PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Nivolumab (Opdivo) for Metastatic Renal Cell Carcinoma

September 1, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Nivolumab (OPDIVO®) is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.
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:

x __ agrees ___ 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 overall clinical benefit with nivolumab compared to everolimus based on statistically significant and clinically meaningful improvements in overall survival and objective response rate, as well as meaningful improvement in the toxicity profile.

The Committee was satisfied that nivolumab also aligned with patient values.

Bristol-Myers Squibb Canada is committed to working with the provinces to facilitate access to Canadian patients with advanced renal cell carcinoma.

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.

__x__	Support conversion to final recommendation.	____	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
Page 3,4	Economic Evaluation. Section 1.3 Submitted and EGP reanalyses estimates	Paragraph 2 and 4	Bristol-Myers Squibb Canada believes that the following assumptions or clarifications are pertinent to the cost-effectiveness analysis or to the decision to be made based on the EGP re-analyses: 1. The use of an average patient weight of 82.4 Kg does not take into account the Canadian patient demographics in terms of gender distribution. In Checkmate 025 study,[1] the majority of patients were male (75%), which is higher than that of reported value in the Canadian patient population (62.9%).[2] Using the Canadian gender distribution provides a more realistic estimate, which is an average weight of 80.5 Kg. The resulting ICER would be $165,932 instead of $172,242 reported by the EGP group. 2. The use of the utility values from the axitinib trial is not appropriate due to the high degree of heterogeneity between the population in this trial[3] and the CheckMate 025[1]: • The population in the axitinib trial included 33% of the poor MSKCC risk group[3], while these patients comprised only 15% of the total trial population in the Checkmate 025[1]. • Prior therapy in the axitinib trial[4] included cytokines for 35% of the population, while in the CheckMate 025 the prior therapy was limited to VEGF targeted therapy only (sunitinib, pazopanib, axitinib). • In addition to the heterogeneity between the patients in the two trials, the safety profiles were different. The pCODR initial clinical guidance report stated in page 3, paragraph 5: "In contrast to TKIs or mTOR inhibitors, nivolumab is very well tolerated..." • In the appraisal of the Afinitor submission to NICE, the progressive state utility score used for Afinitor[5] was 0.68. This

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			was higher compared to the value used in the EGP re-analysis (0.61). • Most importantly the pCODR initial clinical guidance report stated in page 2, last paragraph: "Nivolumab was very well tolerated with a significant benefit in quality of life over everolimus". Therefore the use of axitinib utility data significantly underestimate the quality of life demonstrated by nivolumab in the CheckMate 025. The use of axitinib data as a base case for nivolumab cost-effectiveness analysis is not considered evidence based. The quality of life data generated in the CheckMate 025, which was appraised as a high quality randomized trial (pCODR initial clinical guidance page 15, paragraph 2), should remain the basis for the cost-effectiveness analysis.

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

References

1. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med 2015;373:1803-13.
2. Canadian Cancer Statistics. Canadian Cancer Society, 2015. (Accessed 2016-02-09, 2016, at http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf?la=en.)
3. Cella D, Escudier B, Rini B, et al. Patient-reported outcomes for axitinib vs sorafenib in metastatic renal cell carcinoma: phase III (AXIS) trial. Br J Cancer 2013;108:1571-8.
4. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet 2011;378:1931-9.
5. Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma Peninsula Technology Assessment Group (PenTAG) 2009. 2015, at https://www.nice.org.uk/guidance/ta219/documents/renal-cell-carcinoma-second-line-metastatic-everolimus-acd-evidence-review-group-report2.)

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.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 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.

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.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. 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.