Canadian Journal of Health Technologies

CADTH

December 2021 Volume 1 Issue 12

CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: In combination with platinum and fluoropyrimidine–based chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the esophagogastric junction (tumour centre 1 cm to 5 cm above the gastric cardia)

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda should be reimbursed by public drug plans for the treatment of esophageal or human epidermal growth factor receptor 2 (HER2)-negative esophagogastric junction (EGJ) cancer that cannot be removed by surgery or is metastatic, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat adult patients who have not received previous treatment for advanced or metastatic esophageal or EGJ cancer and who have good performance status.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed in combination with platinum and fluoropyrimidine–based chemotherapy and given by a clinician who is experienced in treating cancer. The price of Keytruda must be lowered to be cost-effective and affordable.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Keytruda combined with cisplatin and 5-fluorouracil (5-FU) improved survival compared with cisplatin and 5-FU alone. Keytruda also had manageable side effects, which is an outcome identified as important by patients.

Based on public list prices, Keytruda is not considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) for patients included in the indication approved by Health Canada, relative to cisplatin plus 5-FU. Economic evidence suggests that the price of Keytruda needs to be reduced by 75% for it to be cost-effective at a $50,000 per QALY threshold.

Based on public list prices, Keytruda is expected to cost the public drug plans $91 million over 3 years.

Additional Information

What Is Esophageal and EGJ Cancer?

Esophageal cancer occurs in the esophagus — a muscular tube that connects the throat to the stomach — and EGJ cancer occurs where the esophagus and the stomach join. The cancer is considered locally advanced if it spreads in the esophagus or GEJ or metastatic if it spreads to another part of the body. Approximately 5% of patients diagnosed with advanced esophageal cancer are expected to be alive in 5 years.

Unmet Needs in Esophageal and EGJ Cancer

Many patients do not respond to available treatment options. Even in patients who do respond, the duration of response is often short, and their survival is quite limited.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $8,472.27 per cycle of pembrolizumab in combination with 5-FU and cisplatin at the sponsor's assumed relative dose intensities.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy be reimbursed for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or human epidermal growth factor receptor 2 (HER2)-negative adenocarcinoma of the esophagogastric junction (EGJ) (tumour centre 1 cm to 5 cm above the gastric cardia) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, randomized, double-blind, placebo-controlled trial demonstrated that treatment with pembrolizumab plus cisplatin and 5-fluorouracil (5-FU) resulted in added survival benefit when used for the first-line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced or metastatic Siewert type I adenocarcinoma of the EGJ. The KEYNOTE-590 trial (N = 749) demonstrated that, when compared with placebo plus cisplatin and 5-FU, treatment with pembrolizumab plus cisplatin and 5-FU was associated with a statistically significant improvement in progression-free survival (PFS) (hazard ratio [HR] = 0.65; 95% confidence interval [CI], 0.55 to 0.76; P < 0.0001) and a statistically and clinically significant improvement in overall survival (OS) (HR = 0.73; 95% CI, 0.62 to 0.86; P < 0.0001). Input from patient groups indicated that patients desire new effective therapies that prolong OS, improve quality of life (QoL), reduce disease symptoms, and have tolerable side effects. Given all the evidence, pERC concluded that pembrolizumab plus cisplatin and 5-FU met some of the needs identified by patients because it provides an additional treatment option with improved OS and a manageable safety 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 in combination with 5-FU and cisplatin was $170,819 per quality-adjusted life-year (QALY) compared with 5-FU plus cisplatin alone. At this ICER, pembrolizumab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for first-line treatment of patients with locally advanced unresectable or metastatic cancer of the esophagus or HER2-negative adenocarcinoma of the EGJ. A reduction in price of at least 75% 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
Initiation	
1. Treatment with pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy should be initiated only in adult patients who have all of the following: 1.1. Histologically or cytologically confirmed locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus, or advanced or metastatic Siewert type I adenocarcinoma of the esophagogastric junction 1.2. ECOG PS of 0 or 1.	Evidence from the KEYNOTE-590 trial demonstrated that pembrolizumab plus cisplatin and 5-FU resulted in significant improvements in PFS and OS in patients with characteristics listed in this condition.
2. Pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy should be initiated in patients with no history of receiving anti–PD-1, anti–PD-L1, or anti–PD-L2 therapies, or an agent directed to another co-inhibitory T-cell receptor.	No evidence was available to support the efficacy of pembrolizumab plus cisplatin and 5-FU in patients previously treated with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent, or with an agent directed to another co-inhibitory T-cell receptor because these patients were excluded from the KEYNOTE-590 trial.
Renewal	
3. Assessment for renewal of pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy should be based on clinical and radiographic evaluation every 9 weeks (2 months).	In KEYNOTE-590, assessment of response to therapy was performed every 9 weeks, and more frequently if clinically indicated.
4. Treatment with pembrolizumab may be reimbursed for a maximum of 24 months (i.e., completion of 35 administrations).	In KEYNOTE-590, a benefit of pembrolizumab was observed for up to 24 months (i.e., completion of 35 administrations).
Discontinuation	
5. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 5.1. documented disease progression as per RECIST 1.1 5.2. unacceptable toxicity.	The CADTH review identified no evidence that continuing treatment with pembrolizumab in patients whose disease has progressed is effective. Patients who are unable to complete treatment with pembrolizumab due to unacceptable toxicity would likely not be able to receive further treatment with pembrolizumab.
Prescribing	
6. Pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy should only be administered under the supervision of clinicians experienced in the treatment of cancer.	To ensure pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
7. Pembrolizumab should be prescribed in combination with platinum and fluoropyrimidine–based chemotherapy for eligible patients.	Pembrolizumab was administered in combination with cisplatin and 5-FU in the KEYNOTE-590 trial; the CADTH review identified no evidence to suggest an additional benefit of pembrolizumab as monotherapy.

Reimbursement condition	Reason
Pricing	
8. A reduction in price.	The ICER for pembrolizumab in combination with 5-FU and cisplatin is $170,819 per QALY when compared with 5-FU plus cisplatin alone. A price reduction of 75% would be required for pembrolizumab to be able to achieve an ICER of $50,000 per QALY compared with 5-FU plus cisplatin.
Feasibility of adoption	
9. The feasibility of adoption of pembrolizumab must be addressed.	At the submitted price, the budget impact of pembrolizumab is expected to be greater than $40 million in year 3.

5-FU = 5-fluorouracil; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PD-L2 = programmed cell death ligand 2; PFS = progression-free survival; QALY = quality-adjusted life-year; RECIST = Response Evaluation Criteria in Solid Tumours.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by pERC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance from pERC

Condition # from Table 1	Implementation considerations and guidance
1	KEYNOTE-590 included patients with previously treated brain metastases who were radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging) and clinically stable without requirement of steroid treatment for at least 14 days before the first dose of trial treatment. As a result, pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to treat patients with metastatic esophageal or EGJ cancer who have controlled CNS metastases with pembrolizumab plus chemotherapy, if the patient is otherwise eligible to receive combination therapy with pembrolizumab plus platinum and fluoropyrimidine–based chemotherapy and does not require steroids (equivalent of prednisone 10 mg/day or higher).
1	Patients with an ECOG PS score of 2 were not eligible for inclusion in KEYNOTE-590. pERC agreed with the clinical experts that the magnitude of benefit in this population is uncertain and noted that the decision to use pembrolizumab plus cisplatin and 5-FU in these patients should be left to the discretion of the treating clinician.
2	KEYNOTE-590 excluded patients with a history of receiving anti–PD-1, anti–PD-L1, or anti–PD-L2 therapies. pERC agreed with the clinical experts consulted by CADTH that it may be reasonable to re-treat patients who received prior adjuvant therapy with a PD-1, PD-L1, or PD-L2 inhibitor with pembrolizumab plus platinum and fluoropyrimidine–based chemotherapy in the locally advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy.
3	In KEYNOTE-590, formal assessments were conducted every 9 weeks. pERC agreed with the clinical experts consulted by CADTH that clinical and radiographic evaluations can be conducted every 8 weeks to 12 weeks, and more frequently, if needed, at the discretion of the treating physician.
4	pERC agreed with the clinical experts that it would be reasonable to re-administer pembrolizumab (up to 17 additional administrations), with or without chemotherapy, at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.

Condition # from Table 1	Implementation considerations and guidance
6	pERC agreed with the clinical experts that pembrolizumab may be added to other first-line chemotherapy platinum and fluoropyrimidine–based regimens (e.g., FOLFOX or CAPOX). If patients cannot tolerate the chemotherapy combination and do not have any grade 3 or higher immune-related adverse events, it would be reasonable to continue with pembrolizumab monotherapy. The patient must have received at least 1 cycle of chemotherapy concurrently with pembrolizumab before changing to pembrolizumab monotherapy.
6	pERC agreed that it would be reasonable to permit the addition of pembrolizumab as a time-limited option for patients who are currently receiving a first-line chemotherapy regimen for the indication under review, and who have not progressed on chemotherapy. Applicable first-line chemotherapy regimens would include first- line platinum plus fluoropyrimidine–based chemotherapy. Patients who have recently completed chemotherapy without disease progression would also be suitable. The clinical experts consulted by CADTH indicated that there is no time frame specified to add pembrolizumab for patients on chemotherapy alone or those who have recently completed chemotherapy as long as there is lack of progression. Patients should otherwise meet the inclusion criteria for the KEYNOTE-590 trial. pERC noted that the population of patients who would fall into this category will be quite small.

5-FU = 5-fluorouracil; CAPOX = capecitabine plus oxaliplatin; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; EGJ = esophagogastric junction; FOLFOX = folinic acid, 5-FU, plus oxaliplatin.

Discussion Points

- pERC deliberated on the results of the pivotal KEYNOTE-590 trial and agreed that first-line treatment with pembrolizumab plus cisplatin and 5-FU was associated with a clinically meaningful and statistically significant improvement in OS, compared with placebo plus cisplatin and 5-FU, in adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the EGJ (tumour centre 1 cm to 5 cm above the gastric cardia). pERC discussed that, although the PFS benefit observed in the KEYNOTE-590 trial was statistically significant, the difference in median PFS between the 2 study groups (6.3 months in the pembrolizumab group versus 5.8 months in the placebo group) was not considered clinically meaningful.
- In the KEYNOTE-590 trial, response rates were greater in patients with squamous cell carcinoma histology and a programmed cell death 1 ligand 1 (PD-L1) combined proportion score (CPS) of 10 or higher. However, the study showed a clinically meaningful and statistically significant survival benefit in favour of pembrolizumab for the entire study population. Therefore, pERC agreed that the full patient population in the funding request (i.e., adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the EGJ [tumour centre 1 cm to 5 cm above the gastric cardia]) should be eligible for treatment with pembrolizumab.
- pERC acknowledged that the standard first-line chemotherapy regimens for the patient population under review include a platinum and fluoropyrimidine–based chemotherapy. Although the platinum and fluoropyrimidine–based chemotherapy used in KEYNOTE-590 (i.e., cisplatin and 5-FU) represents 1 of these chemotherapy regimens, pERC agreed that it would be reasonable to add pembrolizumab to other chemotherapy backbones used in the first-line setting that are interchangeable with cisplatin plus 5-FU, including capecitabine plus cisplatin, CAPOX (capecitabine and oxaliplatin), and FOLFOX (folinic acid, fluorouracil, and oxaliplatin).

- pERC agreed with the clinical experts consulted by CADTH that access to PD-L1 CPS testing would be ideal, and testing should be performed when a patient presents with metastatic or advanced carcinoma of the esophagus or EGJ. It was noted that PD-L1 testing results can provide meaningful information for the clinicians to discuss the anticipated benefits of treatment with patients and their families.

Background

Pembrolizumab in combination with platinum and fluoropyrimidine–based chemotherapy has a Health Canada indication for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the EGJ (tumour centre 1 cm to 5 cm above the gastric cardia). Pembrolizumab is an IgG4 monoclonal anti–programmed cell death 1 (PD-1) antibody. The Health Canada–approved dose is 200 mg every 3 weeks or 400 mg every 6 weeks administered as an IV infusion until disease progression, unacceptable toxicity, or up to 24 months.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial in patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced or metastatic Siewert type I adenocarcinoma of the EGJ
- patients' perspectives gathered by 3 patient groups: Colorectal Cancer Canada (CCC), the Gastrointestinal (GI) Society, and My Gut Feeling – Stomach Cancer Foundation of Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- three clinical specialists with expertise diagnosing and treating patients with esophageal carcinoma and EGJ adenocarcinoma
- input from 2 clinician groups, including 1 joint submission by 6 clinicians on behalf of the Medical Advisory Board of My Gut Feeling, the Canadian Gastrointestinal Oncology Evidence Network, and the Medical Advisory Board of CCC and 1 joint submission from 4 clinicians on behalf of the Ontario Health-Cancer Care Ontario Gastrointestinal Drug Advisory
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient and from clinical expert(s) consulted by CADTH for the purpose of this review. As well, issues identified by the Provincial Advisory Group that may impact their ability to implement a recommendation are summarized.

Patient Input

Three patient groups co-created 1 patient input for this review: CCC, the GI Society, and My Gut Feeling – Stomach Cancer Foundation of Canada.

According to the patient and caregiver respondents (N = 33), most patients were diagnosed with esophageal adenocarcinoma (77.42%); 12.90% of patients were diagnosed with esophageal squamous cell carcinoma (ESCC). All patient and caregiver respondents (except 1 patient) reported patients experienced the following symptoms before diagnosis: trouble swallowing, heartburn, weight loss, fatigue, worsening indigestion, frequent choking on food, hiccups, and indigestion.

Two patient respondents had experience with the drug under review (pembrolizumab) and reported treatment-related side effects. One patient reported abdominal pain, diarrhea, rash, shortness of breath, and constipation; the other patient reported fatigue, itching, and some allergic reactions. One patient respondent noted that pembrolizumab manages coughing, back pain, hoarseness, and vomiting less effectively than existing therapies. However, both respondents reported that pembrolizumab did manage certain symptoms better than existing therapies. One patient reported pain behind the breastbone or in the throat, black stool, and weight loss (1 patient); the other patient reported fatigue and vomiting. Both patients indicated that they expected the following key outcomes to be improved by pembrolizumab: prolonging OS, delaying the need for chemotherapy, and having a convenient route of administration.

Patient and caregiver respondents highlighted that given the poor and short survival rates for most patients with esophageal cancer, it is necessary for patients to have access to new effective therapies that prolong OS, improve QoL, reduce disease symptoms, and have tolerable side effects. It was also noted that given the severity of disease symptoms, improved QoL is an important outcome to consider in this setting. Additionally, when asked to indicate trade-offs in respect to treatment outcomes in choosing a new therapy, almost all patient and caregiver respondents indicated that they were willing to take a drug that has been proven to improve QoL even if it would not prolong OS.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts agreed that the full patient population included in the indication (adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative adenocarcinoma of the EGJ [tumour centre 1 cm to 5 cm above the gastric cardia]) should be eligible for treatment with pembrolizumab. However, the clinical experts noted that some patients are more likely to respond to treatment with pembrolizumab than others (e.g., ESCC histology and a PD-L1 CPS > 10). The clinical experts identified patients with autoimmune diseases are at increased risk of autoimmune disease flares and immune-related adverse events when treated with immunotherapy. However, the clinical experts agreed that for patients with well-controlled autoimmune disease, immunotherapy may still represent an appropriate treatment option for these patients after a discussion of the risks and benefits between clinician and patient. The clinical experts reiterated that the full patient population included in the indication should be eligible for treatment with pembrolizumab.

According to the clinical experts, pembrolizumab added to chemotherapy has the potential to represent a standard of care for patients with esophageal cancer or EGJ Siewert type I.

The clinical experts felt that pembrolizumab added to chemotherapy would certainly be a standard of care for patients with ESCC and for patients with a CPS of 10 or greater. The clinical experts also felt that pembrolizumab, added to chemotherapy, would be an appropriate treatment option for Siewert type I HER2-negative adenocarcinoma of EGJ and for tumours with CPS less than 10.

The clinical experts identified prolonged life and improved health-related QoL to be important outcomes and goals for treatment. The clinical experts noted that not all patients respond to available treatment options, and patients ultimately become refractory to current therapies. As a result, there is a need for more effective treatment options with a manageable safety profile.

To the clinical experts, a clinically meaningful response to treatment would be improved OS and a reduction in the frequency or severity of symptoms (improved QoL). The clinical experts expressed that for patients treated with immunotherapy, a long-term plateau of the survival curve would also be considered a significant benefit since current median survival for this patient population is less than 12 months. As well, the clinical experts stated that if the addition of an agent to an established regimen did not cause a detriment to QoL and improved survival, that would also be considered a clinically meaningful response to treatment.

Clinician Group Input

Overall, 2 clinician group inputs were provided for the review: 1 joint submission by 6 clinicians on behalf of the Medical Advisory Board of My Gut Feeling, the Canadian Gastrointestinal Oncology Evidence Network, and the Medical Advisory Board of CCC and 1 joint submission from 4 clinicians on behalf of the Ontario Health-Cancer Care Ontario Gastrointestinal Drug Advisory.

Both clinician groups emphasized that all patients with esophageal cancers and EGJ adenocarcinomas (Siewert type I) would greatly benefit from this treatment. The clinician group emphasized that all patients with locally advanced unresectable or metastatic esophageal carcinoma or HER2-negative EGJ adenocarcinoma have poor prognosis and therefore all patients should be eligible for the addition of pembrolizumab to first-line platinum and fluoropyrimidine chemotherapy.

The clinician groups identified prolonged life and improved or maintained health-related QoL as the goals of treatment. Additional goals of treatment identified by the Ontario Health-Cancer Care Ontario Gastrointestinal Drug Advisory clinicians were delay disease progression and ensure adequate nutritional intake.

To the clinician groups, a clinically meaningful response to treatments would be a reduction in symptoms or, at minimum, a stabilization of symptoms (e.g., less pain, weight gain or cessation of weight loss, less fatigue). Additionally, an overall improvement in the ability to perform daily activities and a reduction in the caregiver burden would also be considered clinically meaningful responses to treatment.

In summary, although the clinician groups and clinical experts noted that patients with a PD-L1 CPS of 10 or higher, and patients with ESCC and a PD-L1 CPS of 10 or higher are more likely to respond to pembrolizumab than the intention-to-treat population (any PD-L1 CPS and esophageal cancer or EGJ Siewert type I), all patients with esophageal cancers and esophagogastric junction adenocarcinomas (Siewert type I) would benefit from

pembrolizumab. As a result, both the clinician groups and clinical experts expressed that the full patient population in the indication submitted for reimbursement (i.e., esophageal cancer and HER2-negative EGJ Siewert type I) should be eligible for treatment with pembrolizumab.

Drug Program Input

Input from the Provincial Advisory Group (PAG) identified factors pertaining to relevant comparators, consideration for initiation of therapy, consideration for discontinuation of therapy, generalizability, care provision, system issues, and economic considerations. pERC weighed evidence from the KEYNOTE-590 trial and other clinical considerations, including input from clinical experts consulted by CADTH, to provide responses which are presented in Table 3.

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
First-line therapies in this indication include platinum plus fluoropyrimidine–based doublet or triplet regimens (e.g., CF, CX, ECX, EOX, FOLFOX, FOLFIRI). Comparator in study (CF) is funded in most provinces as a first-line option. How does pembrolizumab-CF compare with other first-line chemotherapies? Can trial results be generalized to other first-line chemotherapy combinations if a patient is not able to tolerate or receive a platinum-based combination?	pERC agreed with the clinical experts consulted by CADTH that pembrolizumab may be added to other first-line chemotherapy combinations. CAPOX and FOLFOX are considered as interchangeable chemotherapy backbones with cisplatin plus 5-FU. For patients who are not eligible for cisplatin, carboplatin would be a reasonable substitute. The clinical experts confirmed that this is consistent with standard practice in multiple cancer sites in Canada. If patients cannot tolerate the chemotherapy combination and do not have any grade 3 or higher immune-related adverse events, it would be reasonable to continue with pembrolizumab monotherapy. The patient must have received at least 1 cycle of chemotherapy concurrently with pembrolizumab before changing to pembrolizumab monotherapy. pERC noted that FOLFIRI is not a commonly used first-line treatment.
Considerations for initiation of therapy	
If treatment is discontinued before evidence of progressive disease, can pembrolizumab be administered at time of relapse? If re-treatment is permitted at time of relapse, would therapy consist of pembrolizumab monotherapy or pembrolizumab plus chemotherapy?	pERC agreed with the clinical experts that pembrolizumab may be added to other first-line chemotherapy platinum and fluoropyrimidine–based regimens (e.g., FOLFOX or CAPOX). pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to re-administer pembrolizumab (up to 17 additional administrations) at the time of relapse, with or without chemotherapy at the discretion of the treating physician, in the following instances: • treatment is discontinued before disease progression • disease progression occurs during a treatment break.

Implementation issues	Response
Would patients with CNS metastases be eligible for pembrolizumab plus chemotherapy?	Patients with active or uncontrolled CNS metastases were not included in KEYNOTE-590; thus, the magnitude of benefit for combination therapy with pembrolizumab is unclear. However, KEYNOTE-590 included patients with previously treated brain metastases who were radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging) and clinically stable without requirement of steroid treatment for at least 14 days before the first dose of trial treatment. As a result, pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to treat patients with metastatic esophageal or EGJ cancer who have controlled CNS metastases with pembrolizumab plus chemotherapy, if the patient is otherwise eligible to receive combination therapy with pembrolizumab plus platinum and fluoropyrimidine–based chemotherapy and does not require steroids (equivalent of prednisone 10 mg/day or higher).
Considerations for discontinuation of therapy	
What is the recommended definition or parameters to use in determining when to stop pembrolizumab therapy?	pERC noted that, in the KEYNOTE-590 trial, the study treatments continued unless the following discontinuation criteria were met: documented confirmed progressive disease, unacceptable adverse events, intercurrent illness that prevents further administration of treatment, investigator decision to discontinue treatment, patient withdrawal of consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, a total of 35 administrations (approximately 2 years) of study medication, or administrative reasons requiring cessation of treatment. pERC acknowledged the clinical experts' response that treatment with pembrolizumab should be discontinued in the presence of disease progression on CT scan, deterioration in clinical status precluding continuation of treatment, withdrawal of patient consent, severe adverse events, or grade 3 or higher immune-related adverse events. They also agreed with the clinical experts with the addition of discontinuing treatment if the patient receives 35 administrations (approximately 2 years) of pembrolizumab.
If there is disease progression during a treatment break, can pembrolizumab therapy be resumed?	pERC agreed with the clinical experts consulted by CADTH that it would be reasonable to re-administer pembrolizumab at the time of relapse, with or without chemotherapy, at the discretion of the treating physician in the following instances: treatment is discontinued before disease progression or disease progression occurs during a treatment break.
If a patient cannot tolerate the chemotherapy combination, are they able to continue with pembrolizumab monotherapy? Is there a minimum number of chemotherapy cycles that must be given concurrently with pembrolizumab?	pERC agreed with the clinical experts consulted by CADTH that for patients who cannot tolerate the chemotherapy combination and do not have any grade 3 or higher immune-related adverse events, it would be reasonable to continue with pembrolizumab monotherapy. At least 1 cycle of chemotherapy should be given concurrently with pembrolizumab before changing to pembrolizumab monotherapy.

Implementation issues	Response
Generalizability	
Should patients with an ECOG PS score of 2 or greater be eligible?	Patients with an ECOG PS score of 2 were not eligible for inclusion in KEYNOTE-590. However, 2 (out of 749) patients in the trial appear to have been included with an ECOG PS score of 2. pERC agreed with the clinical experts that the magnitude of benefit in this population is uncertain and noted that the decision to use pembrolizumab plus cisplatin and 5-FU in these patients should be left to the discretion of the treating clinician.
There is a time-limited need to allow patients currently on platinum plus fluoropyrimidine–based chemotherapy, or alternate chemotherapy, to add pembrolizumab. What time frame is appropriate to add pembrolizumab for patients on chemotherapy alone or who recently completed chemotherapy?	The clinical experts consulted by CADTH suggested that it would be reasonable to permit the addition of pembrolizumab as a time-limited option for patients who have not progressed on first-line therapy. Applicable first-line chemotherapy regimens would include first-line platinum plus fluoropyrimidine or alternate doublet chemotherapy (e.g., FOLFOX or CAPOX); patients who had completed treatment without progression would also be suitable. There is no time frame specified as long as there is lack of progression. Patients should otherwise meet the inclusion criteria for the KEYNOTE-590. The population of patients who would fall into this category will be quite small.
Care provision issues	
Is companion diagnostic testing CPS for PD-L1 required to determine eligibility of patients?	Although it is not required for eligibility, pERC agreed with the clinical experts consulted by CADTH that access to PD-L1 CPS testing would be ideal and should be performed when a patient presents with metastatic or advanced disease. PD-L1 testing results provide meaningful information for the clinicians to discuss the anticipated benefits of treatment with patients and their families.
System and economic issues	
PAG notes that the uptake of pembrolizumab in this setting vs. existing systemic therapies is likely to be immediate leading to a considerable increase in budget impact in a reimbursement scenario and also notes that reimbursement of pembrolizumab in the first-line setting would likely shift other systemic therapies to later lines of therapy, representing an added cost. Health care providers are already familiar with the preparation, administration, and monitoring of pembrolizumab infusions.	pERC agreed with the clinical experts consulted by CADTH that adding pembrolizumab in the first-line setting would not cause a shift in the sequencing of therapies because pembrolizumab is not standard of care in Canada.

5-FU = 5-fluorouracil; CAPOX = capecitabine and oxaliplatin; CF = cisplatin plus 5-fluorouracil; CNS = central nervous system; CPS = Combined Proportion Score; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EGJ = esophagogastric junction; FOLFOX = folinic acid, 5-FU, and oxaliplatin; FOLFIRI = irinotecan, fluorouracil, and oxaliplatin; PD-L1 = programmed cell death ligand 1; vs. = versus.

Clinical Evidence

Clinical Trials

Description of Studies

Keynote 590 is a phase III, randomized, double-blind, placebo-controlled, multicentre, superiority study comparing pembrolizumab plus cisplatin and 5-FU to placebo plus cisplatin and 5-FU for the first-line treatment of patients with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced or metastatic Siewert type I adenocarcinoma of the EGJ. A total of 749 patients were randomized in a 1:1 ratio to receive pembrolizumab plus cisplatin and 5-FU (373 patients) or placebo plus cisplatin and 5-FU (376 patients). The first patient was randomized on July 25, 2017, and the last patient was randomized on July 2, 2020. This is an ongoing study with interim (primary analysis) results using a Global Study Population which included both the Global Cohort and the China Extension Study. These interim results represent the final analysis, with a data cut-off date of July 2, 2020, because the study end points were met for both PFS and OS.

The co-primary outcomes were:

- OS among
  - patients with ESCC whose tumours are PD-L1 biomarker-positive (CPS ≥ 10)
  - patients with ESCC
  - patients with PD-L1 CPS of 10 or higher
  - all patients
- PFS per RECIST 1.1 among
  - patients with ESCC
  - patients with PD-L1 CPS of 10 or higher
  - all patients.

Secondary and exploratory outcomes included objective response rate, duration of response, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), EORTC Quality of Life Questionnaire Oesophageal Module (EORTC QLQ-OES18), safety and EuroQol 5-Dimensions 5-Levels (EQ-5D-5L).

The demographic and baseline characteristics were well-balanced between groups, except for age (65 years or older) and stage IV B (distant lymph nodes and/or other organs) disease. There were more patients aged 65 years or older in the pembrolizumab plus cisplatin and 5-FU group (46.1%) compared with the placebo plus cisplatin and 5-FU group (39.9%). There were more patients with a current disease stage of IV B in the pembrolizumab plus cisplatin and 5-FU group (17.4%) compared with the placebo plus cisplatin and 5-FU group (10.9%). The majority had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (99.7%: ECOG PS 0% to 39.9% and ECOG PS 1% to 59.8%, respectively) and had metastatic disease (91.2%). Most patients were male (83.4%), had an ESCC primary diagnosis (73.2%), and approximately half were Asian (53.4%), enrolled in Asia (52.5%), and had tumour-expressed PD-L1 CPS of 10 or higher (51.1%).

The results for both PFS and OS are deemed final based on interim analysis because both primary end points met the prespecified stopping boundary for statistical significance.

However, the study is ongoing; therefore, long-term efficacy and safety data are anticipated to be available in the future.

Efficacy Results

As of the data cut-off date (July 2, 2020), the median follow-up duration for patients in the pembrolizumab plus cisplatin and 5-FU group was 12.6 months (range = 0.1 to 33.6) and the median follow-up duration for patients in the placebo combined with cisplatin and 5-FU group was 9.8 months (range = 0.1 to 33.6).

In all patients, there was a 27% reduction in the risk of death in favour of pembrolizumab plus cisplatin and 5-FU. The OS HR was 0.73 (95% CI, 0.62 to 0.86; P < 0.0001), which met the statistical significance threshold in the analysis. The median OS was 12.4 months (95% CI, 10.5 to 14.0) for the pembrolizumab plus cisplatin and 5-FU group compared with 9.8 months (95% CI, 8.8 to 10.8) for the placebo plus cisplatin and 5-FU group. A statistically significant OS benefit in favour of pembrolizumab plus cisplatin and 5-FU was also observed in the following subgroups: patients with ESCC whose tumours expressed PD-L1 CPS of 10 or higher, patients with ESCC, and patients whose tumours expressed PD-L1 CPS of 10 or higher.

In all patients, there was a 35% reduction in risk of death and disease progression in favour of pembrolizumab plus cisplatin and 5-FU. The PFS HR was 0.65 (95% CI, 0.55 to 0.76; P < 0.0001), which met the statistical significance for statistical significance. The median PFS was 6.3 months (95% CI, 6.2 to 6.9) for the pembrolizumab plus cisplatin and 5-FU group compared with 5.8 months (95% CI, 5.0 to 6.0) for the placebo plus cisplatin and 5-FU group. A statistically significant PFS benefit in favour of pembrolizumab plus cisplatin and 5-FU was also observed in subgroups of patients with ESCC and patients whose tumours expressed PD-L1 CPS of 10 or higher.

In the patient-reported outcome (PRO) full set analysis population (i.e., all randomized patients who have at least 1 PRO assessment available for the specific end point and have received at least 1 dose of the study intervention), the least squares mean change from baseline to week 18 for EQ-5D VAS score was similar between the 2 groups. The mean change from baseline in global health status or QoL (using the EORTC QLQ-C30 scale) remained stable over time for the pembrolizumab plus cisplatin and 5-FU group compared with the placebo plus cisplatin and 5-FU group, and the median time to deterioration for global health status or QoL was not reached for both groups.

Harms Results

Overall, any adverse events, treatment-related adverse events, grade 3 to 5 adverse events, and any serious adverse events were comparable between the pembrolizumab plus cisplatin and 5-FU group and the placebo plus cisplatin and 5-FU group. The most commonly reported adverse events reported in each group, respectively, were nausea (67.3% versus 62.7%), anemia (50.5% versus 56.2%), decreased appetite (44.3% versus 38.1%), fatigue (40.3% versus 34.1%), and constipation (40.0% versus 40.3%).

The number of deaths due to an adverse event and deaths due to a treatment-related adverse events were low and similar between the 2 groups.

Immune-mediated adverse events and infusion reactions (25.7% versus 11.6%), hypothyroidism (10.8% versus 6.5%) and hyperthyroidism (5.7% versus 0.8%), pneumonitis (6.2% versus 0.5%), grade 3 or higher treatment-related adverse events (71.9% versus

67.6%), serious treatment-related adverse events (31.6% versus 26.2%), and discontinuation due to treatment-related adverse events (19.5% versus 11.6%) were higher among the pembrolizumab plus cisplatin and 5-FU group versus the placebo plus cisplatin and 5-FU group.

Critical Appraisal

Notable limitations of the KEYNOTE-590 trial are highlighted below:

- There is a potential risk of bias because of missing data on secondary and exploratory end points (e.g., duration of response, EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L), particularly on the QoL measures. In addition, for subjective outcomes (e.g., PROs) may have differential recall bias. For example, drug-related adverse events, such as immune-mediated events (25.7% in the pembrolizumab plus cisplatin and 5-FU group versus 11.6% in the placebo plus cisplatin and 5-FU group), particularly hypothyroidism (symptoms including fatigue, increased sensitivity to cold, muscle weakness) and hyperthyroidism (symptoms including nervousness, anxiety, fatigue, weight loss) might have led to unblinding and patients' awareness of their treatment assignment, potentially leading to biased assessment of the PROs. Overall, the magnitude and direction of the impact of missing data and imbalances is unknown.
- The platinum and fluoropyrimidine–based chemotherapy used in KEYNOTE-590 (i.e., cisplatin and 5-FU) represents 1 of the standard first-line chemotherapies regimens; other relevant treatment regimens (listed in the Systematic Review Protocol) were not considered in the KEYNOTE-590 trial. An overall beneficial effect of the combination therapy with pembrolizumab was present. However, it would remain uncertain if such benefit could be generalizable to different combinations of chemotherapy regimens. Moreover, the study excluded patients with poor ECOG PS scores (> 1). This further compromised the generalizability of the findings on efficacy and, particularly, safety to those patients who may receive this first-line combination therapy in practice.
- The reported OS and PFS results are deemed final based on interim analysis according to prespecified stopping criteria. However, whether the "actual" final efficacy results would conform with these interim results is unknown. There are case reports that discuss an early stop of a trial to claim statistical significance according to prespecified stopping rule had suffered type I error with the interim results, and the estimates of effects could not be the repeated at the final analysis after the trial was completed.

Indirect Comparisons

No indirect treatment comparisons were included in the sponsor's submission to CADTH or identified in the literature search. The sponsor conducted a feasibility assessment[3] of estimating the comparative efficacy and safety of pembrolizumab plus cisplatin and 5-FU versus other competing interventions using data obtained from a systematic literature review.

The submitted feasibility assessment was summarized and critically appraised by the CADTH clinical review team. Ultimately, the CADTH clinical review team concluded that a standard network meta-analysis was not feasible due to a lack of network connectivity and an unanchored MAIC would likely be biased, and it would not be possible to quantify or identify the direction of the bias.

Other Relevant Evidence

Two studies (KEYNOTE-062 and KEYNOTE-859) were identified as relevant. However, the study populations of these trials were slightly different from the population of interest in this review. Both the KEYNOTE-062 and KEYNOTE-859 trials enrolled patients with HER2-negative EGJ cancer without any Siewert classification, whereas only patients with HER2-negative Siewert type I EGJ cancer are of relevance to the reimbursement request. The trials also did not include patients with ESCC or adenocarcinoma of the esophagus, which are relevant populations for the reimbursement request. For the KEYNOTE-062 trial, patients had to be PD-L1 positive (i.e., CPS ≥ 1), whereas PD-L1 status is not an eligibility criterion for reimbursement for this submission. Both trials used alternative platinum and fluoropyrimidine–based chemotherapy backbones for the intervention and comparator compared with the KEYNOTE-590 trial. In the KEYNOTE-062 trial, cisplatin and 5-FU or cisplatin and capecitabine were offered as the chemotherapy backbone for the intervention and comparator, whereas in the KEYNOTE-859 trial, cisplatin and 5-FU or oxaliplatin and capecitabine were offered.

KEYNOTE-062 is a phase III, randomized, partially blinded, multicentre study comparing pembrolizumab as monotherapy and pembrolizumab in combination with cisplatin plus 5-FU or cisplatin plus capecitabine versus placebo, in combination with cisplatin plus 5-FU or cisplatin plus capecitabine, as first-line treatment for patients with advanced gastric or EGJ adenocarcinoma. The results from the prespecified subgroup analysis of the primary location (EGJ) were only available for OS, and safety data were reported for the entire study population (gastric and EGJ adenocarcinoma).In the overall study population (patients with gastric and EGJ adenocarcinoma), there was no difference in OS between the pembrolizumab combination and chemotherapy groups for patients with a PD-L1 CPS of 1 or higher (OS HR = 0.85; 95% CI, 0.7 to 1.03). The prespecified OS subgroup analyses of the primary location for EGJ were consistent with the overall study population results (OS HR = 0.96; 95% CI, 0.67 to 1.36). The EGJ subgroup OS results were exploratory, underpowered, and not reflective of the entire reimbursement population; therefore, these results should be interpreted with caution. Results for the primary location (EGJ adenocarcinoma) subgroup for other important efficacy outcomes were not available. In the overall population (patients with gastric and EGJ adenocarcinoma), more adverse events leading to discontinuation and immune-mediated adverse events and infusion reactions were reported in the pembrolizumab combination group compared with the chemotherapy group (27.6% versus 18.0% and 24.0% versus 7.8%, respectively).

KEYNOTE-859 is a phase III, multicentre study comparing pembrolizumab plus chemotherapy (cisplatin and 5-FU or oxaliplatin and capecitabine) versus placebo plus chemotherapy (cisplatin and 5-FU or oxaliplatin and capecitabine) as first-line treatment for patients with advanced gastric or EGJ adenocarcinoma. Currently, only study design details are available. The study is still ongoing, and no results are available at this time.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients (aged 18 years and older) with locally advanced unresectable or metastatic, cancer of the esophagus or HER2-negative esophagogastric junction. Aligns with reimbursement request.
Treatments	Pembrolizumab in combination with 5-FU and cisplatin
Submitted price	Pembrolizumab IV infusion: $4,400 per 4 mL vial
Treatment cost	The total cost per cycle of pembrolizumab in combination with 5-FU and cisplatin was $8,472.27 at the sponsor's assumed relative dose intensities
Comparators	• 5-FU and cisplatin • Blended chemotherapy, consisting of ◦ 5-FU + cisplatin ◦ capecitabine + cisplatin ◦ 5-FU + oxaliplatin + leucovorin (FOLFOX) ◦ capecitabine + oxaliplatin (CAPOX)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (20 years)
Key data source	KEYNOTE-590 trial was used to inform PFS, OS, TTD, and health utility values
Key limitations	• The reported results for both PFS and OS from the KEYNOTE-590 trial were considered final by the sponsor based on an interim analysis. However, as noted in case reports for other conditions, whether the actual final efficacy results would conform with the interim results is unknown. Thus, the magnitude of any survival benefit, and maintenance of treatment effect beyond the short-term treatment duration, is uncertain. This uncertainty is compounded by the sponsor's choice of a partitioned survival model, and poor-fitting parametric survival curves. As such, the results of the submitted economic evaluation are associated with uncertainty. • The cost-effectiveness of the blended chemotherapy comparator should be interpreted with caution because the sequential analyses lacked regimen-specific comparative efficacy and safety parameters for the individual treatment regimens. As such, the cost-effectiveness of pembrolizumab in combination with 5-FU and cisplatin relative to the individual chemotherapy regimens is unknown. • The sponsor's model considered pembrolizumab in combination with 5-FU and cisplatin and did not consider other backbone chemotherapies that may be prescribed with pembrolizumab (e.g., FOLFOX or CAPOX). • CADTH identified a programmatic error in the sponsor's model regarding incorrect calculation of drug administration fees for FOLFOX and CAPOX considered in the blended chemotherapy comparator; inappropriate list prices for 5-FU, oxaliplatin, and leucovorin; and underestimated dose for leucovorin.

Component	Description
CADTH reanalysis results	• CADTH revised the sponsor's model by correcting programmatic errors, revising the leucovorin dose, and using public listed prices for 5-FU, oxaliplatin, and leucovorin. Additionally, the CADTH base case used Canadian end-of-life costs specific to esophageal adenocarcinoma, reduced the proportion of patients requiring subsequent treatments to 10%, and incorporated a treatment waning effect (per a scenario provided by the sponsor). • Based on CADTH's base case, compared with 5-FU in combination with cisplatin, pembrolizumab in combination with 5-FU and cisplatin was associated with an ICER of $170,819 per QALY.[a] • A price reduction of at least 75% would be needed for pembrolizumab in combination with 5-FU and cisplatin to be cost-effective at a WTP threshold of $50,000 per QALY.

5-FU = 5-fluorouracil; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; TTD = time to discontinuation; WTP = willingness to pay.

[a]Due to limitations with the use of a blended comparator and concerns about the validity of the sponsor's calculations, the blended comparator was not considered within the CADTH reanalysis.

Budget Impact

CADTH identified uncertainty in the assumed referral rate to a medical oncologist and the HER2-negative oncology treatment rate.

CADTH reanalysis included aligning market share assumptions with the economic evaluation, assuming lower rate of transitioning to second-line treatments, assuming higher referral rate to medical oncologists, and assuming a higher HER2-negative treatment rate.

Based on CADTH reanalyses, the budget impact to the public drug plans of introducing pembrolizumab, in combination with platinum and fluoropyrimidine–based chemotherapy, is expected to be $7,281,922 in year 1, $33,335,288 in year 2, and $50,440,428 in year 3 (a 3-year total of $91,057,638).

pCODR Expert Review Committee 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 13, 2021

Regrets: One expert committee member did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.