



**pan-Canadian Oncology Drug Review
Submitter or Manufacturer Feedback on a
pCODR Expert Review Committee Initial
Recommendation**

**Rituximab (Rituxan) for Acute Lymphoblastic
Leukemia**

August 31, 2017

1. Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): **Rituximab**
 Role in Review (Submitter and/or Manufacturer): **Submitter**
 Organization Providing Feedback: **CancerCare Manitoba**

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

1.1 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 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.

We thank pCODR for their comprehensive review and recommendations. However, we would like to highlight certain elements of the clinical review with which we disagree. We believe that further clarification of these elements may assist pCODR in revising their recommendations about the role of rituximab in CD20+ Philadelphia chromosome negative B-cell Acute lymphoblastic leukemia (Ph- B-ALL).

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 two (2) Business Days after the end of the feedback deadline date.

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 Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity

1.2 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
2	pERC Clinical Considerations	1.2	<p>Use of EFS as the primary endpoint in the GRAALL-R trial.</p> <p>pCODR considers that OS is an important outcome for ALL. pCODR notes no overall survival (OS) advantage in favour of Rituximab-based regimens, and that the cited Randomized Controlled Trial (RCT) [1] was not powered for OS as a primary outcome.</p> <p>EFS, as defined by the GRALLL-R trial, is the elapsed time from randomization to one of: failure of complete remission induction; relapse; and death [1]. We emphasize that EFS is a clinically relevant and valuable endpoint in frontline trials for ALL, and that EFS remains the standard, and preferred outcome for frontline RCTs in ALL.</p> <p>Multiple rigorously designed and conducted RCTs evaluating frontline therapy in ALL for children, adolescents or younger adults with ALL, all of which have used or will use EFS as their primary outcome; those completed studies have uniformly been practice changing:</p> <ul style="list-style-type: none"> • CCG 1882: Superiority of Augmented Berlin-Frankfurt-Munster (BFM) therapy for high-risk pediatric ALL patients with slow, early (day 7) response to induction, with better 5-year EFS compared with standard therapy (72.6% ± 3.9% vs. 57.0 ± 4.2%; p = 0.0008) [2]. • CCG 1922: Superiority of dexamethasone in induction and maintenance compared with prednisone for standard risk ALL; 6-year EFS of 85.5% ± 1.7% in pediatric ALL patients randomized to dexamethasone and 79.1% ± 1.9% in patients randomized to prednisone (p = 0.002) [3]. This was subsequently supported by Medical Research Council and BFM trials [4,5]. • CCG-1961: More Intensive but not longer post-induction intensification (augmented BFM

Page #	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			<p>regimen without second delayed intensification) is superior for high-risk pediatric ALL patients with a rapid, early (day 7) response to induction therapy with 5-year EFS $82.2 \pm 1.6\%$ for intensive vs. $72.5 \pm 1.9\%$ for standard post-induction therapy, respectively ($p = 0.0001$) [6].</p> <ul style="list-style-type: none"> • CCG-1991: Escalating intravenous methotrexate is superior to oral methotrexate during interim maintenance in standard-risk ALL; 5-year EFS $92.6 \pm 1.2\%$ versus $88.7 \pm 1.4\%$, respectively ($p = 0.009$) [7]. • COG AALL0232: Superiority of high-dose methotrexate over Capizzi methotrexate in high-risk pediatric ALL; 5-year EFS $82.0 \pm 3.4\%$ and $75.4 \pm 3.6\%$, respectively ($p = 0.006$) [8]. • Younger adult ALL: The recently activated frontline Alliance for Clinical Trials in Oncology RCT in B-ALL (A041501), evaluating the role of Inotuzumab ozogamicin, uses the primary endpoint of EFS. This trial's design was approved by the US National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) [9]. <p>We are not aware of recent published frontline RCTs in pediatric, adolescent, or young adult ALL that have adopted OS as the primary outcome.</p> <p>While we agree that OS provides the most solid result when evaluating a new treatment oncology in ALL, OS may not be practical, reasonable, or ethical for evaluating frontline therapies in ALL: Failure to achieve CR, or relapse represent clinically significant, highly undesirable events that usually imply the need to switch regimens, exposing the patient to potentially longer and/or more toxic therapy. Such events also result in substantial psychosocial and economic burden to patients and their caregivers. As reflected in a follow-up GRAALL-R publication, those patients who experienced remission induction failure or relapse (i.e. "events") fared poorly, despite having to undergo complex and arduous therapy [10]. Similar outcomes were seen in a Canadian cohort treated upfront with a modified DFCI regimen [11]. As reflected in these publications, the marked variation in subsequent therapies following refractory or relapse ALL can have an effect on OS.</p> <p>Overall, we contend that EFS provides sufficient power to detect a clinically relevant and meaningful difference for</p>

Page #	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			patients, caregivers and health care professionals.
2	pERC Clinical Considerations	1.2	<p>Applicability of the GRAALL-R comparator to Canadian Practice:</p> <p>pCODR raised concerns that the comparator in the GRAALL-R [1] was inappropriate for the Canadian setting.</p> <p>The submitter has no reason to believe that the multi-agent, pediatric-inspired regimen deployed by the GRAALL group offers any meaningful difference in clinical outcomes to those regimens that are commonly offered in Canada. Shared by all of these regimens is prolonged and repeated exposure to classic anti-leukemic drugs such as corticosteroids, anthracyclines, L-Asparaginase, vincristine, and methotrexate. There are no randomized trials that demonstrate the superiority of one of these frontline multi-agent ALL regimens over another, and the decision to adopt ALL regimens such as DFCI, hyper-CVAD, or others in Canada, is based primarily on familiarity and convention, without high level evidence.</p> <p>We contend that the addition of rituximab onto any multi-agent ALL backbone whose construct is at least similar to that of the GRAALL regimen would produce similar results and similar effect size. Such regimens would include hyperCVAD or DFCI [12,13].</p>
3	Summary of pERC deliberations	P2 L12-14	<p>Although quality of life was not directly measured in the GRAALL-R study, we encourage pERC to consider the impact of the disease on patients and the associated quality of life benefits of event free survival.</p> <p>The addition of rituximab to standard chemotherapy regimens improved event-free survival significantly.</p> <p>To put it into context of what this means for patient quality of life, death has an associated utility of 0, while relapse has a utility of 0.30[14]. However, complete response/remission, sustained (e.g. EFS) is associated with a utility of 0.86 [14]. Complete response thus a very desirable health state.</p> <p>Although pERC focused their deliberation on relapse and death, they did not give much discussion to its inverse. Survivors of relapsed ALL have a lower general health score than survivors of non-relapsed ALL[15].</p> <p>Patients <i>prefer not</i> to relapse; they <i>prefer</i> to be in complete remission. This aforementioned data is based on direct elicitations. The addition of rituximab to standard chemotherapy regimens aligns with this preference.</p> <p>Toxicity was identified as an important patient value. We</p>

Page #	Section Title	Paragraph, Line Number	Comments related to Submitter or Manufacturer-Provided Information
			would like to highlight pERC's conclusion that the addition of rituximab would result in added but manageable toxicities. Whilst there are manageable toxicities, there are also considerable benefits in event-free survival; events that are <i>all</i> important, as previously discussed.

1.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments

References:

1. Maury S, Chevret S, Thomas X, et al. Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia *N Engl J Med*. 2016 Sep 15;375(11):1044-53
2. Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N Engl J Med*. 1998;338(23):1663-1671.
3. Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101(10):3809-3817.
4. Mitchell CD, Richards SM, Kinsey SE, et al. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005;129(6):734-745
5. Schrappe M, Zimmermann M, Moricke A, et al. Dexamethasone in induction can eliminate one third of all relapses in childhood acute lymphoblastic leukemia (ALL): results of an international randomized trial in 3655 patients (Trial AIEOP-BFM ALL 2000).. Presented at: 50th Annual Meeting of the American Society of Hematology; San Francisco, CA, USA. 6-9 December.2008.
6. Seibel NL, Steinherz PG, Sather HN, et al. Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group. *Blood*. 2008;111(5):2548-2555.
7. Matloub Y, Bostrom BC, Hunger SP, et al. Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report for the children's oncology group. *Blood*. 2011;118(24):243-251.
8. Larsen EC, Salzer WL, Devidas M, et al. High dose methotrexate (Hd-MTX) as compared with Capizzi methotrexate plus asparaginase (C-MTX/asnase) improves event-free survival (EFS) in children and young adults with high-risk acute lymphoblastic leukemia: a report

from the Children's Oncology Group study AALL0232. Presented at: Annual Meeting of American Society of Clinical Oncology; Chicago, IL, USA. 3-7 June 2011.

9. Inotuzumab Ozogamicin and Frontline Chemotherapy in Treating Young Adults With Newly Diagnosed B Acute Lymphoblastic Leukemia:
<https://clinicaltrials.gov/ct2/show/NCT03150693>
 10. Acute lymphoblastic leukemia relapsing after first-line pediatric-inspired therapy: a retrospective GRAALL study. Desjonquères A, Chevallier P, Thomas X, et al. *Blood Cancer J.* 2016 Dec 9;6(12)
 11. Liew E, Atenafu EG, Schimmer AD, et al. Outcomes of adult patients with relapsed acute lymphoblastic leukemia following frontline treatment with a pediatric regimen. *Leuk Res.* 2012 Dec;36(12):1517
 12. DeAngelo DJ, Stevenson KE, Dahlberg SE et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia.* 2015 Mar;29(3):526-34.
 13. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol.* 2010 Aug 20;28(24):3880-9.
 14. Aristides M, Barlev A, Barber B, Gijzen M, Quinn C. Population preference values for health states in relapsed or refractory B-precursor acute lymphoblastic leukemia in the United Kingdom. *Health and Quality of Life Outcomes.* 2015;13(1):1-7.
 15. Essig S, von der Weid NX, Strippoli M-PF, et al. Health-Related Quality of Life in Long-Term Survivors of Relapsed Childhood Acute Lymphoblastic Leukemia. *PLOS ONE.* 2012;7(5):e38015.
-

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.