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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: In combination with fluoropyrimidine- and platinum-containing chemotherapy, the drug is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

Canada's Drug Agency recommends that Keytruda should be reimbursed by public drug plans for the treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric or gastroesophageal junction (GEJ) adenocarcinoma if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients who have not received previous treatment for HER2-negative advanced or metastatic gastric or GEJ cancer and who have good performance status.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed in combination with fluoropyrimidine- and platinum-containing chemotherapy by a clinician with expertise and experience in treating gastric and GEJ cancer, and the cost of Keytruda in combination with chemotherapy is reduced so that it does not exceed the drug program cost of treatment with nivolumab in combination with chemotherapy.

Why Did We Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that patients treated with Keytruda, when added to fluoropyrimidine- and platinum-containing chemotherapy, resulted in improved survival and could delay cancer progression.
- Keytruda meets patient needs of delaying disease progression and prolonging survival and was unlikely to worsen health-related quality of life (HRQoL).
- Based on our assessment of the health economic evidence, Keytruda does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Keytruda in combination with chemotherapy compared with nivolumab in combination with chemotherapy.
- Based on public list prices, Keytruda, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is estimated to cost the public drug plans approximately $2.1 million over the next 3 years.

Summary

Additional Information

What Is Gastric or GEJ Cancer?

Gastric and GEJ cancers occur in the stomach, where the esophagus and stomach join, respectively. Most gastric and GEJ cancers are adenocarcinomas. The cancer is considered locally advanced if it spreads in the stomach or GEJ and metastatic if it spreads to another part of the body. The 5-year survival rate for patients diagnosed with gastric and GEJ cancer living in Canada is 29%. For patients with metastatic gastric or GEJ cancer, the 5-year survival rate is 6.6%.

Unmet Needs in Gastric or GEJ Cancer

Many patients with HER2-negative gastric or GEJ cancer do not respond to available treatment options. Even in patients who do respond to treatment, their survival remains limited.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per patient per 28-day cycle.

Recommendation

The pCODR Expert Review Committee (pERC) recommends that pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, be reimbursed for adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) negative gastric or GEJ adenocarcinoma only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III double-blind randomized controlled trial (KEYNOTE-859; N = 1,579) demonstrated that pembrolizumab, when added to fluoropyrimidine- and platinum-containing chemotherapy results in added clinical benefit in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. The KEYNOTE-859 trial demonstrated that, compared to chemotherapy alone, treatment with pembrolizumab plus chemotherapy was associated with statistically significant and clinically meaningful improvements in overall survival (OS) in patients with programmed death-ligand1 (PD-L1) combined positive score (CPS) of 10 or greater (hazard ratio [HR] = 0.65; 95% confidence interval [CI], 0.53 to 0.79), in patients with PD-L1 CPS of 1 or greater (HR = 0.74; 95% CI, 0.65 to 0.83), and in all randomized patients regardless of PD-L1 CPS (stratified HR = 0.78; 95% CI, 0.70 to 0.87). Results for the progression-free survival (PFS) were supportive of OS findings (stratified HR for all randomized patients = 0.76; 95% CI, 0.67 to 0.85). Immunotherapy-mediated adverse events were more frequent in the pembrolizumab group; however, pERC considered the safety profile of pembrolizumab in combination with chemotherapy to be manageable and consistent with the known safety profile of pembrolizumab. Conclusion on HRQoL could not be drawn due to the exploratory nature of these outcomes in the trial, absence of minimally important difference (MID) estimates in patients with gastric or GEJ cancer and substantial proportion of missing data. However, the trial results suggested that HRQoL was not worse in the pembrolizumab plus chemotherapy group and may likely improve pain-related symptoms, when compared to placebo plus chemotherapy.

Patients identified the need for more effective and accessible treatment options that prolong survival, minimize side effects and improve quality of life for patients and caregivers, and allow for more convenient therapy administration. pERC noted that the addition of pembrolizumab to chemotherapy met some of the needs identified by patients because it provides an additional treatment option with improved OS, may results in little or no deterioration in HRQoL, and has 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 chemotherapy was $153,779 per quality-adjusted life-year (QALY) gained compared with chemotherapy alone and had similar costs and QALYs when compared to nivolumab in combination with chemotherapy. At this ICER, pembrolizumab in combination with chemotherapy is not cost-effective at a $50,000 per QALY gained willingness-to-pay (WTP) threshold for patients with gastric or gastroesophageal junction adenocarcinoma compared to chemotherapy alone. The total drug cost of pembrolizumab plus chemotherapy should not

exceed the total drug cost of nivolumab plus chemotherapy, as the 2 treatment regimens are considered similarly effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy should be initiated in patients who have all of the following: 1.1. 18 years of age or older 1.2. previously untreated HER2 negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.	Evidence from the KEYNOTE-859 trial demonstrated statistically significant OS and PFS benefits in patients who fulfilled the characteristics listed in this condition.	—
2. Patients must not have: 2.1. active CNS metastases 2.2. history of therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy, in the advanced or metastatic setting.	The KEYNOTE-859 trial excluded patients with active CNS metastasis, and those who had received prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy or an drug directed to another stimulatory or coinhibitory T-cell receptor. As such, the potential benefit of pembrolizumab plus chemotherapy therapy in these patients has not been demonstrated.	pERC agreed with the clinical experts that it may be reasonable to re-treat patients who received prior adjuvant therapy with a PD-1, PD-L1, or PDL2 inhibitor with pembrolizumab plus chemotherapy in the advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy.
3. Patients must have good performance status.	The KEYNOTE-859 trial included patients with an ECOG performance status of 0 or 1.	pERC agreed with the clinical experts that patients with an ECOG Performance Status more than 1 may be treated at the discretion of the treating physician.
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity 4.3. completion of 24 months of treatment (e.g., 35 cycles, administered every 3 weeks).	Patients in the KEYNOTE-859 trial discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice. Patients in the KEYNOTE-859 trial were treated with pembrolizumab for a maximum of 35 cycles (approximately 24 months).	pERC agreed with the clinical experts that it would be reasonable to re-administer pembrolizumab at the time of recurrence (up to 17 additional every-3-week doses, or 12 months) at the discretion of the treating physician for patients who have discontinued pembrolizumab with the completion of 2 years of treatment and before any disease progression, or after achieving a complete response.
5. One component of the treatment can be discontinued at the discretion of the treating physician in case of adverse events.	In the KEYNOTE-859 trial, 1 component of the treatment (pembrolizumab or chemotherapy) could be interrupted or discontinued, due to toxicity, and the other components could be continued.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
6. Pembrolizumab in combination with and chemotherapy should be prescribed by clinicians with expertise and experience in treating gastric or GEJ cancers. The treatment should be delivered in institutions with expertise in systemic therapy delivery and management of immunotherapy-related side effects.	This condition is to ensure that treatment 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 fluoropyrimidine- and platinum-containing chemotherapy.	In the KEYNOTE-859 trial, pembrolizumab was administered in combination with 5-fluorouracil plus cisplatin or capecitabine plus oxaliplatin. No evidence was available to support the clinical benefit of pembrolizumab monotherapy.	—
Pricing		
8. Pembrolizumab in combination with chemotherapy should be negotiated so that it does not exceed the drug program cost of treatment with nivolumab in combination with chemotherapy.	The results of the network meta-analysis, clinical expert opinion, and the output of the pharmacoeconomic model concluded that OS and PFS is similar between patients receiving treatment with either pembrolizumab or nivolumab in combination with chemotherapy. As such, there is insufficient evidence to justify a cost premium for pembrolizumab over nivolumab for the treatment of gastric or gastroesophageal junction adenocarcinoma.	—

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; QALY = quality-adjusted life-year.

Discussion Points

- pERC deliberated on the results of the phase III KEYNOTE-859 trial which showed that first-line treatment with pembrolizumab, when used in combination with fluoropyrimidine- and platinum-containing chemotherapy in adult patients with locally advanced unresectable or metastatic HER2-negative of GEJ adenocarcinoma, resulted in improved OS and PFS compared to chemotherapy alone. pERC further noted that the risk difference in OS benefit at 12 months [redacted] and 30 months [redacted] met the expert-identified threshold for clinical meaningfulness (i.e., 10% to 15%) in favour of pembrolizumab plus chemotherapy. The lower bounds of the corresponding 95% confidence intervals were compatible with little-to-no clinically important difference at 12 months. However, the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment of the evidence suggested with high certainty that adding pembrolizumab to chemotherapy results in a

clinically important increase in the probability of survival at 30 months compared with placebo plus chemotherapy.

- pERC noted that the KEYNOTE-859 trial enrolled patients regardless of their tumour PD-L1 expression status. However, over 78% of patients in both treatment groups had documented PD-L1 CPS of 1 or more. pERC noted that the results from the full study population and those from the PDL1 positive subgroup were consistent, and that the clinical benefit observed in the full study population appeared to be driven by the PD-L1 positive subgroup. pERC also noted that, in the KEYNOTE-859 trial, patients with PD-L1 CPS greater than 10 appeared to derive most benefit from treatment with pembrolizumab.
- In the absence of a direct comparison of pembrolizumab and nivolumab for the indication of interest, pERC considered evidence from a sponsor-submitted indirect treatment comparisons that suggested there was minimal or no differences in OS and PFS outcomes between pembrolizumab and nivolumab, when added on to fluoropyrimidine- and platinum-containing chemotherapy in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. However, pERC noted that the indirect evidence was associated with uncertainty due to clinical and methodological heterogeneity between the studies included in the network. pERC agreed with the clinical experts that the choice between pembrolizumab and nivolumab, in clinical practice, will depend on the preference of treating physician and patient.
- pERC noted that HER2 testing would be required for the implementation of a reimbursement recommendation for pembrolizumab in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. pERC further discussed that chemotherapy may be initiated pending results of HER2 testing and pembrolizumab added upon confirmation of HER2-negative status. If HER2 status cannot be determined (e.g., insufficient tissue for testing), patients may be considered for the treatment with pembrolizumab plus chemotherapy.
- The committee discussed that, although PD-L1 testing is not required for the implementation of a reimbursement recommendation for pembrolizumab in this patient population; where available, the PD-L1 test results can provide meaningful information for the clinicians to discuss the anticipated benefits of treatment with patients and their families. pERC also considered the patient group input that emphasized the importance of biomarker testing to be accessible on the onset of patients' disease experience across all jurisdictions and treatment centres.

Background

Gastric cancer is a growth of abnormal cells that starts in the stomach. In 2023, an estimated 4,100 Canadians were projected to be diagnosed with gastric cancer. Gastric cancers are generally classified into 2 topographical subsites. Cardia gastric cancers include the upper part of the stomach adjoining the esophagus. Noncardia gastric cancer occurs in the more distal regions of the stomach. GEJ cancer develops in the area where the esophagus meets the gastric cardia. The risk for developing gastric and GEJ cancer increases with age, is greatest after 50 years of age, and occurs more frequently among men than women.

Approximately 90% of noncardia cancers are attributable to a *Helicobacter pylori* infection. Early-stage gastric and GEJ cancer are potentially curable. However, most patients present with symptoms that are usually nonspecific, and early diagnosis of gastric and GEJ cancers is challenging. As a result, most patients present with advanced-stage III or stage IV disease at the time of diagnosis when curative treatments may not possible. Patients with unresectable advanced or metastatic disease typically experience high symptom burden, impaired quality of life (QoL), and frequent bouts of anxiety and depression. The 5-year survival rate for patients diagnosed with gastric and GEJ cancer living in Canada is 29%, reflecting that the majority of patients are diagnosed with advanced-stage disease that is associated with poor prognosis. Among those with metastatic gastric or GEJ cancer, the 5-year survival rate is 6.6%.

Between 90% and 95% of gastric and GEJ cancers are histologically classified as adenocarcinoma. Gastric cancers may contain oncogenic driver mutations that leads to uncontrolled cell growth and proliferations. The most common driver mutation is human epidermal growth factor receptor 2 (HER2), a transmembrane tyrosine kinase receptor. As HER2 has been found to be overexpressed or amplified in approximately 20% of patients with gastric or GEJ cancers, most patients living in Canada have HER2-negative disease. Based on projections from the Canadian Cancer Statistics Advisory Committee, an estimated 3,060 new cases of gastric or GEJ cancers are expected in 2025, of which 81% will be classified as HER2-negative. Despite currently available treatments, the prognosis for patients with advanced unresectable or metastatic gastric or GEJ adenocarcinoma remains poor with a 5-year survival rate at least 10%. Although the prognostic significance of HER2 status is not as well established in gastric cancer as in other cancers (i.e., breast cancer), its presence or absence is a predictive biomarker for choice of first-line systemic therapy in the advanced and metastatic setting.

Pembrolizumab has been approved by Health Canada, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. Pembrolizumab is a high affinity antibody that works against programmed cell death protein 1 (PD-1) which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumour cells. It is available as solution for IV infusion and the dosage recommended in the product monograph is 200 mg every 3 weeks or 400 mg every 6 weeks.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized control trial (RCT) in adult patients with HER2-negative advanced gastric or adenocarcinoma; and 1 indirect treatment comparisons in the form of a network meta-analysis (NMA)
- patients' perspectives gathered by 1 patient group, My Gut Feeling — Stomach Cancer Foundation of Canada
- input from public drug plans and cancer agencies that participate in our review process

- input from 2 clinical specialists with expertise diagnosing and treating patients with gastric or GEJ cancers
- input from 1 clinician group, Ontario Health — Cancer Care Ontario (OH-CCO) Gastrointestinal Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

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

Patient Input

Patient group input was submitted by 1 patient advocacy group, My Gut Feeling — Stomach Cancer Foundation of Canada. Patient input was collected from an international online survey (March 12 to March 25, 2024) and it included responses from 39 patients (79.6%) and 10 caregivers (20.4%). Overall, 69.4% of responders were residing in Canada, 29.6% residing in the US and 1% residing outside of North America. However, the patient group submission did not include a distinct breakdown of data from patient's living in Canada. All patients who responded to the survey experienced at least 1 symptom before diagnosis, with most common being changes in weight loss (61.2%), changes in appetite (59.2%), pain (46.9%), reflux (42.9%), nausea or vomiting (36.7%) and difficulty swallowing (34.7%). Most patients (95%) reported that their cancer diagnosis had a significant impact on their QoL, including physical and mental health, ability to eat and work, finances, social life, identity, and personal image. Both patient and caregiver respondents, specifically those with metastatic disease, reported a significant decline in their mental health due to the cancer diagnosis and its treatment. In addition, changes in identity and family dynamics due to cancer diagnosis were reported to further impact psychosocial well-being and exacerbated any pre-existing mental health conditions such as depression and anxiety in both patients and caregivers. Respondents also indicated that cancer and its treatments had financial implications on the patient and caregiver. All patients who completed the survey experienced at least 1 treatment-related side effect. The most reported treatment-related side effects included fatigue (89.8%), weight loss (83.7%), appetite changes (79.6%), nausea or vomiting (75.5%), chemo brain (73.5%), taste changes (69.4%), neuropathy (67.3%), hair loss (65.3%), diarrhea (61.2%), abdominal pain (51%) and insomnia (46.9%). Overall, 8.2% of respondents reported discontinuing treatment due to an adverse event resulting in hospitalization, 16.4% reported receiving a dose reduction in treatment, and 16.4% reported delaying or skipping a treatment cycle. Patients and caregivers who completed the survey indicated that the following outcomes were important in considering treatment options: QoL, treatment side effects, cost of treatment, convenience of treatment, duration of treatment and the survival benefit. Patients and caregivers added that equitable access, convenience of administration (e.g., oral versus IV, less frequent travel to hospital, shorter chair time to receive treatment), and more options from which to choose based on their values and preferences were important. Input from the patient

group emphasized the patients' demand for biomarker testing to be accessible for patients in Canada at the onset of their disease across all centres and provinces.

Clinician Input

Input From Clinical Experts Consulted on This Review

The clinical experts consulted for the purpose of this review emphasized that locally advanced and metastatic HER2-negative gastric or GEJ cancer is associated with considerable unmet needs. Treatment with nivolumab in combination with chemotherapy is the only available first-line option for locally advanced metastatic HER2-negative gastric or GEJ cancer; however, OS remains poor (median OS 13 to 15 months). The clinical experts suggested that the addition of pembrolizumab to chemotherapy would represent an alternative to combination therapy with nivolumab plus chemotherapy in the first-line setting for patients with locally advanced and metastatic HER2-negative gastric or GEJ cancer. The clinical experts noted that, if approved for funding, the addition of pembrolizumab to chemotherapy offers patients an alternative treatment schedule of every 6 weeks versus every 2 to 4 weeks with nivolumab. As per the Health Canada indication, the clinical experts agreed that patients who have HER2-negative gastric or GEJ adenocarcinoma that is metastatic or not amenable to curable resection should be considered for first-line treatment with pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy. Currently, CPS testing for PD-L1 expression is not required for patients with HER2-negative disease. The clinical experts noted the following factors should be used to determine response to treatment: patient reported symptoms and side effects and response on cross-sectional imaging via CT scans or MRI. The clinical experts suggested that patients should be assessed by a clinician after every 2 to 3 cycles of treatment. Clinician assessment may occur more frequently if the patients report the occurrence of bothersome symptoms or side effects. The clinical experts suggested that patients should undergo CT scans every 2 to 3 months. Tumour markers can be used as per clinical judgment to supplement a fulsome patient assessment. The clinical expert stressed, however, that the only truly clinically meaningful end points across all oncology types are OS and QoL. The clinical experts suggested that the decision to discontinue treatment with pembrolizumab should be based on patient reported symptoms, patient preference, side effects and well-being, in combination with assessment of treatment response and disease progression, either radiologic or clinical. The clinical experts suggested that pembrolizumab should only be prescribed by or under the supervision of a practitioner in medical oncology with expertise in the management of immunotherapy side effects.

Clinician Group Input

One clinician group input was submitted by the Ontario Health — Cancer Care Ontario (OH-CCO) Gastrointestinal Drug Advisory Committee. A total of 4 clinicians provided input for this review on behalf of OH-CCO's Drug Advisory Committee.

The clinician group pointed out that patients with advanced, HER2-negative gastric cancer are offered chemotherapy (e.g., FOLFOX, XELOX) plus nivolumab as a currently available standard of care combination therapy in Canada. The clinician group mentioned that the goals of treatment in the palliative setting include improvements of QoL and OS. The clinician group indicated that the addition of pembrolizumab

would give clinicians an alternative option to nivolumab, which is currently approved. The clinician group providing input added that patients with HER2-negative advanced gastric cancer would be best suited for treatment with pembrolizumab. Referring to studies CheckMate-649 and KEYNOTE-859, the clinician group suggested that those patients with PD-L1 CPS of more than 5% or at least 10% may derive most benefit from pembrolizumab; whereas patients with PD-L1 CPS lower than 1% may derive little benefit. The clinician group indicated that clinical response or symptoms are used to determine whether a patient is responding to treatment in clinical practice. The input further suggested that CT scans should be done regularly, as per clinician discretion. The clinician group indicated that the decision to continue or discontinue treatment with pembrolizumab should be based on disease response and immune-related toxicities, and functional status.

Drug Program Input

The clinical expert we consulted provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
For patients who are unable to receive or tolerate fluoropyrimidine plus platinum-based chemotherapy, is it reasonable to combine pembrolizumab with alternative chemotherapy?	The clinical experts consulted on this review noted that fluoropyrimidines, capecitabine or fluorouracil, are the backbones of all the chemotherapies used in clinical practice in Canada for the patient population under review. pERC agreed with the clinical experts that raltitrexed may be used in patients with a contraindication to the receipt of fluoropyrimidine chemotherapy.
Considerations for initiation of therapy	
Patients eligible for inclusion in KEYNOTE-859 had adenocarcinoma histology. Should patients with squamous cell or undifferentiated gastric cancer be considered eligible for pembrolizumab with chemotherapy?	Patients with squamous cell or undifferentiated gastric cancer were excluded from the KEYNOTE-859 trial. pERC agreed with the clinical experts that, while it is relatively rare for patients with gastric cancers to present with squamous cell and undifferentiated histology, it would be reasonable for these patients to be considered eligible for treatment with pembrolizumab.
Should eligibility to receive pembrolizumab plus chemotherapy be determined by PD-L1 combined positive score; and/or dMMR or MSI-H?	pERC agreed with the clinical experts that eligibility to receive pembrolizumab plus chemotherapy should not be tied to a patient's PD-L1 combined positive score or dMMR or MSI-H status. pERC noted that this would be aligned with the eligibility criteria for combination therapy with nivolumab in the patient population under review. pERC further discussed that chemotherapy may be initiated pending results of HER2 testing and pembrolizumab added upon confirmation of HER2-negative status. If HER2 status cannot be determined (e.g., insufficient tissue for testing), patients may be considered for the treatment with pembrolizumab plus chemotherapy.

Implementation issues	Response
The duration of treatment for pembrolizumab is until disease progression, unacceptable toxicity or up to 24 months (35 cycles administered every 3 weeks). If pembrolizumab is discontinued for reasons other than progression or intolerance after the initial 24 months, are patients eligible for an additional 12 months (17 cycles every 3 weeks) at the time of disease progression in alignment to other indications for pembrolizumab?	pERC agreed with the clinical experts that in the event pembrolizumab is discontinued after the initial 24 months of treatment, for reasons other than disease progression or intolerability, it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 12 months) at the discretion of the treating physician.
Should re-treatment consist of pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy?	pERC agreed with the clinical experts that re-treatment with pembrolizumab, alone or in combination with chemotherapy, should be based on a joint decision-making process between the oncologist and patient, considering disease burden, residual treatment side effects, and patient symptoms, values, and preferences.
PAG notes that nivolumab in combination with chemotherapy was reviewed by us for the treatment of adult patients with advanced or metastatic gastric, GEJ or esophageal adenocarcinoma.	Comment from the drug program to inform pERC deliberations.
Considerations for discontinuation of therapy	
If there is disease progression during a treatment break, can pembrolizumab with or without chemotherapy be resumed?	pERC agreed with the clinical experts that pembrolizumab with or without chemotherapy can be resumed, at the treating physician's discretion, for patients who stopped pembrolizumab before any disease progression and if disease progression occurred during the treatment break.
Considerations for prescribing of therapy	
For consistency, jurisdictions would plan on implementing pembrolizumab as weight-based dosing up to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg or 4 mg/kg every 6 weeks to a maximum of 400 mg), similar to other indications.	Comment from the drug program to inform pERC deliberations.
The trial allowed pembrolizumab to be continued if 1 or more chemotherapy drugs was discontinued. Is there a minimum number of chemotherapy cycles that must be given concurrently with pembrolizumab?	The clinical experts noted that, in alignment with other immunotherapies, at least 1 cycle of chemotherapy should be administered concurrently with pembrolizumab. pERC agreed with the clinical experts.
Generalizability	
Can the results from KEYNOTE-859 be generalizable to patients with: • ECOG performance status of 2 or greater be eligible? • CNS metastases? thereby allowing them to be eligible for treatment with pembrolizumab with chemotherapy?	Patients with untreated CNS metastases and those with ECOG Performance Status of more than 1 were excluded from the KEYNOTE-859 trial. pERC agreed with the clinical experts that although the magnitude of benefit in patients with ECOG Performance Status of more than 1 or greater is uncertain, eligibility of these patients should be left to the discretion of the treating clinician. Consistent with the clinical experts' opinion, pERC also noted it would be appropriate to consider patients with controlled CNS metastases for eligibility.

Implementation issues	Response
Funding algorithm	
How does pembrolizumab-chemotherapy compare with nivolumab-chemotherapy?	The sponsor-submitted indirect treatment comparisons suggested that there may to be little-to-no difference in efficacy outcomes between pembrolizumab in combination with chemotherapy and nivolumab in combination with chemotherapy in the patient population under review. pERC agreed that the choice between pembrolizumab and nivolumab will be determined by the treating physician's preference.
Care provision issues	
Is PD-L1 CPS testing and MSI testing required to determine eligibility for treatment with pembrolizumab plus chemotherapy?	The clinical experts indicated that PD-L1 CPS and MSI testing should not be required to determine eligibility for treatment with pembrolizumab in combination with chemotherapy or this patient population.

CNS = central nervous system; CPS = combined positive score; dMMR = deficient mismatched repair; ECOG = Eastern Cooperative Oncology Group; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; MSI = microsatellite instability; MSI-H = microsatellite instability-high; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review expert review committee; PD-L1 = programmed death-ligand 1.

Clinical Evidence

Systematic Review

Description of Studies

One study was included in the sponsor-conducted systematic review: the KEYNOTE-859 trial.

KEYNOTE-859 (NCT03675737) is an on-going multicentre (207 sites across 22 countries), placebo-controlled, randomized (1:1) double-blind, phase III trial evaluating the efficacy and safety of adding pembrolizumab to fluoropyrimidine- and platinum-containing chemotherapy as first-line therapy in adult patients with HER2-negative advanced gastric or GEJ adenocarcinoma. Patients were randomly allocated to receive either pembrolizumab 200 mg every 3 weeks (N = 790) or saline placebo (N = 789) each in combination with chemotherapy (cisplatin and 5-fluorouracil [FP] or capecitabine and oxaliplatin [CAPOX]). Randomization was stratified by geographic region (Western Europe, Israel, North America and Australia versus Asia versus rest of the world), investigator's choice of chemotherapy regimen (FP versus CAPOX), and PD-L1 expression at baseline (CPS ≥ 1 versus CPS < 1). PD-L1 expression was determined at a central laboratory using the Agilent PD-L1 IHC 22C3 pharmDx kit and the tests were conducted at a central laboratory. The primary efficacy end point in the KEYNOTE-859 trial was OS. Secondary end points were PFS, overall response rate and duration of response per RECIST 1.1 by blinded independent central review (BICR), and harms outcomes. Exploratory end points included in the following HRQoL measures: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-STO22 (EORTC QLQSTO22), and the EQ-5D-5L.

The mean ages of patients randomized to the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group were 59.5 (standard deviation [SD], 11.9) years and 60.0 (SD, 11.8) years, respectively. In terms of disease characteristics, 18.9% of patients in the pembrolizumab plus chemotherapy group presented with adenocarcinoma of the GEJ and 81.0% presented with adenocarcinoma of the stomach. In the placebo plus chemotherapy group, 23.4% and 76.4% of patients presented with adenocarcinomas of the GEJ and stomach, respectively. Approximately 78% of patients in both treatment groups had documented PD-L1 CPS of 1 or more.

Efficacy Results

Results presented are based on the planned interim analysis 1 (IA1) with the data cut-off date of October 3, 2022. At the time of IA1, the primary and secondary end points met the prespecified criteria for superiority of pembrolizumab plus chemotherapy versus placebo plus chemotherapy, and the null hypotheses were rejected. No further hypothesis testing will be performed at the final analysis.

Overall Survival

At the time of the data cut-off, patients were followed for a median of 12.0 months (range 0.1 to 24.9 months). The median follow-up duration was 12.9 months (range, 0.2 to 45.9 months) in the pembrolizumab with chemotherapy group, and 11.6 months (range, 0.1 to 45.5 months) in the placebo and chemotherapy group.

The proportions of observed deaths at the time of IA1 were 76.5% and 84.4% in the pembrolizumab plus chemotherapy group and placebo plus chemotherapy group, respectively. The median OS was 12.9 months (95% CI, 11.9 to 14.0 months) in the pembrolizumab plus chemotherapy group, and 11.5 months (95% CI, 10.6 to 12.1 months) in the placebo and chemotherapy group. The stratified HR for OS was 0.78 (95% CI, 0.70 to 0.87; P < 0.0001) in favour of pembrolizumab plus chemotherapy, when compared with placebo plus chemotherapy. Risk differences in OS between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups were [redacted] at 12 months; [redacted] at 24 months; and [redacted] at 30 months.

The subgroup analyses of OS were indicative of a differential treatment effect among subgroups of patients based on PD-L1 status. More specifically, no difference in OS was observed among patients with PD-L1 CPS less than 1 (HR 0.92; 95% CI, 0.73 to 1.17), indicating that the difference in OS observed in the overall study was driven primarily by patients with PD-L1 CPS of 1 or greater (HR, 0.73; 95% CI, 0.65 to 0.83). The treatment effect on OS was more pronounced among patients with PD-L1 of 10 or greater (HR, 0.64; 95% CI, 0.52 to 0.7) relative to patients with PD-L1 CPS less than 10 (HR, 0.86; 95% CI, 0.75 to 0.98). The subgroup analyses also showed that the treatment effect on OS was likely more pronounced among patients who had MSI-H tumours (HR, 0.35; 95% CI, 0.18 to 0.66) relative to patients whose tumours were non-MSI-H (HR, 0.79; 95% CI, 0.7 to 0.89).

Progression-Free Survival

Disease progression or death on or before the IA1 data cut-off date was observed in 72.4% of patients in the pembrolizumab plus chemotherapy group and 77.1% of patients in the placebo plus chemotherapy group.

The median PFS was 6.9 months (95% CI, 6.3 to 7.2 months) in the pembrolizumab plus chemotherapy group and 5.6 months (95% CI, 5.6 to 5.7 months) in the placebo plus chemotherapy group. The HR for PFS was 0.76 (95% CI, 0.67 to 0.85; P < 0.0001) in favour of pembrolizumab plus chemotherapy, when compared with placebo plus chemotherapy. Risk differences in PFS between the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups were [redacted] at 6 months; [redacted] at 12 months; [redacted] at 24 months; and [redacted] at 30 months.

Health-Related Quality of Life

EORTC QLQ-C30

EORTC QLQ-C30 is a cancer-specific HRQoL tool consisting of 30 items to assess 5 functional dimensions (physical function, role function, emotional function, cognitive function, and social function), 3 symptoms items (fatigue, nausea or vomiting, and pain), 5 single-item measures assessing additional symptoms commonly experienced by patients with cancer (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and 1 scale assessing global health status and global QoL. Based on input from the clinical experts consulted on this review, global health and the nausea or vomiting scales assessed in KEYNOTE-859 were most relevant to patients with GEJ cancers. Scores for each scale and item ranged from 0 to 100 with higher scores indicative of greater QoL or a greater degree of symptoms. Improvement and deterioration were defined as a change of 10 or more points in the relevant direction.

Baseline EORTC QLQ-C30 was completed by 743 patients (96.2%) in the in the pembrolizumab plus chemotherapy group and 749 patients (97.1%) in the placebo plus chemotherapy group. By week 18, 608 patients (78.8% of randomized patients) were available in the pembrolizumab plus chemotherapy group; of whom, 504 patients (65.3% of randomized patients) completed the questionnaire for a compliance rate of 82.9%. In the placebo plus chemotherapy group, 592 patients (76.8% of the randomized patients) were available; of whom, 506 patients (65.6% of the randomized patients) completed the questionnaire for a compliance rate of 85.5%.

For global health status, between group difference in least square change from baseline to week 18 was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement in global health status was reported in 35.4% in the pembrolizumab plus chemotherapy group and 30.9% of patients in the placebo plus chemotherapy group. The between group difference in global health improvement was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement or stability in global health status was reported in 73.4% of patients in the pembrolizumab plus chemotherapy group and 72.9% of patients in the placebo plus chemotherapy group. The between-group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. The stratified HR for time to deterioration of the global health scale at 12 months was 0.87 (95% CI, 0.72 to 1.04; P = 0.1337) for pembrolizumab plus chemotherapy relative to placebo plus chemotherapy.

For nausea and vomiting symptoms, between group difference in least square change from baseline to week 18 was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement in nausea and vomiting symptoms was reported in 24.5% in the pembrolizumab plus chemotherapy group and 24.4% of patients in the placebo plus chemotherapy group. The between group difference in improvement of nausea and vomiting symptoms was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement or stability in nausea and vomiting symptoms was reported in 71.4% of patients in the pembrolizumab plus chemotherapy group and 74.2% of patients in the placebo plus chemotherapy group. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. The stratified HR for time to deterioration of the nausea and vomiting symptom scale at 12 months was 0.95 (95% CI, 0.9 to 1.14; P = 0.5698) for pembrolizumab plus chemotherapy relative to placebo plus chemotherapy.

EORTC QLQ-ST022

EORTC QLQ-ST022 is a HRQoL measure specific to gastric cancer, that consists of 22 items to assess symptoms of dysphagia (4 items), pain or discomfort (3 item), upper gastrointestinal GI symptoms (3 items), eating restrictions (5 items), emotional (3 items), dry mouth, hair loss and body image (1 item each).[30] Scores for each symptom scale range from 0 to 100 with higher scores indicative worsening symptoms. Improvement and deterioration were defined as a decrease or increase of 10 or more points, respectively. Results from the EORTC QLQ-ST022 pain scale were assessed in KEYNOTE-859. Scores for each scale and item ranged from 0 to 100 with higher scores indicative of a greater degree of symptoms. Improvement and deterioration were defined as a change of 10 or more points in the relevant direction.

Baseline EORTC QLQ-ST022 was completed by 701 (91.4%) patients in the pembrolizumab plus chemotherapy group and 696 (91.5%) in the placebo and chemotherapy group. By week 18, 595 patients (77.6% of the randomized patients) were available in the pembrolizumab plus placebo group; of whom, 488 patients (63.6% of the randomized patients) completed the questionnaire for a compliance rate of 82.0%. In the placebo plus chemotherapy group, 577 patients (75.8% of the randomized patients) were available; of whom, 489 patients (64.3% of the randomized patients) completed the questionnaire for a compliance rate of 84.7%.

For pain symptoms, between group difference in least square change from baseline to week 18 was [redacted] favouring treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement in pain symptoms was reported in 36.5% in the pembrolizumab plus chemotherapy group and 31.1% of patients in the placebo plus chemotherapy group. The between group difference in improvement in pain symptoms was [redacted] favouring treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. Improvement or stability in pain symptoms was reported in 77.8% of patients in the pembrolizumab plus chemotherapy group and 76.1% of patients in the placebo plus chemotherapy group. The between group difference in improvement or stability was [redacted]

following treatment with pembrolizumab plus chemotherapy versus placebo plus chemotherapy. The stratified HR for time to deterioration on the pain symptoms scale at 12 months was 0.76 (95% CI, 0.58 to 0.98; P = 0.0378) favouring pembrolizumab plus chemotherapy compared to placebo plus chemotherapy.

Harms Results

Adverse Events

The proportion of patients with at least 1 adverse event (AE) was reported to be 98.9% in the pembrolizumab plus chemotherapy group and 98.0% in the placebo plus chemotherapy group. The 5 most frequently reported AEs in the pembrolizumab plus chemotherapy group were nausea (46.4%), anemia (41.9%), diarrhea (35.7%), vomiting (33.6%) and decreased appetite (29.4%). In the placebo plus chemotherapy nausea, the 5 most reported AEs were nausea (46.3%), anemia (36.3%), diarrhea (32.3%), decreased appetite (28.6%), and vomiting (26.7%).

Grade 3 or worse AEs were reported in 75.3% of patients in the pembrolizumab plus chemotherapy group and 69.6% of patients in the placebo plus chemotherapy group. The most common grade 3 or worse AEs reported in the pembrolizumab plus chemotherapy group were: anemia (12.1%), neutrophil count decreases (9.8%), neutropenia (7.4%), platelet count decreased (7.1%), diarrhea (6.4%), hypokalemia (6.4%), vomiting (5.2%), and fatigue (5.0%). The most common grade 3 or worse AEs reported in the placebo plus chemotherapy group were anemia (9.1%), neutrophil count decreased (8.1%), neutropenia (8.6%), platelet count decreased (5.0%), diarrhea (5.1%), vomiting (5.3%), and fatigue (5.1%).

Serious Adverse Events

Serious adverse events were AEs resulting in death, or those that were life-threatening, required inpatient hospitalization or prolonged of existing hospitalization, resulted in persistent or significant disability and/or incapacity, congenital anomaly and/or birth death, or other important medical events.

The proportion of patients with at least 1 serious adverse event (SAE) was reported to be 45.2% in the pembrolizumab plus chemotherapy group and 40.2% in the placebo plus chemotherapy group. SAEs reported by 2% or more of patients in the pembrolizumab plus chemotherapy group were diarrhea (3.9%), pneumonia (3.8%), vomiting (2.4), and colitis (2.0%). SAEs reported by 2% or more of patients in the placebo plus chemotherapy group were diarrhea (3.2%) and vomiting (2.9%).

Withdrawal of Treatment Due to Adverse Events

Discontinuation of treatment due to AEs occurred in 32.7% of patients in the pembrolizumab group and 25.9% of patients in the placebo plus chemotherapy group.

In the pembrolizumab plus chemotherapy group, 14.8% of patient discontinued treatment with pembrolizumab, 30.2% discontinued treatment with any backbone chemotherapy and 8.5% discontinued all therapies in their treatment regimen. AEs leading to treatment discontinuation in 1% or more of patients in the pembrolizumab plus chemotherapy group included peripheral sensory neuropathy (3.6%), neuropathy peripheral (3.3%), diarrhea (1.9%), palmar-plantar erythrodysesthesia syndrome (1.7%), neutrophil count decreases (1.5%), platelet count decreased (1.5%), neutropenia (1.4%), (1.1%) and fatigue (1.0%).

In the placebo plus chemotherapy group, 10.9% discontinued treatment with placebo, 25.0% discontinued treatment with any backbone chemotherapy and 7.5% discontinued all therapies in their treatment regimen. AEs leading to treatment discontinuation in 1% or more of patients in the placebo plus chemotherapy group were neuropathy peripheral (4.1%), peripheral sensory neuropathy (2.7%), platelet count decreased (1.8%), palmar-plantar erythrodysesthesia syndrome (1.1%), and neutropenia (1.0%).

Mortality

Deaths due to AEs were documented in 8.2% of patients in the pembrolizumab plus chemotherapy group and 7.4% of patients in the placebo plus chemotherapy group.

Notable Harms

Immune-mediated adverse events were of interest to the clinical review team. At least 1 immune-mediated AE was documented in [redacted] of patients in the pembrolizumab plus chemotherapy group and [redacted] of patients in the placebo group plus chemotherapy group. Grade 3 or worse immune-mediated AEs were reported in [redacted] of patients in the pembrolizumab plus chemotherapy group and [redacted] of patients in the placebo plus chemotherapy group.

Critical Appraisal

The KEYNOTE-859 trial is a randomized, placebo-controlled, parallel-group, multicentre, double-blinded phase III study. The stratification factors for randomization appeared to be appropriate, as they addressed important prognostic factors identified by the clinical experts consulted on this review; and the baseline characteristics between the treatment groups were generally well balanced. The use of concomitant and subsequent therapies was comparable between the treatment groups. There was a greater proportion of patients in placebo plus chemotherapy group who discontinued from the study (85.8% versus 77.1% in the pembrolizumab plus chemotherapy group) or discontinued from the study medication during the treatment period of the trial (94.3% versus 87.3% in the pembrolizumab plus chemotherapy group). Duration of exposure to chemotherapy was consistently longer among patients in the pembrolizumab plus chemotherapy group (3,666.2 person-month versus 2,093.2 person-month in the placebo plus chemotherapy group). A relatively longer treatment exposure to chemotherapy could introduce bias the study results in favour of pembrolizumab. However, the observed difference in chemotherapy exposure may have also been due to earlier dropouts (e.g., due to deaths) in the placebo group, when compared to the pembrolizumab group. Although re-treatment was permitted, it is unknown how many patients had received re-treatment, which also could have biased the results in favour of pembrolizumab.

Risk of bias to due to missing outcome data for OS and PFS appeared to be low as losses to follow-up for reasons other than death were low, and sensitivity analyses with different censoring rules for PFS in the overall population were consistent. HRQoL was assessed as an exploratory outcome using EORTC QLQ-30 and EROTC QLQ-ST022. Despite no notable differences observed between the 2 groups, the HRQoL results were compromised by a sizable proportion of patients with incomplete data of the questionnaires.

Analysis of efficacy results followed a defined statistical plan and employed appropriate censoring criteria. The efficacy end points of OS and PFS were addressed using a multiplicity hierarchical testing procedure,

which controlled from type I error across multiple end points and interim analyses. Both PFS and OS were modelled using a proportional hazards assumption. Although the hazards assumption underlying the HRs for OS and PFS was not tested, based on visual inspection, the curves appeared to be relatively parallel. Of note, OS and PFS results were based on interim analyses, which may have overestimated the treatment effect estimates. Given the relatively large sample size and number of events, the effect estimate and confidence interval are not likely to be highly unstable. Although reassuring, overestimation of the treatment effects cannot be completely excluded.

GRADE Summary of Findings and Certainty of the Evidence

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

- probability of OS at months 12 and 30
- probability of PFS at months 6, 12 ad 30
- HRQoL as measured by the EORTC QLQ-C30 (global QoL and nausea or vomiting scales) and EORTC QLQ-ST022 (pain symptoms scale) at week 18
- notable harms, including immune-mediated adverse events and grade 3 or worse immune-mediated adverse events.

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

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

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The presence or absence of an important effect for OS was based on threshold informed by the clinical experts consulted for the purpose of this review, while the presence or absence of an important effect on HRQoL was based on MID estimates identified in the literature. For all other outcomes, the presence or absence of an important effect was based on the non-null effect.

Table 3 presents the GRADE summary of findings for pembrolizumab in combination with chemotherapy versus saline placebo in combination with chemotherapy.

Table 3: Summary of Findings for Pembrolizumab in Combination With Fluoropyrimidine- and Platinum-Containing Chemotherapy Versus Saline Placebo in Combination With Fluoropyrimidine- and Platinum-Containing Chemotherapy for Adult Patients with HER2-Negative Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + chemotherapy	Pembrolizumab + chemotherapy	Difference		
Overall survival							
Probability of survival at 12 months [a] Median follow-up: 12.9 and 11.6 [b]	1,579 (1 RCT)	NR	46.7 per 100 (43.2 to 50.2 per 100)	52.7 per 100 (49.1 to 56.1 per 100)	[redacted]	Moderate [c]	The addition of pembrolizumab to chemotherapy likely results in a clinically important increase in OS when compared to placebo plus chemotherapy at 12 months.
Probability of survival at 30 months [a] Median follow-up: 12.9 and 11.6 [b]	1,579 (1 RCT)	NR	13.1 per 100 (10.6 to 15.9 per 100)	22.8 per 100 (19.6 to 26.1 per 100)	[redacted]	High [d]	The addition of pembrolizumab to chemotherapy results in a clinically important increase in OS when compared to placebo plus chemotherapy at 30 months.
Progression-free survival per RECIST v1.1 by BICR							
Probability of PFS at 6 months [a] Median follow-up: 12.9 and 11.6 [b]	1,579 (1 RCT)	NR	44.8 per 100 (41.1 to 48.4 per 100)	55.3 per 100 (51.6 to 58.9 per 100)	[redacted]	High [e]	The addition of pembrolizumab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 6 months. The clinical importance of the increase is unclear.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + chemotherapy	Pembrolizumab + chemotherapy	Difference		
Probability of PFS at 12 months [a] Median follow-up: 12.9 and 11.6 [b]	1,579 (1 RCT)	NR	19.3 per 100 (16.3 to 22.4 per 100)	28.9 per 100 (25.5 to 32.4 per 100)	[redacted]	High [e]	The addition of pembrolizumab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 12 months. The clinical importance of the increase is unclear.
Probability of PFS at 30 months [a] Median follow-up: 12.9 and 11.6 [b]	1,579 (1 RCT)	NR	9.0 per 100 (6.5 to 11.8 per 100)	15.3 per 100 (12.4 to 18.6 per 100)	[redacted]	High [e]	The addition of pembrolizumab to chemotherapy results in an increase in PFS when compared to placebo plus chemotherapy at 30 months. The clinical importance of the increase is unclear.
Health-related quality of life (scale 0 to 100; greater score indicates greater QoL, greater functioning or a greater degree of symptoms)							
Change in LS mean EORTC QLQ-C30 global health status/QoL scale from baseline to week 18, points Median follow-up: 12.9 and 11.6 [b]	1,492 (1 RCT)	NR	−0.85 (−2.62 to 0.93)	0.40 (−1.37 to 2.18)	[redacted]	Low [f]	The addition of pembrolizumab to chemotherapy may result in little-to-no clinically important difference in HRQoL global health at week 18 compared to placebo plus chemotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + chemotherapy	Pembrolizumab + chemotherapy	Difference		
Change in LS mean EORTC QLQ-C30 nausea or vomiting item from baseline to week 18, points Median follow-up: 12.9 and 11.6 [b]	1,492 (1 RCT)	NR	1.36 (−0.45 to 3.16)	1.06 (−0.75 to 2.87)	[redacted]	Low [g]	The addition of pembrolizumab to chemotherapy may result in little-to-no clinically important difference in nausea or vomiting at week 18 compared to placebo plus chemotherapy.
Change in LS mean EORTC QLQ ST022 pain symptom scale from baseline to week 18, points Median follow-up: 12.9 and 11.6 [b]	1,492 (1 RCT)	NR	−5.64 (−7.34 to −3.94)	−8.21 (−9.91 to −6.51)	[redacted]	Moderate [h]	The addition of pembrolizumab to chemotherapy likely results in decreased (improved) pain symptoms when compared to placebo plus chemotherapy at 18 months. The clinical importance of the increase is unclear.
Harms							
Immune-mediated AEs [a] Median follow-up: 12.9 and 11.6 [b]	1,572 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High [i]	The addition of pembrolizumab to chemotherapy results in an increase in immune-mediated AE when compared with placebo plus chemotherapy.
Grade 3 or worse immune-mediated AEs [a] Median follow-up: 12.9 and 11.6 [b]	1,572 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High [i]	The addition of pembrolizumab to chemotherapy results in an increase in Grade 3 or worse immune-mediated AE when

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + chemotherapy	Pembrolizumab + chemotherapy	Difference		
							compared with placebo plus chemotherapy.

BICR = blinded independent central review; CI = confidence interval; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-STO22 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-STO2;2L GEJ = gastroesophageal junction; LS = least squares; OS = overall survival; MID = minimally important difference; NR = not reported; PFS = progression-free survival; SD = standard deviation.

[a]Between-group differences were requested from the sponsor to aid in interpretation and were not part of the sponsor's analysis plan.

[b]Median follow-up time at the time of data cut-off (October 3, 2022) was 12.9 months (range, 0.2 to 45.9) in the pembrolizumab plus chemotherapy group and 11.8 months (range, 0.1 to 45.5) in the placebo and chemotherapy group.

[c]Rated down1 level for serious imprecision. Although the point estimate suggests a clinically important benefit (exceeding the 5 to 10% threshold suggested by the clinical experts consulted on this review), the lower bounds of the 95% CI is compatible with little-to-no difference in clinical benefit.

[d]The point estimate and 95% CI exceeded the threshold of a clinically important benefit (5 to 10%) suggested by the clinical experts consulted on this review.

[e]The clinical experts consulted on this review indicated a lack of clarity about a threshold of clinical importance therefore the null was used. Although the certainty of evidence was not rated down for serious indirectness, there were concerns about the clinical importance of PFS.

[f]Rated down 1 level for serious study limitation because of risk of bias due to missing data as results were available for 65.3% of patients by week 18. Rated down1 level for serious imprecision. There was no MID estimate specific to patients with advanced gastric or GEJ adenocarcinoma that was identified or provided by the sponsor. Between group difference in MID ranged between 3 to 9 points for improvement, and −4 to −13 points for deterioration on the global QoL scale across various cancer types. Using the MID established for other cancer types, the treatment effect and the 95% CI included the possibility of no difference in global health/QoL, and the lower bound of the 95% CI included the potential for decrease in (worsening of) global health or QoL.

[g]Rated down 1 level for serious study limitation because of risk of bias due to missing data as results were available for 65.3% of patients by week 18. Rated down1 level for serious imprecision. There was no MID estimate specific to patients with advanced gastric or GEJ adenocarcinoma that was identified or provided by the sponsor. Between group difference in MID ranged between 5 to 7 points for improvement, and −5 to −8 points for deterioration on the nausea or vomiting scale across various cancer types. Using the MID established for other cancer types, the 95% CI included the possibility of no difference in nausea/vomiting, and the upper bound of the 95% CI included the potential for increasing (worsening) nausea or vomiting.

[h]Rated down1 level for serious study limitation because of risk of bias due to missing data as results were available for 65.3% of patients by week 18. No MID estimate specific to patients with advanced gastric or GEJ adenocarcinoma was identified; therefore, the null was used. Although the certainty of evidence was not rated down for serious indirectness, there were concerns about the clinical importance of the between group difference on the pain symptom scale.

[i]The clinical experts consulted on this review indicated a lack of clarity about a threshold for clinical importance, therefore the null was employed.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Note: Data cut-off date October 3, 2022.

Source: Clinical Study Report for KEYNOTE-859.[36] Additional information request. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were included in this submission.

Indirect Comparisons

In the absences of direct head-to-head trials evaluating the comparative efficacy of pembrolizumab versus relevant comparators for first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric and GEJ adenocarcinoma, the sponsor submitted 1 indirect treatment comparison, in the form of a NMA, indirectly comparing the treatment effect of first-line treatment pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy versus other first-line therapies.

Description of Studies

For the purpose of this review, the sponsor summary of the clinical evidence focused on the comparators relevant to the practice setting in Canada. The adaptation of the NMA in Canada consisted of 2 trials evaluated 2 interventions, including pembrolizumab in combination with fluoropyrimidine and platinum doublet chemotherapy (KEYNOTE-859) and nivolumab in combination with fluoropyrimidine and platinum doublet chemotherapy (CheckMate-649), connected by the comparison to fluoropyrimidine and platinum doublet combination chemotherapy alone.

Efficacy Results

Overall Survival

The NMA for OS was constructed using a fixed-effects model (deviance information criterion [DIC], 7.36; deviance, 3.35). The treatment response of adding pembrolizumab or nivolumab to chemotherapy on OS were favoured over chemotherapy alone. The credible intervals (CrIs) for the comparisons between pembrolizumab plus chemotherapy versus nivolumab plus chemotherapy presented little-to-no difference in OS between the treatments (HR, 0.99; 95% CrI, 0.85 to 1.15).

Progression-Free Survival

The NMA for PFS was constructed using a fixed model (DIC, 5.37; deviance, 2.36). The treatment response of adding pembrolizumab or nivolumab to chemotherapy on PFS were favoured over chemotherapy alone. The CrIs for the comparisons between pembrolizumab plus chemotherapy versus nivolumab plus chemotherapy presented little-to-no difference in PFS between the treatments (HR, 0.96; 95% CrI, 0.82 to 1.13).

Critical Appraisal

The sponsor-submitted NMA was based on studies identified from a systematic literature review of relevant evidence. The systematic literature review was based on population, intervention, control, and outcomes that were defined a priori. The systematic literature review involved multiple searches in electronic databases, clinical registries, and supplementary sources. As the search and selection of relevant studies were restricted to trials published in English, relevant non-English publications may have been excluded. Funnel plot assessment for publication bias was not conducted and thus publication bias cannot be fully ruled out. While the risk of bias of the comparator trials was assessed, risk of bias was not assessed by outcome. Several

sources of clinical and methodological heterogeneity were identified. The most notable were differences in the primary analysis population, distribution of PD-L1 expression and study design. The primary analysis population were different between the trials. The analysis population in KEYNOTE-859 consisted of patients with PD-L1 CPS of 1 or more, CPS of 10 or more, and all enrol patients regardless of PD-L1 expression. In CheckMate-649, the analysis population consisted of patients with PD-L1 CPS of 5 or more and all enrolled patients regardless of PD-L1 expression. To mitigate the differences in analysis population between the trials, the NMA was conducted using all enrolled patients, regardless of PD-L1 expression. However, a greater proportion of patients in the CheckMate-649 trial had a PD-L1 CPS of 10 or more relative to KEYNOTE-859 (49% versus 35%). The lack of stratified results of PD-L1 expression of CPS of 5 or more and CPS of 10 or more in both trials precluded sensitivity analysis to explore this potential bias or adjustment for this difference. In terms of study design, KEYNOTE-859 employed a double-blinded study design; whereas CheckMate-649 was an open-label trial. To minimize any bias inherent in open-label trials, efficacy results were based on BICR. Finally, the NMA results were based on the final analysis CheckMate-649 (completion date May 2020) and interim analysis from KEYNOTE-859 (data cut-off date October 3, 2022). Accordingly, the review team was not able to rule out the possibility that final analysis results from KEYNOTE-859, if available, would have impacted the indirect comparison of pembrolizumab versus nivolumab differently. The aforementioned sources of clinical and methodological heterogeneity may have introduced intransitivity, which may have biased effect estimates. To account for changes in hazards ratio over time, the sponsor provided both constant HR and time-varying HR methods for NMA. The time-varying HRs for pembrolizumab plus chemotherapy versus nivolumab plus chemotherapy remained consistent over time and were concordant with the result of the constant NMA for OS and PFS. Accordingly, the assumption of proportional hazards was likely met. The adaptation of the NMA in Canada was limited by the available data. With only 1 trial informing each comparison, random effects were not feasible and the results from the fixed effect analysis were predicated on an assumption of minimal between study heterogeneity. NMA results were presented only for OS and PFS; harms outcomes and other outcomes of relevance to patients (e.g., HRQoL) were not reported.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps in the evidence from the systematic review were included in this submission.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target populations	Adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma
Treatment	Pembrolizumab plus fluoropyrimidine- and platinum-containing chemotherapy[a] (hereafter referred to as pembrolizumab plus chemotherapy)
Dose regimen	Pembrolizumab: 200 mg IV administered every 3 weeks for up to 35 cycles
Submitted price	Pembrolizumab: 100 mg/4 mL: $4,400 per vial
Submitted treatment cost	Pembrolizumab: $5,638 every 3 weeks[b]
Comparators	• Nivolumab plus fluoropyrimidine- and platinum- containing chemotherapy (hereafter referred to as nivolumab plus chemotherapy) • Fluoropyrimidine- and platinum-containing chemotherapy alone (hereafter referred to as chemotherapy)
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	KEYNOTE-859 trial informed PFS, OS, time on treatment, and health state utility values Sponsor-submitted network meta-analysis to inform OS and PFS comparison between pembrolizumab and nivolumab.
Submitted results	• ICER (pembrolizumab plus chemotherapy vs. chemotherapy alone) = $144,318 per QALY gained (incremental costs = $71,912; incremental QALYs = 0.50). • ICER (pembrolizumab plus chemotherapy vs. nivolumab plus chemotherapy) = pembrolizumab plus chemotherapy dominates (cost savings = $2,809; incremental QALYs = 0.02).
Key limitations	• It is uncertain whether pembrolizumab plus chemotherapy is less costly and more effective than nivolumab plus chemotherapy. The cost difference between the 2 treatments is small and the evidence underlying the relative effectiveness of pembrolizumab compared to nivolumab is statistically and clinically insignificant. The clinical experts we consulted noted that in practice the clinical effectiveness of nivolumab plus chemotherapy is considered comparable to that of pembrolizumab plus chemotherapy. • The pattern of use for chemotherapy regimens in the sponsor's base case was inconsistent with clinical practice in Canada, according to the clinical experts we consulted. • The dose and scheduling frequency of pembrolizumab and nivolumab in the sponsor's base case was inconsistent with clinical practice in Canada according to the clinical experts we consulted. • The health state utility values adopted by the sponsor lacked face validity, in that the utility value for the progression-free health state was higher than the general population value for the same age group. • Relative dose intensity (RDI) was used to reduce drug costs; however, this assumes a direct link between RDI and drug cost which may not hold in practice.

Component	Description
Our reanalysis results	• In our base case, we assumed: equal efficacy for OS and PFS for pembrolizumab compared with nivolumab; changed the percentage use of chemotherapy regimens and dosing frequency for the immunotherapies to be reflective of clinical practice in Canada; adopted 100% relative dose intensity; and, applied aged-based health utility decrements. Our reanalysis also corrected the cost of oxaliplatin. • The results of our reanalysis suggested that pembrolizumab plus chemotherapy was more costly and more effective than chemotherapy alone and was slightly more costly than nivolumab plus chemotherapy with similar QALYs in probabilistic analysis. • The incremental cost and QALYs between the 2 combination therapy comparators was comparatively small in our analysis and the sponsor's analysis, suggesting that the difference between the 2 regimens may not be meaningfully different given the clinical uncertainty within the economic analysis.

ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; LY = life-year; PFS = progression-free survival; OS = overall survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RDI = relative dose intensity; WTP = willingness to pay.

[a]Chemotherapy was assumed by the sponsor to comprise CAPOX plus 5-fluorouracil and cisplatin (CISPFU) for the pembrolizumab plus chemotherapy and chemotherapy only arms and CAPOX and leucovorin, 5-fluorouracil and oxaliplatin (FOLFOX) for the nivolumab plus chemotherapy arm.

[b]A weight-based dose assuming 2mg/kg, 65.5 kg patient, vial sharing and 95.3% relative dose intensity.

Budget Impact

We identified the following key limitations with the sponsor's analysis: The unit price of oxaliplatin used was outdated, the use of RDI to estimate actual drug costs was inappropriate, the distribution of chemotherapy regimens was not aligned with clinical practice in Canada, the dosing frequency of pembrolizumab and nivolumab was not aligned with the backbone chemotherapy, the market share of comparators did not reflect clinical practice, and the allocation of market share to clinical trials was inappropriate. Additionally, the number of patients eligible to receive pembrolizumab was uncertain.

We corrected the price of oxaliplatin using the most recent prices. Our reanalysis included: assuming 100% RDI for all drugs, revising the distribution of chemotherapy backbones to align with clinical practice, aligning the dosing frequency of pembrolizumab and nivolumab doses with backbone chemotherapy and revising the market share of comparators.

Based on our base case, the 3-year budget impact is expected to be $2,108,315 (year 1: $324,871; year 2: $847,679; year 3: $935,765) should the public drug plans reimburse pembrolizumab for use in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, 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: August 14, 2024

Regrets: Four expert committee member(s) did not attend.

Conflicts of interest: None

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