pCODR 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 metastatic Urothelial Cancer

March 2, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	pembrolizumab (KEYTRUDA®) For the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy
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 clinical initial recommendation for pembrolizumab (KEYTRUDA®) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

Merck Canada does not agree with the EGP Reanalysis Estimates in the Economic Guidance Report, (page 4 Table 1.3)

Time Horizon: In order to find the proper time horizon that covers a lifetime horizon of urothelial carcinoma, the median overall survival is not a statistic that should be used as a portion of patients can respond for a long time. When looking at the 5-year survival probabilities of patients with distant stage bladder cancer, 5% of patients are still alive after 5 years.[1] This statistic is based on current standard of care and does not show the benefit of pembrolizumab yet. The base case of the model that was provided, models a 5-year survival rate of 6.5% for SOC which is conservative based on the 5-year survival rate shown in real world with the SEER database (5%). For patients on pembrolizumab, the model forecasts that 16.5% of patients would still be alive after 5 years. After 10 years, the model estimates that 3.3% of patients on SOC would still be alive and 9.9% for patients that received pembrolizumab. Based on the SEER data, a 5 year time horizon is clearly too

[1] National Cancer Institute. SEER Program. Cancer Stat Facts: Bladder (2017). https://seer.cancer.gov/statfacts/html/urinb.html. Accessed June 22, 2017.

short. Based on the extrapolation of the data of KN045, a 10-year time horizon still does not appear to cover a lifetime horizon for every patient. In the absence of long-term data, Merck considers a ten year time-horizon is a conservative assumption, and it could require to be even longer.

OS without adjustment for crossover: Pembrolizumab is currently not reimbursed as a treatment option for UC in Canada and therefore should not be available as a subsequent treatment for the comparator arm. Therefore, the OS of the comparator arm should be adjusted for the crossover of patients.

Merck Canada would also like to reinforce the fact that pembrolizumab was assessed using a 200mg fixed dose Q3W and that there are no clinical evidence to support the usage of pembrolizumab with a 2mg/kg dose in the UC population. Furthermore, the 200mg fixed dose Q3W is the dose approved in the Canadian product monograph for this 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.

Support conversion to final recommendation.		_X___	Do not support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.			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

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.

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.