PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (previously untreated)

November 3, 2016

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

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3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	IMBRUVICA® (ibrutinib) for the treatment of patients with previously untreated chronic lymphocytic leukemia and small lymphocytic lymphoma for whom flurdarabine-based treatment is considered inappropriate.
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Janssen Inc.

**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

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.*

Janssen Inc. agrees with the committee that 'there is an unmet need for more effective and tolerable treatment options for patients with previously untreated CLL/SLL'

- The majority of patients with CLL are elderly and/or have comorbidities, and may be unsuitable to receive fludarabine-based treatment. Many of these patients would benefit from less intensive treatment options.
- Current treatment options for patients who are considered inappropriate for fludarabine-based treatment are associated with lower toxicity compared to fludarabine, but they provide limited efficacy. There is therefore a gap for treatment options that render long lasting remission with an acceptable tolerability profile.

Janssen Inc. agrees with the committee that 'ibrutinib demonstrated an overall net clinical benefit based on clinically meaningful and statistically significant improvement in progression-free survival, improvement in overall survival, improvement in quality-of-life and a moderate but manageable toxicity profile.'

- Ibrutinib is therefore an oral, targeted therapy that offers a new mechanism of action and fulfills the current treatment gap in previously untreated CLL/SLL.

Janssen does not agree with the EGP reanalysis where two very unlikely assumptions

were applied to derive the upper ICER range. To derive the upper range, the EGP assumed that 1) HR for both PFS and OS are equal to 1 at the end of the trial duration; and 2) subsequent idelalisib treatment cost are applied for 50% of ibrutnib patients.

Regarding the first assumption (HRs=1 at end of trial period):

- Janssen does not agree with this reanalysis as it is inconsistent with the available evidence:
- The OS HR observed in the Phase 3 study was 0.16 (95% CI, 0.05-0.56, p=0.001) compared to chlorambucil, after a median follow up of 18.4 months. At study closure, remaining study participants were transferred to the non-randomized observational study (PCYC-1116). The HR for OS for this collective data-set at the latest interim analysis was 0.44 (95% CI, 0.21-0.92), after a median follow up of 28 months. At this time, 41% of chlorambucil patients had crossed over into the ibrutinib group. This evidence therefore suggests that treatment benefit continues over time despite crossover.
- Further, in the three year follow up of the Phase 1b/2 data of 31 patients with previously untreated CLL/SLL, the estimated PFS rate was 96% (95% CI, 76.5-99.5%) at 30 months, and estimated OS rate was 97% (95% CI, 78-99.5%) at 30 months. This evidence therefore suggests that treatment benefit continues with longer follow up.
- In light of this evidence — treatment benefit continuing beyond 30 months in the phase 1b/2 study, and treatment benefit continuing despite significant crossover in the collective randomized and non-randomized data-set, it is very unlikely that all treatment benefit should stop at the end of the study period. Instead, the evidence suggests that that treatment benefit will continue for some time and then attenuate over time.

Regarding the second assumption (subsequent idelalisib treatment cost are applied for 50% of ibrutinib patients).

- Janssen does not agree with coupling this assumption with the first assumption, as it is very unlikely that all ibrutinib benefit should stop at end of study, and within the same scenario, patents initially treated with ibrutinib should incur the cost of high-cost subsequent therapy.
- In addition, idelalisib is not currently widely funded for R/R CLL. Current clinician experience does not suggest that 50% of patients are being treated with idelalisib in the R/R CLL setting.

As such, while Janssen acknowledges the application of testing assumptions, Janssen does not agree with assuming both of these assumptions for the upper range. Instead, the best case estimate of the upper range is more likely made up of one but not both of these assumptions.

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
			NO COMMENTS

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 COMMENTS

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
			NO COMMENTS

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.