pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Provincial Advisory Group (PAG) Feedback on a pCODR Expert Review Committee Initial Recommendation

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

November 3, 2016

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s): Ibrutinib (Imbruvica) for CLL, previously untreated

Endorsed by: Provincial Advisory Group Chair

Feedback was provided by all nine provinces (Ministries of Health and/or provincial cancer agencies) and federal drug plans participating in pCODR.

3.1 Comments on the Initial Recommendation

a) Please indicate if the PAG (either as individual PAG members and/or as a group) agrees or disagrees with the initial recommendation:

_____ Agrees _____ Agrees in part __x__ Disagree

PAG does not agree with the recommendation. This recommendation is difficult to implement as the comparator used in the trial is not what is being used in current Canadian practice. Although pERC identified benefits of ibrutinib when compared to chlorambucil, the lack of evidence to inform whether ibrutinib is better, the same or worse than treatments used in current practice leads to a situation where price arrangements to improve cost-effectiveness cannot be determined.

b) Notwithstanding the feedback provided in part a) above, please indicate if the PAG 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.

PAG is requesting reconsideration since pERC was unable to determine the magnitude of clinical benefit and thus, cost-effectiveness, compared to Canadian standard of care. Without comparative evidence to current standards of care, combined with no information on sequencing chemo-immunotherapy after ibrutinib failure, PAG members considered that eligibility for ibrutinib in previously untreated patients should be limited to those with del(17p) or for those where chemo-immunotherapy is not an option. PAG identified the unmet need is in the small number of patients with the del(17p) who do not respond to chemo-immunotherapy. pERC noted that patients with del(17) were excluded from the RESONATE-2 trial but considered evidence from a small phase II non-randomized trial in treatment-naïve patients with del(17p).

PAG identified that the budget implications may be quite significant and it was noted from clinician feedback that shifting current first line treatments downstream will be expected.

On both issues, where evidence that directly compares ibrutinib with current first line treatments and evaluates clinical benefit of treatment options following ibrutinib, PAG members indicated that trials are feasible to answer these questions and evidence generation should not be the responsibility of the provinces.

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
5	Summary of pERC Deliberations	paragraph #6, last two sentences	Although PAG agrees that testing for del(17p) will not be required in front-line treatment with ibrutinib given the benefits are the same for patients with or without del(17p), PAG noted that testing for del(17p) would still be important: • patients with del(17p) do not respond to chemo-immunothearapy and physicians may wish to treat these patients with ibrutinib upfront • testing for del(17p) would be conducted at subsequent relapses since the mutation can develop over the course of the disease • del(17p) status is important in the collection of prospective evidence regarding benefit (outcome) and cost-effectiveness of all CLL therapies.
2	Potential Next Steps	Collecting Prospective Evidence	PAG felt that evidence from trials comparing ibrutinib to current standard of care should be submitted to assess cost-effectiveness rather than the provinces collecting prospective to inform cost-effectiveness post-marketing, for front-line treatment of CLL given the availability of treatments.

3.2 Comments related to PAG input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on the PAG input provided at the outset of the review on potential impacts and feasibility issues of adopting the drug within the health system.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial PAG input
			Although issues associated with the recommendation have been made clear, most notably on the lack of comparative data with current standard of care and no information on whether current standards of care

			are of benefit in ibrutinib failures, there are significant adoption feasibility challenges with: • negotiating a substantial price reduction for ibrutinib where cost-effectiveness against current treatments is not known • decisions on whether to or not reimburse current first line therapies in the second line setting where clinician input favors this scenario, but where there is a lack of evidence for benefit and unknown whether the existing negotiated price point is appropriate as a downstream therapy (e.g. obinutuzumab plus chlorambucil was given a conditional recommendation from pCODR for which a negotiated price based on economic evaluation in the first line setting was established)

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
4 11	Overall Clinical Benefit Economic Evaluation	Paragraph 3, Line 2 Paragraph on Drug Costs, Line 3	 Correction: chlorambucil is an oral therapy, not intravenous
			PAG noted that the dose of chlorambucil used in the RESONATE-2 trial may be different than in Canadian practice.

About Completing This Template

pCODR invites the Provincial Advisory Group (PAG) to provide feedback and comments on the initial recommendation made by the pCODR Expert Review Committee. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR re view 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 pERC 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 PAG, either as individual PAG members and/or as a group, agrees or disagrees with the pERC 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 pERC 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 pERC final 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 a pERC final 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 pERC final 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 members of the PAG can provide feedback on the pERC initial recommendation; delegates must work through the PAG representative to whom they report.
    a. Please note that only one submission is permitted for the PAG. Thus, the feedback should include both individual PAG members and/or group feedback.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the pERC 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 *Provincial Advisory Group (PAG) Feedback on a 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. PAG 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, PAG 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.