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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3–4N2) non–small cell lung cancer (NSCLC) in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgery.

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

Canada's Drug Agency (CDA-AMC) recommends that Keytruda be reimbursed by public drug plans for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3 to 4N2) non–small cell lung cancer (NSCLC), in combination with platinum-containing chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgery, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat adult patients who have stage II, IIIA, or IIIB (T3 to 4N2) NSCLC with tumours that can be surgically removed, are in relatively good health (as measured by performance status), have no prior treatment with drugs that change how the immune system works, and have no known *EGFR* or *ALK* gene abnormalities.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed by clinicians with expertise in managing patients with NSCLC and if the cost of Keytruda is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda in combination with platinum-based chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, was better at improving survival and lowering the chances of cancer returning when compared to neoadjuvant platinum-based chemotherapy.
- Keytruda may meet some of the needs identified as important to patients, including improving survival and delaying their disease from recurring, which may delay the onset of symptoms from recurrent disease, maintaining their health-related quality of life (HRQoL) and having a manageable safety profile.
- 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 $17 million over the next 3 years.

Summary

Additional Information

What Is NSCLC?

In lung cancer, cells in the lungs grow uncontrollably and may spread to nearby lymph nodes and other organs. It is the most common cancer and the leading cause of cancer-related deaths in Canada. NSCLC is the most frequent type, accounting for about 88% of lung cancer cases. In Canada, the 5-year prevalence of NSCLC is approximately 92 to 98 cases per 100,000 people. About 30% to 35% of NSCLC cases are detected early enough to potentially benefit from surgical removal of tumours.

Unmet Needs in NSCLC

Major unmet needs include the need of new therapies that can enhance symptom control, achieve cure, improve quality of life, and maintain disease stability, even in cases where a cure is not possible.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $13,495 per patient in the neoadjuvant setting, and $8,800 per 21-day cycle in the adjuvant setting.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3 to 4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 randomized, phase III, placebo-controlled trial (the KEYNOTE-671 trial, N = 797) in adult patients with resectable stage II, IIIA, or selected stage IIIB (T3 to 4N2) NSCLC demonstrated that pembrolizumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by pembrolizumab monotherapy as adjuvant treatment (hereinafter referred to as *perioperative pembrolizumab treatment*), resulted in clinically meaningful benefits in overall survival (OS) and event-free survival (EFS) when compared to placebo with platinum-based chemotherapy as neoadjuvant treatment followed by placebo in the adjuvant setting. The study showed an improvement in the median OS with a hazard ratio (HR) of 0.72 (95% confidence interval [CI], 0.56 to 0.93; P = 0.00517) in the pembrolizumab group compared to the placebo group. The Kaplan-Meier (KM)-estimated between-group differences in probability of being alive at 36 months and 48 months were [redacted] and [redacted] in favour of the pembrolizumab group, respectively, when compared to the placebo group. The study showed an improvement in the median EFS with an HR of 0.59 (95% CI, 0.48 to 0.72; P < 0.00001) in favour of the pembrolizumab group. The KM-estimated between-group differences in probability of EFS at 36 weeks and 48 weeks were [redacted] and [redacted] in favour of the pembrolizumab group, respectively, when compared to the placebo group. More than half of the patients reported stable or improved HRQoL over time in the study, as assessed by global health status or quality of life (QoL) score, with a slightly higher proportion favouring pembrolizumab over placebo (58.7% versus 51.8%; between-group difference = 7.0% [95% CI, 0.1% to 13.9%]). The adverse effect profile of pembrolizumab is manageable and consistent with the known side effects of immune checkpoint inhibitors (ICIs).

pERC considered the needs expressed by patients for treatment options that improve survival and QoL, delay symptom onset, and reduce caregiver burden. pERC determined that pembrolizumab met several of these needs, including improvements in OS and EFS that may delay the onset of symptoms from recurrent disease, maintenance of HRQoL, and a manageable safety profile. pERC also considered the fact that the use of perioperative (neoadjuvant followed by adjuvant) ICI therapy in combination with chemotherapy is not an established or accessible option in Canada at this time and noted that perioperative pembrolizumab therapy may meet an unmet need in improving clinical outcomes.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for perioperative pembrolizumab was $119,365 per quality-adjusted life-year (QALY) gained, compared with neoadjuvant nivolumab plus chemotherapy. At this ICER,

pembrolizumab is not cost-effective at a $50,000 per QALY gained willingness-to-pay (WTP) threshold for patients with resectable stage II, IIA, and IIIB (T3 to 4N2) NSCLC. A price reduction is required for pembrolizumab to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Neoadjuvant treatment with pembrolizumab in combination with platinum-based chemotherapy, followed by adjuvant pembrolizumab, should be reimbursed in adult patients with stage II, IIIA, or IIIB (T3 to 4N2) NSCLC whose tumours are resectable.	Evidence from the KEYNOTE-671 study demonstrated clinical benefit from neoadjuvant treatment with pembrolizumab, followed by adjuvant pembrolizumab monotherapy after surgery (referred to as "perioperative" pembrolizumab). The population outlined reflects the patient population of the KEYNOTE-671 study.	In the KEYNOTE-671 study, disease staging was based on the AJCC staging system (eighth edition). No evidence on the safety of adjuvant pembrolizumab when used along with other anticancer treatments was included in this review. In the neoadjuvant setting, patients who experience intolerable adverse events attributable to platinum-based chemotherapy may receive the remainder of treatment with pembrolizumab monotherapy, and vice versa.
2. Patients must have good performance status.	Patients enrolled in the KEYNOTE-671 study had an ECOG performance status of 0 or 1 at baseline.	Based on clinical expert input, selected patients with an ECOG performance status of more than 1 could be considered for treatment at the discretion of the treating physician.
3. Patients are ineligible for neoadjuvant treatment with pembrolizumab in combination with platinum-based chemotherapy if they have any of the following: 3.1. prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, anti–CTLA-4, or any other immune-modulating agent 3.2. known *EGFR* mutations or *ALK* translocations.	In the KEYNOTE-671 study, patients who received prior treatment with an anti–PD-1, anti–PD-L1, anti–PD-L2, anti-CD137, anti–CTLA-4, or any other immune-modulating agent were excluded. The proportion of patients with known *EGFR* mutations or *ALK* translocations included in the KEYNOTE-671 study was small (< 5%), and the clinical experts expressed caution in including patients with these characteristics when other treatment options are available (i.e., adjuvant *EGFR or ALK* inhibitor therapy).	Rapid molecular testing is needed to identify patients with NSCLC carrying molecular mutations who should not undergo perioperative chemoimmunotherapy.
Discontinuation		
4. Neoadjuvant treatment with pembrolizumab in combination with platinum-based chemotherapy, followed by adjuvant pembrolizumab, should be discontinued upon the occurrence of any of the following:	In the KEYNOTE-671 study, treatments were continued until disease progression, recurrence unacceptable toxicity, or completion of a total of 17 cycles of pembrolizumab 200 mg every 3 weeks treatment (i.e., 4 and 13 cycles in the neoadjuvant and adjuvant settings, respectively). According to clinical experts, clinical and	—

Reimbursement condition	Reason	Implementation guidance
4.1. disease progression or recurrence 4.1.1. patients should be assessed for evidence of disease progression during treatment as per local standard practice 4.2. unacceptable toxicity 4.3. completion of 1 year of pembrolizumab-based therapy administered either every 21 days or every 42 days, with 12 weeks of therapy provided in the neoadjuvant setting and the remainder in the adjuvant setting (e.g., 4 cycles of neoadjuvant and 13 cycles adjuvant therapy).	biological evaluations are performed at every cycle of therapy as per standard practice in oncology similarly as patients undergoing chemoimmunotherapy in the advanced disease setting.	
Prescribing		
5. Neoadjuvant treatment with pembrolizumab in combination with platinum-based chemotherapy, followed by adjuvant pembrolizumab, should be prescribed by clinicians with expertise in managing patients with NSCLC.	This is meant to ensure that pembrolizumab is prescribed for appropriate patients and adverse events are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	The ICER for perioperative pembrolizumab is $119,365 when compared with neoadjuvant nivolumab. A price reduction of 30% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained compared to neoadjuvant nivolumab. The identified internal validity concerns within the sponsor's NMA and the lack of direct comparative evidence against neoadjuvant nivolumab means that a higher price reduction may be warranted.	—

AJCC = American Joint Committee on Cancer; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; NSCLC = non–small-cell lung cancer; PS = performance status; QALY = quality-adjusted life-year.

Discussion Points

- **Identified treatment needs**: Patients and clinicians emphasized the value of new therapies that can enhance symptom control, achieve cure, improve HRQoL, and maintain disease stability, even in cases where a cure is not possible. pERC noted that the use of perioperative (neoadjuvant followed by adjuvant) ICI in combination with chemotherapy is not currently an established or widely accessible treatment option in Canada. In this context, pembrolizumab may address an important unmet need of improving surgical outcomes, optimizing cure rates and pathological complete response (pCR), and targeting micrometastatic disease.
- **Efficacy and safety considerations**: pERC acknowledged the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of the evidence from the pivotal KEYNOTE-671 trial, which demonstrated moderate and high certainty that perioperative pembrolizumab in combination with chemotherapy improves OS and EFS compared to neoadjuvant chemotherapy alone. Perioperative pembrolizumab also showed little to no effect on HRQoL, as indicated by the trial's findings. pERC weighed these benefits against the evidence of little to no difference in overall adverse events (AEs), while acknowledging the high and moderate certainty of an increased risk of serious adverse events (SAEs) and adverse events of special interest (AESIs), respectively, with perioperative pembrolizumab treatment compared to neoadjuvant chemotherapy. There were also slightly more overall deaths with perioperative pembrolizumab treatment (6.6% versus 3.8% neoadjuvant chemotherapy). pERC considered the clinical expert input noting that the adverse effects of pembrolizumab are generally manageable, and concluded that the associated risks may be acceptable given the potential benefits.
- **Generalizability considerations**: pERC identified ongoing uncertainties regarding the generalizability of the KEYNOTE-671 study results, particularly for patients with *EGFR* or *ALK* mutations and those who achieve a pCR. Notably, less than 5% of the trial population had *EGFR* or *ALK* mutations, and existing evidence suggests that other adjuvant targeted therapies may provide significant benefits for these patients. Additionally, the committee highlighted that the potential added benefit of adjuvant ICI therapy following the neoadjuvant phase, especially among those patients achieving a pCR with surgery, remains unclear, as this question is not adequately addressed by the current body of evidence.
- **Indirect evidence**: No direct comparative evidence between perioperative pembrolizumab versus existing treatments (other than neoadjuvant chemotherapy) was submitted. pERC discussed the results of a network meta-analysis (NMA) submitted by the sponsor, which suggested that the efficacy of perioperative pembrolizumab plus chemotherapy could potentially be similar to neoadjuvant nivolumab plus chemotherapy, a relevant comparator; however, the results were uncertain due to methodological limitations. The exclusion of adjuvant trials and emerging therapies from the network also diminishes the relevance of the findings in the context of the Canadian treatment landscape (e.g., comparisons to adjuvant chemotherapy followed by pembrolizumab or atezolizumab are unavailable). Overall, based on the submitted evidence, pERC noted that the comparative efficacy

and safety of perioperative pembrolizumab versus alternative treatments (other than neoadjuvant chemotherapy) in the patient population under review is inconclusive.

- **Timely access to molecular testing**: pERC noted that molecular testing for driver mutations (*EGFR* and *ALK*) is important for selecting appropriate treatment. While molecular testing is performed in a timely manner in most treatment centres in Canada, it remains a challenge in some centres with a long turnaround time. Improved timeliness of access to molecular testing is important to optimize disease management.

Background

Lung cancer is the most common malignancy and the leading cause of cancer-related death in Canada, with NSCLC accounting for approximately 88% of cases. It was estimated that, in 2024, 32,100 Canadians would be diagnosed with lung cancer and 20,700 deaths would occur due to the disease. Most NSCLC cases are diagnosed at an advanced stage, but about 30% to 35% are classified as early stage and potentially resectable. Despite surgery or definitive chemoradiotherapy being the only potentially curative options, high recurrence rates — ranging from 30% to 70%, depending on the stage — remain a major challenge, and 5-year survival rates for stage II and III NSCLC are poor at 39% and 16%, respectively. Immunotherapy has been integrated into treatment regimens to improve outcomes, with agents like nivolumab and atezolizumab demonstrating benefits in neoadjuvant or adjuvant settings. However, unmet needs persist, particularly in reducing recurrence and improving survival in resectable NSCLC.

Pembrolizumab has been approved by Health Canada for the treatment of adult patients with resectable stage II, IIIA, or IIIB (T3 to 4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery. Pembrolizumab is a monoclonal antibody targeting PD-1. It is available as solution for infusion (100 mg/4 mL). The recommended dosage in the product monograph is 200 mg every 3 weeks or 400 mg every 6 weeks.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized, double-blind, placebo-controlled trial in patients with resectable stage II, IIIA, or stage IIIB (T3 to 4N2) NSCLC, and 1 indirect treatment comparison (ITC) using an NMA
- a joint submission of patients' perspectives by the Canadian Cancer Survivor Network (CCSN), Lung Cancer Canada (LCC), and the Lung Health Foundation (LHF)
- input from 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 the LCC Medical Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group input was received as a joint submission by the CCSN, LCC, and the LHF regarding the use of pembrolizumab (Keytruda) for resectable stage II, IIIA, or IIIB NSCLC. Together, these organizations gathered patient perspectives through a survey conducted from August 1, 2024, to September 16, 2024, which included responses from 3 patients and 1 caregiver, all of whom were from Canada. All respondents reported having experience with pembrolizumab; however, it was unclear whether their use aligned specifically with the indication under review (resectable stage II, IIIA, or IIIB NSCLC), as pembrolizumab is approved for multiple indications in lung cancer and may have been used in different phases of treatment.

The patients reported varying stages of NSCLC, ranging from stage IB to stage IV. They had undergone various treatments, including surgery, radiation, chemotherapy, immunotherapy, and participation in clinical trials. Symptoms such as cough, shortness of breath, fatigue, and nausea were commonly reported, with significant impacts on their daily lives, including their ability to work, pursue hobbies, perform household tasks, and engage in physical activities. Emotional well-being, family relationships, and financial burdens were also identified as being impacted by the disease.

When asked about their experiences with current treatments, patients highlighted both the benefits and challenges of their therapies. They reported that pembrolizumab, in combination with other treatments, helped reduce fatigue, manage cough, and improve appetite, energy, and pain levels. However, side effects such as fatigue, low energy, edema, and weight gain were noted. Despite these side effects, most respondents found them manageable with medications, allowing them to continue participating in daily activities. While 1 respondent faced access challenges, such as travel costs and availability of targeted therapies, others reported no significant barriers to treatment.

Respondents emphasized that new treatments should focus on improving symptom control, QoL, and maintaining stability, even when a cure is not possible. Reduced cost was also a priority. Pembrolizumab was viewed positively, with 1 patient noting that it provided them with additional time to spend with loved ones and continue with their daily life. The extended EFS reported in clinical trials was seen as particularly valuable, offering patients more time to enjoy meaningful activities.

Adverse effects such as colitis, hypothyroidism, and rheumatoid arthritis were reported, but most respondents found these side effects tolerable in exchange for the benefits of pembrolizumab. Overall, the treatment was rated favourably, with respondents appreciating its ability to control their disease and improve their QoL.

The patient groups acknowledged the small sample size of this submission but emphasized that the responses still highlight the positive impact of pembrolizumab for lung cancer patients. The groups emphasized that the option to use pembrolizumab as part of a perioperative treatment plan offers patients a valuable new approach to managing their disease at multiple stages.

Clinician Input

Input From Clinical Experts Consulted for This Review

Clinical experts consulted for this review highlighted several unmet needs in the treatment of resectable NSCLC, particularly in stages II, IIIA, and IIIB, where optimizing cure rates and targeting micrometastatic disease are critical. Current therapies, such as neoadjuvant chemoimmunotherapy with nivolumab, have demonstrated efficacy but leave substantial room for improvement, according to the clinical experts. However, the clinical experts mentioned that the added value of adjuvant immunotherapy after neoadjuvant therapy remains unproven. Additional gaps were noted, such as uncertainties regarding the benefits of immunotherapy in PD-L1–negative tumours and specific subgroups within the early-stage NSCLC population.

Regarding pembrolizumab's place in therapy, the experts indicated it would serve as an alternative to nivolumab in the neoadjuvant chemoimmunotherapy setting, particularly for stages II and IIIA, with potential applicability in stage IIIB. The experts emphasized the importance of assessing neoadjuvant response through imaging, while recognizing challenges such as nodal immune flare (NIF), which could mimic progression. The clinical experts noted that discontinuation due to progression or severe toxicity may occur, but also acknowledged that an immune phenomenon can sometimes be difficult to immediately distinguish from progression.

Clinician Group Input

Two clinician groups including a total of 25 clinicians — the OH-CCO Lung Cancer Drug Advisory Committee and the LCC Medical Advisory Committee — provided input for this review.

According to both groups, the current standard treatment for patients with resectable stage II or III NSCLC includes neoadjuvant platinum-based chemotherapy, often combined with nivolumab. However, there is no access to adjuvant immunotherapy for patients who have undergone neoadjuvant chemoimmunotherapy. The treatment goals include curing the disease, improving OS, and reducing the chance of recurrence, as measured by disease-free survival (DFS).

The clinician groups noted that a key unmet need is the lack of adjuvant immunotherapy for patients who have received neoadjuvant chemoimmunotherapy.

Regarding place in therapy, pembrolizumab combined with chemotherapy would represent an alternative to neoadjuvant chemoimmunotherapy with nivolumab. The clinician groups suggested that pembrolizumab could be a potential option for patients with resectable stage II or III disease who do not have *EGFR* or *ALK* mutations and have no contraindications to immunotherapy. Patients least suited for treatment would include those with significant comorbidities, poor surgical candidacy, or contraindications to immunotherapy.

The clinician groups stated that treatment response would be assessed using imaging, including CT scans, both before surgery and during follow-up to monitor for disease recurrence. In the adjuvant phase, CT scans should be performed every 3 to 6 months. Treatment discontinuation would occur due to disease progression, severe AEs, or completion of the treatment course.

The clinician groups also noted that the appropriate treatment setting for pembrolizumab is in an outpatient clinic under the supervision of medical oncologists and thoracic surgeons experienced in managing thoracic malignancies. Surgery remains a key part of the treatment plan, and perioperative pembrolizumab is expected to improve surgical outcomes by increasing R0 resections and improving lymph node downstaging.

Drug Program Input

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
The KEYNOTE-671 study compared neoadjuvant pembrolizumab-cisplatin doublet therapy followed by surgery and adjuvant pembrolizumab to neoadjuvant cisplatin doublet therapy followed by surgery and placebo. At the time of this input, adjuvant platinum chemotherapy followed by pembrolizumab (if PD-L1 TPS < 50%) or perioperative durvalumab are under review. Funded comparators include: • neoadjuvant chemotherapy with or without nivolumab followed by surgery with or without adjuvant platinum chemotherapy • neoadjuvant chemotherapy with or without nivolumab followed by surgery with or without adjuvant osimertinib if *EGFR*-positive • surgery followed by platinum chemotherapy and either adjuvant atezolizumab if PD-L1 TPS ≥ 50% and *EGFR*- or *ALK*-negative, or adjuvant osimertinib if *EGFR*-positive.	This is a comment to inform pERC deliberations.
Considerations for initiation of therapy	
Less than 5% of the population with pembrolizumab were either *EGFR*-positive or had *ALK* translocation. Can pERC confirm whether patients with *EGFR* mutation or *ALK* translocation should be eligible for perioperative pembrolizumab?	The clinical experts consulted by CDA-AMC expressed a preference against using this treatment in this population due to the limited representation of patients with these specific characteristics in the trial. While acknowledging that some patients from this subgroup were included in the KEYNOTE-671 trial, they noted that the small sample size makes it challenging to draw definitive conclusions about the treatment's efficacy for this subgroup. pERC agreed with the clinical experts and noted that patients with *EGFR* mutation or *ALK* translocation would not be eligible for perioperative pembrolizumab.

Drug program implementation questions	Clinical expert response
Under what clinical circumstances might perioperative pembrolizumab be preferred over perioperative durvalumab, neoadjuvant nivolumab, adjuvant atezolizumab, or adjuvant pembrolizumab?	The clinical experts indicated that while each of these immunotherapy options has shown some potential benefits in certain settings, the data are still evolving, and direct comparisons between these treatments are limited. Consequently, they emphasized the need for more robust evidence to determine clear clinical advantages for 1 approach over another in the perioperative or adjuvant setting.
Can pembrolizumab be administered with alternate chemotherapy if a patient cannot receive or tolerate platinum-based chemotherapy in the neoadjuvant phase?	If a patient is unable to receive or tolerate platinum-based chemotherapy in the neoadjuvant phase, the experts clarified that platinum-based chemotherapy is essential for achieving the intended efficacy of the treatment regimen. If an alternative to cisplatin is needed due to tolerance issues or specific contraindications, the experts would recommend carboplatin as a substitute when used in combination with pembrolizumab. They believed that carboplatin may provide a more tolerable option for some patients while maintaining the treatment's effectiveness, as it still falls within the platinum-based category critical to the therapeutic protocol. pERC agreed with the clinical experts and noted that no evidence for the use of pembrolizumab in combination with non–platinum-based chemotherapy in the neoadjuvant phase was reviewed by the committee.
Perioperative durvalumab is also under review. Where possible, the reimbursement criteria should align.	This is a comment to inform pERC deliberations.
Considerations for prescribing of therapy	
PAG would like to inform pERC that most jurisdictions use weight-based dosing up to a cap for pembrolizumab (2 mg/kg up to 200 mg every 3 weeks, or 4 mg/kg up to 400 mg every 6 weeks).	This is a comment to inform pERC deliberations.
Would patients be eligible for pembrolizumab for downstream immunotherapy in the following situations? • The patient's disease progresses during neoadjuvant pembrolizumab. • The patient receives neoadjuvant pembrolizumab but is not able to proceed to surgery. • The patient's disease progresses during or recurs shortly after adjuvant pembrolizumab. • The patient has started but is not able to complete adjuvant pembrolizumab for reasons other than disease progression.	In these various scenarios, the experts outlined specific considerations: • For patients whose disease progresses during neoadjuvant pembrolizumab, the experts would not recommend continuing pembrolizumab if progression occurs during the neoadjuvant phase, as this would indicate a lack of response to the therapy, and further immunotherapy would likely be ineffective. • For patients who receive neoadjuvant pembrolizumab but are unable to proceed to surgery, the experts noted that eligibility would depend on the reason for not proceeding with surgery. If surgery is cancelled due to disease progression or patient health issues, further immunotherapy may not be suitable. However, specific details of the case could affect this decision. • For patients whose disease progresses during or recurs shortly after adjuvant pembrolizumab, experts would consider re-treating with pembrolizumab if the recurrence occurs 6 months or more after completing the initial adjuvant therapy, as this suggests a delayed progression. If recurrence

Drug program implementation questions	Clinical expert response
	happens within 6 months, additional pembrolizumab would likely not be effective. • For patients unable to complete adjuvant pembrolizumab for reasons other than disease progression, re-treatment could be considered if a reasonable interval has passed since the last dose, allowing some recovery time. However, eligibility would again depend on the specific circumstances, with a preference for longer intervals before reinitiating therapy. Overall, the experts suggest a cautious approach, emphasizing response to prior treatment, interval duration since the last immunotherapy, and the specific clinical context in determining re-treatment eligibility. pERC agreed with the clinical experts' input in the aforementioned scenarios.
Generalizability	
Should patients with an ECOG PS score > 1 be eligible? Should the ability to continue to surgery following neoadjuvant therapy be a consideration?	The experts suggested that patients with an ECOG score of 2 could potentially be eligible for neoadjuvant pembrolizumab, especially those with resectable stage III disease who are otherwise young and relatively fit. However, they clarified that patients with an ECOG score of 3 should not be considered eligible, as the level of functional impairment would likely make them unsuitable candidates for such intensive therapy. The experts emphasized that the key criterion for neoadjuvant treatment is a patient's suitability for surgery (i.e., if a surgeon has assessed a patient and determined they are fit for a thoracotomy, it implies a sufficient performance status for neoadjuvant therapy). Consequently, they would not place excessive emphasis on minor differences in ECOG status if a patient is deemed surgically operable. For the experts, the primary consideration is ensuring that the patient's overall condition allows them to complete the treatment pathway, which includes both neoadjuvant therapy and subsequent surgery. pERC determined that patients must have good performance status. Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.
Should patients who are currently on or who were previously treated with neoadjuvant nivolumab plus chemotherapy be eligible for a switch to perioperative pembrolizumab?	The experts indicated that while this scenario may arise infrequently, it could be a viable option. They noted that patients could potentially benefit from adjuvant immunotherapy provided in the perioperative pembrolizumab regimen. Given that most patients initially receive neoadjuvant nivolumab plus chemotherapy, the number of patients needing or opting for a switch is expected to be small. However, they agreed that if a clinician decided that a switch was appropriate for a particular patient, it could be considered within the same eligible population (i.e., personalized treatment adjustments based on the clinical judgment of the treating physician). pERC emphasized that treatment selection should be determined upfront, before initiation. Switching from

Drug program implementation questions	Clinical expert response
	neoadjuvant nivolumab plus chemotherapy to perioperative pembrolizumab may be allowed as long as the decision is not based on treatment response. Specifically, patients who experience disease progression or an incomplete response during neoadjuvant nivolumab plus chemotherapy should not be eligible for a switch to perioperative pembrolizumab.
System and economic issues	
The sponsor estimated a 3-year incremental budget of $17.4 million ($930,000 in year 1, $6.3 million in year 2, and $10.1 million in year 3). This is significantly lower than the estimated 3-year incremental budget impact of $65.2 million for perioperative durvalumab (which was not considered in Merck's BIA for perioperative pembrolizumab). PAG is concerned that if these estimates are low, there would be a resulting higher budget impact.	This is a comment to inform pERC deliberations.
Durvalumab, atezolizumab, and nivolumab have confidential prices negotiated.	This is a comment to inform pERC deliberations.

BIA = budget impact analysis, CDA-AMC = Canada's Drug Agency; ECOG = Eastern Cooperative Oncology Group; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = performance status; TPS = Tumor Proportion Score.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal study was included in this submission. The KEYNOTE-671 trial was a phase III, randomized, double-blind, placebo-controlled trial that evaluated pembrolizumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by pembrolizumab monotherapy as adjuvant treatment, in patients with resectable stage II, IIIA, or stage IIIB (T3 to 4N2) NSCLC. A total of 797 patients were randomized 1:1 to receive either pembrolizumab or placebo, each in combination with chemotherapy for 4 cycles, followed by up to 13 cycles of pembrolizumab monotherapy or placebo after surgery. The co-primary end points were EFS and OS. Other outcomes included HRQoL and safety measures. The study aimed to assess the efficacy of pembrolizumab in reducing the risk of recurrence, progression, or death, and in improving long-term survival in this population.

The baseline characteristics of the study population were well balanced between treatment arms. The median age of participants was approximately 64 years, with the majority being male (74%). Most patients had stage IIIA disease (53%) and had an ECOG performance status score of 0 or 1. Both squamous and nonsquamous histologies were well represented, and around one-third of the participants had a PD-L1 Tumor Proportion Score (TPS) greater than or equal to 50%.

Efficacy Results

In the KEYNOTE-671 trial, pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in OS compared to placebo. At the second interim analysis (IA2), the HR was 0.72 (95% CI, 0.56 to 0.93; P = 0.00517). The median OS was not reached in the pembrolizumab arm, whereas it was 52.4 months in the placebo arm. At 48 months, [redacted] of patients in the pembrolizumab arm were alive compared to 51.5% in the placebo arm, an absolute difference of [redacted]

EFS, a co-primary end point in the KEYNOTE 671 study, also showed significant improvement with pembrolizumab. At IA2, the median EFS in the pembrolizumab arm was 47.2 months (95% CI, 32.9 to not reached) compared to 18.3 months (95% CI, 14.8 to 22.1) in the placebo arm, representing an approximate 29-month extension. At 48 months, the EFS rate was [redacted] for pembrolizumab versus 26.2% for placebo, a risk difference of [redacted] The HR for EFS was 0.59 (95% CI, 0.48 to 0.72; P < 0.00001). Kaplan-Meier curves showed separation beginning at approximately 5 months, with consistent benefits across prespecified subgroups, emphasizing pembrolizumab's efficacy in reducing disease recurrence and progression.

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) ranges from 0 to 100, with higher scores indicating better health status. The difference in least squares (LS) mean change from baseline in global health status for pembrolizumab versus placebo was 1.43 points (95% CI, −1.64 to 4.49) at neoadjuvant week 11, and 2.22 points (95% CI, −0.58 to 5.02) at adjuvant week 10. Physical and role functioning scores showed declines in the neoadjuvant phase in both arms but stabilized during the adjuvant phase. Overall, most patients reported stable or improved global health status or QoL scores, with a slightly higher proportion favouring the pembrolizumab arm (58.7% versus 51.8%), with a between-group difference of 7.0% (95% CI, 0.1 to 13.9).

Harms Results

AEs were nearly universal in both treatment groups, with rates of 99.5% in the pembrolizumab arm and 98.7% in the placebo arm. Common AEs included nausea, decreased neutrophil counts, and anemia, with slightly higher incidences observed in the pembrolizumab group. Fatigue, decreased appetite, and rash were more frequent with pembrolizumab, whereas asthenia was marginally more prevalent in the placebo arm. SAEs occurred in 41.7% of patients in the pembrolizumab arm, compared to 33.3% in the placebo arm, with pneumonia and pulmonary embolism being the most common SAEs in both groups.

AEs led to higher treatment discontinuation rates in the pembrolizumab group, with 21.5% discontinuing pembrolizumab or placebo and 25.8% discontinuing any drug in the regimen, compared to 9.5% and 17.5% in the placebo arm, respectively. Pneumonitis, anemia, and decreased neutrophil counts were among the most common reasons for discontinuation in the pembrolizumab arm. Mortality related to AEs was also higher in the pembrolizumab group (6.6%) compared to the placebo group (3.8%). AESIs, particularly immune-mediated events such as hypothyroidism (10.9%) and pneumonitis (6.1%), were notably more frequent in the pembrolizumab arm. The impact of AEs on surgical outcomes was also highlighted, as 6.3% of patients in the pembrolizumab arm were unable to undergo in-study surgery due to AEs, compared to 4.3% in the placebo arm.

Critical Appraisal

The KEYNOTE-671 trial had a rigorous double-blind, placebo-controlled design and robust randomization process, which was stratified by disease stage, PD-L1 TPS, histologic features, and geographic region. These measures minimized bias and ensured methodological rigour. Baseline characteristics were well balanced between treatment arms, supporting valid comparisons. The study assessed OS and EFS using robust statistical methods, including a stratified Cox regression and Kaplan-Meier survival analysis, with appropriate control for multiplicity. However, potential unblinding due to the distinct AE profiles of pembrolizumab may have introduced bias in subjective outcomes like HRQoL. The higher rates of treatment discontinuation and differences in subsequent antineoplastic therapy utilization between the arms could also confound long-term outcome assessments, particularly OS. There was an increased risk of bias for HRQoL end points at longer follow-up (adjuvant week 10), where the amount of missing outcome data exceeded 30% in both groups. HRQoL analyses were unadjusted for multiplicity; therefore, statistically significant results for any subscale are at increased risk of type I error (i.e., erroneously rejecting the null hypothesis).

For external validity, the trial enrolled a population reflective of patients with resectable stage II, IIIA, or IIIB NSCLC, aligning broadly with Canadian clinical practice, although an underrepresentation of Black patients may slightly limit its generalizability. Differences in the standard of care comparator used in the study versus current Canadian practice, such as the widespread use of neoadjuvant chemoimmunotherapy with nivolumab, may affect the applicability of the results. The clinical experts mentioned that the comparator arm of KEYNOTE-671 does not fully align with current Canadian practice, leaving unanswered questions about pembrolizumab's potential advantages over existing standards of care. The design of the trial does not provide the ability to separate the effects of using pembrolizumab in the neoadjuvant and/or adjuvant phases. Additionally, the inclusion of patients with *EGFR* or *ALK* mutations, reliance on cisplatin-based chemotherapy, and the ineligibility of some patients with comorbidities or contraindications to immunotherapy further constrain the trial's relevance to certain patient subgroups. These factors highlight the need for careful interpretation when applying the trial findings to diverse real-world populations and evolving treatment landscapes.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and randomized controlled trials (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.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- OS at 24, 36, and 48 months
- EFS at 24, 36, and 48 months
- HRQoL
- harms

- AESIs.

For the GRADE assessments, findings from the pivotal KEYNOTE-671 study were evaluated and summarized by outcome. Where deemed appropriate by the CDA-AMC team, outcomes were presented narratively, reflecting the similarity across studies in terms of population, interventions, design, and outcome measures. In such cases, a single narrative statement was used to represent the overall body of evidence, providing a cohesive and streamlined interpretation.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for neoadjuvant pembrolizumab versus placebo and chemotherapy for patients with NSCLC.

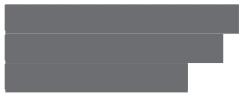
OS and EFS end points were assessed at 24, 36, and 48 months, as these time points were deemed important by experts consulted by CDA-AMC.

For OS, the 48-month end point assessment was considered to be of high certainty and to have an effect of clinical importance. The estimates at 24 and 36 months were rated down 1 level for imprecision because the estimates showed wide CIs that included a threshold of benefit.

All EFS estimates were deemed to be of high certainty. HRQoL presented estimates with 95% CIs that included the null effect but did not cross any threshold of a minimally important difference of 10 points, likely denoting little to no difference in effects between groups.

For AEs, the evidence showed that pembrolizumab results in little to no difference in the number of patients with at least 1 AE between pembrolizumab and placebo and chemotherapy (high certainty), and more SAEs in the pembrolizumab arm (high certainty). Also, pembrolizumab increased the number of AESIs, such as hyperthyroidism, pneumonitis, or hypothyroidism (moderate certainty).

Table 3: Summary of Findings for Perioperative Pembrolizumab vs. Chemotherapy for Patients With NSCLC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Chemotherapy	Pembrolizumab	Difference (95% CI)		
Survival (median follow-up = 29.8 months; range, 0.4 to 62.0 months)							
Overall survival probability at 24 months	797 (1 RCT)	NA	747 per 1,000			Moderate[a]	Pembrolizumab likely results in a clinically important increase in overall survival when compared with chemotherapy.
Overall survival probability at 36 months	797 (1 RCT)	NA	640 per 1,000			Moderate[a]	Pembrolizumab likely results in a clinically important increase in overall survival when compared with chemotherapy.
Overall survival probability at 48 months	797 (1 RCT)	NA	515 per 1,000			High	Pembrolizumab results in a clinically important increase in overall survival when compared with placebo and chemotherapy.
EFS probability at 24 months	797 (1 RCT)	NA	414 per 1,000			High[b]	Pembrolizumab results in a clinically important increase in EFS when compared with chemotherapy.
EFS probability at 36 months	797 (1 RCT)	NA	354 per 1,000			High[b]	Pembrolizumab results in a clinically important increase in EFS when compared with chemotherapy.
EFS probability at 48 months	797 (1 RCT)	NA	262 per 1,000			High[b]	Pembrolizumab results in a clinically important increase in EFS when compared with chemotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects			Certainty	What happens
			Chemotherapy	Pembrolizumab	Difference (95% CI)		
Health-related quality of life							
Health-related quality of life, EORTC QLQ-C30 and EORTC QLQ-LC13 Follow-up: mean 11 weeks	785 (1 RCT)	Assessment of EORTC QLQ-C30 global health status showed no evidence of difference of effects on HRQoL scores between treatment groups (1.43; 95% CI, −1.64 to 4.49), with CIs including the null effect but not above or below an MID of 5.				Moderate[c]	Pembrolizumab may result in little to no difference in health-related quality of life when compared with chemotherapy.
Harms							
AEs Follow-up: median 48 months	797 (1 RCT)	AEs were overall similar between groups. At least 1 AE was reported in 394 patients (99.5%) in the pembrolizumab arm and 394 (98.7%) in the placebo and chemotherapy arm. The most common AEs (> 15% of patients) were nausea (58% vs. 53%), decreased neutrophils (44% vs. 42%), constipation (39% vs. 37%), fatigue (32% vs. 25%), decreased appetite (29% vs. 25%), decreased white blood cells (28% vs. 25%), vomiting (21% vs. 17%), diarrhea (20% vs. 19%), and dyspnea (18% vs. 13%).				High	Pembrolizumab results in little to no difference in AEs when compared with chemotherapy.
SAEs Follow-up: median 48 months	797 (1 RCT)	SAEs were more frequent in the pembrolizumab arm, with 165 patients (41.7%) having at least 1 SAE, compared to the placebo arm (133 patients [33.3%]). Pneumonia, pulmonary embolism, anemia, pyrexia, and elevated liver enzymes were the most commonly reported.				High[d]	Pembrolizumab results in an increase in SAEs when compared with chemotherapy. The clinical relevance of the difference is uncertain.
AESIs Follow-up: median 48 months	797 (1 RCT)	In the pembrolizumab arm compared to the placebo and chemotherapy arm, the following AEs were more commonly reported: hypothyroidism (11% vs. 1.5%), pneumonitis (6.1% vs. 1.8%), hyperthyroidism (5.1% vs. 2%), severe skin reactions (2% vs. 0%), and colitis (1.3% vs. 0%).				Moderate[e]	Pembrolizumab likely results in more AESIs when compared with chemotherapy.

AE = adverse event; AESI = adverse event of special interest; CI = confidence interval; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EORTC QLQ-LC13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Lung Cancer; RCT = randomized controlled trial; SAE = serious adverse event; vs. = versus.

[a]A threshold of 50 more patients surviving per 1,000 treated with pembrolizumab (vs. placebo and chemotherapy) was considered clinically meaningful. The 95% CI crosses this threshold, denoting imprecision for establishing a meaningful effect at the 24-month and 36-month time points but not at 48 months, where the estimate and its 95% CI include a clinically meaningful effect without imprecision.

[b]A threshold of 100 more patients surviving without events (EFS, as defined in the study) per 1,000 treated with pembrolizumab (vs. placebo and chemotherapy) was considered clinically meaningful. The 95% CI excludes this threshold, denoting no imprecision at this time point.

[c]All estimates of effects from all assessments showed CIs that included the null effect but did not cross a conservative estimate of a minimally important difference (MID) of 5 points; hence, the effects were not rated down for imprecision but 1 level for risk of bias (due to more than 30% missing data [nonrandomly missing]).

[d]Total sample size is above a conservative estimate of a review information size of 400 patients per study. Furthermore, the total number of events was deemed appropriate for the outcome.

[e]Although the total sample size is above a conservative estimate of a review information size of 400 patients per study, the total number of events was deemed appropriate for some outcomes, but other events are too small in number to draw strong conclusions. Hence, the overall effect was rated down 1 level for imprecision.

Note: 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.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension study materials were submitted by the sponsor.

Indirect Comparison

Description of Studies

The ITC employed an NMA of 8 RCTs to evaluate the efficacy and safety of pembrolizumab in the perioperative treatment of resectable NSCLC. The included studies were identified through a systematic literature review and selected based on predefined criteria, including patient population, interventions, comparators, and outcomes (PICO). The trials assessed therapies across various stages of early-stage resectable NSCLC, with a focus on EFS as the end point of interest.

Given that nonproportional hazards were identified for some comparisons, a fractional polynomial NMA allowing for time-varying hazards was also presented, including the same studies.

Efficacy Results

The constant hazards NMA demonstrated favourable EFS outcomes for perioperative pembrolizumab compared to surgery alone [redacted] However, when compared to chemotherapy [redacted] chemoradiotherapy [redacted] and neoadjuvant nivolumab ([redacted]), no statistically significant differences were observed, with wide credible intervals (CrIs) that included the null effect.

Among the best-fitting fractional polynomial models was the time-varying second-order fractional polynomial (p1 = 0, p2 = 0) with treatment effects on scale and first shape. Results suggested that pembrolizumab was favoured over chemotherapy (time windows after 6 months), chemoradiotherapy (time windows after 12 months), and surgery alone. Earlier time windows for the chemotherapy and chemoradiotherapy comparisons had CrIs that were crossing the null. Comparisons to neoadjuvant nivolumab had wide CrIs on both sides of the null in all time windows.

Harms Results

No harm effects were assessed in the ITC and NMA submitted.

Critical Appraisal

The ITC was conducted using a rigorous systematic literature review with prespecified PICO criteria, dual independent reviews, and quality assessment using the Cochrane risk of bias tool. Key limitations include the exclusion of adjuvant trials due to differences in end points (EFS versus DFS) and patient populations, which restricts comparisons with important treatment strategies (e.g., comparisons to adjuvant chemotherapy followed by pembrolizumab or atezolizumab). Differences in randomization timing (e.g., pretreatment in the KEYNOTE-671 study versus postsurgery in adjuvant trials) and the noninterchangeability of surrogate end points violate assumptions of similarity, homogeneity, and consistency, resulting in potentially biased estimates of relative treatment effects.

Imbalances in treatment effect modifiers, such as PD-L1 status, disease stage, and regional enrolment, further undermine the transitivity assumption and limit the robustness of the ITC findings. Additionally, full information on treatment effect modifiers was not always available to allow for a comprehensive assessment of the heterogeneity. Methodological choices — including assumptions regarding the pooled chemotherapy node and reliance on the constant HR model, despite proportional hazard violations in some trials — exacerbate the uncertainty. The second-order fractional polynomial NMA would overcome violations of the proportional hazards assumption but cannot overcome the heterogeneity and other concerns previously noted. Additionally, interpretation is limited to discrete time windows, and the sponsor noted that sample sizes were decreased at longer follow-up durations, introducing uncertainty into the comparative effect estimates. The exclusion of OS, HRQoL, and AE data reduces the analysis's comprehensiveness, while the omission of emerging therapies weakens its relevance in the evolving Canadian treatment landscape. The estimates relative to the most relevant comparator, neoadjuvant nivolumab, were particularly affected by wide CrIs, which further increased the uncertainty. Although the ITC provides some insights into pembrolizumab's perioperative efficacy, its utility for clinical decision-making is constrained by methodological challenges, violations of key assumptions, and significant gaps in the evidence.

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 resectable stage II, IIIA, or IIIB (T3 to 4N2) NSCLC
Treatment	Neoadjuvant pembrolizumab plus chemotherapy[a] followed by adjuvant pembrolizumab
Dose regimen	• Neoadjuvant pembrolizumab: 200 mg every 3 weeks for up to 4 cycles. • Neoadjuvant chemotherapy: 75 mg/m^2 of cisplatin administered every 3 weeks with either 500 mg/m^2 of pemetrexed or 1,000 mg/m^2 of gemcitabine every 3 weeks. Repeat for a maximum of 4 cycles. • Adjuvant pembrolizumab: 200 mg every 3 weeks for up to 13 cycles.
Submitted price	Pembrolizumab: $4,400.000 per 100 mg/4mL vial
Submitted treatment cost	• Neoadjuvant pembrolizumab plus cisplatin and pemetrexed: $13,495 per cycle • Neoadjuvant pembrolizumab plus cisplatin and gemcitabine: $9,745 per cycle • Adjuvant pembrolizumab: $8,800 per cycle

Comparators	• Neoadjuvant chemotherapy
	  ◦ cisplatin plus gemcitabine (squamous) or pemetrexed (nonsquamous)
	• Neoadjuvant nivolumab plus chemotherapy, followed by optional adjuvant chemotherapy
	  ◦ chemotherapy: gemcitabine plus cisplatin or paclitaxel plus carboplatin (squamous), pemetrexed plus cisplatin or paclitaxel (nonsquamous)

Component	Description
	◦ adjuvant chemotherapy: carboplatin, cisplatin, docetaxel, gemcitabine, paclitaxel, pemetrexed, or vinorelbine • Surgery only; no neoadjuvant or adjuvant therapies
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (36.9 years)
Key data source	KEYNOTE-671 trial, sponsor-submitted NMA
Submitted results	• ICER (neoadjuvant pembrolizumab plus chemotherapy with adjuvant pembrolizumab vs. neoadjuvant nivolumab plus chemotherapy) = $119,365 per QALY gained (incremental costs = $59,658; incremental QALYs = 0.50) • Neoadjuvant chemotherapy and surgery alone were dominated (less costly, more effective) by neoadjuvant pembrolizumab plus chemotherapy with adjuvant pembrolizumab
Key limitations	The sponsor's submitted model used a multistate model to estimate relative efficacy for neoadjuvant pembrolizumab and all comparators. While relative efficacy was informed by the sponsor's NMA, the multistate modelling approach uses a distinct set of methods to estimate survival. While the approach is appropriate for the decision problem, the literature informing the use of these methods is still evolving. In addition to the methodological concerns, there were model transparency concerns that created barriers to validating some key assumptions. Due to resource and time constraints, CDA-AMC was unable to verify whether the calculations used to predict the transition probabilities from the event-free state were consistent with the selected methodology.
CDA-AMC reanalysis results	The sponsor's base case was maintained. The ICER was $119,365 per QALY gained (incremental costs: $59,658; incremental QALYs: 0.50). CDA-AMC did not identify any limitations which could be addressed through reanalysis. At least a 30% reduction in the price of pembrolizumab is needed for neoadjuvant pembrolizumab plus chemotherapy with adjuvant pembrolizumab to be considered cost-effective compared to neoadjuvant nivolumab at a WTP threshold of $50,000 per QALY gained. The identified internal validity concerns within the sponsor's NMA and the lack of direct comparative evidence against neoadjuvant nivolumab means that a higher price reduction may be warranted.

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life-year; NMA = network meta-analysis; NSCLC = non–small cell lung cancer; PSM = partitioned survival model; QALY = quality-adjusted life-year; WTP = willingness to pay.

[a]Includes squamous (cisplatin plus gemcitabine) or nonsquamous (cisplatin plus pemetrexed) chemotherapy.

Budget Impact

CDA-AMC did not perform a reanalysis of the budget impact, but did perform 2 scenario analyses. The first explored how a 33% market share for perioperative pembrolizumab would affect the estimated budget impact. The second considered the impact of a 30% price reduction for pembrolizumab. In the submitted base case, the budget impact from the introduction of perioperative pembrolizumab was estimated to be $931,612 in year 1, $6,329,996 in year 2, and $10,092,729 in year 3. The 3-year net budget impact was estimated to be $17,354,337. Findings from the CDA-AMC scenario analyses illustrated how an increase in market share will increase the budget impact, while a decrease in the unit price of pembrolizumab will lower the budget impact.

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: February 12, 2025

Regrets: None

Conflicts of interest: None

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