CADTH

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

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

January 3, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Pembrolizumab/sq NSCLC
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Registered Clinician Feedback Cancer Care Ontario Lung DAC

**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

The CCO Lung DAC disagrees with the conclusion that there is insufficient information about the benefit of therapy. This trial shows a similar relative benefit to all the trials of chemo + IO. Keynote 189 HR for OS was 0.49. The HR is 0.64. There is a 4 month absolute difference in OS which is clinical meaningful. The current decision is inconsistent with other recent decisions in NSCLC. The DAC also notes that pCODR was concerned regarding the short followup, and uncertainty with how the result would hold up with time. There is evidence from the ESMO 2019 poster that continued to show the same benefit (HR of 0.71 for OS). Further, the DAC was unsure why pCODR was concerned that the cost comparisons were chemotherapy and not pembrolizumab alone for the high PD-L1 patients. In the PDL1 >50%, there will be zero difference in terms of budget impact as these patients are already treated (less the $1000 or so for 4 cycles of carbo/taxol). If pCODR wants the economic analysis on the PDL1 <50% subset it would be feasible for them to do (HR for OS for <1 is ~0.79 (33% of patients), and HR for OS for 1-49 is ~0.59. (33% of patients).

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

☐ agrees ☐ agrees in part ☐ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the provisional algorithm. Please note that comments should relate* ***only to the proposed place in therapy of the drug under review*** *in the provisional algorithm. If feedback includes New Information or about other therapies that are included in the provisional algorithm, the information will not be considered and will be redacted from the posted feedback. Substantive comments on the provisional algorithm will preclude early conversion of the initial recommendation to a final recommendation.*

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

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.

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 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.

CADTH

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

January 3, 2020

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Squamous NSCLC For the treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC cancer.
Eligible Stakeholder Role in Review (Sponsor and/or Manufacturer, Patient Group, Clinical Organization Providing Feedback	Clinical Group Lung 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

The initial recommendation of the pCODR Expert Review Committee regarding funding of pembrolizumab in combination with carboplatin plus paclitaxel or nab-paclitaxel resulted in strong concerns among the physicians of the Lung Cancer Canada's (LCC) Medical Advisory Committee. We ask that pCODR to strongly reconsider the initial negative funding recommendation. We believe strongly that the improvements in objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQoL) in the context of a double-blind randomized controlled trial (KEYNOTE-407) are more than adequate to indicate clinical benefit with the addition of pembrolizumab.

The objection to this recommendation is based on the following points:

1. The study design was robust – A randomized controlled, double-blind, placebo controlled trial is the gold standard for determination of drug efficacy.
2. There was consistent improvement with the addition of pembrolizumab both across outcomes and subgroups – KEYNOTE-407 demonstrated improvements with the addition

of pembrolizumab in: ORR (57.9% v 38.4%), PFS (6.4 v 4.8 months, 0.56; 95% CI, 0.45 to 0.70; P<0.001), and OS (15.9 v 11.3 months, 0.64; 95% CI, 0.49 to 0.85; P<0.001). The OS benefit was seen regardless of PD-L1 level (Figure A)

3. There was central, independent review of progression to help reduce investigator bias.

4. Allowed crossover to PD-1/PD-L1 inhibitor (including pembrolizumab) in the control group biased the trial towards null.

5. Rigorous statistical methods were used to ensure that calling a benefit at an interim analysis would be done conservatively. The trial used a p-value of 0.008 to define the threshold of statistical significance at the second interim analysis. The efficacy boundaries were met.

6. A recent update at ESMO, showed that the improvement in OS with adding pembrolizumab has only increased with additional follow-up (now median 14.3 months) - OS (median [95% CI], 17.1 [14.4–19.9] vs 11.6 [10.1–13.7] months)

7. If there is a delay in approval waiting for resubmission with new data, there will be lung cancer patients not getting a therapy that could help them. The process for resubmission is a lengthy one, however, if they were to reassess now that would lessen the harm for lung cancer patients.

8. The initial recommendation already acknowledges that the therapy aligns with patient interests.

The deliberative framework guiding pCODR states overall clinical benefit is defined as: A measure of the net health benefit of using the drug to diagnose or manage a cancer related condition (e.g., lung cancer) or cancer care related issue (e.g., skeletal related events in metastatic disease). There are subcategories of Effectiveness, Safety, Burden of Illness, and Need. As detailed above, the physicians of the LCC MAC believe the effectiveness of the treatment is established using the principles of evidence-based medicine. The risk of grade 3+ adverse events in the KEYNOTE-407 trial were similar between the experimental and control arms, speaking to safety. Lung cancer is the leading cause of cancer-related death both in Canada and worldwide. Squamous cell carcinoma accounts for approximately 30% of diagnoses of non-small cell lung cancer (NSCLC) and more than 50% of patients are diagnosed when their disease is already metastatic and incurable. There is no question that there is a high burden of disease. In terms of need, the improvements seen in metastatic NSCLC treatment over the last decade have largely been enjoyed by patients with non-squamous NSCLC due to the relative lack of targetable mutations in squamous cell carcinoma. While second line PD-1/PD-L1 inhibitors are available, the benefits seen in KEYNOTE-407 despite crossover clearly demonstrate that second line treatment is not a substitute and a high need remains.

The pERC decision is also inconsistent with previous decisions on PD-1/PD-L1 inhibitors used in the treatment of solid tumours. As seen in Table A, the hazard ratio of 0.64 seen in KEYNOTE-407 is equivalent to or superior to those seen with previous positive recommendations.

Figure A

Table A

Drug	Disease	Line	Fund?	Year	mOS diff	HR
Ipilimumab	Melanoma	2	Yes	2012	3.6	0.68
Ipilimumab	Melanoma	1	Yes	2015	2.1	0.72
Pembrolizumab	Melanoma	1/2	Yes	2015	NR	0.63-0.69
Nivolumab (vs Ipi)	Melanoma	1/2/3	Yes	2016	NR/NS	0.42/0.93
Nivolumab	NSCLC	2/3	Yes	2016	2.8	0.73
Nivolumab	Renal	2/3	Yes	2016	5.4	0.73
Pembrolizumab (2 doses)	NSCLC	2/3	Yes	2016	1.9/4.2	0.71/0.61
Pembrolizumab	NSCLC (PDL1 50+%)	1	Yes	2017	NR	0.60
Nivolumab	HNSCC	2	Yes	2017	2.43	0.70
Nivo + Ipi (vs either alone)	Melanoma	1	Yes	2017	NR for NI/N	0.55 v Ipi 0.88 NS v N
Pembrolizumab	Urothelial	2	Yes	2018	2.9	0.73
Avelumab	Merkel	2	Yes	2018	12.6 (1 arm)	N/A
Atezolizumab	NSCLC	2/3	Yes	2018	3.8	0.73
Nivo + Ipi	Renal	1	Yes	2018	NR	0.63
Nivolumab	HCC	2	No	2018	15.6 (1 arm)	N/A
Nivolumab	Melanoma	Adj	Yes	2019	RFS	0.65
Durvalumab	NSCLC (stg III)	Cons	Yes	2019	NR	0.68

Pembrolizumab + chemo	NSCLC (nSq)	1	Yes	2019	NR	0.49
Pembrolizumab	Urothelial (CPS 10+)	1	No	2019	18.5 (1 arm)	N/A
Atezolizumab + chemo	SCLC	1	No	2019	2.0	0.70

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☐ 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.

The LCC MAC believe that the negative funding recommendation for pembrolizumab added to chemotherapy for incurable squamous NSCLC patients, runs counter to the principles of

"rigorous and consistent evidence-based clinical and pharmacoeconomic reviews" and "A review process that is cost-efficient, effective, and streamlined (i.e., reduced duplication)" enshrined in pCODR's guiding principles. We ask for a reconsideration of the recommendation to allow Canadians with lung cancer to access this important and clinically effective therapy.

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