CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Registered Clinician Feedback on a pCODR Expert Review Committee Initial Recommendation

Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia

March 2, 2018

3 Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Venetoclax a**s monotherapy for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)**
Name of registered clinician(s):	Dr. Tom Kouroukis, Dr. Jordan Herst, Dr. Janet MacEachern, Dr. Anca Prica

**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 registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part X disagree

The Cancer Care Ontario Hematology Drug Advisory Committee (CCO Hem DAC) does not agree with the pERC initial recommendation for the following reasons:

First, the appropriate comparator referenced by pERC (rituximab monotherapy or rituximab with HDMP) is, in the Hem DAC's opinion, a sub-optimal comparator that is not widely used in practice. A more suitable comparator may be idelalisib with rituximab.

The Hem DAC also acknowledged pERC's concern regarding the need for intensive monitoring and prophylactic measures to prevent tumour lysis syndrome (TLS) in patients. The Hem DAC feels that in a real world setting, TLS induced by venetoclax is manageable. Therefore, the Hem DAC would not expect all these patients to be admitted to the hospital. Intensive monitoring of blood counts and chemistry (in the outpatient setting) may be sufficient.

For patients who have a 17p deletion, the Hem DAC would like venetoclax to be considered following ibrutinib for use as a bridge to allogenic stem cell transplant (allo). By comparison, idelalisib has significantly greater pro-inflammatory effects which may result in additional complications following an allo (e.g. GVHD). Venetoclax has fewer pro-inflammatory effects and would thus be preferred in this setting.

Finally, the Hem DAC would like to reiterate that patients who fail TKIs have a very short life expectancy and no other viable treatment options. Venetoclax is the only agent with documented efficacy in this population.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur two (2) Business Days after the end of the feedback deadline date.

___	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.

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 the Registered Clinician(s) Input

Please provide feedback on any issues not adequately addressed in the initial recommendation based on registered clinician(s) input provided at the outset of the review on outcomes or issues important that were identified in the submitted clinician input. Please note that new evidence will be not considered during 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 program.

Examples of issues to consider include: Are there therapy gaps? Does the drug under review have any disadvantages? Stakeholders may also consider other factors not listed here.

Page Number	Section Title	Paragraph, Line Number	Comments related to initial registered clinician input

3.3 Additional comments about the initial recommendation document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

1 About Completing This Template

pCODR invites those registered clinicians that provided input on the drug under review **prior** to deliberation by the pCODR Expert Review Committee (pERC), to also 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 registered clinician(s) agree or disagree 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, including registered clinician(s), agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation two (2) Business Days after the end of the feedback deadline date. 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.

2 Instructions for Providing Feedback

a) Only registered clinician(s) that provided input at the beginning of the review of the drug can provide feedback on the initial recommendation. If more than one submission is made by the same registered clinician(s), only the first submission will be considered.

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 during this part of the review process; however, it may be eligible for a Resubmission.

c) The template for providing *pCODR Clinician Feedback on a 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. Registered clinician(s) 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

registered clinician(s) 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 initial pERC recommendations 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). Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be new references. New evidence is not considered during 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 by logging into www.cadth.ca/pcodr and selecting "Submit Feedback" by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca. Information about pCODR may be found at www.cadth.ca/pcodr.

Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.

Feedback on pERC Initial Recommendation

Name of the drug indication(s):	Venetoclax for CLL after BCRi failure
Name of registered clinician(s):	Carolyn Owen, David Spaner, Kerry Savage, Nathalie Johnson, Anthea Peters, Versha Banerji, Pamela Skrabek, John Kuruvilla, Mona Shafey, Mohamed Elemary, Sue Robinson

**pCODR may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by pCODR.*

Comments on the Initial Recommendation

a) Please indicate if the registered clinician(s) agrees or disagrees with the initial recommendation:

____ agrees ____ agrees in part __**X**__ disagree

Please explain why the registered clinician(s) agrees, agrees in part or disagrees with the initial recommendation.

As physicians who treat patients with CLL, we disagree with this recommendation and with your interpretation of the evidence in this patient population. We agree with the recommendations of the Clinical Guidance Panel who have made a thorough and thoughtful review of the evidence and the clinical need. This negative decision will lead to lack of access for Canadian CLL patients to the most effective AND best tolerated agent in relapsed/refractory CLL, thereby exposing patients to more toxic and ineffective alternatives or to rapid disease progression and death. This decision also removes an effective agent that could provide a bridge to allogeneic stem cell transplantation in eligible patients.

We are disappointed that your assessment appears to disregard the data from the publication of the M14-032 study. The pERC acknowledged receipt of the manuscript and recognised that the manuscript had been peer-reviewed and accepted for publication. Despite this fact, pERC appears to have not considered the manuscript, instead that the data supporting venetoclax is "immature" and "only available in abstract form". We respectfully request that pERC review the peer-reviewed data from the M14-032 study (now published and available online).

Additionally, we are concerned that though pERC acknowledged that "there is no accepted standard treatment option to use as a comparator", the committee still concluded that venetoclax did not demonstrate a clear clinical benefit over "appropriate comparators". As there are no

appropriate comparators, this conclusion is not valid. We agree with the Clinical Guidance Panel that it would be unethical to conduct a comparative study in which half of patients would be exposed to an ineffective therapy (it would also not be possible to select an acceptable comparator given the lack of evidence for any other therapy in this clinical situation). The efficacy of venetoclax has been clearly demonstrated through impressive PFS data and MRD negativity rates, as reported in the M14-032 manuscript. There is no alternative therapy that has ever been demonstrated to provide any clinical benefit in CLL patients who have failed a BCR inhibitor. Rather than acknowledge the lack of any appropriate comparator, pERC declares that current treatment options would include "single agent rituximab" or "rituximab plus high dose methylprednisolone (HDMP)". There is no evidence that single agent rituximab has any benefit in relapsed/refractory CLL – the use of such a therapy would be inappropriate and wasteful. While data exists for HDMP +/- rituximab in refractory CLL, this data is from many years ago, before the introduction of kinase inhibitors. The duration of response for HDMP +/- R is short, the data is derived from a small number of old studies with small patient numbers and the therapy is associated with a high incidence of infectious complications. It would be unethical to expose modern patients who have failed BCRi to an unproven and risky therapy just because it is cheaper than a proven alternative.

We were also dismayed to read pERC's comments regarding the M14-032 quality of life (QoL) data that stated, "there were no data to determine the impact of venetoclax on patient quality of life compared with available options". When there are no available options for a disease, the alternative option is progression of disease and death. Clearly, it would be unethical to ask dying patients to complete QoL forms to present data for a 'comparator' group. If pERC insists on claiming that HDMP is an appropriate comparator, there is no data on the QoL impact of this therapy; however, HDMP is associated with a high risk of infectious toxicities, its use requires multiple concomitant medications to treat and prevent these infections and it results in significant GI intolerance (far worse than the mild diarrhea caused by venetoclax). It is unreasonable to assume that QoL would be better with HDMP than with venetoclax monotherapy and there is no data to support that supposition. Similarly, the pERC opinion states that venetoclax only "partially" aligns with patient values. This is untrue as patients recognise the lack of other treatment options for CLL progressing after BCRi therapy and the therapy is very well tolerated.

Venetoclax is the only agent with any data for efficacy and safety in r/r CLL patients who have failed a BCRi. This therapy is extremely well tolerated, better than therapy with BCR inhibitors and significantly better than chemotherapy or HDMP. The slow dose ramp up has resulted in negligible rates of tumour lysis syndrome (TLS) and only rare laboratory TLS, which is very manageable. This is the only reasonable therapy for these patients and it provides a life-extending therapy to a small group of needy patients.

If pERC is not willing to accept Phase 2 data for a rare ("orphan") disease, then their opinion should reflect that absolute requirement for Phase 3 data. We feel that pERC's recommendation does not appropriately consider all the data provided and suggests gaps in the data that are not accurate (ignoring the peer-reviewed publication). The absolute requirement for Phase 3 data is not reasonable for these types of rare diseases and deprives needy patients of the opportunity to access valuable, new, effective therapies.

In summary, the conclusion that venetoclax does not demonstrate net clinical benefit over appropriate comparators is not accurate because there are no appropriate comparators and this

therapy is highly effective and very tolerable for CLL patients that have failed a BCR inhibitor—a small group of patients who have no other treatment options and a very short survival without this therapy. On behalf of CLL patients, we strongly support reimbursement for venetoclax in these patients.

b) Notwithstanding the feedback provided in part a) above, please indicate if the registered clinician(s) 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.