pan-Canadian Oncology Drug Review

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

Obinutuzumab (Gazyva) for Follicular Lymphoma

June 2, 2017

1 Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s):	GAZYVA (obinutuzumab) for Follicular Lymphoma
Role in Review (Submitter and/or Manufacturer):	Submitter and Manufacturer
Organization Providing Feedback	Hoffmann-La Roche Limited

**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 __X__ 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.*

Hoffmann-La Roche (Roche) agrees with the clinical recommendations of pERC to fund GAZYVA in combination with chemotherapy for patients with follicular lymphoma who are refractory to rituximab as defined in the GADOLIN study (i.e. failure to respond to, or progression during, any previous rituximab-containing regimen, or progression within 6 months of the last rituximab dose, in the induction or maintenance treatment settings).

As noted by pERC, evaluation of the treatment effect of GAZYVA should consider both phases together. The clinical benefit of GAZYVA observed is based on its use in the GADOLIN trial where the median progression-free survival was 25.3 months versus 14.0 months (hazard ratio 0.52; 95% CI 0.39-0.69). The pattern of separation in the Kaplan-Meier curves has been seen in studies of iNHL patients receiving rituximab-based immunochemotherapy, i.e. small or no separation after induction, followed by significant separation later.[1,2] In addition, there are few events in either arm early in the trial.

Roche supports the pERC's assessment of the potential benefit of GAZYVA in combination with chemotherapy for patients with ECOG status $\geq$ 2 and select patients with comorbidities as determined by the treating physician. Given the limited treatment options for patients with refractory disease, patients for whom physicians feel GAZYVA is an option should be considered for and have access to the therapy.

While Roche agrees with the clinical recommendations, there are some concerns with the approach taken by the Economic Guidance Panel in their assessment of the cost-effectiveness of GAZYVA which are discussed in further detail in the sections that follow.

References

1. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005;105:1417–23.
2. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121–7.

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.

Recommendation does not require reconsideration by pERC.

_____ Do not support conversion to final recommendation.

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
Pg5	Summary	P1 L1-3	pERC concluded that the same risk of post-progression survival for both treatment arms favoured obinutuzumab. This statement is factually incorrect. The EGP had access to a model in which post-progression survival could be modelled independently for each arm of the trial. The results were not reported in the EGR but we report them here. With post-progression survival modelled independently, the ICER ***improves*** to $42,953/QALY vs. bendamustine and $53,800/QALY vs. chemo alone. This result disproves the premise of the EGP and pERC on common risk of post-progression survival between the two trial arms resulting in a bias in favor of obinutuzumab.

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
Pg5 Pg10	Economic Evaluation	P1 L3-5 P3 L10-15	pERC concluded obinutuzumab plus chemotherapy is unlikely to be cost-effective, citing, in part, limitations listed by the EGP. pERC summarizes the guidance from the EGP on the time horizon and the post-progression distribution; both of which were inputs into the aforementioned conclusion by pERC. Regarding the time horizon, the EGP submitted an arbitrary time horizon to pERC. As per CADTH guidelines, where the outcome is survival, the time horizon should correspond to the time when survival is zero – the time of the last death in the population. At 10 years, ~20% and ~10% of intervention and comparator arms, respectively, are projected to be alive. The model explored alternative distributions which led to alternative survivals. This was part of the sensitivity analysis which was not noted by the pERC or EGP. The EGP uses an arbitrary time horizon in order to "mitigate" or "reduce" uncertainty, a practice embraced by the pERC. This practice, however, does not achieve the stated objective. The only way to reduce uncertainty, where it is even possible, is to *collect more information*. Merely ignoring patient outcomes beyond year 10 does not mean there is less uncertainty. Roche is concerned about the pattern of conclusions from the EGP and pERC that are made from arbitrary time horizons and/or for reducing uncertainty. pERC accepted the EGP recommendation to use the lognormal distribution for post-progression survival on the basis that it had the best goodness of fit and the most conservative estimate of incremental overall

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
			survival. Roche challenges both premises for the selection of the lognormal distribution. Regarding the goodness of fit, first, the fit statistics were not very different between Weibull and lognormal distribution. Second, internal fit is just one decision criterion. As per CADTH guidelines and their cited NICE DSU guidance, external plausibility is also a factor. With a lognormal distribution, roughly 20% are surviving at 20 years (30% if you use only a 10-year time horizon). Regarding incremental overall survival, a distribution should not be chosen with the express aim of producing "the most conservative estimate of incremental overall survival". The CADTH Guidelines and NICE DSU guidance do no prescribe such practice. Roche recommends pERC not accept such practice in the future. Again, Roche disagrees with the conclusion that GAZYVA in combination with chemotherapy is unlikely to be cost-effective based on this premise.

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

3.3 Additional Comments About the Initial Recommendation Document

Please provide any additional comments:

Page Number	Section Title	Paragraph, Line Number	Additional Comments
Pg4	Summary	P1 L10-13	Roche highlights the importance of the pERC and CGP's conclusions that for patients with follicular lymphoma, the treatment effect of the intervention cannot be interpreted separately according to induction and maintenance phases of treatment.

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.