CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

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

Nivolumab (Opdivo) for Melanoma Adjuvant Therapy

March 7, 2019

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Nivolumab (Opdivo) for the adjuvant treatment of adult patients after complete resection of melanoma with regional lymph node involvement, in transit metastases/satellites without metastatic nodes, or distant metastases.
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer, Patient Group, Clinical Group):	Manufacturer
Organization Providing Feedback	

**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 pCODR.*

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

Bristol-Myers Squibb (BMS) agrees in part with the initial recommendation to reimburse nivolumab (Opdivo) for the adjuvant treatment of patients with completed resected melanoma.

BMS agrees with pERC recommendation to reimburse nivolumab (Opdivo) and that the eligible patients should continue treatment until disease progression or a maximum of one year, whichever comes first. BMS also agrees that nivolumab is cost-effective at the listed price compared with observation. However, BMS disagrees with the proposed eligible population described by pERC on page 1 of the pCODR Expert Review Committee Initial Recommendation which reads as follows:

> "Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D (with the exception of regional lymph nodes with micrometastases) and stage IV melanoma (8th edition of the AJCC melanoma staging system)."

BMS noted a discrepancy between the proposed eligible population by pERC and the patient population who benefited from nivolumab in the clinical trial CheckMate 238 (NEJM 2017;377:1824-1835). This discrepancy pertains to the applicable pERC deliberative quadrant "Clinical Benefit".

In order to align with the patient population from the clinical trial CheckMate 238, BMS proposes to revise the eligible population to read as follows:

> **"Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D and stage IV melanoma (8th edition of the AJCC melanoma staging system). However, for patients with regional lymph**

nodes with micrometastases, completion lymph node dissection is not required."

The proposed revisions to the eligible population reflects:

- the Committee's agreement on the generalizability of the CheckMate 238 trial results to the 8th edition of the AJCC melanoma staging system on page 2 of the Initial Recommendation
- the conclusion of the CGP on page 12 of the Clinical Guidance Report
- the CGP comments on the deferral of completion lymph node dissection found on page 14: " the CGP agreed that completion lymph node dissection for patients with micrometastatic lymph node involvement detected on sentinel lymph node biopsy should not be a requirement for consideration of treatment with nivolumab as adjuvant therapy to surgery."

b) 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) 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	Para 1, line no. 4	*BMS proposes to edit the eligible population as follows: "Reimbursement should be for the adjuvant treatment of patients with completely resected stage IIIB/C/D ~~(with the exception of regional lymph nodes with micrometastases)~~ and stage IV melanoma (8th edition of the AJCC melanoma staging system). However, for patients with regional lymph nodes with micrometastases, completion lymph node dissection is not required."*
14	pERC recommendation-Appendix 1	Row 1, second column, third bullet	As per CheckMate 238 study inclusion criteria, and as noted in the third bullet of the left column (PAG Implementation Questions), patients in the trial were BRAF mutation positive or negative. For this reason, BMS suggests the following revision: "The CGP agreed that patients with completely resected BRAF-mutated melanoma ~~who otherwise met the CheckMate 238 inclusion criteria~~ should be offered treatment with nivolumab as adjuvant therapy to surgery."
13	Clinical Guidance	Third bullet	Same comment as above.

	report		
14	Clinical Guidance report	Second bullet	As per CheckMate 238 study inclusion criteria, patients were included in the study regardless of PD-L1 status. For this reason, BMS suggests the following revision: "the CGP agreed that there were insufficient data to support this practice, and recommended consideration of treatment with nivolumab as adjuvant therapy to surgery for patients ~~who otherwise met the CheckMate 238 inclusion criteria,~~ regardless of PD-L1 testing;

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, 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
13	pERC recommendation-Appendix 1	Row 4	BMS noted that PAG requested clarity on the use of a faster infusion time of 30 minutes. BMS confirms that the infusion time of 30 minutes is approved by Health Canada for the adjuvant melanoma indication.

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). (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 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), 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. 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.

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 pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

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

- The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
    - The Submitter 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)
- 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.
- 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.)
- 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.
- 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.
- 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.
- 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.
- The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.
- 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.