CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

CABOZANTINIB (Cabometyx)

(Ipsen Biopharmaceuticals Canada Inc.)

Indication: Cabometyx 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 RCC

October 20, 2023

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0312-000
Brand name (generic)	Cabometyx (cabozantinib)
Indication(s)	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
Organization	Ontario Health (Cancer Care Ontario) Genitourinary Cancer Drug Advisory Committee ("GU DAC")
Contact information[a]	Name: Dr Girish Kulkarni

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. The GU DAC would like it to be clarified that patients can be treated if they **completed** adjuvant or neoadjuvant therapy 6 months prior (not just received).		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
If yes, please detail the help and who provided it. OH-CCO provided a secretariat function to the group.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Girish Kulkarni • Dr. Aly-Khan Lalani • Dr. Reeta Barua		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Akmal Ghafoor
Position	Genitourinary Drug Advisory Committee Member
Date	10-10-2023
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	Dr. Sebastien Hotte
Position	Genitourinary Drug Advisory Committee Member
Date	12-10-2023
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Ipsen	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	Dr. Christina Canil
Position	Genitourinary Drug Advisory Committee Member
Date	17-10-2023
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Ipsen	☒	☐	☐	☐
BMS	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	Dr. Urban Emmenegger
Position	Genitourinary Drug Advisory Committee Member
Date	13-10-2023
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0312-000
Brand name (generic)	Cabometyx (cabozantinib) + Opdivo (nivolumab)
Indication(s)	for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC
Organization	Kidney Cancer Research Network of Canada
Contact information[a]	Name: Dr. Dominick Bossé [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

KCRNC agrees with the recommendation of pERC that cabozantinib in combination with nivolumab be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease

Re: "*pERC noted that since cabozantinib monotherapy is currently reimbursed as a second and third-line therapy for patients with advanced or metastatic RCC, use of cabozantinib-nivolumab as a first-line treatment for RCC would impact subsequent treatment sequencing. Further, it is unclear which treatments would be appropriate as second- or third-line treatment options. pERC suggested the provisional funding algorithm for advanced or metastatic RCC be updated to address these treatment gaps.*" (p. 6 of draft recommendation).

KCRNC supports updating the provisional funding algorithm for advanced or metastatic RCC. As per national consensus of RCC experts published by Canil et al. in CUAJ 2021, second line option should include axitinib.

Re: *"What evidence is available to support downstream sequencing after cabozantinib-nivolumab and what should the sequencing look like?"* (Table 2, p. 10)

The Kidney Cancer Research Network of Canada (KCRNC) annually produces an evidence-based consensus statement based on the deliberations and conclusions of key Canadian opinion leaders in the management of advanced renal cell cancer. The 2021 consensus statement can be found here:

https://www.kidneycancercanada.ca/wp-content/uploads/2021/04/CUA-guidelines-Management-of-Advanced-Kidney-Cancer.pdf

As per this national consensus published by Canil et al. in CUAJ 2021, second line option should include axitinib. KCRNC will, at such time CADTH issues a notice of a provisional funding algorithm project for advanced or metastatic RCC, provide further input and evidence addressing the question of sequencing of treatments following cabozantinib + nivolumab.

KCRNC agrees with extending the favorable recommendation to non clear cell RCC, recognizing that cabozantinib targets MET alterations often reported in patients with papillary RCC and based on the PAPMET trial (Pal et al, Lancet, 2021) showing that cabozantinib is the preferred TKI to treatment such patients, cabozantinib + nivolumab may become the favored treatment for papillary RCC for multiple clinicians. It will be important to ensure access to second line therapy.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
If not, please provide details regarding the information that requires clarification.		

Re: Table 1. **Reimbursement Conditions and Reasons** (p.2): "*Patients must not have any of the following: 3.1. Active central nervous system metastases…*"

We suggest to leave to clinicians expert in treatment of RCC the need to assess suitability of using nivolumab + cabozantinib in patients with active brain metastases. They are no strong rational to exclude these patients as recommended by CADTH. Retrospective evidence published by Hirsch et al. in Jama Oncol 2021 suggest that cabozantinib alone has intracranial objective response rate of 55% (95% CI, 36%-73%) without concurrent brain directed therapy and 47% (95% CI, 33%-61%) in a cohort of patients treated with concurrent radiotherapy. In addition, nivolumab single agent also demonstrated modest activity in the brain in a subset analysis of the NIVOREN trial, with an intracranial response rate of 12% (Flippot et al, J Clin Oncol 2019). This suggest that cabozantinib +nivolumab may indeed be the favored regimen for patient with brain metastasis.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

for Clinician Groups

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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0312
Name of the drug and Indication(s)	Cabozantinib in combination with nivolumab for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC)
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons

Version: 1.0
Publication Date: TBC
Report Length: 2 Pages

Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. The algorithm will need to be updated (rapid algorithm) 2. PAG is asking about downstream sequencing after first-line cabozantinib-nivolumab
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0312-000
Brand name (generic)	Cabometyx (cabozantinib) + Opdivo (nivolumab)
Indication(s)	for the first-line treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic RCC
Organization	Kidney Cancer Canada
Contact information[a]	Name: Christine Collins

Stakeholder agreement with the draft recommendation

1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

While KCC generally agrees with the recommendation, we request that CADTH/pERC re-visit the recommendation as is applies to "*Initiation*", specifically, "*Patients must not have any of the following: 3.1. Active central nervous system metastases…*"

We are aware of evidence demonstrating that patients with brain metastasis would benefit from the cabozantinib component of this treatment combination, as well as evidence that demonstrates *modest* efficacy on brain metastasis from nivolumab. We advise that CADTH rely on the expert advice and recommendations from the Kidney Cancer Research Network of Canada with respect to the use of this treatment combination for patients with active central nervous system metastases.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

If not, what aspects are missing from the draft recommendation?

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

KCC agrees with expert committee's recommendation that the provisional funding algorithm for mRCC undergo a comprehensive review to address treatment sequencing. For expert opinion on algorithm development, we recommend that CADTH refer to the consensus statements produced

annually by the Kidney Cancer Research Network of Canada (KCRNC). The KCRNC produces evidence-based consensus statement based on the deliberations and conclusions of key Canadian opinion leaders in the management of advanced renal cell cancer. Here is a link to the 2021 consensus statement:

https://www.kidneycancercanada.ca/wp-content/uploads/2021/04/CUA-guidelines-Management-of-Advanced-Kidney-Cancer.pdf

Further, KCC would like to highlight that implementation of this recommendation in certain provinces (Ontario and Atlantic Canada) will be complicated due to this regimen being a mixed regimen (IV + oral). Reimbursement and treatment access processes in Ontario and Atlantic Canada pose significant barriers to patients who are under the age of 65 who are trying to access oral/take-home cancer treatments.

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

If not, please provide details regarding the information that requires clarification.

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

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A. Patient Group Information	
Name	*Christine Collins*
Position	*Executive Director*
Date	*October 19, 2023*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BMS	☐	☐	☐	☒
Eisai	☐	☐	☒	☐
IPSEN	☐	☐	☐	☒
Merck	☐	☐	☐	☒
Pfizer	☐	☐	☐	☒

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

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Company	**Check Appropriate Dollar Range**			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0312
Brand name (generic)	Cabometyx® (cabozantinib) in combination with Opdivo® (nivolumab)
Indication(s)	For the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or metastatic renal cell carcinoma (RCC) who have had no prior systemic therapy for metastatic disease
Organization	Ipsen Biopharmaceuticals Canada Inc.
Contact information[a]	Anna Liovas [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Ipsen Biopharmaceuticals Canada Inc. agrees with pERC's recommendation that Cabometyx® in combination with Opdivo® (CABO+NIVO) be reimbursed for the treatment of adult patients with advanced (not amenable to curative surgery or radiation therapy) or mRCC who have had no prior systemic therapy for metastatic disease and supports conversion of draft to final recommendation. Ipsen is committed to working with pCPA to facilitate access to the small population that can benefit from this combination.

Ipsen disagrees with this statement on page 5 under Feasibility of Adoption that "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."

- This statement requires a broader interpretation as it can be taken out of context. This assessment is based on list price comparisons. This is artificial as confidential pricing drives the true impact. Minimal budget impact is anticipated.
- Further, first line use of CABO+NIVO will come from patients that would have been given a funded combination such as LEN+PEM or AXI+PEM. Therefore, the total spend on aRCC first line treatment will change very little with the funding of CABO+NIVO.

Ipsen also disagrees with elements in the Summary of Economic Evaluation.

- pERC has decreased the time horizon to 10 years. In the model, patients are still alive at 10 years. A longer time horizon would have yielded an improved ICER.
- The delta QALY vs LEN or AXI in combination with PEM in all and intermediate/poor populations is very small, indicating similar efficacy. However, as a denominator in an ICER equation, this contributes to a larger ICER.

- A more appropriate description would be that CABO+NIVO is similar to the currently funded IO/TKI combinations, and any additional cost needs to be reported in a more balanced way as list prices are used.

Expert committee consideration of the stakeholder input

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Ipsen continues to disagree with the following statement as cabozantinib and sunitinib have similar tolerability and management: 'pERC considered the safety profile of cabozantinib-nivolumab to be manageable, albeit more burdensome, than sunitinib.'

Though it does not appear to be incorporated into the implementation guidance, Ipsen disagrees with the comments from the clinician chosen by CADTH that characterized patients with least disease burden most likely to respond.

- Under Patient population on page 8, the clinical expert conversely indicated that patients who are best suited for CABO+NIVO are those with IMDC intermediate or poor risk prognosis, while patients with IMDC favourable risk prognosis remain candidates for a single agent VEGF-TKI.
- This is further inconsistent with the input of both clinician groups (which Ipsen agrees with). Specifically, in Clinician Group Input page 9, both groups agreed that untreated patients with ANY IMDC prognostic risk score would be potentially eligible for systemic treatment with CABO+NIVO. The clinician groups indicated that CABO+NIVO would be an additional first-line treatment option for patients with aRCC, and this combination therapy could potentially address unmet needs for some patients.

Finally on Page 15, under Indirect Comparisons, Critical Appraisal, Ipsen agrees there is a high degree of uncertainty surrounding comparative effectiveness of CABO+NIVO with relevant comparators. It must be acknowledged that conducting an NMA evaluating primary therapy in aRCC is challenging, given the heterogeneity of the clinical trial evidence. Two of the most relevant challenges included violations of the proportional hazards assumption and heterogeneity between trials. To overcome these, a Bayesian fractional polynomial NMA was undertaken, where fractional polynomials were fitted along with the fixed effects and random effects with heterogeneity for the intercept. Furthermore, Ipsen included a scenario analysis in the final report where Bayesian fractional polynomial NMA was substituted with an NMA, with trial level covariate adjustments. The scenario analysis with trial level adjustment covariates, which mitigates the effect of heterogeneity, CABO+NIVO dominated LEN+PEM and had comparable effectiveness to AXI+PEM. Notwithstanding, the NMA confirmed that all three IO-TKI combination therapies had comparable efficacy. Therefore, the sensitivity of the ICERs is an artifact of comparable efficacy between regimens- not due to the NMA. The submitted NMA used sound methodology and provided the best available evidence for the indirect comparison.

Clarity of the draft recommendation

3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

Yes, however one statement warrants clarification within the Rationale for the Recommendation on page 3. "(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-nivolumab compared with sunitinib."

- This should read "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 progression or death with cabozantinib-nivolumab compared with sunitinib at any time point.

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

Yes, however, there are several inconsistencies that require clarification.

- On page 10, under Drug Program Implementation Questions, Ipsen disagrees with the Clinical Expert Response "Cabozantinib-nivolumab should not be used for patients with poor performance status." This statement, although a clinical opinion, is inconsistent with other comments made by the same expert and may pose challenges for implementation of funding and treatment choices.
- On page 8, the clinician consulted by CADTH states CABO+NIVO is best suited for IMDC intermediate or poor risk and comments that patients with the least disease burden are most likely to respond. Note that CABO+NIVO has demonstrated and proven efficacy regardless of IMDC status. Checkmate 9ER was not powered to assess the efficacy of subgroups and demonstrated statistically significant advantage in PFS and OS in all subgroups.
- This causes confusion and further inconsistency with the recommendation that the criteria for CABO+NIVO should be like that of LEN+PEM and AXI+PEM.

Ipsen disagrees with the clinician's comments on page 10: "The clinician noted a lack of strong evidence that CABO+NIVO is better than other 1st-line options or has a more favourable toxicity profile, there is no rationale for switching." Rather Ipsen agrees with pERC's assessment. The following statements should be noted for accuracy, consistency, and implementation.

- LEN+PEM needs to be added to: "The clinical expert noted that both IPI + NIVO and AXI+PEM have more obvious sequencing strategies,
- not yet 'apparent' is miseading: "a clear second-line and beyond strategy is not yet *apparent* (should say consistent)."

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

Ipsen agrees, however, a few items require clarification for consistency in funding implementation.

On page 9, pERC considered that it would be reasonable to re-administer nivolumab only up to 1 year, with or without CABO. The guidance around retreatment after relapse requires clearer language

On Page 4, under Condition #5, the statement is untrue 'There is *no data supporting the efficacy and safety* when either component is initially used as monotherapy for the first-line treatment of advanced or mRCC.' Cabometyx® though not funded, is indicated for monotherapy in 1st line aRCC.

[a] CADTH may contact this person if comments require clarification.