CADTH

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Manufacturer)

Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma

October 3, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Pembrolizumab (KEYTRUDA®) As a monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (Combined Positive Score (CPS)) ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Organization Providing Feedback	Submitter and Manufacturer Merck Canada

**The pCODR program may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by the pCODR program.*

3.1 Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Merck agrees with pERC regarding the "substantial unmet need for effective and tolerable treatments in patients who are cisplatin ineligible, especially in those who are not eligible for any platinum-based chemotherapy and have locally advanced or metastatic UC". However, Merck does not agree with pERC's decision not to recognize the clinical benefit of pembrolizumab for these patients. Merck also notes that the pERC initial recommendation does not align with the pCODR Clinical Guidance Panel (CGP) assessment and the feedback received by clinicians and patients.

To ensure consistency in HTA assessment and equity across patients facing similar unmet medical needs, Merck respectfully request that pERC reconsider their recommendation for the locally advanced or metastatic urothelial carcinoma cisplatin-ineligible patients. Especially for the platinum ineligible patients that have no

effective treatment option and for whom no phase III evidence will be available compared to the currently used treatment. Merck kindly asks pERC to recommend the reimbursement of pembrolizumab for these patients.

1- (Page 1, pERC Recommendation, 2nd paragraph; Clinical Benefit)
pERC was not satisfied that there is a net clinical benefit of pembrolizumab compared with gemcitabine plus carboplatin or single-drug chemotherapy given the limitations in the evidence from the available phase II clinical trial. The Committee concluded that there was considerable uncertainty in the magnitude of clinical benefit of pembrolizumab compared with appropriate comparators.

In the past, pERC has recognized net clinical benefit in other indications where the evidence was based on non-comparative trials, despite considerable uncertainty as to the magnitude of the clinical benefit. In recent reviews, pERC recommended reimbursement of pembrolizumab and nivolumab in patients with refractory or relapsed classical Hodgkin lymphoma (cHL) and of avelumab for the treatment of metastatic Merkel cell carcinoma (mMCC). Evidence for these files was also based on Phase II non-comparative trial and showed similar outcomes in settings with substantial unmet need.

Of note, the CGP mentions that the results of KEYNOTE-052 compare favorably to currently available chemotherapies in both subgroups of UC cisplatin ineligible patients and that the duration of response and tolerability compared with chemotherapy strongly supports the role of pembrolizumab in cisplatin-unfit metastatic UC patients. The registered clinicians reported that in contrast (to chemotherapy), pembrolizumab is less toxic and can provide significant and durable benefits. They also stated that "There is general agreement that pembrolizumab should be the preferred first-line treatment for the target population".

2- (Page 3, Summary of pERC Deliberations, 2nd and 3rd paragraphs; Clinical Benefit)
In addition, pERC considered that the magnitude and durable nature of objective tumour responses observed with pembrolizumab were important and agreed with the CGP on the safety of pembrolizumab. The Committee considered that incidence and severity of adverse reactions appear manageable and consistent with the safety profile of pembrolizumab in other cancer trials. However, pERC was not satisfied that there is a net clinical benefit for pembrolizumab.

The CGP mention that in the platinum-ineligible patients, pembrolizumab showed a clinically meaningful overall response rate and prolonged durability of responses, with a toxicity profile that is better than that experienced with chemotherapy. Furthermore, they concluded that the platinum-ineligible patients have no effective treatment options, stating that "This patient population is often not well enough to receive any treatment with no hope of benefit, or receiving no treatment or single agent gemcitabine only, that have dismal response rate of 10% or less". By comparison, the objective response rate to pembrolizumab in the platinum ineligible patient population was 26.2% (95% CI, 19.3 – 34.2) and the median duration of response (DOR) was not reach after a median follow up of 11.5 months. This is substantially superior to gemcitabine.

The CGP also noted the importance of prolonged responses for both the cisplatin ineligible with PD-L1 CPS ≥ 10 and platinum ineligible subgroups. As reported by O'Donnell et al., at ASCO 2019, in the final update for KEYNOTE-052, the median DOR with pembrolizumab for the total population is 30.1 months (95% CI: 18.8-NR). In patients who are cisplatin ineligible and PD-L1 CPS ≥ 10, the median DOR was not reached. These patients experienced clinically meaningful response rates with an ORR of 47.3% and median overall survival (OS) of 18.5 months. (O'Donnell PH, Balar AV, Vuky J, et coll. KEYNOTE-052: Phase 2 study evaluating first-line pembrolizumab in cisplatin-ineligible advanced urothelial cancer (UC): updated response and survival results) Importantly, examination of the Kaplan-Meier curve for these patients show a prolonged tail stretching out passed 24 months at approximately 40% overall survival (Figure 6B, O'Donnell et al ASCO 2019).

The CGP also specifically mentions that for the platinum-ineligible patients, new therapies showing tumour response with improved toxicity are urgently needed. Again, pERC agrees that the magnitude and durable nature of objective tumour responses observed with pembrolizumab were important and agree with the CGP

on the safety of pembrolizumab. Based on the CGP assessment and pERC's agreement, pembrolizumab's clinical benefit does address the unmet need in this subpopulation. In their report, the CGP clearly mention that "The KEYNOTE 052 trial is an important trial that showed pembrolizumab has both efficacy and tolerability in patients who are cisplatin-ineligible".

3- (Page 3, Summary of pERC Deliberations, 2nd paragraph; Clinical Benefit) pERC mention that "There are ongoing phase III trials with pembrolizumab in the two target patient populations that may provide clarity on the comparative effectiveness of pembrolizumab in relation to alternative treatment options."

Merck wants to clarify that for the platinum-ineligible patients (one of the target patient population) there will be no phase III trial comparing pembrolizumab to chemotherapies nor best supportive care (BSC). As mentioned by the Committee, "conducting a phase III trial with pembrolizumab compared with standard of care (palliative care or single-drug gemcitabine) would likely not be feasible in the patient population that is platinum ineligible due to rapidly deteriorating patients and equipoise considerations." As such, uncertainty in the magnitude of the clinical benefit of pembrolizumab compared to the suboptimal treatment for the platinum ineligible patients will persist.

In addition, on page 2 of the recommendation, in Potential Next Steps For Stakeholders, pERC mention that for the platinum-ineligible patients subgroup, higher-quality evidence could form the basis of a resubmission to pCODR. Assuming pCODR is referring to MK-7902-011 trial (pembrolizumab vs pembrolizumab + lenvatinib in patients with advanced UC who are cisplatin-ineligible), given that pembrolizumab is used in both arms and the lack of a chemotherapy-alone arm, this study will not address the uncertainty in the magnitude of clinical benefit. Note that this study is not expected to readout before the end of 2022. As such, the urgency for new therapies will not be addressed by this study. With respect to KEYNOTE-361, as it does not include platinum ineligible patients, it can only inform as to the magnitude of the pembrolizumab-containing arms compared to carboplatin/gemcitabine for the patients that can tolerate that treatment.

4- (Page 6, Key efficacy results, 3rd paragraph; Clinical Benefit) pERC is stating that "Data on median DOR as assessed by IRR using RECIST 1.1 for platinum ineligible patients were not reported".

Merck wants to point out that in the clinical guidance report initially sent by pCODR, the document erroneously reported a median DOR of 2.1 months for the platinum ineligible patients. Merck then clarified that the 2.1 months is a time to response not median DOR. This data was submitted by Merck based on the request by pCODR for a time to response for the platinum ineligible patients. The error was erased from the published report. The median DOR for these patients was in fact not reached (95%CI: 2.8, 27.6+ months) at the 30-nov-2017 data cut-off, which is a duration of response significantly different than what was mistakenly considered by the CGP and pERC; and much longer then what is observed with chemotherapies. Merck asks that pERC consider the accurate median DOR for the platinum ineligible patient in their reconsideration and believes that it will mitigate the uncertainty in the magnitude of the clinical benefit in these patients.

5- (Page 3, Summary of pERC Deliberations, 2nd paragraph; Clinical Benefit)
pERC noted that ORR is an uncertain surrogate for survival in most solid tumours.

Merck agrees that ORR is not a good surrogate marker for survival in chemotherapy. However, there is a strong suggestion that ORR is a good surrogate marker in PD-1 inhibitors. Recently, Fradet et al, in an updated analysis of KEYNOTE 045, examined OS by best overall response (Poster ASCO 2018) and showed that patients who experienced a complete or partial response when treated with pembrolizumab had significantly longer OS (HR = 0.14 (95% CI 0.06-0.33, p<0.00001) and PFS (HR=0.27, 95% CI 0.14-0.51, p<0.0001) compared to chemotherapy. Similar results were not seen in patients experiencing stable or progressive disease. Similarly, median OS in patients with advanced hepatocellular carcinoma was not reached among patients responding to nivolumab compared to those with stable or progressive disease (El-Khoudry et al, ASCO GI 2017) as compared to those with stable disease. This suggests that patients who respond to

immunotherapy do experience significantly longer survival. This is certainly reflected in the prolonged DOR seen among patients who respond to pembrolizumab, which in turn is reflected in the long tails of PFS curves, as opposed to the median PFS.

6- (Page 3, Summary of pERC Deliberations, 2nd paragraph; Clinical Benefit)
pERC mention that PFS is the main deciding factor in treatment selection in the current era.

The CGP mention that the disease response is a meaningful endpoint for patients because it often results in improvement of symptoms and quality of life. They further state that responses in this patient population (UC cisplatin-ineligible patients) are important because of the accompanying improvement in distressing disease symptoms and improvement in performance status. Moreover, the CGP state that the "Response rate is a reasonable primary outcome for this study and that critical outcomes including PFS and OS were secondary endpoint" in their assessment of the appropriateness of primary and Secondary Outcomes of KEYNOTE 052. They also acknowledge that "response rate reflects the ability of therapy to inhibit the target and consequently would be associated with benefit". Plus, CGP notes that in current era, the duration of disease control has become one of the main deciding factors in treatment selection.

7- Merck considers that the EGP's best-case scenario ICERs for the platinum ineligible population are overestimated. In this patient population, the EGP prolongs pembrolizumab's maximum treatment duration from 2 to 3 years, therefore increasing the treatment costs without increasing the expected clinical benefit. However, Merck considers this methodology inappropriate since, in all patient populations and scenario analyses, the model includes an OS waning effect where the treatment effect (hazard ratio) for pembrolizumab versus comparators decreases linearly until reaching 1 between Year 4 and Year 6. This assumption was implemented to compensate for long term OS uncertainty. The 4-year cut point was selected because Kaplan-Meier data is available until around 3.5 years for KEYNOTE-052 (based on O'Donnell 2019 publication) and the extrapolated OS curves are aligned with available KM data. Increasing treatment duration to 3 years goes against pembrolizumab treatment protocols and furthermore, doing so without modifying the assumption on OS waning effect is inadequate.

In summary, with clinically meaningful overall response rate, prolonged durability of responses and a favourable safety profile, Merck strongly believe that pembrolizumab addresses the unmet need for the UC platinum-ineligible patients and that pERC should recognize the net clinical benefit of pembrolizumab for these patients. For the cisplatin ineligible and PD-L1 CPS ≥ 10 UC patients, Merck agrees that evidence from a phase III randomized controlled trial is coming later and could form the basis of a resubmission. However, the moment of availability of this data is uncertain. A resubmission with these results would probably not happen soon. As stated by the CGP, effective therapies with improved toxicity are urgently needed in this setting. Pembrolizumab showed a clinically meaningful overall response rate, prolonged durability of responses, excellent early overall survival and favourable safety profile in these patients. Consequently, Merck believe that pembrolizumab also address the unmet need for the cisplatin ineligible and PD-L1 CPS ≥ 10 UC patients.

Based on all the above, Merck kindly asks pERC to reconsider their initial position and recommend the reimbursement of pembrolizumab as a monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (Combined Positive Score (CPS)) ≥ 10) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

b) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the provisional algorithm:

☐ agrees ☐ agrees in part ☐ disagree

Not applicable

c) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence or provisional algorithm) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
4	Summary of pERC Deliberations	2nd paragraph, 3rd line	pERC acknowledged that there is a need for additional effective treatments in this setting. However, many platinum-ineligible patients will only receive BSC. For them, the need is not for an additional treatment option, but for an effective and tolerable treatment option. No conclusion on the clinical benefit of pembrolizumab compared to BSC is made. On this, the CGP mention that "more patients with platinum ineligible disease may be considered for first-line treatment where before they would have only received best supportive care".
3	Summary of pERC Deliberations	2nd paragraph, last sentence	pERC mention that they could not confidently conclude that pembrolizumab addresses the need for more effective treatment options" in the platinum ineligible patients. However, pERC already recognized that the substantial unmet need is for effective and tolerable treatments and CGP mentions that the platinum-ineligible patients have no effective treatment options and that new therapies that show tumour response with improved toxicity are urgently needed.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder 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.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder 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 program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, including the provisional algorithm, 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.

Please see comments in Section 3.1 a)

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

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 rational 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 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 Submitter 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 Submitter 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.