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 Follicular Lymphoma

September 29, 2016

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	Zydelig (idelalisib) for the treatment of patients with follicular lymphoma (FL) who have received at least two prior systemic regimens and are refractory to both rituximab and an alkylating agent.
Role in Review (Submitter and/or Manufacturer):	Manufacturer
Organization Providing Feedback	Gilead Sciences Canada, 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 ____ agrees in part X__ 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. disagrees with the pERC initial recommendation not to fund Zydelig (idelalisib) as a monotherapy in patients with follicular lymphoma (FL) who have received at least two prior systemic regimens and are refractory to rituximab and an alkylating agent for the following reasons:

1) Net clinical benefit of idelalisib in a population of high unmet need

The common pattern of disease course in FL is one of relapse and remission, with each relapse becoming more difficult to treat and each remission period shorter than the preceding one. Although FL is considered an indolent disease, the median duration of response to treatment is only 6 months with a median overall survival of 1.2 years once the patient reaches his/her third line of therapy.[1] By this stage, patients have a disease that is very serious and in need of treatment options which are currently lacking. However, Study 101-09 demonstrated that in patients with FL who were refractory to rituximab and an alkylating agent, and who had a median of 4 prior lines of therapy and were treated with idelalisib monotherapy, achieved an ORR of 55.6%, median PFS of 11 months, and a median OS that was not reached after a median follow up of 19.4 months.[2] These outcomes far exceed those expected with available therapies as well as when compared with a median PFS of 4.6 months reported for the last therapy received prior to entry into Study 101-09.

The toxicity profile also was acceptable in this heavily pretreated, refractory patient population. The pERC noted the 5 patients (7%) with FL who discontinued Study 101-09 due to death. The causes of death in these 5 patients were reported as follows: heart failure, cardiac arrest, splenic infarct/acute abdomen, drug-induced pneumonitis, and unknown (n=1 each).[2] This incidence of mortality is not unexpected: as noted by the patient input in the Clinical Guidance Report, available treatment options in Canada for relapsed disease tend to be associated with increased toxicity, and reduced anti-tumor activity and tolerability. For example, deaths considered to be possibly treatment related occurred in 6 rituximab-refractory iNHL patients (6%) with a median of 2 prior therapies who received chemotherapy,[3] despite these patients reflecting a less heavily pre-treated population than the alkylating agent-refractory patients evaluated in Study 101-09.

Consistent with the opinion of the pERC (and described in the Clinical Guidance Report), and the regulatory authorities in their approval of Zydelig (idelalisib) in Canada, the United States and the European Union, is the recognition of a significant lack of treatment options and effective therapies for patients with FL who are refractory to rituximab and an alkylating agent. Data from Study 101-09 was compelling enough to gain conditional approval for this indication. The risk factors associated with increased serious and/or fatal infections, as recently identified in a frontline CLL study and two early relapse iNHL studies of idelalisib in combination with other agents, are absent within the current idelalisib monotherapy indication and reimbursement request. Furthermore, the Committee for Medicinal Products for Human Use (CHMP) recently issued a positive opinion for idelalisib in the European Union, endorsing the Pharmacovigilance Risk Assessment Committee (PRAC) conclusion that the benefit-risk balance in the authorized indications for idelalisib in refractory FL and relapsed CLL remained positive.

Given the significant unmet need for this specific subset of patients with FL who have relapsed following previous (including multiple lines of) therapy and become refractory to rituximab and an

alkylating agent, the evidence in Study 101-09 strongly supports the conclusion that idelalisib is active and offers a net clinical benefit in this population.

2) Patient population in Study 101-09 were in need of treatment

The pERC has limited the definition of treatable patients to only those who are 'symptomatic' as defined by B symptoms (eg. fever, weight loss, night sweats) and other symptoms (eg. skin lesions, pruritus, etc) and failed to consider other patient- and disease-related criteria that drive treatment decisions. According to Canadian and international treatment guidelines and clinical practices, B symptoms are not always present in FL and represent only one of the potential criteria to consider when determining initiation of treatment.[4-6] As per the GELF and BNLI criteria, as well as the Alberta Health Services Lymphoma Treatment Guidelines, additional considerations for immediate treatment include any of the following: bulky disease, involvement of ≥3 nodal sites, any systemic or B symptoms, cytopenias, organ compression, splenic enlargement, pleural effusion, performance status, or rapid lymphoma progression.[4-6] These additional considerations and patient characteristics were not acknowledged by the pERC in their statements and overall evaluation. Therefore, the conclusions drawn by the pERC regarding the population of patients that should be treated (i.e. limited to only those patients who are symptomatic) are misguided. Indeed, the fact that patients in the 101-09 study were relapsed with a median of 4 prior treatments indicates that clinicians had already identified these patients as having progressive disease requiring treatment. Moreover, the fact that a benefit from idelalisib treatment was observed supports the notion that idelalisib in this setting is appropriate.

The patients enrolled in Study 101-09 were in need of treatment. The patients were all refractory to rituximab and an alkylating agent; 83.3% had Ann Arbor stage III-IV disease, 29% had elevated LDH, 22% had bulky disease, 54% had a high-risk FLIPI score at baseline, 18.1% had disease-related symptoms, and 30.6% had baseline cytopenias. Notably, the patients enrolled also had rapidly progressing disease, with a median time since completion of their last therapeutic regimen of 4.3 months and with 86% of patients being refractory to this regimen. Based on the guidelines and clinical practice mentioned, this patient population would not be considered appropriate for an observational management approach.

3) 101-09 study design was appropriate given no standard of care and highly specific patient population refractory to rituximab and an alkylating agent never previously investigated in a comparative clinical trial setting

Gilead Sciences Canada Inc. did not receive any specific questions related to the validity of the study design, sample size, or post hoc analysis throughout the review process and therefore had no opportunity to address the concerns now raised by the pERC. Furthermore, when Gilead sought feedback from pCODR regarding whether to include the iNHL analysis, FL analysis or both, pCODR responded that both analyses be provided and that the funding request be focused on the FL population. Gilead proceeded accordingly.

The data submitted to pCODR for refractory iNHL (N=125) demonstrate an ORR of 57.6% and median PFS of 11 months. The results submitted for the FL subset (n=72), which represents the majority of patients enrolled, are consistent with this overall analysis (ORR of 55.6%; median PFS of 11 months).

The pERC noted that a randomized controlled trial could have been conducted with heavily pre-treated FL patients who were refractory to rituximab and an alkylating agent and that, in contrast to Study 101-09 such a trial would provide unequivocal results. Until Study 101-09, there had not been a clinical trial conducted in this specific FL population. Thus, there is no standard therapy for this patient population and patients are typically treated pragmatically with chemotherapies that also have never been evaluated in a clinical trial setting. Given that there is no standard therapy to serve as an adequate control, a randomized, blinded, controlled trial was not feasible at the time the study protocol was developed. In Study 101-09, there were 47 different prior therapeutic regimens documented as the most recent therapy prior to study entry, reflecting the heterogeneity

and lack of consensus in treating these patients. The median PFS with idelalisib was more than double that reported for patients on the last therapy received prior to study entry, which far surpasses outcomes expected in current clinical practice. Contrary to the point in the Clinical Guidance Report and made by the pERC, patients were not required to be refractory to their immediate last prior regimen for entry into Study 101-09; thus these data do serve as a reasonable reference for outcomes in a similar real-world population that would be appropriate for idelalisib monotherapy.

pERC also noted that a randomized controlled trial would have been feasible, given the large number of patients diagnosed each year with FL. Although we agree that a large number of patients are diagnosed, number of diagnoses does not translate directly into the number of patients who will become refractory to rituximab and an alkylating agent. To date, since the NOC/c for idelalisib in Canada on March 27, 2015, the Gilead Oncology Patient Support Program which is open to all patients with FL who have received at least 2 prior systemic regimens and are refractory to both rituximab and an alkylating agent, has received 90 enrollments from physicians requesting access to idelalisib for their patients. This is significantly less than the 2800 patients diagnosed in Canada in 2015 referenced in the Clinical Guidance Report.

4) **The pERC initial recommendation not aligned with the clinical interpretation of experts reflected in the pCODR Clinical Guidance Report**

Based on the pCODR Clinical Guidance Report, the panel concluded that there may be a net overall clinical benefit to idelalisib in the treatment of FL. Although it was noted that without a comparator, the magnitude of benefit is difficult to determine, the conclusion stated "it is clear that idelalisib is an active drug in FL based on the ORR and PFS reported, with an 11 month PFS in the refractory patient population likely of clinically meaningful benefit". The report also concluded that based on the data submitted from Study 101-09, "idelalisib is a reasonable option for patients with FL when other treatment options have been exhausted". The reason for the significant discrepancy between the recommendations of the pERC and the conclusions stated in the Canadian expert panel's Clinical Guidance Report is not clear to Gilead Sciences Canada Inc.

Summary

Idelalisib monotherapy is considered and is currently administered to patients with FL as a viable option to help control disease that is refractory to rituximab and an alkylating agent. Patients receiving idelalisib may achieve durable responses, and idelalisib is a recommended option for specific patients in treatment guidelines for FL.[7] Based on the:

- compelling efficacy results from Study 101-09,
- acceptable and manageable safety profile,
- significant unmet need in this patient population,
- strong alignment to stated patient values,
- conclusions stated by Canadian experts within the Clinical Guidance Report, and
- prior precedent for positive funding recommendations based on ORR in single-arm trials,

Gilead Sciences Canada Inc. considers the evidence provided adequate to support the use of idelalisib as monotherapy for the treatment of patients with FL who have received at least two prior systemic regimens and are refractory to rituximab and an alkylator, a population which has to date not been studied specifically in a comparative clinical trial setting. Orally administered idelalisib monotherapy represents an important therapeutic option with a novel mechanism of action in the treatment of this incurable, serious, life-threatening disease. Limiting the access and reimbursement of idelalisib as an option for clinicians and appropriate patients leaves no viable alternative other than supportive and palliative care.

Gilead Sciences Canada Inc. respectfully requests that pCODR reconsider its initial recommendation and issue a positive clinical decision for the use of idelalisib monotherapy in this patient population in their final recommendation.

- 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.

- 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
p.2 p.4 p. 5	Summary of pERC Deliberations Patient populations: Mostly asymptomatic patients Safety: High risk of significant toxicity, including death	P 2, L 11-17 Whole section P 1, L 2	As per the information provided already to pCODR, the statements by the pERC relating to the 101-09 study population being mostly 'asymptomatic' are misguided. Please refer to the "Comments on the Initial Recommendation" section of this document. With this reiteration and given the numerous erroneous references to the 101-09 population being 'asymptomatic', the clinical benefit in Study 101-09 should be re-evaluated.
p. 2 p. 5	Summary of pERC Deliberations Safety: High risk of significant toxicity, including death	P 3, L1 P 1, L1	To clarify, what the pERC is referring to are discontinuations that occurred due to death. The following were reported as the cause of death in the 5 patients: heart failure, cardiac arrest, splenic infarct/acute abdomen, drug-induced pneumonitis, and unknown (n=1 each).
p.2 p. 5	Summary of pERC Deliberations Key efficacy results: Exploratory	P 2, L10-11 P 1, L1	To clarify, the reported one-sided alpha level of 0.1 by the pERC is erroneous and potentially misleading, implying that this alpha level increased the chance of detecting a statistical difference when there is no real difference. Using Simon's optimum 2-stage design, a sample size of 100 patients had power >0.90 to achieve

	secondary end point in a subgroup analysis		a one-sided alpha level of <0.005 (two-sided significance level of 0.01).

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

References

1. Johnson PWM, Rohatiner, A.Z.S., Whelan, J.S., Price, C.G.A., Love, S., Lim, J., Matthews, J., Norton, A.J., Amess, J.A.L., Lister, T.A. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single-center. Journal of Clinical Oncology 1995;13:140-7.

2. Gilles Salles, Stephen J. Schuster, Sven de Vos, Nina D. Wagner-Johnston, Andreas Viardot, Christopher R. Flowers, Matthias Will, Madlaina Breuleux, Wayne R. Godfrey, Bess Sorensen, Ajay K. Gopal. Idelalisib Efficacy and Safety in Follicular Lymphoma Patients From a Phase 2 Study. In: ASCO Annual Meeting. May 29-June 2, 2015, Chicago, IL.

3. Kahl BS, Bartlett, N.L., Leonard, J.P., Chen, L., Ganjoo, K., Williams, M.E., Czuczman, M.S., Robinson, S., Joyce, R., van der Jagt, R.H., Cheson, B.D. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. Cancer 2010;116:106-14.

4. Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. J Clin Oncol. 1997. 15:1110-7.

5. Ardeshna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003 Aug 16. 362(9383):516-22.

6. Alberta Health Treatment Guidelines. LYMPHOMA. Protocol Number LYHE-002 Version 8. December 2014. Accessed: December 2015. http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf.

7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphoma 2015.

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.