pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Obinutuzumab (Gazyva) for Chronic Lymphocytic Leukemia

January 27, 2015

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TABLE OF CONTENTS

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of obinutuzumab (Gazyva) in combination with chlorambucil as compared to an appropriate comparator (eg. chlorambucil, chlorambucil plus rituximab) in patients with previously untreated chronic lymphocytic leukemia (CLL) where fludarabine-based therapy is considered inappropriate.

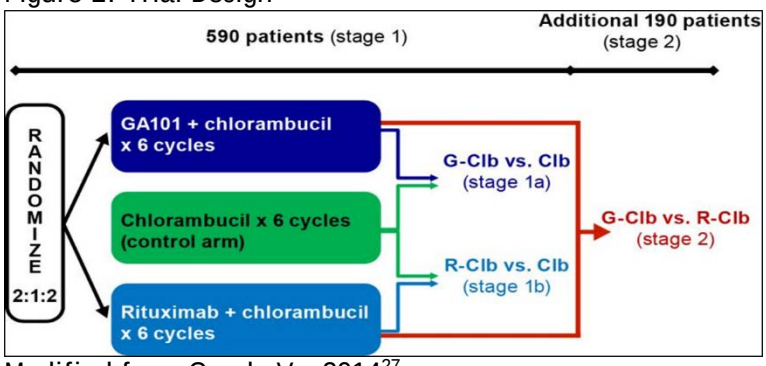
Obinutuzumab is a glycoengineered, humanized type II anti-CD20 monoclonal antibody which directly triggers programmed cell death. Health Canada's approved indication for obinutuzumab is in combination with chlorambucil for the treatment of patients with previously untreated CLL.[1] Health Canada's recommended dosage of obinutuzumab is 1000 mg administered on day 1-2, day 8, and day 15 of the first 28 day treatment cycle followed by a fixed dose of 1000 mg administered on day 1 only for each subsequent treatment cycle (cycles 2 to 6).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label three-armed randomized controlled trial CLL11 (N=781) compared obinutuzumab-chlorambucil (ObChl, n=238) vs. chlorambucil alone (Chl n=118) in Stage 1a, rituximab-chlorambucil (RChl, n=233) vs. chlorambucil alone (n=118) in Stage 1b, and obinutuzumab-chlorambucil (additional 95 patients for a total of n=333) vs. rituximab-chlorambucil (additional 97 patients for a total of n=330) in Stage 2, in previously untreated CLL patients with coexisting conditions.

Figure 2. Trial Design



Modified from Goede V., 2014[27]

Enrollment in the CLL11 trial was preceded by a safety run-in phase administering ObChl to 6 patients to assess safety of this combination. Thereafter, enrollment was opened to all three treatment arms of ObChl, Chl, or RChl, stage one (ObChl vs. RChl vs. Chl) followed by stage two (ObChl vs. RChl). Demographic and diagnostic/prognostic characteristics were well balanced, the median age was 73 years, median Cumulative Illness Rating Scale (CIRS) score was 8 at baseline, and 82% of patients had more than three coexisting conditions. There were differences in circulating lymphocyte counts, in that there was a higher proportion of lower lymphocyte counts ($<25x10^9$ cells/L) in the RChl arm in stage 1b (RChl vs. Chl). There were differences in del(17)p but they were not statistically significant.

Efficacy

The primary endpoint was investigator-assessed progression free survival (PFS) with overall survival (OS) and response rates as secondary endpoints.

A significant improvement in PFS was found in both antibody treatment arms in stage 1a/b, of ObChl and RChl compared to Chl alone. Median PFS was 26.7 months for ObChl vs. 11.1 months for Chl alone (hazard ratio (HR)=0.18, 95%CI: 0.13-0.24, p<0.001). The median PFS was 16.3 months for RChl vs. 11.1 months for Chl alone (HR=0.44, 95%CI: 0.34-0.57, p<0.001). This benefit was seen in all analyzed subgroups, except in patients with del(17)p. In stage 2, there was a significant prolongation in PFS in ObChl with 26.7 months vs. RChl with 15.2 months (HR=0.39, 95%CI=0.31-0.49, p<0.001). PFS results were confirmed with an independent review committee.

OS medians were not reached at the time of analysis (May 9th, 2013). A significant improvement in OS was associated with ObChl compared to Chl (HR=0.41, 95%CI: 0.23-0.74, p=0.002). Rates of deaths were 9% and 20%, respectively. No significant benefit in OS was found in RChl vs. Chl or ObChl vs. RChl. Overall response rates at 3 months after treatment were increased with ObChl (77%) and RChl (66%) compared to Chl (31%). In stage 2, overall response rates were higher in the ObChl arm (78%) vs. RChl (65%).

Harms

In stage 1, the proportion of patients who died were 9%, 15%, and 20% for the ObChl, RChl, and Chl arms respectively. During stage 2, there were 8% and 12% in the ObChl and RChl arms respectively. Deaths due to adverse events in stage 2 occurred in 4% of the ObChl arm and 6% in the RChl arm. No deaths were due to infusion reactions.

During stage 2 treatment-related adverse events (grade ≥3) occurred in 70% and 55% of patients in the ObChl and RChl arms respectively. Neutropenia was the most frequently occurring hematologic adverse event and similar rates of febrile neutropenia were seen in both arms (≤2%). Infusion-related reactions occurred most frequently in the ObChl arm in both stages of the study (20%), they occured within the first cycle of obinutuzumab.

No statistically significant differences were noted between all arms for both safety and global measures of quality of life, however the study was not powered to detect statistical differences in these parameters.

1.2.2 Additional Evidence

pCODR received input on obinutuzumab (Gazyva) for chronic lymphocytic leukemia from three patient advocacy groups, Chronic Lymphocytic Leukemia Patient Advocacy Group (CLL PAG), the Leukemia and Lymphoma Society of Canada (LLSC), and Lymphoma Foundation Canada (LC). 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

CLL represents the most common leukemia in western countries and is characterized by a long natural history with a median survival from diagnosis of 10 or more years. Treatment is normally reserved for patients with symptomatic disease as cure is not a realistic goal with current modalities. For patients in good health and under the age of 65, the standard of care is fludarabine, cyclophosphamide and rituximab (FCR). However the toxicity of this regimen is too great for the majority of patients with CLL to manage. Patients over the age of 65 with comorbidities benefit from less toxic regimens such as chlorambucil but the response rate and survival is less than FCR.

The addition of an anti-CD20 monoclonal antibody (i.e. rituximab or ofatumumab) to chlorambucil or other chemotherapy regimen such as bendamustine, has improved PFS but there has been no improvements in OS. While rituximab-chlorambucil is only funded in a limited number of provinces, the Clinical Guidance Panel agreed that it is likely used more broadly in clinical practice and constitutes as a clinically relevant treatment option for patients where fludarabine based therapy is unsuitable.

There was a statistically significant PFS benefit with obinutuzumab-chlorambucil when compared to chlorambucil alone (absolute benefit of 15.6 months) and rituximab-chlorambucil (absolute benefit of 11.5 months). Overall survival advantage was seen for obinutuzumab-chlorambucil over chlorambucil alone. Obinutuzumab-chlorambucil is the first combination to demonstrate a survival advantage in first-line therapy over chlorambucil alone in symptomatic CLL patients over the age of 65 with comorbidities or reduced renal function, this cohort of patients represents the majority of CLL patients. There was no survival advantage when compared to rituximab-chlorambucil, however OS medians have not been reached.

The study reported no deterioration in quality of life in the obinutuzumab-chlorambucil arm.

Obinutuzumab-chlorambucil had higher rates of infusion-related reactions, these reactions only occurred in the first cycle. Neutropenia was also more common in the obinutuzumab-chlorambucil arm compared to both chlorambucil and rituximab-chlorambucil. Despite the increased rate of neutropenia, rate of febrile neutropenia was low (2%). Higher rates of adverse events were seen with obinutuzumab-chlorambucil due primarily to the increased frequency of infusion-related reactions, but given the use of other monoclonal antibodies such as rituximab there is familiarity in managing these predictable toxicities.

1.3 Conclusions

The pCODR Hematology Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of obinutuzumab plus chlorambucil in the first line treatment of CLL patients unfit for FCR chemotherapy. This is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival compared to chlorambucil and a clinically and statistically significant benefit in PFS compared to both chlorambucil and rituximab-chlorambucil. Although there is an increased rate of grade 3 or greater adverse events with the use of obinutuzumab, this is primarily due to infusion reactions at the time of the first infusion. This and other toxicities are predictable and manageable.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Although randomized controlled trials with a similar patient population comparing chlorambucil to other anticipated therapies and compounds for CLL (bendamustine, fludarabine, and other anti-CD20 monoclonal antibodies plus chlorambucil) have been conducted and it is not possible to compare between trials; within the broader study inclusion criteria of 18 years of age, obinutuzumab-chlorambucil is the first regimen thus far to demonstrate an overall survival advantage compared to chlorambucil in the first-line setting in the patient population over 65 years with comorbidities.
- The PFS benefit of obinutuzumab-chlorambucil compared to rituximab-chlorambucil is significant, and satisfies the feedback from patient advocacy groups wishing for treatments with longer and deeper remissions, and a

manageable side effect profile. Longer follow-up is necessary to determine the full magnitude of benefit.

- In addition to the obinutuzumab-chlorambucil data, Stage 1 of this trial provides the only randomized phase III data comparing rituximab-chlorambucil to chlorambucil alone. The trial demonstrates a small but statistically significant PFS benefit of rituximab-chlorambucil compared to chlorambucil alone, with no overall survival advantage. This is a relevant outcome of this study due to provincial variation in the use of rituximab-chlorambucil in the first-line setting.
- There is no data directly comparing obinutuzumab-chlorambucil to bendamustine.
- Evidence for obinutuzumab-chlorambucil has only been demonstrated in the first line setting and results cannot be generalized to use in subsequent lines of therapy, with other compounds other than chlorambucil, retreatment in a subsequent line of therapy, and treatment beyond 6 cycles (use as maintenance therapy). There is no data showing benefit in these scenarios.
- For young, fit patients, standard of care remains FCR, obinutuzumab has not been studied in this patient population.
- Quality of life appears unaffected but data are limited.

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 obinutuzumab used in combination with chlorambucil for patients with previously untreated chronic lymphocytic leukemia where fludarabine based therapy is considered unsuitable. 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 obinutuzumab 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 obinutuzumab and a summary of submitted Provincial Advisory Group Input on obinutuzumab 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. CLL is characterized by a clonal expansion of morphologically mature but immunologically incompetent B lymphocytes, leading to a progressive accumulation of abnormal B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Chlorambucil with or without corticosteroids has been the most frequently used treatment for CLL. Other treatments such as adding an anti-CD20 monoclonal antibody (i.e. rituximab or ofatumumab) or by using other chemotherapy regimens such as bendamustine have been utilized in this population. Obinutuzumab (GA101; RO5072759) is a recombinant humanized and glycoengineered Type II anti-CD20 monoclonal antibody. Obinutuzumab in combination with chlorambucil provides a new treatment option for patients with previously untreated CLL.[2]

Generally patients can be classified with "aggressive" or "indolent" CLL. Some patients can survive for long periods without treatment, while others require more immediate treatment.[3] 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.[2] Although the majority of patients with CLL are of advanced age, these patients have not been well represented in past clinical trials. Improvements in prognostic categorization have resulted in identification of "high risk" and "low risk" patients. 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.[3] Treatment including the nucleoside analog fludarabine was compared with chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS.[31] 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 of severe infection.[5] 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 fludarabine and cyclophosphamide.[6] Patients who cannot tolerate toxicity associated with aggressive chemotherapy, for whom fludarabine is unsuitable, and are the population of focus in this review.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of obinutuzumab in combination with chlorambucil, on patient outcomes compared with appropriate comparators in treatment of patients with previously untreated chronic lymphocytic leukemia where fludarabine-based therapy is considered unsuitable. Only randomised controlled trials were considered for inclusion in this review. Overall survival, progression free survival, response rate, hematologic/non-hematologic, ≥grade 3 adverse events (AEs), infusion reactions, infections, fatigue, hepatitis B virus (hep-B)/cytomegalovirus (CMV)/ herpes simplex virus (HSV) reactivations are outcomes of interest.

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 (CLL11) met the eligibility criteria for this review, the trial evaluated obinutuzumab in combination with chlorambucil (ObChl) versus chlorambucil in combination with rituximab (RChl) versus chlorambucil monotherapy (Chl) in 781 patients.[4] Enrollment was preceded by a safety run-in phase administering ObChl to 6 patients to assess safety of this combination. This is a three arm trial which randomized patients on a 1:2:2 basis: Chl, ObChl, or RChl. During stage one 118 patients were enrolled in the chlorambucil monotherapy arm, 238 in chlorambucil/obinutuzumab arm, and 233 in the chlorambucil/rituximab arm. During phase two an additional 95 patients, were enrolled in the ObChl arm bringing total enrollment to 333. An additional 97 patients were enrolled in the, RChl arm bringing total enrollment to 330. Demographic and diagnostic/prognostic characteristics were well balanced between arms although there were differences in circulating lymphocyte counts and del(17p) in stage one in the RChl versus Chl arms. Differences were significant in the case of circulating lymphocytes with those in the RChl arm having higher proportion of lower lymphocyte counts (<25x10^9 cells/L). Differences in del(17p) were not indicated as statistically significant.

Progression free survival (PFS) is the primary endpoint in this study. Both investigator assessments and independent assessments were conducted for PFS. Overall response rate, overall survival, safety/toxicity, and quality of life were secondary endpoints. In stage one, PFS was found to be significantly prolonged for both combination arms, 26.7 months with ObChl and 16.3 months with RChl, compared with 11.1 months with chlorambucil monotherapy (ObChl results: HR=0.18, 95%CI 0.13-0.24, p<0.001; RChl results: HR=0.44, 95%CI 0.34-0.57, p<0.001).

Progression free survival was significantly extended in stage two of the trial with ObChl compared to RChl (HR=0.39, 95%CI 0.31-0.49, p<0.001). In stage one overall survival was found to be significantly in favour of ObChl compared to Chl with HR=0.41, 95%CI 0.23-0.74, p=0.002. There was no significant prolongation in overall survival during stage one for RChl versus Chl where HR=0.66, 95%CI 0.39-1.11, p=0.11; or during stage two for ObChl versus RChl where HR=0.66, 95%CI 0.41-1.06, p=0.08. However, it is important to note that median overall survival has not been reached for stage two.

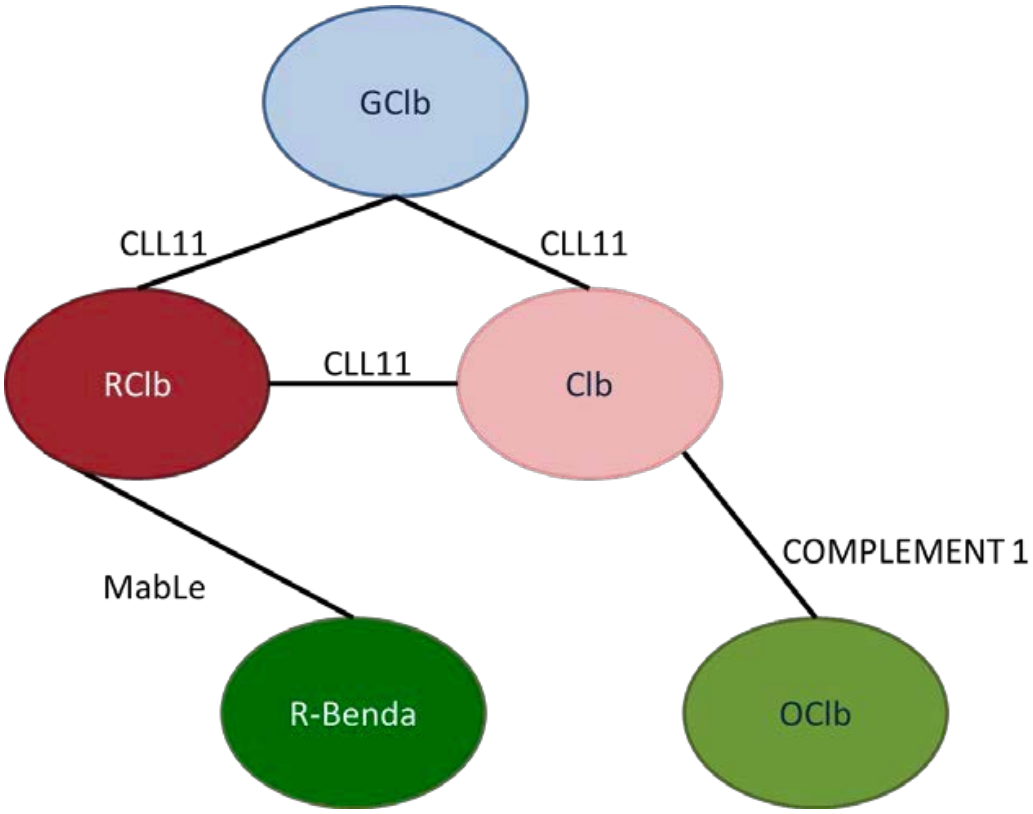
During stage one treatment-related ≥ grade 3 adverse events (AE) occurred in 73% and 56% of patients in the ObChl and RChl arms respectively. In stage two the equivalent ≥ grade 3 AE's occurred in 70% and 55% of patients in ObChl and RChl arms respectively.[4] There were 21 (6.4%) deaths due to AEs in the RChl group, 15 (4.5%) deaths due to AEs in the ObChl group and 11 (9%) deaths due to AEs in the Chl alone group.[4] Neutropenia was the most frequently occurring hematologic AE occurring in 33% versus 28% of patients in the ObChl versus RChl arms respectively.[4] Febrile neutropenia was similar between groups and stages.[4] Infusion related reactions occurred most frequently in the ObChl arm, in both stages of the study. Twenty-one percent vs 4% had an event in the ObChl versus RChl arms respectively during stage one, and 20% of patients versus 4% in stage two.[4] Infections occurred in 12% and 14% of patients during stage 2 of the study and fatigue was similar with 8% and 9% having events in ObChl and RChl arms, respectively.[2] No statistically significant differences were noted between arms for both safety and global measures of quality of life, however the study was not powered to detect statistical differences in these parameters.

The main limitations associated with this study are that it is open label, that patient crossover to ObChl from the Clb arm was allowed (if progression during or within 6 months of treatment completion) and could impact the OS results, and that there were slight differences in prognostic characteristics that could influence survival and response outcomes. Furthermore, due to the fact that stage two is ongoing and OS medians have not yet been reached, results are not final and could change considerably throughout the course of follow-up. Assessment of disease progression and response was confirmed by an independent review committee, indicating investigator results are robust.

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.

A network meta-analysis was submitted for indirect comparison of obinutuzumab plus chlorambucil to bendamustine monotherapy. The network of evidence included a total of 16 randomized controlled trials (including the CLL11 study which is under review in this report), encompassing 14 different pharmacological interventions to estimate the indirect comparative effectiveness of obinutuzumab against 13 other comparators for progression-free survival. The following diagram highlights the network for the studies enrolling only patients ineligible to fludarabine-based therapy. The Knauf trial comparing bendamustine to chlorambucil is excluded in this network meta-analysis as patients are believed to have been enrolled regardless of their (in)eligibility to fludarabine-based therapy.[3] Further, MabLe will only be added to this network meta-analysis once trial results become available, though it is represented in the diagram.



ClB: Chlorambucil; G: Obinutuzumab; R: Rituximab; O: Ofatumumab: Benda: Bendamustine

Given the current funding of bendamustine, a brief assessment was made by pCODR to determine the appropriateness of an indirect comparison between obinutuzumab 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:

- Obinutuzumab plus chlorambucil versus rituximab plus chlorambucil versus chlorambucil in the three-arm CLL11 trial[4], 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 (study under review in this Clinical Guidance Report).
- Bendamustine versus chlorambucil in the 02CLLIII trial[19], 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).
- Ofatumumab plus chlorambucil versus chlorambucil in the COMPLEMENT-1 trial[23], 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.

The submitter, through their network meta-analysis, concluded that obinutuzumab was the most effective treatment against any of the above comparators.

However, the CGP concluded that an indirect comparison between obinutuzumab plus chlorambucil, bendamustine and ofatumumab plus chlorambucil is not appropriate. This is due to different eligibility criteria and patient populations between the trials included in the indirect comparison and systematic differences in dosing of chlorambucil. 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.

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

	Obinutuzumab plus chlorambucil	Bendamustine	Ofatumumab plus chlorambucil
N	238	162	221
Median age (range)	74 (39-88)	63 (58-70)	69 (35 – 92)
WHO/ECOG PS, n (%) **0** **1** **2**	 NR Median ECOG PS = 1 NR	 113 (69.8) 43 (26.5) 3 (1.9)	 87 (39) 115 (52) 17 (8)
Binet stage, n (%) **A** **B** **C**	 55 (23) 98 (41) 85 (36)	 0 116 (71.6) 46 (28.4)	 77 (35) 74 (33) 70 (32)

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 (%)

	CLL11		Knauf et al.		COMPLEMENT-1	
	ObChl	Chl	B	Chl	OChl	Chl
Overall response	184 (77.3)	37 (31.4)	110 (68)	48 (31)	NR (82)	155 (69)
Median progression-free survival (months)	26.7	11.1	21.6	8.3	22.4	13.1

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

	CLL11		Knauf et al.		COMPLEMENT-1	
	ObChl	Chl	B	Chl	OChl	Chl
Grade ≥3 AEs	73%	50%	NR	NR	50%	43%
Neutropenia grade ≥3	35%	16%	23%	11%	26%	14%
Infusion-related grade ≥3	21%	N/A	NR	N/A	10%	N/A
Infections grade ≥3	11%	14%	1.9%	1%	15%	14%

AE = adverse event; N/A = not applicable

A separate publication in abstract form, 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.[6] 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

	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 obinutuzumab plus chlorambucil and relevant comparators was done by pCODR 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.

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 correct for spelling or grammar.

Patient Advocacy Group Input

From a patient perspective, patients seek individualized choice in treatment that will offer disease control, deeper and longer lasting remissions and an improved quality of life while offering minimal toxicity and manageable side effect profiles relative to other treatments. Patients seek access to new therapies that produce quick favourable outcomes with relatively mild side effects compared to other forms of existing treatment. Because respondents' 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, and in particular with age often comes comorbidities and this also impacts whether or not a patient can tolerate existing treatments; patient advocacy groups report that CLL patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a broad range of patients, including those that have the poorest prognostic factors and those who are of advanced age with existing co-morbidities. While there are side-effects with the drug under review, respondents reported that the obinutuzumab drug regimen has changed their long-term

health and well-being, and for the most part has provided improvement in the quality of life.

PAG Input

Input on the review of obinutuzumab (Gazyva) 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 or bendamustine monotherapy would be the treatment option for previously untreated CLL in patients who are medically unfit. PAG noted the flat dosing of obinutuzumab 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. 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.

2.2 Interpretation and Guidance

Burden of Illness and Need

CLL is a disease of the elderly, with a median age at diagnosis of 72 years. With a median survival from diagnosis of 10 or more years, its long natural history results in an extended period of watchful waiting in most patients. Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities.

For patients in good health and under the age of 65, the standard of care for symptomatic or advanced stage CLL is combination therapy with fludarabine, cyclophosphamide and rituximab (FCR). However, the toxicity of this regimen is too great for the majority of patients with CLL to manage. Patients over the age of 65 with comorbidities or reduced renal function benefit from less toxic chemotherapy regimens but the response rate, and progression free survival is less than FCR. The cornerstone of therapy in this less fit population has been chlorambucil. Previous attempts to improve outcomes by adding in an anti-CD20 monoclonal antibody (i.e. rituximab or ofatumumab), or by using other chemotherapy regimens such as bendamustine, have improved progression free survival (PFS), but there has been no improvement in overall survival. Obinutuzumab-chlorambucil is the first chemoimmunotherapy combination to demonstrate a survival advantage in first line therapy over chlorambucil alone for symptomatic CLL patients over the age of 65 with comorbidities or reduced renal function. This cohort of patients represents the majority of CLL patients.

Effectiveness

Overall Survival (OS):

The study under review demonstrates an OS advantage of obinutuzumab plus chlorambucil over chlorambucil alone. This is a secondary endpoint of the study. The magnitude of the survival is both statistically and clinically significant. There is a slight imbalance in the baseline prognostic markers of CLL. Unmutated Immunoglobulin variable region (IGHV) was slightly higher in the obinutuzumab-chlorambucil arm compared to chlorambucil alone

(61% vs. 59%), potentially biasing results in favour of chlorambucil. Conversely, del(17p) was higher in the chlorambucil arm (8% vs. 10%), which would bias results in favour of obinutuzumab-chlorambucil. It is unlikely that these differences are significant and do not impact the conclusions of the study. There was no overall survival benefit seen when obinutuzumab-chlorambucil was compared with rituximab-chlorambucil, however OS medians have not been reached.

Progression-free survival (PFS):

The primary endpoint of this study was PFS. The analysis was done at a predetermined checkpoint summarized in Table 3, section 6.3.2.2. Highlighting the pertinent findings for this review, there is a statistically significant PFS when obinutuzumab-chlorambucil was compared to chlorambucil (absolute benefit of 15.6 months). Similarly, when compared to rituximab-chlorambucil, there was an absolute PFS benefit of 11.5 months favoring obinutuzumab-chlorambucil. These results are both statistically and clinically significant providing patients with a significantly longer disease control after therapy.

Quality of life analysis:

The study reports no deterioration in quality of life in the obinutuzumab-chlorambucil arm, but specific details of this analysis are not available.

Safety

Obinutuzumab-chlorambucil had higher rates of infusion reactions compared to rituximab-chlorambucil. These reactions occurred in the first cycle, and did not occur in subsequent cycles. Neutropenia was also more common with obinutuzumab-chlorambucil compared to both chlorambucil and rituximab-chlorambucil. Despite the increased rates of neutropenia, the rate of febrile neutropenia was low (2%), suggesting this toxicity was manageable, and the clinical significance of the neutropenia is low. Other clinically relevant toxicities were balanced between the groups. Due to the widespread use of other monoclonal antibodies such as rituximab, there is familiarity in dealing with infusion-related reactions. Consequently, obinutuzumab plus chlorambucil is a relatively well-tolerated therapy with manageable and predictable toxicities in this less fit patient population.

2.3 Conclusions

The pCODR Hematology Clinical Guidance Panel concluded that there is a net overall clinical benefit to the use of obinutuzumab plus chlorambucil in the first line treatment of CLL patients unfit for FCR chemotherapy. This is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival compared to chlorambucil and a clinically and statistically significant benefit in PFS compared to both chlorambucil and rituximab-chlorambucil. Although there is an increased rate of grade 3 or greater adverse events with the use of obinutuzumab, this is primarily due to infusion reactions at the time of the first infusion. This and other toxicities are predictable and manageable.

In making this conclusion, the Clinical Guidance Panel also considered that:

- Although randomized controlled trials with a similar patient population comparing chlorambucil to other anticipated therapies and compounds for CLL (bendamustine, fludarabine, and other anti-CD20 monoclonal antibodies plus chlorambucil) have been conducted and it is not possible to compare between

trials; within the broader study inclusion criteria of 18 years of age, obinutuzumab-chlorambucil is the first regimen thus far to demonstrate an overall survival advantage compared to chlorambucil in the first-line setting in the patient population over 65 years with comorbidities.

- The PFS benefit of obinutuzumab-chlorambucil compared to rituximab-chlorambucil is significant, and satisfies the feedback from patient advocacy groups wishing for treatments with longer and deeper remissions, and a manageable side effect profile. Longer follow-up is necessary to determine the full magnitude of benefit.
- In addition to the obinutuzumab-chlorambucil data, stage one of this trial provides the only randomized phase III data comparing rituximab-chlorambucil to chlorambucil alone. The trial demonstrates a small but statistically significant PFS benefit of rituximab-chlorambucil compared to chlorambucil alone, with no overall survival advantage. This is a relevant outcome of this study due to provincial variation in the use of rituximab-chlorambucil in the first-line setting.
- There is no data directly comparing obinutuzumab-chlorambucil to bendamustine.
- Evidence for obinutuzumab-chlorambucil has only been demonstrated in the first line setting and results cannot be generalized to use in subsequent lines of therapy, with other compounds other than chlorambucil, retreatment in a subsequent line of therapy, and treatment beyond 6 cycles (use as maintenance therapy). There is no data showing benefit in these scenarios.
- For young, fit patients, standard of care remains FCR, obinutuzumab has not been studied in this patient population.
- Quality of life appears unaffected but data are limited.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Hematology 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 4.8 cases/100 000 population, chronic lymphocytic leukemia (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 or more years) results in an extended period of watchful waiting in most patients [7]. Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities.

A diagnosis of CLL is normally suspected when an unexplained lymphocytosis is noted on blood counts, often done for another reason. The diagnosis is usually made on flow cytometry of peripheral blood demonstrating 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[8]. In the absence of extramedullary involvement there must be $\geq 5 \times 10^9$ cells/L in the peripheral blood with this phenotype for a diagnosis of CLL to be made. 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. The management of CLL and SLL is identical. 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 peripheral lymphomas, such as mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma as treatment of these entities differ from that of CLL/SLL.

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).[9, 10] 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 a poor prognosis and is a commonly accepted indication for treatment.

A large number 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. Blood tests indicating rapid turnover including β2-microglobulin and thymidine kinase have also been confirmed to reflect adverse prognosis.[11]

Patient advocacy groups expressed concern with respect to a rise of the white blood cell count with treatment. There are some compounds used to treat CLL where a progressive lymphocytosis occurs as a side effect of therapy. However, the combination of obinutuzumab-chlorambucil does not cause this response.

Table 1. Accepted staging systems for patients with chronic lymphocytic leukemia.[9, 10]

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.

Immunoglobulin gene rearrangement is also associated with prognosis. During the development of normal B lymphocytes, acquisition of mutations in variable regions of immunoglobulin genes occurs through somatic hypermutation. CLL may arise from either antigen naïve (without immunoglobulin gene somatic hypermutation) or antigen exposed (with somatic hypermutation) B-cells.[11] These two disease subtypes have dramatically divergent clinical courses, with patients with unmutated disease having median survival of 8 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. Although two such markers, CD38 and ZAP-70, are correlated with mutational status, they are insufficiently precise to be solely relied upon for prognostication. [12]

Cytogenetic analysis has also become an important prognostic tool. With fluorescent in-situ hybridization (FISH), genetic mutations are detected in 80% of patients with CLL. Some mutations such as an isolated 13q deletion are associated with a favorable prognosis, while other mutations (deletion 11q or 17p) are associated with a poor prognosis. A prognostic model based on mutation analysis has highlighted the heterogeneity of CLL, with a median overall survival ranging from 32 months to 133 months depending on the particular mutations present.[13]

3.2 Accepted Clinical Practice

Although there are numerous prognostic markers available for CLL as outlined above, their usefulness in guiding treatment decisions is still an area of ongoing investigation. The decision to treat is predominantly based on whether the patient has symptoms related to CLL or advanced disease causing significant cytopenias. Treatment in asymptomatic, early

stage disease has failed to show benefit[14], and a watchful waiting approach is appropriate in this patient group. Common indications to initiate therapy include the development of cytopenias (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling time (< 3 months). Once a need for therapy is established, the choice of first line therapy depends on the age and overall health of the patient.

For patients in good health and under the age of 65, the standard of care for symptomatic or advanced stage CLL is combination therapy with fludarabine, cyclophosphamide and rituximab (FCR). The German CLL Study Group study showed improvement in 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.[15] However, in subgroup analysis, the survival advantage was lost for patients over the age of 65, and there was higher incidence of infections and toxicity in this age group. Consequently, this regimen is typically reserved for patients under the age of 65 with a low comorbidity index.[16]

Patients over the age of 65, or those who are not considered fit enough to receive FCR but are still suitable to receive treatment, may derive benefit from several less intensive regimens. Chlorambucil, an alkylating agent, is well tolerated and has been in use for more than 30 years. It can be given in daily, weekly, biweekly and monthly schedules. However, response rates are low. Attempts to improve response rates using alternate therapies have been associated with increased toxicity and no long-term benefit. Fludarabine was compared to chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS.[17] Patients treated with fludarabine in this study had a higher rate of severe infection and neutropenia[18] and consequently, the toxicity outweighed the benefit. Bendamustine was also compared with chlorambucil.[19] Response rates and PFS were markedly improved with bendamustine as compared to chlorambucil. Overall survival was not significantly increased; however OS was not a primary endpoint of the trial. Toxicity appeared to be increased with bendamustine, although statistical significance was not reported. As a result, bendamustine has entered clinical practice as a treatment option for patients not fit for fludarabine-based therapy. Chlormabucil also remains an option for elderly and less fit patients.

The addition of anti-CD20 monoclonal antibodies have revolutionized treatment for B-cell malignancies. These antibodies can induce cell death by a number of mechanisms such as antibody-dependent cellular cytotoxicity and phagocytosis, by complement-mediated cell death, or by the direct induction of programmed cell death. Rituximab and ofatumumab are Type I monoclonal antibodies that work predominantly by redistribution of the CD20 molecules on the cell membrane which triggers complement mediated destruction. Type II antibodies such as obinutuzumab directly trigger programmed cell death.[20] Both Type I and Type II monoclonal antibodies are equally effective at activating immune effector cells. Obinutuzumab is the first glycoengineered, humanized type II anti-CD20 monoclonal antibody utilized in clinical practice. It can induce significant apoptotic cell death over and above the high degree of spontaneous apoptosis compared to rituximab. This leads to the elimination of malignant B-cells without the requirement of immune effector cells. The activity of obinutuzumab in heavily pre-treated patients was confirmed in a phase I study in patients with B-cell lymphoma suggesting this novel mechanism of action has clinical relevance, and prompted the need for further research with this drug.[21]

In fit individuals with CLL, the addition of an anti-CD20 monoclonal antibody to chemotherapy has a proven survival advantage (FCR vs. FC).[22] Until recently, such a survival advantage had not been demonstrated in patients with comorbidities. In phase III studies, rituximab and ofatumumab demonstrated higher response rates, and complete remission rates compared to chlorambucil alone, but no improvement in OS.[4, 23] The role of obinutuzumab in the treatment of CLL is the topic of this review.

3.3 Evidence-Based Considerations for a Funding Population

The majority of patients with CLL are elderly, and may be unsuitable to receive fludarabine-based treatment, but 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 can 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.[24] Patients with a CIRS above 6, or a creatinine clearance less than 70 ml per minute have generally been considered unsuitability for FCR, and less intensive regimens should be considered.

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. No additional diagnostic tests are required beyond the current standard of care for CLL patients.

3.4 Other Patient Populations in Whom the Drug May Be Used

Aside from a phase I study confirming activity of obinutuzumab in heavily pre-treated patients[21], there is no published data to support the use of obinutuzumab in the relapsed setting.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Three patient advocacy groups, (1) Chronic Lymphocytic Leukemia Patient Advocacy Group ("CLL PAG"), (2) the Leukemia and Lymphoma Society of Canada ("LLSC") and (3) Lymphoma Foundation Canada ("LC"), provided input on obinutuzumab in combination with chlorambucil for previously untreated chronic lymphocytic leukemia where fludarabine-based therapy is considered unsuitable, and their input is summarized below.

CLL PAG and LLSC conducted a joint online survey asking for input from patients who have been diagnosed with chronic lymphocytic leukemia (CLL), are currently in treatment or are in remission ("Survey 1"). Survey 1 was posted on www.cllpag.ca, www.cllcanada.ca and www.LLSCanada.org websites, and distributed through other channels, including social media, online forum and emails. A total of 212 responses were received. The responses came in from respondents worldwide and included: 60 from Canada; 104 from USA; 18 from the United Kingdom; 9 from Australia; 1 from France; 1 from Brazil. 19 respondents did not indicate their country of residence. Of the total responses, 54% of the respondents were female and 46% male. Respondents also provided their age category. The age breakdown of respondents is recorded in the table below (note 17 people did not answer this question):

Answer Options	Response Percent	Response Count
39 or younger	0.5%	1
40-49	9.2%	18
50-59	32.8%	64
60-69	40.0%	78
70-79	16.9%	33
80-89	0.5%	1

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

In addition to the above, a separate survey ("Survey 2") was distributed through the same channels for CLL patients who have experienced with obinutuzumab. There were a total of 7 responses to Survey 2. It was reported that 86% (6/7) of respondents were from the USA, and one was from Canada. The age range included 50-59 years of age - 1 (14.29%), 60-69 years of age - 4 (57.14%) and 70-79 years of age - 2 (28.57%). Four respondents (57.14%) were women.

LC conducted two online surveys (one of patients and one of caregivers) to gather information about the impact of CLL on their lives and the effect of treatments on their disease. The surveys were sent via e-mail to patients and caregivers registered on the LC database, and were also made available via LC Twitter and Facebook accounts. LC reported that nine (9) respondents had direct experience with using obinutuzumab. Three (3) respondents were obtained through the survey. Another three (3) respondents were obtained through an online interview. LC also

conducted telephone interviews with three patients who had direct experience with obinutuzumab to provide meaningful perspectives of the drug under review. These patients were located with the assistance of the Lymphoma Research Foundation in the United States and by using a search of publicly available blogs of patients with obinutuzumab experience. Please see below for a breakdown of the results to the surveys and interview.

Participants by Country		Canada (n, %)	USA (n, %)	UK (n, %)	Australia (n, %)	Skipped (n, %)	Total (n)
Survey	Patients without Obinutuzumab Experience	23 (67.6%)	7 (20.6%)	-	1 (2.9%)	3 (8.8%)	34
	Patients with Obinutuzumab Experience	1 (33.3%)	2 (66.7%)	-	-	-	3
	Total (Patient Survey Respondents)	**24 (64.9%)**	**9 (24.3%)**	**-**	**1 (2.7%)**	**3 (8.1%)**	**37**
Interviews	Patients with Obinutuzumab Experience	2 (33.3%)	4 (66.7%)	-	-	-	6
Survey	Caregivers – none with obinutuzumab Experience	9 (81.8%)	1 (9.1%)	1 (9.1%)	-	-	11
Total	**Survey & Interviews**	**35 (64.8%)**	**14 (25.9%)**	**1 (1.9%)**	**1 (1.9%)**	**3 (5.6%)**	**54**

From a patient perspective, patients seek individualized choice in treatment that will offer disease control, deeper and longer lasting remissions and an improved quality of life while offering minimal toxicity and manageable side effect profiles relative to other treatments. Patients seek access to new therapies that produce quick favourable outcomes with relatively mild side effects compared to other forms of existing treatment. Because respondents' 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, and in particular with age often comes comorbidities and this also impacts whether or not a patient can tolerate existing treatments; patient advocacy groups report that CLL patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a broad range of patients, including those that have the poorest prognostic factors and those who are of advanced age with existing co-morbidities. While there are side-effects with the drug under review, respondents reported that the obinutuzumab drug regimen has changed their long-term health and well-being, and for the most part has provided improvement in the quality of life.

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 CLL

According to LC, patients with early stage CLL who participated in the survey reported minimal symptoms associated with their disease and noted a good quality of life. For those with more advanced disease, the respondents reported their quality of life being impacted more significantly. Fatigue was most commonly reported. Respondents described feeling a depletion of energy and stated that they needed to rest often in order to perform their normal daily activities. Some respondents with CLL expressed difficulties with concentration, emotions, stress levels, insomnia and mood swings. Additional symptoms reported included enlarged lymph nodes, fever, night sweats, peripheral neuropathy and

weight loss. Frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts) were also reported. LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day-activities. Many respondents also had relapsed from previous treatments. Below were some of the direct quotes from the respondents.

> "*My illness has robbed me of so many goals I had for my life and my family. I know I could have grown my business to a much greater level… I couldn't make it to work everyday from the fatigue or was at another Cancer Clinic appointment. The illness plays on your mind and you are angry that it was me it picked. It has impacted my family life in ways that I must depend on my wife and children to help me out to do manual chores or submit paper work to get some reimbursement from insurance companies that structure themselves so that the forms are lengthy and multiple phone calls are required to obtain payment. I have cancelled holidays with family and friends because my platelet counts are too low and I might have a life threatening bleed. My wife and I* plan our lives around my clinic appointments." (male; 45-54; Canada)
>
> *"It is difficult to deal with changes in blood count nos. constantly. It means being on and off treatment and that causes stress."* (female; 65-74; Canada)
>
> "*Loss of 25 lbs sure impacted my physical strength and endurance. Have to have a sleep during the day, many days moderate to heavy fatigue. Don't sleep nearly as well at night*." (male; 65-74; Canada)
>
> *"My main symptom initially was an inability to swallow and frequent choking due to enlarged nodes in the neck and throat…I experienced extreme fatigue, weakness and loss of taste, some hair loss…After my immunotherapy my major symptom… was and remains peripheral neuropathy in my feet, upsetting my sense of balance and changes in my walking gait… I experienced loss of concentration and mood swings."* (male; 75 years or older; Canada)

CLL PAG and LLSC asked respondents to rate the disease symptoms as having significant impact on their quality of life (giving the symptom a rating of 5, 6 or 7 on a scale of 1-7, where 1 indicates little impact and 7 indicates severe impact). Respondents reported:

- Fatigue = 46%
- Increasing White Blood Count (leading to weakened immune systems and frequent infections) = 38%
- Enlarged lymph nodes = 27%

A respondent stated: "*CLL is insidious. I didn't know how ill I was until I started receiving treatment and began to have more energy and started feeling so much better. Previously, I thought my fatigue and struggle through my days was normal*." Another respondent said "*My ability to mix socially is severely curtailed due to the associated risk of infections and the long time it takes me to recover from them*."

Respondents also reported the following psychosocial symptoms as having significant impact on their quality of life (giving the symptom a rating of 5, 6 or 7 on a scale of 1-7, where 1 indicates little impact and 7 indicates severe impact):

- Stress = 40%
- Anxiety = 39%
- Depression = 28%

One respondent said: "*I'm a nervous wreck waiting for symptoms. Reading about others stories has given me depression. My hair is falling out I am so stressed.*" Some other notable comments included: "*People expect me to die suddenly since they know I have cancer. Friends talk to me differently and hesitate to ask how I am,*" and "*It's like holding your breath. It is a secret illness that messes with your mind.*"

A number of respondents who are still of working age commented on the effects of CLL on their ability to work. For example, one respondent said: "Fatigue and infections required I stop working in my forties. I could have been a more productive member of society - if the CLL effects were controlled." Another said "My whole life has been wrecked, lost my career, can do little of anything I used to anymore," while another with a similar experience said CLL "shortened my professional career, into early retirement." And lastly, "I am a 46 year old parent of two and my job is the main source of income and insurance for our family. The stress of living with this "time bomb" of a disease can be overwhelming. However, it is comforting to know that there are new treatments out there to help keep my cancer in its place and keep me healthy to see my children grow up."

4.1.2 Patients' Experiences with Current Therapy for CLL

CLL PAG and LLSC found that 43% (91/212) of respondents have received treatment; while 57% (121/212) of respondents are in a watch & wait phase. Many patients refer to 'Watch and Wait' as 'Watch and Worry'. One respondent said "*Watch and wait has been very difficult. Everything we know about cancer (early detection, early treatment) doesn't necessarily apply to CLL. As a young person (44; dx @ 41) it's emotionally difficult to just wait around to get sick.*"

93% (85/91) of respondents who have received treatment responded to questions asking about treatment type(s). The list of therapies is set out below; this includes 2 respondents who are in clinical trials for non-marketed drugs:

Treatment Given	# Patients treated first-line	# Patients treated second-line	# Patients treated third-line
Bendamustine	0	3	2
BR - Bendamustine Rituxan	7	3	3
BR + ibrutinib	0	2	1
Campath	1	0	0
Chlorambucil	5	0	0
CR - Chlorambucil Rituxan	1	0	0
CVP	1	0	0
CVP + R	0	2	11
DHAP	0	0	1
Fludarabine	0	1	0
FC	0	1	0
FCR	35	4	1
FR	8	2	0
Ibrutinib	6	4	4
Ibrutinib Rituxan	2	1	0
Obinutuzumab	1	2	0
PCR	3	0	0

Treatment Given	# Patients treated first-line	# Patients treated second-line	# Patients treated third-line
R-CHOP	0	1	0
Revlimid	2	0	0
Rituxan	13	0	0
TOTAL	85	28	14

Seven respondents have received fourth line treatment (obinutuzumab, ibrutinib, bendamustine and rituximab, R-Chop, CVP-R, CHOP, FCR). Five have received fifth line treatment (two on ibrutinib, two BR, one R-CHOP) and three have received sixth-line treatment, all on ibrutinib.

According to LC, respondents reported having experience with the following therapies:

Current Treatment N= 25	Response Count* (n, %)	Current Treatment	Response Count* (n, %)
FCR	7 (28.0%)	Radiation	3 (12.0%)
Rituximab alone	4 (16.0%)	Stem cell transplant	2 (8.0%)
CVP chemotherapy	3 (12.0%)	Splenectomy	1 (4.0%)
CHOP	2 (8.0%)		
Chlorambucil alone	1 (4.0%)		
Other current treatments: ibrutinib (3, 12.0%); idelalisib (1, 4.0%); R-CHOP (1, 4.0%); FR (1, 4.0%); IVIG (2, 8.0%); blood transfusions (1, 4.0%); anti-nausea (1, 4.0%) and anti-anxiety (1, 4.0%). ***Total response count exceeds total respondents to this question (N=25) because some patients indicated using more than one current treatment.**			

CLL PAG and LLSC noted that 94% (84/89) of respondents that have had treatment and responded to this question reported side effects. The most common were fatigue (73%) and low blood counts (62%). Forty-four percent had nausea and about a third experienced anemia, diarrhea, mouth sores and skin rashes.

One respondent stated: "*Hard to tolerate, but overwhelmingly happy with the results!*" while another was "*Grateful to be alive but now have arthritis, pain, nervousness, numbness, tingling, worse fatigue than before treatment.*" Patients understand that all treatments have some degree of side effects. One said: "*negative cannot be avoided in terms of side effects or the physical low experienced with this disease; positive equals remission which equivocates to a beautiful life.*"

According to LC, respondents listed both positive (disease control) and negative side effects (disease progression; adverse events; dose interruptions due to side effects) of current treatments. Highlighted below were the comments from three respondents.

> *"Short or no benefit from multiple therapies. Infusion reactions, rashes, joint pain, nausea and vomiting, diarrhea, hair loss, infections, insomnia, stomach pains, high blood pressure, liver inflammation, severe fatigue, isolation and prolonged hospitalization."*(male; 55-64; USA)

> *"I had hoped that the therapies would keep my red cell count up longer than it does. I am not able to maintain good nos. over a period of time. That means going on and off treatment often."* (female; 65-74; Canada)

> *"All treatments wiped out my good blood components and made me tired. As treatment went on with each of these therapies I developed more complications that made it unsafe for me to continue to receive treatment. Hence I endured the chemo treatments but had complications like low platelets; low neutrophils and was*

unable to finish the full treatment of each of these lines of therapy…My remissions were short before the leukemia came back…" (male; 45-54; Canada)

CLL PAG and LLSC found that 84% of respondents could access treatment in their own community; however, 16% of respondents could not and had to travel.

LC also conducted a similar survey where respondents were asked how difficult it was to access their most current therapy(ies). According to LC, 37% of respondents who answered this question experienced difficulties. Difficulties expressed by patients and caregivers included the need to: travel great distances to receive treatments in Canada; meet specific provincial drug funding criteria; pay out-of- pocket costs for treatments and associated travel.

Level of Difficulty with Access	N (%)	Level of Difficulty with Access	N (%)
Not at all difficult	9 (33.3%)	Somewhat difficult	6 (22.2%)
Not very difficult	8 (29.6%)	Very difficult	4 (14.8%)
			Response Count: 27

Some notable comments from respondents include:

"Access was easy - difficulty was paying for it." (female; 55-64, Canada)

"I live 130 Kilometres from Ottawa so I had to drive in order to get the treatments." (female, 75 years or older, Canada)

"I started treatment in February of this year, and by the time we were done in May, our credit cards were maxed out and we were beginning to fall behind. On short term disability I only received 2/3 of my regular pay, and they were not very prompt with their payment. But there were drug costs, travel costs (I am treated 100 miles from home), accommodation costs (my treatment was 3 days per month)."(female; 45-54; Canada)

"Financial implications re: travelling costs to treatments and checkups; parking at hospital(minimum of $25.00 each time); loss of income due to absence from work/etc."(female; 75 or older; Canada)

According to CLL PAG and LLSC, 76% of respondents reported their experience with treatment to date as being positive as they obtained remission and their quality of life improved during remission. If remission lasted less than 2 years, most respondents counted their experience as being negative. Moreover, 79% of respondents said their treatment adequately managed their CLL symptoms. Patients overall understand their disease is currently non-curative and length of remission varies greatly between patients.

Respondents to the LC survey were asked to rate their level of agreement with how much their current therapy(ies) are able to manage symptoms associated with their CLL, on a scale of 1 (Strongly Disagree) to 10 (Strongly Agree). Those respondents who identified as having relapsed/refractory disease rated substantially lower (rating average 6.4, n= 5) than those patients without relapsed/refractory disease (rating average 7.5, n = 13).

When considering treatment, respondents to the LC survey were asked how important is it for them and their physician to have choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 (Not Important As Long There Is At Least One Treatment Choice) to 10 (Extremely Important To Have Choice of Treatment). 65.4% (17/26) of respondents who answered this question gave this a rating of 8 or higher. The rating average was 7.9, which according to LC means a large proportion felt that choice was very important based on the known side effects and

expected outcomes of a drug. Respondents were also asked if they feel there is currently a need for more choice in drug therapy(ies) for patients with CLL. All 23 respondents who answered this question feel there is a definitive need for more therapies.

4.1.3 Impact of CLL and Current Therapy on Caregivers

Respondents to the LC survey were asked to rate on a scale of 1 (No Impact) to 10 (Very Significant Impact) how caring for the person with CLL has impacted their "day-to-day life." Differences in ratings were reported based on a caregiver's retirement status. Five (45.5%) respondents were retired at the time of completing the survey and 6 (54.5%) were still working.

Impact on Day-to-Day Life of Retired Caregivers (N=5)*	Rating of 7 or Higher N (%)	Rating Average	Impact on Day-to-Day Life of Non-Retired Caregivers (N=6)*	Rating of 7 or Higher N (%)	Rating Average
Ability to travel	4 (80%)	7.2	Ability to volunteer	3 (50%)	6.2
Ability to volunteer	3 (60%)	5.8	Ability to exercise	2 (33.3%)	5.0
Ability to spend time with family and friends	2 (40%)	5.2	Ability to concentrate	2 (33.3%)	4.5
Ability to concentrate	2 (40%)	4.8	Ability to travel	1 (16.7%)	4.5
Ability to fulfill family obligations	2 (40%)	4.8	Ability to spend time with family and friends	1 (16.7%)	4.3
Ability to exercise	2 (40%)	4.4	Ability to contribute financially to household expenses	1 (16.7%)	4.2
Ability to attend household chores	1 (20%)	4.0	Ability to attend household chores	1 (16.7%)	4.0
Ability to contribute financially to household expenses	1 (20%)	2.2	Ability to fulfill family obligations	1 (16.7%)	4.0
***All 11 respondents answered questions relating to day-to-day life impact and retirement status**					

Other common challenges faced by caregivers related to "anxiety". Below are the perspectives from two caregivers.

> *"Cancelled weekend away with friends due to anxiety about being out-of-town and too far away from mother. Have not taken time to workout…Sleep pattern is minimal since eating*

habit has changed and has affected my quality of sleep." (child; female 45-54; not retired; Canada)

"The worst part is the stress and also "the unknown" about what will happen next, how long will the remission last…When treatment is underway, it takes over your life, always watching for bad side effects during the chemo and knowing how to best offer support…very emotionally and physically draining. Life sort of stops while all this is happening." (spouse/partner; female; 65-74; retired; Canada)

According to LC, caregivers also reported difficulties managing 'side effects' of treatment. The most commonly reported side effects related to emotional (moods) and safety (physical mobility) issues. Below are comments provided by two caregivers.

"There were many days when my husband's mental state was such that I was subjected to shouting, being ignored and similar treatment, all due to drug side effects." (spouse/partner; female; 65-74; retired; Canada)

"No strength in mother's legs has presented safety and falling issues in house- I often strain myself trying to assist lifting her" (child; female; 45-54; not retired; Canada)

In addition to the above, caregivers reported difficulties with "accessibility". The most commonly reported factors were financial burden and distance to drug. Some caregivers had to take time off work to assist in taking care of the patient (loss of income). Other caregivers reported the drug was difficult to access because they had to travel to a cancer centre far from home (travel to United States for a drug not available in Canada; travel to another province to receive drug; travel long distance from remote community). Below were comments received from two caregivers in response to this issue.

"There were many additional expenses we had to cover: travel, sometimes accommodation, infusion charges, doctor and hospital fees, parking, etc…Since we are both retired and on pensions we suffered no loss of income but had a significant increase in costs, approximately $1,000 per month! Travel alone took an entire day when he had to be in the Buffalo clinic. The drug he was on is not available in Canada." (spouse/ partner; female; 65-74; retired; Canada)

"Have taken time off work - compassionate leave which has effected finances and ability to pay bills and going to declare bankruptcy." (child; female 45-54; not retired; Canada)

CLL PAG and LLSC reported caregiver challenges include mental stress and emotional turmoil brought on by their exhausting care-taking duties. These duties included doing research on line in journal articles, online postings and interviews to discover potentially available treatments for their ailing partners, becoming familiar with side effects of various therapies and how to deal with those. Caregivers have to ensure the patients attended their medical appointments, accompany them during often very time consuming therapy sessions, ensure that the patients followed their physicians' instructions and monitor their condition round the clock. "*I try to keep abreast of developing therapies such as the targeted treatments and to provide such information as my husband might want*".

In addition, caregivers had to take on all previously shared household duties including meal preparation, shopping, etc. Their own careers suffered because caregivers were too exhausted to fully concentrate on their own careers and sometimes had to give up their jobs to take care of their partners. "*I quit my job to take care of parent with CLL*".

The potential for exposing patients to infectious diseases was cited as a major reason for reduced social contacts with family and friends and sacrificing vacations and attending public events. *"We rarely entertain guests, fear of infection and not wanting to share that he is ill."*

Dealing with their partners' often serious treatment induced side effects was mentioned as major reasons for stress as was the worry over the effectiveness of current treatments. *"Unfortunately 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."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Obinutuzumab

According to CLL PAG and LLSC, 96% of respondents indicated it was important to have choices available for CLL treatment (assigning a rating of 5, 6 or 7 on a scale of 1-7, where 1 indicate as not important and 7 indicate as very important). 84% of respondents rated this as a 7.

One respondent noted: *"A heterogeneous disease like CLL needs to have choices in available treatments. One size does not fit all,"* and *"Since CLL is a manifestation of many different underlying mutations, one size will DEFINITELY not fit all,"* and *"Right now CLL is a fatal, incurable disease. There is NO truly effective treatment."*

When respondents were asked what they knew about obinutuzumab in combination with chlorambucil, they responded as follows with 1=know nothing and 5=well informed:

1	2	3	4	5	Response Count
75	38	42	21	31	207

When asked what was important to them in any new treatment, 95% of respondents indicated they wanted longer remissions with less toxicity, with the remainder noting having treatment choices and more knowledge on the treatments. Respondents reported the following:

> *"As CLL usually requires frequent treatments in a patient's lifetime, I would want a drug that gives you longer remissions and of course what we all want, a permanent cure. Drugs must be affordable or only the rich will live. I don't sleep worrying about how I will afford the drugs I will need to save my life".*
>
> *"CLL progresses differently in each patient. It seems that the best treatment is individualized to the patient and the disease, not one treatment for all patients".*
>
> *"Getting information about actual side effects and how they are related to the various "strains" of CLL".*
>
> *"Minimal side affects, oral therapy rather than chemo".*

According to LC, respondents were asked on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) and to rate the extent they would be

willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their CLL. 48.6% (17/35) of respondents gave a rating of 8 or higher (rating average 6.5). Many respondents described that they would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. The respondents reported the following:

"Because if I got my life back the side effects would be a reasonable trade off." (female; 65-74; USA)

"To get a deep and long remission, I would put up with most side effects."(female; 45-54; USA)

"Debilitating side effects are a major concern with any new drug and should be minimal with the use of any new drug." (male; 75 or older; Canada)

Below is a summary of responses from respondents on their opinion as to how obinutuzumab has changed or is expected to change their long-term health and well-being.

Long-term Health or Well-being	Survey (n, %)	interviews	Response Count
Live longer	3 (100%)	**3 (100%)**	6
Improve blood counts	**3 (100%)**	**3 (100%)**	6
Control disease and side effects	**3 (100%)**	**3 (100%)**	6
Improve quality of life	**3 (100%)**	**3 (100%)**	6
Bring about a remission	**3 (100%)**	**3 (100%)**	6

Respondents to the LC survey were asked to rate on a scale of 1 (Not Important To Control) to 10 (Very Important To Control), and to rate how important is it for a new drug to be "able to control" specific aspects associated with their disease. According to LC, it can be seen that the vast majority of respondents who answered this question assigned ratings of a '10' to all aspects.

Level of Importance of a New Drug to be able to Control	Rating of 10 n (%)	Rating Average	Response Count
Live longer	23 (92.0%)	9.92	25
Improve Quality of Life	22 (88.0%)	9.84	25
Control disease and side effects	21 (84.0%)	9.76	25
Improve blood counts	21 (84.0%)	9.68	25
Bring about a remission	21 (84.0%)	9.48	25

Below were some of the comments that were provided by the respondents.

"Size of lymph nodes, as I have some that are impacting my abdomen and bowel."(female; 65-74; Canada)

"Quality of life and a longer life pretty much covers it all!" (female; 65-74; Canada)

Respondents to the CLL PAG and LLSC survey were also asked to rate what side effects were most important to control. The table below summarized the key ranking to control side effects.

Answer Options	1	2	3	4	5	6	7	Response Count	% Rated 5-7
Fatigue, lack of energy	6	1	6	17	23	37	115	205	85%
Frequent infections	16	7	10	14	21	44	89	201	77%
Increasing white blood cell counts	8	11	9	23	13	31	104	199	74%
Enlarged lymph nodes	18	11	7	27	38	43	60	204	69%
Enlarged spleen/discomfort or dragging feeling on upper left side of stomach	21	12	12	19	38	41	57	200	68%
Shortness of breath	26	18	12	16	32	35	59	198	64%
Pain	31	14	13	21	29	38	51	197	60%
Night sweats	30	12	16	29	30	34	47	198	56%
Fever	43	10	13	22	33	30	49	200	56%
Weight loss	52	18	23	30	23	24	23	193	36%

LC reported that a total of 9 patients (3 survey respondents; 3 telephone interviews; 3 online interviews) had direct experience with obinutuzumab.

Most respondents did not receive previous treatment prior to starting obinutuzumab. One respondent had switched from therapy to therapy as his disease kept relapsing; he was deemed rituximab refractory. Since starting treatment with obinutuzumab, it was reported that their blood counts have returned to normal and their quality of life has improved dramatically. Survey respondents and interviewees were asked to rate using a scale from 1 (No Improvement) to 10 (Very Significant Improvement) how much symptoms associated with CLL had shown improvement with obinutuzumab. According to LC, the majority of respondents provided a ranking of 9 or higher which means that they are experiencing significant improvement in their symptoms and quality of life (see Table below). All 9 (100%) patients are tolerating obinutuzumab very well and those interviewed by LC (3) did not report any dose interruptions. None of the patients have had a relapse of their disease.

Improvement in symptoms associated with CLL since taking obinutuzumab	Rating of 10 N (%)	Rating of 9 N (%)	Rating Average	Response Count
Enlarged lymph nodes	6 (100%)	-	10	6
White blood cell counts	5 (100%)	-	10	5 (1 Skipped)
Fatigue	6 (100%)	-	10	6
Platelet counts	5 (83.3%)	1 (16.7%)	9.83	5 (1 Skipped)
Red blood cell count (anemia)	4 (80%)	1 (20%)	9.80	5 (1 Skipped)

According to CLL PAG and LLSC, 71.43% (5/7) of respondents felt they were well informed about obinutuzumab.

Respondents were asked which symptoms of CLL the obinutuzumab drug regimen managed for them. Please see the table below for a summary of managed symptoms.

CLL Symptom	% respondents whose symptom was managed	Total Number of respondents
Enlarged lymph nodes	85.71%	6
Fatigue, lack of energy	57.14%	4
Enlarged spleen	57.14%	4
Increasing white count	57.14%	4
Pain	28.57%	2
Night sweats	28.57%	2
Did not manage any symptoms	14.29%	1

Respondents were subsequently asked which symptoms of CLL the obinutuzumab drug regimen did not manage for them. Please see the table below for a summary of symptoms that were not managed.

CLL Symptom	% respondents whose symptom was not managed	Total Number of respondents
Shortness of breath	42.88%	3
Fatigue, lack of energy	28.57%	2
Frequent infections	28.57%	2
Enlarged lymph nodes	14.29%	1
Weight loss	14.29%	1
Pain	14.29%	1
All symptoms managed	14.29%	1

According to CLL PAG and LLSC, respondents reported the following side effects that they were willing to tolerate.

Drug regime Side effect	% respondents willing to manage side effect	Total Number of respondents
Anemia or neutropenia	42.86%	3
Cough	42.86%	3
Diarrhea	28.57%	2
Fever	28.57%	2
Fatigue	28.57%	2
Back pain	28.57%	2
Low platelets	28.57%	2
Breathing difficulties	28.57%	2

Tumour lysis syndrome	28.57%	2
Viral reactivation	28.57%	2
Nausea	14.29%	1
Rash or itching	14.29%	1
Irregular heartbeat	14.29%	1
Small bowel obstruction	14.29%	1
None of the above	14.29%	1

Based on the responses from the LC survey, when asked about the side effects experienced with obinutuzumab, respondents stated that the side effects were mild and quickly dissipated with minimal tolerability issues. Side effects initially experienced by respondents included an initial infusion reaction that did not recur during subsequent doses and anemia, cough and fever that went away shortly after starting treatment. As expressed by two respondents,

> "*The very first day I had an infusion reaction…they just had to stop the dose and wait 20 minutes and give me a little more benedryl and then they could start it up again. They had to go slow the first day"…I had basically two side effects. The drug made me temporarily a little more anemic then I was. So, in the first few weeks I needed a transfusion of red cells to bring my haemoglobin up a little bit. And that resolved over a few weeks and my haemoglobin bounced back to normal levels…the only other issue I had with it is that I got a fairly bad cough from the antibody…that lasted the first six weeks or so, I controlled it with hydrocodone cough syrup…no side effects lingered past the first 6 weeks of treatment."* (male; 56; USA; finished treatment with obinutuzumab in May 2014; no dose interruptions)

> "*In many ways easier, no terrible stomach upset, and I didn't lose my hair, which may seem like nothing, but it was a huge thing for me…I haven't experienced them* [similar side effects*] since taking only obinutuzumab."* [Compared to R-CHOP] (male; 55-64; Canada)

CLL PAG and LLSC noted that 29% (2/7) of respondents were able to access treatment in their own community. Of those unable to access treatment in their community, 40% (2/5) indicated that treatment was not available in their province or state. 20% (1/5) did not have a local cancer centre, 20% (1/5) did "not have local expertise with the drug" and 20% (1/5) was in a clinical trial that was not offered locally.

Below were the overall experiences with the obinutuzumab that were reported by respondents.

> "*Excellent, minimum side effects / Lymphocyte # down to 4 in 24 hrs., now normal*"

> "*Nodes shrank rapidly & pain gone. Some lung inflammation, resolving with nebulizer, still need 3 more cycles. Overall, feel much better, more energy. 1st infusion, felt nauseous and flu like, now just slight fatigue for a few days after*."

> "*I have a partial remission using obinutuzumab by itself. The treatment was uncomfortable but do-able. The trial is on-going at this time*"

"*Wonderful recovery, infusion reactions are difficult to handle*"

"*First treatment caused a severe drug reaction including intense rigors*"

"*mediocre*"

Respondents noted that the obinutuzumab drug regimen has changed their long-term health and well-being:

"*It has made a huge difference: my haemoglobin is higher than it's been in years, lymph nodes normal, no infections, all normal blood counts two years post treatment*"

"*My labs are normal, migraines gone, pain under ribs from cluster of nodes gone, more energy, no longer hot & cold. I HAVE hope for my future & almost feel normal even though I have not completed the full treatment. It is a miracle!*"

"*So far, things are much improved with energy being available. I still have little resistance to infections*"

"I was supposed to die a few months ago"

"Brought down my spleen, took a year though"

"Helped me to continue to buy time"

Below are some of the personal perspectives collected from the CLL PAG and LLSC surveys and LC interviews:

"*treatment was so much easier to tolerate that I expected and results were faster than expected*"

"*I am grateful for new medications that are becoming available, it gives me hope for my future. I felt flu like, fatigued, frequent migraines/vertigo & quality of life poor before treatment. I am grateful beyond words to have my life back. I hope the results of Gazyva (US patient) last for many years, but that remains to be seen*"

"*I didn't anticipate any personal advantage to taking part in this trial, I just wanted to "do my bit" towards possibly finding a cure. I have been rewarded with an improved quality of life*"

"*Without these new drugs I would have died 4 to 5 years ago and I am very grateful"*

"*In January my white count had escalated to 379,000, my haemoglobin had dropped to 9.5, so they started me on the new monoclonal antibody obinutuzumab. So I started that in January cycle one - day 1, 8 and 15…I felt fine. I was very fortunate I had no infusion reaction, no tumour lysis syndrome, no complications and actually I did not even know they were doing it other than the fact I had an IV in my arm. I felt perfectly fine throughout the whole treatment plan…The first day [of treatment] my white count, actually split and I only got a 100 milligrams the first day. The next morning my white count had dropped a 100,000…For me, it was like, we are on to something here. This is good. For my wife, my family that was a big positive for them also. It was very exciting*"

"*Two years ago my white blood cell count had tripled and I had a node in my neck the size of a golf ball…I really did not hesitate to participate in the clinical trial. It was a no-brainer actually…It worked perfectly for me. It changed my body chemistry and brought it to normal overnight after the 5% of the first dose…I have leukemia and I am lucky because the drug came in time for me, it all kind of all cosmically timed out right*."

"My quality of life has been positively impacted because I was so anemic going in. You know, I was pretty fatigued. Even walking to my car after work, which was a 2-3 minute walk got me out of breath. My doctor did not want me shovelling snow. He said I could have an infarct until the anemia was resolved. In that way once the obinutuzumab started to work and my blood counts came back, I was able to do all those things without any problem again."

"***CHOP nearly killed me. At the time I was heavily burdened with the disease, my nodes were very enlarged. Nurse Karen called me and said they had good news for me: obinutuzumab. I felt like I won the lottery, I knew about this [obinutuzumab] from the year before. I have had three doses now, and I can report it is a very kind medication. I don't feel sick, just a bit weak…I think it will help me, I know it's working on my immune system…On CHOP I was convinced I was going to die…Cancer is a hell of a disease.***"

4.3 Additional Information

No additional information was provided by the patient advocacy groups.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for obinutuzumab (Gazyva) for previously untreated chronic lymphocytic leukemia (CLL). 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 obinutuzumab (Gazyva) 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 or bendamustine monotherapy would be the treatment option for previously untreated CLL in patients who are medically unfit would be an alternate treatment option. PAG noted the flat dosing of obinutuzumab 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. 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 (FCR) is the current first-line treatment option for medically fit patients with CLL. Chlorambucil or bendamustine hydrochloride would be the treatment option for elderly patients and unfit patients, where the chemotherapy combination cannot be used. PAG noted that obinutuzumab is an anti-CD20 monoclonal antibody that would be an option to FCR.

PAG is requesting information on whether there are head-to-head comparisons of obinutuzumab plus chlorambucil with other anti-CD20 drugs and alkylating agents for CLL. Lastly, information on sequential use with other anti-CD20 drugs and information on use of obinutuzumab with other alkylating agents 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 small number of previously untreated CLL patients who require treatment. However, PAG would like pERC to address the broader funding request for previously untreated CLL patients compared to the trial where previously untreated patients who have comorbidities and not suitable for FCR in the first-line setting were enrolled.

PAG has concerns for indication creep for patients with relapsed/refractory CLL, where treatment options are limited. This may be a barrier to implementing obinutuzumab for first-line treatment

of CLL and PAG would like guidance on use of obinutuzumab in the relapsed/refractory setting where there is a larger prevalent population.

In addition, PAG would like information on the use of obinutuzumab after other anti-CD20 monoclonal antibodies and on the use of other anti-CD20 monoclonal antibodies after obinutuzumab in downstream treatments.

5.3 Factors Related to Accessibility

Obinutuzumab, 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

Obinutuzumab dose is flat dosing, regardless of patient's weight or body surface area. PAG noted that the vial sizes available provide these doses without drug wastage. These are enablers to implementation.

PAG has noted that in cycle 1, four doses (on days 1, 2, 8 and 15) are required and has concerns with scheduling chemotherapy chair time and resources to manage the four infusions in the first 28 days of treatment. This is a barrier to implementation.

Treatment with obinutuzumab is for six cycles. The short number of treatments is an enabler from the implementation perspective. However, PAG is seeking information about treatment with obinutuzumab beyond the six cycles.

5.5 Factors Related to Implementation Costs

Obinutuzumab is administered by intravenous infusion over 4 hours and in cycle 1, four doses are required. These are barriers as there would be chemotherapy chair utilization and increased nursing resources. PAG also recognized that there may be additional costs associated with obinutuzumab treatment, such as monitoring for infusion related reactions and other adverse reactions.

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

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 obinutuzumab and monitor for infusion related reactions.

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

Obinutuzumab 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.

5.6 Other Factors

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

There are several drugs for 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.

PAG has concerns with the potential for drug errors due to the look-alike, sound-alike drug names of obinutuzumab and ofatumumab, given that they are both monoclonal antibodies indicated for the treatment of CLL and both require refrigeration for storage. The consequences of these look-alike, sound-alike drugs would have serious patient implications as the drugs have different dosing schedules in the first cycle and different total number of cycles.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety/toxicity of obinutuzumab when used in combination with chlorambucil compared with current standards in the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) where fludarabine is inappropriate and require therapy.

No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group (PAG) 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	Fludarabine inappropriate, Previously untreated CLL patients requiring therapy. Subgroups: 17p,11q deletions, agent, age (≥ 65)	Obinutuzumab AND Chlorambucil	Chlorambucil ***OR*** Chlorambucil ***AND*** Other monoclonal antibody (ofatumumab, rituximab) ***OR*** Alkylating agent (bendamustine, or cyclophosphamide) ***OR*** Alkylating agent (bendamustine, or cyclophosphamide) ***AND***	**Overall survival (OS)**, progression free survival (PFS), complete response (CR) rate, overall response rate (ORR), grade 3-4 adverse events, withdrawal due to adverse events, **rash, fatigue**, CMV reactivation, HSV reactivation, Hep-B reactivation, Progressive Multifocal Leukoencephalopathy (PML), PML resulting in death, infusion reactions, infections, hematologic adverse events, non-hematologic adverse events, treatment related deaths, tumor lysis, **quality of life**

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
			Other monoclonal antibody (ofatumumab, rituximab)	
Overall survival (OS), progression free survival (PFS), complete response (CR) rate, overall response rate (ORR)				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

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-December 2014) with in-process records & daily updates via Ovid; EMBASE (1980-December 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 Obinutuzumab and chronic lymphocytic leukemia.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical 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 December 8th, 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), European Society for Medical Oncology (ESMO), and American Society of Hematology (ASH) were limited to the last five years. 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:

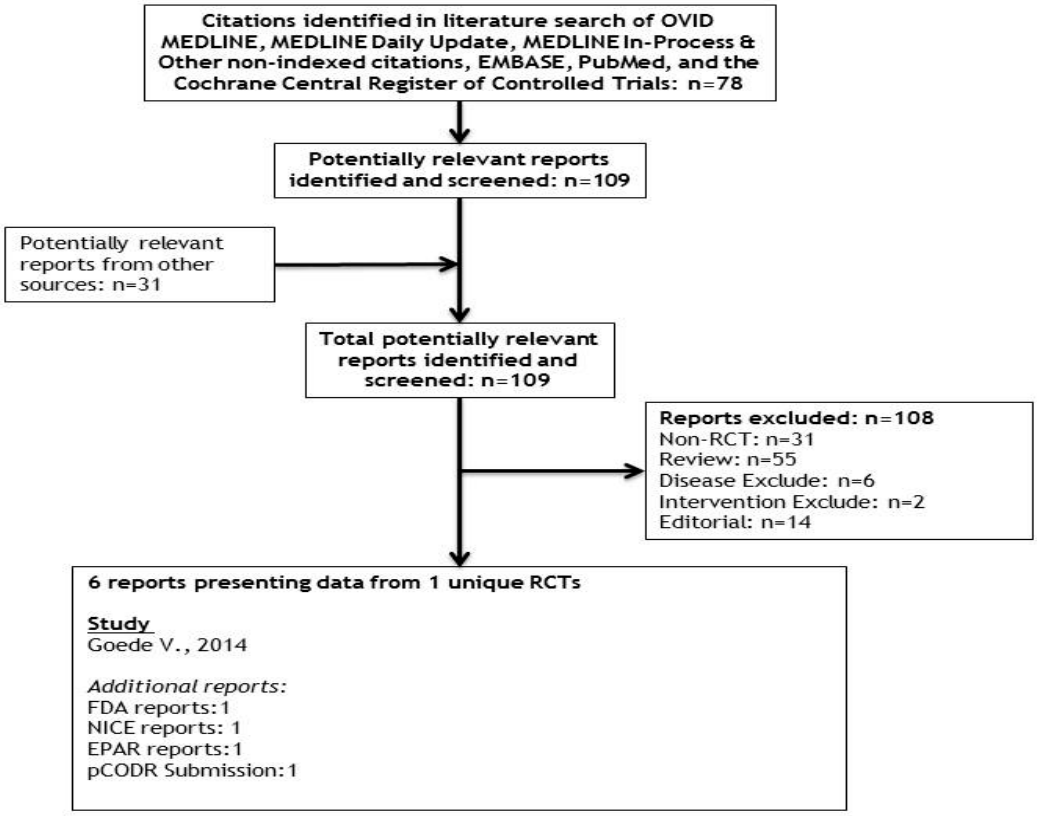
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

Of the 109 potentially relevant reports identified, one study was included in the pCODR systematic review[4] and 108 studies were excluded. Studies were excluded because they were non-RCT (n=33), they were reviews or editorial (n=69), they included the wrong intervention (n=2), or they reviewed the wrong disease (n=6). An exploratory search found the FDA review[25], and EPAR review.[26] The pCODR submission file[2] was also included.

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



Note: Additional data related to studies Goede V., 2014[4] were also obtained through requests to the Submitter by pCODR

6.3.2 Summary of Included Studies

One randomized trial was eligible for inclusion in this review.[3] This trial evaluated the use of obinutuzumab in combination with chlorambucil versus chlorambucil alone versus rituximab in combination with chlorambucil in patients with previously untreated CLL requiring therapy, where fludarabine is not appropriate. Further results and information from this trial was provided by the submitting company upon request. Further information was also available in the assessment reports completed by the FDA, NICE, and EPAR.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included Study[4]

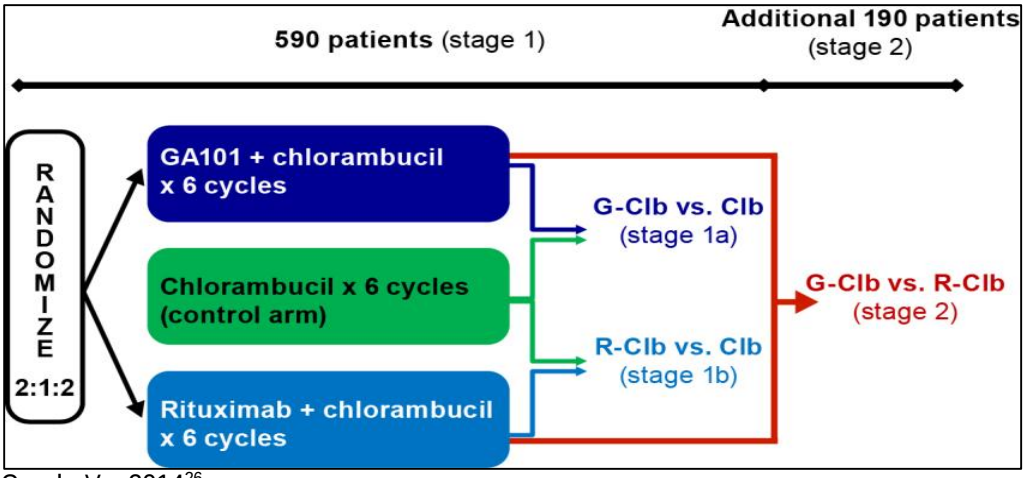
Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Goede V., 2014[4] Randomized Control trial with safety phase in stage. N=781 Funded by: Hoffman LaRoche	Patients with: Documented CD20+ B-CLL •Previously untreated CLL requiring treatment •Total CIRS score >6 and/or creatinine clearance <70 mL/min •Absolute neutrophil count ≥1.5 × 10^9 /L and platelets ≥75 × 10^9/L unless cytopenia was caused by the underlying disease, i.e., no evidence of additional bone marrow dysfunction •Age ≥18 years •Life expectancy >6 months •Able and willing to provide written informed consent and to comply with study protocol procedures <u>Exclusion criteria:</u> Previous CLL therapy • Transformation of CLL to aggressive NHL (Richter's transformation) • One or more individual organ/system impairment score of 4 as assessed by the CIRS definition, excluding the eyes, ears, nose, throat and larynx organ system • Inadequate renal function: Creatinine clearance <30 mL/min • Inadequate liver function • History of other malignancy that could have affected compliance with the protocol or interpretation of results • Active bacterial, viral, or fungal infection requiring systemic treatment • Known infection with human immunodeficiency virus or human T-cell leukemia virus 1 • Positive hepatitis serology: Patients with positive serology for hepatitis B could be included if hepatitis B viral DNA was not detectable.	chlorambucil, obinutuzumab plus chlorambucil, or rituximab plus chlorambucil	Primary end point: investigator-assessed progression-free survival Secondary end points: progression-free survival as assessed by an independent review committee, response rates and the rate of negative testing for minimal residual disease after the end of treatment, event-free survival, time to new treatment, overall survival, adverse events, and patient-reported outcomes

Table 2. Summary of Trial characteristics of the included Study[4]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
	Patients with positive hepatitis C serology unless HCV (RNA) was confirmed negative • History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products • Hypersensitivity to Chl or to any of the excipients • Women who were pregnant or lactating • Fertile men or women of childbearing potential unless: (1) Surgically sterile or ≥2 years after the onset of menopause; (2) Willing to use highly effective contraceptive method during study treatment and in female patients for 12 months after end of antibody treatment and male patients for 6 months after end of chlorambucil treatment • Vaccination with a live vaccine a minimum of 28 days prior to randomization		
CR= complete response; DB= double-blind; PC= placebo controlled; PR= partial response; RECIST= Response Evaluation Criteria in Solid Tumours; RCT= randomized controlled trial; CIRS=Cumulative Illness Rating Scale			

a) Trials

One open label randomized control trial was found for this review.[4] This trial is a comparative superiority trial that included a safety run-in phase. Patients were randomized on a 1:2:2 basis: chlorambucil alone (Chl), obinutuzumab plus chlorambucil (ObChl), or rituximab plus chlorambucil (RChl). After 118 patients had been assigned to the Chl group, this group was closed on the basis of a predefined stopping criteria, and randomization to the two antibody groups was performed on a 1:1 basis. Randomization was stratified according to geographic region and Binet stage. Patients from the Chl arm, in whom progressive disease developed during treatment or 6 months following were allowed to cross over to the ObChl arm. The primary endpoint in the study is progression free survival, with overall survival and response rates included as secondary endpoints. This study was conducted in 26 countries with 189 centers.

Figure 2. Trial Design



Goede V., 2014[26]

Populations

There were 781 patients enrolled and treated with Chl alone, ObChl or RChl. Age and clinical characteristics were well balanced between arms – see Figure 3 below. Patients had a median age of 73 years, with median age range of 72-74 years through each group. Median creatinine clearance was 62 ml per minute, median CIRS score was 8 at baseline, and median ECOG was 1. Eighty-two percent of patients had more than three coexisting conditions while 27% had at least one condition that was not well managed. There was a higher proportion of male patients in each of the treatment arms. Prognostic characteristics were also well balanced.

Figure 3. Patient Characteristics

Characteristic	Stage 1			Stage 2	
	Chl (N=118)	ObChl (N=238)	RChl (N=233)	ObChl (N=333)	RChl (N=330)
Age (Median)	72	74	73	74	73
Cumulative Illness Rating Score – Median (range)	8 (0–18)	8 (1–20)	8 (0–18)	8 (0–22)	8 (0–18)
Unmutated *IGHV* — no./total no. (%)	58/99 (59)	129/210 (61)	126/204 (62)	188/305 (62)	182/298 (61)
del(17p) on FISH — no./total no. (%)	10/96 (10)	16/203 (8)	9/196 (5)	22/295 (7)	20/287 (7)

Interventions

Patients received Chl alone, ObChl, or RChl in six 28-day cycles. Chlorambucil was administered orally at a dose of 0.5 mg per kilogram of body weight on days 1 and

15 of each cycle (equivalent to the median dose in a previous trial showing noninferiority of chlorambucil to fludarabine in elderly patients with CLL).[28] Obinutuzumab was administered intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6. The first infusion of obinutuzumab was administered over a period of 2 days following amendment of study protocol. Rituximab was administered intravenously at a dose of 375 mg per square meter of body-surface area on day 1 of cycle 1 and 500 mg per square meter on day 1 of cycles 2 through 6. Fluid intake and premedication with allopurinol, paracetamol (acetaminophen), antihistamines, and glucocorticoids were included as prophylactic treatment for infusion related reactions.

For patients where follow up treatment was necessary, either due to progression, or relapse, the following second line treatments were used by treating physician. These treatments are second-line and are not related to first-line therapy, or results, in any way. These included: alkylating agents, monoclonal antibodies, antimetabolites, antineoplastic agents, corticosteroids, vinca alkaloids, cytotoxic antibiotics, immunomodulators, non-steroidal anti-inflammatories, and tyrosine kinase inhibitors.

Patient Disposition

There were 21 (6.5%) deaths due to adverse events in the RChl group, 15 (4.5%) deaths due to adverse events in the ObChl group and 11 (9%) deaths due to adverse events (AEs) in the Chl alone group. There was no reporting on whether the differences between the groups in the number of deaths due to AEs was statistically significant.[5] There was a higher proportion of patients who withdrew from the Chl arm compared with antibody treatment arms (stage 1 and stage 2) during follow up. During stage 2 there was a higher proportion of patients who withdrew in the RChl arm compared to the ObChl arm.

Limitations/Sources of Bias

I. Goede V., 2014[4] is an open label RCT. Being open label, there is no blinding of investigators or participants. This can lead to introduction of bias and reduces validity of trial results.

II. Stage 2 results are not yet final. Study is ongoing therefore cannot make final statements regarding comparative efficacy of ObChl versus RChl. The latest data-cut was March 2014 and overall survival medians had still not been reached at that time.

III. Hazard ratio for overall survival (ObChl versus RChl) may be compromised due to patients' crossing over from the Chl arm to ObChl arm following progression. This would most likely reduce the magnitude of difference in overall survival between ObChl and RChl, assuming that there is an overall survival benefit associated with obinutuzumab-chlorambucil.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 3. Efficacy Outcomes

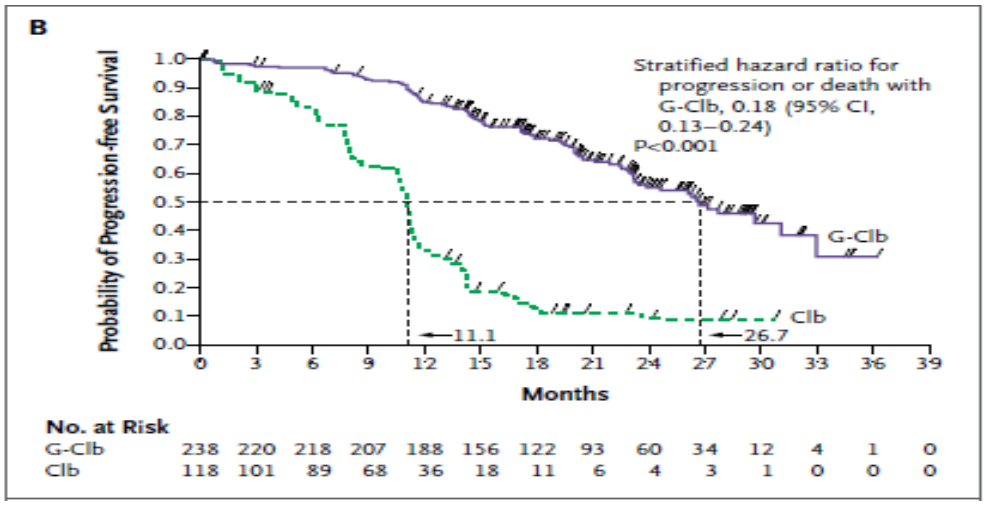
Efficacy Outcomes, Goede V., 2014[4]						
	Stage 1				**Stage 2**	
	Stage 1a		**Stage 1b**			
Outcome	**ChI (n=118)**	**ObChI (n=238)**	**ChI (n=118)**	**RChI (n=233)**	**RChI (n=330)**	**ObChI (n=333)**
PFS - Median PFS HR, (95%CI)	11.1 months	26.7 months HR=0.18, 95%CI (0.13-0.24); p<0.001	11.1 months	16.3 months HR=0.44, 95%CI (0.34-0.57); P<0.001	15.2 months	26.7 months HR=0.39, 95%CI (0.31-0.49); *p*<0.001
Overall Response Rate (ORR)	31.4%	77.3%	31.4%	65.7%	65.1%	78.4%
Complete Response Rate (CR)	0%	22.3%	0%	7.3%	7.0%	20.7%
Overall Survival (OS)	Death rate 20%	Death rate 9% HR=0.41, 95%CI (0.23- 0.74); P = 0.002	Death rate 20%	Death rate 15% HR=0.66, 95%CI (0.39-1.11); P = 0.11	Death rate 12%	Death rate 8% HR=0.66, 95%CI (0.41-1.06); P = 0.08

Goede V., 2014[4]

Progression Free Survival (PFS)

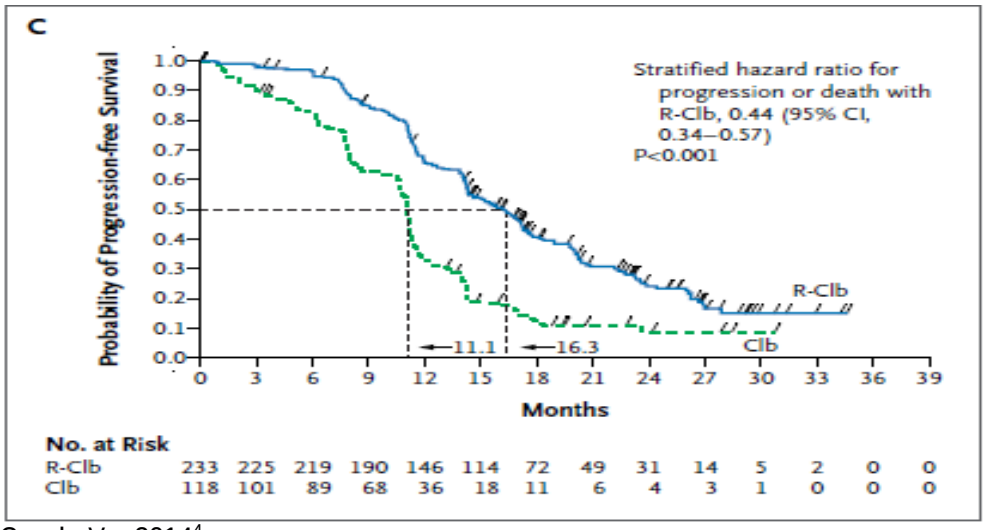
Progression free survival was the main endpoint in this study. A significant extension in PFS was found in both antibody treatment arms; Stage one ObChl and RChl compared to Chl alone. Median PFS was 26.7 months for ObChl versus 11.1 months with Chl alone (HR for progression or death of 0.18, 95%CI: 0.13-0.24, p<0.001). Median PFS was 16.3 months for RChl versus 11.1 months for Chl (HR=0.44, 95%CI: 0.34-0.57, p<0.001). This benefit was seen in all analyzed subgroups, except in patients with del(17p).

Figure 4. Progression free survival (Investigator) – Stage 1
ObChl vs. Chl



Goede V., 2014[4]

Figure 5. Progression free survival (investigator) – Stage 1
RChl vs. Chl

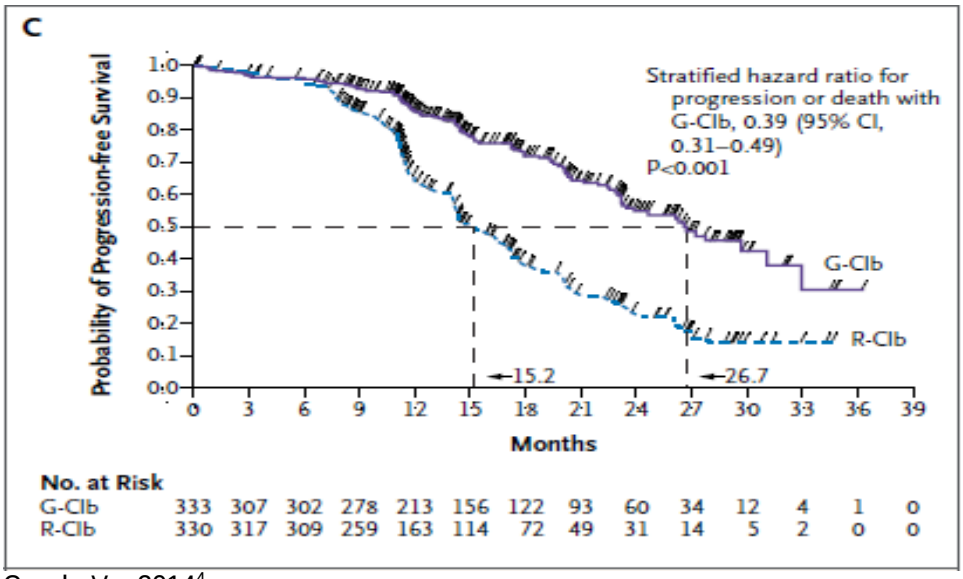


Goede V., 2014[4]

There was a significant prolongation in PFS found in the ObChl treatment arm compared with RChl treatment arm during stage two. Median PFS was 26.7 months

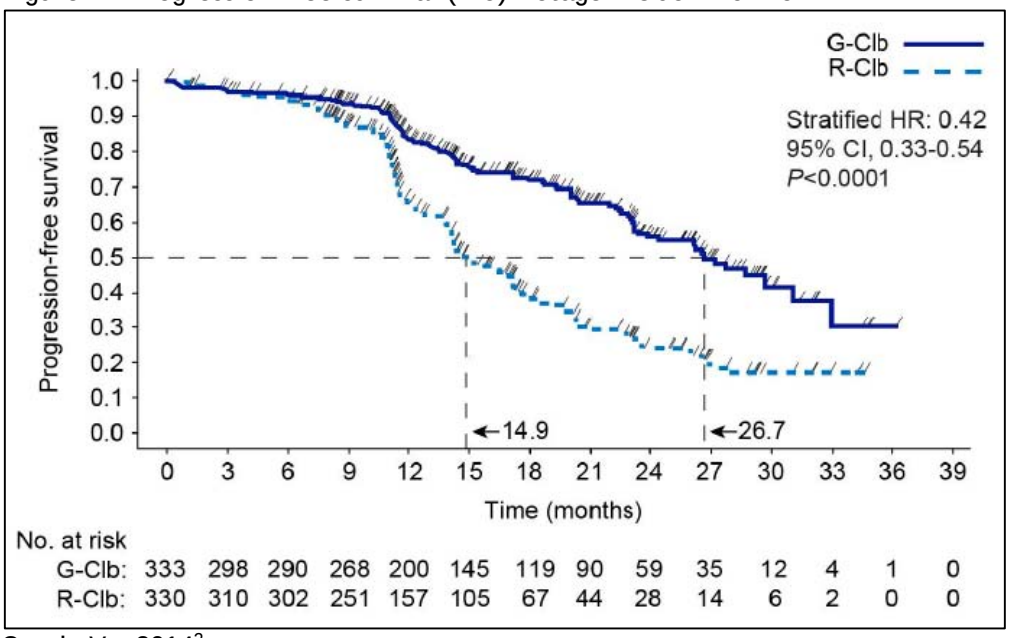
versus 15.2 months The PFS benefit with ObChl as compared with RChl was supported in all preplanned subgroup analyses, although the hazard ratios for patients with del(17p) or other karyotypes had 95% confidence intervals that included 1. All PFS results were confirmed through subsequent survival analysis conducted by independent review committee (IRC), for both stage one and two. There was a good concordance between investigator and IRC assessment of PFS, and the finding of primary analysis was supported by all relevant sensitivity analyses. Thus, the efficacy results were considered robust.

Figure 6. Progression free survival (Investigator) – Stage 2
ObChl vs. RChl



Goede V., 2014[4]

Figure 7. Progression free survival (IRC) – Stage 2 ObChl vs. RChl

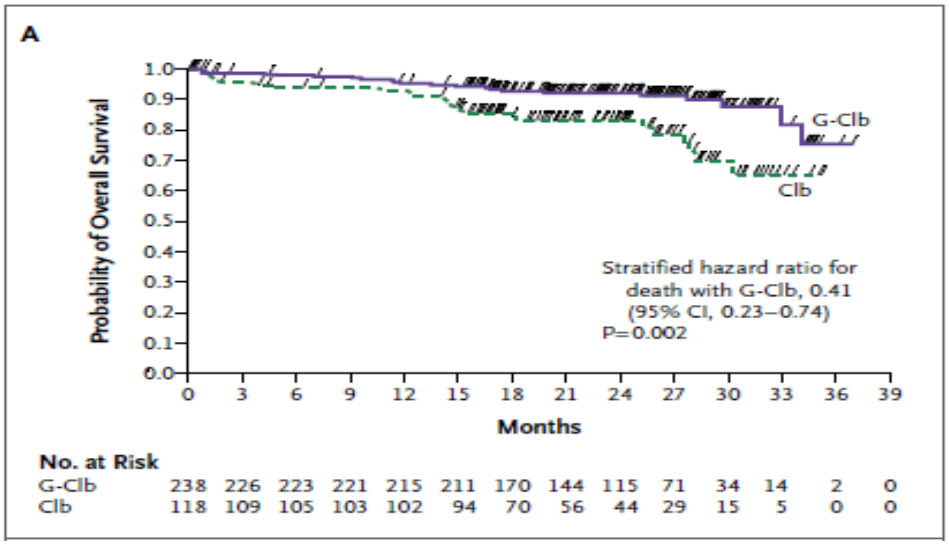


Goede V., 2014[2]

Overall Survival (OS)

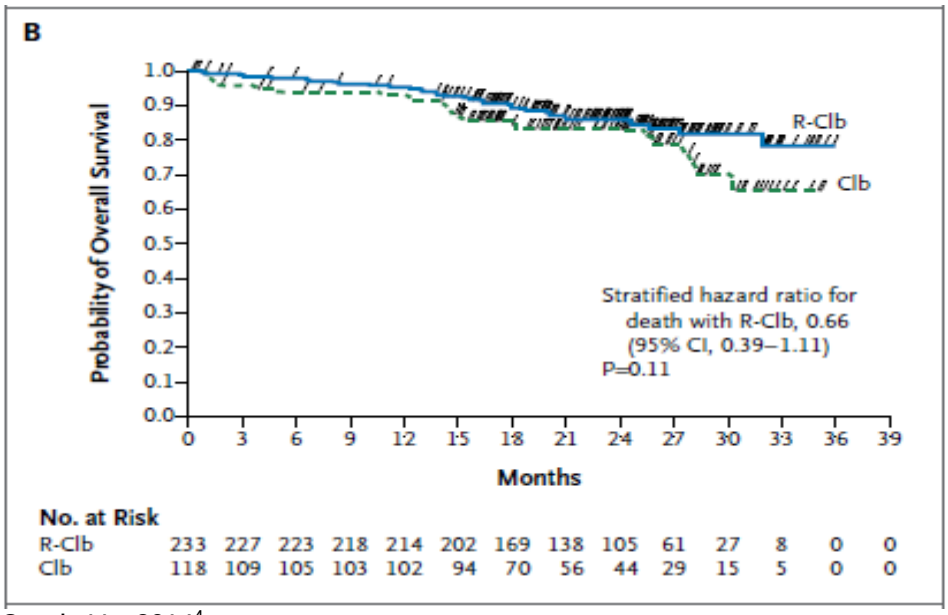
Overall survival medians were not reached at time of analysis. At the May 9th, 2013 clinical cutoff an assessment of stage one OS results indicated a statistically significant extension in OS associated with ObChl compared with Chl monotherapy (HR=0.41, 95%CI: 0.23-0.74, p=0.002). Rates of death were 9% and 20%, respectively. No significant benefit in OS was found for RChl versus Chl alone (HR=0.66, 95%CI: 0.39-1.11, p=0.11). Rates of death were 15% and 20%, respectively.

Figure 8. Overall survival – Stage 1 Chl vs. ObChl



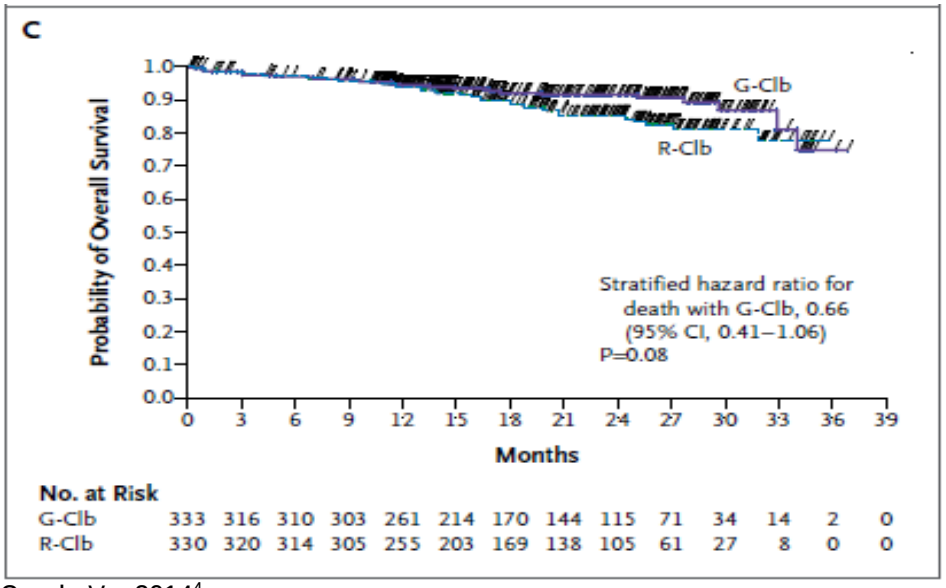
Goede V., 2014[4]

Figure 9. Overall survival – Stage 1 Chl vs. RChl



Goede V., 2014[4]

Figure 10. Overall survival – Stage 2 ObChl vs. RChl



Goede V., 2014[4]

No significant prolongation in overall survival was found between ObChl versus RChl treatment arms during stage two (HR=0.66, 95%CI: 0.41-1.06, p=0.08). Reported death rates in these treatment arms were 8% and 12%, respectively.

Overall Response Rate (ORR)

Overall response rates at 3 months after the end of treatment were higher in the ObChl and RChl groups as compared with the Chl alone group. The response to therapy at 3 months after the end of treatment and the status with respect to remission during follow-up were assessed according to the guidelines of the International Workshop on Chronic Lymphocytic Leukemia. Complete and partial responses were confirmed by means of computed tomographic scanning, and complete responses were confirmed by means of bone marrow biopsy.

In stage one, ORRs were significantly higher in the study arms using antibody treatment versus those with Chl alone. In stage two ORRs were higher in the ObChl arm, 78.4%, versus the RChl arm, 65.1% ($p<0.001$).

Complete Response Rate (CRR)

Complete responses were seen exclusively in study arms using antibody treatment. Stage one results showed higher CRRs in ObChl arm compared with the RChl arm with rates of 22.3% versus 7.3% respectively. There were no complete responses in the Chl alone arm. Stage 2 results revealed higher CCRs in the ObChl arm versus the RChl arm with rates of 20.7% versus 7.0% respectively. Statistical significance was not reported in the trial.

Harms Outcomes

Patient Deaths

There were 21 (6.5%) deaths due to AEs in the RChl group, 15 (4.5%) deaths due to AEs in the ObChl group and 11 (9%) deaths due to AEs in the Chl alone group. There was no reporting on whether the differences between the groups in the number of deaths due to AEs was statistically significant.[5] No deaths were related to infusion reactions.

Discontinuation of treatment

During the stage 1 treatment period, 29 (12%), 48 (20%), and 40 (34%) of patients withdrew from treatment for the RChl, ObChl, and Chl alone arms.[29] In stage 2 there were 43 (13%), and 67 (20%) of patients who withdrew from treatment for the RChl and ObChl arms[29], respectively. The main cause of withdrawal was AEs or intercurrent illness with rates of 25 (8%) and 44 (13%) during stage 2 for the RChl and ObChl arms respectively. In stage one 61% patients in the ObChl arm experienced AEs leading to dose modification of any study medication compared to 20% in the Chl arm. In stage 2 63% patients in the ObChl arm experienced AEs leading to dose modification of any study medication compared to 49% in the RChl arm.[30]

Table 4. Safety Outcomes

Safety Outcomes, Goede V., 2014[4,26]						
	Stage 1				**Stage 2**	
	Stage 1a		**Stage 1b**			
Adverse Events of Grade 3 or higher*	**Chl (n=116)**	**ObChl) (n=241)**	**Chl (n=116)**	**(RChl) (n=225)**	**(ObChl) (n=336)**	**(RChl) (n=321)**
Any Event	58 (50%)	175 (73%)	58 (50%)	125 (56%)	235 (70%)	177 (55%)
Infusion related reactions**	NA	51 (21%)	NA	9 (4%)	67 (20%)	12 (4%)
Neutropenia	18 (16%)	84 (35%)	18 (16%)	60 (27%)	111(33%)	91 (28%)
Thrombocytopenia	5 (4%)	27 (11%)	5 (4%)	8 (4%)	35 (10%)	10 (3%)
Anemia	5 (4%)	11 (5%)	5 (4%)	10 (4%)	14 (4%)	12 (4%)
Leukopenia	0%	13 (5%)	0%	3 (1%)	15 (4%)	3 (1%)
Infections	16 (14%)	27 (11%)	16 (14%)	30 (13%)	40 (12%)	44 (14%)
Pneumonia	4 (3%)	8 (3%)	4 (3%)	11 (5%)	13 (4%)	17 (5%)
Febrile Neutropenia	5 (4%)	4 (2%)	5 (4%)	4 (2%)	8 (2%)	4 (1%)
Death Due to AE	9%	4%	9%	6%	NA	NA
Other Adverse Events of Interest Goede V., 2014[26]						
Adverse Events of Interest - Any grade	**Chl (n=118)**	**(ObChl) (n=238)**	**Chl (n=118)**	**(RChl) (n=233)**	**(ObChl) (n=333)**	**(RChl) (n=330)**
Fatigue	12 (10%)	17 (7%)	12 (10%)	20 (9%)	27 (8%)	30 (9%)
Rash	3 (3%)	8 (3%)	3 (3%)	13 (6%)	8 (2%)	19 (6%)
Tumor Lysis Syndrome	1 (<1%)	10 (4%)	1 (<1%)	0	14 (4%)	0
Cardiac Failure	2 (2%)	3 (1%)	2 (2%)	0 (0%)	4 (1%)	1 (<1%)
Myocardial Infarction	2 (2%)	4 (2%)	2 (2%)	0 (0%)	4(1%)	0 (0%)

* The safety population included all patients who received at least one dose of study medication. Shown are adverse events of grade 3, 4, or 5 with an incidence of 3% or higher in any treatment group, irrespective of whether the event was considered related or unrelated to treatment by the investigators.; ** There were no grade 5 infusion reactions

Grade 3, 4 Adverse Events

Adverse events occurred more frequently in the antibody treatment arms than in the Chl monotherapy arm. In stage one the incidence of any adverse events was highest in the ObChl arm compared with the RChl arm and Chl arm. In stage 2 the incidence of any adverse event was also greater in the ObChl arm compared to the RChl.

Hematologic Adverse Events

The incidence of grade 3 or 4 neutropenia was highest in ObChl treatment arm and was lowest for Chl monotherapy. Thrombocytopenia also had highest incidence in the ObChl arms in both stages 1 and 2, when compared with both RChl and Chl monotherapy. During stage one autoimmune hemolytic anemia was reported as a serious AE in less than 1% of patients within antibody treatment arms and in 2% of patients in the chlorambucil monotherapy arm. In stage two hemolytic anemia was reported in less than 1% of patients in both treatment arms (ObChl, RChl). Anemia was reported as a grade 3/4 AE evenly throughout treatment groups in both stages at proportions of 4%-5%. Leukopenia was reported as a grade 3 or higher AE more frequently in ObChl arms and was not reported in the Chl monotherapy arm.

Non Hematologic Adverse Events

Non hematologic adverse events were not reported as a group. During stage one pneumonia was reported in 3%, 3% and 5% of patients in the Chl, ObChl, and RChl arms respectively. [4] It was reported in 4% and 5% of patients during stage two, in the ObChl and RChl arms respectively.[4]

Both cardiac arrest and cardiac failure occurred most frequently in the ObChl treatment arm, compared to RChl and Chl treatment arms.[27] Cardiac failure occurred in 3 (1%), 2 (2%), and no (0%) patients during stage one, in the ObChl, Chl, and RChl arms respectively. Myocardial infarctions occurred in 4 (2%), 2 (2%), and no (0%) patients in the ObChl, Chl, and RChl arms respsectively. During stage two, cardiac failure was reported in 4 (1%) and 1 (<1%) patients, while myocardial infarction was reported in 4 (1%) and 0 (0%) for the ObChl and RChl arms, respectively.

Rash

Incidence of rash occurred at a higher rate in RChl arms compared to Chl and OBChl arms. Rash occurred most frequently in RChl arms during both stages of the trial.

Fatigue

Fatigue was reported as an adverse event with no grade specified. Rates of fatigue were similar across all treatment arms with lowest occurring in stage one in the ObChl arm (7%). The highest proportion of patients per group was found in the Chl arm in stage one with a proportion of 10%. No testing for significance of difference was completed for fatigue.

Infusion reactions

Infusion related reactions occurred exclusively in the antibody treatment arms. Grade 3 or higher infusion reactions occurred most frequently in the ObChl arms.

The number of patients in stage one was 51 (21%) versus 9 (4%) in the ObChl versus RChl arms respectively.[4] In stage 2 the number of patients was 67 (20%) versus 12 (4%).[4] There were no Grade 5 infusion related reactions reported. An important observation was that all grade 3 or 4 infusion-related reactions occurred during the first infusion of obinutuzumab but not during subsequent infusions.

Tumor lysis

Tumor lysis syndrome was reported as a serious adverse event of any level in 10 (4%), 1 (<1%), 0, and 1 (<1%) of patients in the ObChl, Chl, and RChl arms in stage one.[2] In stage 2 tumor lysis syndrome was reported in 14 patients (4%) and no patients in the ObChl and RChl arms respectively.[2] It is noted that of the 15 cases reported, all were resolved.[4]

Infections

Infections were reported more frequently in the antibody treatment arms, and did not differ significantly between treatment arms or stage. Rates of grade 3 to 5 infection ranged from 11% to 14%.[4] Most reported infections were of bacterial origin, and were one of the most frequently occurring serious adverse events.

Progressive Multifocal Leukoencephalopathy (PML)

There were no cases of PML reported in patients treated with ObChl.

CMV reactivation

There were no reported cases of CMV reactivation in the study.

HSV reactivation

No data on HSV reactivations was reported in the study.

Hepatitis-B reactivation

There were no cases of Hep-B reactivation reported in patients treated with ObChl. Two cases were reported in the RChl arm but these were considered unrelated to treatment.

Quality of life (QoL)

The EORTC Quality of Life Questionnaires QLQ-C30 and QLQ-CLL-16 was used to assess patient reported outcomes (PRO) and symptom burden. It was reported that quality of life did not deteriorate during or after treatment with antibody therapy compared to chlorambucil alone. No notable differences in any of the subscales was observed, health-related QoL assessment specific to fatigue during the treatment period showed no statistically significant difference, however the study was not powered to detect statistical differences in these parameters.

6.4 Ongoing Trials

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study ID#: NCT01980875 Estimated Enrollment: 306 Study Start Date: 02/2015 Estimated Study Completion Date: 02/2025 A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Obinutuzumab Compared to Chlorambucil in Combination With Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia	Inclusion Criteria • Not candidates for standard dose bendamustine + rituximab or fludarabine + cyclophosphamide + rituximab therapy • Documented diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) • No prior therapy for CLL other than corticosteroids for disease complications. • CLL that warrants treatment • Presence of measurable lymphadenopathy • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2	Idelalisib + obinutuzumab vs Obinutuzumab + chlorambucil	**Primary Outcome Measures:** Progression-free survival **Secondary Outcome Measures:** Overall survival, overall response, complete response, nodal response, Minimal residual disease negativity rate

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 obinutuzumab (Gazyva)for previously untreated patients with CLL where fludarabine is unsuitable. 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 the 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Hematology Clinical Guidance Panel is comprised of hematologists 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. RO5072759.rn,nm.
4. (Obinutuzumab or GA101 or RO5072759).ti,ab,rn,nm,sh,hw,ot.
5. *obinutuzumab/
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. 1or/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

"Chronic lymphocytic leukemia AND obinutuzumab OR GA101 OR GAYZA"

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"Chronic lymphocytic leukemia AND obinutuzumab OR GA101 OR GAYZA"

Grey Literature Search via
-Select International agencies (EMA)
-Conference Abstracts (ASCO, ASH, ESMO)

"Chronic lymphocytic leukemia AND obinutuzumab OR GA101 OR GAYZA

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