

## CADTH Reimbursement Recommendation

# Nivolumab (Opdivo)

**Indication:** In combination with fluoropyrimidine- and platinum-containing chemotherapy, for the treatment of adult patients with human epidermal growth factor receptor 2–negative advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

**Sponsor:** Bristol Myers Squibb Canada

**Final recommendation:** Reimburse with conditions

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## What Is the CADTH Reimbursement Recommendation for Opdivo?

CADTH recommends that Opdivo be reimbursed by public drug plans for the first-line treatment of human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic gastric adenocarcinoma (GAC), gastroesophageal junction adenocarcinoma (GEJAC), or esophageal adenocarcinoma (EAC) if certain conditions are met.

### Which Patients Are Eligible for Coverage?

Opdivo should only be covered to treat patients who have not received previous treatment for advanced or metastatic GAC, GEJAC, or EAC, and who have good performance status. The price of Opdivo must be lowered to be cost-effective and affordable.

### What Are the Conditions for Reimbursement?

Opdivo should only be reimbursed if prescribed in combination with fluoropyrimidine- and platinum-containing chemotherapy by a clinician experienced in treating cancer.

### Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that adding Opdivo to fluoropyrimidine- and platinum-containing chemotherapy improved survival.
- Based on public list prices, Opdivo is not considered cost-effective at a willingness to pay (WTP) of \$50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to chemotherapy alone.
- Economic evidence suggests that a 95% price reduction is needed to ensure Opdivo is cost-effective at a \$50,000 per QALY WTP threshold.
- Based on public list prices, the 3-year budget impact is \$198,898,038.

## Additional Information

### What Are GAC, GEJAC, and EAC?

Gastric, gastroesophageal junction, and esophageal cancers are those that occur in the stomach, where the esophagus and stomach join, and in the esophagus, respectively. Most gastric, gastroesophageal junction, and esophageal cancers are adenocarcinomas. There are approximately 6,600 new cases of gastric, gastroesophageal junction, or esophageal cancer every year.

### Unmet Needs in GAC, GEJAC, and EAC

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

### How Much Does Opdivo Cost?

Treatment with Opdivo in combination with fluoropyrimidine- and platinum-containing chemotherapy is expected to cost approximately \$9,833 to \$10,618 per patient per 28 days of treatment.

## Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy be reimbursed for the first-line treatment of adult patients with HER2 negative advanced or metastatic gastric, gastroesophageal junction or esophageal adenocarcinoma only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

Evidence from a phase III, open-label randomized controlled trial (RCT), demonstrated that treatment with nivolumab plus chemotherapy (leucovorin, fluorouracil, and oxaliplatin [FOLFOX], or capecitabine and oxaliplatin [XELOX]) resulted in added clinical benefit over chemotherapy alone in patients with previously untreated, HER2-negative advanced or metastatic GAC, GEJAC, or EAC. The CheckMate-649 trial (N = 1,581) demonstrated that, compared with chemotherapy alone, treatment with nivolumab plus chemotherapy was associated with a statistically significant and clinically meaningful improvement in overall survival (OS) in patients with programmed death-ligand 1 (PD-L1) combined positive score (CPS) of 5 or greater (hazard ratio [HR] = 0.71; 98.4% confidence interval [CI], 0.59 to 0.86;  $P < 0.0001$ ), in patients with a PD-L1 CPS of 1 or greater (HR = 0.77; 99.3% CI, 0.64 to 0.92;  $P < 0.0001$ ), and in all randomized patients regardless of PD-L1 CPS (HR = 0.80; 99.3% CI, 0.68 to 0.94;  $P = 0.0002$ ). Results for progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR) across different PD-L1 cut-offs were supportive of the OS findings. Conclusions on health-related quality of life (HRQoL) outcomes could not be drawn due to the absence of formal statistical testing, the potential for bias in an open-label trial, and the high proportions of missing data, but the results suggested that HRQoL was not worse in the nivolumab plus chemotherapy arm. Although the notable harms associated with nivolumab were appreciable, they were in line with previous experience with nivolumab and considered to be manageable with supportive care. The patient input received for this review indicated that patients need new therapies that prolong survival, reduce risk of disease progression, improve HRQoL, allow for more convenient administration of therapy, and minimize side effects. Given the totality of the evidence, pERC concluded that treatment with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy met some of the needs identified by patients because it prolongs survival and has a manageable safety profile.

Using the sponsor-submitted price for nivolumab plus FOLFOX or XELOX and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for nivolumab plus FOLFOX or XELOX was \$398,312 per QALY when compared with FOLFOX or XELOX. At this incremental cost-effectiveness ratio, nivolumab plus FOLFOX or XELOX is not cost-effective at a \$50,000 per QALY WTP threshold for adult patients with HER2-negative advanced or metastatic GAC, GEJAC, or EAC. A reduction in price of at least 95% is required for nivolumab plus FOLFOX or XELOX to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason
<b>Initiation</b>	
1. Treatment with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy should only be reimbursed in adult patients who have all of the following: <ul style="list-style-type: none"> <li>1.1. Previously untreated, HER2-negative, advanced or metastatic GC, GEJC, or EC with histologically confirmed predominant adenocarcinoma</li> <li>1.2. Good performance status</li> </ul>	<p>Evidence from the CheckMate-649 trial demonstrated that nivolumab plus FOLFOX or XELOX resulted in statistically significant and clinically meaningful benefit in overall survival in patients with previously untreated advanced or metastatic GC, GEJC, or EC with histologically confirmed predominant adenocarcinoma and ECOG Performance Status of 0 or 1. The relevant Health Canada indication for nivolumab specifies that patients must have HER2-negative disease.</p> <p>pERC agreed with the clinical experts that though the magnitude of benefit in patients with ECOG Performance Status of 2 or greater is uncertain, eligibility of these patients should be left to the discretion of the treating clinician.</p>
2. Patients should not have either of the following: <ul style="list-style-type: none"> <li>2.1. a contraindication to immunotherapy</li> <li>2.2. uncontrolled CNS metastases.</li> </ul>	<p>Patients with a contraindication to immunotherapy and patients with untreated CNS metastases were excluded from the CheckMate-649 trial. pERC considered it appropriate to consider patients with controlled CNS metastases for eligibility.</p>
<b>Renewal</b>	
3. Assessment for renewal should be based on clinical and radiographic evaluation every 2 to 4 months.	<p>In the CheckMate-649 trial, tumour response was assessed every 6 weeks for the first 48 weeks, followed by every 12 weeks. According to clinical expert input, imaging assessments are performed approximately every 2 to 4 months.</p>
4. Treatment with nivolumab may be reimbursed for a maximum of 24 months.	<p>In the CheckMate-649 trial, patients in the nivolumab plus chemotherapy arm received nivolumab up to a maximum of 24 months.</p>
<b>Prescribing</b>	
5. Treatment should be prescribed by clinicians with expertise and experience in treating GC, GEJC, or EC. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects.	<p>This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.</p>
6. Nivolumab should be prescribed only in combination with fluoropyrimidine- and platinum-containing chemotherapy.	<p>Nivolumab was administered in combination with FOLFOX or XELOX in the CheckMate-649 trial; no evidence was available to support the clinical benefit of nivolumab monotherapy.</p>
<b>Pricing</b>	
7. A reduction in price.	<p>The ICER for nivolumab plus FOLFOX or XELOX is \$398,312 per QALY when compared with FOLFOX or XELOX.</p> <p>A price reduction of 95% would be required for nivolumab plus FOLFOX or XELOX to be able to achieve an ICER of \$50,000 per QALY compared to FOLFOX or XELOX alone.</p>

Reimbursement condition	Reason
<b>Feasibility of adoption</b>	
8. The feasibility of adoption of nivolumab must be addressed.	At the submitted price, the budget impact of nivolumab is expected to be greater than \$40 million in each of year 1, year 2, and year 3.

CNS = central nervous system; EC = esophageal cancer; ECOG = Eastern Cooperative Oncology Group; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; GC = gastric cancer; GEJC = gastroesophageal junction cancer; HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; XELOX = capecitabine and oxaliplatin.

## Implementation Guidance

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

**Table 2: Implementation Guidance From pERC**

Condition number in Table 1	Implementation considerations and guidance
1	For patients whose disease has unknown HER2 status, pERC considered it appropriate for these patients to begin chemotherapy alone and add nivolumab upon confirmation of HER2-negative status.
1	pERC agreed that it would be appropriate to permit the addition of nivolumab as a time-limited option for patients who are currently receiving a first-line chemotherapy regimen for the indication under review, and who have not progressed on chemotherapy. Applicable first-line chemotherapy regimens would include first-line fluoropyrimidine- and platinum-containing chemotherapy. Patients who have recently completed chemotherapy without disease progression would also be suitable. pERC did not consider it necessary to establish a time frame from initiation of chemotherapy for eligibility and noted that the population of patients who would fall into this category will be quite small.
2	The CheckMate-649 trial excluded patients with a history of receiving an anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy, or a drug directed to another co-inhibitory T-cell receptor. 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 PD-L2 inhibitor with nivolumab 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.
4	pERC agreed with the clinical experts that it would be reasonable to re-administer nivolumab to patients whose disease progresses while off treatment. pERC considered that it would be reasonable to allow for re-treatment with nivolumab, alone or in combination with chemotherapy, for up to an additional 12 months.
6	pERC considered that for patients who discontinue platinum drugs due to hypersensitivity, treatment may continue with the other components of the treatment regimen.
6	pERC considered that for patients who cannot tolerate the chemotherapy combination and do not have any grade 3 or higher immune-related adverse events, it would be reasonable to continue with nivolumab monotherapy. The patient must have received at least 1 cycle of chemotherapy concurrently with nivolumab before changing to nivolumab monotherapy.
6	pERC agreed that weight-based dosing up to a cap, similar to other immunotherapy policies, may be appropriate for dosing with nivolumab (i.e., nivolumab 3 mg/kg up to 240 mg every 2 weeks or nivolumab 4.5 mg/kg up to 360 mg every 3 weeks).

HER2 = human epidermal growth factor receptor 2; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; pERC = pan-Canadian Oncology Drug Review Expert Review Committee.

## Discussion Points

- In the CheckMate-649 trial, the comparative efficacy of nivolumab plus chemotherapy versus chemotherapy was dependent upon PD-L1 status, with greater OS benefit observed with higher PD-L1 CPS cut-offs. However, there was a clinically meaningful and statistically significant OS benefit in favour of nivolumab plus chemotherapy for all randomized patients; as such, pERC agreed that patients should not be required to have a minimum PD-L1 CPS to be eligible for treatment with nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy.
- pERC considered that access to PD-L1 CPS testing would be ideal, and testing should be performed when a patient presents with metastatic or advanced GAC, GEJAC, or EAC. It was noted that PD-L1 testing results can provide meaningful information for the clinicians to discuss the anticipated benefits of treatment with patients and their families.

## Background

Nivolumab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, has a Health Canada indication for the treatment of adult patients with HER2 negative advanced or metastatic gastric, gastroesophageal junction or esophageal adenocarcinoma. It is also noted in the Health Canada indication that a positive association was observed between PD-L1 CPS score and the magnitude of the treatment benefit. Nivolumab is an anti-programmed cell death protein 1 antibody. It is available as a 10 mg/mL solution for IV infusion and the Health Canada-approved dosage is 240 mg every 2 weeks or 360 mg every 3 weeks.

## Sources of Information Used by the Committee

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

- a review of 1 RCT in patients with previously untreated, HER2-negative (or HER2-unreported) advanced or metastatic GAC, GEJAC, or EAC.
- 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 the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with advanced or metastatic GAC, GEJAC, or EAC
- input from 2 clinician groups, including the Ontario Health Gastrointestinal Cancer Drug Advisory Committee and the Canadian Gastrointestinal Oncology Evidence Network (CGOEN) and other physicians treating gastroesophageal cancers
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Group Input

Input was provided by 1 patient group for this review (My Gut Feeling – Stomach Cancer Foundation of Canada). My Gut Feeling is the first non-profit organization in Canada dedicated to providing support, awareness, education, information, and advocacy to patients with gastric cancer (GC), gastroesophageal junction cancer (GEJC), and esophageal cancer (EC) as well as survivors and caregivers. My Gut Feeling distributed a survey via email, social media, and online forums to patients with GC, GEJC, or EC as well as their caregivers between August 20, 2021, and September 9, 2021. Among the 62 respondents (half patients and half caregivers), most (79%) were female, resided in Canada or the US (63% and 29%, respectively), and had received or were caring for someone who had received a diagnosis of GC (74.2%) and adenocarcinoma (82.3%). The number of respondents with advanced or metastatic disease was unclear.

Most respondents (90.3%) reported a significant impact of their cancer on HRQoL, with adverse effects on physical health, mental health, ability to eat, ability to work, finances, social life, identity, and self-image. Some of these impacts extended to caregivers and families, as well. Symptoms frequently included weight loss, change in appetite, pain, fatigue, reflux, nausea, vomiting, difficulty swallowing, shortness of breath, bleeding, anemia, ascites, and dumping syndrome. Patients highlighted the limited treatment options for GC, GEJC, and EC and their experiences with prior therapies (surgery, radiation, chemotherapy, and immunotherapy), including variable effectiveness in delaying disease progression and controlling symptoms as well as significant side effects impacting HRQoL (e.g., fatigue, nausea and vomiting, appetite changes exacerbating weight loss). Twelve respondents had experience with nivolumab and felt that the drug controlled their disease, improved HRQoL, and was more convenient and tolerable than surgery or chemotherapy.

According to patients, an ideal therapy for GC, GEJC, and EC would, when compared to standard care, prolong survival while maintaining or improving HRQoL. Delaying recurrence or progression and manageable side effects were also important factors for patients, who identified an unmet need for equitable access to therapies that may prolong life, improve symptoms, reduce risk of recurrence, and have improved tolerability. Such treatment options should be available barrier free for all patients in Canadian with GC, GEJC, or EC who could potentially benefit.

### Clinician Input

#### Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of advanced or metastatic GAC, GEJAC, and EAC.



## ***Unmet Needs***

According to the clinical experts consulted by CADTH for this review, all currently used treatment approaches for advanced or metastatic GAC, GEJAC, and EAC are palliative in nature, and survival is typically less than 1 year. Only a minority of patients respond to currently used combination chemotherapy regimens; these responses are usually short-lived and very few patients live beyond 15 to 18 months. There is clearly an unmet need for more effective therapies for advanced or metastatic GAC, GEJAC, and EAC that can be administered with similar or lower toxicity than current chemotherapy options.

## ***Place in Therapy***

According to the clinical experts, prior experience in other cancers has shown that when immunotherapy alone is ineffective, combining it with chemotherapy may lead to better treatment outcomes with no or limited additional toxicity. According to the experts as well as the sponsor, nivolumab would be administered in combination with fluoropyrimidine- and platinum-based chemotherapy for first-line treatment of most patients who are HER2 negative with advanced or metastatic GAC, GEJAC, or EAC who are able to tolerate chemotherapy. It would not be appropriate for patients to receive other treatments before nivolumab plus chemotherapy: according to the clinical experts, the most effective interventions should be used first line as there is significant attrition and many patients do not receive second or subsequent lines of therapy. Nivolumab would not be used in patients who are intolerant to or have failed on chemotherapy. The clinical experts stated that all patients with EAC would be eligible for nivolumab if funded irrespective of the availability of HER2 testing. Nivolumab attempts to address the underlying disease process by potentiating antitumour immune responses but there are many shortcomings to this approach. Reimbursement of nivolumab plus chemotherapy would not shift the treatment paradigm as most patients would receive chemoimmunotherapy rather than fluoropyrimidine- and platinum-based chemotherapy alone in the first line, with second and subsequent lines remaining the same.

## ***Patient Population***

Unfortunately, the patients who are most in need of intervention have the most advanced disease, poor PS, and do not generally respond well to immunotherapy and are thus excluded from clinical trials. According to the clinical experts consulted by CADTH for this review, the available data from trials provide evidence regarding the use of nivolumab plus chemotherapy in patients with advanced or metastatic GAC, GEJAC, and EAC and Eastern Cooperative Oncology Group (ECOG) PS of 0 and 1, but administration in additional patients (ECOG PS of 2 or potentially even 3) may be possible if judged appropriate by the treating clinician. In the opinion of the clinical experts, nivolumab plus chemotherapy should be available for all patients with advanced or metastatic GAC, GEJAC, or EAC for whom local or curative treatment is not possible and in whom chemotherapy is a treatment option. The site of metastasis or presence of symptoms would not affect patient selection. Diagnosis and staging (based on biopsy and CT or PET imaging) are standard and misdiagnosis is unlikely.

According to the clinical experts, patients with a good PS (ECOG PS of 0 or 1) are most likely to respond to nivolumab plus chemotherapy. In addition, the clinical experts emphasized that PD-L1 expression is an established biomarker of response and patients with higher PD-L1 CPS are more likely to respond to nivolumab. PD-L1 CPS testing of biopsy specimens is now routinely performed for other cancer types and could easily be adapted for patients with GAC, GEJAC, or EAC, although this is not routinely done at present. According to the clinical experts, the minor proportion of patients (3% to 5%) with high microsatellite instability are also much more likely to respond to immunotherapy including nivolumab. The clinical experts

viewed patients with poor PS and PD-L1 CPS of less than 1 as least likely to benefit from nivolumab, and stated that patients with active autoimmune diseases are least suitable for treatment due to safety concerns.

### ***Assessing Response to Treatment***

Imaging (e.g., CT and PET scans) is used to evaluate response to therapy. In clinical practice, imaging assessments are performed approximately every 3 months (in contrast with the trial setting in which they were performed every 6 weeks). Survival is the most important indicator of response, with improvement in symptoms and HRQoL also being important parameters in assessing response. Weight and PS may also give an indication of treatment response and are evaluated at each clinic visit.

### ***Discontinuing Treatment***

Treatment should be discontinued in patients with clear objective progressive disease assessed by imaging. Treatment intolerance or significant toxicity may also require discontinuation of therapy.

### ***Prescribing Conditions***

Diagnosis of GAC, GEJAC, or EAC and initial workup is typically performed by surgeons and gastroenterologists. Patients are then transferred to the care of a medical oncologist for systemic therapy. Palliative and supportive care specialists as well as dietitians would also follow these patients. Treatment would be administered in outpatient centres with professionals experienced in delivering systemic therapy (including chemotherapy and immunotherapy). Most centres already have significant experience with nivolumab and the accompanying chemotherapy regimens.

### ***Additional Considerations***

The clinical experts emphasized that most oncologists already have significant experience with administering nivolumab, including combinations with chemotherapy, for other indications.

### **Clinician Group Input**

Two clinician groups provided input for this review: the Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (5 clinicians) and the CGOEN, as well as other physicians treating gastroesophageal cancers (7 clinicians). No major contrary views were presented. Both clinician groups echoed the limited efficacy of available systemic therapies for advanced or metastatic GAC, GEJAC, and EAC and the short DOR in many patients. In contrast with the clinical experts consulted by CADTH for this review, clinicians from the CGOEN felt that patients with PD-L1 CPS lower than 5 (rather than lower than 1) would be least suitable for treatment with nivolumab plus chemotherapy, while those from the Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee felt that although patients with PD-L1 CPS of 5 or greater and 1 or greater are more likely to respond, all patients with GAC, GEJAC, or EAC can benefit from the addition of nivolumab to chemotherapy.

### **Drug Program Input**

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

**Table 3: Responses to Questions From the Drug Programs**

Implementation issues	Response
<b>Relevant comparators</b>	
How do FOLFOX and XELOX compare with other first-line chemotherapies with regard to efficacy and safety?	<p>pERC agreed with the clinical experts that FOLFOX and XELOX (and to a lesser extent FOLFIRI) are the preferred chemotherapy backbones in Canada and that FOLFOX is often preferred by clinicians due to patients' difficulties in swallowing capecitabine tablets.</p> <p>According to the clinical experts, there is jurisdictional variation in chemotherapy regimens; in some jurisdictions, cisplatin plus 5-FU would be used instead, but clinician preference would be for FOLFOX or XELOX due to lower toxicity, more convenient administration, and potentially enhanced efficacy.</p> <p>pERC acknowledged this input and considered that with the availability of generic oxaliplatin products, FOLFOX and XELOX will likely be funded in more jurisdictions in the near future.</p>
Can the results of the CheckMate-649 trial be generalized to first-line chemotherapy combinations other than FOLFOX and XELOX in patients who are unable to tolerate platinum-based combinations?	<p>The clinical experts indicated uncertainty around this as the only data available are from the CheckMate-649 trial that used FOLFOX and XELOX. According to the clinical experts, clinicians might consider administering nivolumab in combination with other chemotherapy regimens, but the efficacy of such combinations is unknown.</p> <p>pERC agreed with the clinical experts that a small percentage of patients who start on platinum- and fluoropyrimidine-containing chemotherapy may discontinue the platinum drug due to hypersensitivity but can continue receiving the other components (which was also in accordance with treatment in the CheckMate-649 trial). pERC noted that patients should initiate nivolumab therapy with platinum- and fluoropyrimidine-containing chemotherapy before discontinuing the platinum drug or switching to an alternative regimen due to intolerance or unacceptable toxicity of platinum agents.</p>
<b>Considerations for initiation of therapy</b>	
Nivolumab (plus chemotherapy) was administered for a maximum of 2 years in the CheckMate-649 trial. Should re-treatment be offered to patients who complete up to 2 years whose disease progresses while off treatment? If so, what should the re-treatment duration be, and would re-treatment consist of nivolumab plus chemotherapy or nivolumab monotherapy?	<p>The clinical experts stated that based on past immunotherapy trials in other cancers, re-treatment should be offered to these patients after a gap of 6 months or longer. The re-treatment duration would be 1 to 2 years. In the absence of data, it is uncertain whether re-treatment would be with nivolumab alone or nivolumab plus chemotherapy and there is likely to be variation in clinical practice.</p> <p>pERC agreed with the experts that it would be reasonable to offer re-treatment with nivolumab, with or without chemotherapy, for up to 1 year for patients who experience relapse while off treatment.</p>

Implementation issues	Response
<p>Nivolumab for adjuvant treatment of completely resected esophageal and GEJ cancer is also under CADTH review (PC0253). In other solid tumours, patients 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 same principle be applied in this setting?</p>	<p>According to the clinical experts, the same principle would apply in this setting unless proven otherwise.</p> <p>pERC agreed with the experts that patients who received a PD-1 or PD-L1 inhibitor in the adjuvant setting can receive nivolumab with platinum- and fluoropyrimidine-containing chemotherapy for advanced or metastatic disease provided that disease recurrence occurs more than 6 months from the last dose of adjuvant PD-1 or PD-L1 inhibitor therapy.</p>
<p>PAG noted that pembrolizumab in combination with fluoropyrimidine- and platinum-based chemotherapy for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the esophagus or HER2-negative Siewert type I GEJ adenocarcinoma is under review by CADTH (PC0250). PAG noted the differences in the funding requests for these 2 reviews (e.g., squamous cell vs. adenocarcinoma histology, first-line therapy vs. treatment line-agnostic, and inclusion and exclusion of gastric cancer).</p>	<p>pERC noted that for the treatment of advanced or metastatic gastroesophageal cancers, only pembrolizumab would be used for squamous cell cancers and only nivolumab would be used for gastric cancers. Although the relevant indication for pembrolizumab specifies use of first-line treatment and the indication for nivolumab does not, both treatments should only be used for first-line treatment in this setting.</p>
Considerations for discontinuation of therapy	
<p>In the CheckMate-649 trial, patients randomized to receive nivolumab plus chemotherapy could continue to receive nivolumab monotherapy (if chemotherapy was discontinued) or chemotherapy alone (if nivolumab was discontinued). Would these treatment discontinuation parameters be applied in clinical practice?</p>	<p>The clinical experts indicated that these treatment discontinuation parameters would be applied in clinical practice, although it is more likely that patients would discontinue chemotherapy and continue with immunotherapy rather than vice-versa.</p> <p>pERC agreed with the experts that some patients can discontinue chemotherapy and continue with nivolumab monotherapy. pERC considered that for patients who cannot tolerate the chemotherapy combination and do not have any grade 3 or higher immune-related adverse events, it would be reasonable to continue with nivolumab monotherapy. The patient must have received at least 1 cycle of chemotherapy concurrently with nivolumab before changing to nivolumab monotherapy.</p>
Considerations for prescribing of therapy	
<p>PAG anticipated that as with previous CADTH reviews of immune checkpoint inhibitors, jurisdictions will implement weight-based dosing for nivolumab up to a maximum dose cap. Dosing frequency of nivolumab (e.g., every 2 or 3 weeks) will correspond to the chemotherapy regimen schedule used in combination.</p>	<p>pERC agreed that weight-based dosing up to a cap, similar to other immunotherapy policies, may be appropriate for dosing with nivolumab (i.e., nivolumab 3 mg/kg up to 240 mg every 2 weeks or nivolumab 4.5 mg/kg up to 360 mg every 3 weeks).</p>

Implementation issues	Response
<p>PAG noted the ongoing CADTH review of pembrolizumab plus chemotherapy in a similar patient population (PC0250) and noted that pembrolizumab and nivolumab have different dosing intervals; pembrolizumab may be administered every 21 or 42 days while nivolumab may be administered every 14, 21, or 28 days. How would prescribers choose which immunotherapy (e.g., pembrolizumab vs. nivolumab) to use for advanced or metastatic gastric, gastroesophageal junction, or esophageal cancer?</p>	<p>According to the clinical experts, this would depend in part on funding of these immunotherapies (nivolumab and pembrolizumab) as well as availability of PD-L1 testing. Patients with gastric cancer would likely receive nivolumab plus chemotherapy. Patients with esophageal squamous cell carcinoma would likely receive pembrolizumab plus chemotherapy. For patients who are candidates for both nivolumab and pembrolizumab, the decision would be up to the treating physician.</p> <p>pERC did not have additional comments other than to note the differences in the relevant indications between nivolumab and pembrolizumab as mentioned in the response under Considerations for initiation for therapy.</p>
Generalizability	
<p>Should patients with an ECOG PS of 2 or greater be eligible for nivolumab plus chemotherapy?</p>	<p>The clinical experts stated that some patients with an ECOG PS of 2 (or potentially even 3) would receive nivolumab plus chemotherapy. Some younger patients may be good candidates despite an ECOG PS of 2; treatment must be tailored to each patient and such decisions would be made by the treating physician. Fragile patients with poor PS who are unlikely to respond and may suffer adverse effects without deriving clinical benefit would not be good candidates for nivolumab.</p> <p>pERC agreed with the clinical experts that the magnitude of benefit in this population is uncertain and noted that the decision to use nivolumab plus fluoropyrimidine- and platinum-containing chemotherapy in these patients should be left to the discretion of the treating clinician.</p>
<p>For patients currently receiving fluoropyrimidine- and platinum-based chemotherapy with no evidence of progressive disease, there is a time-limited need for addition of nivolumab. What time frame from initiation of chemotherapy would be appropriate to add nivolumab for patients currently receiving chemotherapy or who recently completed chemotherapy?</p>	<p>The clinical experts stated that the addition of nivolumab to chemotherapy should occur before any detected disease progression for patients currently receiving chemotherapy. The experts expressed uncertainty around what time frame would be appropriate and suggested that, in the absence of data, arbitrary cut-offs of 2 to 3 cycles, or at least before the first scan at 3 months, would likely be used. The expert also noted that there is likely to be variation in clinical practice.</p> <p>pERC agreed that it would be reasonable to permit the addition of nivolumab as a time-limited option for patients who are currently receiving a first-line chemotherapy regimen for the indication under review, and who have not progressed on chemotherapy. Patients who have recently completed chemotherapy without disease progression would also be suitable. pERC did not consider it necessary to establish a time frame from initiation of chemotherapy for eligibility.</p>
Funding algorithm	
<p>PAG noted that reimbursement of nivolumab for this indication may change the place in therapy of drugs reimbursed in subsequent lines (e.g., ramucirumab plus paclitaxel and trifluridine and tipiracil).</p>	<p>pERC did not expect the place in therapy for drugs currently reimbursed in subsequent lines to be affected by the reimbursement of nivolumab for this indication, aside from a small percentage of patients who may receive re-treatment with nivolumab.</p>

Implementation issues	Response
<b>Care provision issues</b>	
PAG noted that addition of nivolumab to chemotherapy would require additional time to administer treatment and adds admixtures for pharmacy preparation. However, because nivolumab is used in many other indications, it is anticipated that vial sharing and dose rounding would be possible, especially in larger centres.	This input was acknowledged by pERC in its discussion.

5-FU = fluorouracil; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = fluorouracil, leucovorin, and irinotecan; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; PAG = Provincial Advisory Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = Performance Status; vs. = versus; XELOX = capecitabine plus oxaliplatin.

## Clinical Evidence

### Pivotal Studies and Protocol Selected Studies

#### Description of Studies

CheckMate-649 was a phase III, open-label, multi-centre RCT (N = 1,581)<sup>13</sup> whose primary objective was to compare the efficacy of first-line therapy with nivolumab plus FOLFOX or XELOX versus FOLFOX or XELOX alone in prolonging OS and PFS per blinded independent central review (BICR) in patients with advanced or metastatic GAC, GEJAC, or EAC (all with a PD-L1 CPS of  $\geq 5$ ). Secondary objectives included comparing OS and PFS by BICR in patients with a PD-L1 CPS of  $\geq 1$  (OS hierarchically tested), all randomized patients (OS hierarchically tested), and patients with a PD-L1 CPS of 10 or greater and comparing ORRs in patients with a PD-L1 CPS of 5 or greater, patients with a PD-L1 CPS of 1 or greater, all randomized patients, and patients with a PD-L1 CPS of 10 or greater. Changes in HRQoL (measured using the patient-reported EQ-5D-3 Levels [EQ-5D-3L] and functional assessment of cancer therapy – gastric [FACT-Ga] instruments, including the FACT-Ga gastric cancer subscale [GaCS]), were assessed in exploratory fashion. Patients had to be 18 years or older with inoperable advanced or metastatic, HER2-negative or HER2-unreported GAC, GEJAC, or EAC previously untreated in the advanced or metastatic setting and have an ECOG PS of 0 or 1. Patients were enrolled at 175 sites in 29 countries, and were randomized 1:1:1 to receive either nivolumab 360 mg plus XELOX every 3 weeks or nivolumab 240 mg plus FOLFOX every 2 weeks; XELOX (every 3 weeks) or FOLFOX (every 2 weeks); or 4 cycles of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) every 3 weeks followed by nivolumab monotherapy 240 mg every 2 weeks. The nivolumab plus ipilimumab and nivolumab monotherapy arm was closed to recruitment on June 5, 2018.

■■■ data for these patients were not relevant to this review and are not included. Patients were treated until disease progression, unacceptable toxicity, study withdrawal, or death, whichever came first. Treatment with nivolumab plus chemotherapy beyond initial, investigator-assessed progressive disease was allowed if the patient had investigator-assessed clinical benefit and was tolerating treatment. Further progression (i.e., increase in tumour burden of  $\geq 10\%$ ) resulted in discontinuation of nivolumab plus chemotherapy. For patients receiving nivolumab plus chemotherapy, the maximum treatment period was 24 months. Following treatment discontinuation, patients entered survival follow-up (every 3 months until study withdrawal, death, or data cut-off, whichever came first).

The mean ages of study participants were █ years and █ years in the nivolumab plus chemotherapy and chemotherapy alone arms, respectively. Approximately 70% of patients were male, approximately 70% were White, and approximately 60% were enrolled at sites outside of North America and Asia. Approximately 70% of patients had GAC █. Almost all patients (approximately 96%) had metastatic disease while a minority (approximately 4%) had locally advanced or recurrent disease. Only a minority of patients (10% to 20%) had received prior surgery, █. Approximately 60% had HER2-negative tumours, while in approximately 40% of patients HER2 status was not reported. Approximately 83%, 61%, and 49% of patients had a PD-L1 CPS of 1 or greater, 5 or greater, and 10 or greater, respectively. Baseline demographic and disease characteristics were generally well balanced between study arms.

### Efficacy Results

At the database lock of July 10, 2020 (minimum follow-up of 12.1 months; mean follow-up of █ months [standard deviation = █ months] in the nivolumab plus chemotherapy arm and █ months [standard deviation = █ months] in the chemotherapy alone arm), the coprimary efficacy analyses of OS and PFS in patients with a PD-L1 CPS of 5 or greater showed that patients in the nivolumab plus chemotherapy arm had longer OS and PFS than those in the chemotherapy alone arm. Median OS was 14.39 months (95% CI, 13.11 months to 16.23 months) in the nivolumab plus chemotherapy arm versus 11.10 months (95% CI, 10.02 months to 12.09 months) in the chemotherapy alone arm ( $P < 0.0001$ ). The HR for OS comparing nivolumab plus chemotherapy with chemotherapy was 0.71 (98.4% CI, 0.59 to 0.86). Median PFS was 7.69 months (95% CI, 7.03 to 9.17 months) in the nivolumab plus chemotherapy arm versus 6.05 months (95% CI, 5.55 to 6.90 months) in the chemotherapy alone arm ( $P < 0.0001$ ). The HR for PFS comparing nivolumab plus chemotherapy with chemotherapy was 0.68 (98% CI, 0.56 to 0.81). The hierarchically tested secondary analyses of OS in patients with a PD-L1 CPS of 1 or greater and all randomized patients also showed that patients in the nivolumab plus chemotherapy arm had longer OS than those in the chemotherapy alone arm. Among patients with a PD-L1 CPS of 1 or greater, median OS was 13.96 months (95% CI, 12.55 to 14.98 months) in the nivolumab plus chemotherapy arm versus 11.33 months (95% CI, 10.64 months to 12.25 months) in the chemotherapy alone arm ( $P < 0.0001$ ). The HR comparing nivolumab plus chemotherapy with chemotherapy alone was 0.77 (99.3% CI, 0.64 to 0.92). Among all randomized patients, median OS was 13.83 months (95% CI, 12.55 to 14.55 months) in the nivolumab plus chemotherapy arm versus 11.56 months (95% CI, 10.87 to 12.48 months) in the chemotherapy alone arm ( $P = 0.0002$ ). The HR comparing nivolumab plus chemotherapy with chemotherapy alone was 0.80 (99.3% CI, 0.68 to 0.94). The results of the coprimary and hierarchically tested secondary OS analyses were clinically relevant according to the clinical experts consulted by CADTH for this review, based on their judgment that a 6-week improvement in survival represents a clinically meaningful improvement in this patient population.

OS and PFS analyses were conducted as secondary end points across other PD-L1 CPS cut-offs. Median OS in patients with a PD-L1 CPS of 10 or greater was █ months (95% CI, █ months) in the nivolumab plus chemotherapy arm and █ months (95% CI, █ months) in the chemotherapy alone arm; the HR for OS comparing nivolumab plus chemotherapy with chemotherapy alone was 0.66 (95% CI, █). Among patients with a PD-L1 CPS of 10 or greater, median PFS was █ months (95% CI, █ months) in the nivolumab plus chemotherapy arm and █ months (95% CI, █ months) in the chemotherapy alone arm; the HR for PFS comparing nivolumab plus chemotherapy with chemotherapy alone was █ (95% CI, █). Among patients with a PD-L1 CPS of 1 or greater, median PFS was



7.49 months (95% CI, 7.03 to 8.41 months) in the nivolumab plus chemotherapy arm and 6.90 months (95% CI, 6.08 to 7.03 months) in the chemotherapy alone arm; the HR for PFS comparing nivolumab plus chemotherapy with chemotherapy alone was 0.74 (95% CI, 0.65 to 0.85). Among all randomized patients, median PFS was 7.66 months (95% CI, 7.10 months to 8.54 months) in the nivolumab plus chemotherapy arm and 6.93 months (95% CI, 6.60 to 7.13 months) in the chemotherapy alone arm; the HR for PFS comparing nivolumab plus chemotherapy with chemotherapy alone was 0.77 (95% CI, 0.68 to 0.87).

Subgroup analyses of OS by PD-L1 CPS showed decreasing treatment effects with nivolumab plus chemotherapy versus chemotherapy with lower PD-L1 CPS cut-offs as follows: PD-L1 CPS lower than 10: HR = 0.94 (95% CI, 0.80 to 1.10); PD-L1 CPS of 10 or greater: HR = 0.65 (95% CI, 0.55 to 0.78); PD-L1 CPS of lower than 5: HR = 0.94 (95% CI, 0.78 to 1.13); PD-L1 CPS of 5 or greater: HR = 0.70 (95% CI, 0.60 to 0.81); PD-L1 CPS of lower than 1: HR = 0.92 (95% CI, 0.70 to 1.23); and PD-L1 CPS of 1 or greater: HR = 0.76 (95% CI, 0.67 to 0.87). Subgroup analyses of PFS followed a similar pattern.

EQ-5D-3L utility index scores, EQ-5D visual analogue scale (VAS) scores, FACT-Ga total scores, and GaCS scores at baseline were similar among all randomized patients in the 2 treatment arms. Mean values for EQ-5D-3L utility index scores, EQ VAS scores, FACT-Ga total scores, and GaCS scores were numerically higher (improved) at post-baseline assessments during the treatment period compared with the baseline assessment among all randomized patients in both treatment arms.

Comparisons of ORR and DOR also favoured nivolumab plus chemotherapy over chemotherapy alone. According to the clinical experts consulted by CADTH for this review, differences in these outcomes, which were outside the statistical hierarchy, had uncertain clinical significance on their own but were supportive of the clinically meaningful difference in OS in favour of nivolumab plus chemotherapy.

## Harms Results

Adverse events (AEs) occurred in almost all patients treated with nivolumab plus chemotherapy and chemotherapy alone (99.2% versus 98.0%). Serious AEs and withdrawals due to AEs occurred in larger proportions of patients receiving nivolumab plus chemotherapy than those receiving chemotherapy alone (54.1% versus 43.7% and 47.4% versus 32.7%, respectively). A total of 68.8% of patients treated with nivolumab plus chemotherapy and 74.6% of patients treated with chemotherapy alone died during the study period.

Select AEs, immune-mediated AEs (IMAEs), and other events of special interest (protocol-defined to capture the expected toxicity profile of nivolumab) occurred more frequently in the nivolumab plus chemotherapy arm than in the chemotherapy alone arm. Select AEs affecting the gastrointestinal system (40.3% in the nivolumab plus chemotherapy arm and 33.9% in the chemotherapy alone arm), select AEs affecting the hepatic system (34.1% and 24.3%), select AEs affecting the skin (33.5% and 17.9%), select AEs affecting the endocrine system (15.0% and 1.8%), and hypersensitivity and infusion reactions (15.1% and 5.9%) were the most common select AEs in the nivolumab plus chemotherapy arm. Hypothyroidism and thyroiditis (9.5% in the nivolumab plus chemotherapy arm and 0.8% in the chemotherapy alone arm), rash (6.5% and 0.5%), pneumonitis (4.2% and 0%), diarrhea and colitis (3.3% and 0%), hyperthyroidism (2.9% and 0.3%), and hepatitis (2.4% and 0%) were the most common immune-mediated AEs in the nivolumab plus chemotherapy arm.



## Critical Appraisal

A notable limitation of the CheckMate-649 trial was its open-label design and the potential sources of bias associated with this design. Randomization was stratified by tumour PD-L1 expression ( $\geq 1\%$  versus  $< 1\%$ ) while the coprimary OS and PFS analyses were conducted in patients with a PD-L1 CPS of 5 or greater, eliminating the protection of stratified randomization. Although outcome assessment of tumour response and progression was performed by BICR using objective Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria, patient-reported HRQoL data and assessment of harms outcomes may have been impacted to some degree by knowledge of treatment allocation. The open-label design may also have resulted in more frequent discontinuation before receiving any study therapy (nivolumab plus chemotherapy arm = 0.9% versus chemotherapy alone arm = 3.2%), discontinuation of therapy during the treatment phase (patient request: nivolumab plus chemotherapy arm = 1.7% versus chemotherapy alone arm = 4.6%; withdrawal of consent: nivolumab plus chemotherapy arm = 2.6% versus chemotherapy alone arm = 5.3%), and discontinuation from the study (withdrawal of consent: nivolumab plus chemotherapy arm = 2.6% versus chemotherapy alone arm = 4.7%) by patients randomized to the chemotherapy alone arm. The open-label design could have altered treatment exposure in either or both study arms due to investigator biases, especially as treatment beyond progression was allowed for nivolumab plus chemotherapy but not chemotherapy alone. According to the clinical experts consulted by CADTH for this review, treatment with nivolumab plus chemotherapy beyond progression is clinically appropriate in some patients; although, in most patients, therapy would be discontinued at the first objective determination of progressive disease. According to the clinical experts consulted for this review, the frequency of treatment beyond progression in the CheckMate-649 trial (■■■■■) was higher and the duration of treatment beyond progression was longer than expected based on current clinical practice in Canada; the impact of extended administration of nivolumab on OS was uncertain, although the clinical experts were of the opinion that post-progression treatment was unlikely to significantly influence OS or the interpretation of OS data. The absence of formal statistical comparison and high amounts of missing HRQoL data (due to deaths and low questionnaire completion rates following treatment discontinuation) limited interpretation of these end points. In addition, the GaCS has not been validated as a standalone scale and the degree to which it specifically measures changes in symptomology versus general HRQoL changes was unclear. The study had very high power for the coprimary efficacy analyses and would likely have been capable of detecting smaller treatment effects than originally anticipated with uncertain clinical relevance. The magnitude of OS differences between the nivolumab plus chemotherapy and chemotherapy alone arms in the primary analysis population (PD-L1 CPS of  $\geq 5$ ) was statistically and clinically significant according to the clinical experts consulted by CADTH for this review, but smaller differences in PFS were of uncertain clinical relevance.

The demographic and disease characteristics of the CheckMate-649 trial population were broadly reflective of the Canadian population with GAC, GEJAC, or EAC. Of note, there were major unresolved questions of generalizability to some of the patient groups that would be covered by the Health Canada indication and the reimbursement request submitted for CADTH's review. The CheckMate-649 trial enrolled patients with an ECOG PS of 0 or 1 and no prior systemic therapy in the advanced or metastatic setting. This review identified no evidence regarding administration of nivolumab plus chemotherapy beyond first-line therapy or in patients with an ECOG PS of 2 or greater. Critically, the study was not designed to conclusively identify the PD-L1 expression thresholds required for therapeutic benefit. Analyses of OS and PFS using different PD-L1 CPS cut-offs, as well as subgroup analyses by

tumour cell PD-L1 expression, pointed toward potentially important differences in efficacy according to PD-L1 status.

## Indirect Comparisons

### Description of Studies

One sponsor-submitted indirect treatment comparison (ITC) contributed evidence to this review. The purpose of the ITC was to compare the efficacy of nivolumab plus chemotherapy to relevant comparators (chemotherapy alone regimens: fluoropyrimidine, fluoropyrimidine plus platinum, taxane plus platinum, fluoropyrimidine plus topoisomerase inhibitor, fluoropyrimidine plus taxane, platinum plus topoisomerase inhibitor, taxane plus topoisomerase inhibitor, fluoropyrimidine plus platinum and taxane, or fluoropyrimidine plus platinum and anthracycline) for first-line treatment of advanced or metastatic GC, GEJC, or EAC. Pembrolizumab plus chemotherapy was not considered a relevant comparator by the ITC authors.

Following a literature search, 31 studies presenting data on OS and PFS and with relevant treatment comparisons were considered for inclusion in the network meta-analysis. Of these, 23 were used in the PFS network and 28 were used in the OS network. The ATTRACTION-4 study was excluded from the main ITC. Studies were connected in drug class-based networks for OS and PFS outcomes to indirectly compare nivolumab plus chemotherapy to other relevant therapies among all-comers (irrespective of PD-L1 status). A Bayesian framework was conducted with non-informative priors. As both fixed- and random-effects models were used, models were compared using the deviance information criterion. Scenario analyses were conducted based on the heterogeneity observed across trials included in the networks.

### Efficacy Results

Pairwise comparisons for OS and PFS did not show differences between nivolumab plus fluoropyrimidine and platinum and the following treatments of interest: fluoropyrimidine plus platinum, fluoropyrimidine plus topoisomerase inhibitor, and fluoropyrimidine plus platinum and anthracycline. Scenario analyses were generally consistent with the primary analyses for PFS and OS for all relevant comparisons.

### Harms Results

The sponsor-submitted ITC did not assess harms outcomes.

### Critical Appraisal

Studies of pembrolizumab plus chemotherapy were not included in the ITC; while pembrolizumab is currently not funded outside special access programs across Canadian jurisdictions, it was still considered a clinically relevant comparator by the clinical experts consulted for this review. Substantial heterogeneity was observed across patient and trial characteristics. While multiple scenario analyses were conducted to explore the impact of certain effect modifiers, others could not be investigated. A risk of bias assessment conducted by the sponsor revealed that most studies included in the ITC were of low to medium quality, and scenario analyses that excluded low-quality studies produced more precise estimates. The sponsor's ITC also did not include outcomes other than OS and PFS, such as toxicities or HRQoL, both of which are important outcomes to patients. Overall, the ITC had limitations associated with clinical and statistical heterogeneity that

increased the uncertainty of estimates and may have prevented detection of differences between treatments.

## Other Relevant Evidence

No other relevant evidence was identified for this review.

## Conclusions

Evidence from the CheckMate-649 trial suggested that compared with FOLFOX or XELOX alone, first-line administration of nivolumab plus FOLFOX or XELOX contributed to statistically significant and clinically meaningful prolongation of OS among patients who were HER2 negative and had GAC, GEJAC, or EAC. This finding was consistent across patients with a PD-L1 CPS of 5 or greater, patients with a PD-L1 CPS of 1 or greater, and all randomized patients. Administration of nivolumab plus FOLFOX or XELOX also resulted in statistically significant prolongation of PFS among patients with a PD-L1 CPS of 5 or greater, though the clinical relevance of the difference in PFS was unclear. Other analyses of PFS, ORR, and DOR across different PD-L1 CPS cut-offs also favoured nivolumab plus chemotherapy and were supportive of the OS results. Results for patient-reported HRQoL and symptom scores (EQ-5D-3L, FACT-Ga) could not be interpreted due to absence of formal statistical testing, potential for bias in an open-label trial, and high rates of missing data at later time points post-baseline. There were signals from the trial that the comparative efficacy of nivolumab plus chemotherapy versus chemotherapy alone in patients with GAC, GEJAC, or EAC was dependent upon PD-L1 status. Despite this, prolongation of OS by nivolumab plus chemotherapy, which was acknowledged as the most important outcome of therapy by both patients and clinicians, was statistically and clinically significant among all randomized patients. A sponsor-submitted ITC did not provide evidence of differences in efficacy between nivolumab plus fluoropyrimidine- and platinum-based chemotherapy and other chemotherapy regimens and did not include pembrolizumab plus chemotherapy as a comparator. Notable harms associated with nivolumab (including immune-mediated AEs) were appreciable but were expected and generally manageable in most patients with supportive care.

## Economic Evidence

**Table 4: Cost and Cost-Effectiveness**

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population(s)	Adult patients (aged 18 years and older) with HER2-negative advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma. Aligns with reimbursement request.
Treatments	Nivolumab in combination with XELOX (every 21 days) or nivolumab in combination with FOLFOX (every 14 days)
Submitted price	Nivolumab, 10 mg per mL, solution: \$19.55 per mg (\$782.22 per 40 mg vial) Nivolumab, 10 mg per mL, solution: \$19.55 per mg (\$1955.56 per 100 mg vial)

Component	Description
<b>Treatment cost</b>	Nivolumab = \$9,387 per 28 days of treatment Nivolumab plus XELOX = \$9,833 per 28 days of treatment Nivolumab plus FOLFOX = \$10,618 per 28 days of treatment
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• 5-FU + oxaliplatin + leucovorin (FOLFOX) or capecitabine + oxaliplatin (XELOX)</li> <li>• 5-FU + irinotecan and leucovorin (FOLFIRI)</li> <li>• 5-FU + cisplatin</li> <li>• Capecitabine + cisplatin</li> <li>• 5-FU + epirubicin + cisplatin</li> </ul>
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcomes</b>	QALYs, LYs
<b>Time horizon</b>	Lifetime (25 years)
<b>Key data source</b>	CheckMate-649 trial was used to inform parameter values for progression-free survival, overall survival, time to discontinuation, and health state utility
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• Some comparator treatments were deemed to be non-reflective of current clinical practice.</li> <li>• The long-term comparative efficacy of nivolumab is uncertain. The long-term efficacy of nivolumab plus FOLFOX or XELOX compared to FOLFOX or XELOX alone was uncertain, and the clinical experts consulted by CADTH deemed the sponsor's long-term extrapolation of survival curves to be too optimistic. The sponsor's model also did not consider treatment effectiveness waning over time.</li> <li>• The sponsor's model results suggested that patients receiving nivolumab plus FOLFOX or XELOX lived longer following relapse than those receiving no active therapy. This post-relapse survival benefit lacks face validity and was not supported by the clinical evidence. This structural issue produces an estimate of incremental effectiveness that is likely biased in favour of nivolumab.</li> <li>• Pembrolizumab has been approved by Health Canada for a similar indication and is available to some patients under special access programs. The sponsor did not include pembrolizumab in the cost-utility analysis as a comparator. The cost-effectiveness of nivolumab plus FOLFOX or XELOX compared to pembrolizumab is unknown.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• CADTH made the following revisions to the sponsor's pharmacoeconomic model: corrected programming errors, removed irrelevant comparators, used publicly listed prices for relevant drug costs, set all dose intensities to 100%, used Kaplan-Meier plots for the first 33 months and alternative parametric survival extrapolations beyond 33 months.</li> <li>• Based on CADTH's base case, nivolumab plus FOLFOX or XELOX was associated with an ICER of \$398,312 per QALY compared to FOLFOX or XELOX.</li> <li>• A price reduction of at least 95% would be needed for nivolumab plus FOLFOX or XELOX to be cost-effective at a WTP threshold of \$50,000 per QALY.</li> </ul>

5-FU = fluorouracil; HER2 = human epidermal growth factor receptor 2; ICER = incremental cost-effectiveness ratio; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; LY = life-years; QALY = quality-adjusted life-year; WTP = willingness to pay; XELOX = capecitabine plus oxaliplatin.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: meaningful uncertainty in estimated population size; inappropriate modelling of drug plan perspective and omission of drug wastage; outdated unit costs and inappropriate dosing; treatment cost of nivolumab was underestimated; the market share of nivolumab and comparators may not reflect likely use; and uncertainty in the treatment duration of nivolumab in combination with chemotherapy.

CADTH conducted reanalysis that included assuming 85% of patients have HER2-negative status, including drug wastage, assuming flat dosing of nivolumab, and excluding fluorouracil plus irinotecan and leucovorin from the market mix.

Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing nivolumab is expected to be \$198,898,038 (year 1: \$57,115,126; year 2: \$66,231,528; year 3: \$75,551,384). The estimated budget impact is sensitive to nivolumab dosing (weight-based versus flat dosing) and recurrence rate of HER2-negative advanced or metastatic GAC, GEJAC, or EAC.

## pERC Information

### Members of the Committee

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

**Meeting date:** January 12, 2022

**Regrets:** None

**Conflicts of interest:** None