CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

enfortumab vedotin (Padcev)

(Seagen Canada Inc.)

Indication: In combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer (la/mUC).

June 3, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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Patient Group Input

Name of Drug: enfortumab vedotin (Padcev)

Indication: In combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer (la/mUC).

Name of Patient Group: Bladder Cancer Canada

Author of Submission: Adam Waiser

1. About Your Patient Group

Bladder Cancer Canada (BCC) was formed in 2009 by two bladder cancer survivors who found that there was no one to talk to about their treatments, experiences and fears. Today, BCC is a registered national charity and the only organization in Canada serving those facing a bladder cancer diagnosis. Our objectives are to help bladder cancer patients and their support teams address the day-to-day issues of this disease; to increase awareness of bladder cancer among the general public and medical community; and to fund research which pursues the diagnosis, treatment and elimination of bladder cancer. www.bladdercancercanada.org

2. Information Gathering

Bladder Cancer Canada (BCC) collected the data for this submission from an online survey as well as one-to-one interviews.

The online survey was conducted between April 17 and May 29, 2024. The survey asked questions about the impact of locally advanced and metastatic urothelial carcinoma (la/mUC) on the lives of patients, the effect of current treatments and the patient experience with enfortumab vedotin (Padcev). Potential respondents were identified through messages to the BCC mailing list. Messages were posted on Facebook, LinkedIn and Twitter as well as the Cancer Connection and Cancer Survivors Network online discussion boards. Many of these posts were shared by the Bladder Cancer Advocacy Network and the World Bladder Cancer Patient Coalition. Investigators from the EV301 and EV302 clinical trials were also asked to relay the survey to patients. Nonetheless, BCC found it very difficult to identify patients with appropriate la/mUC and Padcev treatment experience.

A total of 9 people completed the survey – 7 patients and 2 caregivers responding on behalf of a patient. 7 of these respondents were from Canada (representing Alberta, British Columbia and Ontario), 1 was from the United States and 1 didn't answer. All of the respondents had experience with la/mUC. 7 had treatment experience with Padcev in combination with pembrolizumab (Keytruda).

4 people agreed to participate in telephone interviews to elaborate on their survey responses. All had treatment experience with Padcev in combination with Keytruda.

3. Disease Experience

1 respondent was diagnosed in 2023, 3 were diagnosed in both 2022 and 2021, 1 was diagnosed in 2019 and 1 was diagnosed in 2015.

The most commonly reported cancer symptoms were: blood in urine (88%, n=8), 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.

4. Experiences With Currently Available Treatments

Respondents had treatment experience with gemcitabine, cisplatin, carboplatin, paclitaxel, radiation, TURBT procedures, radical cystectomy and neobladder reconstruction. 6 had received platinum-based chemotherapy, while the other 3 had received Padcev as their first IV treatment.

Respondents were asked to rate their agreement with the statement "My current therapies are able to manage my cancer symptoms" on a scale of 1 (strongly disagree) to 10 (strongly agree). The average score was exactly 7 and only one respondent gave a score lower than 5, suggesting that current therapies are broadly adequate for managing patient symptoms.

The most commonly reported side effects of these treatments were fatigue (67%, n=9) as well as loss of appetite, neuropathy and hair loss (44% each). Fatigue and neuropathy were most frequently cited as 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.

5. Improved Outcomes

When respondents were asked whether they would be willing to tolerate new side effects from drugs that can control disease progression or improve overall survival on a scale of 1 (will not tolerate side effects) to 10 (will tolerate significant side effects), the average score was 8.6 (n=9), suggesting that patient values strongly prioritize health outcomes and are willing to accept more aggressive side effects to reach them. This conclusion is supported by some of the comments made during the interviews:

- I would redo all my treatments in a heartbeat, no second thoughts.
- If there was something that could make this cancer go away, extend my life a lot longer, I'm more than willing to deal with pain that comes along with the treatment. I need to keep fighting for my wife and kids.
- It's like having a baby. At first you think - oh my god I'll never do this again, but six months later you're willing to do it again I would do it again in a heartbeat.

6. Experience With Drug Under Review

7 respondents had treatment experience with Padcev in combination with Keytruda – 5 as patients and 2 as a caregiver. 3 patients and 1 caregiver participated in telephone interviews to elaborate on their feedback.

Patient A was diagnosed in 2021. She was treated with Padcev in combination with Keytruda for 6-12 months, but terminated the treatment because it did not control the cancer. She subsequently received 3 cycles of gemcitabine and cisplatin, but her oncologist would not allow to complete the full 6 cycles due to the side effects. She is currently awaiting participation in a phase 1 trial. She did not participate in a telephone interview.

Patient B was diagnosed in 2015. He is currently receiving Padcev in combination with Keytruda, but had been on this treatment for less than 3 months. He has an extensive treatment history including (chronologically) 1) targeted radiation and chemo (cisplatin, carboplatin, gemcitabine), 2) BCG treatment combined with a TURBT, 3) bladder removal and neobladder reconstruction, 4) carboplatin, 5) radiation and 6) Padcev in combination with Keytruda. He is waiting to see the results of his treatment with Padcev.

Patient C was diagnosed in 2023. He has been treated with Padcev in combination with Keytruda for 3-6 months. He underwent a TURBT procedure last year, followed by Padcev in combination with Keytruda as his first line of IV treatment. He is currently receiving Padcev.

Patient D was diagnosed in 2019. She had no evidence of cancer cells following surgery until a recurrence in 2021. She received 8 rounds of Padcev in combination with Keytruda. The Keytruda caused an adrenal crisis that required the removal of her pituitary gland. She had one further round of treatment with Padcev and currently has no evidence of recurrent or metastatic disease.

Patient E was diagnosed in 2022. They were treated with Padcev in combination with Keytruda for 3-6 months prior to and following a radical cystectomy. They were only given 1 cycle of pembrolizumab due to its impact on liver function and they did not receive all of the post-surgery cycles because the disease metastasized. They subsequently received radiation therapy and are now screening for a study.

Caregiver A cared for her husband who was diagnosed in 2022. He received Padcev in combination with Keytruda for 3-6 months, but discontinued treatment because it did not control the bone metastases. Subsequent treatments include a TURBT procedure, gemcitabine in combination with cisplatin, paclitaxel and repeated rounds of radiation. The patient for whom she was caring has since passed away.

Caregiver B cared for a patient who was diagnosed in 2022. They received Padcev in combination with Keytruda as their first line of treatment. This treatment was discontinued because it did not control bone metastases. They subsequently received cisplatin & gemcitabine followed by paclitaxel.

Treatment

Patients were asked to rate how their life had changed on Padcev compared to other therapies that they had received on a scale of 1 (much worse) to 5 (much better). Every criterion was rated as an improvement except for preventing recurrence. The greatest impact was on maintaining quality of life and drug side effects.

Change on Padcev	Average Score (n=7)
Maintaining quality of life	4.3
Drug side effects	4.1
Cancer symptoms	3.7

Controlling disease progression	3.3
Preventing recurrence	2.9

Comments include:

- Much easier - more tolerable than doing the cisplatin and carboplatin. (Patient B)
- He wasn't as tired on Padcev compared to chemo – more energy (Caregiver A)

Two different respondents noted that while this treatment was effective of soft-tissue tumours, it failed to control the growth of bone metastases.

Side Effects

Hair loss and nausea were the most commonly reported side effects (43% each, n=7).

When respondents asked to rate the tolerability of the side effects associated with Padcev on a scale from 1 (completely tolerable) to 10 (completely intolerable), the average score was 6.0 However, this result represented a stark dichotomy between Patients B, C & E as well as Caregiver B who gave a score of 1 and Patients A & D as well as Caregiver A who gave a score of 8 or higher.

Caregiver A indicated that the worst side effects occurred during the first week of treatment and largely cleared up afterwards. By contrast, Patient D indicated that the side effects built over time and that her skin issues became sufficiently severe that removing a band-aid would take the skin with it.

Only Patient E required any dose reductions as a result of adverse events. However, Patient C indicated that his oncologist had suggested a future reduction due to concern about peripheral neuropathy.

Patients were also asked to rate how the side effects associated with Padcev had affected different aspects of their life on a scale of 1 (much worse) to 5 (much better). 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. However, it should be noted that these results showed a similar dichotomy between patients who did not report significant side effects and those who did.

Change to quality of life on Padcev	Average Score
Ability to sleep	3.0 (n=7)

Ability to work	2.3 (n=5)
Ability to spend time with family and friends	2.0 (n=7)
Ability to perform household chores	1.9 (n=7)
Ability to care for children	1.33 (n=3)

Comments included:

- Slowed disease progression is a plus, which for the most part allowed me to live a normal life, for the most part. Negatively the Neuropathy is still here but manageable. (Patient A)
- It's allowed me to venture out more from the house. To be able to do things with the children, not just laying on the couch feeling nauseous. (Patient B)
- It's been easy to tolerate. I consider it a godsend. (Patient C)
- Due to the fatigue, I am unable to continue to work, I find I am unable to tolerate more than 3-4 hours of steady activity. But have learned how to adjust my meds and rest, then I am able to continue my reduced active day. (Patient D)
- Quality of life wasn't all that great. (Caregiver A)

Local Treatment

Patient D lives in rural Alberta and had to travel to a major city for treatment. She emphasized that a drug that can be taken at home or at a regional treatment centre would present great advantages for people in her situation:

- I would benefit greatly if this treatment was offered closer to home for sure. As a senior, it is stressful to make that trip 6 times a month while in treatment.
- It was a bit of a challenge in the bad weather, my children would sometimes take time off work to drive me. It was all worth it.

7. Companion Diagnostic Test

n/a

8. Anything Else?

When asked if they would recommend Padcev to other patients with bladder cancer, six respondents said that they would. Comments included:

- If my cancer returned, I would ask for it in a heartbeat. (Patient D)
- We could save some bladders that way. (Patient C)
- I would do it all over again, even with the same side effects all in a heartbeat, to cure my cancer and give me life. (Patient D)

Patient E was unsure about a recommendation and commented: “I had hoped it would increase the effectiveness of the radical cystectomy treatment but it did not. I was happy not to suffer too many side effects but wonder if i could have continued with a lower dose of pembro if it would have been more effective.”

It should be added that Caregiver A indicated that she does not think that Padcev should have been her husband’s first line of treatment due to its lack of effect on his bone metastases.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, prepared this submission with the assistance and oversight of Bladder Cancer Canada staff.

1. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, created the clinician surveys, oversaw survey distribution and collection, and analyzed the data for this submission with the assistance and oversight of Bladder Cancer Canada staff.

2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
None				

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Michelle Colero
Position: Executive Director
Patient Group: Bladder Cancer Canada
Date: June 3, 2024

Clinician Group Input

CADTH Project Number: PC0353-000

Generic Drug Name (Brand Name): Enfortumab vedotin (Padcev)

Indication: In combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer (la/mUC).

Name of Clinician Group: Bladder Cancer Canada

Author of Submission: Adam Waiser

1. About Your Clinician Group

Bladder Cancer Canada (BCC) was formed in 2009 by two bladder cancer survivors who found that there was no one to talk to about their treatments, experiences and fears. Today, BCC is a registered national charity and the only organization in Canada serving those facing a bladder cancer diagnosis. Our objectives are to help bladder cancer patients and their support teams address the day-to-day issues of this disease; to increase awareness of bladder cancer among the general public and medical community; and to fund research which pursues the diagnosis, treatment and elimination of bladder cancer. www.bladdercancercanada.org

2. Information Gathering

Bladder Cancer Canada collected the information for this submission from online surveys conducted between April 27 and May 29, 2024. The survey asked clinicians about their experience treating locally advanced or metastatic urothelial carcinoma (la/mUC) patients with enfortumab vedotin in combination with pembrolizumab as well as other therapies. It also asked questions about their treatment goals, current unmet needs and the potential role of enfortumab vedotin within the treatment paradigm. Potential respondents were identified from EV301 and EV302 clinical trial investigators as well as the members of the BCC medical advisory board.

A total of 5 clinicians completed the survey. All 5 respondents are from Canada (representing Alberta, Manitoba, Ontario & Quebec). All respondents had experience treating patients with la/mUC and 3 had experience treating la/mUC patients with enfortumab vedotin in combination with pembrolizumab.

3. Current Treatments and Treatment Goals

The current standard of care for eligible patients with la/mUC is platinum-based chemotherapy followed by avelumab maintenance (for patients who do not progress on chemotherapy). For patients who progress on chemotherapy, the standard subsequent treatment is pembrolizumab. 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).

Erdafinitinb and enfortumab vedotin were both prescribed after Health Canada approval, but prior to provincial funding through patient support programs.

For patients who received neoadjuvant chemotherapy with residual high-risk disease, or patients that are unfit or ineligible for adjuvant chemotherapy, the standard of care would be adjuvant nivolumab.

When asked for their impression of current la/mUC treatments, one clinician gave this response:

- Slow improvements in outcomes have been made over the past 5 years. Some patients do not respond to chemotherapy and then quickly progress and are not well enough for further therapy.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The most commonly reported unmet need was durable disease control – one respondent indicated “Sometimes toxicity limits duration of therapy and majority of patients do not have long lasting benefit”. Quality of life and complete response were also cited as treatment gaps.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

All of the respondents who answered this question indicated that enfortumab vedotin in combination with pembrolizumab would become the first-line standard of care due to the magnitude of benefit seen compared to the current standard of care.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

All of the respondents indicated that it is not currently possible to identify which patients will most benefit from this treatment due to the absence of any identified biomarkers. Patients with an active autoimmune disease or organ transplants would not be able to receive this treatment due to the effects of pembrolizumab.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

All respondents indicated that prolonged survival should be considered a clinically meaningful response and a majority also cited delay of recurrence and the ability to perform activities of daily living. A smaller number of respondents cited reduced cancer symptoms and prevention of recurrence.

4 respondents indicated that treatment response should be reassessed with imaging every 3 months, while the fifth respondent said that it should happen clinically every 3-weeks prior to each subsequent treatment cycle.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

All respondents cited adverse events as a factor that should be considered when deciding to discontinue treatment. Severe neuropathy or rash were identified as the most common adverse events that might require discontinuation. A smaller number of respondents also cited recurrence of disease, disease progression and burden of treatment.

5.5 What settings are appropriate for treatment with enfortumab vedotin? Is a specialist required to diagnose, treat, and monitor patients who might receive enfortumab vedotin?

A majority of respondents said that cancer centre outpatient clinics were appropriate for treatment with enfortumab vedotin. Other respondents identified hospital outpatient clinics and private infusion clinics. Less formal settings were not considered appropriate due to the risk of adverse events.

6. Additional Information

When asked if they would recommend enfortumab vedotin in combination with pembolizumab to patients with la/mUC based on their personal observations, the respondents **unanimously** said that they would.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

3. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Adam Waiser, an independent consultant, prepared this submission with the assistance and oversight of Bladder Cancer Canada staff.

4. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   Adam Waiser, an independent consultant, created the clinician surveys, oversaw survey distribution and collection, and analyzed the data for this submission with the assistance and oversight of Bladder Cancer Canada staff.

5. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Susanna Cheng

Position: Medical oncologist staff

Date: 27-04-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			
Astra Zeneca	X			
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Nimira Alimohamed

Position: Medical Oncologist

Date: 07-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

Seagen	X			
Pfizer	X			
EMD Serono	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Zineb Hamilou

Position: MD

Date: 07-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Jeff Graham

Position: Medical Oncologist

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
EMD	X			
Pfizer	X			
Merck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Ricardo Fernandes

Position: Medical Oncologist

Date: 29-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
None				

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: **PC0353-000**

Generic Drug Name (Brand Name): **Enfortumab vedotin (Padcev)**

Indication: **In combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer (la/mUC).**

Name of Clinician Group: **Bladder Cancer Canada**

Author of Submission: **Adam Waiser**

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www.bladdercancercanada.org

2. Information Gathering

Bladder Cancer Canada collected the information for this submission from online surveys conducted between April 27 and May 8, 2024. The survey asked clinicians about their experience treating locally advanced or metastatic urothelial carcinoma (LAMUC) patients with enfortumab vedotin in combination with pembrolizumab as well as other therapies. It also asked questions about their treatment goals, current unmet needs and the potential role of enfortumab vedotin within the treatment paradigm. Potential respondents were identified from ******** clinical trial investigators and the members of the BCC medical advisory board.

A total of 4 clinicians completed the survey. All 4 respondents were from Canada (representing Alberta, Manitoba, Ontario & Quebec). All respondents had experience treating patients with LAMUC and 3 had experience treating LAMUC patients with enfortumab vedotin in combination with pembrolizumab.

3. Current Treatments

The current standard of care for LAMUC is first-line platinum-based chemotherapy follower by avelumab maintenance. One respondent also included gemcitabine in combination with the chemotherapy. The second-line treatments are pembrolizumab if the patient progressed on chemo or erdafinitib, especially if the cancer is FGFR altered. Two identified enfortumab as the standard of care for second line treatment.

There is no alternative treatment for patients who received neoadjuvant chemotherapy, or patients that are unfit or ineligible for adjuvant chemotherapy. No off-label treatments were identified, and special access programs were limited to nivolumab. Several respondents identified nivolumab as the standard of care when it was available.

When asked for their impression of current MIUC treatments, one clinician gave this response:

- Adjuvant gem/cis delays progress. Have observed some surprisingly favourable outcomes. But many patients recover poorly from surgery and are not fit for adjuvant chemo.

4. Treatment Goals

Bladder Cancer Canada asked clinicians to evaluate the importance of different outcomes for bladder cancer treatment on a scale of 1 (not important) to 5 (very important). Medical outcomes like preventing metastases, increasing overall survival and controlling disease progression were rated more highly than quality of life outcomes like reducing severity of symptoms and minimizing adverse events.

Importance of outcome	Average (n=6)
Increasing overall survival	4.83
Preventing metastases	4.83
Controlling disease progression	4.50
Maintaining quality of life	4.00
Minimizing adverse events	3.33
Reducing severity of symptoms	3.33

5. Treatment Gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

There is an unmet need for patients who receive neoadjuvant chemotherapy, but still have significant residual disease at the time of radical resection. These patients are at very high risk of disease recurrence, metastatic disease and death. A substantial percentage of patients will also relapse under the current standard of care, especially those with lymph node involvement at resection. For patients who are ineligible for adjuvant chemotherapy, there is no alternative treatment.

Some respondents also indicated that they lacked robust evidence for the use of adjuvant chemotherapy following radical resection.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Clinicians identified patients who are cisplatin-ineligible and patients with significant residual disease following resection as having the greatest unmet need; more specifically, patients who have pT2+ or N+ at the time of resection.

6. Place in Therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Nivolumab would be used as adjuvant therapy following radical resection for patients with a high risk of recurrence with or without neoadjuvant cisplatin-based chemotherapy, or for patients who are unfit or ineligible for adjuvant cisplatin-based chemotherapy and did not receive neoadjuvant chemotherapy. This would be an additional option for patients. There are currently no recommended treatments for high-risk patients after neoadjuvant chemotherapy.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

No other treatment would be recommended for patients who fit the indications identified in 6.1. There are currently no recommended treatments for high-risk patients after neoadjuvant chemotherapy or patients who are ineligible for adjuvant chemotherapy.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Nivolumab would fill a gap in the current standard of care. As such, it would not affect the sequencing of therapies for MIUC.

6.4. Which patients would be best suited for treatment with the drug under review?

The patients best suited for treatment with nivolumab are all those eligible for the CheckMate 274 clinical trial (multiple clinicians presented their response in these terms).

6.5. How would patients best suited for treatment with the drug under review be identified?

Patients would be identified based on post-operative pathology reports of cystectomy specimens.

6.6. Which patients would be least suitable for treatment with the drug under review?

Patients who responded well to neoadjuvant chemotherapy and patients with contraindications for immunotherapy would be least suitable for treatment with nivolumab.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

PDL1+ patients may have enhanced outcomes, but this is not adequate for making treatment decisions and is not done in practice. Upper tract urothelial carcinoma would be prioritized for adjuvant chemotherapy. Patients with prior neoadjuvant chemotherapy appear to respond best.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Survival time and time to recurrence/metastatic disease would be the outcome used to determine whether patients are responding to treatment with nivolumab.

6.9. What would be considered a clinically meaningful response to treatment?

All 6 respondents identified delay of recurrence, delay of metastases and prolonged survival as clinically meaningful treatment responses. 5 respondents also included prevention of recurrence and prevention of survival as clinically meaningful responses.

6.10. How often should treatment response be assessed?

5 respondents, including the 3 respondents with nivolumab treatment experience, said that treatment response should be assessed every three months. The sixth respondent said that treatment should be assessed every six months.

6.11. What factors should be considered when deciding to discontinue treatment?

All six respondents said that adverse events should be factor when deciding to discontinue treatment. However, it should also be noted that the adverse effects of nivolumab in the adjuvant setting were in line with the profile of nivolumab in other cancer settings. 5 respondents said recurrence of disease should be a factor; the lone dissenter did not indicate why he disagreed. Two respondents said burden of treatment should also be a factor.

6.12. What settings are appropriate for treatment with the drug under review?

A majority of respondents said that hospital outpatient clinics and private infusion clinics were the appropriate settings for treatment with nivolumab. A smaller number of respondents also said that medical clinics and CLSCs would be an appropriate.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Not applicable

7. Additional Information

When asked if they would recommend use of nivolumab for patients with MIUC following radical resection based on clinical evidence of disease-free survival benefits in the absence of overall survival data, all 6 respondents said that they would.

Comments include:

- Progression means a lot to patients - this is a clinically relevant endpoint; and the treatment is well tolerated
- A helpful option for patient who have received neoadjuvant chemo and an alternative for patients unfit for adjuvant chemotherapy

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

6. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, prepared this submission with the assistance and oversight of Bladder Cancer Canada staff.

7. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, created the clinician surveys, oversaw survey distribution and collection, and analyzed the data for this submission with the assistance and oversight of Bladder Cancer Canada staff.

8. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Michel Pavic

Position: Oncologue médical

Date: 26-02-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
BMS	X			
EMD Serono	X			
Merck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Wassim Kassouf

Position: Professor of Urology

Date: 04-03-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
BMS – ad board	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Peter Black

Position: Urologic Oncologist

Date: 08-03-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
BMS	X			
GNE	X			
EMD-Serono	X			
Merck	X			
Pfizer	X			
Janssen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Aly-Khan Lalani

Position: Medical Oncologist

Date: 08-03-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**

AbbVie	X			
Astellas	X			
BMS	X			
Eisai	X			
Ipsen	X			
Janssen	X			
Merck	X			
Novartis	X			
Pfizer	X			
Roche	X			
TerSera	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Ramy Saleh

Position: Med Onc staff

Date: 08-03-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Nimira Alimohamed

Position: Medical Oncology

Date: 11-03-2022

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Pfizer	X			
EMD Serono	X			
Seagen	X			

* Place an X in the appropriate dollar range cells for each company.

CADTH Project Number: PC0353

Generic Drug Name (Brand Name): enfortumab vedotin (Padcev)

Indication: In combination with pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer

Name of Clinician Group: Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee ("GU DAC")

Author of Submission: Dr. Girish Kulkarni

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH(CCO)'s Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered by videoconference.

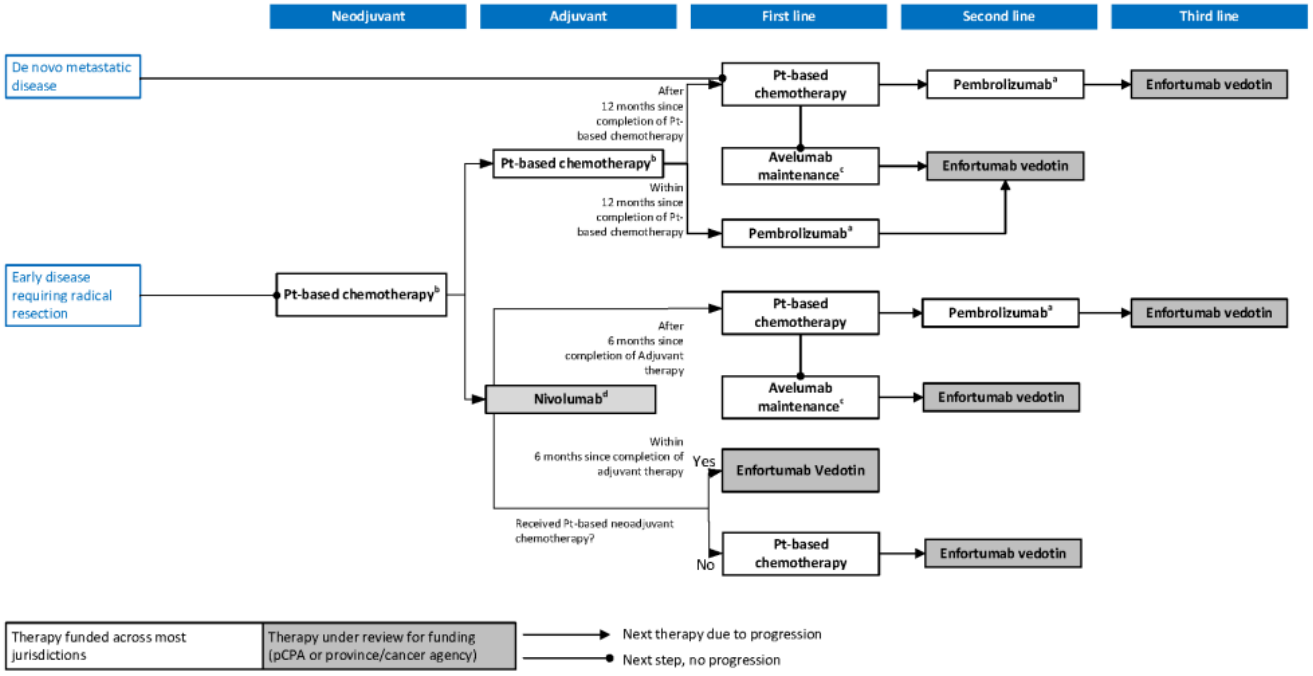
3. Current Treatments and Treatment Goals

Current treatments for first line include platinum-based chemotherapy and avelumab.

As a first line treatment, enfortumab vedotin in combination with pembrolizumab will become a new standard option, including patients who received neoadjuvant/adjuvant chemotherapy, and/or adjuvant nivolumab.

Treatment goals include to improve overall survival, progression-free survival, and improved response rate including complete response with potential for long term remission.

Figure 1: Provisional Funding Algorithm Diagram for MUC



4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The trial data shows improved overall survival (HR=0.47) and improved chance of long term durable responses. This is also a non-chemotherapy option.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

As a first line treatment, enfortumab vedotin in combination with pembrolizumab will become a new standard option, including patients who received neoadjuvant/adjuvant chemotherapy, and/or adjuvant nivolumab.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients best suited include those who are deemed eligible by a physician for immunotherapy-based regimens.

Any patient with urothelial cancer should be eligible irrespective of the histology. Any patient cohort in the trial seems to benefit.

Patients with a contraindication to immunotherapy are least suitable.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Routine clinical and radiographic assessment as per standard of care.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Clinically significant disease progression, unacceptable toxicity.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

In outpatient cancer centers under the advisement of a medical oncologist.

6. Additional Information

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.

7. Conflict of Interest Declarations

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9. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH (CCO) provided a secretariat function to the group.

10. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

    No.

11. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Girish Kulkarni

Position: Ontario Health (Cancer Care Ontario) GU DAC Lead

Date: 08-05-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

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Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Aly-Khan Lalani

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Seagen Canada Inc		X		
Merck		X		

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Sebastien Hotte

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Seagen Canada Inc	X			
Merck	X			
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Chris Morash

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				

Add company name				
Add or remove rows as required				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Dr. Christina Canil

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Seagen Canada Inc	X			
Merck	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Dr. Urban Emmenegger

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 6

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 7

Name: Dr. Reeta Barua

Position: Ontario Health (Cancer Care Ontario) GU DAC member

Date: 08-05-2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 7

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				

* Place an X in the appropriate dollar range cells for each company.