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## Reimbursement Recommendation

# 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.

**Final recommendation:** Reimburse with conditions

# Summary

## What Is the CDA-AMC Reimbursement Recommendation for Padcev?

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that public drug programs reimburse Padcev, in combination with pembrolizumab, for treating patients with locally advanced urothelial cancer (UC) or metastatic urothelial cancer (mUC).

### Which Patients Are Eligible for Coverage?

Padcev, in combination with pembrolizumab, should only be covered to treat adult patients with unresectable locally advanced UC or mUC with no prior systemic therapy for mUC and who are in relatively good health. Eligible patients include those who have received chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant) and experienced disease recurrence more than 12 months after the completion of treatment or received adjuvant immunotherapy with nivolumab and experienced disease recurrence more than 6 months after the completion of treatment.

### What Are the Conditions for Reimbursement?

Padcev, in combination with pembrolizumab, should only be reimbursed if prescribed by a clinician who has experience treating patients with locally advanced UC or mUC and if the price of Padcev is reduced.

### Why Did CDA-AMC Make This Recommendation?

- Evidence from a phase III clinical trial demonstrated that Padcev in combination with pembrolizumab resulted in improved survival compared to standard chemotherapy (platinum plus gemcitabine chemotherapies) and was associated with good response to treatment, which are outcomes identified as important by patients.
- Based on the assessment of the health economic evidence by Canada's Drug Agency (CDA-AMC), Padcev, in combination with pembrolizumab, does not represent good value to the health care system at the public list price. A price reduction is therefore required. Based on the public list price, Padcev, in combination with pembrolizumab, is estimated to cost the public drug plans approximately $329 million over the next 3 years.

## Additional Information

### What Is Locally Advanced UC or mUC?

Locally advanced UC or mUC is a type of bladder cancer. Bladder cancer is the fifth most common cancer in Canada, with an estimated 13,400 new cases diagnosed in 2023. UC is the most common form of bladder cancer

# Summary

and accounts for more than 90% of all cases. Although most UC cases are superficial, an estimated 25% are muscle invasive, and 11% are locally advanced or metastatic at diagnosis.

### Unmet Needs in Locally Advanced UC or mUC

An estimated 30% to 50% of patients with locally advanced UC or mUC are not a candidate for, or do not respond to, the standard of care for the first-line treatment with platinum-based chemotherapy. It has been reported that overall survival (OS) in patients treated with first-line platinum-based chemotherapy ranges between 9 and 15 months. There is a significant unmet need for new therapies with a manageable safety profile that increases survival and improves quality of life (QoL).

### How Much Does Padcev in Combination With Pembrolizumab Cost?

Treatment with Padcev is expected to cost approximately $15,747 per patient per 28-day cycle. When used in combination with pembrolizumab, the 28-day cost per patient for Padcev plus pembrolizumab is $24,547 when using a weight-based dose for pembrolizumab.

## Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that enfortumab vedotin in combination with pembrolizumab be reimbursed for the treatment of adult patients with locally advanced urothelial cancer (UC) 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 1 open-label, phase III randomized controlled trial (RCT) involving a total of 886 patients with locally advanced UC or mUC (Study EV-302) showed that treatment with enfortumab vedotin in combination with pembrolizumab demonstrated a clinically meaningful benefit compared to platinum plus gemcitabine chemotherapy in improving OS (hazard ratio [HR] = 0.468; 95% confidence interval [CI], 0.376 to 0.582; P < 0.00001), progression-free survival (PFS) (HR = 0.450; 95% CI, 0.377 to 0.538; P < 0.00001), and objective response rate (ORR) (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 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) global health status 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 plus 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 OS and PFS.

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 UC or mUC. 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 | The Study EV-302 included patients with adjuvant or neoadjuvant chemotherapy with recurrence | The clinical expert stated that as per standard clinical practice with other regimens after immunotherapy, patients |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| unresectable locally advanced urothelial cancer or metastatic urothelial cancer with no prior systemic therapy.<br>2. For additional clarity, the following patients who have received the following are also eligible:<br>2.1. neoadjuvant chemotherapy, but experienced recurrence more than 12 months after neoadjuvant chemotherapy was completed<br>2.2. adjuvant chemotherapy following cystectomy, but experienced recurrence more than 12 months after adjuvant chemotherapy was completed<br>2.3. adjuvant nivolumab, but experienced recurrence more than 6 months after nivolumab treatment was completed. | 12 months after completion of treatment. | with adjuvant and/or neoadjuvant 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.<br>pERC agreed with the clinical expert. |
| 3. Patients should have a good performance status. | Study EV-302 included patients with ECOG performance status of 0, 1, or 2. | pERC agreed with the clinical experts who indicated that ECOG should not be too prescriptive. pERC determined that adequate performance status should be based on clinical judgment. |
| 4. Treatment with enfortumab vedotin in combination with pembrolizumab should not be initiated in patients with:<br>4.1. active CNS metastases<br>4.2. uncontrolled diabetes<br>4.3. prior enfortumab vedotin or other MMAE-based ADCs. | Study EV-302 excluded patients with these characteristics and this 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 before treatment on baseline scans. However, patients with leptomeningeal disease should not be treated with enfortumab vedotin. |
| **Renewal** | | |
| 5. Patients should be assessed by the treating clinician before 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 needs to be 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:<br>6.1. documented disease progression<br>6.2. unacceptable toxicity<br>6.3. note that pembrolizumab may be used up to 24 months in patients without disease progression, | In Study EV-302, enfortumab vedotin in combination with pembrolizumab was discontinued if patients experienced disease progression or unacceptable toxicity, and this 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 AEs attributable only to enfortumab vedotin may continue pembrolizumab monotherapy for a maximum of 24 months, and patients who experienced an unacceptable AE attributable only to pembrolizumab may |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| according to the pembrolizumab product monograph. | | continue enfortumab vedotin monotherapy.<br>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.<br>7.1. Given the known complications associated with enfortumab vedotin in combination with pembrolizumab, initial treatment must be administered in centres where there is experience using a drug at risk for extravasation. | Ensuring 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 should not be used in combination with other anti-cancer drugs in routine clinical practice for locally advanced urothelial cancer or metastatic urothelial cancer. | Study EV-302 did not include patients receiving other anti-cancer drugs for locally advanced urothelial cancer or metastatic urothelial cancer, and this 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.<br>The cost-effectiveness of enfortumab vedotin in combination with pembrolizumab is dependent on the price paid for both enfortumab vedotin and pembrolizumab.<br>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. | — |

| Reimbursement condition | Reason | Implementation guidance |
|---|---|---|
| **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. | — |

ADC = antibody drug conjugate; AE = adverse event; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; MMAE = monomethyl auristatin E; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; QALY = quality-adjusted life-years.

## Discussion Points

- pERC deliberated whether patients currently receiving alternate first-line therapy for locally advanced UC or mUC 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 have 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 Study EV-302, enfortumab vedotin in combination with pembrolizumab should not be offered to patients who have completed or progressed on first-line chemotherapy. The committee agreed with the clinical expert that patients who are receiving avelumab for maintenance therapy are, by definition, either in remission or have stable disease, and those who progress on avelumab will be eligible for enfortumab vedotin as third-line single drug therapy, which is 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 (AEs) observed in Study 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 one-third of 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 the emergence of avelumab data during this trial. The committee considered that 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 programmed death receptor-1 (PD-1) or programmed death-ligand 1 (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), harbouring susceptible *FGFR3* (fibroblast growth factor receptor) genetic alterations, with disease progression during or following at least 1 line of a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor therapy including within 12 months of neoadjuvant or adjuvant therapy. 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, and accounts for approximately 90% of all bladder cancer cases. Bladder cancer is the fifth most common cancer in Canada, and in 2023, it was estimated there were 13,400 new cases of bladder cancer. The goal of treatment for locally advanced UC or mUC is to delay disease progression, prolong life while minimizing symptoms, improve HRQoL, increase the ability to maintain employment and maintain independence, and reduce the burden on caregivers. Platinum plus gemcitabine followed by avelumab treatment is considered the first-line treatment for patients in Canada who responded to platinum plus gemcitabine 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 QoL.

Enfortumab vedotin is an antibody drug conjugate directed against nectin-4, an adhesion protein located on the surface of most UC cells. Enfortumab vedotin is an anti-neoplastic drug. When given in combination with pembrolizumab, the recommended dose of enfortumab vedotin is 1.25 mg/kg (to a maximum of 125 mg for patients ≥ 100 kg) administered as an IV 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 UC or 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 UC or mUC
- patients' perspectives gathered by patient groups, Bladder Cancer Canada (BCC)

- input from public drug plans and cancer agencies that participate in the CDA-AMC review process
- 2 clinical specialists with expertise diagnosing and treating patients with locally advanced UC or mUC
- input from 2 clinician groups, including BCC and Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee (OH[CCO]-GU DAC)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

# Stakeholder Perspectives

## Patient Input

CDA-AMC received 1 submission from BCC. BCC is a registered national charity in Canada serving patients facing a bladder cancer diagnosis. Their objectives are to help patients with bladder cancer 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 the US, and 1 unknown. All survey respondents had experience with locally advanced UC or mUC, and 7 respondents (5 patients and 2 caregivers) 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 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 respondent's answers, current therapies were 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. Three respondents reported screening problems that delayed access to treatment and may have affected health outcomes. One respondent reported difficulties in accessing treatment due to the distance from the nearest large urban centre. BCC noted that respondents strongly prioritized health outcomes and were 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 they had received, 7 respondents gave the highest average score for maintaining QoL, 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 did not control the growth of bone metastases. BCC reported that hair loss and nausea were the most 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 because of AEs, 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 the ability to sleep, followed by the ability to work, the ability to spend time with family and friends, the ability to perform household chores, and the 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 CDA-AMC

The clinical experts indicated that the goal of the treatment for patients with incurable locally advanced UC or mUC is to reduce cancer burden and improve quantity and QoL. Only about one-half of patients respond to the standard of care of platinum-based combination chemotherapy (platinum plus gemcitabine). With chemotherapy alone, the average survival of these patient is 14 to 18 months, and this improves to about 16 to 20 months with the addition of avelumab maintenance therapy. These treatments also have adverse effects that can diminish QoL, and almost no patients are cured. One clinical expert indicated that although we have had slow some advances in mUC, most patients die swiftly from their disease. Treatments that significantly prolong OS (especially in an unselected population) are needed. 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 UC or mUC 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), platinum plus gemcitabine followed by avelumab for maintenance treatment is considered the first-line treatment in this setting. The clinical experts indicated that, technically, the most relevant comparator is chemotherapy followed by maintenance immunotherapy in patients who are not progressing. Patients who progress despite chemotherapy are offered immunotherapy with pembrolizumab. Supportive treatments may also include analgesics for pain, palliative radiotherapy, bisphosphonates, and referral for palliative care. Patients with progressive cancer despite immunotherapy may be offered enfortumab vedotin monotherapy or, if their tumour has a *FGFR* alteration, erdafitinib 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 sulphate, doxorubicin hydrochloride (Adriamycin), and cisplatin chemotherapy, which includes

granulocyte colony-stimulating factor support. The clinical experts also noted that there is data from a randomized trial that added concurrent and maintenance nivolumab to gemcitabine-cisplatin and showed OS benefit (Checkmate 901 trial). Although not approved for this indication, nivolumab is available in Canada and commonly used for many other cancers. It could also be considered a comparator for patients who are eligible for cisplatin. One clinical expert indicated that economic comparators must include avelumab for the maintenance therapy portion of first-line treatment. At a gross estimate, 65% to 75% of patients would not progress on platinum-based chemotherapy and would be offered or eligible for avelumab maintenance therapy until progression. One expert indicated that in real clinical practice, not all patients who are eligible for avelumab receive it. Roughly about 30% of patients with platinum plus gemcitabine treatment received avelumab in real world.

The clinical experts emphasized that enfortumab vedotin plus pembrolizumab has the highest reported tumour response rate in incurable UC. In addition, the median OS was almost doubled in the enfortumab vedotin plus pembrolizumab arm when compared to platinum plus gemcitabine chemotherapy. It can be given to patients who are not eligible for cisplatin and who constitute up to one-half of patients with advanced UC. The clinical experts indicated that based on the results of the EV-302 trial, it is expected that enfortumab vedotin plus pembrolizumab will become the de facto standard of care for incurable UC.

The clinical expert indicated that all patients with incurable UC 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. Enfortumab vedotin 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, access should not be restricted to patients who would have met inclusion criteria for the clinical trial (i.e., regarding performance status and preexisting autoimmune conditions). Rather, enfortumab vedotin in combination with pembrolizumab should be the standard first-line consideration if the care providers consider them appropriate candidates.

The clinical experts indicated that OS, EORTC QLQ-C30, ORR, safety, PFS, and duration of response are commonly used for assessing the treatment response (benefit) for locally advanced UC or mUC. Additionally, 1 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 UC. This treatment is quite suitable for outpatient administration. One clinical expert indicated that medical oncologists should initially be assessing and prescribing. Ongoing care can likely be safely continued and prescribed by general practice oncologists for patients receiving care outside of major cancer centres.

## Clinician Group Input

CDA-AMC received input from 2 clinician groups BCC and 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 OS, PFS, and improved ORR including complete response with potential for long-term remission.

According to BCC, the unmet needs were durable disease control, toxicity of the treatment, QoL, and complete response. OH(CCO)-GU DAC noted OS 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 considered eligible by a physician for immunotherapy-based regimens are best suited for treatment with the drug under review, and any patient with UC should be eligible irrespective of the histology. OH(CCO)-GU DAC added that patients with a contraindication to immunotherapy are the least suitable. According to BCC, it is not currently possible to identify which patients will 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 before 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 AEs and recurrence of the disease as other factors.

OH(CCO)-GU DAC noted that outpatient cancer centres 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, re-treatment 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 CDA-AMC 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** | |
| **Issues with the choice of comparator in the submitted trial(s)**<br>In the EV-302 trial, enfortumab vedotin plus pembrolizumab was compared to platinum-based chemotherapy (cisplatin or carboplatin plus gemcitabine) in previously untreated locally advanced UC or mUC.<br>Platinum-based chemotherapy with gemcitabine is funded for previously untreated locally advanced UC or 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.<br>Avelumab maintenance is also funded if there has been no disease progression following completion of first-line platinum-based chemotherapy.<br>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.<br>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 locally advanced UC or mUC patients whose cancer is stable or had responded to platinum plus gemcitabine chemotherapy is the current standard of care in Canada. In EV-302 trial, it was reported that 135 of 444 of patients (30.4%) in the control arm used avelumab at their investigator's discretion. Both clinical experts indicated that, in the setting in Canada, while about 50% to 60% patients who receive platinum plus gemcitabine could be potentially eligible for avelumab, real-word data indicates that only about 30% of patients treated with first-line platinum-based chemotherapy receive avelumab maintenance. Therefore, the reported 30% of patients who received avelumab in Study EV-302 is likely close to clinical practice in Canada.<br>pERC agreed with the clinical experts' responses. |
| **Considerations for initiation of therapy** | |
| **Disease diagnosis, scoring, or staging for eligibility**<br>In Study EV-302, patients were required to have histologically documented, unresectable locally advanced UC 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 enfortumab vedotin plus pembrolizumab if recommended for reimbursement. | Confirmed.<br>pERC agreed with the clinical expert's response. |
| **Other patient characteristics for eligibility (e.g., age restrictions, comorbidities)**<br>Patients with an ECOG PS of 0, 1, or 2 were eligible for Study EV-302, but patients with ECOG PS of 2 were required to have a hemoglobin ≥ 100 g/L, GFR ≥ 50 mL/min and could not have NYHA class III heart failure. | One clinical expert indicated yes for patients with ECOG of 2 by trial criteria, and no for full dose enfortumab vedotin for patients with ECOG of 3.<br>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. |

| Drug program implementation questions | Clinical expert response |
|---|---|
| Should the same criteria apply for patients with ECOG PS of 2 to be eligible for enfortumab vedotin plus pembrolizumab?<br>Should patients with PS ≥ 2 be eligible if the physician feels they can tolerate treatment? | pERC agreed with the clinical expert's responses and indicated that adequate performance status should be based on physician's clinical judgment. |
| **Prior therapies required for eligibility**<br>Patients were not eligible to participate in Study EV-302 if they had received prior PD-1 or PD-L1 inhibitor therapy, including for earlier stages of UC.<br>Should patients who previously received adjuvant nivolumab and experience relapse ≥ 6 months from completion be eligible for enfortumab vedotin plus pembrolizumab? | Yes.<br>pERC agreed with the clinical expert's response and indicated that it is reasonable to be aligned with other reviews. |
| **Eligibility for re-treatment**<br>Pembrolizumab was administered for a maximum of 35 cycles (every 3 weeks) in Study EV-302.<br>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)?<br>If re-treatment is permitted, would this be as pembrolizumab monotherapy or in combination with enfortumab vedotin? | Yes.<br>Re-treatment with EV should depend on why it was discontinued.<br>pERC noted that in a study (KEYNOTE 052) supporting the reimbursement recommendation for pembrolizumab monotherapy in patients with locally advanced UC or mUC, patients who stopped study treatment after 24 months, for reasons other than progressive disease or intolerability, or participants who attained a complete response and stopped study treatment, were eligible for up to 1 year of re-treatment upon experiencing progressive disease. pERC decided that re-treatment decisions should be based on the professional judgment of the attending clinicians and patient factors since there is limited data to guide a standardized re-treatment protocol. |
| **Dosing, schedule or frequency, and dose intensity**<br>PAG would like to inform pERC that they plan to implement weight-based dosing up to a cap for pembrolizumab (2 mg/kg to a maximum of 200 mg every 3 weeks or 4 mg/kg to a maximum of 400 mg every 6 weeks), similar to other cancer sites. | No objection.<br>pERC agreed with the clinical experts' response. |
| **Generalizability** | |
| **Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review**<br>Should patients currently receiving alternate first-line therapy for locally advanced UC or mUC be switched to enfortumab vedotin plus pembrolizumab on a time-limited basis at the time of implementation? | According to the clinical experts, patients who have not started or completed platinum-based first-line chemotherapy may be eligible candidates to receive enfortumab vedotin plus pembrolizumab. One expert stated that patients who are initiating avelumab maintenance are, by definition, either in remission or have stable disease. Starting a new treatment for them is not necessary; however, if they progress on avelumab they will be eligible for enfortumab vedotin as third-line single drug therapy, which is already approved and funded.<br>pERC agreed with the clinical experts' 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 |

| Drug program implementation questions | Clinical expert response |
|---|---|
| Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products | Yes |
| **System and economic issues** | |
| **Concerns regarding the anticipated budget impact and sustainability**<br>PAG notes the sponsor projected a 3-year BIA (incremental costs) is more than $321 million and is concerned about budget impact and sustainability. | This is a comment from the drug programs to inform pERC deliberations.<br>Noted. |
| **Presence of confidential negotiated prices for comparators**<br>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.<br>Noted. |

BIA = budget impact analysis; ECOG PS = Eastern Cooperative Oncology Group Performance Status; GFR = glomerular filtration rate; mUC = metastatic urothelial cancer; N/ A = not applicable; NYHA = New York Heart Association; PAG = provincial advisory group; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 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

Study EV-302 is a global, phase III, open-label, 2-arm RCT comparing enfortumab vedotin plus pembrolizumab versus platinum plus gemcitabine (i.e., cisplatin plus gemcitabine or carboplatin plus gemcitabine) chemotherapy, which represents the current standard of care for patients in Canada as first-line treatment for locally advanced UC or 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 end points of PFS by the blinded independent central review (BICR) and OS between the enfortumab vedotin plus pembrolizumab arm and the platinum plus gemcitabine arm.

Patients with locally advanced UC or mUC were randomized 1:1 using interactive response technology to receive enfortumab vedotin plus pembrolizumab 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 enfortumab vedotin plus pembrolizumab (n = 442) or platinum plus gemcitabine (n = 444). There were 47 patients enrolled at 11 sites in Canada.

### Efficacy Results

After a median follow-up of 17.2 months PFS by BICR showed a statistically significant and clinically meaningful improvement in the enfortumab vedotin plus pembrolizumab arm compared with the platinum plus gemcitabine arm. The relative hazard of developing a disease progression event in the enfortumab vedotin plus pembrolizumab arm showed a clinically meaningful reduction by 55% as compared to the

platinum plus gemcitabine arm (HR = 0.450; 95% CI, 0.377 to 0.538; 2-sided P <0.00001). Patients in the enfortumab vedotin plus pembrolizumab arm also demonstrated a longer clinically meaningful median PFS than in the platinum plus gemcitabine arm (treatment group difference of 6 months). According to the clinical experts consulted for this review, compared with the platinum plus gemcitabine used as the first-line treatment, enfortumab vedotin plus pembrolizumab used as the first-line treatment showed a higher clinically meaningful 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 enfortumab vedotin plus pembrolizumab versus platinum plus gemcitabine. The relative hazard of death in the enfortumab vedotin plus pembrolizumab arm showed a clinically meaningful reduction of 54.2% as compared to the platinum plus gemcitabine arm (HR = 0.468; 95% CI, 0.376 to 0.582; 2-sided P <0.00001). The median OS in the enfortumab vedotin plus pembrolizumab arm was 15.4 months longer than that in the platinum plus gemcitabine arm, which is considered clinically meaningful by the clinical experts consulted for this review. Furthermore, according to the clinical experts, compared with the platinum plus gemcitabine first-line treatment, enfortumab vedotin plus pembrolizumab used as the first-line treatment showed a higher clinically meaningful 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 the enfortumab vedotin plus pembrolizumab arms achieved the ORR than that observed in the platinum plus gemcitabine arm, which is considered a clinically meaningful improvement according to clinical experts consulted for this review. Subgroup analyses showed consistent ORR benefits favouring enfortumab vedotin plus pembrolizumab across all prespecified 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 the observed HRQoL in terms of EORTC QLQ-C30 was not clinically meaningfully different between-group (enfortumab vedotin plus pembrolizumab versus platinum plus gemcitabine) or intragroup. The clinical experts consulted for this review highlighted that a significant improvement is not expected in QoL with the anti-cancer 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 a clinically meaningful intragroup and intergroup difference from week 8 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 enfortumab vedotin plus pembrolizumab combination is a relatively new treatment regimen for this population and a limited number of oncologists in Canada have experience using enfortumab vedotin plus pembrolizumab to treat locally advanced UC or mUC. Also, the duration of the treatment of the enfortumab vedotin plus pembrolizumab in Study EV-302 was relatively short and future PFS data are needed to better understand the efficacy of subsequent treatments (e.g., subsequent platinum plus gemcitabine chemotherapy, immunotherapy, and so on).

## Harms Results

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

In summary, according to the clinical experts consulted for this review, the harms profile of enfortumab vedotin plus pembrolizumab as reported in the EV-302 trial was generally consistent with previously known AEs associated with enfortumab vedotin and pembrolizumab in the treatment of patients with locally advanced UC or mUC; 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.

Due to the open-label study design of the 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 investigator’s knowledge of treatment assignment. In addition, use of concomitant medications and concomitant cancer-related procedures were slightly imbalanced between the 2 arms, which could impact the comparative efficacy assessment of the HRQoL measures (e.g., EORTC-

QLQ-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-QLQ-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 UC or mUC for enfortumab vedotin plus pembrolizumab treatment in clinical settings in Canada, except that patients with central nervous system metastases would be eligible for treatment if their disease was controlled. In addition, the clinical experts indicated that, in clinical practice, the measurable disease according to the Response Evaluation Criteria in Solid Tumours Version 1.1 (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 enfortumab vedotin plus pembrolizumab should be based on the judgment of the oncologist treating the patient, not restricted to patients with ECOG Performance Status of 2 or less. According to the clinical experts consulted for this review, based on the demographic and disease characteristics of participants in the EV-302 trial, there is no major generalizability concern about how findings may translate in the clinical practice context in Canada.

### Indirect Comparisons

No indirect evidence was included in the sponsor's submission to CDA-AMC 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 CDA-AMC.

## Economic Evidence

### Cost and Cost-Effectiveness

#### Table 3: Summary of Economic Evaluation

| Component | Description |
|---|---|
| **Type of economic evaluation** | Cost-utility analysis<br>PSM |
| **Target population** | Patients with histologically confirmed locally advanced UC or 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 |

| Component | Description |
|---|---|
| **Dose regimen** | Enfortumab vedotin: 1.25 mg/kg (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<br>Pembrolizumab: 2 mg/kg (to a maximum of 200 mg) on day 1 of a 21-day cycle |
| **Submitted price** | Enfortumab vedotin: $1,181 per 20 mg vial<br>Enfortumab vedotin: $1,772 per 30 mg vial |
| **Submitted treatment cost** | Enfortumab vedotin: $15,747 per 28 days<br>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 |
| **Submitted results** | ICER = $103,466 per QALY gained (incremental costs = $165,909; incremental QALYs = 1.60; incremental LYs = 2.16) |
| **Key limitations** | • The long-term comparative efficacy of enfortumab vedotin plus pembrolizumab vs. platinum-based chemotherapy for OS and PFS is uncertain due to the reliance on extrapolated data from the EV-302 trial (approximately 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 enfortumab vedotin plus pembrolizumab were likely overestimated.<br>• The sponsor used median PFS to estimate ToT for both enfortumab vedotin 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 enfortumab vedotin plus pembrolizumab. 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.<br>• The sponsor assumes there is no drug wastage for enfortumab vedotin. Given the limited vial sizes (20 mg to, 30 mg), the maximum dose of 125 mg, and small size of the patient population who will receive enfortumab vedotin, drug wastage is likely. |
| **CDA-AMC reanalysis results** | • To address the identified limitations, CDA-AMC used alternate models to extrapolate long-term OS and PFS, derived treatment duration for enfortumab vedotin plus pembrolizumab using data on time to discontinuation from the trial and assumed drug wastage for enfortumab vedotin.<br>• In the CDA-AMC base case, enfortumab vedotin plus pembrolizumab is associated with an ICER of $290,563 per QALY gained compared with platinum-based chemotherapy. |

CDA-AMC = Canada's Drug Agency; ICER = incremental cost-effectiveness ratio; LY = life year; mUC = metastatic urothelial cancer; OS = overall survival; PFS = progression-free survival; PSM = partition survival model ; QALY = quality-adjusted life-year; ToT = time on treatment; vs. = versus.

## Budget Impact

In the CDA-AMC base case, the cost of enfortumab vedotin plus pembrolizumab was adjusted to be consistent with the 1-, 2-, and 3-drug acquisition costs in the CDA-AMC base case reanalysis of the pharmacoeconomic evaluation; the prevalence and starting population assumptions were adjusted; the number of eligible patients with de novo locally advanced UC or mUC was estimated using incidence; the proportion of patients diagnosed with each stage of urothelial carcinoma was adjusted; and the proportion

of patients receiving a first-line therapy was adjusted. In this analysis, the budget impact of reimbursing enfortumab vedotin plus pembrolizumab for the treatment of adult patients with previously untreated locally advanced UC or mUC is expected to be $329,107,647 (year 1 = $67,775,713, year 2 = $115,386,675, year 3 = $145,945,258).

# 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


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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.