CADTH

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

Atezolizumab & Bevacizumab for Hepatocellular Carcinoma

November 17, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Atezolizumab (Tecentriq) and Bevacizumab (Avastin) for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy.
Eligible Stakeholder Role	Manufacturer/Sponsor
Organization Providing Feedback	Hoffmann-La Roche Limited

** 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

Hoffmann-La Roche Limited (Roche) agrees with pERC's initial recommendation for reimbursement of atezolizumab in combination with bevacizumab for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC) who require systemic therapy. Roche supports conversion of the initial recommendation to a final recommendation.

<u>Clinical Benefit and Patient-Based Values</u>

- Roche fully agrees with pERC that there is a net clinical benefit of atezolizumab + bevacizumab compared with sorafenib, as demonstrated by the statistically significant and clinically meaningful survival benefit shown in the IMbrave150 trial.
- Roche agrees that the combination of atezolizumab + bevacizumab aligns with patient values of improvement in OS, delay in time to deterioration in QoL, and manageable toxicity profile compared with sorafenib.
- Roche agrees that eligibility for funding should be aligned with the Health Canada-approved population. Assessment of risk of bleeding should align with the Health Canada product monograph and local practice.
- Roche suggests that the following be included in the final recommendation: patients who are currently receiving sorafenib or lenvatinib but who otherwise would have been able to receive atezolizumab + bevacizumab as per the IMbrave150 trial, may be considered for time-limited funding once the combination becomes publicly-funded (as noted in pERC's response to PAG implementation questions, page 14). Switching would be a decision made between the patient and their treating physician.

<u>Economic Evaluation and Adoption Feasibility</u>

- Roche respectfully believes that the ICER estimate provided by the EGP is likely overestimated, due to conservative choices for OS extrapolation that result in an EGP base case greater than 75% of all other scenarios when all else is unchanged.
    - We believe that the EGP's selection of OS parametric survival distributions for both atezolizumab + bevacizumab and sorafenib are overly conservative. For example, the EGP model estimates a 40-month OS for sorafenib at <1%, which is far lower than expected based on existing evidence. The fact that the EGP's model is inconsistent with observed evidence suggests poor fit and face validity. This is further illustrated by the relatively poor goodness of fit of the EGP selections, as measured by AIC/BIC, compared with other possible distributions.

- Using the deterministic framework, we attempted to recreate the EGP's stepped analysis applying the EGP values or assumptions for all steps except for the OS parametric survival distributions. The EGP base case is at the high end of the range of scenarios when all else remains unchanged. More than 75% of scenarios are below the CADTH base case result.
- Given the model's sensitivity to selected survival extrapolations, the EGP's cost-effectiveness conclusions should be interpreted with caution.

- Roche suggests that the conclusions regarding price reductions for atezolizumab and bevacizumab to fall below a willingness-to-pay (WTP) threshold of $50,000 per QALY should be interpreted with caution.
  - These price reductions have been calculated based on the EGP ICER, which Roche believes is likely to be overestimated.
  - Conclusions based on a $50,000/QALY threshold alone may not be appropriate for all therapies, especially cancer therapies. pCODR reports have historically included both $50,000/QALY and $100,000/QALY thresholds in order to give jurisdictions a range of information to support their decision-making. Furthermore, a 2018 publication by Skedgel, et al. has found evidence of a maximum acceptable threshold of approximately $140,000/QALY for oncology therapies reviewed by pCODR[1].

Notwithstanding our economic comments, Roche supports the conversion of the initial recommendation to a final recommendation to expedite access for patients with HCC. Roche is committed to working with the jurisdictions via the pCPA process to ensure that patients have access to this new standard of care as soon as possible.

b) 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) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
1	pERC Recommendation	Paragraph 5, line 6	Suggested revision from "pERC also concluded that the submitted budget impact analysis was underestimated and that the budget impact of atezolizumab plus bevacizumab at the submitted price would be substantial" to "pERC also concluded that the budget impact of atezolizumab plus bevacizumab at the submitted price would be substantial" given that the Economic Guidance Panel concluded that the incremental budget impact would be similar to the submitted amount.
9	Economic Evaluation	Paragraph 2, line 13	Correction of "In the sponsor's base case, atezolizumab plus bevacizumab was associated with an ICER of $332,281 per QALY gained." to "In the sponsor's base case, atezolizumab plus bevacizumab was

			associated with an ICER of $328,622 per QALY gained.”

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, 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

References:

1. Skedgel, C., Wranik, D. & Hu, M. The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017. PharmacoEconomics 36, 467–475 (2018). https://doi.org/10.1007/s40273-018-0610-0

Template for Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

1 About Stakeholder Feedback

CADTH invites eligible stakeholders to provide feedback and comments on the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) initial recommendation.

As part of the CADTH's pan-Canadian Oncology Drug Review (pCODR) 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 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), 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. 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.

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.

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

- 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)
- 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.
- Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.
- References may be provided separately; however, these cannot be related to new evidence.
- CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback must be disclosable and will be posted on the CADTH website.
- The template must be filed with CADTH as a Microsoft Word document by the posted deadline.
- If you have any questions about the feedback process, please e-mail requests@cadth.ca