CADTH

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation

(Patient Advocacy Group)

Pembrolizumab (Keytruda) for Metastatic Urothelial Carcinoma

October 3, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Pembrolizumab
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Patient Group Bladder Cancer 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

Bladder Cancer Canada is concerned about the PERC recommendation not to reimburse pembrolizumab for first line cisplatin-unfit metastatic urothelial carcinoma (UC). There is a clear unmet need for effective and tolerable treatment options for patients with locally advanced or metastatic UC who are not eligible for cisplatin containing chemotherapy. The unmet need is even greater and more urgent in patients who are ineligible for any platinum-based regimens. For this subgroup there are no effective and well-tolerated treatment options available except best supportive or palliative care. It is our view that PERC should be less stringent for this platinum ineligible sub-group of patients in general. It will be very difficult in this group to obtain phase III data and to our knowledge none is expected soon.

We noted that clinicians providing input indicated that metastatic UC is an area of clear unmet need owing to suboptimal treatment options. The average age of patients with metastatic UC is 72, meaning many have comorbidities, and renal dysfunction that preclude their ability to tolerate standard cisplatin-based chemotherapy. Pembrolizumab is a much less toxic and well tolerated drug that can provide significant and even durable benefits in many of these patients. In this setting physicians would feel comfortable treating their patients with pembrolizumab and feel it is the optimal treatment approach, and warrants funding in this setting.

According to one clinician, use of pembrolizumab in cisplatin-ineligible population would be safer than subjecting unfit patients to chemotherapy in order to gain access to second line pembrolizumab. In addition, given the rapid progression of this disease, many patients do not even get to second line treatment. We strongly urge PERC to consider this scenario that could occur in future considering its initial recommendation.

We noted that the clinical guidance panel considered these platinum unfit patients in two distinct groups: 1) Cisplatin-unfit – PDL1 positive and 2) platinum-unfit

Here is the information from page 21:

(2) Platinum-ineligible, irrespective of PD-L1 status subgroup: The CGP concluded that there may be a clinically meaningful net clinical benefit to pembrolizumab compared with standard care, chemotherapy (gemcitabine monotherapy) or best supportive care in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for platinum-containing chemotherapy irrespective of the PD-L1 status. This conclusion is based on evidence from a post-hoc analysis from the noncomparative phase II KEYNOTE 052 clinical trial, which showed a clinically meaningful overall response rate and prolonged durability of responses, with a toxicity profile that is better than that experienced with chemotherapy. Prolonged responses in this patient population are important because this patient population is often not well enough to receive any treatment with no hope of benefit, or only single agent gemcitabine with a dismal response rate of 10% or less. The CGP acknowledges that it is challenging to draw firm conclusions on the efficacy of pembrolizumab based on the data obtained from an exploratory post-hoc analysis based on a non-comparative phase II study with primary tumour response outcomes. However, this particular subgroup of patients has no effective treatment options and new therapies that show tumour response with improved toxicity are urgently needed in this disease setting.

Alternatively, it appears that the PERC decision doesn't align with the clinical guidance report. The PERC recommendation does not consider this sub-group of platinum unfit patients separately. The decision is stated by PERC as follows:

pERC does not recommend the reimbursement of pembrolizumab (Keytruda) 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 programmed death•ligand 1 (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.

We would urge PERC to clearly break up the 2 patient populations in the final recommendation.

1) Cisplatin-unfit – PDL1 positive
2) Platinum-unfit

We note that Bladder Cancer Canada has reached out to 15 patients with pembrolizumab and 34 patients overall. There is strong support for this treatment; some having had a significant benefit.

Quote from a real patient over one year on treatment:

> *When I started taking Pembrolizumab I was in palliative care getting morphine every two hours and cancer tumours were located throughout my body. After seven treatments with pembrolizumab all signs of cancer were gone. Pembrolizumab is truly a miracle drug! It gives the patient an absolutely wonderful quality of life.*

SUMMARY

In May 2017 the FDA in the US announced funding first-line pembrolizumab:

https://www.fda.gov/drugs/resources-information-approved-drugs/pembrolizumab-keytruda-advanced-or-metastatic-urothelial-carcinoma

In June 2018 NICE and EMA did the same with restriction on level of expression of PD-L1:

https://www.nice.org.uk/guidance/ta522

https://www.ema.europa.eu/en/news/ema-restricts-use-keytruda-tecentriq-bladder-cancer

Noting the information above, PERC's decision not to recommend funding this drug is below standard of care.

Furthermore, limiting first-line access for patients may then limit access to second-line clinical trials for these patients

Overall the fifteen patients we surveyed and/or spoke with who had experience with pembrolizumab had an improved and excellent quality of life and reported durable responses.

We ask that further to its initial recommendation, PERC evaluate the subgroup of patients who are platinum ineligible separately from the cisplatin ineligible group. We strongly urge PERC recommend funding for the platinum ineligible group of patients. This only represents a very small percentage of the overall group of patients with metastatic urothelial carcinoma currently having no other effective treatment options and whose survival is 6-12 months at best.

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

☐ agrees ☐ agrees in part ☐ disagree

n/a

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
			See above

3.2 Comments Related to Eligible Stakeholder ProvidedInformation

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.

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.