CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Cabozantinib (Cabometyx) for Renal Cell Carcinoma (Resubmission)

February 20, 2019

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis **submitted to pCODR by IPSEN** compared cabozantinib to standard of care for patients with locally advanced or metastatic renal cell carcinoma (RCC) who have received prior VEGF targeted therapy.

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	Patients with locally advanced or metastatic RCC who have received prior VEGF targeted therapy.
Type of Analysis	*CUA & CEA*
Type of Model	*Partitioned-survival model*
Comparator*	*Axitinib (assumed to have equal efficacy to everolimus)* *Everolimus* *Nivolumab* *Best supportive care*
Year of costs	*2018*
Time Horizon	*10 years (cycle length of 28 days)*
Discount rate	*1.5% for both costs and outcomes*
Perspective	*Government*
Cost of cabozantinib	The recommended dose of cabozantinib is 60mg per day taken orally. Treatment is to continue until patient no longer experiences clinical benefit or unacceptable toxicity. Cabozantinib costs: • $293.33 per 20, 40 or 60mg tablet • $269.57 per day • Economic model uses cost of $7,548.05 per 28 day (accounting for trial dose intensity)
Cost of nivolumab	The recommended dose of nivolumab is 3 mg/kg for 60-minute every 2 weeks. Nivolumab costs: • $58.67 per 3mg • $327.69 per day • Economic model uses cost of $9,175.40 per 28 day (accounting trial dose intensity)
Cost of axitinib	The recommended dose of axitinib is 5 mg twice daily. Axitinib costs: • $194.26 per 10mg tablet • $198.15 per day • Economic model uses cost of $5,548.07 per 28 day (accounting for trial dose intensity)
Cost of everolimus	The recommended dose of everolimus is 10mg per day. Everolimus costs: • $202.652 per 10mg tablet • $188.87 per day • Economic model uses cost of $5,288.35 per 28 day (accounting for trial dose intensity)
Model Structure	The model was comprised of three health states: progression-free, progressed disease and death. All patients enter the model in the

	progression-free health state, having progressed on a previous VEGFR treatment.
Key Data Sources	*METEOR phase III clinical trial (cabozantinib and everolimus)* *Narrow network meta-analysis*[1]
Key Assumptions	*Equal efficacy assumed for axitinib and everolimus. The CGP agreed this assumption was reasonable.*

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, however, axitinib and nivolumab are considered current relevant comparators and are reimbursed options in the second-line setting in almost all provinces. The Submitter did include these comparisons as part of the submitted base case using a network meta-analysis.

- Relevant considerations/issues identified by the CGP include:
  - *There is a net overall clinical benefit to cabozantinib in the second-line treatment of advanced and metastatic RCC. The current evidence supports the use of cabozantanib as second- or third-line therapy.*
  - *Quality of life was measured in the METEOR trial and overall and it appears that HRQoL was maintained for patients treated with cabozantinib and everolimus.*
  - *Current second line options for this patient population include nivolumab, everolimus and axitinib. These comparisons were included in the economic analysis, though the efficacy of axitinib was assumed to be equivalent to everolimus. The CGP agreed that this is justified by available phase III evidence as well as the available evidence from clinical practice on the efficacy and safety of axitinib and everolimus.*
  - *The results of the submitted NMA indicate that patients on cabozantinib had a greater likelihood of PFS and OS as compared to those treated with the other comparators (everolimus and nivolumab). The overall conclusions of the NMA are however limited because there were considerable differences in the study design and baseline population characteristics of the included studies. Therefore, the NMA should be interpreted with caution.*
  - *Although acknowledging the rapidly changing treatment landscape for RCC, the CGP noted that patients who were previously treated with sunitinib or pazopanib in the front line setting may qualify for cabozantinib or nivolumab second line, cabozantinib or nivolumab third line (depending on which agent was used second line) and everolimus or axitinib fourth line. For patients treated with nivolumab plus ipilimumab in the front line setting, second line agents may include sunitinib or pazopanib, cabozantinib third line and everolimus or axitinib in the fourth line setting.*
  - *Cabozantinib should be used for treatment of patients until disease progression, and treatment may continue beyond disease progression. The economic model incorporates treatment duration as time until treatment discontinuation, which accounts for the time patients spent on treatment and not the time until progression.*

Summary of registered clinician input relevant to the economic analysis
Registered clinician input (which included two clinicians and a pharmacist) identified cabozantinib to be a relevant option as a second- or further line of therapy. Though improvements in PFS and OS were observed in the METEOR trial, they noted that the toxicity of cabozantinib could be a potential challenge over other TKI therapies. The clinician input supported the superiority of cabozantinib over everolimus; as cabozantinib has not been compared to nivolumab or axitinib, they were unable to comment on the comparative efficacy and safety compared to these comparators.

Summary of patient input relevant to the economic analysis

Patients with kidney cancer considered that having a choice of treatment options is important. Patients ranked access to treatments that are more effective at slowing or stopping the spread of kidney cancer in the body as a priority. Patients with experience with cabozantinib stated that it was effective in controlling their cancer for the most part, with relatively fair tolerability and impact on their quality of life. Patients stated that the side effect profile was similar to previous therapies they had received. Survival, adverse events and quality of life were taken into consideration in the economic model.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for cabozantinib which are relevant to the economic analysis:

- Comparison with current relevant comparators, which are axitinib and nivolumab as both are funded choices in the second line setting for almost all provinces. The EGP was able to address these comparisons.
- The sequencing with currently available treatments and upcoming treatments is uncertain. The EGP was able to explore scenarios of various subsequent treatments.
- Cost-effectiveness of cabozantinib versus relevant comparators should nivolumab be funded in the third line. A scenario where nivolumab is available as a third line treatment was explored by the EGP.
- Treatment duration of cabozantinib. In the economic model, treatment duration was modeled using time to treatment discontinuation data from the METEOR trial, as patients could continue treatment beyond progression.
- Dosing of cabozantinib and any possible wastage due to dose reductions. The economic model accounts for dose intensity as per the METEOR trial, but the submitted base case did not include any potential wastage for oral tablets. The EGP was able to explore possible wastage by increasing the dose intensity to 100% in scenario analyses.
- As cabozantinib is administered orally, no chemotherapy units or chair time are needed, which is an enable to implementation.
- Flat pricing of cabozantinib. The EGP explored the impact of price reductions on the EGP re-analysis.

1.3 Submitted and EGP Reanalysis Estimates

As per CADTH guidelines, economic models should be conducted using probabilistic analyses. CADTH guidelines also state that when more than one comparator is appropriate, a sequential analysis should be undertaken. The submitter provided a sequential analysis, however, the analysis that was presented in the economic model was deterministic and not probabilistic. The EGP therefore disregarded the sequential analysis results submitted, and presented a series of pair-wise comparisons using the probabilistic results.

Table 2. Submitted and EGP Reanalysis Estimates, cabozantinib versus everolimus, NMA efficacy data, probabilistic (5,000 iterations)

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	0.50	0.45	N/A
Progression-free	0.45	0.40	
Post-progression	0.05	0.05	
ΔE (QALY)	0.39	0.30	N/A
Progression-free	0.36	0.27	
Post-progression	0.03	0.03	

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔC ($)	$70,086	$62,940	N/A
ICER estimate ($/QALY)	$177,876	$206,933	

N/A: not available

Table 3. Submitted and EGP Reanalysis Estimates, cabozantinib versus axitinib, NMA efficacy data, probabilistic (5,000 iterations)

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	0.50	0.45	N/A
Progression-free	0.45	0.40	
Post-progression	0.05	0.05	
ΔE (QALY)	0.40	0.31	N/A
Progression-free	0.36	0.28	
Post-progression	0.04	0.03	
ΔC ($)	$72,193	$65,661	N/A
ICER estimate ($/QALY)	$181,359	$214,709	

N/A: not available

Table 4. Submitted and EGP Reanalysis Estimates, cabozantinib versus nivolumab, NMA efficacy data, probabilistic (5,000 iterations)

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	0.29	0.10	N/A
Progression-free	0.33	0.30	
Post-progression	-0.04	-0.20	
ΔE (QALY)	0.23	0.08	N/A
Progression-free	0.26	0.20	
Post-progression	-0.03	-0.12	
ΔC ($)	-$16,841	-$1,786	N/A
ICER estimate ($/QALY)	Dominant	Dominant	

N/A: not available

The main assumptions and limitations with the submitted economic evaluation were:

- *Sequential analysis:* CADTH guidelines state that the submitted base case analysis should be done probabilistically. CADTH guidelines also state that when more than one comparison is to be included in the economic analysis, a sequential analysis should be done. The submitter was requested to provide a sequential analysis, however, the sequential analysis provided was based on the deterministic results and not the probabilistic results. The EGP elected to present pair-wise comparisons of the probabilistic results as the deterministic sequential analysis does not capture all the uncertainty present in a model. Given the uncertainty surrounding efficacy, a sequential analysis using the deterministic analysis is not reasonable.
- *Equal effectiveness assumption between everolimus and axitinib:* The assumption of equal effectiveness between everolimus and axitinib was necessary, as it was not possible to include axitinib in the network meta-analysis due to large underlying differences in trial design (notably that the axitinib trial, TARGET, did not provided cross-over adjusted results). Though the submitter stated that this assumption is likely conservative, and the CGP validated that it is a reasonable assumption, it is a weakness of the submitted economic model.
- *Network meta-analysis*: Though the overall quality of the NMA was good, there were underlying differences in baseline characteristics in the included studies. This included an

imbalance of effect modifiers. These effect modifiers were the type and number of previous therapies and baseline prognostic factors. The critical appraisal of the NMA concluded that the NMA should be interpreted with caution given the considerable differences in study design and baseline population characteristics between included studies.

- *Sequencing of treatments:* The treatment landscape for RCC is rapidly changing. The CGP noted that patients who were previously treated with sunitinib or pazopanib in the front line setting may qualify for cabozantinib or nivolumab in the second-line setting, followed by cabozantinib or nivolumab in the third-line setting (depending on which agent is used in second line). However, for patients treated with nivolumab plus ipilimumab in the front line setting, they would not be eligible for single agent nivolumab in subsequent settings. The EGP recognized the importance of treatment sequencing and the impact this has on the ICER. A scenario analysis with no nivolumab provided in later settings was explored.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model for all comparators:

- Duration of treatment effect: In the submitted base case, the transition probabilities over time retain the relative benefit for the duration of the time horizon. As there is no clinical evidence to support this assumption, an equal transition probability from 2 – 10 years was explored.
- Subsequent treatments: The CGP indicated that sorafenib is rarely used in Canada for mRCC. The submitter provided a scenario analysis of subsequent treatments based on clinical practice in Canada, which excluded sorafenib. The CGP confirmed that the exclusion of sorafenib better aligns with clinical practice in Canada. The EGP, however, made further changes to subsequent treatments based on additional feedback from the CGP. Given the current changing treatment landscape in RCC, the EGP, based on feedback from the CGP explored lower nivolumab in the 3rd line, and more patients as one likely scenario.
- Utilities: The utilities in the submitted base case were collected in the METEOR trial. The utility value in the post-progression state was calculated based on the progression-free survival state, by applying a utility decrement. This utility value was relatively high, with a value 0.765. In the re-analysis, the EGP used the utility values used in a cost-effectiveness analysis of axitinib for the treatment of advanced renal cell carcinoma in patients who had failed prior systemic therapy.
- No upper bound: The Methods team concluded that the results of the NMA should be interpreted with caution, given some of the underlying limitations in the data informing the NMA. Further, the submitted sequential analysis did not incorporate the probabilistic analysis, by allowing the probabilistic analysis to be run across all comparators simultaneously. For these reasons, the EGP could not quantify the uncertainty in the economic model and elected to not place an upper bound.

A. Cabozantinib versus everolimus

Table 5. EGP Reanalysis Estimates, cabozantinib versus everolimus, NMA efficacy data, probabilistic (5,000 iterations)

	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Submitted base case	$70,086	0.39	0.50	$177,876	--
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Duration of treatment effect - 2 years	$70,157	0.35	0.45	$198,768	$20,892
Subsequent treatments - **Error! Reference source not found.**	$62,970	0.40	0.50	$158,446	-$19,430
Utilities - AXIS trial	$70,063	0.34	0.50	$206,022	$28,146
Best estimate of above 3 parameters (95% CI)	**$62,940** ($39,892, $90,220)	**0.30** (0.11, 0.50)	**0.45** (0.15, 0.75)	**$206,933**	**$29,057**
UPPER BOUND					
No upper bound					

B. Cabozantinib versus axitinib

Table 6. EGP Reanalysis Estimates, cabozantinib versus axitinib, NMA efficacy data, probabilistic (5,000 iterations)

	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Submitted base case	$72,193	0.40	0.50	$181,359	--
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Duration of treatment effect - 2 years	$72,137	0.36	0.45	$201,891	$20,532
Subsequent treatments - **Error! Reference source not found.**	$65,700	0.40	0.50	$165,549	-$15,810
Utilities - AXIS trial	$72,175	0.34	0.50	$209,827	$28,468
Best estimate of above 3 parameters (95% CI)	**$65,661** ($40,709, $93,154)	**0.31** (0.11, 0.50)	**0.45** (0.14, 0.76)	**$214,709**	**$33,350**
UPPER BOUND					
No upper bound					

C. Cabozantinib versus nivolumab

Table 7. EGP Reanalysis Estimates, cabozantinib versus nivolumab, NMA efficacy data, probabilistic (5,000 iterations)

	ΔC	ΔE QALYs	ΔE LYs	ICUR	Δ from baseline submitted ICER
Submitted base case	-$16,841	0.23	0.29	Dominated	--
EGP's Reanalysis for the Best Case Estimate					
LOWER BOUND					
Duration of treatment effect - 2 years	-$16,962	0.08	0.10	Dominant	
Subsequent treatments - **Error! Reference source not found.**	-$792	0.23	0.29	Dominant	
Utilities - AXIS trial	-$16,077	0.20		Dominant	
Best estimate of above 3 parameters (95% CI)	**-$1,786** (-$50,238, $40,978)	**0.08** (-0.18, 0.32)	**0.10** (-0.32, 0.49)	**Dominant**	
UPPER BOUND					
No upper bound					

1.5 Evaluation of Submitted Budget Impact Analysis

The factors that most influence the budget impact analysis include:

- Anticipation of the funding of nivolumab 1st line. Decreasing the proportion of patients who receive nivolumab in the 2nd line (assuming patients would receive it in the 1st line as a combination agent) increases the 3-year budget impact by 800%.
    - For the purposes of this review, the EGP explored the above assumption (nivolumab-ipilimumab use for some patients in the 1st line) and thus the use of nivolumab in 2nd and 3rd line settings would be reduced in the re-analysis.
- Increasing the proportion of patients eligible for public coverage to 100%. When all patients are assumed to have access under publicly funded drug plans, the 3-year budget impact increases by 130%.
- Using the latest available data for 2nd line treatment duration (both published and unpublished sources). When using the latest data, the 3-year budget impact increases by 134%.
- Excluding third-line treatments. Excluding 3rd line treatments reduces the 3-year budget impact by over 60%.
- The proportion of patients who move on to 3rd line treatment following nivolumab. Decreasing the proportion of patients who go to 3rd line treatment following nivolumab by 50% decreases the 3-year budget impact minimally.

Key limitations/challenges of the BIA model include the ability to capture the impact of various sequencing options in the rapidly changing treatment landscape for advanced RCC. Further, wastage of treatments were not factored in the budget impact analysis, however, full dose intensity was assumed for treatment options.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for cabozantinib when compared to everolimus is:

- Between $206,933/QALY and unknown upper bound.
- The extra cost of cabozantinib in the lower bound is $62,940 (ΔC) (95% CI: $39,892, $90,220). *The main factors that influence ΔC are the proportion of patients receiving nivolumab as a subsequent treatment and the cost of everolimus.*
- The extra clinical effect of cabozantinib in the lower bound is 0.30 QALYs (ΔE) (95% CI: 0.11, 0.50). *The main factors that influence ΔE are the duration of treatment effect and the source of utilities (METEOR vs AXIS).*

The EGP's best estimate of ΔC and ΔE for cabozantinib when compared to axitinib is:

- Between $214,709/QALY and unknown upper bound.
- The extra cost of cabozantinib in the lower bound is $65,661(ΔC) (95% CI: $40,709, $93,154). *The main factors that influence ΔC are the proportion of patients receiving nivolumab as a subsequent treatment and the dose intensity of cabozantinib/axitinib.*
- The extra clinical effect of cabozantinib in the lower bound is 0.31 (ΔE) (95% CI: 0.11, 0.50). *The main factors that influence ΔE are the duration of treatment effect and the source of utilities (METEOR vs AXIS).*

The EGP's best estimate of ΔC and ΔE for cabozantinib when compared to nivolumab is:

- Cabozantinib remains dominant over nivolumab in the lower bound.
- Cabozantinib in the lower bound is less costly than nivolumab by -$1,786 (ΔC) (95% CI: -$50,238, $40,978). *The main factors that influence ΔC are the proportion of patients receiving nivolumab as a subsequent treatment and wastage associated with nivolumab.*
- The extra clinical effect of cabozantinib in the lower bound is between 0.08 (ΔE) (95% CI: -0.18, 0.32). *The main factors that influence ΔE are the duration of treatment effect the source of utilities (METEOR vs AXIS).*

Overall conclusions of the submitted model:

- *The economic model relies on a network meta-analysis to inform the efficacy data. The Methods team concluded that the results of the NMA should be interpreted with caution. Therefore, the conclusions around the cost-effectiveness of cabozantinib should be interpreted with caution. This uncertainty is highlighted by the relatively large confidence intervals.*
- *Further, the EGP was unable to conduct a probabilistic analysis of the sequential analysis, and given the uncertainty in the effectiveness data, a deterministic analysis was inappropriate.*

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Renal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of cabozantinib (Cabometyx) for renal cell carcinoma (RCC). A full assessment of the clinical evidence of cabozantinib (Cabometyx) for renal cell carcinoma (RCC) is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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