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
This 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: Ofatumumab (Arzerra) **Submitted Funding Request:** In combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and are inappropriate for fludarabine-based therapy.	
Submitted By: GlaxoSmithKline Inc.	**Manufactured By:** GlaxoSmithKline Inc.
NOC Date: October 2, 2014	**Submission Date:** April 14, 2014
Initial Recommendation: October 30, 2014	**Final Recommendation:** January 29, 2015

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding ofatumumab (Arzerra) plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia (CLL) and for whom fludarabine therapy is considered inappropriate. The Committee made this recommendation because, compared with chlorambucil, ofatumumab plus chlorambucil had only a modest progression-free survival benefit, insufficient information on overall survival and quality of life, moderate but significant toxicities in the studied population, and was not cost-effective. The Committee was also uncertain whether there was an unmet need in light of available therapies (e.g. bendamustine or chlorambucil + rituximab) and concluded that ofatumumab only partially aligned with patient values.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	No next steps were identified

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 may 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 within Canada, patients may also receive chlorambucil plus rituximab. While patients unsuitable for fludarabine therapy have a number of treatment options available, pERC acknowledged the need for more effective and more tolerable treatments in this patient population.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	**PATIENT-BASED VALUES**
ECONOMIC EVALUATION	**ADOPTION FEASIBILITY**

pERC deliberated upon the results of one randomized controlled trial, (COMPLEMENT-1, Hillman 2013), and noted an improvement in median progression free survival (PFS) of 9.3 months favouring ofatumumab + chlorambucil over chlorambucil alone. However, pERC agreed with the Clinical Guidance Panel (CGP), who indicated that for patients with previously untreated CLL, an improvement in median PFS of 9.3 months is modest. pERC also noted that an overall survival benefit has not been demonstrated in the study and the median survivals have not been reached. pERC discussed the toxicity profile of ofatumumab + chlorambucil, noting an increase in grade 3 adverse events, particularly for neutropenia and infusion related reactions. The CGP acknowledged these were expected and manageable adverse events. However, pERC was unsure if the added toxicity of ofatumumab was acceptable in the context of the modest benefit in PFS and no demonstrated benefit in overall survival or quality of life. During reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the Committee's interpretation of improvements in PFS with ofatumumab + chlorambucil as being modest. pERC also considered the submitter's overall feedback the Committee's consistency in its interpretation of clinical data in the current review as compared to a previous pCODR review, in particular of bendamustine in a similar population. pERC discussed that while absolute improvements in relevant outcome measures are important, results are interpreted within the Canadian context, considering both the disease and the relevant treatment options available at the time of a review. However, the majority of pERC members agreed with the CGP that for an indolent disease which now has additional treatment options, a 9.3 month improvement in PFS is modest. pERC members concluded that there was insufficient net clinical benefit to recommend funding ofatumumab + chlorambucil.

There was limited reporting of quality of life data and pERC noted that ofatumumab + chlorambucil demonstrated no global quality of life differences compared to chlorambucil alone. In addition to bendamustine, pERC discussed other available treatment options for patients in whom fludarabine based therapy is clinically inappropriate. pERC agreed with the Clinical Guidance Panel in that while rituximab-chlorambucil is only funded in a limited number of provinces, this combination therapy is likely used more broadly in clinical practice and constitutes a clinically relevant treatment option for patients in whom fludarabine based therapy is inappropriate. pERC also acknowledged that chlorambucil may have been an appropriate comparator at the time of the study design, however, there is currently no direct evidence comparing ofatumumab + chlorambucil to rituximab-chlorambucil or bendamustine monotherapy. While there are indirect comparisons with some of these therapies, pERC agreed with the CGP that there cannot be confidence in the results due to the limitations of these cross trial comparisons. Although a modest PFS benefit was demonstrated, pERC was not convinced that the magnitude of benefit provided by ofatumumab + chlorambucil as compared to chlorambucil monotherapy was clinically meaningful in light of the added toxicity, lack of demonstrated benefit in overall survival or quality of life, short follow up period for study results, and the availability of other treatment options. Upon reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the appropriateness of the treatment comparators used by pERC in its initial deliberations. pERC re-iterated that chlorambucil monotherapy and bendamustine monotherapy are the currently accepted standards of care for patients for whom treatment with a fludarabine based regimen is clinically inappropriate. pERC noted that their deliberations on the net clinical benefit of ofatumumab + chlorambucil were based on the results of the COMPLEMENT-1 study which made a direct comparison to chlorambucil monotherapy. pERC was unable to

comment on the comparative efficacy to bendamustine monotherapy as an indirect comparison was not methodologically appropriate. While pERC acknowledged that bendamustine monotherapy is limited to a "fitter" patient population in clinical practice, there was insufficient evidence presented to suggest that ofatumumab + chlorambucil was efficacious in a specific subgroup of less fit patients. Additionally, the Committee agreed with the CGP that clinical treatment practices change over time and may not always be reflected in the currently accepted standard of care. Therefore, pERC agreed that a clinically relevant treatment option such as rituximab + chlorambucil should be considered relevant comparators within its deliberation process. However, this regimen was not the only or principal comparator considered by pERC in its deliberations.

Upon reconsideration of the initial recommendation, pERC also considered feedback from the submitter regarding the lack of a full publication on the results of the COMPLEMENT-1 study and the potential impact this may have had on the Committee's decision to not recommend funding ofatumumab-chlorambucil. pERC noted that the status of the publication was not a major factor in its deliberations as sufficient information had been provided throughout the review for the Committee to feel confident in their understanding of the trial design and results, although more details on the quality of life evaluation and results would have been helpful. pERC also noted feedback from the submitter questioning the procedural fairness of the steps during the current review. pERC agreed that while it relies on the CGP for interpretation of clinical data, the Committee deliberates and makes its own assessment of the presented evidence. Any procedural disagreements that may arise within a review should be explored through the pCODR Procedural Review mechanism.

pERC discussed patient values and acknowledged that while the availability of ofatumumab + chlorambucil would provide patients with an additional treatment option, the Committee noted that the lack of a demonstrated survival benefit and improvement in quality of life did not fully align with patient expectations for a new therapy. Overall, pERC considered that ofatumumab + chlorambucil aligned only partially with patient values. Upon reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the alignment of ofatumumab + chlorambucil with patient values. pERC re-iterated that ofatumumab + chlorambucil only partially aligned with stated patient values since there was a lack of a demonstrated survival benefit and improvement in quality of life, although ofatumumab + chlorambucil provides a potential additional treatment option.

pERC noted that the quality of the patient input, which was well structured and organized, provided pERC with a better understanding of patients' experiences with CLL and its treatment. pERC noted that feedback was not provided by eligible patient groups on the initial recommendation and agreed that feedback would have been helpful to the Committee's re-deliberations to better understand what patients consider to be a meaningful PFS benefit in this patient population.

pERC discussed the cost-effectiveness of ofatumumab + chlorambucil in the first line treatment of CLL. The Committee noted the Economic Guidance Panel`s (EGP) re-analysis estimates and agreed with changes made to adjust for the short follow up period of the study, the use of a more clinically plausible time horizon for patients, and the incorporation of longer treatment duration. In addition to the drug costs, pERC noted these factors had the largest impact on the re-analysis estimates, which were considerably higher than the manufacturer's estimates. pERC agreed that the EGP's re-analysis estimates were more reliable than those provided by the submitter and concluded that ofatumumab + chlorambucil is not cost-effective compared with chlorambucil alone.

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for ofatumumab + chlorambucil. pERC noted the Provincial Advisory Group's (PAG) concern regarding the relative merit of ofatumumab + chlorambucil compared to other new therapies that are expected in the next 12 months. pERC concluded that an overview of all available therapies in CLL may be helpful at a future date to understand the comparative effectiveness of the new therapies. The Committee, however, noted that the current review is based on the evidence presented for ofatumumab + 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. Lastly, the efficacy of ofatumumab + chlorambucil in relapsed or refractory disease was not within the scope of the current review.

EVIDENCE IN BRIEF

pERC deliberated upon:

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

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (GlaxoSmithKline Inc.)

The pERC initial recommendation was to not recommend funding ofatumumab (Arzerra) plus chlorambucil in patients with previously untreated chronic lymphocytic leukemia (CLL) and for whom fludarabine therapy is considered inappropriate. Feedback on the pERC Initial Recommendation indicated that the manufacturer disagreed with the initial recommendation while pCODR's Provincial Advisory Group agreed with the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The objective of the review was to evaluate the safety and efficacy of ofatumumab (Arzerra) in combination with an alkylating agent as compared to an appropriate comparator in patients with previously untreated chronic lymphocytic leukemia (CLL), for whom fludarabine treatment is considered inappropriate.

Studies included: Data from one RCT available in abstract form

The pCODR systematic review included one open-label randomized controlled trial, COMPLEMENT-1 (Hillman 2013) comparing ofatumumab + chlorambucil (n=221) to chlorambucil (Chl) monotherapy (n=226) in patients with previously untreated chronic lymphocytic leukemia (CLL) who are clinically unsuitable for fludarabine-based therapy. Treatment duration was a minimum of 3 cycles or until best response, up to a maximum of 12 cycles. At the time of the review the study had been published in abstract form, however, sufficient detail was provided by the submitter throughout the review to allow the review team to be able to critically appraise the study design and results, although more details on the quality of life evaluation and results would have been helpful.. Upon reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the absence of a full publication on the results. pERC noted that the publication status was not a major factor in its deliberations.

pERC noted that, within the trial, patients for whom fludarabine treatment is considered inappropriate were classified by the investigator for reasons that included, but were not limited to, advanced age (older than 65 years) or presence of comorbidities. pERC considered that, in addition to age and presence of comorbidities, patients with impaired renal function and/or a Cumulative Illness Rating Scale (CIRS) score > 6, may be considered unsuitable for fludarabine based therapy.

The pCODR review also provided contextual information on the appropriateness of an indirect comparison between COMPLEMENT-1 assessing the efficacy of ofatumumab plus chlorambucil and other relevant comparators (02CLLIII trial: bendamustine monotherapy, CLLL11 trial: obinutuzumab plus chlorambucil). pERC concluded that given 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 ofatumumab in comparison to these other relevant treatment options. pERC agreed with the Clinical Guidance Panel that rituximab-chlorambucil combination therapy is likely used more broadly in clinical practice and constitutes a clinically relevant treatment option for patients in whom fludarabine based therapy is inappropriate. As direct or indirect comparative data were not available, pERC concluded that it was unable to determine the relative

effectiveness of ofatumumab plus chlorambucil in comparison to either bendamustine or chlorambucil + rituximab.

Patient populations: Majority of patients with ECOG 0-1

Population demographics were well balanced between arms. While the COMPLEMENT-1 study did not limit entry criteria based on ECOG PS, the majority of patients had an ECOG PS of 0-1 (92% vs. 91% in the ofatumumab + Chl vs. Chl arms, respectively). A small number of patients had an ECOG PS of 2 (8% in each arm) while no patients had an ECOG PS ≥3. In general, pERC noted that the majority of patients entered into the trial had a good functional status. Disease stage characterization using the Rai system, which provides insight on baseline patient prognosis, showed that 8%, 51%, 40% of patients were in the low, medium and high stage, respectively. Disease stage of patients was balanced between the two arms.

Key efficacy results: Modest improvement in PFS

The key efficacy outcome deliberated on by pERC was progression free survival, the primary endpoint of the COMPLEMENT-1 trial. After a median follow up of 28.9 months, a statistically significant improvement of 9.3 months in median PFS (22.4 vs. 13.1 months, HR=0.57, 95% CI: 0.45-0.72, p<0.001) was observed in favour of the ofatumumab plus chlorambucil arm vs. the chlorambucil alone arm. In agreement with the Clinical Guidance Panel's conclusion, pERC considered this improvement to be modest in this setting of previously untreated patients with CLL. For secondary outcomes, though median survival has not been reached in either arm; the 2 (88.7% vs. 86.7%) and 3 (85.1% vs. 83.2%) year overall survival rates were similar between the ofatumumab + chlorambucil vs. chlorambucil arms, respectively.

pERC considered that ofatumumab demonstrated a modest improvement in progression-free survival compared with chlorambucil while no benefit was seen in overall survival. pERC discussed the value of a 9.3 month improvement in PFS in the absence of survival benefit and in the context of other treatments such as bendamustine monotherapy and rituximab plus chlorambucil in patients unsuitable for fludarabine therapy. pERC was unable to comment on the efficacy of ofatumumab + chlorambucil compared to these therapies. Upon reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the Committee's interpretation of improvements in PFS with ofatumumab + chlorambucil as being modest. pERC discussed that while absolute improvements in relevant outcome measures are important, results must always be interpreted within the Canadian context, considering both the disease and the relevant treatment options available at the time of a review. pERC, therefore, agreed with the CGP that for an indolent disease which now has additional treatment options, a 9.3 month improvement in PFS is modest. pERC also noted that their deliberations on the net clinical benefit of ofatumumab + chlorambucil were based on the results of the COMPLEMENT-1 study which made a direct comparison to chlorambucil monotherapy. pERC also re-iterated that it was unable to comment on the comparative efficacy of ofatumumab + chlorambucil and bendamustine monotherapy as an indirect comparison was not deemed to be methodologically appropriate.

Quality of life: No difference between arms

pERC noted that no differences were seen between arms in terms of global quality of life outcomes. While there were significant differences in emotional functionality and infection subscales in favour of patients receiving ofatumumab + chlorambucil, these differences did not continue beyond the treatment phase. pERC noted that improvement in daily functioning was an important quality of life measure for patients. The study also reported significant improvements in physical functioning in favour of chlorambucil during the follow-up phase. pERC noted that there was limited reporting on quality of life in this study and agreed that follow-up data that have been peer-reviewed may provide greater understanding of the full effect of ofatumumab + chlorambucil on patients' quality of life. Based on the available evidence, the Committee concluded that ofatumumab + chlorambucil did not demonstrate an overall improvement to quality of life.

Safety: Increased neutropenia and infusion related adverse events

pERC discussed the toxicity profile of ofatumumab plus chlorambucil compared to chlorambucil and noted that treatment-related adverse events (> grade 3) were more common in the combination arm although deaths due to adverse events were similar in both arms. Neutropenia (> grade 3) and infusion-related adverse events, however, accounted for much of the difference between the arms, both of which were more common with ofatumumab + chlorambucil. pERC noted that infection complications, including opportunistic infections, were balanced between the arms and no cases of progressive multifocal leukoencephalopathy (PML) were reported.

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 that 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), 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 based on a 13 month increase in PFS over chlorambucil and a reduction in the risk of progression by almost 80% (HR: 0.214). 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 + 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 clinically 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 did not agree that ofatumumab + chlorambucil met this need as it was associated with only a modest improvement in PFS, no overall survival benefit, no difference in quality of life outcomes, and resulted in increased toxicities for patients. Upon reconsideration of the initial recommendation, pERC considered feedback from the submitter regarding the appropriateness of the comparators considered by pERC in its deliberations. pERC re-iterated that chlorambucil and bendamustine monotherapy are the current accepted standards of care for patients for whom treatment with a fludarabine based regimen is inappropriate. pERC agreed there was insufficient evidence to suggest that ofatumumab + chlorambucil was efficacious in a specific subgroup of less fit patients. Additionally, the Committee agreed with the CGP that clinical treatment practices change over time and may not always be reflected in what is deemed the currently stated standard of care. Therefore, pERC affirmed that a clinically relevant treatment options such as rituximab + chlorambucil are considered as a relevant comparators within its deliberative process. However, this regimen was not the only or principal comparator considered by pERC in its deliberations.

PATIENT-BASED VALUES

Experience of patients with chronic lymphocytic leukemia: Significant fatigue and lower quality of life

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 count, enlarged lymph nodes, and night sweats were noted to be the most frequently occurring disease symptoms by patients. The stress of diagnosis, increasing white cell counts, and fatigue have the most impact on patients' lives. Patients' experiences with currently available treatments also vary. Some reported managing their symptoms well with current treatment while others had less favourable experiences. 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 impact of the disease on day-to-day life.

pERC acknowledged patients' experience with CLL and the value of having treatment options that improve or delay deterioration in quality of life. While quality of life reporting was limited in the COMPLEMENT-1 study, pERC noted that there was no difference in global quality of life measures between the two arms. The Committee acknowledged that quality of life was important to patients and agreed that manufacturers should collect and report results of this outcome, preferably in peer-reviewed publications. Based on the available evidence on quality of life, pERC concluded that ofatumumab + chlorambucil only partially aligned with patient values, as it provides another treatment option but not an increase in either survival or quality of life.

Patient values on treatment: Having a choice of treatments important to patients

Patient advocacy group input indicated that patients want treatment options that will extend their life and induce complete remission while maintaining quality of life. Patients indicated the importance of having a treatment option that has reduced toxicity and a side effect profile that is not worse than the disease itself. Patients indicated a greater willingness to tolerate short term side effects, such as nausea, diarrhea, fever, fatigue, and cough, that are manageable with medication, compared to other serious or long term side effects such as tumour lysis syndrome, viral reactivation, bowel obstruction, breathing

difficulties, and irregular heartbeat that require more medical management and monitoring. Upon reconsideration of the Initial Recommendation, pERC noted feedback from the submitter suggested ofatumumab + chlorambucil aligned with the patient value of achieving longer remission. pERC also discussed time to next treatment (TTNT), one of the secondary outcomes from the COMPLEMENT-1 study as being an indicator for longer remission noted by the submitter. In the context of an open label study and better established outcomes such as overall survival and PFS which were identified by the CGP as being outcomes of interest, pERC agreed that the validity of TTNT has not been demonstrated. In addition, longer remission should already be reflected by PFS improvement. The Committee, therefore, concluded that there was insufficient information to consider TTNT as a surrogate outcome for improved survival or quality of life.

pERC considered whether ofatumumab + chlorambucil could be an alternative treatment option for patients, particularly in those who may be considered too frail to be treated with bendamustine and may benefit from alternative treatment options with different side effects. However, pERC noted that there was no evidence evaluating the efficacy of ofatumumab + chlorambucil in this frail population and that COMPLEMENT-1 generally included patients who had better performance status. Overall, the Committee agreed that ofatumumab + chlorambucil did not provide a survival advantage, demonstrated no improvements in quality of life, and was associated with increased toxicity in patients. This led pERC to conclude that ofatumumab + chlorambucil only partially aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: Cost effectiveness and cost-utility analysis

The pCODR Economic Guidance Panel assessed a cost-effectiveness and cost-utility analysis of ofatumumab in combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and for whom fludarabine treatment is considered inappropriate.

Basis of the economic model: Clinical and economic inputs

Costs included drug acquisition costs, monitoring costs, administration costs, adverse event costs, and resource utilization costs for ofatumumab plus chlorambucil as well as subsequent lines of therapy.

The key clinical outcomes considered in the analysis included overall survival, progression free survival, utility estimates and adverse events as from COMPLEMENT-1.

Drug costs: Flat dosing

At the submitted price, ofatumumab costs $3.36/mg and is available in 1000mg/50mL and 100mg/5mL vials. At the recommended dose of 300 mg for the first infusion, followed 1 week later by 1000 mg on day 8, ofatumumab costs $156.00 per day and $4,368.00 per 28 day cycle for the first cycle and $120.00 per day and $3,360.00 per 28 day cycle for the subsequent cycles. pERC noted that ofatumumab is provided as a flat dose, regardless of patient's weight or body surface area. Given that the vial sizes available provide these doses, drug wastage during pharmacy preparation is not a concern.

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

Chlorambucil costs $1.43 per 2mg tablet. At the recommended dose of 10mg/m2 orally days 1-7, chlorambucil costs $3.05 per day and $85.37 per 28 day cycle.

Cost-effectiveness estimates: Time horizon, survival after trial period, treatment duration as key drivers

pERC discussed the cost-effectiveness of ofatumumab + chlorambucil and discussed the EGP's critique of the manufacturer's submitted economic evaluation in the first-line setting. pERC reviewed the incremental cost-effectiveness ratio estimates provided by both the manufacturer and the EGP and agreed with the EGP's estimates. pERC noted that the EGP estimates were considerably higher than the manufacturer's estimates and discussed the assumptions upon which the EGP estimates were based. pERC agreed with the EGP's assessment that the manufacturer's estimated time horizon of 25 years was not

appropriate in this generally older patient population and concluded that a 10 year time horizon was more appropriate. pERC also discussed the EGP's concern with how the submitter had extrapolated overall survival benefit beyond the end of the trial period. Given the relatively short follow up period for the clinical trial, pERC agreed with the EGP's approach to set the hazard ratio for overall survival after the trial period to 1.0 (equal survival between the two treatments, thus, no longer extrapolating the potential benefit of ofatumumab). Lastly, considering that ofatumumab + chlorambucil would be given until best response, pERC agreed with the EGP`sproposed conservative scenario where patients are treated for 9 months, 2 cycles past best response. This was based on input from the CGP. pERC noted that these changes in the estimates of incremental effect had a large impact on the ICER estimate. Therefore, pERC considered that the incremental cost-effectiveness ratio was likely higher than the manufacturer's and concluded that ofatumumab + chlorambucil is not cost-effective relative to chlorambucil alone.

ADOPTION FEASIBILITY

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

pERC discussed factors that could impact the feasibility of implementing a funding recommendation for ofatumumab + chlorambucil. pERC noted PAG`s concern on the relative merit of ofatumumab + 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 ofatumumab + chlorambucil. pERC, however, acknowledged that an overview of all available therapies for CLL may be helpful at a future date to determine the comparative effectiveness with other relevant and upcoming therapies. pERC was also unable to determine the efficacy of ofatumumab + chlorambucil compared to other relevant comparators such as bendamustine monotherapy and chlorambucil + rituximab as direct comparative evidence needed to conduct such an analysis was not available.

pERC noted that the present review considered only the use of ofatumumab in previously untreated patients with CLL. Its use in other populations, including those CLL patients who have been previously treated, those who have received rituximab as part of prior therapy and patients with other B-Cell malignancies (e.g. Mantle Cell Lymphoma) was not addressed. Therefore, pERC was unable to comment on the efficacy of ofatumumab + chlorambucil in other lines of therapy.

pERC noted that infection complications, including opportunistic infections, were balanced between arms and no case of progressive multifocal leukoencephalopathy (PML) was reported in the COMPLEMENT-1 study. pERC also noted that there is currently no information on the optimal sequencing of anti-CD20 agents. Finally, pERC also noted that the incidence and prevalence of CLL, the proportion of those eligible for first-line treatment with ofatumumab plus chlorambucil, treatment duration of ofatumumab and the market share of ofatumumab all had a significant impact on the budget impact analysis.

DRUG AND CONDITION INFORMATION

Drug Information	• Humanized second-generation anti-CD20 monoclonal antibody • 20mg/mL (100mg/5mL and 1000mg/mL) reviewed by pCODR • Recommended dosage of 300 mg administered for the first infusion followed one week later by 1000 mg on day 8 (cycle 1) followed by 1000 mg on day 1 of subsequent cycles until best response or a maximum of 12 cycles (every 28 days).
Cancer Treated	• Previously untreated chronic lymphocytic leukemia
Burden of Illness	• 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	• 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	• 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. Kelvin Chan, Oncologist
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:

- Carole McMahon who did not vote due to her role as a patient member alternate

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

- Scott Berry who was not present for the meeting
- Bill Evans who was not present for the voting
- Kelvin Chan 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

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 Ofatumumab (Arzerra) for Chronic Lymphocytic Leukemia, through their declarations, eight members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and 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

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers 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.

Disclaimer

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report. This document is composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR document).