered in institutions with expertise in systemic therapy delivery, and if the cost is reduced. Keytruda should not be reimbursed in combination with other systemic therapies for dMMR or MSI-H endometrial cancer.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that patients with unresectable or metastatic MSI-H or dMMR endometrial cancer who were treated with Keytruda experienced delayed disease progression and prolonged survival.
- Although it was unclear how Keytruda compared to standard therapies, the trial results suggested that Keytruda may provide patients with a much-needed treatment option that improves survival and has a manageable safety profile.
- Based on CADTH's assessment of the evidence, Keytruda does not represent good value to the health care system at the public list price and a price reduction is required.
- Based on public list prices, Keytruda is estimated to cost the public drug plans $21,400,154 over 3 years.

Additional Information

What Is Endometrial Cancer?

Endometrial cancer is cancer of the lining of the uterus; dMMR or MSI-H tumours have cells that are unable to properly repair certain gene errors. In Canada, it was estimated that 8,000 women would be diagnosed with uterine cancer in 2021 and 1,400 women would die of the disease. Approximately 13% to 20% of patients with endometrial cancer have recurrence, half of whom survive 12 months or less.

Unmet Needs in Endometrial Cancer

There is a need for effective treatments that provide better disease control, improve quality of life, have fewer side effects, and improve survival.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 every 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed as monotherapy for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One single-arm, phase II, open-label, nonrandomized trial (KEYNOTE-158 [KN-158], N = 94) suggested that pembrolizumab has activity in patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. The updated analysis (data cut-off of January 12, 2022) of the KN-158 trial showed that the median overall survival (OS) was 65.4 months (95% confidence interval [CI], 29.5 to not reported [NR]) and the OS rate of patients treated with pembrolizumab at 12 months was 70.0%. The median progression-free survival (PFS) was 13.1 months (95% CI, 4.3 months to 25.7 months) and the PFS rate at 12 months was 50.3%. A total of 47 of 94 patients (50.0%; 95% CI, 39.5 to 60.5) achieved an objective response, which was sustained for 24 months in 70.7% of responders. pERC noted that the harms reported in the KN-158 study seemed generally manageable and consistent with the known safety profile of pembrolizumab.

The patient groups indicated that patients need access to treatments with fewer side effects that would improve symptoms, quality of life, and extend survival. pERC agreed that this is a patient population with a critical unmet need for effective and safe treatment options. pERC concluded that pembrolizumab could meet some of the needs identified by patients by improving OS, while providing a manageable safety profile.

The cost-effectiveness of pembrolizumab relative to physician's choice of chemotherapy (PCC) is unknown in patients with dMMR or MSI-H endometrial cancer owing to the lack of direct comparative clinical effectiveness data, as well as limitations with the pharmacoeconomic model submitted by the sponsor. As such, a base-case cost-effectiveness estimate could not be determined. The committee considered an exploratory analysis conducted by CADTH that produced an incremental cost-effectiveness ratio of $61,200 per quality-adjusted life-year gained when compared with PCC. Based on this exploratory finding, a price reduction is needed for pembrolizumab to be cost-effective at a $50,000 per quality-adjusted life-year willingness-to-pay threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab should only be reimbursed in adult patients with unresectable	Evidence from the KN-158 trial demonstrated a clinical benefit in patients who fulfilled these characteristics.	Intolerance to prior treatment would be according to clinician judgment.

Reimbursement condition	Reason	Implementation guidance
or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy or who are intolerant of prior therapy.		MMR status needs to be determined before treatment.
2. Patients must have good PS.	Patients enrolled in the KN-158 trial had an ECOG PS of 0 or 1.	Based on clinician input, it is reasonable to consider using pembrolizumab for patients with an ECOG PS of 2.
3. Patients must not have any of the following: 3.1. prior treatment with a PD-1 or PD-L1 inhibitor 3.2. active CNS metastases 3.3. active autoimmune disease.	Patients pretreated with an anti-PD-1 or anti-PD-L1, with active untreated CNS metastasis and/or carcinomatous meningitis, as well as active autoimmune disease that had required systemic treatment in the past 2 years were excluded from the KN-158 trial.	Patients with treated or stable CNS metastases should be eligible for treatment. Based on clinician input, it is reasonable for the treating physician to consider treating patients with controlled autoimmune disease with pembrolizumab.
Discontinuation		
4. Discontinuation should be based on a combination of clinical and radiological progression and/or significant adverse events potentially related to pembrolizumab.	Consistent with clinical practice, patients from the KN-158 trial discontinued treatment upon progression or unacceptable toxicity.	—
5. Pembrolizumab should be reimbursed for a maximum of 35 cycles (for 200 mg dosing), or 18 cycles (for 400 mg dosing) or 2 years, whichever is longer.	Patients in the KN-158 trial were treated with pembrolizumab for a maximum of 35 cycles.	It would be reasonable to readminister pembrolizumab (up to 17 additional administrations of 200 mg) at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.
Prescribing		
6. Pembrolizumab should be prescribed in an outpatient oncology clinic; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery.	To ensure that pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	Weight-based dosing and dosing every 6 weeks would be reasonable options. 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.
7. Pembrolizumab should not be used in combination with other systemic therapies for dMMR or MSI-H endometrial cancer.	Pembrolizumab was administered as monotherapy in the KN-158 trial and has a Health Canada indication only as monotherapy for this population.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
8. A reduction in price	The cost-effectiveness of pembrolizumab compared to PCC is unknown. Based on CADTH exploratory analyses, a price reduction of at least 18% would be required to achieve an ICER of $50,000 per QALY relative to PCC. Due to the high degree of uncertainty in the evidence, additional price reductions may be necessary.	—

CNS = central nervous system; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; KN-158 = KEYNOTE-158; MMR = mismatch repair; MSI-H = microsatellite instability-high; PCC = physician's choice of chemotherapy; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1; PS = performance status; QALY = quality-adjusted life-year.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse pembrolizumab as monotherapy for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. pERC discussed each of the issues identified by the sponsor in their request for reconsideration. The issues indicated that the sponsor does not agree that the committee fully considered the unmet need for the patient population or that the original recommendation was supported by the evidence for pembrolizumab. pERC re-examined the limitations of the available evidence for this review, and considered the updated analysis for the reconsideration of the recommendation.
- pERC considered that although endometrial cancer is common, patients with unresectable or metastatic MSI-H or dMMR endometrial cancer represent a small subpopulation of patients with endometrial cancer, and not all patients are well enough for second-line therapy. pERC noted that patients with unresectable or metastatic MSI-H or dMMR endometrial carcinoma whose tumours have progressed following prior therapy represent a patient population with few therapeutic options and therefore, have a significant unmet need for treatment with a better toxicity profile and improved outcomes.
- pERC identified ethical issues related to implementation, which included ensuring access to mismatch repair (MMR) testing and the associated clinical benefits through informed clinical care for individual patients. Additionally, cascade testing of consenting biological family members may better inform potential treatment and prevention strategies for those predisposed to cancer.
- pERC discussed the key limitations of the phase II clinical evidence (the KN-158 trial), which include the lack of hypothesis testing, insufficient sample size, and no comparison with treatments used in the target population. The limitations of the KN-158 trial were revisited during the reconsideration meeting and considered alongside the updated results for median OS of 65.4 months (95% CI, 29.5 to NR) that was reported with the updated data analysis (data cut-off of January 12, 2022). pERC concluded that despite the limitations of the trial, the updated analysis suggests evidence of clinical activity observed in the trial and, due to the strong biological rationale and known safety profile of

pembrolizumab, the available evidence suggests that pembrolizumab has the potential to reduce mortality associated with the disease.

- pERC discussed results of the ITCs because of the lack of direct comparative evidence. Interpretation of the sponsor-submitted ITC was limited due to methodological limitations, including the lack of justification for the selection of the chemotherapy arm of the KEYNOTE-775 (KN-775) trial as the comparator group and for the analytical methods used. Furthermore, the exploration of between-study differences and potential biases were limited by missing information on patient and study characteristics for the 2 data sources. Considering that prognostic factors and effect modifiers are likely imbalanced between treatment groups, the results of the unanchored, unadjusted ITC are subject to an unknown amount of bias. Thus, the findings of the ITC are highly uncertain and conclusions regarding the efficacy of pembrolizumab monotherapy versus chemotherapy cannot be established.
- During the reconsideration meeting, pERC discussed the results of the matching-adjusted indirect comparison (MAIC) and the ECHO study, which were submitted as part of the sponsor's request for reconsideration. The findings from the primary analyses of the MAIC suggested that the results for OS, PFS, and objective response rate (ORR) end points favoured pembrolizumab monotherapy over treatment of PCC (doxorubicin or paclitaxel). The descriptive results of the ECHO study were consistent with the updated analysis of the KN-158 study (data cut-off of January 12, 2022) submitted by the sponsor, suggesting favourable results for PFS, ORR, and duration of response (DOR) in patients who received pembrolizumab. However, interpretation of each of these studies was limited due to methodological limitations; therefore, the findings of the MAIC and the ECHO study are uncertain. As such, conclusions regarding the efficacy of pembrolizumab monotherapy compared to alternative treatments cannot be established and this evidence must be considered supportive only.
- pERC discussed that the quality of evidence for health-related quality of life (HRQoL) outcomes was low and was noncomparative in nature. In view of these limitations, pERC could not draw conclusions regarding the effect of pembrolizumab on HRQoL compared to current treatment for patients with unresectable or MSI-H or dMMR endometrial carcinoma.
- pERC considered the criteria for significant unmet need described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews when deliberating on pembrolizumab. Considering the rarity and severity of the condition, and the absence of clinically effective alternatives, the committee concluded that the available evidence suggests that pembrolizumab has the potential to reduce mortality associated with the disease.

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 commonly assessed molecular cancer biomarkers are microsatellite instability and MMR protein expression. Based on the biomarkers testing, endometrial cancer can be classified into MSI-H (or dMMR), and not MSI-H (or proficient MMR). In clinical practice and in clinical trials, the terms dMMR and MSI-H are often used interchangeably, while non-MSI-H and proficient MMR are also interchangeable. 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.

Pembrolizumab as monotherapy has a Health Canada indication for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. Pembrolizumab is an inhibitor of 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 IV infusion until disease progression or 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 single-arm, phase II, open-label, nonrandomized trial (the KN-158 trial) in patients with advanced MSI-H or dMMR endometrial cancer, and a sponsor-submitted unadjusted (naive) ITC that compared the efficacy of pembrolizumab with doxorubicin or paclitaxel in patients with advanced MSI-H or dMMR endometrial cancer
- patients' perspectives gathered by a joint input of 3 patient groups: the Colorectal Cancer Resource & Action Network (CCRAN), in collaboration with the Canadian Cancer Society (CCS) and the Canadian Cancer Survivor Network (CCSN)
- input from the 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: the Ontario Health (Cancer Care Ontario) Gynecology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor
- information submitted as part of the sponsor's request for reconsideration (described in the following).

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups that responded to CADTH's call for patient input and from the clinical expert(s) consulted by CADTH for the purpose of this review.

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 monotherapy for the treatment of advanced endometrial cancer was provided by CCRAN, in collaboration with CCS and CCSN. CCRAN is a not-for-profit patient advocacy group in Canada 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 Canada (20 patients and 2 caregivers). CCSN conducted an outreach survey on December 5, 2021, and provided feedback from 1 patient in Canada with endometrial cancer. 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 patients with endometrial cancer experience physical symptoms (e.g., vaginal bleeding, pelvic pain, diarrhea, nausea, fatigue) and psychological symptoms (e.g., 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. The CCSN survey and CCRAN interviews outlined a general lack of efficacy and debilitating side effects with standard of care treatments indicated for the management of advanced endometrial cancer.

One patient in Canada had experience with pembrolizumab monotherapy as a second-line treatment through a private insurance plan for 5 months. The patient reported that the monotherapy provided significant resolution of cancer-induced symptoms, disease regression, and superior quality of life. In addition, the patient reported being able to resume daily activities at home and spend time with and care for their loved ones. The patient did not report any adverse effects associated with the treatment under review.

The key outcomes identified by the patient advocacy groups as important to patients with endometrial cancer include 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 pembrolizumab monotherapy as a second-line treatment option for patients with MSI-H or dMMR whose tumour is inoperable, metastatic, or recurrent.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

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

The clinical experts indicated that patients with endometrial cancer who have progressed on platinum chemotherapy currently receive cytotoxic treatments such as carboplatin and paclitaxel, doxorubicin, or pegylated liposomal doxorubicin. Additional chemotherapeutic drugs that can be taken into consideration occasionally include topotecan, gemcitabine, pemetrexed ifosfamide, and hormonal treatments (e.g., megestrol acetate, tamoxifen). The previously described treatments are not considered curative and have low expected response rates and short DORs. Both clinical experts indicated that pembrolizumab would become standard second-line therapy for patients with dMMR endometrial cancer after recurrence or failure of typical platinum-based regimens. This pembrolizumab treatment would address the underlying disease process. The clinical experts felt that it would be preferable to initiate treatment with the drug under review before other therapies. Clinical experts indicated that there is currently no evidence to support re-treatment with the same drug in the case of relapse.

The clinical experts agreed that all patients with dMMR or MSI-H endometrial carcinoma who experience recurrent or progressive disease following platinum-containing chemotherapy and have good PS would benefit most from pembrolizumab treatment (i.e., Eastern Cooperative Oncology Group [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 the treatment response among patients with other histologic types of endometrial cancer (e.g., carcinosarcoma, endometrial leiomyosarcoma, and endometrial stromal sarcomas). One expert indicated that the presence of unstable CNS metastases should be first treated with neurosurgical resection and/or cranial irradiation, before considering treatment with pembrolizumab. 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 indicated that treatment with pembrolizumab would be least suitable for patients with poor PS (i.e., an ECOG PS of 3 or 4). In addition, 1 expert also added that patients with multiple lines of prior chemotherapies, 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 the 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 HRQoL, and symptom control can be considered clinically meaningful responses to a treatment under review. Assessment of treatment response should be conducted every 12 to 16 weeks (i.e., 3 to 4 months).

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

The clinical experts 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 general practitioner oncologist, but under the overview of 1 of the specialists. The experts recommend pembrolizumab be administered in an infusion setting, either a hospital or oncology centre clinic with appropriate monitoring capabilities. In terms

of companion diagnostics, 1 expert noted that the detection of dMMR status through immunohistochemistry staining would be required. In reference to dosing, the clinical experts noted that fixed dosing would be applied for pembrolizumab. One clinical expert expressed that less frequent administrations (i.e., 400 mg, every 6 weeks) 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 PD-1 inhibitors on the market.

Clinician Group Input

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

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. Prolonged life, delayed disease progression, symptomatic relief, partial response (PR), complete response (CR), 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. 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 following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for pembrolizumab:

- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

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

Implementation issues	Response
Considerations for initiation of therapy	
What is the guidance on the maximum number of prior lines of platinum therapy to be eligible for pembrolizumab treatment?	pERC agreed with clinical experts that there is uncertainty regarding the number of previous platinum-based treatments before pembrolizumab monotherapy. As such, pERC did not have evidence to specify eligibility

Implementation issues	Response
	criteria for pembrolizumab based on the number of prior lines of platinum therapy. Clinical experts suggested that pembrolizumab might be preferable to a different treatment after platinum because of the toxicity of alternative chemotherapy options (such as doxorubicin).
What is the guidance on re-treatment?	pERC agreed with the clinical experts that re-treatment with the same regimen is a valid question. pERC noted that it would be reasonable to readminister pembrolizumab (up to 17 additional administrations of 200 mg) at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.
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 every 3 weeks). Should pembrolizumab 4 mg/kg (up to a maximum of 400 mg) IV every 6 weeks be an option?	pERC felt that weight-based dosing up to a maximum dose may be implemented. pERC agreed with the clinical experts that less frequent administrations (i.e., every 6 weeks) would be better for patients, clinicians, and health centres.
Generalizability	
Can pembrolizumab monotherapy used in MSI-H or dMMR endometrial cancer be extended to patients with an ECOG PS > 1?	pERC agreed with the clinical experts that the treatments could be extended to those with an ECOG PS of 2, in an appropriately informed and motivated patient.
The KN-158 study (pembrolizumab monotherapy) excluded patients with sarcomas and mesenchymal tumours, can pembrolizumab monotherapy be extended to patients with endometrial sarcomas?	pERC agreed with the clinical experts that the evidence to date is in carcinomas and they are not aware of benefit in pure sarcomas. However, as carcinosarcomas are a combination, pembrolizumab monotherapy may be extended to patients with carcinosarcomas, though there is no supporting research evidence at the moment.
The KN-158 study (pembrolizumab monotherapy) excluded patients with active CNS metastases. Can pembrolizumab be extended to patients with active CNS metastases?	pERC agreed with the clinical experts that unstable CNS metastasis should be treated with typical methods; presently that is neurosurgical resection and/or cranial irradiation. Subsequently, pembrolizumab treatment may be considered.
Can pERC clarify the instances wherein time-limited funding would be applicable?	pERC agreed with the clinical experts that patients who had started next-line therapy after platinum-based chemotherapy should be given the choice to switch to pembrolizumab on a time-limited basis. However, the preference would be to continue with the current regimen and switch to pembrolizumab when progression occurs, particularly if patients are responding to current treatment.
Care provision issues	
MSI or MMR testing is needed to confirm eligibility for single-drug pembrolizumab monotherapy. Is there a standardized definition of MSI-H or dMMR to guide implementation of eligibility criteria?	pERC agreed with the clinical experts that MMR testing is based on IHC staining of the tumour as a screening test. PCR testing for MSI-H is the next test, and if positive, Lynch syndrome is considered and investigated using germline testing.
When should testing for MSI-H or dMMR take place in patients with endometrial cancer?	pERC agreed with the clinical experts that dMMR status needs to be determined before considering pembrolizumab monotherapy.

CNS = central nervous system; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; IHC = immunohistochemistry; KN-158 = KEYNOTE-158;

MMR = mismatch repair; MSI = microsatellite instability; MSI-H = microsatellite instability-high; PCR = polymerase chain reaction; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

The KN-158 study (i.e., cohort D and cohort K of the KN-158 study) is a single-arm, phase II, open-label, nonrandomized trial in patients with advanced MSI-H or dMMR endometrial cancer. The trial was conducted in 38 centres in 15 countries (including the US, Canada [3 centres], the UK, France, Germany, Australia, and other European, central American, south American, and Asian countries). Enrolment started on February 1, 2016, and is still ongoing. The data cut-off date was October 5, 2020, and the estimated study completion date is on June 18, 2026. The objective of the KN-158 study was to assess the efficacy and safety of pembrolizumab monotherapy for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours had progressed following prior therapy and who had no satisfactory alternative treatment options.

A total of 90 patients were included in the trial. The patients were 18 years and older with dMMR or MSI-H advanced (metastatic and/or unresectable) endometrial carcinoma, which was incurable, and their disease had not responded to prior standard first-line treatments. The primary outcome was ORR, which was defined as the proportion of the patients in the analysis population who had a CR or PR. Response for the primary analysis was determined by independent central radiologic review, with confirmatory assessment as required per the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. DOR, OS, and PFS were assessed as secondary outcomes. HRQoL was assessed as an exploratory outcome (but results were not presented in the Clinical Study Report).

Efficacy Results

At the time of the data cut-off, the median duration of follow-up was 16.5 months (range, 0.5 months to 56.1 months) and the median duration of treatment was 8.3 months (range, 0.03 months to 26.88 months). At this time, 35.7% of patients had died and, based on Kaplan-Meier (KM) estimation, the median OS was not reached (lower bound of 95% CI, 27.2 months). The OS probabilities of patients at 12, 24, 36, and 48 months were 69.4%, 64%, 60.1%, and 60.1%, respectively.

At the time of the data cut-off, there had been 29 (36.7%) PFS events and, based on KM estimation, the median PFS was 13.1 months (95% CI, 4.3 months to 34.4 months). The PFS rates at 12, 24, and 48 months were 51.0%, 41.3%, and 37.0%, respectively.

A total of 38 of 79 patients (48.1%; 95% CI, 36.7 to 59.6%) achieved an objective response. Among these patients, based on the KM method, the median DOR was not reached (range, 2.9 months to 49.7 months). Extended response durations of more than 12, 24, and 36 months were observed in 88.1%, 72.9%, and 68.1% of responders, respectively.

Patient-reported (HRQoL) outcomes were available in a sponsor-submitted conference abstract presented at the 2021 European Society for Medical Oncology (ESMO) Congress. Following treatment with pembrolizumab, European Organization for Research and Treatment

of Cancer-Quality of life-Core 30 global health status (EORTC QLQ-C30 GHS), EORTC QLQ-C30 symptom score, and the 3-level EQ-5D visual analogue scale appeared to be maintained or improved based on the change from baseline to week 9.

Harms Results

Of the 90 patients who received at least 1 dose of pembrolizumab, 95.6% experienced at least 1 treatment-emergent AE. The most common AEs (which occurred in at least 25% of patients) were fatigue (33.3%), diarrhea (32.2%), pruritus (28.9%), arthralgia (27.8%), and nausea (27.8%). A total of 37.8% of patients experienced a serious AE. Each serious AE was reported in 1 patient, except for ascites, chest pain, pneumonia, pyelonephritis, sepsis, and urinary tract infection, which were each reported for 2 (2.2%) patients. AEs leading to study drug discontinuation were reported in 6.7% of patients. These included an increase in transaminases, arthritis, enterocolitis, drug-induced liver injury, and rash. Each occurred in 1 patient (1.1%), except increase in transaminases, which occurred in 2 patients (2.2%).

No deaths due to AEs were reported. Regarding notable harms (i.e., AEs of special interest for this review as identified in the review protocol), hypothyroidism occurred in 14.4% of patients, followed by hyperthyroidism (7.8%), colitis (3.3%), type 1 diabetes mellitus (2.2%), pneumonitis (1.1%), adrenal Insufficiency (1.1%), and hepatitis (1.1%). No hypophysitis or nephritis were reported.

Critical Appraisal

The main limitation of the included pivotal study (KN-158) 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 or standard of care 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. Though inclusion and exclusion criteria were stated, selection procedures were not described; therefore, the potential for selection bias cannot be excluded.

As all results are part of an interim analysis, there is some risk that the efficacy of pembrolizumab has been overestimated. The median OS was not reached at the time of data cut-off; the survival data from the trial were immature, and 36.7% of patients had died at the time of the data cut-off. There is some uncertainty in how the findings may change once data reach maturity. Furthermore, the efficacy assessment was not based on the intention-to-treat population. The efficacy analyses were based on the all patients as treated population for efficacy analysis, defined as patients who received at least 1 dose of the study intervention and had been enrolled at least 26 weeks before the data cut-off. A total of 79 (87.8%) out of 90 patients were included in the efficacy analysis, while 11 (12.2%) patients were not included. As no detailed treatment response information (e.g., disease progression, death, or discontinuation) were provided for those 11 patients, the findings for OS and PFS might be potentially biased. Finally, no formal statistical significance and hypothesis testing were conducted in the analysis; causal inferences cannot be made and this limits the ability to draw robust conclusions from the findings regarding efficacy or safety.

Overall, according to the clinical experts consulted by CADTH, the population enrolled in the trial was consistent with the population expected to be treated in Canadian clinical practice.

No major generalizability issues were noted regarding the findings from the pivotal study. Although patients with CNS metastasis, endometrial sarcomas, and an ECOG PS of 2 or greater were not included in the study, the clinical experts indicated that the patients with CNS metastasis might still benefit from the pembrolizumab treatment after they are treated with radiotherapy first. Similarly, patients with carcinosarcomas and patients with an ECOG PS of 2 may also benefit from pembrolizumab treatment in this clinical setting.

Indirect Comparisons

The sponsor submitted an unadjusted (naive) ITC that compared the efficacy of pembrolizumab monotherapy with doxorubicin or paclitaxel in patients with advanced MSI-H or dMMR endometrial cancer who had received at least 1 prior line of therapy. This analysis estimated the relative time to OS or PFS using individual treatment group data from 2 separate studies (KN-158 and KN-775) based on nonparametric KM methods and unstratified Cox proportional hazards models.

Efficacy Results

For pembrolizumab versus chemotherapy, the hazard ratio for time to OS was 0.34 (95% CI, 0.20 to 0.56; P < 0.001) and the hazard ratio for PFS was 0.42 (95% CI, 0.27 to 0.64; P < 0.001).

Harms Results

The ITC did not assess safety outcomes.

Critical Appraisal

Limitations of the ITC include the lack of justification for the selection of the chemotherapy arm of the KN-775 trial as the comparator group and for the analytical methods used. The exploration of between-study differences and potential biases was limited by missing information on patient and study characteristics for the 2 data sources. Considering that prognostic factors and effect modifiers are likely imbalanced between treatment groups, the results of the unanchored, unadjusted ITC are subject to an unknown amount of bias. Thus, the findings of the ITC are highly uncertain and conclusions regarding the efficacy of pembrolizumab monotherapy versus chemotherapy cannot be established.

The ITC did not assess harms data, thus the comparative safety of pembrolizumab versus chemotherapy is unknown. Other outcomes of importance to patients, such as HRQoL, were not investigated.

Economic Evidence

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Second-line treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy
Treatment	Pembrolizumab
Submitted price	$4,400.50 per 100 mg vial
Treatment cost	$11,733 per 28 days
Comparators	PCC (doxorubicin or paclitaxel)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, Lys
Time horizon	Lifetime (20 years)
Key data source	Keynote-158, a nonrandomized, open-label, multisite phase II study
Submitted results	ICER for pembrolizumab was $39,879 per QALY (incremental costs = $154,373; incremental LYs = 6.04; incremental QALYs = 3.87) compared with PCC
Key limitations	• The clinical evidence available for pembrolizumab was from a single-arm phase II trial (i.e., no comparator arm was included). In the absence of direct comparative trial evidence for pembrolizumab, the sponsor submitted a model with survival parameters based on an ITC. The CADTH Clinical review of the ITC identified several key limitations which precluded drawing conclusions about the comparative effectiveness of pembrolizumab and PCC. • Incremental effectiveness is uncertain as it is based on the sponsor's assumption of a similar trajectory in response patterns observed between pembrolizumab and PCC. The sponsor's method assumed a proportional hazard relationship over the lifetime time horizon that may be inappropriate. • The sponsor's use of a partitioned survival model suggests a postprogression survival bias in favour of pembrolizumab, which was not supported by data from the single-arm phase II trial. • Long-term extrapolations of OS and PFS were highly uncertain and likely overestimated the incremental benefit in favour of pembrolizumab. • Additional issues in the model included the health state utility value for patients in the progressed disease health state, which lacked face validity and likely overestimated patients' quality of life postprogression, in favour of pembrolizumab; incorrect drug prices for the PCC and partial wastage of medications administered by IV, which likely underestimated drug costs of PCC; and uncertainty with the sponsor's methodological approach to including adverse event disutilities, which has an unknown impact on the model's results.
CADTH reanalysis results	• Given the absence of comparative clinical information, as well as the sponsor's use of an inappropriate modelling approach, CADTH was unable to estimate the cost-effectiveness of pembrolizumab in the indicated population. The cost-effectiveness of pembrolizumab compared to currently available treatment options is unknown. • Results from the exploratory analysis estimated an ICER of $61,200 per QALY, and that a price reduction of 18% would be needed for pembrolizumab to be considered cost-effective at a willingness-to-pay threshold of $50,000. The exploratory analysis is still subject to the significant limitations — most

Component	Description
	crucially the absence of comparative clinical information (i.e., no direct evidence, limitations within the indirect evidence) and the high degree of uncertainty around long-term OS that produces a bias in favour of pembrolizumab. As such, additional price reduction may therefore be warranted.

dMMR = mismatch repair deficient; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; MSI-H = microsatellite instability – high; OS = overall survival; PCC = physician's choice of chemotherapy; 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 pembrolizumab is sensitive to dosing strategy (flat versus weight-based dosing); the proportion of advanced or metastatic endometrial cancer is uncertain; and there is uncertainty in the market share of pembrolizumab and comparators as well as the market uptake of pembrolizumab. CADTH reanalysis included updating paclitaxel and doxorubicin costs, revising the market share of pembrolizumab and comparators based on clinical expert opinion, excluding clinical trial from the market mix, and excluding dMMR and MSI-H testing costs.

Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing pembrolizumab for patients with dMMR or MSI-H endometrial cancer in second or subsequent lines of therapy is expected to be $21,400,154 (year 1 = $1,572,345; year 2 = $7,858,502; year 3 = $11,969,306). The estimated budget impact is sensitive to uncertainty in the proportion of advanced or metastatic endometrial cancer and pembrolizumab dosing (weight-based versus flat dosing).

Request for Reconsideration

The sponsor filed a request for reconsideration for the draft recommendation for pembrolizumab (Keytruda) as monotherapy for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. In their request, the sponsor identified the following issues:

- The sponsor believes that the decision to not reimburse pembrolizumab for this indication is not justified based on the evidence that was provided in their submission dossier, and leaves a very important unmet medical need for this vulnerable patient population.
- In regard to CADTH's conclusion that there is uncertainty of the efficacy results at maturity for the KN-158 trial, which was described in the initial recommendation, the sponsor reported that another data cut-off of January 12, 2022, is available and an analysis was run for the endometrial cancer cohorts (D and K) (this provides 464 additional days of follow-up following the October 5, 2020, cut-off date). The sponsor indicated this analysis will be submitted to CADTH for review to address CADTH's concerns regarding the uncertainty of the efficacy results at maturity.
- There is currently no established, standard, effective second-line therapy for the patient population in question and responses are poor with the chemotherapies used for recurrent endometrial cancer, ranging between only 10% and 15% among all available treatment options. The sponsor is of the view that in this setting of important unmet medical need

where no standard treatment is established due to the poor efficacy of the treatment options, a lack of an active comparator should not be a reason not to recognize the clinical benefit of pembrolizumab.

- The initial recommendation mentions that there was a high degree of uncertainty regarding the magnitude of clinical benefit directly attributable to pembrolizumab due to the nonrandomized, noncomparative, open-label study design; the small sample size; short follow-up; and lack of formal hypothesis testing of the submitted evidence. The sponsor referred to the results of the analysis based on the January 12, 2022, data cut-off to address the limitation of short duration of follow-up. The sponsor also submitted a real-world evidence (RWE) analysis (the ECHO Study) to demonstrate the important clinical benefit of pembrolizumab compared to chemotherapies in the treatment of MSI-H or dMMR endometrial cancer.
- The initial recommendation mentions that given the substantial limitations with the ITC (i.e., clinical heterogeneity, imbalance in prognostic and predictive factors, missing information on patient and study characteristics), pERC was unable to determine the comparative efficacy with respect to survival outcomes. The sponsor stated they will be able to address the main concerns by providing a MAIC comparing the KN-158 trial to the chemotherapy arm of the KN-775 trial, which will help CADTH assess the relative therapeutic benefit of pembrolizumab against chemotherapies.
- The sponsor noted that CADTH mentions that single-arm study design and a lack of consideration of confounding variables precludes causal inferences. This limits the ability to draw robust conclusions from the findings regarding efficacy or safety. The sponsor would like to reiterate that the safety of pembrolizumab is well established in thousands of patients through substantial clinical trial experiences and the reference safety dataset.

In the meeting to discuss the sponsor's request for reconsideration, the committee considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission relating to the issues identified by the sponsor
- new information provided by the sponsor to address important gaps in the evidence identified by pERC
- feedback from 2 clinical specialists with expertise diagnosing and treating patients with endometrial cancer
- feedback on the draft recommendation from 2 patient groups: CCRAN and CCS
- feedback on the draft recommendation from 4 clinician groups: the gynecologic and medical oncologists of the McGill University Health Centre, Ontario Health Gynecology Cancer Drug Advisory Committee, the Alberta Gynecologic Oncology Group, and the BC Provincial Gynecologic Cancer Tumour Group
- feedback from public drug plans and cancer agencies that participate in the CADTH review process.

All stakeholder feedback received from patient and clinician groups and the public drug programs in response to the draft recommendation is available on the CADTH website.

Clinical Evidence for the Reconsideration

A MAIC conducted by the sponsor, an analysis of the pivotal trial (KN-158) based on a more recent data cut-off (January 12, 2022), and an RWE study were submitted by the sponsor and summarized as part of the sponsor's request for reconsideration.

Sponsor-Submitted MAIC

Due to the lack of direct comparative evidence between pembrolizumab monotherapy and other existing treatments, the sponsor submitted an unanchored MAIC that evaluated the relative efficacy of pembrolizumab monotherapy in female patients with advanced, recurrent, or metastatic endometrial carcinoma with dMMR who had received at least 1 prior line of therapy. The KN-158 trial was a single-arm trial that required that the sponsor match individual participant data with aggregate data from a comparator trial (the subset of the treatment of physician's choice [TPC] arm in the KN-775 trial) to evaluate the relative efficacy of pembrolizumab against TPC. Five effect modifiers (i.e., age, race, ECOG PS, number of prior lines of therapy, and histology status) were used as matching variables between the KN-158 and the KN-775 trials in the MAIC. After matching for baseline characteristics, findings from the primary analyses suggested that the efficacy of pembrolizumab monotherapy was better than TPC for the OS, PFS, and ORR end points. Sensitivity analyses using a different set of variables for matching for all outcomes were consistent with the primary analyses. However, several limitations were identified in the unanchored MAIC that affect the internal and external validity of the findings. Due to the limitations identified from the unanchored MAIC, no definitive conclusions could be drawn of the relative efficacy of pembrolizumab in female patients with advanced, recurrent, or metastatic endometrial carcinoma with dMMR who have received at least 1 prior line of therapy.

New Data for KN-158 (Data Cut-Off of January 12, 2022)

To support the request for reconsideration, the sponsor provided a descriptive analysis of patients with MSI-H or dMMR endometrial carcinoma receiving pembrolizumab monotherapy (i.e., cohorts D and K of the KN-158 trial). The baseline characteristics were similar except that more patients had an ECOG PS score of 0 in the updated analysis (42 out of 94 patients; 44.7%) compared with what was reported in the original analysis (35 out of 90; 38.9%). The use of prior medication, concomitant medication, and subsequent anticancer drug use appeared similar to what was reported in the original analysis.

The updated results for PFS and ORR (cut-off date of January 12, 2022; median follow-up time of 24.2 months; range, 0.5 months to 71.4 months) appeared consistent with the data originally included in the submission for this review (cut-off date of October 5, 2020; median follow-up time of 16.5 months; range, 0.5 months to 56.1 months). The updated median OS was 65.4 months (95% CI, 29.5 to NR) compared to the original median OS (NR; 95% CI, 27.2 to NR reported for the cut-off date of October 5, 2020; median follow-up time of 16.5 months; range, 0.5 months to 56.1 months).

The safety profile aligned with the original analysis and no additional safety signals were observed. The updated data further confirmed the potential durable response of OS, PFS, ORR in patients with advanced MSI-H or dMMR endometrial carcinoma who have progressive disease following prior systemic therapy and are not candidates for curative surgery or radiation. However, there was uncertainty regarding the magnitude of the clinical benefit directly attributable to pembrolizumab due to the nonrandomized, noncomparative, open-label

study design; the small sample size; and lack of formal hypothesis testing of the submitted evidence. The lack of comparator or adjustment for confounding precludes causal inferences.

RWE Study by Kelkar, et al. (2022)

The RWE study by Kelkar, et al. (2022) (the ECHO study) was summarized as part of the sponsor's request for reconsideration as the sponsor indicated that this may address the gap in evidence regarding the comparison of pembrolizumab to other treatments for patients with dMMR endometrial carcinoma. This multicentre, retrospective, medical chart review study reported OS observed in patients who received pembrolizumab as second-line treatment for advanced endometrial carcinoma, which was consistent with the updated analysis of the KN-158 study (data cut-off of January 12, 2022) submitted by the sponsor. Results for PFS, ORR, and DOR from the ECHO study were favourable for patients who received pembrolizumab; however, these results are subject to limitations such as likely selection bias, potential for bias in outcome measurement, variability between hospitals and clinicians, lack of information on missing data and loss to follow-up, and potential data extraction errors that may have resulted in poor data quality. All results reported in the ECHO study were descriptive and did not include hypothesis testing; therefore, how treatment with pembrolizumab compares to other treatments for patients with dMMR endometrial carcinoma remains unclear.

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

Initial meeting date: May 11, 2022

Regrets: None

Conflicts of interest: None

Reconsideration meeting date: December 7, 2022

Regrets: None

Conflicts of interest: None