PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Bendamustine (Treanda) for indolent Non-Hodgkin Lymphoma and Mantle Cell Lymphoma

November 29, 2012

INQUIRIES

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

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Bendamustine (TREANDA) for indolent non-Hodgkin lymphoma and Mantle cell lymphoma
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Lundbeck Canada Inc.

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

Lundbeck Canada Inc. agrees in part with the initial recommendation related to the following statements made in the pERC initial recommendation:

Summary of the feedback:

- We support the pERC initial recommendations for Bendamustine funding in iNHL and MCL (front-line and relapse) regarding its favourable net clinical benefit and cost-effectiveness.
- We do not believe that prior-rituximab maintenance should be a funding enabler or barrier for Bendamustine reimbursement in the relapsed setting for the reasons outlined in following sections of this feedback document.
- We believe that the ROBIN trial may add additional information on the role of Bendamustine monotherapy in second-line iNHL and may also provide additional clarity for the role of Bendamustine re-treatment in the management of Lymphoma.
- However, pending the ROBIN trial, we believe that Bendamustine monotherapy funding should be made available for patients who have failed prior therapies or are refractory to rituximab and who may not be illegible to enrol in clinical trials and for whom radio-immunotherapy is not an available option. Restricting access to this patient population would create a major funding gap.

pERC RECOMMENDATION: *"There is no clinical evidence available on the clinical benefit of combination bendamustine-rituximab in patients who have either received prior maintenance therapy with rituximab or who are refractory to rituximab." (Page 1, paragraph 2 of the pERC recommendation)*

Prior Rituximab Maintenance: The BR vs. FR trial (Rummel 2010) was conducted between 2003 and 2010 and it was until 2010 that rituximab-maintenance became widely (globally) approved for the front-line management of indolent non-Hodgkin lymphoma, making the requirement for prior-maintenance not feasible.

Also, the fact that rituximab maintenance was not a requirement for patient selection in the Rummel 2010 study should not penalize Bendamustine but in the contrary should add

more certainty in the sense that the derived benefit is strictly related to the interventional arms and may not be confounded by prior rituximab-maintenance.
That being said, we do not believe that such an inclusion or exclusion would have changed the trial general conclusions. In practice, the choice of chemotherapy treatment in iNHL or MCL post-progression does not depend on whether patient has received prior rituximab-maintenance or not. Rather, the prior use of maintenance may guide the treating physician on the course of action regarding the optimal use of anti-CD20 MAB treatment upon relapse.

This standard approach is consistent with the doctrine of differentiating between chemo-sensitivity and immuno-sensitivity. From a biological standpoint, these two classes have different mechanisms of action.

As an example, the Fludarabine-Rituximab combination is currently funded in multiple Canadian jurisdictions in the relapse setting and patients can access it irrespective of whether the patient had prior-maintenance or not. The same applies for Bendamustine recommendations in the relapse setting in the international NCCN and ESMO guidelines as we do not see such a restriction.

Exclusion of Rituximab-refractory population in BR vs. FR: The rituximab-refractory population has been excluded from the study since it is not common in the clinical practice to re-challenge using the same agent if the patient did not respond to it. Hence, it is not surprising to see this exclusion criterion in the Rummel 2010.

Rituximab-refractory population in the Kahl 2009:
The submitted pivotal Kahl 2009 study included patients who are refractory to chemotherapy or rituximab-based therapy. Patient had a median of 2 prior therapies. the trial included the following patients characteristics:

- 25% had already had Radio-immunotherapies
- 1/3 were refractory to their last chemotherapy regimen
- 100% were Rituximab-refractory;
- up to 6 prior therapies

The results show that Bendamustine monotherapy is effective in this area of high unmet need and where patients are running out of options. The only limitation of this study is that it is a single arm study and at the time it was designed and approved there were no proven therapeutic options at this late stage of the disease.
Today, there are still very limited options for these patients and the most commonly reported available options are either clinical trials, if the patient is eligible or radio-immunotherapies if feasible. In the absence of these options, Bendamustine could offer a reasonable alternative to patients.

Moreover, Bendamustine has proven superiority to other chemotherapy regimens in managing iNHL or MCL (in front-line versus CHOP and in relapse vs. Fludarabine). These findings should support its safety and effectiveness in the refractory setting.

Rituximab-refractory population and ongoing ROBIN Trial:
The ongoing ROBIN trial will add additional information about Bendamustine monotherapy in the rituximab-refractory population in the 2nd line setting and may also

provide information about re-treatment with Bendamustine for patients who previously responded to the therapy.

In the same time, we believe that there is a clear benefit to patients in making Bendamustine available as a monotherapy in advanced stages of the disease who may not be candidate for clinical trials or for whom radio-immunotherapy is not available.

SUMMARY OF pERC DELIBERATIONS: ***"It was noted that drug wastage could be an important issue that may limit feasibility, if the 25 mg vials of bendamustine are ever not available, given the short stability of reconstituted bendamustine and increased drug costs that would result from wastage."(Page 3, paragraph 8)***
The manufacturer has already made available the two strengths of 100 mg and 25 mg vials in Canada and plans to continue to do so. The pricing structure is also attractive where the 25mg/vial price is a quarter of the 100mg/vial. Hence, we do not believe that this question should represent a barrier for adoption.

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.

__X__ 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

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional 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.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.