CADTH

pan-Canadian Oncology Drug Review Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Registered Clinician)

Cabozantinib (Cabometyx) for Hepatocellular Carcinoma

April 22, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Cabozantinib (Cabometyx) for Hepatocellular Carcinoma (HCC)
Eligible Stakeholder Role	Clinician (Joint Clinician Input/Feedback)
Organization Providing Feedback	Ad hoc group of HCC-treating physicians Dr. Howard Lim, Medical Oncologist, BC Cancer Agency Dr. Yoo-Joung Ko, Medical Oncologist, Sunnybrook Odette Cancer Centre, Toronto. Dr. Mark Doherty, Medical Oncologist, Sunnybrook Odette Cancer Centre, Toronto. Dr. Eric Chen, Medical Oncologist, Princess Margaret Cancer Centre, Toronto. Dr. Brandon Meyers, Medical Oncologist, Juravinski Cancer Centre, Hamilton Dr. Vincent Tam, Medical Oncologist, Tom Baker Cancer Centre, Calgary.

** CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the initial recommendation:

☒ Agrees ☐ Agrees in part ☐ Disagrees

We agree with the pERC recommendation for reimbursement of cabozantinib (Cabometyx) in adult patients with unresectable hepatocellular carcinoma (HCC) in the second-line setting after progression on sorafenib or lenvatinib, and we agree with the eligibility criteria stated by pERC as they are aligned with the inclusion/exclusion criteria of the CELESTIAL clinical trial, which this group determined to be generally reasonable.

As you will note below in Section 3.2, we also (enthusiastically) support *early conversion to final recommendation* as there is a growing urgency to have in place a funded 2nd line treatment for patients who have received first-line treatment with lenvatinib. In Canada, only regorafenib is available as a 2nd line option, funded only (currently) in some provinces, **but only for patients who were treated in the 1st line with sorafenib**.

In recent months, many of our newly diagnosed patients with advanced and unresectable HCC have been prescribed lenvatinib as the front-line treatment. Recognizing that some of these patients may have disease progression and require a funded 2nd line treatment, we urgently require rapid uptake of pERC's funding recommendation. Thus, we not only support early conversion of the pERC initial recommendation, but as cabozantinib is urgently needed in the 2nd

line, we also urge **rapid negotiation by the pan Canadian Pharmaceutical Alliance, and rapid implementation by all provincial, territorial and federal public drug plans.**

b) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☒ Agrees ☐ Agrees in part ☐ Disagrees

While no explicit provisional algorithm accompanied the pERC Initial Recommendation or the Initial Clinical Guidance Report, we do agree with the pERC recommendation that cabozantinib (Cabometyx) be available to adult patients with unresectable hepatocellular carcinoma (HCC) in the second-line setting after progression on sorafenib or lenvatinib.

For clarity on establishing an algorithm, we wish to reiterate the expert opinion, observations and recommendations regarding optimizing a treatment algorithm in the HCC setting provided in our original Clinician Input Submission for cabozantinib for HCC. Excerpts from that clinician input submission are below:

Excerpts from p.6

> "Clinical research is beginning to focus on optimizing a treatment algorithm in the HCC setting. In the absence of a direct comparison between available second-line options, some aspects of the RCTs help us determine how new treatments should be used. For example:
>
> -regorafenib should not be offered to patients who are sorafenib intolerant.
>
> -due to it's unique molecular pathway, cabozantinib can be administered to patients who are intolerant to sorafenib
>
> - CELESTIAL supports the positioning of cabozantinib as the preferred 2nd or subsequent line agent for the treatment of HCC (BCLC stage C) patients."

Excerpts from p. 7

> "…we do believe that there is a signal of **larger survival benefit with cabozantinib supporting it as a preferred agent in the 2nd line."**

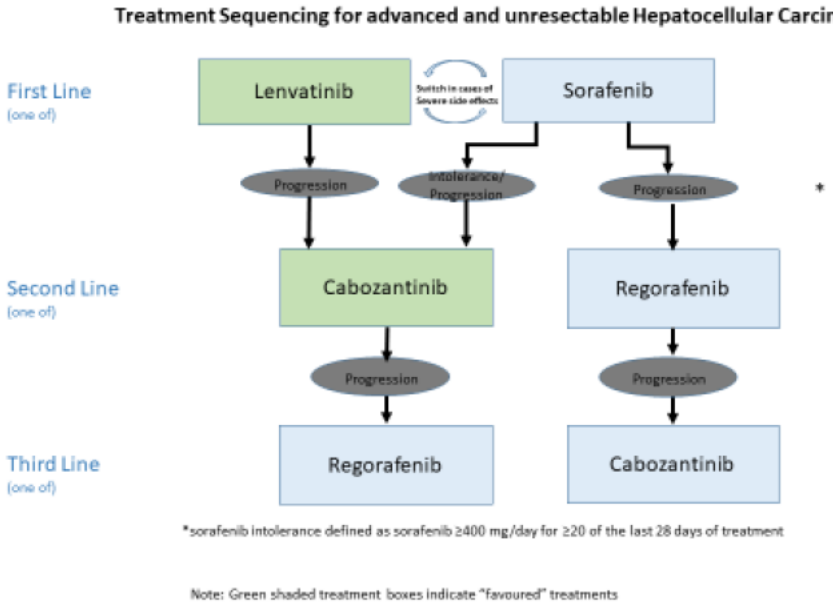
Excerpts from p. 8

> "-for patients who discontinue sorafenib due to toxicity, regorafenib should not be used, with cabozantinib preferred.
>
> -in 2nd line, for patients who have progressed on either sorafenib or lenvatinib, both regorafenib and cabozantinib are options, **with emerging evidence on efficacy favouring cabozantinib as the preferred option."**

and

"Cabozantinib could be used as a third-line TKI treatment since the CELESTIAL trial included patients who had up to two lines of previous treatment (as long as one line was sorafenib)."

Our clinician group has developed the following graphic to represent the treatment algorithm:



c) Please provide editorial feedback on the initial recommendation to aid in clarity. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the stakeholder would support this initial recommendation proceeding to final recommendation ("early conversion"), which would occur two business days after the end of the feedback deadline date.

☒ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

☐ Do not support conversion to final recommendation.

Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a final recommendation, please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the stakeholder during the review.

Please note that new evidence will be not considered at this part of the review process, however, it may be eligible for a resubmission.

Additionally, if the eligible stakeholder supports early conversion to a final recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, the criteria for early conversion will be deemed to have not been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pERC initial recommendation, including the provisional algorithm.

As part of the CADTH's pCODR review process, pERC makes an initial recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. The initial recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 business days within which to provide their feedback on the initial recommendation. It should be noted that the initial recommendation, including the provisional algorithm, may or may not change following a review of the feedback from stakeholders.

CADTH welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The stakeholder feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the initial recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part, or disagree with the initial recommendation, and to provide a rationale for their response. Please note that if a stakeholder agrees, agrees in part or disagrees with the initial recommendation, they can still support the recommendation proceeding to a final recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a final recommendation ("early conversion")?**

   An efficient review process is one of the key guiding principles for CADTH's pCODR process. If all eligible stakeholders support the initial recommendation proceeding to a final recommendation and that the criteria for early conversion as set out in the *Procedures for the CADTH Pan-Canadian Oncology Drug Review* are met, the final recommendation will be posted on the CADTH website two business days after the end of the feedback deadline date. This is called an "early conversion" of an initial recommendation to a final recommendation.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), including the provisional algorithm as part of the feasibility of adoption into the health system, the criteria for early conversion will be deemed to have **not** been met and the initial recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. If the substantive comments relate specifically to the provisional algorithm, it will be shared with CADTH's Provincial Advisory Group (PAG) for a reconsideration. Please note that if any one of the eligible stakeholders does not support the initial recommendation proceeding to a final recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the initial recommendation. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the initial recommendation. If the feedback can be addressed editorially this will done by the CADTH staff, in consultation with pERC, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with PAG.

The final recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit feedback on the initial recommendation:
   - The sponsor and/or the manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - CADTH's Provincial Advisory Group (PAG)

b) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
   - The sponsor and/or the manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Board of Directors of the Canadian Association of Provincial Cancer Agencies

- Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process.
- The template for providing stakeholder is located in section 3 of this document.
- The template must be completed in English. The stakeholder should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply.
- Feedback on the initial recommendation should not exceed three pages in length, using a minimum 11-point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be provided to the pERC for their consideration.
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Organization Providing Feedback	Cancer Care Ontario GI DAC

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Please explain why the stakeholder agrees, agrees in part or disagrees with the initial recommendation. If the stakeholder agrees in part or disagrees with the initial recommendation, please provide specific text from the recommendation and rationale. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.

b) Please indicate if the stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

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Please explain why the stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes new information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

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