Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

pembrolizumab (Keytruda)

Indication: In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥ 1) as determined by a validated test.

Sponsor: Merck Canada Inc.

Recommendation: Reimburse with Conditions

Version: 1.0
Publication Date: May 2024
Report Length: 25 Pages

Single Technology

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

Recommendation

The pCODR Expert Review Committee (pERC) recommends that pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, be reimbursed for adult patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2) positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumours express programmed cell death-ligand 1 (PD-L1) (combined positive score [CPS] $\geq$ 1) as determine by a validated test, 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-811; N=698) demonstrated that pembrolizumab, when added to standard of care (SOC) therapy with trastuzumab and platinum-fluoropyrimidine doublet chemotherapy may result in added clinical benefit in patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinomas, whose tumours express PD-L1 (CPS ≥ 1). The KEYNOTE-811 trial demonstrated that in patients whose tumours express PD-L1 (N= 594) treatment with pembrolizumab plus SOC therapy was associated with statistically significant improvements in progression-free survival (PFS; hazard ratio [HR] = 0.71; 95% confidence interval [CI], 0.59 to 0.86, p = 0.0002) and overall survival (OS) (HR = 0.81; 95% CI, 0.67 to 0.98; p = 0.0142), when compared with placebo plus SOC therapy. The median OS was 20.0 months (95% CI, 17.9 to 22.7 months) in the pembrolizumab plus SOC group and 15.7 months (95% CI, 13.5 to 18.5 months) in the placebo plus SOC group. pERC agreed with the clinical experts that the net improvement in median OS of 4.3 months may be considered clinically meaningful in this patient population, given the poor prognosis of the disease in patients diagnosed at a locally advanced or metastatic stage. Immunotherapy-mediated adverse events were more frequent in the pembrolizumab group; however, pERC considered the safety profile of pembrolizumab in combination with SOC therapy to be manageable and consistent with the known safety profile of pembrolizumab. Conclusions on health-related quality of life (HRQoL) outcomes 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 high proportions of missing data. However, the trial results suggested that HRQoL was not worse in the pembrolizumab plus SOC therapy group, when compared to the placebo plus SOC group.

Patients identified a need for more effective and accessible treatments that prolong survival, reduce risk of disease progression, improve quality of life, allow for more convenient administration of therapy, and minimize side effects. pERC noted that pembrolizumab, when added on to SOC therapy with trastuzumab and platinum-fluoropyrimidine doublet chemotherapy, met some of the needs identified by patients because it may prolong survival, delay disease progression, result 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 plus trastuzumab and chemotherapy was $425,549 per quality-adjusted life-year (QALY) gained compared with trastuzumab and chemotherapy alone using a fixed-dose regimen for pembrolizumab ($297,169 per QALY gained using weight-based dosing). Using either a fixed-dose or weight-based regimen, pembrolizumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold for adults with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma whose tumours express PD-L1. A price reduction for pembrolizumab is required for pembrolizumab plus trastuzumab and chemotherapy to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab, in combination with trastuzumab, 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 positive locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 1.3 Tumour PD-L1 expression (CPS ≥ 1)	Evidence from the KEYNOTE-811 trial demonstrated statistically significant PFS and OS 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 agent in the advanced or metastatic setting	The KEYNOTE-811 trial excluded patients with active CNS metastasis, and those who had received prior anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy. As such, the potential benefit of pembrolizumab plus SOC therapy in these patients has not been demonstrated.	—
3. Patients must have good performance status.	The KEYNOTE-811 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 of 2 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 at a dose of 200 mg every 3 weeks)	Patients in the KEYNOTE-811 trial discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice. Patients in the KEYNOTE-811 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 readminister 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 upon the completion of 2 years of treatment and before any disease progression, or after achieving a complete response.
5. One or more components of the treatment can be discontinued at the discretion of the treating physician in case of adverse events.	In the KEYNOTE-811 trial, 1 or more components of the treatment (pembrolizumab, trastuzumab or chemotherapy) could be interrupted or discontinued, due to toxicity, and continue the other components.	—
Prescribing		
6. Pembrolizumab in combination with trastuzumab and chemotherapy should be prescribed by clinicians with	This condition is to ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
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.		
7. Pembrolizumab should be prescribed in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy.	In the KEYNOTE-811 trial, pembrolizumab was administered in combination with 5-FU plus cisplatin or CAPOX. No evidence was available to support the clinical benefit of pembrolizumab monotherapy.	—
Pricing		
8. A reduction in price	The ICER for pembrolizumab plus trastuzumab and chemotherapy is $425,549 when compared with trastuzumab and chemotherapy alone using a fixed-dose regimen ($297,169 using a weight-based regimen). A price reduction of 85% to 89% for pembrolizumab would be required for pembrolizumab plus trastuzumab and chemotherapy to achieve an ICER of $50,000 per QALY gained compared to trastuzumab and chemotherapy alone.	—

5-FU = 5 fluorouracil, CAPOX = capecitabine plus oxaliplatin; CNS = central nervous system; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; PD-L1 = programmed cell death ligand-1; QALY = quality adjusted life year.

Discussion Points

- Aligned with the input from patient and clinician group, pERC acknowledged that there is an unmet need for effective and safe therapy options in this patient population, as patients who are diagnosed with advanced stage disease have poor prognosis. pERC additionally noted that HER2 overexpression in patients with gastric or GEJ adenocarcinomas may be associated with poorer outcomes and more aggressive disease.

- pERC deliberated on the results of the KEYNOTE-811 trial and noted that the trial's dual primary end points (i.e., OS and PFS) were both statistically significant in favour of the addition of pembrolizumab to trastuzumab plus chemotherapy. pERC discussed that, over a median 38 months of follow-up, treatment with pembrolizumab plus SOC resulted in 3.6 months and 4.3 months incremental improvements in median PFS and OS, respectively over standard treatment alone. pERC discussed that clinical importance of the observed improvement in PFS was unclear, and that there was uncertainty about the validity of PFS as surrogate outcome in predicting the long-term treatment effect on overall survival. However, pERC agreed with the clinical experts that the net improvement in median OS of 4.3 months would be considered clinically meaningful in this patient population with poor prognosis. pERC further noted that the observed difference in OS benefit at 12, 18, and 36 months (point estimates) met the expert-identified threshold for clinical meaningfulness (i.e., 10%-15% at any time point) in favour of pembrolizumab plus SOC, although the lower bounds of the corresponding 95% confidence intervals were compatible with little-to-no clinically important difference. Accordingly, the GRADE assessment of the evidence suggested with a 'moderate' certainty that the addition of pembrolizumab to SOC likely results in a clinically important increase in probability of survival plus SOC at 12, 18, and 36 months, when compared with placebo.

- pERC noted that the KEYNOTE-811 trial enrolled patients regardless of their tumour PD-L1 expression status, but the sponsor's decision to limit the funding request for pembrolizumab plus SOC to patients who have PD-L1 positive disease was based on a subgroup analysis. Although the subgroup analyses based on PD-L1 expression status were pre-specified, they were absent from the statistical testing hierarchy. pERC agreed that, while it presented a risk of inflated type 1 error (i.e., falsely rejecting the null hypothesis), the subgroup of patients with PD-L1 positive tumours represented approximately 85% of the full study population. pERC noted that the results from the full study population (N=698) and those from the PD-L1 positive subgroup (N=594) were consistent, and that the clinical benefit observed in the full study population appeared to be driven by the PD-L1 positive subgroup.
- pERC noted that both HER2 and PD-L1 testing are required for the implementation of a reimbursement recommendation for pembrolizumab in the patient population under review. According to the documentation submitted by the sponsor, HER2 testing is funded across all jurisdictions in Canada, and is currently used for all advanced or metastatic gastric or GEJ tumours across all testing laboratories. However, pERC discussed that some jurisdictions may currently not have a validated PD-L1 testing in place and suggested that those jurisdictions may need to consider operationalizing and funding PD-L1 CPS testing to identify patients eligible for pembrolizumab treatment.

- The pharmacoeconomic analysis which primarily informs pERC's economic rationale for the recommendation considered pembrolizumab as a fixed dose, per the product monograph. pERC discussed the results of the scenario analysis conducted by CADTH where pembrolizumab was assumed to be administered using a weight-based dose. In this analysis, the ICER decreased to $297,169 per QALY gained; a price reduction of 85% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained in such a scenario. pERC noted that this analysis is associated with additional uncertainty given that the treatment was not evaluated as a weight-based dose, as this may influence efficacy and adverse events (AEs).

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. Non-cardia 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, and is greatest after 50 years of age, and occurs more frequently among men than women. Approximately 90% of non-cardia cancers are attributable to Helicobacter pylori infection. Early-stage gastric and GEJ cancer are potentially curable. However, most patients present with symptoms that are usually non-specific. As a result, early diagnosis of gastric and GEJ cancers is challenging. Instead, most patients have advanced stage III or stage IV disease at the time of diagnosis when curative treatments are 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 most 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%.

Approximately 90% to 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 HER2. HER2 is overexpressed or amplified in 25% to 32% of patients with GEJ and between 9.5 and 18% of patients with gastric cancers. HER2 overexpression in patients with gastric cancer is associated with poor outcomes and more aggressive disease. In clinical practice, laboratory tests for both HER2 status and PD-L1 expression are done on a biopsy sample taken from the primary tumour or from metastases. HER2 status can be determined via immunohistochemistry (IHC), which measures the amount of HER2 protein in the cancer cells; or via fluorescence in situ hybridization (FISH), which examines the number of copies of the HER2 gene in the cancer cells. PD-L1 expression determined using a semi-quantitative approach through IHC.

In patients with HER2+ disease, the addition of trastuzumab to the standard first-line platinum-fluoropyrimidine doublet is recommended for all patients based on the phase III ToGA trial, which demonstrated improvements in response rates, PFS, and OS with trastuzumab compared with chemotherapy alone. This regimen is supported by the National Institute for Health and Care Excellence (NICE), the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN),

Cancer Care Ontario (CCO), and Alberta Health Services (AHS). In October 2023, ESMO recommended adding pembrolizumab to the trastuzumab plus chemotherapy SOC for patients with positive PD-L1 expression defined by a combined positive score (CPS) or 1 or more based on the results of the KEYNOTE-811 clinical trial.

Pembrolizumab is a high affinity antibody against programmed cell death protein 1 (PD-1) which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and programmed cell death-ligand 2 (PD-L2), on antigen presenting or tumour cells. Pembrolizumab reactivates tumour specific cytotoxic T lymphocytes in the tumour microenvironment by inhibiting the PD-1 receptors from blinding to its ligands. Pembrolizumab received notice of compliance on February 6, 2024 through the standard review pathway. The Health Canada indication for pembrolizumab, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma, whose tumours express PD-L1 (CPS ≥ 1) as determined by a validated test.

Pembrolizumab has been approved by Health Canada, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for adult patients with locally advanced unresectable or metastatic HER2 positive gastric or GEJ adenocarcinoma, whose tumour express PD-L1 (CPS ≥ 1) as determined by a validated test. Pembrolizumab is available as solution for infusion and the dosage recommended in the product monograph is 200 mg every 3 weeks or 400 mg every 6 weeks by intravenous (IV) infusion.

Sources of Information Used by the Committee

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

- a review of 1 phase III randomized controlled trial (RCT) clinical studies in adult patients with HER2 positive advanced gastric or GEJ adenocarcinoma
- patients perspectives gathered by patient group, My Gut Feeling – Stomach Cancer Foundation of Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 of clinical specialists with expertise diagnosing and treating patients with gastric or GEJ cancers
- input from 2 clinician groups, including the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) and Ontario Health – Cancer Care Ontario Gastrointestinal Drug Advisory Committee (OH-CCO GI DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Patient group input was submitted by one patient advocacy group, My Gut Feeling – Stomach Cancer Foundation of Canada, and included input collected from an international online survey conducted between November 10 and November 24, 2023. The survey included responses from 40 patients (77.5%) and caregivers (22.5%). Of those who responded, 72.5% were from Canada and 15.5% were HER2 positive. All patients who responded to survey experienced at least 1 symptom before diagnosis, with most common being weight loss (57.5%), reflux (55%), change in appetite (50%), pain (47.5%), nausea/vomiting (37.5%), and difficulty swallowing (25%). Most patients (95%) reported that their cancer diagnosis had a significant impact on their QoL, physical and mental health, ability to eat and work, finances, social life, identity, and personal image. Psychosocial impacts such as anxiety, depression, sleep loss, feeling crippled, anticipatory grief, and loss of control were cited by one patient. Caregivers and family members who responded to the survey also reported being impacted by the cancer diagnosis which included feeling hopeless (especially with metastatic disease), stress from the impact of chemotherapy-induced side effects causing stress on other family, and changes to family dynamics that require counselling for children. Other disease- or treatment-related concerns reported by both the patients and caregivers included loss of fertility, feeling isolated, financial difficulty, as well as financial and geographical barriers to accessing treatment, healthcare providers, and information. All patients who completed the survey experienced at least 1 side effect. The most commonly reported treatment-related side effects included fatigue (87.5%), appetite changes (77.5%), alopecia and taste changes (75% each), weight loss and neuropathy (70% each). Approximately 16% of patients reported discontinuing treatment due to an adverse event resulting in hospitalization. Patients and caregivers who completed the survey indicated that the following

outcomes were important in considering new treatments: improved survival, remission, shrinking of cancer, improved symptoms, treatment tolerability, and improved QoL. Patients and caregivers also added that equitable access, convenience of administration (e.g., oral vs. IV, less frequent travel to hospital, shorter chair time to receive treatment), more options from which to choose based on their values and preferences were important. Finally, survey responders from Canada emphasized that biomarker testing should be accessible at the onset of their disease across all centers and provinces.

Clinician Input

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

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for the purpose of this review emphasized that locally advanced and metastatic HER2 positive gastroesophageal cancer is a disease associated with a considerable unmet need. The clinical experts advised that although treatment with trastuzumab combined with chemotherapy is available for locally advanced metastatic HER2 positive gastroesophageal cancer; OS outcomes remain unacceptably poor. Both clinical experts suggested that as per the KEYNOTE-811 clinical trial, pembrolizumab would be added to the current SOC first-line therapy (trastuzumab combined with platinum doublet chemotherapy) for patients with locally advanced and metastatic HER2 positive gastroesophageal cancer. This combination – pembrolizumab combined with trastuzumab and platinum doublet chemotherapy – would represent a new first-line SOC treatment for this patient population. Although patients were eligible to enroll in the KEYNOTE-811 trial regardless of PD-L1 status as measured by CPS, the prespecified subgroup analysis showed that the benefit of adding pembrolizumab to SOC was attributable to the subgroup of patients with PD-L1 CPS of 1 or more (85% of the study population). A clear benefit was not observed in the subgroup of patients with PD-L1 CPS of less than 1, which included a small number of patients. The clinical experts consulted by CADTH opined that the addition of pembrolizumab to first-line treatment for locally advanced and metastatic HER2 positive gastroesophageal cancer should be limited to patients with a PD-L1 CPS of 1 or more. As suggested by the clinical experts, CPS testing should be performed using a validated test. The clinical experts listed three factors, in descending order of clinical importance, used to determine response to treatment: patient reported symptoms and side-effects; cross-sectional imaging via CT scans or MRI; and tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (Ca 19-9). The clinical experts emphasized; however, that the only truly clinically meaningful end points across all oncology types are overall survival and quality of life. The clinical experts added that all other endpoints (e.g., response rate, CEA response, progression-free survival) should be considered surrogates, and are of little relevance if they do not predict improve overall survival or quality of life. The clinical experts suggest that patients should be assessed by a clinician after every 2 to 3 cycles of treatment. The clinical experts suggested that patients should undergo CT scans every 2 to 3 months and that tumour markers should be assessed at least once every 4 weeks. The clinical experts suggested that the decision to discontinue treatment with pembrolizumab should be based on patient reported symptoms, side-effects and well-being, in combination with assessment of treatment response and disease progression, either radiologic or clinical. The clinical experts added that treatment with pembrolizumab should be discontinued in the event of a life-threatening immune-related AEs in accordance with clinical practice guidelines. The clinical experts suggests that pembrolizumab should only be prescribed by or under the supervision of a specialist in medical oncology with expertise in the management of immunotherapy side-effects. The clinical experts noted that immunotherapy and trastuzumab are currently delivered as SOC in all oncology centres and may be safely administered in all centres approved for oncology care.

Clinician Group Input

Clinician group input was submitted by two clinician groups – CGOEN and OH-CCO GI DAC. Input provided by the CGOEN and the OH-CCO GI DAC collated insights from 8 and 2 clinicians, respectively. The clinical groups noted that the are currently limited treatment options for patients with HER2 positive gastric or GEJ cancers, with poor outcomes. The clinician from CGOEN noted that the treatment of HER2 positive gastric cancer has not improved in more than a decade and that immunotherapy is currently only available for patients who are HER2-negative. Based on the input from the OH-CCO GI DAC, the prolonging of OS is the main treatment goal for this patient population. According to input from the CGOEN, patients best suited for treatment with pembrolizumab are those with a PD-L1 CPS of 1 or more as determined by a validated test. Based on input from the CGOEN, response to treatment should be based on routine imaging (during timed intervals for objective assessment), as well as patient preference, tolerability, and

quality of life. Both clinician groups suggested that patients should be evaluated on a regular basis for clinical response and toxicity per current treatment standards. Both clinician groups agreed that the decision to continue or discontinue treatment with pembrolizumab should be based on patient preference, side-effects (including life-threatening immune-related adverse event), radiologic or clinical disease progression or treatment response, and patient reported symptoms and well-being. While input from the CGOEN suggested that said pembrolizumab should be administered in oncology centers, the clinical experts consulted by CADTH noted that pembrolizumab could be safely administered in a hospital or an outpatient clinic.

Drug Program Input

The clinical experts consulted by CADTH 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	
The most used regimens for this patient population are: trastuzumab in combination with cisplatin plus fluoropyrimidine (infusion with 5-FU or capecitabine). Other regimens used in combination with trastuzumab include FOLFOX, CAPOX or carboplatin with fluoropyrimidine). The comparator in the study (trastuzumab plus cisplatin/5-FU or CAPOX) is funded in most provinces as a first line option. Can the trial results be generalized to other first line platinum + fluoropyrimidine-based chemotherapy combination (e.g. FOLFOX, carboplatin + fluoropyrimidine)?	pERC agreed with the clinical experts that the trial results from KEYNOTE-811 could be generalized to other platinum-containing first line chemotherapy combinations.
Considerations for initiation of therapy	
PAG would like to confirm that HER2 positive means HER2 3+ on IHC or HER2 2+ on IHC but positive on FISH.	The clinical experts confirmed that HER2 positive cancer is indicated as either: • IHC 3+ or • IHC 2+ in combination with a positive ISH or FISH as applied in the KEYNOTE-811 study.
Currently patients without HER2 overexpression who receive nivolumab in the adjuvant setting (esophageal or GEJ) are eligible for downstream PD-1/PD-L1 inhibitors provided that disease recurrence occurs more than 6 months from the last dose of adjuvant PD-1 or PD-L1 inhibitors. Can the patients who receive nivolumab in the adjuvant setting, and in whom recurrence occurs more than 6 months from the last dose of adjuvant nivolumab, be eligible to receive pembrolizumab in the first line metastatic setting?	pERC agreed with the clinical experts that patients with HER2 positive gastric or GEJ adenocarcinoma who receive nivolumab in the adjuvant setting, can be considered eligible to receive pembrolizumab in the first line advanced or metastatic setting, if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy with nivolumab.
The requested duration of treatment for pembrolizumab is until disease progression, unacceptable toxicity or up to 24 months (35 cycles at every 3 weeks), whichever is longer, in patients without disease progression. • If pembrolizumab is discontinued for reasons other than disease progression or intolerability after the initial 24 months of treatment, are patients eligible for an additional	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.

Implementation issues	Response
12 months of treatment at the time of disease recurrence, similar to other indications for pembrolizumab? • Should retreatment consist of pembrolizumab monotherapy or pembrolizumab plus trastuzumab or pembrolizumab plus trastuzumab and chemotherapy?	The clinical experts noted that retreatment 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.
Should patients with CNS metastases be eligible for pembrolizumab plus trastuzumab and chemotherapy?	pERC agreed with the clinical experts that patients with stable CNS metastases should be eligible for treatment with pembrolizumab in combination with trastuzumab and chemotherapy, as per the KEYNOTE-811 eligibility criteria in which patients with previously treated brain metastases were allowed to participate in the trial provided they were radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging performed during study screening), and clinically stable, without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
Considerations for discontinuation of therapy	
If there is disease progression during a treatment break, can pembrolizumab and trastuzumab therapy be resumed?	pERC agreed with the clinical expert that therapy with pembrolizumab may be resumed at the discretion of the treating physician for patients who stopped pembrolizumab before any disease progression, and if disease progression occurred during the treatment break.
If a patient cannot tolerate one of the components of the treatment (i.e., pembrolizumab, trastuzumab or chemotherapy) are they able to continue with remaining components?	In the KEYNOTE-811 trial patients were allowed discontinue 1 or more components of the study treatment in case of serious adverse events and continue the other components. The clinical experts noted that, if a patient cannot tolerate one of the components of treatment (i.e., pembrolizumab, trastuzumab or chemotherapy), the decision to continue treatment with the remaining components should be based on the discretion of the treating physician. pERC agreed with the clinical experts.
Is there a minimum number of chemotherapy cycles and trastuzumab that must be given concurrently with pembrolizumab?	pERC agreed with the clinical experts that patients should undergo at least 1 cycle of chemotherapy and trastuzumab concurrently with pembrolizumab.
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 programs to inform pERC deliberations
Generalizability	
The populations of interest match the indication but with insufficient data. • Are the data generalizable to patients with esophageal adenocarcinoma? (Some/most provinces currently fund trastuzumab-fluoropyrimidine-platinum for gastric, GEJ, and esophageal adenocarcinoma)	pERC agreed with the clinical experts that results from the KEYNOTE-811 trial could be generalized to patients with esophageal adenocarcinomas that are HER2 positive. The clinical experts noted that, and that generalizing results patients with gastric or GEJ adenocarcinoma to patients with esophageal adenocarcinoma has been done for other treatments, such as trastuzumab and trifluridine-tipiracil.

Implementation issues	Response
• KEYNOTE-811 eligibility criteria included ECOG PS 0 or 1. Should patients with ECOG performance status of 2 or greater be eligible?	pERC agreed with the clinical experts that patients with an ECOG PS score status of 2 or greater may be considered for treatment in selected cases, at the discretion of the treating physician.
• KEYNOTE-811 enrolled patients with gastric or GEJ adenocarcinoma. Are the study results generalizable to squamous cell histology?	The clinical experts did not consider the KEYNOTE-811 trial results to be generalizable to patients with squamous cell histology. pERC was unable to comment as the committee did not review any evidence to support treatment with pembrolizumab plus SOC in patients with squamous cell gastric or GEJ cancers.
• Are the study results generalizable to Siewert types I, II and III adenocarcinomas?	pERC agreed with the clinical experts that the results from KEYNOTE-811 are generalizable to patients with Siewart types I, II and III and esophageal adenocarcinomas that are HER2 positive.
• Can biosimilar trastuzumab be used?	pERC agreed that biosimilar trastuzumab may be used in combination with pembrolizumab.
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? For patients who initiate chemotherapy, can pembrolizumab and trastuzumab be added once HER2 positivity and PD-L1 CPS ≥ 1 are confirmed?	pERC agreed with the clinical experts that addition of pembrolizumab to current SOC treatment regimen is appropriate for those who are currently on platinum- plus fluoropyrimidine-based chemotherapy. pERC agreed with the clinical experts that, for patients who have already initiated chemotherapy, pembrolizumab and trastuzumab can be added to the treatment regimen once HER2 positive and PD-L1 CPS status is confirmed.
Funding algorithm	
Consideration should be given to updating existing algorithm to include HER2+ disease	Comment from the drug programs to inform pERC deliberations
Care provision issues	
PD-L1 CPS testing needs to be operationalized and funded in some jurisdictions on or before pembrolizumab implementation.	Comment from the drug programs to inform pERC deliberations
System and economic issues	
Trastuzumab biosimilars have confidential net prices.	Comment from the drug programs to inform pERC deliberations
Trastuzumab in this combination will be a biosimilar trastuzumab.	Comment from the drug programs to inform pERC deliberations

5-FU = Fluorouracil; CAPOX = Capecitabine + oxaliplatin; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in situ hybridization; FOLFOX = Fluorouracil + leucovorin + oxaliplatin; GEJ = Gastroesophageal junction; HER2 = Human epidermal growth factor receptor 2; IHC = Immunohistochemistry; pERC = pan-Canadian Oncology Drug Review expert review committee; PD-L1 = Programmed cell death-ligand 1; PS = performance status

Clinical Evidence

Systematic Review

Description of Studies

One study was included in the sponsor-conducted systematic review: KEYNOTE-811.

KEYNOTE-811 is an on-going multicenter (92 sites across 19 countries), placebo-controlled, randomized (1:1 ratio), double-blind, phase III study evaluating the efficacy and safety of adding pembrolizumab (200 mg every 3 weeks) to SOC therapy with

trastuzumab and platinum-fluoropyrimidine doublet chemotherapy as first-line therapy for HER2-positive advanced gastric or GEJ cancer in adult patients. Patients were randomly allocated to receive either pembrolizumab (full study population n = 350; PD-L1 CPS ≥1 subgroup n = 298) or placebo (full study population n = 348; PD-L1 CPS ≥ 1 subgroup n = 296) each in combination with SOC therapy (trastuzumab in combination with cisplatin/5-FU [FP] or capecitabine/oxaliplatin [CAPOX]). Randomization was stratified by geographic region (Australia, Europe, Israel, and North America vs. Asia vs. rest of the world), investigator's choice of chemotherapy regimen (FP vs. CAPOX), and PD-L1 expression at baseline (CPS ≥ 1 vs. < 1). HER2 status and PD-L1 expression were determined by FDA approved assays, and were conducted at a central laboratory. KEYNOTE-811 assessed progression-free survival (PFS) per RECIST 1.1 assess by Blinded Independent Central Review (BICR) and overall survival (OS) as dual primary efficacy endpoints, in which the study success is claimed if a statistically significant analysis results are demonstrated for at least one of the two primary end points. Secondary end points included overall response rate (ORR) and duration of response per RECIST 1.1, and harms. Exploratory end points included the following health-related quality of life (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.

KEYNOTE-811 met the protocol defined criterion of success (1-sided alpha-level testing 0.0013) at the second interim analysis (IA2; data cut-off date May 25, 2022) in which the stratified hazard ratio (HR) for PFS was 0.72 (95% CI, 0.60 to 0.87; p = 0.0002) in favour of pembrolizumab plus SOC (median, 10.0 months; 95% CI 8.6 to 11.7 months) versus placebo plus SOC (median, 8.1 months; 95% CI, 7.0 to 8.5 months). Pre-specified subgroup analysis noted that the treatment effect of pembrolizumab plus SOC on PFS compared to placebo plus SOC was attributable to the PD-L1 CPS of 1 or more 1 subgroup, who made up 85.1% of the total population. A clear benefit was not observed in the subgroup of patients with PD-L1 CPS of less than 1, which included relatively few patients. Among patients with PD-L1 CPS of 1 or more (hereafter referred to as the subgroup of patients who have PD-L1 positive disease), PFS was statistically longer in the pembrolizumab plus SOC group than in placebo plus SOC group (HR, 0.70; 95% CI, 0.58 to 0.85). Based on analyses conducted at IA2, the sponsor proposed that the indication population be limited to patients who had the subgroup of patients who have PD-L1 positive disease. Accordingly, this CADTH review of KEYNOTE-811 will present data from both the full study population and the subgroup of patients who had PD-L1 positive disease as per the Health Canada indication.

The mean age of all patients enrolled in KEYNOTE-811 was 60.4 years (SD, 11.8 years) and 61.7 years (SD, 10.8) in the pembrolizumab plus SOC and placebo plus SOC group, respectively. PD-L1 positive disease was documented in 85.1% of patients in both the pembrolizumab plus SOC and placebo plus SOC group. Among patients in KEYNOTE-811 who were PD-L1 positive, the mean age of patients randomized to the pembrolizumab plus SOC and placebo plus SOC group were 60.6 (SD, not reported [NR]) and 61.4 (SD, NR) years, respectively. In terms of disease characteristics of the study participants with PD-L1 positive disease, 32.6% of patients in the pembrolizumab plus SOC group presented with adenocarcinoma of the GEJ and 67.4% presented with adenocarcinoma of the stomach; in the placebo plus SOC group, 33.4% and 66.6% of patients presented with adenocarcinoma of the GEJ and stomach, respectively.

Efficacy Results

Overall Survival

Full study population

The median duration of follow-up in the full study population at IA2 (data cut-off May 25, 2022) was 16.1 months (range, 0.6 to 41.6 months) and 14.8 months (range 0.3 to 41.2 months) in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The median duration of follow-up at the time of the third interim analysis (IA3; data cut-off March 29, 2023) was not reported for the full study population.

In KEYNOTE-811, the proportion of observed death at the time of IA3 (March 29, 2023) was 70.0% and 73.6% in the pembrolizumab plus SOC and placebo plus SOC groups, respectively. The median OS was 20.0 months (95% CI, 17.8 to 22.1 months) in the pembrolizumab plus SOC group and 16.8 months (95% CI, 15.0 to 18.7 months) in the placebo plus SOC group. The stratified HR for OS was 0.84 (95% CI, 0.70 to 1.01; p = 0.0292) following treatment with pembrolizumab plus SOC versus placebo plus SOC. Risk difference in OS in the full study population following treatment with pembrolizumab plus SOC when compared to placebo plus SOC at months 12, 18 and 36 were [redacted] respectively

PD-L1 positive subgroup

The median duration of follow-up in the PD-L1 positive subgroup at IA2 was 17.0 months (range, 0.6 to 41.6) and 13.9 months (range, 0.3 to 41.2 months) in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The median duration of follow-up at the time of IA3 was not reported for the PD-L1 positive subgroup.

Among patients in the PD-L1 positive subgroup, the proportion of observed death at the time of IA3 (March 29, 2023) was 68.5% and 73.6% in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The median OS was 20.0 months (95% CI, 17.9 to 22.7 months) in the pembrolizumab plus SOC group and 15.7 months (95% CI, 13.5 to 18.5 months) in the placebo plus SOC group. The HR for OS was 0.81 (95% CI, 0.67 to 0.98; p = 0.0142) in favour of treatment with pembrolizumab plus SOC versus placebo plus SOC. Risk difference in OS in the PD-L1 positive subgroup following treatment with pembrolizumab plus SOC when compared to placebo plus SOC at months 12, 18 and 36 were [redacted] respectively.

Progression-free survival

Full study population

In KEYNOTE-811, the protocol defined criterion of success was met at IA2 with 80% of the total events expected for the analysis (information fraction) having accrued (data cut-off date May 25, 2022). The stratified HR for PFS was 0.72 (95% CI, 0.60 to 0.87; p = 0.0002; 1-sided superiority boundary was p = 0.0013) in favour of pembrolizumab plus SOC. The stratified HR for PFS based on BICR assessment from sensitivity analyses 1, 2 and 3 using alternative censoring rules were 0.74 (95% CI, 0.62 to 0.88; p = 0.0003), 0.74 (95% CI, 0.62 to 0.87; p = 0.0001) and 0.73 (95% CI, 0.61 to 0.87; p = 0.0003), respectively.

Disease progression or death on or before the IA3 data cut-off date (March 29, 2023) was observed in 72.3% of patients in the pembrolizumab plus SOC group and in 75.0% of patients in the placebo plus SOC group. The median PFS in the pembrolizumab plus SOC and placebo plus SOC group was 10.0 months (95% CI, 8.6 to 12.2 months) and 8.1 months (95% CI, 7.1 to 8.6 months), respectively. The stratified HR for disease progression or death was 0.73 (95% CI, 0.61 to 0.87, p = 0.0002) in favour of pembrolizumab plus SOC versus placebo plus SOC. Risk difference in PFS in the full study population following treatment with pembrolizumab plus SOC when compared to placebo plus SOC at months 12, 18 and 36 were [redacted] respectively.

PD-L1 positive subgroup

Among patients in the PD-L1 positive subgroup, disease progression or death on or before the data cut-off date (March 29, 2023) was observed in 72.8% of patients in the pembrolizumab plus SOC group and in 76.0% of patients in the placebo plus SOC group. The median PFS in the pembrolizumab plus SOC and placebo plus SOC group was 10.9 months (95% CI, 8.5 to 12.5 months) and 7.3 months (95% CI, 6.8 to 8.5 months), respectively. The HR for disease progression or death was 0.71 (95% CI, 0.59 to 0.86, p = 0.0002) in favour of pembrolizumab plus SOC versus placebo plus SOC. Risk difference in PFS in the PD-L1 positive subgroup following treatment with pembrolizumab plus SOC when compared to placebo plus SOC at months 12, 18 and 36 were [redacted] respectively.

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 quality of life. Based on input from the clinical experts consulted by CADTH, global health, physical functioning and appetite loss were scale items most relevant to patients with gastroesophageal cancers. Scores for each scale and item ranged from 0 to 100 with higher scores indicative of greater quality of life, greater physical functioning or a greater degree of symptoms. Improvement and deterioration were defined as change of 10 or more points in the relevant direction.

Full study population

In KEYNOTE-811, analysis of the EORTC QLQ-C30 in the full study population was based on IA2 (data cut-off date May 25, 2022). Overall, baseline EORTC QLQ-C30 was completed by 320 (92.8%) patients in the pembrolizumab plus SOC group and 339 (99.7%) patients in the placebo plus SOC group. By week 24, 231 (67.0%) of the available 265 (76.8%) of patients in the pembrolizumab plus SOC group completed the questionnaire for a compliance rate of 87.2%. In the placebo plus SOC group, 190 (55.9%) of the available 235 (69.1%) patients completed the questionnaire for a compliance rate of 80.9%.

In the full study population, the between group difference in least square mean change from baseline to week 24 for global health status was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement in global health status was reported in 31.6% and 31.8% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in global health status was reported in 71.9% and 71.5% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. The stratified HR for time to deterioration on the global heath status scale at 12 months was 1.14 (95% CI, 0.84 to 1.55; p = 0.3951) for pembrolizumab plus SOC relative to placebo plus SOC.

For physical function, the between group difference in least square change from baseline to week 24 was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement in physical function was reported in 14.8% and 15.9% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in physical function was reported in 73.0% and 72.4% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. The stratified HR for time to deterioration on the physical function scale at 12 months was 1.05 (95% CI, 0.78 to 1.47; p = 0.7663) for pembrolizumab plus SOC relative to placebo plus SOC.

For the single item appetite loss, the between group difference in least square change from baseline to week 24 was [redacted]. Improvement in appetite loss was reported in 32.5% and 26.6% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in appetite loss was reported in 77.4% and 72.6% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. The stratified HR for time to deterioration on the single item appetite loss at 12 months was 1.18 (95% CI, 0.87 to 1.60; p = 0.2898) for pembrolizumab plus SOC relative to placebo plus SOC.

PD-L1 positive subgroup

Among patients in the PD-L1 positive subgroup, analysis of the EORTC QLQ-C30 was based on IA3 (data cut-off date March 29, 2023). Baseline EORTC QLQ-C30 was completed by 272 (93.5%) patients in the pembrolizumab plus SOC group and 274 (95.8%) patients in the SOC group. The number of patients available for completing the measure diminished over time. By week 24, 223 (76.6%) patients were available in the pembrolizumab plus SOC group; of those 196 (67.0%) patients completed the questionnaire for a compliance rate of 87.4%. In the placebo plus SOC group, 151 (52.8%) of the available 192 (67.1%) patients completed the questionnaire for a compliance rate of 78.6%.

In the PD-L1 positive subgroup, the between group difference in least square mean change from baseline to week 24 for global health status was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement in global health status was reported in 31.6% and 32.5% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in global health status was reported in 71.5% and 71.0% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus

SOC. The HR for time to deterioration on the global heath status scale at 12 months was 1.16 (95% CI, 0.83 to 1.61; p = 0.3756) for pembrolizumab plus SOC relative to placebo plus SOC.

For physical functioning, the between group difference in least square change from baseline to week 24 was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement in physical functioning was reported in 15.1% and 17.5% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in physical functioning was reported in 74.9% and 71.7% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. The HR for time to deterioration on the physical functioning scale at 12 months was 0.99 (95% CI, 0.72 to 1.38; p = 0.9615) for pembrolizumab plus SOC relative to placebo plus SOC.

For the single item appetite loss, the between group difference in least square change from baseline to week 24 was not reported. Improvement in appetite loss was reported in 32.6% and 28.3% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in appetite loss was reported in 78.0% and 72.4% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. The HR for time to deterioration on the single item appetite loss at 12 months was 1.23 (95% CI, 0.88 to 1.70; p = 0.2344) for pembrolizumab plus SOC relative to placebo plus SOC.

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 GI symptoms (3 items), eating restrictions (5 items), emotional (3 items), dry mouth, hair loss and body image (1 item each). 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 were included in the clinical report as supportive analyses.

Full study population

In KEYNOTE-811, analysis of the EORTC QLQ-ST022 was based IA2 (data cut-off date May 25, 2022). Overall, baseline EORTC QLQ-ST022 was completed by 319 (92.5%) patients in the pembrolizumab plus SOC group and 320 (94.1%) patients in the placebo plus SOC group. The number of patients available for completing the measure diminished over time. By week 24, 229 (66.4%) of the available 265 (76.8%) patients in the pembrolizumab plus SOC group completed the questionnaire for a compliance rate of 86.4%. In the placebo plus SOC group, 190 (55.9%) of the available 235 (69.1%) patients completed the questionnaire for a compliance rate of 80.9%.

In the full study population, the between group difference in least square mean change from baseline to week 24 on the pain symptom scale of the EORTC QLQ-ST022 was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement in pain symptoms was reported in 40.0% and 32.1% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] favouring treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in pain was reported in 82.0% and 78.2% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. Deterioration on the pain symptom scale was recorded in 11.3% and 10.6% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The stratified HR for time to deterioration on the pain symptom scale at 12 months was 0.99 (95% CI, 0.62 to 1.58; p = 0.9681) for pembrolizumab plus SOC relative to placebo plus SOC.

PD-L1 positive subgroup

Among patients in the PD-L1 positive subgroup, analysis of the EORTC QLQ-ST022 was based on IA3 (data cut-off date March 29, 2023). Baseline EORT QLQ-ST022 was completed by 271 (93.1%) patients in the pembrolizumab plus SOC group and 273 (95.5%)

patients in the placebo plus SOC group. The number of patients available for completing the measure diminished over time. By week 24, 193 (66.3%) of the available 223 (76.6%) patients in the pembrolizumab plus SOC group completed the questionnaire for a compliance rate of 86.5%. In the placebo plus SOC group, 152 (79.2%) of the available 192 (67.1%) patients completed the questionnaire for a compliance rate of 79.2%.

In the PD-L1 positive subgroup, the between group difference in least square mean change from baseline to week 24 for pain symptom scale of the EORTC QLQ-ST022 was not reported. Improvement in pain symptoms was reported in 40.2% and 32.9% of patients in the pembrolizumab plus SOC and standard care group, respectively. The between group difference in improvement was [redacted] following treatment with pembrolizumab plus SOC versus placebo plus SOC. Improvement or stability in pain was reported in 83.2% and 78.3% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The between group difference in improvement or stability was [redacted] following treatment with pembrolizumab plus SOC compared to placebo plus SOC. Deterioration on the pain symptom scale was recorded in 11.4% and 10.6% of patients in the pembrolizumab plus SOC and placebo plus SOC group, respectively. The HR for time to deterioration on the pain symptom scale at 12 months was 1.00 (95% CI, 0.60 to 1.66; p = 0.9943) for pembrolizumab plus SOC relative to placebo plus SOC.

Harms Results

Adverse Events

Full study population

In KEYNOTE-811, at least 1 AE was reported by 99.4% and 100% of patients in the pembrolizumab plus SOC group and the placebo plus SOC group, respectively. Among patients randomized to receive pembrolizumab plus SOC, the 5 most common reported AEs were diarrhoea (52.6%), nausea (48.3%), anaemia (45.4%), vomiting (33.1%), and decreased appetite (32.3%). In the placebo plus SOC group, the 5 most common reported AEs were nausea (48.3%), diarrhoea (47.1%), anaemia (46.2%), decreased appetite (32.4%) and vomiting (28.6%).

In the full study population, AEs that were classified as Grade 3 or higher were reported in 71.7% of patients in the pembrolizumab plus SOC group and in 65.9% of patients in the placebo plus SOC group. The most common AEs that were classified as Grade 3 or higher (reported in more than 5% of patients) in the pembrolizumab plus SOC group were anemia (12.6%), diarrhea (9.7%), decreased neutrophil count (8.3%), neutropenia (6.6%), decreased platelet count (6.3%) and hypokalemia (5.7%). The most common AEs that were classified as Grade 3 or higher (reported in more than 5% of patients) in the placebo plus SOC group were anemia (10.1%), decreased neutrophil count (8.7%), diarrhea (8.4%), decreased platelet count (6.9%), hypokalemia (5.8%), nausea (5.5%), and neutropenia (5.2%),

PD-L1 positive subgroup

Among patients in the PD-L1 positive subgroup, at least 1 AE was reported by 99.3% and 100% of patients in the pembrolizumab plus SOC group and the placebo plus SOC group, respectively. Among patients who were PD-L1 positive and randomized to receive pembrolizumab plus SOC, the 5 most common reported AEs were diarrhoea (53.7%), nausea (50.7%), anaemia (46.3%), vomiting (35.2%), and decreased appetite (33.2%). In the placebo plus SOC group, the 5 most common reported AEs were nausea (48.5%), diarrhoea (46.8.1%), anaemia (46.8%), vomiting (30.5%) and decreased appetite (30.2%).

In the PD-L1 positive subgroup, AEs that were classified as Grade 3 or higher were reported in 73.8% of patients in the pembrolizumab plus SOC group and in 65.8% of patients in the placebo plus SOC group. The most common AEs that were classified as Grade 3 or higher (reported in more than 5% of patients) in the pembrolizumab plus SOC group were anemia (12.8%), diarrhea (10.7%), decreased neutrophil count (8.4%), neutropenia (7.7%), decreased platelet count (7.4%) and hypokalemia (6.0%). The most common AEs that were classified as Grade 3 or higher (reported in more than 5% of patients) in the placebo plus SOC group were anemia (10.2%), decreased neutrophil count (9.2%), diarrhea (8.5%), decreased platelet count (5.8%), and nausea (5.8%)

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.

Full study population

In the full study population, at least 1 serious AE was reported in 46.0% of patients in each the pembrolizumab plus SOC group, and in the group of patients who received placebo plus SOC. In the pembrolizumab plus SOC group, the following SAEs were reported in more than 2% of patients: pneumonia (5.1%), diarrhea (4.9%), and pulmonary embolism (2.9%). In the placebo plus SOC group, the following SAEs were reported in more than 2% of patients: diarrhea (4.6%) and vomiting (2.6%).

PD-L1 positive subgroup

In the PD-L1 positive subgroup, at least 1 serious AE was reported in 48.0% and 47.8% of patients in each the pembrolizumab plus SOC group, and placebo plus SOC group, respectively. Details of incident SAEs were not reported by the sponsor.

Withdrawals of Treatment Due to Adverse Events

Full study population

In the full study population, treatment with any of the study drugs was stopped in 41.4% and 38.4% of patients in the pembrolizumab plus SOC and the SOC group, respectively. In the pembrolizumab plus SOC group, pembrolizumab, trastuzumab and any chemotherapy were discontinued due to AEs in 13.1%, 13.1%, 38.9% of patients, respectively. In the placebo plus SOC group, placebo, trastuzumab and chemotherapy were discontinued in 10.7%, 9.2% and 38.2% of patients, respectively. Overall, 6.3% of patients in the pembrolizumab plus SOC group and 6.9% of patients in the SOC group discontinued all drugs in the regimen.

PD-L1 positive subgroup

In the PD-L1 positive subgroup, treatment with any of the study drugs was stopped in 42.6% and 36.6% of patients in the pembrolizumab plus SOC and the SOC group, respectively. In the pembrolizumab plus SOC group, pembrolizumab, trastuzumab and any chemotherapy were discontinued due to AEs in 14.1%, 14.1%, 40.3% of patients, respectively. In the placebo plus SOC group, placebo, trastuzumab and chemotherapy were discontinued in 11.5%, 10.5% and 36.3% of patients, respectively. Overall, 6.7% of patients in the pembrolizumab plus SOC group and 7.8% of patients in the placebo plus SOC group discontinued all drugs in the regimen.

Mortality

Full study population

In the full study population, death due to adverse events were documented in 6.6% of patients who received pembrolizumab plus SOC group and in 6.1% of patients who received placebo plus SOC.

PD-L1 positive subgroup

In the PD-L1 positive subgroup, death due to adverse events were documented in 6.7% of patients who received pembrolizumab plus SOC group and in 6.8% of patients who received placebo plus SOC.

Notable Harms

Immune-mediated adverse events were of interest to the CADTH clinical review team.

Full study population

In the full study population, at least 1 immune-mediated AE were documented in [redacted] of patients who received pembrolizumab plus SOC and placebo plus SOC, respectively. Grade 3 or worse immune-mediated AEs were reported in [redacted] of patients in the pembrolizumab plus SOC group and in [redacted] of patients in the placebo plus SOC group.

PD-L1 positive subgroup

In the full study population, at least 1 immune-mediated AE were documented in [redacted] of patients who received pembrolizumab plus SOC and placebo plus SOC, respectively. Grade 3 or worse immune-mediated AEs were reported in [redacted] of patients in the pembrolizumab plus SOC group and in [redacted] of patients in the placebo plus SOC group.

Critical Appraisal

KEYNOTE-811 is a randomized, placebo-controlled, parallel-group, multicentre, double-blinded phase III study. Patients were randomized centrally using interactive response technology, which is typically adequate for concealing allocation until treatment assignment. The stratification factors for randomization appeared appropriate, as they addressed important prognostic factors identified by the clinical experts consulted by CADTH; and the baseline characteristics between the treatment groups were generally well balanced. Of note, since PD-L1 status (CPS ≥ 1 versus CPS < 1) was a stratification factor, the CADTH review team assumed that the randomization and prognostic balance hold in this subgroup of interest. In both the full study population and PDL1 positive subgroup between group imbalances were noted in the concomitant use of loperamide and unspecified herbal and traditional medicine. However, according to the clinical experts consulted by CADTH for the purpose of this review, the use of loperamide or unspecified herbal and traditional medicine is not likely to lead to any meaningful impact on treatment response. In the PD-L1 positive subgroup, a greater proportion of patients who received placebo plus SOC received subsequent therapy relative to the pembrolizumab plus SOC group. Given that the reasons for treatment discontinuation was primarily disease progression and AE (which were similar in proportion between the intervention groups), risk of unblinding driving the use of subsequent therapies appeared to be low.

The dual primary outcomes in the KEYNOTE-811 trial were PFS and OS. An appropriate analysis set (intention-to-treat) was used to measure the effect of treatment on OS and PFS. To minimize risk of measurement bias, the study investigators were masked to patients' responses to treatment, and tumour response was confirmed by radiologic evidence and based on BICR as per RECIST 1.1 objective criteria. Sensitivity analysis of PFS demonstrated consistency between the BICR and investigator's assessment of tumour response, suggesting that the procedures employed to minimize bias associated with knowledge of group assignment were adequate. OS is considered an objective outcome, and it not prone to bias due to knowledge of group assignment. 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. KEYNOTE-811 assessed HRQoL – outcomes deemed important by patients and clinicians – as exploratory outcomes. The double-blind nature of the trial minimized risk of bias in the measurement of the subjective items on the EORTC QLQ-30 and EROTC QLQ-ST022. However, comparative efficacy conclusions based on HRQoL outcomes are limited due to the diminishing number of patients available for completion of the questionnaires. The results pertaining to HRQoL are at risk of attrition bias. Finally, since the completion rates were not balanced between the group, there is also a risk that attrition bias may favour one of the treatment groups over the other. The extent and direction of the bias; however, cannot be determined since it is not clear if those patients who completed the questionnaires were systematically different from those who did not.

Analysis of efficacy results followed a defined statistical plan and employed appropriate censoring criteria. There was adequate control for multiplicity (type 1 error) across the dual efficacy endpoints of PFS and OS and interim analyses in the full study population using a hierarchical testing procedure. Both PFS and OS were modeled using a proportional hazards assumption. Although the proportional hazards assumption underlying the HRs for OS and PFS was not tested, based on visual inspection, the curves appeared to be relatively parallel. The choice to limit treatment with pembrolizumab plus SOC to patients who have PD-L1 positive disease, was based on subgroup analysis. Although the subgroup analyses were pre-specified, they were absent from the statical testing hierarchy. While this presents a risk of type 1 error (i.e., falsely excluding the null), the subgroup of patients who were determined to be PD-L1 positive represented approximately 85% of the full study population. The results observed in the full study population appeared to be driven by the PD-L1 positive subgroup; qualitatively, the results of the full population and PD-L1 positive subgroup were similar. Finally, results were based on interim analyses, which may have overestimated the treatment effect estimates. However, given the relatively large sample size and number of events with a 75% information fraction, the effect estimate and confidence are not likely to be highly unstable. Although reassuring, overestimation of the treatment effect 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 and PFS at months 12, 18 and 36.
- HRQoL as measured by the EORTC QLQ-C30 (global quality of life, physical functioning and appetite loss) at week 24.
- 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 CADTH's 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 by CADTH for the purpose of this review, while the presence of absence of an important effect on HRQoL was based on MID estimates identified in the literature. For all other outcomes, the presence or absence for of an important effect was based on the non-null effect.

Results of GRADE Assessment

Error! Reference source not found. Table 3 presents the GRADE summary of findings for pembrolizumab in combination with SOC versus placebo in combination with SOC.

Table 3: Summary of Findings of Pembrolizumab in Combination with Standard of Care versus Saline Placebo in Combination with Standard of Care for Patients with HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma in the PD-L1 CPS ≥ 1 Subgroup

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus SOC	Pembrolizumab plus SOC	Difference		
Overall Survival							
Probability of survival at 12 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	60.8 per 100	69.5 per 100 (63.9 to 74.4 per 100)	[redacted]	Moderate [c]	The addition of pembrolizumab to SOC likely results in a clinically important increase in OS when compared with placebo plus SOC at 12 months.
Probability of survival at 18 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	45.6 per 100	55.7 per 100 (49.9 to 61.1 per 100)	[redacted]	Moderate [c]	The addition of pembrolizumab to SOC likely results in a clinically important increase in OS when compared with placebo plus SOC at 18 months.
Probability of survival at 36 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	24.5 per 100	31.3 per 100 (25.8 to 36.9 per 100)	[redacted]	Moderate [c]	The addition of pembrolizumab to SOC likely results in a clinically important increase in OS when compared with placebo plus SOC at 36 months.
Progression-Free Survival per RECIST v1.1 by BICR							
Probability of progression-free survival at 12 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	33.2 per 100	46.0 per 100 (40.0 to 51.7 per 100)	[redacted]	High [d]	The addition of pembrolizumab to SOC results in an increase in PFS when compared with placebo plus SOC at 12 months. The clinical importance of the increase in unclear.
Probability of progression-free survival at 18 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	20.4 per 100	29.5 per 100 (24.1 to 35.0 per 100)	[redacted]	High [d]	The addition of pembrolizumab to SOC results in an increase in PFS when compared with placebo plus SOC at 18 months. The clinical importance of the increase in unclear.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus SOC	Pembrolizumab plus SOC	Difference		
Probability of progression-free survival at 36 months [a] Median follow-up: NR [b]	594 (1 RCT)	NR	10.3 per 100	18.0 per 100 (13.3 to 23.3 per 100)	[redacted]	High [d]	The addition of pembrolizumab to SOC results in an increase in PFS when compared with placebo plus SOC at 36 months. The clinical importance of the increase in unclear.
Health Related Quality of Life (Scale 0 to 100; greater score indicates greater quality of life, greater functioning or a greater degree of symptoms)							
Change in LS mean EORTC QLQ-C30 global health status/QoL scale from baseline to week 24, points Median follow-up: NR [b]	546 (1 RCT)	NA	2.06 (-0.67 to 4.79)	0.78 (-1.71 to 3.26)	[redacted]	Low [e]	The addition of pembrolizumab to SOC may result in little to no clinically important difference in HRQoL global health at week 24 compared to placebo plus SOC.
Change in LS mean EORTC QLQ-C30 physical functioning scale from baseline to week 24, points Median follow-up: NR [b]	546 (1 RCT)	NA	-2.01 (-4.01 to -0.01)	-2.03 (-3.91 to -0.15)	[redacted]	Low [e]	The addition of pembrolizumab to SOC may result in little to no clinically important difference in physical function at week 24 compared to placebo plus SOC.
Change in LS mean EORTC QLQ-C30 single item appetite loss from baseline to week 24	546 (1 RCT)	NA	NR	NR	NR	NA	Outcome data were not reported by the sponsor.
Harms							
Immune-mediated AEs[a] Median follow-up: NR [b]	593 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	High [f]	The addition of pembrolizumab to SOC results in an increase in immune-mediated AEs when compared with placebo plus

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus SOC	Pembrolizumab plus SOC	Difference		
							SOC. The clinical importance of the increase in unclear.
Grade 3 or worse immune-mediated AEs[a] Median follow-up: NR [b]	593 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Moderate [g]	The addition of pembrolizumab to SOC likely results in an increase in Grade 3 or worse immune-mediated AEs when compared with placebo plus SOC. The clinical importance of the increase in unclear.

BICR = Blinded independent central review; CI = Confidence interval; CPS = Combined positive score; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR = Hazard ratio; IA = Investigator assessed; LS = Least-squares; OS = Overall survival; MID = minimally important difference; NR= not reported; PD-L1 = Programmed death-ligand 1; PFS = Progression free survival; SD = Standard deviation; SOC = Standard of care

[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 IA3 for both the full study population and in the subgroup patients with PD-L1 positive disease was not reported.

[c] -1 level for serious imprecision. The 95% CI is compatible with little to no difference and a clinically important benefit (exceeding the 5 to 10% threshold suggested by the clinical experts consulted by CADTH).

[d] The clinical experts consulted by CADTH 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.

[e] -2 levels for very serious study limitations because of risk of bias due to missing data as results were available to less than 60% of patients by week 24.

[f] The clinical experts consulted by CADTH indicated a lack of clarity about a threshold of clinical importance, therefore the null was employed.

[g] -1 level for serious imprecision. The clinical experts consulted by CADTH indicated a lack of clarity about a threshold of clinical importance, therefore the null was employed. No threshold was crossed but there was a small number of events contributing to the estimated treatment effect.

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: Results based on interim analysis 3 (data cut-off date March 29, 2023)

Source: Clinical Study Report for KEYNOTE-811, Statistical Report KN811 IA3, PRO Report. 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

No indirect treatment comparisons were included in this submission. The sponsor conducted a feasibility assessment of estimating the comparative efficacy and safety of pembrolizumab combined with SOC therapy (trastuzumab in combination with FP or CAPOX) versus other fluoropyrimidine- and platinum- containing chemotherapies used in combination with trastuzumab in Canada, mainly FOLFOX (5-FU plus leucovorin and oxaliplatin) and capecitabine plus cisplatin. The availability of relevant studies to perform an indirect comparison was informed by a systematic literature review. This review located 1 trial (ToGA) within which some patients in one arm received capecitabine plus cisplatin and trastuzumab. However, an indirect comparison was not possible because this arm was pooled with another (5-FU plus cisplatin and trastuzumab) in the analysis. Therefore, an indirect comparison was not deemed possible. A review of the feasibility appraisal by CADTH is in agreement with this conclusion. .

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

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target populations	Adults with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours express PD-L1
Treatment	Pembrolizumab in combination with trastuzumab plus fluoropyrimidine- and platinum- containing chemotherapy[a] (hereafter referred to as pembrolizumab plus trastuzumab and chemotherapy)
Dose regimen	Pembrolizumab: 200 mg IV administered every 3 weeks for up to 35 cycles
Submitted price	Pembrolizumab: $4,400 per 100 mg/4 mL vial
Submitted treatment cost	$8,316 every 3 weeks for pembrolizumab (fixed dose). When used in combination with trastuzumab and chemotherapy, at the sponsor's assumed dose intensities for each drug, the total regimen cost per cycle was $10,324, assuming a fixed dose for pembrolizumab.
Comparator	Trastuzumab plus fluoropyrimidine- and platinum- containing chemotherapy (hereafter referred to as trastuzumab plus chemotherapy)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data source	KEYNOTE-811 trial informed PFS, OS, time on treatment, and health state utility values
Key limitations	• It is uncertain whether pembrolizumab plus trastuzumab and chemotherapy will improve long-term survival (i.e., beyond the observed data). Approximately 93% of the incremental QALYs predicted by the sponsor's model were accrued after the KEYNOTE-811 trial on the basis of extrapolation, and clinical experts consulted by CADTH noted that the survival predicted by the sponsor's model is likely overestimated. • The distribution of subsequent treatments following disease progression used in the sponsor's base case was inconsistent with Canadian clinical practice according to clinical experts consulted by CADTH.

Component	Description
	• 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. • The dosage regimen of pembrolizumab adopted by the sponsor is not aligned with the public drug plan's implementation strategy (i.e., weight-based dosing). Clinical experts consulted by CADTH agreed that a weight-based dosing strategy would be appropriate for this indication.
CADTH reanalysis results	• In the CADTH base case, CADTH adopted KM data for OS and PFS for the trial period and alternative survival models for extrapolation of PFS and OS, alternative subsequent treatment distributions, 100% relative dose intensity, and aged-based health utility decrements. • Results of the CADTH base case suggest that pembrolizumab plus trastuzumab and chemotherapy is more costly (incremental costs: $153,454) and more effective (incremental QALYs: 0.36) than trastuzumab and chemotherapy alone, resulting in an ICER of $425,549 per QALY gained. A price reduction of at least 89% for pembrolizumab would be needed for pembrolizumab plus trastuzumab and chemotherapy to be considered cost-effective at a WTP threshold of $50,000 per QALY gained. • Results of a scenario analysis adopting a weight-based dose for pembrolizumab suggest that that ICER for pembrolizumab plus trastuzumab and chemotherapy would be $297,169 compared with trastuzumab and chemotherapy alone. A price reduction of at least 85% would be required for pembrolizumab plus trastuzumab and chemotherapy to be considered cost-effective at a WTP threshold of $50,000 per QALY gained if a weight-based strategy is adopted.

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; WTP = willingness to pay.
[a] Chemotherapy was assumed by the sponsor to comprise capecitabine and oxaliplatin (CAPOX) plus 5-fluorouracil and cisplatin (CISPFU).

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: Use of RDI to estimate actual drug costs is inappropriate; The proportion of patients eligible to receive pembrolizumab is uncertain; The attribution of market share to "clinical trials" is inappropriate; The market uptake of pembrolizumab may be underestimated; The use of fixed dosing for pembrolizumab is not aligned with the public drug plans' implementation strategy; The distribution of doublet chemotherapy regimens does not align with Canadian clinical practice.

CADTH reanalysis included: assuming 100% RDI for all drugs, removing market share attributed to clinical trials and adopting a distribution of chemotherapies aligned with Canadian clinical practice.

Based on the CADTH base case, the 3-year budget impact is expected to be $38,095,911 (year 1: $1,927,523; year 2: $13,060,487; year 3: $23,107,901) should the public drug plans reimburse pembrolizumab for use in combination with trastuzumab and chemotherapy for the first-line treatment of locally advanced unresectable or metastatic HER2-positive, PD-L1 positive 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: May 8, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None