



CADTH Reimbursement Recommendation

Cabozantinib (Cabometyx)

Indication: Cabozantinib, in combination with nivolumab, is indicated for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma.

Sponsor: Ipsen Biopharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions



Summary

What Is the CADTH Reimbursement Recommendation for Cabometyx in Combination With Opdivo?

CADTH recommends that Cabometyx in combination with Opdivo be reimbursed by public drug plans for the treatment of adults with advanced or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease if certain conditions are met.

Which Patients Are Eligible for Coverage?

Cabometyx in combination with Opdivo should be covered in patients aged 18 years and older with RCC that is not amenable to curative surgery or radiation therapy, or has spread to other organs; who have not received prior cancer treatment targeting the entire body for advanced RCC; and who are in relatively good health (i.e., have good performance status). Cabometyx in combination with Opdivo should not be reimbursed to treat patients who have active tumours in the brain or spinal cord from the cancer spreading or active autoimmune disease.

What Are the Conditions for Reimbursement?

Cabometyx in combination with Opdivo should be reimbursed if prescribed by a clinician with expertise in treating RCC in an outpatient oncology clinic or institution and the total drug cost of Cabometyx in combination with Opdivo does not exceed the total drug cost of the lowest-cost alternative combination regimen.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that people with advanced or metastatic RCC treated with Cabometyx in combination with Opdivo experienced a delay in the spread of cancer and lived longer compared to those who were treated with sunitinib.

Based on CADTH's assessment of the health economic evidence, Cabometyx in combination with Opdivo does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Cabometyx in combination with Opdivo than for alternative combination regimens.

Based on public list prices, Cabometyx in combination with Opdivo is estimated to cost the public drug plans approximately \$8 million over the next 3 years.



Summary

What Is RCC?

RCC is a cancer that begins from the lining of the kidney tubules, the main function of which is to filter and clean blood. People with advanced or metastatic RCC have cancer that has spread to other organs or body parts, such as the bones, adrenal glands, brain, and liver.

Unmet Needs in RCC

Patients with advanced RCC expressed a need for alternative treatment options that can stop disease progression and improve health outcomes and quality of life.

How Much Does Cabometyx Cost?

Treatment with Cabometyx is expected to cost \$8,436 per patient per 28-day cycle and \$17,823 per patient per 28-day cycle when in combination with Opdivo.

Recommendation

The CADTH pan-Oncology Drug Review Expert Review Committee (pERC) recommends that cabozantinib plus nivolumab be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC who have had no prior systemic therapy for metastatic disease only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

One multicentre, randomized, open-label, phase III trial (CheckMate 9ER, N = 651) demonstrated that treatment with cabozantinib plus nivolumab resulted in added clinical benefit in progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) compared with sunitinib in adults with advanced or metastatic RCC of all International Metastatic RCC Database Consortium (IMDC) risk groups who have not received prior treatment. The hazard ratio (HR) for PFS was 0.51 (95% confidence interval [CI], 0.41 to 0.64), representing a 49% reduction in the risk of PFS with cabozantinib plus nivolumab compared with sunitinib at any particular time point. The HR for OS was 0.60 (98.89% CI, 0.40 to 0.89), representing a 40% reduction in the risk of death with cabozantinib plus nivolumab compared with sunitinib at any particular time point. For ORR, the between-group difference was 28.6% (95% CI, 21.7 to 35.6) and the estimated odds ratio between groups was 3.52 (95% CI, 2.51 to 4.95; $P < 0.0001$) in favour of cabozantinib plus nivolumab. Although pERC was unable to draw definitive conclusions regarding the effects of cabozantinib plus nivolumab on health-related quality of life (HRQoL) compared to sunitinib due to the absence of formal statistical testing and the open-label design of the trial, they noted that the descriptive assessments suggest HRQoL was maintained with cabozantinib plus nivolumab. Due to limitations of the indirect treatment comparisons, pERC was unable to draw definitive conclusions on the relative efficacy of cabozantinib plus nivolumab compared to other combination therapies currently reimbursed for the treatment of RCC in this patient population in Canada.

Patients indicated that there is a need for additional treatment options that can stop disease progression, improve overall outcomes, and improve HRQoL. pERC concluded that cabozantinib plus nivolumab provides another effective treatment option that delays disease progression, improves OS, and potentially maintains HRQoL, and thus meets some of the needs identified by patients.

At the sponsor-submitted price for cabozantinib and publicly listed price for all other drugs, cabozantinib plus nivolumab was more costly than currently funded comparator regimens. As there is no evidence to suggest cabozantinib plus nivolumab is more effective than other immunotherapy plus tyrosine kinase inhibitor (TKI) or double immunotherapy regimens indicated as first-line treatment of adults with advanced or metastatic RCC, the total drug cost of cabozantinib plus nivolumab should not exceed the total drug cost of the lowest-cost alternative combination regimen.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (18 years or older) with all of the following: <ul style="list-style-type: none"> 1.1. advanced OR metastatic RCC <ul style="list-style-type: none"> 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. 	Evidence from the CheckMate 9ER trial demonstrated a clinical benefit in patients with these characteristics.	Patients with non-clear cell histology may be treated in the same manner as those with clear cell histology due to the absence of standard treatment options for patients with non-clear cell histology. Patients can be treated if they received adjuvant or neoadjuvant therapy at least 6 months prior and had no previous tyrosine kinase inhibitor therapy.
2. Patients should have good performance status.	Patients with a KPS of $\geq 70\%$ were included in the CheckMate 9ER trial.	Treating patients with a KPS of $< 70\%$ may be at the discretion of the treating clinician.
3. Patients must not have any of the following: <ul style="list-style-type: none"> 3.1. active central nervous system metastases 3.2. active autoimmune disease. 	The CheckMate 9ER trial excluded patients with active CNS metastases and autoimmune disease; therefore, there is no evidence to suggest these patients will benefit from treatment with cabozantinib + nivolumab.	Patients with treated or stable CNS metastases should be eligible for treatment. Treatment of patients with autoimmune disease may be at the discretion of the treating physician.
Discontinuation		
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.	Consistent with clinical practice, patients from the CheckMate 9ER trial discontinued treatment upon progression or unacceptable toxicity. Patients in the CheckMate 9ER trial were treated with nivolumab for a maximum of 2 years.	—
Prescribing		
5. Cabozantinib + nivolumab should be prescribed by a clinician with expertise in treating RCC in an outpatient oncology clinic.	This will ensure that cabozantinib + nivolumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
6. Cabozantinib + nivolumab should only be reimbursed when administered in combination.	There is no data supporting the efficacy and safety of cabozantinib + nivolumab when used in combination with additional anticancer drugs, or when either component is initially used as monotherapy for the first-line treatment of advanced or metastatic RCC.	As stated in condition 4, cabozantinib can continue as monotherapy after the 2 years of nivolumab.

Reimbursement condition	Reason	Implementation guidance
7. Nivolumab should be reimbursed for a maximum of 2 years. Cabozantinib can be continued beyond this time.	Patients in the CheckMate 9ER trial were treated with nivolumab for a maximum of 2 years.	It would be reasonable to readminister nivolumab up to 1 year, with or without cabozantinib, at the discretion of the treating physician for patients who have discontinued nivolumab at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break.
Pricing		
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.	There is insufficient evidence to justify a cost premium for cabozantinib + nivolumab over the least expensive immunotherapy plus TKI or double immunotherapy regimen reimbursed for the treatment of advanced or metastatic RCC.	—
Feasibility of Adoption		
9. The feasibility of adoption of cabozantinib + nivolumab must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate.	—

CNS = central nervous system; KPS = Karnofsky performance status; OS = overall survival; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

Discussion Points

- pERC discussed the generalizability of the trial results to all RCC histologies (e.g., clear cell and non-clear cell variants). pERC noted that patients with non-clear cell tumours were excluded from the CheckMate 9ER trial. However, pERC expected all histologies to respond to cabozantinib plus nivolumab, as they do with other therapies in this setting. Therefore, tumour histology should not be a limiting factor for reimbursement of this regimen, and all advanced RCC histologies should be covered.
- pERC noted that other combination therapies, such as pembrolizumab-axitinib, pembrolizumab-lenvatinib, and nivolumab-ipilimumab, are currently available for advanced and metastatic RCC. pERC discussed the results of the indirect treatment comparison reviewed by CADTH, which compared cabozantinib plus nivolumab to other combination therapies. Interpretation of the sponsor-submitted network meta-analyses (NMA) was limited due to methodological issues, such as connections being limited to 1 study, concerns with potential bias due to effect modifiers, trial population heterogeneity, and lack of reporting of study quality assessment. Due to these limitations in the NMA, approaches

used and uncertainty in their estimates, pERC could not draw definitive conclusions on the relative efficacy and safety of cabozantinib plus nivolumab versus combination therapies. However, pERC agreed with the clinical expert that cabozantinib plus nivolumab would provide a viable alternative treatment option for patients who are candidates for first-line combination therapy.

- pERC noted that patients with advanced RCC identified a need for alternative treatment options with a different or better toxicity profile and improved outcomes across all IMDC risk groups. pERC considered the safety profile of cabozantinib plus nivolumab to be manageable, albeit more burdensome, than sunitinib. pERC could not draw conclusions regarding the safety profile of cabozantinib plus nivolumab compared to other combination therapies due to limitations of the indirect evidence, although it considered the safety profile of cabozantinib plus nivolumab to be similarly manageable to other combination therapies.
- pERC noted that as cabozantinib monotherapy is currently reimbursed as a second-line and third-line therapy for patients with advanced or metastatic RCC, use of cabozantinib plus nivolumab as a first-line treatment for RCC would impact subsequent treatment sequencing. Furthermore, it is unclear which treatments would be appropriate as second-line or third-line treatment options. pERC suggested the provisional funding algorithm for advanced or metastatic RCC be updated to address these treatment gaps.

Background

RCC is the most common form of kidney cancer, accounting for approximately 90% of all cases around the world. Approximately 8,100 people in Canada were diagnosed with kidney and renal pelvis cancer in 2022, of which 85% of cases were attributed to RCC. RCCs are further classified into different subtypes based on histology (clear cell, papillary, chromophobe, clear cell papillary, collecting duct, medullary, and unclassified). The clear cell component subtype is the most prevalent form of RCC and represents more than 70% of all RCC cases in practice. More than one-third of cases identified at initial diagnosis have metastatic disease, due to the fact that most patients experience few or no symptoms at earlier stages. Common symptoms consist of flank pain, visible blood in the urine, a noticeable mass in the abdomen, loss of appetite, fatigue, pain, and anemia. Patients who have progressed to an advanced stage of RCC generally face a poor prognosis, with reported 5-year survival rates ranging from 0% to 20% for those with metastatic disease.

Treatment options for untreated advanced clear cell RCC are guided by prognostic risk models, particularly the IMDC risk group classification (i.e., favourable, intermediate, and poor).⁹ Over 80% of patients with metastatic disease are classified as intermediate and poor risk.¹⁰ There is no standard therapy for non-clear cell RCC, and it is generally accepted that patients with non-clear cell histology should be treated similarly to patients with clear cell histology. For patients who fall under the IMDC favourable-risk category, the preferred treatments, according to the Kidney Cancer Research Network of Canada (KCRNC) guidelines, are a combination of immunotherapy and vascular endothelial growth factor receptor (VEGF) TKI.⁹ These include pembrolizumab plus axitinib, pembrolizumab plus lenvatinib or cabozantinib plus nivolumab, with sunitinib or pazopanib as alternative options for patients who have a contraindication to immunotherapy or who are

unable to tolerate combination therapy. For patients who fall under the IMDC intermediate-risk or poor-risk categories, the preferred treatments according to the KCRNC guidelines are ipilimumab plus nivolumab, pembrolizumab plus axitinib, cabozantinib plus nivolumab, or pembrolizumab plus lenvatinib, with sunitinib, pazopanib, or cabozantinib monotherapy as alternative options.⁹

Cabozantinib is approved by Health Canada for the following indication: in combination with nivolumab, for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC. Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. The recommended dose for advanced or metastatic RCC is cabozantinib 40 mg, taken orally once daily, plus nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III randomized clinical trial in patients with advanced or metastatic RCC and 1 sponsor-submitted indirect treatment comparison
- patients' perspectives gathered by 1 patient group, Kidney Cancer Canada (KCC)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 1 clinical specialist with expertise diagnosing and treating patients with advanced or metastatic RCC
- input from 2 clinician groups, the Ontario Health (Cancer Care Ontario) (OH-CCO) Genitourinary Cancer Drug Advisory Committee (GU DAC) and KCRNC
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that responded to CADTH's call for input and from the clinical expert consulted by CADTH for the purpose of this review.

Patient Input

One patient group, KCC, submitted input for this review. KCC reported that patients in Canada do not have access to cabozantinib plus nivolumab; therefore, the group could not gather information on patients' feedback or experiences with this therapy. Their submission was based on a survey of 2,213 respondents, of which 139 were from Canada, including 111 (80%) patients diagnosed with kidney cancer.

From the patients' perspective, there is a need for access to new and effective treatment options that can stop disease progression, control drug resistance, and improve overall outcomes and quality of life. The

patient group indicated that cabozantinib plus nivolumab could fill an unmet need in papillary RCC and for patients with brain metastases, where additional treatment options are needed.

Clinician Input

Input From the Clinical Expert Consulted by CADTH

Unmet Needs

The clinical expert noted that the unmet needs of patients with advanced RCC include reducing side effects, particularly having access to less toxic therapies, and that available treatments do not have curative potential. The expert also noted that the available treatments are considered palliative, and that most patients' disease progresses, and next lines of therapy are sought.

Place in Therapy

The clinical expert noted that cabozantinib plus nivolumab would compete with other first-line options (i.e., single-drug VEGF TKI, TKI-checkpoint inhibitor, or dual checkpoint inhibitor therapy). The expert also indicated that use of cabozantinib plus nivolumab would challenge the existing treatment paradigm as it is unclear what drugs would be effective as second-line treatment after disease progression.

Patient Population

The clinical expert indicated that those with IMDC intermediate-risk or poor-risk prognoses are best suited for cabozantinib plus nivolumab, while patients with IMDC favourable-risk prognosis remain candidates for a single-drug VEGF TKI. The expert also noted that it is not clear from the available data which patients are most likely to respond, although they indicated that it is probable those with the least disease burden are most likely to respond.

Assessing Response to Treatment

The clinical expert noted that measures of response would include radiologic evidence and symptom assessment, conducted every 8 to 12 weeks. Responses include stability of the known sites of disease without worsening of disease-related symptoms and without intolerable side effects.

Discontinuing Treatment

The clinical expert noted that progressive disease should be a definitive indication to discontinue treatment as should significant side effects. The clinical expert also indicated that, in their opinion, there is a need to rule out "pseudoprogression," a common phenomenon that suggests early radiologic progression, by allowing the treatment to continue for at least 1 more assessment time point. The types of side effects that could lead to treatment discontinuation would include severe hypertension, severe diarrhea, severe fatigue, liver dysfunction, and any immune mediated adverse events (IMAEs).

Prescribing Considerations

The clinical expert noted that a medical oncologist with experience managing immunotherapy and TKI therapies should be required to diagnose, treat, and monitor patients who might receive cabozantinib plus nivolumab in designated community settings.

Clinician Group Input

Two clinician groups, OH-CCO's GU DAC and KCRNC, submitted input for this review. Input was provided by 7 clinicians, 3 for OH-CCO and 4 for KCRNC. KCRNC highlighted the need for drug development and increasing clinical trial options for patients with non-clear cell histology, developing biomarkers for predicting response to the treatment, decreasing the attrition of patients, and optimizing treatment for brain metastases. OH-CCO's GU DAC pointed to the lack of further options for refractory disease. Both clinician groups agreed that patients with any IMDC prognostic risk score who have not had treatment would be potentially eligible for systemic treatment with cabozantinib plus nivolumab. The clinician groups indicated that cabozantinib plus nivolumab would be an additional first-line treatment option for patients with advanced RCC, and this combination therapy could potentially address unmet needs for some patients. Both groups indicated that treatment should be discontinued in the case of disease progression or unacceptable toxicity.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process.

The clinical expert consulted by CADTH provided advice on the potential implementation issues raised by the drug programs (refer to [Table 2](#)).

Table 2: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
<p>The trial compared cabozantinib + nivolumab against sunitinib. Currently funded first-line options include pembrolizumab + axitinib (any risk category), ipilimumab + nivolumab (intermediate-risk or poor-risk categories), and single-drug sunitinib or pazopanib. At the time of this input, pembrolizumab + lenvatinib is under negotiation.</p> <p>How does cabozantinib + nivolumab compare to either pembrolizumab + axitinib, pembrolizumab + lenvatinib, ipilimumab + nivolumab, or pazopanib?</p>	<p>The clinical expert noted that, in their opinion, cabozantinib + nivolumab is superior to a first-line single-drug VEGF TKI (sunitinib and pazopanib), and it appears comparable to the other combination therapies listed.</p> <p>pERC was unable to draw conclusions on the comparative efficacy and safety of cabozantinib + nivolumab to other active treatments (including combination therapies and pazopanib), due to limitations of the indirect treatment comparisons.</p>
Considerations for initiation of therapy	
<p>The trial included patients who had 1 previous adjuvant or neoadjuvant therapy for completely resectable RCC, provided the drug did not target VEGF or VEGFR receptors and that recurrence is at least 6 months from the last dose of adjuvant and/or neoadjuvant therapy.</p> <p>Adjuvant pembrolizumab is currently in negotiations. Should patients with prior adjuvant or neoadjuvant therapy be eligible for cabozantinib + nivolumab provided there has been a disease-free interval of 6 months or greater in between?</p>	<p>The clinical expert indicated that patients should be eligible for first-line systemic therapy if they received adjuvant or neoadjuvant therapy at least 6 months prior. The clinical expert noted that there has so far been modest uptake of perioperative systemic therapy in renal carcinoma, given limited evidence of a survival advantage with this treatment.</p> <p>pERC agreed with the clinical expert that it would be reasonable to reinstate treatment if a patient completed or discontinued pembrolizumab in the curative setting without disease progression and had a disease-free interval of 6 months or greater.</p>

Drug program implementation questions	Clinical expert response
<p>Should patients who complete 2 years of nivolumab and experience disease progression or recurrence off nivolumab be eligible for re-treatment with nivolumab? If yes, what is the duration for the nivolumab re-treatment?</p> <p>Should nivolumab re-treatment be given with cabozantinib or can it be given as monotherapy?</p>	<p>The clinical expert noted that there is no clear approach, but believes expert opinion would suggest that a trial with a checkpoint inhibitor (e.g., nivolumab) alone is reasonable if the patient has been off nivolumab for at least 3 to 6 months. If there is a response, treatment should continue until progression or 2 years.</p> <p>pERC noted that the CheckMate 9ER trial did not permit re-treatment at recurrence. However, pERC acknowledged the clinical expert's response and considered that 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.</p>
<p>Should the following patients be considered for cabozantinib + nivolumab:</p> <ul style="list-style-type: none"> • those with stable CNS metastases • those with non-clear cell histology • those with poor performance status? 	<p>The clinical expert indicated that patients with stable CNS metastases were included in the CheckMate 9ER trial and should be eligible for cabozantinib + nivolumab. The trial required a component of clear cell histology, and this criterion should be maintained, although patients with non-clear cell histology are generally treated with the same regimens tested on those with clear cell histology in regular practice. The clinical expert noted that data to support this approach is lacking but some studies have demonstrated that the non-clear cell malignancies respond to these therapies, but to a lesser extent. Cabozantinib + nivolumab should not be used for patients with poor performance status.</p> <p>pERC recommended that patients with non-clear cell histology may be treated in the same manner as those with clear cell histology due to the absence of standard treatment options for patients with non-clear cell histology.</p>
<p>Should the criteria for cabozantinib + nivolumab be similar to that of pembrolizumab + lenvatinib or pembrolizumab + axitinib?</p>	<p>The clinical expert indicated that the criteria should be similar.</p>
Considerations for prescribing of therapy	
<p>PAG would like to inform pERC that jurisdictions will implement weight-based dosing up to a cap for nivolumab, similar to other immunotherapy policies (i.e., 3 mg/kg up to 240 mg every 2 weeks or 6 mg/kg up to 480 mg every 4 weeks).</p>	<p>Comment from the drug plans to inform pERC deliberations.</p>
<p>In the trial, if 1 drug had to be discontinued for reasons other than disease progression, treatment could continue with the other drug.</p>	<p>Comment from the drug plans to inform pERC deliberations.</p>
Generalizability	
<p>Should patients currently receiving an alternative first-line therapy, who have not yet progressed, be eligible to switch to cabozantinib + nivolumab?</p>	<p>The clinical expert noted that given the lack of strong evidence, cabozantinib + nivolumab is better than other first-line options or has a more favourable toxicity profile, so there is no rationale for switching.</p> <p>pERC noted that no switching should be required if a patient is</p>

Drug program implementation questions	Clinical expert response
	responding adequately. 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 exercised.
Funding algorithm	
<p>Cabozantinib + nivolumab would be an alternative first-line option.</p> <p>Under what circumstances would cabozantinib + nivolumab be preferred over pembrolizumab + axitinib, pembrolizumab + lenvatinib, or ipilimumab + nivolumab?</p> <p>What evidence is available to support downstream sequencing after cabozantinib + nivolumab and what should the sequencing look like?</p>	<p>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.</p> <p>The clinical expert noted that both ipilimumab + nivolumab and pembrolizumab + axitinib have more obvious sequencing strategies; therefore, the clinical expert indicated that 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.</p>
System and economic issues	
<p>The cost of cabozantinib + nivolumab should not exceed the drug program cost of the least costly tyrosine kinase inhibitor plus immunotherapy regimen reimbursed for this indication.</p>	<p>Comment from the drug plans to inform pERC deliberations.</p>

CNS = central nervous system; PAG = Provincial Advisory Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; RCC = renal cell carcinoma; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

Clinical Evidence

Pivotal Studies and Randomized Controlled Trial Evidence

Description of Studies

One trial, CheckMate 9ER (N = 651), met the inclusion criteria for the systematic review conducted by the sponsor. The objectives of the CheckMate 9ER trial were to evaluate the efficacy and safety of cabozantinib plus nivolumab versus sunitinib in adults with previously untreated advanced RCC with a clear cell component. Patients had any IMDC prognostic risk score and a Karnofsky performance status score of at least 70 (on a scale from 0 to 100, with lower scores indicating greater disability), and were randomized in a 1:1 ratio stratified by IMDC prognostic risk score, geographic region, and tumour expression of the programmed cell death 1 ligand 1 (PD-L1). Eligible patients were randomized to receive cabozantinib 40 mg, taken orally once daily, plus nivolumab 240 mg IV every 2 weeks or sunitinib 50 mg, taken orally once daily, for 4 weeks, followed by 2 weeks off, per 6-week cycle. The primary outcome was PFS assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumours Version 1.1. (RECIST 1.1), and the secondary outcomes were OS, ORR, and safety. HRQoL measured by the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) and 3-Level EQ-5D visual analogue scale (EQ-5D-3L VAS) questionnaires was included as an exploratory outcome. Key baseline patient characteristics were generally balanced between treatment groups. The population was predominately white (82%) and

male (71% to 77%), with an approximate mean age of 60 years. Most patients had a Karnofsky performance status score of 90 or 100 (74% to 80%) and the majority (approximately 57%) had an intermediate-risk IMDC score. A similar proportion of patients in both groups had prior radiotherapy (14%) or nephrectomy (approximately 70%).

Efficacy Results

PFS by BICR

In total, 335 PFS events had occurred in both groups by interim analysis 1 (data cut-off of March 30, 2020). At a median follow-up of 18.1 months for OS (range, 10.6 to 30.6), the median PFS was 16.6 months (95% CI, 12.5 to 24.9) with cabozantinib plus nivolumab and 8.3 months (95% CI, 7.0 to 9.7) with sunitinib (logrank test $P < 0.001$), with a between-group HR of 0.51 (95% CI, 0.41 to 0.64). The probability of PFS at 9 months was 68.3% (95% CI, 62.6% to 73.2%) and 47.8% (95% CI, 41.7% to 53.6%), respectively. The findings at the interim analysis 2 extended follow-up (data cut-off of June 24, 2021) were consistent with those of interim analysis 1. The results of the sensitivity analyses were consistent with the primary analysis, and the efficacy results were consistent across IMDC prognostic risk categories (favourable, intermediate, and poor risk).

Overall Survival

By interim analysis 1 (data cut-off of March 30, 2020), the median OS was not reached in either group (logrank test $P = 0.001$). An HR of 0.60 (98.89% CI, 0.40 to 0.89) was estimated. The median follow-up for OS was 18.1 months (range, 10.6 to 30.6). OS rates at 9 months were higher in the cabozantinib plus nivolumab group than in the sunitinib group: 89.9% (95% CI, 86.0% to 92.8%) versus 80.5% (95% CI, 75.7% to 84.4%). The findings at the interim analysis 2 extended follow-up (data cut-off of June 24, 2021) were consistent with those of interim analysis 1.

ORR by BICR

By interim analysis 1 (data cut-off of March 30, 2020), the ORR in the cabozantinib plus nivolumab group was 55.7% (95% CI, 50.1% to 61.2%) and 27.1% (95% CI, 22.4% to 32.3%) in the sunitinib group, with a between-group difference of 28.6% (95% CI, 21.7% to 35.6%). The estimated odds ratio between groups was 3.52 (95% CI, 2.51 to 4.95; $P < 0.0001$) in favour of cabozantinib plus nivolumab. The findings at the interim analysis 2 extended follow-up (data cut-off of June 24, 2021) were consistent with those of interim analysis 1.

Health-Related Quality of Life

The exploratory HRQoL outcomes of FKSI-19 total and DRS and EQ-5D-3L VAS scores were assessed at the first interim analysis (data cut-off of March 30, 2020) and were not controlled for multiplicity. Mean changes from baseline through week 91 were generally stable for the cabozantinib plus nivolumab group, whereas patients in the sunitinib group had a trend toward decreased scores, and at times were in excess of the minimum important difference (MID) of 3 points.¹¹ In addition, FKSI-DRS score improved from baseline in patients in the cabozantinib plus nivolumab group, whereas patients in the sunitinib group had a decline from baseline after week 7 through week 91. For EQ-5D-3L VAS, patients in the cabozantinib plus nivolumab group had a trend toward improvement, while patients in the sunitinib group remained relatively stable with a trend

toward decline through week 91. The mean changes from baseline in both groups did not meet the MID of 7¹² through week 91. HRQoL was not assessed at the interim analysis 2 extended follow-up.

Harms Results

At least 1 treatment-emergent adverse event (TEAE) was reported in almost all patients in both treatment groups (99.7% of patients in the cabozantinib plus nivolumab group and 99.1% of patients in the sunitinib group). The most common TEAEs in the nivolumab plus cabozantinib group and sunitinib group were diarrhea (65.3% versus 50%, respectively), palmar-plantar erythrodysesthesia syndrome (40.3% versus 41.9%, respectively), hypertension (38.4% versus 37.5%, respectively), hypothyroidism (36.9% versus 31.6%, respectively), and fatigue (33.8% versus 35.6%, respectively). At least 1 serious adverse event (AE) was reported in 53.1% of patients in the cabozantinib plus nivolumab group and 42.2% of patients in the sunitinib group. The most common serious AE in both groups was malignant neoplasm progression (4.7% and 4.4% in the cabozantinib plus nivolumab and sunitinib groups, respectively). Overall, 37.2% of patients in the cabozantinib plus nivolumab group versus 20.9% in the sunitinib group discontinued treatment due to TEAEs. Deaths were reported in 37.2% of patients in the cabozantinib plus nivolumab group and 45.9% of patients in the sunitinib group. Most deaths were attributed to disease progression in both treatment groups (25.0% with cabozantinib plus nivolumab and 34.7% with sunitinib). Most notable harms occurred in similar percentages of patients in both groups, with hypertension being the most frequently reported notable harm in both study groups (39.7% versus 39.4% in the cabozantinib plus nivolumab and sunitinib groups, respectively). Thrombotic events occurred in 13.4% versus 6.3% of patients treated with cabozantinib plus nivolumab versus sunitinib, respectively. In terms of IMAEs, the cabozantinib plus nivolumab group had a higher incidence compared to the sunitinib group for all IMAEs, with hypothyroidism and/or thyroiditis being the most frequently observed IMAE in the cabozantinib plus nivolumab and sunitinib groups (28.1% and 9.4%, respectively).

Critical Appraisal

CheckMate 9ER was an open-label, phase III, randomized, multicentre trial. The open-label design introduces a potential bias in the assessment of PFS and ORR, and a potential reporting bias of the subjective outcomes of HRQoL and safety. However, this bias was mitigated by use of a BICR for PFS and ORR. Randomization procedures, including stratification by IMDC prognostic risk score, tumour PD-L1 expression, and region, were appropriate and conducted by interactive response technology. In general, the baseline characteristics of the patients appeared balanced between groups, indicating that randomization was successful. To minimize the risk of differential measurement error, the trial performed tumour assessments using RECIST 1.1 criteria and radiographic scans were assessed by BICR. There was low selective reporting bias as the data were analyzed in accordance with the prespecified statistical plan. All interim analyses conducted were planned a priori with appropriately specified alpha spending methods, and secondary outcomes were adjusted for multiplicity. The censoring rules for PFS were prespecified, and sample size and power calculations were based on PFS. All planned outcomes were reported, and the intention-to-treat analysis was conducted for the primary (PFS) and secondary outcomes (OS and ORR). Multiplicity adjustments were not conducted for exploratory outcomes, including the analysis of prespecified subgroups. HRQoL was assessed as an exploratory outcome using the FKSI-DRS and EQ-5D-3L questionnaires. The FKSI-DRS questionnaire

has been validated in patients with RCC with evidence of reliability, responsiveness, and a MID. Although the EQ-5D-3L has been widely used in oncology trials in different cancer populations, it has not been validated in patients with advanced RCC.

The population requested for the reimbursement aligns with the Health Canada indication, and the dosing and administration of cabozantinib plus nivolumab was consistent with the Health Canada–approved product monograph. The clinical expert consulted by CADTH considered the eligibility criteria and baseline characteristics of the CheckMate 9ER trial generalizable to adults with advanced RCC with a clear cell component in the Canadian setting. The expert also noted that sunitinib, an approved treatment option for untreated patients with advanced RCC in Canada, was an appropriate comparator. The trial included outcomes that were important to patients and clinicians. The patient group indicated that stopping disease progression and improving overall outcomes and HRQoL are important to them.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Studies Addressing Gaps in the Evidence in the Pivotal and Randomized Controlled Trial Evidence

No additional studies addressing gaps in the pivotal and randomized controlled trial evidence were submitted by the sponsor.

Indirect Comparisons

One sponsor-submitted NMA was included in the submission to inform the pharmacoeconomic model and to identify indirect comparisons that fill gaps in the evidence for other first-line treatments of interest for advanced RCC. The objective of the NMA was to indirectly compare the efficacy and safety of cabozantinib plus nivolumab to other relevant comparators, including sunitinib, pazopanib, ipilimumab plus nivolumab, axitinib plus avelumab, axitinib plus pembrolizumab, and lenvatinib plus pembrolizumab, in treatment-naive patients with advanced RCC.

Description of NMA

Out of 10 eligible trials, 6 were included in the NMA. The rest were excluded due to a lack of relevant data. In total, 5 different NMA approaches were used to generate estimates for PFS, OS, and AEs. For the purpose of this review, the results of the survival end point meta regression for the prognostic risk NMA, fractional polynomial NMA, and standard NMA for AEs are reported. The survival end point meta regression for the prognostic risk NMA attempted to address some sources of heterogeneity across the studies in the network by including patients in the intermediate-risk and poor-risk categories as a covariate, the fractional polynomial NMA was used to inform the pharmacoeconomic model and attempted to address the violation of the proportional hazards assumption that was identified in most trials, and the standard NMA for AEs was the only NMA approach that reported on safety. The fifth approach (the piecewise exponential NMA) was exploratory and did not attempt to address any additional gaps in the other methods and is therefore not reported in this review.

Efficacy and Harm Results

All the connections within the network were limited to 1 study and the comparisons of interest within the network were limited to indirect estimates only. In general, the estimates across the different NMA approaches varied with wide credible intervals. The survival end point meta regression for the prognostic risk NMA results for PFS favoured cabozantinib plus nivolumab versus the comparators during the observed period from the trial. After 5 years' predictive time horizon, the results favoured nivolumab plus ipilimumab, followed by avelumab plus axitinib and cabozantinib plus nivolumab. The fractional polynomial NMA results for PFS favoured lenvatinib plus pembrolizumab followed by cabozantinib plus nivolumab during the observed period from the trial. After 5 years' predictive time horizon, the results favoured nivolumab plus ipilimumab, followed by cabozantinib plus nivolumab. For OS, the survival end point meta regression for the prognostic risk NMA results favoured axitinib plus pembrolizumab and lenvatinib plus pembrolizumab followed by cabozantinib plus nivolumab during the observed trial period. After 10 years' predictive time horizon, the results favoured ipilimumab plus nivolumab followed by cabozantinib plus nivolumab. The fractional polynomial NMA results for OS favoured lenvatinib plus pembrolizumab, followed by cabozantinib plus nivolumab. After the observed period, the results favoured lenvatinib plus pembrolizumab, followed by axitinib plus pembrolizumab and cabozantinib plus nivolumab. For harms, the results for cabozantinib plus nivolumab were less favourable versus other treatments, with nivolumab plus ipilimumab as most favourable.

Critical Appraisal

The methods used to conduct the systematic literature review were prespecified and appropriate to search databases, select studies, extract data, and assess the quality of the included studies. In total, 5 different NMA approaches were used to generate estimates for PFS, OS, and AEs. However, clear rationale for these approaches was not provided by the sponsor. Out of 10 eligible trials, 6 were included in the NMAs; 4 trials were excluded due to lack of relevant data. The authors noted that the NMAs may have been impacted by these exclusions. Based on quantitative and qualitative assessment, the exchangeability assumption was violated as there were several notable sources of heterogeneity and missing data for potential effect modifiers across the included trials, which further limited the ability to assess heterogeneity across the studies. This included patient histology, disease stage, brain metastases, study drug dosing, and follow-up duration. These sources of heterogeneity were not explored sufficiently in any of the NMA approaches, and none addressed the violation of the exchangeability and proportional hazards assumptions collectively. In addition, risk of bias at the individual study level on effect estimates was not explicitly assessed or discussed. Due to these limitations in the NMA approaches used and uncertainty in their estimates, no definitive conclusions could be drawn on the relative treatment effects of cabozantinib plus nivolumab versus other comparators.

Conclusions

Evidence from 1 phase III open-label randomized controlled trial showed that treatment with cabozantinib plus nivolumab resulted in clinically important improvements in PFS, OS, and ORR compared to sunitinib in adults with previously untreated advanced RCC. These results addressed key treatment outcomes noted

as important by both patients and clinicians. For HRQoL, no definitive conclusions can be drawn due to the exploratory nature of the outcomes and open-label design of the trial. Due to limitations of the indirect treatment comparisons, no conclusions can be drawn on the relative efficacy and safety of cabozantinib plus nivolumab compared to other active treatments.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	Base case: adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC who have not been previously treated (i.e., no restriction by IMDC risk) Key scenario (intermediate or poor risk): adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC with intermediate-risk or poor-risk disease (according to IMDC) who have not been previously treated
Treatment	cabozantinib + nivolumab
Dose regimen	cabozantinib 40 mg once daily plus 240 mg of nivolumab intravenously every 2 weeks for a maximum period of 24 months
Submitted price	cabozantinib 20 mg, 40 mg, and 60 mg: \$301.29 per tablet
Treatment cost	28-day cycle cost for cabozantinib: \$8,436 28-day cycle cost for nivolumab: \$9,327 28-day cycle cost for cabozantinib + nivolumab is \$17,823
Comparators	Base case: sunitinib, axitinib + pembrolizumab, lenvatinib + pembrolizumab, pazopanib Intermediate-risk or poor-risk scenario: ipilimumab + nivolumab, axitinib + pembrolizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs and LYs
Time horizon	Lifetime (45 years)
Key data source	CheckMate 9ER trial (cabozantinib + nivolumab vs. sunitinib) Sponsor-conducted NMA used to inform comparison with rest of comparators
Key limitations	<ul style="list-style-type: none"> PFS and OS in the sponsor's model were informed by an NMA that was associated with uncertainty. There is limited evidence to support a difference between cabozantinib + nivolumab and other combination therapies, which are deemed the most relevant comparators, for these outcomes. The model results are heavily influenced by the choice of parametric assumptions, as the alternative survival estimates derived from the NMA produce different incremental cost and QALY estimates that affect the results observed. The sponsor's time horizon of 45 years was not justifiable in a real-world setting as survival beyond 10 years is exceedingly rare in this patient population. The sponsor applied several assumptions that had an impact on the estimation of drug costs. First,

Component	Description
	<p>the sponsor incorporated an RDI of less than 100% for some comparators and not others. Second, they assumed there would be no wastage of IV therapies; however, some wastage is expected with these drugs. Third, the sponsor assumed a price for lenvatinib that does not align with the least costly option. Overall, these assumptions likely biased drug costs in favour of cabozantinib + nivolumab in comparison with other dual-therapy regimens.</p> <ul style="list-style-type: none"> The proportion of patients receiving subsequent therapies upon progression and the type of subsequent therapy received in the sponsor's model did not align with Canadian clinical practice.
CADTH reanalysis results	<ul style="list-style-type: none"> CADTH undertook reanalyses to address identified limitations by reducing the time horizon to 10 years; incorporating an RDI of 100% for all comparators, assuming wastage of IV medications in single-use vials, revising the price of lenvatinib and other comparator drugs with updated public list prices, and revising the subsequent therapies used to better align with clinical expectations and provincial funding algorithms. In the CADTH base case, for the proposed Health Canada–indicated population regardless of IMDC risk status, cabozantinib + nivolumab is not a cost-effective strategy (dominated) given its higher cost (+\$48,917) and fewer QALYs (-0.02) compared to lenvatinib + pembrolizumab. <ul style="list-style-type: none"> When compared with axitinib + pembrolizumab and lenvatinib + pembrolizumab (most relevant comparators), a price reduction of at least 35% for cabozantinib is required for cabozantinib + nivolumab to be the most cost-effective treatment option at a \$50,000 per QALY gained threshold. When considering all relevant comparators, including the single-drug treatment regimens pazopanib and sunitinib, cabozantinib + nivolumab was not a cost-effective therapy at a \$50,000 per QALY gained willingness-to pay-threshold regardless of the price reduction for cabozantinib. In a scenario analysis of the subgroup of patients in the intermediate-risk or poor-risk categories, which included ipilimumab + nivolumab as a comparator, cabozantinib + nivolumab remained dominated by axitinib + pembrolizumab (\$96,186 more expensive and 0.036 fewer QALYs).

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; LY = life-years; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; RCC = renal cell carcinoma; RDI = relative dose intensity.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for first-line systemic therapy was underestimated, the estimated treatment durations were not consistent with those of the pharmacoeconomic evaluation, the allocation of market shares to clinical trials is inappropriate, the modelled population does not represent the full Health Canada indication, the eligible Non-Insured Health Benefits program population was inappropriately calculated, less expensive pricing for the lenvatinib dose used in the model is available, the assumption that ipilimumab plus nivolumab will not be displaced by newer treatment options is inappropriate, and its market share may have been overestimated.

CADTH reanalyses included assuming that patients at intermediate-high to high risk of progression after nephrectomy were originally diagnosed with nonadvanced RCC, assuming treatment duration aligned with PFS, removing clinical trials as a comparator, lowering the cost of lenvatinib to the least expensive option, and assuming that cabozantinib plus nivolumab will also displace ipilimumab plus nivolumab in the intermediate-risk or poor-risk subpopulations. CADTH also made several corrections to the sponsor's model but was unable to correct the calculation of the eligible Non-Insured Health Benefits program population.

CADTH reanalyses suggest that the reimbursement of cabozantinib plus nivolumab for the first-line treatment of advanced or metastatic clear cell RCC would be associated with a budgetary increase of



\$1,113,684 in year 1, \$2,559,415 in year 2, and \$4,938,052 in year 3, for a 3-year incremental budgetary cost of \$8,611,151.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik

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Regrets: None

Conflicts of interest: None



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