

## CADTH Reimbursement Recommendation

# Nivolumab (Opdivo)

**Indication:** For the adjuvant treatment of completely resected esophageal or gastroesophageal junction cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy

**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 adjuvant treatment of completely resected esophageal or gastroesophageal junction (GEJ) cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (CRT) if certain conditions are met.

## Which Patients Are Eligible for Coverage?

Opdivo should only be covered to treat adult patients who have esophageal or GEJ cancer; who have been treated with chemoradiation followed by surgery to remove the cancer, but still have some cancer cells present; and who have a good performance status.

## What Are the Conditions for Reimbursement?

Opdivo should only be reimbursed if it is prescribed by a clinician who is experienced in treating cancer. Opdivo should not be used in combination with other adjuvant anti-cancer drugs. The price of Opdivo must be lowered to be cost-effective and affordable.

## Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that Opdivo was better than placebo in allowing patients to remain free of esophageal or GEJ cancer from returning.

Based on public list prices, Opdivo is not considered cost-effective at a willingness-to-pay threshold of \$50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to surveillance. A price reduction is therefore required. Economic evidence suggests that at least a 36% price reduction is needed to ensure Opdivo is cost-effective at a \$50,000 per QALY threshold.

Based on public list prices, the 3-year budget impact is \$122,873,802.

## Additional Information

### What Are Esophageal and GEJ Cancers?

Esophageal cancer occurs in the esophagus – a muscular tube that connects the throat to the stomach – and GEJ cancer occurs where the esophagus and the stomach join. About 70% to 75% of patients with esophagus or GEJ cancer still have some cancer cells present even after having been treated with chemoradiation followed by surgery, and do not live as long as patients who have no cancer cells present after chemoradiation and surgery.

### Unmet Needs in Patients With Esophageal and GEJ Cancers

Currently, there are no drugs available to treat patients who have esophageal or GEJ cancer that have been treated with chemoradiation followed by surgery, but still have some cancer cells present. The only treatment option after surgery is surveillance. For many of these patients, the cancer will return and spread in the esophagus or GEJ or to another part of the body.

### How Much Does the Opdivo Adjuvant Treatment Cost?

Treatment with Opdivo is expected to cost approximately \$9,387 per patient per 28-day cycle.

## Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that nivolumab be reimbursed for the adjuvant treatment of completely resected esophageal or GEJ cancer in patients who have residual pathologic disease following prior neoadjuvant CRT only if the conditions listed in Table 1 are met.

## Rationale for the Recommendation

One ongoing, phase III, double-blind, randomized controlled trial (CheckMate 577; N = 794) comparing nivolumab with placebo for the adjuvant treatment of completely resected esophageal or GEJ cancer in patients who had residual pathologic disease following prior neoadjuvant chemoradiotherapy demonstrated that treatment with nivolumab (240 mg given every 2 weeks by IV infusion for 16 weeks, followed by 480 mg every 4 weeks for a total duration of 1 year) resulted in added clinical benefit with a statistically significant and clinically meaningful improvement in disease-free survival (DFS; hazard ratio [HR] = 0.69; 96.4% confidence interval, 0.56 to 0.86; P = 0.0003) compared to placebo. No mature overall survival (OS) data were available; however, pERC agreed with the clinical experts that DFS was a meaningful outcome for patients on its own and is likely to be correlated with OS in the adjuvant setting. pERC also noted that nivolumab was associated with a manageable toxicity profile.

pERC agreed that there was a significant unmet need for this rare patient population in this setting given the poor prognosis of patients with residual pathologic disease after neoadjuvant therapy and complete resection, as well as the high risk of recurrence, and the lack of effective therapies for patients after neoadjuvant CRT and surgical resection. Patients identified a need for effective and convenient treatment options that could result in longer survival, improved quality of life, and fewer side effects. Given the totality of the evidence, pERC concluded that adjuvant therapy with nivolumab meets some of the needs identified by patients, including a need for effective treatments with manageable side effects and DFS benefit.

Results of the CheckMate 577 trial suggested no deterioration in health-related quality of life (HRQoL) during the treatment period with nivolumab; however, pERC was unable to draw any conclusions on the effect of nivolumab on HRQoL due to the exploratory nature of patient-reported outcomes in the trial.

Using the sponsor-submitted price for nivolumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio for nivolumab was \$79,241 per QALY compared with active surveillance. At this incremental cost-effectiveness ratio, nivolumab is not cost-effective at a \$50,000 per QALY willingness-to-pay threshold for completely resected patients with esophageal or gastroesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy. A reduction in price of at least 36% is required for nivolumab to be considered cost-effective at a \$50,000 per QALY threshold.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason
<b>Initiation</b>	
<p>1. Adjuvant treatment with nivolumab should only be initiated in adult patients who have all of the following:</p> <ul style="list-style-type: none"> <li>1.1. histologically confirmed predominant adenocarcinoma or squamous cell carcinoma of esophagus or GEJ</li> <li>1.2. completed neoadjuvant CRT</li> <li>1.3. complete resection of the tumour</li> <li>1.4. residual pathologic disease with a tumour and node classification status of ypT1 or ypN1, at minimum.</li> </ul>	<p>Evidence from the CheckMate 577 trial demonstrated that nivolumab resulted in a statistically and clinically significant improvement in disease-free survival in patients with the characteristics listed in this condition.</p>
<p>2. Patients should have a good performance status.</p>	<p>The CADTH review identified no evidence to demonstrate the benefit of adjuvant therapy with nivolumab in patients with an ECOG PS greater than 1. The CheckMate 577 trial included patients with an ECOG PS of 0 or 1. Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.</p>
<p>3. Treatment with nivolumab should be initiated within 4 to 16 weeks of complete resection.</p>	<p>Evidence from the CheckMate 577 trial demonstrated that nivolumab resulted in significant clinical benefit in patients who receive the drug within 4 to 16 weeks after complete surgical resection.</p>
<b>Renewal</b>	
<p>4. Patients should be assessed by the treating physician with diagnostic imaging conducted every 3 to 6 months.</p>	<p>Imaging assessments for the CheckMate 577 trial were performed every 12 weeks (approximately every 3 months). According to the clinical expert input, in clinical practice, patients would be assessed for disease progression every 3 to 6 months.</p>
<p>5. Nivolumab can be continued for an equivalent of 1 year of treatment; i.e., a maximum of:</p> <ul style="list-style-type: none"> <li>5.1. 17 cycles if administered at a dose of 240 mg over 30 minutes every 2 weeks for 16 weeks, followed by 480 mg over 30 minutes every 4 weeks beginning at week 17</li> <li>5.2. 13 cycles if administered at a dose of 480 mg over 30 minutes every 4 weeks for 16 weeks, followed by 480 mg over 30 minutes every 4 weeks beginning at week 17.</li> </ul>	<p>In the CheckMate 577 trial, patients were treated with nivolumab (started on 240 mg every 2 weeks for 16 weeks; cycles 1 to 8) followed by 480 mg every 4 weeks until disease progression or unacceptable toxicity for a total treatment period of 1 year (i.e., 17 cycles). When there were dose delays, patients could continue their treatment for up to 17 cycles (with a maximum dose delay of 6 weeks during cycles 1 to 8 and a maximum dose delay of 10 weeks for the remainder of the treatment).</p>

Reimbursement condition	Reason
<b>Prescribing</b>	
6. Nivolumab should be prescribed by clinicians with experience and expertise in treating advanced esophageal or GEJ cancer. The treatment should be supervised and delivered in outpatient specialized oncology clinics with expertise in systemic therapy and immunotherapy delivery.	To ensure that nivolumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.
7. Nivolumab should not be used in combination with other adjuvant anti-cancer drugs.	Nivolumab was administered as monotherapy in the CheckMate 577 trial; the CADTH review identified no evidence on the safety and potential benefits of combining nivolumab with any other treatments.
<b>Pricing</b>	
8. A reduction in price	The ICER for nivolumab is \$79,241 per QALY when compared with active surveillance.  A price reduction of at least 36% would be required for nivolumab to achieve an ICER of \$50,000 per QALY compared to active surveillance.
<b>Feasibility of adoption</b>	
9. 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 years 2 and 3. Furthermore, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.

CRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GEJ = gastroesophageal junction; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; ypN1 = pathologic lymph node stage 1; ypT1 = pathologic tumour stage 1.

## 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 from Table 1	Implementation considerations and guidance
3	The CheckMate 577 trial included patients within 4 to 16 weeks after complete resection of tumour. The clinical experts felt that it may also be reasonable to offer nivolumab, at the discretion of the treating clinician, to those patients who might fall just outside of the 16 week maximum time frame specified in the trial. However, in the absence of supporting evidence, pERC was unable to provide evidence-based guidance on the use of nivolumab after 16 weeks.

Condition number from Table 1	Implementation considerations and guidance
5	The CheckMate 577 trial did not permit dose modifications due to toxicity. However, nivolumab could be interrupted or delayed for a maximum of 6 weeks during the first 16 weeks or for a maximum of 10 weeks during the remainder of the treatment period. pERC noted that nivolumab should not be restarted if there is a treatment break of more than 8 to 10 weeks resulting from severe drug toxicity.
5	pERC agreed with the clinical experts that patients who receive nivolumab in the adjuvant setting may be rechallenged or retreated with a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting if the patient experiences a disease recurrence after a disease-free interval of 6 months or greater after completion of adjuvant therapy.
5	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 3mg/kg up to 240 mg every 2 weeks for the first 16 weeks followed by nivolumab 6mg/kg up to 480 mg every 4 weeks beginning 2 weeks after the last 3mg/kg dose).

PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

## Discussion Points

- Based on the input from clinical experts and patients, pERC acknowledged this is a rare patient population with a significant unmet medical need for new, effective, and safe adjuvant treatment options as patients with completely resected esophageal or GEJ cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy only follow-up option is currently post-operative surveillance. pERC agreed with the clinical experts that these patients have a high risk of recurrence, which is associated with an increased mortality rate and poor quality of life.
- pERC discussed the results of a randomized phase III (CheckMate 577) trial that demonstrated that nivolumab was associated with a significant improvement in DFS compared to placebo. The OS data were not mature at the time of the analysis. The clinical experts consulted by CADTH indicated that the goal of adjuvant treatment is primarily to improve the cure rate (i.e., reduce the risk of relapse). There was a doubling of median DFS in the trial, and the clinical expert indicated that this was likely to correlate with OS. DFS on its own is a meaningful end point for many patients.
- The CheckMate 577 trial included patients with stage II or stage III carcinoma of the esophagus or GEJ (per American Joint Committee on Cancer criteria, 7th edition), and patients with clinical stage I disease were excluded from the trial. pERC agreed with the clinical experts that in clinical practice, most patients with stage I disease would undergo upfront surgery without chemoradiation; however, a very small number of patients may end up receiving chemoradiation. pERC noted that, in those rare instances, it may be reasonable to consider treating patients who would otherwise meet the criteria for the CheckMate 577 trial with adjuvant immunotherapy.
- pERC noted that, in the CheckMate 577 trial, patients were required to have complete resection (R0), meaning they were surgically rendered free of disease with negative margins on resected specimens defined as no vital tumour present within 1 mm of the proximal, distal, or circumferential resection margins. The committee agreed with the clinical experts that, although the pivotal trial excluded patients with R1 resection, adjuvant therapy might be considered in clinical practice for patients with microscopic positive

margins because these patients are at a higher risk of recurrence with no other effective adjuvant therapy options.

- Patients indicated a need for effective treatment options that can prolong life, minimize adverse effects, and improve quality of life. pERC concluded that adjuvant therapy with nivolumab could meet some of the patients' needs by offering a clinically effective treatment with manageable side effects and DFS benefit. The CheckMate 577 trial results suggested no deterioration in HRQoL; however, pERC was unable to make any conclusions from the available data due to the exploratory nature of the patient-reported outcomes in the trial and substantial missing data on these outcomes.
- The Health Canada–recommended dose for nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks for 16 weeks, both followed by 480 mg of nivolumab every 4 weeks (all doses administered by IV over 30 minutes) until disease progression or unacceptable toxicity for a total treatment duration of 1 year. pERC noted that, although the pivotal trial used an every 2 weeks dosing schedule (i.e., 240 mg every 2 weeks for 16 weeks [cycles 1 to 8] followed by 480 mg every 4 weeks beginning at week 17 [cycles 9 to 17] for a total duration of 1 year), the 480 mg every 4 weeks dosing schedule may be adopted by some clinicians in clinical practice to reduce burden on clinic resources and patients (e.g., travel costs, chair time).
- pERC discussed the possibility of retreatment with downstream programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1) inhibitors in the advanced metastatic setting and its potential impact on nivolumab's cost-effectiveness, though acknowledged that exploring retreatment in the advanced metastatic setting would be considered out of scope. The impact is unknown as it was not explored in the sponsor's pharmacoeconomic submission.

## Background

Nivolumab has a Health Canada indication for the adjuvant treatment of completely resected esophageal or GEJ cancer in patients who have residual pathologic disease following prior neoadjuvant CRT. Nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to a PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, therefore blocking PD-1 pathway-mediated inhibition of T-cell antitumour immune response and reactivating T-cell antitumour immune response. It is available as 40 mg/4mL and 100 mg/10 mL (10 mg nivolumab/mL) single-use vials. The Health Canada–approved dose is 240 mg every 2 weeks or 480 mg every 4 weeks administered as IV infusion over 30 minutes. After completing 16 weeks of therapy, nivolumab is administered as 480 mg every 4 weeks until disease progression or unacceptable toxicity for a total treatment duration of 1 year.

## Sources of Information Used by the Committee

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

- a review of 1 ongoing, phase III, randomized, double-blind, placebo-controlled, multicenter superiority study in adult patients with esophageal or GEJ cancer who had residual pathologic disease following prior neoadjuvant CRT

- 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
- input from 2 clinical specialists with expertise in diagnosing and treating patients with esophageal carcinoma and GEJ adenocarcinoma
- input from 1 clinician group (Ontario Health – Cancer Care Ontario Gastrointestinal Drug Advisory Committee)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

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

### Patient Input

One patient group, My Gut Feeling – Stomach Cancer Foundation of Canada, provided input for this review. The patient group, which includes patients with esophageal or GEJ cancer, aims to support patients and caregivers by providing them with information, mentorship, and a platform to voice their opinions. The information collected in this input was based on an international survey, which was conducted between June 29, 2021, and July 16, 2021, with 11 patients and 4 caregivers (total of 15 respondents). Of the 15 participants, 1 patient who had surgically resected cancer and chemoradiation had been treated with nivolumab.

Regarding clinical symptoms, patient respondents with esophageal or GEJ cancer and caregiver respondents indicated that before diagnosis, most symptoms experienced were changes in appetite and pain. Other significant symptoms included weight loss, difficulty swallowing, nausea and vomiting, dumping syndrome, and reflux. Less frequently reported symptoms included bleeding, feeling a mass, ascites, bowel obstruction, food regurgitation, and shortness of breath. Respondents commented that these symptoms impacted their day-to-day life.

Regarding current treatment, more than half of patient respondents (60%) agreed to some degree that current treatment helped them manage their cancer symptoms. The remainder of patient respondents (40%) were neutral or dissatisfied with their treatments. The patient group noted that many aspects of patients' and caregivers' lives, such as physical, mental, social, financial, and occupational, have deteriorated as a result of diagnosis and treatment. All patients experienced at least 1 side effect from their therapies. Some side effects were well tolerated, but some led to hospitalization and/or delay in the subsequent treatment.

One patient respondent accessed nivolumab through a hospital special access program. The patient respondent indicated that no evidence of disease was confirmed by PET scan at 3 months following the nivolumab therapy. The respondent did not experience any new side

effects or exacerbation of side effects from surgery or chemoradiation, and they expressed strong satisfaction on improvement of quality of life.

Overall, the patient group indicated that there is an unmet need for the treatment of patients with esophageal or GEJ cancer. The patient group strongly supports the use of nivolumab for the adjuvant treatment of completely resected esophageal or GEJ cancer in patients who have residual pathologic disease following prior neoadjuvant chemoradiotherapy. The patient group expressed that patients and caregivers should have equitable access to treatment options that have the potential to improve quality and duration of life.

## Clinician Input

### Input From Clinical Experts Consulted by CADTH

The clinical experts consulted for this review indicated that the treatment goals include improving DFS, reducing the adverse effects, improving or maintaining HRQoL, and improving OS. There is currently no adjuvant therapy for patients with completely resected esophageal or GEJ cancer who do not achieve a pathologic complete response to neoadjuvant CRT. Nivolumab is the first adjuvant therapy based on phase III evidence that has demonstrated a significant DFS benefit. The clinical experts agreed that nivolumab would represent the new standard of care for adjuvant therapy for patients who do not achieve a pathologic complete response following neoadjuvant CRT. Given that no other treatment is available for this population, it would not be appropriate to recommend that patients try other treatments before initiating treatment with nivolumab adjuvant therapy.

The clinical experts indicated that all patients who receive neoadjuvant CRT and an esophagectomy with pathology showing no pathological complete response should be assessed for adjuvant nivolumab. Patients would need to have an Eastern Cooperative Oncology Group Performance (ECOG PS) of 0 or 1. Although not supported by clinical trial evidence, the experts also indicated that the treatment can be extended to patients with an ECOG PS of 2. Patient should have no contraindication to nivolumab. The clinical experts indicated that nivolumab is contraindicated for patients with an ECOG PS of 3 or 4. According to the clinical experts, it is not possible to identify those patients who are most likely to benefit from treatment with nivolumab. The clinical experts noted that based on the CheckMate 577 trial criteria, patients with R1 resection (e.g., patients with positive circumferential, distal, or proximal margins) would be excluded, and highlighted that the clinical management of patients with R1 resection may be similar to patients with R0 resection given the lack of available effective treatment options for patients with R1 resection. The clinical experts indicated that in clinical practice, clinicians may wish to use nivolumab for patients with R1 resection.

The clinical experts indicated that the goal of adjuvant treatment is primarily to improve the cure rate (i.e., reduce the risk of relapse), and believed that DFS would be a relevant and clinically meaningful outcome for the purpose of this review. The clinical experts indicated that an improved DFS was likely to correlate with an improvement in OS and, therefore, DFS may be considered as a surrogate for OS in adjuvant treatment. CT scans every 3 to 6 months, while on treatment, can be used to determine if a patient has disease recurrence and thus is no longer benefiting from nivolumab.

The clinical experts indicated that nivolumab should continue for 17 cycles or a total duration of 1 year (with a maximum dose delay of 10 weeks, as per the trial protocol) and

may be discontinued early if confirmed evidence of disease recurrence or unacceptable toxicity occurs.

The clinical experts indicated that nivolumab should be prescribed at an outpatient oncology clinic. Treatment should be supervised and delivered in institutions trained in chemotherapy delivery and administration.

According to the clinical experts, adjuvant treatment with nivolumab for this population represents a huge advance in the care of patients with esophageal and GEJ cancers. There is no adjuvant treatment for this population and nivolumab fulfills a major unmet need.

### Clinician Group Input

The Ontario Health – Cancer Care Ontario Gastrointestinal Drug Advisory Committee recognized the unmet needs in the current treatment algorithm for completely resected esophageal or GEJ cancer in patients who have residual pathologic disease following prior neoadjuvant CRT where the only option is post-operative surveillance. The clinician group indicated that this patient population has a high risk of recurrence associated with an increased mortality rate and poor quality of life. The clinician group expressed that patients should be offered nivolumab if they meet the eligibility criteria of the clinical trial and noted that outpatient chemotherapy suite settings were appropriate treatment settings for patients. The most important treatment goals identified by patients were to prolong life, delay disease progression, reduce the severity of symptoms, minimize adverse effects, and improve quality of life. The clinician group also highlighted that drug toxicity and disease recurrence are factors that should be considered when deciding to discontinue treatment. Finally, the clinician group expressed that nivolumab sets a new standard of care for this patient population.

### Drug Program Input

Input from PAG identified factors pertaining to relevant comparators, considerations for initiation of therapy, discontinuation of therapy, generalizability, care provision, system issues, and economic impacts. pERC weighed evidence from the CheckMate 577 trial and other clinical considerations, including input from the clinical experts consulted by CADTH, to provide responses that are presented in Table 3.

**Table 3: Summary of Implementation Questions From the Drug Plan and Clinical Expert Responses**

Implementation issues	Advice from CADTH
<b>Considerations for initiation of therapy</b>	
<p>In the CheckMate 577 trial, patients were randomized to receive either nivolumab or placebo within 4 to 16 weeks after surgery.</p> <p><b>What is considered the maximum time frame since surgical resection to initiate nivolumab?</b></p>	<p>The clinical experts consulted by CADTH noted that the pivotal trial included patients within 4 to 16 weeks after surgery and there was a significant benefit observed in the nivolumab arm even in the patients who received the drug 10 to 16 weeks after complete resection.</p> <p>pERC noted that it did not review data on the maximum time allowance for initiation of nivolumab after complete resection; however, pERC agreed with the clinical experts that it would be reasonable to initiate nivolumab within 16 weeks after surgery, as soon as the patient’s clinical condition permits, at the discretion of the treating physician.</p>

Implementation issues	Advice from CADTH
<p>PAG noted that pembrolizumab for the first-line treatment of locally advanced unresectable or metastatic esophageal or esophagogastric junction is also under CADTH review.</p> <p>PAG highlighted that in other solid tumours (e.g., lung, melanoma), patients are eligible for downstream PD-1 or PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of an adjuvant PD-1 or PD-L1 inhibitor.</p> <p><b>Can the same principle be applied in this setting?</b></p>	<p>The clinical experts consulted by CADTH acknowledged that currently there is emerging data for first-line therapy, as PD-1 or PDL-1 inhibitors have only recently been added to the treatment algorithm for metastatic esophageal cancer. The clinical experts noted that the 6-month window for rechallenge or retreatment is based on expert opinion as opposed to clinical trial data.</p> <p>While acknowledging that the optimal treatment for patients who progress on or after single immunotherapy is not known, pERC agreed with the clinical experts that it would be reasonable to consider rechallenge or retreatment if the relapse happens after a disease-free interval of 6 months or greater after completion of adjuvant therapy, which is consistent with common oncologic practice.</p>
<b>Considerations for discontinuation of therapy</b>	
<p>Although the CheckMate 577 trial did not permit dose modifications due to toxicity, nivolumab could be interrupted or delayed for a maximum of 6 weeks during the first 16 weeks or for a maximum of 10 weeks during the remainder of the treatment period.</p> <p>If treatment interruptions occur, should the remainder of the doses be given even if it will take more than a year to deliver the treatments, provided there has been no disease progression in between? For example:</p> <p><b>Scenario 1: The patient has received 2 months' worth of doses but had to take 5 months off. Should the remaining 10 months' worth of doses be given when the patient resumes treatment?</b></p> <p><b>Scenario 2: The patient has received 10 months' worth of doses but had to take 5 months off. Should the remaining 2 months' worth of doses be given when the patient resumes treatment?</b></p>	<p>The clinical experts consulted by CADTH noted that in both scenarios, a 5-month delay goes beyond the window of dose delay and therefore treatment should be discontinued. The clinical experts support treatment duration and delays as per the CheckMate 577 protocol that indicates patients are permitted to receive 52 weeks of nivolumab (as this allows for q2w or q4w dosing) with a maximum delay of 10 weeks.</p> <p>pERC noted that nivolumab should not be restarted if there is a treatment break of more than 8 to 10 weeks due to severe toxicity.</p>
<b>Considerations for prescribing of therapy</b>	
<p>PAG noted that jurisdictions will implement weight-based dosing up to a cap, similar to other immunotherapy policies (i.e., nivolumab 3mg/kg up to 240 mg every 2 weeks for the first 16 weeks followed by nivolumab 6mg/kg up to 480 mg every 4 weeks beginning 2 weeks after the last 3mg/kg dose).</p>	<p>The clinical experts acknowledge PAG's pragmatic weight-based dosing with a cap approach and noted PAG's dosing approach for this indication is not supported by phase III clinical trial evidence.</p> <p>pERC agreed that a weight-based dosing up to the cap, similar to other immunotherapy policies, may be appropriate for dosing with nivolumab.</p>
<b>Generalizability</b>	
<p>Eligibility criteria for the CheckMate 577 trial included patients with an ECOG PS of 0 or 1. Patients with an ECOG PS of greater than 1 were excluded from the trial.</p> <p><b>Can nivolumab use be extended to patients with an ECOG PS of greater than 1?</b></p>	<p>Although not supported by the clinical trial evidence, pERC agreed with the clinical experts consulted by CADTH indicated that patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.</p>

Implementation issues	Advice from CADTH
<p>PAG noted that the current standard of care after surgery is surveillance.</p> <p><b>For patients who are already in active surveillance, is there a maximum time frame since surgical resection to allow such patients access to nivolumab?</b></p>	<p>As previously noted, the clinical experts consulted by CADTH highlighted that there is no data to support a maximum time from surgery. The clinical experts noted that up to 16 weeks could be considered as the reference time frame, though, it would also be reasonable to allow for physician's discretion (for those patients who fall just outside of 16 weeks). However, pERC was unable to provide guidance in the absence of any supporting evidence.</p>
Funding algorithm	
<p>As highlighted previously, PAG noted that the current standard of care after surgery is surveillance and that pembrolizumab for the first-line treatment of locally advanced unresectable or metastatic esophageal or esophagogastric junction is also under CADTH review.</p> <p><b>Do you expect that nivolumab would impact the treatment paradigm such that surveillance and subsequent lines of therapy (i.e., in the locally advanced unresectable or metastatic esophageal or esophagogastric junction setting) will be impacted?</b></p>	<p>The clinical experts consulted by CADTH highlighted that nivolumab would represent the new standard of care for adjuvant therapy for patients who do not achieve a pathologic complete response following neoadjuvant CRT, as nivolumab is the first adjuvant therapy based on phase III trial evidence that has demonstrated a significant disease-free survival benefit.</p> <p>pERC agreed with the clinical experts that the future treatment paradigm will be impacted if pembrolizumab and/or nivolumab are funded in the first-line metastatic setting. Patients who receive nivolumab in the adjuvant setting and progress or relapse within 6 months may not warrant retreatment with a PD-1 or PD-L1 inhibitor.</p>
System and economic issues	
<p>The sponsor estimates a 3-year pan-Canadian budget of \$53.7 million, based on the market share uptake of ██████████, respectively, in years 1 to 3. The uptake is likely to be much more rapid because nivolumab will become the new standard of care for an aggressive disease that is associated with a high risk of recurrence.</p>	<p>The clinical experts consulted by CADTH indicated that in the absence of adjuvant treatment options for completely resected esophageal cancer or gastroesophageal junction cancer in current clinical practice, there is an unmet need in these patients. Therefore, clinical experts anticipated a rapid market uptake.</p> <p>pERC agreed with the clinical experts that complete market uptake may not be reached, as some patients may not be eligible for nivolumab due to pre-existing immune conditions, a deterioration of health, or delayed recovery after complete resection. Further, a small minority of patients may refuse treatment altogether.</p>

CRT = chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; PAG = Provincial Advisory Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; q2w = 240 mg every 2 weeks for 16 weeks (cycles 1 to 8) followed by 480 mg every 4 weeks beginning at week 17 (cycles 9 to 17); q4w = 480 mg every 4 weeks.

## Clinical Evidence

The CheckMate 577 trial is an ongoing, phase III, randomized, double-blind, placebo-controlled, multicenter superiority study comparing nivolumab with placebo for the adjuvant treatment of completely resected esophageal or GEJ cancer in adult patients who have residual pathologic disease following prior neoadjuvant CRT. Patients were required to be rendered free of disease (defined as no vital tumour present within 1 mm of the proximal, distal, or circumferential resection margins) with a complete resection performed within 4 to 16 weeks before randomization.

The trial was conducted in 170 sites in 29 countries (including Canada, US, UK, Australia, and other European, South American, and Asian countries).

The primary objective of the CheckMate 577 trial was to compare DFS of nivolumab versus placebo in patients with completely resected esophageal or GEJ cancer. The secondary objective was to compare OS of nivolumab versus placebo. The main exploratory objectives included assessment of overall safety and tolerability, distant metastasis-free survival (DMFS), EQ-5D 3-Levels and Visual Analogue Scale, and patient's cancer-related quality of life using the Functional Assessment of Cancer Therapy – Esophageal (FACT-E) questionnaire and selected components such as the esophageal cancer subscale (ECS), Functional Assessment of Cancer Therapy – General (FACT-G), and Functional Assessment of Cancer Therapy – General 7 (FACT-G7).

A total of 1,085 patients were screened, and 794 patients were randomized in a 2:1 ratio to receive nivolumab (n = 532) or placebo (n = 262). Randomization was done centrally using the Interactive Web Response System. Randomization was stratified by the following 3 factors: histology (squamous versus adenocarcinoma), pathologic lymph node status (positive [ $\geq$  ypN1] versus negative [ypN0]) and tumour cell PD-L1 status ( $\geq$  1% versus < 1% or indeterminate or non-evaluable). The first patient was randomized on July 14, 2016, and the last patient was enrolled in August 2019. A total of 792 patients received at least 1 dose of nivolumab or placebo, as assigned. While all patients in the nivolumab arm received at least 1 dose, 2 patients in the placebo arm did not receive the treatment.

Prespecified interim analysis results (cut-off date of July 3, 2020) for the primary outcome, DFS, were provided in the sponsor's submission. The sponsor indicated that the interim DFS result was considered as the final result because the DFS interim analysis met the prespecified statistical significance criteria.<sup>3</sup> The study is ongoing, with an estimated study completion date of October 11, 2025.

## Efficacy Results

At the interim analysis as of database lock (July 3, 2020), nivolumab demonstrated a statistically significant and clinically meaningful improvement in DFS compared with placebo (HR = 0.69; 95% CI, 0.56 to 0.86; P value = 0.0003), which implies a 31% reduction in the risk of recurrence or death with the nivolumab adjuvant treatment compared with placebo (the current standard of care is active surveillance). The observed median DFS was twice as long in the nivolumab arm compared with the placebo arm (22.41 months versus 11.04 months in the nivolumab and placebo arms, respectively). DFS rates at 6 months were higher in the nivolumab arm compared with the placebo arm (72.3% versus 63.4%). In addition, the results from various subgroup analyses and sensitivity analyses were consistent with the primary analysis.

As the secondary outcome, the OS was not mature at the data-cut-off; therefore, OS is not available for this review.

Patient-reported and HRQoL outcomes were assessed as exploratory outcomes. Overall, the study demonstrated no deterioration or maintenance from baseline in HRQoL with the treatment of nivolumab or placebo.

The improved benefit of nivolumab over placebo was also supported by the DMFS results, as the median DMFS was numerically longer in the nivolumab arm than the placebo arm (28.32 months versus 17.61 months), with an HR of 0.74 (95% CI, 0.60 to 0.92). However, DMFS was an exploratory outcome in the CheckMate 577 study.

### Harms Results

Overall, the frequency of any grade adverse events and serious adverse events were similar in both nivolumab and placebo arms. The most common adverse events ( $\geq 20\%$  in either of the arms) were “investigations” including [REDACTED], [REDACTED], diarrhea (29.1% versus 29.2%), fatigue (27.1% versus 24.2%), and nausea (22.7% versus 21.2%). More patients treated with nivolumab experienced treatment-related adverse events and serious adverse events than patients treated with placebo. Numerically, more patients discontinued from treatment due to adverse events or treatment-related adverse events in the nivolumab arm compared with the placebo arm. Notable adverse events, including pneumonitis and myocarditis, were less than 5% in any arms [REDACTED]. Of note, pneumonitis and myocarditis were all-causality adverse events [REDACTED]. Overall, the clinical experts indicated that the nivolumab safety profile in this study was acceptable, manageable, and consistent with the known safety profile of nivolumab, and no additional safety signals were identified with adjuvant nivolumab monotherapy.

### Critical Appraisal

The included pivotal study (CheckMate 577) was a double-blind, randomized, placebo-controlled study. Overall, it was well-designed. OS data were not mature at the time of the data-cut-off; however, according to the clinical experts consulted by CADTH, DFS is a relevant and clinically important primary outcome for the adjuvant treatment in this population and is likely to be correlated with OS in the adjuvant setting.

The patient-reported and HRQoL outcomes (i.e., ECS, FACT-E, FACT-G7, FACT-G, and ED-5D-3L) were assessed as exploratory outcomes. No formal statistical analysis was performed to compare the patient-reported and HRQoL outcomes between the 2 treatment arms. In addition, there is a potential risk of bias because of substantial missing data on these outcomes. As well, there may have been differential recall bias. Overall, the magnitude and direction of the impact of these missing data and recall bias on the patient-reported and HRQoL outcomes is unknown. Therefore, these patient-reported outcomes and HRQoL findings were inconclusive.

No major generalizability issue was noted regarding the findings from the pivotal study.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 4: Summary of Economic Evaluation**

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Completely resected patients with esophageal or gastroesophageal cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy

Component	Description
<b>Treatment</b>	Nivolumab
<b>Submitted price</b>	Nivolumab, 40 mg and 100 mg single-use vials: \$782.22 per 4 mL vial (\$19.56 per mg) \$1,955.56 per 10 mL vial (\$19.56 per mg)
<b>Treatment cost</b>	At the submitted price, the average 28-day cost of nivolumab is estimated to be \$9,387 per patient.
<b>Comparator</b>	Active surveillance (no systemic treatments)
<b>Perspective</b>	Canadian publicly funded health care payer
<b>Outcomes</b>	QALYs; LYs
<b>Time horizon</b>	30 years
<b>Key data source</b>	CheckMate-577 trial: Transitions from pre-recurrence to post-recurrence based on DFS, pre-recurrence to death based on the risk of death among trial participants (up to 3 years) Netherlands Comprehensive Cancer Organization: Transition from post-recurrence to death
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>• The long-term survival benefits of nivolumab were associated with high uncertainty due to immature OS data. The clinical experts consulted by CADTH advised that predicted DFS was not aligned with clinical expectations and felt that this was overestimated beyond 3 years.</li> <li>• The sponsor used DFS data, which captures first recurrence or death, to inform the transition from pre-recurrence to post-recurrence, and as the model also accounts for death in the pre-recurrence health state, the death events are double-counted. This limitation may introduce a survival benefit favouring nivolumab as the risk of death was likely higher among patients in the active surveillance arm. Although it is more appropriate to use time-to-recovery data to derive transition probabilities of recurrence, these data were not submitted as part of a clinical study report.</li> <li>• The sponsor's model included a terminal care cost up to the cure point (i.e., 3 years). This approach underestimated the total cost of care. Terminal care costs should be applied to all patients who transition to death regardless of their cure status, otherwise downstream costs in those cured are not being accurately captured.</li> <li>• CADTH identified limitations regarding the health utility values used by the sponsor. The sponsor's estimates did not adjust for the baseline utility in regression analyses. The imbalance in mean baseline utility between trial arms may cause misleading ICERs.</li> <li>• The sponsor used a weight-based approach to calculate the cost of nivolumab. The clinical experts consulted by CADTH advised that it was more appropriate to use the dosage regimen indicated in a Health Canada-approved product monograph for drug cost calculation.</li> </ul>
<b>CADTH reanalysis results</b>	<ul style="list-style-type: none"> <li>• In CADTH's base case, the following revisions were made: corrected subsequent chemotherapy regimens and unit costs; assumed no vial sharing; used a flat dose for nivolumab; applied the same proportions of patients requiring subsequent chemotherapy to both nivolumab and active surveillance; assigned a terminal care cost to any patient who transitions to death; used 5 years as a cure time point; and used a 2-knot spline hazard to predict DFS for nivolumab.</li> <li>• In CADTH's base case, compared to active surveillance, nivolumab was associated with an ICER of \$79,241 per QALY. A price reduction of at least 36% would be needed for nivolumab to be cost-effective at a WTP threshold of \$50,000 per QALY.</li> <li>• The cost-effectiveness of nivolumab was sensitive to the assumption regarding the cure time point, followed by parametric models used to extrapolate DFS data.</li> </ul>

DFS = disease-free survival; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; WTP = willingness to pay.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of individuals eligible for nivolumab treatment was underestimated; treatment acquisition costs of nivolumab and subsequent chemotherapies were underestimated, with some missing regimens and errors in cost calculations; and there was significant uncertainty in the market share of nivolumab.

CADTH conducted reanalyses that included: including patients with stage I esophageal or GEJ cancer, aligning assumptions made in estimating nivolumab's treatment cost with the product monograph, assuming a higher market share of nivolumab, and assuming no difference in the distribution of patients on subsequent chemotherapies.

Although the sponsor suggested that nivolumab would be associated with a budget impact of \$53,674,419 over the 3-year time horizon, based on the CADTH reanalysis, the budget impact of introducing nivolumab to the public drug plans is expected to be \$33,999,272 in year 1; \$44,194,197 in year 2; and \$44,680,333 in year 3; for a 3-year total of \$122,873,802.

## pan-Canadian Oncology Drug Review Expert Review Committee Information

### Members of the Committee

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

**Meeting date:** December 1, 2021

**Regrets:** None

**Conflicts of interest:** None