CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review

Stakeholder Feedback on a pCODR Expert Review Committee Initial Recommendation (Manufacturer)

Obinutuzumab (Gazyva) for Follicular Lymphoma

November 1, 2018

3 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	GAZYVA (obinutuzumab) Indication: GAZYVA in combination with chemotherapy, followed by GAZYVA monotherapy in patients achieving a response, is indicated for the treatment of patients with previously untreated stage II bulky (>7cm), III or IV follicular lymphoma (FL)
Eligible Stakeholder Role in Review (Submitter and/or Manufacturer,	Submitter/Manufacturer
Organization Providing Feedback	Hoffmann-La Roche Ltd.

**The pCODR program 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 eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

☐ agrees ☐ agrees in part ☒ disagree

Please explain why the Stakeholder *agrees, agrees in part or disagrees with the Initial Recommendation. If the Stakeholder agrees in part or disagrees with the Initial Recommendation, please provide specific text from the recommendation and rational. Please also highlight the applicable pERC deliberative quadrants for each point of disagreement. The points are to be numbered in order of significance.*

Hoffmann-La Roche (Roche) disagrees that the initial recommendation is in the best interest of patients, or the healthcare professionals who treat and manage these patients. GALLIUM is the first head-to-head phase III randomized study in previously untreated FL to demonstrate the superiority of GAZYVA (G)-based regimens over the current standard of care of Rituxan (R)-based regimens. As agreed by pERC, treatment with GAZYVA + chemotherapy followed by GAZYVA monotherapy (G-chemo) aligns with patient values and provides an improvement in PFS which translates to longer remission. The following text highlights points of disagreement with the Initial Recommendation along with supporting rationale:

1. *CLINICAL BENEFIT: "modest improvement in PFS, no proven OS"; "difficult to determine whether the small improvement in PFS observed...is clinically meaningful." (Pg 3. Summary of pERC Deliberations, Para 2, lines 11-14)*

The results from the GALLIUM trial are clinically meaningful, especially for patients with previously untreated follicular lymphoma (FL) with greater disease severity and therefore higher risk of progression, as defined by a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or higher (Intermediate and High FLIPI). Although G-chemo is indicated for all patients with previously untreated FL, based on the GALLIUM trial, Roche requests that pERC consider funding G-chemo for FL patients with Intermediate or High FLIPI score (high-risk group). The positive NICE (National Institute for Health and Care Excellence) appraisal in the UK was based upon this same population (intermediate to high FLIPI patients, i.e. patients with FLIPI score >2), in which the clinical benefit of G-chemo was recognized as being meaningful for these patients. [1] These patients are at higher risk of relapse and have the greatest clinical unmet need as they have a significantly shorter duration of response to subsequent treatments and thus substantially higher mortality. [2,3] In this high-risk group, the benefit of G-chemo was clearly demonstrated by superior and consistent progression free survival (PFS) over rituximab + chemotherapy followed by rituximab maintenance (R-chemo). This is evidenced by the consistent hazard ratios (HR) between the high-risk subgroups groups and narrower confidence intervals (CI) around the estimates. The GALLIUM study was stratified by FLIPI as per the protocol/statistical analysis plan (SAP). At the September 10, 2016 data cut-off, the Investigator-assessed PFS by patient FLIPI score (available in the Clinical Study Report) is summarized as follows: The HR for PFS in the FLIPI-Intermediate subgroup was 0.62 (95% CI: 0.41, 0.94) and the HR for PFS in the FLIPI-High subgroup was 0.64 (95% CI: 0.46, 0.89). In contrast, the HR for PFS in the FLIPI-Low score subgroup was 1.11 (95% CI: 0.62, 1.99). [4] As reflected by the wide confidence interval in this low-risk population, the HR is associated with greater uncertainty. These data suggest that G-chemo may work better than R-chemo in high-risk previously untreated FL patients.

Progression of disease at 24 months (POD 24) may be a relevant endpoint to FL trials and may help to further characterize clinical benefit. In the National Lymphocare study, POD24 in FL patients receiving immunochemotherapy was associated with decreased overall survival. The sooner progression occurred, the higher risk in mortality. [5] In the GALLIUM trial, G-chemo was associated with a 34% (95% CI: 12.8, 49.8) reduction in the risk of a PFS event and a 46% (95% CI: 25, 61) reduction in the risk of POD event relative to R-chemo at 24 months, based on an exploratory analysis. [6] The risk of death was found to be 26-fold higher following POD24. [6] A study by Jurinovic et al., in a German based FL cohort and a Canadian FL cohort from a patient registry in British Columbia, explored the correlation between patient outcomes and POD 24 event. The study reports that progression of disease within 24 months is an accurate predictor of poor OS. It also demonstrates a correlation between high disease severity as measured by FLIPI score and higher number of POD 24 events in these patients. [7] Patients with a higher FLIPI score have a higher risk of relapse and they

relapse significantly earlier than those patients with a FLIPI score of 0-1. [8] This reaffirms the importance of treating high-risk patients with alternative and novel therapies such as G-chemo to avoid early relapse and improve patient outcomes.

Furthermore, the clinical benefit observed in GALLIUM can be expected to be relevant to a Canadian population, whereby the standard of care as noted by pERC, is R-bendamustine (R-benda). The trial was not designed to compare the three different chemotherapy regimens used in the study (CHOP, CVP or bendamustine) because the allocation of chemotherapy was not randomized at the patient level. However, pre-planned subgroup analyses of investigator-assessed PFS HRs showed G-benda reduced the risk of progression, relapse, or death as compared to R-benda by 37% (HR = 0.63 [95% CI, 0.46, 0.88]; p = 0.0062). [9] In comparison, G-CHOP reduced the risk of progression, relapse, or death as compared to R-CHOP by 28% (HR = 0.72 [95% CI, 0.48, 1.10]; p = 0.1266) and G-CVP reduced the risk of progression, relapse, or death as compared to R-CVP by 21% (HR = 0.79 [95% CI, 0.42, 1.47]; p = 0.4560). [9] If applied to the Canadian market, these data suggest that since the majority of eligible Canadian patients would be treated with G-benda, there is potential for an even greater and clinically meaningful benefit for Canadian patients with previously untreated FL.

2. CLINICAL BENEFIT: *"The committee noted that FL is an indolent disease and patients have long survival with currently available treatments." (Pg 3. Summary of pERC Deliberations, Para 1, lines 8-10)*

While FL is an indolent disease, the clinical course is heterogeneous, characterized by a high response rate to first line therapy and subsequent relapses that require additional therapy lines or eventually, re-challenge with previous lines. [10] The advent of biological agents such as rituximab, the improvement of supportive care and availability of different chemotherapy regimens improved the prognosis of FL in the last decades, [11-15] with an expected median survival approaching or even exceeding 20 years. [5, 16] Since patients with FL usually have a long life expectancy, the time to median PFS can be long and often times not fully realized in clinical trials within reasonable timelines to ensure patient access to effective therapies. Median PFS is not to be expected within the context of the primary analysis of any 1L FL trial. GAZYVA, an optimized anti-CD20 antibody, significantly impacts the natural history of FL by reducing the risk of progression, death, or relapse even further compared to currently available treatments. [17,18] As such, the time to median PFS is not expected to be reached over a short period of time. To address this challenge, Coverage with Evidence Development (CED) could provide a solution whereby efficacy data is collected in Canadian patients under a risk-sharing framework and evaluated over time.

3. CLINICAL BENEFIT *"...rate of secondary malignancies in patients …obinutuzumab + bendamustine…much higher than in patients who received rituximab + bendamustine" (Pg 4. Summary of pERC Deliberations, Para 1, lines 8-10)*

Second malignancies are considered important potential risks associated with obinutuzumab. In GALLIUM, although a numerically higher incidence of second malignancies, as a group of events (defined as using the SMQ "Malignant and unspecified tumors" starting 6 months after the first study drug intake), has been observed in the obinutuzumab-bendamustine arm compared to rituximab-bendamustine arm, it should be emphasized that upon review of the nature and severity of the individual events, there was no notable imbalance in incidence between obinutuzumab exposed patients and rituximab exposed patients. The most frequent second malignancies were squamous cell carcinoma and basal cell carcinoma, both clinically manageable or curable diseases.

Review of the whole clinical trial experience from all obinutuzumab pivotal trials as well as post marketing safety data, did not identify any secondary malignancies as causally associated with obinutuzumab with the exception of squamous cell carcinoma. This event is included in the obinutuzumab label and by its nature is clinically manageable. [18] Overall, with the exception of squamous cell carcinoma, obinutuzumab is not associated with any other second malignancies. Given the clinical impact of a potential association, Roche remains vigilant and considers second

malignancies as an important potential risk with associated pharmacovigilance activities. No risk minimization activities are implemented.

4. *ECONOMIC EVALUATION: "ICER estimate assumed 5 year duration of treatment effect…..Committee agreed that true ICER may be even higher...no proven difference in OS.." (Pg 4. Summary of pERC Deliberations, Para 3, lines 12-15; Pg 8. Economic Evaluation, Para 5, lines 7-10)*

The assumption of no PFS treatment effect beyond the GALLIUM study follow up period of 5 years is implausible for antiCD20 treatments. Due to the indolent nature of FL, long-term follow-up data reaching median PFS as observed for R-chemo in PRIMA was 10.46 years after the initiation of maintenance rituximab following induction with CHOP or CVP. [19] For Gazyva, data in 1st line FL is limited to the maximum available follow up period of up to 5 years in the GALLIUM study (September 2016 clinical cut-off date). However, based on the experience with Gazyva in other settings and the common CD20 target with rituximab there is no evidence in the literature for a finite treatment effect:

Gazyva has also demonstrated longer term treatment effect versus rituximab in the treatment of chronic lymphocytic leukaemia (CLL) as there appears to be an ongoing treatment effect of Gazyva over rituximab after 6 months induction therapy in the CLL11 study with median follow up of 43 months, significantly beyond median PFS. [20]

In addition to the PRIMA study (that investigated R maintenance versus observation only), long-term follow up from R-chemo induction studies in 1st line FL was identified from studies investigating R-chemo versus chemo induction therapy. These studies do not show evidence of a finite duration of treatment effect: Bachy et al. [21] and Herold et al. [22] report long-term follow up in R-chemo induction versus chemo with 8.4 years and up to 8.7 years of median follow up, respectively.

Furthermore, the Economic Guidance Report Page 3, Section 1.3, bullet #1 states "in the submitted analysis the use of data from the PRIMA trial may underestimate the benefit of obinutuzumab". This statement directly contradicts the text in the initial recommendation whereby the duration of treatment effect is suggested to be 5 years or less which does not align with the statement made by the EGP. Roche agrees with the EGP that the benefit of obinutuzumab would be underestimated, especially by using the trial duration of 5 years to limit the duration of treatment effect.

5. *ECONOMIC EVALUATION: "frequency of maintenance therapy of every 3 months instead of every 2 months in the comparator arm to reflect Canadian clinical practice"...(Pg 8. Economic Evaluation, Para 4, lines 12-13)*

The EGP reanalysis of the ICER changed the rituximab maintenance schedule to every 3 months based on clinical practice in some provinces. Roche disagrees with this approach as it biases the results in favor of rituximab by simply reducing the cost of the treatment yet assuming the same magnitude of clinical benefit with a lower dose.

6. *ADOPTION FEASIBILITY: "Submitted budget impact is underestimated and actual budget impact will be substantial"...(Pg 8. Adoption Feasibility, Para 1, lines 10-11); "pERC noted that the factors that influenced the budget impact analysis include…increasing the size of the eligible FL population…"(Pg 9. Adoption Feasibility, Para 1, line 12-14)*

The proposed request to limit the population to high-risk patients (Intermediate and High FLIPI) would help to address the adoption feasibility concerns suggested by pERC. By limiting the population to high-risk patients by FLIPI score (a simple and reproducible prognostic index), the budget impact would be expected to be reduced by a factor of approximately 20-30% [3, 17].

References:

1. National Institute for Health and Care Excellence (NICE) – Technology Appraisal Guidance [TA513], Published 21 March 2018; https://www.nice.org.uk/guidance/TA513/chapter/1-Recommendations

2. Nooka AK, et al. "Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices." Ann Oncol 2013; 24(2): 441-448.
3. Solal-Celigny P, et al. "Follicular lymphoma international prognostic index." Blood 2004; 104(5): 1258-1265.
4. Roche. Updated GALLIUM clinical study report (Report No. 1075139). May 2017.
5. Casulo C, et al. Disease characteristics, treatment patterns, and outcomes of follicular lymphoma in patients 40 years of age and younger: an analysis from the National Lymphocare Studydagger. Ann Oncol. 2015;26(11):2311
6. Launonen, A et al. "Early Disease Progression Predicts Poorer Survival in Patients with Follicular Lymphoma (FL) in the GALLIUM Study." Blood 130.Suppl 1 (2017): 1490.
7. Jurinovic V, et al. Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy. Blood. 2016;128(8):1112-1120.
8. Goldman M. L., et al. High-Risk FLIPI Score at Diagnosis Is Associated with Early Relapse in the Rituximab Era for Patients with Follicular Lymphoma. Blood, 2017 130(Suppl 1), 5158
9. Hiddemann W. Immunochemotherapy with obinutuzumab or rituximab in previously untreated follicular lymphoma in the randomised phase III GALLIUM study: analysis by chemotherapy regimen. International Conference on Malignant Lymphoma 14th ICML; 2017; Switzerland.
10. Pavanello F, et al. Systemic Front Line Therapy of Follicular Lymphoma: When, to Whom and How. Mediterr J Hematol Infect Dis. 2016; 8(1): e2016062.
11. Conconi, et al. Patterns of survival of follicular lymphomas at a single institution through three decades. Leuk Lymphoma.Leuk Lymphoma. 2010;51(6):1028–34.
12. Tan D, et al. Improvements in observed and relative survival in follicular grade 1–2 lymphoma during 4 decades: the Stanford University experience. Blood. 2013;122(6):981–7
13. Casulo C, et al. Disease Characteristics, Treatment Patterns, and Outcomes of Follicular Lymphoma in Patients 40 Years of Age and Younger: An Analysis from the National LymphoCare Study. National LymphoCare Study. 2014;124:3044–3044.
14. Junlen HR, et al. Follicular lymphoma in Sweden: nationwide improved survival in the rituximab era, particularly in elderly women: a Swedish Lymphoma Registry study. Leukemia. 2015;29(3):668–76.
15. Armitage JO, Longo DL. Is watch and wait still acceptable for patients with low-grade follicular lymphoma?, Blood. 2016;127(23):2804–8.
16. Conconi A, et al. Life expectancy of young adults with follicular lymphoma. Ann Oncol. 2015;26(11):2317–22.
17. Marcus R, Davies A, Ando K, et al. Obinutuzumab for the First-Line Treatment of Follicular Lymphoma. N Engl J Med. 2017;377(14):1331-1344.
18. Roche. GAZYVA® (obinutuzumab) Health Canada Product Monograph. 2018.
19. Salles GA, et al. Long Term Follow-up of the PRIMA Study: Half of Patients Receiving Rituximab Maintenance Remain Progression Free at 10 Years. Blood 2017; 130:486.
20. Goede V, et al. Updated Survival Analysis from the CLL11 Study: Obinutuzumab Versus Rituximab in Chemoimmunotherapy-Treated Patients with Chronic Lymphocytic Leukemia. Blood 2015; 126:1733.
21. Bachy E, et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. Haematologica 2013; 98, 1107-14.
22. Herold M, et al. Longterm follow-up of rituximab plus first-line mitoxantrone, chlorambucil, prednisolone and interferon-alpha as maintenance therapy in follicular lymphoma. J Cancer Res Clin Oncol 2015; 141, 1689-95.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. 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	Summary of pERC Deliberations	Para 2, lines 11-14	*"INV PFS (absolute difference of 6.7%)... IRC PFS (absolute difference of 4%)...Sept 10, 2016 data cut-off…INV PFS (absolute difference of 7%)...IRC PFS (absolute difference 4%)"* There are limitations with presenting the absolute clinical benefit at one specific time-point of obinutuzumab compared with rituximab considering the nature of this indolent disease. In the "Summary of pERC Deliberations" presenting the estimated 3-year PFS benefit in absolute terms at one specific time-point and in the absence of the statistically significant PFS results and corresponding hazard ratios shows a fraction of the picture and introduces bias. Roche requests the data be summarized in alignment with the text found on pages 5 and 6 of the recommendation (section heading: Key Efficacy Results, paragraph 1), which reports the PFS and hazard ratios as well.

3.2 Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder 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. Recommendation does not require reconsideration by pERC.	☒	Do not support conversion to Final Recommendation. Recommendation should be reconsidered by pERC.

If the eligible stakeholder does not support conversion to a Final Recommendation, please provide feedback on any issues not adequately addressed in the Initial Recommendation based on any information provided by the Stakeholder 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 program.

Additionally, if the eligible stakeholder supports early conversion to a Final Recommendation; however, the stakeholder has included substantive comments that requires further interpretation of the evidence, the criteria for early conversion will be deemed to have not been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information

1 About Stakeholder Feedback

pCODR invites eligible stakeholders to provide feedback and comments on the Initial Recommendation made by the pCODR Expert Review Committee (pERC). (See www.cadth.ca/pcodr for information regarding review status and feedback deadlines.)

As part of the pCODR review process, pERC makes an Initial Recommendation based on its review of the clinical benefit, patient values, economic evaluation and adoption feasibility for a drug. (See www.cadth.ca/pcodr for a description of the pCODR process.) The Initial Recommendation is then posted for feedback from eligible stakeholders. All eligible stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation. It should be noted that the Initial Recommendation may or may not change following a review of the feedback from stakeholders.

pERC welcomes comments and feedback from all eligible stakeholders with the expectation that even the most critical feedback be delivered respectfully and with civility.

A. Application of Early Conversion

The Stakeholder Feedback document poses two key questions:

1. **Does the stakeholder agree, agree in part, or disagree with the Initial Recommendation?**

   All eligible stakeholders are requested to indicate whether they agree, agree in part or disagrees with the Initial Recommendation, and to provide a rational for their response.

   Please note that if a stakeholder agrees, agrees in part or disagrees with the Initial Recommendation, the stakeholder can still support the recommendation proceeding to a Final Recommendation (i.e. early conversion).

2. **Does the stakeholder support the recommendation proceeding to a Final Recommendation ("early conversion")?**

   An efficient review process is one of pCODR's key guiding principles. If all eligible stakeholders support the Initial Recommendation proceeding to a Final Recommendation and that the criteria for early conversion as set out in the *pCODR Procedures* are met, the Final Recommendation will be posted on the CADTH website 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.

   For stakeholders who support early conversion, please note that if there are substantive comments on any of the key quadrants of the deliberative framework (e.g., differences in the interpretation of the evidence), the criteria for early conversion will be deemed to have **not** been met and the Initial Recommendation will be returned to pERC for further deliberation and reconsideration at the next possible pERC meeting. Please note that if any one of the eligible stakeholders does not support the Initial Recommendation proceeding to a Final pERC Recommendation, pERC will review all feedback and comments received at a subsequent pERC meeting and reconsider the Initial Recommendation.

B. Guidance on Scope of Feedback for Early Conversion

Information that is within scope of feedback for early conversion includes the identification of errors in the reporting or a lack of clarity in the information provided in the review documents. Based on the feedback received, pERC will consider revising the recommendation document, as appropriate and to provide clarity.

If a lack of clarity is noted, please provide suggestions to improve the clarity of the information in the Initial Recommendation. If the feedback can be addressed editorially this will done by the pCODR staff, in consultation with the pERC chair and pERC members, and may not require reconsideration at a subsequent pERC meeting.

The Final pERC Recommendation will be made available to the participating federal, provincial and territorial ministries of health and provincial 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) The following stakeholders are eligible to submit Feedback on the Initial Recommendation:
   - The Submitter making the pCODR Submission, or the Manufacturer of the drug under review;
   - Patient groups who have provided input on the drug submission;
   - Registered clinician(s) who have provided input on the drug submission; and
   - The Provincial Advisory Group (PAG)

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 *Stakeholder Feedback on pERC Initial Recommendation* can be downloaded from the pCODR section of the CADTH 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 Stakeholder 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.

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 provided to the pERC for their consideration.

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 program.

h) The comments must be submitted via a Microsoft Word (not PDF) document to pCODR by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail pcodrsubmissions@cadth.ca

Note: CADTH is committed to providing an open and transparent cancer drug review process and to the need to be accountable for its recommendations to patients and the public. Submitted feedback will be posted on the CADTH website (www.cadth.ca/pcodr). The submitted information in the feedback template will be made fully disclosable.