pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Registered Clinician)

Brentuximab (Adcetris) for Hodgkin Lymphoma - Resubmission

March 7, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Brentuximab/HL
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient	Registered Clinician Feedback
Organization Providing Feedback	Cancer Care Ontario Hematology DAC

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

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☒ agrees ☐ agrees in part ☐ disagree

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 rational. 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 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

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 pERC Recommendation ("early conversion"), which would occur two (2) 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 in the submission or as additional information 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. If you are unclear as to whether the information you are providing is eligible for a Resubmission, please contact the pCODR program.

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

1 About Stakeholder Feedback

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pERC 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 disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder 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 pCODR's key guiding principles. 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 *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website two (2) 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 pERC 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

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2 Instructions for Providing Feedback

a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
   - The Submitter making the pCODR Submission, 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 Provincial Advisory Group (PAG)

b) 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, however, it may be eligible for a Resubmission.

c) The template for providing *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

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f) 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.

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(Registered Clinician)

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March 7, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Brentuximab Vedotin for adult patients with Hodgkin's Lymphoma that have received at least 2 prior regimens and are not Stem Cell Transplant eligible
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician

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3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

1. "The committee made this recommendation because it was unable to conclude that there is a net clinical benefit of brentuximab vedotin compared with single-agent chemotherapy given the limitations in the evidence from the phase IV clinical trial."

The data in the field of relapsed / refractory Hodgkin's lymphoma (RR-HL) are limited due to the lack of large prospective, randomized clinical trials. The trial defining the role of autologous stem cell transplant (ASCT; the goal of care for eligible patients in the second line setting) is a small academic trial that would be unlikely to meet modern scrutiny to fund new therapies. There have been no randomized trials to define salvage therapy in this patient population and thus clinical practice is driven largely by phase II studies, registry or institutional experience. In the absence of such data, it is not reasonable to attach a higher bar to novel therapies that could better serve this population. The phase IV data are consistent with other brentuximab data that suggest approximately 50% of patients with refractory disease may be salvaged with subsequent therapy. Heterogeneity in the population prevents any further interpretation. There are no other therapies available that appear more effective based on available data.

From a toxicity perspective, the recommendation does not address the effects of salvage therapies that are routinely employed in this setting. Our group at Princess Margaret has published extensively in the area and the available Canadian data speak to the ineffectiveness and significant toxicities of traditional chemotherapy strategies in patients with disease that has not responded to platinum-containing chemotherapy. Subsequent therapies such as mini-BEAM or other regimens are associated with significant toxicities (high rates of significant nausea and vomiting, febrile neutropenia and other

hematologic adverse events) and decrements in health-related quality of life. Given the historic nature of these regimens, this has not been formally assessed in the current era. As outlined in the prior response to pCODR, these are typically short-term toxicities as responding patients are immediately moved towards ASCT which provides the opportunity for definitive cure.

2. "While pERC noted that there is a significant need for more effective treatment options in this setting and that brentuximab vedotin produces anti-tumout activity, the Committee concluded that there was considerable uncertainty in the evidence available on outcomes important to decision-making, such as rates of subsequent ASCT, overall survival (OS) and progression-free survival (PFS)

Once again, the additional data presented to the Committee is consistent with the other available data in this setting. Given the limitations noted above, there will be no additional high quality data to fill this void. Brentuximab vedotin is a standard therapy in this setting and frequently employed by expert centres in this setting around the world. There is no logical reason to believe that the outcomes of responders to brentuximab that go onto to ASCT will be inferior to a similar population that had received more traditional therapies. Importantly, Canadian experts who treat RR-HL use brentuximab vedotin in this setting preferentially if they are able to access it and thus from a clinical decision-making perspective, it is clearly THE currently preferred option.

3. "Furthermore, the Committee was unable to determine how brentuximab vedotin compares with current treatment options given the lack of robust comparative data on outcomes important to decision-making.

This statement merely reiterates the point that was made repeatedly throughout the review. It would appear that "robust comparative data" based on what is discussed by the Committee would be a randomized controlled trial reporting overall and progression-free survival with quality of life and pharmacoeconomic endpoints. Such a study will NOT be performed in this setting – particularly since Canada is one of the few jurisdictions where such a trial might be requested. Other approaches to try to develop evidence in the Canadian environment (such as the Cancer Care Ontario Evidence Building Program) have been pursued unsuccessfully.

While there is some potential access to brentuximab vedotin in this setting on some clinical trials, compassionately through Seattle Genetics or potentially at the hospital or provincial level at a case by case basis, this is not uniform and leads to inequity of access to potentially curative therapy. This is clearly an untenable situation for patients in Canada.

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