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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

Canada's Drug Agency (CDA-AMC) recommends that Keytruda be reimbursed by public drug plans for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients aged 6 months and older who have solid tumours with MSI-H and/or dMMR mutations that cannot be removed by surgery, or whose tumours have spread to other parts of the body; who have not responded to previous therapy and have no other treatment options available; and who are in relatively good health.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if it is prescribed by clinicians with expertise in treating advanced cancer and the cost of Keytruda is reduced. It should not be given in combination with other anticancer drugs, as well as in patients who have a history of treatment with an anti–PD-1, anti–PD-L1, or anti–PD-L2 drug.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 3 clinical trials suggested that treatment with Keytruda caused tumours to shrink or disappear on imaging, and response to treatment was durable.
- Keytruda may meet some important patient needs by providing another treatment option with manageable side effects; however, there was not enough evidence to show that Keytruda would improve health-related quality of life (HRQoL).
- Testing for MSI-H and/or dMMR status is available as a routine part of care in many solid tumours, but not for rarer cancer types, or pediatric cancer. Implementation of testing in tumour types where testing is not part of routine practice may have an impact on the health system.
- Based on the assessment of the health economic evidence by CDA-AMC, Keytruda may not represent good value to the health care system at the public list price, given the substantial amount of uncertainty in the evidence. A price reduction is therefore required.

Summary

- Based on public list prices, Keytruda is estimated to cost public drug plans approximately $21 million over the next 3 years.

Additional Information

What Are Solid Tumours With MSI-H or dMMR Mutations?

MSI-H or dMMR mutations have been reported in more than 30 different types of cancers in adults and children, with some cancers showing a higher prevalence of mutations (endometrial, colorectal, small intestine, and gastric cancers) than others (cervical, esophageal, bladder or urothelial, lung, and skin cancers). Solid tumours with MSI-H or dMMR mutations have cells that are unable to properly repair certain DNA errors. Patients with solid tumours with MSI-H or dMMR mutations tend to have a worse course of disease compared to patients whose tumours are not MSI-H or dMMR, although this varies based on tumour type.

Unmet Needs in Patients With MSI-H or dMMR Solid Tumours

There is a need for safe and effective treatments for MSI-H and/or dMMR solid tumours once standard of care (SOC) fails that result in durable responses, prolonged survival, alleviated symptoms, and improved quality of life.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per 28 days when using a fixed dose (200 mg every 21 days) or $8,155 per 28 days when using a weight-based dose (2 mg/kg to 200 mg every 21 days).

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed as monotherapy for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

pERC acknowledged that the collection of evidence for any solid tumours with MSI-H and/or dMMR mutations is particularly challenging as individual tumours harbouring this mutation are rare, and sample sizes are small, particularly in pediatric patients, which contributes to the additional uncertainty in the clinical evidence available to assess the effects of pembrolizumab.

Evidence from 3 open-label, single-arm studies in adult patients (KEYNOTE-158 [N = 373] and KEYNOTE-164 [N = 124]) and pediatric patients (KEYNOTE-051 [N = 7]) with unresectable or metastatic solid tumours with MSI-H and/or dMMR mutations demonstrated a clinically meaningful benefit of pembrolizumab based on the objective response rate (ORR) in adult patients (KEYNOTE-158: ORR = 33.8%; 95% confidence interval [CI], 29.0% to 38.8%; KEYNOTE-164: ORR = 33.9%; 95% CI, 25.6% to 42.9%), but not in pediatric patients (KEYNOTE-051: ORR = 0%), and durability of response (KEYNOTE-158: duration of response [DOR] = 63.2 months; KEYNOTE-164: DOR = not reached). However, pERC noted that there was considerable heterogeneity in the antitumour activity of pembrolizumab on different tumour types and substantial uncertainty in the magnitude of the observed response rate. The results of the studies also suggested that treatment with pembrolizumab resulted in a clinically meaningful improvement in median overall survival (OS) among adult patients (KEYNOTE-158: OS = 19.8 months; 95% CI, 14.5 to 25.8 months; KEYNOTE-164: OS = 36.1 months; 95% CI, 24.0 months to not reached) and pediatric patients (7.7 months; 95% CI, 1.9 months to not reached). pERC noted that the harms reported in the included trials were considered manageable and consistent with the known safety profile of pembrolizumab. The sponsor-submitted indirect treatment comparisons suggested improved progression-free survival (PFS) and OS compared to SOC; however, there were significant limitations that impacted the internal validity of the findings which precluded pERC from drawing conclusions on the comparative efficacy and safety of pembrolizumab.

Patients and clinicians identified a need for new, effective treatments to treat unresectable or metastatic MSI-H and/or dMMR solid tumours once SOC or salvage chemotherapy fails, that result in durable responses, prolonged survival, alleviated symptoms, and improved HRQoL. pERC concluded that pembrolizumab may meet some of the needs identified by improving response rate and DOR, while providing a manageable safety profile. pERC could not draw any conclusions on HRQoL due to the exploratory nature of the outcome, the limited availability of evidence (only assessed in the KEYNOTE-158

study), high proportion of missing data, and the widely variable response (in terms of improved, stable, or deteriorated HRQoL).

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab was $32,001 per quality-adjusted life-year (QALY) compared with SOC. This represents a weighted ICER derived from all eligible tumour sites. However, results from the analyses were considered highly uncertain due to the absence of robust clinical evidence to inform the analysis; uncertain testing costs to identify all eligible patients across all tumour sites; and disproportional weight given to tumour sites where pembrolizumab is already covered under other indications. Price reductions are required to reduce uncertainty regarding cost-effectiveness.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab should only be initiated in patients who: 1.1. have unresectable or metastatic solid tumours harbouring MSI-H or dMMR mutations as determined by validated test that has progressed following prior treatment and who have no satisfactory alternative treatment options 1.2. are aged 6 months or older.	Evidence from the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies demonstrated a clinical benefit in patients who fulfilled the characteristics listed in this condition.	pERC and the clinical experts noted that in line with the Health Canada indication, reimbursement request, and trial populations, at least 1 line of prior therapy would be required before initiating pembrolizumab monotherapy. pERC noted that testing for MSI-H and/or dMMR mutations is available as a routine part of care in many solid tumours where ICIs are used as SOC; however, testing for MSI-H or dMMR mutations will also be required for tumours where ICI are not standard of care in earlier lines of therapy, as well as in most pediatric patients.
2. Patients must not have: 2.1. active CNS metastases 2.2. history of therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 drug.	The KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies excluded patients with active CNS metastasis, and those who received prior anti–PD-1, anti–PD-L1, or anti–PD-L2 therapy. As such, the potential benefit of pembrolizumab in these patients has not been demonstrated.	pERC agreed with the clinical experts that patients with CNS metastases could be eligible for pembrolizumab once the CNS metastases were considered clinically stable or managed. pERC agreed with the clinical experts that patients who have progressed following treatment with immune checkpoint inhibitor therapy would not be eligible for re-treatment with pembrolizumab.
3. Patients must have good performance status.	The KEYNOTE-158 and KEYNOTE-164 studies included adults with an ECOG PS of 0 or 1. The KEYNOTE-051 study included pediatric patients with a Lansky Play Scale or Karnofsky Performance Scale score ≥ 50.	pERC agreed with the clinical experts that adult patients with an ECOG PS of more than 1 may be treated at the discretion of the treating physician. It should be noted that ECOG PS is not used in the pediatric population and another adequate performance score should be used.

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity 4.3. completion of 24 months of treatment (e.g., 35 cycles administered every 3 weeks).	Patients in the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice. Patients in the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies were treated with pembrolizumab for a maximum of 35 cycles (approximately 24 months).	pERC agreed with the clinical experts that re-treatment with pembrolizumab (up to 1 year of therapy at the time of progressive disease) would be reasonable to consider for patients who completed a prior course of pembrolizumab (e.g., up to a maximum of 2 years of therapy) in whom progressive disease did not occur either during or within 6 months of completing pembrolizumab. However, according to the clinical experts, in cancers where pembrolizumab is already first-line or second-line SOC, if a patient did not respond to, or progressed on pembrolizumab, rechallenging with pembrolizumab would not be recommended.
Prescribing		
5. Pembrolizumab should be prescribed by clinicians with expertise and experience in treating unresectable or metastatic cancers. The treatment should be delivered in institutions with expertise in systemic therapy delivery and management of immunotherapy related side effects.	This condition is to ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	Using a weight-based dose at the public list price, pembrolizumab may be considered cost-effective versus current SOC, at a $50,000 per QALY gained willingness-to-pay threshold. However, evidence used to determine this conclusion was highly uncertain given the absence of robust clinical data, uncertain testing costs, and disproportional weight given to tumour sites where patients already have access to pembrolizumab. A reduction in price is required to reduce the uncertainty regarding the cost-effectiveness of pembrolizumab in this setting.	—
Feasibility of adoption		
7. The feasibility of adoption of pembrolizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of	—

Reimbursement condition	Reason	Implementation guidance
	adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	
8. The organizational feasibility of conducting testing for solid tumours with MSI-H or dMMR mutations must be addressed.	Testing for MSI-H or dMMR mutations is required to determine eligibility for pembrolizumab.	pERC noted that implementation of testing for patients with MSI-H or dMMR mutations where ICI is not funded as SOC may have a substantial impact to the health system (e.g., in consideration of need for patient eligibility assessment, personnel and infrastructure requirements, and cost).

CDA-AMC = Canada's Drug Agency; CNS = central nervous system; dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICI = immune checkpoint inhibitor; MSI-H = microsatellite instability-high; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year; SOC = standard of care.

Discussion Points

- **Unmet needs:** pERC discussed the poor prognosis for patients with MSI-H and/or dMMR solid tumours who have exhausted all satisfactory treatment options creating an unmet need for new and effective treatments, and a general need for new treatments in the pediatric population. pERC noted that no input from pediatric patients or caregivers was included as part of this review, thus, their perspective remains unknown. Specifically, pERC considered the input from patient (all adults) and clinician groups, noting the need for treatments that prevent progression and recurrence, prolong survival, have a durable response, and improve HRQoL. As noted, the committee felt that pembrolizumab may meet some of these needs, providing an additional treatment with clinically meaningful and durable responses, although the magnitude of this difference across different tumour types and versus currently available SOC treatments is uncertain. pERC also recognized the breadth of clinical experience with pembrolizumab which indicates it is generally better tolerated with fewer and less severe adverse effects compared to conventional chemotherapy. pERC also discussed the rarity of the indication under review and noted that many of the individual tumours evaluated in the evidence were not considered rare, although, tumours harbouring MSI-H or dMMR mutations may be considered rare. The committee noted that there may be an increase in genetic testing for rarer tumour types and in the pediatric setting.
- **Place in therapy:** pERC discussed the many solid tumour cancers (e.g., colorectal, endometrial, kidney, non–small cell lung, gastric, urothelial, and other cancers) that are currently treated with pembrolizumab or other immune checkpoint inhibitors as SOC in earlier lines of therapy. Additionally, pERC noted that in the available evidence, patients who had previously received anti–PD-1, anti–PD-L1, or anti–PD-L2 drugs were excluded, thus, there are no data to support re-treatment with pembrolizumab after failure of immune checkpoint inhibitors (ICIs) in this population. The committee noted that given the current treatment landscape, the number of patients in Canada who will be eligible to receive pembrolizumab in later lines of therapy is questionable. Pembrolizumab could

represent a new treatment option for rarer cancers and in pediatric patients where there are limited options and ICIs are not used, although the evidence is highly uncertain.

- **Testing procedure considerations:** pERC discussed the requirement of testing for MSI-H and/or dMMR status when determining eligibility for pembrolizumab. pERC noted that microsatellite instability (MSI) and/or mismatch repair (MMR) testing is available as part of the SOC for the most common unresectable or metastatic solid tumour types in adult patients (e.g., colorectal or endometrial cancer) evaluated in the pivotal studies. pERC recognized that MSI and/or MMR testing is available in other solid tumour types not evaluated in the pivotal evidence (e.g., incorporated within genomic panels for breast, prostate, and lung cancers). However, pERC noted that testing for MSI-H and/or dMMR status may not be part of the SOC for rarer cancer types, or any pediatric patients with cancer in Canada. As such, in more common tumour types, pERC agreed with the clinical experts that a potential increase in testing requirements is not anticipated to be an implementation or access barrier. Nevertheless, the committee anticipated that increases in testing might be observed for some cancers where first or second-line treatment with ICI is not funded, and noted that this may have substantial impact to the health systems, including but not limited to the cost of testing to identify all potentially eligible adult and pediatric patients with solid tumours for which MSI and/or MMR testing is not currently performed. pERC also noted the potential impact of increased testing on capacity of human and other health care resources (e.g., testing infrastructure and equipment to conduct and analyze test results) to allow timely and equitable access to testing. pERC noted that there will be additional costs associated from broadening the testing requirement in adult and pediatric populations, and capacity for testing across some jurisdictions remains a concern. Furthermore, pERC noted that the availability of pembrolizumab may also increase use of testing in many other solid tumour types.
- **Certainty of evidence:** pERC discussed the pivotal evidence submitted for this review which consisted of 3 open-label, single-arm trials (KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051) that included multiple different advanced solid tumour types (including adrenocortical, brain, breast, cervical, cholangiocarcinoma, colorectal, endometrial, gastric, mesothelioma, neuroendocrine, ovarian, pancreatic, prostate, renal, salivary, sarcoma, small cell lung cancer, small intestine, thyroid, urothelial, and other rarer cancer types). pERC deliberated on the results of these trials which demonstrated that pembrolizumab was associated with clinically meaningful and durable responses (KEYNOTE-158: ORR = 33.8% and DOR = 63.2 months; KEYNOTE-164: ORR = 33.9% and DOR = not reached). Furthermore, pERC noted that there was notable heterogeneity in the response rates of individual tumour types (ranging from 4.8% to 59.3%), although the interpretability was limited given small sample sizes for some tumour types (ranging from 21 to 124 patients). Finally, pERC emphasized that the results for the pediatric population are highly uncertain due to the small sample size and the lack of patients who responded. pERC highlighted that the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment of the evidence suggested that the certainty of these results was very low, primarily due to the lack of comparator which precluded the ability to draw conclusions on the relative efficacy of pembrolizumab versus any other treatments.

- **Additional sources of uncertainty and generalizability:** The committee noted the considerable heterogeneity in response across small samples of different tumour types from the KEYNOTE-158 study, the challenges with interpreting these data, and the uncertainty of whether the results represent true differences or natural statistical variation. pERC acknowledged that the study likely represents the natural prevalence of the MSI-H and/or dMMR biomarkers and that enrolling a large number of patients for each tumour type may not have been feasible. As the KEYNOTE-051 study included only 7 pediatric patients, primarily with brain cancers, pERC discussed how the results of the trial may not adequately represent the broader patient population in terms of age, tumour type, performance status, and disease stage and restricts the ability to draw robust conclusions about the efficacy and safety of pembrolizumab across the broader pediatric population with MSI-H or dMMR tumours. The committee acknowledges that the prevalence of MSI-H or dMMR mutations in the pediatric population is likely much lower compared to adults and that the most common types of solid tumours in pediatric patients differs from adult patients.
- **Indirect evidence:** In the absence of a direct comparison between pembrolizumab and comparators for the indication of interest, pERC considered evidence from 5 sponsor-submitted indirect treatment comparisons for colorectal, endometrial, small intestine, and gastric cancers. While the results generally favoured pembrolizumab over SOC, which the clinical experts believed was plausible, the indirect evidence was associated with uncertainty due to various methodological issues including the indirect treatment comparison (ITC) designs (naive indirect comparisons and unanchored matching-adjusted indirect comparison[(MAICs]), and the lack of MSI-H and/or dMMR status information in comparator studies. Moreover, patients with colorectal, endometrial, or gastric cancer likely have already received immunotherapy in the first-line setting reducing the relevance of the results. Lastly, the indirect evidence did not include pediatric patients and comparative efficacy, and safety remained unknown for this patient population.
- **Additional evidence:** pERC considered the results of 2 additional datasets: the International Replication Repair Deficiency Consortium (IRRDC) (N = 18) dataset and whole exome sequencing (WES) pooled datasets (N = 21), that included pediatric and adult patients with MSI-H status tumours who received pembrolizumab. pERC noted that results were generally consistent with the pivotal studies, supporting the use of pembrolizumab in adult and pediatric patients with MSI-H tumours, but were affected by similar limitations as the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies.
- **Ethical and equity considerations:** pERC discussed the physical and psychosocial burdens of living with and undergoing treatment for unresectable or metastatic MSI-H or dMMR solid tumours. The committee acknowledged the limited clinical benefit and cumulative toxicity of existing treatment options and the unmet need for effective and tolerable treatments for patients with these types of cancers. pERC noted that reimbursing pembrolizumab for the proposed tumour-agnostic indication could alleviate current inequities in access to treatment options experienced by people with MSI-H or dMMR tumours for which pembrolizumab is not currently reimbursed. The committee discussed how some groups, including notably children and people with rare tumour types, were underrepresented

or had limited representation in the clinical trial data. pERC acknowledged that clinical experts said they would prescribe pembrolizumab for eligible children, despite limited efficacy evidence, due to unmet need and an established safety profile in adults. The committee also highlighted the importance of robust consent conversations to ensure patients and their caregivers understood the uncertain benefits and risks of treatment with pembrolizumab, and limited experience using pembrolizumab, especially for groups who were underrepresented or with limited representation in clinical trials, including children.

- **Ethical and equity considerations for health systems implementation:** pERC acknowledged that, given the very low proportion of patients with MSI-H and/or dMMR status in some tumour sites that are not currently tested, testing costs to identify 1 eligible patient can be high. The committee noted that the additional capacity and resources (including human resources and costs of testing) required to test for MSI-H and/or dMMR status across all tumour types raises concerns about the opportunity costs to health systems, including beyond oncology. pERC acknowledged that while the infrastructure required to prescribe, administer, and monitor pembrolizumab is already in place, children may experience disproportionate difficulty accessing the drug, since few pediatric providers have experience with the treatment. They also acknowledged the importance of mitigating geographic barriers to access by providing support for patients who reside far from infusion centres. pERC discussed the need for long-term efficacy data to further support clinical and health systems decision-making, including to understand opportunity costs and how the treatment will impact health system sustainability in the context of finite resources.
- **Cost-effectiveness**: pERC acknowledged that although weighted results across all tumour sites from the economic analysis suggested an ICER of less than $50,000 per QALY gained, this was driven by results in tumour sites where pembrolizumab is already funded and used. As there is limited evidence in tumour sites where pembrolizumab is currently not funded, the results from the economic analysis are challenging to interpret. The committee acknowledged that in the absence of robust clinical evidence the ICER may be substantially higher than what was presented for the tumour sites for which evidence is available.

Background

MMR and dMMR results in an inactivation of the DNA repair system and can be caused by mutations in genes encoding proteins that are responsible for detecting and correcting errors in mismatched base pairs. Microsatellites are repetitive stretches of 1 to 6 base pairs that can result from a defective MMR system or inactivation of the MMR system. dMMR can be observed by comparing the variation in length of the microsatellite in the tumour tissue versus the same patient’s healthy tissue. This is often termed as MSI and large variation in microsatellite length is referred to as MSI-H. Cancers that are MSI-H or dMMR tend to have a high tumour mutational load and are more responsive to PD-1 based immunotherapy. ICIs, such as pembrolizumab, prevent tumour cells from evading the immune system, which are then recognized by T

cells, and can trigger an antitumour immune response. MSI-H and dMMR status can be assessed by next-generation sequencing and immunohistochemistry, respectively.

MSI-H or dMMR mutations have been detected in more than 30 cancers. It was reported in a meta-analysis from 2022 that there is an estimated pooled prevalence of 2.7% for MSI-H status and 2.9% for dMMR status across different solid tumour types in adults. Endometrial, colorectal, small intestine, and gastric cancers showed a higher prevalence of MSI-H (8.5% to 21.9%), compared to cervical, esophageal, bladder or urothelial, lung, and skin cancers, which showed a lower prevalence of MSI-H (less than 5%). According to the clinical experts consulted for this review, patients with metastatic solid tumours that have confirmed MSI-H or dMMR status have inferior outcomes when treated with conventional therapies and tend to show improved outcomes with ICIs. As a group, these patients have a worse prognosis compared to those whose tumours are not MSI-H or dMMR, although prognosis varies based on tumour type.

There is high variability in first-line treatments and SOC in solid tumours expressing MSI-H or dMMR mutations. In some instances, immunotherapy has become the SOC. In patients with MSI-H or dMMR unresectable or metastatic colorectal cancer, pembrolizumab received a recommendation to reimburse as a first-line therapy and is the currently funded SOC. Also, pembrolizumab received a recommendation to reimburse as a second-line or later therapy in adult patients with MSI-H or dMMR unresectable or metastatic endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options and is currently funded in most jurisdictions. Regardless of tumour type, patients with unresectable or metastatic MSI-H or dMMR cancers who have progressed after prior standard systemic therapy have a very poor prognosis, and the SOC for these patients is typically chemotherapy-based regimens, which provide limited clinical benefit and are associated with significant cumulative toxicity.

Pembrolizumab has been approved by Health Canada as monotherapy for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by a validated test, which have progressed following prior treatment and who have no satisfactory alternative treatment options. Pembrolizumab is a high-affinity antibody against PD-1 that reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment. It is available as a solution for infusion (100 mg per 4 mL vial) that is administered as an IV infusion over 30 minutes. The dosage recommended in the product monograph in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks until unacceptable toxicity or disease progression, or up to 24 months or 35 doses of 200 mg or 18 doses of 400 mg, whichever is longer, in patients without disease progression. The recommended dosage in pediatric patients is 2 mg per kg (to a maximum of 200 mg) every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months or 35 doses, whichever is longer, in patients without disease progression.

Sources of Information Used by the Committee

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

- a review of 3 single-arm studies of pembrolizumab in different solid tumours; 4 indirect treatment comparisons in different solid tumours; and 2 real-world datasets included in the Studies Addressing Gaps in Systematic Review Evidence section
- patients' perspectives gathered by 2 patient groups, Colorectal Cancer Canada and Colorectal Cancer Resource & Action Network working in collaboration with Canadian Cancer Survivor Network, Craig's Cause Pancreatic Cancer Society, Canadian Breast Cancer Network, and Ovarian Cancer Canada
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 3 clinical specialists with expertise diagnosing and treating patients with MSI-H or dMMR solid tumours
- input from 5 clinician groups, the Society of Gynecologic Oncology of Canada and 4 Ontario Health (Cancer Care Ontario) Drug Advisory Committees (for genitourinary cancer, breast cancer, gynecology cancer, and central nervous system cancer)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to pembrolizumab.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Patient group input was submitted from Colorectal Cancer Canada and Colorectal Cancer Resource & Action Network (working in collaboration with Canadian Cancer Survivor Network, Craig's Cause Pancreatic Cancer Society, Canadian Breast Cancer Network, and Ovarian Cancer Canada) for this review. The groups collected information through patient and caregiver interviews and online surveys. All contributions were from adult patients and/or their caregivers and did not include the perspectives of pediatric patients.

According to the respondents, symptoms of the disease as well as the side effects of the SOC treatments they received had the greatest impact on their physical, mental, and social health. The impact of diagnosis, disease recurrence, and treatment was felt by patients' family, friends, and communities.

The most important outcomes noted by patients and caregivers included preventing disease progression and disease recurrence, prolonging survival, having a durable response, and improving HRQoL and symptoms.

Patients who received pembrolizumab noted many benefits, including symptom relief, quick response to treatment, minimal adverse effects, being easier to receive than conventional treatments, better HRQoL, and feeling that they avoided long-term toxicities associated with conventional chemotherapies.

The groups emphasized the importance of wide and equitable access to biomarker testing, treatments for those with appropriate biomarker status (i.e., MSI-H or dMMR) that go beyond tumour type, and drugs to treat rare and pediatric cancers.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts highlighted the heterogeneity and aggressive phenotype of MSI-H and dMMR solid tumours. For adult patients with MSI-H and/or dMMR metastatic cancer, there is a need for effective therapeutic options once SOC, or salvage chemotherapy fails. Meanwhile, for pediatric patients there is a general need for new treatments, as the current treatment options in both the front-line and relapsed setting are limited for this population.

The clinical experts highlighted that pembrolizumab is already indicated for use as SOC in non–MSI-H and/or dMMR tumours (e.g., kidney, urothelial, gastric, lung, biliary tract cancers) and in some cancers with specification for MSI-H and/or dMMR mutations (e.g., colorectal or endometrial cancers), thus, this may not be considered in later lines of therapy, depending on prior response. For the pediatric population, 1 clinical expert highlighted that pembrolizumab and ICIs, in general, are less frequently used, and experience is limited. In adult and pediatric patients, the clinical experts highlighted that, for the indication under review, pembrolizumab is intended for use after first-line therapy specific to the solid tumour site, although the ideal sequencing of treatments is unknown. The clinical experts noted that pembrolizumab would not be used in combination with existing treatments for any indication in this setting based on currently available data.

The experts considered patients most likely to benefit from treatment with pembrolizumab to be those with confirmed MSI-H and/or dMMR positivity, as at this time, there are no other validated biomarkers or clinical factors that can better predict treatment benefit for these patients than MSI-H and/or dMMR status. The clinical experts highlighted that underdiagnosis due to lack of testing is a risk, particularly for rarer cancers, where next-generation sequencing or immunohistochemistry are not reflexively tested, or in pediatric patients, where testing is even more limited. One expert highlighted that up to 50% of patients will not benefit from treatment despite biomarker positivity. Additionally, the experts highlighted that, particularly for rarer cancers, treatment with SOC does not result in long-term benefits. The clinical experts also highlighted that patients least suitable for pembrolizumab are those who test negative for the MSI-H and/or dMMR biomarker, those who have previously received and/or did not respond to an ICI during a previous line of therapy, as well as those with severe active autoimmune disease. In the pediatric setting, 1 clinical expert highlighted the population of patients with high-grade gliomas, for which MSI and MMR mutations are known, and testing is more routine, would benefit from pembrolizumab. Conversely, the prevalence of MSI-H and/or dMMR mutations appears much lower in pediatric patients, thus, testing for MSI-H and/or dMMR mutations is uncommon (except for high-grade gliomas) as they do not often treat patients with some of the more common adult cancers that harbour MSI-H or dMMR mutations (e.g., colorectal, endometrial, or pancreatic cancers).

In both the adult and pediatric populations, the primary aim of treatment is disease control and prolongation of survival, with low toxicity. The clinical experts noted that complete responses are uncommon for these patients, thus, durability and stability are also important. Per the clinical experts, treatment tolerance is generally evaluated at each appointment, with radiologic response assessments typically occurring every 2 to 3 treatment cycles, or approximately every 9 to 12 weeks, depending on local protocols.

There is extensive experience with pembrolizumab in oncology. The clinical experts highlighted that treatment with pembrolizumab is generally discontinued due to intolerable adverse events (AEs), and clear evidence of disease progression. One concern highlighted by the clinical experts is the potential risk of premature discontinuation due to pseudoprogression, where treating physicians must carefully weigh the need to identify true disease progression against the risk of prematurely halting a therapy that may still offer significant clinical benefit to patients.

As noted, ICIs have become SOC in the treatment of many adult cancers, and there is growing experience in their use across various health care settings including academic and community settings; however, in the pediatric setting this is likely limited to specialist tertiary hospitals. Specialists, such as medical oncologists (as well as pediatric oncologists in the case of pediatric patients), are needed to select appropriate patients for treatment, and oversee the management of therapy.

Clinician Group Input

Five clinician groups submitted input for this review: the Society of Gynecologic Oncology of Canada and 4 Ontario Health (Cancer Care Ontario) Drug Advisory Committees (for genitourinary cancer, breast cancer, gynecology cancer, and central nervous system cancer).

Input from the clinician groups aligned with that of the clinical experts consulted for this review with regards to treatment goals, the unmet needs of this patient population, assessing treatment response, the drug's place in therapy, deciding when to discontinue treatment, which specialists should manage these patients, and where patients should be treated with pembrolizumab. The clinician groups noted that access to biomarker testing varies based on tumour type and jurisdiction.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The included studies (KEYNOTE-164, KEYNOTE-158, and KEYNOTE-151) did not have active comparator treatments and only included cohorts that received pembrolizumab monotherapy. The KEYNOTE-164 study included patients with colorectal cancer. Later-line treatment options for this population can	pERC and the clinical experts agreed that all tumour types with MSI-H and/or dMMR mutation should be eligible for treatment with pembrolizumab. pERC and the clinical experts also highlighted that although there was no formal comparator in the available evidence, results from the sponsor-submitted studies, as well as other studies, have demonstrated that pembrolizumab is

Implementation issues	Response
include: • multiagent chemotherapy with or without bevacizumab • multiagent chemotherapy with or without *EGFR* inhibitors • encorafenib + *EGFR* inhibitors • trifluridine-tipiracil + bevacizumab. The KEYNOTE-158 study included several tumour type cohorts that have a broad range of available treatment options (e.g., endometrial cancer, small intestinal cancer, and gastric cancer). In endometrial cancer, later-line treatment options include: • pembrolizumab monotherapy (funded by most jurisdictions in dMMR and/or MSI-H) • single agent chemotherapy. In small intestinal cancer, later-line treatment options include: • anti-*VEGF* + chemotherapy • taxane-based chemotherapy. In gastric cancer, late line treatment options include: • ramucirumab + paclitaxel • multiagent or single agent chemotherapy. The KEYNOTE-051 study is an ongoing trial designed to establish dosing for pediatric patients and tolerability for pembrolizumab. All patients enrolled (7 of which have dMMR and/or MSI-H) received pembrolizumab monotherapy. How does pembrolizumab monotherapy compare to existing later-line therapies in other indications? Would all solid tumour types with MSI-H or dMMR mutation be eligible for treatment for this indication?	associated with good response rate and duration of response versus historical treatments. However, pERC and the clinical experts acknowledged the limitations in combining very different diseases, and further highlighted that, in general, the results with SOC or conventional chemotherapy are underwhelming.
Considerations for initiation of therapy	
In the KEYNOTE-164 study, patients in cohort A received 2 or more prior lines of therapy and patients in cohort B received 1 or more prior lines of therapy. In the KEYNOTE-158 study, patients must have received at least 1 prior line of therapy, except cohort K (patients with colorectal cancer) who must have received 2 prior lines of therapy. In the KEYNOTE-051 study, pediatric patients could have had any number of prior therapies. How many lines of prior therapy should patients receive before pembrolizumab monotherapy?	pERC and the clinical experts noted that in line with the Health Canada indication, reimbursement request, and trial populations, at least 1 line of prior therapy would be required before pembrolizumab monotherapy.
Should patients who complete 2 years of treatment and experience disease progression and/or recurrence be eligible for up to 1 year of pembrolizumab re-treatment?	pERC and the clinical experts stated that rechallenging with a therapy proven to be previously highly effective is routine in oncology and should be considered standard in this setting as well. They also highlighted that most trials and health jurisdictions are now routinely permitting rechallenge at progression. Conversely, pERC and the clinical experts agreed that in cancers where pembrolizumab is already first-line or second-line SOC, if

Implementation issues	Response
	a patient did not respond to treatment with pembrolizumab, they should not be rechallenged later.
Would patients with CNS metastases be eligible for pembrolizumab monotherapy?	pERC agreed with the clinical experts that patients with CNS metastases could be eligible for pembrolizumab if or once their CNS metastases were considered clinically stable or managed.
Pembrolizumab monotherapy was previously reviewed by CDA-AMC 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.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for prescribing of therapy	
For consistency, jurisdictions would plan on implementing pembrolizumab as weight-based dosing to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg in adult and pediatric patients) or 4 mg/kg every 6 weeks to a maximum of 400 mg (in adult patients only), similar to other indications.	This is a comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients with ECOG PS of 2 or greater be eligible?	pERC agreed with the clinical experts that patients with an ECOG PS of 0 to 2 would be considered eligible for treatment with pembrolizumab provided they were able to tolerate therapy. The experts noted that, situationally, patients with an ECOG PS of 3 may be considered eligible, for example, if they were young without comorbidities, and/or if due to cancer-related symptoms that may be alleviated with other treatments or local management. However, the clinical experts noted that ECOG is not used in the pediatric population, and they would use another adequate performance score. pERC agreed with the clinical experts.
Should patients with ampullary cancer, sarcomas, or mesenchymal tumours be eligible?	pERC and the clinical experts agreed that despite the exclusion of these patients from the trials, they highlighted that if the MSI-H and/or dMMR biomarker is present in these patients, then patients should be eligible for treatment with pembrolizumab. The clinical experts also noted that sarcomas represent a larger proportion of solid tumours in pediatric patients.
Should patients actively on alternative later-line therapies be eligible to switch to pembrolizumab monotherapy?	pERC and the clinical experts agreed that patients who are doing well on current treatment should not be switched.
Funding algorithm	
Pembrolizumab monotherapy is currently funded by most jurisdictions as first-line therapy in dMMR and/or MSI-H colorectal cancer. In the KEYNOTE-164 study, patients were excluded if they had received prior anti–PD-1, anti–PD-L1, or anti–PD-L2 therapy. Should patients who have previously received prior anti–PD-1, anti–PD-L1, or anti–PD-L2 therapy be eligible for pembrolizumab.	If patients progressed following treatment of immune checkpoint inhibitor therapy, they would not be eligible for re-treatment with pembrolizumab.

Implementation issues	Response
Care provision issues	
Currently testing for MSI-H and/or dMMR mutations is in place for unresectable or metastatic colorectal cancer and endometrial cancers. In the KEYNOTE-158 study, cohorts A through J completed PCR-based central testing evaluating the 5 mononucleotide loci (*BAT25*, *BAT26*, *NR21*, *NR24*, and *Mono27*) to retrospectively identify enrolled patients with MSI-H and/or dMMR, while cohort K (patients with colorectal cancer) was performed locally. In clinical practice, how should MSI-H and dMMR testing be conducted for all patient populations when determining eligibility?	MSI-H and/or dMMR testing would be conducted using locally funded and standardized testing as available, which generally includes NGS, PCR, or IHC. While both tests are adequate for identifying this biomarker, IHC tends to be more readily accessible across regions (i.e., in community or hospital settings). However, the clinical experts also noted that the standard adult MSI panel is known to be inaccurate in pediatric populations, thus, they felt that there should be flexibility in the type of tests conducted to determine biomarker status.
System and economic issues	
Confidential prices exist for pembrolizumab, bevacizumab, encorafenib, panitumumab, ramucirumab, and trifluridine-tipiracil.	This is a comment from the drug programs to inform pERC deliberations.

CDA-AMC = Canada's Drug Agency; CNS = central nervous system; dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group Performance Status; *EGFR* = epidermal growth factor receptor; IHC = immunohistochemistry; MSI = microsatellite instability; MSI-H = microsatellite instability-high; NGS = next-generation sequencing; PCR = polymerase chain reaction; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SOC = standard of care; *VEGF* = vascular endothelial growth factor.

Clinical Evidence

Systematic Review

Description of Studies

Three studies were included in this review: KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051. All were single-arm trials that evaluated pembrolizumab in different solid tumours. The KEYNOTE-158 study enrolled adult patients with advanced MSI-H or dMMR solid tumours (noncolorectal cancer) who had disease progression following prior therapy. The KEYNOTE-164 study enrolled adult patients with advanced MSI-H or dMMR colorectal cancer that progressed following prior therapy, in 2 cohorts. Cohort A included patients who had previously been treated with 2 or more lines of SOC therapies, which must have included fluoropyrimidine, oxaliplatin, and irinotecan. Cohort B included patients with at least 1 line of prior systemic SOC therapy. The KEYNOTE-051 study enrolled pediatric patients with MSI-H or dMMR cancers whose disease had progressed following prior therapy. Patients who had previously received anti–PD-1, anti–PD-L1, or anti–PD-L2 drugs were excluded from all trials. The primary end point for the KEYNOTE-158 and KEYNOTE-164 studies was ORR and the secondary end points were DOR, PFS, OS, safety, and tolerability. For the KEYNOTE-051 study, the primary end point was safety, tolerability, and ORR and the secondary end points were DOR, PFS, and OS.

The KEYNOTE-158 study enrolled 373 patients with a variety of MSI-H and/or dMMR solid tumours, primarily endometrial (25%), gastric (14%), small intestine and ovarian (7% each), among other rarer cancers (26%)

who had disease progression after prior treatments. The mean age was 59.2 years (standard deviation [SD] = 13.1 years), and most patients (56%) had 2 or more prior lines of therapy. The KEYNOTE-164 study enrolled 124 patients (61 in cohort A and 63 in cohort B) with MSI-H or dMMR colorectal cancer who received 1 or more prior lines of therapy, although the majority received 2 or more (76%). The mean age of included patients was 56.1 years (SD = 14.9 years), and there were slightly more males (56%) than females (44%). The KEYNOTE-051 study included 7 pediatric patients with a mean age of 11 years (SD = 4.3 years), mostly with brain tumours (n = 6, 86%). In total 57% of patients received 1 prior therapy, while 29% received 2 or more lines of therapy.

Efficacy Results

Response Rate

Adult

In the KEYNOTE-158 study, the median duration of follow-up was 17 (range, 0.2 to 71.4) months. The ORR per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1) was 33.8% (95% CI, 29.0% to 38.8%). The best objective response included a complete response (CR) in 40 patients (10.7%) and a partial response (PR) in 86 patients (23.1%). The tumour-specific ORR in the KEYNOTE-158 study showed varied response rates, ranging from 4.8% (brain) to 59.3% (small intestine) across different types of cancer. Tumours with higher ORRs compared to the pooled result included endometrial, gastric, small intestine, cholangiocarcinoma, urothelial, and salivary cancers. Tumours with lower ORRs included ovarian, pancreatic, brain, sarcoma, breast, cervical neuroendocrine, prostate, adrenocortical, mesothelioma, thyroid, small cell lung, and renal cancers.

For the KEYNOTE-164 study, the median duration of follow-up was 31.4 (range, 0.2 to 65.2) months for cohort A and 52.7 (range, 0.1 to 56.6) months for cohort B. The pooled ORR (cohort A and B) was 33.9% (95% CI, 25.6% to 42.9%); 9.7% had a CR and 24.2% had a PR. The ORR in cohort A was 32.8% (95% CI, 21.3% to 46.0%). The objective response included a CR in 3 patients (4.9%) and a PR in 17 patients (27.9%). The ORR in cohort B was 34.9% (95% CI, 23.3% to 48.0%). The objective response included a CR in 9 patients (14.3%) and a PR in 13 patients (20.6%).

Pediatric

In the KEYNOTE-051 study, the median duration of follow-up was 5.2 (range, 0.3 to 28.2) months, and the ORR was 0% (95% CI, 0.0% to 41.0%). No patients achieved CR or PR, 1 patient (14.3%) had stable disease, and 5 patients (71.4%) experienced progressive disease. Tumour-specific ORR results were not analyzed in the KEYNOTE-051 study, as all but 1 patient had brain cancer.

Duration of Response

Adult

Among 126 patients in the KEYNOTE-158 study with a response, the median DOR was 63.2 (range, 1.9 to 63.9) months. Both ends of the range represent patients who were ongoing in the study without the event at the time of the data cut-off. Tumour-specific median DOR was as follows (for tumours represented by at least 10 patients): endometrial (63.2 months), gastric cancer (not reached), and small intestine cancer

(not reached). The DOR event-free probability at 6, 12, and 24 months was 95.2%, 88.5%, and 72.3%, respectively.

In the KEYNOTE-164 study, among 42 patients with a response in the overall population, the median DOR was not reached (range, 4.4 to 58.5 [patients ongoing with response] months). The DOR event-free probability at 6, 12, and 24 months was 97.6%, 95.1%, and 92.2%, respectively. Similarly, the median DOR in cohorts A (n = 20) and B (n = 22) were not reached (range, 6.2 to 58.5 [patient ongoing with response]) months and not reached (range, 4.4 to 52.4 [patient ongoing with response]) months, respectively.

Pediatric

DOR was not measured in the KEYNOTE-051 study as there were no patients with a response.

Overall Survival

Adult

A total of 230 of 373 patients (61.7%) in the KEYNOTE-158 study died, with a median OS of 19.8 (95% CI, 14.5 to 25.8) months. The OS event-free probability at 6, 12, and 24 months was 72.1%, 58.6%, and 46.5%, respectively.

In the KEYNOTE-164 study, 63 of 124 patients (50.8%) died, with a median OS of 36.1 (95% CI, 24.0 to not reached) months. The OS event-free probability at 12 and 24 months was 74.2% and 59.1%, respectively. In cohort A, 38 of 61 patients (62.3%) died, with a median OS of 31.4 (95% CI, 21.4 to 58.0) months. In cohort B, 31 of 63 patients (49.2%) died, with a median OS of 47.0 (95% CI, 19.2 to not reached) months.

Pediatric

In the KEYNOTE-051 study, 5 of 7 patients (71.4%) died, representing a median OS of 7.7 (95% CI, 1.9 to not reached) months. The OS event-free probability at 6, 12, and 18 months was 50.0%, 33.3%, 33.3%, respectively.

Progression-Free Survival

Adult

A total of 275 of 373 patients (73.7%) in the KEYNOTE-158 study experienced a PFS event, with a median PFS of 4.0 (95% CI, 2.4 to 4.3) months. The PFS event-free probability at 6, 12, and 24 months was 43.2%, 35.1%, and 28.8%, respectively.

In the KEYNOTE-164 study, 83 of 124 patients (66.9%) experienced a PFS event, with a median PFS of 4.0 (95% CI, 2.1 to 7.4) months. The PFS event-free probability at 6, 12, and 24 months was 45.8%, 37.5%, and 33.8%, respectively. In cohort A, 44 of 61 patients (72.1%) had a PFS event, with a median PFS of 2.3 (95% CI, 2.1 to 8.1) months. In cohort B, 40 of 63 patients (63.5%) had a PFS event, with a median PFS of 4.1 (95% CI, 2.1 to 18.9) months.

Pediatric
In the KEYNOTE-051 study, 6 of 7 patients (85.7%) experienced a PFS event, with a median PFS of 1.7 (95% CI, 0.4 to not reached) months. The PFS event-free probability at 6 months was 16.7% and for 12 months it was not estimable.

Health-Related Quality of Life

Adult
In the KEYNOTE-158 study, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status scale and quality of life scale score (range, 0 [worst] to 100 [best]) had a baseline mean of 64.40 (SD = 20.12) points across 364 patients. By week 9, the mean global health status scale and quality of life scale score was 67.48 (SD = 22.48) points in 265 patients, and the least squares mean change from baseline of 3.08 (95% CI, 0.32 to 5.84) points. A total of 57 patients (21.5%) experienced a deterioration in HRQoL at week 9. Deterioration was defined as a negative change of 10 points or more for each EORTC QLQ-C30 scale or subscale.

HRQoL was not assessed in the KEYNOTE-164 study.

Pediatric
HRQoL was not assessed in the KEYNOTE-051 study.

Harms Results

Adult

In the KEYNOTE-158 study, 96% of patients experienced at least 1 AE, with the most common being diarrhea (25%), fatigue (24%), nausea (21%), asthenia (20%), vomiting (19%), and pruritus (19%). At least 1 serious AE (SAE) was reported in 133 of 373 patients (36%). SAEs reported in at least 2% of patients included sepsis (2%) and pneumonia (2%). A total of 49 of 373 patients (13%) discontinued pembrolizumab in the KEYNOTE-158 study, and 20 patients (5.4%) died due to AEs.

In the KEYNOTE-164 study, 100% of patients experienced AEs, with the most frequent being fatigue (34%), diarrhea (32%), nausea (31%), abdominal pain (27%), and vomiting (26%). At least 1 SAE was reported in 56 of 124 patients (45%). SAEs reported in at least 2% of patients included dyspnea (4%), sepsis (4%), abdominal pain (3%), small intestinal obstruction (3%), urinary tract infection (3%), and ileus (2%). In total, 10 of 124 patients (8%) discontinued treatment due to AEs, and 4 of 124 patients (3%) had an AE that resulted in death.

Pediatric

In the KEYNOTE-051 study, all patients experienced at least 1 AE, with the most common being anemia (71.4%), headache (71.4%), vomiting (57.1%), decreased lymphocyte count (42.9%), pyrexia (42.9%), and rash (42.9%). At least 1 SAE was reported in 6 of 7 patients (85.7%). The most common SAE was vomiting (28.6%). A total of 2 of 7 patients (28.6%) discontinued treatment due to AEs. There were no deaths due to AEs.

Critical Appraisal

KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 are all single-arm trials, which raised several important considerations due to the lack of any relevant comparison group. Single-arm trials are inherently limited in their ability to provide causal inferences, making it difficult to distinguish between treatment effects and natural disease progression. Only ORR and DOR can be definitively attributed to the antitumour activity of pembrolizumab, as a response is unlikely to occur spontaneously. This absence of a direct comparator creates challenges in interpreting time-to-event end points (PFS or OS) and HRQoL. The open-label design may also introduce a risk of performance bias, although there is no clear evidence that this was a concern in the trials. There is a risk of bias in the measurement of the outcomes, particularly HRQoL and subjective AEs, because knowledge of the intervention can impact patient expectations and perceptions about the benefits and harms of treatment. This risk of bias in the outcome assessment was mitigated for the response outcomes (PFS, ORR, or DOR) in the KEYNOTE-158 and KEYNOTE-164 studies, where they were assessed by an independent review committee. OS is an objective outcome unlikely to be affected by such bias. The assessment of HRQoL in the KEYNOTE-158 study was at high risk of bias due to missing outcome data. Despite high adherence among available patients, there were close to 30% missing outcome data at week 9. The results of the KEYNOTE-158 study, which included adult patients with varying tumour types, showed considerable heterogeneity in response across tumour types. Many tumour types were represented by very small numbers (< 20) of patients. The interpretation of the potential differences in response across small samples of different cancer types is therefore challenging, as these may represent either actual differences in treatment effects or natural statistical variation. The Health Canada review report also acknowledged the variation in therapeutic benefit across tumour types, citing small sample sizes and that the number of patients recruited each histology reflects the natural prevalence of the MSI-H and/or dMMR biomarker and that enrolling a larger number of patients may not have been feasible given the broad indication. The Health Canada review report also noted that the use of a pooled ORR and DOR in the KEYNOTE-158 study is reasonable for pursuing a tissue-agnostic indication. There was a small degree of heterogeneity across cohorts A and B in the KEYNOTE-164 study. In the KEYNOTE-051 study, only 7 patients were included, which limits the reliability of assessing the efficacy and safety of pembrolizumab.

In the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies, patients who had previously received anti–PD-1, anti–PD-L1, or anti–PD-L2 drugs were excluded. Clinical experts consulted by CDA-AMC indicated that only a small proportion of patients in Canada would meet this eligibility criterion, as most MSI-H and/or dMMR solid tumours are treated with anti–PD-1 or anti–PD-L1 drugs as SOC in earlier lines of therapy. This limits the generalizability of the trial results to the smaller population of patients with cancer with MSI-H or dMMR tumours in Canada who would not have received anti–PD-1 or anti–PD-L1 drugs in an earlier line. For cancers such as colorectal, endometrial, and non–small cell lung, pembrolizumab is already used in earlier treatment stages. Additionally, other ICIs are widely used in solid tumours like gastric, mesothelioma, breast, small cell lung, and biliary tract cancers, regardless of MSI-H or dMMR status. The KEYNOTE-051 study included only 7 patients, primarily with brain cancers which also limits the generalizability of findings. This small cohort is unlikely to adequately represent the broader patient population in terms of age, sex, performance status, disease stage, and other factors. Furthermore, HRQoL

was not assessed in 2 trials (KEYNOTE-164 and KEYNOTE-051), thus, the generalizability of any HRQoL results to other indications or populations remains uncertain.

GRADE Summary of Findings and Certainty of the Evidence

For the pivotal studies identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for the outcomes considered most relevant to inform CDA-AMC's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE working group. Although GRADE guidance is not available for noncomparative studies, the review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies (or populations), indirectness, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials starts at very low certainty with no opportunity for rating up.

Table 3 presents the GRADE summary of findings for pembrolizumab assessed in the KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051 studies. The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- response (ORR [CR and PR], and DOR)
- survival (OS and PFS)
- HRQoL (EORTC QLQ-C30)
- notable harms (AEs of special interest: immune-mediated AEs, infusion-related reactions).

Table 3: GRADE Summary of Findings for Pembrolizumab for Patients With Unresectable or Metastatic MSI-H and/or dMMR Solid Tumours

Outcome and follow-up (months)	Patients (studies), N	Effect	Certainty[a]	What happens
Response (RECIST 1.1)				
ORR (CR or PR) Median follow-up = 17 (range, 0.2 to 71.4)	373 adults with mixed solid tumours (1 single-arm trial)	33.8 per 100 (95% CI, 29.0 per 100 to 38.8 per 100)	Very low[b,c]	The evidence is very uncertain about the effects of pembrolizumab on ORR vs. any comparator.
ORR (CR or PR) Median follow-up = 31.4, (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	124 adults with colorectal cancer (1 single-arm trial)	33.9 per 100 (95% CI, 25.6 per 100 to 42.9 per 100)	Very low	The evidence is very uncertain about the effects of pembrolizumab on ORR vs. any comparator.
ORR (CR + PR) Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	0 per 100 (95% CI, 0 per 100 to 41.0 per 100)	Very low	The evidence is very uncertain about the effects of pembrolizumab on ORR vs. any comparator.
CR Median follow-up = 17 (range, 0.2 to 71.4)	373 adults with mixed solid tumours (1 single-arm trial)	10.7 per 100 (95% CI, 7.8 per 100 to 14.3 per 100)	Very low[b,c]	The evidence is very uncertain about the effects of pembrolizumab on CR vs. any comparator.
CR Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	124 adults with colorectal cancer (1 single-arm trial)	8.9 per 100 (95% CI, NR)	Very low	The evidence is very uncertain about the effects of pembrolizumab on CR vs. any comparator.
CR Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	0 per 100 (95% CI, 0 per 100 to 41 per 100)	Very low	The evidence is very uncertain about the effects of pembrolizumab on CR vs. any comparator.
Duration of response among responders				
DOR Median follow-up = 17 (range, 0.2 to 71.4)	126 adults with mixed solid tumours (1 single-arm trial)	Median = 63.2 months (range, 1.9 to 63.9[d] months) Event-free probability: 12 months: 88.5 per 100 (95% CI, NR) 24 months: 72.3 per 100 (95% CI, NR)	Very low[b,c]	The evidence is very uncertain about the effects of pembrolizumab on DOR vs. any comparator.

Outcome and follow-up (months)	Patients (studies), N	Effect	Certainty[a]	What happens
DOR Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	42 adults with colorectal cancer (1 single-arm trial)	Median = not reached (range, 4.4 to 58.5[d] months) Event-free probability: 12 months: 95.1 per 100 (95% CI, NR) 24 months: 92.2 per 100 (95% CI, NR)	Very low	The evidence is very uncertain about the effects of pembrolizumab on DOR vs. any comparator.
DOR Median follow-up = 5.2 (range, 0.3 to 28.2)	0 children with mixed solid tumours (1 single-arm trial)	NA	NA	There is no evidence about the effects of pembrolizumab on DOR; no patient had a response.
OS and PFS				
OS Median follow-up = 17 (range, 0.2 to 71.4)	373 adults with mixed solid tumours (1 single-arm trial)	Median = 19.8 months (95% CI 14.5 to 25.8) Event-free probability: 12 months: 58.6 per 100 (95% CI, NR) 24 months: 46.5 per 100 (95% CI, NR)	Very low[b,c]	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.
OS Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	124 adults with colorectal cancer (1 single-arm trial)	Median = 36.1 months (95% CI 24.0 months to not estimable) Event-free probability: 12 months: 74.2 per 100 (95% CI, NR) 24 months: 59.1 per 100 (95% CI, NR)	Very low	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.
OS Follow-up = not reported Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	Median = 7.7 months (95% CI 1.9 months to not estimable) Event-free probability: 12 months: 33.3 per 100 (95% CI, NR) 24 months: not estimable	Very low	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.
PFS Median follow-up = 17 (range, 0.2 to 71.4) months	373 adults with mixed solid tumours (1 single-arm trial)	Median = 4.0 months (95% CI, 2.4 to 4.3 months) Event-free probability: 12 months: 35.1 per 100 (95% CI, NR) 24 months: 28.8 per 100 (95% CI, NR)	Very low[b,c]	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.
PFS Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A	124 adults with colorectal cancer (1 single-arm trial)	Median = 4.0 months (95% CI 2.1 to 7.4 months) Event-free probability:	Very low	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.

Outcome and follow-up (months)	Patients (studies), N	Effect	Certainty[a]	What happens
Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B		12-month rate: 37.5 per 100 (95% CI, NR) 24-month rate: 33.8 per 100 (95% CI, NR)		
PFS Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	Median = 1.7 months (95% CI, 0.4 months to not estimable) Event-free probability 6-month rate: 16.7 per 100 (95% CI, NR) 12-month rate: not estimable	Very low[b]	The evidence is very uncertain about the effects of pembrolizumab on OS vs. any comparator.
HRQoL[b]				
EORTC QLQ-C30 (global health status scale and quality of life scale score), least squares mean change from baseline, points (0 [worst] to 100 [best]) Follow-up = to week 9	364 adults with mixed solid tumours (1 single-arm trial)	3.08 (95% CI, 0.32 to 8.84)	Very low[e]	The evidence is very uncertain about the effects of pembrolizumab on EORTC QLQ-C30 (global health status scale and quality of life scale score) vs. any comparator.
Harms				
Patients with ≥ 1 AEOSI Median follow-up = 17 (range, 0.2 to 71.4) months	373 adults with mixed solid tumours (1 single-arm trial)	22 per 100	Very low[c]	The evidence is very uncertain about the effects of pembrolizumab on AEOSIs vs. any comparator.
Patients with ≥ 1 AEOSI Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	124 adults with colorectal cancer (1 single-arm trial)	30 per 100	Very low	The evidence is very uncertain about the effects of pembrolizumab on AEOSIs vs. any comparator.
Patients with ≥ 1 AEOSI Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	28.6 per 100	Very low	The evidence is very uncertain about the effects of pembrolizumab on AEOSIs vs. any comparator.
Patients with ≥ 1 SAE Median follow-up = 17 (range, 0.2 to 71.4) months	373 adults with mixed solid tumours (1 single-arm trial)	36 per 100	Very low[c]	The evidence is very uncertain about the effects of pembrolizumab on SAEs vs. any comparator.

Outcome and follow-up (months)	Patients (studies), N	Effect	Certainty[a]	What happens
Patients with ≥ 1 SAE Median follow-up = 31.4 (range, 0.2 to 65.2) for cohort A Median follow-up = 52.7 (range, 0.1 to 56.6) for cohort B	124 adults with colorectal cancer (1 single-arm trial)	45 per 100	Very low	The evidence is very uncertain about the effects of pembrolizumab on SAEs vs. any comparator.
Patients with ≥ 1 SAE Median follow-up = 5.2 (range, 0.3 to 28.2)	7 children with mixed solid tumours (1 single-arm trial)	85.7 per 100	Very low	The evidence is very uncertain about the effects of pembrolizumab on SAEs vs. any comparator.

AEOSI = adverse events of special interest (immune-mediated events and infusion-related reactions); CI = confidence interval; CR = complete response; dMMR = mismatch repair deficient; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GRADE = Grading of Recommendations, Assessment, Development and Evaluation; HRQoL = health-related quality of life; MSI-H = microsatellite instability-high; NA = no assessment; NE = not evaluable; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1; SAE = serious adverse event; vs. = versus.

[a]In the absence of a comparator group, conclusions about efficacy relative to any comparator cannot be drawn and the certainty of evidence is started at very low and cannot be rated up.

[b]Rated down 1 level for serious study limitations as results are based on an interim analysis. There is a risk of overestimating treatment effects.

[c]Rated down 1 level due to inconsistency for ORR, CR, and DOR. The KEYNOTE-158 study included a mixed solid tumour population. There was heterogeneity in the effects across different solid tumours for these outcomes; there was not subgroup information for OS, PFS, nor harms to make this judgment.

[d]For DOR in the patient was ongoing in the study without the event at the time of analysis.

[e]HRQoL data were not reported for the KEYNOTE-164 study (adults with colorectal cancer) and the KEYNOTE-051 study (children with mixed solid tumours). Rated down 2 levels for study limitations due to risk of bias in assessment of the outcome (open-label with subjective assessment) and due to missing outcome data.

Source: The KEYNOTE-158 CSR, KEYNOTE-164 CSR, and KEYNOTE-051 CSR.

Long-Term Extension Studies

No long-term extension studies were provided by the sponsor.

Indirect Comparisons

To support the economic evaluation for tumour-agnostic submissions, the sponsor submitted several ITCs, each focusing on comparing pembrolizumab to other relevant treatments in 4 different solid tumour types: colorectal, endometrial, small intestine, and gastric cancers. In the colorectal cancer ITC, pembrolizumab was compared to pooled chemotherapy and anti-vascular endothelial growth factor (*VEGF*) plus chemotherapy using naive indirect comparison, and trifluridine and tipiracil (TAS-102) via unanchored MAIC. In the endometrial cancer ITC, an unanchored MAIC was conducted to compare pembrolizumab with the treatment of physician's choice (TPC) (doxorubicin or paclitaxel). For the small intestine cancer ITC, a naive indirect comparison was used to compare pembrolizumab with nanoparticle albumin-bound paclitaxel (nab-paclitaxel). The gastric cancer ITC conducted a naive indirect comparison to compare pembrolizumab with leucovorin calcium (folinic acid) + fluorouracil + irinotecan hydrochloride (FOLFIRI), ramucirumab plus paclitaxel, ramucirumab monotherapy, paclitaxel, and irinotecan.

Efficacy Results

Colorectal Cancer

The colorectal cancer ITC included 2 naive ITCs comparing pembrolizumab to chemotherapy and chemotherapy plus anti-*VEGF* and 1 MAIC comparing pembrolizumab to TAS-102. Only PFS and OS were reported. In both naive ITCs the pembrolizumab group had a lower median age and had fewer patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 compared to the comparator group. In the unanchored MAIC, matching factors included age, sex, and ECOG PS.

The naive ITC for OS estimated a hazard ratio (HR) of 0.30 (95% CI, 0.24 to 0.39) when compared to chemotherapy alone, and 0.37 (95% CI, 0.29 to 0.48) when compared to chemotherapy in combination with an anti-*VEGF*, favouring pembrolizumab. The naive ITC for PFS estimated an HR of 0.43 (95% CI, 0.34 to 0.54) when compared to chemotherapy alone and 0.53 (95% CI, 0.42 to 0.67) when compared to chemotherapy in combination with an anti-*VEGF*, favouring pembrolizumab.

In the unanchored MAIC comparing pembrolizumab to TAS-102, the estimated HR of OS was 0.21 (95% CI, 0.15 to 0.30) and for PFS was 0.32 (95% CI, 0.23 to 0.45), both favouring pembrolizumab.

Endometrial Cancer

For the endometrial cancer ITC, an unanchored MAIC was conducted to compare pembrolizumab to TPC (doxorubicin or paclitaxel). ORR, PFS, and OS were reported. Matching factors included age, race, ECOG PS, number of prior lines of therapy, and histology status.

In the unanchored MAIC, the estimated response ratio was 4.27 (95% CI, 2.11 to 8.64) for ORR, favouring pembrolizumab. The estimated HR was 0.31 (95% CI, 0.19 to 0.53) for PFS and 0.24 (95% CI, 0.13 to 0.45) for OS, both favouring pembrolizumab compared to TPC. In each case, sensitivity analyses yielded results that aligned with the main analysis in both the direction and magnitude of effect.

Small Intestine Cancer

For the small intestine cancer ITC, a naive ITC was conducted to compare pembrolizumab to nab-paclitaxel. Only PFS and OS were presented. The pembrolizumab group had a similar median age and a greater number of patients with an ECOG PS of 0 compared to the comparator group.

The naive ITC estimated an HR of 0.18 (95% CI, 0.07 to 0.45) for OS and 0.22 (95% CI, 0.09 to 0.52) for PFS, both favouring pembrolizumab.

Gastric Cancer

For the gastric cancer ITC, a naive ITC was conducted to compare pembrolizumab to FOLFIRI, ramucirumab plus paclitaxel, ramucirumab monotherapy, paclitaxel, and irinotecan. Only OS and PFS were presented. The pembrolizumab group had a higher median age and a greater number of patients with an ECOG PS of 0 patients compared to all comparator groups.

For OS, the naive ITC estimated an HR of 0.43 (95% CI, 0.26 to 0.69) versus FOLFIRI, 0.35 (95% CI, 0.22 to 0.53) versus ramucirumab, 0.44 (95% CI, 0.29 to 0.66) versus ramucirumab plus paclitaxel, and 0.38 (95% CI, 0.26 to 0.56) versus irinotecan, all favouring pembrolizumab. The evidence was insufficient to demonstrate a difference between pembrolizumab and paclitaxel.

For PFS, the naive ITC estimated an HR of 0.43 (95% CI, 0.28 to 0.67) versus FOLFIRI, 0.37 (95% CI, 0.24 to 0.58) versus ramucirumab, 0.45 (95% CI, 0.31 to 0.65) versus ramucirumab plus paclitaxel, and 0.33 (95% CI, 0.23 to 0.47) versus irinotecan, all favouring pembrolizumab. The evidence was insufficient to demonstrate a difference between pembrolizumab and paclitaxel.

Harms Results

No harms were evaluated in the submitted ITCs.

Critical Appraisal

The sponsor conducted systematic literature reviews to identify studies for inclusion in 4 ITCs. Although these reviews appeared comprehensive, an a priori protocol was not provided, which prevented the evaluation of the risk of selective reporting based on the magnitude, direction, or statistical significance of the effects. The included comparator studies were deemed to be primarily at low or unclear risk of bias. Additionally, the searches for colorectal, endometrial, and small intestine cancer were conducted between July and August 2023. It is not clear whether new relevant studies would have become available since this time. Violations of the proportional hazards assumption in most comparisons further undermine the validity of the estimated HRs.

The majority of ITCs, except for the endometrial cancer ITC, included comparator studies that did not evaluate MSI-H or dMMR status, as this was not feasible. According to clinical experts consulted by the review team, patients with dMMR or MSI-H status typically have a worse prognosis compared to those whose tumours are not MSI-H or dMMR, although prognosis varies based on tumour type. Without the dMMR or MSI-H status of patients in the comparator arms, the impact cannot be quantified. Naive indirect comparisons were used due to substantial reductions in effective samples size when attempting to match

baseline characteristics; however, such methods are highly susceptible to confounding bias from differences in patient characteristics and study methodologies. Unanchored MAICs were employed in other cases. These matched on a small number of factors. Although these factors were relevant according to clinical experts consulted by the review team, it is unlikely that these represent all known and unknown prognostic and effect modifying variables. As a result, there is a high risk of residual confounding. Small effective samples sizes after matching and differences in patient characteristics, such as ECOG PS scores, reduce the reliability of the results.

The colorectal, endometrial, and gastric cancer comparisons may no longer be highly relevant due to changes in the current SOC, as patients are likely to have already received immunotherapy in the first-line setting. This shift means that comparisons may not accurately reflect current patient populations or outcomes. Additionally, the analyses did not assess harms or HRQoL outcomes.

Studies Addressing Gaps in the Evidence From the Systematic Review

Description of Studies

The IRRDC data came from an observational, registry-based study of pediatric patients (N = 18, including 1 patient aged 24 years with a total of 20 tumours) with confirmed or suspected DNA replication repair deficiency. The type of cancer patients had was categorized as either central nervous system tumours or noncentral nervous system tumours. Patients were treated with pembrolizumab between May 2015 and March 2019. Objective tumour response was the outcome of interest. The data cut-off date was March 2022.

The WES data were obtained from across the clinical development program and data were evaluated from 7 trials of pembrolizumab monotherapy. Patients (N = 21) consisted of adults (median age was 65 years) with advanced solid tumours (gastric or gastroesophageal junction cancer, prostate cancer, cholangiocarcinoma, head and neck squamous cell carcinoma, or triple-negative breast cancer) who had previously received at least 1 systemic treatment. End points of interest included ORR, DOR, PFS, and OS.

Efficacy Results

From the IRRDC dataset (pediatric patients), 17 tumours had measurable disease at baseline (3 tumours were not measurable). Based on the 17 tumours, 4 patients (23.5%) experienced objective treatment response, and 9 patients (52.9%) experienced stable disease. Four tumours (23.5%) continued to progress. Furthermore, 11 of 20 tumours (55.0%) had not progressed by 6 months and 15 of 18 patients (83.3%) were alive at 12 months.

In the WES dataset (adults), ORR was 52.4% (95% CI, 29.8% to 74.3%). Median PFS was 17.8 months (95% CI, lower limit of 4.3 months and upper limit not reached) while PFS rates were 56.7% and 45.9% at 12 and 36 months (there were no CIs), respectively. Median DOR and median OS were not achieved. The OS rates were 66.7% and 61.5% at 12 and 24 months (there were no CIs), respectively.

Harms Results

Collection of safety data were not a specific intent of the IRRDC study (pediatric patients), therefore harms data are limited. According to the summary of clinical safety, no new safety signals were identified, and

pancreatitis was the only harm that occurred in more than 1 patient (N = 2). The following harms were reported in 1 patient each: diarrhea, pneumonia, gastritis, dry skin, transient hypothyroidism, tolerable intermittent elevations in liver enzymes, skin rash, severe headaches, and seizure.

Safety data were not reported for the WES dataset (adults).

Critical Appraisal

Although the datasets provide more efficacy information on pediatric and adult populations with MSI-H cancers, they are small, noncomparative, and do not address the lack of direct or indirect evidence for pembrolizumab in this setting. Moreover, no protocols were available for review and methods were not well described, thus, there is a risk of selective reporting. It was noted that for the IRRDC study, treatment of patients was at the discretion of the clinical team and changes to dosages may not have been standardized across patients making it challenging to interpret the results. Outcome measures were reviewed centrally by a blinded, independent committee, which can lower the risk of bias in the outcome measurement. The tumour types in these datasets generally cover the same as those in the pivotal trials (i.e., the datasets provide limited additional information to what is already available). Based on the available information, more than one-half of patients had an ECOG PS of 1, which may not be representative of patients who were not as healthy and who could receive pembrolizumab for MSI-H or dMMR tumours in clinical practice in Canada. There were few pediatric patients contributing to the pivotal trial evidence and the IRRDC dataset provides a modest increase to the available information for younger patients. There was limited reporting of harms and only for the IRRDC dataset; assessments of HRQoL were not reported. Despite the use of real-world registry data, which could improve the generalizability of the results, the internal and external validity issues minimize the use and applicability of the findings to clinical practice.

Ethical Considerations

Patient group, clinician group, and drug plan input, as well as consultation with clinical experts, were reviewed to identify ethical considerations specific to the use of pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Diagnosis, Treatment, and Experiences of People Living With MSI-H or DMMR Solid Tumours

- As reported in the Testing Procedure Considerations section of the Clinical Review Report, testing for MSI-H and/or dMMR alterations is routinely performed across Canada for all adult patients with solid tumour types for which immunotherapy or other targeted treatment is already SOC for metastatic disease. However, testing is not routinely performed in the context of pediatric or adult cancers where targeted therapies (including pembrolizumab) are currently not authorized or reimbursed. Should pembrolizumab be funded for the proposed tumour-agnostic indication, testing all people

with unresectable or metastatic solid tumours that could have MSI-H and/or dMMR alterations would enable equitable access to targeted therapy. Testing for such alterations can also benefit patients and families by providing opportunities to pursue genetic testing and counselling for related hereditary tumour syndromes.

- The clinician groups and clinical experts reported that people with unresectable or metastatic MSI-H and/or dMMR solid tumours that have progressed following prior treatment typically only have chemotherapy-based regimens associated with limited clinical benefit and significant cumulative toxicity as treatment options. Living with and undergoing treatment for unresectable or metastatic MSI-H or dMMR solid tumours causes substantial physical and psychosocial burdens that adversely impact patients' and their caregivers' HRQoL. Patient group input detailed how physical symptoms and side effects of treatments (especially chemotherapy) can be intolerable and limit functioning in daily activities. Psychosocial impacts of these cancers include experiencing anxiety, fear, sadness, and hopelessness about the future. Additional impacts include a reduced ability to engage in employment, exercise, and social activities.
- Patients with MSI-H and/or dMMR tumour types for which pembrolizumab is currently not funded may experience emotional distress knowing that a targeted therapy such as pembrolizumab exists, but that it is only funded currently for selected MSI-H and/or dMMR tumour types. People with such cancers have a high unmet need and desire for effective treatments with manageable toxicity that can increase their OS and PFS and improve HRQoL.

Clinical Evidence Used in the Evaluation of Pembrolizumab

- The safety and efficacy of pembrolizumab was evaluated in 3 single-arm, multicentre, nonrandomized, open-label, multicohort studies: KEYNOTE-158, KEYNOTE-164, and KEYNOTE-051. The KEYNOTE-158 study was a phase II, basket trial that enrolled 373 adult patients with various types of MSI-H and/or dMMR tumours. The KEYNOTE-164 study was a phase II trial that enrolled 124 adults with MSI-H and/or dMMR colorectal cancer. The phase I and II KEYNOTE-051 study basket trial included 7 pediatric patients with MSI-H and/or dMMR tumours, 6 of whom had brain tumours. ITCs for colorectal, endometrial, small intestine, and gastric cancers evaluated comparative efficacy versus SOC treatments among adult patients. These ITCs consisted of naive indirect comparisons and unanchored MAICs. The Clinical Review Report provides further details on these 3 studies and the ITCs.
- Durable response to treatment, improved OS and PFS, and improved HRQoL are important outcomes to patients and clinicians. The clinical experts believed that the KEYNOTE-158 and KEYNOTE-164 studies demonstrated clinically meaningful and durable improvements in ORR compared to what is typically observed with SOC treatments. They also felt the evidence regarding OS and PFS was promising based on the natural history of the disease and their clinical practice experience. However, the Clinical Review Reports that there is uncertainty regarding the efficacy of pembrolizumab relative to SOC across tumour sites due to the trials' single-arm designs. ITCs suggested pembrolizumab improved OS and PFS compared to SOC. However, the Clinical Review Reports that the ITCs had significant limitations that impacted the validity of the findings

and precluded definitive conclusions about comparative efficacy. Responses to pembrolizumab were heterogenous across specific cancer types, and patients with some cancer types had limited representation or small sample sizes in the trials, limiting the generalizability of the results.

- None of the trials identified new safety signals. However, because the ITCs did not include comparative safety data, the safety of pembrolizumab compared to SOC treatments for MSI-H and/or dMMR solid tumours is unknown. The clinical experts emphasized the breadth of experience using pembrolizumab in other cancers and perceived that pembrolizumab is better tolerated and has fewer and less severe side effects than conventional chemotherapy. The median follow-up times at data cut-off for ORR in the clinical trials ranged from 52.7 months (for the cohort of participants in the KEYNOTE-164 study who had received at least 1 line of prior systemic SOC therapy for colorectal cancer) and 5.2 months (for participants in the KEYNOTE-051 study). Follow-up times for ORR of individual participants across all trials ranged from 0.1 to 71.4 months. The clinical experts highlighted that further safety data may not be necessary to inform decision-making, given the body of pre-existing research on the use of pembrolizumab for various cancers. However, they acknowledged the potential benefit of the ongoing collection of efficacy data on its use for the proposed indication (e.g., through registries) to further support decision-making in clinical and health systems.
- The available evidence also raises ethical considerations related to limited representation or underrepresentation in clinical trials. It is difficult to ascertain the potential benefit or harms of pembrolizumab in pediatric patients, given the small number of participants and single-arm design of the KEYNOTE-051 study. Clinical experts also acknowledged the underrepresentation of racialized persons (with 77% of pooled participants with MSI-H and/or dMMR tumours in the KEYNOTE-158 and KEYNOTE-164 studies [14% Asian, 5% other or missing, and 3% Black or African American], and 86% in the KEYNOTE-051 study reported as being white [14% Asian]). Cancers where MSI-H is more common (i.e., colorectal, endometrial, and gastric cancer) had the greatest representation in the KEYNOTE-158 and KEYNOTE-164 data, while the representation of other cancers in this data were lower. The experts and patient group input reported that these groups frequently have underrepresentation or limited representation in clinical trials and research about cancer therapies. Underrepresentation or limited representation of children, racialized persons, and people with rarer MSI-H and/or dMMR tumours may limit the generalizability of findings to these groups.

Clinical Use of Pembrolizumab

- The clinical experts reported they would use pembrolizumab for the treatment of adult and pediatric patients with metastatic, unresectable MSI-H or dMMR solid tumours who have progressed following prior treatment and who have no effective and tolerable alternative treatment options. They supported this tumour-agnostic indication, emphasizing the substantial unmet need for effective and tolerable treatments for these patients despite uncertain, although promising, evidence for patient-important and clinician-important outcomes such as durable improvement in ORR and improved OS and PFS.
- Clinical expert and patient group input provided insight into how pembrolizumab could lead to improvements in HRQoL for patients. Patients with MSI-H or dMMR solid tumours reported positive experiences with pembrolizumab, which they described as life-changing when reducing tumour

burden and, in turn, alleviating cancer symptoms and prolonging survival. Patients who received treatment with pembrolizumab reported experiencing reduced physical and psychosocial burdens related to cancer. They appreciated the ease of use of pembrolizumab compared to chemotherapy: fewer additional medications to manage AEs, quicker infusion times, and no need for infusion pumps at home. Clinical experts and patients generally perceived adverse effects associated with the use of pembrolizumab as manageable, especially when compared to chemotherapy.

- The experts and patient group input noted that reimbursing pembrolizumab for the proposed tumour-agnostic indication could alleviate current inequities in access to treatment options for people with MSI-H and/or dMMR tumours where treatment with pembrolizumab is not currently reimbursed.
- The clinical experts anticipated that most adult patients with MSI-H and/or dMMR solid tumours eligible for pembrolizumab in Canada would not have trouble accessing the treatment, were it reimbursed, given that the infrastructure required to prescribe, administer, and monitor the drug is already in place. However, since pembrolizumab is administered in hospitals or outpatient settings via a 30-minute IV infusion, people without access to transportation or living far from these settings may experience barriers to access. While these considerations are not novel in the context of cancer treatment, they emphasize the importance of providing patient supports to facilitate equitable access.
- The clinical experts anticipated that children would experience disproportionate difficulty accessing pembrolizumab, as fewer pediatric providers would have experience with the treatment. These providers may also require educational supports to identify and treat eligible patients. Pediatric patients would likely receive their infusions at specialist centres, which may be especially challenging to access for those living far away.
- To promote autonomous, informed decision-making, robust consent conversations should include disclosures about the uncertain benefits and risks of treatment with pembrolizumab. Clinical experts reported they would prescribe pembrolizumab for eligible patients from groups that were underrepresented or had limited representation in clinical trials (i.e., eligible racialized persons, children, and people with rare tumour types) due to unmet need. However, clinicians should disclose limitations in evidence available for these groups as well as their limited experience using pembrolizumab to treat children and people with cancers for which it formerly was not authorized or reimbursed. Consent conversations should also consider the vulnerabilities for patients with life-limiting conditions and uphold appropriate processes for obtaining consent and assent from pediatric patients. Disclosing that pembrolizumab is not a curative therapy may also be important to mitigate harms associated with unmet expectations. Finally, people without satisfactory alternative treatment options and who are not eligible for pembrolizumab may need appropriate psychosocial supports.

Health Systems Impact

- The Pharmacoeconomic Report found that pembrolizumab may be cost-effective at a $50,000 per QALY gained threshold, relative to current SOC. However, due to the absence of direct evidence or robust indirect evidence, there is uncertainty regarding the magnitude of benefit pembrolizumab provides versus SOC across all tumour sites. In some tumour sites, no evidence is available.

This makes the estimation of cost-effectiveness highly uncertain and, in turn, may challenge understandings of opportunity costs and decision-making about the fair allocation of limited health system resources. Further collection of long-term data on efficacy and safety outcomes following pembrolizumab's use for the proposed indication in the real world may better inform this decision-making.

- As detailed in the Testing Procedure Considerations section, the clinical experts anticipated there would only be a small number of patients who would require MSI-H and/or dMMR testing but would not already receive it as standard care. For this reason, they did not anticipate additional testing required for implementing pembrolizumab for the proposed indication would substantially increase health system resource utilization. Still, the Pharmacoeconomic Report details that while testing costs associated with the tumour-agnostic indication are uncertain, costs would vary substantially by tumour type. Given the very low proportion of patients with MSI-H and/or dMMR status in some tumour sites, testing costs to identify 1 patient can be high. However, making MSI-H and/or dMMR testing standard for potentially eligible children and people with cancers for which targeted therapy is not already available would ensure these groups have equal opportunity to benefit from pembrolizumab.
- The experts did not anticipate the administration of pembrolizumab for the proposed indication in Canada would require new health system structures or substantially greater use of health system resources. Providers already administer pembrolizumab and similar immunotherapies to adults with numerous solid tumour types in hospitals and clinics across Canada. Additionally, clinical experts anticipated that many otherwise eligible patients with common tumour types may have already accessed pembrolizumab or other ICIs in earlier lines of therapy.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options
Treatment	Pembrolizumab
Dose regimen	200 mg every 3 weeks (every 3 weeks) for up to 35 cycles or until progression
Submitted price	Pembrolizumab: $4,400 per 100 mg/4 mL vial
Submitted treatment cost	$8,800 per cycle ($308,000 for 35 cycles)

Component	Description
Comparators	SOC defined by tumour site: • colorectal – pooled FOLFOX-FOLFIRI; anti-*VEGF* + chemotherapy; trifluridine-tipiracil • endometrial – paclitaxel; doxorubicin • gastric – paclitaxel; irinotecan; ramucirumab + paclitaxel; FOLFIRI; ramucirumab • small intestine – nanoparticle albumin-bound paclitaxel; anti-*VEGF* + chemotherapy; taxane-based
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	KEYNOTE-158 and KEYNOTE-164 studies ITCs for pembrolizumab and comparator treatments based on tumour site
Key limitations	• The comparative clinical efficacy of pembrolizumab vs. SOC across all tumour sites is uncertain due to the lack of head-to-head clinical trial evidence for the target population. The model relied on indirect treatment comparisons that were associated with limitations and may not accurately reflect the relative effect of pembrolizumab vs. current SOC. • The long-term survival benefit associated with pembrolizumab is uncertain. The sponsor assumed the mortality risk for some patients would eventually match the general population. This would indicate that some patients are not only cured but there is no excess mortality associated with having had metastatic cancer. There is no evidence to support this assumption and was considered unlikely by clinical experts consulted for this review. • The dosing of pembrolizumab (fixed) adopted by the sponsor is not aligned with the public drug plan's implementation strategy (weight-based dosing). Weight-based dosing is associated with a lower cost under the assumption of vial sharing. • The sponsor's approach to estimate time on treatment was different for pembrolizumab vs. SOC. The approach assumed individuals who received pembrolizumab could discontinue before progression whereas individuals who received SOC would be treated until progression. This underestimates the incremental cost of pembrolizumab vs. SOC. • The sponsor assumed no additional testing costs as testing is part of routine practice. Based on the submitted budget impact analysis, testing uptake may increase due to pembrolizumab funding as testing is not routine across all tumour sites.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by making changes in model parameter values and assumptions, in consultation with clinical experts: alternative distributions to extrapolate long-term OS data for those receiving pembrolizumab; applied weight-based dosing 2 mg/kg for pembrolizumab; and, set TTD equal to PFS up to 104 weeks after which pembrolizumab was discontinued. • In the CDA-AMC base case, pembrolizumab is associated with a weighted ICER of $32,001 per QALY gained compared to SOC (incremental costs: $77,054; incremental QALYs: 2.41) across all tumour sites.

CDA-AMC = Canada's Drug Agency; dMMR = mismatch repair deficient; FOLFIRI = leucovorin calcium (folinic acid) + fluorouracil + irinotecan hydrochloride; FOLFOX = leucovorin calcium (folinic acid) + fluorouracil + oxaliplatin; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; LY = life-year; MSI-H = microsatellite instability-high; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; SOC = standard of care; TTD = time to discontinuation; vs. = versus.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the market uptake of pembrolizumab is associated with uncertainty but was likely overestimated by the sponsor in tumour sites where ICIs (e.g., pembrolizumab or nivolumab) are available in previous lines of therapy, and drug

acquisition costs were updated as outlined in the CDA-AMC critical appraisal of the cost-utility model. The CDA-AMC base case estimated that the 3-year budget impact of reimbursing pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options would cost $4,480,035 in year 1; $7,614,489 in year 2; and $8,777,897 in year 3, for a 3-year cumulative total of $20,872,421 across all tumour sites.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villneuve, and Danica Wasney.

Meeting date: December 4, 2024

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Canada's Drug Agency
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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.