PAN-CANADIAN ONCOLOGY DRUG REVIEW

Pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Ofatumumab (Arzerra) for Chronic Lymphocytic Leukemia

January 29, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

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

Ofatumumab is a fully humanized second-generation anti-CD20 monoclonal antibody that binds a more proximal domain on the CD20 molecule and binds more tightly than rituximab. Ofatumumab has a Health Canada approval for use in combination with chlorambucil, for the treatment of patients with chronic lymphocytic leukemia (CLL) who have not received prior therapy and for whom fludarabine-based therapy is considered inappropriate.[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label randomised controlled trial, COMPLEMENT-1[2] comparing ofatumumab + chlorambucil (n=221) to chlorambucil (Chl) monotherapy (n=226) in patients with previously untreated chronic lymphocytic leukemia (CLL) for whom fludarabine treatment is considered inappropriate. Patients for whom fludarabine treatment was considered inappropriate by the investigator included, but were not limited to those with advanced age or presence of comorbidities.

Patient characteristics were reported to be well balanced between arms. Although the trial did not limit inclusion of patients by ECOG performance status, the majority of patients had a 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.

Treatment duration was a minimum of 3 cycles or until best response, up to a maximum of 12 cycles. The study has only been published in abstract form.

Efficacy

The primary outcome in the COMPLEMENT-1 study was progression free survival (PFS) with overall response rate (ORR), overall survival (OS), safety/toxicity, and quality of life (QoL) as secondary endpoints.

After a median follow up of 28.9 months, PFS was increased by 9.3 months in favour of the ofatumumab + Chl arm. Median progression free survival was 22.4 vs. 13.1 months in the ofatumumab + Chl vs Chl arms, respectively (HR=0.57 95% CI: 0.45-0.72, p<0.001).

Two and 3 year OS was similar among the ofatumumab + Chl vs Chl arms, respectively ((88.7% and 86.7% at 2 years and 85.1% and 83.2% at 3 years, odds ratio 0.91 (0.57 – 1.43), p=0.666). Overall response was assessed by an independent review committee. Improved response rates were observed in favour of the ofatumumab + Chl arm (82% vs. 69%, OR 2.16 (1.36 – 3.42), p<0.001).

No statistically significant differences were noted between the two treatment arms for global quality of life scale. Statistically significant differences were found in the emotional functionality, B-symptom score and infection scales during the treatment phase in favour of the ofatumumab arm but were not sustained in the follow up phase.

Overall, among the secondary outcomes, while ORR was statistically improved in favour of the ofatumumab arm, OS and global quality of life was similar between the two arms.

Harms

Adverse events leading to death were reported in 23 (11%) vs 14 (6%) of patients in the ofatumumab + Chl arm vs. chlorambucil arm, respectively. However, only 3 and 2 patient deaths, respectively, were deemed to be treatment-related. Infection complications, including opportunistic infections, were balanced between arms and no case of PML was reported.

There was a higher incidence of Grade ≥3 events in the ofatumumab plus chlorambucil arm: Overall 50% versus 43%; treatment related 45% versus 29%; and 10% of patients had Grade ≥3 infusion related reactions. Among the most commonly reported grade 3/4 AE's neutropenia events were more common in the ofatumumab plus chlorambucil arm (Ofa+Chl, 26%; Chl, 15%), whereas the incidence of thrombocytopenia was greater in the chlorambucil monotherapy arm (Ofa+Chl 5%, Chl 10%).

Neutropenia (≥ grade 3) and infusion-related adverse events account for much of the difference between the arms, both of which were more common in the ofatumumab containing arm. Infection complications, including opportunistic infections, were balanced between arms and no case of progressive multifocal leukoencephalopathy (PML) was reported in the study.

1.2.2 Additional Evidence

pCODR received input on ofatumumab (Arzerra) for chronic lymphocytic leukemia from two patient advocacy group, Chronic Lymphocytic Leukemia Patient Advocacy Group (CLL PAG) and the Leukemia and Lymphoma Society of Canada (LLSC). Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

Burden of Illness and Need:

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the western world, and affects 4.2 people/100 000 population per year. Although the disease has an indolent course and most patients can be safely observed without treatment for many years, cure of this disease is not a reasonable expectation and most affected patients will eventually die as a result of their disease. The median survival from the time patients require treatment for CLL is approximately 4 years.

The two classes of drugs most often used to treat CLL are nucleoside analogues and alkylating agents. The majority of CLL patients are however older and not considered suitable candidates for intensive chemotherapy regimens (patients older than 65, with concurrent illnesses, impaired renal function and those with Cumulative Illness Rating Scale (CIRS) score ≥ 6). Older patients have few options and usually receive treatment with single agents, occasionally in combination with rituximab. Chlorambucil, an alkylating agent, has been in use for more than 30 years and can be given in daily, weekly, biweekly and monthly schedules. Bendamustine in previously untreated patients with CLL has been widely adopted in this population based on demonstrated improvements in PFS compared to chlorambucil monotherapy while rituximab, in combination with regimens commonly used to treat CLL, has also been shown to improve overall and progression-free survival. While it is not widely funded, rituximab plus chlorambucil is likely used more broadly in clinical practice and constitutes a clinically relevant treatment option for patients

unsuitable for fludarabine based therapy. The Clinical Guidance Panel agreed that there is currently no data suggesting the optimal use of available therapies in patients for whom treatment with a fludarabine based regimen is inappropriate. Although not uniformly used, chlorambucil monotherapy, bendamustine monotherapy and rituximab-chlorambucil are all valid treatment options in this setting, and the CGP concurred it would be appropriate to include all relevant comparators in addition to chlorambucil monotherapy. Most patients will receive multiple lines of chemotherapy and will experience shorter remissions after each cycle as the disease becomes more resistant to treatment.

Effectiveness:

Patients in the ofatumumab arm achieved a modest nine month improvement in progression-free survival when compared to patients in the standard treatment arm. Differences were largely due to improved response rates in the experimental arm. Two and 3 year overall survival was similar between the two treatment arms. The results of the systematic review suggest that ofatumumab may have a place in the front-line management of patients who are not eligible for fludarabine. However, the relative effectiveness of ofatumumab in combination with chemotherapy compared with rituximab in combination with chemotherapy needs to be determined in this population as well as the relative effectiveness and safety of ofatumumab plus chlorambucil compared with that of bendamustine monotherapy.

Globally no differences were seen between the arms in terms of quality of life. There were significant differences in Emotional Functionality and Infection subscales for patients on treatment but these differences did not persist beyond the treatment phase. During follow up there were no differences in Global QOL measures, but significant improvements were seen in functioning and financial sub-scales in the ofatumumab and chlorambucil arm. The meaning of these differences in an open label study of this design is unclear. Longer range quality of life measures included improved physical functioning in the chlorambucil arm and higher rates of financial burden in the ofatumumab arm.

Safety:

Treatment-related adverse events ($\geq$ grade 3) were more common in the combination arm although deaths due to adverse events were similar. Neutropenia ($\geq$ grade 3) and infusion-related adverse events account for much of the difference between the arms, both of which were more common in the ofatumumab arm.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be net clinical benefit to providing ofatumumab to patients with untreated CLL who are ineligible for treatment with fludarabine. The panel based its conclusion on a single open label, randomized study showing a modest nine month improvement in progression-free survival.

In reaching this conclusion the Panel also considered that:

- The burden of the described treatment, including time to attend for infusions and higher rates of adverse effects, is difficult to justify for in light of the modest benefit reported.
- The quality of life data seems to suggest reduced quality of life in some domains for individuals treated with ofatumumab.
- The panel discussed the appropriateness of having chlorambucil as the comparator, versus bendamustine, and felt that some of the patients in the comparator arm may have been eligible for bendamustine.
- The clinical trial has yet to be fully published and the role of the manufacturer in the design and conduct of the study is difficult to elucidate from the published abstract.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ofatumumab (Arzerra) for previously untreated patients with Chronic Lymphocytic Leukemia who require therapy and for whom fludarabine treatment is considered inappropriate. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding ofatumumab (Arzerra) conducted by the Hematology Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ofatumumab (Arzerra) and a summary of submitted Provincial Advisory Group Input on ofatumumab (Arzerra) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Chronic lymphocytic leukemia (CLL) involves the development of abnormal lymphocytes. In 2010 there were 2,195 new cases of CLL diagnosed, 61% of those cases were male and 39% were female.[3] In 2011, there were 600 deaths related to CLL, 62% of those were male patients and 38% were female.[4] Statistics Canada reported a 5 year relative survival of patients with CLL of 80% (80% for men and 81% for women).[5]

About three quarters of all CLL patients are over the age of 65, and about 50% of all CLL patients are over the age of 75. The incidence of CLL for this group is increasing significantly and median age of diagnosis is 72 years.[6] Although the majority of patients with chronic lymphocytic leukaemia (CLL) are of advanced age, these patients have not been well represented in past clinical trials. The combination of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care for young, otherwise healthy patients given the results of a recent German CLL Study Group study showing improved PFS (51.8 vs. 32.8 months, $p<0.0001$) and OS (87% vs. 83%, $p=0.012$) with the addition of rituximab to FC. [7]

Patients for whom fludarabine treatment is considered inappropriate cannot tolerate toxicity associated with aggressive chemotherapy and are the population of focus in this review. It is estimated that 30-40 percent of CLL patients fall into this category.[8] The addition of anti-CD20 monoclonal antibodies to conventional chemotherapy drugs has resulted in improved overall survival among patients with CLL or indolent lymphoma. Ofatumumab is a human monoclonal antibody that binds specifically to the CD20 loop domains, inducing cell death through complement-dependent cytotoxicity.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of ofatumumab (Arzerra), in combination with chlorambucil, on patient outcomes compared with appropriate comparators in treatment of patients with previously untreated chronic lymphocytic leukemia (CLL), for whom fludarabine treatment is considered inappropriate.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

One trial met the eligibility criteria for this review.[2] Hillmen et al., evaluated ofatumumab in combination with chlorambucil versus chlorambucil alone. Four hundred forty seven patients were included in this study; 226 in chlorambucil monotherapy; 221 in chlorambucil/ofatumumab arm. Population demographic and diagnostic/prognostic characteristics were well balanced between arms with notable differences listed below. 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. Primary endpoint was progression free survival. Overall response rate, overall survival, safety/toxicity, and quality of life were secondary endpoints. Progression free survival was determined to be significantly prolonged (P<0.001) when ofatumumab was added to treatment, with benefits also found in response rate and overall survival. Treatment related ≥ grade 3 AE's occurred in 29% and 45% of patients and there were 2 and 3 deaths in the chlorambucil versus chlorambucil and ofatumumab arms respectively. Neutropenia was the most frequently occurring hematologic AE occurring in 15% versus 26% of patients in the chlorambucil versus chlorambucil and ofatumumab arms respectively. Non hematologic AE's were most frequently reported as rash, nausea, and fever and occurred in ≥5% of patients in each arm. The most common infusion reactions were rash, nausea, hives, and fever occurring in 67% of all cases. No statistically significant differences were noted between arms for both safety and global measures of quality of life. Although some quality of life subscales demonstrated improvement, there is no indication that results were powered to detect differences in subscales.

The main limitations associated with this study are; that it is open label, that it has only been published in abstract form, that there could be limitations on generalizability of results to Canadian patients due to race of populations; that there were slight differences in prognostic characteristics that could create bias in survival and response outcomes, and association investigators had with the submitter. Assessment of disease progression, and response, was undertaken by independent review committee increasing robustness of results.

Table 2. Efficacy Outcomes

Efficacy Outcomes for patients on the COMPLEMENT-1 study [2, 9]				
Median follow up	**Outcome**	**CHL + Ofatumumab**	**CHL**	**Comparative Statistic (95% CI) for HR/OR**
28.9 ms	**Median PFS (95%CI)**	22.4ms (19.0-25.2)	13.1ms (10.6-13.8)	HR=0.57 (0.45-0.72) (p<0.001)
	Overall Response Rate (ORR)	182 (82%)	155 (69%)	OR=2.16 p<0.001 95% CI: 1.36 - 3.42
	Overall Survival (OS)	2 yr-88.7%, 3 yr-85.1%	2 yr-86.7%, 3 yr-83.2%	3 year HR=0.91 (0.57-1.43) p=0.666

Table 3. Safety Outcomes

Safety Outcomes for patients on the COMPLEMENT-1 study[2, 9]		
	CHL + Ofatumumab	CHL
Grade ≥3/ AE's	50%	43%
Treatment-related Grade ≥3 AE	97(45%)	66(29%)
Hematologic (≥3) AEs occurring in ≥ 5% of patients		
	CHL + Ofatumumab	CHL
Neutropenia	57(26%)	34(15%)
Thrombocytopenia	10(5%)	23(10%)
Anemia	11(5%)	12(5%)
All AEs associated with other cytopenias	20 (9%)	8(4%)
SAEs associated with other cytopenias	1 (<1%)	0(0%)
Non -Hematologic occurring in ≥ 5% of patients		
	CHL + Ofatumumab	CHL
Grade ≥3 Infusion Reactions	22(10%)	NA

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team identified the following relevant literature providing supporting information for this review.

The submitter examined whether an indirect comparison of ofatumumab to other current therapies in CLL was appropriate. These other comparators included bendamustine monotherapy, rituximab monotherapy, GA101 in combination with chlorambucil, rituximab in combination with chlorambucil, and rituximab in combination with bendamustine. The submitter concluded that an indirect comparison was not appropriate between the trials, for the following reasons:

- systematic differences in the doses and durations of chlorambucil treatment;
- systematic differences among the patient populations; and
- systematic differences in the definition and ascertainment of the endpoints.

Given the current funding of bendamustine, an assessment was made by the pCODR review team to determine the appropriateness of an indirect comparison between ofatumumab and other relevant comparators. Three trials providing data on these other comparators and with the most relevance to this review are summarized below. In each of the trials, chlorambucil monotherapy was used as the comparator:

- Ofatumumab plus chlorambucil versus chlorambucil in the COMPLEMENT-1 trial[2], a randomized phase III trial. Chlorambucil was dosed at 10 mg/m^2 on days 1-7, every 28 days with a total dose per cycle of 122 mg (study under review in this Clinical Guidance Report)
- Bendamustine versus chlorambucil in the 02CLLIII trial[10], a randomized phase III trial. Chlorambucil was dosed at 0.8 mg/kg orally on days 1 and 15 every 4 weeks, with a total dose per cycle of 112 mg (based on 70 kg).
- Rituximab plus chlorambucil versus obinutuzumab plus chlorambucil versus chlorambucil in the three-arm CLLL11 trial[11], a randomized phase III trial. Chlorambucil was dosed 0.5 mg/kg orally on day 1 and 15 of every 28-day cycle with a total dose per cycle of 70 mg.

Given differences in patient populations and systematic differences in dosing of chlorambucil, it was concluded that an indirect comparison between ofatumumab plus chlorambucil, obinutuzumab plus chlorambucil and bendamustine is not appropriate. This conclusion was supported by the CGP. Further, it was uncertain whether the safety profiles of the three drugs were similar. Due to these differences in the abovementioned three trials, results obtained through an indirect comparison were not considered to be appropriate.

Description of patients and response rates of the above three trials have been summarized in the following tables for information purposes only.

Table 1. Summary of the patients in the intervention arms for studies considered relevant

	Ofatumumab plus chlorambucil	Bendamustine	Obinutuzumab plus chlorambucil
N	221	162	238
Median age (range)	69 (35 – 92)	63 (58-70)	74 (39-88)
WHO/ECOG PS, n (%) **0** **1** **2**	 87 (39) 115 (52) 17 (8)	 113 (69.8) 43 (62.5) 3 (1.9)	 NR Median ECOG PS = 1 NR
Binet stage, n (%) **A** **B** **C**	 77 (35) 74 (33) 70 (32)	 0 116 (71.6) 46 (28.4)	 NR (23) NR (41) NR (36)

WHO = World Health Organization; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NR = not reported

Table 2. Summary of response rates for intervention and control groups for studies considered relevant, n (%)

	COMPLEMENT-1		Knauf et al.		CLL11	
	OChl	Chl	B	Chl	ObChl	Chl
Overall response	NR (82)	155 (69)	110 (68)	48 (31)	NR (75.5)	NR (30.2)
Median progression-free survival (months)	22.4	13.1	21.6	8.3	23.0	10.9

OChl = ofatumumab plus chlorambucil; Chl = chlorambucil; B = bendamustine; ObChl = obinutuzumab plus chlorambucil; NR = not reported

The following table summarizes the safety profile of the three trials considered relevant.

Table 3. Summary of adverse events for intervention and control groups

	COMPLEMENT-1		Knauf et al.		CLL11	
	OChl	Chl	B	Chl	ObChl	Chl
Grade ≥3 AEs	50%	43%	NR	NR	67%	41%
Neutropenia grade ≥3	26%	14%	23%	11%	34%	15%

	COMPLEMENT-1		Knauf et al.		CLL11	
	OChl	Chl	B	Chl	ObChl	Chl
Infusion-related grade ≥3	10%	N/A	NR	N/A	21%	N/A
Infections grade ≥3	15%	14%	1.9%	1%	6%	11%

AE = adverse event; N/A = not applicable

A separate publication in abstract form,[12] conducted by authors with affiliations in the pharmaceutical industry, carried out an indirect treatment comparison of ofatumumab plus chlorambucil versus bendamustine versus obinutuzumab plus chlorambucil. The indirect comparison was done using fixed-effects network meta-analysis. The following are the results of the indirect treatment comparison, which includes HR and 95% confidence intervals obtained from the three trials summarized above:

Table 4. Summary of results of indirect treatment comparisons[13]

	Hazard ratio	95% confidence interval
Obinutuzumab plus chlorambucil versus bendamustine	0.53	0.35-0.77
Obinutuzumab plus chlorambucil versus ofatumumab plus chlorambucil	0.33	0.22-0.47

Conclusion

A brief assessment of the appropriateness of an indirect comparison between ofatumumab plus chlorambucil and relevant comparators was done by the pCODR review team and concluded that due to differences in patient populations and systematic differences in dosing of chlorambucil, an indirect comparison is not appropriate. This conclusion was supported by the CGP. Further, it was uncertain whether the safety profiles of the three drugs were similar. Due to these differences in the abovementioned three trials, results obtained through an indirect comparison were not considered to be appropriate.

While a separate abstract was published providing HR and 95% CI for the abovementioned three trials, the submitter of the current submissions also examined whether indirect comparison of ofatumumab to other current therapies in CLL was appropriate and concluded that an indirect comparison was not appropriate between the trials. This was due to systematic differences in the doses and durations of chlorambucil treatment, systematic differences among the patient populations and systematic differences in the definition and ascertainment of the endpoints.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

Patient Advocacy Group Input

From a patient perspective, patients' personal experience with CLL varies a great deal, with some patients going many years with 'watch and wait' management of the disease and others requiring treatment right away. The patient advocacy group CLL PAG survey reported that about 41% of respondents who received treatment strongly agree that their treatment is able to manage their CLL symptoms; 59% provided a less than strongly agree to neutral response. LLSC reported that 73% of respondents said the treatment did adequately manage symptoms, while 27% said it did not. The majority of respondents from both CLL PAG and LLSC who have received chemotherapy reported post-treatment issues. Both CLL PAG and LLSC noted that it is important to very important to have choices in CLL treatment. Respondents indicated that they are willing to tolerate side effects that are manageable with medication and are short term especially if the treatment results in a longer remission. It was reported that the majority of respondents know little to nothing about ofatumumab. Only two respondents had experience with ofatumumab. It was noted that the expectation for the drug under review would meet the need for patients who are not suitable for fludarabine based treatments and the expected side effects would be manageable; and would provide clinically meaningful improvements over current therapies.

PAG Input

Input on the review of ofatumumab (Arzerra) for previously untreated CLL was received from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, chlorambucil monotherapy would be the treatment option for previously untreated CLL in patients where fludarabine-based chemotherapy is not suitable and ofatumumab plus chlorambucil would be an alternate treatment option. PAG noted the flat dosing of ofatumumab and has no concerns with drug wastage with the vial sizes available. These are enablers to implementation. The barriers to implementation identified include the four hour infusion time, the monitoring of infusion related reactions and indication creep into the relapsed/refractory setting or as a replacement to fludarabine-based therapy. In addition, PAG noted that there are several drugs for the first-line treatment of CLL anticipated in the next six to 12 months and PAG would like an assessment of the relative merits of these treatments based on clinical benefits and cost-effectiveness.

Other

The product monograph[1] provided by the manufacturer (GSK) provides the following serious warnings and precautions:

- Infusion Reactions: Arzerra administration can result in serious, including fatal infusion reactions. Health Canada recently endorsed a public communication regarding a post-marketing case of a fatal infusion reaction reported in a patient with chronic

lymphocytic leukemia (CLL) who received intravenous ofatumumab and who had no known history of cardiac disease.[45]

- Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including Arzerra, in some cases resulting in fulminant hepatitis, hepatic failure, and death.
- Progressive Multifocal Leukoencephalopathy (PML) resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including Arzerra.
- Cardiovascular: Serious and/or fatal cardiovascular events have been reported following the administration of Arzerra.
- Infections: Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of therapy with Arzerra.

2.2 Interpretation and Guidance

Burden of Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the western world, and affects 4.2 people/100 000 population per year. CLL is a disease of the elderly, with a median age at diagnosis of 72 years, and its long natural history (median survival from diagnosis is 10+ years) reflects an extended period of watchful waiting in most patients.[14] Although the disease has an indolent course and most patients can be safely observed without treatment for many years, cure of this disease is not a reasonable expectation and most affected patients will eventually die as a result of their disease. Young patients may benefit from intensive chemotherapy regimens and possibly from stem cell transplantation, but the majority of patients with CLL are older and so are not considered suitable candidates for these modalities. Older patients have few options and usually receive treatment with single agents, occasionally in combination with rituximab. Most patients will receive multiple lines of chemotherapy and will experience shorter remissions after each cycle as the disease becomes more resistant to treatment. The median survival from the time patients require treatment for CLL is approximately 4 years.

Treatment of Chronic Lymphocytic Leukemia

In broad terms, the two classes of drugs most often used to treat CLL are nucleoside analogues and alkylating agents. These agents were developed in the middle decades of the twentieth century, and have well known safety profiles. The pivotal trial that compared fludarabine and chlorambucil in untreated patients with CLL demonstrated a 6-month improvement in median PFS (20 vs. 14 months, $p<0.001$) with similar overall survival with both agents. Subsequent comparisons in elderly patients failed to demonstrate clinical benefit with fludarabine over chlorambucil, potentially due to increased toxicity in this population. Chlorambucil, an alkylating agent, has been in use for more than 30 years and can be given in daily, weekly, biweekly and monthly schedules. The use of bendamustine in previously untreated patients with CLL, previously reviewed with pCODR, has been widely adopted based on the results of a phase III, randomized study that demonstrated significant improvements in PFS compared to chlorambucil monotherapy While targeted therapy with small molecule inhibitors has not entered clinical practice in Canada, inhibitors of Bruton's tyrosine kinase (PCI-32765) and immunomodulatory drugs such as lenalidomide are in clinical trials currently.

The monoclonal anti-CD20 antibody rituximab has been shown to improve overall and progression-free survival when added to regimens commonly used to treat CLL.[7] While rituximab-chlorambucil combination therapy is only funded in a limited number of provinces, it is likely used more broadly in clinical practice and constitutes as a clinically relevant treatment option for patients unsuitable

for fludarabine-based therapy. The development of newer generations of anti-CD20 antibodies has raised the possibility of improved outcomes for patients with CLL. The present application considers ofatumumab, a second-generation anti-CD20 with properties favouring antibody-directed cellular cytotoxicity and complement-mediated cytotoxicity. It is felt that these properties may lead to longer disease-free intervals and improved health outcomes for patients with CLL.

Complement-1

The systematic review was able to identify one open-label, randomized, active control study comparing standard treatment with chlorambucil to the combination of chlorambucil and ofatumumab in previously untreated patients with CLL[2]. Diagnosis was made according to standard criteria and the decision to treat was based on accepted criteria established by the NCI Working Group on CLL. Patients were unsuitable to receive fludarabine-based treatment based on age and/or comorbid conditions. This report has only been published in abstract form and the full details of the trial were not available to the Clinical Guidance Panel. Some of the missing information was provided by the manufacturer upon request.

In Complement-1, 447 patients were randomized to the standard (n=226) or experimental (n=221) arms. For baseline characteristics, the groups were slightly unbalanced with respect to cytogenetic risk categories (more unfavourable risk del (11q) and favourable risk del(13q) in the experimental arm vs. more neutral (no aberration) in the standard arm) but overall were comparable for the outcomes of interest. The primary outcome of Complement 1 was Progression-Free Survival. Patients in the experimental arm achieved nine more months of PFS than patients in the standard treatment arm (PFS 22.4 (19.0 – 25.2) months vs. 13.1 (10.6 – 13.8) months, HR 0.57 (0.45 – 0.72), p<0.001). Differences were largely due to improved response rates in the experimental arm (82% vs. 69%, OR 2.16 (1.36 – 3.42), p<0.001). Two-year Overall Survival was similar between the arms (88.7% vs. 86.7%). Treatment-related adverse events (≥ grade 3) were more common in the combination arm (45% vs. 29%), although deaths due to adverse events were similar. Neutropenia (≥ grade 3) and infusion-related adverse events account for much of the difference between the arms, both of which were more common in the ofatumumab arm.

Quality of life was assessed during this study. Globally no differences were seen between the arms. There were significant differences in Emotional Functionality and Infection subscales for patients in the ofatumumab arm but these differences did not persist beyond the treatment phase. The meaning of these differences in an open label study of this design is unclear. Longer range quality of life measures included improved physical functioning in the chlorambucil arm and higher rates of financial burden in the experimental arm.

Summary

CLL is a common disease with a long natural history, and patients with this condition receive treatment on an intermittent basis as dictated by the activity and symptoms of their illness. Patient groups indicate that there is a need for more treatment options throughout the course of their disease. While the standard of care for young, fit patients is gradually shifting to moderately intensive combination regimens (i.e. fludarabine-cyclophosphamide-rituximab, FCR) there is no standard of care for older or less fit patients. The results of the systematic review suggest that ofatumumab may have a place in the front-line management of patients who are not eligible for fludarabine.

The review raises several questions for future study:

- The relative effectiveness of ofatumumab in combination with chemotherapy compared with rituximab in combination with chemotherapy needs to be determined in this population.

- The effectiveness of ofatumumab in combination with other chemotherapy backbones (alternative alkylating agents, nucleoside analogues or combinations) is unknown.
- The relative effectiveness and safety of ofatumumab and chlorambucil compared with that of bendamustine monotherapy is currently unknown.
- The impact of biological risk factors such as deletions of 17p or 11q, IgH mutational status and ZAP-70 expression on outcome with ofatumumab should be examined in future studies.
- The present review considers the use of ofatumumab in previously untreated patients with CLL. Its use in other populations, including those CLL patients who have been previously treated and those who have received rituximab as part of prior therapy was not addressed in this review. The panel also did not consider the use of ofatumumab in other B-Cell malignancies.

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be net clinical benefit to providing ofatumumab to patients with untreated CLL who are ineligible for treatment with fludarabine. The panel based its conclusion on a single open label, randomized study showing a modest nine month improvement in progression-free survival.

In reaching this conclusion the Panel also considered that:

- The burden of the described treatment, including time to attend for infusions and higher rates of adverse effects, is difficult to justify for in light of the modest benefit reported.
- The quality of life data seems to suggest reduced quality of life in some domains for individuals treated with ofatumumab.
- The panel discussed the appropriateness of having chlorambucil as the comparator, versus bendamustine, and felt that some of the patients in the comparator arm may have been eligible for bendamustine.
- The clinical trial has yet to be fully published and the role of the manufacturer in the design and conduct of the study is difficult to elucidate from the published abstract.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Leukemia/Lymphoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

With an age-adjusted incidence rate of 4.2 cases/100,000 population, CLL represents the most common leukemia in western countries. CLL is a disease of the elderly, with a median age at diagnosis of 72 years, and its long natural history (median survival from diagnosis is 10+ years) reflects an extended period of watchful waiting in most patients.[14] Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities. While survival from diagnosis in CLL may exceed 10 years, survival from the onset of treatment is only 4 years and contrary to widely held belief, 70% of patients with CLL die of causes related to their disease. New, more effective treatments for patients with this disease are desperately needed.

A diagnosis of CLL is normally suspected when an unexplained lymphocytosis is noted on blood counts, often done for another reason. Examination of a peripheral blood film demonstrates lymphocytes that are slightly larger than normal lymphocytes, with clumped chromatin and a thin crescent of pale cytoplasm. Prolymphocytes are infrequent, and the presence of > 55% prolymphocytes suggests a diagnosis of B-cell prolymphocytic leukemia.[15] Further testing demonstrates the characteristic immunophenotype of CLL cells, which are typically kappa- or lambda-restricted CD19+, CD5+, CD23+, CD10-, CD11cdim, CD20dim, sIg dim B-cells with absent or dim expression of FMC-7 and CD79a. The 2008 WHO Classification indicates that in the absence of extramedullary involvement there must be $\geq 5 \times 10^9$ cells/L with this phenotype for a diagnosis of CLL to be made.[16] Lymph node infiltration by B-lymphocytes with a CLL phenotype may occur in the absence of peripheral lymphocytosis: When this occurs a diagnosis of small lymphocytic lymphoma (SLL) is made. CLL and SLL are generally considered to be indolent lymphomas based on the mature appearance of the malignant cells and their similarity to other mature B-cell neoplasms. It is important to distinguish CLL from other peripheralizing lymphomas, such as mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma as treatment of these entities differs from that of CLL.

CD20 expression by CLL is variable and dim but is generally understood to be present in all cases. There is no correlation between CD20 expression levels in CLL and response to anti-CD20 antibodies and it is recommended that this marker not be used to determine eligibility for anti-CD20 antibody treatment in otherwise eligible patients.

Two staging systems have been in use for CLL, with a strong preference for the Rai staging system in North America and for the Binet system in Europe (see Table 1).[17, 18] Both staging systems reflect the gradual infiltration of CLL target organs, lymph nodes, spleen and bone marrow by disease cells, with higher stages indicating impairment of bone marrow function. Advanced CLL with bone marrow impairment (Rai stage 3 or 4, Binet stage C) has poor prognosis and is a commonly accepted indication for treatment.

Table 1. Accepted staging systems for patients with chronic lymphocytic leukemia.

Staging System	Stage	Definition	Median OS (mo)
Rai	0	Blood/marrow lymphocytosis	126
	1	Lymphadenopathy	92
	2	Splenomegaly	53
	3	Anemia (Hb < 110)	23
	4	Thrombocytopenia (Plt < 100)	20
Binet	A	< 3 lymph node areas*	128
	B	≥ 3 lymph node areas	47
	C	Anemia (Hb < 100) or thrombocytopenia (Plt < 100)	24

* Lymph node areas for Binet staging are unilateral or bilateral cervical, axillary or inguinal lymph nodes, liver and spleen.

A large numbers of factors have been associated with adverse prognosis in CLL. Rapid cell turnover, reflected by a short lymphocyte doubling time, is associated with an aggressive clinical course and shortened survival. Plasma factors indicating rapid turnover including LDH, β2- microglobulin and thymidine kinase have also been confirmed to reflect adverse prognosis.[19]

Early work examining the status of the immunoglobulin domain of CLL B-cells indicated that CLL may arise from either antigen naïve (without immunoglobulin gene somatic hypermutation) or antigen exposed (with somatic hypermutation) B-cells.[20, 21] These two disease subtypes have dramatically divergent clinical courses, with patients with unmutated disease having median survival of 8-9 years, compared with > 20 years for patients with mutated immunoglobulin domains. The cumbersome nature of the technology necessary to determine the mutation status of IgH domains has limited the clinical utility of this assay and has instead led to the investigation of surrogate markers associated with these changes. Two such markers, CD38 and ZAP-70, have shown an imperfect correlation with mutational status, but nonetheless remain important and relevant prognostic factors in their own rights. [22-24]

Metaphase cytogenetics in CLL is hampered by the low mitotic rate of these cells in tissue culture. Interphase FISH has become a powerful tool in such situations, and allows the detection of clonal cytogenetic abnormalities on fixed tissue without the need to prepare metaphase spreads. Isolated 13q deletions are associated with favourable prognosis while deletions of 11q or 17p are associated with unmutated IgH and poor prognosis. Some studies have suggested that with appropriate treatment the prognosis of del (11q) cases can approach that of more favourable subgroups. [25]

3.2 Accepted Clinical Practice

Common indications to treat patients with CLL include the development of cytopenias (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< 3 months). The nucleoside analog fludarabine was compared with

chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS. [26] Patients treated with fludarabine in this study had higher rates of severe infection and neutropenia, and the combination of fludarabine and chlorambucil has been associated with unacceptably high rates on severe infection. [27] The combination of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care for young, otherwise healthy patients given the results of a recent German CLL Study Group study showing improved PFS (51.8 vs. 32.8 months, p<0.0001) and OS (87% vs. 83%, p=0.012) with the addition of rituximab to FC. [7]

Table 2. Results of selected chemotherapy trials in chronic lymphocytic leukemia.

Regimen	Entry Criteria	Response Rate (CR+PR)	Overall Survival
Chlorambucil vs. obs.[28]	Untreated, Stage A	76%	76% vs. 80% (5-year)
Chlorambucil vs. obs.[29]	Untreated, Stage A	68%	75% vs. 82% (5-year)
Chlorambucil vs. COP[30]	Untreated, B or C	59% vs. 61%	44% vs. 43% (5-year)
Chlorambucil vs. ChOP[31]	"Advanced"	89.5% vs. 75%	68% vs. 47% (5-year)

Patients who are not considered fit enough to receive FCR (those older than 65, patients with concurrent illnesses, impaired renal function and those with Cumulative Illness Rating Scale (CIRS) score $\geq$ 6) but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Chlorambucil, an alkylating agent, has been in use for more than 30 years and can be given in daily, weekly, biweekly and monthly schedules. Extramedullary toxicity is generally mild and transient. The use of bendamustine in previously untreated patients with CLL, previously reviewed with pCODR, has been widely adopted based on the results of a phase III, randomized study comparing bendamustine with chlorambucil. This study demonstrated improved PFS in patients treated with bendamustine (21.6 months) versus chlorambucil (8.3 months) (p<0.001). Rituximab-chlorambucil combination therapy is funded in a limited number of provinces for patients in whom fludarabine therapy is inappropriate. This combination regimen is, however, likely used more broadly in clinical practice and the CGP concurred it constitutes a clinically relevant treatment option for patients unsuitable for fludarabine-based therapy. Other alkylator-based regimens, such as cyclophosphamide and prednisone or CVP have been described in CLL (see Table 2). Other alkylating agents, such as busulfan and melphalan, are of limited value in treating patients with CLL. Novel agents such as lenalidomide[32] have been evaluated in CLL but have yet to find their place in the therapeutic arsenal for this disease.

3.3 Evidence-Based Considerations for a Funding Population

Patients who are considered unsuitable to receive fludarabine-based treatment may derive benefit from less intensive regimens. This population includes patients who are older, those with comorbidities and patients with significant autoimmune cytopenias (common in CLL) that may be exacerbated by the immune dysregulation that may occur following treatment with fludarabine. The CIRS (Cumulative Illness Rating Scale) score is commonly used to identify patients who may not derive benefit from fludarabine and fludarabine-containing regimens due to higher rates of toxicity. [33] Patients who have received

fludarabine previously and either not responded or progressed within six months of treatment are also considered unsuitable for further treatment with nucleoside analogues.

The addition of anti-CD20 monoclonal antibodies to conventional chemotherapy drugs has resulted in improved overall survival among patients with CLL or indolent lymphoma. [7, 34, 35]. Ofatumumab is a fully humanized second-generation anti-CD20 monoclonal antibody with target binding properties that differ from those of rituximab. It binds a more proximal domain on the CD20 molecule and binds more tightly than rituximab. It translocates CD20 to lipid rafts that favour complement-mediated and antibody-directed cellular killing over direct cytotoxicity. Early clinical development has demonstrated a favourable safety profile and prolonged B-Lymphocyte depletion following treatment.[36] Other second generation anti-CD20 monoclonal antibodies include obinotuzumab (GA-101) and veltuzumab; clinical development of third generation monoclonal antibodies with enhanced FcγIIIR binding has begun. [37]

3.4 Other Patient Populations in Whom the Drug May Be Used

In contrast to initial treatment, there is no established treatment for patients with relapsed or refractory disease. While the disease may respond to regimens similar to those used for induction, responses are generally of lesser quality and duration in previously treated patients. The use of Ofatumumab in combination with chemotherapy has been reported in two small non-comparative studies enrolling previously-treated patients. Response rates between 40 – 72.3% and median progression-free survival was between 8.1-23.6 months. [38, 39]

CLL that is refractory to both nucleoside analogues and alkylating agents has an especially poor prognosis. Alemtuzumab has been used successfully as a bridge to allogeneic stem cell transplantation in this setting. Responses are generally brief and are frequently associated with opportunistic infection as a result of the intense immunosuppression associated with this agent.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient advocacy groups are invited to provide input on drug reviews to ensure patients' experiences of living with cancer and undergoing treatment are routinely considered as part of the pCODR Review Process. The patient advocacy groups are independent of pCODR. The following patient advocacy group(s) provided input on ofatumumab (Arzerra) used in therapy for patients with previously untreated CLL, for whom fludarabine treatment is considered inappropriate, at the beginning of the review process and their input is summarized below: The following two patient advocacy groups, Chronic Lymphocytic Leukemia Patient Advocacy Group (CLL PAG) and the Leukemia and Lymphoma Society of Canada (LLSC), provided input on ofatumumab (Arzerra) 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 and their input is summarized below.

CLL PAG designed and conducted two online surveys to gather information about the patient and caregiver experience with CLL and the drug under review. CLL PAG stated that the typical CLL patient is male and 72 years old at diagnosis. CLL PAG noted that this group is less likely to engage in surveys like this, and found that it was reflected in the survey response based on the age of respondents (majority of respondents were under 69 years) and gender of the respondents (57% of respondents in both surveys were female).

A total of 35 CLL patients and 14 caregivers participated in the two surveys by CLL PAG. The surveys sought information about patients' or caregivers' experience with CLL and related treatments, including ofatumumab and chlorambucil. Due to the rarity of CLL and the difficulties in identifying Canadian patients with experience with ofatumumab, CLL PAG requested participation in the survey from patients in Canada and from other countries. 28 participants were from Canada, 13 were from the U.S.A., 1 was from Australia, 5 were from the UK, and one patient each was from Brazil and France.

LLSC also conducted two separate online surveys (LLSC Survey #1 and LLSC Survey #2) to gather information about the patient and caregiver experience with CLL and the drug under review. The LLSC Survey #1 was posted on the LLSCanada.org website and distributed via social media. There were 23 responses, all of which were Canadian patients (52% female and 48% males). Two respondents were in the 36-50 years of age category, 9 were in the 51-65 age category and 12 were age 65+ years.

In LLSC Survey #2, the survey was open to all blood cancer patients and caregivers on their cancer experience. Of the respondents to this survey, 137 were Canadian CLL patients and 16 were caregivers. 36% of the respondents were male, 34% were female and 30% did not identify themselves by gender; seven were in the 36-50 years of age category, 50 were in the 51-65 age category and 39 were age 65+ years. 41 respondents did not reveal their age bracket.

From a patient perspective, patients' personal experience with CLL varies a great deal, with some patients going many years with 'watch and wait' management of the disease and others requiring treatment right away. The CLL PAG survey reported that about 41% of respondents who received treatment strongly agree that their treatment is able to manage their CLL symptoms; 59% provided a less than strongly agree to neutral response. LLSC reported that 73% of respondents said the treatment did adequately manage symptoms, while 27% said it did not. The majority of respondents from both CLL PAG and LLSC who have received chemotherapy reported post-treatment issues. Both CLL PAG and LLSC noted that it is important to very important to have choices in CLL treatment. Respondents indicated that they are willing to tolerate side effects that are manageable with medication and are short term especially if the treatment results in a longer remission. It was reported that the majority of respondents know little to nothing about ofatumumab. Only two respondents had experience with ofatumumab. It was noted that the expectation for the drug under review would meet the need for patients who are not suitable for

fluradibine based treatments and the expected side effects would be manageable; and would provide clinically meaningful improvements over current therapies.

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not corrected for spelling or grammar.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Chronic Lymphocytic Leukemia (CLL)

According to LLSC, patients' personal experience with CLL varies a great deal, with some patients going many years with 'watch and wait' management of the disease and others requiring treatment right away. Survival varies widely dependent on the genetic mutation that triggers the disease, with some patients' disease being resistant to existing therapies. With age often comes comorbidities and this also impacts whether or not a patient can tolerate existing treatments.

Based on the information from LLSC Survey #1, patients experienced the following disease symptoms most frequently:

- 77% fatigue
- 73% increased White Blood Count
- 60% enlarged lymph nodes
- 50% night sweats

Two patients recently went through treatment and are currently in remissions, and reported no symptoms.

According to the CLL PAG survey, 50% of respondents (17/34) indicated they are currently in "Watch and Wait (or Worry)", and although this is considered to be positive, the following common themes were voiced:

> "*The psychological stress of having cancer caused severe depression. Not being able to do anything but watch and wait was frustrating, always wondering when I will need treatment*"
>
> "*Watch and wait runs contrary to our normal approach to illness*"
>
> "*I have become hypersensitive being around sick people. If someone coughs, it sends shudders up my back. Sometimes I feel paranoid and a bother to be around. It has impacted my traveling, having guests over, being in large crowds etc*."
>
> "*Exhaustion forced treatment with FR which caused work disruption, but mostly it was exhaustion that made me stop doing anything outside of what absolutely needs to be done*"

CLL PAG reported on how the disease has impacted on the quality of life, and found that stress of diagnosis and fatigue had the most impact on respondents' lives. Patient respondents were asked to rate how the following symptoms impacted their quality of life, using a scale of 1 to 7, with 7 representing an extremely high rate of impact. The table below summarizes the most impactful symptoms.

CLL Symptom	% Respondents who rated a "7"	# Respondents	Rating average
Stress of Diagnosis	19.35%	31	5.03
Increasing White Count	19.35%	31	4.16
Fatigue	19.35%	31	4.00
Psychological issues	10.34%	29	3.55
Enlarged Lymph nodes	22.58%	31	3.48

In addition to the above, 25% of patient respondents cited "frequent infections and risk of infection" that limited their activities and travel before and after treatment.

According to LLSC, 67% (14/21) indicated the disease symptoms currently impacted their quality of life, mainly due to extreme fatigue. Abnormal white blood counts also lead to weakened immune systems and increased infections. One patient said "*Fatigue interferes with ability to carry out planned activities. I retired from a job I loved that involved children because of risk of getting infections*." Another said "*Tiredness and infections interfere with being able to do day-to-day activities or to do them in a timely and efficient manner*." 23% (5/21) of respondents indicated the disease symptoms do not have quality of life impact.

Results from LLSC Survey #1 found that 20 of the patient respondents (~87%) also indicated an emotional impact from their diagnosis. 10 express fear (e.g., when the disease will flare up, when they will need treatment, how long remission will last), 9 experience anxiety, 9 experience stress and 7 are depressed. One patient said: "*I wonder when I'll get sick and need treatment; how long I'll live; whether I should have children or not*." Others said: "*Chronic illnesses are emotionally challenging" and "It is depressing to live with a chronic condition*." Results from LLSC Survey #2 found that 86 patients noted an emotional impact to the disease (63%), 27 patients said they did not experience negative emotional responses (20%) and 24 (17%) did not answer the question. One patient said "*It's a lonely illness. I feel like crying every day but it doesn't look like anything is wrong with me*." LLSC found that the key emotions experienced by respondents in LLSC Survey #2 matched the results in LLSC Survey #1, which are fear; anxiety; depression.

According to LLSC Survey #1, 13 patients had no financial impact to the disease; 3 patients experienced loss of income; 2 had travel costs associated with treatment; 2 had medication costs; and 3 patients did not respond to this question. While in LLSC Survey #2, 83 patients did not experience financial stresses due to their CLL; 27 patients reported a loss of income; 13 had out-of-pocket drug expenses; 23 had travel costs associated with treatment.

LLSC also asked respondents about returning to work post diagnosis. 59 indicated this question was not applicable to them due to the fact they were not working when diagnosed. 27 were able to return to work, but 4 had to change to part-time hours or take different role as they could no longer do their previous job, 16 were not able to return to work due to symptoms of the disease.

4.1.2 Patients' Experiences with Current Therapy for CLL

According to LLSC, 70% of the total survey respondents (both surveys) have received treatment; 30% are in a watch & wait phase.

In LLSC Survey #1, 50% (11) had treatment. All had IV chemotherapy; 5 have received first line treatment only; 6 have received multiple lines of treatment; 7 were able to receive treatment in their community; two could not and indicated being away from home for over 9 months each. 10 patients indicated their treatments were easy to access; 1 had difficulty accessing the recommended treatment.

Of the 11 patients that have had treatment, all experienced side effects.

- Fatigue 100%
- Low blood counts 73%
- Nausea 45%

In LLSC Survey #2, 60 patients had treatment. All had IV chemotherapy. Thirty five also had oral chemotherapy, 6 had radiotherapy. Forty nine patients indicated they are on Watch & Wait. 40 patients indicated they have to travel to visit their cancer center; 56 are treated within their community.

According to CLL PAG, the therapies that patient survey respondents used are as follows:

Therapy (17 respondents)	First-line	Second- Line	Subsequent therapy
Fludarabine	1	1	
Fludarabine/Rituxan	4		
Fludarabine Cyclophosphamide/Rituxan	3		
Chlorambucil/Prednisone	4	1	
Bendamustine or B/Rituxan	1	2	
Ibrutinib	2	1	
RCHOP		1	
Lenalidomide	1		
Ofatumumab		1	
Cytoxan			1
Rituxan		1	
Radiotherapy			1
VCP	1		

According to CLL PAG, 41% (7/17) of respondents who received treatment strongly agree that their treatment is able to manage their CLL symptoms. 59% provided a less than strongly agree to neutral response.

LLSC reported that patients who have had chemotherapy as well as those who are in watch and wait were asked if their treatment adequately managed their CLL symptoms. 73% said the treatment did adequately manage symptoms; 27% said it did not. All realized their disease symptoms would reappear and any treatment relief of symptoms was temporary.

According to LLSC, of the 60 patients who have received chemotherapy, 57 reported post-treatment issues.

- 52 decreased energy
- 50 fatigue
- 28 trouble concentrating
- 25 memory issues
- 18 pain

74 reported post-treatment concerns, with 73% indicating their #1 concern was when the disease would recur.

Respondents indicated that they are willing to tolerate side effects that are manageable with medication and are short term especially if the treatment results in a longer remission. Adverse effects experienced by respondents are itemized below:

Therapy (17 respondents)	Adverse Effects
Fludarabine	Relapsed after 10 months
Fludarabine/Rituxan	Allergic reaction (2), Acute tubular necrosis, nausea, tiredness
Fludarabine Cyclophosphamide/Rituxan	None, nausea (2), vomiting, neutropenia, thrombocytopenia/ITP, allergic reaction, low IgG levels, refractory
Chlorambucil/Prednisone	Sepsis
Bendamustine or B/Rituxan	Diarrhea, severe nausea, rigors from Rituxan, Campylobacter infection, neutropenia, thrush, fever
Ibrutinib	Heart arrhythmias, eye issues, facial angioedema, mild diarrhea, itching, joint pain, fatigue
RCHOP	Cardiac, neural damage, shingles reactivation
Lenalidomide	Neuropathy
Ofatumumab	Reaction required decreased rate
Cytoxan	None reported
Rituxan	Decrease in immunoglobulins, heart arrhythmia, sinus problems
Radiotherapy	None reported
VCP	Ineffective

CLL PAG reported that 47% (8 respondents) rated access as difficult to extremely difficult with the average rating 3.47 out of 7. These 8 respondents, (4 Canadians) indicated they needed to travel outside their community to access treatment. Two respondents travelled to the US (one from France and one from Ontario) to access treatment not available otherwise. Respondents stated that they do not understand why payment for drugs is limited based on previous treatment or age. One respondent stated: "*that living in Ontario limits me from accessing Rituxan for second line or subsequent treatment because the province does not fund it*". Another respondent noted that "*because I opted to take the pill form of fludarabine, I had to pay for a great part of my treatment as I did not want to spend another day at the hospital for an infusion. I feel this is very unfair and these costs should be covered*."

According to CLL PAG, 79% (26/33) of respondents felt it is "very important to have" a choice in what drugs to take. Payment for drugs as first-line or second-line treatment drugs only, reduces choices patients have.

One respondent stated: "*Day-to-day quality of life for CLL patients seems to be poorly understood and a very low priority on the research agenda. Since death is inevitable, this needs to change*."

4.1.3 Impact of CLL and Current Therapy on Caregivers

CLL PAG reported that 14 caregivers responded to their caregiver's survey. Approximately 93% (13/14) of respondents were a spouse/partner and 7% of respondents (1/14) were a child of a CLL patient. 50% of respondents had provided caregiving during treatment, 50% of caregivers were in watch and wait with their patient, and 93% (13/14) of caregivers were female and 85% were older than 60 years.

Based on the survey, 92% of caregivers cited stress, anxiety and emotional issues as an impact of being a caregiver for a CLL patient. Watch and wait is difficult for caregivers as well as patients. Below are some of the responses that were received:

> "*Our lives have been turned upside down – now the center of our lives is focused on the health of my husband*"

> "*Constant worry about losing the love of my life and having to watch him suffer through chemo was difficult. CLL never truly goes away so we're constantly on edge wondering when it will return again and what treatment will be available to him when it does and whether we'll be able to afford the treatment*"

> "*I worry constantly about my husband's health, what treatment regime he should choose and how we will pay for his treatment, I also worry about widowhood*"

Both CLL PAG and LLSC noted that the demands on caregivers' time can be significant. Formerly shared household duties, such as shopping and cooking, can become the sole responsibility of the caregiver. The caregiver has to ensure that the patient attends medical appointments, they are expected to provide transportation and accompany the patient and take time off from work to do this. Caregivers will often do research into the disease, other available treatments, drug trials, etc. Caregivers with outside careers worry about being able to safeguard their jobs for which they now lack necessary time and concentration. The social life of caregivers also suffers. Vacations and travel are very much restricted and so are social interactions with others for fear of contracting infections and not wanting to share that the patient is ill. The CLL patient's wellbeing often becomes the caregiver's primary focus. One caregiver stated: "*It puts you in limbo - difficult to plan anything while undergoing treatment. Have to assume most household chores. Difficult to have social interaction with friends.*" A comment from a patient regarding their caregiver "*The caregiver loses a great deal of independence as many hours each day are spent at the patient's side…either for companionship, reassurance, or providing sustenance.*"

Based on the survey from CLL PAG, 54% or more of caregivers indicated they are willing to help their CLL patient manage treatment side effects such as nausea, fatigue, diarrhea, respiratory infections, breathing difficulties, rash, viral reactivation and fever. 30% or more would help their CLL patient manage infusion reactions, anemia, neutropenia and Tumour Lysis Syndrome. Respondents stated:

> "*I am prepared to do whatever is necessary to help my husband have a better quality of life*"

> "*I will help with any side effects to the best of my ability*"

According to LLSC, of the 15 caregivers who responded to the LLSC Survey #2, 14 indicated a negative emotional response to their loved one's diagnosis. All of them felt anxiety, 10 reported fear and 6 reported depression. 8 of the 15 said they felt like they had good personal support mechanisms for themselves; 7 did not.

Moreover, 8 of the caregiver's experienced financial difficulties related to their loved one's diagnosis (7 loss of income; 6 medication costs; 6 travel costs). Six said they did not have any financial concerns associated with CLL and 1 did not answer the question.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Ofatumumab

According to LLSC, the majority of respondents know little to nothing about ofatumumab.

Based on the results from LLSC Survey #1, 95% (19) patients indicated it is important to very important to have choices in CLL treatment; 1 patient indicated it was not important.

Respondents felt that the most important factors were:

- That it manages my CLL symptoms and I have payment for it by my province
- I would like to have better quality of life, greater chance of survival and greater chance of chronic condition not becoming acute. Also, targeted treatments that will impact cancerous cells with minimal impact on healthy cells.
- Reduced toxicity, because of my age, is an important factor
- The goal of remission is very important. Along with that a tolerable lifestyle In terms of energy and lack of pain are important.
- Drug not to be worse than disease itself

According to CLL PAG, the ofatumumab and chlorambucil regime would meet a need for patients who are not suitable for fludarabine based treatments. It would be expected that the drugs under review would be suitable for an older population of unfit CLL patients, and the expected side effects would be manageable. Treatment with this regime would provide clinically meaningful improvements over current therapies.

Respondents were asked to rate on a scale of 1 to 7, how important it is for ofatumumab and chlorambucil to control each of the following symptoms.

CLL Symptom	% respondents who rated a "7"	Number of respondents	Rating Average
Viral reactivations	70.00%	20	6.05
Frequent infections	66.675	21	6.14
Enlarged lymph nodes	65.22%	23	6.17
Elevated white count	60.87%	23	5.83
Decreased platelets	52.38%	21	5.90
Pain	47.37%	19	5.16
Fatigue	42.86%	21	5.33
Anemia	42.86	21	5.43
Fever	40.00%	20	5.15
Low IgG levels	38.10%	21	5.38
Night sweats	33.33%	21	4.81
Weight loss	21.055	19	4.11

Based on the results from the LLSC Survey #1, the majority (79%) indicated the number one symptom to control was fatigue. This was followed by increasing white blood counts/infections, and then enlarged lymph nodes.

Because ofatumumab requires an IV infusion, it is not as easy to use as oral drugs such as single agent chlorambucil. CLL PAG noted that infusion related side effects are well

documented for this drug regime. When patients are made aware of side effects, they are willing to manage them as needed. CLL PAG reported that 82% of respondents would be willing to tolerate potential adverse effects resulting from the ofatumumab and chlorambucil if it were to improve their overall daily functioning.

Possible Adverse Effect	% respondents who rated their willingness to tolerate the adverse effect a "7" out of 7
Fatigue	60.71%
Nausea	50.00%
Diarrhea	39.29%
Rash	35.71%
Neutropenia	25%
Vomiting	21.43%

According to LLSC, the majority of respondents indicated they are willing to tolerate short-term side effects like nausea; diarrhea; fever; fatigue; cough. They are less likely to want to tolerate more severe side effects like tumour lysis syndrome; viral reactivation; bowel obstruction; breathing difficulties; irregular heartbeat.

LLSC reported that one respondent who had experience with ofatumumab & chlorambucil. The only negative reaction that the respondent experienced resulting from the treatment was extreme weight loss.

CLL PAG also reported one respondent who had experience with chlorambucil/prednisone first-line and ofatumumab second-line. The respondent reported that: "*I greatly reacted to Ofatumumab. I had to have the rate of infusion slowed down and it took days to do. I had to have many anti-rejection drugs to reduce the reactions. I had to be hospitalized. On a positive note, my enlarged lymph nodes disappeared immediately*." Viral reactivation was a noted side effect of this drug regime by this user.

4.3 Additional Information

Based on the survey responses, CLL PAG believes that CLL patients are looking for options in treatment and retreatment. The survey attracted younger patients than would be generally appropriate for ofatumumab/chlorambucil; which supports their view that patients are becoming more aware that they need choices and drug treatment should not be one size fits all.

LLSC submits that these patients are facing a diagnosis and treatment for an incurable cancer. Available treatments are life-extending for some, but non-curative. Due to the average age of patients, they often have comorbidities that limit what drugs can be administered. Toxicity of new treatments is of prime concern for patients who are older with comorbidities, who are looking for more options for life extension while scientists continue to search for cures. Research studies have a tendency to have age limits below that of the average age of diagnosis for CLL and not include patients with comorbidities or drug–resistant disease, yet these populations are a significant portion of CLL patients.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group at the beginning of the review as factors that potentially affect the feasibility of implementing a funding recommendation for ofatumumab (Arzerra) for previously untreated CLL patients for whom fludarabine treatment is considered inappropriate. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the review of ofatumumab (Arzerra) for previously untreated CLL was received from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, chlorambucil monotherapy would be the treatment option for previously untreated CLL in patients where fludarabine-based chemotherapy is not suitable and ofatumumab plus chlorambucil would be an alternate treatment option. PAG noted the flat dosing of ofatumumab and has no concerns with drug wastage with the vial sizes available. These are enablers to implementation. The barriers to implementation identified include the four hour infusion time, the monitoring of infusion related reactions and indication creep into the relapsed/refractory setting or as a replacement to fludarabine-based therapy. In addition, PAG noted that there are several drugs for the first-line treatment of CLL anticipated in the next six to 12 months and PAG would like an assessment of the relative merits of these treatments based on clinical benefits and cost-effectiveness.

Please see below for details on individual parameters.

5.1 Factors Related to Comparators

The chemotherapy combination of fludarabine, cyclophosphamide and rituximab (FC-R) is the current first-line treatment option for medically fit patients with CLL. PAG noted that chlorambucil or bendamustine would be the treatment option for elderly patients and unfit patients, where the chemotherapy combination cannot be used. Chlorambucil would be one of the appropriate comparators in this subgroup of patients.

PAG noted that the funding request specifies chlorambucil as the alkylating agent to be used in combination with ofatumumab. However, at the time the submission was made the Health Canada indication did not specify the alkylating agent. PAG would like the use of other alkylating agents (such as busulfan, melphalan, cyclophosphamide, bendamustine) be addressed by PERC as the alkylating agent used would impact cost-effectiveness. In addition, PAG requested information on whether there are head-to-head comparisons of ofatumumab plus chlorambucil with other anti-CD agents and alkylating agents. Lastly, information on sequential use with rituximab will be important to understand from an implementation perspective.

5.2 Factors Related to Patient Population

As hematologic malignancies tend to be less common than solid tumors overall, PAG recognized that there may be a very small number of previously untreated CLL patients who are not suitable for fludarabine-based or rituximab-based chemotherapy. Ofatumumab would be an anti-CD20 monoclonal antibody option for these patients. This

would be an enabler. However, it may be a challenge to clearly identify patients who are ineligible or unsuitable for fludarabine-based or rituximab-based chemotherapy.

PAG noted that ofatumumab has a Notice of Compliance with condition for the treatment CLL refractory to fludarabine and alemtuzumab, which is not part of this funding request. As such, PAG has concerns for indication creep for patients with relapsed/refractory CLL, where treatment options are limited. This may be a barrier to implementing ofatumumab for first-line treatment of CLL and PAG would like information or guidance on use of ofatumumab in the relapsed/refractory setting where there is a larger prevalent population.

In addition, PAG would like information on the use of ofatumumab after rituximab-based therapy and on the use of rituximab after ofatumumab in downstream treatments, as both are anti-CD20 monoclonal antibodies.

5.3 Factors Related to Accessibility

Ofatumumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of infusion related reactions. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients which is an enabler. However, in some areas, patients would need to travel far to an outpatient chemotherapy center, which would be a barrier to implementation.

5.4 Factors Related to Dosing

Ofatumumab dose is flat dosing, regardless of patient's weight or body surface area. PAG noted this as an enabler, given that the vial sizes available provide these doses without drug wastage.

5.5 Factors Related to Implementation Costs

Ofatumumab is administered by intravenous infusion over 4 to 4.5 hours. This would be a barrier as there would be chemotherapy chair utilization, increased pharmacy preparation time and increased nursing resources. PAG also recognized that there may be additional costs associated with ofatumumab treatment, such as monitoring for infusion related reactions and other adverse reactions.

PAG noted that ofatumumab requires refrigeration for storage and in some centers, refrigerator space may be an issue.

Ofatumumab is available in solution and thus, reconstitution is not required prior to adding to the infusion solution. This is an enabler from the perspective of pharmacy preparation time. However, PAG noted that an equivalent volume must be withdrawn from the infusion solution prior to adding the drug. PAG has concerns that this additional step may be overlooked.

PAG noted that cancer centers would be familiar with administration of anti-CD20 monoclonal antibodies and the required pre-medications. This would be an enabler. However, smaller cancer centers and rural communities may not have the expertise or the resources to prepare and administer ofatumumab and monitor for infusion related reactions.

PAG also noted that there is no specific companion diagnostic associated with ofatumumab and that the test for CD20 antigen would already have been done at the time of diagnosis.

5.6 Other Factors

PAG noted that there were reported cases of death associated with progressive multifocal leukoencephalopathy (PML) and with Hepatitis B infection reactivation in patients treated with ofatumumab. PAG would like the risks versus the overall benefits of treatment with ofatumumab addressed by pERC.

There are several drugs for the first-line treatment of CLL anticipated within the next six to 12 months. PAG is requesting information on the relative merits of these drugs based on clinical benefits and cost-effectiveness.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety/toxicity of ofatumumab (Arzerra) when used in combination with an alkylating agent, in comparison with current standards in the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) requiring therapy, for whom fludarabine treatment is considered inappropriate.

No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or Unpublished Randomized controlled trials	Previously untreated CLL patients requiring therapy for whom fludarabine treatment is considered inappropriate. Subgroups: 17p mutation, alkylating agent.	Ofatumumab AND Alkylating agent (chlorambucil (Chl), bendamustine, busulfan, melphalan or cyclophosphamide)	Alkylating agent (chlorambucil (CHL), bendamustine, or cyclophosphamide) OR Alkylating agent (chlorambucil, bendamustine, or cyclophosphamide) AND Other monoclonal antibody (rituximab, (GA101: obinutuzumab**)	OS, PFS, CR, ORR ***Adverse Events:*** Grade 3-4 adverse events ***WDAE*** **Fatigue** **Infusion related toxicity** **Infections** Hep-B reactivation PML Hematologic adverse events Non-hematologic adverse events Tumor lysis syndrome QOL

Abbreviations: Chl=Chlorambucil; PML: Progressive multifocal leukoencephalopathy; CLL=Chronic Lymphocytic Leukemia; ; OS=overall survival; PFS=progression-free survival; CR=complete response; QOL=quality of life
* Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
** *Identified as agent of interest although not currently available in Canada*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-2014) with in-process records & daily updates via Ovid; EMBASE (1980-2014) via Ovid; the Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Ofatumumab (Arzerra) and chronic lymphocytic leukemia.

Methodological filters were applied to limit retrieval to randomized controlled trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of November 6, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were not limited by date. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.

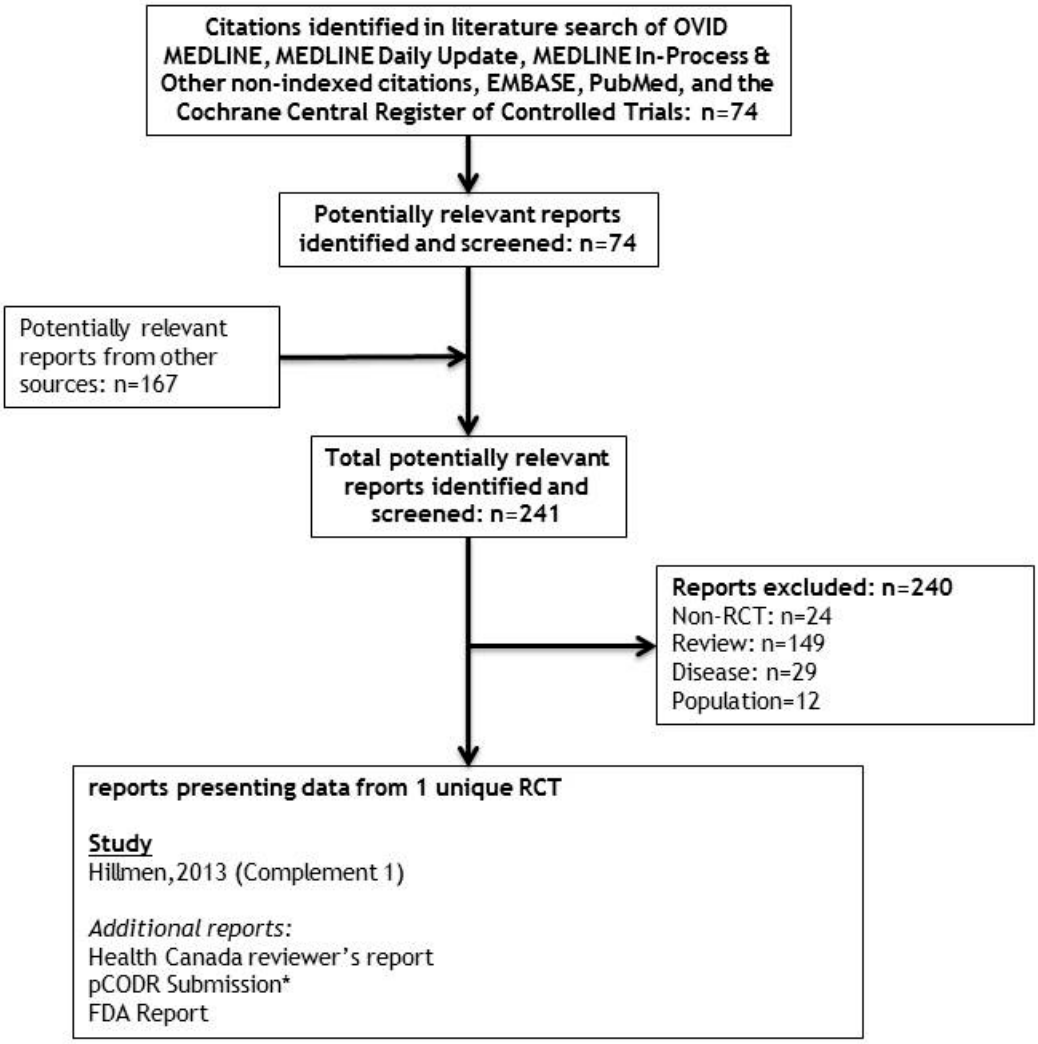
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

A total of 241 unique citations were identified through searches of MEDLINE (OVID), MEDLINE Daily Update (OVID), MEDLINE In-Process & Other Non-Indexed Citations (OVID), EMBASE (OVID), Cochrane Central Register of Controlled Trials, and PubMed (Figure 1). Of the 241 potentially relevant reports identified, 1 study was included in the pCODR systematic review and 240 studies were excluded. Studies were excluded because they were unrelated by study or treatment type, were not correct study type, did not cover correct patient population, or did not contain relevant comparator interventions. Twenty three additional references were found when databases were searched again on November 6th, 2014. None of these references were phase III trials and most did not study previously untreated patients.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the study was also obtained through requests to the submitter by pCODR[40]

6.3.2 Summary of Included Studies

One randomized trial was eligible for inclusion in this review.[2] This trial evaluated the use of Ofatumumab in combination with chlorambucil versus chlorambucil alone in patients with previously untreated CLL requiring therapy, for whom fludarabine treatment is considered inappropriate. The document retrieved for this reference was in abstract form. The submitter has informed pCODR that a manuscript is pending publication. Further results and information from this trial was provided by submitting company and identified in the FDA assessment report.

Table 2. Detailed Trial Characteristics

Table 5. Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Interventions	Outcomes
Hillmen, 2013 Phase III, Open label multicenter RCT Industry sponsored - **Funded by: GlaxoSmithKline** **Centres in Europe, North America, India & Brazil** **Trial Type:** Comparative phase III trial with no cross over. **Sample Size:** n=477, 221 - CHL/O, 226 - CHL	**Inclusion criteria:** 1. Confirmed diagnosis of CLL, active disease, and indication for treatment based on IWCLL-updated NCI-WG guidelines 2. Not previously treated for CLL 3. For whom fludarabine treatment is considered inappropriate by the investigator for reasons that included, but were not limited to, advanced age or presence of comorbidities **Exclusion criteria:** 1. Chronic or current active infectious disease requiring systemic treatment, positive serology for hepatitis B (HBsAg-positive), or known to be (HIV)-positive. 2. cardiac disease, cerebrovascular disease, other past or current malignancy, or abnormal laboratory values indicating significantly compromised renal or liver function 3. Glucocorticoid use (unless given in doses ≤100 mg/day hydrocortisone or equivalent dosage of another glucocorticoid for < 7 days for exacerbations other than CLL 4. Significant infections and other conditions that could impact the primary endpoint 5. Use of high-dose steroids for any condition (because of their known anti-CLL properties, which would compromise the efficacy assessment)	Chlorambucil & Ofatumumab Vs. Chlorambucil • CHL was given orally (10mg/m^2 at days 1-7 of each 28 day cycle) • O was administered as intravenous infusions (Cycle 1: 300mg day 1 and 1000mg day 8, subsequent cycles: 1000mg at day 1) • Treatment given for 3 cycles min, until best response to a maximum of 12 cycles.	PFS, ORR, OS, Grade 3|4 adverse event, hematologic and non-hematologic adverse events, Safety, QOL

CLL= Chronic Lymphocytic Leukemia; CHL=Chlorambucil; O=Ofatumumab, PFS=Progression free survival; ORR=Overall response rate; OS=Overall survival; QOL=Quality of Life

a) Trials

One open label randomized trial was found for this review. Complement 1[2] is a comparative superiority trial that includes progression free survival as the primary endpoint. None of the participants or investigators were blinded and patients were randomized 1:1 to receive ofatumumab plus chlorambucil or chlorambucil alone.

b) Populations

Four hundred forty seven patients were randomized from 16 different countries. Analyses were carried out based upon intention to treat principle.

Patient characteristics were reported to be well balanced between arms. Median age - 69 yrs, Rai stage - low 8%, med 51%, high 40%, unmutated IgVH - 56%, 17p deletions - 6%, β-2-microglobulin level ≥ 3500ug/L - 75%. The trial did not limit inclusion of patients by ECOG performance status.

Figure 2. Patient Characteristics

Category	Demographic or Disease Characteristics	Chlorambucil (N = 226)	Ofatumumab Plus Chlorambucil (N = 221)	Total (N = 447)
Region, n (%)	European	N/A	N/A	357 (80%)
	North America/Canada	N/A	N/A	42 (9%)
	Brazil and India	N/A	N/A	48 (11%)
Age, years	Median (min-max)	70 (36-91%)	69 (35-92%)	69 (35-92%)
	< 65, n (%)	71 (31%)	69 (31%)	140 (31%)
	≥ 65, n (%)	155 (69%)	152 (69%)	307 (69%)
	≥ 70, n (%)	117 (52%)	104 (47%)	221 (49%)
	≥ 75, n (%)	63 (28%)	56 (25%)	119 (27%)
Sex, n (%)	Male	140 (62%)	142 (64%)	282 (63%)
	Female	86 (38%)	79 (36%)	165 (37%)
Race, n (%)	White	201 (89%)	196 (89%)	397 (89%)
	Asian	22 (10%)	21 (10%)	43 (10%)
	African American/African	2 (<1%)	4 (2%)	6 (1%)
B Symptoms, n (%)	Yes	120 (53%)	118 (53%)	238 (53%)
Rai Stage, n (%)	Low risk (0)	21 (9%)	16 (7%)	37 (8%)
	Intermediate (I, II)	116 (51%)	113 (51%)	229 (51%)
	High risk (III, IV)	89 (39%)	92 (42%)	181 (40%)
Binet Stage, n (%)	A	70 (31%)	77 (35%)	147 (33%)
	B	87 (38%)	74 (33%)	161 (36%)
	C	69 (31%)	70 (32%)	139 (31%)
ECOG PS, n (%)	0,1	205 (91%)	204 (92%)	409 (91%)
	2	19 (8%)	17(8%)	36 (8%)
	3-5	0	0	0

Manufacturer submission[8], N/A: not available

Prognostic factors and patient comorbidities are also an important consideration in determining validity of results as these characteristics have the ability to confound

comparative results. Most prognostic factors were found to be similar between treatment arms with notable differences in the 11q, 17p, and 13q deletions between the CHL and CHL & O arms respectively. The 11q and 17p deletion prognostic markers have been found to correlate with shorter survival and response outcomes, while the 13q is associated with improved relative survival. Overall, this could create bias in survival outcomes.

Subgroup analysis was conducted and included reasons for which patients were considered for whom fludarabine treatment is considered inappropriate. Reasons provided were advanced age, presence of comorbidity, advanced age and comorbidity, and other. The reason, other refers to "Other" includes patient's choice, medical decision, financial constraint, and fludarabine availability (not standard of care).

Figure 3. Baseline Prognostic Markers

Prognostic Markers	Chlorambucil (N = 226)	Ofatumumab Plus Chlorambucil (N = 221)	Total (N = 447)
11q deletion, n (%)	24 (11%)	40 (19%)	64 (15%)
12q trisomy, n (%)	34 (16%)	35 (17%)	69 (16%)
17p deletion, n (%)	17 (8%)	10 (5%)	27 (6%)
13q deletion, n (%)	105 (49%)	122 (58%)	227 (53%)
No aberration, n (%)	64 (37%)	41 (26%)	105 (31%)

European Medicines Agency Assessment Report [9]

Comorbidities were also found to be similar between arms. Proportions of patients with comorbidities were evenly distributed through both treatment arms. A total of 87% of patients had at least one condition. The following conditions were most commonly reported: Vascular disorders (inc. hypertension), Mild renal impairment, Metabolic disorders, musculoskeletal disorders, respiratory disorders (asthma, COPD, dyspnea), GI disorders (diarrhea, GI reflux, constipation) and cardiac disorders.

c) Interventions

Complement 1 is a two arm study comparing chlorambucil combined with ofatumumab to chlorambucil alone. Chlorambucil was given orally (10mg/m^2 at days 1-7 of each 28 day cycle) and ofatumumab was administered as intravenous infusions (Cycle 1: 300mg day 1 and 1000mg day 8, subsequent cycles: 1000mg at day 1). Ofatumumab premedication included acetaminophen, antihistamine and glucocorticoid. Treatment duration was a minimum of 3 cycles, until best response up to a maximum of 12 cycles. It was noted by both PAG and the CGP that there is no specific companion diagnostic associated with ofatumumab and that the test for CD20 antigen would already have been done at the time of diagnosis.

d) Patient Disposition

All analyses were conducted on the intent-to-treat population of 447 patients. For the safety analysis all patients that received at least one dose of the study drug were included - 444 patients. For the follow-up analysis 71% of patients continue to participate while ~29% are no longer participating due to death or withdrawal. Among patients no longer participating, 15% vs. 18% (34 vs. 40) have died, 0% vs. 1% (0 vs. 1) completed the follow up period, and 11% vs. 13% (25 vs. 30) withdrew from the study in the ofatumumab + Chl vs. Chl arms, respectively.

e) Limitations/Sources of Bias

Open label trials lack blinding of all participants and investigators in the trial. Bias is possible but extent/severity and direction not clear. On the other hand, assessment of disease progression, and response, was undertaken by independent review committee which decreases the likelihood of investigator bias, thereby increasing strength of results.

Differences in prognostic characteristics were noted for those with 11q and 17p deletions, between treatment arms. There was a higher proportion of patients with the 11q deletion in the Chl/O arm, a lower proportion of 17p deletion in the Chl/O arm, and higher proportion of 13q deletion in the Chl/O arm. These mutations are correlated with worse survival and response outcomes [41] and may introduce bias.

To date this information has only been published in "abstract" form. Subsequent information was made available through submission materials and regulatory reports, but it is not clear whether information has been verified through a peer-reviewed publication of the trial information and whether reporting is complete. Gaps related to patient follow-up and measurements of quality of life have been noted as needing further review.

Comparative therapies: Currently, there are no studies comparing chlorambucil and ofatumumab with chlorambucil and rituximab, or with bendamustine. Given the use of these therapies in clinical practice, studies assessing the comparative efficacy would be informative.

Given the discrepancy between progression free survival and overall survival it is necessary to examine longer follow up to determine whether overall survival will begin to improve in the treatment arm.

The COMPLEMENT 1 study was conducted worldwide. Eighty percent of participants were enrolled in Europe, 11% were enrolled in "Brazil and India" and 9% in North America/Canada. Due to the small proportion of North American enrollment, any differences in disease course or response to treatment found in other populations or regional treatment patterns could affect generalizability to the Canadian population.

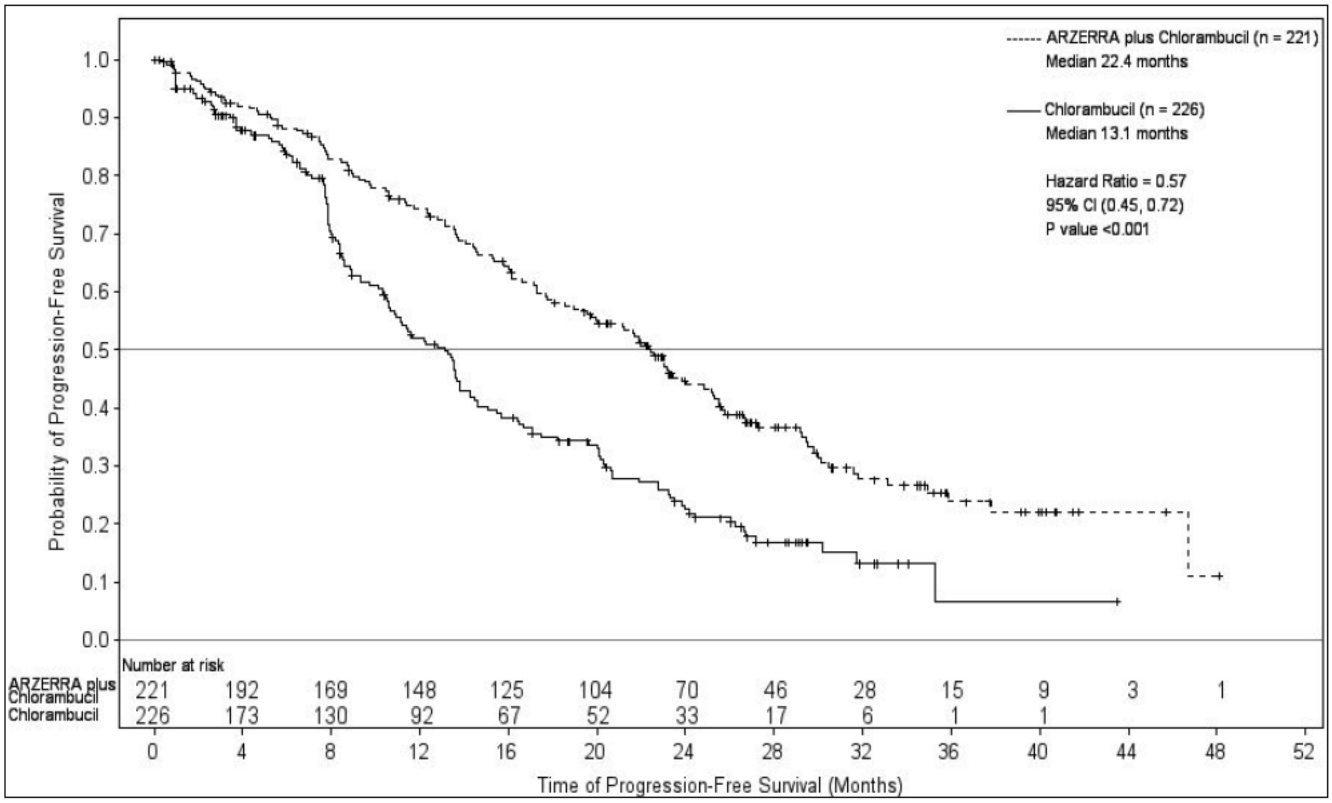
Trial investigators were reported to have associations with GSK. Most frequently, relationships were described as research funding or consultancy.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 3. Primary and Secondary Efficacy Outcomes

Efficacy Outcomes for patients on the COMPLEMENT-1 study[2, 9]				
Median follow up	**Outcome**	**CHL + Ofatumumab**	**CHL**	**Comparative Statistic (95% CI) for HR/OR**
28.9 ms	**Median PFS (95%CI)**	22.4ms (19.0-25.2)	13.1ms (10.6-13.8)	HR=0.57 (0.45-0.72) (p<0.001)
	Overall Response Rate (ORR)	182 (82%)	155 (69%)	OR=2.16 p<0.001 95% CI: 1.36 - 3.42
	Overall Survival (OS)	2 year 88.7% 3 year 85.1%	2 year 86.7% 3 year 83.2%	3 yr HR=0.91 (0.57-1.43) p=0.666

Figure 4. Kaplan-Meier plot, IRC assessed, Progression Free Survival



FDA Summary[42]

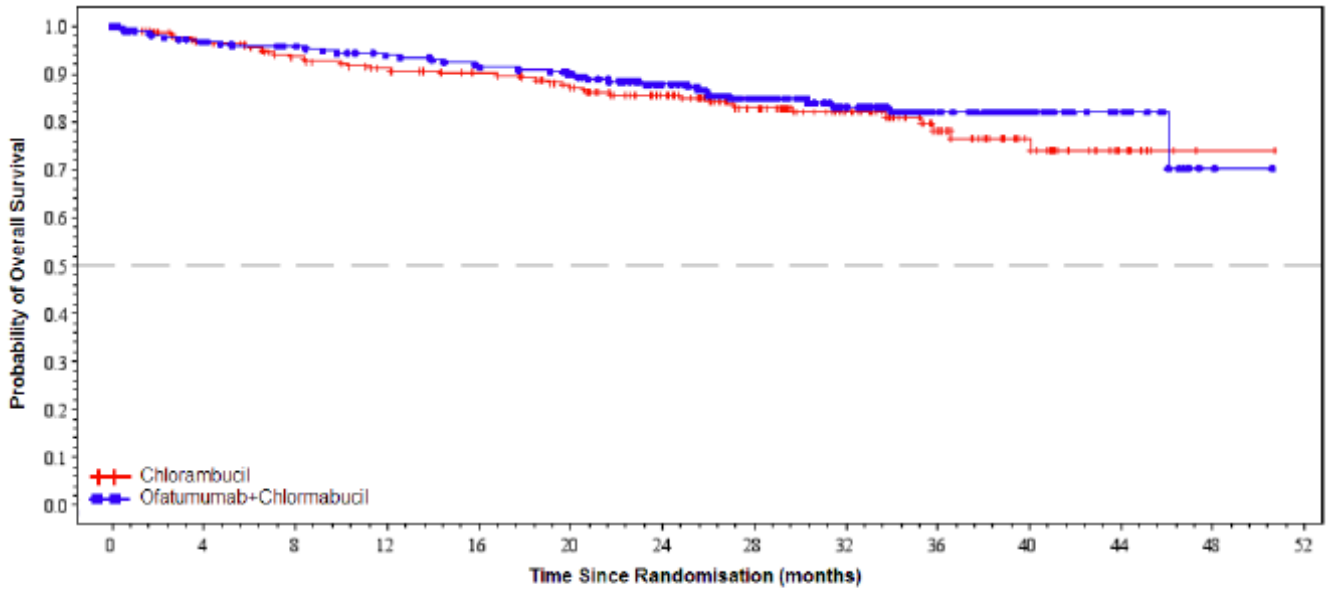
Progression Free Survival (PFS)

Progression free survival was main endpoint in the Complement 1 study. Results were analysed by an independent review committee and showed a statistically significant prolongation of PFS when ofatumumab was combined with chlorambucil. With a median follow up period of 28.9 months, there was a median increase of 9.3 months in the chlorambucil & ofatumumab arm. Individually, the chlorambucil & ofatumumab arm had median progression free survival of 22.4 months and a 95% confidence interval from 19 months to 25.2 months. The chlorambucil monotherapy arm had median PFS of 13.1 months with a 95% confidence interval between 10.6 and 13.8 months. The resulting hazard ratio was 0.57 (95% CI 0.45 – 0.72) and the associated a p-value was < 0.001 indicating a significant increase in progression free survival.

PFS subgroup analysis demonstrated a statistically significant benefit in PFS with the addition of Arzerra regardless of gender, age, constitutional symptoms, Rai stage, number of co-morbidities, or disease stage, CIRS scare, 11q/6q/12q/13q/no aberration, IGHV mutational status, Beta 2 microglobulin, and SAP70. Statistical significance was not seen for geographical distribution – India/Brazil, North America, Binet stage B & C, 17p deletion cytogenetic status and the category of "Other" (reason used by investigators to identify patients for whom fludarabine treatment was considered inappropriate). It should be noted that there is no evidence that subgroup analysis was powered to provide results that are statistically relevant, and that some subgroups were very small**.**

Overall Survival (OS)

Two and 3 year OS proportions were reported along with the 3 year survival proportion, hazard ratio and p-value. Two year rates were 88.7% and 86.7% in the chlorambucil and ofatumumab versus chlorambucil alone arms respectively. Three year rates were 85.1% and 83.2% for the same groups generating a hazard ratio of 0.91, a 95% confidence interval from 0.57 to 1.43 and a p-value of 0.666.[9]



Subjects at Risk

C	226	209	199	191	183	172	146	112	84	53	32	12	1
O+C	221	207	201	193	188	182	153	119	90	57	36	14	2

European Medicines Agency Assessment Report[9]

Overall Response Rate (ORR)

Overall response rate was analysed by independent review committee. Overall response was defined according to response criteria found in the IWCLL-updated NCI-WG guidelines[43], and was a key secondary endpoint in the COMPLEMENT 1 phase 3 randomized controlled trial. With a 82% response rate in the CHL/O arm and a 69% response rate in the CHL alone arm the difference in ORR was determined to be statistically significant (p=0.001). Investigator assessment of ORR and CR/CRi: investigator-assessed ORR was 88% for patients receiving ofatumumab and chlorambucil, compared to 81% for those receiving chlorambucil only (P = 0.044). The rate of CR/CRi was substantially higher in the ofatumumab plus chlorambucil arm (49%) compared with chlorambucil monotherapy arm (21%).[9]

Complete Response (CR)

Complete response was analysed by independent review committee. No comparative evaluation results were provided by treatment arm. Complete response was reported in 12% and 1% of patients in the ofatumumab + chlorambucil versus chlorambucil arms respectively. Complete response and complete response with incomplete bone marrow recovery (CR/Cri) rates were reported to much higher in the CHL/O arms versus CHL alone arm, in the investigator led analysis.[44]

Harms Outcomes

Deaths

Patient deaths were reported as follows: 23 (11%) adverse events leading to death in the ofatumumab plus chlorambucil arm, compared to 14 (6%) adverse events leading to death in the chlorambucil arm, but only 3 and 2 of those, respectively, were deemed to be treatment-related. Adverse events' reporting requires an outcome to be reported along with time and frequency. It is described that an event with a "fatal" outcome is an adverse event leading to death. No detail regarding what event led to death was provided. [44]

Discontinuation of Treatment

Adverse events leading to discontinuation of treatment were 13% in the CHL/O treatment arm versus 14% in the CHL alone arm. Dose reductions were required in 17% of patients in both arms. Interruptions or delay in treatment was 28% in the CHL alone arm versus 69% in the CHL/O arm. No comparative testing was completed for these results, but notable differences exist between treatment arms for adverse events causing treatment interruption or delay. [8]

Adverse Events

Most patients in both treatment arms experienced at least one adverse event (95% vs. 89% in the ofatumumab plus chlorambucil vs. chlorambucil arms, respectively). Treatment related adverse events were also reported in 84% vs. 65% of patients in the ofatumumab plus chlorambucil vs. chlorambucil arms, respectively.

Figure 5. Adverse Events of Special Interest

Adverse Events of Special Interest, n (%)	Chlorambucil (N = 227)	Ofatumumab Plus Chlorambucil (N = 217)
AEs associated with decreased neutrophil count[a]	56 (25)	69 (32)
Neutropenia	41 (18)	59 (27)
Grade ≥3 neutropenia	33 (15)	58 (26)
SAEs associated with decreased neutrophil count[a]	13 (6)	12 (6)
AEs associated with decreased hemoglobin[b]	35 (15)	30 (14)
Anemia	30 (13)	20 (9)
Grade ≥3 anemia	12 (5)	11 (5)
Anemia hemolytic autoimmune	3 (1)	2 (<1)
SAEs associated with decreased hemoglobin[b]	11 (5)	8 (4)
AEs associated with decreased platelet count[c]	67 (30)	40 (18)
Thrombocytopenia	59 (26)	30 (14)
Grade ≥3 thrombocytopenia	23 (10)	10 (5)
SAEs associated with decreased platelet count[c]	3 (1)	2 (<1)
All AEs associated with other cytopenias[d]	8 (4)	20 (9)
SAEs associated with other cytopenias[d]	0	1 (<1)
Infusion reactions	N/A	146 (67)
Grade ≥3 infusion reactions	N/A	22 (10)
Serious infusion reactions	N/A	6 (3)

Manufacturer Submission[8]

Table 5. Safety Outcomes

Safety Outcomes for patients on the COMPLEMENT-1 study [2, 9, 42]		
	CHL + Ofatumumab	**CHL**
Any Adverse Events (AE)	206 (95%)	203 (89%)
Treatment Related AE's	182 (84%)	148 (65%)
Non-Hematologic AE's occurring in ≥ 5% of patients	**CHL + Ofatumumab**	**CHL**
Infusion related reactions	**146 (67%)**	**0 (0%)**
Grade ≥3 infusion related reactions	**10%**	**NA**
Serious Infusion related reactions	**3%**	**NA**
SAE's leading to death	23 (11%)	14 (6%)
Fatal SAE's related to treatment	3	2
AE's associated with decreased neutrophil count (including neutropenia, febrile neutropenia, neutropenia sepsis, decreased neutrophil count, and pancytopenia)	69 (32%)	56 (25%)
Hematologic (≥3) AEs occurring in ≥ 5% of patients	**CHL + Ofatumumab**	**CHL**
Neutropenia	57(26%)	34(15%)
Thrombocytopenia	10(5%)	23(10%)
Anemia	11(5%)	12(5%)
All AEs associated with other cytopenias	20 (9%)	8(4%)
SAEs associated with other cytopenias	1 (<1%)	0(0%)

Grade 3, 4 Adverse Events

There was a higher incidence of Grade ≥3 events in the ofatumumab plus chlorambucil arm, with 10% related to infusion reactions. The most frequently reported Grade ≥3 events in the ofatumumab plus chlorambucil arm were neutropenia, thrombocytopenia, and anemia. Neutropenia events were more common in the ofatumumab plus chlorambucil arm (Ofa+Chl, 26%; Chl, 15%), whereas the incidence of thrombocytopenia was greater in the chlorambucil monotherapy arm (Ofa+Chl: 5%, Chl: 10%). Anemia occurred in 5% of patients, in both treatment arms.

Hematologic Adverse Events

Neutropenia events were more common in the ofatumumab plus chlorambucil arm (Ofa+Chl, 26%; Chl, 15%), whereas the incidence of thrombocytopenia was greater in the chlorambucil monotherapy arm (Ofa+Chl 5%, Chl 10%). Anemia incidence was similar in both arms (5%). The frequency of hematologic autoimmune adverse events was 1% in both treatment arms. Although adverse events related to thrombocytopenia was lower in the CHL/O arms, other cytopenias were reported to be more common in the CHL/O arm. No comparative testing was conducted on these results.

Non Hematologic Adverse Events

Neutropenia, rash, nausea, and fever were reported in ≥5% of patients in each treatment arm. The frequency of nausea was comparable between treatment arms, while neutropenia was more common in the ofatumumab plus chlorambucil arm. Mucocutaneous reactions (events pertaining to or affecting mucous membranes and skin) were reported in a higher proportion of O+CHL subjects than CHL subjects, but the majority of these were Grade 1-2 rash, urticaria, and pruritus. The higher incidence in the O+CHL arm was due to overlap of infusion reaction and mucocutaneous reaction terms.

No case of tumor lysis syndrome meeting the Cairo-Bishop criteria was reported.

Infection complications, including opportunistic infections, were balanced between arms and no case of PML was reported.

Fatigue

As is described in the quality of life section no significant differences in the Fatigue scale of the EORTC QLQ-CLL16.

Infusion Reactions

Infusion reactions were only noted in the Ofatumumab/Chlorambucil combination arm and this is expected due to the fact that these reactions are associated with monoclonal antibody infusions. The most commonly reported infusion reactions included rash, nausea, urticaria, and fever/pyrexia. These primarily occurred during the first 2 cycles and were clinically manageable with the supportive care guidelines provided in the protocol. Most infusion reactions were considered mild to moderate in severity (10% Grade ≥3), decreased in frequency over subsequent cycles, and led to permanent discontinuation of study treatment only in a small proportion of subjects (3%). There were no fatal infusion reactions.

Quality of life (QoL)

Comparison of Health Related Quality of Life was evaluated using EORTC QLQ-C30 Global Health scores (increase from baselines) and EORTC QLQ-CLL16 Fatigue scores (decrease from baseline), which were prespecified as the principal QOL outcomes. Quality of life outcomes were reported for treatment phase and follow up phase.

Table 6. Quality of Life

Treatment phase No significant differences for Global Health scale of the EORTC QLQ-C30 or the Fatigue scale of the EORTC QLQ-CLL16 Significant differences (p<0.05) favoring chl + o arm for: • Emotional Functionality scale of the EORTC QLQ-C30 • Infection scale of the EORTC QLQ-CLL16 • B-symptoms score
Follow-up phase No significant differences for Global Health scale of the EORTC QLQ-C30 or the Fatigue scale of the EORTC QLQ-CLL16. Significant differences (p<0.05) for: • Physical functioning (favoring CHL arm) • Financial difficulties (favoring CHL + O arm)

6.4 Ongoing Trials

There were 57 results returned from the clinicaltrials.gov search on the following search terms: Chronic lymphocytic leukemia and ofatumumab, searched on May 28th, 2014. One trial matched inclusion criteria and is summarized below.

Table 7: Study NCT01678430 - A Randomised Investigation of Alternative Ofatumumab-containing Regimens in Less Fit Patients With CLL

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study ID #: NCT01678430 **Official Title:** A Randomised Investigation of Alternative Ofatumumab-containing Regimens in Less Fit Patients With CLL **Trial Type:** Phase III RCT **Sponsors:** University of Liverpool GlaxoSmithKline Napp Pharmaceuticals Limited Chugai Pharma USA **Sample Size** 670 **Expected End Date** December 2017	Patients with Chronic Lymphocytic Leukemia, requiring treatment, who are considered, not fit enough for rituximab, fludarabine & cyclophosphamide (R-FC). CLL/SLL requiring treatment defined by NCI/IWCLL 2008 criteria and must satisfy at least one of the following criteria: • Progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. • Massive (i.e. 6 cm below the left costal margin) or progressive or symptomatic splenomegaly. • Massive (i.e. 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy. • Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. • No prior cytotoxic or targeted therapy for CLL • Full-dose R-FC considered inappropriate for at least one of the following reasons: • Age 75 or greater • WHO performance status 2 or 3 • Cardiac impairment (NYHA class II) • Respiratory impairment (bronchiectasis or moderate COPD) • Renal impairment (estimated Glomerular Filtration Rate (eGFR) 10-30 ml/min) • Any other significant co-morbidity or factor that makes R-FC inappropriate • Considered able to tolerate Chl at the dose used in the LRF CLL4 trial (10mg/m2 d1-7) • Written informed consent	ofatumumab & chlorambucil (O-Chl) vs. ofatumumab & bendamustine (O-B)	**Primary Endpoints:** • PFS **Secondary Endpoints:** • Duration of response • OS • Toxicity • Dose • Quality of life

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Hematology Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ofatumumab (Arzerra) for previously untreated patients with CLL for whom fludarabine treatment is considered inappropriate. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Hematology Clinical Guidance Panel is comprised of hematologist and oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

Literature search via OVID platform

1. lymphocytic leukemia/ or Leukemia, Lymophocytic, Chronic/
2. (chronic lymphocytic leukemia: or CLL:).ti,ab,rn,nm,sh,hw,ot.
3. 679818-59-8.rn,nm.
4. (ofatumumab or arzerra).ti,ab,rn,nm,sh,hw,ot.
5. *ofatumumab/
6. 1 or 2
7. or/3-5
8. 6 and 7
9. exp animals/
10. exp animal experimentation/
11. exp models animal/
12. exp animal experiment/
13. nonhuman/
14. exp vertebrate/
15. or/9-14
16. exp humans/
17. exp human experiment/
18. or/16-17
19. 15 not 18
20. 8 not 19
21. (randomized controlled trial or controlled clinical trial).pt.
22. randomized controlled trial/
23. randomized controlled trials as topic/
24. controlled clinical trial/
25. controlled clinical trials as topic/
26. randomization/
27. random allocation/
28. double-blind method/
29. double-blind procedure/
30. double-blind studies/
31. single-blind method/
32. single-blind procedure/
33. single-blind studies/
34. placebos/
35. placebo/
36. control groups/
37. control group/
38. (random: or sham or placebo:).ti,ab,hw.
39. ((singl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
40. ((tripl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
41. (control: adj3 (study or studies or trial:)).ti,ab.
42. (nonrandom: or non random: or non-random: or quasi-random: or quasirandom:).ti,ab,hw.
43. allocated.ti,ab,hw.
44. ((open label or open-label) adj5 (study or studies or trial:)).ti,ab,hw.
45. or/21-44
46. 20 and 45
47. remove duplicates from 46
48. limit 47 to english language

Literature search via PubMed

"Ofatumumab or Arzerra AND chronic lymphocytic leukemia"

Cochrane Library

Grey Literature Search via
- ClinicalTrials.guv
- ASCO, ESMO, ASH Conference Abstracts

"Ofatumumab OR Arzerra AND chronic lymphocytic leukemia"

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