

pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

The 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-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation

Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Obinutuzumab (Gazyva)

Submitted Funding Request: In combination with chlorambucil for previously untreated chronic lymphocytic leukemia (CLL) where fludarabine-based therapy is considered inappropriate

Submitted By:
Hoffmann-La Roche Limited

Manufactured By:
Hoffmann-La Roche Limited

NOC Date:
November 25, 2014

Submission Date:
August 11, 2014

Initial Recommendation:
January 9, 2015

Final Recommendation:
January 27, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding obinutuzumab (Gazyva) in combination with chlorambucil in patients with previously untreated chronic lymphocytic leukemia (CLL) and adequate renal function, for whom fludarabine-based treatment is considered inappropriate.

The Committee made this recommendation because it was satisfied that there is a net clinical benefit of obinutuzumab plus chlorambucil compared with chlorambucil monotherapy based on improvements in overall survival and progression-free survival and has a manageable toxicity profile. pERC was also satisfied that obinutuzumab plus chlorambucil is cost-effective compared to chlorambucil monotherapy in this patient setting.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Optimal Sequencing of Obinutuzumab and Other Therapies Unknown
pERC concluded that the optimal sequencing of obinutuzumab and other therapies in previously untreated CLL is currently unknown. In the absence of direct evidence, pERC was unable to make an informed recommendation. However, pERC recognized that the provinces will need to address this issue upon implementation of obinutuzumab plus chlorambucil funding in the first-line setting and noted that collaboration among provinces to develop a common approach would be of value.

Time-Limited Need for Obinutuzumab Plus Chlorambucil

At the time of implementing a funding recommendation for obinutuzumab plus chlorambucil, jurisdictions may consider addressing the short-term, time-limited need for obinutuzumab plus chlorambucil for patients who are currently receiving other therapies for first line treatment of CLL. pERC noted that this time-limited access should be for patients who would otherwise meet the eligibility criteria for obinutuzumab plus chlorambucil.

Affordability Will Likely Impact Adoption Feasibility

pERC concluded that obinutuzumab plus chlorambucil is cost-effective compared to chlorambucil based on the information provided. However, the Committee acknowledged that individual provinces will need to consider the potentially large budget impact of funding obinutuzumab plus chlorambucil as the cost of the drug and the number of patients that may be eligible for treatment could be high.

Uncertainty of Cost-Effectiveness Compared to Bendamustine

pERC noted that the provinces may need to consider the cost-effectiveness of obinutuzumab plus chlorambucil compared to bendamustine in this setting. pERC, however, also noted that at this time there is no direct evidence comparing the efficacy of obinutuzumab plus chlorambucil versus bendamustine. While there is an indirect comparison of these therapies, pERC agreed that there cannot be confidence in the results due to a number of methodological limitations of this cross trial comparison.

SUMMARY OF pERC DELIBERATIONS

Chronic lymphocytic leukemia (CLL) is a common leukemia with a long natural history. Therefore, the burden of illness for patients with this disease can be substantial. pERC discussed that in the first-line treatment setting of CLL, medically-fit patients are often treated with fludarabine-based regimens such as FCR (fludarabine, cyclophosphamide, rituximab). Patients who are not candidates for fludarabine are frequently treated with chlorambucil and more recently bendamustine monotherapy. Where available, patients may also receive chlorambucil plus rituximab. While patients not eligible for fludarabine therapy have other treatment options available, pERC acknowledged the need for more effective and more tolerable treatments in this patient population.

pERC deliberated upon the results of one large randomized controlled trial (CLL11) that compared obinutuzumab plus chlorambucil (ObChl), rituximab plus chlorambucil (RChl), and chlorambucil monotherapy (Chl). pERC determined that there was an overall net clinical benefit for ObChl compared to Chl. This was based on a statistically and clinically significant improvement in both overall survival and progression-free survival in patients with CLL in favour of the ObChl arm compared to the Chl arm. pERC agreed with the Clinical Guidance Panel (CGP) that the magnitude of benefit was meaningful. pERC also noted that there was a statistically significant improvement in progression-free survival in patients receiving ObChl vs. RChl. There was no significant difference in overall survival for ObChl compared to RChl; however, the median overall survival had not been reached for any of the treatment arms at the time of the published analysis. pERC discussed the specific eligibility criteria in the CLL11 study, which included a Cumulative Illness Rating Scale (CIRS) score >6 or creatinine clearance of 30-69 ml per minute. It was pERC's understanding that the CIRS score is not commonly used in Canadian practice, but they acknowledged that adequate renal function is a key criterion for eligibility for treatment with obinutuzumab plus chlorambucil. pERC concluded that eligibility should be left to the treating physician, however, adequate renal function should be considered.

pERC discussed the toxicity profile of obinutuzumab and noted that there were more infusion reactions in the ObChl arm compared to the other 2 treatment arms; however, these reactions typically only occurred in the first cycle of treatment. pERC agreed with the Clinical Guidance Panel (CGP) that the infusion reactions were predictable and manageable in centres with experience in administering anti-CD20 monoclonal bodies. There were no deaths associated with infusion reactions. The rates of infection (grade 3-5) in the CLL11 study were similar among the 3 arms. While quality of life data were collected in the study, detailed information was not reported. The Committee expressed a strong interest in having access to better quality of life data in large trials being used for funding and regulatory decisions, such as the CLL11 trial. pERC acknowledged that, from available data, there was no deterioration in quality of life with ObChl compared to Chl alone. Based on the improvement in overall survival and progression-free survival, and manageable toxicity compared to chlorambucil monotherapy, pERC concluded that there was an overall net clinical benefit of obinutuzumab plus chlorambucil in previously untreated patients with CLL who are not suitable for treatment with fludarabine.

pERC deliberated on the alignment of obinutuzumab plus chlorambucil with patient values. The Committee reviewed input from 3 patient advocacy groups on patient and caregiver experiences. pERC noted that the high quality of the patient input, which was well structured and organized, provided pERC with a rich understanding of patients' experiences with CLL and its treatment. pERC noted that patients with CLL may experience prolonged periods of "watch and wait" while others require treatment right away. Patients with elevated white blood cell counts most frequently experienced fatigue and enlarged lymph nodes. pERC discussed that patients wanted to have longer remissions, more choice in treatment options, and manageable toxicity. pERC also recognized the challenges that caregivers experience when caring for ill loved ones over long periods of time, including exhaustion, stress, anxiety, and financial burden. pERC concluded that obinutuzumab plus chlorambucil aligns with patient values, as it provides a significant improvement in survival compared to chlorambucil, it offers patients another choice in first-line treatment for CLL, and has a manageable toxicity profile.

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

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the potential cost-effectiveness of obinutuzumab plus chlorambucil in comparison with chlorambucil alone and determined that it was cost-effective. pERC agreed with the Economic Guidance Panel's (EGP's) incremental cost effectiveness estimates for ObChI versus ChI as the EGP believed the economic model provided was valid. The EGP considered multiple scenarios that consistently resulted in a favourable cost-effectiveness estimate. While it is not clear what treatments patients will receive in the second-line setting, pERC noted that the submitted model assumed that patients progressing on the chlorambucil arm would receive additional costly treatments in the second-line setting. pERC noted that this substantially increased costs in the chlorambucil arm but concluded that this is not expected to have a large impact on the cost-effectiveness estimates. In addition, pERC agreed with the EGP's cost-effectiveness estimates for ObChI compared to RChI, and concluded that, in this scenario, ObChI was cost-effective as well. pERC also noted that the cost-effectiveness of ObChI compared to bendamustine is unknown, although bendamustine could be considered a reasonable comparator. Finally, pERC acknowledged the potential budget impact of obinutuzumab plus chlorambucil is unknown given the significant cost of the drug and the uncertainty in the number of patients who are not suitable to receive fludarabine-based therapy.

pERC considered the feasibility of implementing a funding recommendation for obinutuzumab plus chlorambucil. The Committee noted that obinutuzumab is associated with substantial infusion reactions particularly during the first infusion. For this reason, pERC noted the importance of treatment administration at centres with experience administering anti-CD20 monoclonal bodies.

pERC noted the Provincial Advisory Group's (PAG) concern regarding the relative place in therapy of obinutuzumab plus chlorambucil compared to other new therapies that are expected in the next 12 months. pERC concluded that an overview of all available therapies for CLL may be helpful at a future date to understand the comparative effectiveness. The Committee, however, noted that the current review is based on the evidence presented for obinutuzumab plus chlorambucil and must be considered on its own merits. pERC agreed there are no data available to comment on the optimal sequencing of anti-CD20 agents. The efficacy of obinutuzumab plus chlorambucil in other lines of therapy was not within the scope of the current review pERC acknowledged that the overall survival outcomes for ObChI versus RChI may be of particular interest to the provinces, as there is a subsequent entry biologic for rituximab expected in the future. That comparison was outside of the scope of the current review and pERC's recommendation, but could be pursued when mature data become available.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from three patient advocacy groups (CLL Patient Advocacy Group, The Leukemia & Lymphoma Society of Canada, and Lymphoma Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- three patient advocacy groups (Lymphoma Canada, CLL Patient Advocacy Group, and Leukemia & Lymphoma Society of Canada)
- the Submitter (Hoffmann-La Roche Limited)

The pERC initial recommendation was to fund obinutuzumab (Gazyva) in patients with previously untreated chronic lymphocytic leukemia (CLL) and adequate renal function, for whom fludarabine-based treatment is considered inappropriate

Feedback on the pERC Initial Recommendation indicated that the manufacturer, patient advocacy groups and pCODR's Provincial Advisory Group agreed with the initial recommendation.

The pERC Chair and designated pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of this review is to evaluate the safety and efficacy of obinutuzumab (Gazyva) in combination with chlorambucil compared to an appropriate comparator in patients with previously untreated chronic lymphocytic leukemia (CLL), for whom fludarabine treatment is considered inappropriate.

pCODR review scope

The objective of this review is to evaluate the safety and efficacy of obinutuzumab (Gazyva) in combination with chlorambucil compared to an appropriate comparator in patients with previously untreated chronic lymphocytic leukemia (CLL), for whom fludarabine treatment is considered inappropriate.

Studies included: One large three-armed randomized trial

The pCODR systematic review included one open-label three-armed randomized controlled trial CLL11 (Goede et al, 2014, n=781) comparing obinutuzumab + chlorambucil (ObChI, n=238) vs. chlorambucil monotherapy (ChI n=118) in stage 1a of the trial, rituximab + chlorambucil (RChI, n=233) vs. ChI (n=118) in stage 1b of the trial, and ObChI (additional 95 patients for a total of n=333) vs. RChI (additional 97 patients for a total of n=330) in stage 2. Patients were previously untreated for CLL and were considered unsuitable treatment with fludarabine.

The pCODR review also provided contextual information on the appropriateness of an indirect comparison across CLL11 and other trials assessing the efficacy of ObChI and other relevant comparators, including bendamustine monotherapy, and ofatumumab plus chlorambucil. The Clinical Guidance Panel (CGP) concluded that given the differences in patient populations and systematic differences in dosing of

chlorambucil among trials, an indirect comparison would not be appropriate. Therefore, pERC concluded that it was unable to determine the relative effectiveness of obinutuzumab in comparison to these other relevant treatment options through an indirect comparison.

pERC agreed with the CGP that RChI is also available for patients in some jurisdictions. Therefore the Committee concluded that RChI is likely used somewhat broadly in clinical practice and constitutes a clinically relevant treatment option for patients for whom fludarabine based therapy is inappropriate.

Patient populations: Older patients with comorbidities, considered ineligible for fludarabine

Baseline demographic and diagnostic/prognostic characteristics were well balanced between the treatment arms. The eligibility criteria for the CLL11 study included patients with a Cumulative Illness Rating Scale (CIRS) score > 6 (CIRS range, 0 to 56, with higher scores indicating worse health status) or a creatinine clearance of 30 to 69 ml per minute. The median age of patients across the three arms was 73 years, median CIRS score was 8 at baseline, and 82% of patients had > 3 coexisting conditions. Differences in the treatment arms were noted in circulating lymphocyte counts with patients in the RChI arm having a significantly higher proportion of low lymphocyte counts. pERC discussed the specific eligibility criteria in the CLL11 study, which included a Cumulative Illness Rating Scale (CIRS) score >6 or creatinine clearance of 30-69 ml per minute. It was pERC's understanding that the CIRS score is not commonly used in Canadian practice, but they acknowledged that adequate renal function is a key criterion for eligibility for treatment with obinutuzumab plus chlorambucil. pERC concluded that eligibility should be left to the treating physician, however, both fitness for fludarabine-based therapy and adequate renal function should be considered. Guidance on what constitutes adequate renal function for the safe administration of obinutuzumab can be obtained from the product monograph and input from local physician experts who have experience administering and managing anti-CD20 therapies.

Key efficacy results: Clinically significant improvement in overall survival and progression-free survival

pERC noted the significant improvement in overall survival (OS) for ObChI compared to ChI (hazard ratio (HR) 0.41, 95%CI: 0.23-0.74, p=0.002) in the CLL11 study. pERC agreed that the magnitude of the survival benefit is both statistically significant and clinically meaningful. Though slight imbalances between treatment arms were present in the baseline prognostic markers of CLL, pERC agreed that it is unlikely these differences would impact the conclusions of the study. There was no overall survival benefit seen when ObChI was compared with RChI, however, medians for OS had not been reached for any arm of the study at the time of the analysis.

In addition to the improvement in overall survival, pERC discussed the significant improvement in progression-free survival (PFS) in the ObChI treatment arm in comparison to the ChI arm. PFS was the primary outcome of the study. Median PFS was 26.7 vs. 11.1 months for ObChI vs. ChI, respectively (hazard ratio (HR) 0.18, 95% CI: 0.13-0.24, p<0.001). This benefit was seen in all analyzed subgroups, except in patients with del(17)p. However, there were only 42 patients in the del(17)p subgroup, so it was insufficiently powered to detect a difference in survival in this subgroup. In stage 2 of the study, there was a significant prolongation in PFS of 26.7 vs. 15.2 months in the in ObChI vs. RChI arms, respectively (HR 0.39, 95% CI=0.31-0.49, p<0.001), representing an improvement of 11.5 months. PFS results were confirmed by an independent review committee. pERC agreed that these results were clinically significant.

There was also a significant improvement in PFS for patients in the RChI arm compared to those in the ChI arm (with median PFS of 16.3 vs. 11.1 months for RChI vs. ChI, respectively HR 0.44, 95% CI: 0.34-0.57, p<0.001).

Quality of life: Limited reporting, no differences among treatment arms

No statistically significant differences were noted among arms for both safety and global measures of quality of life, however the study was not powered to detect differences in these parameters. While the study reported no deterioration in quality of life in the ObChI arm, specific details of this analysis were not available.

pERC noted that improvement in quality of life is an important outcome for patients. While quality of life data were collected in the study, there was limited reporting of the data in the study publication. The

Committee agreed that additional quality of life data would likely provide a greater understanding of the full effect of ObChI on patients' quality of life.

Safety: Increased but manageable and predictable toxicity profile

pERC discussed the toxicity profile of ObChI and RChI compared to ChI and noted that the proportions of patients who died during stage 1 of the trial due to adverse events were 9%, 15%, and 20% for the ObChI, RChI, and ChI arms respectively. The proportions of deaths in stage 2 for the ObChI and RChI arms were similar to those in stage 1. As were deaths due to adverse events in stage 2 occurred in 4% vs. 6% of patients in the ObChI vs. RChI arms, respectively. pERC considered these rates to be comparable between study arms and to therapies in current use.

While patients in the ObChI arm had higher rates of infusion reactions compared to those in the RChI arm, no deaths were reported due to this adverse event. pERC also noted that clinicians who treat CLL are familiar with infusion-related reactions due to the widespread use of other monoclonal antibodies such as rituximab. pERC considered the clinical significance of the increased rates of neutropenia in the ObChI arm compared to other arms. The Committee agreed that while rates of neutropenia were higher, the rate of febrile neutropenia was low (2%), suggesting this toxicity was manageable. Other clinically relevant toxicities were balanced between the groups.

pERC noted that infections were reported more frequently in the monoclonal antibody treatment arms, but did not differ significantly between treatment arms or stage of the trial. Rates of grade 3 to 5 infection ranged from 11% to 14%. No cases of progressive multifocal leukoencephalopathy (PML) were reported in the ObChI arm.

Need: Improved efficacy and reduced toxicity profile

pERC noted that in the first-line treatment of CLL, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is the standard of care for younger, otherwise healthy patients, but due to significant toxicity, this regimen is often deemed unsuitable for older or less medically-fit individuals. As CLL primarily affects older individuals (median age 72 years at diagnosis), most patients may also not be candidates for stem cell transplants. Those patients who are not candidates for fludarabine-based regimens often receive treatments such as chlorambucil. Bendamustine monotherapy has been widely adopted in this population. pERC noted that some patients may be considered too frail to be treated with bendamustine and may benefit from alternative treatment options with more tolerable side effects. Rituximab plus chlorambucil is also available for patients in some jurisdictions and is likely used more broadly in clinical practice. pERC agreed this combination therapy constitutes a clinically relevant treatment option for patients in whom fludarabine based therapy is inappropriate. In considering the available treatment options, pERC agreed that there is a need for more effective and better tolerated agents that demonstrate a clinical benefit relative to treatments currently used in clinical practice.

The Committee agreed that ObChI met this need as it was associated with clinically and statistically significant improvements in PFS and OS in comparison to ChI. ObChI also provided a clinically and statistically significant improvement in PFS when compared to RChI while no OS benefit has yet been demonstrated. While toxicities were increased for patients treated with ObChI, the Committee agreed that they were expected and manageable.

PATIENT-BASED VALUES

Experiences of patients with CLL: Anxiety of “watch and wait” for both patients and caregivers

Patient advocacy group input indicated that patients with CLL may experience prolonged periods of “watch and wait” while others require treatment right away. Fatigue, increased white blood cell count and enlarged lymph nodes were noted to be the disease symptoms that have significant impact on their quality of life. These were also the most important disease symptoms patients would like controlled with any new treatment.

Input from caregivers discussed the impact of CLL on caregiver's quality of life both in terms of the stress associated with watching a loved one coping with the illness and the financial/social impact of additional responsibilities in caring for an ill loved one. pERC appreciated the information provided regarding both

the patient and caregiver experiences, and noted the importance that patients and caregivers placed not only on overall survival, but on progression-free survival as well.

Patient values on treatment: Longer remission, more treatment options, minimal toxicity

Patients indicated value in having a treatment option that will offer disease control, deeper and longer lasting remissions and an improved quality of life while offering minimal toxicity and manageable side effect profiles relative to other treatments. Patients expressed a desire to access targeted therapies with proven efficacy in treating a broad range of patients, including those that have the poorest prognostic factors and those who are older age with existing co-morbidities. A large proportion of patients expressed the view that choice in treatment is very important based on the known side effects and expected outcomes of a drug. Patients indicated that they would be willing to tolerate side effects if they could live longer, achieve remission, have control of their disease and have an improved quality of life.

pERC considered the current experiences of patients receiving treatment for CLL, and noted that the most common treatment-related side effects experienced with current therapies were fatigue and low blood counts. Patients experienced both positive (disease control) and negative side effects (disease progression; adverse events; dose interruptions due to side effects) associated with current treatment options. In the majority of instances, most patients stated that their experience with the treatment was negative if their remission lasted less than 2 years.

Sixteen of the patients surveyed by patient groups had direct experience with obinutuzumab. pERC noted this was a small sample size, but provided helpful information. The majority of patients noted that ObChI improved their symptoms associated with enlarged lymph nodes, low blood counts, and fatigue. While there are side effects associated with obinutuzumab, respondents reported that they were quickly resolved and that the drug regimen has changed their long-term health and well-being, and for the most part had provided improvement in their quality of life.

ECONOMIC EVALUATION

Economic model submitted: Cost effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-effectiveness and cost-utility analysis of ObChI vs. ChI and RChI vs. ChI, in previously untreated patients with chronic lymphocytic leukemia (CLL) for whom fludarabine-based therapy is considered inappropriate.

Basis of the economic model: Clinical and economic inputs

Costs considered in the analysis included drug costs, administration costs, supportive care, subsequent treatment costs, and adverse event costs.

The key clinical outcomes considered in the analysis included progression-free survival, overall survival, adverse events, and utility estimates from the CLL11 study.

Drug costs: Flat dosing for obinutuzumab

Obinutuzumab costs \$5,275.54 per 1,000 mg vial. At the recommended dose of 1,000 mg on days 1, 8, and 15, followed by 1,000 mg on day 1 of cycles 2-6, obinutuzumab costs \$565.23 per day and \$15,826.50 per 28 day on cycle 1 and \$188.41 per day and \$5275.50 per 28 day cycle for subsequent cycles. pERC noted that drug wastage is not anticipated to be an issue as administration of the drug is based on a flat dose regardless of patient's weight or body surface area. The cost of obinutuzumab is based on the list price submitted by the manufacturer.

Rituximab costs \$453.10 for a 100 mg vial, and \$2,265.50 for a 500 mg vial. At the recommended dose of 375 mg/m² on day 1 of cycle 1, followed by 500 mg/m² on day 1 of cycles 2-6, rituximab costs \$103.16 per day and \$2888.51 per 28 day cycle for cycle 1 and \$137.55 per day and \$3851.35 per 28 day cycle for subsequent cycles.

Chlorambucil costs \$1.44 per 2 mg tablet. At the trial recommended dose of 0.5mg/kg on days 1 and 15, chlorambucil costs \$1.79 per day and \$50.22 per 28 day cycle.

Bendamustine costs \$312.50 and \$1,250.00 per 25mg/vial and 100mg/vials. At the recommended dose of 100mg/m² iv on days 1 & 2 every 28 days, bendamustine costs \$151.79 per day and \$4,250.00 per 28 day cycle.

Cost-effectiveness estimates: Cost-effective compared to chlorambucil monotherapy

pERC deliberated upon the cost-effectiveness of obinutuzumab plus chlorambucil compared to chlorambucil monotherapy and discussed the pCODR Economic Guidance Panel's (EGP) critique of the submitted model and cost-effectiveness estimates. pERC agreed with the EGP's re-analysis estimates and concluded that ObChI was cost-effective compared to ChI and RChI. pERC agreed with the EGP's conclusion that a 10 year time horizon was appropriate for the submitted model and that the main cost drivers were overall survival, cost of obinutuzumab, time horizon, and post-progression survival.

pERC discussed the uncertainties highlighted by the EGP, including immaturity of the overall survival data from CLL11 study, post-progression survival estimates, and potential uncertainty regarding second-line therapy. For the comparison of obinutuzumab plus chlorambucil versus chlorambucil monotherapy, the EGP conducted reanalyses using the upper bound of the 95% confidence interval for overall survival. Additionally, for the comparison of obinutuzumab plus chlorambucil to rituximab plus chlorambucil, the EGP wanted to explore the impact of no benefit in overall survival between the two treatments as the 95% confidence interval crossed 1.0. The EGP also analyzed the impact of post-progression survival and conducted a reanalysis by changing the hazard ratio for overall survival to 1.0 after the end of the clinical trial period. pERC noted that these multiple scenarios considered by the EGP did not significantly impact the cost-effectiveness estimates and concluded that obinutuzumab is cost-effective. pERC, however, noted that even though the economic model demonstrated an ICER that is considered to be cost-effective, the results of the model are dependent on the treatments that patients receive in second-line therapy. The economic model assumed that patients receiving chlorambucil would progress and receive additional costly treatments in the second-line setting, driving up the cost in the chlorambucil arm of the model. Currently, the treatment options in second-line and the number of patients receiving second-line therapy is uncertain.

pERC also noted that the EGP provided re-analysis estimates for the ObChI vs RChI comparison. pERC agreed with the EGP's estimates and concluded that ObChI is cost-effective when compared to RChI. This model had a similar design to the ObChI versus ChI model. pERC noted that there was no cost-effectiveness analysis comparing ObChI to bendamustine monotherapy, which is also a relevant comparator. Thus the cost-effectiveness of ObChI compared to bendamustine is unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Comparative efficacy with other treatment options unknown

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for obinutuzumab plus chlorambucil. pERC noted the Provincial Advisory Group's (PAG) concern on the relative merit of obinutuzumab plus chlorambucil in a landscape that is rapidly changing with new therapies expected in the next 12 months. pERC noted that evaluation of evidence in this review is based on the evidence presented for ObChI. pERC also noted that evidence was available through the CLL11 trial that addressed the comparative efficacy of ObChI to RChI, a treatment option that is relevant to the Canadian clinical practice setting. pERC, however, noted that direct comparative evidence was not available in comparison to bendamustine monotherapy. pERC, acknowledged that a future overview of all available therapies for CLL would be helpful to determine comparative effectiveness with other relevant and upcoming therapies.

pERC noted that the present review considered only the use of obinutuzumab in previously untreated patients with CLL for whom fludarabine-based therapy is inappropriate. pERC noted that the management of small lymphocytic lymphoma (SLL) is identical to that of CLL as they are generally considered to be the same disease. The use of obinutuzumab in CLL patients who are previously untreated and may qualify for FCR or the use of obinutuzumab in previously treated patients was not addressed. Therefore, pERC was unable to comment on the efficacy of obinutuzumab plus chlorambucil in other lines of therapy. pERC also noted that there is currently no information on the optimal sequencing of anti-CD20 agents nor the use of obinutuzumab in combination with other alkylating agents, other than chlorambucil.

pERC noted that wastage will not be a concern as obinutuzumab is administered as a flat dose regardless of the patient's weight or body surface area. pERC however acknowledged that additional health care resources would be required in terms of chemotherapy chair time and nursing resources, particularly in the first cycle where patients require one dose per week for 28 days. pERC noted that there is no evidence to support the use of obinutuzumab beyond the recommended 6 cycles nor as a maintenance therapy. pERC noted the increased rate of grade 3 or greater adverse events with the use of obinutuzumab, primarily due to infusion reactions, and agreed that monitoring for infusion related reactions and other adverse reactions will require additional hospital resources. pERC also noted that the first infusion with obinutuzumab should be undertaken in treatment facilities with familiarity in the usage of monoclonal antibody therapy.

pERC noted that no cases of progressive multifocal leukoencephalopathy (PML) or hepatitis B reactivation were reported in the obinutuzumab arm of the CLL11 trial.

pERC agreed that due to the similarity in the names of obinutuzumab with other new drugs for CLL, jurisdictions may consider labelling obinutuzumab using Gazyva, its brand name. pERC noted that this may help to avoid possible prescribing and/or administration errors.

pERC noted that the budget impact analysis was most sensitive to an increase in price of the drug, the proportion of patients considered eligible for the treatment, and the proportion of patients ineligible for fludarabine-based therapies. pERC, however, noted that as new agents are entering this therapeutic area, market shares have the potential to change rapidly, including these agents that are not currently in use. Therefore, an accurate assessment of the budget impact of obinutuzumab may not have been provided in the submitted analysis.

DRUG AND CONDITION INFORMATION

Drug Information	<ul style="list-style-type: none"> Humanized type II anti-CD20 monoclonal antibody 25mg/mL (1000mg/40mL) reviewed by pCODR Recommended dosage of 1000 mg administered as an intravenous infusion on Day 1-2, Day 8, and Day 15 for the first 28 day treatment cycle followed by a fixed dose of 1000 mg administered on Day 1 for each subsequent treatment cycle (Cycles 2 to 6)
Cancer Treated	<ul style="list-style-type: none"> Previously untreated chronic lymphocytic leukemia
Burden of Illness	<ul style="list-style-type: none"> Most common leukemia in western countries with age-adjusted incidence rate of 4.2 cases/100, 000 population and median age at diagnosis of 72 years Due to advanced age or presence of co-morbidities, patients may not be considered fit enough to receive fludarabine, chlorambucil and rituximab (FCR) (standard of care in first line)
Current Standard Treatment	<ul style="list-style-type: none"> Single agent Chlorambucil Single agent Bendamustine Rituximab + chemotherapy (not the standard of care in most jurisdictions but likely used in clinical settings)
Limitations of Current Therapy	<ul style="list-style-type: none"> Limited effectiveness or tolerability of available treatment options in older or less medically fit patients who are not eligible for fludarabine based therapy.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
 Dr. Maureen Trudeau, Oncologist (Vice-Chair)
 Dr. Scott Berry, Oncologist
 Bryson Brown, Patient Member
 Dr. Matthew Cheung, Oncologist
 Mario de Lemos, Pharmacist
 Dr. Sunil Desai, Oncologist
 Mike Doyle, Economist

Dr. Bill Evans, Oncologist
 Dr. Allan Grill, Family Physician
 Dr. Paul Hoskins, Oncologist
 Danica Wasney, Pharmacist
 Carole McMahon, Patient Member Alternate
 Jo Nanson, Patient Member
 Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Sunil Desai who was not present for the meeting
- Bill Evans who was excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee 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 chronic lymphocytic leukemia, through their declarations, six 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

The pCODR Expert Review Committee 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 their 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 the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

Use of this recommendation

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