

Provisional Funding Algorithm

Indication: Metastatic Urothelial Carcinoma

This report supersedes the Provisional Funding Algorithm report for metastatic urothelial carcinoma dated January 11, 2023. Please always check [Provisional Funding Algorithms](#) to ensure you are reading the most recent algorithm report.

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Background

Following a request from jurisdictions, Canada's Drug Agency (CDA-AMC) may 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:

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

Note 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 CDA-AMC website for more details.

Provisional funding algorithms also 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 CDA-AMC following changes to drug funding statuses. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CDA-AMC Provisional Funding Algorithm on metastatic urothelial carcinoma. 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

CDA-AMC first published a provisional funding algorithm for urothelial carcinoma in March 2022. This was a rapid algorithm with the aim to incorporate the [CDA-AMC recommendation for enfortumab vedotin \(Padcev\)](#) for the treatment of adult patients with unresectable, locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and programmed death receptor-1 or programmed death-ligand 1 inhibitor therapy.

A second provisional funding algorithm report was later released on January 11, 2023, to incorporate the 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.

Jurisdictional cancer drug programs have recently requested to update this rapid algorithm to incorporate the [CDA-AMC recommendation for erdafitinib \(Balversa\)](#) for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma (UC) harboring susceptible FGFR3 genetic alterations who have disease progression during at least one line of prior therapy as well as [CDA-AMC recommendation for enfortumab vedotin \(Padcev\)](#) in combination with pembrolizumab for the treatment of adult patients with locally advanced urothelial cancer (UC) or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC.

Table 1: Relevant Previous Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Enfortumab Vedotin (Padcev)	December 17, 2024	<p>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 following conditions are met:</p> <ul style="list-style-type: none">• Enfortumab vedotin in combination with pembrolizumab should be reimbursed for the treatment of adult patients with unresectable locally advanced urothelial cancer or metastatic urothelial cancer with no prior systemic therapy.• For additional clarity, the following patients who have received the following are also eligible:

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<ul style="list-style-type: none"> ○ Neoadjuvant chemotherapy, but experienced recurrence more than 12 months after neoadjuvant chemotherapy was completed ○ Adjuvant chemotherapy following cystectomy, but experienced recurrence more than 12 months after adjuvant chemotherapy was completed ○ Adjuvant nivolumab, but experienced recurrence more than 6 months after nivolumab treatment was completed. • Patients should have a good performance status • Treatment with enfortumab vedotin in combination with pembrolizumab should not be initiated in patients with: <ul style="list-style-type: none"> ○ Active CNS metastases ○ Uncontrolled diabetes ○ Prior enfortumab vedotin or other MMAE-based ADCs. • Patients should be assessed by the treating clinician before each treatment cycle with diagnostic imaging conducted every 2 to 3 months. • Treatment should be discontinued in patients with any of the following: <ul style="list-style-type: none"> ○ Documented disease progression ○ Unacceptable toxicity ○ Note that pembrolizumab may be used up to 24 months in patients without disease progression, according to the pembrolizumab product monograph. • Treatment with enfortumab vedotin in combination with pembrolizumab should only be initiated by a medical oncologist with experience treating incurable urothelial cancer. <ul style="list-style-type: none"> ○ 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. • 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. • A reduction in price. • The feasibility of adoption of enfortumab vedotin must be addressed. <p>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.</p> <p>pERC noted that enfortumab vedotin in combination with pembrolizumab should not be offered to patients who have completed or progressed on first-line chemotherapy.</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>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.</p> <p>pERC agreed with the clinical expert that as per standard clinical practice with other regimens after immunotherapy, patients 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.</p> <p>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.</p> <p>pERC agreed with the clinical expert that 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 continue enfortumab vedotin monotherapy.</p>
Erdafitinib (Balversa)	January 28, 2025	<p>pERC recommends that erdafitinib be reimbursed for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma (UC) harbouring susceptible FGFR3 genetic alterations, who have disease progression during or following at least 1 line of prior therapy, including within 12 months of neoadjuvant or adjuvant therapy, only if the following conditions are met:</p> <ul style="list-style-type: none"> • Erdafitinib should be reimbursed in patients with a diagnosis of locally advanced or metastatic UC harbouring susceptible FGFR3 genetic alterations who have disease progression during or following at least 1 line of prior therapy, including within 12 months of neoadjuvant or adjuvant therapy. • Erdafitinib should not be reimbursed in patients who are eligible for but have not received prior PD-1 or PD-L1 inhibitor therapy. • Treatment with erdafitinib should be initiated following confirmation of a susceptible FGFR3 genetic alteration using a validated test. • Reimbursement of erdafitinib should be discontinued upon evidence of: <ul style="list-style-type: none"> ○ Clinically significant disease progression as assessed by imaging and clinical criteria. ○ Intolerable or unmanageable drug toxicity. • Erdafitinib should be prescribed by clinicians with expertise in treating patients with UC.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<ul style="list-style-type: none"> • A reduction in price. • The feasibility of adoption of erdafitinib must be addressed. <p>The organizational feasibility of conducting FGFR3 testing must be addressed.</p>
Nivolumab (Opdivo)	October 17, 2022	<p>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.</p> <p>Treatment with nivolumab should only be reimbursed when initiated in patients who have all of the following:</p> <ul style="list-style-type: none"> • Pathologic evidence of urothelial carcinoma at high risk of recurrence based on pathologic staging of radical surgery tissue in patients who have either: <ul style="list-style-type: none"> ○ 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: <ul style="list-style-type: none"> ○ 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 <p>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.</p> <p>pERC noted that patients who recur more than 6 months after receiving adjuvant treatment with nivolumab would be treated according to the established treatment algorithm (i.e., eligibility for downstream enfortumab vedotin).</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Enfortumab (Padcev)	January 24, 2022	<p>pERC recommends that enfortumab vedotin be reimbursed for the treatment of adult patients with unresectable locally advanced or MUC who have previously received:</p> <ul style="list-style-type: none"> • 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 <p>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.</p>
Avelumab (Bavencio)	March 23, 2021	<p>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:</p> <ul style="list-style-type: none"> • cost-effectiveness is improved to an acceptable level • feasibility of adoption (budget impact) is addressed. <p>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.</p>

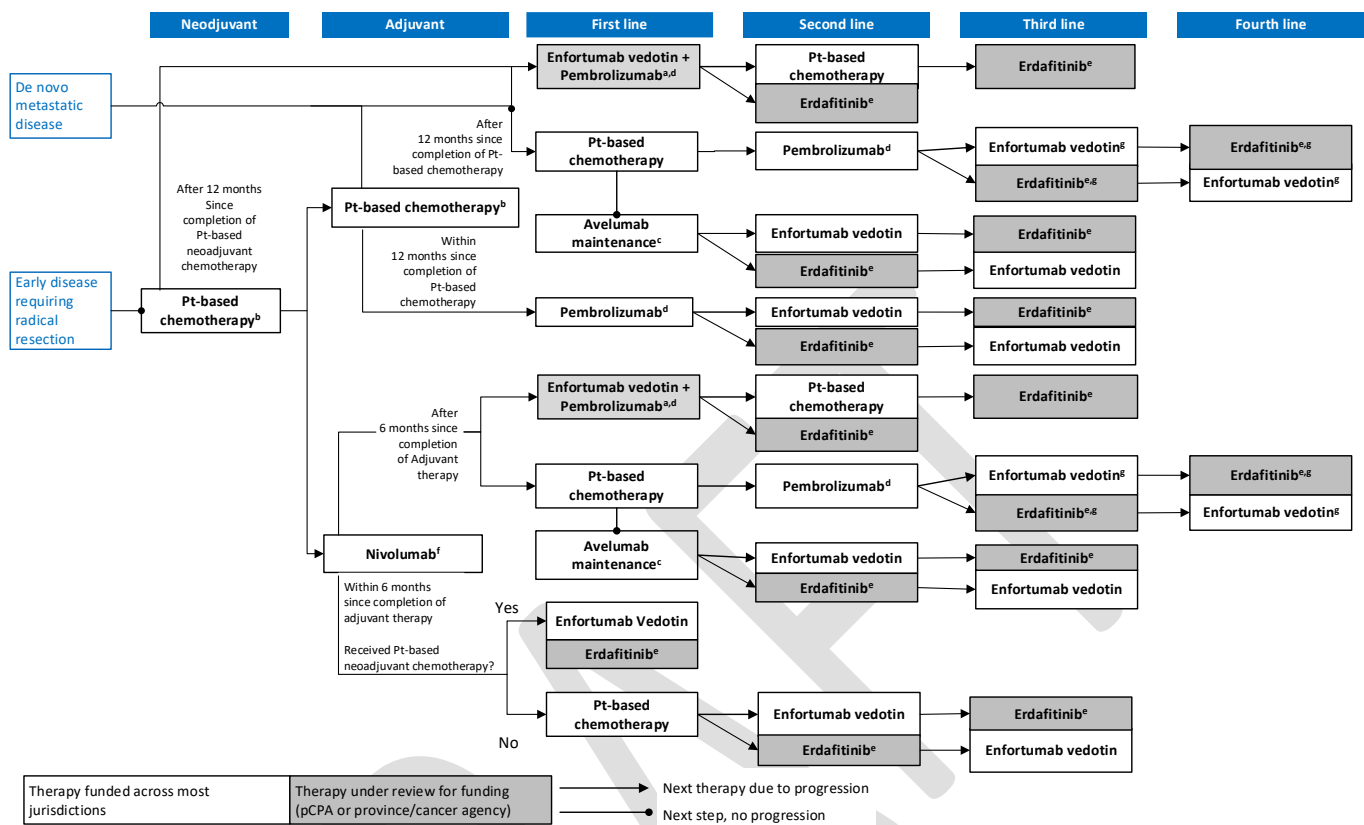
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>pERC agreed with the CGP that patients who progressed on avelumab maintenance treatment should not be treated with subsequent anti-PD1 therapy. For patients who stop treatment with avelumab for reasons 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.</p> <p>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.</p> <p>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.</p>
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 two years of pembrolizumab therapy, whichever comes first.

ADC = antibody drug conjugate; AE = adverse event; BSC = best supportive care; CGP = Clinical Guidance Panel; CNS = central nervous system; pERC = pCODR Expert Review Committee; MMAE = monomethyl auristatin E; MUC = metastatic urothelial carcinoma; PD-1 = programmed death receptor-1; PD-L1 = programmed death-ligand 1; UC = urothelial carcinoma

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Metastatic Urothelial Carcinoma

Alt Text: A flow diagram depicting the therapies that are funded or under review for funding across most jurisdictions for patients with MUC across adjuvant, first line, second line, and third line. A full description can be found below the figure.



MUC = metastatic urothelial carcinoma; pCPA = pan-Canadian Pharmaceutical Alliance; pt = platinum; UC = urothelial carcinoma

^a Patients who experience unacceptable adverse events attributable only to enfortumab vedotin may continue pembrolizumab monotherapy for a maximum of 24 months, and patients who experienced unacceptable adverse events attributable only to pembrolizumab may continue enfortumab vedotin monotherapy.

^b Note that in usual practice, individuals would not receive 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 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.

^e Treatment with erdafitinib should be initiated following confirmation of a susceptible FGFR3 genetic alteration using a validated test.

^f For patients with muscle-invasive UC who are at high risk of recurrence after undergoing radical resection. Treatment with nivolumab should be initiated within 120 days after completion of therapy.

^g Patients who progress on enfortumab vedotin in the third line may now receive erdafitinib in the fourth line, and those who progress on erdafitinib in the third line may now receive enfortumab vedotin in the subsequent treatment line.

Description of the Provisional Funding Algorithm

Patients with de novo metastatic disease

For patients with de novo metastatic disease, several first-line therapy options are available. One option is enfortumab vedotin in combination with pembrolizumab, which has been recommended for use in the advanced setting and is currently under review for funding. Upon disease progression on or after this combination therapy, platinum-based chemotherapy or erdafitinib, currently under review for funding, are available as second-line options. For patients who have completed second-line platinum-based chemotherapy, the third-line option is erdafitinib, which is under review for funding.

Another option for first-line therapy is platinum-based chemotherapy, which may be administered with or without subsequent avelumab maintenance therapy. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, pembrolizumab is available until disease progression. Patients who discontinue pembrolizumab treatment after two years for reasons other than disease progression or intolerability may receive up to one additional year of pembrolizumab treatment. After progression on pembrolizumab, enfortumab vedotin or erdafitinib, both currently under review for funding, become available. Patients who progress on enfortumab vedotin in the third line may now receive erdafitinib in the fourth line, while those who progress on erdafitinib in the third line may now receive enfortumab vedotin in the subsequent treatment line. For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line options are enfortumab vedotin or erdafitinib.

Patients with early disease requiring radical resection and neoadjuvant / adjuvant treatment

For patients with early disease, platinum-based chemotherapy is an option in the neoadjuvant setting prior to surgical resection, with cisplatin-based chemotherapy being the preferred choice in most jurisdictions. In the adjuvant setting, therapy options following surgery include platinum-based chemotherapy and nivolumab.

Patients who have received neoadjuvant chemotherapy

In the neoadjuvant setting, patients may receive platinum-based chemotherapy prior to 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 which includes platinum-based chemotherapy and more recently nivolumab which has been recommended for use in the adjuvant setting.

For patients who have received neoadjuvant chemotherapy and experienced recurrence more than 12 months after completing treatment, one option is enfortumab vedotin in combination with pembrolizumab, which has been recommended for use in the advanced setting and is currently under review for funding. Upon disease progression on or after this combination therapy, platinum-based chemotherapy or erdafitinib, currently under review for funding, are available as second-line options. For patients who have completed second-line platinum-based chemotherapy, the third-line option is erdafitinib, which is under review for funding.

Another option for first-line therapy is platinum-based chemotherapy, which may be administered with or without subsequent avelumab maintenance therapy. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, pembrolizumab is available until disease progression. Patients who discontinue pembrolizumab treatment after two years for reasons other than disease progression or intolerability may receive up to one

additional year of pembrolizumab treatment. After progression on pembrolizumab, enfortumab vedotin or erdafitinib, both currently under review for funding, become available. Patients who progress on enfortumab vedotin in the third line may now receive erdafitinib in the fourth line, while those who progress on erdafitinib in the third line may now receive enfortumab vedotin in the subsequent treatment line.

For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line options are enfortumab vedotin or erdafitinib. Patients who progress on enfortumab vedotin in the second line may now receive erdafitinib as a third-line treatment, while those who progress on erdafitinib in the second line may now receive enfortumab vedotin in the subsequent treatment line.

Patients who have received adjuvant chemotherapy

For patients who have received adjuvant chemotherapy and experienced recurrence more than 12 months after completing treatment, several first-line therapy options are available. One option is enfortumab vedotin in combination with pembrolizumab, which has been recommended for use in the advanced setting and is currently under review for funding. Upon disease progression on or after this combination therapy, platinum-based chemotherapy or erdafitinib, currently under review for funding, are available as second-line options. For patients who have completed second-line platinum-based chemotherapy, the third-line option is erdafitinib, which is under review for funding.

Another option for first-line therapy is platinum-based chemotherapy, which may be administered with or without subsequent avelumab maintenance therapy. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, pembrolizumab is available until disease progression. Patients who discontinue pembrolizumab treatment after two years for reasons other than disease progression or intolerability may receive up to one additional year of pembrolizumab treatment. After progression on pembrolizumab, enfortumab vedotin or erdafitinib, both currently under review for funding, become available. Patients who progress on enfortumab vedotin in the third line may now receive erdafitinib in the fourth line, while those who progress on erdafitinib in the third line may now receive enfortumab vedotin in the subsequent treatment line.

For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line options are enfortumab vedotin or erdafitinib. Patients who progress on enfortumab vedotin in the second line may now receive erdafitinib as a third-line treatment, while those who progress on erdafitinib in the second line may now receive enfortumab vedotin in the subsequent treatment line.

For patients who progress 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 for reasons other than disease progression or intolerability, up to an additional year of pembrolizumab treatment is available. Second-line options include enfortumab vedotin or erdafitinib, both of which are currently under review for funding. Patients who progress on enfortumab vedotin in the second line may now receive erdafitinib as a third-line treatment, and those who progress on

erdafitinib in the second line may now receive enfortumab vedotin in the subsequent treatment line.

Patients who have received adjuvant nivolumab

For patients who have received adjuvant nivolumab, which is used for those with a high risk of recurrence after surgical resection, therapy options depend on the timing of progression. For patients who progress to metastatic urothelial carcinoma (MUC) after more than six months, one option is enfortumab vedotin in combination with pembrolizumab, which has been recommended for use in the advanced setting and is currently under review for funding. Upon disease progression on or after this combination therapy, platinum-based chemotherapy or erdafitinib, currently under review for funding, are available as second-line options. For patients who have completed second-line platinum-based chemotherapy, the third-line option is erdafitinib, which is under review for funding.

Another option for first-line therapy is platinum-based chemotherapy, which may be administered with or without subsequent avelumab maintenance therapy. For patients who have completed first-line platinum-based chemotherapy without subsequent avelumab maintenance treatment, pembrolizumab is available until disease progression. Patients who discontinue pembrolizumab treatment after two years for reasons other than disease progression or intolerability may receive up to one additional year of pembrolizumab treatment. After progression on pembrolizumab, enfortumab vedotin or erdafitinib, both currently under review for funding, become available. Patients who progress on enfortumab vedotin in the third line may now receive erdafitinib in the fourth line, while those who progress on erdafitinib in the third line may now receive enfortumab vedotin in the subsequent treatment line.

For patients who have completed first-line platinum-based chemotherapy with subsequent avelumab maintenance treatment, the second-line options are enfortumab vedotin or erdafitinib. Patients who progress on enfortumab vedotin in the second line may now receive erdafitinib as a third-line treatment, while those who progress on erdafitinib in the second line may now receive enfortumab vedotin in the subsequent treatment line.

For patients who progress to MUC within six months of receiving adjuvant nivolumab, the first-line therapy depends on whether they have previously received platinum-based neoadjuvant chemotherapy. For those who have received platinum-based neoadjuvant chemotherapy, the first-line options are enfortumab vedotin or erdafitinib. For those who have not received platinum-based neoadjuvant chemotherapy, platinum-based chemotherapy is the first-line therapy, followed by enfortumab vedotin or erdafitinib as second-line options. Patients who progress on enfortumab vedotin in the second line may now receive erdafitinib as a third-line treatment, while those who progress on erdafitinib in the second line may now receive enfortumab vedotin in the subsequent treatment line.

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