PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Pembrolizumab (Keytruda) for Classical Hodgkin Lymphoma

January 5, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	*pembrolizumab (KEYTRUDA®)* *refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, in adults who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.*
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Merck Canada

**pCODR 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

____ agrees **X** agrees in part ____ disagree

Merck Canada agrees with pERC's initial recommendation for pembrolizumab (KEYTRUDA®) for patients with refractory or relapsed classical Hodgkin Lymphoma (cHL). The pERC considered that KEYTRUDA® provides a net overall clinical benefit based on: the rates of complete remission in a heavily pre-treated population, a favourable toxicity profile, the potential to improve quality of life and the substantial need for treatment options in a small population who have had multiple relapses. pERC also recognized that KEYTRUDA® is aligned with patient values.

Merck Canada generally agrees with the ICER assessment in the Economic Guidance Report, however disagrees with the 10 year time horizon proposed by the Economic Guidance Panel (EGP). The panel justified a 10 versus 20 year time horizon by the fact that it would be highly unlikely for these patients to be living beyond 10 years and the lack of data to inform the long term survival in this population. Merck Canada agrees with a time horizon below 20 years but argues it should be longer than the 10 years proposed by the panel, based on the following facts:

- For Brentuximab Vedotin after ASCT, the time horizon established by INESSS and pCODR are 20 and 15 years respectively
- The mean age of patients in the KN-087 trial is 39 years old. Considering the difference between the mean age of patients in KN-087 and the mean age of death reported by Statistics Canada for cHL (62 years old), we believe that a time horizon longer than 10 years is appropriate.

In addition, Merck Canada recommends a rectification to the stated gemcitabine dosing so it reflects what is usually recommended for this drug (should be 3 times every 28 days cycle). Finally Merck Canada recommends aligning the gemcitabine cost used in the model

to the gemcitabine cost listed in the economic input summary table.

Merck Canada supports this initial recommendation proceeding to early conversion, but would like to reinforce the fact that KEYTRUDA® for refractory or relapsed classical Hodgkin Lymphoma (cHL) was assessed using a 200mg fixed dose Q3W and that there are no clinical evidence to support the usage of KEYTRUDA® with a 2mg/kg dose in the cHL population. Furthermore, the 200mg fixed dose Q3W is the dose approved in the Canadian product monograph for the cHL indication.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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.

X	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.

c) Please provide feedback on the initial recommendation. 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 Submitter or Manufacturer-Provided Information

Please provide feedback on any issues not adequately addressed in the initial recommendation based on any information provided by the Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Secretariat.

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
Initial Economic Guidance Report, Page 1	Table 1 Submitted Economic Model Cost of gemcitabine	Row 9: *"Gemcitabine costs $270 per 1000mg •At the recommended dose of 1000mg/m2 every 4 weeks, pembrolizumab costs: o$16.39 per day o$459 per 28-day course"*	– The recommended dose of gemcitabine is 1000mg/m2, three times (days 1, 8, 15), per 28-day cycle[1]. Therefore, the statement on the dosage as well as calculations of the cost per day and the cost per 28-day course of gemcitabine should be rectified. – Correct the following: "gemcitabine costs" instead of "pembrolizumab costs".
Initial Economic Guidance Report, Page 3	Section 1.4 Detailed Highlights of the EGP Reanalysis	Table 2 Submitted and EGP Estimates Row 9: EGP Reanalysis Lower Bound – ICER estimate ($/QALY)	The pCODR recommendation reports a cost of gemcitabine of $270 per 1000mg and was retrieved from QuintilesIMS DeltaPA database. However, this cost was not used in the EGP Reanalysis of their ICER estimate. The data used in the pCODR recommendation should be consistent and therefore, pCODR's cost of gemcitabine should be used in the economic model and the EGP estimated ICER should be updated to reflect that cost (correcting the cost of gemcitabine changes the ICER to 186,439/QALY).
Initial Economic Guidance Report, Page 4	Section 1.4 Detailed Highlights of the EGP Reanalysis	Paragraph 2: The time horizon was changed from 20 years to 10 years (CGP see it as highly unlikely that patients would live beyond 10 years).	A time horizon of 10 years as chosen in EGP reanalysis appears to be too short. In the pCODR recommendation of brentuximab vedotin in cHL[4], the EGP chose a time horizon of 15 years (the time horizon was shortened to 15 years to mitigate any long-term impact of extrapolating based on poor quality data). In their reimbursement review of brentuximab vedotin for cHL, INESSS chose a time horizon of 20 years[5]. Additionally, the mean age in the KN-087 trial is 39 years[2]. Considering the difference between the mean age of patients in KN-087 and the mean age of death reported by Statistics Canada for cHL (62 years old)[3], we believe that a time horizon longer than 10 years

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			would be appropriate.
Initial Economic Guidance Report, Page 3	Summary of PAG input relevant to economic analysis (under Barriers)	Line 1: PAG reported additional chair time as a factor to consider if implementing a funding recommendation	We suggest improving the clarity of this statement as it may lead to confusion. A dose of pembrolizumab is administered intravenously over 30min per cycle. In contrast, gemcitabine is given over 90min per cycle (3x30min). If additional chair time is being assumed as a result of pembrolizumab being an additional line of therapy (as suggested in the CGR, p.29, section 4.4), it should be specified.

About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

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

Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

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 *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.cadth.ca/pcodr for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) 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 forwarded to the pERC.

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.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is 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 considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

1. Cancer Care Ontario. Hodgkin's Lymphoma Regimens. November 2016.
2. Merck. Data on file. 2016.
3. Table 102-0522 - Deaths, by cause, Chapter II: Neoplasms (C00 to D48), age group and sex, Canada, annual (number).
4. Pan-Canadian Oncology Drug Review Final Economic Guidance Report. Brentuximab Vedotin (Adcetris) for Hodgkin Lymphoma. August 29, 2013
5. INESSS recommendation. Adcetris - Hodgkin Lymphoma. June 2014.