CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Enfortumab vedotin (Padcev)

Indication: In combination with pembrolizumab, for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC
Sponsor: Seagen Canada Inc.

Recommendation: Reimburse with Conditions

Version:	1.0
Publication Date:	October 2024
Report Length:	17 Pages

Single Technology

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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.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that enfortumab vedotin in combination with pembrolizumab be reimbursed for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from one open-label phase III randomized controlled trial involving a total of 886 patients with locally advanced or metastatic urothelial cancer (Study EV-302) showed that treatment with enfortumab vedotin in combination with pembrolizumab demonstrated a clinically meaningful benefit compared to platinum plus gemcitabine chemotherapy (PLAT + GEM) in improving overall survival (HR: 0.468 [95% CI: 0.376, 0.582]; P < 0.00001), progression-free survival (HR = 0.450, 95% CI: 0.377, 0.538; P < 0.00001), and objective response rate (Difference = 23.3 % [95% CI, 16.8 % to 29.6%]; P < 0.00001) with high certainty. The safety profile of enfortumab vedotin in combination with pembrolizumab was consistent with the known safety profiles of enfortumab vedotin monotherapy and pembrolizumab monotherapy.

The EORTC QLQ-C30 GHS results from Study EV-302 indicated that treatment with enfortumab vedotin in combination with pembrolizumab may result in little-to-no clinically important difference in patients' health-related quality of life (HRQoL) compared with platinum + gemcitabine. However, pERC considered the HRQoL results to be immature with low completion rates and, therefore, insufficient for drawing a definitive conclusion about the effect of enfortumab vedotin in combination with pembrolizumab on HRQoL. Based on the totality of the evidence, pERC concluded that enfortumab vedotin in combination with pembrolizumab is an effective treatment option with an acceptable safety profile that meets some of the unmet needs identified by patients, such as improved overall survival and progression-free survival.

Using the sponsor-submitted price for enfortumab vedotin and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for enfortumab vedotin in combination with pembrolizumab was $290,563 per quality-adjusted life-year (QALY) gained, compared with initiating platinum-based chemotherapy in patients with locally advanced or metastatic urothelial cancer. At this ICER, enfortumab vedotin in combination with pembrolizumab is not cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained. Therefore, a reduction in the price of enfortumab vedotin in combination with pembrolizumab is required.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason	Implementation Guidance
Initiation		
1. Enfortumab vedotin in combination with pembrolizumab should be reimbursed for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer with no prior systemic therapy. 2. For additional clarity, the following patients are eligible: 2.1. Received neoadjuvant chemotherapy, but experienced recurrence more than12 months after neoadjuvant chemotherapy was completed; or 2.2. Received adjuvant chemotherapy following cystectomy, but experienced recurrence more than 12 months after adjuvant chemotherapy was completed; or 2.3. Received adjuvant nivolumab, but experienced recurrence more than 6 months after nivolumab treatment was completed	The Study EV-302 included patients with adjuvant or neoadjuvant chemotherapy with recurrence 12 months after completion of treatment; and the clinical expert stated that as per standard practice with other regimens after immunotherapy, patients with adjuvant neo/adjuvant immune checkpoint inhibitors who experienced relapse at least 6 months after treatment completion should be eligible to be treated with enfortumab vedotin in combination with pembrolizumab.	
3. Patients should have a good performance status	The EV-302 study included patients with ECOG performance status of 0, 1, or 2.	pERC agreed with the clinical experts indicated that ECOG should not be too prescriptive. because a pERC determined that adequate performance status should be based on clinical judgement.
4. Treatment with enfortumab vedotin in combination with pembrolizumab should not be initiated in patients with: 4.1. Active CNS metastases 4.2. Uncontrolled diabetes 4.3. Prior enfortumab vedotin or other MMAE based ADCs	Study EV-302 excluded patients with these characteristics and the CADTH review did not identify any evidence to demonstrate the safety and potential benefits in such patients.	pERC determined that patients with CNS metastases may be eligible for treatment with enfortumab vedotin in combination with pembrolizumab, if they have stable brain metastases prior to treatment on baseline scans. However, patients with leptomeningeal

Reimbursement Condition	Reason	Implementation Guidance
		disease should not be treated with enfortumab vedotin.
Renewal		
5. Patients should be assessed by the treating clinician prior to each treatment cycle with diagnostic imaging conducted every 2 to 3 months.	Imaging assessments for Study EV-302 were performed every 9 weeks (approximately every 2 months) from the first dose of study treatment throughout the study until radiological disease progression.	pERC agreed with the clinical expert that in clinical practice, imaging assessment should not be too prescriptive and that it could vary based on prescriber experience, patient factors, and whether treatment is at the early or late stage.
Discontinuation		
6. Treatment should be discontinued in patients with any of the following: 6.1. Documented disease progression 6.2. Unacceptable toxicity	In Study EV-302, enfortumab vedotin in combination with pembrolizumab was discontinued if patients experienced disease progression or unacceptable toxicity, and the CADTH review did not identify any evidence to demonstrate the safety and potential benefits in such patients.	pERC agreed with the clinical expert that as per the Study EV-302, patients who experience unacceptable AE attributable only to enfortumab vedotin may continue pembrolizumab monotherapy up to a maximum of 35 cycles, and patients who experienced an unacceptable AE attributable only to pembrolizumab may continue enfortumab vedotin monotherapy. pERC noted that the decisions to discontinue treatment should be made in consultation with the patient.
Prescribing		
7. Treatment with enfortumab vedotin in combination with pembrolizumab should only be initiated by a medical oncologist with experience treating incurable urothelial cancer. 7.1. Given the known complications associated with enfortumab vedotin in combination with pembrolizumab, initial treatment must be administered in centers where there is experience using a drug at risk for extravasation.	To ensure that enfortumab vedotin in combination with pembrolizumab is initiated only for appropriate patients and adverse effects are managed in an optimized and timely manner.	pERC agreed with the clinical expert that after the initial prescription, ongoing care may be continued by general practice oncologists for patients receiving care outside of major cancer centres.
8. Enfortumab vedotin in combination with pembrolizumab	The Study EV-302 did not include patients on other anti-cancer	-

Reimbursement Condition	Reason	Implementation Guidance
should not be used in combination with other anti-cancer drugs for with locally advanced or metastatic urothelial cancer.	drugs for with locally advanced or metastatic urothelial cancer, and the CADTH review did not identify any evidence to demonstrate the safety and potential benefits of enfortumab vedotin in combination with pembrolizumab in such patients.	
Pricing		
9. A reduction in price	The ICER for enfortumab vedotin in combination with pembrolizumab is $290,563 per QALY gained when compared to initiating platinum-based chemotherapy. The cost-effectiveness of enfortumab vedotin in combination with pembrolizumab is dependent on the price paid for both enfortumab vedotin and pembrolizumab. A price reduction of 78% for both enfortumab vedotin and pembrolizumab would be required for enfortumab vedotin in combination with pembrolizumab to achieve an ICER of $50,000 per QALY gained when compared to platinum-based chemotherapy.	
Feasibility of Adoption		
10. The feasibility of adoption of enfortumab vedotin must be addressed	At the submitted price, the incremental budget impact of enfortumab vedotin in combination with pembrolizumab is greater than $40 million in years 1, 2 and 3 with a total 3-year budget impact of $329 million.	

CNS = central nervous system; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER; incremental cost-effectiveness ratio; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand 1; PFS= progression-free survival; ORR = overall response rate; OS = overall survival; QALY = quality-adjusted life years; RECIST= Response Evaluation Criteria in Solid Tumours; UC = urothelial carcinoma

Discussion Points

- pERC deliberated whether patients currently receiving alternate first-line therapy for locally advanced or metastatic urothelial cancer could be switched to enfortumab vedotin in combination with pembrolizumab on a time-limited basis at the time of implementation. The committee decided that patients who have not started or not completed platinum-based first-line chemotherapy may be eligible candidates to receive enfortumab vedotin plus pembrolizumab. pERC noted that based on the inclusion criteria of the EV-302 study, enfortumab vedotin in combination with pembrolizumab should not be offered to patients who have completed or progressed on 1st-line chemotherapy. The committee agreed with the clinical expert that

patients who are initiating maintenance avelumab are, by definition, either in remission or have stable disease, and those who progress on avelumab will be eligible for enfortumab vedotin as 3rd-line single agent therapy, already approved and funded.

- pERC discussed the patient group input indicating that patients strongly prioritize health outcomes and are willing to accept more significant side effects. pERC determined that given that adverse events observed in EV-302 were consistent with that known to be associated with enfortumab vedotin monotherapy and pembrolizumab monotherapy, indicating that the safety profile of enfortumab vedotin in combination with pembrolizumab are predictable, acceptable and clinically manageable in most patients.
- The comparator used in Study EV-302 was standard of care chemotherapy (i.e., cisplatin plus gemcitabine or carboplatin plus gemcitabine), with about a third of the patients (30.4%) on avelumab for maintenance therapy. pERC noted that this was consistent with the sequencing of treatments in Canada and aligned with the newly recommended listing for avelumab as maintenance therapy following the first-line platinum-based chemotherapy in the locally advanced or metastatic setting. However, the Committee agreed with the clinical experts that the use of avelumab in the control arm of study EV-302 may be less than expected in a contemporary setting due to emergence of avelumab data during this trial. The committee did consider the potential for overestimating the benefit of enfortumab vedotin in combination with pembrolizumab versus the control could not be ruled out.
- pERC discussed the public drug plans' request for clarification on whether erdafitinib could be considered as a relevant comparator in patients with fibroblast growth factor receptor (*FGFR)* genetic alterations who have previously received PD-1 or PD-L1 inhibitors and chemotherapy. pERC noted that erdafitinib is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC), whose tumors have susceptible FGFR2 or FGFR3 genetic alterations and who have disease progression during or following at least one line of prior chemotherapy, including within 12 months of neoadjuvant or adjuvant chemotherapy. The Committee concluded that the indication under review for reimbursement of enfortumab vedotin in combination with pembrolizumab is different and it may be premature to determine that erdafitinib is a relevant comparator for that indication.

Background

Urothelial carcinoma can begin in the renal collecting duct, the ureters, or urethra in addition to the bladder, accounts for approximately 90% of all bladder cancer cases. Bladder cancer is the 5th most common cancer in Canada, and in 2023, it was estimated that there were 13,400 new cases of bladder cancer. The goal of the treatment of la/mUC is to delay disease progression, prolong life while minimizing symptoms, improve health-related quality of life, increase the ability to maintain employment and maintain independence, and reduce burden on caregivers. In Canada, Plat +Gem followed with avelumab treatment is considered the first line treatment for patients who responded to Plat +Gem without progression (i.e., achieved a complete response, partial response, or stable disease). Despite current treatments, patients with metastatic disease have a 5-year survival rate of 5%. There is a significant unmet need for new therapies that increase survival with a manageable safety profile and maintain quality of life (QoL).

Enfortumab vedotin is an antibody drug conjugate (ADC) directed against Nectin-4, an adhesion protein located on the surface of most urothelial cancer cells. Enfortumab vedotin is an antineoplastic agent. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) administered as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

Enfortumab vedotin in combination with pembrolizumab has a Health Canada indication for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC.

Sources of Information Used by the Committee

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

- A review of 1 open-label, phase III RCT in patients with locally advanced or metastatic urothelial cancer
- Patients' perspectives gathered by patient groups, 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 locally advanced or metastatic urothelial cancer

- Input from 2 clinician groups, including Bladder Cancer Canada (BCC) and Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee.
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received 1 submission from Bladder Cancer Canada (BCC). BCC is a registered national charity in Canada serving those facing a bladder cancer diagnosis. Their objectives are to help bladder cancer patients and their support teams, to increase awareness of bladder cancer, and to fund research.

BCC collected data from 7 patients and 2 caregivers through an online survey conducted between April 17 and May 29, 2024. Overall, 7 survey respondents were from Canada, 1 from US and 1 unknown. All of the survey respondents had experience with locally advanced or metastatic urothelial cancer (la/mUC), and 7 respondents (5 patients and 2 care givers) had treatment experience with Padcev in combination with pembrolizumab.

According to the BCC, the most reported cancer symptoms were blood in urine (88%), fatigue (63%) and bone pain (50%). Blood in urine and frequent urination were cited in interviews as the most difficult symptoms to tolerate. It was also noted that frequent urination could interfere with the patient's ability to sleep.

BCC noted that respondents had treatment experience with gemcitabine, cisplatin, carboplatin, paclitaxel, radiation, transurethral resection of bladder tumour (TURBT) procedures, radical cystectomy and neobladder reconstruction. Among the respondents, 6 had received platinum-based chemotherapy, while 3 had received Padcev as their first IV treatment. BCC added that based on respondents answers current therapies are broadly adequate for managing patient symptoms, and the most reported side effects of these treatments were fatigue (67%), loss of appetite (44%), neuropathy (44%) and hair loss (44%). Fatigue and neuropathy were the most difficult side effects to tolerate. 3 respondents reported screening problems that delayed the patient's access to treatment and may have affected health outcomes. 1 respondent reported difficulties in accessing treatment due to her distance from the nearest large urban centre. BCC noted that respondents strongly prioritize health outcomes and are willing to accept more aggressive side effects.

BCC stated that when patients were asked to rate how their life had changed on enfortumab vedotin in combination with pembrolizumab compared to other therapies that they had received, among 7 respondents, the highest average score was for maintaining quality of life, followed by drug side effects, cancer symptoms, controlling disease progression, and preventing recurrence. BCC added that 2 respondents noted that while this treatment was effective for soft-tissue tumours, it failed to control the growth of bone metastases. BCC reported that hair loss and nausea were the most commonly reported side effects (43% each, n=7).

BCC noted that when respondents were asked to rate the tolerability of the side effects associated with enfortumab vedotin in combination with pembrolizumab on a scale from 1 (completely tolerable) to 10 (completely intolerable), the average score was 6.0 (3 patients and 1 caregiver scored 1, while 2 patients and 1 caregiver scored 8 or higher). Additionally, BCC reported that 1 caregiver indicated that the worst side effects occurred during the first week of treatment and largely cleared up afterwards, by contrast, 1 patient indicated that the side effects built over time. BCC added that 1 patient reported dose reductions as a result of adverse events, and 1 patient reported dose reduction due to concern about peripheral neuropathy.

BCC stated that when patients were asked to rate how the side effects associated with Padcev had affected different aspects of their life, the highest average score was for ability to sleep, followed by ability to work, ability to spend time with family and friends, ability to perform household chores, and ability to care for children. BCC added that the treatment was seen to have a moderately negative effect in most areas of life, but this effect was particularly dramatic on the respondents' ability to care for children.

According to BCC, 1 patient reported lack of geographical accessibility.

Clinician Input

Input from Clinical Experts Consulted by CADTH

The clinical experts indicated that the goal of the treatment for patients with incurable locally advanced or metastatic urothelial cancer is to reduce cancer burden and improve quantity and quality of life. Only about half of patients respond to the standard of care of Platinum-based combination chemotherapy (Plat +Gem). With chemotherapy alone, the average survival of these patient is 14-18 months, and this improves to about 16-20 months with the addition of avelumab maintenance therapy. These treatments also have adverse effects that can diminish quality of life, and almost no patients are cured. One clinical expert indicated that although we have had slow some advances in mUC, the majority of patients die from their disease swiftly. Treatments that significantly prolong OS (especially in an unselected population) are needed. So better treatments providing more frequent and prolonged disease control are needed.

The clinical expert mentioned that the first line of the standard of care pharmaceutical therapy for patients with incurable locally advanced or metastatic urothelial cancer is Platinum-based combination chemotherapy. The Clinical expert emphasized that, for patients who do not progress during or after platinum-based chemotherapy (i.e., achieved a complete response, partial response, or stable disease), Plat +Gem followed by the avelumab maintenance treatment is considered as the first line treatment in this setting. So, the clinical experts indicated that, technically, the most relevant comparator is chemotherapy followed by maintenance immunotherapy in non-progressing patients. Patients who progress despite chemotherapy are offered immunotherapy with pembrolizumab. Supportive treatments may also include analgesics for pain, palliative radiotherapy, bisphosphonates, and palliative care referral. Patients with progressive cancer despite immunotherapy may be offered enfortumab vedotin monotherapy or, if their tumor has a fibroblast growth factor receptors (FGFR) alteration, erdafinitib may be offered. The clinical experts stated that Platinum-based chemotherapy typically consists of gemcitabine with either cisplatin or carboplatin, or less commonly dose-intense methotrexate, vinblastine sulfate, doxorubicin hydrochloride (Adriamycin), and cisplatin (MVAC) chemotherapy, which includes Granulocyte colony-stimulating factor (G-CSF) support. The Clinical experts also noted that there is also data from a randomized trial that added concurrent and maintenance nivolumab to gemcitabine/cisplatin and showed overall survival benefit (Checkmate 901). Although not approved for this indication, nivolumab is available in Cananda and commonly used for many other cancers, so could also be considered a comparator for cisplatin eligible patients. One clinical expert indicated that economic comparators must include the maintenance avelumab portion of first line treatment. At a gross estimate, 65-75% of patients would fail to progress on platinum-based chemo and would be offered or eligible for maintenance avelumab until progression. One expert indicated that in real clinical practice, not all patients who are eligible for avelumab actually receive avelumab. It is roughly about 30% of the patients with the Plat +Gem treatment actually received avelumab in real world.

The clinical experts emphasized that EV+P has the highest reported tumor response rate in incurable urothelial cancer. In addition, the mOS was almost doubled in EV+P arm when compared to PLAT +GEM chemotherapy. It can be given to patients who are cisplatin ineligible, who constitute up to half of advanced urothelial cancer patients. The clinical experts indicated that based on the results of the EV-302 trial, it is expected that EV+P will become the de facto standard of care for incurable urothelial cancer.

The clinical expert indicated that all patients with incurable urothelial cancer should be considered for enfortumab vedotin in combination with pembrolizumab as the first consideration for treatment. Patients with contraindications to immunotherapy might not be able to receive pembrolizumab. EV has dermatological, neuropathic and diabetogenic risks that might be contraindications in some patients. One clinical expert indicated that given the significant survival advantages with enfortumab vedotin in combination with pembrolizumab, it should not restrict access to only patients who would have met inclusion criteria for the clinical trial (i.e. with regard to performance status, pre-existing autoimmune conditions). Rather, enfortumab vedotin in combination with pembrolizumab should be the standard first line consideration if the care providers deem them appropriate candidates.

The clinical experts indicated that Overall Survival (OS), European Organisation for Research and Treatment of Cancer Quality of Life Core 30 (EORTC QLQ-C30), Objective Response Rate (ORR), Safety, Progression-Free Survival (PFS), Duration of Response (DOR) are commonly used for assessing the treatment response (benefit) for la/mUC. Additionally, one clinical expert noted that it should not be too prescriptive about frequency of assessments that will vary from prescriber to prescriber; from patient to patient; it also depends on whether it is at the early stage or late stage in the patient's treatment course.

The clinical experts indicated that treatment should be discontinued if there is cancer progression despite treatment, severe or intolerable adverse effects, deterioration in the patient's condition due to other factors, or at the patient's request.

The clinical experts indicated that patients should be assessed for this treatment by a medical oncologist with experience treating incurable urothelial cancer. This treatment is quite suitable for outpatient administration. One clinical expert indicated that medical oncologist should be assessing and prescribing initially. Ongoing care can likely be safely continued and prescribed by general practice oncologists (GPOs) for patients receiving care outside of major cancer centres.

Clinician Group Input

CDA received input from 2 clinician groups. Bladder Cancer Canada (BCC) and Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee [OH(CCO)-GU DAC].

The clinician groups believed that the first line of treatment includes platinum-based chemotherapy and avelumab. BCC added that for patients who progress on chemotherapy, the standard subsequent treatment is pembrolizumab, and once patients have progressed on immunotherapy (avelumab or pembrolizumab), the standard of care for second-line treatment is enfortumab vedotin monotherapy, or erdafinitib (for FGFR-altered cancers).

OH(CCO)-GU DAC noted that treatment goals are to improve overall survival, progression-free survival, and improved response rate including complete response with potential for long term remission.

According to BCC the unmet needs were durable disease control, toxicity of the treatment, quality of life and complete response. OH(CCO)-GU DAC noted overall survival and durable responses as treatment gaps.

Both clinician groups stated that enfortumab vedotin in combination with pembrolizumab would become the first-line standard of care.

OH(CCO)-GU DAC mentioned that patients who are deemed eligible by a physician for immunotherapy-based regimens are best suited for treatment with the drug under review, and any patient with urothelial cancer should be eligible irrespective of the histology. OH(CCO)-GU DAC added that patients with a contraindication to immunotherapy are least suitable. According to BCC it is not currently possible to identify which patients will most benefit from this treatment due to the absence of any identified biomarkers. BCC added that patients with an active autoimmune disease or organ transplants would not be able to receive this treatment due to the effects of pembrolizumab.

OH(CCO)-GU DAC believed that patient response assessment is based on clinical and radiographic assessment as per standard of care. BCC mentioned that survival time, recurrence of disease, ability to perform activities of daily living, and reduction of cancer symptoms would be the outcomes used to determine whether patients are responding to treatment, and BCC explained that among the survey respondents, 4 clinicians suggested assessment every 3 months and 1 suggested every 3 weeks prior to each subsequent treatment cycle.

According to OH(CCO)-GU DAC clinically significant disease progression and unacceptable toxicity are the factors that should be considered when deciding to discontinue treatment. BCC added adverse events and recurrence of the disease as other factors.

OH(CCO)-GU DAC noted that outpatient cancer centers under the advisement of a medical oncologist are appropriate settings for this treatment. BCC added the hospital outpatient clinics and private infusion clinics to the list.

OH(CCO)-GU DAC explained that for patients who completed their initial course of 2 years of pembrolizumab, at the time of confirmed disease recurrence, retreatment with pembrolizumab should be funded for up to an additional 1 year (i.e., up to 17 additional doses every 3 weeks or 9 additional doses every 6 weeks) provided pembrolizumab was not previously discontinued due to disease progression.

Drug Program Input

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

Table 2. Responses to Questions from the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
a) Issues with the choice of comparator in the submitted trial(s) In the EV-302 trial, enfortumab vedotin + pembrolizumab (EV+P) was compared to platinum-based chemotherapy (cisplatin or carboplatin + gemcitabine) in previously untreated la/mUC. Platinum-based chemotherapy with gemcitabine is funded for previously untreated la/mUC, including those presenting with unresectable locally advanced or de novo metastatic disease, patients who previously received adjuvant platinum-based therapy and experienced relapse ≥12 months from completion of chemotherapy, and those who experienced relapse ≥6 months from adjuvant nivolumab in eligible patients. Avelumab maintenance is also funded in patients if there has been no disease progression following completion of first-line platinum-based chemotherapy. Pembrolizumab is funded as a second-line option in patients who have not previously received avelumab and/or are not resistant to a PD-1 inhibitor if applicable (e.g., adjuvant nivolumab). Pembrolizumab is also funded for first-line treatment of mUC in patients who experience early relapse (e.g., <12 months) after adjuvant platinum-based chemotherapy. Enfortumab vedotin is funded as a second- or third-line option in patients who have previously received platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor, including patients who experience early relapse (e.g., <6 months) after adjuvant nivolumab.	One clinical expert indicated that the trial was designed without including avelumab maintenance therapy (i.e., without formally incorporating maintenance into the protocol. However, it was allowed at the investigators' discretion). Avelumab maintenance therapy for la/mUC patients whose cancer is stable or had responded to gemcitabine/platinum chemotherapy is the current standard of care in Canada. In EV-302 trial, it was reported that 135/444 (30.4%) of control arm patients used avelumab at their investigator's discretion. Both clinical experts indicated that, in the Canadian setting, while about 50-60% patients who receive Plat +Gem could be potentially eligible for avelumab, real word data indicates that only about 30% of patients treated with first-line platinum-based chemotherapy actually receive avelumab maintenance. Therefore, the reported 30% of patients who received avelumab in EV-302 is likely close to Canadian clinical practice. *pERC agreed with the clinical expert responses*
Considerations for initiation of therapy	
a) Disease diagnosis, scoring or staging for eligibility In the EV-302 study, patients were required to have histologically documented, unresectable LA or mUC (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Patients with squamous or sarcomatoid differentiation or mixed cell types were eligible. Please confirm if this should be the same eligibility for EV + P if recommended for reimbursement.	Confirmed. *pERC agreed with the clinical expert responses*
b) Other patient characteristics for eligibility (e.g., age restrictions, comorbidities) Patients with an ECOG PS of 0, 1, or 2 were eligible for the EV-302 study, but patients with ECOG PS 2 were required to have a	One clinical expert indicated: Yes, for patients with ECOG 2 by trial criteria, and No, for full dose enfortumab vedotin for patients with ECOG 3.

Drug program implementation questions	Clinical expert response
hemoglobin ≥ 100 g/L, GFR ≥ 50 mL/min and couldn't have NYHA Class III heart failure. *Should the same criteria apply for patients with ECOG PS 2 to be eligible for EV + P?* *Should patients with PS ≥2 be eligible if the physician feels they can tolerate treatment?*	The other clinical expert mentioned that using ECOG status should not be too prescriptive because a lot more goes into determining a treatment plan for a patient than their ECOG. *pERC agreed with the clinical expert responses and indicated that "adequate performance status" should be based on physician's clinical judgement.*
c) Prior therapies required for eligibility Patients were not eligible to participate in the EV-302 study if they had received prior PD-1 or PD-L1 inhibitor therapy, including for earlier stages of UC. *Should patients who previously received adjuvant nivolumab and experience relapse ≥6 months from completion be eligible for EV + P?*	Yes *pERC agreed with the clinical expert responses and indicated that it is reasonable to be aligned with other reviews.*
d) Eligibility to re-treatment Pembrolizumab was administered for a maximum of 35 cycles (every 3 weeks) in the EV-302 study. *Should patients who complete 35 cycles or 2 years of therapy be eligible to receive an additional 1 year of treatment with pembrolizumab at time of relapse if it was initially discontinued without any evidence of disease progression (similar to how pembrolizumab is currently funded in several other advanced cancers, including mUC)?* *If retreatment is permitted, would this be as pembrolizumab monotherapy or in combination with EV?*	Yes. Retreatment with EV should depend on why it was discontinued. *pERC agreed with the clinical experts, noting that as per the Study EV-302, patients who experience unacceptable adverse events attributable only to enfortumab vedotin may continue pembrolizumab monotherapy up to a maximum of 35 cycles, and patients who experienced an unacceptable adverse events attributable only to pembrolizumab may continue enfortumab vedotin monotherapy.* *pERC noted that the decisions to discontinue treatment should be made in collaboration between clinician and patient.*
a) Dosing, schedule/frequency, dose intensity PAG would like to inform pERC that they plan to implement weight-based dosing up to a cap for pembrolizumab (2 mg/kg up to a maximum of 200 mg every 3 weeks or 4 mg/kg up to a maximum of 400 mg every 6 weeks), similar to other cancer sites.	No objection. *pERC agreed with the clinical expert responses*
Generalizability	
a) **Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review** *Should patients currently receiving alternate first-line therapy for la/mUC be switched to EV + P on a time-limited basis at the time of implementation?*	Only if they have not started or completed platinum-based first-line chemotherapy. *pERC agreed with the clinical expert responses*
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs	Yes
Drug may change place in therapy of drugs reimbursed in subsequent lines	Yes
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products	Yes

Drug program implementation questions	Clinical expert response
System and economic issues	
a) Concerns regarding the anticipated budget impact and sustainability PAG notes the manufacturer projected 3-year BIA (incremental costs) is over $321 million and is concerned about budget impact and sustainability.	*This is a comment from the drug programs to inform pERC deliberations.* Noted.
b) Presence of confidential negotiated prices for comparators Confidential prices exist for pembrolizumab and avelumab. There are generic versions of cisplatin, carboplatin and gemcitabine available.	*This is a comment from the drug programs to inform pERC deliberations.* Noted.

BIA = budget impact analysis; ECOG PS = Eastern Cooperative Oncology Group; EV = enfortumab vedotin; GFR = Glomerular Filtration Rate; la/mUC = Locally Advanced or Metastatic Urothelial Cancer; N/ A = not applicable; NYHA = New York Heart Association; p = pembrolizumab; PAG = Provincial Advisory Group; PD-1 = Programmed Death Receptor-1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PS = Performance Status; UC = Urothelial Carcinoma.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

EV-302 is a global, phase 3, open-label, 2-arm randomized controlled study (Figure 1) comparing EV+P versus platinum plus gemcitabine (Plat +Gem – i.e., cisplatin plus gemcitabine or carboplatin plus gemcitabine) chemotherapy, which represents the current standard of care for Canadian patients as first-line treatment for la/mUC. The choice of cisplatin or carboplatin in the chemotherapy arm was based on the investigator's assessment of whether a given patient was eligible for cisplatin or carboplatin. The primary objectives were to compare the dual primary endpoints of PFS by BICR and OS between the EV+P arm and the platinum plus gemcitabine arm.

Patients with la/mUC were randomized 1:1 using interactive response technology to receive EV+P or platinum plus gemcitabine with stratification according to cisplatin eligibility (eligible or ineligible), PD-L1 expression (low or high), and liver metastasis (present or absent). At the data cut-off (August 8, 2023), a total of 886 patients across both arms had been randomized to receive EV+P (n = 442) or platinum plus gemcitabine (n = 444); Of these, 47 patients were enrolled at 11 Canadian sites.

Efficacy Results

After a median follow up of 17.2 months PFS by BICR showed a statistically significant and clinically meaningful improvement in the EV+P arm compared with the platinum plus gemcitabine arm. The relative hazard of developing a disease progression event in EV+P arm was clinical meaningfully reduced by 55% as compared to Plat +Gem arm (HR = 0.450). The patients in EV+ P arm also demonstrated a clinically meaningful longer median PFS than that in Plat +Gem arm (treatment group difference: 6 month). According to the clinical experts consulted for this review, compared with the Plat +Gem used as the first line treatment, EV+P used as the first line treatment showed a clinical meaningful higher PFS rate starting from 12 months and sustained to 18 months. Subgroup analyses and sensitivity analyses of PFS appeared consistent with the primary analysis.

The analysis of OS revealed a statistically significant and clinically meaningful improvement in OS with EV+P versus platinum plus gemcitabine. The relative hazard of death in EV+P arm was clinical meaningfully reduced by 54.2 % as compared to Plat +Gem arm (HR = 0.468). The median OS in EV+P arm was 15.4 month longer than that in Plat +Gem arm, which is considered clinical meaningful by the clinical experts consulted for this review. Furthermore, according to the clinical experts, compared with the Plat +Gem first line treatment, EV+P used as the first line treatment showed a clinical meaningful higher OS rate starting from 12 months and sustained to 18 months. Subgroup analyses and Sensitivity analyses of OS appeared consistent with the primary analysis.

After an overall median follow-up of 17.2 months, 23.3% more patients in EV+P arms achieved the ORR than that observed in Plat +Gem arm, which is considered clinically meaningful improvement according to clinical experts consulted for this review. Subgroup analyses showed consistent ORR benefits favoring EV+P across all pre-specified subgroups.

The patient-reported and HRQoL outcomes were identified as important by patients. The findings of EORTC QLQ-C30 assessed at week 26 showed that no apparent HRQoL worse observed in terms of EORTC QLQ-C30 at week 26. And no clinical meaningful between-group (EV+P vs. Plat +Gem) or intra-group difference or were observed. The clinical experts consulted for this review highlighted that it is not expected to see a significant improvement in quality of life with the anticancer treatment for this population. Other patient reported and HRQoL outcomes including Time to Pain Progression and Worst Pain Scores and Change from Baseline and EQ-5D-5L also did not show an clinical meaningful intra-group and intergroup difference from week 8 up to week 71. Notably, a significant number of patients were not included in the analyses of patient-reported outcomes, and HRQoL outcomes, which is an important limitation and a source of uncertainty in those outcomes.

The clinical experts consulted for this review indicated that the EV+P combination is a relatively new treatment regimen for this population and a limited number of Canadian oncologists have experience using EV+P to treat la/mUC. Also, the duration of the treatment of the EV+P in the EV-302 was relatively short and future PFS2 data are needed to better understand the efficacy of subsequent treatments (e.g., subsequent Plat-Gem chemotherapy, immunotherapy, etc.).

Harms Results

The harms outcome was based on the data cut-off of Aug. 23, 2023, which represented a median follow up of 17.2 months. The overall rates of AEs were similar in both the EV+P and Plat +Gem arms. However, some AE (e.g., peripheral sensory neuropathy and pruritus) occurred more often in the EV+P arm than in Plat +Gem arm, whereas others such as anemia, neutropenia, and nausea were more frequent with Plat +Gem than with EV+P. Fewer patients in EV+P arm than in the Plat + Gem are reported that Grade 3 to 5 TEAEs. However, more patients in EV+P arm experienced SAEs than those in Plat +Gem arm. Arm. The clinical experts consulted indicated that overall, the type and distribution of AEs observed in the EV-302 were not unexpected compared in clinical practice. In addition, it was noted the proportion of patients who discontinued treatment because of AEs was higher in the EV+P arm compared to the Plat +Gem arm. Peripheral sensory neuropathy was the most common AEs that caused treatment discontinuation in EV+P arm. Anemia was the most common AEs that caused treatment discontinuation in Plat +Gem arm. TEAE leading to death appeared similar in both arms. The clinical experts consulted for this review indicated that, of the reported AEs of special interest for EV, skin reactions and hyperglycemia are the most clinically important. The incidence of skin reactions and hyperglycemia was higher in EV+P arm than that in Plat +Gem arm. The clinical experts consulted for this review also noted that hepatitis is the most clinically important AEs of special interest for pembrolizumab. In the EV-302 trial, the incidence of hepatitis was clinically meaningfully higher in EV+P arm than in the Plat +Gem arm.

In summary, according to the clinical experts consulted for this review, the harms profile of EV+P as reported in EV-302 trial was generally consistent with that previously known AEs associated with EV and pembrolizumab in the treatment of patients with locally advanced or metastatic urothelial cancer; with no new safety signals or adverse drug reactions identified. Overall, most AEs were predictable, acceptable and clinically manageable in most patients.

Critical Appraisal

Study EV-302 was a phase III, open-label RCT. Appropriate methods for randomization were reported. The outcomes assessed are clinically relevant and statistical analyses were done using standard methods. The risk of selection bias, confounding bias and detection bias are considered very low for the key objective outcomes (i.e., OS, PFS and ORR). However, several potential limitations are discussed below:

Due to the open-label study design of EV-302 trial, subjective patient reported outcomes, such as HRQoL (e.g., EORTC QLQ-C30), and some of the harms outcomes (e.g., skin reaction) may have been biased or influenced by the patient or investigators knowledge of treatment assignment. In addition, use of concomitant medications, concomitant cancer-related procedures were slightly

imbalanced between the two arms, which could impact the comparative efficacy assessment of the health-related quality of life measures (e.g., EORTC-QOQ-C30), although the direction and the magnitude of the bias were unknown. Furthermore, a significant number of patients were not included in the analysis of EORTC-QOQ-C30. No statistical analysis was done to identify statistical differences in HRQoL between treatments.

The clinical expert consulted for this review noted that the inclusion and exclusion criteria for Study EV-302 were generally similar to the criteria for selecting eligible patients with locally advanced or metastatic UC for EV+P treatment in Canadian clinical settings, except that patients with CNS metastases would be eligible for treatment if their disease was under control. In addition, the clinical experts indicated that, in clinical practice, the measurable disease according to RECIST v1.1 is usually not a necessary criterion for selecting patients for the treatment, since the treatment response can be assessed based on clinical response, such as symptom reduction. The clinical experts emphasized that treatment with EV+P should be based on the judgement of the treatment oncologist not restricted to patients with ECOG PS ≤2. According to the clinical experts consulted for this review, based on the demographic and disease characteristics of participants in EV-302 trial, there is no major generalizability concern about how its findings may translate in the Canadian clinical practice context.

Indirect Comparisons

No indirect evidence was included in the sponsor's submission to CADTH or identified in the literature search that matched the inclusion and exclusion criteria of this review.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Histologically confirmed la/mUC who had not received prior systemic therapy, including those who had received neoadjuvant chemotherapy (or adjuvant chemotherapy after cystectomy) with recurrence >12 months from treatment completion.
Treatments	Enfortumab vedotin in combination with pembrolizumab (EV+P)
Dose regimen	Enfortumab vedotin: 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. Pembrolizumab: 2 mg/kg (up to a maximum of 200 mg) on Day 1 of a 21-day cycle.
Submitted price	Enfortumab vedotin: $1,181 per 20-mg vial Enfortumab vedotin: $1,772 per 30-mg vial
Submitted treatment cost	Enfortumab vedotin: $15,747 per 28-days Enfortumab vedotin in combination with pembrolizumab: $24,547 per 28-days
Comparator	Platinum-based chemotherapy (gemcitabine plus carboplatin or gemcitabine plus cisplatin)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	15 years
Key data source	EV-302 trial, a phase III randomized, open-label trial

Component	Description
Submitted results	ICER = $103,466 per QALY gained (incremental costs: $165,909; incremental QALYs: 1.60; incremental life years: 2.16)
Key limitations	• The long-term comparative efficacy of EV+P versus platinum-based chemotherapy for OS and PFS is uncertain due to the reliance on extrapolated data from the EV-302 trial (~37 months maximum follow-up). Based on best modelling practices and feedback from clinical experts consulted for this review, the assumptions that inform these extrapolations were considered overly optimistic as they resulted in 7% of patients surviving beyond 20 years. This meant that OS and PFS benefit for EV+P were likely overestimated. • The sponsor used median PFS to estimate time on treatment (ToT) for both EV and pembrolizumab individually. Rates of treatment discontinuation for all therapies were available from the trial which is the most appropriate data to inform ToT. The approach taken by the sponsor underestimates drug costs for EV+P. Long- term progression rates were also not considered when estimating long term treatment discontinuation. Given progression is a primary reason for treatment discontinuation progression and ToT are likely correlated. • The sponsor assumes there is no drug wastage for EV. Given the limited vial sizes (20 mg, 30), the maximum dose of 125 mg, and small size of the patient population who will receive EV, drug wastage is likely.
CADTH reanalysis results	• To address the identified limitations, CADTH used alternate models to extrapolate long-term OS and PFS, derived treatment duration for EV+P using data on time to discontinuation from the trial and assumed drug wastage for EV. • In the CADTH base case, EV+P is associated with an ICER of $290,563 per QALY gained compared with platinum-based chemotherapy.

Budget Impact

In the CADTH base case, the cost of EV+P was adjusted to be consistent with the 1-, 2-, and 3- drug acquisition costs in the CADTH base case reanalysis of the pharmacoeconomic evaluation; the prevalence and starting population assumptions were adjusted; the number of eligible patients with de novo la/m uC was estimated using incidence; the proportion of patients diagnosed with each stage of UC was adjusted; and the proportion of patients receiving a 1L therapy was adjusted. In this analysis, the budget impact of reimbursing EV+P for the treatment of adult patients with previously untreated la/m UC is expected to be $329,107,647 (year 1: $67,775,713, year 2: $115,386,675, year 3: $145,945,258).

pCODR Expert Review Committee (pERC) Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, Danica Wasney.

Meeting Date: October 9, 2024

Regrets

Two expert committee members did not attend.

Conflicts of Interest

None