pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Provincial Advisory Group (PAG) Feedback on a pCODR Expert Review Committee Initial Recommendation

Nivolumab (Opdivo) with Ipilimumab (Yervoy) for Metastatic Melanoma

November 30, 2017

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s): **Nivolumab + Ipilimumab for metastatic melanoma**

Contact person*: **PAG Chair**

3.1 Comments on the Initial Recommendation

a) Please indicate if the PAG (either as individual PAG members and/or as a group) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __x__ disagree

PAG disagrees with the recommendation and does not support early conversion of recommendation to final. PAG identified that this recommendation would be difficult to implement for the following reasons:

- In the absence of knowing the value of the nivolumab/ipilimumab combination as a first line therapy compared to current standards of care for first line treatment of advanced melanoma that have been implemented based on previous pCODR recommendations, there is overall uncertainty in the magnitude and duration of survival benefit for the combination, with the following considerations:
    - the combination was not compared against pembrolizumab, previously recommended by pCODR as first line immunotherapy over ipilimumab, independent of BRAF mutation status. Pembrolizumab has been implemented as first line, standard of care therapy in most Canadian jurisdictions.
    - the combination was not compared against BRAF/MEK targeted agents, previously recommended by pCODR for first line treatment in patients with BRAF mutation. A number of jurisdictions do not allow sequencing of BRAF/MEK inhibitors after immunotherapy, thus is the first line standard of care for patients with BRAF mutated tumors.
    - the recommendation indicated the combination as compared to nivolumab may provide similar net benefits, however there was uncertainty in the magnitude of these benefits. Nivolumab as first line immunotherapy was previously recommended by pCODR only in the subset of patients with BRAF wild-type tumors. The choice of nivolumab as a first line immunotherapy for advanced melanoma is not common given the BRAF restriction and its every 2 weeks administration schedule as compared to pembrolizumab without BRAF restriction and an every 3 week administration schedule. Thus, nivolumab

would not be the primary standard of care comparator for the combination.

- In addition, in the absence of knowing the value of sequential immunotherapy, particularly with BRAF/MEK inhibitors, there are significant challenges for implementation, as combination BRAF targeted therapies have only been recommended as first line therapies. The recommendation for the combination is for treatment naïve patients and does not specifically address the sequence of treatments for BRAF mutation positive patients – whether sequencing of the nivolumab and ipilimumab combination with BRAF/MEK inhibitors should or should not be recommended and, if recommended, is there an optimal order of sequencing? The recommendations for pembrolizumab and nivolumab addressed this issue and PAG is requesting consistency in this recommendation. It was noted in the clinician input, that the combination can be given as first line immunotherapy or second line, post BRAF targeted therapy.
- PAG members are requesting clarity with regards to the place in therapy for the combination given current first line treatment standards.
- Although the economic analysis suggests that the combination is cost effective, the analysis did not use the appropriate comparator. Ipilimumab is no longer a valid comparator in Canada and nivolumab is recommended only for BRAF wild type tumors. Pembrolizumab is the most relevant standard of care for advanced melanoma as it is recommended for patients independent of BRAF status with a more favorable administration schedule. It is noted that there were concerns with the use of an indirect comparison against pembrolizumab. However, clinicians have repeatedly indicated that pembrolizumab and nivolumab are considered clinically/therapeutically equivalent. In addition, there was no comparison with BRAF targeted therapies for BRAF mutation positive patients. PAG is requesting specific economic guidance for the combination against the current standard of care, and in the absence of information disagrees with the overall recommendation that the combination is cost-effective.
- To minimize waste and budget impact, the recommendation should specify that during the nivolumab monotherapy phase (after completion of the combination therapy), the recommended dose of 3 mg/kg (capped at 240 mg) IV every 2 weeks be consistent with other recent recommendations for pembrolizumab and nivolumab.
- The economic analysis also did not account for the re-initiation of single agent nivolumab (after discontinuation of the combination due to toxicities or after treatment break), which would likely occur in actual practice.
- PAG expressed concern with the recommendation in patients with 'good performance status' which is usually interpreted to be ECOG 0 to 2. Given the incremental and often significant toxicity of the combination, PAG members felt the recommendation should specifically state ECOG 0 or 1 as per the clinical trial.

b) Notwithstanding the feedback provided in part a) above, please indicate if the PAG 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
2	Next Steps	Budget Impact	The dose during the monotherapy phase is 3mg/kg – PAG is requesting whether 3mg/kg to maximum dose of 240mg to maximize drug cost efficiencies could be addressed as it may alter the economic analysis and budget impact analysis. A flat dose of 240mg for all patients would lead to higher drug costs.
3	Next Steps	Time Limited Need	The recommendation only speaks to a time limited need for combination therapy for patients on ipilimumab monotherapy or nivolumab monotherapy. PAG is seeking a recommendation on switching patients who started on pembrolizumab monotherapy to nivolumab/ipilimumab combination if there is no disease progression on pembrolizumab monotherapy, or alternatively, those patients who are receiving BRAF targeted therapy without disease progression (may depend on sequencing guidance)
6			The recommendation states "appears cost-effective", but then later in the body of the report, it states that it is cost effective – suggest "is" be replaced with "may" on page 6. It is difficult to state that the combination is cost effective. Although the OS benefit of the combination is better than ipilimumab alone, the majority of patients are receiving PD-1 inhibitor in the first line setting, so the recommendation needs to reflect the uncertainty around the appropriate comparator in the Canadian setting currently (nivolumab for BRAF negative and pembrolizumab for BRAF negative or positive).
			It was mentioned that if nivolumab/ipilimumab combination therapy is discontinued due to toxicities, treatment with nivolumab monotherapy would likely occur after toxicity resolution. However, clarification of re-starting treatment with nivolumab monotherapy in the clinical scenarios of toxicity resolution with no disease progression, or after disease progression during a treatment break would be helpful.

			Also, PAG is requesting guidance on whether a re-initiation of the combination therapy should be considered and in what clinical setting, for example would combination re-induction be allowed in cases where the patient completed the 12 weeks of combination followed by monotherapy for a prolonged period (e.g., 2 years) and then develops a recurrence during this long-term nivolumab monotherapy, or in a patient who had discontinued nivolumab after prolonged treatment and recurred in the time period after stopping nivolumab.

3.2 Comments related to PAG input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on the PAG input provided at the outset of the review on potential impacts and feasibility issues of adopting the drug within the health system.

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.

Examples of issues to consider include: what are the operational, capital, human resources, legislative, regulatory factors that may either important enablers or barriers to recommendation implementation.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial PAG input
			The clinical trials only allowed patients with PS 0-1, but the clinical guidance panel discussed "good performance status" for patient eligibility. PAG noted that this statement is usually interpreted to include patients with PS 2, and given the much higher toxicity of this combination regimen, should PS be restricted to PS 0-1?
			There are some patients who would have received four doses of ipilimumab as first line treatment and continue to be disease free (the tail on the OS curve of the original single-agent ipilimumab trial). Would these patients be eligible for nivolumab/ipilimumab combination when their disease recurs?
			Since pembrolizumab is given every 3 week dosing schedule and is used regardless of BRAF status, there will likely be requests to use pembrolizumab after induction with nivolumab/ipilimumab instead of nivolumab. PAG is seeking information on whether this is clinically reasonable or not.
			PAG members indicate that requests will be made in clinical practice to add ipilimumab to a patient's therapy at the time of progression on

			nivolumab or pembrolizumab monotherapy, as these patients would have missed their window of opportunity for the combination. Clarity on this issue would be helpful for PAG, or at least a comment regarding next steps for stakeholders.

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
2	pERC Recommendation		The actual budget impact would be substantially greater given that the uptake of the combination may be significantly higher given jurisdictions have previously made a decision not to fund subsequent ipilimumab after PD-1 immunotherapy. The budget impact would be less if sequencing of ipilimumab had been funded.
	Next Steps		PAG noted there is information on using nivolumab at a dose of 6 mg/kg every 4 weeks to a maximum dose of 480mg. Although this information was not provided by the submitter at the time of the review, this dose may have an impact on the ICER and the health system delivery of the treatment.
			PAG is requesting guidance on extrapolation of eligibility to patients with ocular melanoma and whether the results of combination therapy could be generalized to include these patients or should they be excluded from the funding recommendation as they were excluded from the trial.

1 About Completing This Template

pCODR invites the Provincial Advisory Group (PAG) to provide feedback and comments on the initial recommendation made by the pCODR Expert Review Committee. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The pERC initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the PAG, either as individual PAG members and/or as a group, agrees or disagrees with the pERC initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the pERC initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a pERC final recommendation 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.

If any one of the invited stakeholders does not support the initial recommendation proceeding to a pERC final recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The pERC final recommendation will be made available to the participating provincial and territorial ministries of health and 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) Only members of the PAG can provide feedback on the pERC initial recommendation; delegates must work through the PAG representative to whom they report.
    a. Please note that only one submission is permitted for the PAG. Thus, the feedback should include both individual PAG members and/or group feedback.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the pERC initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Provincial Advisory Group (PAG) Feedback on a pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. PAG 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. Similarly, PAG should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) 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 forwarded to the pERC.

f) 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.

g) 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 Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.