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Reimbursement Review

Pembrolizumab (Keytruda)

Indication: In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma

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, in combination with pemetrexed and platinum chemotherapy, be reimbursed by public drug plans for the treatment of unresectable advanced or metastatic malignant pleural mesothelioma (MPM), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda plus pemetrexed and platinum chemotherapy should only be covered to treat adult patients who have not received prior systemic treatment for MPM and who are in relatively good health (as measured by performance status) at the start of treatment.

What Are the Conditions for Reimbursement?

Keytruda plus pemetrexed and platinum chemotherapy should only be reimbursed if it is prescribed by clinicians with experience in immune-oncology and in treating MPM, and if the cost is not higher than the drug program cost of treatment with nivolumab plus ipilimumab.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda plus pemetrexed and platinum chemotherapy compared with chemotherapy alone improved overall survival in adults with unresectable advanced or metastatic MPM with good performance status and who had not received prior MPM treatment.
- Based on the CDA-AMC assessment of the health economic evidence, Keytruda does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Keytruda compared with nivolumab plus ipilimumab over the duration of treatment.
- Based on public list prices, Keytruda is estimated to save the public drug plans approximately $488,202 over the next 3 years. However, the actual budget impact is uncertain and dependent on relative dose intensity assumptions, the dosing regimen, and the market share of pembrolizumab.

Summary

Additional Information

What Is MPM?

MPM is a rare cancer of the pleural mesothelium, a layer of cells that surrounds the lungs. Exposure to asbestos, often many years before diagnosis, is implicated in most cases. In Canada (excluding Quebec), there were 460 cases of MPM in 2019, mostly in men. MPM is an aggressive cancer. The prognosis of patients diagnosed with MPM is poor, with a median survival (when half of people with this cancer are still alive) of approximately 1 year.

Unmet Needs in MPM

Patients often have advanced disease by the time symptoms develop and are not candidates for surgery. Despite chemotherapy, survival is still poor. New treatment options for MPM that can allow patients to live longer with a good quality of life are needed.

How Much Does Keytruda Plus Chemotherapy Cost?

Treatment with Keytruda plus pemetrexed and platinum chemotherapy is expected to cost between $9,655 and $10,235 per patient every 21 days.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab, in combination with pemetrexed and platinum chemotherapy, be reimbursed for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

pERC determined that there is a need for additional first-line treatment options for unresectable advanced or metastatic MPM, given the poor prognosis and substantial morbidity of this disease. Evidence from 1 phase II/III, open-label, randomized controlled trial (RCT) (the KEYNOTE-483 trial, N = 440) demonstrated that pembrolizumab in combination with chemotherapy is likely to extend how long people live compared with chemotherapy alone. The Kaplan-Meier estimated probability of overall survival (OS) at 24 months and 36 months was 6.2% (95% confidence interval [CI], –2.8% to 15.2%) and 8.1% (95% CI, –0.2% to 16.4%) higher, respectively, in those who received pembrolizumab plus chemotherapy compared with chemotherapy alone. The probability of OS at both time points exceeded the threshold of 5% considered clinically important by the consulted clinical experts, although the lower bounds of the CIs crossed zero, introducing uncertainty. The hazard ratio (HR) for OS favoured combination therapy with pembrolizumab plus chemotherapy compared with chemotherapy alone (HR = 0.79; 95% CI, 0.64 to 0.98). Regarding health-related quality of life (HRQoL), pembrolizumab plus chemotherapy may result in little to no difference in HRQoL compared to chemotherapy alone, although this is based on low-certainty evidence that was associated with imprecision and indirectness due to the short follow-up period of 15 weeks. The trial showed that treatment with pembrolizumab plus chemotherapy likely results in an increase in the proportion of patients who experience serious adverse events (SAEs) and treatment discontinuation due to adverse events (AEs) when compared with chemotherapy alone. However, pERC considered the adverse effects of the combination to be important but manageable, given that treatment is expected to be prescribed and overseen by clinicians who are experienced in treating MPM.

In the absence of a direct head-to-head comparison, pERC considered an indirect treatment comparison (ITC) provided by the sponsor, which estimated the comparative efficacy of pembrolizumab plus chemotherapy with nivolumab plus ipilimumab. pERC highlighted limitations with the ITC, including potentially unaccounted-for heterogeneity (e.g., disease stage at baseline) between the included trials, and variation in results based on the analysis model used and whether the proportional hazards assumption for the time-to-event analyses held. Although pERC was aware that the point estimates for OS generally favoured nivolumab plus ipilimumab and estimates for progression-free survival (PFS) favoured pembrolizumab plus chemotherapy, differences were not statistically significant based on wide CIs that included no difference in treatment effects. Therefore, it could not be determined with certainty that there is a difference in efficacy between these regimens for OS and PFS. The ITC did not provide comparisons for HRQoL and harms data, and the comparative effects of pembrolizumab plus chemotherapy versus nivolumab plus ipilimumab on these outcomes remained unknown.

Patients identified a need for accessible and effective treatment options that reduce symptoms related to MPM, delay disease progression, prolong life, have an improved and durable response, improve HRQoL, and minimize adverse effects. pERC concluded that pembrolizumab plus chemotherapy meets some important needs identified by patients, as it provides an additional first-line treatment option with improvements in OS, PFS, and objective response rate (ORR), and the potential for fewer immune-related AEs compared with dual immunotherapy with nivolumab plus ipilimumab. At the sponsor-submitted price for pembrolizumab plus chemotherapy and publicly listed price for nivolumab plus ipilimumab, pembrolizumab plus chemotherapy was less costly than nivolumab plus ipilimumab. As pembrolizumab plus chemotherapy is considered similarly effective to nivolumab plus ipilimumab, the total drug cost of pembrolizumab plus chemotherapy should not exceed the total drug cost of nivolumab plus ipilimumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin) should be reimbursed in patients who have not received prior systemic treatment for MPM.	In the KEYNOTE-483 trial, treatment with pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (cisplatin or carboplatin) demonstrated a clinical benefit relative to chemotherapy alone in patients who had not received prior treatment for MPM. Patients who had received prior treatment for MPM were excluded from the KEYNOTE-483 trial.	Prior therapy for MPM that led to patient exclusion from the KEYNOTE-483 trial was defined in the study protocol as prior chemotherapy for advanced or metastatic disease; prior immunotherapy at any stage of disease; prior treatment with targeted small molecule therapies, biologics, viral therapies, or angiogenesis inhibitors for advanced or metastatic disease; and prior thoracic radiotherapy, unless clear disease progression was demonstrated and confirmed. Participants who had received previous (neo)adjuvant cisplatin-based systemic chemotherapy were excluded, unless the last dose was administered at least 12 months before registration.
2. Patient must have good performance status.	The KEYNOTE-483 trial excluded patients who had an ECOG PS score greater than 1 at baseline. Clinical expert input to pERC noted that patients with ECOG PS scores of 2 or greater could be considered for treatment with pembrolizumab plus chemotherapy because ECOG PS may be related to tumour symptoms that may respond to treatment.	—
Discontinuation		
3. Reimbursement of treatment should be discontinued for disease progression based on mRECIST criteria, or uncontrollable or serious treatment-associated toxicity.	In the KEYNOTE-483 trial, pembrolizumab and chemotherapy were discontinued upon disease progression or unacceptable toxicity.	—

Reimbursement condition	Reason	Implementation guidance
4. The maximum duration of reimbursement for pembrolizumab is 2 years.	Patients in the KEYNOTE-483 trial were treated with pembrolizumab 200 mg every 3 weeks for up to 35 cycles (2 years) in combination with pemetrexed and platinum chemotherapy for up to 6 cycles.	—
Prescribing		
5. Pembrolizumab in combination with pemetrexed and platinum chemotherapy should be prescribed by clinicians and centres with experience in immuno-oncology and treating MPM.	To ensure the appropriate patients receive treatment with pembrolizumab plus chemotherapy and to optimize toxicity management.	—
Pricing		
6. Pembrolizumab plus chemotherapy should be negotiated so that it does not exceed the drug program cost of treatment with nivolumab plus ipilimumab.	The CDA-AMC Clinical Review determined that the available evidence did not establish whether pembrolizumab plus chemotherapy was superior, inferior, or equivalent to nivolumab plus ipilimumab. The sponsor's ITC showed that OS results favoured nivolumab plus ipilimumab over pembrolizumab plus chemotherapy, while PFS favoured pembrolizumab plus chemotherapy over nivolumab plus ipilimumab; however, in both cases, the difference was not statistically significant. Other outcomes, such as ORR and HRQoL, were not included in the sponsor's economic analysis of pembrolizumab plus chemotherapy. As such, there is insufficient evidence to justify a cost premium for pembrolizumab plus chemotherapy over nivolumab plus ipilimumab.	—

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HRQoL = health-related quality of life; ITC = indirect treatment comparison; MPM = malignant pleural mesothelioma; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Discussion Points

- **PFS:** There was evidence of moderate certainty (via Grading of Recommendations Assessment, Development and Evaluation [GRADE] assessment) that pembrolizumab plus chemotherapy likely results in an increase in PFS compared to chemotherapy alone. The Kaplan-Meier estimated difference in PFS probability at 12 months from the KEYNOTE-483 trial was 9.1% (95% CI, 0.8% to 17.4%) in favour of pembrolizumab plus chemotherapy, which was higher than the threshold of 5% for clinical significance, although the lower CI was lower than the threshold. However, the median

PFS was 7.1 months in both treatment groups, and the upper limit of the 95% CI for the proportional hazards analysis was very close to including no treatment effect (HR = 0.80; 95% CI, 0.65 to 0.99). pERC noted that the variability and imprecision in between-group differences suggest that pembrolizumab in combination with chemotherapy may not provide the level of benefit anticipated for PFS, and there is uncertainty whether the treatment effect is durable.

- **Symptom relief is uncertain:** Patients and clinicians highlighted the importance of a treatment that shrinks tumour size and may relieve symptoms related to MPM, notably chest pain. A higher percentage of patients treated with pembrolizumab plus chemotherapy achieved an objective response compared with those receiving chemotherapy alone, with a between-group difference of 23.5% (95% CI, 14.6% to 32.0%) at the latest data cut-off date. While the consulted clinical experts considered this difference clinically meaningful (they suggested 10% as a minimal important difference [MID] threshold), the result did not translate into observable improvement in HRQoL compared with chemotherapy alone. The least squares mean difference between groups on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health and quality of life domain was 0.99 points (95% CI, −2.88 to 4.86), indicating that pembrolizumab plus chemotherapy may result in little to no difference in HRQoL compared with chemotherapy alone (MID = 4 points). However, the time point for the analysis of HRQoL of 15 weeks was likely too short a duration of follow-up to derive robust results, especially considering the median follow-up duration for all participants was nearly 18 months in the trial. Thus, the longer-term impact of the objective response and impacts on HRQoL are unclear.
- **Greater benefit for patients with nonepithelioid histology:** Subgroup analyses suggested that patients with nonepithelioid histology experienced greater treatment benefits with pembrolizumab plus chemotherapy versus chemotherapy alone for OS, PFS, and objective response compared to those with epithelioid histology. However, the trial was not designed to support causative inferences on subgroups.
- **Safety and unmet needs:** pERC discussed 1 of the potential advantages of pembrolizumab plus chemotherapy that may address an unmet need identified by patients: a lower frequency and severity of AEs compared with existing therapies like dual immunotherapy with nivolumab plus ipilimumab. However, the reviewed ITC did not compare the regimens for harms outcomes because the sponsor indicated that the comparison was not feasible, due to heterogeneity in the AE profiles between the 2 therapies. pERC concluded that while there is sound clinical rationale for this potential advantage, which was supported by the clinical experts, there remains no comparative evidence to validate it.
- **Economic considerations:** The submitted economic base case, which was accepted by CDA-AMC, suggests that pembrolizumab is cost-saving and results in a lower budget impact compared to nivolumab plus ipilimumab. pERC noted that these cost-savings are highly uncertain, given the nature of the comparative evidence and the distribution of subsequent therapies, among other factors. The uncertainty around the market share of nivolumab plus ipilimumab and chemotherapy adds additional uncertainty to the conclusion of cost-savings and reduced budget impact.

- **Cost-effectiveness comparison to chemotherapy:** The sponsor chose to submit a cost-minimization analysis (CMA) comparing pembrolizumab plus chemotherapy with nivolumab plus ipilimumab. As a result, pERC noted the lack of clinical and economic evidence comparing pembrolizumab to platinum-based chemotherapy within the indicated population, which was deemed a relevant comparator in a small subset of patients, and the sponsor's approach did not allow pERC to assess cost-effectiveness. The price reduction needed to achieve cost-effectiveness compared to chemotherapy at a given willingness-to-pay threshold may be different from the reduction needed to achieve cost equivalence to nivolumab plus ipilimumab.
- **Appropriateness of economic analysis:** pERC noted that the sponsor submitted a CMA based on an indirect comparison to nivolumab and ipilimumab. A CMA necessarily requires evidence supporting the equivalence of all relevant treatment outcomes between comparators, including survival and HRQoL. The ITC submitted for this review was not sufficiently robust to support the assumption of equivalence between these 2 therapies. CMA was therefore felt to be an inappropriate form of economic analysis for this review. Further price reduction may be warranted.

Background

MPM is a rare neoplasm that develops in the pleural cavity. The epithelioid subtype is the most common (present in 60% to 70% of patients with MPM) and is generally associated with better prognosis compared with sarcomatoid or mixed histologies.

MPM is primarily associated with occupational inhalational exposure to asbestos, with a latency period of 10 to 50 years. Symptoms include chest-wall pain, pleuritic pain, cough, pneumothorax, difficulty breathing, and unexplained weight loss, which can affect daily functioning and HRQoL. Diagnosis may consist of laboratory blood tests, imaging with chest X-ray or CT scan of the chest and upper abdomen, PET scan, and thoracentesis. The overall prognosis of mesothelioma is poor, and cure with treatment is rare. The median OS for patients with MPM has been estimated to be less than 1 year.

The primary goals of treatment are to improve symptoms, enhance HRQoL, and extend survival. Due to its long latency period and nonspecific symptoms, MPM is often diagnosed at an advanced stage, making it difficult to treat. Systemic therapy is the main treatment modality for MPM. First-line systemic therapies for unresectable advanced MPM include chemotherapy with pemetrexed plus cisplatin (or carboplatin), or combination immunotherapy with nivolumab plus ipilimumab.

Pembrolizumab, in combination with pemetrexed and platinum chemotherapy, has been approved by Health Canada for the first-line treatment of adult patients with unresectable advanced or metastatic MPM. Pembrolizumab is a monoclonal antibody that blocks PD-1 receptors on T cells, preventing PD-1 pathway–mediated inhibition of the antitumour immune response. It is available as a solution (100 mg/4 mL vials) for IV infusion, and the dosage recommended in the product monograph is 200 mg every 3 weeks or 400 mg every 6 weeks in patients aged 18 years and older.

Sources of Information Used by the Committee

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

- a review of 1 phase II/III randomized, open-label controlled trial in patients with unresectable advanced and/or metastatic MPM, and 1 ITC using Bucher and network meta-analysis (NMA) approaches
- a joint submission of patients' perspectives by the Lung Health Foundation, Lung Cancer Canada, and the Canadian Cancer Survivor Network
- input from public drug programs that participate in the Reimbursement Review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with MPM
- input from 1 clinician group, the Ontario Health — Cancer Care Ontario Lung Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Patients who responded to the 3 patient groups' requests for input reported significant challenges in obtaining an accurate and timely diagnosis. Symptoms such as fatigue, shortness of breath, cough, nausea, and pain affected daily life, limiting work, physical activity, and hobbies while contributing to emotional distress and concerns about caregiver burden. While prior treatments provided symptom relief and prolonged survival, many patients struggled with lingering adverse effects like fatigue, neuropathy, and nausea, as well as financial barriers to accessing further treatment. Key concerns included better symptom and adverse effect management, along with treatment effectiveness in slowing or stopping disease progression with minimal toxicity.

Patients with MPM with experience using pembrolizumab reported experiencing tumour reduction and symptom relief, with 1 seeing rapid improvement after starting pembrolizumab in a clinical trial. However, disease progression eventually led to treatment switches, highlighting the need for sustained efficacy in advanced disease.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

The clinical experts indicated that current treatments for MPM include chemotherapy and combination immunotherapy, but both have limitations, particularly for patients who cannot tolerate immunotherapy's adverse effects. Pembrolizumab plus chemotherapy offers a first-line alternative that combines immunotherapy with chemotherapy in a more tolerable manner. Clinical experts emphasized its potential benefit for patients who may not tolerate nivolumab plus ipilimumab, which is associated with a much higher

rate of immune-related AEs. While nivolumab plus ipilimumab remains preferred for nonepithelioid MPM, pembrolizumab plus chemotherapy could serve as an alternative in this subgroup.

MPM remains incurable, with treatment primarily aimed at prolonging survival, maintaining HRQoL, and preventing disease progression. Oncologists monitor patients at each treatment cycle, assessing side effects, functional status, and tumour response with imaging every 2 to 4 cycles. Treatment discontinuation is recommended for disease progression, severe toxicity, or after 2 years, per the product monograph. Experts agreed that prescribing should be limited to experienced clinicians to ensure appropriate use and toxicity management.

Clinician Group Input

The clinician group identified nivolumab plus ipilimumab as the standard first-line treatment for MPM, with platinum plus pemetrexed chemotherapy preferred for patients contraindicated to immunotherapy. Despite available treatments, OS remains poor, and patients experience a high symptom burden, highlighting the need for more effective and tolerable options. Pembrolizumab plus chemotherapy is expected to serve as a first-line alternative for patients with advanced, unresectable MPM, with treatment decisions guided by patient and physician choice in the absence of direct comparative data. Regular clinical and radiological assessments are recommended to monitor treatment response, with tumour stability or shrinkage seen as meaningful outcomes for improving symptoms and HRQoL. Treatment should be administered under medical oncologist supervision and discontinued upon serious toxicity, disease progression, or completion of therapy.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for pembrolizumab. 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

Drug program implementation questions	Clinical expert response
Relevant comparators	
When is pembrolizumab plus chemotherapy preferable to nivolumab plus ipilimumab?	Combination immunotherapy with nivolumab plus ipilimumab may be too toxic for certain patients. Pembrolizumab plus platinum-based chemotherapy offers an alternative to all-immunotherapy or all-chemotherapy approaches, leveraging the known effectiveness of both types of regimens in MPM while providing a different adverse effect profile. Pembrolizumab plus chemotherapy is a well-tolerated regimen in patients with NSCLC, where there is substantial experience with the regimen. The clinical experts noted that although no head-to-head comparisons exist for pembrolizumab plus chemotherapy, clinicians may prefer combination immunotherapy (nivolumab plus ipilimumab) over a chemotherapy-containing regimen for patients with nonepithelioid histology. Nonepithelioid tumours are associated with higher symptom burden, poorer prognosis, and a

Drug program implementation questions	Clinical expert response
	weaker response to chemotherapy than to immunotherapy. pERC agreed with the clinical experts.
Are the trial results generalizable to allow patients to switch from nivolumab plus ipilimumab to pembrolizumab plus chemotherapy if there are adverse effects without disease progression?	There is currently no evidence to support switching treatments, including from the KEYNOTE-483 trial. However, the clinical experts noted that switching may be considered in practice, particularly if adverse effects from nivolumab plus ipilimumab are serious or difficult to manage. They emphasized that the different adverse effect profile of pembrolizumab plus chemotherapy, combined with its expected benefit, could justify switching in such cases. pERC agreed with the clinical experts.
Considerations for initiation of therapy	
For disease diagnosis, scoring or staging for eligibility, is PD-L1 status required or applicable?	Oncologists who treat MPM do not routinely test for PD-L1, as it is not considered a key factor in treatment decision-making. This is based on findings from the CheckMate 743 trial, which showed no clear association between PD-L1 expression and outcomes with nivolumab plus ipilimumab in MPM. Similarly, the KEYNOTE-483 trial did not indicate a subgroup effect based on PD-L1 status. The clinical experts stated that reimbursement for pembrolizumab plus chemotherapy should not be linked to a patient's PD-L1 status. They noted that this would be consistent with the reimbursement criteria for nivolumab plus ipilimumab in the same patient population. pERC agreed with the clinical experts.
The KEYNOTE-483 trial eligibility included the following criteria: • age 18 years or older • histologically confirmed unresectable advanced and/or metastatic MPM • had not received prior chemotherapy for any stage of advanced or metastatic disease or prior immunotherapy for any stage of disease • ECOG PS score of 0 to 1. Would these criteria be appropriate to apply for identifying patients who are eligible for reimbursement of pembrolizumab plus chemotherapy?	The eligibility criteria for the KEYNOTE-483 trial are generally appropriate for identifying the target population for pembrolizumab treatment. However, the clinical experts noted that patients with an ECOG PS score of 2 or higher would be considered for pembrolizumab plus chemotherapy because performance status could be influenced by tumour-related symptoms that may improve with treatment. This approach is also applied when considering treatment with nivolumab plus ipilimumab. The clinical experts agreed that the reimbursement initiation conditions specified in the pERC recommendation for nivolumab plus ipilimumab could similarly be applied to pembrolizumab plus chemotherapy if recommended for public reimbursement. pERC agreed with the clinical experts.
Would patients who had partial tumour resection be eligible for the pembrolizumab and chemotherapy regimen?	The clinical experts noted that the KEYNOTE-483 trial did not include patients who had undergone initial resection; however, it was also noted that a partial resection, by definition, is not curable. The experts indicated that it would be reasonable to offer treatment with pembrolizumab plus chemotherapy to patients with a tumour that has undergone partial resection upon disease progression following resection or symptomatic progression following resection. pERC agreed with the clinical experts.

Drug program implementation questions	Clinical expert response
The KEYNOTE-483 trial excluded patients with the following: • evidence of interstitial lung disease • known history or any evidence of active noninfectious pneumonitis • active CNS metastases and/or carcinomatous meningitis. Would patients with these trial exclusion criteria be eligible treatment with pembrolizumab with chemotherapy?	Interstitial lung disease and noninfectious pneumonitis are not absolute contraindications to pembrolizumab, but they are considered risk factors that require careful consideration and monitoring, including treatment modifications as per the product monograph. The clinical experts noted that CNS metastases are very rare in MPM and that patients with stable and asymptomatic brain metastases would be eligible for pembrolizumab plus chemotherapy. pERC agreed with the clinical experts.
If pembrolizumab is discontinued for reasons other than disease progression or toxicity, would patients with advanced MPM be considered eligible for an additional 12 months of treatment at the time of disease recurrence? Should re-treatment consist of pembrolizumab monotherapy or pembrolizumab plus chemotherapy?	The clinical experts indicated that re-treatment with pembrolizumab plus chemotherapy may be considered in this scenario, especially if a patient had been off pembrolizumab for at least 6 months without disease progression, indicating an initial strong objective and durable response to treatment. However, they were not aware of evidence to inform the use of pembrolizumab re-treatment in patients with advanced MPM. In clinical practice, decisions would be informed by experience with pembrolizumab re-treatment in NSCLC. The clinical experts noted that very few patients with advanced MPM would meet these criteria, making this scenario rare. It was the opinion of the clinical experts that — in this scenario — rechallenge with the combination would be preferred to pembrolizumab monotherapy. There is evidence for and considerable clinical experience demonstrating that some patients can achieve repeated responses to platinum-based chemotherapy with pemetrexed, suggesting no strong rationale for withholding this treatment upon disease recurrence. While the role of immunotherapy in the rechallenge setting remains uncertain due to limited direct evidence, chemotherapy is expected to provide clinical benefit in this context. However, for patients who previously achieved a durable response to pembrolizumab and did not experience disease progression while receiving it, rechallenge with both pembrolizumab and chemotherapy would be a clinically justifiable option. pERC agreed with the clinical experts, noting that re-treatment for 1 year should be an option for patients progressing after completion of 2 years of treatment with pembrolizumab plus chemotherapy and a reasonable off-treatment period. The decision for re-treatment with pembrolizumab monotherapy vs. pembrolizumab plus chemotherapy should be at the discretion of the treating clinician.
Consider alignment with reimbursement conditions for nivolumab plus ipilimumab for MPM.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for discontinuation of therapy	
If there is disease progression during a treatment break, can pembrolizumab and chemotherapy be resumed? If a patient cannot tolerate 1 of the components of the treatment, would treatment continue with remaining	The clinical experts stated that if disease progression occurred during a treatment break, then they would resume pembrolizumab plus chemotherapy treatment. The clinical experts indicated that continuing treatment with

Drug program implementation questions	Clinical expert response
components? Is there a minimum number of chemotherapy cycles that must be given concurrently with pembrolizumab?	pembrolizumab alone would be clinically appropriate if the patient experiences an adverse event from chemotherapy, in the absence of disease progression. This approach was permitted in the KEYNOTE-483 trial and would align with current treatment practices. Monotherapy with the remaining agent should stop if the patient experiences serious adverse effects or has disease progression, or after completion of 2 years of therapy. The clinical experts noted that at least 1 cycle of chemotherapy should be administered concurrently with pembrolizumab. In cases where an infusion reaction to platinum-based chemotherapy occurred in the first cycle, then switching to nivolumab plus ipilimumab may be considered; however, the experts noted that is typically a rare scenario. pERC agreed with the clinical experts.
Consider alignment with reimbursement conditions for nivolumab plus ipilimumab for MPM.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for prescribing of therapy	
Jurisdictions would plan on implementing pembrolizumab as weight-based dosing up to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg) if reimbursed for MPM, similar to other indications.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Can pembrolizumab and chemotherapy also be given to patients with advanced peritoneal mesothelioma?	Malignant peritoneal mesothelioma is not currently an approved indication for pembrolizumab. Patients with malignant peritoneal mesothelioma and other nonpleural mesotheliomas were not included in the KEYNOTE-483 trial. The clinical experts indicated that malignant peritoneal mesothelioma is a distinct disease from MPM. No high-level studies (i.e., RCTs) have evaluated pembrolizumab with or without chemotherapy in patients with unresectable malignant peritoneal mesothelioma. Currently, evidence on the effects of pembrolizumab in this population is limited to retrospective data.[34] However, accumulating clinical evidence and guideline recommendations suggest a potential role for this regimen in peritoneal mesothelioma. The clinical experts noted that UK practitioners have extrapolated data from the CheckMate 743 trial (evaluating ipilimumab plus nivolumab) to peritoneal mesothelioma. Increasing clinical experience with this regimen is helping to shift perspectives on the role of these treatments in peritoneal mesothelioma. Additionally, the NCCN guidelines[4] list both nivolumab plus ipilimumab and pembrolizumab plus chemotherapy as treatment options for peritoneal mesothelioma. The study by Marmarelis et al., while small and retrospective, reported objective response rates that are clinically important in the experts' opinions. It was noted that peritoneal mesothelioma is more commonly epithelioid in nature, making chemotherapy a key component of treatment. The clinical experts also noted that given the rarity of

Drug program implementation questions	Clinical expert response
	peritoneal mesothelioma, randomized studies are less likely to be conducted. However, the accumulation of smaller studies, clinical experience, and evolving guidelines increasingly support a clinical rationale for using pembrolizumab plus chemotherapy in this setting. pERC agreed with the clinical experts.
Could patients actively receiving alternative first-line systemic treatment for MPM and who have not experienced disease progression and otherwise meet eligibility criteria be switched to pembrolizumab plus chemotherapy?	The clinical experts noted that there is no evidence to inform switching from chemotherapy or nivolumab plus ipilimumab to pembrolizumab plus chemotherapy. However, it was their opinion that patients who had received fewer than 4 cycles of chemotherapy without disease progression or toxicity could be switched to pembrolizumab plus chemotherapy to potentially improve the likelihood of an objective response and delay progression. Switching from nivolumab plus ipilimumab before completing the regimen would primarily be considered for patients who experienced serious adverse effects or toxicity from dual immunotherapy. pERC agreed with the clinical experts' input stating that it would be appropriate to consider switching from nivolumab plus ipilimumab to pembrolizumab plus chemotherapy due to serious adverse effects or toxicity.
Funding algorithm	
Drug may change place in therapy of comparator drugs.	This is a comment from the drug plans to inform pERC deliberations.

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MPM = malignant pleural mesothelioma; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RCT = randomized controlled trial.

Clinical Evidence

Systematic Review

Description of Studies

One RCT, the KEYNOTE-483 trial, was included in the sponsor's systematic review. This open-label, multicentre, phase II/III study randomly assigned patients 1:1 to either pembrolizumab plus pemetrexed and cisplatin (or carboplatin) (N = 222) or pemetrexed plus platinum chemotherapy alone (N = 218), stratified by histology. Patients in the KEYNOTE-483 trial were enrolled across 54 centres in 3 countries, including 13 study sites in Canada.

Patients had to be aged 18 years or older with histologically confirmed unresectable advanced and/or metastatic MPM and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1. Enrolled patients were primarily male (77%) and white (79%), with a median age of 70 years.

The primary objective of the study was to evaluate whether pembrolizumab improves OS when added to standard chemotherapy in MPM.

Efficacy Results

At the data cut-off on September 16, 2022, with a median follow-up of 17.4 months (range, 0.8 months to 60.3 months), 175 patients (80.3%) in the chemotherapy-alone group and 167 patients (75.2%) in the pembrolizumab-plus-chemotherapy group had died. The Kaplan-Meier estimated differences in OS probabilities between groups favoured pembrolizumab plus chemotherapy by 6.2% (95% CI, –2.8% to 15.2%) at 24 months and 8.1% (95% CI, –0.2% to 16.4%) at 36 months.

PFS based on Modified Response Evaluation Criteria in Solid Tumors (mRECIST) by blinded independent central review (BICR) was achieved in 190 patients (85.6%) in the pembrolizumab-plus-chemotherapy group and 166 patients (76.1%) in the chemotherapy-alone group. The Kaplan-Meier estimated difference in PFS probability at 12 months was 9.1% (95% CI, 0.8% to 17.4%) in favour of pembrolizumab plus chemotherapy.

A higher percentage of patients receiving pembrolizumab plus chemotherapy achieved an objective response (per mRECIST by BICR) compared with those receiving chemotherapy alone, with a between-group difference of 23.5% (95% CI, 14.6% to 32.0%) at the data cut-off.

Subgroup analyses suggested that patients with nonepithelioid histology experienced greater treatment benefits with pembrolizumab plus chemotherapy versus chemotherapy alone for OS, PFS, and ORR compared to those with epithelioid histology. However, the trial was not designed to support causative inferences on subgroups.

HRQoL was assessed using several subscales of the EORTC QLQ-C30 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13). No significant between-group differences were observed on any subscale.

Harms Results

A higher percentage of patients randomized to pembrolizumab plus chemotherapy experienced AEs compared with those who received chemotherapy alone (96.3% versus 91.4%). More patients treated with pembrolizumab plus chemotherapy experienced grade 3 and higher AEs of any cause. SAEs were reported more frequently in patients treated with pembrolizumab plus chemotherapy (40.2%) compared with chemotherapy alone (19.0%). More patients treated with pembrolizumab plus chemotherapy discontinued treatment for any AE (withdrawal due to adverse events [WDAEs]) (34.4%) compared with the chemotherapy-alone group (17.2%). A higher percentage of patients treated with pembrolizumab plus chemotherapy experienced death coded as an AE (7.1%) compared to those in the chemotherapy-alone group (2.2%). The most common cause of death was sepsis, occurring in 4 patients (1.7%) in the pembrolizumab plus chemotherapy group and 2 patients (0.9%) in the chemotherapy-alone group. Nearly 27% of patients in the pembrolizumab plus chemotherapy group and 7% in the chemotherapy-alone group experienced notable harms. The most frequently reported notable harms in the pembrolizumab group were immune-mediated (e.g., hypothyroidism).

Critical Appraisal

Internal Validity

The KEYNOTE-483 trial employed a web-based randomization system with stratification by histology, ensuring balance for this key prognostic factor. However, baseline imbalances in smoking history and prior therapies could introduce residual confounding, although clinical experts deemed these differences unlikely to impact results significantly. The open-label design introduced risks of performance, detection, and reporting bias, particularly for subjective end points like HRQoL and AEs, although OS — the primary end point — is less prone to bias. A key concern is the higher post-trial use of nivolumab in the chemotherapy-alone group, which may have diluted the treatment effect of pembrolizumab plus chemotherapy, yet no sensitivity analysis assessed this potential impact. Delayed separation of Kaplan-Meier curves for OS and PFS suggests possible violations of the proportional hazards assumption, complicating interpretation of the HRs. Additionally, the study's original power calculations overestimated the expected treatment benefit, raising questions about whether the trial was sufficiently powered to detect smaller, yet clinically meaningful, effects. Subgroup analyses suggested differential efficacy by histology and by geographic region (Europe versus Canada) on OS and PFS, raising questions about potential variability in treatment effects. However, these analyses were exploratory, lacked formal interaction testing, and did not include confounder analyses, increasing the risk of spurious or misleading findings due to multiple comparisons. The validity of conclusions drawn from the subgroup analyses remains uncertain.

External Validity

The trial population was generally representative of real-world patients receiving first-line treatment for advanced MPM, but the exclusion of patients with ECOG PS scores greater than or equal to 2 limits generalizability to those with poorer performance status. The comparator, pemetrexed plus platinum chemotherapy, aligned with standard clinical practice, with an appropriate distribution of carboplatin and cisplatin use. While the trial measured key outcomes relevant to patients, the short duration of HRQoL assessments (15 weeks) limits conclusions about long-term impacts on patient-reported outcomes.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor’s systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for OS, PFS, ORR, SAEs, WDAEs, and fatal AEs were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review (Table 3). The reference point for the certainty of the evidence assessment for EORTC QLQ-C30 global health status and quality of life score was set according to the presence or absence of an important effect based on a threshold that was informed by the literature.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor for this review.

Indirect Comparisons

One sponsor-provided ITC was included to evaluate the comparative effectiveness and harms of pembrolizumab plus chemotherapy versus nivolumab plus ipilimumab in the first-line treatment of unresectable advanced or metastatic MPM.

Description of Studies

A systematic literature search was conducted, which identified 3 reports from 2 RCTs that met the inclusion criteria for the ITC: the KEYNOTE-483 study and the phase II IND.227 study for pembrolizumab plus chemotherapy, and the CheckMate 743 study for nivolumab plus ipilimumab.

Two analyses were reported:

- The main analyses (base case) used Bucher's ITC method and included 2 studies (the KEYNOTE-483 and CheckMate 743 studies) reporting OS, PFS, and ORR.
- Sensitivity analyses were performed via a Bayesian NMA and included 3 studies (the KEYNOTE-483, CheckMate 743, and IND.227 studies) reporting OS, PFS, and ORR.

HRQoL and AE end points were not included in the ITC analyses.

Models were analyzed under both proportional hazards and nonproportional hazards assumptions for OS and PFS.

Table 3: Summary of Findings for First-Line Pembrolizumab Plus Chemotherapy Versus Chemotherapy Alone for Adult Patients With Unresectable Advanced or Metastatic Malignant Pleural Mesothelioma

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty[a]	What happens
			Chemotherapy	Pembrolizumab + chemotherapy	Difference		
Overall survival							
Probability of OS at 24 months Median (range) follow-up in months: Pembrolizumab + chemotherapy 17.4 (0.8 to 60.3) Chemotherapy 16.8 (0.8 to 59.3)	440 (1 RCT)	NR	328 per 1,000	389 per 1,000 (325 to 453 per 1,000)		Moderate[b]	Pembrolizumab plus chemotherapy likely results in an increase in OS compared to chemotherapy alone at 24 months.
Probability of OS at 36 months Median (range) follow-up in months: Pembrolizumab + chemotherapy 17.4 (0.8 to 60.3) Chemotherapy 16.8 (0.8 to 59.3)	440 (1 RCT)	NR	173 per 1,000	253 per 1,000 (193 to 318 per 1,000)		Moderate[b]	Pembrolizumab plus chemotherapy likely results in an increase in OS compared to chemotherapy alone at 36 months.
PFS per mRECIST by BICR							
Probability of PFS at 12 months Median (range) follow-up in months: Pembrolizumab + chemotherapy 17.4 (0.8 to 60.3) Chemotherapy 16.8 (0.8 to 59.3)	440 (1 RCT)	NR	171 per 1,000	263 per 1,000 (204 to 324 per 1,000)		Moderate[c]	Pembrolizumab plus chemotherapy likely results in an increase in PFS compared to chemotherapy alone at 12 months.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty[a]	What happens
			Chemotherapy	Pembrolizumab + chemotherapy	Difference		
ORR per mRECIST by BICR							
ORR (mRECIST by BICR) Median (range) follow-up in months: Pembrolizumab + chemotherapy 17.4 (0.8 to 60.3) Chemotherapy 16.8 (0.8 to 59.3)	440 (1 RCT)	[redacted]	294 per 1,000	527 per 1,000 (459 more to 594 more per 1,000)	[redacted]	High[d]	Pembrolizumab plus chemotherapy results in a higher percentage of patients experiencing an objective response compared to chemotherapy alone.
Health-related quality of life							
Mean change from baseline in EORTC QLQ-C30 Global Health Status or Quality of Life Time point: 15 weeks	440 (1 RCT)	NR	–3.86 points (–6.80 to –0.92)	–2.87 points (–5.68 to –0.07)	LS mean difference 0.99 points (−2.88 to 4.86)	Low[e, f]	Pembrolizumab plus chemotherapy may result in little to no difference in HRQoL compared with chemotherapy alone.
Harms							
SAEs Follow-up: NR Time point: End of trial	473 (1 RCT)	NR	190 per 1,000	402 per 1,000	[redacted]	High[d]	Pembrolizumab plus chemotherapy results in an increase in SAEs compared to chemotherapy alone.
WDAEs Follow-up: NR Time point: End of trial	473 (1 RCT)	NR	172 per 1,000	344 per 1,000	[redacted]	Moderate[g]	Pembrolizumab plus chemotherapy likely results in an increase in WDAEs compared to chemotherapy alone.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty[a]	What happens
			Chemotherapy	Pembrolizumab + chemotherapy	Difference		
Deaths as AEs Follow-up: NR Time point: End of trial	473 (1 RCT)	NR	22 per 1,000	71 per 1,000	[redacted]	Low[h]	Pembrolizumab plus chemotherapy may result in an increase in deaths as AEs compared to chemotherapy alone.

AE = adverse event; BICR = blinded independent central review; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HRQoL = health-related quality of life; LS = least squares; MID = minimal important difference; mRECIST = Modified Response Evaluation Criteria in Solid Tumors; NR = not reported; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RR = relative risk; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a]Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[b]Rated down 1 level for imprecision. In the absence of a validated MID, the threshold was informed by clinical experts consulted for this review. A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 24 and 36 months was considered clinically significant by the clinical experts. While the point estimate and upper CI exceeded this threshold, the lower CI crossed zero, indicating uncertainty. The risk difference includes both meaningful benefit and the possibility of no effect. Certainty was not downgraded further for imprecision despite variations in the magnitude and statistical significance of OS estimates across different metrics — including median OS, Cox proportional hazards (HR), and the difference in RMST at 24 months and by histology — because the direction of the treatment effect remained consistent.

[c]Rated down 1 level for imprecision. In the absence of a validated MID, the threshold was informed by clinical experts consulted for this review. A between-group absolute risk difference of 5% (50 fewer or more events per 1,000 patients) at 12 months was considered clinically significant by the clinical experts. While the point estimate and upper CI exceeded this threshold, the lower CI did not, indicating uncertainty. The risk difference includes both meaningful benefit and the possibility of no effect.

[d]In the absence of a validated MID, the threshold was informed by clinical experts consulted for this review. A between-group absolute risk difference of 10% (100 fewer or more events per 1,000 patients) was considered clinically significant by the clinical experts. The point estimate and entire CI exceeded the threshold.

[e]Rated down 1 level for imprecision due to the wide CI, which includes both no effect and the published MID of 4 points. This uncertainty limits confidence in whether the observed effect is clinically meaningful.

[f]Rated down 1 level for indirectness because the final analysis was conducted at 15 weeks, while the median follow-up duration for all participants was nearly 18 months. This discrepancy raises concerns about whether the reported results accurately reflect the longer-term impact on HRQoL.

[g]Rated down 1 level for imprecision. In the absence of a validated MID, the threshold was informed by clinical experts consulted for this review. A between-group absolute risk difference of 10% (100 fewer or more events per 1,000 patients) was considered clinically significant by the clinical experts. Although the point estimate and upper CI exceed the clinician-defined threshold for clinical significance, the lower CI is slightly below this threshold, introducing uncertainty.

[h]Rated down 2 levels for imprecision. In the absence of a validated MID, the threshold was informed by clinical experts consulted for this review. A between-group absolute risk difference of 3% (30 fewer or more events per 1,000 patients) was considered clinically significant by the clinical experts. Although the point estimate and upper CI exceed the clinician-defined threshold for clinical significance, the lower CI is slightly below this threshold, introducing uncertainty. Additionally, the number of deaths was low, making the effect estimate unstable and susceptible to meaningful changes with small variations in event counts.

Efficacy Results

The base-case Bucher ITC analysis indicated that the HR for OS favoured nivolumab plus ipilimumab over pembrolizumab plus chemotherapy (However, the difference was not statistically significant because the 95% CIs crossed unity (upper CI was > 1).

The Bucher ITC analysis indicated that the HR for PFS favoured pembrolizumab plus chemotherapy over nivolumab plus ipilimumab (. However, the difference was not statistically significant, as the 95% CI crossed unity (lower CI < 1).

The Bucher ITC analysis indicated that the odds ratio for ORR favoured pembrolizumab plus chemotherapy over nivolumab plus ipilimumab

Harms Results

Harms results were not estimated.

Critical Appraisal

The systematic literature review and ITC of pembrolizumab versus nivolumab plus ipilimumab, using chemotherapy as the common comparator, aligned with Reimbursement Review requirements. The ITC aimed to estimate relative treatment effects for OS, PFS, and ORR, rather than formally test for superiority, equivalence, or inferiority. Key ITC assumptions — similarity and transitivity — were assessed and generally met, but no adjustments were made for baseline imbalances, and no subgroup analyses were conducted on important effect modifiers such as histology, reducing interpretability. The sponsor employed fixed-effect models for all analyses due to the small number of trials, which was deemed acceptable but may not fully capture treatment effect heterogeneity. Long-term extrapolations (up to 15 years) introduced uncertainty, as survival in advanced MPM is much shorter, and comparisons at this time point may not be generalizable. No comparisons for HRQoL or AEs were conducted, limiting insights into patient-centred outcomes and potential differences in tolerability between regimens. Overall, while the ITC followed standard methodology, concerns about long-term extrapolations, lack of HRQoL and AE assessments, and potential baseline imbalances impact the robustness of its conclusions.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies were submitted.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evidence

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target population	Proposed: In combination with pemetrexed and platinum chemotherapy, for the first-line treatment of adult patients with unresectable advanced or metastatic MPM
Treatment	Pembrolizumab plus chemotherapy (i.e., pemetrexed and cisplatin or carboplatin)
Dose regimen	Pembrolizumab was administered at 200 mg every 3 weeks for up to 2 years, pemetrexed at 500 mg/m^2 every 3 weeks for 6 cycles, and cisplatin at 75 mg/m^2 every 3 weeks for 6 cycles. In cases where cisplatin was contraindicated, carboplatin was substituted at an AUC of 5 to 6 for 6 cycles.
Submitted price	Pembrolizumab, 25 mg/mL, solution for infusion: $4,400 per 100 mg vial
Submitted treatment costs	$8,800 per patient per 28-day cycle
Comparator	Nivolumab plus ipilimumab
Perspective	Canadian publicly funded health care payer
Time horizon	Lifetime (31 years)
Key data source	An ITC was conducted to evaluate the efficacy of pembrolizumab plus chemotherapy compared to nivolumab plus ipilimumab. The ITC compared evidence from the CheckMate 743 trial and the KEYNOTE-483 trial. The KEYNOTE-483 trial was a phase II/III randomized controlled study that assessed the efficacy and safety of pembrolizumab plus chemotherapy vs. pemetrexed plus cisplatin or carboplatin alone in patients with advanced or metastatic MPM.
Costs considered	Drug acquisition and administration costs.
Key limitations	• The CDA-AMC Clinical Review determined that there is uncertainty regarding similar efficacy between pembrolizumab plus chemotherapy and nivolumab plus ipilimumab for the treatment of MPM. Despite this uncertainty, evidence from the ITC did not indicate a sufficiently clear difference in OS or PFS between pembrolizumab plus chemotherapy and nivolumab plus ipilimumab to assert nonsimilarity for either treatment. • The sponsor used publicly available list prices, introducing uncertainty into the estimated cost-savings for pembrolizumab plus chemotherapy. If the actual list prices of the comparators are lower than anticipated, this could negate cost-savings associated with pembrolizumab plus chemotherapy and potentially increase overall costs to the public payer. • The sponsor estimated RDI values of 95.1% to 98.6% for pembrolizumab and chemotherapy, respectively, using trial data. The sponsor assumed that patients receiving pembrolizumab plus chemotherapy would use a lower proportion of the recommended dose compared to patients in the comparator arm, who were assumed to use the maximum dose. Because RDI influences drug utilization, this assumption reduced the total cost attributed to pembrolizumab plus chemotherapy. Given the uncertainty around actual RDI, this approach may introduce bias in favour of pembrolizumab plus chemotherapy and overestimate its cost-saving. • Clinical experts consulted by CDA-AMC indicated that the proportion of patients receiving subsequent therapies for either treatment would likely differ from those observed in the

Component	Description
	trial. As a result, the proportion of patients not receiving subsequent therapy increased to 60% from 46% in a scenario analysis. Furthermore, clinical experts anticipated that patients receiving pembrolizumab plus chemotherapy or nivolumab plus ipilimumab would be less likely to be rechallenged with the same immunotherapy after discontinuation. • The sponsor's base-case model assumed a fixed dosing regimen of pembrolizumab at 200 mg intravenously every 3 weeks. However, CDA-AMC noted that, in line with other pembrolizumab reviews, jurisdictions would likely implement a weight-based dosing regimen. This assumption overestimated the treatment cost of patients receiving pembrolizumab plus chemotherapy.
CDA-AMC reanalysis results	CDA-AMC did not perform reanalyses for the base case and accepted the sponsor's submitted base case. Based on publicly available list prices, pembrolizumab plus chemotherapy is cost-saving compared with nivolumab plus ipilimumab. The cost-savings associated with pembrolizumab plus chemotherapy is contingent on confidentially negotiated prices. If the actual price paid for nivolumab plus ipilimumab is lower than the publicly listed price, reimbursing pembrolizumab at the price submitted by the sponsor could result in higher costs for the public health payer. Changes to the RDI assumptions resulted in cost-savings for nivolumab plus ipilimumab, with pembrolizumab plus chemotherapy being associated with higher costs. All other scenario analyses, including weight-based dosing and the proportion of patients receiving subsequent therapy, resulted in cost-savings.

AUC = area under the curve; CDA-AMC = Canada's Drug Agency; ITC = indirect treatment comparison; MPM = malignant pleural mesothelioma; OS = overall survival; PFS = progression-free survival; RDI= relative dose intensity.

Budget Impact

CDA-AMC identified the following key limitations from the sponsor's analysis: the market share of pembrolizumab may be underestimated, fixed dosing for pembrolizumab is not reflective of clinical practice, RDI obtained for pembrolizumab may be inappropriate, and the impact of subsequent therapy was excluded from the budget impact analysis.

CDA-AMC did not conduct a base-case reanalysis. In the sponsor's analysis, the 3-year budget impact of reimbursing pembrolizumab plus chemotherapy for the first-line treatment of patients with advanced or metastatic MPM was –$488,202 (year 1: –$180,818; year 2: –$277,114; year 3: –$30,270).

Budget impact analysis results were sensitive to all scenarios undertaken by CDA-AMC (i.e., incremental budget impact when pembrolizumab's market share was increased, increased cost-savings when the weight-based dosing was applied to pembrolizumab, and increased budget expenditure when RDI assumptions were changed).

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Kelvin Chan (Vice Chair), Dr. Phillip Blanchette, 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 Villeneuve, and Danica Wasney.

Meeting date: May 14, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@cda-amc.ca.