# pCODR EXPERT REVIEW COMMITTEE (pERC)
# FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

**pERC Final Recommendation**
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

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| **Drug:** Cabozantinib (Cabometyx)<br>**Submitted Reimbursement Request:**<br>For the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior therapy. | |
| **Submitted By:**<br>Ipsen Biopharmaceuticals Canada Inc. | **Manufactured By:**<br>Ipsen Biopharmaceuticals Canada Inc. |
| **NOC Date:**<br>September 14, 2018 | **Submission Date:**<br>September 17, 2018 |
| **Initial Recommendation:**<br>January 31, 2019 | **Final Recommendation:**<br>February 20, 2019 |

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| **Approximate per Patient Drug Costs, per Month (28 Days)** | Cabozantinib costs $293.33 per 20 mg, 40 mg, or 60 mg tablet. At the recommended dose of cabozantinib is 60 mg per day taken orally, cabozantinib costs $293.33 per day and $7,548.05 per 28-day cycle (assuming the METEOR trial dose intensity). |

## pERC RECOMMENDATION

pERC recommends the reimbursement of cabozantinib (Cabometyx) 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 is improved to an acceptable level.

If the aforementioned condition cannot be met, pERC does not recommend reimbursement of cabozantinib. Reimbursement should be for patients who have been previously treated with at least 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

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| | 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.<br><br>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 compared with nivolumab. |
| POTENTIAL NEXT STEPS FOR STAKEHOLDERS | **Pricing Arrangements to Improve Cost-Effectiveness**<br>Given that there is a net clinical benefit of cabozantinib compared with everolimus and axitinib, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of cabozantinib to an acceptable level. pERC further noted that the incremental benefit between cabozantinib and nivolumab is small and the direction and magnitude of this benefit is unclear, therefore, pERC was unable to estimate the cost effectiveness of cabozantinib compared with nivolumab.<br><br>**Optimal Sequencing of Cabozantinib and Other Therapies Unknown**<br>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.<br><br>**Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Benefit and Cost-Effectiveness**<br>Given the considerable uncertainty in the magnitude of clinical benefit of cabozantinib compared with nivolumab in patients with RCC who are previously treated, pERC concluded that the collection of prospective evidence to inform the comparative efficacy between these two drugs would better inform the true cost-effectiveness of cabozantinib compared with nivolumab.<br><br>**Please note:** Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1. |

# SUMMARY OF pERC DELIBERATIONS

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6,600 new cases and 1,900 deaths related to kidney cancer in Canada. About 90% of kidney cancers are RCCs, 80% of all RCCs are of clear cell histology, and 20% are classified as non-clear cell cancers. In localized stages of RCC, survival rates range from 70% to 90%, but drop to 50% to 60% for patients with more extensive tumours. The current standards of care for patients with advanced or metastatic, clear cell RCC who have had one prior VEGF-targeted therapy include nivolumab and axitinib. With the availability of these two drugs, the use of everolimus, previously a standard of care, has declined substantially. Despite current treatment options, long-term survival and cure are still rare for patients with metastatic RCC, particularly in the second-line setting, with less than 10% of patients with metastatic disease surviving for five years or longer. pERC concluded that there is a need for more effective and less toxic therapies that overcome disease resistance, delay disease progression, and improve OS.

| pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria: | |
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| CLINICAL BENEFIT | PATIENT-BASED VALUES |
| ECONOMIC EVALUATION | ADOPTION FEASIBILITY |

pERC deliberated upon the results of one large randomized, open-label phase III trial (METEOR) comparing cabozantinib with everolimus in patients with advanced RCC who had been previously treated with at least one previous VEGFR TKI. pERC concluded that there is a net clinical benefit of cabozantinib over everolimus based on statistically significant and clinically meaningful improvements in PFS and OS. pERC noted that OS was immature at the time of the first planned interim analysis and that two subsequent analyses performed were unplanned. pERC, however, recognized that the magnitude of effect reported for OS in these unplanned analysis was large, confirming that cabozantinib provides a significant benefit to patients. The benefit in PFS and OS was also maintained across most subgroups, including patients with bone metastases. pERC noted that cabozantinib did not result in the deterioration of patients' QoL. The Committee discussed the safety profile of cabozantinib relative to everolimus and noted that the incidence of grade 3 or higher toxicities was higher with cabozantinib. pERC, however, felt that the toxicities with cabozantinib are well known and manageable. Therefore, pERC concluded that there is a net overall clinical benefit with cabozantinib, based upon statistically significant and clinically meaningful improvements in PFS and OS, maintenance of QoL, and a manageable toxicity profile compared with everolimus.

pERC discussed the generalizability of the overall trial results in patients with advanced or metastatic RCC. Although the METEOR trial only compared cabozantinib with everolimus, pERC noted that the efficacy and safety outcomes with everolimus are similar and therefore generalizable to those of axitinib, a relevant comparator in the Canadian setting. Therefore, pERC concluded that the trial results are generalizable to the Canadian population. pERC also discussed that the METEOR trial included only patients with clear cell RCC and there was no evidence presented on the efficacy and safety of using cabozantinib in patients with non-clear cell histology. pERC noted that in clinical practice patients with non-clear-cell RCC are managed the same way as patients with clear-cell RCC and therefore agreed that it is reasonable to generalize the METEOR trial results to patients with non-clear-cell RCC. pERC noted that the METEOR trial excluded patients with a Karnofsky Performance Status scale score of less than 70 (approximately an Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 2) and that patients with ECOG PS 2 or greater are typically excluded from trials. pERC therefore felt that the treatment of patients with poorer performance statuses should be left to the discretion of the treating oncologist. pERC further agreed that the use of cabozantinib should be restricted to patients who have had previous treatment with a TKI, regardless of whether or not patients have had prior treatment with immunotherapy or an mTOR (mammalian target of rapamycin) inhibitor.

pERC deliberated on a manufacturer-submitted network meta-analysis (NMA) comparing the efficacy and safety of cabozantinib with nivolumab. pERC noted that the results of the NMA favoured cabozantinib for PFS and OS. Given the considerable differences in the study design and baseline patient characteristics of the studies forming the NMA, pERC agreed with the Methods team that the results of the NMA should be interpreted with caution.

pERC deliberated upon input from one patient advocacy group (Kidney Cancer Canada) concerning cabozantinib and noted that patients value having an additional treatment option with demonstrated efficacy in delaying disease progression and improving survival. Patients noted the burden of bone progression and skeletal-related events and expressed a desire for treatments that control bone metastases. Given that cabozantinib demonstrated statistically significant and clinically meaningful improvements in PFS and OS, including the subgroup of patients with bone metastases; had a manageable toxicity profile; and no deterioration in QoL, pERC agreed that cabozantinib aligned with patient values.

pERC deliberated upon the cost-effectiveness of cabozantinib compared with everolimus and axitinib and concluded that, at the submitted price, cabozantinib is not cost-effective. pERC also concluded that the cost-effectiveness of cabozantinib compared with nivolumab is uncertain given the uncertainty in the estimates of clinical effectiveness that were derived through the NMA. Uncertainty regarding the duration of treatment effect, estimates for utilities, and distribution of subsequent drugs was considered in the reanalysis estimates by the pCODR Economic Guidance Panel (EGP). pERC agreed with the EGP's changes to the economic model to assume smaller gains in QoL benefit (utilize alternative utility values) and to shorten the duration of the treatment effect with cabozantinib, both of which were overestimated in the submitted base-case incremental cost-effectiveness ratio (ICER). Changes to the distribution of subsequent treatments resulted in a decrease in the ICER. pERC also noted that the incremental cost and quality-adjusted life-years gained with cabozantinib when compared with nivolumab was small and that a small change in either input could dramatically alter the ICER. pERC further noted that the upper bound of the ICER could not be estimated for any of the comparisons presented given the uncertainty in the clinical effect estimates between cabozantinib and all relevant comparators, which were derived through an NMA. Overall, pERC concluded that cabozantinib is not cost-effective when compared with everolimus and axitinib, and that the cost-effectiveness is uncertain when compared with nivolumab.

pERC discussed the feasibility of implementing a reimbursement recommendation for cabozantinib for patients with previously treated RCC. pERC noted that the most substantial factor that influenced the budget impact was the distribution of subsequent treatment options (inclusion or exclusion of nivolumab as a subsequent drug and eligible patient population). pERC further noted that the treatment landscape for RCC is rapidly changing with the use of nivolumab likely shifting to first-line treatment as a combination drug with ipilimumab for intermediate and poor risk patients. pERC therefore highlighted that the budget impact of adding cabozantinib to the sequence of treatments for advanced RCC will be large as the cost of nivolumab will be shifted earlier to first-line treatment.

The Committee noted input from pCODR's PAG, which requested guidance and clarification on the implementation of cabozantinib. For patients who are currently on an mTOR inhibitor with everolimus and who have not experienced disease progression, pERC noted that oncologists will likely opt to keep patients on a treatment to which they are responding. In case of intolerance or progression, pERC agreed that it is reasonable to treat patients who have previously been treated with an mTOR inhibitor or an immunotherapy with cabozantinib. pERC noted various requests from PAG for clarity on the place in therapy of cabozantinib and guidance on sequencing. pERC agreed with the pCODR Clinical Guidance Panel that cabozantinib is likely to be a second- or third-line treatment option for patients depending on the first-line treatment that patients receive. pERC, however, felt that patients need to have been treated with at least one VEGF TKI to be eligible for cabozantinib as this aligns with the patient population in the METEOR trial. pERC further highlighted that the optimal sequencing of cabozantinib and other treatments now available for the treatment of patients with advanced RCC who have received prior therapy is currently unknown. pERC therefore recognized that provinces would need to address treatment sequencing upon implementation of cabozantinib reimbursement and noted that collaboration among provinces to develop a common approach would be of value.

# EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the pCODR Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from the pCODR clinical and economic review panels
- input from one patient advocacy group (Kidney Cancer Canada)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- One clinician group, (Cancer Care Ontario GU DAC, CCO)
- The PAG
- The submitter (Ipsen Biopharmaceuticals Canada Inc.)

The pERC Initial Recommendation was to recommend reimbursement of cabozantinib (Cabometyx) 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. Feedback on the pERC Initial Recommendation indicated that the manufacturer, and registered clinician group agreed with the Initial Recommendation. Feedback was not received from the patient advocacy group.

The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

### pCODR review scope

The purpose of this review is to evaluate the safety and efficacy of cabozantinib (Cabometyx) for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior therapy.

### Studies included: Large randomized controlled trial

The pCODR systematic review included one large, multi-centre, open-label, phase III randomized controlled trial, METEOR, which randomly enrolled 658 patients in a 1:1 ratio to receive 60 mg per day of cabozantinib (n = 330) once a day or 10 mg per day of everolimus (n = 328).

This pCODR review also provided contextual information on a critical appraisal of a manufacturer-submitted network meta-analysis (NMA), which provided evidence of the efficacy of cabozantinib as compared with other active therapies (everolimus and nivolumab) in patients with advanced RCC in the second-line setting. Although the results of the NMA favoured cabozantinib for PFS and OS, given the considerable differences in the design and baseline patient characteristics of the studies forming the NMA, pERC was unable to make firm conclusions about the comparative effectiveness of cabozantinib and nivolumab. pERC agreed with the Methods team that the results of the NMA should be interpreted with caution. The NMA did not report on comparative safety or quality of life data.

### Patient populations: Prior tyrosine kinase inhibitor

Key eligibility criteria required that patients be 18 years of age, have advanced or metastatic clear-cell RCC, measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, had received at least one prior VEGFR TKI and must have progressed within 6 months of their most recent VEGFR TKI and within 6 months of randomization. pERC noted that the METEOR trial excluded patients with a Karnofsky Performance Status (KPS) scale score of less than 70 (approximately an Eastern Cooperative Oncology Group [ECOG] performance status [PS] of 2) and that patients with ECOG PS 2 or greater are typically excluded from trials. Notably, 92% of patients on the trial had a KPS of 80 or greater. Given that the toxicity profile of cabozantinib is well known and manageable (which is typical of TKIs), pERC agreed that the treatment of patients with poorer performance statuses should be left to the discretion of the treating oncologist. The majority of patients enrolled in the trial were male (75%), white (81%), and had a favourable (45.5%) or intermediate (41.5%) Memorial Sloan-Kettering Cancer Center

status. Additionally, 70.5% of patients had previously been treated with one line of VEGFR TKIs and the majority had received sunitinib (63%) or pazopanib (42.5%). A small minority of patients (less than 6% per treatment group) had received an immunotherapy as a prior treatment. pERC further agreed that the use of cabozantinib should be restricted to patients who have had previous treatment with a VEGFR TKI, regardless of whether or not patients have had prior treatment with an immunotherapy or an mTOR inhibitor.

pERC discussed that the METEOR trial excluded patients with non–clear cell RCC and therefore, there was no evidence presented on the efficacy and safety of using cabozantinib in this patient population. pERC noted that patients with non–clear cell RCC are managed the same way as patients with clear cell RCC. Therefore, pERC agreed that it is reasonable to generalize the METEOR trial results to patients with non-clear cell RCC. pERC further discussed that the METEOR trial only compared cabozantinib with everolimus, however the efficacy and safety outcomes with everolimus are similar and therefore generalizable to those of axitinib, a relevant comparator in the Canadian setting. Therefore, pERC agreed that the trial results are generalizable to the Canadian population.
Patients continued to receive treatment as long as they experienced clinical benefit as assessed by the study investigator or until unacceptable toxicity, the need for subsequent anticancer therapy, or other withdrawal criteria. Patients who progressed as per RECIST1.1 could still continue treatment if the investigator believed that the patient would receive clinical benefit. Crossover was not permitted.

### Key efficacy results: statistically significant and clinically meaningful improvements in progression-free survival and overall survival

The key efficacy outcome deliberated on by pERC was PFS, while the secondary outcomes were OS and objective response rate. The trial was initially designed to conduct one interim analysis in order to assess OS and PFS. However, at the first interim analysis (May 22, 2015, data cut-off), OS was immature, and thus the manufacturer conducted an unplanned interim analysis on December 31, 2015, and an updated analysis of OS on October 2, 2016, but the results of this second unplanned analysis have not been published.

pERC agreed that there is a net clinical benefit of cabozantinib over everolimus based on statistically significant and clinically meaningful improvements in PFS and OS. At the first interim analysis the median PFS for the cabozantinib was 7.4 months and 3.8 months in the everolimus group. Cabozantinib was associated with a longer PFS as compared with everolimus (hazard ratio [HR]: 0.58; 95% confidence interval [CI], 0.45 to 0.75; $P \leq 0.001$). Similar estimates were observed at the December 31, 2015, analysis (HR: 0.51; 95% CI, 0.41 to 0.62; $P = \leq 0.0001$). Cabozantinib was associated with a significantly longer OS as compared with everolimus (median: 21.4 months versus 16.5 months, respectively; HR: 0.66; 95% CI, 0.53 to 0.83; $P = 0.00026$). At the later OS analysis (October 2, 2016), cabozantinib was again associated with a significantly longer OS as compared with everolimus therapy (HR: 0.70; 95% CI, 0.58 to 0.85; $P = 0.0002$). Even though OS was immature at the time of the first planned interim analysis, pERC agreed that the magnitude of effect reported for OS in the two subsequent unplanned analysis was large, confirming that cabozantinib provides a significant benefit to patients. The benefit in PFS and OS was also maintained across most subgroups, including patients with bone metastases.

### Patient-reported outcomes: No significant or clinically meaningful difference

Health-related QoL was assessed as a tertiary outcome and was measured using the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI-19) and the EuroQol 5-Dimensions 5-Levels (EQ-5D-5L) questionnaires. For the FKSI-19 total score analysis, the difference between treatment groups (i.e., the estimated least squares mean in change from baseline) was –0.13 (standard deviation [SD] pooled: 9.768; $P < 0.0001$). On the other hand, the difference between treatment groups for the EQ-5D-5L scale (i.e., the estimated least squares mean in change from baseline) was –0.009 (SD pooled: 0.196; $P = 0.825$) and –0.003 (SD pooled: 16.809; $P = 0.921$) for the EQ-5D-5L visual analogue scale. Neither one of these differences was considered statistically significant or clinically significant (minimally important difference of 0.30 or greater).

Overall, it appears that health-related QoL was maintained for patients treated with cabozantinib and everolimus and there were no apparent differences between the FKSI-19 and EQ-5D-5L scales over time.

### Safety: Manageable toxicity profile

Safety was a tertiary outcome in the METEOR trial. The Committee discussed the safety profile of cabozantinib relative to everolimus and noted that the incidence of grade 3 or higher toxicities was higher with cabozantinib (71% versus 60%). At the December 31, 2015, cut-off, serious adverse events (AEs) occurred equally across the two treatment groups (cabozantinib: 39% and everolimus: 40%).

More dose reductions occurred in the cabozantinib group as compared with the everolimus group (62% versus 25%). The proportion of patients who discontinued treatment due to an AE not related to disease progression was similar between the two groups (cabozantinib: 12% and everolimus: 11%). One treatment-related death occurred in the cabozantinib group but the cause of death was not specified. In the everolimus group, two treatment-related deaths occurred due to Aspergillus infection and aspiration pneumonia. pERC, however, agreed that the toxicities with cabozantinib are well known and manageable.

### Need and burden of illness: Greater efficacy and less toxicity in new treatment options

Kidney cancer accounts for approximately 3% of all cancers in Canada. In 2017, there were 6,600 new cases and 1,900 deaths related to kidney cancer. About 90% of kidney cancers are RCCs, 80% of all RCCs are of clear cell histology, and 20% are classified as non-clear cell cancers. In localized stages of RCCs, survival rates range from 70% to 90%, but drop to 50% to 60% for patients with more extensive tumours. Until recently, the most commonly used first-line treatment options were the oral VEGFR TKIs sunitinib and pazopanib. However, based on the recent data showing superiority of the combination of the CTLA4 checkpoint inhibitor (ipilimumab) and the PD1 checkpoint inhibitor (nivolumab) over sunitinib in patients with intermediate or poor risk disease, nivolumab plus ipilimumab is quickly becoming a new first-line option in this patient population. The current standard of care for patients with advanced or metastatic clear cell RCC who have had one prior VEGF-targeted therapy includes nivolumab and axitinib. With the availability of these two drugs, the use of everolimus, previously a standard of care, has declined substantially. Despite current treatment options, long-term survival and cure are still rare for patients with metastatic RCC, particularly in the second-line setting, with less than 10% of metastatic patients surviving for five years or longer. pERC agreed that there is a need for more effective and less toxic therapies that overcome disease resistance, delay disease progression, and improve OS.

### Registered clinician input: Superiority in progression-free survival, overall survival, and manageable toxicity profile

pERC deliberated on input from two registered clinicians and one pharmacist. The incidence of patients who may be eligible for cabozantinib as second- or third-line therapy is expected to be low (one-third of patients who receive a TKI as first-line therapy). Registered clinician input indicated that everolimus, which has been shown to be inferior to both nivolumab and cabozantinib, is now rarely used in Canadian jurisdictions, making nivolumab or axitinib the most relevant therapies in this setting. Feedback from registered clinicians on the pERC Initial recommendation reiterated that everolimus monotherapy is not an agent that is used widely in this setting.

Input from these health professionals indicated that the improvements in survival and response rates demonstrated with cabozantinib are important. The toxicity profile was reported to be comparable with those seen with TKIs. While cabozantinib has not been compared with axitinib or nivolumab, which are options after first-line TKI therapies, the health professionals emphasized the superiority of cabozantinib over everolimus based on PFS and OS. Input indicated that cabozantinib would be used in patients after first-line TKI therapy. Feedback from registered clinicians on the pERC Initial recommendation stated that nivolumab should be available to patients after axitinib and/or cabozantinib. Additionally, registered clinicians noted cabozantinib should also be available after nivolumab. pERC considered input received from registered clinicians and a pharmacist and agreed that it aligned with the conclusions reached by the pCODR Clinical Guidance Panel.

## PATIENT-BASED VALUES

### Values of patients with RCC: Manageable toxicity profile, effective options that can manage bone metastases

pERC deliberated upon input from one patient advocacy group (Kidney Cancer Canada) concerning cabozantinib. Patients noted that experiencing a complete response to treatment with a single drug is rare. While some first-line treatments are effective at halting the progression of RCC, patients eventually

experience resistance; Kidney Cancer Canada stated that more effective treatments in further lines of therapy are greatly needed to help overcome the drug resistance. Patients also described an unmet need based on a lack of suitable or effective treatments for all patient subgroups, lack of treatments that prevent progression to other parts of the body, especially progression to bones, and poor control of skeletal-related events. Approximately 85% of patients experience skeletal-related events, such as bone pain, fractures, and spinal cord compression, which can result in hospitalizations and surgery, leading to great burden on the health care system in addition to the burden experienced by the patient.

The majority of patients providing input reported that they had received sunitinib followed by nivolumab, pazopanib, everolimus, and axitinib in prior lines of therapy. Most patients find current drugs to be generally tolerable. About one-third of patients reported having stopped first or second line treatment due to side effects and not due to disease progression.

Kidney Cancer Canada identified recurring themes from prior patient input submissions made to pCODR which included: the importance of having a choice among therapies when considering a new therapy, giving patients an opportunity to have an informed choice on treatment based on known side effects, and the lack of efficacy of current treatment options. Given that cabozantinib is an effective treatment option that demonstrated statistically significant and clinically meaningful improvements in PFS and OS, including the subgroup of patients with bone metastases; had a manageable toxicity profile; and no deterioration in QoL, pERC agreed that cabozantinib aligned with patient values.

### Patient values on treatment: Individualized treatment plan and choice of different options, control bone metastases

Patients indicated that gaps present in the management of RCC include a need for better therapies to improve outlooks for patients with advanced disease, more effective predictive and prognostic biomarkers to guide treatment and detect disease at earlier stages, treatments that control or overcome treatment resistance mechanisms for advanced disease, and for treatments with greater effectiveness on bone metastases. Patients ranked the need for drugs to better stop or slow the spread of kidney cancer as a top priority.

Although patients acknowledge the important breakthrough in new immunotherapies, survival benefit from these drugs is not realized in the majority of kidney cancer patients and some patients find the treatment causes unexpected and sometimes serious side effects, unlike the side effects typically seen with more established/familiar treatments. Patients thus indicated that having more treatment options allows them and their oncologists to better individualize treatment plans according to specific disease/treatment history and contraindications, leading to the best possible outcomes and QoL for the patient. Patients reported that their highest overall priority was to have access to drugs that have a greater effect on treating RCC and on stopping the spread of kidney cancer (metastasis).

Information was collected from 13 patients with experience using cabozantinib as single-drug therapy, two of whom were on the METEOR trial. Patients considered cabozantinib to be fairly effective in controlling their kidney cancer; none of the patients reported that cabozantinib was not effective at all. On a scale of 1 to 5 (1 = low and 5 = high QoL), patients indicated a weighted average score of 3.08 regarding the impact of cabozantinib on QoL. While none of the patients indicated the QoL with cabozantinib being high, two patients did report a very low QoL. Most patients reported a score between 2 and 4 in regard to the tolerability of cabozantinib; none of the patients thought cabozantinib was very tolerable; however, one patient did indicate cabozantinib as being completely intolerable. The patients in this survey who had experience with cabozantinib reported the tolerability and QoL related to experienced side effects as generally consistent with the patient-rated tolerability of other drugs used to treat RCC. A subpopulation of patients who had cancer that had spread to their bones reported that the drug has a positive effect on that site of metastases.

## ECONOMIC EVALUATION

### Economic model submitted: Cost-effectiveness and cost-utility analyses

The pCODR Economic Guidance Panel (EGP) assessed cost-effectiveness and cost-utility analyses comparing cabozantinib with everolimus, axitinib, and nivolumab.

### Basis of the economic model: Network meta-analysis to inform clinical effect estimates

Costs included were drug acquisition costs, subsequent treatment costs, disease management costs, AEs management, end of life care costs, and wastage.

Key clinical effect estimates considered in the analysis include PFS, OS, time to treatment discontinuation, AEs, and utilities.

### Drug costs:

Cabozantinib costs $293.33 per 20 mg, 40 mg, or 60 mg tablet. At the recommended dose of 60 mg per day, cabozantinib costs $269.57 per day and $7,548.05 per 28-day cycle (accounting for trial dose intensity).

Nivolumab cost $58.67 per 3 mg. At the recommended dose of 3 mg/kg for 60-minute every two weeks, nivolumab costs $327.69 per day and $9,175.40 per 28-day cycle (accounting for trial dose intensity).

Axitinib costs $194.26 per 5 mg tablet. At the recommended cost of 5 mg twice daily, axitinib costs $198.15 per day and $5,548.07 per 28-day cycle (accounting for trial dose intensity).

Everolimus costs $202.652 per 10 mg tablet. At the recommended dose of 10 mg per day, everolimus costs $188.87 per day and of $5,288.35 per 28-day cycle (accounting for trial dose intensity).

### Cost-effectiveness estimates: No upper limit to incremental cost-effectiveness ratio

pERC deliberated upon the cost-effectiveness of cabozantinib compared with everolimus and axitinib and concluded that, at the submitted price, cabozantinib is not cost-effective. Uncertainty regarding the duration of treatment effect, estimates for utilities, and distribution of subsequent drugs were considered in the reanalysis estimates by EGP. pERC agreed with changes made to the economic model to utilize alternative utility values that reflected lower QoL as patients progress on treatment and shorten the duration of treatment effect with cabozantinib, both of which were overestimated in the submitted base-case incremental cost-effectiveness ratio(ICER). Changes to the distribution of subsequent treatments, which removed sorafenib and lowered the proportion of patients who would receive nivolumab in subsequent lines, resulted in a decrease in the ICER.

pERC also concluded that the cost-effectiveness of cabozantinib compared with nivolumab is uncertain given the uncertainty in the estimates of clinical effectiveness that were derived from the submitted NMA. Given the small incremental cost and quality-adjusted life-years gained with cabozantinib when compared with nivolumab, pERC noted that a small change in either input could dramatically alter the ICER. pERC further noted that the upper bound of the ICER could not be estimated for any of the comparisons presented given the uncertainty in the clinical effectiveness estimates between cabozantinib and all relevant comparators, which were derived through an NMA. Overall, pERC agreed that cabozantinib is not cost-effective when compared with everolimus and axitinib and the cost-effectiveness is uncertain when compared with nivolumab.

pERC noted the EGP's inability to perform a sequential analysis through a probabilistic sensitivity analysis and agreed that such an analysis would be appropriate to incorporate the uncertainty associated with the clinical effect estimates.

## ADOPTION FEASIBILITY

### Considerations for implementation and budget impact: Rapidly changing treatment landscape

pERC discussed the feasibility of implementing a reimbursement recommendation for cabozantinib for patients with previously treated RCC. pERC noted that the biggest factor that influenced the budget impact analysis was the distribution of subsequent treatment options (inclusion or exclusion of nivolumab as a subsequent drug) and eligible patient population. pERC further noted that the treatment landscape for RCC is rapidly changing, with nivolumab use likely shifting to first-line treatment as a combination drug with ipilimumab. pERC therefore agreed that the budget impact of adding cabozantinib to the sequence of treatments will be large as the cost of nivolumab will be shifted up to first-line treatment.

The Committee noted input from pCODR's Provincial Advisory Group, which requested guidance and clarification on the implementation of cabozantinib. For patients who are currently on an mTOR inhibitor

with everolimus and who have not experienced disease progression, pERC agreed that oncologists will likely opt to keep patients on a treatment to which they are responding. In case of intolerance or progression, pERC agreed that it is reasonable to treat patients who have previously been treated with an mTOR inhibitor or an immunotherapy with cabozantinib. pERC noted various requests for clarity on the place in therapy of cabozantinib and for guidance on sequencing. pERC agreed with the pCODR Clinical Guidance Panel that cabozantinib is likely to be a second- or third-line treatment option for patients depending on the first-line treatment patients receive. pERC, however, agreed that patients need to have been treated with a VEGF TKI to be eligible for cabozantinib as this aligns with the patient population in the METEOR trial. pERC further highlighted that the optimal sequencing of cabozantinib and other treatments now available for the treatment of patients with advanced RCC who have received prior therapy is currently unknown. pERC therefore recognized that provinces would need to address treatment sequencing upon implementation of cabozantinib reimbursement and noted that collaboration among provinces to develop a common approach would be of value.

# DRUG AND CONDITION INFORMATION

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| Drug Information | • Multiple receptor tyrosine kinase inhibitor<br>• 20 mg, 40 mg, and 60 mg reviewed by CADTH pan-Canadian Oncology Drug Review<br>• Recommended dosage 60 mg daily |
| Cancer Treated | • Renal cell carcinoma |
| Burden of Illness | • In 2017 there were 6,600 new cases and 1,900 deaths due to the disease<br>• Approximately one-quarter of patients present with metastases at diagnosis and at least one-half of all patients will eventually develop advanced disease<br>• Metastatic disease is rarely cured |
| Current Standard Treatment | • Nivolumab<br>• Axitinib<br>• Everolimus |
| Limitations of Current Therapy | • No curative treatment options for metastatic renal cell carcinoma<br>• Need for novel treatment strategies |

# ABOUT THIS RECOMMENDATION

### The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan and Dr. Winson Cheung, who were not present for the meeting
- Dr. Henry Conter and Dr. Christian Kollmannsberger, who were excluded from voting due to a conflict of interest
- Valerie McDonald, who did not vote due to her role as a patient member alternate on this specific review.

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

### Avoidance of conflicts of interest

All members of pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of cabozantinib (Cabometyx) for renal cell carcinoma, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members was excluded from voting.

### Information sources used

pERC is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

### Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

### Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

### Disclaimer

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## APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PROVINCIAL ADVISORY GROUP IMPLEMENTATION QUESTIONS

| PAG Implementation Questions | pERC Recommendation |
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| • PAG is seeking guidance on the sequencing of nivolumab after cabozantinib, if cabozantinib is chosen as a second-line TKI option over axitinib.<br>• PAG is seeking guidance on the place in therapy for cabozantinib and which patient population would benefit most from the therapy and which patient population would be best suited for treatment with other available therapies.<br>• Patients who have started second-line treatment with everolimus but wish to switch to cabozantinib prior to disease progression.<br>• Patients who have recently failed everolimus or temsirolimus, and who are not candidates for nivolumab, as the METEOR trial did not enrol patients with previous mTOR inhibitor therapy. | • pERC further highlighted that the optimal sequencing of cabozantinib and other treatments now available for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior therapy is currently unknown.<br>• 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.<br>• pERC agreed with CGP that patients currently on everolimus and who have not had disease progression should not switch to cabozantinib but rather should wait until disease progression. This is based on clinicians' desire to optimize treatment options available and to keep treating a patient with a drug they are tolerating well. pERC, however, agreed that patients intolerant to everolimus should be able to switch to cabozantinib. |
| • In provinces where everolimus, axitinib, and nivolumab are not funded, data comparing cabozantinib with sorafenib would be an enabler to implementation in those provinces. | • 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 two 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. |
| • PAG noted that the funding request does not specify the histologic type of renal cell carcinoma. PAG noted that the METEOR trial enrolled only patients with clear cell histology. PAG is seeking clarity on the patient population who would be eligible for treatment with cabozantinib. | • pERC noted that patients with non-clear cell carcinoma are treated according to clear cell cancer guidelines and it is expected that cabozantinib will have activity in non-clear cell RCC. Cabozantinib should therefore be made available to patients with non-clear cell histology. Therefore, pERC agreed that it is reasonable to generalize the METEOR trial results to patients with non-clear-cell RCC. |
| • Funding request is for treatment until patient no longer has clinical benefit. PAG is seeking clarity on this statement and how it will affect treatment duration and criteria for treatment discontinuation. | • pERC noted that the trial allowed patients to continue treatment as long as they experience clinical benefit in the opinion of the investigator or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment. pERC agreed that treatment beyond progression would likely occur in exceptional circumstances as it is unusual to treat patients beyond progression with a TKI. |
| • PAG is seeking information on the dose intensity and the frequency of dose adjustments.<br>• PAG is seeking information on the cost and noted that flat pricing of all tablet strengths is more expensive for patients who are dispensed the lower strengths and adjusting dose by adjusting the number of tablets. | • pERC noted that the submitted base-case results were based on the trial dose intensity (43mg daily (IQR: 36 to 56) with dose reductions occurring in 62% of patients in the cabozantinib group), which likely reflects the clinical setting as patients are unlikely to maintain 100% dose intensity given the toxicities of cabozantinib and the proportion of patients who required dose reductions on the METEOR trial. pERC, however, acknowledged that the ICER was sensitive to alteration to the dose intensity.<br>• pERC acknowledged that flat pricing of cabozantinib would not result in any cost savings when patients are dose reduced. |

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| • PAG would appreciate guidance as to whether patients who have a documented intolerance to one or both sunitinib or pazopanib (funded first-line TKIs) without disease progression should be eligible for cabozantinib funding.<br>• PAG is seeking information on if and when a submission for first-line use would be submitted to Health Canada and to pCODR. | • 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.<br>• 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. |

CGP = pCODR Clinical Guidance Panel; ICER = incremental cost-effectiveness ratio; mTOR = mammalian target of rapamycin; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; PFS = progression-free survival; RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGFR = vascular endothelial growth factor receptor.