pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Obinutuzumab (Gazyva) **Submitted Reimbursement Request:** In combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (≥ 7 cm), III or IV follicular lymphoma	
Submitted by: Hoffmann-La Roche Limited	**Manufactured by:** Hoffmann-La Roche Limited
NOC Date: July 5, 2018	**Submission Date:** March 15, 2018
Initial Recommendation: August 30, 2018	**Final Recommendation:** November 1, 2018

Drug Costs	
Approximate per Patient Drug Costs	**Obinutuzumab costs $5,429 per 1,000 mg vial (fixed dose)** • Induction: At the recommended dose of 1,000 mg on days 1, 8 and 15 of the first 28-day cycle followed by 1,000 mg on day 1 of each of the 5 subsequent 28-day cycles, obinutuzumab costs $258.52 per day and $7,238.67 per 28-day course. • Maintenance: At the recommended dose of 1,000 mg once every 2 months for 2 years, obinutuzumab costs $89.24 per day and $2,498.83 per 28-day course.

pERC RECOMMENDATION	**pERC does not recommend reimbursement of obinutuzumab in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (≥ 7 cm), III or IV follicular lymphoma (FL).** **pERC made this recommendation because, compared with rituximab, obinutuzumab had a modest improvement in progression-free survival (PFS), no proven difference in overall survival (OS), and moderate but significant toxicities (including infusion-related reactions, neutropenia, infections, and second malignancies). pERC was uncertain about whether obinutuzumab adequately addresses the need for more effective therapies. pERC agreed with the pCODR Clinical Guidance Panel (CGP) that**

	it was difficult to determine whether the small improvement in PFS observed with obinutuzumab was clinically meaningful. pERC concluded that obinutuzumab aligned with patient values of providing a modest increase in PFS and no detriment to quality of life (QoL), compared with rituximab. pERC noted that at the submitted price, obinutuzumab compared with rituximab cannot be considered cost-effective in this population. pERC also highlighted that the potential budget impact of obinutuzumab is underestimated and likely to be substantial.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified.

SUMMARY OF pERC DELIBERATIONS

FL is the most common type of indolent non-Hodgkin lymphoma, with an estimated incidence of more than 2,800 Canadians diagnosed every year. For patients with previously untreated FL, the standard of care in Canada is bendamustine plus rituximab followed by rituximab maintenance every three months for up to two years. CHOP plus rituximab can be an alternative option for patients with FL. The Committee noted that FL is an indolent disease and patients have long survival with currently available treatments. pERC noted that there is a need for more effective therapies that provide patients with a treatment option that will prolong the remission period for patients who will eventually need to be retreated.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon the results of a phase III, open-label, international, multi-centred randomized controlled trial (GALLIUM) that compared induction treatment with obinutuzumab to rituximab, each combined with chemotherapy, and followed by maintenance treatment (with the same antibody), in previously untreated patients with advanced indolent non-Hodgkin lymphoma, including FL. The Committee noted that the majority of patients in the trial had FL, and that the requested reimbursement population by the submitter was specifically for patients with previously untreated FL. The GALLIUM trial was designed to evaluate the primary outcome of PFS in the subgroup of patients with FL. pERC considered that PFS is a clinically relevant end point for FL considering the indolent nature of the disease. pERC noted a statistically significant improvement in PFS associated with obinutuzumab in the subgroup of patients with FL. The Committee discussed that the estimated three-year PFS by investigator was 80.0% in patients treated with obinutuzumab compared with 73.3% in patients treated with rituximab, an absolute difference of 6.7%. The estimated three-year PFS by independent review was 81.9% in patients treated with obinutuzumab compared with 77.9% in patients treated with rituximab, with a smaller absolute difference of 4.0%. The Committee also noted that an updated efficacy analysis with an additional 6.5 months of follow-up demonstrated a sustained treatment benefit in PFS in favour of the obinutuzumab treatment group. While the difference in PFS was statistically significant between treatment groups, in discussion, pERC noted that the observed difference in favour of obinutuzumab was modest in the context of the natural history of previously untreated advanced FL. pERC agreed with the pCODR CGP's opinion that the clinical meaningfulness of the small PFS benefit observed in the trial is difficult to determine. pERC also agreed with the pCODR CGP that it is difficult to determine the magnitude of absolute clinical benefit of obinutuzumab compared with rituximab considering the short follow-up period in the GALLIUM trial.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the submitter requesting that pERC consider limiting reimbursement of obinutuzumab to patients with FL with intermediate- or high-risk Follicular Lymphoma International Prognostic Index (FLIPI) scores (high-risk group). The submitter commented that subgroup analyses by patient FLIPI score for investigator-assessed PFS were conducted and suggest that obinutuzumab may be more effective than rituximab in the subgroup of high-risk, previously untreated patients with FL.

pERC discussed clarification provided by the pCODR Methods team in the pCODR Final Clinical Guidance Report and noted that subgroup analyses were conducted by FLIPI risk score, which showed a benefit in independently assessed PFS in favour of obinutuzumab in patients with intermediate- and high-risk FLIPI scores, but not for low-risk patients. pERC considered that no adjustments for multiplicity were made and the risk of type I error associated with these subgroup analyses makes it difficult to interpret whether there is a true difference in treatment effect based on FLIPI score. Additionally, pERC noted that an economic analysis for the high-risk subgroup was not submitted for this review and agreed that a submission would be required to consider reimbursement of obinutuzumab for high-risk patients with FL.

Furthermore, upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the submitter that suggested there would be a greater and clinically meaningful benefit for Canadian

patients based on preplanned subgroup analyses of investigator-assessed PFS by chemotherapy backbone given that the majority of patients in Canada would be treated with obinutuzumab plus bendamustine.

pERC considered that bendamustine plus rituximab followed by rituximab maintenance is the most commonly used regimen in Canada. However, the Committee noted that the GALLIUM trial was not designed to compare different chemotherapy regimens, patients were not randomized to chemotherapy regimens in the trial, and the subgroup analyses based on the chemotherapy backbones were considered exploratory. Overall, the Committee reiterated that the GALLIUM trial was designed to evaluate PFS in the subgroup of patients with FL, irrespective of FLIPI score or chemotherapy backbone, and it was difficult to determine whether the small improvement in PFS observed with obinutuzumab was clinically meaningful.

pERC further discussed that while the complete response rate at the end of induction treatment was higher in the rituximab group, there was no statistically significant difference between the groups at the primary analysis. Furthermore, pERC noted that the three-year OS rates between treatment groups were similar, but that OS was not formally tested for statistical significance due to the hierarchical testing design of the trial. pERC noted input from the registered clinicians that it is expected that there would be no OS difference between the groups, as patients with FL have a relatively long survival, making it unlikely to detect any difference with short follow-up. However, the Committee also noted that even with sufficient follow-up, any OS data will be confounded by post-trial treatments. pERC also discussed QoL and noted both treatment groups showed clinically meaningful improvements from baseline in all scales from the end of induction treatment onwards, although there were no differences between the treatment groups. The Committee agreed that there appeared to be no detriment to QoL with treatment with obinutuzumab.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback provided by the submitter that noted progression of disease at 24 months (POD24) may be a relevant end point in FL trials that may help further characterize clinical benefit.

pERC discussed clarification provided by the pCODR Methods team and the pCODR CGP in the pCODR Final Clinical Guidance Report that there is currently insufficient evidence to support the use of POD24 as a surrogate end point for OS. The Committee discussed the analysis of POD24 in the GALLIUM trial, and noted that it was considered exploratory and would require prospective evaluation and validation as a surrogate outcome. Overall, the Committee agreed that longer-term follow-up data are necessary to draw definitive conclusions on the clinical benefit of obinutuzumab in previously untreated patients with FL.

The Committee discussed the safety of obinutuzumab compared with rituximab, and noted that overall, obinutuzumab was associated with a higher incidence of adverse events (AEs) and serious AEs. The Committee noted that the most common grade 3 to5 AEs during induction were neutropenia, infections, and infusion-related reactions. The most common grade 3 to 5 AEs during maintenance treatment were neutropenia and pneumonia. pERC considered that the frequency of secondary malignancies was higher in patients treated with obinutuzumab compared with rituximab. The Committee noted the pCODR CGP's concern that in the follow-up phase of the trial the rate of secondary malignancies in patients who received treatment with the combination of bendamustine and obinutuzumab was much higher than in patients who received the bendamustine and rituximab combination. The Committee agreed that this safety concern requires further follow-up in future studies. Overall, pERC agreed with the pCODR CGP that there may be a net clinical benefit of obinutuzumab compared with rituximab based on a modest improvement in PFS, no proven difference in OS, a manageable but significant toxicity profile, and the lack of detriment to QoL during treatment. The Committee was uncertain whether the modest improvement in PFS demonstrated by obinutuzumab was clinically meaningful and adequately addressed the need for more effective therapies for patients with FL.

pERC deliberated upon input from one patient advocacy group concerning obinutuzumab. pERC appreciated the considerable effort the patient advocacy group made to prepare a written summary of the GALLIUM trial in order to determine patients' values in the context of first-line therapy and the treatment under review. The Committee agreed that the approach taken by the patient advocacy group was impressive, and, overall, informative for their deliberations. pERC noted that patients felt that current standard of care for first-line therapy is relatively effective. The Committee noted that patients valued longer survival, longer remission, improvement in QoL, and symptom control in the context of first-line treatment. The Committee discussed that obinutuzumab was associated with a modest improvement in PFS and that there was no

detriment to QoL compared with rituximab. Overall, the Committee concluded that obinutuzumab aligned with patient values.

The Committee deliberated upon the cost-effectiveness of obinutuzumab. pERC noted that the pCODR Economic Guidance Panel (EGP) estimates were higher than the submitter's estimates, and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's reanalysis, which included a shortened time horizon, a truncated duration of treatment effect, an increased proportion of rituximab administered subcutaneously, frequency of maintenance therapy in the comparator arm that reflects current Canadian practice where rituximab is given every three months instead of every two months, and the price of intravenous biosimilar rituximab. The Committee noted that these changes increased the incremental cost-effectiveness ratio (ICER) estimates. pERC discussed the fact that the submitter used data from another clinical trial to inform post-progression survival because of the lack of mature OS data from the GALLIUM trial. pERC noted that at the time of the primary analysis and the updated analysis, there were no differences in OS between the treatment groups in the GALLIUM trial. The Committee discussed that the EGP's upper bound ICER estimate assumed a five-year duration of treatment effect based on the duration of follow-up in the GALLIUM trial. However, the Committee agreed that the true ICER may be even higher than the EGP's upper bound ICER estimate because there was no proven difference in OS observed between the two treatment groups. The Committee also noted that the secondary malignancies observed during follow-up of the GALLIUM trial were not incorporated into the economic analysis. Overall, pERC noted that the magnitude of any long-term benefit associated with obinutuzumab is unknown given the lack of long-term data. pERC noted that, at the submitted price, obinutuzumab compared with rituximab cannot be considered cost-effective in this population.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the submitter regarding issues raised around some of the assumptions in the pCODR EGP reanalyses.

pERC discussed clarification provided by the pCODR EGP in the Economic Guidance Report regarding two assumptions in the EGP's reanalyses. Firstly, the submitter noted that the assumption of no PFS treatment effect beyond the GALLIUM study follow-up period of five years is implausible for anti-CD20 treatments. However, the Committee noted that, in the absence of mature OS data to confirm the long-term effects of treatment with obinutuzumab, the EGP elected to truncate the duration of the treatment effect of obinutuzumab to five years in the reanalysis. pERC agreed with this approach to explore uncertainty in the ongoing benefit of obinutuzumab (due to the extrapolation of long-term estimates from data with a shorter follow-up period) and the impact of this benefit on OS, given the use of indirect data from another FL trial to inform post-progression survival, which may not reflect the course of illness of a patient being treated with obinutuzumab therapy. The EGP chose to truncate the treatment effect to five years as it corresponds to the duration of follow-up in the GALLIUM trial, assuming no incremental treatment effect of obinutuzumab beyond the GALLIUM trial follow-up of five years. The EGP noted that this analysis could represent the worst-case scenario and therefore included it as part of its upper bound ICER estimate. pERC reiterated that this was an appropriate approach to demonstrate the impact of the unknown long-term treatment effect of obinutuzumab on OS and the ICER. The Committee reiterated that the magnitude of the long-term benefit associated with obinutuzumab is uncertain given the short follow-up in the GALLIUM trial.

Secondly, the submitter provided feedback and noted that changing the rituximab maintenance schedule to every three months to reflect clinical practice biases the results in favour of rituximab. The Committee agreed with the CGP and EGP and reiterated that the inclusion of administration of maintenance therapy of rituximab every three months reflects the current standard of care in Canadian clinical practice.

pERC discussed factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for obinutuzumab for the treatment of adults with previously untreated FL. The Committee agreed with the pCODR Provincial Advisory Group (PAG) that the enablers to implementation include flat dosing with no drug wastage, and that the barriers to implementation include increased chair time in the first month of treatment and in the maintenance phase, increased resource use, and the high cost of obinutuzumab. pERC also discussed PAG's request for clarity on sequencing using rituximab plus chemotherapy after first-line treatment with obinutuzumab, but noted that there is currently no evidence to inform sequencing of available therapies. Finally, pERC considered that the submitted Ontario-specific budget impact analysis is underestimated and will likely be substantial, given the

prevalence of FL in the first-line setting, and the possibility of extending treatment with obinutuzumab to other indolent lymphomas.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the Clinical Guidance Report that provided clinical context
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from the pCODR clinical and economic review panels
- Input from one patient advocacy group, Lymphoma Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- the submitter, Hoffmann-La Roche Limited
- registered clinicians
- PAG.

The pERC Initial Recommendation was to not recommend reimbursement of obinutuzumab (Gazyva) in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (≥ 7 cm), III or IV follicular lymphoma (FL). Feedback on the pERC Initial Recommendation indicated that PAG and registered clinicians agreed with the Initial Recommendation. The submitter did not agree with the Initial Recommendation. The patient advocacy group, Lymphoma Canada, did not provide feedback on the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of obinutuzumab (Gazyva), in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (≥ 7 cm), III or IV FL.

Studies included: One randomized phase III trial

The pCODR systematic review included one phase III, ongoing, open-label, multi-centred randomized trial, GALLIUM, which evaluated the efficacy and safety of induction treatment with obinutuzumab (N = 601) compared with rituximab (N = 601), each combined with chemotherapy, and followed by maintenance treatment (with the same antibody) in previously untreated patients with advanced indolent non-Hodgkin lymphoma (iNHL). pERC noted that the primary objective of the study was to evaluate the primary outcome, progression-free survival (PFS), in patients with FL. pERC noted that this aligned with the reimbursement request for previously untreated patients with FL.

Patient populations: Previously untreated, CD20-positive, indolent B-cell NHL, which included FL

Key eligibility criteria for the GALLIUM trial included advanced stage (Ann Arbor stage III or IV, or stage II with bulky disease, and tumour ≥ 7 cm in greatest dimension) FL (grade 1 to3a), at least one lesion assessable by bidimensional measurement (> 2 cm by CT or MRI), Eastern Cooperative Oncology Group (ECOG) status of 0 to 2, and indication for treatment according to Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.

The median age of patients was 59 years. The majority of patients had an ECOG performance status of 0 to 1 (97%),were Ann Arbor disease stage III (35%) or IV (57%), and were classified as Follicular Lymphoma

International Prognostic Index (FLIPI) intermediate-risk (37%) or high-risk (42%). Bone marrow involvement, extranodal involvement, and bulky disease (tumour ≥ 7 cm) were present in 52%, 67%, and 44% of patients, respectively. The distribution of patients by chemotherapy regimen was also balanced among the two treatment groups, with approximately 57% of patients receiving bendamustine, 33% CHOP, and 10% CVP.

Key efficacy results: Modest statistically significant improvement in PFS; No difference in complete response rate at the end of induction treatment between the groups; No proven difference in overall survival between the groups

The key efficacy outcomes deliberated on by pERC included the investigator-assessed (INV) PFS and independently assessed (IRC) PFS in the FL subgroup. pERC noted a statistically significant improvement in PFS associated with obinutuzumab in the subgroup of patients with FL, at the third planned interim analysis, which was considered the primary analysis of the trial (by crossing the pre-specified boundary of superiority). At the primary analysis, with a median follow-up of 34.5 months, a statistically significant improvement in PFS by INV was demonstrated in the obinutuzumab-based treatment group (hazard ratio [HR] = 0.66; 95% confidence interval [CI], 0.51 to 0.85; *P* = 0.001). Median INV PFS was not reached. The estimated three-year PFS by INV was 80% (95% CI, 75.9 to 83.6) in patients treated with obinutuzumab versus 73.3% (95% CI, 68.8 to 72.2) in patients treated with rituximab (absolute difference of 6.7%). The estimated three-year PFS by IRC was 81.9% (95% CI, 77.9 to 85.2) in patients treated with obinutuzumab versus 77.9% (95% CI, 73.8 to 81.4) in patients treated with rituximab (absolute difference of 4%).The updated efficacy analysis (September 10, 2016, data cut-off date with a median follow-up of 41.1 months) performed after an additional 6.5 months of follow-up showed a sustained treatment benefit in PFS in the obinutuzumab treatment group in the patients with FL population (HR = 0.68; 95% CI, 0.54-0.87; *P* = 0.0016). The estimated three-year PFS by INV was 82.0% (95% CI, 78 to 86) in patients treated with obinutuzumab versus 75.0% (95% CI, 71 to 78) in patients treated with rituximab (absolute difference of 7.0%). The estimated three-year PFS by IRC was 83.0% (95% CI, 80 to 86) in patients treated with obinutuzumab versus 79.0% (95% CI, 75 to 82) in patients treated with rituximab (absolute difference of 4.0%). At both analysis time points, results of the IRC assessment of PFS were consistent with the primary analysis. pERC noted that the improvement in PFS observed in patients treated with obinutuzumab compared with rituximab was statistically significant, but also noted that the observed benefit was modest considering the natural history and disease context of patients with previously untreated FL. pERC also noted the pCODR Clinical Guidance Panel's opinion that the clinical significance of the small PFS benefit observed in the trial is difficult to determine.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted feedback from the submitter requesting that pERC consider reimbursing obinutuzumab for patients with FL with intermediate- or high-risk FLIPI scores (high-risk group). The submitter commented that subgroup analyses for PFS by INV by patient FLIPI score were conducted and inferred that the FLIPI score subgroup data suggest obinutuzumab may work better than rituximab in the subgroup of high-risk, previously untreated patients with FL.

Subgroup analyses were conducted by FLIPI risk score at the primary analysis (January 31, 2016, data cut-off date) and showed a PFS by INV benefit in favour of obinutuzumab in patients with intermediate- (HR = 0.59; 95% CI, 0.37 to 0.92) and high-risk FLIPI scores (HR = 0.58; 95% CI, 0.41 to 0.84), but not for low-risk patients (HR = 1.17; 95% CI, 0.63 to 2.19). pERC noted that the effect estimate in the low-risk group should be interpreted with caution due to small sample size and low event rates. Additionally, the test for interaction for the FLIPI score subgroup analysis was not statistically significant (*P* = 0.14), suggesting no difference in treatment effect between FLIPI risk categories. Furthermore, the lack of adjustment for multiplicity and risk of type I error associated with these analyses make it difficult to interpret whether there is a difference in treatment effect based on FLIPI score.

Additionally, upon reconsideration of the pERC Initial Recommendation, the Committee noted feedback from the submitter that suggested there is a greater and clinically meaningful benefit for Canadian patients based on preplanned subgroup analyses of investigator-assessed PFS based on chemotherapy backbone given that the majority of patients in Canada would be treated with obinutuzumab plus bendamustine.

pERC considered that bendamustine plus rituximab followed by rituximab maintenance is the most commonly used regimen in Canada. The Committee noted the pre-specified subgroup analyses by chemotherapy regimen (bendamustine, CHOP, or CVP) demonstrated a consistent treatment benefit in

favour of obinutuzumab at both analysis time points, with the greatest magnitude of treatment benefit observed with obinutuzumab combined with bendamustine (HR = 0.63; 95% CI, 0.46 to 0.88) compared with obinutuzumab combined with CHOP (HR = 0.72; 95% CI 0.48 to 1.10) or obinutuzumab combined with CVP (HR = 0.79; 95% CI 0.42 to 1.47) at the updated analysis. However, the Committee noted that the GALLIUM trial was not designed or powered to compare efficacy by type of chemotherapy backbone as the choice of chemotherapy was not randomized but chosen by trial sites at the start of the trial. Overall, the Committee reiterated that the GALLIUM trial was designed to evaluate PFS in the subgroup of patients with FL, irrespective of FLIPI score or chemotherapy backbone, and it was difficult to determine whether the small improvement in PFS observed with obinutuzumab was clinically meaningful.

At the end of induction treatment the complete response (CR) rate was higher in the rituximab treatment group (23.8%) compared with the obinutuzumab group (19.5%); the difference between the groups (4.3%) was not statistically significant (*P* = 0.07). Since the difference in CR did not reach statistical significance at the primary analysis, the remaining secondary outcomes specified in the hierarchical testing scheme were not formally tested. These end points, which included overall survival (OS), showed no differences between groups at the primary and updated analyses (HR = 0.75; 95% CI, 0.49 to 1.17; *P* = 0.21; and HR = 0.82; 95% CI, 0.54 to 1.22; *P* = 0.32; respectively). The estimated three-year OS rate at the primary analysis was 94.0% (95% CI, 91.6 to 95.7) in patients treated with obinutuzumab compared with 92.1% (95% CI, 89.5 to 94.1) in patients treated with rituximab. The estimated three-year OS rate at the updated analysis was 94.0% (95% CI, 92 to 96) in patients treated with obinutuzumab compared with 92.0% (95% CI, 90 to 94) in patients treated with rituximab.

The submitter provided feedback on pERC's Initial Recommendation, and noted that progression of disease at 24 months (POD24) may be a relevant end point to consider in FL trials that may help to further characterize clinical benefit. The submitter noted that in the GALLIUM trial obinutuzumab combined with chemotherapy was associated with a reduction in the risk of a POD event relative to rituximab-chemotherapy at 24 months, based on an exploratory analysis. The submitter suggested that POD within 24 months is an accurate predictor of poor OS.

pERC noted clarification provided by the pCODR Methods team and the pCODR Clinical Guidance Panel (CGP) in the pCODR Final Clinical Guidance Report in response to the feedback from the submitter. Specifically, the CGP commented that there is currently insufficient evidence to support the use of POD24 as a surrogate end point for OS and that the analysis of POD24 in the GALLIUM trial was considered exploratory and would require prospective evaluation and validation. Furthermore, pERC noted that POD24 was not considered an outcome of interest of the systematic review performed by the pCODR Methods Team and the pCODR CGP, and therefore data on POD24 was not reported in the Initial pCODR Final Clinical Guidance Report. Overall, the Committee agreed that longer-term follow-up data are necessary to draw definitive conclusions on the clinical benefit of obinutuzumab in previously untreated patients with FL.

Patient-reported outcomes: Clinically meaningful improvements in HRQoL from the end of induction treatment onward from baseline in all scales in both treatment groups; however there are no clear differences between the treatment groups in any FACT-LYM scale scores

Patient-reported health-related quality of life (QoL) was measured using the Functional Assessment of Cancer Therapy - Lymphoma (FACT-LYM) instrument. Compliance in completing questionnaires was high at baseline in both treatment groups (92.5% in the obinutuzumab group versus 91.5% in the rituximab group) but declined over the course of treatment and follow-up. pERC noted that at baseline, mean FACT-LYM scores were similar in both treatment groups for all scales, with all patients in both groups demonstrating some degree of impairment of physical function, functional well-being, and emotional and social function. pERC noted both treatment groups showed clinically meaningful improvements from the end of induction treatment onward from baseline in all scales, although there were no differences between treatment groups at any time point. Overall, there appeared to be no detriment to QoL with treatment with obinutuzumab.

Safety: Manageable toxicity profile; higher frequency of second malignancies in the obinutuzumab treatment group

pERC noted that the most common grade 3 to 5 adverse events (AEs) during induction (obinutuzumab versus rituximab) were neutropenia (37.1% versus 34%), leukopenia (7.7% versus 8%), and infusion-related reactions (6.6% versus 3.5%), while the most common serious AEs were infusion-related reactions (4.4% versus 1.8%),

neutropenia (2.9% versus 3.2%), febrile neutropenia (3% versus 2.2%), and pyrexia (2.5% versus 2.7%). The most common grade 3 to 5 AEs and serious AEs during maintenance treatment were neutropenia (16.4% versus 10.7%) and pneumonia (2.4% versus 3%), respectively.

Over the course of the trial the frequency of second malignancies (occurring at least six months after the start of treatment) was higher in the obinutuzumab treatment group (n = 43, 7.2% with obinutuzumab versus n = 30, 5% with rituximab), particularly non-melanoma skin cancers (n = 18, 3% versus n = 14, 2%) and hematologic malignancies (n = 6, 1% versus 0). In the follow-up phase of the study, 5.2% of patients receiving bendamustine in combination with obinutuzumab developed secondary malignancies compared with 0.8% of patients receiving bendamustine in combination with rituximab.

A total of 81 deaths had occurred by the primary analysis data cut-off date; of these, 24 (4%) in the obinutuzumab treatment group and 20 (3.4%) in the rituximab group were attributed to AEs.

Need and burden of illness: Indolent disease with long survival; Standard of care in Canada is bendamustine plus rituximab with rituximab maintenance

FL is the most common type of iNHL. For previously untreated patients with FL, the standard of care in Canada is bendamustine plus rituximab with rituximab maintenance every three months for up to two years. CHOP plus rituximab can be an alternative option for patients with FL. The Committee noted that FL is an indolent disease and patients with FL have long survival with currently available treatments. pERC noted that there is a need for more effective therapies that provide patients with a treatment option that will prolong the time between treatments for patients with FL who will eventually need to be retreated.

Registered clinician input: Need for a treatment option that will prolong time between treatment; obinutuzumab associated with greater toxicity and infusion reactions

Clinicians providing input noted that obinutuzumab meets current clinical needs for patients with FL, and that obinutuzumab may provide patients with a treatment option that will prolong time between treatments (compared with rituximab) for patients who will eventually need to be retreated. The clinicians providing input noted that first-line therapy for patients with FL in Canada is chemotherapy and rituximab, specifically bendamustine and rituximab, and that CHOP and rituximab can be used as an alternative option. Clinician input noted that obinutuzumab results in greater toxicity and infusion reactions compared with rituximab. Furthermore, clinicians noted that there is no evidence regarding sequencing of therapies after treatment with chemotherapy plus obinutuzumab.

PATIENT-BASED VALUES

Patient values on treatment: Longer survival, longer remission, improved quality of life, reduced side effects

pERC noted patient input that explored patient values for first-line treatment. Patients valued as extremely important longer survival (87%), longer remission (79%), improvement in QoL (69%), and fewer side effects. (44%). pERC noted that patients felt that the current standard of care for first-line therapy is relatively effective. Fatigue, diarrhea, nausea and vomiting, hair loss, mouth sores, and neutropenia were the most commonly reported side effects of currently available treatments. Fatigue, nausea and vomiting, and pain were reported as being the most difficult to tolerate. pERC noted only six patient respondents reported having experience with obinutuzumab treatment, and all reported that their treatment was able to manage most of their disease symptoms. The Committee noted that fatigue was reported as the most difficult side effect to manage with treatment with obinutuzumab.

pERC appreciated the considerable effort the patient advocacy group Lymphoma Canada made to prepare a written summary of the GALLIUM trial for respondents in order to determine patients' values in the context of first-line therapy and the treatment under review. pERC noted that the approach taken by the patient advocacy group was impressive, and, overall, informative in its deliberations. The Committee noted that obinutuzumab was associated with a modest improvement in PFS and that there was no detriment to QoL compared with rituximab.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed the cost-effectiveness and cost-utility analyses comparing induction obinutuzumab plus chemotherapy followed by maintenance obinutuzumab monotherapy compared with induction rituximab plus chemotherapy followed by maintenance rituximab monotherapy.

Basis of the economic model: Clinical and cost inputs

Costs included were drug-acquisition, supportive care, subsequent therapies, AEs, and clinical visits.
Key clinical effect estimates considered in the analysis included OS, PFS, duration of treatment, utilities, and disutilities. pERC noted that post-progression survival data were sourced from another clinical trial, the phase III PRIMA trial, which examined rituximab maintenance after first-line treatment in patients with FL receiving an induction rituximab plus chemotherapy regimen.

Drug costs: High drug cost

Obinutuzumab costs $5,429 per 1,000 mg vial (fixed dose). The total regimen cost of induction treatment with bendamustine plus obinutuzumab is $68,510. The total maintenance cost of obinutuzumab every two months for two years is $65,153.

Rituximab costs $2,352.59 per 500 mg vial (dosing based on body surface area calculated as mg/m^2). The total regimen cost of induction treatment with bendamustine plus rituximab is $42,794. The total maintenance cost of rituximab every three months for two years is $23,108.

Cost-effectiveness estimates: Not cost-effective at the submitted price

The Committee deliberated upon the cost-effectiveness of obinutuzumab. pERC noted that the EGP estimates (lower bound: $76,261 per quality-adjusted life-year [QALY]; upper bound: $133,801 per QALY) were higher than the submitter's estimate ($49,562 per QALY) and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's reanalysis, which included:

- a shortened time horizon from 40 years to 30 years to better align with the expert opinion of the pCODR Clinical Guidance Panel
- a truncated duration of treatment effect from nine years to five years to reflect the duration of the follow-up period in the GALLIUM trial
- an increased proportion of rituximab administered subcutaneously to reflect that some provinces in Canada administer rituximab subcutaneously
- frequency of maintenance therapy of every three months instead of every two months in the comparator arm to reflect current Canadian practice
- rituximab intravenous price to reflect the future biosimilar price with a discount of 35%.

The Committee noted that these changes to the estimates of the incremental effect and costs increased the ICER estimates. The Committee noted that post-progression survival data were sourced from another clinical trial, the phase III PRIMA trial, which examined rituximab maintenance after first-line treatment in patients with FL receiving an induction rituximab plus chemotherapy regimen, due to the lack of mature OS data from the GALLIUM trial. pERC noted that there is no evidence of long-term OS in patients treated with obinutuzumab from the GALLIUM trial. The Committee noted that the EGP's upper bound ICER estimate assumed a five-year duration of treatment effect based on the duration of follow-up of the GALLIUM trial. However, pERC noted that the true ICER may be even higher than the EGP's upper bound ICER estimate because there was no proven difference in OS observed between the two treatment groups. The Committee also noted that the secondary malignancies observed during follow-up of the GALLIUM trial were not incorporated into the economic analysis. Furthermore, pERC also noted that granulocyte-colony stimulating factors (G-CSF) is not a standard of care for the treatment of neutropenia, and the use of G-CSF to manage neutropenia in patients treated with obinutuzumab would increase the ICER. Overall, pERC noted that the magnitude of any long-term benefit associated with obinutuzumab is unknown given the lack of long-term data from the GALLIUM trial. pERC noted that at the submitted price, obinutuzumab compared with rituximab cannot be considered cost-effective in this population.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted feedback from the submitter regarding issues raised around some of the assumptions in the pCODR EGP reanalyses.

Clarification was provided by the pCODR EGP in the Economic Guidance Report regarding two assumptions in the Economic Guidance Report reanalyses. Firstly, the submitter noted that the assumption of no PFS treatment effect beyond the GALLIUM study follow-up period of five years is implausible for anti-CD20 treatments. The Committee noted that in the absence of mature OS data to provide a full picture of the long-term effects of treatment with obinutuzumab, the EGP elected to truncate the duration of the treatment effect of obinutuzumab to five years in the reanalysis. pERC agreed with this approach as a means of exploring uncertainty in the ongoing benefit of obinutuzumab (due to the extrapolation of long-term estimates from data with a shorter follow-up period) and the impact of this benefit on OS, given the use of indirect data from the phase III PRIMA trial to inform post-progression survival, which may not reflect the course of a patient being treated with obinutuzumab therapy. The EGP chose to truncate the treatment effect to five years as it corresponds to the duration of follow-up in the GALLIUM trial. The Committee noted that in truncating the treatment effect at five years, the EGP assumed no incremental treatment effect of obinutuzumab beyond the GALLIUM trial follow-up of five years. The EGP noted that this analysis could represent the worst-case scenario and therefore included it as part of its upper bound ICER estimate. pERC reiterated that this was an appropriate approach to demonstrate the impact of the unknown long-term treatment effect of obinutuzumab on OS and the ICER. The Committee reiterated that the magnitude of the long-term benefit associated with obinutuzumab is uncertain given the short follow-up in the GALLIUM trial.

Secondly, the submitter provided feedback regarding the EGP's reanalysis using three-monthly dosing of rituximab to reflect current Canadian clinical practice. The submitter noted that this approach biases the results in favour of rituximab by reducing the incremental cost between the two treatments, while assuming the same magnitude of clinical benefit for rituximab plus chemotherapy with a lower frequency of administration. pERC noted that in the EGP's reanalysis, the EGP changed the frequency of maintenance therapy of rituximab to every three months to reflect current Canadian clinical practice. The Committee agreed with the CGP and EGP and reiterated that the inclusion of administration of maintenance therapy of rituximab every three months reflects the current standard of care in Canadian clinical practice.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Submitted budget impact is underestimated and actual budget impact will be substantial

pERC noted factors that could impact the feasibility of implementing a positive conditional reimbursement recommendation for obinutuzumab for the treatment of adults with previously untreated FL. The Committee agreed with PAG that the enablers to implementation include flat dosing with no drug wastage, and that the barriers to implementation include increased chair time in the first month of treatment and in the maintenance phase, increased resource use, and the high cost of obinutuzumab. pERC also discussed PAG's request for clarity on sequencing using rituximab plus chemotherapy after first-line treatment with obinutuzumab, but noted there is no evidence to inform sequencing of available therapies. Finally, pERC noted that the Ontario-specific budget impact was underestimated, and the actual budget impact will be substantial, given the prevalence of FL in the first-line setting. pERC noted that the factors that influenced the budget impact analysis include the frequency of maintenance therapy (rituximab maintenance frequency every three months versus every two months), increasing the size of eligible the FL population, market share of obinutuzumab, and assuming the biosimilar cost of all rituximab products.

DRUG AND CONDITION INFORMATION

Drug Information	• Recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype • Administered as an intravenous infusion • For induction obinutuzumab treatment, the recommended dosage is 1,000 mg administered on day 1, day 8, and day 15 for the first 28-days of the treatment cycle followed by 1,000 mg administered on day 1 only for each subsequent 28-day treatment cycle (cycles 2 to 6) • For maintenance treatment, the recommended dose is 1,000 mg alone once every two months until disease progression or for up to two years (whichever occurs first)
Cancer Treated	• Previously untreated follicular lymphoma
Burden of Illness	• Estimated incidence of more than 2,800 Canadians newly diagnosed every year • Indolent incurable disease with long survival
Current Standard Treatment	• Rituximab plus bendamustine, followed by maintenance rituximab every three months for two years
Limitations of Current Therapy	• Need for new effective therapies to improve quality of life and prolong time between treatments for patients who will eventually need to be retreated

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Christopher Longo, Economist
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Avram Denburg, Dr. Anil Abraham Joy, and Cameron Lane, who were not present for the meeting
- Dr. Catherine Moltzan, who had a conflict of interest.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Cameron Lane, Patient Member
Dr. Christopher Longo, Health Economist
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Winson Cheung and Dr. Anil Abraham Joy, who were not present for the meeting
- Dr. Catherine Moltzan, who had a conflict of interest
- Daryl Bell, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR pERC must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website, and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of obinutuzumab (Gazyva) for follicular lymphoma (previously untreated), one member had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting. For the Final Recommendation, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR Guidance Reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR Guidance Reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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