pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: **Avelumab (Bavencio)** Submitted **Reimbursement** Request: For the first-line maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy.	
Submitted By: Pfizer	Manufactured By: Pfizer
NOC Date: December 10, 2020	Submission Date: December 10, 2020
Initial Recommendation: March 4, 2021	Final Recommendation: March 23, 2021

Approximate per Patient Drug Costs, per Month (28 Days)	Avelumab costs $1,325 for a 10 mL (20 mg/mL) vial. At the recommended dose of 10 mg/kg administered as IV infusion over 60 minutes on day 1 and day 15 of every 4-week cycle, avelumab costs $10,600 per 28-day cycle.

pERC RECOMMENDATION

☐ **Reimburse**

☒ **Reimburse with clinical criteria and/or conditions***

☐ **Do not reimburse**

*If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted reimbursement request.

pERC conditionally recommends reimbursement of avelumab (Bavencio) plus best supportive care (BSC) for the first-line maintenance treatment of patients with histologically confirmed, unresectable, locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy if the following conditions are met:

- cost-effectiveness is improved to an acceptable level
- feasibility of adoption (budget impact) is addressed.

Eligible patients should have good performance status with documented locally advanced unresectable or stage IV disease before having received first-line chemotherapy. First-line chemotherapy should be platinum-based, and patients must have received 4 to 6 cycles of treatment with chemotherapy. Patients must not have experienced disease progression (i.e., they must have had an ongoing complete response, partial response, or stable disease). Patients may continue to receive avelumab until confirmed disease progression or unacceptable toxicity, whichever comes first.

pERC made this recommendation because it was satisfied that there is a net clinical benefit of avelumab plus BSC compared to BSC only based on statistically significant and clinically meaningful improvements in overall survival, progression-free survival, a manageable toxicity profile, and no

	apparent detriment in quality of life. pERC agreed that avelumab aligns with the following patient values: preventing recurrence, controlling disease and maintaining quality of life. pERC concluded that avelumab in combination with BSC is not considered cost-effective at the submitted price versus BSC alone. This is driven largely by the high cost of avelumab. CADTH's reanalysis of the sponsor's budget impact analysis suggests that the budget impact of introducing avelumab to the market is substantial and significantly underestimated by the sponsor.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness and Decrease Budget Impact** Given that pERC was satisfied that there is a net clinical benefit of avelumab, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of avelumab. pERC noted that a substantial reduction in the price of avelumab would be required to improve the cost-effectiveness to an acceptable level and to decrease the anticipated impact on budgets. **Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

SUMMARY OF pERC DELIBERATIONS

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

Bladder cancer is the most common malignancy involving the urinary system. In addition to the bladder, urothelial carcinoma (UC) may also be found in the renal pelvis, ureter, or urethra. Bladder cancer is the fifth most commonly diagnosed cancer in males and the 12th most commonly diagnosed cancer in females. A total of 12,200 new cases of bladder cancer were diagnosed in Canada in 2020, and bladder cancer was the eighth most common cause of cancer-related death. Patients with bladder cancer typically have a prognosis of 6 months if it is left untreated. Current first-line treatments typically include a platinum-based chemotherapy involving cisplatin and gemcitabine, although up to 50% of patients may be intolerant to cisplatin due to advanced age, hearing loss, peripheral neuropathy, or renal impairment. In such cases, carboplatin may be administered as an alternative. The median survival of patients who are treated with chemotherapy is approximately 15 months. However, for some patients with bone and liver metastases or poor performance status, treatment may only lead to survival of approximately 4 months. Overall, pERC agreed with the Clinical Guidance Panel (CGP), the registered clinicians, and the patient groups that there is unmet need for therapies that increase patient survival.

pERC deliberated on the results of 1 randomized, multi-centre, multi-national, open-label phase III trial (JAVELIN Bladder 100) that evaluated the efficacy and safety of avelumab plus best supportive care (BSC) in adult patients with histologically confirmed, unresectable locally advanced or metastatic UC. pERC noted that the results of the JAVELIN Bladder 100 trial were based on a pre-specified interim analysis, which showed that the efficacy boundaries for overall survival (OS) had been crossed and that the interim analysis was therefore considered final. pERC discussed that, compared to BSC alone, avelumab plus BSC showed statistically significant and clinically meaningful improvement in OS and progression-free survival (PFS). pERC also noted that overall response rate (ORR) was greater in the avelumab plus BSC group compared to the BSC group, with a greater number of patients in the avelumab plus BSC group having a confirmed or partial response. Overall, the Committee agreed with the CGP, registered clinicians, and the patient advocacy group (PAG) providing input for this submission that avelumab plus BSC maintenance provides a net clinical benefit for patients compared to maintenance with BSC alone.

pERC deliberated on the safety data from the JAVELIN Bladder 100 trial and noted adverse events (AEs) were more common among patients treated with avelumab plus BSC versus BSC alone. pERC noted that immune-related AEs and infusion-related reactions were common AEs among the avelumab plus BSC group of the trial. pERC discussed the high frequency of infusion-related reactions. Although the majority of infusion-related reactions during the trial were grade 1 or 2 in severity, the frequency of events was acknowledged to be disruptive to the administration of treatment, and potentially negatively impact patients' quality of life. Aside from the frequency of infusion-related reactions, pERC agreed with the CGP that avelumab is a well-tolerated treatment. Overall, pERC agreed with the CGP and patient advocacy groups providing input for this submission that avelumab plus BSC had a manageable safety profile.

pERC discussed the available patient-reported outcome data from the JAVELIN Bladder 100 trial, including the National Comprehensive Cancer Network–Functional Assessment of Cancer Therapy FACT-Bladder Cancer Symptom Index-18 (NCCN-FACT FBlSI-18), EuroQol 5 Dimensions 5-levels (EQ-5D-5L), and visual analogue scale (VAS). pERC noted that patients in both treatment groups of the JAVELIN Bladder 100 trial showed similar improvement throughout the trial in all health-related quality of life (HRQoL) questionnaires; improvement in HRQoL questionnaires were observed to occur similarly for patients in

both treatment groups. pERC discussed that the time to deterioration analysis revealed that HRQoL may be somewhat lower for patients treated with avelumab plus BSC during treatment, potentially due to adverse reactions. However, overall time to deterioration did show improvement among patients treated with avelumab plus BSC maintenance. In general, pERC agreed that avelumab plus BSC did not result in any detriment to patient's quality of life.

pERC also discussed the generalizability of treatment with avelumab plus BSC to patients with poorer performance status, as poor performance status may be due to chemotherapy effects and treatment of these patients should be at the discretion of the treating physician. pERC agreed with the CGP that consideration of avelumab plus BSC as maintenance treatment for patients with poorer performance status may be reasonable, as long as patients' disease has not progressed.

In summary, based on statistically significant and clinically meaningful improvements in OS and PFS, pERC concluded that avelumab plus BSC compared to BSC alone showed a net clinical benefit for patients with histologically confirmed, unresectable locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy. In addition, the toxicity profile of avelumab was considered to be manageable, with no apparent detriment to quality of life.

pERC deliberated on the patient advocacy group input from Bladder Cancer Canada (BCC). According to BCC, blood in urine, fatigue, difficulty urinating, and burning during urination were common symptoms of concern related to UC. pERC discussed that, according to BCC, patients are faced with a high likelihood of disease recurrence and a low 5-year survival rate. Patients reported that the severity of the side effects of avelumab were mild to moderate. Patients also indicated a willingness to tolerate moderate to severe side effects for the benefit of receiving new treatment options that could result in improved survival. Overall, pERC concluded that avelumab aligns with patient values because it is a treatment that can be used to prevent recurrence, control disease, and maintain quality of life.

pERC deliberated on the cost-effectiveness of avelumab compared with BSC. pERC noted that the CADTH results were similar to the sponsor-submitted results. They recognized that although avelumab would generate some cost savings due to a reduction in pembrolizumab use, these cost savings were significantly less than the cost associated with avelumab. pERC noted the extent of pembrolizumab use in those who start on avelumab would be limited, however the entire removal of this cost had minimal changes to the ICER. pERC concluded it is highly unlikely that avelumab would be considered cost-effective at a willingness-to-pay threshold of $50,000 per quality-adjusted life-year (QALY) and substantial price reductions would be required.

pERC also discussed the budget impact analysis. pERC noted the uncertainty about the level of cost savings that would arise through reduced use of pembrolizumab. Regardless, pERC acknowledged that any cost savings would only provide a partial offset to the increased cost of avelumab and that the budget impact would be substantial

The Committee deliberated on the input from PAG regarding factors related to currently funded treatments, the eligibly population, implementation factors, and sequencing and priority of treatment. Refer to the summary in Appendix 1 for more details.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from 1 patient advocacy group: Bladder Cancer Canada (BCC)
- One joint input from 2 registered clinicians (1 on behalf of Ontario Health [Cancer Care Ontario] Genitourinay [GU] Drug Advisory Committee, and 1 oncologist in practice at an Ontario health centre)
- input from CADTH's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group: BCC
- One registered clinician group: Cancer Care Ontario
- The PAG
- The sponsor: Pfizer

The pERC Initial Recommendation was to recommend reimbursement of avelumab plus BSC for the first line maintenance treatment of patients with locally advanced or metastatic UC whose disease has not progressed with first line platinum-based induction chemotherapy, conditional on the cost-effectiveness being improved to an acceptable level, and the feasibility of adoption (budget impact) being addressed.

Feedback on the pERC Initial Recommendation indicated that the sponsor, the PAG and the registered clinician group all agreed with the Initial Recommendation and supported early conversion to a Final Recommendation. The patient advocacy group greed in part with the Initial Recommendation and supported early conversion to a Final Recommendation.

The pERC Chair and pERC members reviewed the stakeholder feedback and it was determined that the pERC Initial Recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of avelumab for the first-line maintenance treatment of patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy.

Studies included: One open-label, phase III randomized trial (JAVELIN Bladder 100)

The CADTH systematic review included 1 international, multi-centre, randomized, open-label, parallel-arm phase III trial (JAVELIN Bladder 100) that compared the efficacy and safety of maintenance treatment with avelumab plus BSC versus BSC alone in adult patients with unresectable locally advanced or metastatic UC after completion of first-line platinum-based chemotherapy (gemcitabine plus cisplatin or gemcitabine plus carboplatin) without evidence of disease progression. The trial was conducted at 197 sites across 29 countries, which included 25 patients from Canada. Patients were randomized in a 1:1 ratio to receive either avelumab plus BSC or BSC alone. The trial was open-label; however, disease progression was determined and confirmed by an expedited blinded independent central review (BICR) based on radiological assessments from pre-chemotherapy and post-chemotherapy confirmatory scan(s).

Crossover was not permitted within the original protocol of the JAVELIN Bladder 100 trial. However, at the pre-specified interim analysis the primary end point of OS demonstrated superiority in both co-

primary populations. Based on this, and with recommendation from an external data monitoring committee, a protocol amendment was made to allow the remaining patients in the BSC group to be offered crossover to avelumab if they met the eligibility criteria specified in the amended trial protocol. Two co-primary populations of interest were evaluated in the JAVELIN Bladder 100 trial; the Overall Population (all patients who underwent randomization) and the PD-L1–Positive Population (patients with PD-L1–positive tumours).

Patient populations: Baseline characteristics well-balanced in both co-primary populations

A total of 700 patients met the requirements and were enrolled in the JAVELIN Bladder 100 trial (350 patients in each treatment group in the Overall Population). Within the PD-L1–positive population,189 patients were randomized to the avelumab plus BSC group and 169 patients were randomized to the BSC group. In the Overall Population, the baseline characteristics were similar for both treatment groups. The median age was 68 years (range = 37 to 90) in the avelumab plus BSC group and 69 years (range = 32 to 89) in the BSC group. Baseline demographic characteristics were similarly reported in the PD-L1–positive population.

In the Overall Population, the same proportions of patients were reported to have a visceral (54.6%) or non-visceral (45.4%) site of baseline metastasis before receipt of chemotherapy in both treatment groups. More patients had a complete or partial response to first-line chemotherapy (avelumab plus BSC: 72.3%; BSC: 72.0%) versus patients who had a stable disease (avelumab plus BSC: 27.7%; BSC: 28.0%). Overall, 54.0% of patients in the avelumab plus BSC group and 48.3% of patients in the BSC group had PD-L1–positive status tumours. A smaller proportion of patients had tumours with unknown PD-L1 status in the avelumab plus BSC group (6.3%) compared with the BSC group (14.3%). Slightly fewer patients received gemcitabine plus cisplatin as their first-line chemotherapy regimen in the avelumab plus BSC group compared with the BSC group (52.3% versus 58.9%, respectively), and more patients received gemcitabine plus carboplatin in the avelumab plus BSC group (42.0% versus 34.9%, respectively). A greater proportion of patients had an upper tract tumour as the primary site of the disease in the avelumab plus BSC group (30.3%) compared with the BSC group (23.1%).

In the PD-L1–positive population, baseline characteristics were balanced across treatment groups. Most patients had either a complete response or partial response to their first-line chemotherapy (avelumab plus BSC: 73.5%; BSC: 75.7%). A slightly lower proportion of patients had visceral disease (avelumab plus BSC: 46.6%; BSC: 46.7%) versus non-visceral disease (53.4% and 53.3%, respectively). Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 (avelumab plus BSC: 60.3%; BSC: 63.3%) or 1 (39.2% and 36.1%, respectively). Most patients also had the primary site of their tumour in the lower tract (avelumab plus BSC: 76.6%; BSC: 79.3%). Compared to the Overall Population, a greater proportion of patients in the PD-L1–Positive Population had baseline metastasis in non-visceral sites (53.4% in the avelumab plus BSC group and 53.3% in the BSC group) than in visceral sites (46.6% for both treatment groups).

Key efficacy results: Clinically meaningful improvements in the primary and key efficacy outcomes in favour of avelumab plus BSC

The key efficacy outcome deliberated on by pERC was OS. The secondary efficacy outcomes included BICR-assessed PFS, ORR, disease control rate, and time to recovery. The results of the primary and secondary end points from the JAVELIN Bladder 100 trial were based on a median follow-up for OS of 19.6 (95% CI, 18.0 to 20.6) months for patients in the avelumab plus BSC group and 19.2 (95% CI, 17.4 to 21.6) months for patients in the BSC group within the Overall Population. The median follow-up for OS was 18.3 (95% CI, 16.0 to 20.2) months and 20.0 months (95% CI, 17.1 to 22.2) for the avelumab plus BSC and BSC groups, respectively, in the PD-L1–positive population.

In the Overall Population, the median OS was longer in the avelumab plus BSC group at 21.4 months compared with the BSC group which had a median OS of 14.3 months (HR = 0.69; 95% CI, 0.56 to 0.86). In the PD-L1–positive population, the median OS in the avelumab plus BSC group was not estimable and was

17.1 months (HR = 0.56; 95% CI, 0.40 to 0.79) in the BSC group. Overall, the results of the key secondary efficacy outcomes were consistent with the primary outcome: the results demonstrated an improvement on avelumab plus BSC compared with BSC alone. For PFS, in the Overall Population and the PD-L1–positive population, the HR was 0.62 (95% CI, 0.52 to 0.75) and 0.43 (95% CI, 0.33 to 0.55), respectively, in favour of avelumab plus BSC. For ORR, in the Overall Population and the PD-L1–Positive Population, the stratified odds ratio was 7.46 (95% CI, 2.82 to 24.45) and 12.70 (95% CI, 3.16 to 114.12), respectively, in favour of avelumab plus BSC. For disease control rate, in the Overall Population and in the PD-L1–positive population, the proportion of patients with a best overall response was greater in the avelumab plus BSC group than the BSC group (41.1% versus 27.4%, and 43.9% versus 27.8%, respectively). For time to recovery, in the Overall Population, the median was 2.0 months for both treatment groups, and in the PD-L1–positive population, the median was 2.0 months in the avelumab plus BSC group and 2.8 in months the BSC group.

Patient-Reported outcomes: HRQoL is maintained and/or improved on both avelumab plus BSC and BSC alone

In the JAVELIN Bladder 100 trial, HRQoL was assessed using the following tools: the NCCN-FACT, NCCN-FACT FBlSI-18, EQ-5D-5L, and VAS.

In the Overall Population, the mean FBlSI-18 total score at baseline was similar in both the avelumab plus BSC group and in the BSC alone group. During on-treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group), FIBISI-18 total scores showed improvement in both treatment groups. Changes in the FIBISI-18 total and subscale scores from baseline were similar between the avelumab plus BSC group and the BSC group. The median time to deterioration (assessed with the FBISI DRS-P subscale) was not reached (95% CI, 13.9 months to not reached) in the avelumab plus BSC group and was 13.8 months (95% CI, 12.9 months to not reached) in the BSC group (HR = 1.26; 95% CI, 0.90 to 1.77).

The mean EQ-5D-5L and VAS scores at baseline were similar in the avelumab plus BSC group and in the BSC group. During on-treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group), EQ-5D-5L scores showed improvement in both treatment groups. During on-treatment assessments with sufficient data from at least 10 patients (through cycle 31 for the avelumab plus BSC group and cycle 25 for the BSC group), VAS scores increased (i.e., indicating a better health state) for both treatment groups. Changes from baseline were similar between both the avelumab and BSC groups in the EQ-5D-5L index and VAS scores. Results for the PD-L1–Positive Population were similar to those of the Overall Population for all HRQoL analyses.

Limitations: Open-label trial design had the potential to introduce biases

The main limitations outlined by the CADTH Methods Team and discussed by pERC were the following:

The JAVELIN Bladder 100 trial was conducted using an open-label study design, which is susceptible to reporting and performance biases. Patients and investigators were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of the active treatment if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. However, the use of an interactive response technology system used for randomization, implementation of a BICR for assessment of outcomes (i.e., PFS and ORR), and the use of objective diagnostic criteria (RECIST v1.1) and radiological assessments were appropriate to mitigate potential biases related to the open-label nature of the trial. However, patients' awareness of treatment assignment may have biased measurement of patient-reported outcomes, favouring maintenance treatment with the investigational therapy (avelumab plus BSC) over the control group in the trial (BSC alone).

Other limitations included analysis of patient-reported outcomes without standard minimally important differences to aid in the interpretation of clinically meaningful changes in quality of life for patients between treatment groups; a lack of stratification by PD-L1 status for efficacy outcomes because efficacy analyses in the trial were conducted in 2 co-primary populations including the Overall Population and the

PD-L1–positive population; a large amount of censoring for efficacy analyses which may have inflated benefit observed from avelumab; and subgroup analyses were not powered for detection of differences between treatment groups and were not adjusted for multiplicity.

Safety: The use of avelumab in this setting appears safe with low rates of severe adverse effects

In general, AEs of all categories occurred more frequently in the avelumab plus BSC group versus the BSC group. AEs of any grade occurred in 98.0% of patients in the avelumab plus BSC group and in 77.7% of patients in the BSC group. Grade 3 or higher AEs occurred in 47.4% of patients in the avelumab plus BSC group and 25.2% of patients in the BSC group. The most commonly occurring grade 3 or higher AEs in the avelumab plus BSC group compared with the BSC group were urinary tract infection (4.4% versus 2.6%) and anemia (3.8% versus 2.9%). Serious AEs (SAEs) occurred in 27.9% of patients in the avelumab plus BSC group versus 20.0% in the BSC group. The most common SAE was urinary tract infection, which occurred in 16 patients (4.7%) in the avelumab plus BSC group and 7 patients (2.0%) in the BSC group. Treatment-related AEs of any grade occurred in 77.3% of patients in the avelumab plus BSC group and in 1.2% of patients in the BSC group. The most common treatment-related AEs in the avelumab plus BSC group were pruritus (13.7%), hypothyroidism (10.5%), diarrhea (10.2%), and infusion-related reactions (10.2%). None of these treatment-related AEs occurred in the BSC group. Treatment-related AEs of grade 3 or higher were reported in 16.6% of patients in the avelumab plus BSC group; of these, 3 patients (0.9%) experienced a grade 4 treatment-related AE. No patients in the BSC group experienced a grade 3 or higher treatment-related AE.

An immune-related AE of any grade was reported in 29.4% of patients in the avelumab plus BSC group and in 1.4% of patients in the BSC group. Grade 3 immune-related AEs occurred in 7.0% of patients in the avelumab plus BSC group and 0.3% of patients in the BSC group. One patient (0.3%) in the BSC group experienced a serious immune-related AE which was due to diabetes mellitus. Discontinuation of treatment due to immune-related AEs occurred in 19 patients (5.5%) in the avelumab plus BSC group. Infusion-related reactions (referring to the composite category) occurred in [redacted]% of patients in the avelumab plus BSC group, and in no patients in the BSC group. Three patients (0.9%) experienced grade 3 or higher infusion-related reactions. Serious infusion-related reactions in the avelumab plus BSC group were reported in [redacted] patients ([redacted]%), all of whom discontinued study treatment with avelumab. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Deaths were mainly due to progression of disease, and occurred in [redacted] patients ([redacted]%) in the avelumab plus BSC group versus [redacted] patients ([redacted]%) in the BSC group. Based on investigator assessment, 2 patients (0.6%) in the avelumab plus BSC group experienced death related to toxicity of trial treatment. One of the patients experienced sepsis following a urinary tract infection and possible central venous catheter infection after having received 11 infusions of avelumab. The second patient died from an ischemic stroke which occurred 100 days after having received 1 dose of avelumab and after disease progression and AEs of limb venous thrombosis, pulmonary embolism, and acute myocardial infarction. *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this information not be disclosed pursuant to the Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review. This information will remain redacted until notification by the sponsor that it can be publicly disclosed).*

Need and burden of illness: Improved treatment options for these patients are needed and highly relevant

In 2019, UC resulted in 2,500 deaths among Canadians, making it the eighth most common cause of cancer-related death and the fifth most common cause of cancer in males. UC typically arises in the bladder but may develop in the urothelium lining the renal pelvis, ureter, and proximal and prostatic urethra as well. Although first-line platinum-based combination chemotherapy has reasonably high ORR

and is associated with improved OS and second-line immunotherapy with pembrolizumab has modestly improved OS, virtually all patients with recurrent, metastatic, or locally advanced incurable UC die of their disease. The effectiveness of immunotherapy as second-line treatment has led to investigation of immunotherapy-based first-line treatment strategies for incurable urothelial cancer. Improved treatment options for these patients are needed and highly relevant.

Registered clinician input: Avelumab fulfills an unmet need for maintenance treatment following good response to platinum-based induction chemotherapy

One joint clinician input was provided from 2 medical oncologists. One oncologist provided input on behalf of Ontario Health (Cancer Care Ontario) GU Drug Advisory Committee, and the other was an oncologist in practice at an Ontario health centre. Overall, the registered clinicians felt that the patient population in the reimbursement request aligned with the need identified in their clinical practice. They would use avelumab maintenance therapy in patients who have received first-line platinum-containing regimen and experienced stable disease or regression. The clinicians felt that avelumab fulfills an unmet need for maintenance treatment following good response to platinum-based induction chemotherapy. Currently, these patients are monitored and given BSC. In the event of disease progression, patients are treated with pembrolizumab. Avelumab maintenance therapy would be a replacement of pembrolizumab in these patients.

PATIENT-BASED VALUES

Perspectives of patients with UC: Blood in urine a key symptom; other symptoms included fatigue, difficulty urinating, and a burning sensation during urination

One patient advocacy group input was submitted by BCC. The most frequently reported cancer symptoms by the survey respondents were blood in urine (49%), fatigue (38%), difficulty urinating (22%), and a burning sensation during urination (20%). Approximately 11% to 15% of patients also reported abdominal pain, nausea, shortness of breath, and loss of appetite. Four patients reported that they had no symptoms before diagnosis and before treatments started. Several patients believed their symptoms were caused by the cancer treatments and/or stress related to their diagnosis and were not directly caused by their UC. Few respondents reported difficulty accessing current treatments; however, they did report the following challenges: travel distance, treatment cost, and parking and travel costs. Respondents reported additional financial challenges such as accommodation costs and low income caused by absences from work. Six patients required financial assistance due to the cost of UC or its treatments.

Patient values on treatment: Preventing disease recurrence, controlling progression, and maintaining their quality of life

Two of the patients included in the patient group's survey had treatment experience with avelumab. One patient reported mild to moderate side effects and was able to complete the full course the treatment, whereas the other patient reported that they initially experienced few side effects but had to discontinue the treatment after 6 months due to a sudden onset of side effects. However, both patients concluded that they would recommend avelumab to other patients.

Overall, patients valued preventing disease recurrence, controlling progression, and maintaining their quality of life. Most patients reported that they would tolerate moderate to severe adverse effects if a treatment controlled disease progression or prevented recurrence. BCC commented that, if funded, avelumab would addresses an unmet need and that it aligns with patient values.

ECONOMIC EVALUATION

Avelumab is given in 4-week cycles at a dose of 10 mg/kg intravenously (IV) over 60 minutes on day 1 and day 15 of each cycle until disease progression or unacceptable toxicity. Each 200 mg vial costs $1,325, for a total cost of $10,600 per 4-week cycle.

The sponsor submitted a cost-utility analysis of avelumab with BSC for first-line treatment of patients with locally advanced or metastatic UCs whose disease has not progressed with first-line platinum-based induction chemotherapy compared with BSC alone. The sponsor submitted a 3-state partitioned survival model based on Kaplan-Meier data and parametric survival curves. The 3 mutually exclusive states were progression-free, progressed disease, and death. Time spent in each state was based on direct modelling of OS and PFS curves, which the sponsor extrapolated over the time horizon of the analysis using parametric methods. In the model, the patient could also progress onto a subsequent line of therapy, at which point the costs of treatment were changed to reflect subsequent therapy. The types of subsequent therapies available and the proportion of patients receiving each type were based on the JAVELIN Bladder 100 trial. This trial was the primary source of efficacy data in the model. The sponsor's analysis was conducted from the perspective of a Canadian publicly funded health care payer over a 10-year time horizon.

The following key limitations were identified:

- Long-term survival for both BSC and avelumab with BSC was deemed optimistic by the clinical experts consulted by CADTH given the lack of long-term data outcomes beyond the trial duration.
- After treatment discontinuation, a proportion of patients receive a second-line therapy due to disease progression or treatment intolerance. The proportions and types of subsequent therapies used in the model were not in line with data from the trial.
- Disutility associated with AEs was not considered, including events such as immune-mediated pneumonitis, hyperthyroidism, and immune-mediated diabetes. Costs incurred from moderate AEs were omitted.
- Costs for BSC were omitted. Although BSC costs would appear in both treatment arms, patients on avelumab with BSC live for longer, excluding these costs underestimates the costs in the avelumab arm.
- The time horizon used was not reflective of a lifetime time horizon.

CADTH's reanalysis included the following changes: the OS curves for both the BSC and avelumab with BSC treatment arms were changed from generalized gamma curves to exponential curves, the percentage of patients initially receiving avelumab who receive pembrolizumab as subsequent therapy was updated to reflect the JAVELIN Bladder 100 trial, the time horizon was extended from 10 years to 15 years, and the percentage of patients on avelumab who received subsequent therapy after treatment discontinuation was increased from 68.52% to 79% to align with the JAVELIN Bladder 100 trial. According to CADTH's reanalyses, the incremental cost-effectiveness ratio (ICER) for avelumab with BSC versus BSC alone in patients with locally advanced or metastatic UCs whose disease has not progressed with first-line platinum-based induction chemotherapy was $278,373 per QALY. At a willingness-to-pay threshold of $50,000 per QALY, a price reduction of at least 83% is required for avelumab with BSC to be cost-effective. As there remains some outstanding uncertainty within the model regarding potential cost and health consequences associated with adverse events, subsequent treatment costs and utility post disease progression, the resulting ICER may overestimate the cost-effectiveness of avelumab, and the price reduction may be underestimated.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Budget impact substantial and underestimated

CADTH reanalysis suggests that the sponsor-submitted budget impact of introducing avelumab to the market is underestimated. CADTH was unable to obtain reliable estimates from the sponsor's budget

impact analysis and therefore could only conduct a reanalysis that excluded cost savings from subsequent treatment costs. The 3-year budget impact from this reanalysis estimated an increase to budgets of $312,553,246.

Factors related to currently funded treatments, the eligible patient population, implementation, and sequencing and priority of treatments are described in Appendix 1.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member
Dr. Jennifer Bell, Bioethicist
Dr. Kelvin Chan, Oncologist
Dr. Michael Crump, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger, Oncologist
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Maureen Trudeau who did not vote due to her role as pERC Chair
- Dr. Christian Kollmannsberger due to a conflict of interest

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of avelumab plus BSC for adult patients with locally advanced or metastatic UC whose disease has not progressed with first-line platinum-based induction chemotherapy, through their declarations, 2 members had a real, potential or perceived conflict and based on application of the pCODR Conflict of Interest Guidelines, but 1 of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the pCODR Disclosure of Information Guidelines. The sponsor, as the primary data owner, did not agree to the disclosure of efficacy and safety information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

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Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the pCODR Disclosure of Information Guidelines.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

PAG implementation questions	pERC Recommendation
Eligible patient population	
In view of the characteristics of the patient population and exclusion criteria in the JAVELIN Bladder 100 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with avelumab: • Patients on alternative non-platinum chemotherapy (e.g., gemcitabine plus paclitaxel) due to intolerance or contraindications. • Patients having experienced prior adjuvant or neoadjuvant systemic therapy within the past 12 months and who are candidates for re-treatment with chemotherapy in the advanced setting. • Patients who experience intolerance and are unable to complete at least 4 cycles of platinum-based chemotherapy as first-line treatment.	• In real-world practice, some patients may receive alternative non-platinum chemotherapy, and pERC agreed with the CGP that maintenance therapy with avelumab is reasonable for these patients, provided they have received a minimum 12 weeks (4 to 6 cycles) of treatment and had not shown evidence of progressive disease on or after treatment. • pERC agreed with the CGP that patients with potentially curable urothelial cancer, those who have received adjuvant or neoadjuvant systemic therapy within 12 months, and those who have had prior treatment with PD-1 plus PD-L1 inhibitors or who have received second-line chemotherapy for incurable disease should not be considered candidates for avelumab maintenance therapy. Pembrolizumab is currently approved for second-line treatment in this patient population. • pERC agreed with the CGP that shorter durations of treatment with chemotherapy in the first line (> 4 cycles) may be eligible for treatment with avelumab plus BSC maintenance. However, patients receiving fewer than 4 cycles of chemotherapy due to intolerance should have no evidence of disease progression on or after treatment, and reasons for shortened chemotherapy exposure should be clearly justified so as not to encourage inadequate exposure to chemotherapy treatment.
PAG seeks to understand if there are histologies other than transitional cell in UC and, if so, whether they would they qualify for avelumab.	pERC agreed with the CGP that these data are generalizable to patients with incurable UC of predominantly transitional histology, as long as there was no evidence of disease progression on or after first-line chemotherapy. The JAVELIN Bladder 100 results should not be generalized to patients with predominantly non-transitional histologies.
Implementation factors	
The recommended dose of avelumab is 10 mg/kg body weight by IV infusion over 60 minutes every 2 weeks in 4-week cycles. It is proposed that the drug should continue to be administered until disease progression or unacceptable toxicity. PAG seeks advice on a definition of progression and related	In the JAVELIN Bladder 100 trial, disease progression was determined by BICR assessment based on RECIST v1.1 criterion. Radiological tumour assessments were conducted at baseline (within 28 days before randomization), at 8 weeks after randomization, every 8 weeks for 12 months from randomization, and every 12

criteria for discontinuation. PAG noted that the use of single-use 200 mg vials may result in wastage, particularly in low volume or rural institutions where vial sharing is not feasible and weight-based dosing is used. For a 70 kg patient, the 10 mg/kg dose would be 700 mg, which requires 4 vials to be used; the unused portion (100 mg) would be discarded if vial sharing could not occur. PAG remarked that a fixed dose of 800 mg avelumab was used in some clinical trials and was approved by the FDA. PAG seeks advice on implementing weight-based dosing up to a maximum of 800 mg, as it would minimize waste and be consistent with how nivolumab and pembrolizumab are currently implemented.	weeks thereafter until documented disease progression regardless of whether patients received subsequent anti-cancer therapy. pERC agreed with the CGP that in clinical practice, radiological tumour assessments are more commonly performed every 12 weeks (compared to the more frequent assessments performed in the trial). pERC agreed with the CGP that weight-based dosing would be reasonable to minimize wastage up to a maximum of 800 mg.
PAG commented that the q.2.w. schedule has potential impacts on chemotherapy room utilization, nursing resources, and patient commitment to the treatment schedule. Consequently, PAG seeks evidence and guidance on administering avelumab on a different schedule (e.g., every 4 weeks) for patient convenience and to minimize visits to the cancer treatment centre.	pERC agreed with the CGP that there is no evidence to support a different dosing schedule. Additionally, there is the concern of an increased risk for infusion-related reactions if less frequent administration schedules lead to patients receiving larger doses of avelumab.
Sequencing and priority of treatment	
PAG is seeking guidance on the appropriate place in therapy of avelumab for UC and on sequencing with other drugs for this condition. PAG seeks to understand what options would be available after failure of avelumab. Based on that, PAG raised the question of the appropriateness of subsequent immune checkpoint inhibitors in cases of progression on avelumab maintenance and whether it would be preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress.	pERC agreed with the CGP that there is currently no evidence to support the use of a second-line immune checkpoint inhibitor following first-line avelumab maintenance given that they work through similar mechanisms of action. There remains a lack of evidence-based therapies for these patients; however, chemotherapy and clinical trials may be appropriate. In terms of whether it would preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress, the CGP noted that the JAVELIN Bladder 100 clinical trial investigated whether patients treated with avelumab plus BSC had better outcomes than patients treated with BSC only. Given the results of the trial, pERC agreed with the CGP that it would be preferable to give avelumab for maintenance therapy

	rather than wait and give pembrolizumab to patients who progress.
If subsequent anti-PD1 therapy is permitted, PAG would like to determine the minimum progression-free interval to qualify for such therapy (e.g., patients who progress during or within 6 months of stopping avelumab would not be eligible for further anti-PD1 therapy).	pERC agreed with the CGP that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy. For patients who stop treatment with avelumab for reasons related to infusion reaction or unrelated to progression after a short duration of exposure (i.e., <6 months) and who then experience disease progression after a progression free interval of >6 months, pERC agreed with the CGP that subsequent treatment with pembrolizumab may be considered.
PAG mentioned that patients may interrupt avelumab maintenance for personal reasons and seeks guidance (e.g., adequacy, timing) on restarting avelumab therapy in case of disease progression or giving pembrolizumab instead.	pERC agreed with the CGP that treatment with avelumab should only be continued if the disease is still in remission. If the disease had progressed, then the patient would receive the next line of treatment for their disease.
Companion diagnostic testing	
PAG would like confirmation that PD-L1 testing is not required and that no PD-L1 expression subgroup derives a distinct benefit from avelumab.	pERC agreed with the CGP that PD-L1 testing is not required. The results of the JAVELIN Bladder 100 trial showed a positive effect of avelumab treatment in the Overall Population, and that these results were not limited just to patients who were PD-L1 positive.

CGP = Clinical Guidance Panel; PAG = Provincial Advisory Group; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; q.2.w. = every 2 weeks; UC = urothelial carcinoma.