PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Patient Advocacy Group Feedback on a pCODR Expert Review Committee Initial Recommendation

Nivolumab (Opdivo) for Metastatic Melanoma

Melanoma Network of Canada

April 1, 2016

1 Feedback on pERC Initial Recommendation

Name of the drug indication(s): _Opdivo (Nivolumab)_____

Name of registered patient advocacy: Melanoma Network of 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.*

1.1 Comments on the Initial Recommendation

a) Please indicate if the patient advocacy group agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __X__ disagree

Please explain why the patient advocacy group agrees, agrees in part or disagrees with the initial recommendation.

The Melanoma Network of Canada is deeply concerned with this recommendation and is not in agreement with the recommendations of pERC regarding qualified support for approval of the use of Nivolumab (Opdivo) only for treatment of patients with unresectable of metastatic melanoma with the wild-type mutation.

The basis upon which the decision was made to recommend funding (subject to better price negotiations) only for treatment of patients with unresectable or metastatic BRAF wild-type melanoma is unclear. We see no substantive evidence, research based or otherwise to make the conclusion that Nivolumab has no net clinical benefit for patients with BRAF V-600 mutation or for those previously treated with Ipilimumab. Quite the contrary, in *the New England Journal of Medicine,* July, 31, 2015 **Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma,** the conclusions reached were quite different. Page 31 concludes:

'In this randomized, double-blind, phase 3 study involving patients with previously untreated advanced melanoma, treatment with nivolumab alone or with the combination of nivolumab and ipilimumab resulted in significantly longer progression-free survival and higher objective response rates than did treatment with ipilimumab alone. In the two nivolumab-containing groups, as compared with ipilimumab, these results were observed independently of PD-L1 tumor status, *BRAF* mutation status, or metastasis stage.'

As well,

"Two phase 3 trials have shown superior efficacy of nivolumab, as compared with chemotherapy, in previously untreated patients with wild-type *BRAF* tumors or in patients with either mutant or wildtype *BRAF* tumors after progression during ipilimumab therapy and, in patients with tumors positive for *BRAF* mutation, after progression during treatment with a BRAF inhibitor." And;

Analyses of progression-free survival in prespecified subgroups showed consistently longer progression-free survival with nivolumab or with nivolumab plus ipilimumab than with ipilimumab, including in subgroups defined according to PD-L1 status, *BRAF* mutation status, and metastasis stage (Fig. 1B and 1C, and Fig. S2 in the Supplementary Appendix). In the

nivolumab-plus ipilimumab group, the median progression-free survival was 11.7 months (95% CI, 8.0 to not reached) among patients with a *BRAF* mutation and 11.2 months (95% CI, 8.3 to not reached) among patients with wild-type *BRAF*.

It is our belief, based upon available data, that it is premature to make a decision to exclude BRAF mutated patients, patients with prior treatment with targeted inhibitors or PD-L1 status.

There is little doubt that the impact of these new anti-PD1 immunotherapies is significant in the world of cancer treatment. Patients have been waiting for the outcomes of this trial for nearly a decade, and many have not lived long enough to benefit from these new breakthroughs. I personally find it shocking and I know our organization shares my concerns that of the 17 members of the pERC committee, only 8 were present to vote on this important breakthrough therapy. In addition, out of 9 oncologists, only 4 participated in the meeting. These are supposed to be our experts, who provide context and meaning to the decisions and recommendations. This does not add credibility to your decision making process or recommendations. Our hope is that in future deliberations, the committee will be present, well informed and understand the impact of the recommendations.

b) Notwithstanding the feedback provided in part a) above, please indicate if the patient advocacy group would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

____ Support conversion to final recommendation.
Recommendation does not require reconsideration by pERC.

_X___ Do not support conversion to final recommendation.
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
1	pERC Recommendation	Paragraph 1,3, 4	While the recommendations are clear, the available scientific evidence does not appear to align with the recommendations. There is a net clinical benefit to all patients, regardless of BRAF status. Results are even better when combined with Ipilimumab. It is also a well-known fact now that dacarbazine or other traditional chemotherapies are virtually ineffective in treating melanoma. We are strongly encouraging pharmaceutical companies to not use chemotherapy in trial arms as we believe with the evidence available today, that it is unethical when there are known better therapies for treatment. We don't know

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			why you would even comment that the committee is unable to determine how Nivolumab compares to chemotherapy. Numerous studies have proven the ineffectiveness of chemotherapy in the treatment of melanoma.
2	pERC Recommendation	Paragraph 2	pERC has concluded that Nivolumab is not cost effective in comparison to Ipilimumab. It is an unfair comparison. These are not apples to apples as the treatment protocol is completely different. It is like comparing aspirin to insulin (which is taken for life in most cases – and I would assume is a substantial cost impact to the medical system). The committee will prematurely bias provincial decisions by your wording. Let provinces fairly negotiate the pricing with pharma and don't bias discussions, that may ultimately result in a negative impact for patient access. We do not believe that is the role of the committee. This wording must be changed.

1.2 Comments Related to Patient Advocacy Group Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on patient advocacy group input provided at the outset of the review on outcomes or issues important to patients that were identified in the submitted patient input. Please note that new evidence will be not considered during 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 impacts of the condition on patients' daily living? Are the needs of patients being met by existing therapies? Are there unmet needs? Will the agents included in this recommendation affect the lives of patients? Do they have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial patient advocacy group input

1.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			As a patient group, we do not have the resources or time to adequately assess and address the outcomes of these types of recommendations within the timelines provided. We do not have access to analysts or economists. We are purely and simply part of the public that has the misfortune of having to deal with this disease. Up until the last few years, we have had nothing that has been effective in treatment of melanoma. Arguably, with currently approved therapies having 20 to 30% response rates, we are still dealing with lack of options and poor outcomes. Patients have been waiting for years (those that have survived long enough to be lucky to be in a trial or have another therapy span the gap until a better therapy comes along) for this therapy. This recommendation, which does not appear to be grounded in the research, seems to be more about budgets than the basis of benefit this therapy can bring to all patients, regardless of BRAF status. We do not believe that this is historically the well-balanced approach of pCODR or the pERC committee and the reasoned decision making we have come to know and respect. We are deeply concerned and hope you will revisit this troubling recommendation and consider the input of experts in the area and the scientific data to date.

About Completing This Template

pCODR invites those registered patient advocacy groups that provided input on the drug under review **prior** to deliberation by the pCODR Expert Review Committee (pERC), to also provide feedback and comments on the initial recommendation made by pERC. (See www.cadth.ca/pcodr 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.cadth.ca/pcodr for a description of the pCODR process.) The 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 patient advocacy groups agree or disagree with the 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 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, including registered patient advocacy groups, agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. 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 final pERC 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 final pERC 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.

Instructions for Providing Feedback

a) Only registered patient advocacy groups that provided input at the beginning of the review of the drug can provide feedback on the initial recommendation.

- Please note that only one submission per patient advocacy group is permitted. This applies to those groups with both national and provincial / territorial offices; only one submission for the entire patient advocacy group will be accepted. If more than one submission is made, only the first submission will be considered.
- Individual patients should contact a patient advocacy group that is representative of their condition to have their input added to that of the group. If there is no patient advocacy group for the particular tumour, patients should contact pCODR for direction at www.cadth.ca/pcodr.

b) 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 during this part of the review process; however, it may be eligible for a Resubmission.

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

d) At this time, the template must be completed in English. Patient advocacy groups 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 to their group. Similarly, groups 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 initial pERC recommendations **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 new references. New evidence is not considered during 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 by logging into www.cadth.ca/pcodr and selecting "Submit Feedback" by the posted deadline date.

i) Patient advocacy group feedback must be submitted to pCODR by **5 P.M. Eastern Time** on the day of the posted deadline.

j) If you have any questions about the feedback process, please e-mail pcodrinfo@cadth.ca. For more information regarding patient input into the pCODR drug review process, see the *pCODR Patient Engagement Guide*. Should you have any questions about completing this form, please email pcodrinfo@cadth.ca

Note: Submitted feedback is publicly posted and also may be used in other documents available to the public. The confidentiality of any submitted information at this stage of the review cannot be guaranteed.