pan-Canadian Oncology Drug Review

Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

Nivolumab (Opdivo) for Classical Hodgkin Lymphoma

May 30, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Nivolumab (OPDIVO) for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous stem cell transplantation (ASCT) and brentuximab vedotin or three or more lines of systemic therapy including ASCT.
Role in Review (Submitter and/or Manufacturer):	Submitter and manufacturer
Organization Providing Feedback	Bristol-Myers Squibb 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

Bristol-Myers Squibb Canada agrees with the pERC initial recommendation for nivolumab (OPDIVO®) and with pERC's acknowledgement of the net clinical benefit of nivolumab in patients with cHL who have relapsed or progressed after ASCT followed by brentuximab vedotin (BV). However, the pERC initial recommendation for patients with cHL who have relapsed or progressed after 3 or more lines of systemic therapy including ASCT is not aligned with the approved Health Canada indication, nor the pCODR Clinical Guidance Panel (CGP) assessment, nor the clinicians who provided input for this submission.

Indeed, based on the evidence from the clinical trial Checkmate 205, Health Canada approved the use of nivolumab for patients with cHL who have relapsed or progressed after 3 or more lines of systemic therapy including ASCT. Patients in cohort A of Checkmate 205 progressed after ASCT and were BV naïve before receiving nivolumab. These patients demonstrated an objective response rate of 65%, and the longest duration of response assessed by an independent radiographic review committee (median 20.5 months) as well as the longest progression free survival (median 18.3 months, 1-year PFS rate: 55%) of the three cohorts of patients included in the trial.

In addition, the CGP reported that the results from the Checkmate 205 trial demonstrated that nivolumab would address the unmet medical need of a larger patient population including those with relapsed or progressed cHL who are 1) ASCT ineligible and BV naïve, 2) not candidates for BV and 3) ASCT ineligible and have received BV. This small group of patients (about 100 patients per year) who are in most of the cases fairly young in age have no effective treatment options and will die from their cHL whereas they could return to work if their cancer was put into remission.

As reported by the Committee, not all patients with cHL are eligible to BV due to its

toxicity profile or lack of funding. For these patients, chemotherapy is their only treatment option and is consequently the comparator to assess the net overall clinical benefit of nivolumab. Again, as reported by the Committee, equipoise between nivolumab and chemotherapy agent does not exist.

This clinical scenario was modelled as a comparison between nivolumab and the best supportive care (BSC). Bristol-Myers Squibb Canada has included such scenarios in the submission. Scenario 6 and 7 for Decision Problem 1 (Sections 8.8.6 and 8.8.7) compare post-ASCT / BV-naïve patients from Cohort A to the population of Canadian patients from British Columbia (BCCA) and Ontario (Dhamko et al., 2015) registries. The cost of BSC is calculated as a weighted average of all chemotherapy drugs (with exclusion of BV) from a Canadian treatment pattern study. OS and PFS survival curves were fitted from the patient level data in CA209205 trial and survival curves from BC and ON registry data. Utility values were calculated from Checkmate 205 trial data. Under these assumptions, nivolumab is cost-effective when compared to BSC with ICUR between $60,000 and $65,000 / QALY on a model horizon of 15 years.

In addition, in the clinical guidance review, patients with experience with nivolumab reported that nivolumab had a positive impact on their ability to work, attend school, travel, participate in activities, and on their personal relationships.

For all the reasons mentioned above, Bristol-Myers Squibb Canada kindly asks the pERC Committee to include their assessment of the generalization of Checkmate 205 results to patients with cHL that has relapsed or progressed after 3 or more lines of systemic therapy including ASCT and who are not eligible to BV in their funding recommendation. By doing so, the pERC's recommendation would align with the Committee review and would help to address the substantial unmet medical need of this small group of patients.

Bristol-Myers Squibb Canada is committed to working with the provinces to facilitate access to Canadian patients with cHL.

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 within 2(two) business days of the end of the consultation period.

____	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
8	Overall clinical benefit	2nd paragraph 5th line	The reported definition of cohort A and cohort B from Checkmate 205 was reversed. Correct definition of patients in Checkmate 205: Participants were patients who progressed after ASCT and were brentuximab naïve (cohort A), who progressed after ASCT and brentuximab (cohort B), who progressed after ASCT prior to or subsequent to brentuximab (cohort C)
14	Adoption feasibility	4th paragraph 1st line	We suggest to align the pERC's recommendation with the Committee review by adding the following patients: *Patients who have cHL that has relapsed or progressed after three or more lines of systemic therapy including ASCT and are not eligible to receive BV.*

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

1 About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (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 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 Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees 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 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.

1 Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

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 at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on 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. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) 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 Submitter (or the Manufacturer

of the drug under review, if not the Submitter) 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.