PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

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

Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia

August 18, 2015

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Idelalisib (ZYDELIG™) for the treatment of patients with relapsed chronic lymphocytic leukemia in combination with rituximab
Role in Review:	Submitter/Manufacturer
Organization Providing Feedback	Gilead

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:

____X agrees ____ 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.*

Gilead Sciences Canada Inc. agrees with the recommendation of the pERC to fund idelalisib (ZYDELIG™) when used in combination with rituximab for the treatment of patients with relapsed CLL. We agree that ZYDELIG plus rituximab has demonstrated a clinically meaningful improvement in progression-free survival (PFS) and overall survival (OS), improved quality of life, and has a manageable toxicity profile compared to rituximab plus placebo in Study 116. These improvements were significant and observed across subgroups, including in those with poor prognostic factors such as 17p deletion/TP53 mutation. We also agree that ZYDELIG plus rituximab is aligned to patient values for treatments, in that it provides improvements in PFS, OS, quality of life, and offers another choice in treatment with a different side effect profile. Gilead Sciences Canada Inc. considers ZYDELIG plus rituximab cost-effective based on the submitted estimates of the incremental cost-effectiveness ratio (ICER). Gilead agrees with pERC and the EGP assessment that the model used the most conservative approach by comparing with chlorambucil, the least expensive treatment option. We acknowledge that altering other key assumptions within the submitted model may impact estimates of cost-effectiveness. The submitted cost effectiveness model was prepared based on the Health Canada approved CLL indication and reimbursement request (consistent with the pERC recommendation). The budget impact analysis model submitted was prepared based on assessment of the anticipated market dynamics at the time of submission. Gilead Sciences Canada Inc. looks forward to refining the budget impact assumptions reflecting changes in the environment since the submission was made as the discussions with various jurisdictions take place.

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 #	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
3	Summary of Deliberations	Paragraph 2, line 9-11	The pERC noted that the population in Study 116 was likely more fit than patients who would be considered candidates for ZYDELIG plus rituximab in the real world setting and noted concern regarding the generalizability of the study population. To note, the CLL patient population and disease characteristics are heterogeneous, with patients often diagnosed at an advanced age and affected by concurrent comorbidities. This was reflected in the relapsed CLL population within Study 116. Previously, the relapsed CLL patient population included in Study 116 had not been well represented in clinical trials, making the optimal treatment strategy unclear. Patient preferences, age, and lack of evidence-based options for treating CLL patients who are elderly and/or have comorbidities are considered factors that lead to under-treatment in this population. As submitted, the patient population in Study 116 was also heterogeneous, with a median age of 71 (range 47-92) and a median CIRS score of 8 (range 1-18). Comorbidities were common across organ systems - 51.8% respiratory, 41.8% endocrine/metabolic, 39.5% renal, 36.8% cardiac and ~35% had poor bone marrow function. Considering this information and context, we believe that the patients in study 116 do in fact reflect the real world population. Given the population included, we agree with the pERC's statement that they were impressed by the PFS

			and OS reported in Study 116. However, remains somewhat unclear as to why pERC would assess the patients to be more fit in Study 116 than in the general CLL population.
5	Overall Clinical Benefit (Studies Included)	Paragraph 2, line 1	We agree with the pERC that there is currently no standard of care for relapsed CLL in Canada. Treatment decisions are often made on an individual basis dependent upon specific patient and disease characteristics. As such, it is difficult to define the comparator in Study 116 as "inappropriate", particularly from a clinical perspective. As included in the pCODR submission, dose-dense rituximab is one of many possible treatment options and was chosen as the comparator for the following reasons: • Single agent rituximab has documented activity in previously-treated CLL. Dose-dense rituximab was included as a treatment option in the National Comprehensive Cancer Network (NCCN) guidelines for patients with significant comorbidities. • Clinical practice data show that rituximab is a commonly prescribed treatment in other jurisdictions for this patient population. Rituximab monotherapy is used in 23- 26% of patients in the second-, third- and fourth-line settings. • Patients enrolled in Study 116 were deemed by their clinicians to be inappropriate for cytotoxic chemotherapy due to bone marrow damage from previous chemotherapy, renal impairment, or comorbidities. Dose-dense rituximab monotherapy would be a viable treatment option for these patients. Data from Study 116 showed that rituximab monotherapy benefitted a number of patients, thus confirming it as a reasonable comparator.
3	Summary of Deliberations	Paragraph 1, line 18-21	As noted by the pERC, patients who are on anti-coagulants or those who have recently experienced a stroke or a serious bleeding episode may be candidates for treatment with ZYDELIG plus rituximab. The benefit of ZYDELIG plus rituximab, however, is not limited to this subset of patients and was observed across the

			broader relapsed CLL population that was included in Study 116. ZYDELIG plus rituximab meets an unmet need in the relapsed CLL patient population. As submitted to pCODR, the CLL patient population and disease characteristics are heterogeneous, with patients often diagnosed at an advanced age and affected by concurrent comorbidities. Many patient and disease related factors are considered when choosing the most appropriate treatment for a given patient, such as age, type and severity of comorbidities, stage, and cytogenetics. Therefore, given the individual differences among patients living with CLL, treatment options are highly needed for physicians and patients. We agree with the pERC that ZYDELIG plus rituximab is aligned to patient values for treatments, in that it provides improvements in PFS, OS, quality of life, and offers another choice in treatment with a different side effect profile.

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 #	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
3 6	Summary of pERC Deliberations Overall Clinical Benefit	Paragraph 3, line 8 Paragraph 4, line 3	As per information submitted to pCODR as well as the ZYDELIG Health Canada Product Monograph, suggest “hepatotoxicity” rather than “hepatitis”.

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.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.