pan-Canadian Oncology Drug Review

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

Pembrolizumab (Keytruda) for Non-small Cell Lung Cancer

November 3, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	*pembrolizumab (KEYTRUDA®)* For the treatment of patients with metastatic NSCLC whose tumours express PD-L1 (as determined by a validated test) and who have disease progression on or after platinum-containing chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumour aberrations should have disease progression on authorized therapy for these aberrations prior to receiving pembrolizumab. Funding is being requested for patients with a TPS (Tumour Proportion Score) of PD-L1 ≥1%.
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Merck Canada Inc.

**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

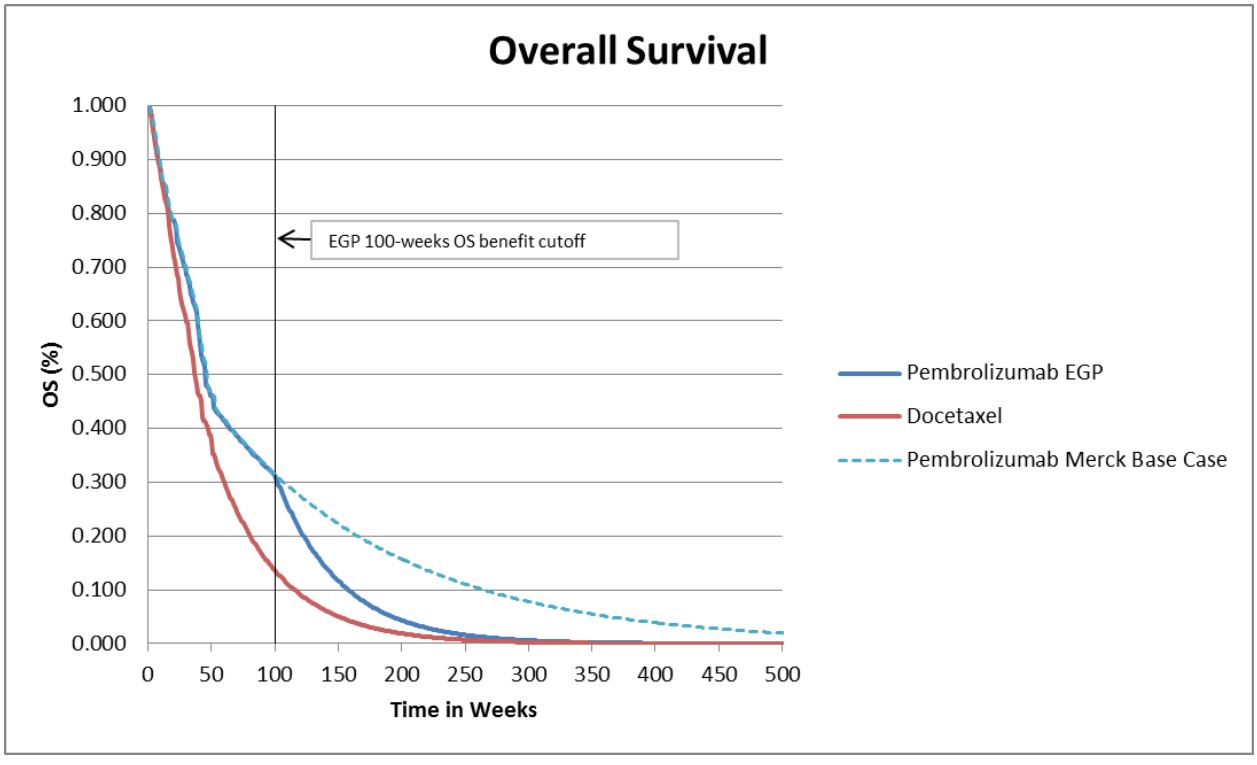
Merck Canada agrees with pERC's clinical assessment and recommendation on the net overall clinical benefit of pembrolizumab (KEYTRUDA®) compared to docetaxel, based on statistically significant and clinically meaningful improvements in overall survival (OS), durable response, meaningful improvements in toxicity profile, and no detriment in quality of life. In addition the Committee was satisfied that pembrolizumab aligned with patient values.

Merck Canada disagrees with pERC and the EGP that the true ICER is likely towards the upper bound of their reanalysis due to the application of a 100 week treatment effect cap and no more than one subsequent line of therapy *(Pages 5, 12; Summary of pERC deliberations; Economic Evaluation; Section 1.4 EGP Reanalysis and Section 1.6 Conclusions)*.

This underestimates the clinical value of pembrolizumab (KEYTRUDA®) based on the currently available data. The shorter treatment effect cap results in a less appropriate extrapolation of OS compared to that submitted in the Merck base case.

It is unlikely that patients would suddenly lose their overall survival benefit over docetaxel immediately at the primary completion date of the study. KEYNOTE 010 was designed to follow overall survival for three years and the current submission included data from the September 2015 cutoff. The estimated completion date of the study is March 2019. Therefore, updates to the data will continue to validate the accuracy of the extrapolation in the base case.

The EGP's assumption for overall survival has been modeled below:



- The extrapolation of overall survival in the base case displays a more natural curve that will be validated as the clinical trial follow-up progresses compared to the EGP scenario which represents the worst case scenario.
- Provided below are the ICER estimates with the inclusion of the EGP assumptions at different treatment effect cap.

Treatment effect CAP	No CAP assumed (base case)	208 weeks (4 years)	156 weeks (3 years)	100 weeks (trial period)
ICER	$149,342	$159,272	$182,836	$254,945

Furthermore, the EGP and pERC indicated that the model does not account for more than one line of subsequent therapy. Merck Canada would like to point out that less than 10% of patients in KEYNOTE 010 received more than one line of subsequent therapy. Both treatment arms had comparable proportion of patients requiring more than one line of subsequent therapy. Therefore, the impact of modeling more than one line of subsequent therapy would likely be minimal and any further modeling would not result in a significant change in ICER.

Merck Canada believes that the assumptions provided in the Merck base case are conservative and representative of the scenario most likely to be reflective in clinical practice.

Merck Canada is committed to working with the provinces to facilitate access to Canadian patients with metastatic non-small cell lung cancer (NSCLC).

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 within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.

Recommendation does not require reconsideration by pERC.

_X_ 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

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.