

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

**Nivolumab (Opdivo) with Ipilimumab
(Yevroy) for Metastatic Melanoma**

November 30, 2017

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s): Ipilimumab-Nivolumab
Name of registered clinician(s): Dr. Teresa Petrella (on behalf of CCO Skin Drug Advisory Committee)
Contact person*: Dr. Teresa Petrella
Title: Medical Oncologist; Associate Professor at University of Toronto; Ontario Skin Cancers Lead at Cancer Care Ontario

**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 registered clinician(s) agrees or disagrees with the initial recommendation:

agrees agrees in part disagree

We disagree with pCODR's recommendation to limit funding to treatment naïve patients. There is published data (http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.9522, see attached abstract) available to suggest that ipilimumab-nivolumab offers clinical benefit in patients previously treated with BRAF inhibitors; hence we strongly support the use of nivolumab-ipilimumab either as a first line immunotherapy or second line post-BRAF targeted therapy. The latter would also be consistent with Ontario's funding for single agent immunotherapies.

We disagree that the 'actual budget impact would be substantially greater.' The increased uptake of the combination is not due to greater familiarity with managing AEs, but rather the lack of funding of subsequent ipilimumab after nivolumab or pembrolizumab. Funding reconsideration of subsequent ipilimumab should mitigate concerns about the uptake for the combination. Also the budget impact may be improved with nivo/ipi as most patients would get 3 treatments or less of the ipi/nivo combination and one-third receive nivolumab maintenance, which is less than they would receive with pembrolizumab or nivolumab alone. We think that real world data should be collected to better understand how many patients will continue on single agent Nivolumab post combination.

We also support the treatment of patients with stable brain metastases.

[Overall survival \(OS\) analysis from an expanded access program \(EAP\) of nivolumab \(NIVO\) in combination with ipilimumab \(IPI\) in patients with advanced melanoma \(MEL\).](#)

[David Hogg, Paul B. Chapman, Mario Sznol, Christopher D. Lao, Rene Gonzalez, Gregory A. Daniels, Show More](#)

Abstract Disclosures ASCO Abstract #9522

Background: NIVO (anti-PD-1) and IPI (anti-CTLA-4), alone and in combination, are approved for the treatment of MEL. Phase II and III trials showed improved efficacy for NIVO+IPI versus IPI alone, but with a higher frequency of adverse events (AEs). In the phase II CheckMate 069 trial, the 2-year OS rate was 63.8% for all patients (pts) in the NIVO+IPI group. We report the first OS analysis, as well as updated safety data, from a North American EAP of NIVO+IPI in pts with MEL (CheckMate 218; NCT02186249). **Methods:** CheckMate 218 included pts with MEL who could have progressed on other therapies, but were anti-CTLA-4 and anti-PD-1 treatment-naive. Pts received NIVO 1 mg/kg + IPI 3 mg/kg Q3W x 4, followed by NIVO 3 mg/kg Q2W until disease progression or a maximum of 48 weeks from the first monotherapy dose. We assessed OS in the US cohort (n = 580) and safety in all pts (n = 732). Pts were followed for a minimum of 1 year in the USA and 6 months in Canada. **Results:** Of 732 pts, 43% had a *BRAF* mutation, 84% stage IV MEL, 51% M1c disease, 31% LDH > ULN (9% LDH > 2x ULN), and 13% received ≥1 prior systemic therapy in the metastatic setting. All pts received a median of 3 doses each for NIVO (range: 1–4) and IPI (range: 0–4) in the induction phase; 34% of pts received at least 1 dose of NIVO maintenance. The 1- and 2-year OS rates were 78.6% (95% CI: 74.2–82.4) and 65.3% (95% CI: 56.1–73.0), respectively. AEs of any grade occurred in 717 pts (98%), with grade 3/4 AEs in 470 pts (64%). Immune-modulating medications were used to manage any grade AEs, including grade 1/2 skin and gastrointestinal AEs, in 538 of 717 pts (75%), and to manage grade 3/4 AEs in 279 of 470 pts (59%). The most common treatment-related AEs of any grade were diarrhea (39%), pruritus (26%), and an increase in aspartate aminotransferase level (23%). Treatment-related deaths in 2 pts were reported as drug-induced liver injury and myocardial infarction. **Conclusions:** In this EAP, which included pts who had received prior systemic therapies for MEL and pts with poor prognostic factors generally not included in clinical trials, NIVO+IPI treatment demonstrated survival outcomes and a safety profile consistent with clinical trial data. [Clinical trial information: NCT02186249.](https://clinicaltrials.gov/ct2/show/study/NCT02186249)

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) 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.

<input checked="" type="checkbox"/> Support conversion to final recommendation.	<input type="checkbox"/> 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	Evidence Generation	Sentence 2 to 4	We agree that patients should be allowed to continue single agent nivolumab after a temporary interruption and support the suggestion to collect real world evidence to collect data to better understand the optimal duration of therapy.

3.2 Comments Related to the Registered Clinician(s) Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on registered clinician(s) input provided at the outset of the review on outcomes or issues important that were identified in the submitted clinician 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 program.

Examples of issues to consider include: Are there therapy gaps? Does the drug under review have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial registered clinician input
10	Registered clinician input	Last paragraph, 2 nd last sentence	We had previously indicated that the combination can be given as first line immunotherapy or second line post-BRAF targeted therapy. There is data to suggest clinical benefit in patients previously treated with targeted agents.

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
3	Time-limited Need	Last paragraph	We disagree with imposing restrictions on the time-limited need. Time-limited need for the combination should be extended to patients who would have otherwise been eligible, based on the clinical discretion of the treating physician.
Page 8	Patient populations	1 st & 2 nd paragraph, last sentence	There were statements that ocular melanoma was excluded in CheckMate 067 and 069, however, it may be clinically reasonable to extend use to this group of patients, consistent with existing policies for immunotherapies and CheckMate 218 (Expanded Access Program, did not exclude ocular melanoma)

1 About Completing This Template

pCODR invites those registered clinicians 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 registered clinician(s) 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 clinician(s), agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC 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 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.

2 Instructions for Providing Feedback

- a) Only registered clinician(s) that provided input at the beginning of the review of the drug can provide feedback on the initial recommendation. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.
- 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 Clinician 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. Registered clinician(s) 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, the

registered clinician(s) 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). 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) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca. Information about pCODR may be found at www.cadth.ca/pcodr.

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