



**pan-Canadian Oncology Drug Review
Stakeholder Feedback on a pCODR Expert
Review Committee Initial Recommendation
(Sponsor)**

**Pembrolizumab (Keytruda) for Renal Cell
Carcinoma**

April 2, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	pembrolizumab (KEYTRUDA®) For the treatment of patients with advanced or metastatic renal cell carcinoma (RCC) with axitinib, in adults with no prior systemic therapy for metastatic RCC
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer 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 agrees in part disagree

Merck Canada agrees with pERC’s clinical initial recommendation for pembrolizumab (KEYTRUDA®) in combination with axitinib, for the treatment of patients with advanced renal cell carcinoma.

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

Attenuating relative treatment effect: Merck Canada consider this to be an inappropriate analysis, as there is no clinical support for such a limited period of treatment. This is further supported by the clinically implausible long term-survival estimates when implementing a 5 years treatment effect cap, shown in Table 1 below.

Table 1. OS estimates implementing clinically implausible treatment waning assumption

Years	Merck Canada's Base Case		EGP's 5 years treatment waning		10 years treatment waning,	
	P+A	S	P+A	S	P+A	S
1	88.3%	79.9%	88.3%	79.9%	88.3%	79.9%
2	78.0%	63.9%	78.0%	63.9%	78.0%	63.9%
3	68.7%	50.9%	67.5%	50.9%	68.2%	50.9%
5	53.5%	32.5%	46.0%	32.5%	50.6%	32.5%
10	28.7%	10.6%	15.0%	10.6%	19.2%	10.6%
15	15.4%	3.4%	4.9%	3.4%	6.2%	3.4%

The results shown above substantiate Merck Canada's opinion that the implementation of a treatment waning effect at 5 years produces clinically nonsensical results, showing minimal survival benefit on pembrolizumab in combination with axitinib versus sunitinib. Using a treatment waning at 10 years yields more plausible results.

- 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.

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
9	Registered clinician input	2 nd to last sentence	<p>Although it indicates that another PD-1 inhibitor may be used if time exceeds 6 months after stopping pembrolizumab, no where in the recommendation does it mention that as per study protocol, patients could receive up to 12 months of pembrolizumab after stopping the initial treatment due to a confirmed complete response or 35 cycles of pembrolizumab.</p> <p>A re-treatment statement, as per the study protocol and as other previous KEYTRUDA® recommendations (NSCLC 1L & 2L) should be included in the pERC recommendation section</p>

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
2	Potential Next Steps Factors affecting Budget..	2 nd paragraph, 3 rd line	<p>Although the following phrase: “potential for re-treatment with pembrolizumab” suggests the possibility for re-treatment, it is not clearly included in the pERC recommendation section</p> <p>As per the study protocol, patients could receive up to 12 months of pembrolizumab if they experienced an investigator-determined confirmed radiographic disease progression, according to immune-related response criteria after stopping their initial treatment with pembrolizumab due to achievement of a confirmed complete response or having experienced 35 administrations of pembrolizumab.</p> <p>A re-treatment statement, as per the study protocol and as other previous KEYTRUDA® recommendations (NSCLC 1L & 2L) should be included in the pERC recommendation section</p>

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC), including the provisional algorithm. (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation, including the provisional algorithm may or may not change following a review of the feedback from stakeholders.

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 rationale 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), including the provisional algorithm as part of the feasibility of adoption into the health system, 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. If the substantive comments relate specifically to the provisional algorithm, it will be shared with PAG for a reconsideration. 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. Please also note that substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will be done by the CADTH staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting. Similarly if the feedback relates specifically to the provisional algorithm and can be addressed editorially, CADTH staff will consult with the PAG chair and PAG members.

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

2 Instructions for Providing Feedback

- a) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
 - The Sponsor 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) The following stakeholders are eligible to submit Feedback on the provisional algorithm:
 - The Sponsor 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 Board of Directors of the Canadian Provincial Cancer Agencies
- c) 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.
- d) 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.)
- e) At this time, the template must be completed in English. The Stakeholder 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.
- f) 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 provided to the pERC for their consideration.
- g) 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, and should not contain any language that could be considered disrespectful, inflammatory or could be found to violate applicable defamation law.

- h) 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 program.
- i) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.
- j) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.