pan-Canadian Oncology Drug Review

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

Nivolumab (Opdivo) for Metastatic Melanoma

April 1, 2016

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Nivolumab (Opdivo®) for the treatment of patients with unresectable or metastatic melanoma, regardless of BRAF status
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Bristol-Myers Squibb Canada

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	✓	agrees in part	____	disagree

- Bristol-Myers Squibb (BMS) agrees in part with the pERC's initial recommendation to fund nivolumab conditional to cost-effectiveness being improved to an acceptable level.
- BMS's decision to agree in part aims at supporting an early conversion of the initial recommendation to the final recommendation in order to initiate the pCPA negotiation, with a goal of reducing patient access delays for a drug that would significantly improve survival and quality of life in patients struggling with a life threatening disease.
- BMS supports unreservedly the pERC's initial recommendation to fund nivolumab for the first-line treatment of patients with unresectable or metastatic BRAF wild-type melanoma.
- BMS is surprised at pERC's recommendation not to fund nivolumab for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. We would like to comment on submitted clinical data and show how it supports the claims and leads to a better understanding of the evidence.
- BMS is also surprised at pERC's initial recommendation not to fund nivolumab for the treatment of patients with unresectable or metastatic melanoma previously treated with ipilimumab. We would also want to offer comments on this part of the recommendation.
- BMS understands that pERC's conclusions and recommendations in these two instances originating from subgroup analyses to determine between-subgroup treatment effect of nivolumab to assess net clinical benefit. However, inferences drawn from the subgroup analyses are unreliable, since they were performed without a proper interaction test and were underpowered to detect a difference in treatment effect. Hence, interpretations may wrongfully direct management of certain patient groups.
- For instance, pERC's assessment of the clinical efficacy of nivolumab conflicts with the findings of pCODR's own Clinical Guidance Panel (Page 5-6 Section 1.3, Initial Clinical Guidance Report) which clearly support the net clinical benefit of nivolumab for the treatment of unresectable or metastatic melanoma in previously untreated and treated patients (including ipilimumab pre-treated patients). It also stands in contrast to unanimous feedback obtained by other international health authorities and HTA agencies such as NICE.
- BMS respectfully believes that there is sufficient evidence to determine a net clinical benefit in these patient populations, consistent with the conclusions of the Clinical Guidance Panel, and we respectfully ask pERC to support funding for these patient populations in their final recommendation.
- The Economic Guidance Panel's best estimates on cost-effectiveness are based on very conservative assumptions and methods and are among the highest estimates. They do not help address uncertainties in the economic evaluation. BMS intends to collaborate with the pCPA to define a risk sharing approach to address uncertainties and ensures improved cost-effectiveness.
- Interpretation of the clinical value of nivolumab is inconsistent with previous pERC assessments of benefit for similar patient populations (unresectable and metastatic melanoma).

- Assessment of clinical value should be consistent across pCODR submissions, and should take into consideration the totality of evidence to support the use of the treatment for the group of patients.
- BMS noted and is worried that six (40%) voting members of pERC were either absent or did not participate in the deliberation due to conflict of interest. As most of the members who refrained from voting were clinical oncologists, BMS is concerned that the balance of the vote between clinical and non-clinical considerations may have been lost.

Comments re Overall Clinical Benefit and Cost-Effectiveness

A. Clinical Efficacy

1) Nivolumab in First-line Treatment of BRAF V600 Mutation-positive (BRAFm) Patients

We believe that there is strong clinical evidence supporting the net clinical benefit of nivolumab in the BRAF V600 mutation-positive previously untreated unresectable or metastatic melanoma. This corroborates the findings of the Clinical Guidance Panel: ''*The Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated unresectable stage III or IV melanoma compared with ipilimumab*.'' [1]

Interpretation of Subgroups Analyses

The lack of recognition by pERC of the clinical benefit provided by nivolumab monotherapy in BRAFm patients lies mainly on the absence of statistical difference in PFS: "*In a subgroup analysis by BRAF mutation status, pERC noted a statistically significant and clinical meaningful difference in progression-free survival in favour of nivolumab (median 7.89 months) compared with ipilimumab (median 2.83 months; HR 0.50, 95% CI 0.39 to 0.63) in patients with BRAF wild-type disease. However, in patients with BRAF V600 mutation-positive disease, no statistically significant difference was demonstrated (HR 0.77, 95% CI 0.54 to 1.09 in favour of nivolumab).*"[2]

It is widely accepted that subgroup analyses should concentrate on differences from the average overall treatment effect, via tests of heterogeneity or interaction, and that it is inappropriate to assess the effects of treatment on a single subgroup by examination of the 95% CI for that subgroup. Confidence intervals in subgroups are always wider than those for the main effect because of smaller numbers. If the interval for a subgroup crosses the no effect point, this is widely misinterpreted as a lack of effect in the subgroup even where the overall effect is significant.[3] Lack of statistical difference does not equal lack of clinical relevance (especially in small number subpopulations). This is further supported by pCODR clinical experts panel: "*The Clinical Guidance Panel concluded that there is an overall net clinical benefit to nivolumab monotherapy in the treatment of patients with previously untreated unresectable stage III or IV melanoma compared with ipilimumab*." [1]

In CheckMate-067 the benefit of nivolumab on PFS vs ipilimumab was observed regardless of the BRAF status. The median PFS in the nivolumab group was 6.9 months (95%CI: 4.3, 9.5) compared to 2.9 months (95% CI, 2.8, 3.4) with ipilimumab. Analyses of progression-free survival in prespecified subgroups, including BRAF mutation status, showed consistently longer progression-free survival with nivolumab than with ipilimumab. In the nivolumab group, the median progression-free survival was 5.62 months (95% CI, 2.79, 9.46) among patients with a BRAF mutation and 7.89 months (95% CI, 4.86, 12.68) among patients with wild-type BRAF. Although the study was not powered to demonstrate superiority within subgroups, the estimated HR for the co-primary efficacy endpoint was <1 for both mutational status (HR 0.77 BRAFm and 0.50 BRAF WT).[4] Of note, for BRAF mutants, this hazard ratio falls below the 0.80 mark, classically recognized as the surrogate level for clinical benefit.

Use of PFS as a Surrogate for I-O Derived Clinical Benefit

In addition, using PFS as the only end-point to assess efficacy of any immuno-oncology agent should be reconsidered. As stated in the pCODR Initial Clinical Guidance Report: ''*It is also important to highlight that it is unknown whether progression-free survival data are a reliable surrogate for overall survival in trials with immunotherapies such as ipilimumab.*''[1]

In the absence of OS data, PFS should therefore be taken in the context of all available data. In Checkmate-067, the ORR was 43.7% with nivolumab vs 19% with ipilimumab with an unweighted difference vs ipilimumab of 24.6% (95% CI: 17.5-31.4). The benefit of nivolumab on ORR was observed regardless of the BRAF status. Among patients with a BRAF WT status, the ORR was 46.8% in the nivolumab group with an unweighted difference vs ipilimumab of 29.1% (95% CI: 20.5-37.1). In the BRAFm group, the ORR was 36.7% with nivolumab with an unweighted difference vs ipilimumab of 14.7% (95% CI: 2.0-26.8).[5]

Together, these results show that nivolumab resulted in significantly longer progression-free survival and higher objective response rates than did treatment with ipilimumab alone. These results were observed independently of the BRAF mutation status.[4]

Better Safety Profile of Nivolumab vs Ipilimumab

When looking at the net clinical benefit of a drug, safety should be taken into consideration. As stated in the pERC initial recommendation: "*There is a need for more effective treatment options with more favourable toxicity profiles in metastatic melanoma."*[2]

The safety profile of nivolumab compares favourably with the safety profile of ipilimumab. In CheckMate-067, Grade 3 or 4 treatment-related AEs were reported in 16.3% of patients in the nivolumab group and 27.3% of patients in the ipilimumab group. Treatment-related AEs that led to discontinuation of the study drug occurred in 7.7% of patients on nivolumab and 14.8% of patients on ipilimumab.[4] This better safety profile of nivolumab vs ipilimumab was recognized by the pCODR: "*Nivolumab has an excellent safety profile, particularly when compared to ipilimumab."* and pERC: *"the toxicity associated with nivolumab was manageable compared to either ipilimumab or chemotherapy"*. [1,2]

National Comprehensive Care Network (NCCN) Guidelines

The net clinical benefit of nivolumab was recognized by the NCCN. Nivolumab is a preferred systemic therapy option in first-line (category 1) for advanced or metastatic melanoma, regardless of the mutational status according to the NCCN guidelines.[6] These guidelines, are widely followed for the treatment of melanoma internationally.

In conclusion, based on all the available data and on the mechanism of action of nivolumab that is independent of the BRAF status, it is clear that nivolumab has a superior efficacy and a better safety profile than ipilimumab. Therefore, there is no clinical rationale to preclude BRAFm patients from accessing the potential clinical benefit provided by nivolumab. Nivolumab should be considered as a preferred treatment option in patients with previously untreated unresectable stage III or IV melanoma, regardless of their BRAF mutation status. This conclusion if further supported by the NCCN guidelines and the very own pCODR clinical expert reviewers.[1,6]

2) Nivolumab in Patients Previously Treated with Ipilimumab

There is clinical evidence supporting the net clinical benefit of nivolumab in this patient population that supports the findings of the pCODR Clinical Guidance Panel: "*The Clinical Guidance Panel concluded that there is a net overall clinical benefit to nivolumab monotherapy in the treatment of patients with unresectable stage III or IV melanoma that was previously treated with ipilimumab compared with chemotherapy."*[1]

Results of the CheckMate-037 phase 3 trial showed an ORR of 32% in nivolumab treated patients versus 11% in the reference arm of chemotherapy-treated patients. Durable tumor regression was observed, with the majority (95%) of responses ongoing in nivolumab treated patients and a median duration of response that was not reached. In the reference arm, ICC, the median duration of response was 3.5 months, ranging from 1.3+ to 3.5 months. Frequency of grade 3-4 drug related adverse events (AE) was lower with nivolumab (9%) compared to chemotherapy (31%).[7] Clearly, nivolumab should be considered as a new treatment option for patients that have progressed after ipilimumab, or a BRAF inhibitor and ipilimumab if their melanoma is *BRAFV*600-mutated.[7]

These results are further supported by the phase I study with nivolumab in a heavily pre-treated patient population (ORR of 41% with the median duration of response of 22 months (9-27+); survival rates at 1-, 2, 3- and 4-year were 65%, 47%, 41%, and 35% respectively; and mOS of 20.3 months (7.2-NE)).[8] These data demonstrate the unprecedented survival benefit that nivolumab provides to patients in the treatment of advanced melanoma.

We recognize the immaturity of the data mentioned above in relation to the precise OS clinical benefit provided by nivolumab post ipilimumab. However, based on the breath of available data for this molecule across different tumor types, nivolumab treatment has consistently displayed OS benefit vs SOC, both in frontline, and advanced lines of therapy (1stL melanoma, 2L+ NSCLC, 2L+RCC, 2L SCCHN) without any evidence of increased toxicities. [9,10,11,12,13]

In conclusion, there is a high unmet medical need for patients who have previously received treatment with ipilimumab. Based on the clear benefit observed with nivolumab, these patients should be given the opportunity to be treated with nivolumab. This is supported by the pCODR reviewers: "*The progression-free survival data and overall survival data from the CheckMate 037 trial are* immature; however, d*ue to the high clinical burden that this illness poses to patients and based on the higher response rates observed with*

nivolumab monotherapy compared with chemotherapy, the Panel concluded that nivolumab has a net clinical benefit in this patient population." [1]

B. Cost-Effectiveness

The Economic Guidance Panel's best estimates on cost-effectiveness are based on very conservative methods and assumptions and are among the highest estimates. They do not help address uncertainties in the economic evaluation.

1) Overall Survival

A very conservative estimate was made on the extrapolation of overall survival using a decreasing pattern of survival that resulted in a high ICER of $198,776/QALY. This is not consistent with available clinical evidence of cancer immunotherapies in patients with unresectable or metastatic melanoma where survival benefit sustained in a long-term period.

2) Time Horizon

BMS does not agree with the Economic Guidance Panel's assumption to truncate the time horizon of the economic model from 20 years to 10 years, given the experience with cancer immunotherapies and anticipated number of patients to be alive after 10 years. The model's time horizon was designed to be long enough to capture all treatment benefits such that the last event would occur within the time frame. Truncating the time horizon, hinders the model from taking into account any long-term benefits realized by this patient group.

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. Recommendation does not require reconsideration by pERC.	——	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

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
No comment			

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
No comment			

[1] Oncology Drug Review Initial Clinical Guidance Report Nivolumab (Opdivo) for Metastatic Melanoma February 4, 2016.

[2] pCODR expert review Committee (pERC) Initial Recommendation, February 4, 2016.

[3] Cuzick J. Forest plots and the interpretation of subgroups. *Lancet*. 2005 Apr 9-15;365(9467):1308.

[4] Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma.N Engl J Med. 2015 Sep 24;373(13):1270-1.

[5] Larkin et al. Efficacy and Safety in Key Patient Subgroups of Nivolumab Alone or Combined With Ipilimumab Versus Ipilimumab Alone in Treatment-Naïve Patients with Advanced Melanoma (CheckMate 067). ECC/ESMO 2015. Oral Presentation.

[6] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Melanoma: NCCN; Version2.2016.

[7] Weber J, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomized, controlled, open-label, phase 3 trial. Lancet Oncology. Published Online March 18, 2015.

[8] Hodi et al. Long-term Survival of Ipilimumab-naïve Patients with Advanced Melanoma Treated with Nivolumab in A Phase 1 Trial, SMR 2014, Oral presentation.

[9] Robert C, Long GV, Brady B, et al. Nivolumab in Previously Untreated Melanoma without BRAF Mutation. *N Engl J Med.* Nov 16 2014.

[10] Brahmer et al., Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. NEJM May 31, 2015.

[11] Borghaei,et al. (2015) Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer. N Engl J Med 2015.

[12]Motzer et al. (2015) Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. Sept 25, 2015.

[13] CheckMate -141, a Pivotal Phase 3 Opdivo (nivolumab) Head and Neck Cancer Trial, Stopped Early. BMS Press Release, January 28, 2016. http://news.bms.com/press-release/checkmate-141-pivotal-phase-3-opdivo-nivolumab-head-and-neck-cancer-trial-stopped-earl

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.