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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the adjuvant treatment of adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA non-small cell lung cancer who have undergone complete resection and platinum-based chemotherapy

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 adjuvant treatment of adult patients with stage IB (with tumour[s] of 4 cm in diameter or larger), II, or IIIA non–small cell lung cancer (NSCLC) who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 tumour proportion score (TPS) of less than 50%, as determined by a validated test, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients aged 18 years or older who have a diagnosis of stage IB (with tumour[s] of 4 cm in diameter or larger), II, or IIIA NSCLC whose tumours have been completely surgically removed, who have received platinum-based chemotherapy, whose tumours have a PD-L1 TPS of less than 50% as determined by pathology testing, and who are in relatively good health (as measured by performance status). Keytruda should not be covered for patients who have received or planned to receive radiation therapy before or after surgery, and/or who are receiving other drugs before surgery to shrink a tumour or stop its spread. Also, Keytruda should not be covered to treat patients who have had previous treatment with drugs that change how the immune system works.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if it is prescribed by clinicians with expertise in managing lung cancer and the price of Keytruda is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that adjuvant treatment with Keytruda was better than placebo at allowing patients to live longer or delaying the return of their disease.
- Keytruda may meet some of the needs identified as important to patients, such as stopping or delaying their disease from recurring, having manageable side effects, and maintaining their health-related quality of life (HRQoL).
- 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. A price reduction is therefore required.
- Based on public list prices, Keytruda is estimated to cost the public drug plans approximately $32 million over the next 3 years.

Summary

Additional Information

What Is NSCLC?

NSCLC is the most common type of lung cancer, accounting for nearly 90% of all lung cancers in Canada. In those with NSCLC, unusual growth of cells takes place inside the lungs or lining of the airways and forms into tumours. Cancer that is stage I, II, or IIIA is considered early stage, meaning the tumour has not spread to other parts of the body.

Unmet Needs in NSCLC

The intention of surgery for early-stage NSCLC is to cure patients. However, it is possible for the cancer to return for some patients who have had surgery; therefore, there is a need for treatment options that can prevent the cancer from returning.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $8,800 per patient per 28-day cycle.

Recommendation

The pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult patients with stage IB (tumour stage 2a [T2a] ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 TPS of less than 50%, as determined by a validated test, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One triple-blind, phase III randomized controlled trial (RCT) (KEYNOTE-091) demonstrated that adjuvant treatment with pembrolizumab for approximately 1 year (18 doses) resulted in improved disease-free survival (DFS) compared to placebo with active surveillance in adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and adjuvant chemotherapy, and whose tumours have a PD-L1 TPS of less than 50%. After a median follow-up duration of 46.6 months, the median DFS (i.e., time to disease recurrence, new malignancy, or death) was 51.7 months (95% confidence interval [CI], 39.0 to 70.4) for patients who received pembrolizumab and 34.5 months (95% CI, 23.3 to 46.4) for patients who received placebo (hazard ratio [HR] = 0.72; 95% CI, 0.58 to 0.89; P < 0.001). The Kaplan-Meier (KM) estimates of the probability of DFS in the pembrolizumab and placebo groups were 67.2% (95% CI, 61.9 to 71.9) versus 55.0% (95% CI, 49.7 to 60.0) at 24 months; and 51.2% (95% CI, 45.2 to 56.9) versus 42.4% (95% CI, 36.7 to 47.9) at 48 months, respectively. Furthermore, the adverse event (AE) profile of pembrolizumab was considered manageable and consistent with the known side effects of an immune checkpoint inhibitor.

Patients indicated a need for treatments that prolong life, stop or delay disease recurrence, have more tolerable side effects, and improve HRQoL. pERC concluded that pembrolizumab meets their need for improved DFS, side effects that are manageable, and, likely, improved HRQoL, as patients who received pembrolizumab had relatively stable and comparable HRQoLs to the patients who received placebo.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for pembrolizumab was $103,900 per quality-adjusted life-year (QALY) gained compared with active surveillance. At this incremental cost-effectiveness ratio, pembrolizumab is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 TPS of less than 50%, as determined by a validated test. A price reduction is required for pembrolizumab to be considered cost-effective at a $50,000 per QALY gained threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Pembrolizumab should be reimbursed only if all of the following conditions are met:	The KEYNOTE-091 trial demonstrated that adjuvant treatment with pembrolizumab has a clinical benefit compared to placebo	—

Reimbursement condition	Reason	Implementation guidance
1.1. adults aged 18 years or older 1.2. stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC 1.3. undergone complete surgical resection (with negative margins and have no clinical or radiographic evidence of disease) and platinum-based chemotherapy 1.4. PD-L1 TPS score < 50% as determined by pathology testing.	in adults with completely resected stage IB-IIIA NSCLC and a PD-L1 TPS score < 50%. Adjuvant chemotherapy was not mandatory in the KEYNOTE-091 trial but was to be considered for patients with stage IB disease and strongly recommended for those with stage II or IIIA disease, according to local practice and national guidelines, and the majority of patients enrolled in the trial received adjuvant chemotherapy. All patients included in the reimbursement request population had received adjuvant chemotherapy.	
2. Patients must have good performance status.	Patients enrolled in the KEYNOTE-091 trial had an ECOG PS of 0 or 1.	Based on clinical expert input, selected patients with an ECOG PS of more than 1 could be considered for treatment at the discretion of the treating physician.
3. Pembrolizumab should not be reimbursed in patients who meet any of the following criteria: 3.1. received or planned to receive neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy 3.2. prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or CTLA-4 modulator, or any other immunomodulating drugs.	In the KEYNOTE-091 trial, previous neoadjuvant or adjuvant radiotherapy for the current malignancy was not permitted. Patients with prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, or CTLA-4 modulators, or any other immunomodulating drugs were excluded from the trial as well.	—
Discontinuation		
4. Reimbursement of pembrolizumab should be discontinued upon occurrence of any of the following: 4.1. disease recurrence 4.2. unacceptable toxicity 4.3. completion of 1 year of treatment or 18 doses, whichever comes first.	In the KEYNOTE-091 trial, adjuvant treatment with pembrolizumab continued until disease recurrence, new malignancy, unacceptable toxicity, investigator's decision, withdrawal of consent, or completion of 18 cycles (approximately 1 year) of treatment.	—
Prescribing		
5. Pembrolizumab should be prescribed by clinicians with	This is meant to ensure that pembrolizumab is prescribed for appropriate patients and that adverse	—

Reimbursement condition	Reason	Implementation guidance
expertise in managing lung cancer.	effects are managed in an optimized and timely manner.	
Pricing		
6. A reduction in price.	The ICER for pembrolizumab is $103,900 per QALY gained when compared with active surveillance. A price reduction of 54% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained compared with active surveillance.	—

ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; NSCLC = non–small cell lung cancer; PS = performance status; QALY = quality-adjusted life-year; T2a = tumour stage 2a; TPS = tumour proportion score.

Discussion Points

- **Uncertainty in overall survival (OS):** Patients identified a need for treatments that can cure their disease and prolong survival. pERC was unable to definitively conclude that adjuvant treatment with pembrolizumab would meet this need due to the uncertainty in the OS results, although there is a trend toward improved OS in favour of pembrolizumab. After a median follow-up duration of [redacted], the median OS was not reached in either of the reimbursement request population groups ([redacted]), with deaths observed in 23% and 30% of patients in the pembrolizumab and placebo groups, respectively. The KM estimates of the probability of OS in the pembrolizumab and placebo groups were [redacted] at 36 months; and [redacted] at 48 months, respectively.
- **Reimbursement request based on a subset of the KEYNOTE-091 trial population:** The evidence reviewed by pERC and scope of this recommendation were limited to the sponsor's reimbursement request. pERC noted that the Health Canada indication for pembrolizumab does not specify requirements for PD-L1 TPS and that the overall KEYNOTE-091 trial population aligned with the Health Canada indication. pERC raised concerns about the sponsor's submission being limited to a subset of the trial population (i.e., the reimbursement request population) and noted that although subgroup analyses were prespecified by PD-L1 status in 3 groups (TPS < 1%, TPS 1% to 49%, and TPS ≥ 50%), a subgroup analysis pooling together patients with a TPS of less than 50% was not prespecified. The committee emphasized there were limitations to this approach, as the KEYNOTE-091 trial was not powered, nor designed, to test hypotheses for the reimbursement request population; thus, uncertainty remains around the interpretation of the subgroup analyses.
- **Indirect evidence:** The sponsor submitted a Bucher indirect treatment comparison (ITC) comparing pembrolizumab and atezolizumab only in patients with a PD-L1 TPS of 50% or greater to support their reimbursement request for patients with a PD-L1 TPS of less than 50%. pERC members discussed the results of this ITC, which suggested that pembrolizumab is less effective than

atezolizumab in patients with a TPS of 50% or greater, stage II to IIIA disease, and prior adjuvant chemotherapy ([redacted]). However, pERC noted that these results are uncertain because it is unclear if sources of clinical or methodological heterogeneity may have biased effect estimates of ITC as no assessment of homogeneity was conducted. The sponsor did not conduct an additional ITC for the reimbursement request population (i.e., patients with a PD-L1 TPS < 50%) because atezolizumab is not indicated for this subpopulation of patients and therefore not a comparator for patients with a TPS of less than 50%.

- **Testing procedure considerations:** pERC discussed the requirement for PD-L1 testing when determining eligibility for pembrolizumab. Overall, this is not anticipated to be an implementation barrier, as PD-L1 TPS testing at diagnosis is the current standard of care for all patients with NSCLC.
- **Patients with driver mutations:** In the KEYNOTE-091 trial, some patients who meet the defined reimbursement request population had known driver mutations, specifically *EGFR* (7% to 9%) or *ALK* (1% to 2%) mutations. Overall, the *EGFR* and *ALK* mutation status was unknown for most patients who were enrolled (52% to 66% met the reimbursement request population). pERC noted that therapies targeting specific mutations could be a comparator for the subset of patients with driver mutations, but no comparative evidence of pembrolizumab versus targeted therapies in these patients was submitted. The clinical experts consulted for this review strongly recommend the use of targeted therapies rather than pembrolizumab for adjuvant treatment in patients with *EGFR* or *ALK* mutations, unless the patient had a contraindication to the targeted therapy.

Background

Lung cancer is the most diagnosed cancer and leading cause of cancer deaths in Canada, with an estimated 32,100 new cases of lung cancer diagnosed and 20,700 deaths from lung cancer in 2024. NSCLC accounts for approximately 88% of all lung cancer cases in Canada. It is estimated that 30% to 35% of NSCLCs are diagnosed at an early stage (I to IIIA) and approximately 20% to 25% of patients with NSCLC have surgically resectable disease.

Standard treatment for patients with stage IB to IIIA NSCLC is surgical resection. The clinical experts consulted for this review noted that in the perioperative setting, the current treatment standard for patients with resectable NSCLC without actionable oncogenic alterations is neoadjuvant platinum-doublet chemotherapy in combination with immunotherapy (nivolumab), or adjuvant platinum-doublet chemotherapy followed by immunotherapy (atezolizumab for patients with a PD-L1 TPS ≥ 50%). However, the clinical experts indicated that not all patients receive immunotherapy or platinum-based chemotherapy in the perioperative setting as they may decline, not be offered a referral to medical oncology, or are ineligible. The clinical experts noted that there is a need to reduce recurrence rates in early-stage NSCLC and provide options for those who have not had neoadjuvant immunochemotherapy and are ineligible for adjuvant atezolizumab (e.g., patients with a PD-L1 TPS < 50%) to cure disease, delay disease recurrence, improve survival, and maintain quality of life.

Pembrolizumab has been approved by Health Canada for the adjuvant treatment of adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy. The sponsor requested reimbursement for pembrolizumab as monotherapy for the adjuvant treatment of adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC, and with a PD-L1 TPS of less than 50% who have undergone complete resection and platinum-based chemotherapy, as determined by a validated test. Pembrolizumab is a PD-1 blocking antibody. It is available as a solution for infusion 100 mg/4 mL vial and the dosage recommended in adults in the product monograph is 200 mg every 3 weeks or 400 mg every 6 weeks, administered as an IV infusion over 30 minutes.

Sources of Information Used by the Committee

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

- a review of 1 phase III, placebo-controlled RCT in adults with completely resected stage IB to IIIA NSCLC, and 1 ITC
- patients' perspectives gathered by a joint submission of 3 patient groups, the Lung Health Foundation (LHF), Lung Cancer Canada (LCC), and the Canadian Cancer Survivor Network (CCSN)
- input from the public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with lung cancer
- input from 2 clinician groups, the Ontario Health (Cancer Care Ontario) (OH-CCO) Lung Cancer Drug Advisory Committee and LCC – Clinician Group
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

This review received a joint submission by 3 patient groups, LHF, LCC, and CCSN. The input was based on information collected by LHF from individuals living with lung cancer, which was gathered from 3 interviews with patients from Ottawa, Vancouver, and Toronto who had experience with pembrolizumab, as well as 33 responses to an online survey available between June 2023 and June 2024.

The survey respondents reported similar symptoms and challenges from their lung cancer, some of which included fatigue (53%), shortness of breath (50%), cough (23%), and pain (20%). Most respondents indicated that living with lung cancer negatively impacts their emotional well-being through feelings of isolation, challenges with symptom management, and perceived burden on caregivers and family. The disease aspects that were most important to responders to control included improved management of disease symptoms, as well as pain and side effects from therapy. Patients who previously received surgery reported experiencing deconditioning and chronic fatigue, and medication side effects included extreme itching that affects sleep, brain fog, fatigue, nausea, vomiting, mood changes, diminished appetite, weight

loss, hair loss, anemia, and neuropathy. These patients also experienced challenges accessing some therapies due to high treatment costs, as well as difficulty navigating the health care system and locating disease information and support. The input also noted concerns from patients on targeted therapy related to their ability to access the next line of treatment if or when their current therapy stops working.

The respondents indicated that key treatment outcomes to consider when evaluating new therapies include stopping or slowing disease progression with minimal side effects and effectiveness in advanced disease. Three LHF interviewees had experience with pembrolizumab, though these patients did not fall into the eligible population of the current indication under review, which is limited to stage IB (T2a ≥ 4 cm), II, or IIIA. One interviewee with *EGFR*-positive, stage IV lung cancer was taking pembrolizumab in combination with chemotherapy, though it was unclear if the interviewees with NSCLC were taking pembrolizumab similarly or as monotherapy. One patient discontinued pembrolizumab after 19 months due to progression, while another experienced sufficient tumour shrinkage and inactivity to discontinue pembrolizumab after 3 years, before reinitiating shortly after upon tumour reactivation. After reinitiation of pembrolizumab, the patient's tumours have once again decreased in size. The side effects reported by these patients included nausea, fatigue, muscle soreness, constipation, diarrhea, and worsening of their diabetes, eczema, and liver enzymes. Patients did not feel these side effects impeded their ability to participate in activities of daily living or exercise and overall reported experiencing improved quality of life while on therapy.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

According to the clinical experts consulted by the review team, the key treatment goals for patients with early-stage NSCLC who receive adjuvant therapy following complete surgical resection is to improve cure rates through reducing risk of relapse. The clinical experts noted that there are currently no adjuvant immunotherapy options for the patients with stage IB to IIIA NSCLC who have a PD-L1 TPS of less than 50% in Canada, defining an unmet need for this group. The clinical experts noted that adjuvant pembrolizumab would fill a treatment gap, as currently, patients can only access this treatment after relapse. The clinical experts pointed out that OS is the outcome important to patients. The clinical experts indicated that pembrolizumab treatment should be discontinued if 1 of the following has been met: a total of 18 cycles (1 year) of adjuvant immunotherapy has been completed, disease progression has been detected, or unacceptable toxicity develops. The clinical experts noted that treatment with pembrolizumab should be in a specialty setting that has surgical and medical oncology multidisciplinary staff and expertise to administer systemic therapy, monitor the patient, and manage treatment-related toxicities.

Clinician Group Input

This review received input from 2 clinician groups: the OH-CCO Lung Cancer Drug Advisory Committee and the LCC – Clinician Group. Six clinicians from OH-CCO and 35 clinicians from LCC provided input for this review. The input from the clinician groups aligned with the input from the clinical experts consulted for this review for unmet needs, patient population, key outcomes, discontinuing treatment, and prescribing considerations. The LCC group also highlighted that in patients with early-stage resected IB to IIIA NSCLC, current therapies do not adequately achieve high cure rates or prevent recurrences. The LCC group noted

this as particularly important for patients with NSCLC, as the risk of relapse substantially increases with each subsequent disease stage. The LCC group also emphasized that patient relapse and metastatic disease have substantial costs to patient health, quality of life, use of health care resources, economic loss of productivity, and overall costs to society. The LCC group expects that pembrolizumab will shift the current treatment paradigm as it represents the first adjuvant immunotherapy option for this patient population. The LCC group also highlighted that treatment with pembrolizumab for eligible patients with a sensitizing *EGFR* mutation will require case-by-case consideration by treating clinicians, who will need to weigh the risks and benefits of adjuvant sequential chemotherapy and immunotherapy versus adjuvant osimertinib. The clinician groups agreed that treatment benefit in the adjuvant setting is primarily determined by disease recurrence, which the LCC group noted typically occurs within 2 to 3 years for patients with stage IB to IIIA NSCLC. The LCC group indicated that cure rates, as measured by 5-year OS, can also determine response, but typically require even more years of follow-up. The LCC group suggested implementing clinical and laboratory follow-up every 3 weeks to evaluate toxicity and disease recurrence, as well as imaging scans at 3- to 4-month intervals, given pembrolizumab is administered over 1 year. The LCC group noted that overall, immunotherapies are well tolerated by patients, and autoimmune side effects can often be readily managed by oncologists.

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:

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

The clinical experts consulted for this 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	
Pembrolizumab is an add-on to ACT and other currently available adjuvant therapies and is not expected to replace atezolizumab or osimertinib in the adjuvant setting There was an indirect treatment comparison study vs. atezolizumab. There is no direct comparator for the adjuvant treatment of NSCLC with stage IB (T2a ≥ 4cm), II, or IIIA NSCLC who have undergone complete resections and platinum-based chemotherapy with PD-L1 < 50%.	This is a comment from the drug plans to inform pERC deliberations.

Implementation issues	Response
Considerations for initiation of therapy	
The exclusion criteria in the KEYNOTE-091 study are: • received or planned to receive neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy for the current malignancy • prior treatment with an anti–PD-1, anti–PD-L1 or anti–PD-L2, anti-CD137, CTLA-4 modulator, or any other immune-modulating drugs. Would patients who had planned to receive neoadjuvant or adjuvant radiotherapy, chemotherapy, or immunotherapy be eligible for treatment?	Based on the inclusion and exclusion criteria in the KEYNOTE-091 study, as well as clinical practice in Canada, the clinical experts consulted for this review noted that the following patients would be eligible to receive treatment with pembrolizumab: • patients who are planned for adjuvant chemotherapy or adjuvant radiotherapy • patients undergoing adjuvant chemotherapy • Of note, ACT was not mandatory in the pivotal trial but considered for patients with stage IB disease (T2a ≥ 4 cm) and strongly recommended for stages II and IIIA and was administered according to national and local guidelines. The clinical experts noted that the following patients would not be eligible to receive treatment with pembrolizumab: • patients who received a neoadjuvant immunotherapy or chemotherapy • patients undergoing neoadjuvant chemotherapy • patients who had neoadjuvant therapy or induction radiotherapy • Patients undergoing neoadjuvant or adjuvant radiotherapy. In addition, the clinical experts indicated that adjuvant radiotherapy is not currently the standard of care for the patients in Canada. As such, the impact on application of not recommending patients receiving adjuvant radiotherapy would be minimal. pERC agreed with the clinical experts.
In the KEYNOTE-091 study, patients must undergo complete resection of their NSCLC (lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy) with microscopically free resection margins (R0). Can patients with a partial resection be eligible for treatment? If a patient's complete resection failed, would they be eligible to receive this treatment? In the KEYNOTE-091 study, patients should also complete a maximum of 4 cycles of ACT with a platinum-based regimen. The first dose of pembrolizumab should be administered at least 3 weeks but no more than 12 weeks after the last dose of ACT. If there are delays in treatment or complications with surgery, and so forth, would patients be eligible for treatment > 12 weeks after the last dose of ACT? What conditions and/or time frame would be advisable?	The clinical experts indicated that if a patient does not have a complete resection, they would not be eligible to receive pembrolizumab. The clinical experts pointed out that it is usually recommended to start ACT within 8 weeks surgery; and an immunotherapy (e.g., pembrolizumab) can be started within 12 weeks of ACT completion. The clinical experts noted that for patients who have not had 4 full cycles of platinum-based chemotherapy ACT, there are conditions that may preclude them from having an immunotherapy. Some examples of these conditions include patients' refusal, treatment toxicity (i.e., neurological or auditory AEs), and eligibility for receiving an immunotherapy (e.g., renal issues). The clinical experts noted that patients receiving adjuvant chemotherapy should receive no more than 4 cycles of adjuvant chemotherapy and have their immunotherapy start within 12 weeks of completion of adjuvant chemotherapy, based on the patients included in the KEYNOTE-091 study (i.e., patients who are not receiving adjuvant chemotherapy should receive their immunotherapy within 12 weeks of surgery). pERC agreed with the clinical experts.
Should patients who complete 1 year of treatment and experience disease progression or recurrence off pembrolizumab treatment be eligible for up to 1 year (18 cycles) of pembrolizumab re-treatment?	The clinical experts noted that this question is regarding the management of relapsed disease, and the evidence from the KEYNOTE-091 study is not applicable to address this question. pERC agreed with the clinical experts that patients in the incurable setting would be eligible for downstream immunotherapy provided the

Implementation issues	Response
	patient relapses 6 months or later after completion of their adjuvant immunotherapy.
Considerations for discontinuation of therapy	
The study treated patients for 18 doses of 200 mg every 3 weeks (for approximately 1 year). Should therapy end after 18 doses or 1 year, whichever comes first?	The clinical experts consulted for this review indicated that pembrolizumab should end after 18 doses of 200 mg every 3 weeks or 1 year, whichever comes first. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
Jurisdictions use weight-based dosing to a cap: 2 mg/kg to a maximum of 200 mg every 3 weeks or 4 mg/kg to a maximum of 400 mg every 6 weeks, as is outlined in other indications.	This is a comment from the drug plans to inform pERC deliberations.
Consider alignment with atezolizumab criteria: For patients who have received a full course of treatment with nivolumab (i.e., 3 cycles) in combination with platinum-doublet chemotherapy in the NAT setting, the expert panel acknowledges that further immunotherapy in the adjuvant setting is not supported by the available evidence and most jurisdictions restrict this use for atezolizumab.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
The study was in patients with an ECOG PS of 0 to 1. Can patients with an ECOG status > 1 be eligible to receive treatment?	The clinical experts noted that even though there is a lack of data for patients with an ECOG PS of 2 based on the KEYNOTE-091 study, patients with an ECOG PS of 0 to 2 would be eligible for treatment with pembrolizumab, because in clinical practice in Canada, there is often treatment with pembrolizumab offered to patients with an ECOG PS of up to 2. The clinical experts indicated that clinicians need to evaluate the patients with a PS of 2 thoroughly, and per their assessment, consider the patients' individual status when considering treating those with an ECOG PS of 2 with pembrolizumab and ensure close follow-up and compliance. pERC determined that patients must have good PS. Based on clinical expert input, select patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.
Funding algorithm (oncology only)	
This is a complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
PD-L1 testing is widely available at many institutions.	This is a comment from the drug plans to inform pERC deliberations.

ACT = adjuvant chemotherapy; AE = adverse event; ECOG = Eastern Cooperative Oncology Group; NAT = neoadjuvant treatment; NSCLC = non–small cell lung cancer; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status; vs. = versus.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, multicenter, triple-blind, phase III RCT, KEYNOTE-091 (Total N = 1,177) submitted by the sponsor was included for this review. The study compared pembrolizumab (200 mg IV infusion every 3 weeks for up to 1 year [18 doses] or until disease recurrence or unacceptable toxicity) with placebo as adjuvant therapy for completely resected stage IB to IIIA NSCLC. Eligible patients were adults with pathologically confirmed NSCLC (any histology) of stage IB (T2a ≥ 4 cm), II, or IIIA per the American Joint Committee on Cancer (AJCC) staging system (7th edition) after complete surgical resection (i.e., lobectomy, sleeve lobectomy, bi-lobectomy, or pneumonectomy) and negative margins (R0). Eligible patients had an available tumour sample obtained during resection for PD-L1 assessment, had known PD-L1 expression status, had no evidence of disease on clinical examination and radiographic assessment per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) according to local investigator review after surgery but within 12 weeks before randomization, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and had adequate organ function within 10 days of treatment initiation. Previous neoadjuvant or adjuvant radiotherapy for the current malignancy was not permitted. ACT was not mandatory but was to be considered for patients with stage IB disease and strongly recommended for those with stage II or IIIA disease, according to local practice and national guidelines. Patients with prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, CTLA-4 modulator, or any other immune-modulating drugs were excluded from KEYNOTE-091 study. The subpopulation of interest (i.e., the reimbursement request population [n = 363 in the pembrolizumab group; n = 363 in the placebo group]), were patients with adjuvant chemotherapy and a PD-L1 TPS of less than 50%. The outcomes relevant to this review included OS, DFS, HRQoL, and safety.

The reimbursement request population of the KEYNOTE-091 study had a median age of 64 to 65 years. The proportion of male patients (65% to 68%) was higher than that of female patients (32% to 35%). Most patients were white (77% to 78%), followed by Asian (17% to 18%), among the others. A relatively small proportion of patients had stage IB disease (11% to 12%) and more than half had stage II disease (55% to 59%). Most patients were former smokers (68% to 73%), followed by those who had never smoked (13% to 19%), and current smokers (13% to 14%). More patients had an ECOG PS of 0 (56% to 62%) than an ECOG PS of 1 (38% to 44%). Most patients had the lymph node stage of N0 (no regional lymph node involvement; 41%) or N1 (nearby lymph node involvement; 38%). More patients had nonsquamous disease (62.5% to 72.2%) than squamous disease (27.8% to 37.5%) for histology. The proportion of patients who had the *EGFR* mutation (5.8% to 8.5%) or *ALK* translocation (0.8% to 1.7%) was low. Of note, more than half of the patients had an unknown *EGFR* mutation (51.8% to 57.4%) or *ALK* translocation (56.7% to 66.4%) status.

Efficacy Results

The key efficacy results from the KEYNOTE-091 trial are summarized in Table 3 in order from the most important to the least important outcomes suggested by the clinical expert consulted for this review. The

efficacy and harms outcomes of the KEYNOTE-091 study reported in this review were based on the protocol prespecified third interim analysis, for which the data cut-off date was January 24, 2023.

Overall Survival

As of the data cut-off date (January 24, 2023) and among the reimbursement request population (N = 726), the median duration of follow-up [redacted] for the reimbursement request population. The median OS was not reached in either group ([redacted].The KM estimates of the probability of OS in the pembrolizumab and placebo groups were [redacted] at 36 months; and [redacted] at 48 months, respectively.

Disease-Free Survival

As of the data cut-off date, and among the reimbursement request population, the median DFS was 51.7 months (95% CI, 39.0 to 70.4) for patients treated with pembrolizumab and 34.5 months (95% CI, 23.3 to 46.4) for patients who received placebo (HR = 0.72; 95% CI, 0.58 to 0.89; P < 0.001). The KM estimates of the probability of DFS in the pembrolizumab and placebo groups were 67.2% (95% CI, 61.9 to 71.9) versus 55.0% (95% CI, 49.7 to 60.0) at 24 months; and 51.2% (95% CI, 45.2 to 56.9) versus 42.4% (95% CI, 36.7 to 47.9) at 48 months, respectively.

Health-Related Quality of Life

The HRQoL outcomes assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status/quality of life (QoL), and the EORTC Quality of Life Questionnaire Lung Cancer module 13 (QLQ-LC13) symptom scales at 48 weeks were available among the patient-reported outcome full analysis set population (N = 1,161). The compliance rates for the EORTC QLQ-C30 and EORTC QLQ-LC13 were 98.6% at baseline and 85.8% at week 48 in the pembrolizumab group, and 99.8% at baseline and 90.0% at week 48 in the placebo group, respectively. At week 48, the questionnaire completion rates were 77.9% and 84.9% in the pembrolizumab and placebo groups, respectively.

The proportion of patients with a deteriorated score in EORTC QLQ-C30 global health status/QoL (who had a 10-point or greater deterioration in score from baseline at any time during the trial when the criteria for improved or stable was not met) in the pembrolizumab group was higher than in the placebo group (18.1% and 12.9%, respectively; difference = 5.2%; 95% CI, 1.0 to 9.4; P = 0.015).

At week 48, the proportion of patients with a deteriorated score in EORTC QLQ-LC13 symptom scales was similar between the 2 groups for chest pain (difference = −1.7%; 95% CI, −4.9 to 1.5; P = 0.295), coughing (difference = −0.1%; 95% CI, −3.9 to 3.6; P = 0.945), and dyspnea (difference = 3.2%; 95% CI, −1.5 to 7.8; P = 0.181).

Harms Results

The harms outcomes were available among the all patients as treated population in the KEYNOTE-091 study (N = 1,161). AEs were reported in 96% and 91% of patients in the pembrolizumab and placebo groups,

respectively. The most common AEs were increased weight (23% in the pembrolizumab group and 29% in the placebo group, respectively), pruritus (22% and 13%), and hypothyroidism (21% and 5%). The incidence was higher in the pembrolizumab group than in the placebo group for grade 3 to 5 AEs (34% and 26%), serious AEs (25% and 16%), AEs resulting in treatment discontinuation (20% and 6%), AEs resulting in death (2% and 1%), AEs of special interest (AEOSIs) (i.e., immune-mediated events and infusion-related reactions) (39% and 13%). The most frequently reported AEOSIs in the pembrolizumab and placebo groups were hypothyroidism (21% and 5%, respectively), hyperthyroidism (11% and 3%, respectively), and pneumonitis (7% and 3%, respectively).

Critical Appraisal

In the KEYNOTE-091 study, the review team and the clinical experts consulted for this review did not identify major issues that would impact the validity of the study results with presenting the DFS and OS outcomes through ad hoc analyses in the reimbursement request population, based on the fact that PD-L1 TPS category was 1 of the stratification variables.

The patient demographic and disease characteristics appeared generally balanced between the treatment groups in both the overall population and the reimbursement request population, suggesting that the benefits of the randomization were reasonably maintained in the subpopulation for reimbursement request. The review team noted that histologic status was unbalanced between the 2 groups (squamous = 27.8% in the pembrolizumab group versus 37.5% in the placebo group). To what extent this imbalance could bias the results is unknown. In the reimbursement request population, a higher proportion of patients in the pembrolizumab group (48%) discontinued from the study medication than in the placebo group (37%), mainly due to AEs. The clinical experts commented that the between-group imbalance and the reasons for study medication discontinuation were reasonable and in line with the safety outcomes that higher proportions of patients in the pembrolizumab group experienced AEOSIs than those in the placebo group. In the reimbursement request population, nearly all of the study patients (95%) received at least 1 concomitant medication and the proportion of patients with use of the most medications was similar between treatment groups. However, there was a higher proportion of some concomitant medications (e.g., antihistamines, corticosteroids, and thyroid replacement therapy) in the pembrolizumab group compared to the placebo group, which might have impacted the assessment of HRQoL and biased the results in favour of pembrolizumab, as these concomitant drug uses were most likely for the control or treatment of drug-related side effects associated with pembrolizumab. The proportion of patients with subsequent anticancer treatment during the trial was lower in the pembrolizumab group than in the placebo group for both antineoplastic therapy and immunotherapies. Although these uneven uses of anticancer therapies may have biased the efficacy results against pembrolizumab as compared to placebo group for OS, the extent of any important impact on interpretation of the observed effect could not be determined.

The triple-blind design of the trial likely mitigated risk due to knowledge of group assignment for the previously reported outcomes. Risk of bias due to missing outcome data for OS, DFS, and safety outcomes appeared to be low as losses to follow-up for reasons other than death were low and sensitivity analysis with the different censoring rule for DFS in the reimbursement request population was consistent. Risk of

bias due to missing outcomes data for HRQoL outcome is low as only a small proportion of patients had “no assessment” for the select measures (1% to 6%) in the patient-reported outcome full analysis set population (N = 1,161). OS and DFS were tested by applying a multiplicity hierarchical testing procedure to account for the potential inflated type I error rates across multiple end points and interim analyses. However, OS and DFS results were based on interim analyses, which may have overestimated the treatment effect estimates. The presence and extent of any overestimation that may have been introduced could not be determined.

Patients in the KEYNOTE-091 study were recruited from multiple countries, including Canada. The clinical experts considered the eligibility criteria of patients in the KEYNOTE-091 study to be appropriate and the demographic characteristics of the patients from the diversity aspect in the study were mostly in line with the patients seen in clinical practice in Canada. The clinical experts noted that pembrolizumab is often offered to patients who have an ECOG PS of up to 2 in clinical practice in Canada, and these patients might gain benefit from pembrolizumab, even though only patients with an ECOG PS of 0 to 1 were enrolled in the KEYNOTE-091 trial, per the study inclusion criteria. The clinical experts noted that presenting the survival outcomes among the subgroup of patients in the KEYNOTE-091 study who had a PD-L1 TPS of less than 50% and had adjuvant chemotherapy as appropriate for this review to align with the reimbursement request and address the unmet therapeutic needs.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor’s systematic review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CDA-AMC 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.

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 the expert committee members:

- probability of OS at months 36 and 48
- probability of DFS at months 24 and 48
- HRQoL as measured by the EORTC QLQ-C30 (global health status/QoL) and EORTC QLQ-LC13 symptomatic scales (chest pain, coughing, and dyspnea) at week 48
- grade 3 to 5 AEs.

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

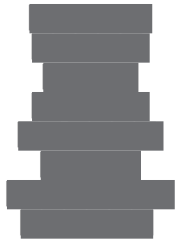
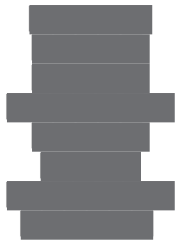
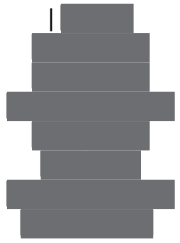
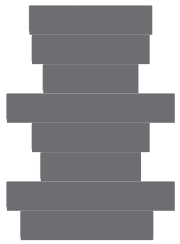
on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

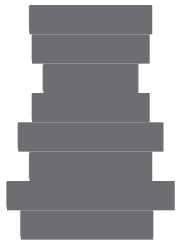
Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for pembrolizumab versus placebo in adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 tumour TPS of less than 50%.

Table 3: Summary of Findings for Pembrolizumab vs. Placebo for Adults With Stage IB, II, or IIIA NSCLC With a PD-L1 TPS of Less Than 50%

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Pembrolizumab	Difference		
Overall survival							
Probability of survival at 36 months Median (range) follow-up: 46.6 (0.6 to 84.2) months	726 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[a]	Pembrolizumab may result in little to no difference in OS compared to placebo at 36 months.
Probability of survival at 48 months Median (range) follow-up: 46.6 (0.6 to 84.2) months	726 (1 RCT)	NR	699 per 1,000 (646 to 745 per 1,000)	778 per 1,000 (729 to 820 per 1,000)	[redacted]	Moderate[b]	Pembrolizumab likely results in an increase in OS compared to placebo at 48 months.
Disease-free survival							
Probability of disease-free survival at 24 months Median (range) follow-up: 46.6 (0.6 to 84.2) months	726 (1 RCT)	NR	550 per 1,000 (497 to 600 per 1,000)	672 per 1,000 (619 to 719 per 1,000)	[redacted]	Moderate[c]	Pembrolizumab likely results in a clinically important increase in DFS compared to placebo at 24 months.
Probability of disease-free survival at 48 months Median (range) follow-up: 46.6 (0.6 to 84.2) months	726 (1 RCT)	NR	424 per 1,000 (367 to 479 per 1,000)	512 per 1,000 (452 to 569 per 1,000)	[redacted]	Moderate[c]	Pembrolizumab likely results in a clinically important increase in DFS compared to placebo at 48 months.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Pembrolizumab	Difference		
HRQoL (measured with EORTC QLQ-C30 and EORTC QLQ-LC13)							
Proportion of patients with a ≥ 10-point deterioration in EORTC QLQ-C30 global health status/ QoL score from baseline (0 [worst] to 100 [best]) Follow-up: 48 weeks	1,161 (1 RCT)	NR	129 per 1,000 (103 to 159 per 1,000)	181 per 1,000 (151 to 215 per 1,000)		High[d,e]	Pembrolizumab results in little to no clinically important difference in EORCT QLQ-C30 global health status/QoL compared to placebo.
Proportion of patients with a ≥ 10-point deterioration in EORTC QLQ-LC13 chest pain score from baseline (0 [best] to 100 [worst]) Follow-up: 48 weeks	1,161 (1 RCT)	NR	91 per 1,000 (69 to 118 per 1,000)	74 per 1,000 (54 to 99 per 1,000)		Low[d,f]	Pembrolizumab may result in little to no clinically important difference in EORTC QLQ-LC13 chest pain compared to placebo.
Proportion of patients with a ≥ 10-point deterioration in EORTC QLQ-LC13 coughing score from baseline (0 [best] to 100 [worst]) Follow-up: 48 weeks	1,161 (1 RCT)	NR	119 per 1,000 (94 to 148 per 1,000)	117 per 1,000 (92 to 147 per 1,000)		Low[d,f]	Pembrolizumab may result in little to no clinically important difference in EORTC QLQ-LC13 coughing compared to placebo.
Proportion of patients with a ≥ 10-point deterioration in EORTC QLQ-LC13 dyspnea score from baseline (0 [best] to 100 [worst]) Follow-up: 48 weeks	1,161 (1 RCT)	NR	189 per 1,000 (158 to 224 per 1,000)	221 per 1,000 (188 to 257 per 1,000)		Low[d,f]	Pembrolizumab may result in little to no clinically important difference in EORTC QLQ-LC13 dyspnea compared to placebo.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo	Pembrolizumab	Difference		
Harms							
Grade 3 to 5 AEs Median (range) follow-up: 46.7 (0.6 to 84.2) months	1,161 (1 RCT)	NR	258 per 1,000 (NR)	341 per 1,000 (NR)		High[d,e]	Pembrolizumab likely results in an increase in grade 3 to 5 AEs compared to placebo.

AE = adverse event; CDA-AMC = Canada's Drug Agency; CI = confidence interval; DFS = disease-free survival; EORTC = European Organization for Research and Treatment of Cancer; HRQoL = health-related quality of life; MID = minimal important difference; NR = not reported; NSCLC = non–small cell lung cancer; OS = overall survival; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-LC13 = Quality of Life Questionnaire Lung Cancer module 13; QoL = quality of life; RCT = randomized controlled trial; TPS = tumour proportion score; vs. = versus.

Note: Data presented in this table were based on analyses at a clinical cut-off date of January 24, 2023. Of note, the OS data were not mature as of January 24, 2023. The between-group differences for all the outcomes in this table were requested from the sponsor to aid in interpretation and were not part of the sponsor's analysis plan. 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 following footnotes.

[a]Rated down 2 levels for very serious imprecision. At the data cut-off date, the OS results data were immature. An empirically derived and validated between-group MID for OS was not identified. Based on a threshold that is usually used by CDA-AMC for an effect assessment of an adjuvant treatment in patients with NSCLC of similar severity or stage, a between-group difference in the probability of OS of 5% might be clinically meaningful. The 95% CI of the absolute effect included the "no effect" threshold of 0, as well as the clinical importance threshold of 5%.

[b]Rated down 1 level for serious imprecision. At data cut-off date, the OS results data were immature. An empirically derived and validated between-group MID for OS was not identified. Based on a threshold that is usually used by CDA-AMC for an effect assessment of an adjuvant treatment in patients with NSCLC of similar severity or stage, a between-group difference in the probability of OS of 5% might be clinically meaningful. At 48 months, the 95% CIs of the absolute effect excluded the "no effect" threshold of 0, and the point estimate and the upper bound of the 95% CI suggest a clinical important increase in OS based on the threshold of 5%.

[c]Rated down 1 level for serious imprecision. An empirically derived and validated between-group MID for DFS was not identified. Based on a threshold that is usually used by CDA-AMC for an effect assessment of an adjuvant treatment in patients with NSCLC of similar severity or stage, a between-group difference in the probability of DFS of 10% might be clinically meaningful. At both 24 months and 48 months, the 95% CIs of the absolute effect excluded the "no effect" threshold of 0, and the upper bound of the 95% CIs suggest a clinical important increase in DFS based on the threshold of 10%.

[d]Indirectness was not rated down. The outcomes data for HRQoL and harms were based on the total population in the KEYNOTE-091 trial. Although there may be uncertainties related to the presence and magnitude of any potential differences in these outcomes between the total population and the reimbursement request population, the review team and the clinical experts consulted for this review did not identify major issues that would impact the study results as PD-L1 TPS category was 1 of the stratification variables, and the patient characteristics appeared balanced between the treatment groups in both overall population and reimbursement request population, suggesting that the benefits of the randomization were reasonably maintained in the subpopulation for reimbursement request.

[e]Imprecision did not result in the level of certainty being rated down, as the 95% CI of the absolute effect excluded the null threshold of 0. The clinical experts consulted for this review could not provide a threshold of important difference; however, the CDA-AMC review team judged that the point estimate and 95% CI of the absolute effect were unlikely to include any important difference.

[f]Rated down 2 levels for very serious imprecision. The review team was unable to identify the MID to assess a between-group difference from the literature or the clinical experts consulted for this review; therefore, the null was used to assess certainty. The 95% CI of the absolute effect included the "no effect" threshold of 0.

Indirect Comparisons

In the absence of direct head-to-head trials evaluating the comparative efficacy of pembrolizumab and atezolizumab for the adjuvant treatment of adults with early-stage NSCLC who have undergone complete resection and platinum-based chemotherapy, the sponsor has conducted 1 ITC including only the subpopulation of participants with a TPS of 50% or greater. The findings from this ITC are used to support the sponsor's reimbursement request and request for a deviation from pharmacoeconomic requirements that excludes this subpopulation.

Description of Studies

The sponsor included 2 studies in their ITC: KEYNOTE-091 and IMpower010. For the KEYNOTE-091 study, the sponsor included only the ongoing trial patients after excluding patients who discontinued treatment. The sponsor did not report the median follow-up duration for this subpopulation; however, the median follow-up time for the intention-to-treat population of patients with a PD-L1 TPS of 50% or greater who were treated with pembrolizumab was 46.8 months (range, 3.4 to 83.5). For the IMpower010 study, from the published data, the median follow-up time for patients with a PD-L1 TPS of 50% or greater who were treated with atezolizumab was 35.98 months (range, 0.2 to 54.2). The sponsor did not report any assessment of homogeneity or any handling of potential effect modifiers.

Efficacy Results

The ITC of pembrolizumab versus atezolizumab in patients with a PD-L1 TPS of 50% or greater, stage II to IIIA disease, and prior adjuvant chemotherapy showed that pembrolizumab appears to be less effective than atezolizumab in this subpopulation with [redacted] ([redacted]).

Harms Results

Harms outcomes were not reported.

Critical Appraisal

The sponsor-submitted ITC was used to support their reimbursement request and request for a deviation from pharmacoeconomic requirements that excludes this subpopulation of adults with early-stage NSCLC who have undergone complete resection and platinum-based chemotherapy and have a PD-L1 TPS of 50% or greater. The sponsor did not conduct an additional ITC for the reimbursement request population (i.e., patients with a PD-L1 TPS < 50%). They did not conduct a systematic literature review for this ITC. There appears to be a 10-month difference in median follow-up time between both trials, which may have an impact on time-to-event outcomes. The clinical experts consulted for this review commented that the baseline patient characteristics from both trials appeared to be well matched. The sponsor, however, did not report or appear to assess homogeneity between the 2 studies, and could only include published aggregate-level data from the IMpower010 study. Therefore, it is unclear if sources of clinical or methodological heterogeneity may have biased effect estimates in the ITC.

Harms outcomes and other outcomes of relevance to patients (e.g., HRQoL) were not reported.

The clinical experts noted that, while there are currently no therapy options available after adjuvant chemotherapy for patients with resected stage IB to IIIA NSCLC who have a PD-L1 TPS of less than 50%,

atezolizumab is currently the treatment of choice for patients with a PD-L1 TPS of 50% or greater. They commented that the results from this ITC support the current therapy guidelines and the sponsor's reimbursement request.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 TPS < 50%, as determined by a validated test.
Treatment	Pembrolizumab
Dose regimen	200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year or until disease recurrence or unacceptable toxicity
Submitted price	Pembrolizumab: $4,400 per 100 mg/4 mL vial
Submitted treatment cost	$8,800 per 21-day cycle ($158,400 for 18 cycles)[a]
Comparator	Active surveillance
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (36 years)
Key data sources	The KEYNOTE-091 trial provided DFS data to estimate transitions from DF to LR, DM, and death for pembrolizumab and active surveillance. A SEER-Medicare RWE study (calibrated with OS data from the KEYNOTE-091 trial) estimated transitions from LR to DM. The KEYNOTE-189 and KEYNOTE-407 trials informed the OS and PFS data used to estimate transitions from DM to death.
Key limitations	• The impact of pembrolizumab on long-term OS is highly uncertain due to immature OS data (median follow-up = 47 months), lack of validated long-term comparative evidence, limitations in the sponsor's modelling approach owing to the use of time-invariant extrapolations across all postprogression health states, and limitations in the sponsor's calibration approach. Approximately 75% of incremental LYs gained by patients treated with pembrolizumab were accrued via extrapolation, representing model-generated outcomes rather than trial-based evidence. • The long-term DFS of active surveillance is highly uncertain due to the sponsor's use of parametric modelling to extrapolate beyond observed data, with approximately 95% of incremental QALYs derived from extrapolation. The sponsor's external validation relied on a population that differed substantially from that in the KEYNOTE-091 trial, raising concerns about the accuracy of long-term DFS predictions. • The cure assumption implemented by the sponsor lacked face validity as it equated the long-term survival outcomes of current or former smokers with those of the average person in Canada,

Component	Description
	disregarding the excess mortality risks associated with smoking and comorbidities. The study used to support this assumption involved a population in which 81% of patients had stage I NSCLC, compared to only 12% of patients with stage I disease at baseline in the KEYNOTE-091 population, indicating differences in disease severity and prognosis. • Due to the underestimation of OS produced by the modelling approach, the sponsor applied a calibration method assuming that patients with LR on active surveillance progress faster than those treated with pembrolizumab in the first 10 years from adjuvant treatment initiation. In the absence of trial data for subsequent transitions, the sponsor's assumptions are speculative, contributing to the uncertainty in the predicted long-term OS outcomes. • The submitted model did not include age-related disutilities, leading to an overestimation of QALYs gained, particularly for older patients. This omission biases the cost-effectiveness results in favour of pembrolizumab by ignoring the natural decline in HRQoL as patients age. • The assumption of a fixed dosage for pembrolizumab (200 mg every 3 weeks) considered by the sponsor is not aligned with the public drug plan's implementation strategy, which uses weight-based dosing. Weight-based dosing is expected to result in lower costs, assuming vial sharing is possible. • Based on clinical expert feedback, adjuvant osimertinib is a relevant comparator for a subset of patients within this indication, specifically those with a sensitizing *EGFR* mutations. As this was not considered by the sponsor, the cost-effectiveness of adjuvant pembrolizumab compared with adjuvant osimertinib is unknown.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by making changes to the following model parameters: adopting an alternative parametric distribution to extrapolate the transition from DF to LR in patients receiving active surveillance; assuming that 82% of patients who are disease free 10 years posttreatment initiation would be considered cured; aligning the time points used for calibration of health state transition rates between adjuvant pembrolizumab and active surveillance with the median and maximum follow-up observed in the KEYNOTE-091 trial; including age-related disutility; and adopting weight-based dosage for pembrolizumab. • In the CDA-AMC base case, adjuvant pembrolizumab is associated with an ICER of $103,900 per QALY gained compared with active surveillance (incremental costs = $75,957; incremental QALYs = 0.73). A price reduction of 54% is required for pembrolizumab to be considered cost-effective relative to active surveillance at a WTP threshold of $50,000 per QALY gained. • The cost-effectiveness of pembrolizumab was sensitive to assumptions concerning cure among patients who achieve long-term DFS and the dosage adopted for pembrolizumab. When removing the cure assumption, the ICER for pembrolizumab increased to $122,164 per QALY gained compared to active surveillance. When adopting a fixed dosage for pembrolizumab based on the product monograph, the ICER for pembrolizumab increased to $135,566 per QALY gained compared to active surveillance.

DF = disease free; DM = distant metastasis; DFS = disease-free survival; ICER = incremental cost-effectiveness ratio; LR = locoregional recurrence; LY = life-year; NSCLC = non–small cell lung cancer; OS = overall survival; QALY = quality-adjusted life-year; RWE = real-world evidence; SEER = Surveillance, Epidemiology, and End Results Program; T2a = tumour stage 2a; TPS = tumour proportion score; WTP = willingness to pay.

[a]The sponsor assumed patients received a fixed pembrolizumab dose of 200 mg every 3 weeks for up to 18 cycles, which incorporated vial sharing.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the proportion of patients tested for PD-L1 expression is underestimated; the market uptake of pembrolizumab is underestimated; the dosage for pembrolizumab is not aligned with the input received from participating public drug plans and expert feedback; and the impact of adjuvant pembrolizumab on subsequent therapy costs is uncertain. CDA-AMC reanalyses included increasing the proportion of patients tested for PD-L1 expression, adopting a rapid uptake of pembrolizumab, adopting a weight-based dosage for pembrolizumab, and aligning the distant

metastasis transition probabilities used in the budget impact analysis with the CDA-AMC base case of the cost-utility analysis to estimate subsequent therapy costs.

Based on the CDA-AMC base case, the 3-year budget impact is expected to be $31,937,001 (year 1 = $5,297,747; year 2 = $12,988,648; year 3 = $13,650,607) should the public drug plans reimburse pembrolizumab for the adjuvant treatment of adult patients with stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection and platinum-based chemotherapy and whose tumours have a PD-L1 TPS of less than 50%, as determined by a validated test. The 3-year total budgetary impact increased to $43,183,321 when a fixed dosage was adopted for pembrolizumab.

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 Villeneuve, and Danica Wasney.

Meeting date: December 4, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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