PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Vemurafenib (Zelboraf) for Advanced Melanoma

June 1, 2012

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	ZELBORAF (vemurafenib). Indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. A validated test is required to identify BRAF V600 mutation status.
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Hoffmann-La Roche Ltd.

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

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) *agrees, agrees in part or disagrees with the initial recommendation.* Manufacturer/Submitter agrees only in part with the initial recommendation, as it limits the use of vemurafenib as first-line therapy for patients with BRAF+ unresectable or metastatic melanoma. Although compelling evidence was provided to demonstrate the efficacy and safety of vemurafenib in previously treated patients (BRIM 2), this was not included in the pERC's systematic review as the trial lacked a comparator treatment group. However, at the time of development and until the availability of vemurafenib, there was no universal standard of care for BRAF+ patients previously treated with other systemic therapy.

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?

No comments provided.

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
1 2 4	Recommendation Summary of pERC Deliberations Evidence In Brief, Overall Clinical Benefit, Studies Included and Patient Population	First Paragraph, lines 3-5 Second paragraph, last line Paragraphs 2 and 3	The pCODR Expert Review Committee (pERC) has recommended funding for vemurafenib as first-line therapy in BRAF V600 mutation-positive unresectable or metastatic melanoma, but not in previously treated patients. Based on positive efficacy and safety data from BRIM 2, the Manufacturer believes that previously treated BRAF V600 mutation-positive patients should not be denied access to treatment with the targeted agent, vemurafenib. In the dose extension cohort of the phase I study evaluating vemurafenib 960mg BID in 32 patients with BRAF V600 positive metastatic melanoma, the response rate was an unprecedented 81% with an estimated median PFS of more than 7 months [1]. With the high response rate in the phase I study, vemurafenib clinical development continued with BRIM 2 - a single-arm phase 2 study in previously treated BRAF V600 mutation-positive unresectable or metastatic melanoma. Given the unprecedented response rates, and meaningful PFS and OS achieved in BRIM 2, it is the Manufacturer's position that a single-arm trial in this patient population was justified. There was no universal standard of care when the trial was conducted, particularly in BRAF+ patients, which hinders the ability to conduct a randomized controlled study. The magnitude of efficacy demonstrated in BRIM 2 supports the broad indication,

Page Number	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			including both previously treated and untreated patients, as approved by Health Canada: *ZELBORAF™ (vemurafenib) is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. A validated test is required to identify BRAF V600 mutation status.* Other regulatory authorities, including the FDA, EMA and Swiss Medic, have recognized the efficacy of vemurafenib in previously treated patients by approving a broad indication for vemurafenib which includes both first and subsequent lines. Until February 2012, there were no regimens approved by Health Canada for previously treated melanoma. Treatments for metastatic melanoma had poor response rates and no benefit in overall survival leaving no good options for patients; the preferred option for metastatic melanoma patients was participation in a clinical trial. Furthermore, in the pERC Initial Recommendation for ipilimumab (Yervoy), the pERC states "…there is currently no standard treatment for metastatic melanoma in previously treated patients…". Therefore, the results of BRIM 2 should inform pERC's decision making on the activity of vemurafenib in previously treated BRAF V600 mutation positive

**** The 3-page limit on feedback for initial recommendations was reached. As the instructions to completing this feedback form indicate, if comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC. ****

References:

1. Flaherty KT, Puzanov I, Kim KB et al. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. 2010: N Engl J Med 2010;363:809-19.

2. Sosman J.A., Kim K.B., Schuchter L. et al. Survival in BRAF V600-Mutant Advanced Melanoma Treated with Vemurafenib. N Engl J Med 2012; 366:707-14.

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.

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.