

## CADTH Reimbursement Recommendation

# Pembrolizumab (Keytruda)

**Indication:** Treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (combined positive score  $\geq 1$ ), as determined by a validated test, in combination with chemotherapy with or without bevacizumab

**Sponsor:** Merck Canada Inc.

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda be reimbursed by public drug plans for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express programmed death ligand 1 (PD-L1) (combined positive score [CPS]  $\geq 1$ ) as determined by a validated test, in combination with chemotherapy with or without bevacizumab if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq 1$ ) are not amenable to curative treatment, who are in relatively good health (i.e., have a good performance status, as determined by a specialist), have not received prior systemic chemotherapy for metastatic or advanced cervical cancer, and are candidates for standard-of-care chemotherapy with or without bevacizumab.

## What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed in combination with platinum-based chemotherapy, with or without bevacizumab, if given by a clinician who is experienced in chemoimmunotherapy administration, and if the cost of Keytruda is reduced.

## Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda combined with the standard-of-care regimen of chemotherapy with or without bevacizumab improved survival and delayed disease progression compared with standard of care alone. Keytruda also had manageable side effects, which is an outcome identified as important by patients.
- Based on CADTH's assessment of the health economic evidence, Keytruda does not represent good value to the health care system at the public list price. A reduction in price is therefore required. Over 3 years, Keytruda is expected to increase drug costs to the public drug plans by approximately \$125,648,400.

## Additional Information

### What Is Cervical Cancer?

Cervical cancer is a type of cancer that most often originates from squamous cells in the cervix. People with persistent, recurrent, or metastatic cervical cancer have been treated unsuccessfully, have been treated and the cancer has returned, or have cervical cancer that has spread to other parts of the body. The majority of cervical cancers are associated with persistent high-risk oncologic HPV-type infections.

### Unmet Needs in Persistent, Recurrent, or Metastatic Cervical Cancer

Patients with persistent, recurrent, or metastatic cervical cancer are treated with chemotherapy with or without bevacizumab; however, not all patients respond to these available treatments, and there is a need for more effective treatments.

### How Much Does Keytruda Cost?

Treatment with Keytruda is estimated to cost approximately \$11,733 per 28 days.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab in combination with chemotherapy with or without bevacizumab be reimbursed for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express programmed death ligand 1 (PD-L1) (combined positive score [CPS]  $\geq 1$ ) as determined by a validated test only if the conditions listed in [Table 1](#) are met.

## Rationale for the Recommendation

One phase III, randomized, multicentre, placebo-controlled study (KEYNOTE-826) demonstrated that pembrolizumab added to chemotherapy, with or without bevacizumab, resulted in added clinical benefits for adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq 1$ ). The results of the KEYNOTE-826 trial demonstrated that the addition of pembrolizumab administered every 3 weeks to the standard-of-care (SoC) regimen of chemotherapy, with or without bevacizumab, for up to 35 cycles of treatment was associated with statistically significant and clinically meaningful improvements in overall survival (OS) compared with placebo plus SoC at a median of 18.3 months of follow-up (hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.50 to 0.81; P value = 0.0001). The addition of pembrolizumab also demonstrated a statistically significant improvement in progression-free survival (PFS) (HR = 0.62; 95% CI, 0.50 to 0.77; P < 0.0001) compared with placebo. Although exploratory, the addition of pembrolizumab to SoC was not associated with a detriment in health-related quality of life (HRQoL). Pembrolizumab was associated with a manageable toxicity profile.

Patients identified a need for access to effective treatments that maintain quality of life, reduce side effects from current standard treatments, and delay the onset of symptoms. pERC concluded that pembrolizumab met some of the needs identified by patients in terms of delaying the onset of symptoms and providing a manageable toxicity profile.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab and SoC was \$272,958 per quality-adjusted life-year (QALY) compared with SoC alone. At this ICER, pembrolizumab is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold for adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq 1$ ) as determined by a validated test. A price reduction is required for pembrolizumab to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Treatment with pembrolizumab in combination with chemotherapy with or without bevacizumab should be only reimbursed when initiated in patients with all of the following:	In the KEYNOTE-826 study, treatment with pembrolizumab demonstrated a clinically meaningful benefit in patients with these characteristics for this condition.	—

Reimbursement condition	Reason	Implementation guidance
1.1. tumour not amenable to curative treatment 1.2. have not been previously treated with systemic chemotherapy for metastatic or advanced disease (except for patients who received concurrent cisplatin with radiation with curative intent) 1.3. candidates for SoC chemotherapy with or without bevacizumab 1.4. good performance status 1.5. tumours express PD-L1 (CPS $\geq 1$ ) as determined by a validated test.		
2. Patients must not have active CNS metastasis or significant autoimmune disease.	Patients enrolled in the KEYNOTE-826 trial did not have active CNS metastasis or significant autoimmune disease. As such, the potential benefit of pembrolizumab in these patients has not been demonstrated.	—
<b>Discontinuation</b>		
3. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 3.1. clinical disease progression 3.2. unacceptable toxicity.	As per KEYNOTE-826 study, clinical expert opinion, and standard clinical practice.	—
4. The maximum duration of reimbursement is up to 105 weeks for patients who receive pembrolizumab every 3 weeks or up to 108 weeks for patients who receive pembrolizumab every 6 weeks for patients who do not meet any of the discontinuation criteria.	In the KEYNOTE-826 trial, pembrolizumab was administered every 3 weeks up to a maximum of 35 cycles. The pembrolizumab product monograph allows for an alternative dosing schedule of every 6 weeks up to a maximum of 18 cycles.	—
<b>Prescribing</b>		
5. Pembrolizumab should be prescribed and administered in an oncology health facility by trained health professionals familiar with chemoimmunotherapy administration.	This is to ensure that pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
6. Pembrolizumab must be prescribed in combination with platinum-based combination therapy with or without bevacizumab.	Pembrolizumab was administered in combination with platinum-based combination therapy with or without bevacizumab in the KEYNOTE-826 trial.	pERC noted that because turnaround times for PD-L1 testing vary across cancer centres, chemotherapy with or without bevacizumab can be initiated first, with a plan to add pembrolizumab when the PD-L1 CPS score becomes available.

Reimbursement condition	Reason	Implementation guidance
<b>Pricing</b>		
7. A reduction in price.	The ICER for pembrolizumab + SoC is \$272,958 compared with SoC alone. A price reduction of 90% would be required for pembrolizumab + SoC to achieve an ICER of \$50,000 per QALY compared with SoC.	—
<b>Feasibility of adoption</b>		
8. The feasibility of adoption of pembrolizumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

AE = adverse event; CPS = combined positive score; CNS = central nervous system; ICER = incremental cost-effectiveness ratio; PD-L1 = programmed death ligand 1; QALY = quality-adjusted life-year; SoC = standard of care.

## Discussion Points

- pERC discussed that although the effect of pembrolizumab on HRQoL was uncertain, there did not appear to be a detrimental effect in patients who received pembrolizumab. The evidence suggests pembrolizumab may extend the time to deterioration in HRQoL measures, although this remains uncertain given the exploratory nature of the end points.
- pERC discussed that the toxicity profile for pembrolizumab is established, and physicians are familiar with mitigating adverse events (AEs).
- pERC discussed that patients who complete their treatment cycles and subsequently experience disease progression may be retreated with the original treatment regimen. Patients who receive re-treatment with pembrolizumab would do so every 3 weeks for a maximum of 17 cycles.
- pERC discussed that similar to the study protocol of the KEYNOTE-826 trial, treatment with pembrolizumab could be discontinued at the treating physician's discretion if the patient has received a minimum of 8 cycles total of treatment (approximately 24 weeks), including 2 cycles following complete response (CR).

## Background

Cervical cancer is commonly grouped into histologic categories of epithelial tumours: squamous, adenocarcinoma, mixed adenosquamous, and other epithelial histologies.<sup>1,2</sup> The majority of cervical cancers are associated with persistent high-risk oncologic HPV-type infections.<sup>1</sup> The organized cervical cytology screening programs across Canada and recent widespread vaccination campaigns against HPV are expected to continue to lower the incidence of cervical cancer and mortality rates well into the future; however, cervical cancer is still a public health concern. According to the 2021 Canadian cervical cancer statistics, approximately 1,450 people in Canada are diagnosed with cervical cancer annually, 12% of

whom are in stage IV. There are also 380 deaths in Canada due to cervical cancer annually.<sup>3</sup> Primary treatment with surgery, radiation, or a combination of both are indicated. Between 10% and 20% of patients will have persistent, recurrent, or metastatic cervical disease after primary treatment. This can have a very high burden on patients and their families, impacting their daily lives, work lives, sexual relationships, physical activity, and sleep patterns.<sup>1,4</sup> The current SoC therapy for persistent, recurrent, or metastatic cervical after primary therapy with surgery and radiation is chemotherapy with or without the addition of bevacizumab, depending on patient contraindications.

The majority of cervical cancer tumours express PD-L1; therefore, this was the basis for studying the use of a checkpoint inhibitor in this disease. Pembrolizumab is a PD1 inhibitor (administered as an IV infusion over 30 minutes) and has been studied in combination with SoC chemotherapy, with or without bevacizumab. The recommended dosage is either 200 mg IV every 3 weeks or 400 mg IV every 6 weeks until disease progression, unacceptable toxicity, or a maximum of up to 24 months, thirty-five 200 mg doses, or eighteen 400 mg doses, whichever is longer.

Pembrolizumab has been approved by Health Canada for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq 1$ ), as determined by a validated test, in combination with chemotherapy with or without bevacizumab. Pembrolizumab is an immune checkpoint inhibitor. It is available as an IV infusion, and the dosage recommended in the product monograph is either 200 mg every 3 weeks or 400 mg every 6 weeks.

## Sources of Information Used by the Committee

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

- a review of 1 randomized, placebo-controlled, clinical study in patients with persistent, recurrent, or metastatic cervical cancer
- patients' perspectives gathered by 1 patient group, HPV Global Action
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with cervical cancer
- input from 1 clinician group, the Ontario Health-Cancer Care Ontario (OH-CCO) Gynecology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

One patient advocacy group, HPV Global Action, in collaboration with the Canadian Cancer Survivor Network (CCSN), provided a joint input for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1

(CPS  $\geq 1$ ) as determined by a validated test. Information was gathered from March to May 2022 through Blue Ribbon Project Inc., who reached out to 24 clinicians via email and 5 international organizations online seeking help to identify advanced cervical cancer patients. Data were collected from 8 patients and caregivers through an online survey, among whom 5 were from Canada and 3 from the US. Among the 8 responders, 6 had been diagnosed with metastatic disease and 1 with stage III disease. Moreover, 3 patients had first-hand experience with the therapy under review.

Fatigue, pain in the pelvic area or lower back, and abnormal vaginal bleeding after menopause were the top 3 physical symptoms identified by the patients; living with uncertainty, anxiety, panic attacks/depression, and feeling isolated or lonely were the top psychosocial problems for the responders.

In response to the survey question on side effects of current treatments, patients described pain during sexual intercourse, difficulty urinating, difficulty having a bowel movement, and leaking of urine or feces from the vagina impacting their daily lives. When asked about their considerations for outcomes while evaluating novel therapies, all metastatic cervical cancer patients chose “maintain quality of life” and “access to a new treatment option” as their preferred outcomes, with “reduce side effects from current medications or treatments” and “delay onset of symptoms” as their second and third preferences. When describing their experiences with the drug under review, 2 of the 3 patients with experience with pembrolizumab achieved a “no evidence of disease” status after therapy and identified it as a “positive effect.” The third patient mentioned having minimal side effects from the drug under review. When describing the negative effects from pembrolizumab, patients mentioned facing grade 2 interstitial nephritis, nausea, feeling unusually tired or weak, diarrhea, rash, joint pain, fever, dry skin, and nail breakage as some of the adverse effects. However, all 3 respondents mentioned that they were able to manage disease progression, it was easy to use, and they had more control of symptoms more effectively while being on the therapy under review. When responding to what side effects from the therapy under treatment would be acceptable for the patients, the 2 patients who responded chose itching, rash, low levels of thyroid hormone, feeling less hungry, and patches of skin that have lost colour (vitiligo) as acceptable ones.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

Two clinical experts with experience treating cervical cancer highlighted the current significant unmet need for further effective options to treat persistent, recurrent, or metastatic cervical disease. The clinical experts agreed that standard outcome measures of treatment response, duration of response, survival statistics, toxicities, and quality-of-life measures are aligned with the outcomes used in the current KEYNOTE-826 clinical trial. The clinical experts agreed that pembrolizumab should be given in a clinical setting where patients can be monitored closely for early detection and management of immune-related toxicities with appropriate patient education.

### Clinician Group Input

One clinician group, OH-CCO Gynecology Cancer Drug Advisory Committee, provided input for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq 1$ ) as determined by a validated test. The clinician group commented that pembrolizumab would improve the efficacy for patients treated within the



submitted indication and meet the unmet needs because no curative treatment is available for the patient population. It was also highlighted that there are very limited second-line options available for patients with persistent, recurrent, or metastatic cervical cancer. The clinical group considered pembrolizumab as the first-line treatment option for patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1, whereas patients with contraindications to pembrolizumab and patients whose tumours do not express PD-L1 are considered to be the least suitable for this treatment. The clinician group noted that they would consider disease progression or toxicity as indications to discontinue treatment with the drug under review.

## Drug Program Input

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

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

Questions	Clinical expert response
<b>Relevant comparators</b>	
<p>The comparator in KEYNOTE-826 was placebo + paclitaxel 175 mg/m<sup>2</sup> + a platinum (either cisplatin 50 mg/m<sup>2</sup> or carboplatin AUC 5) ± bevacizumab 15 mg/kg (added as per local practice) every 3 weeks. A platinum-based doublet ± bevacizumab is the current standard of practice in this setting. Other chemotherapy combinations used can include platinum + topotecan, taxane + topotecan, or single-agent therapy.</p> <ul style="list-style-type: none"> <li>• Are alternative chemotherapy backbones appropriate for combination with pembrolizumab (± bevacizumab) when a patient is unable to receive a platinum agent and/or a taxane?</li> </ul>	<p>The clinical experts consulted by CADTH noted that paclitaxel 175 mg/m<sup>2</sup> + carboplatin AUC 5 with the addition of bevacizumab, if tolerated, is a well-recognized standard of care and is used in 95% or more of patients. Other combinations are rare; however, if a patient is unable to receive either paclitaxel or carboplatin, other agents should be chosen according to patient characteristics.</p>
<p>KEYNOTE-826 underwent a second protocol amendment that resulted in limiting the chemotherapy component of the regimen to 6 cycles of therapy, although patients with ongoing clinical benefit who were receiving chemotherapy without unacceptable side effects could continue beyond 6 cycles after consultation with the sponsor.</p> <ul style="list-style-type: none"> <li>• Is there clinical evidence to support patients with ongoing clinical benefit and no intolerability continuing the chemotherapy backbone beyond 6 cycles?</li> </ul>	<p>pERC agreed with the clinical experts that there is no clinical evidence to support chemotherapy beyond 6 cycles, but this is a common clinical practice. In the clinical trial with pembrolizumab, chemotherapy was permitted to be continued beyond 6 cycles, and clinical experts recommend that the clinical trial treatment schema be followed.</p>
<b>Considerations for initiation of therapy</b>	
<p>Should patients who complete 2 years of treatment and experience disease progression or recurrence off of pembrolizumab treatment be eligible for up to 1 year (17 cycles) of pembrolizumab re-treatment?</p>	<p>pERC agreed with the clinical experts that for patients who have completed 2 years of treatment with pembrolizumab and subsequently experience disease progression or recurrence, re-treatment with pembrolizumab is commonly done with pembrolizumab and expected in the cervical cancer indication as well.</p>

Questions	Clinical expert response
If re-treatment is permitted, would this be as pembrolizumab monotherapy or in combination with chemotherapy?	pERC noted that there is no evidence to suggest whether re-treatment with pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy would be superior. Typically, re-treatment would be done with the full treatment regimen, in this case, pembrolizumab in combination with paclitaxel and a platinum-based chemotherapy with or without bevacizumab.
<b>Considerations for discontinuation of therapy</b>	
If a patient cannot tolerate the chemotherapy combination, are they able to continue with pembrolizumab ± bevacizumab?	pERC agreed with the clinical experts that this decision would be made to be in line with the conduct of KEYNOTE-826. The experts noted that patients who cannot tolerate chemotherapy should continue to receive pembrolizumab, with or without bevacizumab, following discontinuation of chemotherapy.
If a patient cannot tolerate bevacizumab, are they able to continue with pembrolizumab + chemotherapy?	pERC agreed with the clinical experts that if a patient cannot tolerate bevacizumab, they should continue treatment with pembrolizumab + chemotherapy, which is in line with the KEYNOTE-826 protocol.
Is there a minimum number of chemotherapy cycles that must be given concurrently with pembrolizumab?	<p>The clinical experts agreed that the KEYNOTE-826 protocol should be followed. Chemotherapy should be continued up to 6 cycles with treatment; beyond 6 cycles is permitted if there is clinical benefit. If chemotherapy cannot be tolerated and is discontinued before 6 cycles, pembrolizumab should be continued with or without bevacizumab.</p> <p>pERC noted that the patient must have received at least 1 cycle of chemotherapy concurrently with pembrolizumab with or without bevacizumab before changing to pembrolizumab with or without bevacizumab.</p>
<b>Considerations for prescribing of therapy</b>	
<p>Pembrolizumab was administered every 3 weeks in KEYNOTE-826; however, the product monograph indicates that administration either every 3 weeks or every 6 weeks is acceptable for cervical cancer.</p> <ul style="list-style-type: none"> <li>Is a dosing interval for pembrolizumab of every 6 weeks appropriate for this indication?</li> </ul>	pERC agreed with the clinical experts that there is no clinical difference between the 2 dosing options. Although the trial used 200 mg every 3 weeks, some clinicians may choose 400 mg every 6 weeks to reduce the number of visits and chair time.
<p>Comments from the drug plans (response not required):</p> <ul style="list-style-type: none"> <li>If funded, to keep in line with other indications for pembrolizumab, jurisdictions would implement a weight-based dose of 2 mg/kg (up to a maximum of 200 mg) every 3 weeks or 4 mg/kg (up to a maximum of 400 mg) every 6 weeks.</li> </ul>	Comment from the drug programs to inform pERC deliberations.
<b>Generalizability</b>	
Should patients with an ECOG PS of 2 or higher be eligible?	Patients with an ECOG PS score of 2 were not eligible for inclusion in KEYNOTE-826. pERC agreed with the clinical experts that the magnitude of benefit in this population is uncertain and noted that the decision to use pembrolizumab in combination with chemotherapy with or without bevacizumab in these patients should be left to the discretion of the treating clinician.

Questions	Clinical expert response
<p>There is a time-limited need to allow patients currently on platinum-based doublet chemotherapy, or alternate chemotherapy ± bevacizumab, to add pembrolizumab.</p> <ul style="list-style-type: none"> <li>• What time frame is appropriate to add pembrolizumab for patients actively on treatment (chemotherapy ± bevacizumab) or who have recently completed treatment?</li> <li>• Should pembrolizumab be added to bevacizumab if the patient has completed the chemotherapy component?</li> </ul>	<p>pERC agreed with the clinical experts that it is reasonable to add pembrolizumab to treatment for patients already receiving chemotherapy with or without bevacizumab, given that there has been no disease progression.</p>
Care provision issues	
<p>Comments from the drug plans (response not required):</p> <ul style="list-style-type: none"> <li>• Pembrolizumab is already prepared and administered at facilities throughout Canada. Health care professionals have extensive experience with it. Preparation and administration time for pembrolizumab are relatively reasonable and would not be expected to significantly increase health system resources. However, there is the additional cost related to drug wastage because there is only 1 vial size available.</li> </ul>	<p>Comment from the drug programs to inform pERC deliberations.</p>
System and economic issues	
<p>Comments from the drug plans (response not required):</p> <ul style="list-style-type: none"> <li>• Pembrolizumab use as an additional agent in this patient population would introduce a considerable impact to budget vs. chemotherapy alone or chemotherapy + bevacizumab.</li> </ul>	<p>Comment from the drug programs to inform pERC deliberations.</p>

AUC = area under the curve; ECOG PS = European Cooperative Oncology Group Performance Status.

## Clinical Evidence

### Description of Studies

KEYNOTE-826 is an ongoing phase III, randomized, placebo-controlled clinical trial investigating pembrolizumab in combination with SoC compared with placebo plus SoC in the treatment of patients with histologically confirmed persistent, recurrent, or metastatic cervical cancer who have not been treated with prior systemic chemotherapy. Patients were randomized 1:1 to receive pembrolizumab 200 mg plus SoC or a placebo plus SoC. SoC was defined as paclitaxel 175 mg/m<sup>2</sup> plus either cisplatin 50 mg/m<sup>2</sup> or carboplatin area under the curve (AUC) 5, with the addition of bevacizumab 15 mg/kg if there were no contraindications to bevacizumab. Randomization in the KEYNOTE-826 trial was stratified according to metastasis at initial diagnosis, bevacizumab use (according to investigators' choice before randomization), and PD-L1 status (CPS < 1, 1 to < 10, and ≥ 10). There were 6 primary objectives of the study, which were to compare PFS and OS between pembrolizumab plus SoC and placebo plus SoC in patients with PD-L1 with a CPS of 1 or higher, CPS of 10 or higher, and all-comers patients (defined as all randomized patients regardless of PD-L1 status, which included patients with PD-L1 CPS < 1 as well as any with missing PD-L1 status). Secondary objectives included determining overall response rate (ORR), duration of response (DOR), 12-month PFS rate, safety and tolerability, and HRQoL. Overall, 39 (6.3%) were American Indian or Alaska Native, 110 (17.8%) were Asian, 6 (1.0%) were Black or African-

American, 66 (10.7%) were multiple races, 360 (58.3%) were White, 35 (5.7%) not reported, and 1 (0.2%) missing. There were fewer White patients in the pembrolizumab plus SoC arm than the placebo plus SoC arm (56% versus 62.5%) and more patients from the Asia Pacific region in the pembrolizumab plus SoC arm than the placebo plus SoC arm (19.8% versus 13.8%). There were no meaningful differences in baseline characteristics in patients with PD-L1 with a CPS of 10 or higher.

## Efficacy Results

### Health-Related Quality of Life



### Overall Survival

The median OS for patients with PD-L1 with a CPS of 1 or higher was not reached (95% CI, 19.8 to not reached) in the pembrolizumab plus SoC arm and 16.3 months (95% CI, 14.5 to 19.4 months) in the placebo plus SoC arm. The HR for OS comparing pembrolizumab plus SoC and placebo plus SoC was 0.65 (95% CI, 0.50 to 0.81) with a P value of 0.0001 (multiplicity adjusted, 1-sided nominal alpha level = 0.0054906). The OS rate at 12 months was 75.5% (95% CI, 69.7% to 80%) in the pembrolizumab plus SoC arm and 63.1% (95% CI, 57% to 68.5%) in the placebo plus SoC arm.

### Progression-Free Survival

The median PFS for patients with PD-L1 with a CPS of 1 or higher was 10.4 months (95% CI, 9.7 to 12.3 months) in the pembrolizumab plus SoC arm and 8.2 months (95% CI, 6.3 to 8.5 months) in the placebo plus SoC arm. The HR for PFS comparing pembrolizumab plus SoC and placebo plus SoC was 0.62 (95% CI, 0.50 to 0.77) with a P value less than 0.0001 (multiplicity adjusted, 1-sided nominal alpha level = 0.0014426). The PFS rate at 12 months was 45.5% (95% CI, 39.2% to 51.5%) in the pembrolizumab plus SoC arm and 34.1% (95% CI, 28.3% to 40%) in the placebo plus SoC arm.

### Overall Response Rate

The ORR for patients with PD-L1 with a CPS of 1 or higher in the pembrolizumab plus SoC arm was 68.1% (95% CI, 62.2% to 73.6%), including 22.7% of patients that achieved a CR. The ORR in the placebo plus SoC arm was 50.2% (95% CI, 44.1% to 56.2%), including 13.1% of patients that achieved a CR. The difference estimate for pembrolizumab plus SoC compared with placebo plus SoC was 18.0% (95% CI, 10.1% to 25.7%).

### Duration of Response

Of the 186 patients with PD-L1 with a CPS of 1 or higher in the pembrolizumab plus SoC arm that recorded a response, the median time to response was 2.1 months (range, 1.7 to 20.6 months). Of the 138 patients in the placebo plus SoC arm that recorded a response, the median time to response was 2.1 months (range, 1.3 to 7.1 months). The median DOR in

patients in the pembrolizumab plus SoC arm was 18.0 months (range,  $\geq 1.3$  to  $\geq 24.2$  months) while the median DOR in patients in the placebo plus SoC arm was 10.4 months (range,  $\geq 1.5$  to  $\geq 22.0$  months).

## Harms Results

In the safety analysis set at the time of data cut-off, 99.3% of patients with PD-L1 with a CPS of 1 or higher in the pembrolizumab plus SoC arm and 99.4% of the patients in the placebo plus SoC arm reported treatment-emergent AEs. The most common AEs in the pembrolizumab plus SoC arm were anemia (61.2%), alopecia (56.4%), nausea (39.7%), and diarrhea (35.5%). The most common AEs in the placebo plus SoC arm were alopecia (57.9%), anemia (53.4%), nausea (43.7%), and constipation (33%).

The identified notable harms included in the CADTH systematic review with summary data available from the KEYNOTE-826 trial were immune-mediated AEs and infusion reactions. In the pembrolizumab plus SoC arm, immune-mediated AEs occurred in 33.9% of patients with 11.4% of patients reporting AEs of grade 3 or higher. In the placebo plus SoC arm, immune-mediated AEs occurred in 15.2% of patients with 2.9% of patients reporting AEs of grade 3 or higher. Infusion reactions occurred in 13.4% of patients in the pembrolizumab plus SoC arm, with 2.3% reporting grade 3 or higher infusion reactions. In the placebo plus SoC arm, infusion reactions occurred in 12.6%, with 2.3% reporting grade 3 or higher infusion reactions.

## Economic Evidence

**Table 3: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS $\geq 1$ ) as determined by a validated test
Treatment	Pembrolizumab + SoC
Dose regimen	200 mg every 3 weeks or 400 mg every 6 weeks
Submitted price	Pembrolizumab, 100 mg, solution: \$4,400.00 per 100 mg/4 mL vial
Treatment cost	\$11,733 per 28 days
Comparator	SoC (cisplatin/carboplatin + paclitaxel with or without bevacizumab)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	KEYNOTE-826 trial

Component	Description
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• The long-term survival benefit of pembrolizumab is highly uncertain. The vast majority of the survival benefits (incremental LYs and QALYs) were accrued in the PF health state between 10 and 40 years after treatment initiation. The observation period of KEYNOTE-826 was 2.4 years; as such, the predicted gains in survival with pembrolizumab will occur in the period beyond which evidence exists (extrapolated from the clinical trial).</li> <li>• The sponsor's base case presented an implausibly high PFS rate in the PF state over the 40-year time horizon, which does not reflect patient clinical trajectory according to the clinical experts consulted for this review. The fact that many patients remained in the PF state for up to 40 years implied that pembrolizumab could essentially cure patients with persistent, recurrent, or metastatic cervical cancer. However, no evidence was provided by the sponsor to support this assumption.</li> <li>• The transition probabilities from the PF state to death when using log-logistic distribution for PFS and time to progression were observed to be lower than the mortality rate for the general Canadian population at several time points, which lacked face validity.</li> <li>• The sponsor assumed the proportion of patients receiving each of the SoC chemotherapy regimens (cisplatin/carboplatin + paclitaxel with or without bevacizumab) differed by initial treatment (pembrolizumab + SoC or SoC), which aligns with the KEYNOTE-826 trial. Clinical expert feedback suggested there was no clinical reason why patients receiving pembrolizumab + SoC would receive a different chemotherapy regimen than patients receiving SoC alone.</li> <li>• The sponsor assumed that a lower proportion of patients who received pembrolizumab + SoC and had disease progression would receive subsequent treatments. This assumption increased subsequent treatment cost for SoC, favouring pembrolizumab.</li> <li>• The sponsor applied RDI in the derivation of the costs for pembrolizumab, chemotherapy, and bevacizumab. This is inappropriate because RDI can be influenced by many different factors and introduce a bias that favours pembrolizumab.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• CADTH undertook several reanalyses to address limitations relating to overestimation of proportion of patients in PF state over 40 years, use of different chemotherapy regimens among patients receiving pembrolizumab + SoC or SoC alone, and use of different rates of patients undergoing subsequent treatment depending on initial treatment and use of RDI.</li> <li>• In CADTH's base case, for the proposed Health Canada–indicated population, pembrolizumab + SoC was associated with an ICER of \$272,958 per QALY compared with SoC (incremental costs = \$180,957; incremental QALYs = 0.66).</li> <li>• For pembrolizumab + SoC to be cost-effective compared to SoC at a willingness-to-pay threshold of \$50,000 per QALY, a price reduction of 90% is required.</li> </ul>

ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care; PD-L1 = programmed death ligand 1; CPS = combined positive score; PF = progression-free; PFS = progression-free survival; RDI = relative dose intensity.

## Budget Impact

CADTH identified the following key limitations: market uptake may be underestimated, the PD-L1 testing rate may be underestimated, the assumption regarding patient enrolment in clinical trials as a comparator is inappropriate, the relative dose intensity (RDI) and budget impact of patients diagnosed in years 1 to 3 were not fully captured.

CADTH's base case revisions included revising the proportion of patients who were assumed to be in clinical trials to 0%, increased the market uptake to 90%, increased the PD-L1 testing rate to 88%, and set RDI to 100%. CADTH also explored uncertainty in the price reduction, use of a weight-based pembrolizumab dose, and the incident case distribution throughout the year.

Based on CADTH's base case, the expected budget impact for funding pembrolizumab for adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS  $\geq$  1) as determined by a validated test in the drug plan perspective is expected to be \$5,712,761 in year 1, \$25,554,791 in year 2, and \$37,973,976 in year 3, with a 3-year budget impact of \$69,241,528.

Results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to the change to weight-based dosing (3-year budget impact = \$44,771,631) and the timing of when individuals were diagnosed in the model (3-year budget impact = \$125,648,400).

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

**Meeting date:** October 12, 2022

**Regrets:** 3 expert committee members did not attend

**Conflicts of interest:** None