

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 Funding Request:	For the treatment of adults with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen	
Submitted By: Hoffmann-La Roche	Manufactured By: Hoffmann-La Roche	
NOC Date: December 29, 2016	Submission Date: November 4, 2016	
Initial Recommendation: March 30, 2017	Final Recommendation: June 2, 2017	

pERC RECOMMENDATION

pERC recommends reimbursement of obinutuzumab (Gazyva) in combination with chemotherapy followed by obinutuzumab monotherapy conditional on uncertainty in the cost-effectiveness being reduced. Funding should be for the treatment of adults with follicular lymphoma (FL) with disease that is refractory to a rituximab containing regimen as defined in the GADOLIN trial, and with good performance status. Patients with disease response to induction treatment with obinutuzumab plus chemotherapy (i.e. the initial 6 treatment cycles) or who have stable disease should continue to obinutuzumab maintenance. Obinutuzumab maintenance treatment should not be for patients who have progressive disease while on obinutuzumab induction treatment (i.e., obinutuzumab plus chemotherapy for 6 cycles). Maintenance treatment should continue until disease progression or for up to two years whichever occurs first.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of obinutuzumab plus bendamustine based on clinically meaningful improvements in progression-free survival (PFS) and overall survival (OS), manageable toxicities, and at least maintenance in quality of life. pERC felt there is biological plausibility to extend the clinical benefit demonstrated in obinutuzumab in combination with bendamustine to obinutuzumab in combination with chemotherapy. pERC concluded that obinutuzumab aligned with patient values in that it offers disease control, improvement in OS, and it provides patients with an additional treatment option.

pERC was not satisfied that obinutuzumab plus bendamustine is cost-effective compared to bendamustine alone, due to uncertainty about the incremental effect of obinutuzumab that was not accounted for in the submitted economic model. Notably, the Submitter's economic model did not use the trial's OS estimates, but instead, modelled OS indirectly, thus further reducing pERC's confidence in the validity of the submitted cost-effectiveness estimates.

pERC does not recommend reimbursement of obinutuzumab in combination with chemotherapy followed by obinutuzumab monotherapy for the treatment of patients with disease relapse after a rituximab containing regimen and whose disease is not refractory to rituximab.

The committee made this recommendation because there was no clinical evidence to demonstrate benefit or economic data identified to support a recommendation for this population.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS**Collecting Prospective Evidence to Reduce Uncertainty in the Cost-Effectiveness**

pERC was satisfied that obinutuzumab plus bendamustine provided a net clinical benefit for patients with refractory FL, but they noted considerable uncertainty with the inputs used in the submitted economic analysis. As such, pERC concluded that the ongoing collection of overall survival data from the GADOLIN trial and the incorporation of such data in the economic analysis may reduce the uncertainty in the cost-effectiveness estimates. The Committee suggests that the Submitter collect and provide these data to the jurisdictions to reduce uncertainty in the cost-effectiveness.

Generalizability of Results Regarding Eastern Cooperative Oncology Group Performance Status

pERC noted that obinutuzumab plus chemotherapy should be reimbursed for patients with good performance status. However, pERC agreed that patients with declining performance status (i.e., ECOG PS of 2 or more) may benefit from treatment with obinutuzumab plus chemotherapy if the factors affecting performance status are FL-related and are considered to be reversible with treatment. pERC felt treatment selection for these patients requires physician discretion.

Generalizability of Results to Non-Follicular Lymphoma Patients

pERC noted that the extrapolation of iNHL results to non-FL patients, including those with marginal zone lymphoma and small lymphocytic lymphoma, was likely reasonable, as 19% of the patients included in the GADOLIN trial had a non-FL histology; and also because it is unlikely that there will be trials specifically designed for these small groups of patients.

SUMMARY OF pERC DELIBERATIONS

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (iNHL), with an estimated incidence of more than 2800 Canadians newly diagnosed every year.

Treatment of patients with previously treated FL who are refractory to rituximab varies across the jurisdictions and includes fludarabine, brentuximab, bendamustine, cyclophosphamide/ vincristine/ prednisone (CVP) or cyclophosphamide/ doxorubicin/ vincristine/ prednisone (CHOP). For patients who have relapsed on rituximab therapy, rituximab re-treatment is an option depending on time to relapse from last dose of rituximab.

pERC deliberated upon the results of a phase 3, open-label, two-arm parallel, randomized 1:1 study (GADOLIN), which compared obinutuzumab and bendamustine followed by obinutuzumab monotherapy (GB, n= 204) to bendamustine alone (B, n= 209) in patients with rituximab-refractory, indolent non-Hodgkin lymphoma (iNHL). The Committee noted that the majority of patients in the trial had FL (n= 335, 81%), and that the requested reimbursement population by the Submitter was also patients with FL. pERC agreed with the CGP that extrapolation of iNHL results to non-FL patients, including marginal zone lymphoma and small lymphocytic lymphoma, was likely reasonable since it is unlikely that there will be trials specifically designed for these small groups of patients. Secondly, the Committee noted the trial only included rituximab-refractory patients, defined as having no response to, or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy). Patients whose disease had relapsed after rituximab-containing therapy and whose disease was not rituximab-refractory were not included. pERC discussed the fact that the requested reimbursement population included relapsed patients, whereas the GADOLIN trial did not. Therefore, the Committee concluded that there is a lack of evidence to determine the net clinical benefit of obinutuzumab in patients who are not rituximab-refractory and who have disease that has relapsed after a rituximab-containing regimen. Thirdly, the Committee noted that the treatment arm of the trial was bendamustine in combination with obinutuzumab, which is different from the reimbursement criteria of any chemotherapy in combination with obinutuzumab. pERC acknowledged that while enrolling predominantly bendamustine-naïve patients was appropriate at the time of the trial, this patient population no longer reflects clinical practice in Canada today, whereby most patients will receive bendamustine as part of their first line treatment, usually in combination with rituximab. Hence, the use of combination bendamustine in the rituximab-refractory setting would only be relevant to legacy bendamustine-naïve patients. pERC agreed with the Clinical Guidance Panel's (CGP) opinion that the presence of a clinical benefit of using obinutuzumab plus bendamustine would also be as biologically plausible as using obinutuzumab in combination with other chemotherapeutic agents. pERC also agreed with the CGP's opinion that the extent of improvement (that is, the magnitude of the clinical effect) when obinutuzumab is added to chemotherapy is uncertain.

Upon reconsideration, pERC noted feedback from the Provincial Advisory Group (PAG) requesting clarification on the use of obinutuzumab plus bendamustine in patients who are rituximab-refractory after prior therapy with rituximab plus bendamustine. The Committee noted the response from the CGP, which mentioned that in clinical practice in Canada, patients who are refractory to prior therapy with rituximab plus bendamustine would not receive obinutuzumab plus bendamustine (i.e., would not be retreated with bendamustine). pERC reiterated its original conclusion that the presence of a clinical benefit from using obinutuzumab in combination with chemotherapeutic agents other than bendamustine would be as biologically plausible as using obinutuzumab plus bendamustine.

For all interim analyses, pERC noted clinically meaningful improvements in progression-free survival (PFS) associated with obinutuzumab in the subgroup of patients with FL. pERC noted that the FL subgroup analyses were preplanned in the first interim analysis although it is unclear whether the subsequent interim analyses were preplanned, given there was no mention of testing for interaction. In subsequent analyses after the trial publication, the Committee noted statistically significant improvements in overall survival (OS) for the FL subgroup. Although the statistical significance was reached in the FL subgroup only, and not in the iNHL overall population, the Committee felt the point estimates were consistent in

[pERC's Deliberative Framework](#) for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

demonstrating benefit. pERC felt that the absolute differences in PFS and OS reported in the trial would be unlikely to be as favourable to obinutuzumab when used in the real world because the comparator arm, unlike the treatment arm, did not include maintenance therapy, thus likely making the treatment arm appear more favourable. As well, the trial included only a small number of patients (5%) with an ECOG performance status of 2, and excluded patients with active infections, existing cardiovascular or pulmonary disease, elevated creatinine or elevated liver enzymes. For these less healthy patients, pERC felt the degree of benefit from obinutuzumab would likely be smaller than what was reported in the trial. pERC considered that patients with declining performance status (i.e., ECOG PS of 2 or more), who make up about 40% of patients in clinical practice from CGP estimates, may benefit from treatment with obinutuzumab plus chemotherapy if the factors affecting performance status are FL-related and are considered to be reversible with treatment. Although the trial excluded patients with comorbidities, pERC felt obinutuzumab plus chemotherapy may be a reasonable option for select patients with comorbidities, based on the discretion of the treating physician. The Committee discussed whether the effect of obinutuzumab could be attributable to one specific phase of the trial, either induction or maintenance. Specifically, pERC noted little observable separation in the Kaplan-Meier survival curves for PFS and OS at 6 months, which corresponds to the end of the induction period. Furthermore, the survival curves separate after 6 months during the maintenance phase. However, given the GADOLIN trial's design that included maintenance in the treatment arm but not in the comparator arm, the Committee accepted the CGP's conclusion that the treatment effect of the combination of obinutuzumab plus bendamustine followed by obinutuzumab monotherapy should be interpreted altogether, and that the results cannot be interpreted separately according to phase of treatment (i.e., induction and maintenance). In terms of quality of life, pERC noted at least no detriment to quality of life is associated with the obinutuzumab treatment arm compared with the bendamustine monotherapy arm.

pERC discussed the safety of obinutuzumab and noted the higher frequency of serious adverse events in the obinutuzumab plus bendamustine group compared to the bendamustine alone group. However, pERC felt there were no unexpected safety findings from these treatments. pERC felt that infusion-related reactions, which are an adverse event of interest, can be safely managed with proper supervision and pre-medication. In interpreting the safety data, the Committee noted that the higher dose of bendamustine in the comparator arm (120 mg/m^2 as opposed to 90 mg/m^2 in the treatment arm) may increase the risk of myelosuppression (e.g. neutropenia, infectious complications), which may make the combination treatment arm appear more favourable. However, these doses of bendamustine (i.e. monotherapy vs. in combination with anti CD20 therapy) are common to other bendamustine-based regimens for other indications.

pERC deliberated upon input from one patient advocacy group concerning obinutuzumab and noted that the key priorities for patients were to live longer, achieve remission, control disease, and improve quality of life. The Committee agreed that obinutuzumab was associated with a PFS benefit, OS benefit and maintenance of quality of life, and offers patients an additional treatment option. Therefore, the Committee concluded that obinutuzumab aligned with patient values.

The Committee deliberated upon the cost-effectiveness of obinutuzumab and lacked confidence in the submitted information on cost-effectiveness. The Committee expressed considerable uncertainty about the choice of data used in the Submitter's economic model to estimate cost-effectiveness. The Economic Guidance Panel (EGP) had noted that OS data from the GADOLIN trial were not used to directly construct the Submitter's cost-effectiveness analysis, the rationale being that the OS data were not mature. Instead, the PFS and post-progression survival (PPS) curves were used from the 2015 data cut. However, pERC noted that PPS data would theoretically still have used the same death event data (i.e., OS data), which the Submitter considered immature in the first place. The EGP reanalysis suggested less incremental benefit gained (measured in quality-adjusted life years— QALYs) when compared to the Submitter's base case. pERC also discussed the uncertainty of the cost-effectiveness results given the CGP's concerns about the treatment effect size, including concerns related to the National Institute for Health and Care Excellence (NICE)'s reanalysis that found the proportional hazards assumption to be violated. pERC felt that the uncertainty related to the effect size as well as uncertainty from modelling survival using PFS and PPS may have considerable influence on the incremental benefit gained in the economic model. pERC concluded that the ongoing collection of overall survival data from the trial and the direct parameterization of OS in the economic analysis using OS data from the trial may help to reduce the uncertainty in the cost-effectiveness estimates.

Upon reconsideration, pERC noted feedback from the PAG expressing concern that it does not have access to the GADOLIN trial data, and asking pERC to clarify that the Submitter should collect ongoing GADOLIN trial data (e.g., OS) to update the Submitter's economic analysis. pERC agreed that the ongoing collection

of these data is the responsibility of the Submitter and that the economic analysis should be updated as soon as these data become available.

pERC agreed with the limitations of the submitted model noted by the EGP (i.e., highly uncertain input parameters for the secondary analyses) and discussed additional economic considerations. The modeled population was based on the GADOLIN trial and included rituximab-refractory patients only, and not relapsed patients. Given that the trial population was considered bendamustine-naïve, pERC noted the uncertainty in generalizing results to patients today who would receive bendamustine as first-line therapy. Further, the comparator was bendamustine alone, which pERC noted is expensive and would make the incremental costs appear more favourable to obinutuzumab. As described above, pERC felt the absolute difference in clinical benefit between treatment arms in clinical practice is likely smaller than that demonstrated in the trial, thus making the incremental benefit appear more favourable to obinutuzumab. The Submitter assumed that the risk of dying post-progression was the same for both treatment arms, and that the PFS benefit translated directly to an OS benefit in a 1:1 ratio. pERC noted that these assumptions again favoured obinutuzumab. Due to the limitations listed by the EGP and the additional unaccounted sources of uncertainty that were identified by pERC, the Committee felt obinutuzumab plus chemotherapy is unlikely to be cost-effective.

Upon reconsideration, pERC discussed feedback from PAG regarding the uncertainty surrounding the OS assumptions and the inability to provide a best-point estimate for the incremental cost-effectiveness. pERC noted the response from the EGP stating that, to address the uncertainty in the cost-effectiveness, the OS data from the GADOLIN trial would be needed as an input in the economic model. Furthermore, the submitted model could not provide cost-effectiveness estimates utilizing the OS data from the trial.

pERC also discussed feedback from the Submitter regarding the cost-effectiveness of obinutuzumab. First, the Submitter noted that, while its base case assumed that the risk of dying post-progression was the same for both treatment arms, the provided economic model allowed for the risk to be different for each arm (i.e., post-progression survival could be modelled independently for each treatment arm). pERC noted that the EGP confirmed the Submitter's cost-effectiveness estimates, which incorporated the independent modelling of post-progression survival. The Committee also noted and agreed with the EGP's conclusion that this change did not alleviate pERC's main concern regarding the uncertainty in the indirectly modelled OS used to obtain the cost-effectiveness estimates.

Secondly, the Submitter expressed concern regarding the decision to accept a seemingly arbitrary 10-year time horizon rather than the 25-year time horizon assumed by the Submitter. pERC noted the EGP's response, which stated that there was too much potential for inaccurate estimates of the incremental benefits of obinutuzumab when extrapolating the GADOLIN trial results to 25 years (in particular the indirectly modeled OS), due to the relatively short median duration of follow-up in the trial. Therefore, pERC agreed with the EGP's decision to use a 10-year time horizon.

Lastly, the Submitter disagreed with the EGP's decision to use a lognormal model for post-progression survival, as the Submitter felt that statistical fit should not be the only criterion upon which to base the selection of a statistical model, and that a Weibull model provided a more clinically plausible prediction of long-term survival than a lognormal model. pERC noted the EGP's response that more than one criterion should be considered when selecting a statistical model, and that there is subjectivity in the decision regarding which criteria should receive the most weight. The Committee agreed with the EGP's decision to use a lognormal model to estimate post-progression survival. Following discussion of feedback from the Submitter and the PAG on the Initial Recommendation, pERC judged that some uncertainty remained in the cost-effectiveness estimates; therefore, it reiterated its original conclusion that obinutuzumab plus chemotherapy is unlikely to be cost-effective.

pERC also considered factors affecting the feasibility of implementing a conditional positive reimbursement recommendation for obinutuzumab for the treatment of adults with FL who are refractory to a rituximab containing regimen. The Committee agreed with PAG that enablers to implementation include flat dosing, and barriers to implementation include greater chair-time, increased resource use, and the high cost associated with obinutuzumab. The Committee acknowledged PAG's comments that patients who are refractory to rituximab have limited treatment options available, and there is no standard across jurisdictions to address when refractory patients should be retreated with rituximab. The systematic review found no studies comparing obinutuzumab and rituximab retreatment. PAG asked for clarity on the intended group of patients who would be eligible for treatment with obinutuzumab, and pERC re-iterated that obinutuzumab is only recommended for rituximab-refractory patients and not for

relapsed patients. Secondly, pERC discussed PAG's request for clarity on sequencing and reuse of obinutuzumab. pERC could not comment on the use of obinutuzumab in first line treatment, nor could it comment on the reuse of obinutuzumab, as both scenarios were beyond the scope of this review. pERC noted that there is no comparative data on different schedules of drug administration. Furthermore, pERC noted that the dosing of obinutuzumab, like other monoclonal antibody therapies, may be higher than necessary; however, the Committee agreed that the dose and schedule used in the GADOLIN trial should be used in clinical practice unless new evidence is generated on the most appropriate dose and schedule. In terms of the budget impact, pERC noted the submitted analysis included predominantly relapsed patients (79%) and some rituximab-refractory (21%). Excluding relapsed patients would greatly reduce the budget impact.

Upon reconsideration, pERC reiterated its agreement with the CGP that extrapolation of iNHL results to non-FL patients, including marginal zone lymphoma and small lymphocytic lymphoma, was likely reasonable, as it is unlikely that there will be trials specifically designed for these small groups of patients.

EVIDENCE IN BRIEF

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

- A pCODR systematic review
- An evaluation of the manufacturer's economic model and budget impact analysis
- Guidance from pCODR clinical and economic review panels
- Input from one patient advocacy group (Lymphoma Canada [LC])
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, (Lymphoma Canada [LC])
- The PAG
- The submitter (Hoffmann-La Roche Limited).

The pERC Initial Recommendation was to recommend reimbursement of obinutuzumab (Gazyva) in combination with chemotherapy followed by obinutuzumab monotherapy conditional on uncertainty in the cost-effectiveness being reduced. Feedback on the pERC Initial Recommendation indicated that the manufacturer, PAG, and patient advocacy group all agreed in part with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of obinutuzumab in combination with chemotherapy, followed by obinutuzumab monotherapy, in the treatment of adults with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab containing regimen.

Studies included: Phase III, open-label, two-arm parallel, randomized trial

The pCODR systematic review included GADOLIN, a phase 3, open-label, two-arm parallel, randomized 1:1 study, which compared obinutuzumab and bendamustine followed by obinutuzumab maintenance (GB, n= 204) to bendamustine alone (B, n= 209). The GADOLIN trial enrolled patients with rituximab-refractory, indolent non-Hodgkin lymphoma (iNHL) between 2010 and 2015. Canada had the highest recruitment across the ten sites (n= 86). The trial excluded patients who have received treatment with bendamustine within two years of trial start. Of note, the standard of care since 2014 (after trial initiation) has been bendamustine in primary treatment, usually in combination with rituximab. The trial did not include relapsed patients, only rituximab-refractory patients. In the GADOLIN trial, rituximab refractory was defined as having no response to, or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:

- Patients with progressive disease while receiving rituximab monotherapy (after at least one full cycle), rituximab + chemotherapy (after at least one full cycle), or rituximab maintenance treatment (after having received at least one full dose [375 mg/m²] of rituximab)
- Patients with no clinical response (partial response or better) to a rituximab-containing regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Patients with disease relapse (after having achieved a clinical response) within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Rituximab-refractory as defined included patients who were refractory to any prior rituximab containing regimen, not just the most recent regimen containing rituximab.

The primary outcome was progression-free survival (PFS) as assessed by an independent review committee. Other outcomes included overall survival (OS), overall response, duration of response, quality of life, and adverse events (AEs). Dose interruption, delays, discontinuations and infusion rate reduction were allowed.

Patient populations: Similar baseline characteristics; majority with ECOG performance status 0-1; majority with follicular lymphoma

At baseline, prognostic risk factors such as demographic characteristics and previous treatment history were well balanced between the treatment groups, with the exception of a slightly higher proportion of patients in the obinutuzumab plus bendamustine group with extranodal involvement, indicating more advanced disease. The trial population represented a healthier, more selected patient population compared to refractory patients seen in clinical practice. Most patients had ECOG scores of 0 or 1 (n= 391, 95%); approximately 15% of the entire study population had B symptoms (fever, night sweats, weight loss). The majority had FL (n= 335, 81%), which is the population requested for in the reimbursement criteria. At baseline, 327 (79%) patients were refractory to a previous rituximab chemotherapy combination while the remaining patients were refractory to rituximab monotherapy. More than half of the study patients had been exposed to at least two treatment regimens for iNHL, and the mean time from diagnosis to study entry was approximately 4 years. The trial population had no bendamustine two years prior to enrollment. As well, the trial included a small number of patients (5%) with an ECOG performance status of 2, and excluded patients with active infections, existing cardiovascular or pulmonary disease, elevated creatinine or elevated liver enzymes.

Key efficacy results: Clinically meaningful progression-free survival and overall survival data

The key efficacy outcomes deliberated on by pERC were PFS and OS.

In the subgroup of patients with follicular lymphoma, there were statistically significant differences observed in the PFS analyses at the first, second and third interim analyses. The second interim analysis (May 2015, median follow up of 24 months) was unplanned. The most recent analysis (April 2016, median follow up of 32 months) estimated that the median progression free survival was 25.3 months in patients taking obinutuzumab plus bendamustine versus 14.0 months in patients taking bendamustine alone (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001).

At the time of the primary publication of the trial results (September 2014), there were no significant differences in overall survival. From the April 2016 data cut-off, OS estimates in the follicular lymphoma patients favoured the obinutuzumab plus bendamustine group compared to the bendamustine alone group. Median OS for obinutuzumab plus bendamustine was not estimable (NE) and median OS for bendamustine alone was 53.9 months (40.9 months to NE) (HR[95%CI: 0.58[0.39,0.86]; p=0.0061). There were 39 deaths (24%) in the obinutuzumab plus bendamustine group and 64 deaths (37%) in the bendamustine alone group.

The Kaplan-Meier survival curves for the PFS and OS analyses at both cut-off points showed little observable separation in at 6 months, which corresponds to the end of the induction period. In both the PFS and OS plots, the treatment arms crossed one another, suggesting that the proportional hazards assumption may have been violated. pERC noted that NICE also assessed the proportional hazards assumption using Schoenfeld residuals for PFS from the GADOLIN trial, and concluded that there was evidence that the assumption was not valid (spline regression fit, p = 0.0188). These observations about the survival curves and NICE assessment of proportional hazards increase the uncertainty associated with the actual effect size. Secondary analyses, using propensity score methods on data from the GADOLIN trial and a US-based, lymphoma registry, indirectly compared obinutuzumab plus bendamustine with other potentially relevant treatment options in Canada. No conclusions could be drawn due to significant limitations.

Quality of life: Exploratory, low completion rate of FACT-Lym, no notable differences between treatment arms

The GADOLIN trial measured quality of life using two questionnaires: (1) the Functional Assessment of Cancer Therapy for patients with lymphoma (FACT-Lym), and (2) the EuroQol Group EQ-5D. pERC noted quality of life analyses were exploratory and statistical comparisons between treatment arms were not performed for many of the comparisons.

For the FACT-Lym questionnaire, there were no notable differences between the GB and B groups in the total scores and subscale scores in the follicular lymphoma subgroup. In the follicular lymphoma subgroup, median time to deterioration of FACT-Lym Trial Outcome Index (TOI) score, defined as \geq 6-point worsening from baseline, was 5.6 months in the bendamustine group compared to 7.8 months in the bendamustine plus obinutuzumab group (HR[95%CI]: 0.83[0.60,1.13]). A major limitation of the FACT-Lym

data is that questionnaire completion rates decreased substantively over time (completion rates end of induction: GB 77% and B 76%; versus 18 months after end of induction: GB 76% and B 58%).

For the EQ-5D questionnaire, there were comparisons of the two treatment groups at various times throughout the induction phase, but the data for the maintenance phase were only recorded for the obinutuzumab plus bendamustine arm. There were no statistical analyses available for the EQ-5D data.

Safety: Obinutuzumab plus bendamustine associated with more toxicities compared to bendamustine alone; adverse events manageable with proper supervision and pre-medication

At the latest data cut-off (April 2016), Grade 3 to 5 adverse events (AE) were reported in 73% and 66% of the GB and B arms respectively. Myelotoxicity was the most common subtype of AEs, with grade 3 neutropenia occurring in the 35% of the GB versus 27% in the B arm and thrombocytopenia occurring in 11% versus 16% respectively. Grade 3-5 infusion reactions occurred in up to 9% of patients with GB and can be safely managed with proper supervision and pre-medication. Of note, Health Canada had issued black box warnings for infusion reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, tumour lysis syndrome, and cardiovascular adverse events. Infusion rates, for example, can be safely managed with proper supervision and pre-medication.

Interpretation of the adverse event data in the induction phase is complicated by the fact that the bendamustine dose was not the same in both arms (90 versus 120 mg/m² per day for GB and B, respectively). pERC noted that there is uncertainty regarding whether any observed differences in adverse event rates or efficacy during the induction phase may be attributable to the addition of obinutuzumab. Higher doses of bendamustine may increase risk of myelosuppression (e.g. neutropenia, infectious complications). In the induction phase, the study group with bendamustine plus obinutuzumab had a higher rate of serious adverse events (28%) compared to bendamustine (22%). Of note, the treatment arm had a lower planned dose of bendamustine than the comparator arm which had a higher planned dose of bendamustine. Interpretation of the adverse event data beyond the induction phase is complicated by the fact that there was no maintenance treatment in the bendamustine-only treatment group.

Limitations: Potential sources of bias

Firstly, the GADOLIN compromised of patients who were not treated with bendamustine within two years of enrollment, but practices have changed since trial initiation such that first line therapy for FL patients includes bendamustine in primary treatment, usually in combination with rituximab. This limits the direct generalizability of the extent of improvement (effect size) noted in the trial to “legacy patients”, i.e. patients who are rituximab-refractory but are naïve to bendamustine. Secondly, the treatment arms crossed in the PFS Kaplan-Meier plots as well as the OS Kaplan-Meier plots for obinutuzumab plus bendamustine, suggesting the proportional hazards assumption was violated. NICE noted evidence for the violated assumption. This further increases uncertainty associated with the actual effect size. Thirdly, because there was no maintenance therapy in the bendamustine arm of GADOLIN, attributing responsibility for the improvement in PFS and OS to any particular phase of the experimental treatment (induction or maintenance) is challenging.

In reconsidering its Initial Recommendation, pERC considered feedback from PAG regarding the use of obinutuzumab plus bendamustine in patients who are rituximab-refractory after prior therapy with rituximab plus bendamustine. The Committee noted feedback from the CGP which observed that, in clinical practice in Canada, patients who are refractory to prior therapy with rituximab plus bendamustine would not receive obinutuzumab plus bendamustine (i.e., would not be retreated with bendamustine), as all such patients would have previously received bendamustine, likely quite recently prior to the latest lymphoma progression now requiring treatment – making bendamustine an unattractive choice. pERC noted the CGP’s expert opinion that the GADOLIN trial conceptually demonstrated that adding obinutuzumab to cytotoxic chemotherapy overcomes resistance to rituximab, and that bendamustine is currently used in the first-line setting in most Canadian jurisdictions. The Committee also noted the CGP’s expert opinion that obinutuzumab should be combined with chemotherapeutic agents other than bendamustine in patients who are rituximab-refractory after prior treatment with rituximab plus bendamustine.

Registered clinician input: None received

There was no registered clinician input submitted for the review of obinutuzumab for follicular lymphoma.

Need: Absence of reliably effective therapeutic alternatives

For previously treated FL patients with disease that is refractory to rituximab, treatment varies across the jurisdictions and there is no standard of care. Treatments available include fludarabine, bendamustine, cyclophosphamide/vincristine/prednisone (CVP) or cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP). For patients whose disease has relapsed after rituximab therapy, rituximab re-treatment is an option depending on time to relapse from last dose of rituximab.

PATIENT-BASED VALUES

Experience of patients with follicular lymphoma: lower quality of life and complications with relapsed disease

Lymphoma Canada (LC) stated that from a patient's perspective, those with early stage FL who participated in the survey experienced minimal symptoms with their disease and tended to have a good quality of life. However, for those with relapsed disease, quality of life was impacted more significantly. Patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, muscle and joint pain, as well as difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. Furthermore, additional complications included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts). LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities. Patients who responded to the LC survey reported that treatment options for relapsed FL included: single agent or combination chemotherapy, rituximab (alone or in combination), or radiation therapy. LC indicated that these treatment options tend to be associated with increased toxicity, reduced anti-tumour activity and unpleasant side effects.

pERC acknowledged that patient expectations included seeking treatments that will prolong life, offer disease control, bring about remission and improve quality of life.

Caregivers identified the following issues: difficulties managing side effects of treatment, difficulties with accessing treatments (i.e., financial burden and ability to travel to a cancer centre in order to receive treatment), time taken off work (loss of income).

Patient values regarding treatment: Expect more manageable side effects, improvement in disease symptoms and quality of life

Many respondents who did not have experience with obinutuzumab were willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life.

Respondents who had experience with obinutuzumab had fewer and more manageable side effects, as compared to other therapies, as well as improvements in their disease symptoms and in quality of life. LC added that patients who are refractory to rituximab could also benefit from an effective immunotherapy that can be combined with available chemotherapy agents. Finally, LC noted that there are very few effective treatment options for FL patients who have relapsed after initial therapy and that obinutuzumab in combination with chemotherapy followed by obinutuzumab maintenance may potentially improve remissions.

ECONOMIC EVALUATION

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

The cost-effectiveness analysis and cost-utility analysis submitted to pCODR by Hoffman La Roche compared obinutuzumab plus chemotherapy followed by obinutuzumab monotherapy (GB) to bendamustine alone (B) for patients with follicular lymphoma who relapsed or were refractory to rituximab or a rituximab containing regimen (primary analysis). As a secondary analysis, obinutuzumab plus bendamustine was compared to other potentially relevant treatment options in Canada.

Basis of the economic model: Markov model

The Markov model comprised three health states: 1) Alive without progression; 2) Alive post-progression; 3) Dead. The following determined the proportion of patients that would be in each of the health states

every month: PFS (Weibull model; based on GADOLIN trial), mortality rates while progression-free (based on GADOLIN trial), post-progression survival (Weibull model as function of the time since disease progression; based on GADOLIN trial). Overall survival curves were not estimated using the GADOLIN trial patient level data. Instead overall survival was estimated for the two treatment arms using the Markov model by combining PFS, PPS, and probability of death while in PFS. The base case used a time horizon of 25 years. Utility values were taken from a U.K. study of patients with follicular lymphoma (n = 222; Wild et al.), and disutility values for adverse events were also taken from the literature. Unit costs of medications were taken from IMS Brogan (QuintilesIMS).

Drug costs

Obinutuzumab costs \$5,381.01 per 1000 mg (flat pricing). Bendamustine costs \$312.50 per 25 mg vial, and \$1250.00 per 100 mg vial.

Based on the GADOLIN protocol dose, obinutuzumab plus bendamustine costs were \$20,463 per 28-day course (cycle 1), \$9,701 per 28 day course (cycles 2-6), and \$5381 every two months (maintenance up to 2 years). Costs for bendamustine alone were \$5,760 per 28 day course (cycles 1-6). These costs assume a body surface area of 1.92 m² and vial sharing.

Cost-effectiveness estimates: Best estimate driven by the overall survival assumptions in the post-trial period

The main cost drivers of the manufacturer's model were drug acquisition costs and drug administration costs. In the Submitter's model, the acquisition cost of GB versus B was 80% of the total discounted incremental costs (\$60,100 of \$75,229). Other inputs to the model that affected estimates of costs were subsequent treatment costs and the costs of adverse events.

The main drivers of the clinical effect estimates from the model (QALYs, Life Years) were: 1) PFS estimates over time; 2) post-progression survival estimates over time; 3) the time horizon used in the model and 4) the utility values assigned to patients over the duration of the model time horizon. In the secondary analysis, the hazard ratio obtained from the indirect comparison was also a key driver for estimating outcomes.

The EGP provided re-analysis estimates of the cost-effectiveness based on changes to three variables in the model. First, the time horizon was shortened from 25 years to 10 years to reduce possible overestimates of the indirectly constructed overall survival extrapolations. To extrapolate post-progression survival a lognormal model was used in the EGP analysis as it provided the best fit to the trial data. Finally, the EGP changed the Submitter's assumption of no drug wastage, and instead assumed drug wastage in the model.

pERC discussed the main assumptions and limitations of the submitted model identified by the EGP. The Committee noted that the submitter indirectly estimated OS by combining PFS data and post-progression survival (PPS) data from the GADOLIN trial. Furthermore, pERC noted the Submitter's rationale for not using OS data from the GADOLIN trial was that those data were immature. However, the Committee noted that the PPS data would theoretically have the same death event rate as the OS data, and were drawn from the same data cut (i.e., 2015). pERC also noted that the EGP's re-analysis estimates did not address the uncertainty associated with these assumptions and limitations. In the secondary analyses, there was uncertainty associated with the hazard ratio results, due to the limitations of internal validity and external validity of the indirect comparison.

Upon reconsidering its Initial Recommendation, pERC noted feedback from PAG regarding the uncertainty surrounding the OS assumptions and the lack of a best-point estimate for the incremental cost-effectiveness that addressed that uncertainty. pERC noted the response from the EGP that, to address the uncertainty in the cost-effectiveness, the OS data from the GADOLIN trial would be needed to inform the economic model, and that the submitted model could not provide cost-effectiveness estimates utilizing OS data from the trial. Therefore, the EGP could not provide reanalysis estimates that would alleviate pERC's concerns regarding the uncertainty in the indirect modelling of OS.

pERC also noted feedback from the Submitter regarding the cost-effectiveness of obinutuzumab. Firstly, the Submitter noted that, while its base case assumed that the risk of dying post-progression was the same for both treatment arms, the provided economic model allowed for the risk to be different for each arm (i.e., post-progression survival could be modelled independently for each treatment group). pERC noted feedback from the EGP that confirmed the Submitter's cost-effectiveness estimates incorporating

independently modelled post-progression survival. The Committee also noted the EGP conclusion that this change did not alleviate pERC's main concern regarding the uncertainty in the indirectly modelled OS. Secondly, the Submitter was concerned that pERC's decision to accept a 10-year time horizon was arbitrary and not in alignment with the current *CADTH Guidelines for the Economic Evaluation of Health Technologies, 4th Edition*. pERC noted the EGP's response that there is too much potential for inaccurate estimates of the incremental benefits of obinutuzumab when extrapolating the GADOLIN trial results to 25 years, due to the relatively short median duration of follow-up in the trial, the indirect modeling of OS using PFS and PPS and the potential to overestimate benefits over time.

Lastly, the Submitter disagreed that the lognormal model provided the best fit for post-progression survival, as statistical fit is not the only criterion upon which to base the selection of a statistical model. The Submitter felt that a Weibull model provided a more plausible prediction of long-term survival than a lognormal model. pERC noted the EGP's response that more than one criterion should be considered when selecting among statistical models and that there remains subjectivity regarding which criteria should receive the most weight. The EGP concluded that the lognormal model provided the best fit and was, therefore, the best choice to model post-progression survival.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Intravenous administration, restricted to treatment centres with the experience and resources to manage infusion related reactions

PAG noted that for previously treated FL patients who are refractory to rituximab, treatment varies across the jurisdictions and there is no standard of care. Treatments available include fludarabine, bendamustine, cyclophosphamide/ vincristine/ prednisone (CVP) or cyclophosphamide/ doxorubicin/ vincristine/ prednisone (CHOP). For patients who have relapsed after rituximab therapy, rituximab re-treatment is an option depending on time to relapse from last dose of rituximab.

PAG asked for clarity on the generalizability of the GADOLIN trial results to treatment with obinutuzumab in combination with chemotherapy, as the GADOLIN trial was for obinutuzumab with bendamustine. pERC felt the presence of a clinical benefit of using obinutuzumab plus bendamustine would also be as biologically plausible as using obinutuzumab in combination with other chemotherapeutic agents. pERC agreed with the CGP's opinion that the extent of improvement (that is, the magnitude of the clinical effect) when obinutuzumab is added to chemotherapy is uncertain.

PAG noted that a large prevalent number of patients with refractory FL may be eligible to receive treatment, and this would provide a treatment option for patients who are refractory to rituximab.

PAG also noted that the GADOLIN trial included a small number of patients (less than 20%) with marginal zone lymphoma (MZL) and small lymphocytic lymphoma (SLL). The CGP acknowledged that it is unlikely that phase 3 studies will be carried out among the non-FL subtypes given small sample sizes. Although high quality data that the effects of the use of anti-CD20 monoclonal antibodies can be extrapolated from follicular lymphoma to the other indolent small B cell lymphomas are lacking, available indirect comparisons have been consistent with that interpretation and reasonably remain extended to obinutuzumab, until such rigorous evidence becomes available.

PAG identified obinutuzumab's flat dosing (regardless of patient's weight or body surface area), and vial sizes that provide doses without drug wastage as enablers to implementation. PAG noted the following barriers to implementation: high cost of obinutuzumab; route of administration, as there would be chemotherapy chair utilization and increased nursing resources; additional costs associated with obinutuzumab treatment, such as monitoring for infusion related reactions and other adverse reactions; and, in some jurisdictions, the administration of obinutuzumab being restricted to treatment centres with the experience and resources to manage infusion related reactions.

In terms of the budget impact, PAG noted the number of patients eligible for treatment is unknown and that there could be a large incremental budget impact. The Economic Guidance Panel (EGP) noted the following factors that impacted the budget impact analysis the most: estimated number of patients eligible for obinutuzumab, and the market share of obinutuzumab.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody Administered as an intravenous infusion For induction obinutuzumab treatment, the recommended dosage is 1000 mg administered on Day 1, Day 8 and Day 15 of the first 28 day treatment cycle followed by 1000 mg administered on Day 1 only for each subsequent 28 day treatment cycle (Cycles 2 to 6). For maintenance obinutuzumab treatment, the recommended dose is 1000 mg alone once every 2 months until disease progression or for up to two years (whichever occurs first). Recommended IV dosage (above) reviewed by pCODR
Cancer Treated	<ul style="list-style-type: none"> Follicular lymphoma (FL)
Burden of Illness	<ul style="list-style-type: none"> Estimated incidence of more than 2800 Canadians newly diagnosed every year
Current Standard Treatment	<ul style="list-style-type: none"> No current standard of care for the treatment of patients refractory to or relapsing after a rituximab-containing regimen Treatment varies across the jurisdictions and includes fludarabine, brentuximab, bendamustine, cyclophosphamide/vincristine/prednisone (CVP) or cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP). For patients who have relapsed after rituximab therapy, rituximab re-treatment is an option depending on time to relapse from last dose of rituximab.
Limitations of Current Therapy	<ul style="list-style-type: none"> Absence of reliably effective therapeutic alternatives

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:

Dr. Maureen Trudeau, Oncologist (Chair)
 Dr. Paul Hoskins, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Dr. Kelvin Chan, Oncologist
 Dr. Matthew Cheung, Oncologist
 Dr. Craig Earle, Oncologist
 Dr. Allan Grill, Family Physician
 Dr. Marianne Taylor, Oncologist

Don Husereau, Health Economist
 Dr. Anil Abraham Joy, Oncologist
 Carole McMahon, Patient Member
 Valerie McDonald, Patient Member Alternate
 Dr. Catherine Moltzan, Oncologist
 Jo Nanson, Patient Member
 Karen MacCurdy Thompson, Pharmacist
 Danica Wasney, Pharmacist

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

- Jo Nanson, Dr. Scott Berry, and Dr. Craig Earle, who were not present for the meeting
- Dr. Catherine Moltzan who did not vote due to a conflict of interest.

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

- Dr. Paul Hoskins and Dr. Allan Grill, who were not present for the meeting
- Dr. Catherine Moltzan who did not vote due to a conflict of interest
- Jo Nanson who did not vote because of her role as a patient member alternate
- Dr. Scott Berry, who was not present for the voting.

Avoidance of conflicts of interest

All members of 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 for follicular lymphoma, through their declarations, 8 members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members 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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