PAN-CANADIAN ONCOLOGY DRUG REVIEW

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

Pembrolizumab (Keytruda) for Melanoma Adjuvant Treatment

August 1, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	pembrolizumab (KEYTRUDA®) For adjuvant treatment of Stage III melanoma patients following resection; for re-treatment of patients upon loco-regional or distant recurrence more than 6 months following completed adjuvant course of KEYTRUDA®
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 is pleased with pCODR's review of pembrolizumab for the treatment of patients with adjuvant melanoma and pCODR's recognition of the net clinical benefit (relapse-free survival), manageable toxicities with no detriment on quality of life compared with observation (placebo).

Merck also agrees with pERC that pembrolizumab aligns with patient values and fulfils a need for treatment options that provide disease control with manageable side effects.

However, Merck has concerns on the following points:

<u>Weight-based dosing with a cap</u>

pERC states there is no evidence to suggest that the dosing amount of 200mg is superior to 2mg/kg and feels is it therefore reasonable for pembrolizumab to be administered at 2mg/kg up to a total dose of 200mg (dose capped at 200 mg). pERC is basing this on the dose of 2mg/kg used in the initial trials of pembrolizumab.

However, all these initial trials were conducted in metastatic populations. Treatment in the adjuvant setting has a different intent (i.e. curative) and is administered in a different population (i.e. "disease-free" patients who have been completely resected). KEYNOTE-054 uses a 200 mg flat dose of pembrolizumab, administered every 3 weeks for up to 1 year. There is no trial that has assessed pembrolizumab's clinical benefit using a weight-based dosing approach in the melanoma adjuvant setting. We feel caution should be exercised in

recommending a different dosing, for which the impact on recurrence-free survival is unknown.

Additionally, in the recent pCODR assessment for nivolumab in the adjuvant setting, the CGP indicated treatment should generally adhere to the best available evidence, as the intent for adjuvant treatment is curative. Following this input, pERC agreed in its final recommendation, that until there is evidence to confirm the efficacy with a different dosing, that the nivolumab dosing should generally follow the one used in the clinical trial.

To ensure consistency in HTA assessments, we respectfully request that the final recommendation for pembrolizumab be amended to reflect the dosing used in KEYNOTE-054.

Generalization to other populations

For pembrolizumab, the CGP provided input around extrapolation to other populations, namely:

1. although KEYNOTE-054 enrolled patients ≥18 years of age, the CGP felt early data from KN051 did not indicate pembrolizumab would not be safe to use in a younger patient population.
2. The CGP also agreed that pembrolizumab could be considered for patients with pre-existing immune mediated conditions, although these patients were excluded from the trial.

In the nivolumab pCODR assessment for melanoma adjuvant, the CGP had provided similar feedback for these same populations, to which the pERC agreed in their final recommendation. We respectfully ask that pERC applies the same approach in HTA assessments and address the generalization to these 2 populations suggested by the CGP in the final pembrolizumab recommendation.

Sequencing guidance

In the pembrolizumab initial recommendation, pERC stated that "the optimal sequencing of subsequent therapies for patients with metastatic melanoma after disease progression with adjuvant pembrolizumab is unknown" and that therefore pERC is "unable to make an evidence informed recommendation on sequencing of treatment".

However, in the dabrafenib/trametinib recommendation, both the pERC and GCP were comfortable in issuing such guidance:

1. The known efficacy of BRAF-inhibitors in the metastatic setting was used to inform sequencing in the adjuvant setting:

   "There are currently no data to inform treatment decision-making in this scenario, but it is known that BRAF-targeted therapy in the second-line following progression of disease after treatment with PD-1-directed immunotherapy is efficacious. For this reason, pERC agreed with the CGP that the use of dabrafenib plus trametinib as adjuvant treatment to surgery could be considered in patients where previous adjuvant therapy with immunotherapy failed." (dabrafenib/trametinib final recommendation page 16)

2. The CGP referred to the post-study treatments in the COMBI-AD trial to indicate clinicians would likely wish to consider all these options for the relapsed patient

following treatment with adjuvant dabrafenib-trametinib (final Clinical Guidance Report for dabrafenib-trametinib p.16).

In the pembrolizumab recommendation, the CGP also commented on the variety of post-study treatments in the KEYNOTE-054 trial; these treatments included anti-CTLA4, anti PD1/PDL1 and targeted agents. However, the CGP did not take the same approach as taken in the dabrafenib/trametinib recommendation, to then go on and comment on subsequent treatments clinicians would most likely consider after adjuvant pembrolizumab (initial Clinical Guidance Report for pembrolizumab p.18).

Also, in the context of the pembrolizumab recommendation, pERC agreed with the CGP's opinion in answering the Provincial Advisory Group (PAG) questions:

"in patients with BRAF-mutated melanoma who have completed one year of adjuvant dabrafenib-trametinib and have recurred, weather or not their disease has been resected to no evidence of disease, they would be eligible for retreatment with BRAF MEK inhibitors, or PD-1 inhibitors or dual immunotherapy. "(pembrolizumab initial recommendation Appendix 1 page 13).

In doing so, pERC leaves patients with BRAF-wildtype melanoma who have completed their 1-year adjuvant course without guidance if they were to recur.

Merck respectfully requests that pERC/GCP applies the same approach across all HTA assessments and address the sequencing treatments in the pembrolizumab recommendation for all patients (i.e. not only for BRAF-mutated adjuvant patients).

<u>Retreatment guidance</u>

Merck has a few comments surrounding the pERC feedback on our request for retreatment.

1. Historically, pCODR has issued positive recommendations for retreatment with pembrolizumab in NSCLC, to align with the product monograph, even if there was no survival data at the time supporting retreatment in lung cancer (see table below).

	pCODR issued positive recommendation for re-treatment	**Mention of re-treatment in the Pembrolizumab Product Monograph**
NSCLC 2nd Line (KEYNOTE-024)	**Final recommendation, pembrolizumab NSCLC 2nd Line pCODR dossier 10077** "Patients could receive up to 12 months of pembrolizurnab 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."	*"For patients who completed 24 months of therapy or had a complete response, treatment with KEYTRUDA® could be reinitiated for disease progression and administered for up to 1 additional year. "*
NSCLC 1st Line (KEYNOTE-189)	**Final recommendation, pembrolizumab NSCLC 1st line pCODR dossier 10153** "pERC considered the CGP's expert opinion that patients who complete two years of pembrolizumab and discontinue therapy without progression should have the option for treatment with pembrolizumab if there are at least six months between completion of therapy and documented disease progression."	*"Patients without disease progression were treated for up to 24 months or 35 administrations, whichever was longer. Subsequent disease progression could be retreated for up to 1 additional year. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA®."*

Melanoma adjuvant (KEYNOTE-054)		*The study design included reinitiation with KEYTRUDA® for subsequent disease recurrence that occurs >6 months after completion of one year of adjuvant treatment.*

Since the pembrolizumab Product Monograph also includes language around retreatment in the adjuvant melanoma setting, Merck feels pERC should take a consistent approach in addressing retreatment for all pembrolizumab indications.

2. Merck submitted results from the KEYNOTE-006 trial as a "proof-of-concept" to inform retreatment, as it demonstrates the antitumor activity upon re-exposure to pembrolizumab in the metastatic setting. pERC assessed that due to differences in patient populations, the results of KEYNOTE-006 may not be directly applicable to the adjuvant setting and refrained from making re-treatment decisions.

However, in the context of the dabrafenib/trametinib final recommendation (page 16), pERC was comfortable extrapolating the known benefit of BRAF-inhibitors in the metastatic setting (i.e. BRAF-inhibitors' known efficacy after progression on PD-1 inhibitors), to inform their guidance in the adjuvant setting.

As such, it seems the known benefit of retreatment with pembrolizumab in the metastatic setting (KEYNOTE-006) should also be valid to inform retreatment in the adjuvant setting.

We respectfully ask that pERC applies the same approach in across HTA assessments (e.g. leverage efficacy data from metastatic setting to support guidance in the adjuvant setting).

<u>Cost-effectiveness</u>

Merck strongly believes that pembrolizumab is cost-effective at list price in the melanoma adjuvant setting. In its own re-analysis, pCODR's Economic Guidance Panel estimated that within the range of the ICUR, the best estimate would likely be $51,289/QALY (lower bound), which is below the cost-effectiveness threshold (ICER <$100,000). Moreover, EGP reduced the time horizon to 10-25 years in their reanalysis. 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". Given the relatively young age of this patient population and the curative intent of the adjuvant setting, we believe that a lifetime horizon is appropriate.

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