pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Pembrolizumab (Keytruda) for Nonsquamous Non-Small Cell Lung Cancer

May 31, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	pembrolizumab (KEYTRUDA®) KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, for the treatment of metastatic non-squamous NSCLC, in adults with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.
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®) in combination with pemetrexed and platinum chemotherapy, for the treatment of patients with metastatic non-squamous NSCLC, in adults with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

Merck Canada does not agree with the EGP Reanalysis estimates in the Economic Guidance Report, (page 7 Table 3)

OS with 2-stage adjustment for crossover: This modification is included in the reanalysis' lower bound, with the purpose of "assessing the impact of PFS, OS and ToT extrapolation methods". The purpose of a crossover adjustment should be to portray the full extent of the OS benefit of an experimental treatment. However, Merck Canada strongly believes that no crossover adjustment should be implemented here. In fact, CADTH guidelines for the Economic Evaluation of Health Technologies[1] mention that "Current care should be considered" as a comparator for Canadian economic evaluations and that the "comparators should reflect the target population of interest and the jurisdiction for which the decision is being made". The inclusion of a cross-over adjustment is in opposition with the previous statement, since the comparator arm of Merck Canada's submitted base case adequately reflects current care and clinical practice. As of fact, previous to the regulatory approval of KN189 in Canada, clinical practice consisted of the administration of pembrolizumab monotherapy in 1st line for patients whose tumours express PD-L1>=50%, as well as the use of platinum chemotherapy in 1st line and 2nd line immunotherapy after disease progression for patients with PD-L1<50%. By including a cross-over adjustment, the efficacy of 2nd line immunotherapy is taken out of the comparator arm, which makes that comparison invalid as it doesn't represent Canadian practice. Also, by including a cross-over adjustment, the EGP

unrealistically increases the ICER of the target intervention (pembrolizumab combination) by excluding the cost of 2nd line immunotherapy from the comparator arm. This reduces the cost of post-progression treatments in the comparator arm to a level that doesn't reflect current reality, and hence increases the calculated ICER.

In its evaluation of KN024 (pembrolizumab monotherapy for the treatment of with NSCLC whose tumours express PD-L1>=50%)[2], the EGP didn't include a cross-over adjustment. Also, it is mentioned in the current Economic Guidance Report that "the base case analysis of the model utilizes overall survival for the chemotherapy arm without a switching adjustment. **The CGP and EGP considered this appropriate, as it is reflective of the current clinical practice**". Hence, it seems counter-intuitive to use a lower-bound that over-estimates the ICER, doesn't represent clinical practice and therefor can't be used to inform on the cost-effectiveness of pembrolizumab combination therapy.

Time Horizon: CADTH's guidelines mention that "time horizon should be long enough to capture all relevant differences in the future costs and outcomes associated with the interventions being compared". However, the EGP's modification of the time horizon to 5 years seems to go against the previous statement. With this modification, the model that was provided generates a 5-year survival rate of 3.9% for chemotherapy, which is conservative based on a 5-year survival rate estimated by applying KM mortality for the chemotherapy arm within KN189 for year 1, and mortality risks from years 2-5 for metastatic non-squamous NSCLC patients from the real world SEER database (5-year survival of 7.6%)[3]. For patients on pembrolizumab combination, the current model forecasts that 14.1% of patients would still be alive after 5 years. After 10 years, the model estimates that 0.2% of patients on chemotherapy would still be alive and 1.9% for patients that received pembrolizumab. Hence, a 5-year time horizon is too short to adequately capture all the relevant differences in costs and outcomes and therefore right-censors the clinical benefit of the pembrolizumab combination. Based on the extrapolation of the data of KN189, a 10-year time horizon seems to cover a lifetime horizon for almost all patients; Merck Canada considers a 10-year time-horizon adequate.

For comparison, in its evaluation of KN189, NICE considered the submitted 20 years time horizon satisfactory, stating that "A lifetime horizon is in line with NICE reference case[4]. A duration of 20 years **is considered long enough to reflect the difference in costs and outcomes between pembrolizumab combination and SoC as assessed in this submission**." NICE's justification is aligned with CADTH's Economic guidelines, which makes it more unjustified that the EGP would reduce the time horizon to 5 years.

Likewise, in its reanalysis of KN024, the EGP recognized the validity of a 10-year time horizon as it "was felt to be reasonable by the CGP, as this population is previously untreated and there is evidence that patients with previously untreated metastatic NSCLC may live as long as 10 years". In this current evaluation, the EGP notes that there is uncertainty in the clinical benefit because of the median follow-up duration of the trial (13 months). However, in its evaluation of KN-024, a 10-year time horizon was maintained even though the median follow-up duration was shorter (11.2 months). There seems to be inconsistency in the way EGP approaches time horizon.

Merck Canada would also like to reinforce the fact that pembrolizumab, in combination with pemetrexed and platinum chemotherapy was assessed using a 200mg fixed dose Q3W. Furthermore, the 200mg fixed dose Q3W is the dose approved in the Canadian product monograph for this indication and recommended by the CGP.

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
16	Appendix 1	1st paragraph	Patients who are unable to tolerate chemotherapy after starting treatment with pembrolizumab in combination with chemotherapy can stop treatment with the chemotherapy component while continuing to receive single agent pembrolizumab.

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.

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1 CADTH Methods and Guidelines. Guidelines for the Economic Evaluation of Health Technologies: Canada. 4th Edition. Version 1.0. Ottawa, Canada. March 2017

2 pCODR Final Economic Guidance Report, Pembrolizumab (Keytruda) Non-Small Cell Lung Cancer, August 23, 2017. https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_1stln_fn_egr.pdf

3 Insinga RP, Vanness DJ, Feliciano JL, Vandormael K, Traore S, Burke T. Cost-effectiveness of pembrolizumab in combination with chemotherapy in the 1st line treatment of non-squamous NSCLC in the US. J Med Econ. 2018 Dec;21(12):1191-1205.

4 NICE, Single Technology Appraisal, Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer [TA531] Committee papers, July 2018, https://www.nice.org.uk/guidance/ta531/evidence/committee-papers-pdf-4909657501