Reimbursement Review

Provisional Funding Algorithm

Indication: Renal cell carcinoma

This report supersedes the CADTH Provisional Funding Algorithm report for renal cell carcinoma dated September 6, 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:

- CADTH 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 CADTH, 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 CADTH 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 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 renal cell 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

CADTH first published a rapid algorithm report for advanced or metastatic renal cell carcinoma in September 2022. The main focus of this rapid algorithm was to incorporate the CADTH recommendation for lenvatinib and pembrolizumab (Lenvima and Keytruda) for the treatment of advanced or metastatic renal cell carcinoma.

Jurisdictional cancer drug programs have recently requested an update to this rapid algorithm to incorporate the CADTH recommendation for pembrolizumab (Keytruda) as an adjuvant treatment for adult patients with renal cell carcinoma.

Table 1: Relevant CADTH Recommendations

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

Pembrolizumab (Keytruda)	October 18, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, only if the following conditions are met.
		• Treatment with pembrolizumab should only be reimbursed when initiated in adults who have histologically confirmed diagnosis of RCC with a clear cell component, with or without sarcomatoid features, no prior systemic therapy for advanced RCC, intermediate-high risk or high risk of recurrence after nephrectomy, or M1 NED following nephrectomy and resection of metastatic lesions and partial or radical nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion[s] in M1 NED participants) with negative surgical margins ≥ 4 weeks before the initiation of treatment.
		• Patients should have a good performance status.
		• Treatment with pembrolizumab should be initiated within 12 weeks of complete resection.
		• Pembrolizumab should be discontinued upon the occurrence of any of the following:
		  ○ disease recurrence, defined as local recurrence of RCC, occurrence of distant metastases, or occurrence of a secondary systemic malignancy, determined by clinical, pathologic, and radiographic criteria
		  ○ unacceptable toxicity
		  ○ completion of 1 year of treatment (i.e., 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer) in patients without disease recurrence.
		• Patients should be assessed for disease recurrence every 3 to 6 months.
		• Pembrolizumab should be prescribed by clinicians with experience and expertise in the treatment of RCC. The treatment should be

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

		supervised and delivered in specialized clinics with expertise in systemic therapy and immunotherapy delivery.
		• Pembrolizumab can be continued for an equivalent of 1 year (12 months) of treatment, i.e., a maximum of either:
		  ○ 17 cycles if administered at a dosage of 200 mg IV every 3 weeks, or
		  ○ 9 cycles if administered at a dosage of 400 mg IV every 6 weeks.
		• Pembrolizumab should not be reimbursed when used in combination with other adjuvant anticancer drugs.
		• A reduction in price
		• The feasibility of adoption of pembrolizumab must be addressed.
		
		Optimal sequence guidance:
		• pERC agreed with the clinical experts that eligibility of patients with RCC for adjuvant pembrolizumab treatment should be aligned with the inclusion criteria applied in the pivotal KEYNOTE-564 trial. Specifically, the following criteria should be applied:
		  ○ individuals with clear cell RCC, post-nephrectomy, who have intermediate-high risk for recurrence (pT2, grade 4, or sarcomatoid, N0, M0; or pT3, any grade, N0, M0)
		  ○ individuals with clear cell RCC, post-nephrectomy, who have high risk for recurrence (pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0)
		  ○ individuals who present with a primary kidney tumour and soft tissue metastases that could be completely resected either at the time of nephrectomy (synchronous) or ≤ 1 year after nephrectomy (metachronous)
		• The clinical experts noted that, in the clinical practice, TKI agents (e.g., sunitinib, cabozantinib, pazopanib, or axitinib) are offered to patients who experience relapse while on adjuvant pembrolizumab treatment. The clinical experts believed that administration of the ipilimumab-nivolumab or axitinib-pembrolizumab combination should be discouraged in these patients.
		• pERC agreed with the clinical experts that patients who receive pembrolizumab in the adjuvant setting may be rechallenged or retreated with a PD-1 inhibitor combination (e.g., ipilimumab-nivolumab or axitinib-pembrolizumab), in the locally advanced or metastatic setting, if the patient experiences a disease recurrence after a disease-free interval of 6 months or more after completion of adjuvant therapy.
		• pERC agreed with the clinical experts that there is insufficient evidence to support adjuvant treatment with pembrolizumab in patients with kidney cancers of histology other than clear cell. The clinical experts also noted that sarcomatoid features can occur in almost all types of RCC, and that sarcomatoid differentiation is not considered a unique histological subtype of RCC. Notably, presence of sarcomatoid features was considered as a predictor of poor prognosis among patients with RCC, which suggests a need for adjuvant therapy, according to the clinical experts.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• pERC agreed with the clinical experts that treatment with adjuvant pembrolizumab can be administered until confirmed disease progression, unacceptable toxicity, or to a maximum of 17 doses (every 3 weeks), regardless of the time interval. Dose interruptions were permitted in the KEYNOTE-564 trial for management of adverse events, situations such as medical or surgical events, or other logistical reasons. Patients could complete the remaining cycles of treatment upon resolution of adverse events or within 3 weeks of the scheduled interruption.

Lenvatinib and pembrolizumab (Lenvima and Keytruda)	July 12, 2022	pERC recommends that lenvatinib combined with pembrolizumab be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease only if the following conditions are met.
		• Treatment with LEN-PEM should only be reimbursed when initiated in adults (18 years or older) with advanced (not amenable to curative surgery or radiation) RCC who have not received prior systemic therapy for advanced RCC.
		• Patients should have good performance status.
		• Patients must not have any of the following:
		  ○ active CNS metastases
		  ○ active autoimmune disease
		• Discontinuation should be based on a combination of clinical/radiological progression and significant adverse events potentially related to LEN-PEM.
		• Pembrolizumab should be reimbursed for a maximum of 35 cycles (for 200 mg dosing) or 18 cycles (for 400 mg dosing) or 2 years, whichever is longer. Lenvatinib can be continued beyond this time.
		• LEN-PEM should be prescribed in an outpatient oncology clinic; treatment should be supervised and/or delivered in institutions with expertise in systemic therapy delivery.
		• LEN-PEM should only be reimbursed when administered in combination.
		• LEN-PEM should be negotiated so that it does not exceed the drug program cost of treatment with the least costly immunotherapy plus TKI regimen reimbursed for the treatment of adult patients with advanced or metastatic RCC with no prior systemic therapy for metastatic RCC regardless of IMDC risk status.
		• The feasibility of adoption of LEN-PEM must be addressed.
		Optimal sequencing guidance:
		• pERC noted that the CLEAR trial did not permit re-treatment at recurrence. However, pERC considered that it would be reasonable to re-administer pembrolizumab (up to 17 additional cycles), without lenvatinib, at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of relapse, but only if the treatment was discontinued before disease progression or disease progression occurred during a

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		pembrolizumab treatment break. This would be consistent with pERC guidance on pembrolizumab for other indications. • pERC considered that this new therapy would be an alternative first-line option and would not change the place in therapy of other drugs, although it may displace them from the market. • pERC expects subsequent lines of therapy after LEN-PEM to be funded in a similar manner as they currently are after AXI-PEM, since the same principles and data apply.
Pembrolizumab (Keytruda) plus axitinib (Inlyta)	April 2, 2020	pERC conditionally recommends the reimbursement of pembrolizumab (Keytruda) plus axitinib for the treatment of patients with advanced renal cell carcinoma (RCC) as first-line treatment if the following conditions are met: • cost-effectiveness being improved to an acceptable level • feasibility of adoption (budget impact) being addressed Eligible patients should be previously untreated in the advanced or metastatic setting and have a good performance status. Pembrolizumab treatment should continue until confirmed disease progression or unacceptable toxicity to a maximum of 35 cycles (approximately 2 years), whichever comes first. Treatment with axitinib should continue until disease progression or unacceptable toxicity. Optimal sequencing guidance: • pERC agreed with the CGP that the benefits of pembrolizumab plus axitinib with respect to OS and PFS were observed in all IMDC risk groups and PD-L1 expression categories, and as such would be a first-line treatment option available to patients with advanced RCC. • pERC agreed with the CGP that patients with non–clear-cell histology and all IMDC groups would be eligible to receive pembrolizumab plus axitinib. • pERC agreed with the clinician input that combination treatment with pembrolizumab plus axitinib would be for patients with previously untreated advanced or metastatic RCC, regardless of the IMDC risk group. pERC also noted that pembrolizumab plus axitinib would not replace nivolumab plus ipilimumab given that nivolumab plus ipilimumab is specific for the intermediate or poor-risk patient population, and the treatment with pembrolizumab plus axitinib is for all IMDC prognostic risk groups. • pERC agreed with the clinician input that treatment options after progression on pembrolizumab plus axitinib would depend on the duration between stopping pembrolizumab plus axitinib and when progression occurs. pERC noted that if the duration is greater than 6 months after pembrolizumab therapy, another PD1 inhibitor may be efficacious. • pERC agreed that patients who stop pembrolizumab after 35 doses without PD or stop pembrolizumab due to having achieved a complete response may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses

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		(approximately one year) upon experiencing PD as noted in the Keynote-426 protocol.
Cabozantinib (Cabometyx)	February 20, 2019	pERC recommends the reimbursement of cabozantinib (Cabometyx) in patients with advanced renal cell carcinoma (RCC) who have received at least 1 prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy only if the following condition is met: • cost-effectiveness is improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of cabozantinib. Reimbursement should be for patients who have been previously treated with at least 1 prior VEGFR TKI and treatment should continue until clinically meaningful disease progression or unacceptable toxicity. Optimal sequencing guidance: • The current evidence supports the use of cabozantinib as second- or third-line therapy in patients with clear cell or clear cell component carcinoma with at least 1 prior TKI, but could have had exposure to other therapies, including prior immunotherapy or mTOR inhibitor. pERC noted that the number of patients who have previously been treated with an mTOR inhibitor will only be few. • pERC agreed with CGP that patients currently on everolimus and who have not had disease progression should not switch to cabozantinib but rather should wait until disease progression. This is based on clinicians' desire to optimize treatment options available and to keep treating a patient with a drug they are tolerating well. • pERC noted that patients with non–clear cell carcinoma are treated according to clear cell cancer guidelines, and it is expected that cabozantinib will have activity in non–clear cell RCC. Cabozantinib should therefore be made available to patients with non–clear cell histology. Therefore, pERC agreed that it is reasonable to generalize the METEOR trial results to patients with non–clear-cell RCC. • pERC agreed that first-line use of cabozantinib is out of scope for the current review. In the absence of evidence to confirm the efficacy and safety of cabozantinib in the first-line setting, pERC does not support the use of cabozantinib in patients who are intolerant to first-line VEGFR TKI.
Nivolumab and ipilimumab (Opdivo and Yervoy)	November 1, 2018	pERC recommends the reimbursement of nivolumab (Opdivo) plus ipilimumab (Yervoy) in patients with intermediate or poor-risk advanced renal cell carcinoma (RCC) based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria only if the following condition is met: • cost-effectiveness is improved to an acceptable level. If the aforementioned condition cannot be met, pERC does not recommend reimbursement of nivolumab plus ipilimumab. Eligible

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		patients should be previously untreated in the metastatic setting and have a good performance status. Treatment should continue until disease progression or unacceptable toxicity. Optimal sequencing guidance: • pERC noted feedback from the Clinical Guidance Panel clarifying that patients with non–clear cell RCC are managed the same way as patients with clear cell RCC. pERC therefore agreed that it is reasonable to generalize the CheckMate214 trial results to patients with non–clear cell RCC. • pERC agreed that patients who have already been treated with an immunotherapy agent in the metastatic setting should not be eligible for reimbursement.
Axitinib (Inlyta)	June 29, 2017 (Revised recommendation) March 7, 2013 (Initial recommendation)	**Revised Recommendation** Following a Request for Advice, pERC recommends reimbursement of axitinib (Inlyta) as a second-line treatment option for patients with metastatic RCC of clear cell histology after failure of prior systemic therapy with either a cytokine or VEGF receptor TKI treatment. pERC did not deliberate upon patient values, adoption feasibility, and cost-effectiveness of axitinib compared with everolimus, as the Request for Advice question submitted by pCODR PAG was specific to the clinical issue. **Initial Recommendation** The pCODR Expert Review Committee (pERC) recommends funding axitinib (Inlyta) as a second-line treatment for patients with metastatic clear cell renal carcinoma who, based on the mutual assessment of the treating physician and the patient, are unable to tolerate ongoing use of an effective dose of everolimus or who have a contraindication to everolimus. Funding in a broader patient population was not recommended because there is too much uncertainty that the effectiveness of axitinib is similar to everolimus, due to the lack of direct evidence from randomized comparative trials; however, there is a need for other options amongst patients who are either unable to tolerate or who have a contraindication to everolimus. Therefore, while current evidence is insufficient to recommend funding axitinib broadly, pERC considered that there is a need for axitinib in the subgroup of patients defined above and that this would align with patient values. This recommendation assumes similar pricing of standard dosing of the 2 therapies. pERC did not recommend axitinib as an alternative to everolimus or as a third-line option for patients whose disease progresses while receiving everolimus because there was insufficient clinical trial evidence to support these options.
Nivolumab (Opdivo)	September 1, 2016	pERC recommends reimbursement of nivolumab conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) with disease

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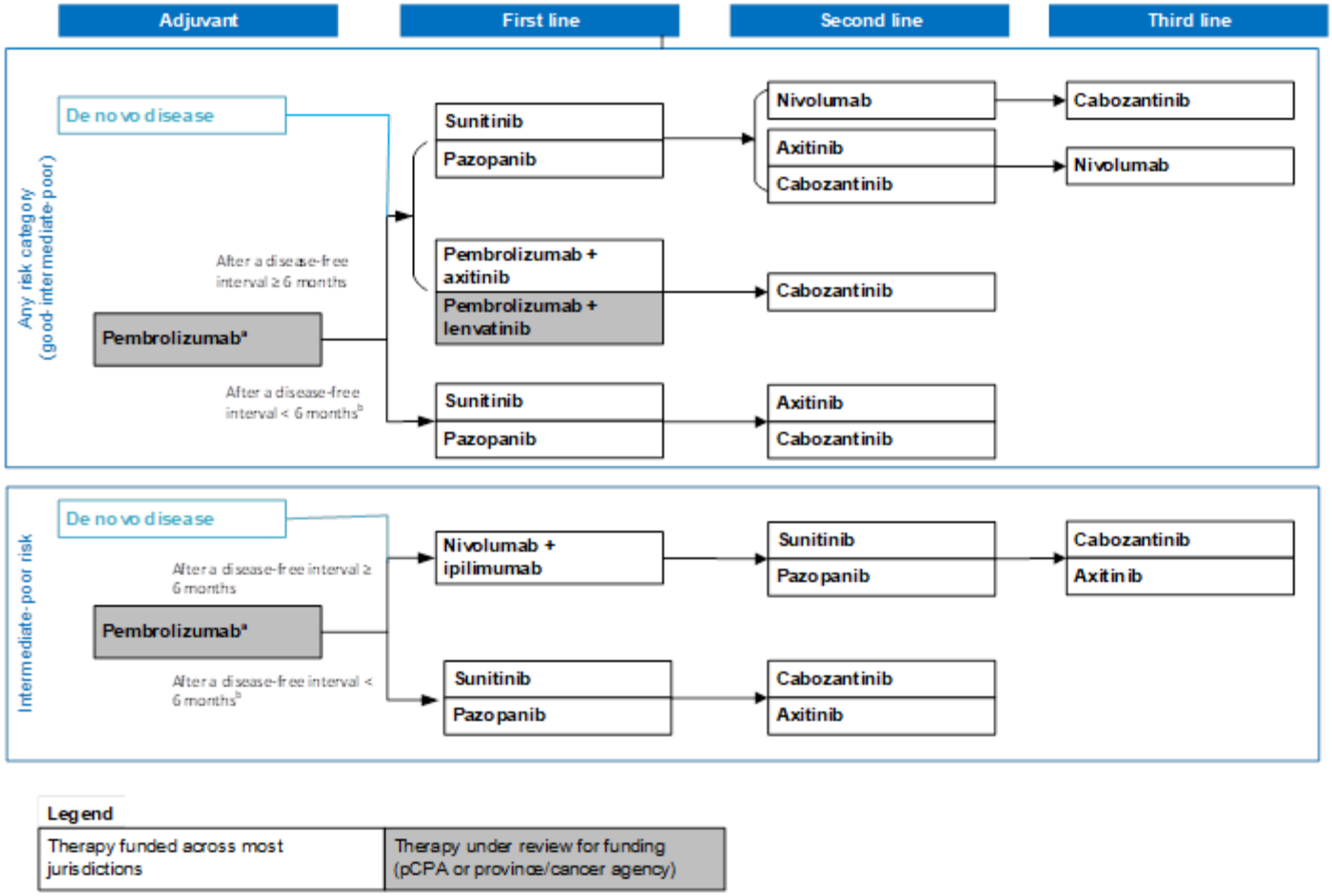
		progression after at least 1 prior anti-angiogenic systemic treatment and who have a good performance status. Treatment should continue until disease progression or unacceptable toxicity. Optimal sequencing guidance: • pERC noted that there is no evidence for the use of nivolumab in the first-line setting, as this was out of the scope of this review. There are, however, ongoing phase III trials evaluating the efficacy and safety of nivolumab in the first-line setting, which can help inform a reimbursement decision. Similarly, the input recognized that there are many treatments available for mRCC in the second-line setting and beyond; thus, a national guideline for the sequencing of these treatments may be helpful.
Pazopanib (Votrient)	August 29, 2013	The pCODR Expert Review Committee (pERC) recommends funding pazopanib hydrochloride (Votrient) as a first-line treatment for patients with advanced or metastatic clear cell renal carcinoma and good performance status. Optimal sequencing guidance: • pERC noted there is no clinical trial evidence to support use of pazopanib if patients experience disease progression on sunitinib while everolimus is an evidence-based treatment option in this patient population. Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from pCODR's Provincial Advisory Group and patient advocacy groups indicating that with the availability of pazopanib in the first-line setting, the appropriate use of second-line treatments such as everolimus, which have only been evaluated after use of first-line sunitinib, is uncertain. • pERC noted that while this is an important consideration, there is no evidence available on the sequential use of treatments for advanced or metastatic clear cell renal carcinoma after pazopanib has been received in the first-line setting. Therefore, pERC considered that the optimal sequencing of these treatments is still unknown and pERC was unable to make an informed recommendation on this issue. However, pERC recognized that provinces will need to address this issue upon implementation of pazopanib funding in the first-line setting and noted that collaboration among provinces to develop a common approach would be of value.

AXI-PEM = axitinib plus pembrolizumab; CGP = clinical guidance panel; CNS = central nervous system; LEN-PEM = Lenvatinib plus pembrolizumab; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; mRCC = metastatic renal cell carcinoma; mTOR = mammalian target of rapamycin; OS = overall survival; PAG = provincial advisory group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; pCODR = pan-Canadian Oncology Drug Review; PD = progressive disease; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression free survival; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Renal Cell Carcinoma



pCPA = pan-Canadian Pharmaceutical Alliance.
Note: The provisional funding algorithm (except for the adjuvant setting) applies to all renal cell carcinoma histologies.
[a] Clear cell renal cell carcinoma at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
[b] Patients who experience disease progression fewer than 6 months from completion of adjuvant pembrolizumab do not qualify for any further immunotherapy in the metastatic setting.

Description of the Provisional Funding Algorithm

Patients in the Adjuvant Setting Following Nephrectomy or Nephrectomy and Resection of Metastatic Lesions

Available treatment options for the adjuvant setting with clear cell RCC include pembrolizumab, which is for adult patients at intermediate-high or high risk of recurrence following nephrectomy alone or following nephrectomy with resection of metastatic

lesions. Pembrolizumab is under consideration for funding by jurisdictions. Intermediate-high risk and high risk are defined by pathological tumour, node, metastasis per the Fuhrman grading status as described under the Additional Remarks section.

Patients in the Advanced or Metastatic Setting of RCC

Available treatment options for advanced or metastatic RCC depend on the patient's risk category (i.e., good, intermediate, or poor) according to the International Metastatic RCC Database Consortium (IMDC) prognostic model classification and prior use with pembrolizumab in the adjuvant setting. The provisional funding algorithm applies to all RCC histologies in the advanced or metastatic setting.

Patients in Any Risk Category

Sunitinib, pazopanib, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib are the treatment options available in the first-line setting for patients with advanced or metastatic RCC.

For patients who have de novo metastatic disease or are 6 months past their last treatment with adjuvant pembrolizumab, the options include sunitinib or pazopanib in the first-line setting. Nivolumab, axitinib, or cabozantinib are available second-line options if a patient's disease progresses. Third-line treatment options include cabozantinib (for patients who received nivolumab as a second-line treatment) and nivolumab (for patients who received axitinib or cabozantinib as second-line treatments).

In this setting, patients may also receive pembrolizumab plus axitinib or pembrolizumab plus lenvatinib in the first-line settling. In these scenarios, cabozantinib is available as a second-line treatment option if their disease progresses. Patients who complete 2 years of pembrolizumab treatment without disease progression or discontinue pembrolizumab due to complete response may receive re-treatment with pembrolizumab for up to 17 additional cycles upon disease progression.

Note that patients who experience disease progression less than 6 months from completion of adjuvant pembrolizumab do not qualify for any further immunotherapy in the metastatic setting. As such, the first-line options in the metastatic setting include sunitinib and pazopanib. The subsequent second-line options if there is disease progression include axitinib and cabozantinib.

Patients in the Intermediate- or Poor-Risk Category

For patients who have de novo metastatic disease or are 6 months past their last treatment with adjuvant pembrolizumab, nivolumab plus ipilimumab is also available as a first-line treatment option for patients who fall under the intermediate- or poor-risk categories, according to the IMDC risk prognostic model classification. Sunitinib or pazopanib are available in the second-line setting for patients whose disease progresses, while cabozantinib or axitinib are available third-line treatments.

Note that patients who experience disease progression less than 6 months from completion of adjuvant pembrolizumab do not qualify for any further immunotherapy in

the metastatic setting. As such, the first-line options in the metastatic setting include sunitinib and pazopanib. The subsequent second-line options if there is disease progression include axitinib and cabozantinib.

Additional Remarks

Intermediate-high risk, high risk, or M1 NED are defined by pathological tumour, node, metastasis; Fuhrman grading status; and presence of sarcomatoid features, as the following:

- Intermediate-high risk RCC:
  - pT2, grade 4 or sarcomatoid, N0, M0
  - pT3, any grade, N0, M0
- High-risk RCC:
  - pT4, any grade, N0, M0
  - pT any stage, any grade, N+, M0
- M1 NED RCC:
  - patients with a primary kidney tumour and solid, isolated, soft tissue metastases that could be completely resected at the time of nephrectomy (synchronous) or 1 year or less from nephrectomy (metachronous)