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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: Treatment of adult patients with FIGO 2014 Stage III-IVA cervical cancer, in combination with chemoradiotherapy

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

Canada's Drug Agency (CDA-AMC) recommends that Keytruda in combination with chemoradiotherapy be reimbursed by public drug plans for the treatment of Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) 2014 stage III to IVA cervical cancer if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda in combination with chemoradiotherapy should only be covered to treat patients who have locally advanced cervical cancer (LACC) (stage III to IVA FIGO 2014 classification) that has not been previously treated, with histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix, and who have a relatively good health (as measured by performance status) at the start of treatment.

What Are the Conditions for Reimbursement?

Keytruda in combination with chemoradiotherapy should only be reimbursed if prescribed by clinicians with experience with immuno-oncology and chemoradiotherapy and in treating cervical cancer, and the cost of Keytruda is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda in combination with chemoradiotherapy compared with placebo in combination with chemoradiotherapy delayed cancer progression and prolonged survival in a subpopulation of adults with LACC (stage III to IVA FIGO 2014 classification) that has not been previously treated.
- Pembrolizumab in combination with chemoradiotherapy may meet some needs identified by patients. The evidence demonstrated a benefit for patients with LACC by improving the spread of cancer and delaying the onset of symptoms.
- 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 $73 million over the next 3 years based on FIGO 2014 staging classifications.

Summary

Additional Information

What Is Cervical Cancer?

Cervical cancer begins in the cells of the cervix in biological females, typically from the lower part of the uterus that connects to the vagina. Most cases of cervical cancer are caused by the human papilloma virus (HPV), a sexually transmitted infection, and only a few cases (5%) are independent of HPV infections. Patients with cervical cancer that has spread beyond the initial location and involve lymph nodes generally have a poorer disease outlook. Cervical cancer is the third most common cancer of the female genital tract in Canada, with 1,600 new diagnoses and 400 deaths reported in 2024.

Unmet Needs in Cervical Cancer

The current standard of care for patients with LACC is chemoradiotherapy alone, which has suboptimal benefits over time with some patients who still experience disease progression or relapse. As such, there is a need for more effective treatments.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per patient per 28 days, based on a fixed-based dosage following the Health Canada–recommended dosing schedule.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the treatment of adult patients with FIGO 2014 stage III to IVA cervical cancer, in combination with chemoradiotherapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-masked study (KEYNOTE-A18) demonstrated that pembrolizumab in combination with chemoradiotherapy resulted in added clinical benefits when compared to chemoradiotherapy for adults with FIGO 2014 stage III to IVA LACC based on a subgroup of the population enrolled in the KEYNOTE-A18 trial. Though median progression-free survival (PFS) and median overall survival (OS) were not reached as of interim analysis 2, the results of the KEYNOTE-A18 trial demonstrated that pembrolizumab in combination with chemoradiotherapy was associated with statistically significant and clinically meaningful improvements in investigator-assessed PFS compared to chemoradiotherapy based on a hazard ratio (HR) of 0.57 (95% confidence interval [CI], 0.43 to 0.76; P < 0.0001). Pembrolizumab in combination with chemoradiotherapy also demonstrated a statistically significant improvement in OS compared to chemoradiotherapy based on an HR of 0.57 (95% CI, 0.39 to 0.83; P = 0.0016). Treatment with pembrolizumab in combination with chemoradiotherapy showed little to no clinically meaningful change in health-related quality of life (HRQoL) compared to chemoradiotherapy. Regarding safety, the addition of pembrolizumab to chemoradiotherapy was associated with a manageable toxicity profile.

Patients identified a need for access to effective treatments that control the spread of cancer, delay symptom onset, improve quality of life, and improve treatment tolerability. pERC concluded that pembrolizumab in combination with chemoradiotherapy met some of the needs identified by patients, as the evidence supports a benefit in terms of controlling the spread of cancer and delaying the onset of symptoms based on the PFS and OS results. pERC also noted that the addition of pembrolizumab to chemoradiotherapy followed by pembrolizumab monotherapy did not appear to worsen HRQoL.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab in combination with chemoradiotherapy was $56,745 per quality-adjusted life-year (QALY) gained compared with chemoradiotherapy. At this ICER, pembrolizumab in combination with chemoradiotherapy is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for adults with FIGO 2014 stage III to IVA cervical cancer. A price reduction is required for pembrolizumab in combination with chemoradiotherapy to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment of pembrolizumab in combination with chemoradiotherapy should only be reimbursed when initiated in patients with all of the following: 1.1. previously untreated FIGO 2014 stage III to IVA locally advanced cervical cancer 1.2. histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix.	In the KEYNOTE-A18 trial, treatment with pembrolizumab in combination with chemotherapy (cisplatin) demonstrated a clinical benefit relative to chemoradiotherapy alone in patients who met these criteria.	As the FIGO 2014 staging system is no longer used in clinical practice in Canada, participating drug plans may consider using the FIGO 2018 staging system for reimbursement. pERC acknowledged that patients with FIGO 2014 stage IB2 to IIB (with node-positive disease) would now be considered stage IIIC per the FIGO 2018 staging system. Though this group was excluded from the subgroup analysis of the KEYNOTE-A18 trial informing this submission (due to the high risk of recurrence and poor prognosis), they may be considered for treatment based on clinician judgment.
2. Patients must have good performance status.	The KEYNOTE-A18 trial excluded patients who had an ECOG PS score greater than 1 at baseline. Clinical expert input to pERC noted that patients with ECOG PS scores of 2 or greater could be considered for treatment with pembrolizumab plus chemoradiotherapy.	—
Discontinuation		
3. Treatment with pembrolizumab plus chemoradiotherapy should be discontinued upon the occurrence of any of the following: 3.1. clinical disease progression 3.2. unacceptable toxicity.	In the KEYNOTE-A18 trial, treatment was discontinued upon radiographic progression or disease recurrence. Discontinuation for these reasons are also aligned with clinical practice in Canada.	—
4. The maximum duration of reimbursement of pembrolizumab is up to 24 months (approximately 105 weeks) for patients who do not meet any of the discontinuation criteria.	In the KEYNOTE-A18 trial, 5 cycles of pembrolizumab 200 mg were administered every 3 weeks, followed by 15 cycles of pembrolizumab 400 mg every 6 weeks. In total, a maximum of 20 cycles, (corresponding to 105 weeks) of pembrolizumab were administered.	
Prescribing		
5. Pembrolizumab should be prescribed by clinicians familiar with cervical cancer and administered in cancer centres that are familiar with immuno-oncology and chemoradiotherapy.	This is to ensure that pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
Pricing		
6. A reduction in price.	The ICER for pembrolizumab in combination with chemoradiotherapy is $56,745 per QALY gained when compared with chemoradiotherapy. A price reduction greater than 10% would be required for pembrolizumab to achieve an ICER below $50,000 per QALY gained compared to chemoradiotherapy. Price reductions for different thresholds are available in Appendix 4 of the Pharmacoeconomic Review report. Notably, the base-case analysis may overestimate QALY gains from pembrolizumab relative to chemotherapy and the associated cost savings, meaning that further price reductions than those presented may be required.	—
Feasibility of adoption		
7. The economic feasibility of adoption of pembrolizumab in combination with chemoradiotherapy must be addressed.	At the submitted price, the incremental budget impact of pembrolizumab in combination with chemoradiotherapy is expected to be nearly $40 million in year 3 using the FIGO 2014 staging system. If the FIGO 2018 stage is applied, the incremental budget impact of pembrolizumab in combination with chemoradiotherapy may exceed $40 million in year 3.	

ECOG PS = Eastern Cooperative Oncology Group Performance Score; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; ICER = Incremental Cost-Effectiveness Ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet need and standard of care:** pERC discussed the unmet need for this condition, as the current standard of care for LACC is chemoradiotherapy alone, which was adopted in 1999. Though chemoradiotherapy has demonstrated benefits in achieving disease-free survival and OS in patients compared to external beam radiotherapy alone, these benefits have remained suboptimal over time with some patients still experiencing disease progression or relapse, particularly patients with advanced FIGO stage disease or nodal involvement.
- **Updated staging for cervical cancer:** pERC discussed the eligibility criteria used for the KEYNOTE-A18 trial, which were based on the FIGO 2014 staging system and are included in the indication approved by Health Canada. Through their discussion, pERC acknowledged that implementing a recommendation based on the 2014 staging system would be challenging as it is impractical to apply an outdated staging system in current clinical practice. The clinical experts

advised that the updated FIGO 2018 system is more commonly used in clinical practice in Canada, which drug plans may wish to consider using for implementation. pERC acknowledged that patients with FIGO 2014 stage IB2 to IIB with nodal involvement would be considered stage IIIC per the FIGO 2018 staging system. Though those patients were excluded from the subgroup analysis of the KEYNOTE-A18 trial that informed this submission, due to the high risk of recurrence and poor prognosis, pERC indicated that patients with stage IIIC per the FIGO 2018 staging system may be considered for treatment based on clinician judgment.

- **Limitations:** The evidence informing this submission is based on a post hoc subgroup analysis of patients with FIGO 2014 stage III to IVA LACC, as well as results from an interim analysis. The median for PFS or OS was not reached for pembrolizumab or placebo. Despite this, the results for PFS and OS were statistically significant, the Kaplan-Meier curves visually document sustained differences, and these results were associated with moderate certainty per the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment, indicating that pembrolizumab in combination with chemoradiotherapy likely results in a clinically important improvement in PFS and OS.
- **HRQoL and treatment tolerability:** Patients identified an improvement in HRQoL and treatment tolerability as important outcomes for new treatments for cervical cancer. The KEYNOTE-A18 trial reported the change from baseline in the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status/QoL item with results up to week 36. pERC discussed that although pembrolizumab plus chemoradiotherapy may result in little to no clinically important difference in HRQoL compared with placebo plus chemoradiotherapy, there did not appear to be a detrimental effect in patients who received pembrolizumab plus chemoradiotherapy as HRQoL scores were maintained over time. pERC also noted that the HRQoL evidence is limited by the lack of robust long-term data beyond 36 weeks.
- **Safety:** pERC discussed that the toxicity profile for pembrolizumab is established and the data from the KEYNOTE-A18 trial were aligned with the expected safety profile. pERC also noted that physicians are familiar with monitoring and managing adverse events (AEs) associated with the treatment with pembrolizumab.
- **Economic considerations:** pERC discussed the cost-effectiveness of pembrolizumab in combination with chemoradiotherapy versus chemoradiotherapy alone. It was noted that postprogression survival is uncertain due to concerns of generalizability as the estimated benefits were informed by the KEYNOTE-A18 and KEYNOTE-826 trials. Given the uncertainty, pERC noted that greater price reductions to pembrolizumab may be required to achieve cost-effectiveness.

Background

Cervical cancer is the fourth most common cancer in females globally, with incidence varying significantly by region. Most cervical cancers are related to HPV infection, making it a highly immunogenic disease, and only 5% are independent of HPV. PD-1 and PD-L1 play a crucial role by inhibiting T cell response to

HPV infection, and PD-L1 expression is a potential biomarker that is overexpressed in cervical cancers and surrounding inflammatory cells. High PD-L1 expression also correlates with poorer OS in patients with cervical cancer, establishing it as a potential prognostic indicator. Other risk factors commonly associated with cervical cancer include smoking, parity, oral contraceptive use, early sexual debut, multiple sexual partners, sexually transmitted infections, autoimmune diseases, and chronic immunosuppression.

Current treatment guidelines recommend cisplatin 40 mg/m^2 IV weekly for 5 to 6 cycles plus external beam radiotherapy followed by brachytherapy for patients with LACC (per FIGO 2014 stage IB2 to IVA or per FIGO 2018 stage IB3 to IVA), and carboplatin (area under the curve 2 IV weekly) as an alternative for patients who are intolerant to cisplatin. Although the current standard of care with chemoradiotherapy is reportedly effective in ensuring disease-free survival and OS, these benefits have remained suboptimal over time, particularly in patients with advanced FIGO stage disease or nodal involvement, hence the need for new treatments that improve OS or cure rates for patients.

Pembrolizumab has been approved by Health Canada for the treatment of adults with FIGO 2014 stage III to IVA cervical cancer, in combination with chemoradiotherapy. Pembrolizumab is a monoclonal antibody PD-1 immune-checkpoint receptor that is available as a 100 mg/4 mL vial solution for infusion and the dosage recommended 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 randomized controlled trial (RCT) in patients with high-risk LACC with FIGO 2014 stage IB2-IIB (node-positive) or stage III to IVA (either node-positive or node-negative) disease
- patients' perspectives gathered by 1 patient group, Colorectal Cancer Resource & Action Network (CCRAN) in collaboration with the Canadian Cancer Survivor Network and HPV Global Action
- input from the public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with cervical cancer
- input from 2 clinician group(s), the Society of Gynecologic Oncology of Canada (GOC) and the Ontario Health (Cancer Care Ontario) (OH [CCO]) Gynecologic Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Input from 1 patient group was submitted for this review by CCRAN in collaboration with the Canadian Cancer Survivor Network and HPV Global Action. CCRAN is a national not-for-profit patient advocacy group

that provides support and education to patients with colorectal cancer to improve longevity and quality of life; CCRAN has expanded its mandate to serve patients outside the colorectal cancer space through collaboration with other tumour type patient advocacy groups. CCRAN also participates in health technology assessment patient evidence submissions, educational events, and advocacy initiatives for patients with cancers outside of the colorectal space. To gather input for this submission, CCRAN conducted telephone interviews with 5 patients (3 from Canada, 2 from the US; representation from Quebec, Ontario, and Alberta). Additional information on patient experiences with the disease and previously available treatments was gathered through a survey conducted between April and May 2022, with 8 responses (5 from Canada and 3 from US; representation from Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia).

CCRAN noted that cervical cancer, which affects only individuals assigned female at birth, has led to significant inequities, including underfunded research and treatments. It disproportionately impacts underserved communities in Canada, who often face barriers such as low health literacy, poor health care access, and lack of culturally appropriate care. Patients interviewed by CCRAN described initial dismissal of their symptoms by health care providers and delays in diagnosis, particularly due to limited access to primary care during the COVID-19 pandemic. Survey respondents identified fatigue (57%); uncertainty about the future (43%); loss of appetite (29%); and anxiety, panic attacks, or depression (29%) as the most pressing symptoms to manage. Many patients shared that receiving their diagnosis felt overwhelming and final, making it difficult to plan for the future or maintain a sense of stability in their personal relationships. The disease requires patients to undergo frequent and intrusive pelvic examinations, including colposcopy. Because cervical cancer is linked to HPV, a sexually transmitted infection, patients often face stigma, guilt, and shame, despite HPV being a common infection that most people acquire at some point in their lives.

Survey respondents reported that prior treatments included cisplatin (29%); carboplatin, paclitaxel, and bevacizumab (14%); palliative care (14%); alternative methods (14%); and pembrolizumab (14%), with most rating these as “somewhat effective.” Interviewees also reported receiving chemotherapy, radiation, brachytherapy, laser therapy, loop electrosurgical excision procedures, hysterectomy, and total pelvic exenteration. Most interviewees indicated that AEs associated with currently available treatments significantly impacted quality of life during treatment. Radiation therapy was also associated with severe toxicity, including fatigue, appetite loss, and rapid weight loss. Patients also highlighted the long-term effects of current treatments, such as impaired sexual and vaginal function from pelvic radiation and loss of fertility following hysterectomy.

Controlling cancer spread was the top priority for most interviewees. Survey respondents also valued improved quality of life, delayed symptom onset, and better treatment tolerability. Across both the interviews and survey, most patients expressed that access to pembrolizumab plus chemoradiation is a key priority. All interviewed patients believed pembrolizumab offered the improvements they sought, particularly strong response rates, short infusion times, and minimal side effects.

Of the interviewees, 4 of 5 had direct experience with pembrolizumab, as did 3 of 8 survey respondents. Surveyed patients reported that while receiving pembrolizumab, they experienced better symptom control, fewer AEs, and easier administration. The most common AEs were nausea, fatigue, diarrhea, rash, joint

pain, fever, and interstitial nephritis. Interviewees were treated with pembrolizumab plus carboplatin and either paclitaxel or radiation for 4 to 6 cycles, followed by pembrolizumab monotherapy, ranging from 2 to 35 cycles. Most reported durable responses: 2 experienced no evidence of disease, 1 experienced aggressive recurrence had no progression, and 1 experienced a 1-year response before developing possible lymph node involvement, requiring bevacizumab. While receiving pembrolizumab, interviewees reported pain relief, reduced mental burden, and a return to normal activities. On a scale of 1 to 10, interviewees rated their quality of life with pembrolizumab at an average of 8.9.

Clinician Input

Input From Clinical Experts Consulted for This Review

Two clinical experts with experience in the diagnosis and clinical management of cervical cancer were consulted by CDA-AMC. They noted that the current standard of care option available to patients is chemoradiation (cisplatin 40mg/m^2 IV weekly for 5 to 6 cycles plus external beam radiotherapy followed by brachytherapy administered for curative intent). Carboplatin and taxol (paclitaxel) in addition to cisplatin (based on evidence from the InterLace trial)[23] were additional chemotherapy treatments highlighted by the experts, although these combinations are not widely adopted by jurisdictions due to challenges involved with radiation administration. The experts noted that pembrolizumab will cause a shift in the current treatment paradigm, as it will become a first-line therapy in combination with chemoradiotherapy. The experts noted that treatment with pembrolizumab addresses the underlying disease process as the HPV infection pathway will be addressed through immunotherapy.

According to the experts, the patients best suited for treatment with concurrent pembrolizumab plus chemoradiotherapy will include those with FIGO 2014 stage III to IVA disease. Given that most patients with stage III to IVA disease enrolled in the trial had a PD-L1 combined positive score of 1 or greater, it was unclear to the experts whether those with a PD-L1–positive tumours combined positive score of lower than 1 will benefit from treatment due to the small number enrolled in the trial.

The most important treatment goals for patients with stage III to IVA cervical cancer highlighted by the experts consulted include improving survival or cure, delaying disease progression, reducing symptoms, and improving HRQoL. Although current treatments (chemotherapy and radiation) prolong life and improve cure rates, they do not modify the underlying disease mechanism; therefore, there is a need for new treatments that ensure long-term cure, reduce toxicity, and have shorter treatment periods. Both clinical experts agreed that they would consider discontinuing treatment if immune-related toxicity is significant during treatment, typically if the liver, gastrointestinal tract, and lungs are affected.

Clinician Group Input

Input from 2 clinician groups, GOC and the OH (CCO) Gynecologic Cancer Drug Advisory Committee, was submitted for this review. GOC is a nonprofit multidisciplinary organization comprised of physicians, nurses, pharmacists, and scientists involved in the treatment and prevention of gynecologic cancer. The OH (CCO) Gynecologic Cancer Drug Advisory Committee provides timely evidence-based clinical and health system guidance on drug-related issues, including the Provincial Drug Reimbursement Programs and the Systemic

Treatment Program. Information was gathered for this submission through a review of published trials and direct clinical experience treating LACC.

The clinician groups indicated that for patients with LACC (stage II, III, and IVA), key treatment goals are to prolong OS and PFS while improving quality of life. The current standard of care treatment for these patients, provided with curative intent, is concurrent cisplatin and external beam pelvic radiation, followed by brachytherapy. The clinician groups agreed that this protocol, which has not been updated since its establishment in 1999, demonstrates only modest OS and PFS benefit; the OH (CCO) Gynecologic Cancer Drug Advisory Committee noted that the OS rate of stage III to IVA cervical cancer is between 32% to 35% in Canada. Thus, the clinician groups highlighted a need for new treatments with improved OS and PFS for this patient population.

The clinician groups agreed that pembrolizumab would be used in the first line for patients with FIGO 2014 stage III or IVA cervical cancer who are undergoing curative intent therapy, regardless of nodal status, as a complement to chemoradiation. The clinician groups anticipate that its approval would shift the current treatment paradigm, such that any eligible patient initiating chemoradiation would also receive pembrolizumab. The groups noted that as a first-line, curative intent therapy, it would not be appropriate to try other treatments before initiating pembrolizumab with chemoradiation. The clinical groups agreed that patients with newly diagnosed FIGO stage III (irrespective of nodal status) or stage IVA, histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix with no previous cancer-directed treatment are most likely to respond to treatment. The patients least suitable for treatment are those who are unable to tolerate radiation, chemotherapy, or immunotherapy.

According to GOC, a clinically meaningful response to treatment would be defined as clinical and radiographic resolution of disease with tolerable toxicity. The clinician groups suggested the use of tumour imaging (per New Response Evaluation Criteria In Solid Tumours version 1.1 [RECIST 1.1] criteria) to determine treatment response. However, the groups had slightly differing suggestions on the schedule for follow-up. The OH (CCO) Gynecologic Cancer Drug Advisory Committee suggested aligning the imaging follow-up schedule with that of the trial (every 12 weeks for years 1 and 2, every 24 weeks in year 3, and once yearly thereafter). GOC suggested initial imaging with pelvic MRI or CT or CT-PET scan, followed by tumour imaging 3 months after chemoradiation completion, and ongoing response assessments by clinical assessment and imaging every 3 to 6 months thereafter. Discontinuation should be considered in the event of disease progression, unacceptable toxicity (especially grade 4 immune-related events), or patient choice. Treatment would be administered as outpatient therapy in a comprehensive cancer setting by specialist physicians, including medical oncologists, radiation oncologists, or gynecologic oncologists with experience treating gynecologic cancer.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CDA-AMC recommendation for pembrolizumab plus chemoradiotherapy:

- considerations for initiation and discontinuation of therapy
- considerations for prescribing therapy
- generalizability
- funding algorithm
- relevant comparators
- care provision issues
- system and economic issues.

The clinical experts consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Response
Relevant comparators	
In the KEYNOTE-A18 trial, patients received 5 cycles of concurrent platinum-based chemoradiotherapy once weekly plus pembrolizumab (or placebo), with an optional sixth dose of chemoradiotherapy at the investigator's discretion, followed by 15 cycles of pembrolizumab (or placebo) monotherapy every 6 weeks. Could pERC confirm the recommended number of cycles for concurrent chemoradiotherapy plus pembrolizumab?	According to the clinical experts consulted for this review, the dosing and number of cycles for chemotherapy and radiation treatment outlined in the trial protocol aligns with clinical practice in Canada. Additional cycles for chemotherapy (up to 6 cycles) will be used at the discretion of the practising physician. According to the experts, the duration of pembrolizumab treatment in practice would align with the procedures outlined in the KEYNOTE-A18 trial. pERC agreed with the clinical experts, noting that 5 doses, with the optional sixth dose, of concurrent chemoradiotherapy is recommended for treatment with pembrolizumab, which aligns with the KEYNOTE-A18 trial.
Considerations for initiation of therapy	
The submitted indication uses the FIGO 2014 staging system to establish the stage III to IVA patient population. Does this align with the FIGO 2018 stage III to IVA patient population? Which FIGO edition is recommended by pERC for staging this patient population?	According to the clinical experts, the 2018 FIGO guidelines are currently used in clinical practice in Canada. Patients who were previously staged as IB2 to IIB with nodal involvement according to the 2014 guidelines would now be considered stage IIIC per 2018 FIGO guidelines. pERC indicated that, for practical reasons, using the 2018 FIGO staging system would be considered reasonable and that patients with stage IB2 to IIB disease with nodal involvement per the 2014 staging system should be eligible for treatment given their prognosis.
Are patients who are treated with pembrolizumab plus chemoradiotherapy in this setting eligible for downstream immunotherapy in the metastatic setting? What would be an appropriate disease-free interval?	The clinical experts noted that due to the lack of evidence for the use of this combination in the metastatic setting, they could not make conclusions on whether downstream use of pembrolizumab will benefit patients or what the appropriate disease-free interval would be. pERC noted that, based on experience in other diseases supporting

Drug program implementation questions	Response
	re-treatment with IO therapies in the metastatic setting, a disease-free interval of 6 months or more between time of completing IO therapy and documented date of progressive disease would be appropriate.
Considerations for discontinuation of therapy	
If there is progression during a drug holiday, can treatment be resumed?	According to the experts, if there is progression during a drug holiday from chemoradiotherapy, then treatment can be resumed. The experts also indicated that radiotherapy is administered immediately after treatment with cisplatin. If there is treatment interruption with chemotherapy due to lack of tolerability or AEs, radiotherapy will be put on hold and administered once treatment resumes. Regarding temporary discontinuation from pembrolizumab, the experts indicated that it would be okay to resume treatment if it was stopped for less than 3 months and the reason was due to toxicity. The severity of the toxicity and clinical guidelines on the safety in this situation would also be considered for restarting treatment. pERC agreed with the clinical experts, and added that temporary discontinuation for reasons other than toxicity or for more than 3 months may also be considered.
If a patient cannot tolerate the chemotherapy combination, are they able to continue with pembrolizumab plus radiotherapy alone?	The experts indicated pembrolizumab plus radiotherapy would be an option for patients who cannot tolerate the chemotherapy combination.
Is there a minimum number of chemoradiotherapy cycles that must be given concurrently with pembrolizumab?	The experts did not believe there is a minimum number of chemoradiotherapy cycles that must be given with pembrolizumab as the chemoradiotherapy cycles administered in practice will likely follow guidelines for standard of care, and pembrolizumab will be used in addition to chemoradiotherapy following the trial's procedures. pERC agreed with the clinical experts.
Considerations for prescribing of therapy	
Pembrolizumab should be implemented using weight-based dosing up to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg, or 4 mg/kg every 6 weeks to a maximum of 400 mg), similar to other indications.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Should patients with an ECOG PS of 2 or greater be eligible?	The experts indicated that they would administer pembrolizumab plus chemoradiotherapy to patients with an ECOG PS of 2 or greater. pERC agreed with the experts, noting that patients with "good performance status" should be eligible.
Should patients who are unable to tolerate platinum-based chemotherapy be eligible for pembrolizumab plus chemoradiotherapy using an alternative chemotherapy?	The experts indicated that if patients are unable to tolerate cisplatin, they could receive another chemotherapy, such as carboplatin or paclitaxel in combination with radiotherapy and pembrolizumab or pembrolizumab plus radiotherapy. pERC noted that evidence from the KEYNOTE-A18 trial supported the use of pembrolizumab plus cisplatin and radiotherapy, and that extrapolation to another platinum-based chemotherapy, such as carboplatin, as an alternative to cisplatin would be reasonable.

Drug program implementation questions	Response
Should pembrolizumab be added for patients currently receiving or who have just completed concurrent chemoradiotherapy?	The experts indicated that there is currently no evidence to support the addition of pembrolizumab for patients who have already received or completed chemoradiotherapy as patients in the KEYNOTE-A18 trial were naive to treatment before receiving the drug combination of interest. However, the experts noted that they would consider adding pembrolizumab for patients in current practice depending on when they began receiving chemoradiotherapy. pERC agreed that there are no data to support initiating pembrolizumab sequentially after completion of chemoradiation (i.e., that was completed without concurrent pembrolizumab). pERC also acknowledged the experts' opinion that consideration would be given to when a patient began receiving chemoradiotherapy, noting that initiation of pembrolizumab shortly after the start of chemoradiotherapy when pembrolizumab was not accessible may be considered. pERC also noted that this is expected to be a very short-term issue upon implementation.
Funding algorithm	
Pembrolizumab in combination with bevacizumab and chemotherapy is indicated in the metastatic setting for cervical cancer.	This is a comment from the drug plans to inform pERC deliberations.
Care provision issues	
Pembrolizumab preparation is familiar to many jurisdictions due to its use in other indications.	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
Feasibility of adoption (budget impact) must be considered as this will become the new standard of care.	This is a comment from the drug plans to inform pERC deliberations.

AE = adverse event; ECOG = Eastern Cooperative Oncology Group Performance Status; FIGO = Fédération internationale de gynécologie et d'obstétrique; IO = immuno-oncology; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Systematic Review

Description of Studies

One RCT, KEYNOTE-A18, was included in the sponsor's systematic review. The KEYNOTE-A18 trial is an ongoing randomized, double-masked, placebo-controlled, phase III trial with a sequential study design evaluating the efficacy and safety of concurrent use of pembrolizumab with and after chemoradiotherapy against placebo and chemoradiotherapy alone in patients with newly diagnosed high-risk (FIGO 2014 stage IB2 to IIB with node-positive disease or stage III to IVA regardless of node status) LACC. The coprimary outcomes assessed in the study were PFS per investigator assessment per RECIST 1.1 and OS. Other outcomes included HRQoL (using the EORTC QLQ-C30 global health status/QoL subscale) and safety.

Overall, patients enrolled in the KEYNOTE-A18 trial were randomized by stratification factors in a 1:1 ratio to pembrolizumab plus chemoradiotherapy and placebo plus chemoradiotherapy groups.

The Health Canada indication is limited to FIGO 2014 stage III to IVA disease and the sponsor's reimbursement request is in line with the Health Canada indication; therefore, this report focuses on the post hoc analyses of the subgroup of patients enrolled in the KEYNOTE-A18 trial who have FIGO 2014 stage III to IVA disease regardless of node status at the interim analysis 2 data cut-off.[24]

At the interim analysis 2 data cut-off (January 8, 2024), 296 patients were included in the PFS analysis in the pembrolizumab plus chemoradiotherapy group versus 305 in the placebo plus chemoradiotherapy group. Baseline demographics and disease characteristics in the FIGO 2014 stage III to IVA subgroup were generally similar for both groups. There were high percentage of patients with a PD-L1–positive tumours combined positive score of 1 or more in both groups (93.9% in the pembrolizumab plus chemoradiotherapy group and 92.1% in the placebo plus chemoradiotherapy group). The majority of patients were aged 65 years or younger (85.8% versus 81.3%) and had disease with positive pelvic and/or para-aortic lymph node involvement (72% in the pembrolizumab plus chemoradiotherapy group versus 69.5% in the placebo plus chemoradiotherapy group).

Efficacy Results

Progression-Free Survival

The HR for PFS by investigator assessment was 0.57 (95% CI, 0.43 to 0.76) in the FIGO 2014 stage III to IVA population. The median PFS was not reached (95% CI, not reached) in the pembrolizumab plus chemotherapy group or the placebo plus chemotherapy group (95% CI, 26.3 to not reached). The Kaplan-Meier–estimated differences in PFS probabilities between groups at 18, 24, and 30 months were 14.8% (95% CI, 7.3% to 22.2%), 16.0% (95% CI, 7.9% to 24.0%), and 17.9% (95% CI, 9.4% to 26.5%), respectively, in favour of pembrolizumab plus chemoradiotherapy. These findings were consistent with PFS by the blinded independent central review analysis and the primary analysis in the overall population (FIGO 2014 stage IB2 to IIB with node-positive disease or stage III to IVA regardless of node status).

Overall Survival

The HR for OS was 0.57 (95% CI, 0.39 to 0.83; nominal P = 0.0016) in the FIGO 2014 stage III to IVA population. The median OS was not reached in either group. The Kaplan-Meier–estimated differences in OS probabilities between groups at 24, 30, and 36 months were 8.9% (95% CI, 2.5% to 15.3%), 11.9% (95% CI, 4.7% to 19.2%), and 11.5% (95% CI, 3.5% to 19.5%), respectively, in favour of pembrolizumab plus chemoradiotherapy. These findings were consistent with the primary analysis of the overall population.

Health-Related Quality of Life

At interim analysis 2, 261 patients in the pembrolizumab plus chemoradiotherapy group and 270 patients in the placebo plus chemoradiotherapy group contributed to the analysis at baseline, and 200 and 198 patients, respectively, were included in the analysis at week 36. The mean change from baseline showed improvements in the EORTC QLQ-C30 global health status/QoL subscale at week 36 in both treatment groups (least squares mean for pembrolizumab plus chemoradiotherapy = 10.67 points [95% CI, 7.73 points

to 13.62 points]; placebo plus chemoradiotherapy = 11.32 points [95% CI, 8.39 points to 14.26 points]), and the between-group risk difference was –0.65 (95% CI,–4.19 to 2.89), with no added benefit observed for pembrolizumab plus chemoradiotherapy compared to placebo plus chemoradiotherapy. These findings were consistent with the primary analysis of the overall population.

Harms

The proportion of overall AEs were comparable between the 2 groups (100% for the pembrolizumab plus chemoradiotherapy group versus 99.3% for the placebo plus chemoradiotherapy group). The most frequently reported AEs (incidence ≥ 25%) were anemia, nausea, diarrhea, and decreased white blood cell counts. Overall, serious adverse events (SAEs) were high in proportion with no major differences between the 2 groups (33.9% in the pembrolizumab plus chemoradiotherapy group versus 32.6% in the placebo plus chemoradiotherapy group). The most frequent SAEs included anemia (4.4%), urinary tract infection (3.1%), and pyrexia (2.0%) in the pembrolizumab plus chemoradiotherapy group, and urinary tract infection (4.3%) and acute kidney injury (2.0%) in the placebo plus chemoradiotherapy group.

Treatment discontinuation rates due to AEs were generally higher in the pembrolizumab plus chemoradiotherapy group than in the placebo plus chemoradiotherapy group (21% versus 15.1%) and include events under system organ class, such as blood and lymphatic system disorders (5.1% in the pembrolizumab plus chemoradiotherapy group and 3.3% in the placebo plus chemoradiotherapy group), gastrointestinal disorders (1.7% in the pembrolizumab plus chemoradiotherapy group versus 2.0% in the placebo plus chemoradiotherapy group), and investigations (6.1% in the pembrolizumab plus chemoradiotherapy group versus 7.2% in the placebo plus chemoradiotherapy group). Deaths due to grade 5 AEs were reported in 4 patients (1.4%) in the pembrolizumab plus chemoradiotherapy group and 6 patients (2.0%) in the placebo plus chemoradiotherapy group. The most frequently reported notable harms in the pembrolizumab plus chemoradiotherapy group were immune-mediated AEs, which were reported by 40.7% of patients compared to 17.8% in the placebo plus chemoradiotherapy group.

Critical Appraisal

Internal Validity

The KEYNOTE-A18 trial is a randomized, double-masked, placebo-controlled, phase III trial in high-risk LACC, which included patients with FIGO 2014 stage IB2 to IIB (with node-positive disease) or stage III to IVA (either node-positive or node-negative) disease. Although the patients enrolled were stratified by FIGO 2014 stage III to IVA at randomization, the subgroup analysis of interest was not prespecified and, as such, the evidence informing this submission is based on a post hoc analysis. There is a potential risk that the statistically significant results may have been due to chance as a result of a lack of statistical adjustments for multiple testing, even though the risk is likely low given that the subgroup results were consistent with those of the primary analysis of the overall population. The trial is ongoing at the time of this review and the data available were based on an interim analysis that could be considered exploratory. There were also concerns about imprecision as evidenced by the wide CIs at various time points for PFS and OS, which included the clinical threshold of important difference suggested by the clinical experts consulted during the review.

Baseline demographic and disease characteristics were generally similar between treatment groups for the FIGO 2014 stage III to IVA subgroup population. This would have ensured that the confounding effect from these factors at baseline is unlikely an explanation of the differences in treatment outcomes between the 2 groups.

The double-masked design minimized the risk of detection bias and reporting bias, particularly for subjective end points like PFS. Results from blinded independent central review for PFS were consistent with the investigator's assessment. This would indicate that the between-group differences in PFS by investigator are unlikely to be attributable to subjective bias in assessment.

The proportion of patients who discontinued the study treatment was high in both treatment groups (39.7% for pembrolizumab plus chemoradiotherapy versus 46.7% for placebo plus chemoradiotherapy). A differential discontinuation from treatment was observed between treatment groups primarily due to radiographic progression (19.3% for pembrolizumab plus chemoradiotherapy versus 30.9% for placebo plus chemoradiotherapy) and AEs (11.2% for pembrolizumab plus chemoradiotherapy versus 4.9% for placebo plus chemoradiotherapy). Although overall treatment exposure appeared to be similar between the treatment arms for the completion of chemoradiotherapy, the shorter duration of exposure to treatment in the placebo arm compared to pembrolizumab (20 months versus 16 months in median duration and 17 months versus 15 months in median treatment cycles) may potentially bias the efficacy results in favour of pembrolizumab plus chemoradiotherapy.

The use of a subsequent anticancer therapy may increase the risk of bias for OS against pembrolizumab plus chemoradiotherapy (e.g., antineoplastic drugs 15.9% for pembrolizumab plus chemoradiotherapy versus 27.6% for placebo plus chemoradiotherapy). Therefore, the benefit on OS may have been underestimated.

External Validity

KEYNOTE-A18 is a multicentre study with 3 sites in Canada. The inclusion and exclusion criteria were considered appropriate for the clinical trial setting and the baseline characteristics of patients enrolled in the overall trial and subgroup did not suggest any notable issues with generalizability to patients in clinical practice in Canada. One exception is that there was uncertainty regarding whether patients with a combined positive score of less than 1 would benefit from this treatment given that the proportion of these patients was low.

The use of chemoradiotherapy was considered appropriate and the number of cycles and doses was reflective of clinical practice. Although carboplatin was not specified as an alternative to cisplatin in the trial and is not frequently prescribed by physicians in clinical practice in Canada, the experts noted that some patients who may not be eligible for cisplatin may receive carboplatin or paclitaxel as an alternative.

Concomitant and subsequent medications were generally reflective of clinical practice, with no discrepancies identified between the medications used in the study and those administered in current practice.

Key outcomes noted as important for clinical decision-making by the clinicians and patient groups consulted by CDA-AMC were investigated in the trial and included PFS, OS, and HRQoL. The assessment time points

considered in the trial were appropriate and the clinical experts consulted by CDA-AMC agreed that 18, 24, and 30 months were clinically meaningful for PFS, and 24, 36, and 36 months were clinically meaningful for OS. PFS assessments by investigator using the RECIST 1.1 criteria reflected current practice settings. The patient groups also indicated that improvements in HRQoL were important. HRQoL (measured using EORTC QLQ-C30 global health status/QoL) was considered clinically relevant and more reflective of changes in quality of life during treatment.

GRADE Summary of Findings and Certainty of the Evidence

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

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

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

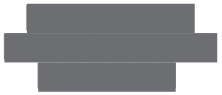
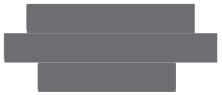
The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: OS, PFS, and HRQoL (EORTC QLQ-C30 global health status/QoL), and safety outcomes (serious AEs, discontinuation due to AEs, and immune-related AEs). The EORTC QLQ-C30 global health status/QoL subscale was determined to be the most appropriate single measure to represent HRQoL for the CDA-AMC assessment of evidence using the GRADE guidelines because it provides a comprehensive, patient-centred measure for overall well-being, integrating physical, emotional, and social aspects of health that were considered most relevant to patients according to the clinical experts.

The reference points for the certainty of evidence assessment for OS, PFS, and safety outcomes (SAEs and immune-related AEs leading to discontinuation) were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts consulted for this review. The reference point for the certainty of the evidence assessment for EORTC QLQ-C30 global health status/QoL score was set according to the presence or absence of an important effect based on a threshold that was informed by the literature.

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for pembrolizumab plus chemoradiotherapy versus placebo plus chemoradiotherapy for the treatment of adults with FIGO 2014 stage III to IVA cervical cancer.

Table 3: Summary of Findings for Pembrolizumab Plus Chemoradiotherapy vs. Placebo Plus Chemoradiotherapy for Patients With FIGO 2014 Stage III to IVA Cervical Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pembrolizumab plus chemoradiotherapy	Placebo plus chemoradiotherapy	Difference		
OS							
OS rate Follow-up: 24 months	601 (1 RCT)	HR = 0.57 (0.39 to 0.83)		780 per 1,000		Moderate[a]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in OS compared to placebo plus chemoradiotherapy at 24 months.
OS rate Follow-up: 30 months				724 per 1,000		Moderate[a]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in OS compared to placebo plus chemoradiotherapy at 30 months.
OS rate Follow-up: 36 months				707 per 1,000		Moderate[a]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in OS compared to placebo plus chemoradiotherapy at 36 months.
PFS by investigator assessment							
PFS rate Follow-up: 18 months	601 (1 RCT)	HR = 0.57 (0.43 to 0.76)		628 per 1,000		Moderate[b]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in PFS compared to placebo plus chemoradiotherapy at 18 months.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pembrolizumab plus chemoradiotherapy	Placebo plus chemoradiotherapy	Difference		
PFS rate Follow-up: 24 months			[redacted]	569 per 1,000	[redacted]	Moderate[b]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in PFS compared to placebo plus chemoradiotherapy at 24 months.
PFS rate Follow-up: 30 months			[redacted]	537 per 1,000	[redacted]	Moderate[b]	Pembrolizumab plus chemoradiotherapy likely results in a clinically important increase in PFS compared to placebo plus chemoradiotherapy at 30 months.
HRQoL							
EORTC QLQ-C30 global health status/QoL LS mean change from baseline Follow-up: Week 36	531 (1 RCT)	NR	[redacted]	11.32 points (8.39 points to 14.26 points)	[redacted]	Low[c]	Pembrolizumab plus chemoradiotherapy may result in little to no clinically important difference in HRQoL compared with placebo plus chemoradiotherapy.
Harms							
Serious adverse events Follow-up: 36 months	599 (1 RCT)	NR	[redacted]	326 per 1,000	[redacted]	Moderate[d]	Pembrolizumab plus chemoradiotherapy likely leads to little to no clinically important difference in serious adverse events compared to placebo plus chemoradiotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Pembrolizumab plus chemoradiotherapy	Placebo plus chemoradiotherapy	Difference		
Withdrawal due to immune-related adverse events Follow-up: 36 months	599 (1 RCT)	NR	[redacted]	7 per 1,000	[redacted]	High[e]	Pembrolizumab plus chemoradiotherapy does not result in a clinically important difference in withdrawals due to immune-related adverse events compared to placebo plus chemoradiotherapy.

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; HR = hazard ratio; HRQoL = health-related quality of life; LS = least squares; MID = minimal important difference; NR = not reported; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; vs. = versus.

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 following footnotes.

[a]Rated down 1 level for imprecision. In the absence of a validated MID, the threshold was informed by the clinical experts consulted for this review. A between-group absolute risk difference of 5% (50 or more events per 1,000 patients) at 24, 30, and 36 months was considered clinically significant by the clinical experts. The 95% CIs included values that were considered unimportant, indicating uncertainty.

[b]Rated down 1 level for imprecision. In the absence of a validated MID, the threshold was informed by the clinical experts consulted for this review. A between-group absolute risk difference of 10% (100 or more events per 1,000 patients) at 18, 24, and 30 months was considered clinically significant by the clinical experts. The 95% CI included values that may be considered unimportant, indicating uncertainty.

[c]Rated down 1 level for imprecision due to the wide 95% CI, which included the published MID of 4 points. Rated down 1 level for risk of bias due to missing data.

[d]In the absence of a validated MID, the null was used. Rated down 1 level for imprecision due to the wide 95% CI, which included the null value.

[e]In the absence of a validated MID, the threshold was informed by the clinical experts consulted for this review. A between-group absolute risk difference of 10% (100 or more adverse events per 1,000 patients) was considered clinically significant by the clinical experts. The point estimate and entire CI did not reach or exclude the threshold.

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

Economic Evidence

Cost and Cost-Effectiveness

- Pembrolizumab is available as a solution for infusion (25 mg/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 following the Health Canada–recommended dosing schedule. This decreases to $8,096 assuming a weight-based dose (2mg/kg) and an average weight of 69 kg.
- Clinical efficacy in the economic analysis was derived from a subgroup analysis of the KEYNOTE-A18 trial, which compared pembrolizumab plus chemoradiotherapy with chemoradiotherapy alone. Evidence submitted by the sponsor indicates that pembrolizumab plus chemoradiotherapy is likely to result in a clinically meaningful improvement for PFS and OS compared with chemoradiotherapy alone among patients with FIGO 2014 stage III to IVA cervical cancer. Although the findings on OS and PFS reported across time points were consistent and considered clinically meaningful, there is uncertainty due to imprecision.
- The results of the CDA-AMC base case suggest:
  - Pembrolizumab plus chemoradiotherapy will be associated with higher costs to the health care system than chemoradiotherapy alone (incremental costs = $99,988), which is primarily driven by increased costs associated with drug acquisition costs.
  - Pembrolizumab plus chemoradiotherapy will be associated with a gain of 2.04 life-years compared to chemoradiotherapy. When the impact on HRQoL is also considered, pembrolizumab plus chemoradiotherapy results in a gain of 1.76 QALYs compared to chemoradiotherapy.
  - The ICER for pembrolizumab plus chemoradiotherapy compared to chemoradiotherapy was $56,745 per QALY gained in the CDA-AMC base case.
  - The trial evidence is only approximately 2 years in length and the incremental benefit is contingent on long-term OS. Given that the evidence used to inform long-term OS was informed from another clinical trial with differing patient characteristics (KEYNOTE-826), the incremental QALYs for pembrolizumab plus chemoradiotherapy predicted in the CDA-AMC base case are uncertain and may be overestimated. Scenario analyses conducted indicate that if postprogression survival is improved such that patients who received chemoradiotherapy only live longer, the ICER for pembrolizumab plus chemoradiotherapy compared to chemoradiotherapy increases to $74,284 per QALY gained.
- CDA-AMC estimates that the budget impact of reimbursing pembrolizumab for use in combination with chemoradiotherapy for the indicated population will be approximately $73 million over the first 3 years of reimbursement compared to the amount currently spent on chemoradiotherapy, with an estimated expenditure of $75 million on pembrolizumab plus chemoradiotherapy over this period. The actual budget impact of reimbursing pembrolizumab plus chemoradiotherapy will depend on the number of people eligible for treatment and the market uptake of pembrolizumab.

pERC Information

Members of the Committee

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

Meeting date: August 13, 2025

Regrets: Six expert committee members did not attend.

Conflicts of interest: None

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