Reimbursement Review

Provisional Funding Algorithm

Indication: Metastatic urothelial carcinoma

This report supersedes the CADTH Provisional Funding Algorithm report for metastatic urothelial carcinoma dated March 28, 2022.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

Publication date: January 2023

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

Background

Following a request from jurisdictions, CADTH will design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

1) CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
2) implementation advice from panels of clinicians convened by CADTH, concerning sequencing of drugs in the therapeutic space of interest
3) existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

It should be noted that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Additionally, provisional funding algorithms delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding statuses. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on metastatic urothelial carcinoma (MUC). However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH first published a provisional funding algorithm for urothelial carcinoma in March 2022. This was a rapid algorithm that aimed to incorporate the CADTH recommendation for enfortumab vedotin (Padcev).

Jurisdictional cancer drug programs have recently requested an update to this rapid algorithm to incorporate the CADTH recommendation for nivolumab (Opdivo) as a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma at high risk for recurrence after undergoing radical resection.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing

Nivolumab (Opdivo)	October 17, 2022	pERC recommends that nivolumab be reimbursed as a monotherapy for the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection of UC. Conditions included a reduction in price and the feasibility of adoption being addressed.
		
		Treatment with nivolumab should only be reimbursed when initiated in patients who have all of the following:
		• pathologic evidence of urothelial carcinoma at high risk of recurrence based on pathologic staging of radical surgery tissue in patients who have either:
		  ○ received cisplatin-based neo-adjuvant chemotherapy (ypT2-pT4a or ypN+)
		  ○ have not received neo-adjuvant cisplatin chemotherapy (pT3-pT4a or pN+) and are ineligible for adjuvant therapy with cisplatin chemotherapy (based on Galsky ineligibility criteria, 2011), or
		  ○ have not received neo-adjuvant cisplatin chemotherapy (pT3-pT4a or pN+) and are eligible for adjuvant cisplatin-based chemotherapy but decline to take it
		• evidence of no recurrence should be confirmed before initiating therapy
		• muscle invasive UC at disease diagnosis
		• patient must not have any of the following:
		  ○ metastatic disease
		  ○ active autoimmune disease
		• patients should have good performance status
		• treatment with nivolumab should be initiated in patients within 120 days after completion of local therapy.
		
		The CheckMate-274 trial did not assess the comparative efficacy of adjuvant nivolumab compared with adjuvant chemotherapy. pERC agreed that given the absence of robust direct or indirect comparison, there is insufficient evidence to ascertain which of the agents (i.e., adjuvant nivolumab or adjuvant chemotherapy) has superior efficacy.
		
		pERC noted that patients who recur more than 6 months after receiving adjuvant treatment with nivolumab would be treated according to the

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		established treatment algorithm (i.e., eligibility for downstream enfortumab vedotin).
Enfortumab (Padcev)	January 24, 2022	pERC recommends that enfortumab vedotin be reimbursed for the treatment of adult patients with unresectable locally advanced or MUC who have previously received: • a PD-1 or PD-L1 inhibitor in the locally advanced or metastatic setting; and • a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting pERC considered the sequencing of treatments given the newly recommended listing for avelumab as maintenance therapy following the first-line platinum-based chemotherapy in the locally advanced or metastatic setting. As per the eligibility criteria of Study EV-301, patients are required to fail platinum-containing chemotherapy, and PD-1/PD-L1 inhibitor therapy. pERC noted that unless there is a re-treatment with a PD-1/PD-L1 inhibitor, patients would fulfill the eligibility criteria for treatment with enfortumab vedotin, thus a significant portion of patients would be eligible to receive enfortumab vedotin as second-line therapy. Conversely, it was also noted that if the treatment-free interval is of sufficient length following treatment with avelumab maintenance therapy, second-line treatment with a PD-1/PD-L1 inhibitor (i.e., pembrolizumab) would be justified prior to enfortumab vedotin.
Avelumab (Bavencio)	March 23, 2021	pERC conditionally recommends reimbursement of avelumab (Bavencio) plus BSC for the first-line maintenance treatment of patients with histologically confirmed, unresectable, locally advanced or metastatic urothelial carcinoma whose disease has not progressed with first-line platinum-based induction chemotherapy if the following conditions are met: • cost-effectiveness is improved to an acceptable level • feasibility of adoption (budget impact) is addressed. pERC agreed with the CGP that there is currently no evidence to support the use of a second-line immune checkpoint inhibitor following first-line avelumab maintenance given that they work through similar mechanisms of action. There remains a lack of evidence-based therapies for these patients; however, chemotherapy and clinical trials may be appropriate. In terms of whether it would be preferable to give avelumab for maintenance or wait and give pembrolizumab to patients who progress, the CGP noted that the JAVELIN Bladder 100 clinical trial investigated whether patients treated with avelumab plus BSC had better outcomes than patients treated with BSC only. Given the results of the trial, pERC agreed with the CGP that it would be preferable to give avelumab for maintenance therapy rather than wait and give pembrolizumab to patients who progress. pERC agreed with the CGP that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy. For patients who stop treatment with avelumab for reasons related to infusion reaction or unrelated to progression after a short duration of exposure (i.e., 6 months) and who then experience disease progression after a progression-free interval of 6 months, pERC agreed with the CGP that subsequent treatment with pembrolizumab may be considered.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		pERC agreed with the CGP that treatment with avelumab should only be continued if the disease is still in remission. If the disease had progressed, then the patient would receive the next line of treatment for their disease. pERC agreed with the CGP that shorter durations of treatment with chemotherapy in the first line (< 4 cycles) may be eligible for treatment with avelumab plus BSC maintenance. However, patients receiving fewer than 4 cycles of chemotherapy due to intolerance should have no evidence of disease progression on or after treatment, and reasons for shortened chemotherapy exposure should be clearly justified so as not to encourage inadequate exposure to chemotherapy treatment.
Pembrolizumab (Keytruda)	September 20, 2017	pERC recommends reimbursement of pembrolizumab (Keytruda) conditional on cost-effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with locally advanced or MUC who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy. Funding should be for patients with a good performance status. Treatment should continue until confirmed disease progression or unacceptable toxicity or after completing 2 years of pembrolizumab therapy, whichever comes first.

BSC = best supportive care; CGP = Clinical Guidance Panel; MUC = metastatic urothelial carcinoma; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; UC = urothelial carcinoma.

Provisional Funding Algorithm

Description of the Provisional Funding Algorithm

Patients With de Novo Metastatic Disease

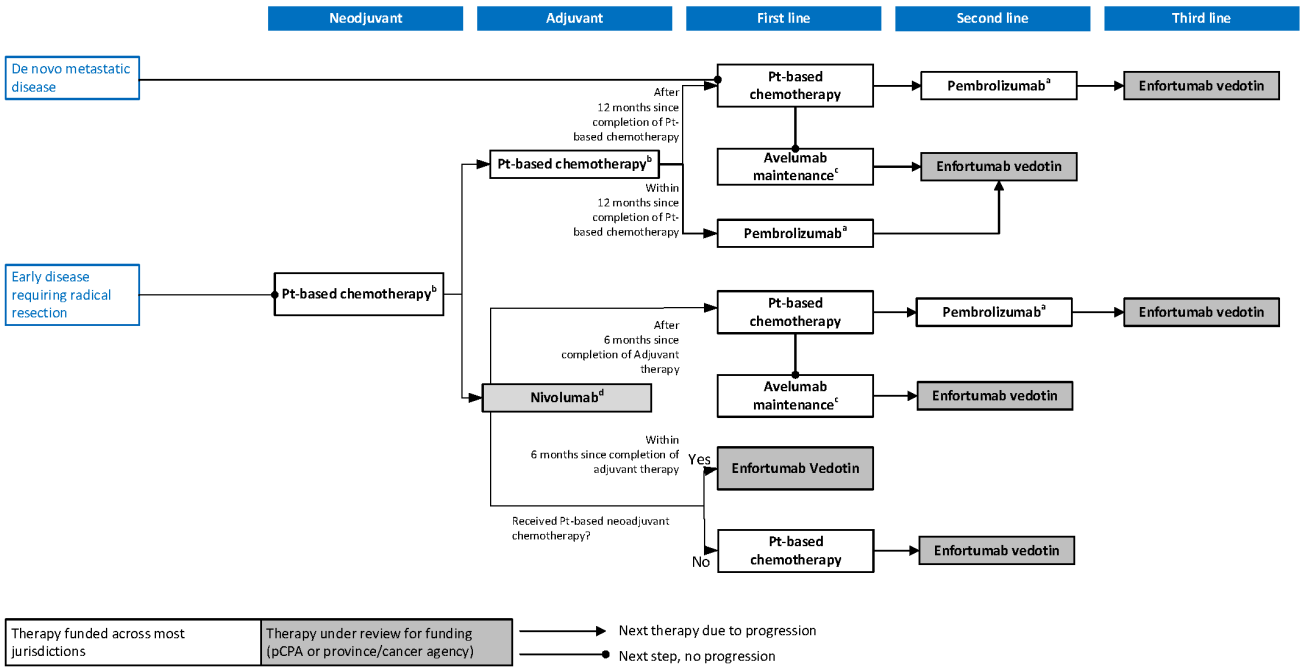
Available first-line therapies include platinum-based chemotherapy with or without subsequent avelumab maintenance treatment. Upon progression on or after chemotherapy without avelumab maintenance, pembrolizumab is available until disease progression. In patients who stop pembrolizumab treatment after 2 years (35 cycles) for reasons other than disease progression or intolerability, up to 1 additional year of pembrolizumab treatment is available. Enfortumab vedotin is available following progression on pembrolizumab or avelumab maintenance therapy.

Patients With Early Disease Requiring Radical Resection and Neoadjuvant or Adjuvant Treatment

In the neoadjuvant setting, patients may receive platinum-based chemotherapy before surgical resection. It is acknowledged that most jurisdictions would start with cisplatin-based chemotherapy in this setting.

Another option is to receive adjuvant treatment after undergoing surgery that includes platinum-based chemotherapy, and more recently nivolumab, which has been recommended for use in the adjuvant setting and is currently under review for funding.

Figure 1: Provisional Funding Algorithm Diagram for MUC



MUC = metastatic urothelial carcinoma; pCPA = pan-Canadian Pharmaceutical Alliance; pt = platinum; UC = urothelial carcinoma.
[a] Patients who stopped pembrolizumab treatment after 2 years (35 cycles) for reasons other than disease progression or intolerability are eligible for up to 1 additional year of pembrolizumab upon relapse.
[b] Note that in usual practice, individuals would not receive the platinum-based chemotherapy both in the neoadjuvant and adjuvant setting sequentially.
[c] If patients received 4 to 6 cycles of chemotherapy without disease progression.
[d] For patients with muscle invasive UC who are at high risk of disease recurrence after undergoing radical resection, treatment with nivolumab should be initiated within 120 days after completion of therapy.

Patients Who Have Received Adjuvant Chemotherapy

For patients who have received adjuvant chemotherapy and have progressed after 12 months, platinum-based chemotherapy with or without subsequent avelumab maintenance treatment is available in the first-line setting. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, the second- and third-line options are pembrolizumab and enfortumab vedotin, respectively. For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line option is enfortumab vedotin.

For patients who have progressed within 12 months of receiving adjuvant platinum-based chemotherapy, the subsequent first-line option is pembrolizumab. In patients who stop pembrolizumab treatment after 2 years (35 cycles) for reasons other than disease

progression or intolerability, up to 1 additional year of pembrolizumab treatment is available. This is followed by a second-line option of enfortumab vedotin.

Patients Who Have Received Adjuvant Nivolumab

Nivolumab is under review for funding in patients with a high risk of recurrence after surgical resection. For patients who have received adjuvant nivolumab and have progressed to MUC after 6 months, platinum-based chemotherapy with or without subsequent avelumab maintenance treatment is available in the first line. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, the second- and third-line options are pembrolizumab and enfortumab vedotin, respectively. For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line option is enfortumab vedotin.

For patients who have received adjuvant nivolumab and have progressed to MUC within 6 months, the first-line option depends on whether they have received platinum-based neoadjuvant chemotherapy. For patients who have previously received platinum-based neoadjuvant chemotherapy, the first-line option is enfortumab vedotin. For patients who have not previously received platinum-based neoadjuvant chemotherapy, the first-line option is platinum-based chemotherapy, followed by a second-line option with enfortumab vedotin.