

CADTH Reimbursement Recommendation

Nivolumab (Opdivo)

Indication: As a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC

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 should be reimbursed by public drug plans as a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

Which Patients Are Eligible for Coverage?

Opdivo should only be covered in patients with UC that spreads into the muscle layer, was removed by surgery, and is at high risk of coming back. Patients should have either received cisplatin-based neoadjuvant chemotherapy or not have received neoadjuvant cisplatin-based chemotherapy and be ineligible or eligible for adjuvant cisplatin-based chemotherapy but decline to take it.

What Are the Conditions for Reimbursement?

Opdivo should only be reimbursed if prescribed by qualified practitioners with expertise in treating UC, systemic therapy delivery, and management of immunotherapy-related side effects, and if the cost of Opdivo is reduced. Patients should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that patients treated with Opdivo experienced a delay until their cancer returned. Opdivo meets the needs of patients for treatments that reduce the risk of UC coming back, maintain quality of life, and have manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Opdivo does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Opdivo is estimated to cost the public drug plans approximately \$180 million over the next 3 years. However, the actual budget impact is uncertain.

Additional Information

What Is UC?

Urothelial cancer (UC) is a type of bladder cancer. It begins in the urothelial cells that line the urethra, bladder, ureter, and renal pelvis. Muscle-invasive UC has spread into the muscle layer, and about 40% to 50% of patients survive no longer than 5 years.

Unmet Needs in UC

Patients with muscle-invasive UC that has been removed by surgery and that has a high risk to come back are in need of treatment options that prevent or delay the cancer from returning, prolong survival with an acceptable toxicity profile, and maintain quality of life.

How Much Does Opdivo Cost?

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

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nivolumab be reimbursed as a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multi-centre, randomized, double-blind, phase III trial (CheckMate-274, N = 709) demonstrated that treatment with adjuvant nivolumab resulted in added clinical benefit compared with placebo in patients with UC who are at high risk of recurrence after undergoing radical resection of muscle-invasive UC (MIUC). The CheckMate-274 trial showed a statistically significant and clinically meaningful improvement in disease-free survival (DFS) with nivolumab compared with placebo, with a hazard ratio (HR) of 0.70 (98.22% CI, 0.55 to 0.90; P = 0.0008). The secondary outcome, non-urothelial tract recurrence-free survival (NUTRS), was supportive of the observed DFS benefit with nivolumab. The adverse event (AE) results from the CheckMate-274 trial indicated that nivolumab was generally well tolerated and pERC considered the AEs to be manageable.

Patients expressed a need for treatments that can prevent recurrence, control disease progression, maintain quality of life, and have manageable side effects. pERC concluded that nivolumab met some of the needs identified by patients as it delays recurrence and controls disease progression compared with placebo, and has manageable side effects. Although patients expressed an unmet need for treatments that maintain quality of life, no definitive conclusion could be reached regarding the effects of nivolumab on health-related quality of life (HRQoL), due to a significant decline in the number of patients available to provide HRQoL assessments over time and a lack of statistical testing.

Using the sponsor-submitted price for nivolumab and publicly listed prices for all other drug costs, in patients who had received neoadjuvant chemotherapy or were not eligible to receive adjuvant chemotherapy, the incremental cost-effectiveness ratio (ICER) for nivolumab was \$112,826 per quality-adjusted life-year (QALY) compared with observation. A price reduction is required for nivolumab to be considered cost-effective at a \$50,000 per QALY threshold. In patients who had not received neoadjuvant chemotherapy and who were eligible to receive adjuvant chemotherapy, nivolumab does not represent a cost-effective treatment; as suggested by the sponsor, nivolumab is less effective and more costly. Given the high cost of treatment and uncertain clinical benefits in this population, even at a 100% price reduction, nivolumab is not a cost-effective treatment.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nivolumab should only be reimbursed when initiated in	Evidence from the CheckMate-274 trial demonstrated that adjuvant treatment	In the CheckMate-274 trial, patients were deemed ineligible for adjuvant cisplatin--

Reimbursement condition	Reason	Implementation guidance
<p>patients who have all of the following.</p> <ol style="list-style-type: none"> 1.1. Pathologic evidence of urothelial carcinoma (UC) at high risk of recurrence based on pathologic staging of radical surgery tissue in patients who have either: <ol style="list-style-type: none"> 1.1.1. received cisplatin-based neoadjuvant chemotherapy (ypT2-pT4a or ypN+) or 1.1.2. not received neoadjuvant cisplatin chemotherapy (pT3-pT4a or pN+) and are ineligible for adjuvant therapy with cisplatin chemotherapy (based on Galsky ineligibility criteria, 2011)^a or 1.1.3. not received neoadjuvant cisplatin chemotherapy (pT3-pT4a or pN+) and are eligible for adjuvant cisplatin-based chemotherapy but decline to take it. 1.2. Evidence of no recurrence confirmed before initiating therapy. 1.3. Muscle-invasive UC (MIUC) at disease diagnosis. 	<p>with nivolumab resulted in a statistically and clinically significant improvement in DFS in patients with characteristics listed in this condition.</p>	<p>based chemotherapy according to the Galsky criteria^a:</p> <ul style="list-style-type: none"> • creatinine clearance (using the Cockcroft-Gault formula) < 60 mL/min • CTCAE version 4, grade 2 or above audiometric hearing loss • CTCAE version 4, grade 2 peripheral neuropathy • ECOG PS 2 • New York Heart Association (NYHA) Class III or IV Heart Failure <p>Patients with a GFR of > 50 mL/min and those with hearing loss may be treated with cisplatin-based chemotherapy at the discretion of the treating clinician and if patients prefer to receive adjuvant chemotherapy after a discussion of the clinical risks.</p> <p>Based on clinical expert opinion, the small patient population with tumours of the urethra who are at high risk of recurrence after undergoing radical resection of UC should also be eligible.</p>
<ol style="list-style-type: none"> 2. Patients must not have any of the following: <ol style="list-style-type: none"> 2.1. metastatic disease 2.2. active autoimmune disease. 	<p>The CheckMate-274 trial excluded patients with metastatic disease and active autoimmune disease. There is no evidence to suggest these patients will benefit from treatment with adjuvant nivolumab.</p>	<p>—</p>
<ol style="list-style-type: none"> 3. Patients should have good performance status. 	<p>Patients with ECOG PS of 0 or 1 were included in the CheckMate-274 trial.</p>	<p>Patients with ECOG PS of 2 may be treated at the discretion of the treating clinician.</p>
<ol style="list-style-type: none"> 4. Treatment with nivolumab should be initiated in patients within 120 days after completion of local therapy. 	<p>The CheckMate-274 trial included patients who had undergone radical surgical resection within 120 days before randomization.</p>	<p>—</p>

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
5. Nivolumab should be discontinued upon the occurrence of either of the following: 5.1. disease recurrence 5.2. unacceptable toxicity.	Consistent with clinical practice, patients in the CheckMate-274 trial discontinued treatment upon progression or unacceptable toxicity.	—
6. Patients should be assessed for disease recurrence every 3 to 6 months.	Consistent with clinical practice, imaging and clinical assessments in the CheckMate-274 trial were performed every 12 weeks until Week 96, every 16 weeks until Week 160, then every 24 weeks).	—
7. Nivolumab should be reimbursed for a maximum of 1 year (240 mg IV every 2 weeks or 480 mg IV every 4 weeks).	Consistent with the product monograph and the CheckMate-274 trial, patients received nivolumab for a maximum of 1 year.	If treatment with nivolumab is interrupted or delayed in the absence of disease progression, it would be reasonable to administer remaining doses of nivolumab.
Prescribing		
8. Treatment should be prescribed by clinicians with expertise and experience in treating urothelial cancer. The treatment should be supervised and delivered in hospital outpatient clinics with expertise in systemic therapy delivery and management of immunotherapy-related side effects.	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	Nivolumab may be given at a dose of 480 mg IV every 4 weeks instead of 240 mg IV every 2 weeks. It can be given based on weight at 3 mg/kg IV every 2 weeks, up to a cap of 240 mg; or 6 mg/kg IV every 4 weeks, up to a cap of 480 mg.
9. Nivolumab should only be reimbursed when administered as monotherapy.	There are no data supporting the efficacy and safety of nivolumab when used in combination with additional anticancer drugs.	—
Pricing		
10. A reduction in price	The ICER for nivolumab is uncertain. In patients who had received neoadjuvant chemotherapy or were not able to receive adjuvant chemotherapy, the ICER for nivolumab was \$112,386 per QALY when compared with observation. A price reduction of at least 56% would be required for nivolumab to be able to achieve an ICER of \$50,000 per QALY compared to observation.	—
11. A reduction in price	The ICER for nivolumab is uncertain. In patients who had not received neoadjuvant chemotherapy and were able to receive adjuvant chemotherapy,	—

Reimbursement condition	Reason	Implementation guidance
	<p>the evidence provided indicated nivolumab was more costly and less effective when compared with adjuvant chemotherapy.</p> <p>Given the poorer clinical outcomes, non-drug costs were such that, with a 100% price reduction for nivolumab, adjuvant chemotherapy remained the optimal treatment at \$50,000 per QALY willingness to pay threshold.</p>	
Feasibility of adoption		
12. The feasibility of adoption of nivolumab must be addressed.	<p>At the submitted price, the budget impact of nivolumab is expected to be greater than \$40 million in each of years 1, 2, and 3.</p> <p>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 estimates.</p>	—

CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER = incremental cost-effectiveness ratio; MIUC = muscle-invasive urothelial carcinoma; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

*Criteria for cisplatin ineligibility by Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. The Lancet Oncology. 2011;12(3):211 to 214.

Discussion Points

- pERC agreed with the clinical experts that muscle-invasive UC is an aggressive disease with poor prognosis for patients who develop metastatic disease after initial therapy. There is an unmet need for effective treatment options in patients at high-risk of disease recurrence after undergoing radical resection of UC.
- pERC discussed the clinical meaningfulness of DFS in the setting of adjuvant therapy post-cystectomy in patients at high risk of recurrence. pERC noted that an increase in DFS has not shown to reliably predict improvement in overall survival (OS) in this patient population. However, pERC agreed with clinicians that DFS is an established clinical end point in the current target setting. The committee agreed that an absolute improvement of 10 months median DFS with nivolumab compared with placebo as observed in the CheckMate-274 trial is clinically meaningful in patients at high risk of recurrence and a median post-recurrence survival of less than 2 years.
- After a median follow-up time of 20.9 months and 19.5 months in the nivolumab and placebo groups, respectively, the number of deaths to trigger the first OS interim analysis had not been reached, leading to uncertainty regarding long-term survival benefits of nivolumab. Even with sufficient follow-up time, OS results may be confounded, as patients were permitted to receive subsequent anticancer therapies including immunotherapies upon recurrence.

- pERC discussed other available treatment options in the requested patient population. pERC noted that there is no consensus regarding the optimal management of patients, who did not receive neoadjuvant chemotherapy and are eligible for cisplatin-based adjuvant chemotherapy. pERC noted that patients may receive adjuvant chemotherapy depending on various factors such as prior therapies, patient values and preferences, comorbidities, and anticipated toxicities from adjuvant treatment. In the absence of a direct comparison of adjuvant nivolumab treatment with adjuvant chemotherapy, pERC considered the results of a sponsor-submitted indirect treatment comparison (ITC). pERC discussed that no firm conclusions could be drawn about the comparative effectiveness of adjuvant nivolumab versus adjuvant chemotherapy based on the results from the ITC due to substantial heterogeneity across study designs and populations. pERC highlighted the importance of patient-centred care, and noted that the choice to initiate adjuvant therapy should be based on shared decision-making and a discussion of clinical evidence on the available treatment options in the adjuvant setting, risks and benefits of treatment options, and the patient's informed preferences.
- pERC discussed the toxicity profile observed in the CheckMate-274 trial, and agreed with the clinical experts consulted by CADTH and the clinician group inputs that incidence and severity of adverse reactions appeared consistent with the known safety profile of nivolumab. The most frequently reported AEs (any grade) with nivolumab included pruritus, diarrhea, fatigue, and [REDACTED], which are manageable by clinicians who are used to dealing with immune-related AEs. No new safety signals were reported with regard to immune-mediated AEs.
- pERC noted that all study participants in the CheckMate-274 trial had MIUC at disease diagnosis. pERC discussed the extension of eligibility to the small patient population with tumours of the urethra, which are part of UC but not MIUC. pERC agreed that it would be reasonable to generalize the CheckMate-274 trial results to patients with tumours of the urethra who are at high risk of recurrence after undergoing radical resection of UC. pERC noted that it is unlikely that there will be trials specifically designed for this small group of patients.
- Based on the CheckMate-274 trial, the estimated proportion of patients who had received prior neoadjuvant cisplatin-based chemotherapy or were not able to receive adjuvant cisplatin-based chemotherapy [REDACTED] to receive adjuvant chemotherapy (though based on the trial population, very few were willing). These proportions may be informative in estimating an overall price reduction for the full patient population.
- pERC noted that nivolumab is a costly treatment, and the estimated budget impact of reimbursing nivolumab may have implications for the feasibility of adoption, particularly if uptake of nivolumab is high, as is expected.

Background

Bladder cancer is the fifth most common cancer in Canada, resulting in an estimated 2,600 deaths in 2020; an estimated 12,500 new cases of bladder cancer were projected in Canada in 2021. The most common histological type of bladder cancer is UC, which typically arises in the bladder but may develop in any location lined with urothelium, including the renal pelvis, ureter, urethra, and prostatic urethra. Approximately 33% to 40% of patients with bladder cancer present with or progress to muscle-invasive disease.

Radical surgery (e.g., cystectomy) with regional lymphadenectomy along with cisplatin-based combination chemotherapy is considered the therapeutic gold standard for MIUC. The Canadian Urological Association guideline recommends that eligible patients with muscle-invasive bladder cancer (cT2-T4a N0 M0) should be considered to receive neoadjuvant cisplatin-based combination chemotherapy. There is a lack of high-quality evidence in patients with upper tract UC (UTUC) due to their small number. However, because both share similar etiology, findings for bladder cancer are generalized to patients with UTUC. The Canadian Urological Association guideline recommends that adjuvant cisplatin-based chemotherapy should be offered to patients with high risk of recurrence (pT3-T4 and/or N+) who are eligible for cisplatin-based chemotherapy and have not received neoadjuvant chemotherapy. The 5-year survival rate has been estimated to be 40% to 50% for patients with high-risk residual disease of pT3-pT4 pN- or any pT pN+ at radical cystectomy followed by cisplatin-based chemotherapy upon recurrence.

The clinical experts and clinician groups consulted by CADTH agreed that there is an unmet need for effective treatment options that improve OS and DFS in patients at high risk of disease recurrence at cystectomy. Specifically, the clinical experts felt that there was an unmet need in patients who have not received neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy, and in patients who present with significant high-risk features at cystectomy after treatment with neoadjuvant cisplatin-based chemotherapy. These patients currently do not have any active adjuvant treatment options.

The reimbursement request submitted by the sponsor for review by CADTH, which is identical to the proposed Health Canada indication, is for nivolumab (240 mg every 2 weeks or 480 mg every 4 weeks, IV administration) as a monotherapy for the adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection of MIUC. Nivolumab is available as IV infusion (sterile solution of injection 40 mg nivolumab/4mL and 100 mg nivolumab/10 mL). The recommended dosage is 240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (60-minute IV infusion).

Sources of Information Used by the Committee

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

- a review of 1 randomized controlled trial (RCT) in patients at high-risk of recurrence after radical resection of MIUC and 1 sponsor-submitted and 1 published ITC
- patients' perspectives gathered by 1 patient group: Bladder Cancer Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise diagnosing and treating patients with MIUC
- input from 2 clinician groups, Bladder Cancer Canada and the Ontario Health (Cancer Care Ontario) Genitourinary (GU) Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient advocacy group, Bladder Cancer Canada, provided input for adjuvant treatment of patients with MIUC who are at high risk of recurrence after undergoing radical resection. The group gathered information through online surveys and one-to-one telephone interviews and responses from a total of 7 patients (6 patients from Canada and 1 patient from the US) were included in the patient input. All patient respondents (N = 7) reported having been diagnosed with MIUC, and 2 patients reported receiving nivolumab (one patient indicated receiving nivolumab for the adjuvant treatment following radical resection and the other patient reported having received nivolumab in combination with ipilimumab).

When Bladder Cancer Canada asked respondents to indicate their experience with treatments they have undergone since diagnosis, most patient respondents (n = 6) reported having received radical cystectomy. Additional treatments received by patient respondents included cisplatin and gemcitabine (received by 3 patients each), transurethral resection (received by 2 patients), and methotrexate, vinblastine, doxorubicin, plus cisplatin and antibody drug conjugates (received by 1 patient each). Patients reported fatigue to be the most common as well as “the most-difficult-to-tolerate” side effect of these treatments, followed by nausea and constipation. Two respondents indicated that they had to be hospitalized due to side effects from treatment.

According to the patient input received, respondents expected new treatments to improve the following key outcomes: preventing recurrence, controlling disease progression, reducing symptoms, maintaining quality of life, and managing side effects. Bladder Cancer Canada indicated that participants rated preventing recurrence as the most important outcome, and managing side effects as the least important outcome. According to Bladder Cancer Canada, the patients’ responses were indicative of a willingness to tolerate side effects if treatment was effective. Furthermore, when Bladder Cancer Canada asked specifically about their willingness to tolerate new side effects from treatment that could control disease progression or prevent recurrence, most patient respondents were supportive of tolerating side effects if the treatment showed benefit.

Patient respondents (n = 2) who had direct experience with nivolumab indicated that, overall, nivolumab was an effective treatment, controlling disease progression and preventing recurrence. One patient also reported having improved cancer symptoms, side effects, and quality of life, while the other patient indicated having slightly worse side effects and quality of life. One patient indicated having experienced the following side effects with nivolumab: itchy skin (pruritus) and fatigue. The other patient reported the following side effects from treatment with nivolumab: diarrhea, joint swelling, colitis, and pneumonitis. In addition, this patient experienced immune-checkpoint inhibitor (ICI)-related interstitial lung disease. However, this patient received both nivolumab and ipilimumab, and the patient reported that the treating respirologist did not indicate which drug caused the lung disease. Overall, 1 patient reported that the side effects of nivolumab were completely tolerable, while the other patient noted that they were somewhat challenging. Overall, both patient respondents noted that they would recommend nivolumab to other patients with MIUC.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH agreed that there is an unmet need for effective treatment options that improve OS and DFS in patients at high risk of disease recurrence, who have not received neoadjuvant chemotherapy and are ineligible for adjuvant cisplatin-based chemotherapy for medical reasons; and in patients who present with residual disease at cystectomy after treatment with neoadjuvant cisplatin-based chemotherapy. The clinical experts noted that data on nivolumab compared to cisplatin-based chemotherapy in patients who have not received neoadjuvant chemotherapy, and are eligible to receive cisplatin-based chemotherapy, were not available from the CheckMate-274 trial. Given the absence of robust comparative data between adjuvant nivolumab and adjuvant chemotherapy, the clinical experts consulted by CADTH were uncertain whether nivolumab addressed an unmet need in patients at high risk of recurrence who are eligible for adjuvant cisplatin-based chemotherapy. The clinical experts anticipated that adjuvant nivolumab would be the preferred treatment over adjuvant chemotherapy in select clinical circumstances only (e.g., gemcitabine allergy or strong patient preference against chemotherapy).

If publicly available, nivolumab could increase the number of patients who receive adjuvant systemic therapy, as some providers may underutilize perioperative systemic chemotherapy, or do not refer their patients for consideration of treatment. In the experts' view, the benefits of perioperative cisplatin-based chemotherapy are well established from RCTs, and only patients who are not candidates for this treatment for specific medical reasons, or those at high risk of recurrence despite neoadjuvant chemotherapy, should be considered for nivolumab.

In the opinion of the clinical experts, an assessment of effectiveness of treatment should primarily be based on OS. DFS may be considered a reasonable surrogate in patients without other treatment options. However, for patients who are eligible for adjuvant chemotherapy, DFS on its own may not be an adequate outcome to guide treatment selection. Patients would be identified based on pathology results following surgery, and knowledge of prior systemic treatments for MIUC. The clinical experts also confirmed that nivolumab should be discontinued if there is disease recurrence or intractable severe adverse effects. As nivolumab is now commonly used and familiar to the oncological community, treatment and monitoring could be done by specialists in community settings.

The pivotal trial, CheckMate-274, also allowed entry of patients "who declined" adjuvant cisplatin-based chemotherapy. Nivolumab would usually have fewer adverse effects than chemotherapy. The clinical experts were of the opinion that an RCT comparing nivolumab to adjuvant chemotherapy (not placebo) should inform treatment of patients who are suitable for but "who declined" standard adjuvant cisplatin-based chemotherapy.

Clinician Group Input

The views of the clinician groups were consistent with the views of the clinical experts consulted by CADTH. Two clinician groups provided input: Bladder Cancer Canada (a registered national charity) surveyed 6 clinicians, and the Ontario Health (Cancer Care Ontario) GU Cancer Drug Advisory Committee included input from 3 clinicians. Clinicians from both groups commented that nivolumab would fill a gap in the standard of care for patients with a high risk of recurrence with or without neoadjuvant cisplatin-based chemotherapy, or for patients who are unfit or ineligible for adjuvant cisplatin-based chemotherapy. The

clinicians from Bladder Cancer Canada highlighted that many patients recover poorly from surgery and are not fit for adjuvant chemotherapy. All UC patients categorized as ypT2 or higher, pT3 or higher, or node positive would be the target population, which constitutes about two-thirds of cystectomy/nephroureterectomy patients. These patients are often frail or have a solitary kidney and thus cannot receive the current standard of adjuvant chemotherapy. The clinicians from Bladder Cancer Canada noted the following important treatment goals in the adjuvant setting (in order of priority): increasing OS, preventing metastases, controlling disease progression, maintaining quality of life, minimizing adverse events, and reducing severity of symptoms. Clinicians from both inputs agreed that there is some debate on the effectiveness of adjuvant chemotherapy and currently poor use of it in clinical practice. Both groups mentioned that nivolumab would change how MIUC would be treated, and that it may become the main drug used in the adjuvant setting for patients.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
<p>Inclusion criteria for the CheckMate-274 trial included:</p> <ul style="list-style-type: none"> • radical surgery (R0 with negative margins) within 120 days of randomization and • pathological evidence of urothelial carcinoma (originating in the bladder, ureter, or renal pelvis) at high-risk of recurrence based on pathological staging of radical surgery tissue, as described in 1 of the following 2 scenarios: • subjects who have not received neoadjuvant cisplatin chemotherapy (pT3-pT4a or pN+) and are not eligible for or refuse adjuvant cisplatin chemotherapy • subjects who received neoadjuvant cisplatin therapy (ypT2-pT4a or ypN+) • evidence of no recurrence should be confirmed before initiating therapy. <p>If recommended for reimbursement, will the trial criteria define the patient population eligible for treatment with nivolumab?</p>	<p>pERC agreed that the trial criteria define the patient population eligible for treatment with nivolumab.</p> <p>pERC noted that the small patient population with tumours of the urethra who are at high risk of recurrence after undergoing radical resection of UC were not included in the CheckMate-274 trial. pERC agreed that it would be reasonable to generalize the CheckMate-274 trial results to these patients as it is unlikely that there will be trials specifically designed for this small group of patients.</p>
<p>Patients in the trial were stratified according to their tumour cell PD-L1 expression level ($\geq 1\%$, $< 1\%$, or indeterminate). Is PD-L1 status required to be eligible for treatment in this setting?</p>	<p>Evidence from the CheckMate-274 trial demonstrated that adjuvant nivolumab resulted in a statistically significant improvement in DFS in all randomized patients, the majority of which had PD-L1 expression status of less than 1% (59.5% and 58.7% of patients had PD-L1 expression status of less than 1% in the nivolumab and placebo groups, respectively).</p> <p>pERC noted that PD-L1 expression level is currently not used to guide treatment decisions in Canadian clinical practice in the present target setting. This area of biomarker analysis is currently still an evolving field of research.</p>

Implementation issues	Response
<p>In the Checkmate 274 trial, subjects were deemed ineligible for adjuvant cisplatin due to any of the following criteria:</p> <ul style="list-style-type: none"> • creatinine clearance (using the Cockcroft-Gault formula) less than 60 mL/min • grade 2 or above audiometric hearing loss • grade 2 peripheral neuropathy • ECOG PS of 2 • NYHA Class III or IV Heart Failure. <p>Are these criteria consistent with those used in clinical practice to determine if a patient is ineligible for cisplatin therapy?</p>	<p>In the CheckMate-274 trial, patients were deemed ineligible for adjuvant chemotherapy according to the Galsky criteria^a. pERC agreed with the clinical experts that the Galsky criteria are clinically established criteria used in clinical trials and clinical practice in the present target population. pERC noted that experienced clinicians may apply some flexibility in terms of using adjuvant chemotherapy in patients with > 50 mL/min and those with hearing loss, if patients prefer to receive adjuvant chemotherapy after a discussion of the clinical risks.</p>
<p>In CheckMate-274, eligible patients must have had radical surgery within 120 days before randomization. What is considered the maximum time frame from surgical resection to initiate nivolumab?</p>	<p>pERC agreed with the clinical excerpts that 120 days is a reasonable maximum time frame.</p>
<p>In other solid tumours (e.g., melanoma), patients are eligible for downstream PD-1/PDL-1 inhibitor, provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of the adjuvant PD-1/PDL-1 inhibitor. If nivolumab is funded in this setting, jurisdictions will permit downstream PD-1/PDL-1 inhibitor used in a manner consistent with other tumour sites.</p>	<p>pERC acknowledged PAG input.</p>
Considerations for discontinuation of therapy	
<p>The Checkmate-274 trial did not permit dose modifications due to toxicity; however, treatment with nivolumab could be interrupted or delayed for a maximum period of 6 weeks.</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)?</p>	<p>In the CheckMate-274 trial, patients received nivolumab 240 mg IV infusion over 30 minutes every 2 weeks for a maximum duration of 1 year. pERC agreed with the clinical experts that if treatment with nivolumab would be interrupted or delayed in the absence of disease progression, it would be reasonable to administer remaining doses of nivolumab, even if it would take more than a year to deliver the complete treatment with nivolumab. pERC agreed with the clinical experts that delivering treatment with nivolumab beyond 2 years would likely not be reasonable.</p>
Considerations for prescribing of therapy	
<p>Nivolumab dose in CheckMate-274 was 240 mg IV every 14 days.</p> <p>If funded, in line with other indications for nivolumab, jurisdictions would implement a weight-based dose (3 mg/kg IV every 14 days, up to a cap of 240 mg).</p> <p>Other indications for nivolumab use extended dosing intervals of every 4 weeks (6 mg/kg, up to 480 mg).</p> <p>Is a nivolumab dosing interval of every 4 weeks appropriate for adjuvant treatment of MIUC?</p>	<p>The CheckMate-274 trial used a nivolumab dose of 240 mg IV every 14 days. pERC agreed with the clinical experts that generalizing the trial results to an alternative nivolumab dosing schedule of 480 every 4 weeks (or weight-based dose of 6 mg/kg IV up to 480 mg) seems reasonable.</p>
Generalizability	
<p>Should patients with ECOG PS of 2 or greater be eligible for nivolumab in this indication?</p>	<p>The CheckMate-274 trial allowed patients to enter the trial if they had an ECOG PS of 0 or 1; patients who did not receive cisplatin--</p>

Implementation issues	Response
	based neoadjuvant chemotherapy and were considered ineligible for cisplatin adjuvant chemotherapy could enter the study with an ECOG PS of 2. Most patients in the trial had an ECOG PS of 0 or 1, and only a few patients had ECOG PS of 2. pERC agreed with the clinical experts that given the generally well-tolerated toxicity profile of nivolumab, it would be reasonable to offer adjuvant nivolumab to patients at high risk of recurrence after radical surgical resection, up to and inclusive of ECOG PS of 2.
Are patients who have undergone a partial cystectomy (or partial nephrectomy in the setting of a renal pelvis tumour) or bladder-preserving chemoradiation eligible for treatment with nivolumab in the adjuvant setting?	<p>The CheckMate-274 trial included patients who had undergone radical surgical resection within 120 days before randomization. Patients who had undergone partial cystectomy or partial nephrectomy were excluded.</p> <p>pERC agreed with the clinical experts that it would be reasonable to generalize the CheckMate-274 trial results to patients who have undergone a partial cystectomy or partial nephrectomy if all other trial eligibility criteria are met, and as long as negative surgical margins are achieved.</p> <p>Adjuvant nivolumab was not studied in patients who received bladder-preserving chemoradiation in the CheckMate-274 trial. pERC agreed with the clinical experts that there is no data to generalize the trial results to patients who received bladder-preserving chemoradiation.</p>
Are patients with bladder cancer of histological subtype other than urothelial carcinoma or transitional cell carcinoma eligible for adjuvant nivolumab?	A minority of patients in the CheckMate-274 trial had a minor histological variant. pERC agreed with the clinical experts that patients with any urothelial component in the histological subtype should be eligible for adjuvant nivolumab.
Are patients with non-muscle-invasive bladder cancer eligible for treatment with adjuvant nivolumab?	The CheckMate-274 trial included patients with muscle-invasive urothelial carcinoma. pERC agreed with the clinical experts that results should not be generalized to patients with non-muscle-invasive bladder cancer, except to the small patient population with tumours of the urethra, as noted above.
The current standard of care after surgery is surveillance. For patients who are already on active surveillance, is there a maximum time frame following surgical resection to allow such patients to access nivolumab?	The CheckMate-274 trial allowed treatment with adjuvant nivolumab within 120 days after surgery, which is a reasonable time frame according to pERC and the clinical experts.
Funding algorithm (oncology only)	
Under what clinical circumstances would adjuvant nivolumab be preferred over adjuvant platinum chemotherapy for those patients who can tolerate platinum?	The CheckMate-274 trial did not assess the comparative efficacy of adjuvant nivolumab compared with adjuvant chemotherapy. pERC agreed that given the absence of robust direct or indirect comparison, there is insufficient evidence to ascertain which of the agents (i.e., adjuvant nivolumab or adjuvant chemotherapy) has superior efficacy. pERC highlighted the importance of patient-centred care and noted that the choice to initiate adjuvant therapy should be based on shared decision-making and a discussion of clinical evidence on the available treatment options in the adjuvant setting, risks and benefits of treatment options, and the patient's informed preferences.

Implementation issues	Response
Can the downstream sequencing be clarified (e.g., re-treatment with downstream PD-1 or PD-L1 inhibitor, provided the disease recurs more than 6 months from the last dose of adjuvant nivolumab; eligibility for downstream enfortumab vedotin)?	pERC noted that patients whose disease recurs more than 6 months after receiving adjuvant treatment with nivolumab would be treated according to the established treatment algorithm.

ECOG PS = Eastern Cooperative Oncology Group performance status; MIUC = muscle-invasive urothelial cancer; NYHA = New York Heart Association; OS = overall survival; PD-1 = programmed death 1 receptor; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; RCT = randomized controlled trial.

*Criteria for cisplatin ineligibility by Galsky MD, Hahn NM, Rosenberg J, et al. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. The Lancet Oncology. 2011;12(3):211 to 214.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

CheckMate-274 was a phase III, randomized, double-blind, placebo-controlled study (N = 709) funded by Bristol Myers Squibb. The primary objective was to compare the DFS for nivolumab versus placebo in all randomized patients and patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells). Secondary objectives included comparing the OS for nivolumab versus placebo in all randomized patients and in patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) as well as evaluating non-urothelial tract recurrence free-survival (NUTRFS) and disease-specific survival (DSS) in each study group in patients with tumours expressing PD-L1 ($\geq 1\%$ membranous staining in tumour cells) and all randomized patients.

After screening, eligible patients were randomized in a 1:1 ratio to the nivolumab or placebo treatment group and stratified by pathologic nodal status (N+ versus N0/x with < 10 nodes removed, versus N0 with ≥ 10 nodes removed), tumour cell programmed death-ligand 1 (PD-L1) expression ($\geq 1\%$, $< 1\%$, indeterminate), and use of cisplatin neoadjuvant chemotherapy (yes versus no). All patients were treated until recurrence of disease, unacceptable toxicity, or withdrawal of consent, with a maximum of 1 year of treatment. Tumour imaging assessments were to be performed every 12 weeks from the date of first dose to Week 96, then every 16 weeks from Week 96 to Week 160, then every 24 weeks until non-urothelial tract recurrence or treatment was discontinued (whichever occurred later) for a maximum of 5 years.

The mean ages of patients in the nivolumab and placebo arms were 65.3 years and 65.9 years, respectively, and the nivolumab group had a slightly larger proportion of patients older than 65 years of age (155 [43.9%] in nivolumab group and 136 [38.2%] in placebo group). Approximately 75% of patients in both groups were White males; almost ■ were enrolled in Europe, and approximately ■ in the US and ■ in the rest of the world, including Canada. Approximately 79% of patients had a primary tumour in the urinary bladder, almost 74% had PT3 or PT4A at resection, and almost 59% had PD-L1 expression of $< 1\%$. Regarding prior cancer therapy, almost 43% of patients had received prior neoadjuvant cisplatin therapy, and of those not treated with cisplatin, ■ patients in the nivolumab group and ■ patients in the placebo group declined to take cisplatin, while the rest were deemed ineligible. Baseline demographic and disease characteristics were generally well balanced between study arms.

Efficacy Results

As of the final primary analysis August 27, 2020 data cut-off date, minimum follow-up time was 5.9 months, and median follow-up time among all randomized patients was 20.9 months and 19.5 months in the nivolumab and placebo groups, respectively. Median treatment durations were 8.77 months (range = 0 to 12.5) in the nivolumab group and 8.21 months (range = 0 to 12.6) in the placebo group. In all randomized patients with tumour cell PD-L1 expression greater than or equal to 1%, the minimum follow-up time was [REDACTED] months, and the median follow-up was [REDACTED] months and [REDACTED] months in the nivolumab and placebo groups, respectively.

OS was a key secondary end point in the CheckMate-274 trial. OS data were immature and not available from the sponsor at the time of this review. Among all treated patients, there were [REDACTED] deaths reported in the nivolumab group and [REDACTED] deaths reported in the placebo group. The primary cause of death was [REDACTED] in the nivolumab group and [REDACTED] in the placebo group.

At the data cut-off date of August 27, 2020, the efficacy analyses of DFS in all randomized patients showed that patients in the nivolumab group had longer DFS than those in the placebo arm. The observed median DFS was longer in the nivolumab group (20.8 months [95% CI, 16.5 to 27.6] versus 10.8 months [95% CI, 8.3 to 13.9]) compared with the placebo group, with HR = 0.70 (98.22% CI, 0.55 to 0.90); log-rank P = 0.0008. The observed median NUTRFS was 22.9 months (95% CI, 19.2 to 33.4) in the nivolumab group and 13.7 months (95% CI, 8.4 to 20.3) in the placebo group, with HR = 0.72 (95% CI, 0.59 to 0.89). [REDACTED]

Among exploratory outcomes, median distant metastasis-free survival (DMFS) was 40.5 months (95% CI, 22.4 to not reached) in the nivolumab group and 29.5 months (95% CI, 16.7 to not reached) in the placebo group with HR = 0.75 (95% CI, 0.59 to 0.94). Time to recurrence (TTR) was [REDACTED] in the nivolumab group and [REDACTED] in the placebo group with a [REDACTED]. Recurrence rates were [REDACTED] in the placebo group ([REDACTED]) than in the nivolumab group ([REDACTED]) at 6 months. [REDACTED]

Results for patient reported outcomes (assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life questionnaire [EORTC QLQ-C30] and EQ-5D-3L) suggested similar overall health status in both study groups.

Harms Results

A total of 347 (98.9%) of patients in the nivolumab group and 332 (95.4%) of patients in the placebo group experienced at least 1 AE, whereas a total of [REDACTED] of patients in the nivolumab group and [REDACTED] patients in the placebo group experienced a grade 3 or greater AE. A total of [REDACTED] of patients in the nivolumab group and [REDACTED] of patients in the placebo group experienced an all-causality serious AE (SAE). The most common SAEs (≥ 2% in either of the arms) in nivolumab versus placebo arms were [REDACTED]

All-causality adverse events leading to study drug discontinuation occurred in [REDACTED] of patients in the nivolumab group versus [REDACTED] in the placebo arm. There were more deaths in the placebo group ([REDACTED]) than in the nivolumab group ([REDACTED]), most commonly due to [REDACTED] in the nivolumab group and [REDACTED] in the placebo arm). There were 3 treatment-related deaths: 2 due to pneumonitis and 1 due to bowel perforation.

Immune-mediated AEs (IMAEs) were identified as notable harms by the clinical experts and were more frequently reported in patients in the nivolumab group than in the placebo arm.

They include [REDACTED]

Critical Appraisal

Internal Validity

In spite of the trial's blind design, it is possible that some AEs, such as IMAEs, allowed the possible detection of the intervention being received by some patients. If trial investigators or patients were aware of the intervention assignment, this may have affected behaviour (such as initiation of subsequent treatment given that DFS was investigator assessed or adherence to treatment), imaging assessments, or perceived HRQoL. Overall survival was considered an outcome of primary importance by the clinical experts consulted by CADTH in guiding treatment selection in clinical practice. The first interim analysis for OS was planned with the February 1, 2021 data cut-off date, at which point OS did not cross the prespecified boundary for declaring statistical significance. No OS data were submitted by the sponsor. [REDACTED]

[REDACTED]. Updated results for DFS, NUTRFS, DMFS, and TTR from the February 1, 2021 data cut-off date were overall consistent with results from the final primary analysis. However, these updated results were only available in poster format (poster presentation at the Society of Urologic Oncology (SUO) congress in December 2021), and no Clinical Study Report was provided for this data cut-off, so the CADTH review team was unable to conduct a rigorous evaluation of the methods and reporting of these analyses. Maintaining quality of life was rated as an important outcome by patients, yet there was no formal statistical comparison and there were missing HRQoL data at later time points post-baseline. The interpretation of results for the HRQoL instruments (i.e., the ability to assess trends over time and to make comparisons across treatment groups) is limited by the significant decline in patients available to provide assessment over time.

External Validity

According to the clinical experts consulted by CADTH for this review, the demographic and disease characteristics of the CheckMate-274 study population were reflective of the Canadian population with MIUC. The study protocol was amended based on findings from the CA209275 study (46% of study patients were PD-L1-positive) to cap PD-L1 negative patients included in the study at 54%. The clinical experts consulted by CADTH noted that the PD-L1 biomarker is currently not used in Canadian clinical practice to guide treatment selection in the target population. The experts noted that research on this biomarker's definitions, methods of measurement, and cut-off values are currently still evolving. The trial capped the proportion of patients with upper tract UC (UTUC) at 20%, as supported by previous studies and confirmed by clinical experts consulted by CADTH. The experts felt that it was reasonable to generalize the CheckMate-274 results to patients with UTUC because of the similar etiology between UTUC and bladder cancer; patients with UTUC were included in the pivotal trial, and they are similarly treated as patients with bladder cancer in Canadian clinical practice. Almost 98% patients taking part in the study had an ECOG performance status (PS) of 0 or 1; however, the experts expected that, in clinical practice, a higher proportion of patients with an ECOG performance status of 2 may receive nivolumab because recurrence of the cancer is high and AEs are tolerable. Cisplatin ineligibility was defined using the Galsky criteria, which are commonly used in clinical trials and clinical practice. The clinical experts consulted by CADTH noted that experienced clinicians may apply some flexibility in terms of using adjuvant chemotherapy in patients with creatinine clearance greater than 50 mL/min and those with

hearing loss, if patients choose to received adjuvant chemotherapy after a discussion of the clinical risks. The reimbursement request is for consideration of nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks; however, the pivotal study only included a dosage of 240 mg every 2 weeks. The clinical experts felt that the results of the CheckMate-274 trial could be generalized to a dosage of 480 mg every 4 weeks, as this regimen has been previously approved for nivolumab as a monotherapy with other indications.

The study included 3 groups of patients at high risk of disease recurrence: patients who received neoadjuvant cisplatin-based therapy and were therefore not eligible for adjuvant cisplatin-based therapy, patients who did not receive neoadjuvant cisplatin-based therapy and were either cisplatin-ineligible [REDACTED] or were cisplatin-eligible but refused adjuvant chemotherapy [REDACTED]. The clinical experts noted that data on adjuvant nivolumab compared to adjuvant cisplatin-based chemotherapy in patients who have not received neoadjuvant chemotherapy and are eligible to receive cisplatin-based chemotherapy were not available from the CheckMate-274 trial. Given the absence of robust comparative data between adjuvant nivolumab and adjuvant chemotherapy, the clinical experts consulted by CADTH were uncertain whether nivolumab addressed an unmet need in patients at high risk of recurrence who are eligible for adjuvant cisplatin-based chemotherapy. The clinical experts noted that more robust direct evidence from a randomized trial is required to address the comparative effectiveness and safety of nivolumab compared with cisplatin-based chemotherapy in the adjuvant setting. The clinical experts anticipated that adjuvant nivolumab would be the preferred treatment over adjuvant chemotherapy in select clinical circumstances only, for example gemcitabine allergy or strong patient preference against chemotherapy. The clinicians from the Ontario Health (Cancer Care Ontario) GU Cancer Drug Advisory Committee providing input for this submission concurred with the clinical experts consulted by CADTH, in that they noted that the comparative effectiveness between adjuvant nivolumab and chemotherapy is unknown at the moment, and it may be possible that patients eligible for cisplatin-based adjuvant chemotherapy may be better suited for chemotherapy than nivolumab. These clinicians noted that currently neither adjuvant nivolumab (long-term OS results are awaited from the CheckMate-274 trial) nor adjuvant chemotherapy have demonstrated an OS benefit versus surveillance. The CheckMate-274 trial was not designed to detect differences in treatment effects across subgroups of cisplatin-eligible versus cisplatin-ineligible patients, and the clinical experts noted that any assumption about the extent to which the subgroup of cisplatin-eligible patients may have influenced the results seen in the overall trial population is speculative.

A review of studies assessing the appropriateness of DFS as a surrogate outcome was conducted. At the individual level, there was a moderate to substantial agreement between DFS and OS. However, in the absence of the trial-level association between DFS and OS in the present target population, it cannot be firmly concluded to what extent the improvements in DFS observed in patients in the nivolumab group of the CheckMate-274 trial would translate into OS benefits. The clinical experts consulted by CADTH anticipated that, in the comparison of adjuvant nivolumab against an active comparator (e.g., adjuvant chemotherapy), primarily OS rather than DFS would guide treatment selection in the adjuvant setting.

Indirect Comparisons

Indirect evidence from 2 NMAs (1 sponsor-submitted NMA and 1 published NMA) evaluated the effectiveness of nivolumab compared to cisplatin-based chemotherapy in the treatment of UC. They address a gap in the pivotal clinical trial, which includes a subgroup of patients who are cisplatin-eligible but who decline to take it.

Description of Studies

A total of [REDACTED] randomized trials comprising [REDACTED] patients were included in the sponsor-submitted ITC. The list of comparators included for the analysis included [REDACTED]

The published NMA included 9 studies comprising 2,444 patients: 2 studies involved an assessment of investigator's choice immunotherapy (nivolumab [n = 353] and atezolizumab [n = 406]) including the pivotal study of this review, 5 studies involved assessment of cisplatin-based chemotherapy (n = 468; regimens included: cisplatin; cisplatin and gemcitabine; cisplatin, vinblastine, and methotrexate; methotrexate, vinblastine, doxorubicin/epirubicin, and cisplatin; and cisplatin, doxorubicin, and cyclophosphamide) in bladder UC patients, and 2 studies involved assessment of cisplatin- or platin-based chemotherapy (gemcitabine with cisplatin or carboplatin) in UTUC patients. The authors conducted an NMA using random and fixed effect models with a Bayesian approach to compare treatments directly and indirectly with observation/placebo as the common comparator arm. Arm-based analyses were performed to estimate OR and 95% credible interval (CrI) to evaluate the disease progression rate in bladder UC and UTUC separately.

Efficacy Results

In the published NMA, in patients with bladder UC, chemotherapy (OR = 0.50; 95% CrI, 0.19 to 1.06), atezolizumab (OR = 1.01; 95% CrI, 0.19 to 5.46), and nivolumab (OR = 0.59; 95% CrI, 0.11 to 3.34) did not lower the likelihood of disease progression compared to observation/placebo. In patients with UTUC, chemotherapy (OR = 0.36; 95% CrI, 0.13 to 0.92) was significantly associated with a lower likelihood of disease progression compared to observation/placebo. On the other hand, atezolizumab (OR = 1.39; 95% CrI, 0.28 to 7.25) and nivolumab (OR = 1.21; 95% CrI, 0.29 to 4.95) were not associated with a lower likelihood of disease progression compared to observation/placebo.

Harms Results

Critical Appraisal

Both NMAs included a limited number of studies with heterogeneity across these studies. In the sponsor-submitted ITC, there was heterogeneity in the tumour staging of patients, definition of end points, treatment doses and regimens, and median follow-up times.

Moreover, [REDACTED] In

the published NMA, there was heterogeneity in the components of the chemotherapy regimen and the median follow-up time. Four trials were older chemotherapy trials with smaller sample sizes and inconsistent reporting of outcomes, which may have led to confounding of the results. In both ITCs, the methodological concerns identified and the observed heterogeneity across study designs and populations precluded drawing definitive conclusions about the comparative effectiveness of adjuvant nivolumab versus adjuvant chemotherapy.

Conclusions

One sponsor-submitted, ongoing, phase III, multinational, double-blind, randomized placebo-controlled trial provided evidence regarding the efficacy and safety of nivolumab compared with placebo in patients at high risk of recurrence after radical resection of MIUC (with primary site either in the bladder or upper urinary tract). Compared to placebo, adjuvant treatment with nivolumab (240 mg every 2 weeks IV infusion until disease recurrence or unacceptable toxicity, for a total treatment duration of 1 year) showed a statistically significant DFS benefit in the treatment of patients (≥ 18 years old) with completely resected MIUC. The absolute difference in median DFS between treatment groups (approximately 10 months) was considered clinically meaningful by the clinical experts consulted by CADTH in patients at high risk of recurrence who are ineligible to receive adjuvant cisplatin-based chemotherapy. Results for OS were not available at the time of this review. While some evidence suggests individual-level associations between DFS and OS, trial-level associations between DFS and OS have not been assessed in the target population. Therefore, it cannot be firmly concluded to what extent the improvements in DFS observed in patients in the nivolumab group of the CheckMate-274 trial would translate into OS benefits. HRQoL analyses were descriptive only and limited by high rates of missing data; thus, changes over time could not be interpreted. Data on adjuvant nivolumab compared to adjuvant cisplatin-based chemotherapy in patients at high-risk of recurrence who are eligible to receive cisplatin-based chemotherapy were not available from the CheckMate-274 trial. Indirect treatment comparisons of nivolumab with cisplatin-based chemotherapy

Given the lack of robust comparative data between adjuvant nivolumab and adjuvant chemotherapy, the clinical experts consulted by CADTH were unsure if adjuvant nivolumab addressed an unmet need in patients who are at high risk of recurrence and eligible for adjuvant chemotherapy.

The safety profile of nivolumab in this study was consistent with the known safety profile of nivolumab, and no additional safety signals were identified with adjuvant nivolumab therapy in this study.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model with 3 health states (disease-free, recurred disease [including regional and distant recurrence], and death)
Target population	Patients with muscle-invasive urothelial carcinoma (MIUC) who are at high risk of recurrence following radical resection
Treatment	Nivolumab
Dose regimen	240 mg every 2 weeks (30-minute IV infusion) or 480 mg every 4 weeks (60-minute IV infusion) as long as clinical benefit is observed or until treatment is no longer tolerated, up to a total treatment duration of 1 year
Submitted price	Nivolumab, single-use vials: <ul style="list-style-type: none"> • \$1,955.56 per 100 mg • \$788.22 per 40 mg
Treatment cost	\$9,387 per patient per 28 days
Comparators	Observation (i.e., no active treatment) Adjuvant chemotherapy
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	30 years
Key data sources	<ul style="list-style-type: none"> • CheckMate-274 trial: disease-free survival data (DFS) from Year 1 to 3, mean number of nivolumab doses, adverse event rates, health utility values • EORTC 30994 (Sternberg et al., 2015): DFS for year 4 to 5 • EORTC study 30986 (De Santis et al., 2012) and EORTC study 30987 (Bellmunt et al., 2012): transitions from recurred disease to death • Naïve comparison to inform nivolumab compared with adjuvant chemotherapy
Key limitations	<ul style="list-style-type: none"> • The long-term survival benefits of nivolumab are highly uncertain. The sponsor assumed that patients received nivolumab for a maximum of 12 months, but the DFS extrapolations assumed that DFS benefit of nivolumab was sustained after treatment discontinuation until year 5. Clinical experts consulted by CADTH indicated that it is unclear whether treatment benefits of adjuvant nivolumab would be maintained after discontinuation to the extent predicted in the sponsor's model. CADTH was also concerned about the use of external data sources to inform DFS data, as it increases the number of required assumptions in the model and associated uncertainty. • The sponsor's 3 health state Markov model is insufficient to capture the care pathway, costs, and outcomes of MIUC patients in the adjuvant setting. Combining locoregional and distant recurrences fails to consider the inherent differences in treatments and prognoses for these patient groups. The sponsor's model only accounted for the impact of the first subsequent line of therapy. Clinical experts noted that MIUC patients may receive up to 3 lines of therapy and that the number of lines of therapy would influence OS. • The sponsor's approach of deriving transition probabilities to recurred disease or death from DFS data introduced structural dependent assumptions between the 2 probabilities, and assumed that improved DFS would translate to survival benefits. This assumption has yet to be proved for nivolumab in this

Component	Description
	<p>patient population, given the lack of OS data from the CheckMate-274 trial.</p> <ul style="list-style-type: none"> • The relative efficacy of nivolumab vs. observation or chemotherapy in the modelled population is uncertain. The sponsor used DFS data from the ITT population of the CheckMate-274 trial to inform a comparison of nivolumab and observation. The ITT population included patients who received prior neoadjuvant cisplatin-based chemotherapy as well as those who did not, which does not adequately reflect MIUC patients in Canada who would be under observation. Data comparing nivolumab and adjuvant chemotherapy were derived by pooling DFS data of cisplatin-eligible patients who did not receive neoadjuvant chemotherapy from the nivolumab and observation arms of the CheckMate-274 trial and naïvely comparing this data with the active immediate chemotherapy arm of the EORTC 30994 study. This naïve comparison is subject to bias as unmeasured patient characteristics may confound the effect of nivolumab on DFS. • Subsequent systematic therapies did not represent currently available treatments in Canada. The sponsor also overestimated the proportion of patients receiving subsequent systematic chemotherapy and those receiving cisplatin-based chemotherapy.
CADTH reanalysis results	<ul style="list-style-type: none"> • In CADTH's base case, the following revisions were made: correcting a terminal care cost and using public listed prices for chemotherapy; reducing the proportions of patients with disease recurrence required subsequent treatment to align with clinical practice; and revising the distribution of the types of treatment, using an alternate approach for DFS prediction for the comparison of nivolumab to observation, and revising end of life costs. • In CADTH's base case, nivolumab was associated with an ICER of \$112,826 per QALY compared to observation (incremental costs: \$78,222; incremental QALYs: 0.70). A price reduction of at least 56% would be needed for nivolumab to be cost-effective at a WTP threshold of \$50,000 per QALY. • Compared to adjuvant chemotherapy, nivolumab was dominated (more costly [\$67,017] and less effective [-1.09 QALYs]). Even with a 100% price reduction for nivolumab, adjuvant chemotherapy was the optimal treatment at \$50,000 per QALY willingness-to-pay threshold, as nivolumab generated fewer QALYs and fewer costs. • The cost-effectiveness of nivolumab was highly sensitive to the approach used for DFS prediction and the cure time point assumption.

Budget Impact

CADTH identified key limitations with the sponsor's analysis. Some treatment costs were based on outdated prices. Further, the number of eligible patients and market share of nivolumab were underestimated. In reanalysis, CADTH updated the number of bladder cancer cases, the proportion of high-risk bladder cancer patients, the proportion of UTUC patients eligible for adjuvant therapy, and the market share of nivolumab. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing nivolumab is expected to be \$180,672,898 (Year 1: \$51,773,325; Year 2: \$60,173,636; Year 3: \$68,725,937). The budget impact model has limited feasibility to estimate the budget impact in subgroups of MIUC population that may or may not be eligible for adjuvant chemotherapy. As such, the estimated budget impact for either subgroup is highly uncertain.

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: August 9, 2022

Regrets: 2 expert committee members did not attend

Conflicts of interest: None