CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Renal cell carcinoma

This report supersedes the CADTH Provisional Funding Algorithm Report for renal cell carcinoma dated January 2023.

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

February 2024

Background

Following a request from jurisdictions, CADTH 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:

- CADTH pan-Canadian Oncology Drug Review (pCODR) 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 status. 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 (RCC) 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 RCC.

Jurisdictional cancer drug programs requested an update to this rapid algorithm report in October 2022 to incorporate the CADTH recommendation for pembrolizumab (Keytruda), and in November 2023 to incorporate the CADTH recommendation for cabozantinib (Cabometyx).

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
First-line setting		
Cabozantinib (Cabometyx) in combination with nivolumab	November 27, 2023	The CADTH pCODR Expert Review Committee (pERC) recommends that cabozantinib in combination with nivolumab be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease only if the following conditions are met: 1. Adults (18 years or older) with all of the following: 1.1. advanced or metastatic RCC 1.1.1. advanced RCC is defined as not amenable to curative surgery or radiation therapy 1.2. have not received prior systemic therapy for advanced RCC. 2. Patients should have good performance status. 3. Patients must not have any of the following: 3.1. active central nervous system metastases 3.2. active autoimmune disease. 4. Reimbursement of cabozantinib-nivolumab should continue until disease progression or unacceptable toxicity. Nivolumab should continue for a maximum of 2 years; cabozantinib can be continued as monotherapy beyond this time. 5. Cabozantinib-nivolumab should be prescribed by a clinician with expertise in treating RCC in an outpatient oncology clinic. 6. Cabozantinib-nivolumab should only be reimbursed when administered in combination. 7. Nivolumab should be reimbursed for a maximum of 2 years. Cabozantinib can be continued beyond this time. 8. Cabozantinib should be negotiated so that the total cost when used in combination with nivolumab does not exceed the drug program cost of treatment with the least costly reimbursed immunotherapy plus TKI or double immunotherapy regimen for the treatment of advanced or metastatic RCC. 9. The feasibility of adoption of cabozantinib in combination with nivolumab must be addressed. **Guidance on sequencing:** Cabozantinib-nivolumab is an additional first-line treatment option. The clinical expert did not indicate circumstances in which cabozantinib-nivolumab would be a preferred first-line option over pembrolizumab-axitinib, pembrolizumab-lenvatinib, or ipilimumab-nivolumab. The clinical expert noted that both ipilimumab-nivolumab and pembrolizumab-axitinib have more obvious sequencing strategies, and

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		therefore the clinical expert indicated these treatment options would be preferred as first-line therapies over cabozantinib-nivolumab, where a clear second-line and beyond strategy is not yet apparent. In addition, it would be reasonable to readminister nivolumab only up to 1 year, with or without cabozantinib. Re-treatment with nivolumab should be at the discretion of the treating physician for patients who have discontinued nivolumab at the time of relapse and only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.
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 renal cell carcinoma (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: 1. Adjuvant treatment with pembrolizumab should only be reimbursed when initiated in adult patients who have all of the following: 1.1. histologically confirmed diagnosis of RCC with a clear-cell component, with or without sarcomatoid features 1.2. no prior systemic therapy for advanced RCC 1.3. intermediate-high risk or high risk of recurrence after nephrectomy, or M1 NED following nephrectomy and resection of metastatic lesions 1.4. 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. 2. Patients should have a good performance status. 3. Treatment with pembrolizumab should be initiated within 12 weeks of complete resection. 4. Pembrolizumab should be discontinued upon the occurrence of any of the following: 4.1. 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 4.2. unacceptable toxicity 4.3. 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. 5. Patients should be assessed for disease recurrence, according to the criteria listed in Condition 4.1, every 3 to 6 months. 6. Pembrolizumab should be prescribed by clinicians with experience and expertise in treating RCC. The treatment should be supervised and delivered in specialized clinics with expertise in systemic therapy and immunotherapy delivery. 7. Pembrolizumab can be continued for an equivalent of 1 year (12 months) of treatment, i.e., a maximum of 1 of the following:

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		7.1. 17 cycles if administered at a dosage of 200 mg IV every 3 weeks 7.2. 9 cycles if administered at a dosage of 400 mg IV every 6 weeks. 8. Pembrolizumab should not be reimbursed when used in combination with other adjuvant anticancer drugs. 9. A reduction in price. 10. The feasibility of adoption of pembrolizumab must be addressed.
Lenvatinib (Lenvima) In combination with Pembrolizumab (Keytruda)	July 12, 2022	The CADTH pCODR Expert Review Committee (pERC) recommends that lenvatinib (LEN) combined with pembrolizumab (PEM) 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: 1. 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. 2. Patients should have good performance status. 3. Patients must not have any of the following: 3.1. active CNS metastases 3.2. active autoimmune disease. 4. Discontinuation should be based on a combination of clinical/radiological progression and significant adverse events potentially related to LEN-PEM. 5. PEM 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. LEN can be continued beyond this time. 6. 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. 7. LEN-PEM should only be reimbursed when administered in combination. 8. 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. 9. The feasibility of adoption of LEN-PEM must be addressed. **Guidance on sequencing:** It would be reasonable to readminister PEM (up to 17 additional administrations of 200 mg), with or without LEN, at the discretion of the treating physician for patients who have discontinued PEM at the time of relapse, only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break. pERC noted that no switching should be required if a patient is responding adequately, although it may depend on the therapy a patient is currently receiving. Switching should be allowed for toxicity reasons as long as the patient has not progressed on the previous treatment or if the patient cannot tolerate an adequate dose of a regimen. Clinician judgment should be

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		exercised. 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 because the same principles and data apply.
Pembrolizumab (Keytruda) In combination with axitinib (Inlyta)	April 2, 2020	The CADTH pCODR Expert Review Committee (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. pERC made this recommendation because it was satisfied that there is a net clinical benefit of pembrolizumab plus axitinib compared with sunitinib based on statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) with manageable toxicities. pERC concluded that the combination of pembrolizumab plus axitinib aligns with patient values in that it offers an improvement in overall survival, delays disease progression, and it provides patients with an effective treatment option with manageable side effects. pERC concluded that at the submitted price, pembrolizumab plus axitinib cannot be considered cost-effective compared with sunitinib. pERC also highlighted that the potential budget impact of pembrolizumab may be underestimated and could be substantial for this small patient population. **Optimal sequencing of available therapies after progression on pembrolizumab plus axitinib:** pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with pembrolizumab plus axitinib. pERC also noted that patients who progress on pembrolizumab plus axitinib are unlikely to be treated with another immunotherapy and may be offered other approved targeted drugs available in the second-line or be enrolled in a clinical trial. **Guidance on sequencing:** pERC agreed with the Clinical Guidance Panel (CGP) that patients who have started first-line treatment and have not yet progressed should not be switched to pembrolizumab plus axitinib; however, patients who are unable to tolerate treatment early on in the therapy may be able to switch to pembrolizumab plus axitinib upon discussion with the patient and in consultation with the treating physician. pERC agreed that patients who stop pembrolizumab after 35 doses without PD or stop pembrolizumab due to having achieved a complete response

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		may be eligible for a second course of pembrolizumab treatment for up to 17 additional doses (approximately 1 year) upon experiencing PD, as noted in the Keynote-426 protocol. 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-risk 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.
Cabozantinib (Cabometyx)	February 20, 2019	The CADTH pCODR Expert Review Committee (pERC) recommends the reimbursement of cabozantinib in patients with advanced renal cell carcinoma (RCC) who have received at least one prior vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) therapy only if the following condition is met: • cost-effectiveness being 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 one prior VEGFR TKI and treatment should continue until clinically meaningful disease progression or unacceptable toxicity. pERC made this recommendation because the committee was confident of the net clinical benefit of cabozantinib based on statistically significant and clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS) compared with everolimus. pERC noted that while everolimus is no longer a relevant comparator in the Canadian setting, the efficacy and safety outcomes of everolimus are also generalizable to those of axitinib, a relevant comparator in the Canadian setting. Cabozantinib had a manageable toxicity profile, and based on the available data, treatment did not result in a decrement in patients' quality of life (QoL). Cabozantinib aligned with the patient values of maintaining QoL, having a manageable toxicity profile, and being an effective treatment option. In addition, the committee considered evidence provided through an indirect treatment comparison with nivolumab, a relevant comparator in this setting. pERC concluded that there may be a net clinical benefit of cabozantinib compared with nivolumab; however, there is considerable uncertainty concerning the magnitude of benefit due to the lack of direct comparative evidence between cabozantinib and nivolumab. pERC noted that both cabozantinib and nivolumab had manageable safety profiles and individually meet patient needs. The lack of direct comparative evidence limited pERC's conclusions on these factors. pERC concluded that cabozantinib could not be considered cost-effective compared with everolimus and axitinib due to its high cost. pERC further concluded that the cost-effectiveness of cabozantinib is uncertain when

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		compared with nivolumab. **Optimal sequencing of cabozantinib and other therapies unknown:** pERC concluded that the optimal sequencing of cabozantinib and other therapies now available for the treatment of patients with advanced RCC who have received prior therapy is currently unknown. pERC was, therefore, unable to make an evidence-informed recommendation on sequencing of treatment with cabozantinib. pERC noted that jurisdictions may want to consider developing a common approach to treatment sequencing of all available drugs in this setting. **Guidance on sequencing:** 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 one 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 clinical practice guidelines (CPGs) 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, however, agreed that patients intolerant to everolimus should be able to switch to cabozantinib. pERC noted that for patients progressing on first-line therapy with sunitinib or pazopanib, second-line options include nivolumab, everolimus, or axitinib with the latter 2 drugs approved based on a PFS benefit only. pERC acknowledged that everolimus has gone out of use in most settings and has been replaced by axitinib and nivolumab. pERC further noted that sorafenib is a treatment option that is not used in Canada. 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. pERC noted that the CABOSUN trial has now reported results on the use of cabozantinib in the first-line setting. It is, however, unclear if this small phase II trial will form the basis of a request for reimbursement.
Lenvatinib (Lenvima) in combination with everolimus	January 4, 2019	pERC does not recommend reimbursement of lenvatinib in combination with everolimus for the treatment of patients with advanced or metastatic, clear-cell renal cell carcinoma (RCC) following one prior vascular endothelial growth factor (VEGF)-targeted therapy.
Nivolumab (Opdivo) In combination with ipilimumab (Yervoy)	November 1, 2018	The CADTH pCODR Expert Review Committee (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 patients should

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		be previously untreated in the metastatic setting and have a good performance status. Treatment should continue until disease progression or unacceptable toxicity. pERC made this recommendation because it was confident that there is a net clinical benefit of nivolumab plus ipilimumab compared with sunitinib based on statistically significant and clinically meaningful improvements in both overall survival and objective response rate. In addition, there was a manageable toxicity profile compared with sunitinib. pERC concluded that the combination of nivolumab plus ipilimumab aligns with patient values in that it offers an improvement in overall survival and it provides patients with another effective and tolerable treatment option. pERC concluded that, at the submitted price, nivolumab plus ipilimumab is not cost-effective compared with sunitinib. **Optimal sequencing of available therapies after progression on nivolumab plus ipilimumab:** pERC noted that there is currently no clinical trial evidence to inform the optimal sequencing of available treatments following progression on first-line treatment with nivolumab plus ipilimumab. pERC also noted that patients progressing on nivolumab plus ipilimumab are unlikely to be treated with another immunotherapy and may instead be offered a targeted drug or be enrolled in a clinical trial. **Time-limited need for nivolumab plus ipilimumab:** When implementing a funding recommendation for nivolumab plus ipilimumab, jurisdictions may consider addressing the time-limited need for this combination treatment in patients currently receiving a targeted drug in the first-line setting and who have not experienced disease progression. pERC noted that this time-limited access should be for previously untreated patients with intermediate or poor-risk RCC with a clear-cell component and who would otherwise meet the eligibility criteria outlined in this recommendation. **Restart of treatment in patients who progress during a treatment break:** pERC noted that treatment breaks are expected to occur more frequently in clinical practice compared with the CheckMate 214 trial, which did not allow treatment breaks. pERC therefore agreed that it is reasonable to restart treatment in patients who progress during a treatment break, and that the decision to restart should be left to the treating oncologist. The committee further noted that this scenario was not explored in the submitted budget impact analysis model or cost-effectiveness analysis. Therefore, pERC noted that the impact of reinitiating treatment in patients who have had a treatment break and develop disease progression is unknown. The committee agreed that jurisdictions will need to consider the uncertainty in these factors upon implementation. **Guidance on sequencing:** For patients who are currently on first-line treatment with sunitinib or pazopanib and who have not experienced disease progression, pERC acknowledged that there may be instances where the treating oncologist may agree it is reasonable to keep the patient on treatment because patients are responding well and it allows the oncologist to maximize the number of available treatment options for patients. pERC, however, agreed that a

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		decision to continue or switch treatment to nivolumab plus ipilimumab should be made with discussions between the treating oncologist and patient. pERC also recognized that provinces would need to address treatment sequencing upon implementation of nivolumab plus ipilimumab reimbursement and noted that collaboration among provinces to develop a common approach would be of value. Although there was some evidence from the CheckMate 214 trial on outcomes with subsequent agents, pERC agreed that the data were not sufficient to make firm conclusions on treatment sequencing.
Axitinib (Inlyta)	June 29, 2017 (Revised recommendation) March 7, 2013 (Initial recommendation)	**Revised recommendation:** Following a Request for Advice, the CADTH pCODR Expert Review Committee (pERC) recommends reimbursement of axitinib (Inlyta) as a second-line treatment option for patients with metastatic renal cell carcinoma (RCC) of clear-cell histology after failure of prior systemic therapy with either a cytokine or vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) treatment. pERC made this recommendation because multiple sources of retrospective evidence demonstrated that there may not be a difference in clinical benefit (based on overall survival, progression-free survival, and safety) between axitinib and everolimus in patients with disease progression after previous sunitinib treatment. Furthermore, pERC considered that there is no randomized controlled trial (RCT) comparing the clinical benefit of axitinib with that of everolimus in this group of patients, and it is highly unlikely that there will be. Although these retrospective studies had several limitations, pERC was satisfied that the results from these multiple sources demonstrated consistent outcomes, and concluded that axitinib is a reasonable treatment alternative to everolimus as a second-line treatment for patients with metastatic RCC. **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 among 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.

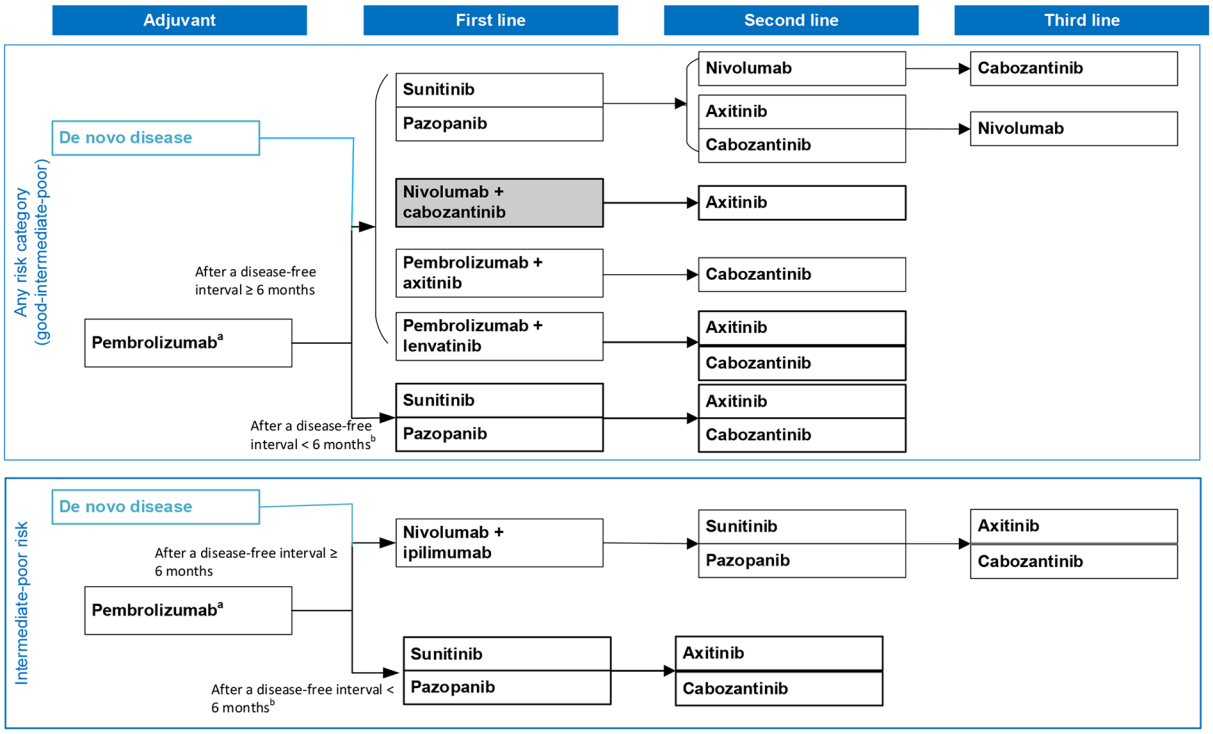
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Nivolumab (Opdivo)	September 1, 2016	The CADTH pCODR Expert Review Committee (pERC) recommends reimbursement of nivolumab conditional on the cost- effectiveness being improved to an acceptable level. Reimbursement should be for the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) with disease progression after at least one prior anti- angiogenic systemic treatment and who have a good performance status. Treatment should continue until disease progression or unacceptable toxicity. The committee made this recommendation because it was satisfied that there is a net clinical benefit with nivolumab compared with everolimus based on statistically significant and clinically meaningful improvements in overall survival and objective response rate and a meaningful improvement in the toxicity profile. pERC also agreed that nivolumab aligned with patient values. The committee concluded that, at the submitted price, nivolumab is not cost-effective in patients with previously treated advanced or metastatic RCC. pERC also noted that there is a potential for a substantial budget impact with nivolumab. **Time-limited need for nivolumab:** At the time of implementing a funding recommendation for nivolumab, jurisdictions may consider addressing the time-limited need for nivolumab for those patients who are currently receiving treatment with everolimus and who have not had disease progression. pERC noted that this time-limited access should be for patients with clear-cell and non–clear-cell histology, who have a good performance status, have had at least one prior treatment, and who would otherwise meet the eligibility criteria of the CheckMate 025 study. **Optimal sequencing of nivolumab and other therapies unknown:** PERC concluded that the optimal sequencing of nivolumab and other treatments now available for the treatment of patients with advanced or metastatic RCC who have had at least one prior treatment is unknown. pERC was therefore unable to make an evidence-informed recommendation on sequencing. However, pERC recognized that provinces would need to address this issue upon implementation of nivolumab reimbursement and noted that collaboration among provinces to develop an evidence-based guideline would be of value.
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. pERC made this recommendation because, based on 2 randomized studies directly comparing pazopanib and sunitinib, the efficacy of the 2 therapies appears similar, the toxicity profiles of the 2 therapies differ, and there is a need for patients to have other treatment options. In addition, pazopanib is cost-effective relative to sunitinib, assuming similar efficacy, standard dosing and the current list prices of the 2 therapies. **Sequencing treatments after first-line pazopanib:** There is currently no evidence available on the sequential use of treatments after pazopanib has been used in the first-line setting for advanced or metastatic clear-cell renal carcinoma. Therefore, pERC considered that the optimal sequencing of these treatments is still unknown and pERC was unable to make an informed recommendation on the sequencing of other

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		treatments following first-line pazopanib. However, pERC recognized that provinces will need to address this issue upon implementation of pazopanib funding and noted that collaboration among provinces to develop a common approach would be of value.
Pazopanib (Votrient)	January 5, 2012	The pCODR Expert Review Committee (pERC) recommends funding pazopanib hydrochloride (Votrient) for patients with advanced or 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 sunitinib. Funding in a broader patient population was not recommended because there is too much uncertainty, due to the lack of direct evidence from randomized comparative trials, that the effectiveness of pazopanib is similar to sunitinib; however, there is a need for other options among patients unable to tolerate sunitinib. Therefore, while current evidence is insufficient to recommend funding broadly, from a clinical perspective, it suggests that pazopanib could have similar efficacy, better tolerability and may be cost-effective relative to sunitinib, assuming similar pricing and standard dosing of the 2 therapies. This led pERC to recommend pazopanib for the defined population of patients who are unable to tolerate sunitinib.

AXI = axitinib; CNS = central nervous system; CPG = clinical practice guideline; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; LEN = lenvatinib; M1 = disease spread to other organs; mTOR = mammalian target of rapamycin; NED = no evidence of disease; OS = overall survival; pCODR = CADTH pan-Canadian Oncology Drug Review; PD = programmed death ligand; PEM = pembrolizumab; pERC = pCODR Expert Review Committee; PFS = progression-free survival; QoL = quality of life; RCC = renal cell carcinoma; RCT = randomized controlled trial; TKI = tyrosine kinase inhibitor; 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 less 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. Intermediate-high risk and high risk are defined by pathological tumour, node, and metastasis per the Fuhrman grading status, as described in 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, cabozantinib plus nivolumab, pembrolizumab plus axitinib, or pembrolizumab plus lenvatinib are the treatment options available in the first-line setting for patients with advanced or metastatic RCC. Cabozantinib plus nivolumab is under review for funding.

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 setting. 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 1 year upon disease progression with or without axitinib or lenvatinib. Note that if the patient has progressed while on axitinib or lenvatinib, re-treatment would be limited to monotherapy with pembrolizumab (for up to 1 year).

In this setting, patients also have the option to receive cabozantinib plus nivolumab in the first-line setting with the option of axitinib as second-line option with disease progression. Cabozantinib plus nivolumab is under review for funding. It would be reasonable to readminister nivolumab only up to 1 year, with or without cabozantinib. Re-treatment with nivolumab should be at the discretion of the treating physician for patients who have discontinued nivolumab at the time of relapse and only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break. Note that if the patient has progressed while on cabozantinib, re-treatment should be limited to monotherapy with nivolumab (for up to 1 year).

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-Risk 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-risk 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 disease spread to other organs (M1) no evidence of disease (NED) RCC is defined by pathological tumour (pT), node (N), and metastasis (M); Fuhrman grading status; and presence of sarcomatoid features, as follows:

- for intermediate-high-risk RCC:
  - pT2, grade 4 or sarcomatoid, N0, M0
  - pT3, any grade, N0, M0
- for high-risk RCC:
  - pT4, any grade, N0, M0
  - pT any stage, any grade, N+, M0
- for 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).

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