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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 [Combined Positive Score (CPS) ≥ 1], as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy

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 should be reimbursed by public drug plans for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (combined positive score [CPS] ≥ 1), as determined by a validated test, as neoadjuvant treatment (before surgery) as monotherapy, continued as adjuvant treatment (after surgery) in combination with radiotherapy (RT) with or without cisplatin, and then as monotherapy, 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 newly diagnosed, locally advanced HNSCC that can be removed by surgery. Their tumours must test positive for PD-L1 (CPS ≥ 1), and they should be in relatively good health (as measured by performance status). Keytruda should not be covered for patients who have more advanced disease (T4b and/or N3 cancer stage or distant spread); cancer outside the mouth, throat, or voice box; or have received prior treatment for head and neck cancer. Exceptions may be made for patients with resectable recurrence more than 6 months after previous treatment.

What Are the Conditions for Reimbursement?

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

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda, used first on its own before surgery (neoadjuvant), then alongside standard treatment after surgery (adjuvant), and continued on its own again after, helped patients live longer and delayed the progression or return of their cancer compared to standard treatment alone.
- Keytruda may help meet some important needs of patients by slowing or preventing the return of their cancer, having manageable side effects, and helping them maintain their health-related quality of life (HRQoL).
- Based on the CDA-AMC assessment of the health economic evidence, Keytruda may not represent good value to the health care system at the public list price due to uncertainty in the evidence. A price

Summary

reduction will reduce the uncertainty regarding the cost-effectiveness of pembrolizumab in this setting.

- Based on public list prices, Keytruda is estimated to cost the public drug plans approximately $72 million over the next 3 years.

Additional Information

What Is HNSCC?

Head and neck cancers start in the mouth, throat, sinuses, or salivary glands. In 2024, approximately 8,100 people in Canada were diagnosed with head and neck cancers, and approximately 2,100 died of these cancers. Most head and neck cancers begin in the thin, flat squamous cells that line these areas, so these cancers are referred to as HNSCC.

Unmet Needs in HNSCC

Patients with HNSCC that is removable by surgery want treatments that help them live longer, delay the cancer from coming back, cause fewer side effects, and improve their HRQoL. Some patients do not respond well to initial treatment and are more likely to have their cancer return. When this happens, surgery or more radiation is often not possible due to side effects from the treatment. Patients with other health problems may also struggle to tolerate usual treatments.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per patient per 28-day cycle using a fixed dosage (200 mg every 21 days) or $8,917 per patient per 28 days using a weight-based dosage (2 mg/kg [up to 200 mg] every 21 days). When pembrolizumab is used in combination with cisplatin, the expected 28-day cost is $12,399 per patient using fixed dosage and $9,583 per patient using weight-based dosage.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the treatment of adult patients with resectable locally advanced HNSCC whose tumours express PD-L1 (CPS ≥ 1) as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as monotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, phase III randomized controlled trial (RCT) (KEYNOTE-689) demonstrated that pembrolizumab as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as monotherapy likely resulted in improved event-free survival (EFS) compared to standard of care (SOC), which is RT with or without cisplatin, in adult patients with resectable locally advanced HNSCC. In the overall study population (N = 714), after a median follow-up duration of 27.1 months, the median EFS (time to disease progression, recurrence, or death) was 51.8 months (95% confidence interval [CI], 37.5 months to not reached; n = 363) for patients who received pembrolizumab plus SOC and 30.4 months (95% CI, 21.8 to 50.1 months; n = 351) for patients who received SOC (hazard ratio [HR] = 0.73; 95% CI, 0.58 to 0.92). The Kaplan-Meier estimates of the probability of EFS in the pembrolizumab plus SOC group and SOC group were 75.1% (95% CI, 70.0% to 79.4%) and 62.5% (95% CI, 56.9% to 67.5%) at 12 months; 57.6% (95% CI, 51.5% to 63.3%) and 46.4% (95% CI, 40.0% to 52.5%) at 36 months; and 52.0% (95% CI, 45.1% to 58.4%) and 44.2% (95% CI, 37.5% to 50.8%) at 48 months, respectively. In patients with PD-L1 CPS of 1 or greater (n = 682), results for EFS were similar at a median follow-up of 27.0 months: the median EFS was 59.7 months (95% CI, 37.9 months to not reached; n = 347) for patients who received pembrolizumab plus SOC compared to 29.6 months (95% CI, 19.5 to 41.9 months; n = 335) for patients who received SOC (HR = 0.70; 95% CI, 0.55 to 0.89). The Kaplan-Meier estimates of the probability of EFS in the pembrolizumab plus SOC group and SOC group were 74.8% (95% CI, 69.6% to 79.2%) and 61.3% (95% CI, 55.5% to 66.5%) at 12 months; 58.2% (95% CI, 51.9% to 64.0%) and 44.9% (95% CI, 38.4% to 51.2%) at 36 months; and 52.1% (95% CI, 45.0% to 58.8%) and 42.8% (95% CI, 35.9 to 49.4) 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 expressed a need for treatments that extend survival, delay disease progression and recurrence, offer more tolerable side effects, and improve HRQoL. pERC concluded that pembrolizumab in combination with the SOC meets these needs for improved EFS, with manageable side effects. HRQoL was likely maintained because patients who received pembrolizumab plus SOC in the KEYNOTE-689 study had relatively stable and comparable HRQoL to that of patients who received SOC.

Using a weight-based dose at the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for neoadjuvant pembrolizumab and adjuvant pembrolizumab plus SOC was $37,888 per quality-adjusted life-year (QALY) gained compared

with SOC. At this ICER, pembrolizumab is cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained for the treatment of adult patients with resectable locally advanced HNSCC. However, long-term overall survival (OS) and EFS benefits are uncertain. A reduction in price will reduce the uncertainty regarding the cost-effectiveness of pembrolizumab in this setting.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Pembrolizumab should be reimbursed only if all the following conditions are met: 1.1. adults aged 18 years or older 1.2. newly diagnosed with histologically confirmed locally advanced (stage III or IVA) HNSCC amenable to primary surgery 1.3. PD-L1 CPS ≥ 1.	The KEYNOTE-689 trial demonstrated that treatment with pembrolizumab as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with RT with or without cisplatin, and then followed as monotherapy likely results in clinically meaningful benefits compared to standard of care alone (adjuvant RT with or without cisplatin) in adult patients with resectable locally advanced HNSCC whose tumours express PD-L1 (CPS ≥ 1).	Patients must have imaging and clinical assessment demonstrating one of the following conditions: • stage III oropharyngeal p16-positive HNSCC that is T4, N0-N2, M0 • stage III or IVA oropharyngeal p16-negative HNSCC • stage III or IVA larynx, hypopharynx, oral cavity HNSCC (independent of p16). Availability of timely CPS testing should be ensured to avoid potential delays in treatment.
2. Patients must have good performance status.	Patients enrolled in the KEYNOTE-689 trial had an ECOG PS score of 0 or 1.	Based on the clinical experts' input, selected patients with an ECOG PS score > 1 could be considered for treatment with pembrolizumab at the discretion of the treating physician.
3. Pembrolizumab should not be reimbursed in patients who have any of the following: 3.1. stage T4b and/or N3 locally advanced HNSCC and/or distant metastases 3.2. cancer outside of the oropharynx, larynx, and hypopharynx or oral cavity 3.3. received prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2 drug or with a drug directed to another co-inhibitory T-cell receptor 3.4. received prior RT treatment or systemic anticancer therapy for head and neck cancer.	In the KEYNOTE-689 trial, patients who had received prior therapy with an anti–PD-1, anti–PD-L1, anti–PD-L2 drug or with a drug directed to another co-inhibitory T-cell receptor, or had prior RT treatment or systemic anticancer therapy, including investigational drugs for their head and neck cancer under study before randomization, were not eligible for inclusion in the trial.	Based on the clinical experts' input, in addition to patients who have not previously received treatment, select patients who experience resectable recurrence 6 months or more after systemic therapy could be considered for treatment at the discretion of the treating physician. This includes patients treated with pembrolizumab for other cancers.
Discontinuation		
4. Reimbursement of pembrolizumab should be discontinued upon occurrence of	In the KEYNOTE-689 trial, neoadjuvant pembrolizumab 100 mg per 4 mL, administered as an IV infusion (either 2	Based on the clinical experts' input, examples of disease progression may include clinically significant deterioration,

Reimbursement condition	Reason	Implementation guidance
any of the following: 4.1. disease progression 4.2. unacceptable toxicity 4.3. completion of 1 year of treatment or 17 doses (200 mg every 3 weeks) or 9 doses (400 mg every 6 weeks), whichever comes first.	doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks, or until disease progression or unacceptable toxicity), was continued as adjuvant pembrolizumab in combination with RT with or without platinum-containing chemotherapy (3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks), followed by 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks as monotherapy, or until disease recurrence or unacceptable toxicity.	inadequate response, or the development of new metastatic lesions. Based on the clinical experts' input, adverse events warranting discontinuation would include immune-related toxicities that are severe (e.g., grade 3 or higher) or persistent despite appropriate management.
Prescribing		
5. Pembrolizumab should be prescribed by clinicians with expertise in managing head and neck cancer.	To ensure that pembrolizumab is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	Using a weight-based dosing and the sponsor-submitted price, pembrolizumab plus SOC may be considered cost-effective vs. SOC at a willingness-to-pay threshold of $50,000 per QALY gained. However, long-term overall survival and event-free survival benefits are uncertain. A reduction in price will reduce the uncertainty regarding the cost-effectiveness of pembrolizumab in this setting.	—

CPS = combined positive score; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HNSCC = head and neck squamous cell carcinoma; QALY = quality-adjusted life-year; RT = radiation therapy.

Discussion Points

- **Unmet needs**: Aligned with the input from the patient group and clinicians, pERC acknowledged there is an unmet need for effective treatment options for patients with resectable locally advanced HNSCC whose tumours express PD-L1 (CPS ≥ 1). Based on currently available evidence from the randomized phase of the KEYNOTE-689 study, pERC concluded that pembrolizumab as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as monotherapy may meet some of the unmet needs by delaying disease progression or recurrence (i.e., improving EFS), with manageable side effects, and maintaining comparable HRQoL compared to SOC alone.
- **Uncertainty in long-term OS:** Patients identified a need for treatments that can cure their disease and prolong survival. As of the data cut-off date (July 25, 2024), median OS was not reached in the pembrolizumab plus SOC group. In the overall population, OS events were observed in 31%

and 37% of patients in the pembrolizumab plus SOC group and SOC group, respectively; in the population with PD-L1 CPS of 1 or greater, OS events were observed in 30.5% and 38.2% of patients, respectively. Pembrolizumab plus SOC is likely associated with a clinically meaningful improvement in OS at 12 months compared to SOC (moderate certainty of evidence). This benefit appeared to extend throughout the available follow-up period; however, the evidence became less certain at 60 months due to few patients remaining at risk (low certainty of evidence). pERC recognized there is a gap in the current evidence regarding OS which may be addressed by the subsequent and final OS analyses.

- **Indication and reimbursement request based on a subpopulation of the KEYNOTE-689 trial population:** Among patients with PD-L1 CPS of 1 or greater (95.5% of the overall KEYNOTE-689 study population), the evidence showed that the EFS, OS, and HRQoL outcomes were generally aligned with those of the overall study population. Because of the small proportion of patients with PD-L1 CPS of less than 1 and the similarity of outcomes in patients with PD-L1 CPS of 1 or greater to those in the overall population, pERC agreed that the efficacy and safety assessment based on the overall population is considered applicable to the subpopulation with PD-L1 CPS of 1 or greater. Furthermore, pERC acknowledged that other studies (e.g., KEYNOTE-040 and KEYNOTE-048) showed a lack of treatment benefit with pembrolizumab in patients with recurrent or metastatic HNSCC who have PD-L1 CPS of less than 1.
- **Side effects**: pERC discussed the safety profile of pembrolizumab plus SOC, acknowledging patients' need for treatments associated with tolerable side effects. pERC agreed with the clinical experts consulted that the harms results in the KEYNOTE-689 trial were consistent with the known AEs identified for pembrolizumab in the HNSCC perioperative and postoperative settings. No long-term extension studies were submitted for this review because the KEYNOTE-689 trial is still ongoing for OS follow-up and there are no other long-term extension studies currently ongoing or completed.
- **Relevant comparators**: No studies with indirect evidence were submitted for this review. pERC acknowledged that the SOC applicable in the Canadian context (RT with or without cisplatin) was used in both treatment arms of the KEYNOTE-689 trial.
- **Testing procedure considerations:** pERC discussed the requirement for PD-L1 CPS testing when determining eligibility for pembrolizumab. The clinical experts consulted for this review noted that PD-L1 CPS testing in patients with resectable locally advanced HNSCC before surgery is not part of the current SOC. They indicated that PD-L1 CPS testing would be necessary to guide treatment decisions, particularly to avoid use in patients with CPS-negative HNSCC in the neoadjuvant setting. pERC discussed the variability of turnaround times for CPS testing across provinces and centres. It was also noted that many patients with HNSCC are referred from community centres with variable testing capacity may only have a fine needle aspiration biopsy available at the time of referral to tertiary care centres. Patients often need a core biopsy for accurate determination of CPS scores, which may lead to delays with initiation of treatment. pERC emphasized that access to timely pathological testing is needed to ensure efficient implementation of the recommendations.

- **Uncertainty in the budget impact due to uncertain uptake:** pERC noted uncertainty in the expected uptake for pembrolizumab in this setting. If uptake is greater than that used in the CDA-AMC base case, the expected budget impact of reimbursing pembrolizumab in this setting is expected to increase.

Background

Head and neck cancers encompass malignancies that originate in the mouth, throat, sinuses, and salivary glands. In Canada, an estimated 8,100 new patients were diagnosed with, and 2,100 deaths were attributed to, head and neck cancers in 2024. More than 90% of head and neck cancers begin in squamous cells, and are termed HNSCCs. Patients with HNSCC experience symptoms of compromised basic physiological functions (e.g., chewing, swallowing, and breathing), reduced senses (e.g., taste, smell, and hearing), and impacted human characteristics (e.g., appearance and voice). Treatment guidelines in Canada support a multimodal approach tailored to patient- and tumour-specific factors to achieve optimal tumour control and survival outcomes while minimizing treatment-related morbidity for resectable, locally advanced HNSCC. For stage III or IVA disease, surgical resection of the primary tumour and involved lymph nodes is the main treatment followed by adjuvant RT or chemoradiotherapy (CRT) based on pathologic risk features such as positive surgical margins or extranodal extension. Patients who are considered to be at high risk typically receive cisplatin (100 mg/m^2 on days 1, 22, and 43) with RT. For patients who cannot tolerate cisplatin, alternatives such as carboplatin with or without 5-fluorouracil or cetuximab are available, although access and the strength of supporting evidence may be limited. Patients with PD-L1 CPS-negative HNSCC generally have a poor prognosis and may respond less favourably to immune checkpoint inhibitors. The complex anatomy of the head and neck often results in lasting disabilities for patients with HNSCC after treatment, with more than half unable to return to work after treatment. These challenges contribute to psychological distress, reduced HRQoL, and increased risk of suicide.

Pembrolizumab received Notice of Compliance on August 11, 2025, from Health Canada for the treatment of adults with resectable locally advanced HNSCC. Pembrolizumab is a PD-1–blocking antibody. It is available as a solution for infusion of 100 mg per 4 mL vial. The dosage recommended in the product monograph is neoadjuvant pembrolizumab 100 mg per 4 mL, administered as an IV infusion (either 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks or until disease progression or unacceptable toxicity), continued as adjuvant pembrolizumab in combination with RT with or without platinum-containing chemotherapy (3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks), followed by 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks as monotherapy or until disease recurrence or unacceptable toxicity.

Sources of Information Used by the Committee

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

- a review of 1 phase III, active-controlled RCT in adults with newly diagnosed, histologically confirmed locally advanced (stage III or IVA) HNSCC amenable to primary surgery
- patients' perspectives gathered by a joint patient group input from the Canadian Cancer Survivor Network and Life-Saving Therapies Network
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with HNSCC
- input from 1 clinician group, Ontario Health (Cancer Care Ontario) Head and Neck Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted by for the purpose of this review.

Patient Input

CDA-AMC received a joint patient group input from the Canadian Cancer Survivor Network and Life-Saving Therapies Network, with their information collected via an online survey conducted between February 24 and March 17, 2025, and follow-up interviews. Eight participants contributed (5 patients who had previously been treated with pembrolizumab, 1 patient in active treatment, and 2 caregivers), who were all based in Canada.

The participants indicated that head and neck cancer significantly affects daily life, causing pain; difficulty with speech, eating, and social activities; and leading to reduced self-esteem. Caregivers are also heavily impacted due to treatment burdens and emotional strain. Patients prioritize treatments that minimize pain, functional impairment, and disfigurement, while preserving quality of life and dignity. They value manageable side effects and the potential for less invasive treatment options. Patient feedback suggests pembrolizumab may offer better tolerability and quality of life compared to traditional treatments. Its use could reduce surgical invasiveness and improve psychological well-being, making it a meaningful option in the Canadian context, especially for recurrent or metastatic disease.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review emphasized that treatment of resectable HNSCC aims for cure and long-term disease control while minimizing toxicity. According to the clinical experts, current SOC involves surgery followed by adjuvant RT with or without chemotherapy (usually cisplatin) or primary RT with or without chemotherapy for organ preservation. Locoregional control is critical, but recurrence (especially

in p16-negative HNSCC) is common, and salvage options such as surgery or re-irradiation are often limited. Comorbidities may also restrict treatment choices. The clinical experts noted that the KEYNOTE-689 trial may shift clinical practice; however, it excluded concurrent chemotherapy with neoadjuvant pembrolizumab, resulting in limited evidence to guide this approach. Nonetheless, the clinical experts suggested that chemotherapy could be added in neoadjuvant settings for patients who are eligible and have good performance status. The clinical experts indicated that pembrolizumab may be best suited for patients with resectable, locally advanced HNSCC not requiring urgent surgery who are medically fit. The clinical experts noted that CPS testing may be needed, particularly if chemotherapy is considered in the neoadjuvant phase, especially for patients with CPS-negative HNSCC or those experiencing more severe symptoms and disease burden. Although OS and HRQoL remain primary goals, improvements in EFS are also meaningful because of the disease's morbidity. Response is assessed through clinical exam, endoscopy, and imaging. The clinical experts consulted by CDA-AMC noted that treatment should be stopped if there is disease progression or severe or persistent AEs. According to the clinical experts, prescribing pembrolizumab would require a multidisciplinary team at a tertiary cancer centre, with a medical oncologist leading treatment and monitoring.

Clinician Group Input

One clinician group, Ontario Health (Cancer Care Ontario) Head and Neck Cancer Drug Advisory Committee, submitted input. The clinician group had similar input as the clinical experts consulted for this review. They agreed the SOC for resectable, locally advanced HNSCC is surgery followed by adjuvant radiation (60 Gy to 66 Gy) with risk-adapted cisplatin chemotherapy (weekly 40 mg/m^2 or high-dose 100 mg/m^2 every 3 weeks) for patients who are considered to be at high risk. The clinician group emphasized the long-term quality-of-life impacts of surgery, radiation, and cisplatin, along with high recurrence rates and limited salvage options, underscoring the need for new treatments to improve survival and reduce recurrence. Although the clinician group felt it was premature to define which patients would benefit most from pembrolizumab without further data, they highlighted the potential role of PD-L1 testing to guide use. The clinician group also noted the need to determine if results from the KEYNOTE-689 trial apply to patients who are not eligible for cisplatin because the trial only included patients who were eligible for cisplatin. The group agreed that treatment should occur in multidisciplinary clinics to reduce risks of disease progression, acknowledged the increased visit burden from the adjuvant pembrolizumab component, and emphasized considering resource implications. For monitoring, the clinician group recommended clinical assessments before each pembrolizumab cycle and surgery, along with cross-sectional imaging (CT or MRI) for restaging. They supported discontinuing pembrolizumab upon disease progression or significant toxicity.

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:

- relevant comparators
- considerations for initiation of therapy

- considerations for prescribing of therapy
- generalizability
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs (Table 2).

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trial For CRT, the preferred chemotherapy regimen is high-dose cisplatin (100 mg/m^2) on days 1, 22, and 43 concurrent with RT. For patients who are not eligible for cisplatin, alternatives include carboplatin with 5-fluorouracil or cetuximab concurrent with RT, as well as hyperfractionated or accelerated RT without chemotherapy. Note that in Canada, cetuximab is only funded for patients with a medical contraindication to cisplatin and carboplatin/5-fluorouracil. This restricted funding positions its use outside the scope of KEYNOTE-689.	The clinical experts consulted for this review agree with this statement. Additionally, the clinical experts noted that low-dose cisplatin (40 mg/m^2 weekly) concurrent with RT may be used as an alternative regimen in clinical practice in Canada. pERC noted that the setting in which cetuximab is indicated is a different setting than the KEYNOTE-689 trial in which both arms had the same design related to CRT. Therefore, the systemic backbone of radiation could be considered a concomitant drug rather than a comparator drug.
Considerations for initiation of therapy	
Other patient characteristics for eligibility KEYNOTE-689 did not include patients who were previously treated (recurrent cases). Should these patients be eligible?	pERC agreed with the clinical experts consulted for this review that patients with recurrent resectable disease could be eligible for treatment with pembrolizumab, depending on their prior therapy history. Specifically, a patient should be considered eligible if their initial treatment occurred a long time ago (e.g., over a year) and they have not received prior systemic therapy. The clinical experts noted that pembrolizumab should be reserved for patients who have not received systemic therapy or patients who had a recurrence more than 6 months after initiation of prior systemic therapy. The clinical experts indicated that because there is currently no approved indication for immunotherapy outside of the noncurative setting, patients previously treated only with local therapies could appropriately be included in trials such as the KEYNOTE-689 trial.
Eligibility for re-treatment Would patients be eligible 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	pERC agreed with the clinical experts that patients would be eligible for downstream immunotherapy in the following scenarios: The clinical experts noted that because only 2 cycles are typically given upfront and pseudoprogression occurs in approximately 20% of patients, continuing treatment and restaging may be appropriate if the patient's disease progresses during neoadjuvant pembrolizumab. The clinical experts indicated that if patients are unable to proceed to surgery after neoadjuvant pembrolizumab, treatment would shift toward a palliative approach or definitive CRT as per trial protocol with curative intent if the patient's disease is amenable to radical radiation. The clinical experts noted that patients would be eligible for re--

Drug program implementation questions	Clinical expert response
adjuvant pembrolizumab for reasons other than disease progression. Should patients who complete 1 year of treatment and experience disease progression or recurrence off pembrolizumab treatment be eligible for re-treatment with pembrolizumab up to 1 year (18 cycles)?	treatment with pembrolizumab if they had discontinued adjuvant pembrolizumab (incomplete adjuvant therapy) for reasons other than disease progression. For disease progression during or shortly after adjuvant pembrolizumab, the clinical experts expressed hesitation, suggesting these patients may have tumours that are considered PD-1 refractory, making further immunotherapy less appropriate. pERC acknowledged that pembrolizumab may be reasonable if disease progresses or recurs at 6 months or more after completion of the originally planned adjuvant treatment with pembrolizumab. In response to the question of whether patients who complete 1 year of pembrolizumab treatment and subsequently experience disease progression or recurrence when off treatment should be eligible for up to 1 additional year (or 18 cycles) of pembrolizumab re-treatment, pERC agreed with the clinical experts who noted that evidence supporting re-treatment is currently lacking because the treatment duration in the KEYNOTE-689 study was limited to approximately 1 year. However, if recurrence occurs 6 months or later after completing treatment with pembrolizumab, the disease may not reflect true PD-1 resistance, and re-treatment with a PD-1–based regimen could be reconsidered.
Considerations for prescribing of therapy	
Dosing, schedule and frequency, dose intensity Neoadjuvant pembrolizumab (2 doses of 200 mg every 3 weeks or 1 dose of 400 mg). Patients receiving neoadjuvant pembrolizumab would continue pembrolizumab post surgery as adjuvant treatment in combination with standard RT or CRT, depending on the risk factors, and then as monotherapy for a total of 1 year. The Oncology Working Group 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).	pERC and the clinical experts agreed with this statement.
Concerns related to combination usage Should pembrolizumab be given with an alternative systemic regimen if the patient cannot receive or tolerate cisplatin?	pERC agreed with the clinical experts that pembrolizumab can be given with an alternative systemic regimen if a patient cannot receive or tolerate cisplatin. The clinical experts indicated a previous study that suggested using a radiosensitizer, regardless of the specific drug, is more beneficial than omitting it entirely.
Generalizability	
Populations of interest matching the indication but with insufficient data 1. Should patients with an ECOG PS score > 1 be eligible? 2. Should the ability to continue to surgery following neoadjuvant therapy be a consideration?	1. The clinical experts indicated that patients with an ECOG PS score > 1 (e.g., ECOG PS = 2) could still be eligible for treatment. The clinical experts noted that in clinical practice in Canada, if the surgeon deems the patient fit for surgery, inclusion of patients with ECOG PS score > 1 in the treatment protocol remains reasonable. 2. The clinical experts agreed that the ability to proceed to surgery after neoadjuvant therapy should be a consideration. The clinical experts emphasized that patients must be fit enough to undergo

Drug program implementation questions	Clinical expert response
	surgery for neoadjuvant treatment to be appropriate. pERC agreed with the clinical experts.
System and economic issues	
Concerns regarding the anticipated budget impact and sustainability There is potential for significant budget impact.	This is a comment from the drug plans to inform pERC deliberations.

CRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RT = radiotherapy.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing, multicentre, open-label, phase III RCT, KEYNOTE-689 (total N = 714; pembrolizumab plus SOC = 363; SOC = 351), was submitted by the sponsor and included for this review. The KEYNOTE-689 trial investigated the efficacy and safety of pembrolizumab as neoadjuvant therapy, followed by postsurgical (adjuvant) treatment combining pembrolizumab and SOC (RT with or without cisplatin) followed by pembrolizumab monotherapy in patients who had not previously received treatment with resectable locally advanced HNSCC. Patients who were eligible for the trial were adults with newly diagnosed, histologically confirmed locally advanced (stage III or IVA) HNSCC amenable to primary surgery. Patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1, adequate organ function, available HPV (p16) results for oropharyngeal tumours, and provided a tumour sample for PD-L1 testing. Patients were not eligible if they had received prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 drug, a drug directed to another co-inhibitory T-cell receptor, or prior RT treatment or systemic anticancer therapy including investigational agents for the head and neck cancer under study before randomization. The outcomes relevant to this review included OS, EFS assessed by blinded independent central review, HRQoL, and safety.

The median age for the overall intention-to-treat (ITT) population in the KEYNOTE-689 study was 60 years. There was a higher proportion of male patients (79%) than female patients (21%). The study population included Asian (13%) and white (78%) participants, with white participants comprising the largest proportion. Most patients currently or previously smoked (78%) and/or used alcohol (68%). In the overall ITT population, 65% of patients had a PD-L1 CPS of 10 or greater, and 95.5% patients had a PD-L1 CPS of 1 or greater. More patients had an ECOG PS score of 0 (57%); 43% had an ECOG PS score of 1. Most patients had a negative HPV status (96%), and stage IVA disease (74%). Most patients had their primary tumour located in the oral cavity (61%), followed by larynx (22%), oropharynx (10%), and hypopharynx (8%).

Efficacy Results

The efficacy and harms outcomes of the KEYNOTE-689 trial reported in this review were based on the protocol prespecified first interim analysis for which the data cut-off date was July 25, 2024. For the overall ITT population (N = 714), the median duration of follow-up was 30.0 months (range, 0.8 to 64.9 months) in the pembrolizumab plus SOC group and 23.4 months (range, 0.5 to 66.5 months) in the SOC group.

Overall Survival

The median OS was not reached (OS = not reached; 95% CI, 61.9 months to not reached) in the pembrolizumab plus SOC group and was 61.8 months (95% CI, 50.1 months to not reached) in the SOC group. The HR was 0.76 (95% CI, 0.59 to 0.98). This was not formally tested. According to the multiple testing strategy of the KEYNOTE-689 trial, formal OS testing was not conducted at the first interim analysis because the statistical significance boundary was not met in the population with PD-L1 CPS of 10 or greater (earlier in the hierarchy). The Kaplan-Meier estimates of the probability of OS in the pembrolizumab plus SOC group and SOC group at 12 months were 86.7% (95% CI, 82.7% to 89.8%) and 77.9% (95% CI, 73.2% to 81.9%), respectively; at 48 months, they were 63.6% (95% CI, 57.4% to 69.1%) and 58.0% (95% CI, 51.6% to 63.9%), respectively.

EFS by Blinded Independent Central Review

In the overall ITT population, the median EFS was 51.8 months (95% CI, 37.5 months to not reached) in the pembrolizumab plus SOC group, and 30.4 months (95% CI, 21.8 to 50.1 months) in the SOC group. The HR was 0.73 (95% CI, 0.58 to 0.92; P = 0.00411). The Kaplan-Meier estimates of the probability of EFS in the pembrolizumab plus SOC group and SOC group were 75.1% (95% CI, 70.0% to 79.4%) and 62.5% (95% CI, 56.9% to 67.5%) at 12 months, respectively; at 36 months, it was 57.6 % (51.5% to 63.3%) and 46.4% (95% CI, 40.0% to 52.5%), respectively; and at 48 months, it was 52.0% (95% CI, 45.1% to 58.4%) and 44.2% (95% CI, 37.5% to 50.8%), respectively.

EORTC QLQ-C30 GHS/QoL score

The between-group differences in least squares mean change from baseline to postadjuvant CRT or RT week 25 and week 51 in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) GHS/QoL scores were [redacted] in a total of 350 patients, and [redacted] in a total of 280 patients, respectively.

Harms Results

The patients in the pembrolizumab plus SOC group had a longer treatment duration per protocol design, with a median of 9.1 months for the pembrolizumab plus SOC group compared to 2.9 months for those in the SOC group.

The harms outcomes were available for the all-participants-as-treated population in the KEYNOTE-689 trial (N = 676). AEs were reported in 96% and 97% of patients in the pembrolizumab plus SOC group and SOC group, respectively. The most common AEs in the pembrolizumab plus SOC group and the SOC group were stomatitis (42% and 55%) and radiation skin injury (40% and 48%), respectively. There were

similar proportions of patients between the pembrolizumab plus SOC group and the SOC group for grade 3 to 5 AEs (76% and 74%, respectively), and AEs resulting in death (7% and 8%, respectively). There were higher proportions of patients with serious AEs in the pembrolizumab plus SOC group than in the SOC group (50% versus 37%), AEs leading to any study treatment discontinuation (24% versus 14%), and AEs of special interest (i.e., immune-mediated events and infusion-related reactions, 44% versus 11%). The most frequently reported AEs of special interest in the pembrolizumab plus SOC group and the SOC group were hypothyroidism (25% and 5%), hyperthyroidism (9% and 3%), pneumonitis (5.5% and 0), colitis (2.5% and 0.3%), and hepatitis (2% and 0.3%), respectively.

Critical Appraisal

The KEYNOTE-689 trial ensured allocation concealment through a central interactive voice- or web-response system. Stratification by key prognostic factors, such as tumour site, disease stage, and PD-L1 tumour proportion score, contributed to ensuring comparability between treatment groups at baseline. Overall, patient characteristics were well balanced, although there was a slight imbalance in smoking status (never smoked: 17.6% in the pembrolizumab plus SOC group versus 23.1% in the SOC group), which clinical experts considered unlikely to influence results. The trial also benefited from the use of centralized, blinded reviews for imaging, pathology, and PD-L1 status, mitigating assessment bias despite the open-label design. Compared to patients in the SOC group, more patients in the pembrolizumab plus SOC group discontinued treatment (pembrolizumab: 54%; SOC: 17%), mainly due to AEs and disease progression. The longer treatment duration (per protocol) in the pembrolizumab group (pembrolizumab: median = 9.1 months; SOC: median = 2.9 months) likely contributed to this difference. Additionally, more patients in the SOC group were randomized but not treated (pembrolizumab: 0.8%; SOC: 10%), mainly due to withdrawal, potentially reflecting concern about not being able to receive pembrolizumab in an open-label trial. This introduces some concern for risk of bias due to deviations from the intended intervention in the SOC group that arose because of the trial context, although the direction and magnitude are unclear. Furthermore, although efficacy outcomes such as EFS and OS were objectively assessed, patient-reported HRQoL measures may be more susceptible to bias under open-label conditions. The handling of missing HRQoL data, which were assumed to be missing at random by the study investigators, is also a notable concern because there were no sensitivity analyses provided to confirm the robustness of the results to different plausible assumptions about the missing data. Finally, the trial's interim OS and EFS analyses introduce uncertainty because HRs may be overestimated, and longer follow-up is needed for robust OS conclusions.

The clinical experts noted that the study population and eligibility criteria in the KEYNOTE-689 trial are reflective of patients seen in clinical practice in Canada. Patients were enrolled from multiple countries, including Canada, and had demographic characteristics consistent with real-world populations. The inclusion of only those patients with an ECOG PS score of 0 to 1 may limit generalizability slightly, although the clinical experts noted that pembrolizumab could also be beneficial in patients with poorer performance status, such as those with an ECOG score of 2. Treatment regimens used in the trial align with clinical practice in Canada, supporting the generalizability of the trial results. However, the small proportion of patients with PD-L1 CPS-negative HNSCC in the study (approximately 4% in each group) limits the certainty of findings for this subgroup. The clinical experts advised caution in using pembrolizumab as neoadjuvant

monotherapy in patients with CPS-negative HNSCC. Because of the limited representation of patients with CPS-negative HNSCC in the KEYNOTE-689 trial and the associated prognostic challenges, further evidence is needed before extending the findings to this population. Moreover, nearly one-third of screened patients did not meet the eligibility criteria and were not included in the study, although the clinical experts felt this did not compromise generalizability. The end points used in the study and reported in this report, including OS, EFS, HRQoL, and safety, were considered clinically relevant and appropriate for decision-making. The use of EFS as a surrogate for OS is supported by good correlations between treatment effects on EFS and OS reported in previous HNSCC meta-analyses, indicating improvements in EFS likely predict OS improvements. However, uncertainties remain regarding the applicability of these findings to the KEYNOTE-689 trial because it is unclear how closely the patient populations, treatment modalities (e.g., inclusion of pembrolizumab, specifics of SOC), and EFS definitions in the KEYNOTE-689 trial align with those in the meta-analyses. Therefore, caution should be exercised when extrapolating EFS findings to long-term survival benefit, especially given OS data remain immature.

GRADE Summary of Findings and Certainty of the Evidence

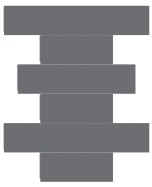
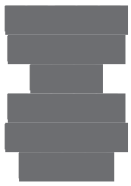
For pivotal studies and RCTs identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), 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 expert committee members:

- probability of OS at 12 months and 60 months
- probability of EFS at 12 months, 36 months, and 48 months
- EORTC QLQ-C30 global health status/QoL at postadjuvant CRT or RT at weeks 25 and 51
- grade 3 to 5 AEs.

Table 3 presents the GRADE summary of findings for pembrolizumab plus SOC versus SOC for adult patients with resectable locoregionally advanced HNSCC.

Table 3: Summary of Findings for Pembrolizumab Plus SOC vs. SOC for Adult Patients With Resectable Locoregionally Advanced HNSCC

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			SOC	Pembrolizumab plus SOC	Difference		
Overall survival							
Probability of survival at 12 months Follow-up: median = 27.1 months (range, 0.5 to 66.5 months)	714 (1 RCT)	NR				Moderate[a]	Pembrolizumab plus SOC likely results in a clinically important increase in OS compared to SOC at 12 months.
Probability of survival at 60 months Follow-up: median = 27.1 months (range, 0.5 to 66.5 months)	714 (1 RCT)	NR				Low[b]	Pembrolizumab plus SOC may result in a clinically important improvement in OS compared to SOC at 60 months.
EFS by BICR							
Probability of EFS at 12 months Follow-up: median = 27.1 months (range, 0.5 to 66.5 months)	714 (1 RCT)	NR				Moderate[c]	Pembrolizumab plus SOC likely results in a clinically important increase in EFS compared to SOC at 12 months.
Probability of EFS at 36 months Follow-up: median = 27.1 months (range, 0.5 to 66.5 months)	714 (1 RCT)	NR				Moderate[d]	Pembrolizumab plus SOC likely results in a clinically important increase in EFS compared to SOC at 36 months.
Probability of EFS at 48 months Follow-up: median = 27.1 months (range, 0.5 to 66.5 months)	714 (1 RCT)	NR				Low[e]	Pembrolizumab plus SOC may result in little to no clinically important difference in EFS compared to SOC at 48 months.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			SOC	Pembrolizumab plus SOC	Difference		
HRQoL (measured with EORTC QLQ-C30)							
LS mean change from baseline in EORTC QLQ-C30 global health status/QoL score (0 [worst] to 100 [best]) Follow-up: postadjuvant CRT or RT week 25	350 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[f]	Pembrolizumab plus SOC may result in little to no clinically important difference on the EORCT QLQ-C30 global health status/QoL compared to SOC at postadjuvant CRT or RT week 25.
LS mean change from baseline in EORTC QLQ-C30 global health status/QoL score (0 [worst] to 100 [best]) Follow-up: postadjuvant CRT or RT week 51	280 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Low[g]	Pembrolizumab plus SOC may result in little to no clinically important difference on the EORCT QLQ-C30 global health status/QoL compared to SOC at postadjuvant CRT or RT week 51.
Harms							
Grade 3 to 5 AEs Follow-up: median = 27.7 months (range, 0.6 to 66.5 months)	676 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate[h]	Pembrolizumab plus SOC likely results in little to no clinically important difference in grade 3 to 5 AEs compared to SOC.

AE = adverse event; BICR = blinded independent central review; CI = confidence interval; CRT = chemoradiotherapy; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HRQoL = health-related quality of life; HNSCC = head and neck squamous cell carcinoma; NR = not reported; OS = overall survival; QoL = quality of life; RCT = randomized controlled trial; RT = radiotherapy; SOC = standard of care.

Notes: Data presented in this table were based on analyses at the clinical cut-off date of July 25, 2024. The median OS data had not been reached in the pembrolizumab plus SOC group as of July 25, 2024. Per protocol design, the pembrolizumab plus SOC group had a longer treatment duration (pembrolizumab plus SOC: median = 9.1 months; SOC: median = 2.9 months).

The between-group difference for grade 3 to 5 AEs presented in this table was requested from the sponsor to aid in interpretation and was not part of the sponsor's analysis plan.

Study limitations (which refer to internal validity or risk of bias), 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.

[a]Rated down 1 level for serious imprecision. At the data cut-off date, there was relatively short follow-up, and the median OS had not been reached in the pembrolizumab plus SOC group. A difference of 5% between the groups was identified by the clinical experts consulted by Canada's Drug Agency (CDA-AMC) as a threshold of clinical importance for this outcome. At 12 months, the 95% CI of the absolute effect includes the possibility of little to no difference and a clinical important increase in OS.

[b]Rated down 2 levels for serious study limitations and imprecision. At the data cut-off date, there was relatively short follow-up, and the median OS had not been reached in the pembrolizumab plus SOC group. A difference of 5% between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome. At 60 months, the 95% CI of the absolute effect includes the possibility of little to no difference and a clinically important benefit; the lower bound of the CI is approaching a threshold of clinically important harm. The estimate is from the tail of the Kaplan-Meier curve where there is a high level of censoring and few patients left at risk.

[c]Rated down 1 level for serious imprecision. A difference of 10% between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome. At 12 months, the 95% CIs of the absolute effect includes the potential for little to no difference and a clinical important increase in EFS.

[d]Rated down 1 level for serious imprecision. A difference of 10% between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome. At 36 months, the 95% CIs of the absolute effect includes the potential for little to no difference and a clinical important increase in EFS.

[e]Rated down 2 levels for serious study limitations and imprecision. A difference of 10% between the groups was identified by the clinical experts consulted by CDA-AMC as a threshold of clinical importance for this outcome. At 48 months, the 95% CI of the absolute effect included the potential for little to no difference and clinically important benefit. The estimate is from the tail of the Kaplan-Meier curve where there is a high level of censoring and few patients left at risk.

[f]Rated down 2 levels for very serious risk bias of due to the open-label nature of the study and the subjective nature of the outcome. A total of 47.1% of the total patient-reported outcome full analysis set population, or 43.5% of the patients with this score assessed at baseline, are missing some data. In the absence of sensitivity analyses, risk of bias cannot be excluded.

[g]Rated down 2 levels for very serious risk bias of due to the open-label nature of the study and the subjective nature of the outcome. A total of 57.7% of the total PRO FAS population, or 54.8% of the patients with this score assessed at baseline, are missing some data. In the absence of sensitivity analyses, risk of bias cannot be excluded.

[h]Rated down 1 level for serious imprecision. The review team was unable to identify the minimal important difference to assess a between-group difference from literature or the clinical experts consulted for this review; therefore, the null was used to assess certainty. The 95% CI of the absolute effect includes the potential for both benefit (reduced AEs) and harm (increased AEs). The CDA-AMC review team assessed that lower boundary of the 95% CI was not a source of serous imprecision, although the upper lower boundary of the 95% CI may indicate an important difference.

Long-Term Extension Studies

No long-term extension studies were submitted for this review because the KEYNOTE-689 trial is still ongoing for OS follow-up.

Indirect Comparisons

No studies with indirect evidence were submitted for this review.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the pivotal and RCT evidence were submitted for this review.

Economic Evidence

Note: The sponsor's application was filed on before the Notice of Compliance was issued and the pharmacoeconomic submission and budget impact analysis is reflective of the indication that was initially submitted to Health Canada and CDA-AMC. The updated indication is not expected to materially impact conclusions on cost-effectiveness. Because the updated indication is narrower than the submitted indication, the budget impact presented is slightly overestimated.

Economic Evaluation and Budget Impact

- Pembrolizumab is available as a solution for infusion (100 mg per 4 mL). At the submitted price of $4,400 per 4 mL vial, the cost of pembrolizumab is expected to be $11,733 per patient per 28 days based on a fixed-based dosage (200 mg once every 3 weeks or 400 mg once every 6 weeks) following the Health Canada–recommended dosing schedule. This decreases to $8,917 per patient

per 28 days, assuming a weight-based dosage (2 mg/kg [up to 200 mg] once every 3 weeks or 4 mg/kg [up to 400 mg] once every 6 weeks) and an average weight of 76 kg.

- Clinical efficacy in the economic analysis was derived from the KEYNOTE-689 trial (date cut-off date: July 25, 2024), which compared pembrolizumab plus SOC with SOC. Evidence submitted by the sponsor indicates that pembrolizumab plus SOC likely results in a clinically important benefit in OS and EFS compared with SOC among adult patients with locally advanced HNSCC. However, long-term comparative efficacy data beyond the pivotal trial period remains limited.
- The results of the CDA-AMC base case suggest:
  - Pembrolizumab plus SOC is predicted to be associated with higher costs to the health care system than SOC (incremental costs = $46,655), primarily driven by increased costs associated with drug acquisition.
  - Pembrolizumab plus SOC is predicted to be associated with a gain of 1.48 life-years compared to SOC and may result in a gain of 1.23 QALYs compared to SOC.
  - The ICER of neoadjuvant pembrolizumab and adjuvant pembrolizumab plus SOC compared to SOC is $37,888 per QALY gained. The estimated ICER was sensitive to long-term extrapolation of EFS. Approximately 75% of the incremental QALYs relative to SOC were gained in the extrapolated period (i.e., after 282 weeks). Because of the lack of evidence beyond this time point, the QALYs gained for patients receiving pembrolizumab plus SOC predicted in the CDA-AMC base case are uncertain.
- CDA-AMC estimates that the budget impact of reimbursing pembrolizumab plus SOC for the treatment of resectable LA HNSCC is predicted to be approximately $72 million over the first 3 years of reimbursement compared to the amount currently spent on SOC, with an estimated expenditure of $85 million on pembrolizumab over this period. The actual budget impact of reimbursing pembrolizumab plus SOC will depend on the number of people eligible for treatment and its uptake.

All feedback received in response to the draft recommendation is available on the CDA-AMC website.

pERC Information

Members of the Committee

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

Meeting date: August 13, 2025

Regrets: Six expert committee members 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.