PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma

February 11, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) as compared to an appropriate comparator in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without del(17)p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.

Ibrutinib is an oral, first-in-class, selective Bruton's tyrosine kinase (BTK) inhibitor developed to specifically target and selectively inhibit BTK in malignant B-cells. Ibrutinib has a Health Canada indication for the treatment of patients with CLL, including those with del(17)p, who have received at least one prior therapy, or for the frontline treatment of patients with CLL with del(17)p.[1] Health Canada's recommended dosage of ibrutinib is 420 mg (three 140 mg capsules) once daily.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label randomised controlled trial, RESONATE, comparing ibrutinib (n=195) to ofatumumab (n=196) in patients with CLL/SLL who had relapsed or refractory disease, had received at least one previous therapy, and for whom treatment or retreatment with purine analog based therapy was considered not appropriate. Patients were considered not suitable by the investigators for reasons that included short progression-free interval after chemoimmunotherapy or coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion.

Patient characteristics were reported to be balanced between arms except for the presence of bulky disease of 5 cm or more (64% vs. 52% in the ibrutinib vs. ofatumumab arms, respectively) and the median time from last therapy (8 vs. 12 months in the ibrutinib vs. ofatumumab arms, respectively).

Efficacy

The primary outcome in the RESONATE trial was progression free survival (PFS) with overall survival (OS) and response rate as secondary endpoints.

After a median follow up of 9.4 months, the median duration of PFS had not been reached in the ibrutinib arm, as compared with a median of 8.1 months in the ofatumumab arm. Ibrutinib significantly improved PFS compared to ofatumumab (hazard ratio (HR) for progression or death of 0.22, 95%CI: 0.15-0.32, p<0.001). The 1 year OS rate was 90% in the ibrutinib arm and 81% in the ofatumumab arm, ibrutinib significantly prolonged the rate of OS (HR=0.43, 95%CI: 0.24-0.79, p=0.005).

Response rates were assessed by an independent review committee, response rates were observed in favour of the ibrutinib arm compared to ofatumumab arm (43% vs. 4%, odds ratio of 17.4, 95%CI: 8.1 to 37.3, p<0.001).

At week 24, clinically meaningful (≥3 points) improvement in fatigue measures occurred in more patients on ibrutinib than ofatumumab. A larger proportion of patients on ibrutinib than ofatumumab showed clinically meaningful improvements on global health scores.

Harms

Six percent of deaths in the ibrutinib arm and 8% in the ofatumumab arm led from treatment emergent adverse events. Grade ≥3 adverse events that occurred during treatment in at least 10% of patients in either group, occurred in 51% of patients in the ibrutinib arm and 39% in the ofatumumab arm.

Adverse events of grade 3 or higher occurred more frequently in the ibrutinib arm than the ofatumumab arm, including diarrhea (4% vs. 2%), neutropenia (16% vs. 14%), thrombocytopenia (6% vs. 4%) and pneumonia (7% and 5%), statistical significance was not reported. Serious adverse events occurred more frequently in the ibrutinib arm compared to ofatumumab arm with 42% and 30% of patients, respectively. Discontinuation of treatment because of adverse events did not differ between groups at 4%, these events were mostly infectious in nature.

1.2.2 Additional Evidence

pCODR received input on ibrutinib (Imbruvica) for CLL/SLL 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 (PAG) input was obtained from nine of the nine provinces participating in pCODR.

The Health Canada indication for front-line treatment of patients with CLL with del(17)p is based on the benefit observed in previously treated CLL patents with del(17)p and the clinical data in the front-line setting are very limited. PAG is seeking guidance on the use of ibrutinib in this front-line setting of patients with del(17)p. Two observational studies were identified by the submitter to support this indication. Results suggest ibrutinib (monotherapy or in combination with rituximab) in this setting is clinically active with disease reduction, response rates, and PFS benefit. However these results should be interpreted with caution since these studies were not identified through a systematic review, had different study designs, different interventions, did not capture PFS and/or OS outcomes consistently, and were of limited sample size.

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

1.2.3 Interpretation and Guidance

Burden of Illness and Need

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. Patients with this condition may receive treatment as dictated by the activity and symptoms of their illness. Patient groups noted that current treatment options for relapsed disease tend to have increased toxicity and reduced anti-tumour activity. While there are greater options for upfront treatment of CLL/SLL, there is no standard of care for older or less fit patients who have refractory or relapsed disease. The outlook of some subgroups of patients with relapsed CLL, including those who are frail and have high risk disease (deletion 17p) is especially poor.

The majority of patients with CLL are elderly and may be unsuitable for purine analogy based therapy, however they may benefit from less intensive regimens. Chlorambucil remains a standard of care in elderly and less fit patients, the addition of an anti-CD20

monoclonal antibody to chlorambucil has been attempted to improve response rates without significantly increasing toxicity. Newer anti-CD20 monoclonal antibodies such as ofatumumab and obinutuzumab may result in improved outcomes for patients with relapsed or refractory disease.

Effectiveness

PFS was significantly improved in the ibrutinib group (median not reached at 9.4 months) compared to the ofatumumab group (8.1 months). Improvements in overall survival were also seen at 12 months and treatment duration was substantially longer in the ibrutinib group compared to ofatumumab group (8.6 vs. 5.3 months).

Quality of life was assessed during this study but were not reported in the published study and are expected to be available in October 2015. At week 24, clinically meaningful (≥3 points) improvement in fatigue measures occurred in more patients on ibrutinib than ofatumumab. A larger proportion of patients on ibrutinib than ofatumumab showed clinically meaningful improvements on global health scores.

Safety

Serious adverse events (≥ grade 3) were more common in the ibrutinib group (42% vs. 30%), although rates of treatment discontinuation for adverse events did not differ between the groups. Serious adverse events included atrial fibrillation and serious infections.

1.3 Conclusions

In conclusion the Clinical Guidance Panel (CGP) felt that treatment with ibrutinib offered net clinical benefit to patients with relapsed and refractory CLL who were ineligible for treatment with purine analogues. The panel based this conclusion on the results of a single, well-conducted randomized comparative trial that enrolled a large number of patients. Evidence in favour of this conclusion includes a substantial number of durable responses among patients in the experimental arm of the RESONATE trial (progression-free survival not reached at 9.4 months with ibrutinib vs. 8.1 months with ofatumumab, HR for progression or death 0.22 (95%CI: 0.15-0.32, p<0.001)). Benefit was seen in all subgroups of patients with CLL, including those with chromosome 17p deletion, bulky disease, advanced stage and disease that was refractory to purine analogues. Adverse events were manageable and generally familiar to physicians who treat this condition.

In reaching this conclusion the panel was unable to comment on the optimal timing of ibrutinib in relation to other available treatments. The panel felt re-treatment with ibrutinib is likely not an issue given the short survival in this relapsed/refractory setting, furthermore administration is until relapse or intolerance to ibrutinib. To the panel's knowledge, there are no trials assessing re-treatment with ibrutinib. The panel noted that ofatumumab is currently only available through its manufacturer's compassionate access program in Canada and that second-line treatments for CLL are generally more toxic and less effective than this agent. As a result it was felt that ibrutinib would offer greater improvements in quality of life and clinical benefit in the Canadian context.

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 ibrutinib used for the treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without deletion 17p (del 17p) who have received at least one prior therapy. 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 Report is based on: a systematic review of the literature regarding ibrutinib conducted by the Hematology Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; and input from the Provincial Advisory Group.

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 ibrutinib and a summary of submitted Provincial Advisory Group (PAG) input on ibrutinib are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

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. Its long natural history (median survival from diagnosis is 10 or more years) reflects an extended period of watchful waiting in most patients. The decision to treat is predominantly based on whether the patient has symptoms related to CLL or advanced disease causing significant cytopenias. The mainstay of chemotherapy is with either an alkylating agent, such as chlorambucil or cyclophosphamide, or a purine analogue (fludarabine), and many combination therapies with these agents have been tried. 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 with CLL who require initial treatment and who are in good health and under the age of 65 include the combination of fludarabine, cyclophosphamide and rituximab (FCR). Patients over the age of 65, or those who are not considered fit enough to receive FCR but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Agents offered to patients in this age group include chlorambucil, an alkylating agent that is well tolerated and has been in use for more than 30 years. However, response rates are low and attempts to improve response rates using alternate therapies have been associated with increased toxicity and no long-term benefit. The addition of a CD20 monoclonal antibody to first-line chlorambucil has been attempted to improve response rates without significantly increasing toxicity. In phase III studies, the CD20 monoclonal antibodies, rituximab, ofatumumab, and obinatuzimab, have all demonstrated higher response rates, and complete remission rates compared to chlorambucil alone, without a significant increase in toxicity.[2,3]

Patients with CLL who have del(17p) karyotypes have an especially poor prognosis. These patients' tumor cells lack functioning p53, an essential cofactor for programmed cell death and are inherently resistant to chemotherapy and radiotherapy. Younger patients may receive alemtuzumab, a CD52 monoclonal antibody, for this condition although significant and prolonged immunodeficiency develops as a result. Alemtuzumab is most often used as

a bridge to definitive therapy with allogeneic stem cell transplantation for eligible patients.

The activity of ibrutinib in CLL has been well documented. Ibrutinib was examined in a phase 1B/2 trial in 85 patients with relapsed or refractory CLL requiring treatment and who had adequate organ function and performance status to enter a clinical trial.[4] Sixty-five percent had advanced disease and 33% had del(17p) karyotypes. Overall responses by traditional response criteria were seen in 71% of patients, although a substantial number of patients in partial response with lymphocytosis converted to complete or partial remissions over several months of observation. The observed response rate obtained by combining these two groups of patients (complete response and partial response) was 65% at one year; the 26 month estimated PFS and OS were 75% and 83%, respectively. Responses did not differ based on traditional disease risk factors such as del(17p), number of prior regimens and age.[4]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness of ibrutinib for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without del 17p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.

See Table 20 in Section 6.2.1 for outcomes of interest and appropriate comparators.

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 open label phase 3 randomized trial (RESONATE) comparing ibrutinib with ofatumumab was identified and included in this Clinical Guidance Report.[5] For a more detailed description of the trial's design and patient characteristics, see Table 20 in the *Systematic Review* (Section 6.3.2.1). The study dose was 420 mg of oral ibrutinib or intravenous ofatumamab at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks.
>
> The primary outcome in this study was progression free survival. Secondary end points included the duration of overall survival and the response rate. Patients from the ofatumumab group were allowed to crossover to the ibrutinib group after disease progression assessed by an independent review committee.[5]
>
> Progression free survival, which was independently assessed, was significantly prolonged with ibrutinib, with the median not reached at a follow-up of 9.4 months (Table 1). The median duration of progression-free survival for ofatumumab was 8.1 months. The hazard ratio for progression or death in the ibrutinib group was 0.22 (95% CI; 0.15 to 0.32; P<0.001). At 6 months, 88% of patients in the ibrutinib group were still alive with no disease progression, as compared with 65% in the ofatumumab group.[5]
>
> In patients with del(17)p, the median duration of progression-free survival was not reached in the ibrutinib group (Table 1). In the ofatumumab group the median duration was 5.8 months (HR for progression or death, 0.25; 95% CI, 0.14 to 0.45).

At 6 months, 83% of the patients in the ibrutinib group, as compared with 49% in the ofatumumab group, were alive with no disease progression.[5]

Overall Survival

Ibrutinib significantly prolonged the rate of overall survival (HR for death in the ibrutinib group, 0.43; 95% CI, 0.24 to 0.79; P=0.005), with the risk of death reduced by 57% compared to ofatumumab (Table 1). The overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group at 12 months. Crossover from ofatumumab to ibrutinib, at confirmed disease progression was permitted in 57 patients at the time of this analysis. Data were censored at the time of crossover, however, the survival effect was also seen in the uncensored analysis (hazard ratio for death, 0.39; P=0.001), with an overall survival rate of 90% in the ibrutinib group and 79% in the ofatumumab group.[5]

There were 12 (6.2%) deaths in the ibrutinib group and 16 (8.4%) in the ofatumumab group leading from treatment emergent adverse events. There were an additional 16 (8.2%) deaths in the ibrutinib group and 33(16.8%) in the ofatumumab group captured from overall survival follow-up.[6]

Response

The response rate was assessed independently. It was significantly higher in the ibrutinib group than in the ofatumumab group. This can be seen in table 1. In the ibrutinib group 43% of the patients had a partial response, as compared with 4% in the ofatumumab group (odds ratio, 17.4; 95% CI, 8.1 to 37.3; P<0.001). The response rates assessed by the investigators differed from the independently assessed response rates in the two groups, there is a bias as there is no blinding in the investigator-assessed responses. The partial response was 43% in the independent assessment and 68% in the investigator led assessment for ibrutinib and 4% for the partial response in the independent assessment and 21% for the investigator response for ofatumumab.[5]

Table 1: Efficacy results from the RESONATE trial

Median follow-up months, range	Outcome	Ibrutinib (n=195)	Ofatumumab (n=196)	Comparative Statistics (95%CI) for HR/OR
9.4 (0.1-16.6)	Median PFS (95%CI)	Not yet reached	8.1 months	HR=0.22 (0.15-0.32) (p<0.001)
	Alive at 6 months with no disease progression (%)	88%	65%	-
	OS at 1 year (%), censored analysis	90%	81%	HR=0.43 (0.24-0.79) (p=0.005)
	OS at 1 year (%), uncensored analysis	90%	79%	HR=0.39 (p=0.001)
	Independently assessed response rate	43%	4%	OR=17.4 (8.1-37.3) (p<0.001)
	Del(17)p subgroup	**Ibrutinib**	**Ofatumumab**	

Median follow-up months, range	Outcome	Ibrutinib (n=195)	Ofatumumab (n=196)	Comparative Statistics (95%CI) for HR/OR
	Median PFS for patients with (95%CI)	Not yet reached	5.8 months	HR=0.25 (0.14-0.45)
	Alive at 6 months with no disease progression (%)	83%	49%	-

Abbreviations: HR=hazard ratio; OR=odds ratio; PFS=progression free survival; CI=confidence interval; OS=overall survival;

Harms Outcomes

For any grade the most frequent non-hematologic adverse events that occurred in at least 20% of the patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group. Overall, 51% of the patients in the ibrutinib group and 39% of the patients in the ofatumumab group had at least one adverse event during treatment. Grade 3 or higher adverse events occurring during treatment were seen in 57% for the ibrutinib group and 47% for the ofatumumab group. Grade 3 and 4 adverse events are in Table 2.[5]

Discontinuation of treatment because of adverse events occurred in 4% of the patients in each study group. Fatal events occurred in 4% of the patients in the ibrutinib group and in 5% of those in the ofatumumab group. These events were most commonly infectious in nature.[5]

Table 2: Grade 3 and 4 Adverse Events reported in the RESONATE trial

Adverse event*	Ibrutinib (n=195)	Ofatumumab (n=191)
	N (%)	N (%)
Any adverse event occurring during treatment	99 (51)	74 (39)
Diarrhea	8 (4)	3 (2)
Fatigue	4 (2)	3 (2)
Nausea	3 (2)	0
Pyrexia	3 (2)	2 (1)
Anemia	9 (5)	15 (8)
Neutropenia	32 (16)	26 (14)
Cough	0	2 (1)
Thrombocytopenia	11 (6)	8 (4)
Pneumonia	13 (7)	9 (5)
Urinary tract infection	7 (4)	1 (1)
Infusion-relation reaction	0	6 (3)

* This is a subgroup of grade 3-4 adverse events that occurred in at least 10% of the patients in either group

Quality of Life

At week 24, clinically meaningful (≥3 points) improvement in FACIT-F occurred in more patients on ibrutinib than ofatumumab (59% vs 46%, p=0.06). Fewer patients in both groups showed clinically meaningful deterioration (14% for ibrutinib vs 24% for ofatumumab, p=0.08).[7] A clinically meaningful improvement (≥10 points) from baseline to week 24 in patients treated with ibrutinib versus ofatumumab was observed for fatigue (median 11 vs 0).

A larger proportion of ibrutinib versus ofatumumab patients showed clinically meaningful improvements on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC-QLQ-C30) global health scores (46% vs 40%).[7]

The results of the EuroQoL Five Dimension- 5L (EQ-5D-5L) questionnaire saw a greater improvement in scores for the ibrutinib group, but it was only significant for week 16. In addition a higher percentage of patients in the ibrutinib group achieved a clinically meaningful improvement in the visual analog scale score compared with the ofatumumab group (53.8% vs 41.8%).[8]

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) input, respectively.

Patient Advocacy Group Input

From a patient perspective, there needs to be individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments.

Patient advocacy groups noted that current treatment options for relapsed disease tend to have increased toxicity and reduced anti-tumour activity. Because respondents' personal experience with CLL/SLL 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/SLL 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. A majority of respondents reported their experience with treatment to date as being positive, as they were able to obtain a remission and their quality of life improved during remission. A large number of respondents were well informed about ibrutinib. Respondents understood that all treatments have some degree of side effects. However, respondents who had experience with ibrutinib

stated that the side effects were mild and quickly dissipated with minimal tolerability issues. In addition, respondents noted the ease of use with ibrutinib as it is an oral drug. Respondents reported on the benefits of no travel time and associated costs to visit clinic, as well as no chemo chair time and greater patient compliance. Respondents also stated that ibrutinib brought their disease under control and makes them feel very similar to the way they did before their diagnosis.

PAG Input

Input on ibrutinib was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, ibrutinib has enablers that include being a new class of drug that fills the gap in therapy for CLL patients and being an oral therapy with once daily dosing schedule that can be easily delivered in the community setting. Key barriers identified include the potentially large budget impact and the possible use in first-line treatment or other indications.

2.2 Interpretation and Guidance

Burden of Illness

Although CLL may be characterized by a long period of expectant waiting after diagnosis, relapsed or refractory CLL has a poor prognosis marked by multiple rounds of increasingly less effective treatment and an increasing burden of illness. The lack of a well-defined standard of care for these patients and poor tolerance of treatment in general further complicates their management. The outlook for some subgroups of patients with relapsed CLL, including those who are medically frail and those with high risk disease (unmutated IgH and del(17)p), is especially poor.

Effectiveness

Progression-free survival (the primary endpoint of this study) was significantly better for patients who received ibrutinib than ofatumumab (not reached at 9.4 months vs. 8.1 months, HR progression or death 0.22 (0.15-0.32, p<0.001)). Overall survival also appeared superior in the ibrutinib arm (90% vs. 81% at 12 months, HR death 0.43 (0.24-0.79, p=0.005). Treatment duration was substantially longer with ibrutinib compared with ofatumumab (8.6 vs. 5.3 months). The improvement in progression-free survival was seen in all subgroups examined, including among patients with del(17)p of whom 83% were alive and progression free at six months, compared with 49% with this deletion in the ofatumumab group.

Safety

Adverse events were generally manageable but more common with ibrutinib. Diarrhea, neutropenia, thrombocytopenia and pneumonia were common in patients treated with ibrutinib compared with ofatumumab. Serious adverse events including atrial fibrillation and serious infections were also more common in this group. Rates of treatment discontinuation for adverse events did not differ between groups at 4% in both arms. A predictable and usually transient rise in the absolute lymphocyte count was noted among patients who received ibrutinib. Clinical benefit (reduction in lymphadenopathy and

organomegaly, improvement in bone marrow function) was noted despite the increasing lymphocytosis.

Despite the higher incidence of bothersome adverse events among patients receiving ibrutinib, the quality of life of these patients was superior numerically to that of patients who received ofatumumab although statistically not significant between arms. As ofatumumab has fewer toxic side effects than the second-line options for CLL currently licensed in Canada the CGP felt that the difference in quality of life would be greater in the Canadian landscape.

2.3 Conclusions

In conclusion the Clinical Guidance Panel felt that treatment with ibrutinib offered net clinical benefit to patients with relapsed and refractory CLL who were ineligible for treatment with purine analogues. The panel based this conclusion on the results of a single, well-conducted randomized comparative trial that enrolled a meaningful number of patients. Evidence in favour of this conclusion includes a substantial number of durable responses among patients in the ibrutinib arm of the RESONATE trial. Benefit was seen in all subgroups of patients with CLL, including those with del(17)p, bulky disease, advanced stage and disease that was refractory to purine analogues. Adverse events were manageable and generally familiar to physicians who treat this condition.

In reaching this conclusion the panel was unable to comment on the optimal timing of ibrutinib in relation to other available treatments. The panel felt re-treatment with ibrutinib is likely not an issue given the short survival in this relapsed/refractory setting, furthermore administration is until relapse or intolerance to ibrutinib. To the panel's knowledge, there are no trials assessing re-treatment with ibrutinib. The panel noted that ofatumumab is currently unavailable in Canada and that second-line treatments for CLL are generally more toxic and less effective than this agent. As a result it was felt that ibrutinib would offer greater improvements in quality of life and clinical benefit in the Canadian context.

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, CLL represents the most common leukemia in western countries. CLL is a disease of the elderly, with a median age at diagnosis of 72 years, and its long natural history (median survival from diagnosis is 10+ years) reflects an extended period of watchful waiting in most patients. Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities.[9]

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 by 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.[10] 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 peripheralizing lymphomas, such as mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma as treatment of these entities differs 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 3).[11,12] Both staging systems reflect the gradual infiltration of CLL target organs, lymph nodes, spleen and bone marrow by disease cells, with higher stages indicating impairment of bone marrow function. Advanced CLL with bone marrow impairment (Rai stage 3 or 4, Binet stage C) has poor prognosis and is a commonly accepted indication for treatment.

A large numbers of factors have been associated with adverse prognosis in CLL. Rapid cell turnover, reflected by a short lymphocyte doubling time, is associated with an aggressive clinical course and shortened survival. Plasma factors indicating rapid turnover including β2- microglobulin and thymidine kinase have also been confirmed to reflect adverse prognosis.[13]

Table 3. Accepted staging systems for patients with chronic lymphocytic leukemia.[11,12]

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

Staging System	Stage	Definition	Median OS (mo)
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 and differentiation of normal B lymphocytes, acquisition of mutations in various immunoglobulin genes occurs through the process of somatic hypermutation. CLL may arise from either antigen naïve (without immunoglobulin gene somatic hypermutation) or antigen exposed (with somatic hypermutation) B-cells. 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.[14,15] 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.[15-17]

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. In Canada, cytogenetic analysis is typically completed shortly before treatment because some genotypes (17p) are associated with greater treatment resistance, and because genetic mutations are dynamic.

Bruton's tyrosine kinase (BTK) is a cytoplasmic non-receptor kinase that participates in several B-Cell receptor pathways. BTK is briefly translocated to the cytoplasmic membrane upon activation of phosphoinositol-3-kinase, where it is fully phosphorylated by the B-Cell receptor-associated proteins LYN and SYK. The resulting "signalsome" influences antiapoptotic and proliferative factors such as NF-kB and MYC while downregulating antiapoptotic BAD and BIM. It has a similar central role in Toll-like receptor and chemokine signaling, pathways associated with enhanced survival and proliferation of B-Cells. Increased levels of phosphorylated BTK have been described in CLL B-Cells. Laboratory studies have confirmed that B-Cell receptor signaling is needed for CLL B-Cell survival.[18]

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 failed to show benefit, 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 (< 3 months). The mainstay of chemotherapy is with either an alkylating agent, such as chlorambucil or cyclophosphamide, or a purine analogue (fludarabine), and many combination therapies with these agents have been tried. 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 with CLL who require initial treatment and who are in good health and under the age of 65 include the combination of 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 fludarabine-cyclophosphamide (FC).[19] Patients over the age of 65, or those who are not considered fit enough to receive FCR but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Agents offered to patients in this age group include chlorambucil, an alkylating agent that is well tolerated and has been in use for more than 30 years. It can be given in daily, weekly, biweekly and monthly schedules. Response rates are low and 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.[20] Patients treated with fludarabine in this study had a higher rate of severe infection and neutropenia and consequently, the toxicity outweighs the benefit. Similarly, bendamustine was compared with chlorambucil.[21] Although the response rates were higher, there was increased toxicity and no benefit in OS. As a result, chlorambucil has remained a standard of care in elderly and less fit patients. The addition of a CD20 monoclonal antibody to first-line chlorambucil has been attempted to improve response rates without significantly increasing toxicity. In phase III studies, the CD20 monoclonal antibodies, rituximab, ofatumumab, and obinatuzimab, have all demonstrated higher response rates, and complete remission rates compared to chlorambucil alone, without a significant increase in toxicity.[2,3] A survival advantage was also demonstrated in the obinutuzumab-chlorambucil study when comparing obinutuzumab-chlorambucil and rituximab-chlorambucil to chlorambucil alone.[2]

Patients with CLL who have del(17p) karyotypes have an especially poor prognosis. These patients' tumor cells lack functioning p53, an essential cofactor for programmed cell death and are inherently resistant to chemotherapy and radiotherapy. Younger patients may receive alemtuzumab, a CD52 monoclonal antibody, for this condition although significant and prolonged immunodeficiency develops as a result. Median progression-free survival for patients with CLL and del(17p) is 2.2 months with chlorambucil compared with 10.7 months with alemtuzumab.[22] Alemtuzumab is most often used as a bridge to definitive therapy with allogeneic stem cell transplantation for eligible patients.

Despite improvements in up-front treatment CLL remains an incurable chronic condition. Little consensus exists on treatment of relapsed or refractory patients with CLL. Options for these patients include retreatment with earlier regimens for patients who had sustained responses without toxicity. In general, treatment decisions for this group of patients should consider age, comorbidities and response to prior therapy. Elderly patients may benefit from chlorambucil or fludarabine, especially if they have not been exposed to these agents previously. Newer monoclonal CD20 antibodies such as ofatumumab and obinutuzumab may result in improved outcomes for patients with relapsed or refractory CLL.

The activity of ibrutinib in CLL has been well documented. In both preclinical and clinical evaluation a pronounced lymphocytosis occurs due to mobilization of tumour cells from the

nursing environment of lymph nodes and spleen to the peripheral blood. Gradual resolution of this lymphocytosis occurs over weeks to months. Ibrutinib was examined in a phase 1B/2 trial in 85 patients with relapsed or refractory CLL requiring treatment and who had adequate organ function and performance status to enter a clinical trial.[4] Sixty-five percent had advanced disease and 33% had del(17p) karyotypes. Overall responses by traditional response criteria were seen in 71% of patients, although a substantial number of patients in partial response with lymphocytosis converted to complete or partial remissions over several month of observation. The observed response rate obtained by combining these two groups of patients (OR + PR with lymphocytosis) was 89% at one year; the 26 month estimated PFS and OS were 75% and 83%, respectively. Responses did not differ based on traditional disease risk factors such as del(17p), number of prior regimens and age.

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 may be exacerbated by the immune dysregulation that may occur following treatment with fludarabine. The CIRS (Cumulative Illness Rating Scale) score is commonly used to identify patients who may not derive benefit from fludarabine and fludarabine-containing regimens due to higher rates of toxicity.[23]

3.4 Other Patient Populations in Whom the Drug May Be Used

It is likely that ibrutinib will become a major agent in the treatment of patients with B-Cell malignancy. Pathways involving BTK are active in lymphoma subtypes including Mantle Cell Lymphoma, Marginal Zone Lymphoma and Lymphoplasmacytic Lymphoma. It is also active the Activated B-Cell phenotype of Large B-Cell Lymphoma and in Multiple Myeloma. Clinical development in these areas lags behind development in CLL, but ibrutinib has received FDA approval for use in patients with Mantle Cell Lymphoma that have received at least one prior line of therapy based on the results of a phase II trial.[24]

Front-line treatment of patients with del(17)p

According to the CGP, there is currently no phase III study limited to front-line therapy for patients with CLL with del(17)p comparing ibrutinib to other therapies. Current therapy options in Canada include: alemtuzumab (with or without steroids), FCR, allogeneic stem cell transplant (alloSCT), and an emerging option of idelalisib.

Alemtuzumab is the main treatment option for front-line therapy of patients with CLL with 17p deletion, this option has a good response rate however these responses are typically brief and associated with a high rate of toxicity (i.e. CMV infections). In Canada, although alemtuzumab is available, there is varying and limited access to alemtuzumab across provinces. Furthermore, a phase III study in this population is challenging to conduct given the low prevalence of del(17)p deletion, short survival of these patients, and different permutations of 17p deletions.

Observational studies of front-line treatment of del(17)p identified by the submitter

The Health Canada indication for ibrutinib is for the treatment of patients with CLL, including those with del(17)p, who have received at least one prior therapy, or for the

frontline treatment of patients with CLL with del(17)p.[1] Clinical effectiveness of ibrutinib in the frontline setting is based on the benefit observed in CLL patients with del(17)p who have received at least one prior therapy. Clinical trial data in the frontline setting are very limited.[8]

According to the submitter, the pivotal studies submitted to Health Canada (RESONATE and PCYC-1102-CA) were not designed to study patients with del(17)p in the frontline setting (RESONATE had no frontline del(17)p, PCYC-1102-CA had two frontline del(17)p).[8] The RESONATE trial was reviewed in this submission. The updated results on the phase 1b/2 study PCYC-1102-CA were presented at the 2014 ASCO Annual Meeting. Efficacy data 3 years following initiation of therapy (420 or 840 mg ibrutinib daily) was independently assessed.[25] Of 132 CLL/SLL patients enrolled, 31 were treatment-naïve (TN) (2 patients had del(17)p). Overall median age was 68 years (range 37-84). The updated overall response rate (ORR) was 78.0% for all-treated patients (83.9% in TN, 76.2% in relapsed/refractory (R/R) disease, and 55.9% for those with R/R with del(17)p)).

Two investigator-initiated studies identified by the submitter, included frontline del (17)p patients.[26,27] The first study was an investigator-initiated phase II, single-center trial of ibrutinib monotherapy prospectively conducted to address the role of ibrutinib in del(17)p CLL irrespective of patient's prior treatment history.[26] The primary endpoint was response after 6 months assessed by computed tomography (CT), bone marrow (BM) biopsy, and routine clinical and laboratory studies. Results reported in abstract form included 53 patients, 24 patients without a del(17)p deletion (nl(17)p) and 29 patients with del(17)p (15 patients were TN, 14 patients had previously treated disease). The median follow-up was 14 months and median age was 66 years (range 33-85). At 6 months, 31 (66%) patients had a partial response (PR) and 13 (28%) had a PR with lymphocytosis (PRL). Responses for del(17)p were 53% PR and 43% PRL. Clinical benefit and disease control in all tissues sites were equal by cohort with nodal response seen in 100% of patients.

The second study identified by the submitter was a single-arm, phase II study conducted to evaluate the safety and activity of ibrutinib plus rituximab for patients with high-risk CLL.[27] All patients enrolled had high-risk cytogenetic abnormalities [(del(17)p, TP53 mutation, or del(11)q), or short PFS (PFS <36 months)] after previous first-line chemoimmunotherapy. Patients received once-daily ibrutinib 420 mg together with rituximab (375 mg/m^2, intravenously, every week during cycle 1, then once per cycle until cycle 6) followed by continuous daily single-agent ibrutinib 420 mg until disease progression or toxicities or complications that precluded further treatment. The primary endpoint was PFS in the intention-to-treat population. Forty patients were enrolled, 20 patients with 17p deletion or TP53 mutations (16 previously treated, 4 untreated). The median follow-up was 16.8 months and the median age was 63.2 years (range 35-82). The 18-month PFS was 78.0% for all subjects and 72.4% for patients with del(17)p/TP53 mutations. Thirty-nine patients were evaluable for response and two patients did not respond, 34 (87%) PR (16 with del(17)p/TP53) and 3 (8%) CR (2 had del(17)p/TP53 and were previously untreated).

The pCODR Review Team identified an abstract from the American Society of Hematology (ASH) 2014 Annual Meeting on the results from the phase II RESONATE-17 trial, the largest prospective trial of patients with del(17)p.[28] Efficacy and safety of single-agent ibrutinib (420 mg daily) in 144 patients with relapsed/refractory del(17)p CLL/SLL was evaluated. The primary endpoint was ORR as assessed by an independent review committee. The median age was 64 years and patients had a median of 2 prior therapies (range 1-7). At a median follow-up of 13.0 months, the median PFS and duration of response had not been

reached. At 12 months, 79.3% were alive and progression-free, and 88.3% of responders were progression-free.

Results of these studies suggest ibrutinib (single agent or in combination with rituximab) appears to be effective against CLL with del(17)p. Clinical benefit (PR and PRL) and disease control in reduction of tumour volume was seen in patients with n(17)p and del(17)p. PFS and response rates for patients with del(17)/TP53 mutations were comparable to patients without these mutations.

Limitations

The observational studies summarized were identified by the submitter and pCODR Review Team and not through a systematic review of the literature. These studies included various populations of patients with CLL, including, but not limited to those with del(17)p for frontline ibrutinib treatment. In addition, the studies had different study designs, different interventions (ibrutinib monotherapy versus combination therapy of ibrutinib plus rituximab), did not capture PFS and/or OS outcomes consistently, and were generally of limited sample size. Two studies were only available in abstract form.[26,28] The quality of these studies were low given the lack of a comparator arm and small sample sizes, conclusions from these studies have a high risk of bias and should be drawn with extreme caution.

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 ibrutinib for the treatment of patients with chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) with or without del 17p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog (e.g., fludarabine), 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 4 below (note 17 people did not answer this question):

Table 4: ages of respondents

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

In addition to the above, a separate survey ("Survey 2") was distributed through the same channels for CLL patients who have experienced with ibrutinib. There were a total of 45 responses to Survey 2. It was reported that 35 respondents were from the USA, 5 were from Canada, one from France and four did not specify their country of origin. The age range included: 40-49 years of age = 1 (2.50%), 50-59 years of age = 10 (25%), 60-69 years of age = 16 (40%) and 70-79 years of age = 13 (33%). 27 (68%) of the respondents were men.

CLL PAG and LLSC also conducted two separate caregiver surveys. 19 respondents responded to the LLSC caregiver survey; while 14 responded to the CLL PAG caregiver survey. 93% (13/14) of respondents were a spouse/partner, and 7% (1/14) was a child of a CLL patient. In the CLL PAG caregiver survey, 93% (13/14) of caregivers were female and 85% were older than 60 years.

LC conducted two online surveys (one of patients and one of caregivers) to gather information about the impact of CLL and SLL 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 11 respondents had direct experience with using ibrutinib. Five patients were obtained through the survey. Another three (3) respondents participated through telephone interview. 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 ibrutinib experience. Another three (3)

respondents were obtained through an online interview. Please see table 5 for a breakdown of the results to the surveys and interview.

Table 5: Participants by Country

Participants by Country		Canada (n, %)	USA (n, %)	UK (n, %)	Australia (n, %)	Skipped (n, %)	N
Survey	Patients without Ibrutinib Experience	33 (71.7%)	7 (15.2%)	-	1 (2.2%)	5 (10.9%)	46
	Patients with Ibrutinib Experience	3 (60%)	2 (40%)	-	-	-	5
	Total (Patient Survey Respondents)	**36 (70.6%)**	**9 (17.6%)**	**-**	**1 (2.0%)**	**5 (9.8%)**	**51**
Interviews	Patients with Ibrutinib Experience	2 (33.3%)	4 (66.7%)	-	-	-	6
Survey	Caregivers - none with Ibrutinib Experience	10 (83.3%)	1 (8.3%)	1 (8.3%)	-	-	12
Total	**Survey & Interviews**	**48 (69.6%)**	**14 (20.3%)**	**1 (1.4%)**	**1 (1.4%)**	**5 (7.2%)**	**69**

From a patient perspective, there needs to be individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. Patient advocacy groups noted that current treatment options for relapsed disease tend to have increased toxicity and reduced anti-tumour activity. Because respondents' personal experience with CLL/SLL 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/SLL 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. A majority of respondents reported their experience with treatment to date as being positive as they were able to obtain a remission and their quality of life improved during remission. A large number of respondents were well informed about ibrutinib. Respondents understood that all treatments have some degree of side effects. However, respondents who had experience with ibrutinib stated that the side effects were mild and quickly dissipated with minimal tolerability issues. In addition, respondents noted the ease of use with ibrutinib as it is an oral drug. Respondents reported on the benefits of no travel time and associated costs to visit clinic, as well as no chemo chair time and greater patient compliance. Respondents also stated that ibrutinib brought their disease under control and makes them feel very similar to the way they did before their diagnosis.

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/SLL

According to LC, patients with early stage CLL or SLL 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 and SLL 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 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)

> *"In my daily life, I have learned to pace myself due to fatigue and shortness of breath experienced even when I am at rest…I alternate between rest and modest activity each day. There are times when I do not feel alert enough to drive the car and then my husband drives. …I estimate that my lifetime job earnings have been reduced by 25% due to my disease. I retired 10 years earlier than planned because I was unable to tolerate the demands of my job due to my disease and because I was not considered competent to continue in my job due to my disease."*(female; 55-64; Canada)

> "*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 every day from the fatigue or was at another Cancer Clinic appointment. 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. 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)

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: "*Being so fatigued, there is little I really want to do*."

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 find it difficult to deal with the uncertainty about my future health and whether or not the new, less toxic drugs will be available when I next need treatment.*"

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 "*Inability to work at my usual level. I have already suffered one hospitalization for multiple infections.*"

4.1.2 Patients' Experiences with Current Therapy for CLL/SLL

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 "*I found the hardest part is "watch & wait". Watching the numbers go up & waiting for the other shoe to drop.*"

93% (85/91) of respondents who have received treatment responded to questions asking about treatment type(s). The list of therapies is set out in table 6; this includes 2 respondents who are in clinical trials for non-marketed drugs:

Table 6: List of therapies

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 (table 7):

Table 7: Previous therapies

Current Treatment N= 25	Response Count* (n, %)	Current Treatment	Response Count* (n, %)
FCR	9 (27.3%)	Stem cell transplant	4 (12.1%)
Rituximab alone	8 (24.2%)	Radiation therapy	3 (9.1%)
CVP chemotherapy	3 (9.1%)	Splenectomy	1 (3.0%)
CHOP chemotherapy	1 (3.0%)		
Chlorambucil alone	1 (3.0%)		
Other current treatments: ibrutinib (3, 9.1%); idelalisib (1, 3.0%); R-CHOP (1, 3.0%); FR (1, 3.0%); IVIG (4, 12.1%); blood transfusions (1, 3.0%); ITP (1, 3.0%); steroids (2, 6.1%); cyclosporine (1, 3.0%); anti-nausea (1, 3.0%) and anti-anxiety (1, 3.0%). ***Total response count exceeds total respondents to this question (N=33) 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%). 44% had nausea and about a third anemia, diarrhea, mouth sores and skin rashes.

One respondent stated: "*Improved quality of life has been worth the limited side effects*" while another was "*The treatment while giving me extra years does not cure the disease nor has it made any difference to the effects of the disease.*" Patients understand that all treatments have some degree of side effects. One said: "*None of these drugs is risk free, but what's the alternative when you have a fatal, incurable disease.*"

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.

> *"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)

"My oncologist reports that my current therapy is a "rescue" therapy. It is meant to control the side effect of my disease that I am currently experiencing, i.e. AIHA [autoimmune haemolytic anemia]. *It does not, he reports, treat my underlying disease. He tells me that I need treatment for my underlying disease very soon, but that standard therapies are unlikely to help me and so I have been referred to be screened for a clinical trial."* (female; 55-64; Canada)

"All treatments wiped out my good blood components and made me tired. As treatment went on with each of these therapies I develop 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, 35% 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. This can be seen in table 8.

Table 8: Difficulties with access

Level of Difficulty with Access	N (%)	Level of Difficulty with Access	N (%)
Not at all difficult	15 (37.5%)	Somewhat difficult	8 (20.0%)
Not very difficult	11 (27.5%)	Very difficult	6 (15.0%)
			Response Count:40

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)

"The life saving drug ibrutinib was not available where I lived so I had to fly to the U.S. to get into a clinical trial to start on the medication that has turned my life around." (male; 55-64; Canada)

"This has been substantial. I have not been able to work since May 11, 2010. I have had assistance but have mounting medical bills due to my long stay in the hospital, surgery, stem cell transplant and monthly visits to the hospital and being unable to work. I was working and got sick within 6 weeks of getting medical coverage because of the 6 month waiting period and so I have had minimal coverage" (female; 45-54; 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 or SLL with 1 (Strongly Disagree) to 10 (Strongly Agree). Those respondents who identified as having relapsed/refractory disease rated substantially lower (rating average 4.9, n= 7) than those patients without relapsed/refractory disease (rating average 7.7, n = 21).

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). 73.7% (28/38) of respondents who answered this question gave this a rating of 8 or higher. The rating average was 8.4, 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 or SLL. All 36 respondents who answered this question feel there is a definitive need for more therapies.

4.1.3 Impact of CLL/SLL 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 (41.7%) respondents were retired at the time of completing the survey and 7 (58.3%) were still working. This can be seen in table 9.

Table 9: Impact of current therapy on caregivers

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	4 (50%)	6.7
Ability to volunteer	3 (60%)	5.8	Ability to exercise	3 (42.9%)	5.1
Ability to spend time with family and friends	2 (40%)	5.2	Ability to concentrate	2 (28.6%)	4.7
Ability to concentrate	2 (40%)	4.8	Ability to travel	1 (14.3%)	4.3
Ability to fulfill family obligations	2 (40%)	4.8	Ability to spend time with family and friends	**2 (28.6%)**	3.9
Ability to exercise	2 (40%)	4.4	Ability to contribute financially to household expenses	**2 (28.6%)**	3.7
Ability to attend household chores	1 (20%)	4.0	Ability to attend household chores	**2 (28.6%)**	3.7
Ability to contribute financially to household expenses	1 (20%)	2.2	Ability to fulfill family obligations	**1 (14.3%)**	3.6
***All 12 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 financial concerns, 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*".

Specifically, 79% (15/19) of respondents who responded to the LLSC caregiver survey cited depression, 42% (8/19) cited fear and 68% (13/19) cited anxiety. 36.8% (7/19) of

respondents experienced financial difficulties. It was noted that 32% (6/19) specifically suffered loss of income due to their partner's cancer diagnosis and treatment, 21% (4/19) cited out of pocket drug costs, and 21 % (4/19) on transportation costs.

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. According to the LLSC survey, 68% (13/19) of caregiver respondents cited fear of recurrence and 32% (6/19) feared that another family member would be diagnosed. *"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 Ibrutinib

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: *"Each "flavour" of CLL is different, it needs to be a patient by patient decision, since the disease is very heterozygous,"* and *"CLL is very complex and you need a range of treatments to meet all complexities."*

When respondents were asked what they knew about ibrutinib, they responded as follows with 1=know nothing and 5=well informed: (table 9)

Table 9: Knowledge of ibrutinib

1	2	3	4	5	Response Count
33	22	28	43	82	208

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:

"Most important thing is to treat the CLL from the perspective that treatment is tailored to my version of the disease - better a scalpel than a chainsaw. Secondly, preserving quality of life while being treated is important...if the treatment is worse that the disease it makes it hard to be optimistic."

"Currently available treatments put me at risk of further reductions in my already badly compromised immunity, both during treatment and after treatment."

"Better remissions. Less side effects. A more hopeful future."

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 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 or SLL. 48.6% (17/35) of respondents gave a rating of 8 or higher (rating average 6.6). 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)

"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)

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 (table 10).

Table 10: Control of a new Drug

Level of Importance of a New Drug to be able to Control	Rating of 10	Rating Average	Response Count
Improve Quality of Life	29	9.79	34
Control disease and side effects	31	9.78	36
Live longer	31	9.77	35
Improve blood counts	30	9.76	34
Bring about a remission	30	9.56	36

Respondents to the CLL PAG and LLSC survey were also asked to rate what side effects were most important to control. The table below summarizes respondents' key ranking with controlling side effects (table 11).

Table 11: Key ranking with controlling 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 11 patients (5 survey respondents; 3 telephone interviews; 3 online interviews) had direct experience with ibrutinib.

Prior to commencing treatment with ibrutinib, all patients had switched from therapy to therapy as their disease kept relapsing which is common with CLL and SLL. Since starting treatment with ibrutinib, respondents 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 or SLL had shown improvement with ibrutinib. 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 (Table 12). Many of the respondents (5, 83.3%) surveyed or interviewed have been taking ibrutinib for two years or longer. Eight (8) of the respondents have not had any dose interruptions and are reported to be tolerating ibrutinib very well. None of the respondents have had a relapse of their disease.

Table 12: Improvement in Symptoms since switching to Ibrutinib

Improvement in symptoms associated with CLL since taking ibrutinib	Rating of 10 N (%)	Rating of 9 N (%)	Rating Average	Response Count
Enlarged lymph nodes	7 (87.5%)	1 (12.5%)	9.9	8

Improvement in symptoms associated with CLL since taking ibrutinib	Rating of 10 N (%)	Rating of 9 N (%)	Rating Average	Response Count
Red blood cell count (anemia)	6 (75%)	2 (25%)	9.8	8
Platelet counts	6 (75%)	2 (25%)	9.8	8
White blood cell counts	6 (75%)	1 (12.5%)	9.1	8
Fatigue	6 (75%)	0 (0%)	8.9	8

According to CLL PAG and LLSC, 71% (32/45) of respondents felt they were well informed about ibrutinib.

Respondents were asked which symptoms of CLL the ibrutinib drug regimen managed for them. Please see the table 13 below for a summary of managed symptoms.

Table 13: Managed symptoms

CLL Symptom	% respondents whose symptom was managed	Number of respondents (total n=45)
Enlarged lymph nodes	80.01%	36
Increasing white count	64.44%	29
Fatigue, lack of energy	51.11%	23
Night sweats	46.7%	21
Enlarged spleen	44.4%	20
Shortness of breath	22.22%	10
Frequent infections	20.00%	9
Did not manage any symptoms	4.44%	2

Respondents were subsequently asked which symptoms of CLL the ibrutinib drug regimen did not manage for them. Please see the table 14 for a summary of symptoms that were not managed.

Table 14: Symptoms that were not managed

CLL Symptom	% respondents whose symptom was not managed	Number of respondents (total n=45)
Fatigue, lack of energy	26.67%	12
Other	20.00%	9
Shortness of breath	11.11%	5
Frequent infections	11.11%	5
Increasing white count	11.11%	5
Weight loss	6.67	3
Pain	6.67	3
All symptoms managed	42.22%	19

Respondents specified other symptoms not managed including:

- Low Platelets (1)
- Low Immunoglobulin levels (2)
- Infections (1)
- Shortness of breath (1)
- Too soon to tell (3)
- Cramps, cold extremities, Raynaud's Syndrome (1)

According to LC, both survey respondents and interviewees reported on how ibrutinib compared in terms of side effects to other treatments they had taken to treat their CLL or SLL on a scale of 1 - 10, with 1 being (Fewer Side Effects) and 10 being (Many More Side Effects). Responses were as follows in table 15:

Table 15: How ibrutinib compared to other treatments for side effects
* One interviewee gave a rating of "zero"

Improvement in Symptoms	Rating of 1 (n, %)	Rating Average	Total Responses
Survey Respondents	4 (100%)	1	4 (1 skipped)
Interview Participants	2 (75%)	0.85*	3*

CLL PAG and LLSC also asked respondents if ibrutinib managed symptoms better than prior treatments. According the results of this survey, 62% (28/45) responded yes, 4% (2/45) responded no and 33% (15/45) had no prior treatment.

According to CLL PAG and LLSC, respondents reported the following side effects (table 16) that they were willing to tolerate.

Table 16: side effect that patients were able to tolerate

Drug regimen Side effect	% respondents willing to manage side effect	Number of respondents (out of 45)
Diarrhea	57.78%	26
Rash or itching	42.42%	19
Fatigue	33.33%	15
Low platelets	33.33%	15
Nausea	28.89%	13
Anemia or neutropenia	22.22%	10
Cough	17.78%	8
Back pain	17.78%	8
Fever	13.33%	6
Breathing difficulties	6.67%	3
Irregular heartbeat	6.67%	3
Tumour lysis syndrome	4.44%	2
Viral reactivation	4.44%	2
Small bowel obstruction	4.44%	3
None of the above	17.78%	8

Other side effects not listed above which respondents were willing to tolerate include: brittle nails (4), mouth sores (2), joint pain (1). One respondent noted that muscle cramps and adult acne are about to make them stop ibrutinib.

Respondents were also asked which side-effects that they have experienced with ibrutinib. Table 17 provides the key side-effects that respondents experienced with the use of ibrutinib.

Table 17: side effects patients experienced with the use of ibrutinib

Ibrutinib side effect	% who experienced this	Number of respondents (total n=45)
Diarrhea	42.22%	19
Rash or itching	31.11%	14
Fatigue	28.89%	13
Low platelets	26.67%	12
None of these	24.44%	11
Anemia or neutropenia	17.78%	8
Cough	15.56%	7
Irregular heartbeat	11.11%	5

Based on the responses from the LC survey, when asked about the side effects experienced with ibrutinib, respondents stated that the side effects were mild and quickly dissipated with minimal tolerability issues. Of the side effects experienced, all eight respondents indicated were willing to accept them as they were far less than chemotherapy or infused/injected drugs and there were minimal tolerability issues. Side effects initially experienced by respondents included stomach upset, diarrhea, heartburn, joint/muscle pain, bruising, and/or an increase in white blood cell counts that returned to normal levels shortly after start of treatment. As expressed by two respondents,

> *"I had more side effects during first 3-6 months- muscle cramps and pains at the beginning of treatment they are resolved now. I had some heartburn over the first several weeks and that went away. I had some very mild diarrhea…I have some persistent easy bruising], but no bleeding problems… …I have not had any infections, low blood count issues, really no other issues."* (male; 63; USA; ibrutinib since May 2012)

> *"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 hospitalizations. On ibrutinib, some joint pains and mild diarrhea, but energy is better- able to get off some of my medication and return to work* (male; 55-64; USA; ibrutinib 2 years)

CLL PAG and LLSC noted that 64% (29/45) of respondents were able to access treatment in their own community. Of those 34.56% (16/45) unable to access treatment in their community, 25% (4/16) indicated treatment was not available in their country. 50% (8/16) indicated that treatment was not available in their province or state. 6.25% (1/16) did not have a local cancer centre, 44% (7/16) indicated they accessed ibrutinib through a clinical trial.

Respondents also reported financial implications. 74.4% (32/43) of respondents indicated they have no other costs, 26% (11/43) indicated they have insurance co-payment costs, travel and accommodation expenses or other costs.

According to CLL PAG and LLSC, 93.33% (42/45) of respondents reported their experience with ibrutinib as positive. Of the remaining 3, one stated "too soon to tell", one thought they were "not experiencing the full effects of the drug" at the 3-month point and one stated "nothing positive or negative". Positive comments include:

> "*I started to feel better immediately and it impacted my lymph nodes very quickly. The side effects so far are minimal and most of my blood counts are in the normal range after a year*".
>
> "*Saved my life. The remarkable thing about most patients in my early Trial for relapsed and refractory patients was how rapidly we all felt so much better". "It has been an incredibly positive experience. Mild & manageable side effects in return for amazing quality of life for more than last 3 yrs & no chemo infusions!!*".
>
> "*No side effects. I had been actively dying. I am alive and active. At this point, my CBCw diff is very near normal. I am not taking Rituxin with ibrutinib. To my eyes, my ibrutinib pill sparkle. I'm very thankful for them. 78 yrs. of age*".
>
> "*It has been a miracle pill for me. My lymph nodes have reduced as much as 50%, I have reduced pain, breathing better, have more energy than before and I am no longer at death's door. My biggest negative is that my white cell count has increased from 4 to 60. I still have fatigue, but I am so much better. Overall it is far easier than any chemotherapy or biologic that I have had before*".

In addition, respondents noted that the ibrutinib drug regimen has changed their long-term health and well-being and provided the following comments:

> "*Regained my health to where I hardly think of having leukemia. I am living my life as if I had no disease whatsoever*."
> "*I was dx with three cancers at once…. breast, fallopian tube and CLL. CLL was the cancer without a hopeful outcome until ibrutinib was available*."
>
> "*Ibrutinib has taken me from an actively dying man to a man who is increasingly active - both physically and mentally. I have hope. I don't see the pain in my wife's eyes. I see joy and hope*."
>
> "*I have had CLL for at least 9 years now. My goal is to see my son become an adult. I need to live for 7 more years to reach that goal. Travelling to the US is costly and stressful for my family, but it is the only way for me to get the Ibrutinib that I need*."
>
> "*I feel like I've been given my life back. I'm not limited in any physical way. What an extraordinary drug this has been*."

The LC survey also reported on respondents' opinion as to how ibrutinib has changed or is expected to change their long-term health and well-being (table 18).

Table 18: how ibrutinib has changed or is expected to change patients' long-term health and well-being

Long-term Health or Well-being	Survey (n, %)	interviews	Response Count
Live longer	5 (100%)	3 (100%)	8
Improve blood counts	5 (100%)	3 (100%)	8
Control disease and side effects	4 (100%)	3 (100%)	7 (1 Skipped)
Improve quality of life	5 (100%)	3 (100%)	8
Bring about a remission	5 (100%)	3 (100%)	8

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

> *"At Ibrutinib Focus group meeting, I was surprised as to all the patients with previous treatments who are now leading normal sick-free lives.... thanks to Ibrutinib".*
>
> *"Getting ibrutinib on a clinical trial before it was approved was life saving"*
>
> *"3 1/2 yrs ago when I relapsed after achieving a CR with FCR treatment, I thought my only real chance at seeing any long term remission was a stem cell transplant with a 50/50 shot of dying. Ibrutinib gave me my life back."*
>
> *"Prior to taking ibrutinib, I had five hospitalizations in a year because my platelets were so low…I had a high risk of haemorrhaging I was bleeding and bruising very easily… at one of those hospitalizations they decided to remove my spleen. It did not really help that I ended up having a major bleed after that…Bone marrow transplant only gave a 6 month remission…When it came back it came back more aggressively…with 17p deletion…Ibrutinib exceeded my expectations within first few days of treatment…within two my lymph nodes had reduced…My energy levels are restored. I have had no infections. My sense of well-being came back within a few weeks…I am living a normal life again. Now my blood work is normal".*
>
> *"Ibrutinib has reduced the size of my lymph nodes so that it is much more comfortable for me to more my arms. My belly is less swollen and I feel better to eat. Finally my platelets have started to climb and I bruise and bleed less. My haemoglobin is improving and I have more energy. I wish the medication was in Canada and I could get it under my drug plan."*
>
> *"It's a horrible, horrible disease. You can feel your body shutting down. I looked like a dead herring [laughs]. I came back from the dead… Two weeks after I started ibrutinib, I went to my niece's wedding in Vancouver… I'm back to normal…That*

drug gave my life back to me… I can exercise, I travel a lot, I cook, I keep myself healthy, I walk faster than anyone I know…I want other people to be well like me. I'm so grateful I'm alive. I was finished... Even if you live only a year, it's a gift."

"*I noticed change right away in my spleen, because my spleen was giving me like severe pain in my left side. Within three days, that was definitely gone. The lymph node on the side of my neck…within two weeks that was completely gone. And my energy, I haven't known what energy is in five years, so that I'm really excited about. That's a big one*."

"*Three times I felt I would be dead within the year; it was hard on my wife to worry all the time . . . [Before ibrutinib] I had problems with the lymph nodes in my neck, they were sizable and I thought people could see them. Now there are no lymph nodes …My white count shot up with ibrutinib, but now they are normal. There are no side effects, not for me. I'm working, I'm playing. I'm normal …I wish everyone could have ibrutinib as a first-line treatment. It's unbelievable, fantastic… My children don't know, I don't want to burden them. If they don't know I'm sick, they won't treat me as sick*."

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 ibrutinib (Imbruvica™) for chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). 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 ibrutinib was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, ibrutinib has enablers that include being a new class of drug that fills the gap in therapy for CLL patients and being an oral therapy with once daily dosing schedule that can be easily delivered in the community setting. Key barriers identified include the potentially large budget impact and the possible use in first-line treatment or other indications.

Please see below for more details.

5.1 Factors Related to Comparators

At the time of the PAG input, ofatumumab was not the current standard of care and thus, not the appropriate comparator. However, it was noted ofatumumab is available through its manufacturer's compassionate access program for CLL patients who are refractory to fludarabine and alemtuzumab.

For previously treated CLL patients, the treatment varies across the jurisdictions and there is no standard of care. In some jurisdictions, the combination of fludarabine/chlorambucil/rituximab (FCR) or rituximab/cyclophosphamide/dexamethasone is available for patients who are rituximab naïve. Other treatments available for previously treated CLL patients include chlorambucil, cyclophosphamide/vincristine/prednisone (CVP), or cyclophosphamide/prednisone.

Alemtuzumab is not used in most of the provinces. Alemtuzumab is available through the manufacturer's compassionate program, at no cost to the patient or cancer clinic, in the few provinces that list alemtuzumab as a treatment option. However, clinicians and patients must be registered in the Mabcampath Access Program, a patient access and monitoring program, to receive drug supply.

PAG noted that, in their experiences, SLL is treated in the same manner as CLL.

5.2 Factors Related to Patient Population

As hematologic malignancies tend to be less common than solid tumors overall, the number of patients diagnosed with CLL and SLL is small. However, given the course of the disease and the limited options for refractory disease, PAG noted that a large prevalent number of previously treated CLL and SLL patients would be eligible to receive treatment with ibrutinib. PAG is seeking clarity on the evidence as it relates to use of ibrutinib after one, two or three or more lines of therapy.

PAG noted that ibrutinib is the first in a new class of drug that could fill the gap in therapy for refractory CLL patients, especially those with 17p deletion and for patients with poor renal function, which precludes use of a purine analog.

PAG also noted that ibrutinib is approved by the Food and Drugs Administration (FDA) in the United States for treatment of mantle cell lymphoma and this indication is not part of the pCODR funding request. PAG also noted that there are many ongoing trials for other lymphomas and for first-line treatment of CLL. Thus, PAG has concerns for indication creep with requests for treatment of previously untreated CLL, mantle cell lymphoma and for other lymphomas as well as requests for re-treatment.

5.3 Factors Related to Accessibility

PAG noted that ibrutinib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation.

However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.4 Factors Related to Dosing

The dose of ibrutinib for treatment of CLL is 420mg (three 140mg capsules) taken orally once daily. The continuous once daily dosing schedule is convenient and could enhance patient compliance. Ibrutinib, being available in only one strength, is easier for patients to manage dosage adjustments and there would be no wastage due to dosage adjustments. These are enablers to implementation.

5.5 Factors Related to Implementation Costs

Ibrutinib is the first in a new class of drug. Health care professionals would need to become familiar with monitoring and managing toxicities and drug-drug interactions associated with ibrutinib, especially since it is metabolized in the liver by the CYP3A and cytochrome P450.

Ibrutinib is a new line of therapy with a potentially large number of patients initially eligible for treatment and is continued until toxicities are no longer tolerated. PAG noted that ibrutinib appears to be fairly tolerated and that few patients discontinue treatment if toxicities are manageable. The unknown number of patients and treatment duration are barriers to implementation as it is difficult to determine the budget impact. PAG noted the high cost of ibrutinib would also be a barrier.

At the time of the PAG input, packaging information is not available for the Canadian market. Ibrutinib is packaged in a bulk bottles in the United States and this packaging is a barrier to implementation for some jurisdictions where local community pharmacies may not have the necessary safety equipment to dispense chemotherapy drugs.

As ibrutinib is an oral drug, there would be no additional resources required to administer ibrutinib in the chemotherapy infusion clinics. This is an enabler to implementation.

PAG is seeking clarity on whether testing for 17p deletion is routinely done upon diagnosis of CLL.

5.6 Other Factors

PAG is requesting information on the relative merits and sequencing of these drugs based on clinical benefits and cost-effectiveness, if available. PAG identified that there will be several drugs for the treatment of CLL anticipated within the next six to 12 months in the Canadian market at a similar time. Therefore, any comparative data of the new drugs would be beneficial to help PAG determine which patient populations would be best suited for each treatment and potential funding criteria for each agent.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness of ibrutinib for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without del(17)p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.

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 table 19 below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 19: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients with CLL or SLL with or without del 17p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog Subgroup analyses: Age (≥65)	Ibrutinib 420 mg/day	-Chemotherapy (chlorambucil, cyclophosphamide) -stem cell transplants, -EGFR-TKI inhibitors, -monoclonal antibodies (ofatumumab, rituximab, obinutuzumab, alemtuzumab) -Alkalating agents (bendamustine)	-OS -PFS -Response rate **-Quality of Life** -Grade 3 or 4 adverse events **(including febrile neutropenia and thrombocytopenia and severe infection and lymphocytosis)** -Withdrawal due to AE's **-Fatigue**
[Abbreviations] CLL= chronic lymphocytic leukemia; EGFR-TKI= epidermal growth factor receptor - tyrosine kinase inhibitor; OS= overall survival; PFS= progression free survival; RCT= randomized controlled trial; SLL= small lymphocytic lymphoma				

- *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- September 2, 2014) with in-process records & daily updates via Ovid; EMBASE (1980- September 2, 2014) via Ovid; The Cochrane

Central Register of Controlled Trials (2014, September) 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 Ibrutinib, Imbruvica or PCI-32765 and 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 4, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and 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 this 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.

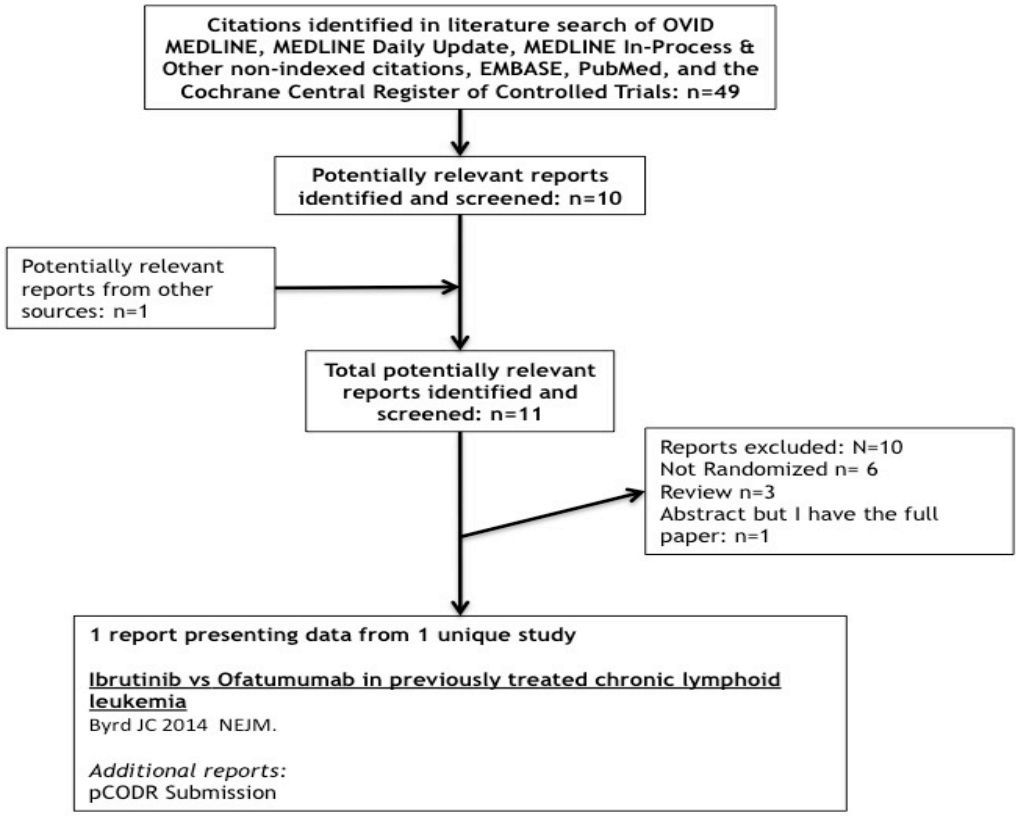
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 11 potentially relevant reports identified, 1 study was included in the pCODR systematic review[5] and 10 studies were [4,29-37] excluded. Studies were excluded because they were not randomized trials, reviews, or abstracts where full publication was available.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Studies.



Note: Additional data related to the study was also obtained through requests to the submitter by pCODR.[6]

6.3.2 Summary of Included Studies

Provide a brief statement summarizing the number and type of included studies.

6.3.2.1 Detailed Trial Characteristics

Table 20. Summary of study characteristics of the included study of ibrutinib in patients with CLL or SLL with or without del 17p who have received at least one prior therapy and are not considered appropriate for treatment or retreatment with a purine analog.[5,38]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
RESONATE NCT01578707 Phase 3 open label multicentre study N=391 Ibrutinib n=195 Ofatumumab n=196 67 centres in 9 countries: Europe, Australia, and North America Patients enrolled from June 2012 to April 2013	**Inclusion Criteria:** • ECOG performance status of 0-1. • Diagnosis of relapsed or refractory CLL or SLL. • Active disease meeting at least 1 of the IWCLL 2008 criteria for requiring treatment. • Must have received at least one prior therapy for CLL/SLL. • Considered not appropriate for treatment or retreatment with purine analog based therapy because they had a short progression-free interval after chemoimmunotherapy or because they had coexisting illnesses, an age of 70 years or more, or a chromosome 17p13.1 deletion. • Measurable nodal disease by CT. • Patients must be able to receive outpatient treatment and laboratory monitoring at the institution that administers study drug for the entire study. **Exclusion Criteria:** • Known CNS lymphoma or leukemia. • No documentation of cytogenetic and/or FISH in patient records prior to first dose of study drug. • Any history of Richter's transformation or prolymphocytic leukemia. • Uncontrolled Autoimmune Hemolytic Anemia or idiopathic thrombocytopenia purpura. • Prior exposure to ofatumumab or to ibrutinib.	Patients were randomly assigned to receive either: • Oral ibrutinib (at a dose of 420 mg once daily) until disease progression or the occurrence of unacceptable toxic effects • Intravenous ofatumumab for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks.	**Primary Outcome Measures:** • PFS **Secondary Outcome Measures:** • OS • Response Rate • Hematological Improvements • Improvement of disease-related symptoms (fatigue, night sweats, and splenomegaly)

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Funded by: Pharmacyclics and Janssen	• Prior autologous transplant within 6 months prior to first dose of study drug. • Prior allogeneic stem cell transplant within 6 months or with any evidence of active graft versus host disease or requirement for immunosuppressants within 28 days prior to first dose of study drug. • History of prior malignancy, with the exception of certain skin cancers and malignancies treated with curative intent and with no evidence of active disease for more than 3 years. • Serologic status reflecting active hepatitis B or C infection. • Unable to swallow capsules or disease significantly affecting gastrointestinal function. • Uncontrolled active systemic fungal, bacterial, viral, or other infection. • History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug. • Requires anticoagulation with warfarin.		

CLL= chronic lymphocytic leukemia; CNS= central nervous system; CT= computerized axial tomography; FISH= fluorescent *in situ* hybridization IWCLL= International Workshop on Chronic Lymphocytic Leukemia; OS= overall survival; PFS= progression free survival; RCT= randomized controlled trial; SLL= small lymphocytic lymphoma

a) Trials

One open label phase 3 randomized trial (RESONATE) was found for this review. Characteristics of the study's design can be found in Table 20. The study was open labelled and not blinded. The patients were centrally randomized 1:1 to each of the treatment arms.[6] The patients were stratified by whether they had resistance to purine analogue chemoimmunotherapy and whether they had a chromosome 17p13.1 deletion. The study was multicentred with 67 sites in 9 countries including Europe, Australia, and North America. The study was sponsored by Pharmacyclics and Janssen.[5]

The primary outcome in this study was progression free survival. This was assessed by an independent review committee, according to the criteria of the International Workshop on Chronic Lymphocytic Leukemia. Progression-free survival was used in the calculation of the study sample size. The number of required events was based on a target hazard ratio for progression or death of 0.60, as calculated with the use of a two-sided log-rank test at an alpha level of 0.05, with a study power of at least 90%.[5]

Secondary end points included the duration of overall survival and the response rate. The criteria of the International Workshop on Chronic Lymphocytic Leukemia require the use of computed tomography to evaluate response and persistent improvement for at least 2 months to confirm response.

The study was not terminated early. The estimated completion date is December 2015.[38] Patients from the ofatumumab group are allowed to crossover to the ibrutinib group after disease progression assessed by an independent review committee. The study protocol was amended to include this change after results from the phase II study were in favour of ibrutinib.[5] It should be noted that this phase 2 trial was also led by the same lead author as the RESONATE trial.

b) Populations

A total of N=391 patients were included in the study. Patients were randomized 1 to 1 to either ibrutinib or ofatumamab.[5] The study baseline patient demographics can be seen in Table 21. Patients were balanced between the two arms except with respect to the presence of bulky disease of 5 cm or more (p=0.04) and the median time from last therapy (p=0.02).

Table 21: Baseline patient demographic and disease characteristics for the RESONATE trial[5]

Characteristics	Ibrutinib N=195	Ofatumumab N=196
Age (years) Median	67	67
< 65 years, n (%)	77 (40)	75 (38)
≥65 years, n (%)	118 (61)	121 (62)
Gender, n (%)		
Male	129 (66)	137 (70)
Female	66 (34)	59 (30)
Race, n (%)		
Asian	3 (2)	2 (1)
Black or African American	8 (4)	9 (5)
White	174 (89)	177 (90)
Multiple	1 (1)	0
Patient declined to answer	9 (5)	8 (4)
Months from initial diagnosis to randomization		
Median	92	91
Histology at diagnosis, n (%)		
CLL	185 (95)	188 (96)
SLL	10 (5)	8 (4)
Baseline ECOG status n (%)		
0	79 (41)	80 (41)
1	116 (59)	116 (59)
Bulky disease, n (%)		
≥ 5 cm	124 (64)	101 (52)
Previous therapies		
Median, n (range)	3 (1-12)	2 (1-13)
≥ 3, n (%)	103 (53)	90 (46)
Type of therapy, n (%)		
Alkylator	181 (93)	173 (88)
Bendamustine	84 (43)	73 (37)
Purine analogue	166 (85)	151 (77)
Anti-CD20	183 (94)	176 (90)

Alemtuzumab	40 (21)	33 (17)
Allogenic transplantation	3 (2)	1 (1)
Median time from last therapy, months (range)	8 (1-140)	12 (0-184)
Resistance to purine analogues, n (%)	87 (45)	88 (45)
Chromosome abnormalities based on local laboratory results, n (%)		
Del11q, n (%)		
Yes	63 (32)	59 (30)
No	127 (65)	132 (67)
Not reported	5 (3)	5 (3)
Del17p, n (%)		
Yes	63 (32)	64 (33)
No	132 (68)	132 (67)
Creatinine clearance < 60ml/min, n (%)	62 (32)	61 (31)
Median hemoglobin g/dl (range)	11 (7-16)	11 (6-16)
Median platelet count, per mm^3 (range)	116,500 (20,000-441,000)	122,000 (23,000-345,000)
Median lymphocyte count, per mm^3 (range)	29,470 (90-467,700)	29,930 (290-551,030)

c) Interventions

Oral ibrutinib was administered at a dose of 420 mg once daily until disease progression or the occurrence of unacceptable toxic effects. Intravenous ofatumumab was administered for up to 24 weeks at an initial dose of 300 mg at week 1, followed by a dose of 2000 mg weekly for 7 weeks and then every 4 weeks for 16 weeks. Patients were allowed to cross over to ibrutinib after disease progression on ofatumumab.[5] In the ibrutinib arm 4.1% of patients had a dose reduction for the management of treatment emergent adverse events (TEAES). In the ofatumumab arm the dose was not administered due to TEAE in 13.6% of subjects. The relative mean dose intensity for ibrutinib was 94.8% and 85.2% for ofatumumab.[6]

d) Patient Disposition

In the RESONATE trial, all 391 randomized patients were included in the final efficacy analysis. Of 195 patients assigned to the ibrutinib arm, all received treatment. A total of 27 patients discontinued ibrutinib (progression during treatment n=9; adverse events/unacceptable toxicity n=8; withdrawal from treatment by patient n=1; death n=8; other, n=1). There are still 168 patients who are still continuing on treatment.[5]

Of 196 patients assigned to the ofatumumab arm, 191 received treatment. Prior to treatment four patients withdrew their consent and one died. A total of 71 patients discontinued ofatumumab (progression during treatment n=38; adverse events n=7; withdrawal from treatment by patient n=6; death n=9; stem cell transplant n=1; not stem cell transplant n=3; other n=7) There were 119 patients who completed the treatment regimen. There is only one patient who is still continuing on treatment.[5]

e) Limitations/Sources of Bias

The study personnel, treating physicians, and patients were not blinded to treatment assignment. This could have affected the results, especially for patient-reported outcomes such as quality-of-life, in favour of whichever arm the assessor (either study personnel or the patient in the case of quality-of-life) felt was likely to provide benefit. Importantly, progression and response assessments were conducted by a blinded and independent committee, which would have resulted in unbiased assessments for the primary outcome, progression free survival.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

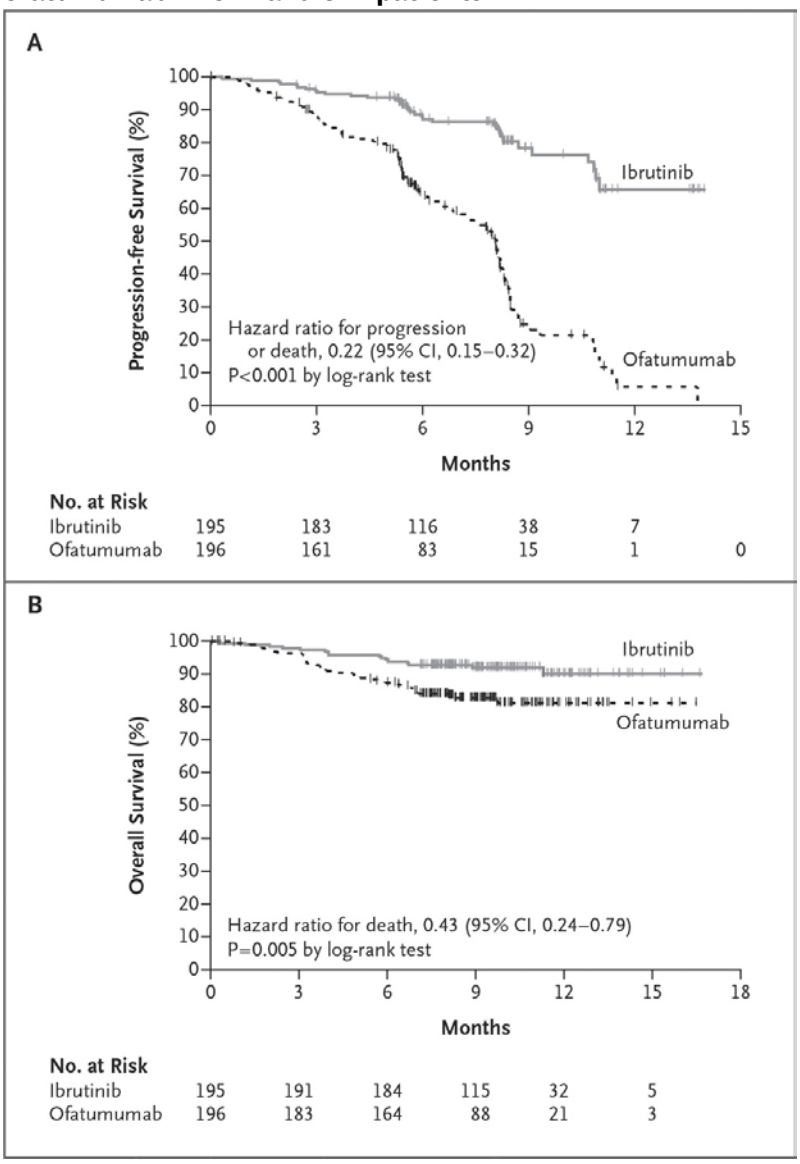
Progression-Free Survival

Progression free survival, which was independently assessed, was significantly extended, with the median not reached at follow-up of 9.4 months. The median duration of progression-free survival for ofatumumab was 8.1 months. The hazard ratio for progression or death in the ibrutinib group was 0.22 (95% CI; 0.15 to 0.32; P<0.001). This signifies a 78% reduction in the risk of progression or death among patients treated with ibrutinib, as compared with ofatumumab. In the ibrutinib group at 6 months, 88% of patients were still alive with no disease progression, as compared with 65% in the ofatumumab group. These results can be seen in figure 2A.[5]

The result of ibrutinib on progression-free survival was demonstrated regardless of baseline clinical characteristics or molecular features. The effect of ibrutinib was visible in spite of the number of previous treatments; less than 3 prior treatments HR 0.19 (95% CI: 0.10-0.36), greater than 3 prior treatments HR 0.21 (95% CI: 0.13-0.34). The only test for heterogeneity that was significant was for geographic region (P=0.02), although treatment effect remained significant within each region (P<0.001). There was no difference in the patients age <65 years HR 0.17 (95% CI; 0.09-0.31) >65 HR 0.24 (95%CI; 0.15-0.40) for progression free survival.[5]

In patients with a chromosome 17p13.1 deletion, the median duration of progression-free survival was not reached in the ibrutinib group. In the ofatumumab group the median duration was 5.8 months (HR for progression or death, 0.25; 95% CI, 0.14 to 0.45). At 6 months no disease progression was seen in 83% of the patients in the ibrutinib group, and 49% of the patients in the ofatumumab group with this deletion. Richter's transformation (CLL that has advanced into an aggressive, rapidly growing large-cell lymphoma) was confirmed in two patients in each study group. An additional patient developed prolymphocytic leukemia in the ibrutinib group.[5]

Figure 2: Progression free survival (A) and overall survival (B) for ibrutinib vs ofatumumab in CLL and SLL patients[5]



Overall Survival

Ibrutinib significantly prolonged the rate of overall survival (HR for death in the ibrutinib group, 0.43; 95% CI, 0.24 to 0.79; P=0.005), with the risk of death reduced by 57% compared to ofatumumab. This can be seen in figure 2B. The overall survival rate was 90% in the ibrutinib group and 81% in the ofatumumab group at 12 months. In this analysis, 57 patients in the ofatumumab group had crossed over to receive ibrutinib after confirmed disease progression. The data were censored at the time of crossover and the survival effect was based on this analysis. However, the survival effect was also observed in the uncensored sensitivity analysis at 12 months (hazard ratio for death, 0.39; P=0.001), with an overall survival rate of 90%

in the ibrutinib group and 79% in the ofatumumab group. The change in overall survival reinforcing the advantage of ibrutinib was retained in all the subgroups (including age <65 years HR 0.24; 95% CI; 0.08-0.73 and >65 HR 0.58; 95%CI; 0.28-1.21) defined according to pre-treatment and genetic features.[5]

Response

The response rate, which was independently assessed, was significantly higher in the ibrutinib group than in the ofatumumab group. Details on the criteria for assessing the response rate was provided in the Supplementary Appendix of the Byrd et al paper. In the ibrutinib group 43% of the patients had a partial response, as compared with 4% in the ofatumumab group (odds ratio, 17.4; 95% CI, 8.1 to 37.3; P<0.001). Moreover, 20% of the patients who received ibrutinib had a partial response with lymphocytosis (resulting in a 63% response rate). Lymphocytosis was noted in 69% of the patients who were treated with ibrutinib and was not considered to be disease progression. This condition resolved in 77% of these patients during follow-up. The response rates assessed by the investigators differed from the independently assessed response rates in the two groups. The partial response was 43% in the independent assessment and 68% in the investigator led assessment for ibrutinib and 4% for the partial response in the independent assessment and 21% for the investigator response for ofatumumab.[5]

Harms Outcomes

The median duration of treatment for patients receiving ibrutinib was longer (8.6 months [range, 0.2 to 16.1]) than those receiving ofatumumab (5.3 months [range, 0 to 7.4]). For any grade, the most frequent nonhematologic adverse events that occurred in at least 20% of the patients were diarrhea, fatigue, pyrexia, and nausea in the ibrutinib group and fatigue, infusion-related reactions, and cough in the ofatumumab group.[5]

Adverse events that were grade 3 or higher were see in 51% of the ibrutinib group and 39% of the ofatumumab group. These can be seen in table 22. Adverse events that occurred more frequently in the ibrutinib group than in the ofatumumab group included diarrhea (4% vs. 2%), neutropenia (16% vs. 14%) and thrombocytopenia (6% vs. 4%). In the ofatumumab group, anemia (8% vs. 5%) and infusion-related reactions (3% vs. 0%) occurred more frequently than in the ibrutinib group.[5]

Serious adverse events with an incidence of ≥2% in either arm by the MedDRA system organ class occurred more frequently in the ibrutinib arm 42% vs 30%. Infections of any grade were more common in the ibrutinib group (70% vs. 54%), whereas the frequency of infections of grade 3 or higher was similar in the two study groups (24% vs. 22%), with urinary tract infections occurring more frequently in the ibrutinib group 4% vs 1%. Pneumonia was by far the most common infection occurring in 8% of ibrutinib patients and 7% of ofatumumab patients (pseudomonas aeruginosa was included in this analysis).[5]

Second malignancies, were seen in 8% of patients treated with ibrutinib, these were most frequently skin cancers. Non skin related malignancies occurred in 3% of the CLL patients.[1] Major hemorrhagic events (those grade 3 and above) occurred in 3% of patients treated with ibrutinib, these include, subdural hematoma, gastrointestinal bleeding, hematuria, and post-procedural haemorrhage.[1]

Table 22: Grade 3 and 4 Adverse Events reported in the RESONATE study[5]

Adverse event	Ibrutinib (n=195)	Ofatumumab (n=191)
	N (%)	N (%)
Diarrhea	8 (4)	3 (2)
Fatigue	4 (2)	3 (2)
Nausea	3 (2)	0
Pyrexia	3 (2)	2 (1)
Anemia	9 (5)	15 (8)
Neutropenia	32 (16)	26 (14)
Cough	0	2 (1)
Thrombocytopenia	11 (6)	8 (4)
Arthralgia	2 (1)	0
Upper respiratory tract infection	1 (1)	3 (2)
Vomiting	0	1 (1)
Headache	2 (1)	0
Dyspnea	4 (2)	1 (1)
Back Pain	2 (1)	1 (1)
Sinusitis	1 (1)	0
Stomatitis	1 (1)	1 (1)
Pain in limb	1 (1)	0
Pneumonia	13 (7)	9 (5)
Urinary tract infection	7 (4)	1 (1)
Myalgia	1 (1)	0
Night sweats	1 (1)	0
Infusion-relation reaction	0	6 (3)
Events of constipation, petechiae muscle spasm, dizziness, contusion, peripheral edema, blurred vision or peripheral sensory neuropathy	0	0
Blood and lymphatic system disorders	8 (4)	11 (6)
Febrile neutropenia	3 (2)	4 (2)
Anemia	2 (1)	4 (2)
Cardiac disorders	13 (7)	6 (3)
Atrial fibrillation	6 (3)	1 (1)
General disorders and administration site conditions	12 (6)	4 (2)
Pyrexia	6 (3)	4 (2)
Infections and infestations	46 (24)	39 (20)
Lung infection	5 (3)	0
Lower respiratory tract infection	4 (2)	2 (1)
Upper respiratory tract infection	1 (1)	4 (2)
Any ≥ grade 3 infection	47 (24)	42 (22)
Pneumonia (includes pseudomonas aeruginosa	16 (8)	14 (7)
Urinary tract infection	7 (4)	1 (1)
Cellulitis	4 (2)	1 (1)
Bronchopulmonary aspergillosis	2 (1)	0
Herpes zoster	1 (1)	3 (2)
Sepsis	2 (1)	2 (1)

Adverse event	Ibrutinib (n=195)	Ofatumumab (n=191)
	N (%)	N (%)
Stenotrophomonas infection	0	2 (1)
Grade 5 infection	6 (3)	9 (5)

Discontinuation of treatment because of adverse events occurred in 4% of the patients in each study group. These events were most commonly infectious in nature.[5]

Quality of Life

Quality of life was assessed using three self-administered questionnaires: The Functional Assessment of Chronic Illness-Fatigue FACIT-Fatigue Scale, The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC-QLQ-C30) and the The EuroQoL Five Dimension- 5L (EQ-5D-5L).8

At week 24, clinically meaningful (≥3 points) improvement in FACIT-F occurred in more patients on ibrutinib than ofatumumab (59% vs 46%, p=0.06). Fewer patients in both groups showed clinically meaningful deterioration (14% for ibrutinib vs 24% for ofatumumab, p=0.08).[7] A clinically meaningful improvement (≥10 points) from baseline to week 24 in patients treated with ibrutinib versus ofatumumab was observed for fatigue (median 11 vs 0).

A larger proportion of ibrutinib versus ofatumumab patients showed clinically meaningful improvements on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30 (EORTC-QLQ-C30) global health scores (46% vs 40%).[7]

The results of the EuroQoL Five Dimension- 5L (EQ-5D-5L) questionnaire saw no significant difference in the scored for time to improvement between both groups (HR=1.142; *P*=0.3714). There was a greater improvement in scores for the ibrutinib group, but it was only significant for week 16. In addition a higher percentage of patients in the ibrutinib group achieved a clinically meaningful improvement in the visual analog scale score (defined as an increase of ≥7 points from baseline to week 24) compared with the ofatumumab group (53.8% vs 41.8%).[8]

Deaths

There were 12 (6.2%) deaths in the ibrutinib group and 16 (8.4%) in the ofatumumab group leading from treatment emergent adverse events. There were an additional 16 (8.2%) deaths in the ibrutinib group and 33(16.8) in the ofatumumab group captured from overall survival follow-up. [6]

6.4 Ongoing Trials

Table 23: Ongoing trials[38]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Ibrutinib Versus Ibrutinib + Rituximab (i vs iR) in Patients With Relapsed Chronic Lymphocytic Leukemia (CLL)			
Study NCT02007044 Randomized, phase 2, open Label, crossover Start date: December 2013 Expected completion date: December 2017 Active: recruiting patients Estimated enrolment: 208 Sponsor: M.D. Anderson Cancer Center Pharmacyclics	**Inclusion Criteria:** • Patients must have a diagnosis CLL/SLL and be previously treated. Patients with 17p del or TP53 mutation will be eligible if they are untreated. • Patients must have an indication for treatment by 2008 IWCLL Criteria. • Patients must be age >/= 18 years • ECOG performance status of 0-2. • Must be willing to practice birth control • Adequate renal and hepatic • Free of prior malignancies for 3 years with exception of patients diagnosed with basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast. • A Urine Pregnancy Test **Exclusion Criteria:** • Pregnant or breast-feeding females. • Prior therapy with ibrutinib or other kinase inhibitors that target BCR signaling (such as idelalisib/GS-1101, CC-292). • Treatment including chemotherapy, chemo-immunotherapy, monoclonal antibody therapy, radiotherapy, high-dose corticosteroid therapy, or immunotherapy within 21 days prior to enrolment or concurrent with this trial. • Investigational agent received within 30 days prior to the first dose of study drug. • Systemic fungal, bacterial, viral, or other infection not controlled • Patients with uncontrolled Autoimmune Hemolytic Anemia (AIHA) or autoimmune thrombocytopenia (ITP). • Patients with severe hematopoietic insufficiency. • Any other severe concurrent disease, or have a history of serious organ dysfunction or disease. • Significant cardiovascular disease • History of stroke or cerebral hemorrhage within 6 months. • Evidence of bleeding diathesis or coagulopathy within 3 months. • Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to enrolment date, anticipation of	4 arms • (Subgroup 1) Ibrutinib started on Day 1 of cycle 1 at dose of 420 mg (3 x 140-mg capsules) orally once daily in each 28 day cycle. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions. • (Subgroup 2) Ibrutinib started on Day 2 of cycle 1 at dose of 420 mg (3 x 140-mg capsules) orally once daily in each 28 day cycle. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions. • (Subgroup 1) + Rituximab Ibrutinib 420 mg (3 x 140-mg capsules) given orally on Day 1 of cycle 1 for each 28 day cycle. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions. Rituximab 375 mg/m2 given intravenously on Day 1, Day 8, Day 15, and Day 22 , and then continued once every 4 weeks only on Days 1 during cycles 2 - 6. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions. • (Subgroup 2) + Rituximab Ibrutinib 420 mg (3 x 140-mg capsules) given orally on Day 2 of cycle 1 for each 28 day cycle. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions.	**Primary outcome** Progression-free Survival (PFS)

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	need for major surgical procedure during the course of the study. •Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to enrollment date. Bone marrow aspiration and/or biopsy are allowed. •Serious, non-healing wound, ulcer, or bone fracture. •Must be off Coumadin for at least 7 days prior to start of the study.	Rituximab 375 mg/m2 given intravenously on Day 1, Day 8, Day 15, and Day 22 , and then continued once every 4 weeks only on Days 1 during cycles 2 - 6. Patients in the iR group alternatingly assigned to subgroups 1 and 2, the purpose is to compare rituximab infusion reactions.	

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
A Study of PCI-32765 (Ibrutinib) Versus Rituximab in Relapsed or Refractory Chronic Leukemia/Lymphoma			
Study NCT01973387 Randomized, phase 3, open Label, Start date: October 2013 Expected completion date: May 2016 Active: recruiting patients Estimated enrolment: 150 Sponsor: Janssen Research & Development, LLC Pharmacyclics	**Inclusion Criteria:** • Eastern Cooperative Oncology Group performance status of 0-1 • Diagnosis of (CLL) or (SLL) • Laboratory values within protocol-defined parameters • Active disease meeting International Workshop on Chronic Lymphocytic Leukemia 2008 criteria • Received at least 1 prior therapy for CLL/SLL and not appropriate for treatment or retreatment with purine analog-based therapy • Measurable nodal disease by computed tomography • Female participants must have a negative serum or urine pregnancy test • Agrees to protocol-defined use of effective contraception **Exclusion Criteria:** • Central nervous system lymphoma or leukemia • Prolymphocytic leukemia or history of or currently suspected Richter's transformation • Refractory to prior rituximab-based therapy • Received any chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days prior to first dose of study drug • Corticosteroid use >20 mg within 1 week prior to first dose of study drug • Radio- or toxin-conjugated antibody therapy within 10 weeks prior to first dose of study drug • Prior autologous transplant within 6 months prior to first dose of study drug • Prior allogeneic stem cell transplant • Major surgery within 4 weeks prior to first dose of study drug • History of prior malignancy according to protocol-defined criteria • Currently active clinically significant cardiovascular disease within 6 months prior to first dose with study drug • Uncontrolled active systemic fungal, bacterial, viral, or other ongoing anti-infective treatment administered intravenously • History of human immunodeficiency virus or active infection with hepatitis B or C • History of stroke or intracranial hemorrhage within 6 months prior to random assignment	Rituximab -Up to 6 cycles (total of 8 doses administered by intravenous infusion): 375 mg/m2 on Day 1 of Cycle 1, 500 mg/m2 on Day 15 of Cycle 1 (Weeks 1-4); 500 mg/m2 on Day 1 and Day 15 of Cycle 2 (Weeks 5-8); and 500 mg/m2 on Day 1 of Cycles 3-6 (Weeks 9-24). Ibrutinib -420 mg capsules administered by mouth daily until disease progression or unacceptable toxicity, whichever occurs first.	**Primary Outcome Measures:** • Progression-free survival Secondary **Outcome Measures:** • Overall response rate • Overall survival • Number of participants demonstrating improvement in hematological laboratory parameters • Number of participants demonstrating improvement and/or resolution of disease-related symptoms • Maximum observed plasma concentration of ibrutinib • Minimum observed plasma concentration of ibrutinib • Time to maximum plasma concentration of ibrutinib • Area under the plasma concentration-time curve of ibrutinib • Elimination half-life of ibrutinib • Number of participants affected by adverse events by MedDRA system organ class (SOC) and Preferred term (PT)

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Pregnant or lactating women • Current life-threatening illness, medical condition, or organ system dysfunction. • Requires or receiving anticoagulation with warfarin or equivalent Vitamin K antagonists • Requires treatment with a strong CYP3A4/5 inhibitor • Uncontrolled autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).		
A Study of Ibrutinib in Combination With Bendamustine and Rituximab in Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma			
Study NCT01611090 Randomized, phase 3, Double Blind Start date: September 2012 Expected completion date: March 2018 Ongoing but not recruiting patients Estimated enrolment: 578 Sponsor: Janssen Research & Development, LLC and Pharmacyclics	**Inclusion Criteria:** • Diagnosis of CLL or SLL • Active disease meeting at least 1 of the International Workshop on Chronic Lymphocytic Leukemia 2008 criteria for requiring treatment • Measurable nodal disease by computed tomography • Relapsed or refractory CLL or SLL following at least 1 prior line of systemic therapy consisting of at least 2 cycles of a chemotherapy-containing regimen • ECOG PS of 0 or 1 • Hematology and biochemical values within protocol-defined limits • Agrees to protocol-defined use of effective contraception • Women must have negative blood or urine pregnancy test at screening **Exclusion Criteria:** • Recent therapeutic interventions within 3 to 10 weeks • Prior treatment with ibrutinib or other Bruton's tyrosine kinase inhibitors or prior randomization in any other clinical study evaluating ibrutinib • The presence of deletion of the short arm of chromosome 17 • Patients previously treated with a bendamustine-containing regimen who did not achieve a response or who relapsed and required treatment within 24 months of treatment with that regimen • Patients for whom the goal of therapy is tumor debulking prior to stem cell transplant • Received a hematopoietic stem cell transplant • Known central nervous system leukemia/lymphoma or Richter's transformation	Experimental: Ibrutinib + BR Ibrutinib 420 mg will be administered orally once daily on a continuous schedule. All subjects will receive background therapy with bendamustine and rituximab (BR) for a maximum of 6 cycles (a cycle is defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication). Placebo Comparator: Placebo + BR Matching placebo will be administered orally once daily on a continuous schedule. All subjects will receive background therapy with BR for a maximum of 6 cycles (a cycle is defined as 28 days, with the exception of Cycle 1, which will be 29 days to allow for rituximab dosing prior to bendamustine and study medication).	**Primary Outcome Measures:** • Progression-free survival **Secondary Outcome Measures:** • Number of participants with adverse events • Overall response rate • Overall survival • Rate of minimal residual disease (MRD)-negative remissions • Number of participants with improvement in hematologic values • Number of participants with improvement in disease-related symptoms • Number of participants with improvement in patient-reported outcome scores • Plasma concentrations of ibrutinib • Plasma concentrations of bendamustine • Plasma concentrations of rituximab • Number of participants with biomarkers related to B-cell receptors

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Patients with uncontrolled autoimmune hemolytic anemia or autoimmune thrombocytopenia • Chronic use of corticosteroids • History of prior malignancy, except: malignancy treated with curative intent and with no known active disease present for >=3 years before randomization • History of stroke or intracranial hemorrhage within 6 months prior to randomization; or clinically significant cardiovascular disease • Requires anticoagulation with warfarin or equivalent vitamin K antagonists or treatment with strong CYP3A4/5 inhibitors • Known history of human immunodeficiency virus or hepatitis C, or active infection with hepatitis B or C • Any uncontrolled active systemic infection or any life-threatening illness, medical condition, or organ system dysfunction • A woman who is pregnant or breast feeding, or a man who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug		

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 ibrutinib (Imbruvica) for treatment of patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with or without deletion 17p (del 17p) who have received at least one prior therapy. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

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

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

1. Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily Update, Ovid EMBASE and Ovid CDSR.

1. exp clinical trial/ or exp clinical trial, phase i/ or exp clinical trial, phase ii/ or exp clinical trial, phase iii/ or exp clinical trial, phase iv/ or exp controlled clinical trial/ or exp randomized controlled trial/ or exp multicentre studies/
2. ibrutinib.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
3. PCI-32765.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
4. PCI 32765.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
5. PCI32765.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
6. Imbruvica.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
7. or/2-6
8. 1 and 7
9. leukemia.mp. [mp=ti, ab, tx, kw, ct, sh, hw, tn, ot, dm, mf, dv, nm, kf, px, rx, ui]
10. 8 and 9
11. remove duplicates from 10

2. Literature Search via PubMed

1. ibrutinib* OR imbruvica* OR PCI-32765* OR PCI - 32765* OR PCI 32765* OR PCI32765
2. publisher[sb]
3. 1 and 2

3. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov
Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: ibrutinib OR imbruvica OR PCI-32765 OR PCI - 32765 OR PCI 32765 OR PCI32765

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: ibrutinib OR imbruvica OR PCI-32765 OR PCI - 32765 OR PCI 32765 OR PCI32765

4. **Conference Abstracts:**

   American Society of Clinical Oncology (ASCO)
   via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

   American Society of Hematology via *Blood* search portal:
   http://www.bloodjournal.org/ash-annual-meeting-abstracts?sso-checked=1

   Search terms: ibrutinib OR imbruvica OR PCI-32765 OR PCI - 32765 OR PCI 32765 OR PCI32765

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