CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ibrutinib (Imbruvica) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (previously untreated)

November 3, 2016

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: info@pcodr.ca
Website: www.cadth.ca/pcodr

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1 GUIDANCE IN BRIEF

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 for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding ibrutinib (Imbruvica) for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) conducted by the Leukemia Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), a summary of submitted Provincial Advisory Group Input on chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and a summary of submitted Registered Clinician Input on chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate. The appropriate comparator for ibrutinib in this treatment setting is multi-agent chemotherapy including, but not limited to, chlorambucil, obinutuzumab plus chlorambucil, and bendamustine.

The patient population under review by pCODR is for adult patients with previously untreated CLL/SLL for whom fludarabine-based treatment is considered inappropriate, consistent with the population of the RESONATE-2 clinical trial, which is a phase III multicenter, open-label study. Ibrutinib is an oral, first-in class Bruton's tyrosine kinase (BTK) inhibitor that offered a new targeted mechanism in the treatment of B-cell malignancies. Ibrutinib received a Notice of Compliance on July 19, 2016.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One clinical trial was identified that met the eligibility criteria of this review and was selected for inclusion (Please see Table 5). RESONATE-2 was a randomized, multi-center, open-label phase 3 study to evaluate the safety and efficacy of ibrutinib versus chlorambucil in treatment naïve CLL patients who are ≥65 years of age.

The primary endpoint of the study was to evaluate the efficacy of ibrutinib compared to chlorambucil based on the independent review committee (IRC) assessment of PFS according to 2008 IWCLL guidelines. Secondary endpoints included ORR, defined as the proportion of patients who achieve CR, CRi, nPR, or PR as per IWCLL 2008 criteria over the

course of the study as assessed by IRC, overall survival, change from baseline FACiT-fatigue score, rate of hematological improvement, and safety events.[1]

Progression-free survival

In the RESONATE-2 trial, during a median follow-up period of 18.4 months, treatment with ibrutinib resulted in significantly longer PFS compared to chlorambucil (median not reached vs. 18.9 months), as assessed by the independent review committee, with a relative risk of progression or death that was 84% lower than that with chlorambucil (HR: 0.16, 95% CI: 0.09 to 0.28; p<0.001). The rate of PFS at 18 months was 90% in the ibrutinib treatment arm versus 52% in the chlorambucil comparator arm.

Overall Survival

Although median OS was not reached in either treatment group, ibrutinib significantly prolonged OS in favour of the ibrutinib group. The overall survival rate at 24 months was 98% with ibrutinib versus 85% with chlorambucil, with a relative risk of death with ibrutinib that was 84% lower than that with chlorambucil (HR: 0.16, 95% CI: 0.05 to 056; p=0.001). Please see Table 1. below for further details. The OS results presented have not been adjusted for crossover. As of the May 28, 2015 cut-off date, 15 months had elapsed after the last patient was randomized, for this reason the RESONATE-2 study was deemed complete and was closed. At the study closure, 25% of patients in the chlorambucil group had crossed into the ibrutinib group.

Upon closure of RESONATE-2, the remaining study patients were transferred to a non-randomized observational study, PCYC-1116, for follow-up and treatment with ibrutinib, as appropriate. An interim analysis was provided for OS for study PCYC-1116. At 28.1 months, the OS rate for the ibrutinib and chlorambucil treatment arms were 94.7% (95% CI: 89.1 to 97.4), and 84.3% (95% CI: 76.7 to 89.6), respectively. The hazard ratio for the collective data set was 0.44 (95% CI: 0.21 to 0.92). At this time, 41% of patients had crossed over into the ibrutinib group.[2]

The final results from PCYC-1116 are not yet available, as the estimated primary completion date is February 2018.[2]

Table 1. Efficacy Outcomes for RESONATE-2

Outcomes	Ibrutinib (n=136)	Chlorambucil (n=133)
Median follow up, months	**18.4**	
On treatment at analysis, n (%)	**87%**	**40%**
Median OS, months	NR	NR
OS rate at 24 months	98%	85%
HR	0.16 (95% CI 0.05-0.56, p=0.001)	
Median PFS, months	NE	18.9
PFS at 18-months	90%	52%
PFS (Hazard Ratio)	0.16 (95% CI 0.09-.028, p<0.001)	
RR	86%	35%
RR (Odds Ratio)	2.42 (95% CI 1.91-3.07, p<0.001)	
Notes: OS = overall survival; PFS = progression-free survival; RR = response rate; ECOG PS= Eastern Cooperative Oncology Group Performance Status		

Adverse Events and Safety

Fatal treatment emergent adverse events were reported in 3 (2.2%) and 4 (3.0%) patients in the ibrutinib and chlorambucil groups, respectively. More patients in the chlorambucil

group discontinued treatment due to an adverse event (9% and 23%) or had a dose reduction due to an adverse event (9.6% and 18.9%).

Any grade 3 or higher drug related adverse event (84.4 and 76.5%) and treatment emergent serious adverse event (33.3% and 20.5%) occurred more frequently in the ibrutinib group.[34] The most common grade 3 or higher AE was neutropenia (10% and 18% in the ibrutinib and chlorambucil groups, respectively). Additionally, anemia occurred in 6% and 8% of patients in the ibrutinib and chlorambucil groups, respectively. Thrombocytopenia (2% and 6%) and fatigue (1% and 5%) occurred more frequently in the chlorambucil group.

Serious adverse events occurring in more than 2% of patients occurred more frequently in the ibrutinib arm for pneumonia (4% and 2%), basal-cell carcinoma (4% and 0) and hyponatremia (2% and 0). Pyrexia, as a serious adverse event, occurred more often in the chlorambucil group (1% and 4%).

Adverse events of interest:

Atrial fibrillation (AF) occurred in 6% (n=8) of patients in the ibrutinib arm (6 within the first 6 months) and in 1 patient in the chlorambucil group. In the ibrutinib group, AF events were mostly grade 1-2. Two of the 8 AF events were grade 3 events. Atrial fibrillation was managed by discontinuation of drug in 2 patients and without dose modification in the remaining 6. No grade 3 or 4 atrial fibrillation occurred in the chlorambucil group. [2,3]

Major hemorrhage (defined as any serious or grade 3 or higher hemorrhage or central nervous system hemorrhage of any grade) was observed in 4% (n=6) of patients in the ibrutinib group. Among these, 3 patients had grade 3 and 1 patient grade 4 hemorrhage. In the ibrutinib arm, 2 major bleeding events occurred within first 6 months, 3 during the next 6-12 months, and 1 during months 12-18. In the chlorambucil group, 2 patients had major hemorrhage with 1 major hemorrhage occurring each in the first 6 months and the next 6-12 months.

Exposure-adjusted infection rate were also reported with 7.5 versus 10.1 per 100 patient-month in the ibrutinib and chlorambucil arms, respectively. Grade ≥3 infections decreased with time for ibrutinib.[4]

Dose reductions due to adverse reactions occurred in approximately 6% of patients.[5] AEs leading to discontinuation of treatment were infrequent in the ibrutinib arm with most occurring during first 6 months. The majority of patients (87%) of continued ibrutinib treatment after a median follow up of 1.5 years.[4]

Patient Reported Outcomes:[4]

The RESONATE-2 study collected patient reported outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30), EuroQoL Five-Dimension (EQ-5D-5L), and FACiT-Fatigue instruments. There were greater improvements in QOL which occurred with ibrutinib vs. chlorambucil in EORTC QLQ-C30 global health status scores by time-dependent mixed-models repeated measures analysis (P=0.0002). Higher rates of clinically meaningful improvement from baseline were also observed with ibrutinib vs. chlorambucil in EORTC QLQ-C30 global health status score (60% vs. 48%; P=0.045). There were no differences in the median time to a minimally important increase and decrease between treatment groups.

Additionally, there were greater improvements in the FACIT-Fatigue scale with ibrutinib vs. chlorambucil (P=0.0004) by time-dependent mixed-models repeated measures analysis. Higher rates of clinically meaningful improvements from baseline were also reported in the ibrutinib group (62% vs. 53%; P=0.164).

Please see section 6.2 of the systematic review for further details on patient reported outcomes.

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, symptoms of CLL/SLL can interfere with a patient's performance, ability to work, travel and day-to-day-activities. Fatigue/lack of energy, increasing lymphocyte, enlarged lymph nodes and frequent infections, among others are commonly reported symptoms. These symptoms, among others, are important symptoms of CLL/SLL to control for patients. Respondents indicated that they would like the benefits of new treatment for CLL/SLL to be long term, and that it is very important to have choice in deciding treatment options. Respondents are currently receiving or have used a variety of therapies to treat CLL/SLL in the first line setting; treatments include: fludarabine/cyclophosphamide and rituximab (FCR), bendamustine and rituximab (BR), chlorambucil, fludarabine and rituximab (FR), and rituximab alone, among others. According to CLLPAG, the current standard drug therapy for CLL/SLL is FCR regime. LC indicated that treatment options currently available tend to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects and relapse. Common side effects of current treatment experienced by respondents included: fatigue, anemia, neutropenia, nausea, low platelets, mouth sores, skin rashes/severer itching, and infections.

Provincial Advisory Group (PAG) Input

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ibrutinib:

Clinical factors:

- Generalizability of results from the submitted trial to the Canadian context as chlorambucil monotherapy is not the current standard of care in Canada
- Sequential use of ibrutinib and other treatments available for CLL/SLL

Economic factors:

- Long duration of treatment
- Large prevalent number of patients potentially eligible for treatment

Registered Clinician Input

Overall, it is felt that ibrutinib provides an oral treatment option, particularly for patients with 17p deletion and patients who are unable to receive intravenous chemotherapy/immunotherapy.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

Two separate studies[6-8] were identified by the Clinical Guidance Panel as relevant to the pCODR review of ibrutinib (Imbruvica) for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate

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[6]

The second study was a phase 1b-2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in patients with relapsed or refractory CLL or small lymphocytic lymphoma[7,8]

Please see section 8 Comparison with other literature section of the systematic review for further details.

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

1.2.3 Factors Related to Generalizability of the Evidence

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	Patients with 17p deletion	In the RESONATE-2 trial, patients with 17p deletion were excluded from the trial Based on the results of two Phase II studies[6-8] Farooukiet al 2015: Phase II, single-arm trial of ibrutinib monotherapy. The study recruited n=51 patients. Among these, n=35 (70%) were previously untreated and n=47/51 (92%) harbored the 17p13.1 deletion. Results were not reported based on del17p status. Results: • 97% of patients achieved objective response (95% CI 86-100) • Estimated OS was 84% (95% CI 72-100) at 24 months. • Estimated cumulative incidence of progression was 9% (1-27) in patients • Grade 3 or worse treatment related adverse events were neutropenia in 12 (24%) patients (grade 4 in one patient), anaemia in seven (14%) patients, and thrombocytopenia in five (10%) patients (grade 4 in one patient). • Grade 3 pneumonia occurred in three (6%) patients, and grade 3 rash in one (2%) patient. O'Brien et al 2014 and Byrd et al 2015: The study recruited 31 previously untreated patients. Among these, n=2/31 (6%) had the 17p13.1 deletion. Therefore, the results of the study are difficult to interpret in the previously untreated population with the 17p13.1 deletion. The overall results do however align with the results of the Farooukiet al study.	Are the trial results generalizable to other patient populations including those with the 17p deletion?	Based on the favorable results of phase 2 studies[6-8] in this population and refractoriness to fludarabine-based regimens, the CGP agrees that the results of the RESONATE-2 study can be generalized into patients with the 17p13.1 deletion. The CGP also acknowledged that it is unlikely that, given the rarity of 17p13.1 -deficient CLL among untreated patients, phase 3 studies will be carried out.

	Patients younger than 65 years of age and for whom treatment with a fludarabine based regimen would be inappropriate due to co-morbidities	In the RESONATE-2 trial, the patient population included only those 65 years of age or greater.	Given that patients younger than 65 years of age may be considered inappropriate for fludarabine treatment due to co-morbidities, are the RESONATE-2 trial results generalizable to this patient population?	The CGP noted that patients below the age of 65 and for who treatment with a fludarabine based regimen would be inappropriate due to co-morbidities, should be eligible for ibrutinib therapy. The CGP agreed that these patients would typically be treated in the same manner as patients who are over the age of 65 and for whom treatment with a fludarabine based regimen would be considered inappropriate.
Comparators	Standard of care	In the RESONATE-2 trial, the comparator was chlorambucil. PAG input highlighted that chlorambucil is no longer a standard treatment option in the Canadian context.	Given that chlorambucil is no longer a standard treatment option for patients in this setting, are the results of the trial applicable in the Canadian setting?	The CGP acknowledged that at the time the RESONATE-2 study was designed, chlorambucil was a standard of care in this setting. However, due to improvements in PFS and OS, obinutuzumab plus chlorambucil has replaced chlorambucil. Although an indirect comparison was not feasible, the CGP noted that PFS with ibrutinib seems substantially longer than with obinutuzumab plus chlorambucil. The results of the trial are therefore applicable to the Canadian setting.

1.2.4 Interpretation

Burden of Illness and Need

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in western countries. In Canada in 2010, the latest year for which statistics are available, 2195 patients were diagnosed with CLL and 600 died of it. 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. While many patients remain in observation for several years before starting treatment overall survival from the time patients start chemotherapy is only four years, with most patients receiving chemotherapy in one form or another for most of this time. Patients with CLL either die as a result of bone marrow failure (typically from infection or bleeding) or as a result of CLL transformation to an aggressive non-Hodgkin lymphoma, a process known as Richter's transformation.

Treatment decisions in CLL are based on age and medical comorbidities, which are surrogates for a patients' ability to tolerate fludarabine-based regimens.[9] In general, patients under the age of 65 with few comorbidities would be offered a combination of fludarabine, cyclophosphamide and rituximab based on the CLL8 clinical trial.[10] Older or frailer patients may be offered chlorambucil, possibly in combination with an anti-CD20 monoclonal antibody like rituximab or obinutuzumab.[11] Although chlorambucil-based treatment results in frequent responses very few of these responses are complete or durable. Patients with CLL who have del(17p) karyotypes have an especially poor prognosis and are inherently resistant to chemotherapy and radiotherapy. Younger patients with the del(17p) mutation may receive alemtuzumab but significant and prolonged immunodeficiency develops as a result. Although responses to alemtuzumab occur in this setting they are typically short-lived and patient's quality of life may be affected by frequent severe infections. As a result, treatments that result in a high rate of complete responses and with long progression-free survival are desperately needed.

In its feedback on the Initial Recommendation, PAG noted that testing for del(17p) would be important for patients with del(17p), as these patients do not respond to chemoimmunotherapy and physicians may wish to treat these patients with ibrutinib upfront. The CGP noted that in some provinces, patients with CLL are routinely tested for del(17p) prior to starting a new line of therapy. The primary reason for doing this is to ensure that patients with TP53 deletions are not exposed to fludarabine or conventional chemotherapy drugs that they will not respond to. The CGP feels that it is inappropriate treat patients with del(17p) mutation with fludarabine or conventional chemotherapy up front or at any point in their clinical course; the opinion of the CGP is that the weight of evidence supports using ibrutinib instead of conventional chemoimmunotherapy in elderly or fludarabine-inappropriate patients. Notwithstanding the well-known limitations of cross-trial comparisons, the reason for this is the longer PFS observed with ibrutinib than with chlorambucil-obinutuzumab (CO), and the lower HR for death when comparing ibrutinib and chlorambucil (HR for death 0.16) versus CO and chlorambucil (HR 0.41).

Effectiveness

The effectiveness of ibrutinib in previously untreated fludarabine-ineligible patients with CLL was evaluated in the RESONATE-2 study, reported in December 2015.[3] This was a randomized, multi-center trial that compared the outcome of 269 patients randomly assigned to ibrutinib (n=136) or chlorambucil (n=133). The two groups were well balanced with respect to prognostic (such as IgH mutational status, presence of bulky disease and Rai stage) and patient factors (such as ECOG performance status and Cumulative Illness

Rating Scale (CIRS) score) at baseline. The primary outcome measure of this trial was progression-free survival, as assessed by an independent review committee. IRC-adjudicated PFS was significantly longer in patients who received ibrutinib compared to those who received chlorambucil (unreached vs 18.9 months, HR 0.16, 95% CI 0.09-0.28, p<0.001). Ibrutinib also significantly prolonged overall survival in this group of patients and at the end of 24 months the relative risk of dying from CLL was 84% lower in patients who received ibrutinib compared with those who were given chlorambucil (98% vs. 85% OS at 24 months, HR 0.16, 95% CI 0.05-0.56, p=0.001).

Measures of quality of life were investigated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaires core 30 (EORTC QLQ30), EuroQoL 3-dimension (EQ5D-5L) and FACiT-fatigue scales. All of these measures showed a clinically-significant difference in quality of life favouring patients treated with ibrutinib compared with chlorambucil. For instance, there were higher rates of clinically-meaningful improvements from baseline for patients who received ibrutinib (60% vs. 48%, p=0.045) as measured by the EORTC QLQ30. Similarly there were greater improvements in quality of life for patients who received ibrutinib as demonstrated by the FACiT-fatigue scale (p=0.0004).

Safety

The most common adverse reactions (≥20%) in the RESONATE-2 trial for patients in the ibrutinib treatment arm included diarrhea, fatigue, cough and nausea. In the chlorambucil group adverse effects included fatigue, nausea, neutropenia and vomiting which occurred in more than 20% of patients. In most cases these reactions were managed by dose adjustment or by briefly withholding the medication. Treatment was discontinued for adverse events more commonly with chlorambucil than ibrutinib (23% vs. 9%, respectively).

The majority of severe adverse events (≥ Grade 3) were seen in patients who received chlorambucil. Grade 3 or 4 hypertension, diarrhea and pneumonia were seen more often in patients who received ibrutinib. Among adverse events of special interest, atrial fibrillation occurred in eight patients in the ibrutinib group. Most atrial fibrillation was grade 1-2 and was managed by discontinuation of drug in two patients and without dose modification in the remaining six patients. Most of these patients had other risk factors for atrial fibrillation, including hypertension, coronary artery disease or myocardial ischemia. Major hemorrhage was also seen more commonly with ibrutinib, with six major bleeding events in the ibrutinib and two events in the chlorambucil arm. It should be noted that the period of exposure to these agents differed between the two groups; median treatment duration for patients in the ibrutinib group was 17.4 months versus 7.1 months in the patients who received chlorambucil.

Additional considerations:

The CGP considered the optimal sequencing of currently available treatments and noted input from registered clinician's indicating that ibrutinib would displace previous first-line therapies to second and third-line use. However, early experience with ibrutinib suggests that progression on ibrutinib may be associated with a more aggressive clinical course (as demonstrated in the second line studies with patients surviving 3 months on average after progression on ibrutinib). The CGP therefore agreed that there is currently no evidence to guide optimal sequencing of treatments following ibrutinib use in the front line setting. Additionally, the utility of FCR, bendamustine, or chlorambucil based therapies in salvage are not well defined and the CGP felt that for aggressive progression, novel therapies targeting different (non B-cell receptor mediated) pathways may be preferable.

In its feedback on the Initial Recommendation, PAG noted that registered clinician input favoured a scenario where current first-line therapies would be funded in the second-line setting if ibrutinib were funded first-line. The CGP noted that the use of other treatments for CLL in sequence after ibrutinib failure is controversial. If ibrutinib were discontinued for adverse effects (as occurred in 9% of patient in the pivotal study), patients should be considered for alternatives such as chlorambucil-obinutuzumab. It is the opinion of the CGP that current evidence suggests that patients with CLL whose disease progresses on ibrutinib have a very low likelihood of responding to subsequent treatments and survival from the time of failure averages about three months. While other treatments may be offered during this phase, it is unlikely that this would have a large budget impact.

In its feedback on the Initial Recommendation, PAG noted that the comparator in the RESONATE-2 trial was not representative of the current standard of care in Canada. The CGP felt that, while a head-to-head comparison would be feasible (this is not a rare disease; treatment indications are fairly standardized; and there is interest in knowing the results), it is doubtful that it will be conducted. At the time the RESONATE-2 study was designed the standard of care for elderly/fludarabine-ineligible patients was single-agent chlorambucil. The standard of care changed to chemoimmunotherapy (largely as a result of the obinutuzumab-chlorambucil vs. rituximab-chlorambucil vs. chlorambucil alone study) while the ibrutinib study was already underway, and it was judged to be impractical to go back and redesign this study. That being said, and acknowledging the well-known limitations of cross-trial comparisons, the response rates and PFS are much better with ibrutinib than they were with chemoimmunotherapy (at 26.7 months 50% of chlorambucil-obinutuzumab patients were progression free, while with ibrutinib 80%+ of patients progression-free at that time point) that the CGP feels that it is unlikely that a head-to-head randomized trial will be done.

1.3 Conclusions

In conclusion, the Clinical Guidance Panel believes there is a net clinical benefit with the use of ibrutinib in patients with previously untreated CLL who are ineligible for treatment with fludarabine. This conclusion is based on the results of a multi-center randomized, controlled clinical trial in this population demonstrating statistically significant and clinically meaningful improvements in progression-free and overall survival, improved quality of life and a favorable adverse effect profile.

In reaching this conclusion, the panel considered:

- That untreated patients with deletions or mutations of TP53 should also be offered treatment with ibrutinib given their refractoriness to fludarabine-based regimens and the favorable results of phase 2 studies in this population. It is unlikely, given the rarity of TP53-deficient CLL among untreated patients, that phase 3 studies will be carried out.[6,7,12]
- The choice of comparator for this study was appropriate at the time the study was designed. Since that time a randomized study has demonstrated improved OS and PFS with the combination of obinutuzumab and chlorambucil compared with chlorambucil alone in this population. Although not compared directly, and acknowledging the limitations of cross-trial comparisons, PFS with ibrutinib seems substantially longer in the RESONATE-2 trial than was seen in the combination arm of the aforementioned study. No benefit was noted with the addition of obinutuzumab to chlorambucil for patients with TP53 deletion.[11]

- Patients younger than 65 and for whom treatment with a fludarabine based regimen is deemed to be inappropriate, due to comorbidities, should be eligible for treatment with ibrutinib.
- The CGP is unaware of any evidence to guide optimal sequencing of treatments following ibrutinib use in the front line setting. Previous evidence for the use of ibrutinib in the second line setting demonstrated poor OS following progression on ibrutinib (3 months on average). Given the immaturity of the current data, the CGP is unable to determine if a similar trend will be observed with upfront use and is therefore unable to comment on the
- The CGP acknowledged that it is possible patients may request the use of an oral therapy in upfront therapy compared to iv chemotherapy. This would be an enabler as it is easier for patients to take and jurisdictions would have less chemotherapy chair time. Given the absence of evidence to inform optimal treatment sequencing, the CGP is unable to comment on whether or not ibrutinib or other available options (anti CD20 agents) should be used in the front line setting.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 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.

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 of 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.[13] 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).[14,15] 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.[16]

Table 3. Accepted staging systems for patients with chronic lymphocytic leukemia.

Staging System	Stage	Definition	Median OS (mo)
Rai	0	Blood/marrow lymphocytosis	126
	1	Lymphadenopathy	92
	2	Splenomegaly	53
	3	Anemia (Hb < 110)	23
	4	Thrombocytopenia (Plt < 100)	20

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.[17,18] 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.[19-21]

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.[22]

2.2 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.

Treatment options for untreated patients with CLL who require 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 FC.[23] After a median follow-up of 5.9 years highly relevant differences in overall survival persist in favor of FCR.[23] 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.[24] 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.[25] 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.[11,26] A survival advantage was also demonstrated in the obinatuzumab-chlorambucil study when compared to chlorambucil alone.[11]

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.[27] 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.[28] 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.

The effectiveness of ibrutinib in the treatment of previously untreated patients with CLL who are inappropriate for fludarabine was assessed in the RESONATE-2 clinical trial, which compared ibrutinib with chlorambucil in this population.[3] Eligible patients were randomly assigned to treatment with ibrutinib or chlorambucil. Treatment was continued until progression or unacceptable side effects occurred. The primary end-point, progression-free survival, was significantly longer in patients who were treated with ibrutinib compared with those treated with chlorambucil (median PFS unreached vs. 18.9 months, HR 0.16 (95% CI 0.09-0.28, p<0.001). Although not the primary outcome of this study, overall survival at 24 months was also noted to be significantly better in patients treated with ibrutinib compared with chlorambucil (OS 98% vs. 85%, HR 0.16, 95% CI 0.05-0.56, p=0.001). Toxicity included diarrhea and fatigue in patient receiving ibrutinib. A higher than expected rate of atrial fibrillation was noted in patients who received ibrutinib, consistent with other findings with this drug.[6,29]

2.3 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.[30]

2.4 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.[31]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy group(s) provided input on ibrutinib (Imbruvica) for chronic lymphocytic leukemia and their input is summarized below: Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG).

LC conducted online surveys and interviews of CLL/SLL patients and caregivers (as noted in the table below). Links to the surveys were sent via e-mail to patients and caregivers registered on the LC database. The links were also made available via LC Twitter and Facebook accounts as well as through the CLL Support Association, online patient forums and blogs. Interviews were conducted with 4 patients who had direct experience with ibrutinib as a monotherapy in the first-line setting. The surveys by LC had a combination of multiple choice, rating and open-ended questions. Skipping logic was also built into the surveys so that respondents were asked questions only relevant to them.

Overall, the perspectives of 76 respondents are represented in this submission: 18 CLL/SLL patients with ibrutinib experience in the first line setting; 46 CLL/SLL patients without ibrutinib experience; and 12 caregivers.

Participants by Country	CAN	USA	UK	AUS	Skipped	N
Patients with Ibrutinib Experience (Survey)	5	8	4	-	1	18
Patients with Ibrutinib Experience (Interviews)	3	1	-	-	-	4*
Patients without Ibrutinib Experience (Survey)	33	7	-	1	5	46
Caregivers (Survey)	10	1	1	-	-	12
* All patients with ibrutinib experience who participated in an interview also completed surveys.						

CLLPAG also conducted online surveys of CLL/SLL patients and caregivers (as noted in the table below). The online surveys were distributed to members of CLLPAG and the CLL Support Association, UK. The survey links were also posted to cllpag.ca, cllcanada.ca, cllsupport.org.uk, social media, and online forums.

CLLPAG reported that patient respondents were diagnosed with CLL/SLL between 1989 and 2016 and 58% patient respondents were diagnosed in the last five years. A total of 86.21% of the caregiver respondents are spouses/partners, 3.45% are children, 6.9% are immediate family, and 3.45% are friends.

Respondents by Country	CAN	USA	UK	AUS	Other*	Skipped	Total
Patients with ibrutinib experience	2	11	2				15
General CLL/SLL patients	63	105	38	3	6	18	233
Caregivers	11	14	3		1		29
*Other includes 1 patient from each of the following: Belgium, Brazil, New Zealand, Norway, Scotland & Sweden; 1 caregiver from Ireland.							

Respondents by Age	21-39	40-49	50-59	60-69	70-79	80-89	90+
Patients with ibrutinib experience		1	2	4	8		
General CLL/SLL patients*	3	17	55	94	43	2	1
Caregivers	2	6	6	9	5	1	
* 18 patients skipped this question							

Respondents by Gender	Male	Female
Patients with ibrutinib experience	5 (33.3%)	10 (66.7%)
General CLL/SLL patients	90 (39.1%)	140 (60.9%)
Caregivers	10 (34.5%)	19 (65.5%)

From a patient's perspective, symptoms of CLL/SLL can interfere with a patient's performance, ability to work, travel and day-to-day-activities. Fatigue/lack of energy, increasing lymphocyte, enlarged lymph nodes and frequent infections, among others are commonly reported symptoms. These symptoms, among other are important symptoms of CLL/SLL to control for patients. Respondents indicated that they would like the benefits of new treatment for CLL/SLL to be long term, and that it is very important to have choice in deciding treatment options. Respondents are currently receiving or have used a variety of therapies to treat CLL/SLL in the first line setting; treatments include: fludarabine/cyclophosphamide and rituximab (FCR), bendamustine and rituximab (BR), chlorambucil, fludarabine and rituximab (FR), and rituximab alone, among others. According to CLLPAG, the current standard drug therapy for CLL/SLL is FCR regime. LC indicated that treatment options currently available tend to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects and relapse. Common side effects of current treatment experienced by respondents included: fatigue, anemia, neutropenia, nausea, low platelets, mouth sores, skin rashes/severer itching, and infections.

Patient respondents described 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. Those respondents who have experience with ibrutinib indicated that the side effect profile of ibrutinib was easy to tolerate by most patient respondents; with the majority of respondent patients stating that the side effects were mild and quickly dissipated. Fatigue, rash or itching, diarrhea, anemia or neutropenia, among others were side effects of ibrutinib experienced by patient respondents. Patient respondents indicated that ibrutinib managed or improved the following symptom of CLL/SLL: enlarged lymph nodes, white blood cell count, and night sweats, among others. LC noted that ibrutinib brought the majority of the patient respondents' disease under control and allowed them to have an improved quality of life. Lastly, as an oral therapy, ibrutinib can be taken in the comfort of a patient's home and there are no infusion times or infusion reactions compared to intravenous (IV) treatment of CLL/SLL.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey and interviews, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

Please see below for a summary of specific input received from the patient advocacy groups.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

LC noted that patients with early stage CLL or SLL who participated in the survey reported minimal symptoms associated with their disease and tended to report a good quality of life. LC also noted that for those with more advanced disease, their quality of life was impacted more significantly. Fatigue was commonly reported; patients described themselves as being void of energy and stated that they needed to rest often in order perform their normal daily activities. Some patients with CLL or 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 states that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day-activities.

Below are quotes from respondents to help illustrate the impact of CLL/SLL symptoms:

- *"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...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. The illness plays on your mind and you are angry that it was me it picked. It has impacted my family life in ways that I must depend on my wife and children to help me out to do manual chores or submit paper work to get some reimbursement from insurance companies that structure themselves so that the forms are lengthy and multiple phone calls are required to obtain payment. I have cancelled holidays with family and friends because my platelet counts are too low and I might have a life threatening bleed. My wife and I plan our lives around my clinic appointments." (Male, 45-54; Canada)*

In their survey, CLLPAG asked which symptoms of CLL/SLL affected patient quality of life at diagnosis. Similar to the findings from LC, the most common symptoms were fatigue/lack of energy, cited by 51.61% (128/248) of respondents; followed by increasing lymphocyte count (47.98%), enlarged lymph nodes (39.11%) and frequent infections (20.97%). However, a total of 22% (56/248) of respondents indicated they did not experience symptoms at diagnosis. Patients reported that CLL was often diagnosed during investigation for another condition or during routine blood work. CLLPAG noted that as the cancer progressed, continuing symptoms included: fatigue (reported by 147/248 respondents, 59.27%), increasing lymphocyte count (91/248, 36.69%), enlarged lymph nodes (65/248, 26.21%), low platelet count (62/248, 25%) and low immunoglobulin levels (60/248, 24.19%).

In their survey, CLLPAG asked respondents to rate which symptoms of CLL/SLL are the most important for treatment to control with 1 = not important and 5 = very important. Below were the results of the responses:

Symptom	1	2	3	4	5	# of responses	% rated 4-5
Frequent infections	13	8	21	39	167	248	83.07
Fatigue/lack of energy	14	8	31	70	125	248	78.63
Viral reactivations	22	11	33	48	134	248	73.38
Low platelet count	16	13	44	65	110	248	70.56
Increasing lymphocyte count	13	13	48	58	116	248	70.16
Anemia	17	7	51	60	113	248	69.75

Symptom	1	2	3	4	5	# of responses	% rated 4-5
Neutropenia	16	11	53	43	125	248	67.74
Enlarged spleen	22	15	44	61	106	248	67.34
Shortness of breath	24	22	36	68	98	248	66.94
Low IgG levels	21	11	51	58	107	248	66.54
Enlarged lymph nodes	14	23	46	74	91	248	66.53
Pain	32	23	35	61	97	248	63.71
Fever	36	30	54	60	68	248	51.61
Night sweats	20	31	88	54	55	248	43.95
Weight loss	55	44	74	37	38	248	30.24

In addition, CLLPAG noted that anxiety was reported as a condition that affected quality of life at diagnosis for about 60% (147/248) of respondents and continues to be an issue for 40% (100/248) of respondents. As well, difficulty sleeping continues to affect about 35% (86/248) patients, which was slightly reduced from the 39% (96/248) that reported this at diagnosis. Depression affected 30% of respondents at diagnosis and continues to affect 23% of patients. Stress of diagnosis was also reported by 75.81% of respondents at diagnosis and continues for 29% of the population.

Below are comments from patient respondents about their diagnosis:

- *"My child was 3 years old at the time of my diagnosis and I worried that I would not survive long enough to raise her."*
- *"I found that the diagnosis affected my relationships and I was in effect written off by some people."*
- *"The diagnosis is devastating. I was diagnosed Dec 2015 and started treatment within days. I was only 45 and have 12 kids (ages 1 year to 25). The emotional toll is hard as well as the financial burden that comes with the diagnosis."*

CLLPAG noted that 144 (58.06%) respondents had received treatment and 104 (41.94%) were in watch & wait. CLLPAG stated that watch & wait management of the disease is often a difficult stage for patients to accept. Below are key responses from patient respondents:

- *"I am finding watch and wait extremely stressful. My numbers are not extreme, yet I can't bring myself to relax and quit stressing."*
- *"Although I am in watch and wait 12 years after diagnosis, CLL affects my life everyday. I require IVIg infusions every 8 weeks to reduce infections and this involves a visit to the hospital. Our lives revolve around this."*
- *"I am using my watch and wait to educate myself about CLL. I find that knowledge is one of the keys to maintaining a healthy perspective when living with CLL."*

According to CLLPAG, patient respondents reported having to retire from work earlier than planned, and being unable to return to work after treatment due to chemo-induced lymphocytopenia.

CLLPAG also found from the responses that ongoing symptoms result in social isolation, especially for those living alone. Below are quotes from patient respondents to support these findings:

- *"I just wish that the fatigue and loss of antibodies could be controlled in the earlier stages of this disease as the loss of social engagements due to fear of getting ill, as well as being too tired to participate does not help a person to be mentally healthy when they live alone."*
- *"its a long road to watch out for everything... your life style changes so much it's hard to handle, just glad there are people who understand out here..."*
- *"I feel unlucky to have been diagnosed with CLL and it is a struggle dealing with this incurable cancer on a daily basis."*

3.1.2 Patients' Experiences with Current Therapy for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

According to CLLPAG, the current standard drug therapy for CLL/SLL is FCR regime. CLLPAG stated that FCR is a toxic regimen that could be ineffective for certain genetic mutations of CLL, such a 17p deletion.

CLLPAG indicated that patient respondents are currently receiving a variety of therapies to treat CLL/SLL, as outlined in the table below:

Treatment Given	# Patients Treated			
	First-line	Second-line	Third-line	Fourth-line
ACP196 (acalabrutinib)	2	2	0	0
Bendamustine	2	2	1	1
BR - Bendamustine rituximab	16	5	2	2
Campath	0	1	0	0
Chlorambucil	10	2	2	1
CVP	1	0	0	0
CVP + R	1	0	0	0
Cytoxan, pentostatin, rituximab	1	0	0	0
Fludarabine, rituximab, lenolidamide	1	0	0	0
Fludarabine	7	0	2	1
FC	2	0	0	0
FCR	37	7	1	0
FR	10	2	1	0
Fludarabine, cytotoxin, ofatumumab	1	0	0	0
GS-9973	0	0	1	0
Ibrutinib	10	22	13	4
Ibrutinib and rituximab	5	0	0	0
Ibrutinib and ubilituximab	0	2	0	0
Idelalisib	1	1	3	0
Obinutuzumab	3	0	0	1
Obinutuzimab and rituximab	1	0	0	0
Obinutuzumab and bendamustine	1	0	0	0
Obinutuzumab/venetoclax	1	0	0	0
Obinutuzumab/venetoclax/ibrutinib	0	1	0	0
Ofatumumab, lenolidamide, dexamethasone	1	0	0	0
PCR	3	1	0	0
R-CHOP	1	3	0	0
Lenalidomide	1	2	0	1
Rituximab / lenalidomide	1	2	0	0
Rituximab	6	15	3	2
Rituximab and HDMP	2	1	0	0
Venetoclax	1	0	1	1
Venetoclax/obinutuzumab	0	0	1	0
TOTAL	144	71	31	14

In addition to these therapies, 7 respondents received fifth line therapy (revlimid, rituximab (2), FCR, ibrutinib (3)) and three respondents received sixth line treatment including Venetoclax, obinutuzumab and ibrutinib.

LC reported the following current treatments used by patient respondents to treat CLL or SLL:

Current Treatment N= 33	Response Count* n (%)	Current Treatment	Response Count* n (%)
FCR	9 (27.3%)	R-CHOP	1 (3.0%)
Rituximab alone	8 (24.2%)	FR	1 (3.0%)
Stem cell transplant	4 (12.1%)	Idelalisib	1 (3.0%)
CVP chemotherapy	3 (9.1%)	Chlorambucil alone	1 (3.0%)
CHOP chemotherapy	3 (9.1%)	FC chemotherapy	1 (3.0%)
Radiation therapy	3 (9.1%)	Splenectomy	1 (3.0%)
*Total response count exceeds total respondents to this question (N=33) because some patients indicated using more than one treatment.			

According to LC, patient respondents listed both positive (disease control) and negative side effects (disease progression; adverse events; dose interruptions due to side effects) of their current treatment. Below are quotes from respondents to illustrate some of the side effects experienced from their treatment:

- *"I had hoped that the therapies would keep my red cell count up longer than it does. I am not able to maintain good nos. over a period of time. That means going on and off treatment often."* (Female; 65-74; Canada)
- *"All treatments wiped out my good blood components and made me tired. As treatment went on with each of these therapies I development 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)

CLLPAG reported the most common side effects of treatment experienced by respondents (137/144 responded) were: fatigue (70.80%), anemia or neutropenia (50.36%), nausea (48.91%), low platelets (39.42%), mouth sores (36.5%), skin rashes/severer itching (32.12%) and infections (32.12%).

CLLPAG asked respondents to agree or disagree with the following statement: "*My current therapy(ies) are able to my manage CLL/SLL symptoms*," with 1 = strongly agree to 5 = strongly disagree. CLLPAG noted that about 50% (69/137) patients provided a rating of 1 or 2.

CLLPAG asked respondents, if you were to consider having treatment for your CLL/SLL, what short term side effects are you willing to tolerate if the treatment improves your overall quality of life? 1 = will not tolerate the side effect to 5 = will tolerate the side effect. 248 patients responded to the question.

Side effect	1	2	3	4	5	% rated 4-5
Fatigue	5.24%	15.31%	20.16%	27.42%	31.85%	59.27%
Cough	6.05%	13.31%	29.44%	24.29%	27.02%	51.21%
Diarrhea	10.89%	12.10%	27.42%	23.39%	26.21%	49.60%
Nausea	10.89%	14.52%	27.02%	20.56%	27.02%	47.58%
Fever	9.68%	14.52%	30.65%	20.97%	24.19%	45.16%
Back pain	14.52%	18.15%	34.75%	18.15%	14.92%	33.07%
Infusion reaction	23.39%	20.97%	24.60%	17.34%	13.71%	31.05%
Rash/severe itching	19.35%	20.16%	30.65%	16.53%	13.31%	29.84%

Side effect	1	2	3	4	5	% rated 4-5
Low platelets	9.68%	24.19%	36.69%	16.94%	12.50%	29.$$%
Irregular heartbeat	26.61%	26.61%	22.58%	17.74%	6.45%	24.19%
Anemia or neutropenia	20.16%	26.61%	29.03%	12.90%	11.29%	24.19%
Tumour Lysis Syndrome	41.53%	15.73%	24.60%	8.87%	9.27%	18.14%
Breathing difficulties or pneumonia	42.74%	26.615	17.74%	6.45%	6.45%	12.90%

CLLPAG stated the above table shows that respondents would be willing to tolerate side effects that are easily treated but less likely to be willing to tolerate more life threatening side effects.

LC indicated that treatment options currently available in Canada tend to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects and relapse. Respondents 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 on a scale of 1 (Strongly Disagree) to 10 (Strongly Agree). Thirty four (34) patients answered this question. The rating average was 6.9.

Respondents were also asked how difficult it was to access their most recent or current therapy(ies). LC reported that many of the 29 Canadian patients who answered this question, (10, 34.5%) experienced difficulties. Difficulties expressed by patients and caregivers included the need to: travel great distances to receive treatments in Canada; meet specific provincial drug funding criteria; pay out-of-pocket costs for treatments and associated travel.

Level of Difficulty With Access	n (%)	Level of Difficulty with Access	n (%)
Not at all difficult	12 (41.4%)	Somewhat Difficult	6 (20.7%)
Not very Difficult	7 (24.1%)	Very Difficult	4 (13.8%)
			Response Count: 29

Below are quotes from respondents to illustrate the difficulties with access to current therapies:

- *"Access was easy - difficulty was paying for it."* (Female; 55-64, Canada)
- *"I live 130 Kilometers from Ottawa so I had to drive in order to get the treatments."* (Female, 75 years or older, 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)

Respondents were also asked by CLLPAG if they could access treatment in own community. A total of 81.02% (111/137) responded "yes" to this question. Of those who could not access treatment locally (26/137), six (23.08%) live in a community without a cancer centre, five (19.23%) couldn't access treatment in their province or state, and 15 (57.60%) indicated other reasons. Two thirds (10) of the other group travelled outside their community to access a clinical trial. Other comments from respondents included: *"I wanted treatment in a specific hospital", "Cancer centre lacked expertise in CLL", "Since last treatment, I have moved to a rural area with no treatment centre, have to travel to attend clinic"*. CLLPAG noted that two thirds of respondents were away from home for less than 4 days; and the longest time away was nine months.

CLLPAG indicated that one patient reported that he received first line ibrutinib treatment for 17p deletion CLL at his own expense. He was then diagnosed with a Richter's transformation and after treatment with R-CHOP, was eligible to receive ibrutinib funded by his provincial health plan.

When considering treatment, respondents were asked how important it is 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). Twenty-eight of the 38 patients (73.7%) who answered this question gave this a rating of 8 or higher. The rating average was 8.4 and according to LC, this means a large proportion felt that choice was very important based on the known side effects and expected outcomes of a drug. Patients 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 respondents (36, 100%) who answered this question feel there is a definite need for more therapies.

Similarly, in their survey, CLLPAG asked: *"If you were to require drug treatment for your CLL/SLL, how important is it for you and your physician to have a CHOICE in deciding what drug(s) to take?"* With 1= not important as long as there is a drug and 5 = very important to have a choice. A total of 91.93% (228/248) patient respondents agreed it was very important, with a 4 or 5 response.

According to CLLPAG, respondents would like the benefits of treatment to be long-term. This was noted in the responses below when asked: *"What is important to you about any new drug or treatment for CLL/SLL?"*

- *"quality of life during and after treatment"*
- *"knowing the effectiveness and response rate of new drugs is important"*
- *"Less side effects, less harmful for the normal cells"*
- *"Minimize toxicity and long term health effects"*
- *"To be more effective and less toxic and side effects"*

3.1.3 Impact of Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma and Current Therapy on Caregivers

The statistical data that was reported have also been reproduced as is according to the submission, without modification. LC asked respondents to rate on a scale of 1 (No Impact) to 10 (Very Significant Impact) how caring for the person with CLL or SLL has impacted their "day-to-day life." LC noted 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 seven (58.3%) were still working. For those factors with a rating average of 5 or more, LC indicated there was a greater than neutral impact on day-to-day life.

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 Not Retired Caregivers (N=7)*	Rating of 7 or Higher n (%)	Rating Average
Ability to travel	4 (80.0%)	7.2	Ability to volunteer	4 (57.1%)	6.7
Ability to volunteer	3 (60.0%)	5.8	Ability to concentrate	3 (42.9%)	5.1
Ability to spend time with family and friends	2 (40.0%)	5.2	Ability to exercise	2 (28.6%)	4.7
Ability to concentrate	2 (40.0%)	4.8	Ability to attend to	2 (28.6%)	3.7
Ability to fulfill family obligations	2 (40.0%)	4.8	Ability to spend time with family and	2 (28.6%)	3.9
Ability to exercise	2 (40.0%)	4.4	Ability to contribute financially to	2 (28.6%)	3.7
Ability to attend to household chores	1 (20.0%)	4.0	Ability to travel	1 (14.3%)	4.3

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 Not Retired Caregivers (N=7)*	Rating of 7 or Higher n (%)	Rating Average
Ability to contribute financially to household expenses	1 (20.0%)	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.					

CLLPAG also expressed that caring for someone with CLL/SLL has a profound impact on the caregivers. CLLPAG received input from a total of 29 caregiver respondents; 65.52% (19) of respondents were female and 34.48% (10) were male.

CLLPAG asked caregivers, *"Have you experienced any of the following conditions as a result of caring for a person with CLL/SLL?"*

Stress of diagnosis	Depression	Difficulty sleeping	Anxiety	Other (includes loss of sleep, anger, worry
68.97% (20)	34.48% (10)	48.28% (14)	89.66% (26)	20.69% (6)

CLLPAG indicated that emotional/psychological burdens of caregiving are faced by caregivers of patients receiving as well as those still awaiting treatment. *"There is an ongoing daily tension … for both patient and caregiver"* one patient noted. Worries include concern that the patient gets a proper diagnosis, the best available treatment and proper updates on progress. The availability of the newer, targeted drugs is a concern.

LC noted that other common challenges faced by caregivers were related to "anxiety". Below are quotes from caregiver respondents to illustrate the anxiety they faced:

- *"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)

LC indicated that caregivers reported difficulties managing "side effects" of treatment. The most commonly reported side effects related to emotional (moods) and safety (physical mobility) issues. Below are quotes from caregiver respondents to illustrate the difficulties of managing side effects of treatment:

- *"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 - strain to myself trying to assist lifting her"* (Child; Female; 45-54; Not retired, Canada)

LC also noted that 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 are quotes from caregiver respondents to illustrate the difficulties of accessing treatment:

- *"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 affected finances and ability to pay bills and going to declare bankruptcy."* (Child, Female 45-54, Not retired, Canada)

CLLPAG also reported that caregivers are faced with exhausting caretaking duties (18/29). They take on previously shared household chores including meal preparation, shopping and upkeep of house and garden. They also face transportation duties accompanying patients to time-consuming and distant medical appointments, taking notes during clinic visits, purchasing drugs and dietary supplements and ensuring doctors' instructions are followed. (*"I had to take over all household duties")*. Many hours are spent understanding CLL/SLL and treatment advances. Despite these burdens, caregivers indicated that they *"will do whatever is necessary."*

CLLPAG highlighted that financial difficulties are another concern raised (12/29) by caregiver respondents. Insufficient insurance coverage of therapeutic drugs is mentioned and there are other related expenses respondents have difficulty meeting, especially when they had to, or decided to, abandon their jobs to care for their patients. *("Financially we lost one income since she cannot work." "All our hard- earned savings disappeared over the next year.")*

CLLPAG stated that patients' compromised immune systems and other treatment side effects were cited (6/29) as the reason for reduced social contact with family and friends for both caregivers and patients, sacrificing vacations and avoiding non-essential social events. One respondent stated: *"Social isolation in part due to fear of germs."* For some caregiving was also cited as having direct physical health implications for caregivers. Most frequently mentioned were trouble sleeping and fatigue. One respondent complained of a back injury due to taking on unfamiliar maintenance duties; one confessed to ignoring her own chronic health problems to attend to the needs of her spouse. Two caregivers indicated that marital relations with their partners had ceased.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Ibrutinib

Expectations with ibrutinib

According to CLLPAG, ibrutinib is expected to provide patients who are unable to benefit from chemotherapy a choice that will be effective in treating their CLL/SLL. Moreover, using ibrutinib first line for CLL patients who will not respond to fludarabine, will improve the lives of these patients. CLLPAG indicated that chemotherapy can have serious adverse effects and that ibrutinib therapy carries risks of serious side effects as well, but patients who do not respond to other treatments because of their genetic profile are willing to tolerate these risks in the hope of extending their life. CLLPAG noted that genetic testing is available to determine who has 17p deletion.

Below are quotes from respondents to illustrate their expectations with ibrutinib:

- *"Gaps are in treatment that doesn't cause serious side effects and long lasting damage to the immune system"*
- *"New and more targeted treatments bring patients hope that quality of life may be better*

while living with the disease and that life may be longer. Living with a Damocles sword hanging over life is very, very hard! More options provide more hope. Non-chemo treatments that lower the chances of a secondary fatal cancer are crucial to patients and their families."

- *"Reduced side effects, greater tolerability ... chemo is like treating CLL with a tank, it takes out everything."*

CLLPAG asked patients compare IV and oral drug treatment for CLL/SL, where 1 = little impact and 5 = severe impact:

	IV Treatment weighted average (120 respondents)	Oral Treatment weighted average (112 respondents)
# of clinic visits	2.58	2.09
Able to tolerate full dose	2.30	2.56
Able to complete all cycles	2.44	2.36
Increased number of infections	2.47	2.16
Increased frequency of infections	2.23	2.08
Ability to do usual activities	2.77	2.43
Too tired to do the things I want to do	2.73	2.56
Infusion time	2.62	NA
Infusion reaction	2.66	NA

According to CLLPAG, oral treatment resulted in less impact than IV treatment in all areas, except the ability to tolerate full dose.

CLLPAG reported that patients are willing to travel away from home to access ibrutinib, as noted by one Canadian patient: *"In order to be in this trial I had to go to Calgary from Vancouver"* and the same patient noted: *"I didn't have difficulty accessing treatment,"* so patients are willing to travel to have access to this drug.

LC asked respondents a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) to rate the extent to which they would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their CLL or SLL. Twelve of the 29 respondents (41.4%) living in Canada who answered this question gave a rating of 8 or higher (rating average 6.3). Many patient respondents described 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. Below are quotes for patients to illustrate their willingness to tolerate side effects:

- *"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)

LC also asked respondents to rate on a scale of 1 (Not Important to Control) to 10 (Very Important to Control), how important it is for a new drug to be "able to control" specific aspects associated with their disease. As depicted in the table, the vast majority of respondents assigned a rating of '10' to all aspects.

Level of Importance of a New Drug to be Able to Control	Rating of 10 n (%)	Rating Average	Response Count
Improve Quality of Life	29 (85.3%)	9.79	34
Control Disease and side effects	31 (86.1%)	9.78	36
Live longer	31(88.6%)	9.77	35
Improve blood counts	30 (88.2%)	9.76	34
Bring about a remission	30 (83.3%)	9.56	36

LC indicated that from a patient's perspective, patients seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. As an oral therapy, ibrutinib is not administered in a hospital or cancer care setting which will lower the risk of patients developing hospital acquired infections. It can be taken in the comfort of a patient's home; a true benefit to patients and caregivers.

Experience with Ibrutinib

LC reported that eighteen (18) patient respondents had experience with ibrutinib in the first-line setting for CLL. Six (6, 33.3%) patients indicated they had 17p deletion and nine (9, 50.0%) respondents indicated they did not. Three (3, 16.7%) respondents did not know if they had 17p deletion. All 18 (100%) patient respondents recommend ibrutinib. One (1, 5.6%) patient respondent discontinued ibrutinib after 10 months due to side effects. The table below summarizes the respondents experiences with ibrutinib.

Start Date	Still Taking	Based on Your Personal Experience with Ibrutinib Would You Recommend Ibrutinib to Other Patients with CLL?
Aug 2012	Yes	*"Yes. Three pills a day and a lifetime to live. So easy. I am so lucky to go straight to Imbruvica and not have to deal with IV treatments."* (Female; 65-74; USA)
Nov 2012	Yes	*"Yes. It worked for me."* (Male; 78; USA)
Apr 2013	Yes	*"Yes. It has dramatically impacted my potential survival without severe side effects. The drug is tolerable and easy to take in pill form."* (Female; 65-74; USA)
Sept 2013	Yes	*"Yes. Because it has changed my life by allowing me to live normally with very few symptoms (at the moment)."* (Male; 65-74; UK)
Apr 2014	Yes	*"Yes. What better options are out there? I never had any sickness with Imbruvica. FCR treatment or any others are extremely toxic."* (Female; age not provided; USA)
Aug 2014	Yes	*"Yes. It is a miracle drug! I highly recommend it as first line therapy. It improved my health extremely fast and if I had taken it earlier before the symptoms became unbearable I would not have realised how sick you can become with CLL. The side effects are none existent if one is healthy and relatively fit as I was. I highly recommend it as first line therapy. It is not a cure but made CLL a really mild chronic condition for me."* (Female; 55-64; UK)
Jan 2015	Yes	*"Yes. Ease of use of taking a pill; minimal side effects. Psychologically, I did not have to go through the horrors of chemo."*(Male; 59; Canada)
Feb 2015	Yes	*"Yes. I have read account of others for whom it has worked wonders; it's been too recent to make the call in my case."* (Female; 55-64; USA)
Feb 2015	Yes	*"Yes. FCR would not have provided a solution for 17p deletion. Going straight on ibrutinib as first line meant that my body was not subject to unnecessary treatment that would not have worked. Ibrutinib was able to reverse the failing blood counts and I was/am able to work and remain productive through out the treatment."* (Male; 55-64; Canada)
Apr 2015	Yes	*"Yes. Imbruvica has saved my life. I suspect that I would be close to death by now without it. Until this drug there was no treatment that had good results for those with 17 p deletion, and those that were used had terrible side effects.* (Female; 65-74; USA)
May 2015	Yes	*"Yes. It may not be a cure but it appears to be a very close second."* (Male; 55-64; UK)
Jul 2015	Yes	*"Yes. It has helped me and I have not had to undergo chemotherapy (yet anyway)."* (Female; 65-74; USA)
May 2015	No	*"Yes. This drug dropped my WBC to well below top numbers in normality. Not every patient on Ibrutinib will experience what I experienced."* (Male; 65-74; USA) Discontinued ibrutinib in March 2016.
Jun	Yes	*"Yes. It does shrink the lymph nodes and is controlling the leukemia and everyone*

Start Date	Still Taking	Based on Your Personal Experience with Ibrutinib Would You Recommend Ibrutinib to Other Patients with CLL?
2015		*is different and will have different side effects, etc. Ibrutinib is the best choice out there for now."* (Female; 65-74; Canada)
Sept 2015	Yes	*"Yes. I most certainly highly recommend it to those who have the 17p deletion."* (Male; 72; Canada)
Oct 2015	Yes	*"Yes. Effective lowering of ALC, relatively minor side effects.* (Male; 54-64; USA)
Nov 2015	Yes	*"Yes, absolutely because it saved my life. Chemo won't help me. Before my lymph nodes were so big I could hardly breathe. My back was achy. It was horrible. I had lots of pain under my arms and in my stomach. If I did not have ibrutinib I would not be here. For me ibrutinib is saving my life."* (Female; 61; Canada)
Mar 2016	Yes	*"Yes. It's effective, it's an oral drug that can be taken at home, and there are few side effects. This means life can carry on with minimal disruption."* (Female; 55-64; UK)

CLLPAG reported that fifteen patients respondents who have experience ibrutinib first line responded to their survey; five of these patients received ibrutinib/rituximab.

CLLPAG asked patients: *"Overall, what is your experience with ibrutinib? Describe the positive and negative."* Below are quote from the respondents:

- *"Excellent. Minimal visits to hospital i.e. once every 3 months. On the negative side my treatment has only been accessed as a trial and involved too many bone marrow biopsies."*
- *"Good on the whole, aches and pains and sore mouth and dry/cracking skin on hands are tolerable."*
- *"While there have been many serious problems along the way, my current status seems to be reasonably stable. So I have to rate the experience a large net positive, as my outlook for survival without treatment was absolutely dismal.",*
- *"I don't have an opinion yet, dealing with the potential expense was very stressful."*
- *"I am very pleased and thankful that I was able to get on a trial for Imbruvica as a treatment naive patient at age 67. I am doing very well."*
- *"Many benefits - reduced or eliminated symptoms (spleen, lymph nodes, wbc)."*
- *"I was thrilled not to face hair loss, or worry about chemo inducing secondary cancers."*
- *"Ibrutinib took my enlarged and painful lymph nodes down drastically just within the first week. Now, after 6 months, I can hardly feel them. And I have had only a few very mild side effects. My WBC is still high, but I feel fine."*

Side Effects with Ibrutinib

LC asked respondents on a scale of 1 - 10, with 1 being (No Side Effects) and 10 being (Many Side Effects), to rate the quantity of side effects with ibrutinib. All 18 respondents answered this question. The rating average was 3.8. When asked about the side effects experienced with ibrutinib, the majority of respondents stated the side effects were mild and quickly dissipated. One (1, 5.6%) respondent discontinued ibrutinib due to side effects (as stated in table above).
Side effects reported by respondents included fatigue (n=8); joint/muscle pain (n=7); bruising (n=6); diarrhoea (n=4); brittle nails (n=3); skin infections (n=2); rash (n=3); stomach upset (n=2); stomach pain (n=1); nosebleeds (n=1); easy bleeding (n=1); petechiae (n=1); nail discoloration (n=1); subconjunctival haemorrhage in both eyes that went away (n=1); skin problems (n=1); dry skin (n=2); itchy skin (n=1); new curly hair (n=1); hair loss (n=1); swelling of feet and ankles (n=1); minor atrial fibrillation (n=1); coughing (n=1); pneumonia (n=1); lowered immunity (n=1); mouth sores (n=1); allergies (n=1); loss of appetite (n=1); cold body temperature (n=1); weight loss (n=1); nausea (n=1); neuropathy (n=1); and increase in white blood cell count at start of treatment only (n=1). Many respondents reported experiencing more than one side effect. According to LC, the side effect profile was easy to tolerate by most. Below are quotes from respondents to help illustrate the side effect profile of ibrutinib:

- *"For me, the side effects of imbruvica seem to lessen over time, and come and go. My life is normal again. With the exception of taking three pills once a day, I would not notice that I have CLL. Imbruvica worked very quickly. I have not missed a day of work because of the disease or drug.* (Female; 67; USA - on ibrutinib since April 2015)
- *"The side effects lessened with continued use and antihistamine drugs prescribed by my doctor until they are no longer of any significance."* (Male; 55-64; Canada)
- *"I know biochemically, hematologically my white blood cell count went up dramatically initially but it did not have an adverse effect on me. I started and my white count was at a 110 and then it went up to 220,000 and now its back down to about 60,000 now."* (Male; 72; Canada)

In their survey, CLLPAG asked: *"Which of the following side effects of ibrutinib have you experienced? and Which of the following side effects are you willing to tolerate?"*

Ibrutinib Side Effect	% respondents who experienced side effect (n=15)	% & # willing to tolerate side effect (n=15)
Fatigue	46.67% (7)	66.67% (10)
Rash or itching	40.00% (6)	53.33% (8)
Diarrhea	26.67% (4)	46.67% (7)
Anemia or neutropenia	26.67% (4)	33.33% (5)
Low platelets	20.00% (3)	46.67% (7)
Back pain	20.00% (3)	40.00% (6)
Cough	20.00% (3)	40.00% (6)
Irregular heartbeat	13.33% (2)	13.33% (2)
None of these	13.33% (2)	6.67% (1)
Nausea	6.67% (1)	33.3% (5)
Tumour lysis	6.67% (1)	6.67% (1)
Pneumonia	6.67% (1)	Not asked
Fever	0% (0)	20.00% (3)
Viral reactivation	0% (0)	6.67% (1)
Breathing difficulties	0% (0)	6.67% (1)
Bowel obstruction	0% (0)	6.67% (1)

Other side effects noted by CLLPAG included weight gain (n=1), cracked fingernails (n=2), finger cuts (n=1), very dry skin (n=1), indigestion (n=2), allergies (n=1), mouth sores (n=2), edema (n=1).

CLLPAG also reported that some respondents outside the survey have reported difficulty swallowing pills.

Improvement in Symptoms with Ibrutinib

LC asked respondents on a scale from 1 (No Improvement) to 10 (Very Significant Improvement) to rate how much several symptoms associated with CLL have improved since starting treatment with ibrutinib.

Improvement in CLL Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	Rating Average	Improvement in CLL Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	Rating Average
Enlarged lymph node(s) N=14	13 (92.9%)	9.2	Night sweats N=8	5 (62.5%)	7.0
White blood cell counts N=14	12 (85.7%)	9.1	Platelet counts N=11	4 (36.4%)	6.4
Fever N=3	2 (66.7%)	8.7	Infections N=12	4 (33.3%)	5.4
Shortness of breath during normal activities N=4	2 (50.0%)	7.5	Chills N=3	1 (33.3%)	5.3
Weight loss N=6	4 (66.7%)	8.0	Fatigue N=16	6 (37.5%)	5.0

Improvement in CLL Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	Rating Average	Improvement in CLL Symptoms Since Taking Ibrutinib	Rating ≥8 n (%)	Rating Average
Red blood cell count N=10	6 (60.0%)	7.2	Immunoglobulin levels N=9	3 (33.3%)	4.3
Discomfort in left side (due to enlarged spleen) N=6	3 (50.0%)	7.2	Aches and pains, N=8	2 (25.0%)	3.3
Not all patients experienced all symptoms. The number of patients who responded to each symptom is shown in the table as indicated by "N".					

LC noted that no respondents reported a relapse in their disease.

CLLPAG asked patients: *"Which symptoms of CLL/SLL does ibrutinib(Imbruvica) manage for you?"*

Symptom	% whose symptom were managed	# of respondents (of 15)
Increasing lymphocyte count	73.33	11
Enlarged lymph nodes	73.33	11
Night sweats	46.67	7
Enlarged spleen	40.00	6
Fatigue, lack of energy	26.67	4
Shortness of breath	20.00	3
Weight loss	20.00	3
Frequent infections	13.33	2
Fever	13.33	2
Did not manage any symptoms	6.67	1
Managed all of my symptoms	40.00	6

CLLPAG indicated that although the respondent who answered *"did not manage any of my symptoms"*, they wrote that, *"I received first line treatment (CLL 17p deletion) at my own expense in early 2015. When I was diagnosed with Richter's Transformation in February 2015, ibrutinib was discontinued and I underwent a full 6 course treatment of RCHOP which was successful. Ibrutinib treatment was recommenced (this time funded under the Special Access Program in Ontario) in July 2015. It (ibrutinib) appears to be controlling my 17p CLL. I'm alive and currently quite stable, so thank you RCHOP and ibrutinib."* This respondent was from Canada.

Long-Term Health and Well-Being with Ibrutinib

LC asked respondents to the survey and interview on how ibrutinib changed or is expected to change their long-term health and well-being. According to LC, most respondents have great expectations for ibrutinib.

Long-Term Health or Well-Being (N=18)	n(%)
Control my CLL and symptoms associated with CLL	16 (88.9%)
Allow me to live longer	14 (77.8%)
Improve my blood counts	13 (77.2%)
Improve my quality of life	13 (77.2%)
Bring about a remission	10 (55.6%)

Quality of Life with Ibrutinib

LC asked respondents on a scale from 1 (Severely Negatively Impacted) to 10 (Normal Living), to rate their Quality of Life while having treatment with ibrutinib. All 18 (100%) respondents answered this

question. The rating average was 7.6. According to LC, ibrutinib brought the majority of the patients' CLL under control and allowed them to have an improved quality of life. Below are quotes from four respondents to help illustrate quality of life with ibrutinib:

- "*Obviously it has improved my life by reducing lymphs and spleen enlargement somewhat and blood counts except platelets have returned to normal. Not a lot has changed in my life except having to take pills every morning and dealing with gastrointestinal issues."*(Female; 65-74; USA)
- *"I started therapy fairly late (blood counts WBC 300; HB 70 and PLT 30,000). My spleen and lymph nodes were very large and most of my joints were very sore and stiff to a point I could not move easily…Within the first week of taking Ibrut my lymph nodes were spectacularly reduced and with the second week my spleen shrank. Stiffness joint pain and joint mobility improved within 6 months. HB went up within a month and it was normal range in about 4 months. I did not have any side effects from taking Ibrut."* (Female; 55-64; UK)
- *"I had nodes popping up all over. My WBC was over 250. I was sweating day and night. I was very scared I would die soon. Now I am in remission. No more worries about dying soon. Can function almost normally."*(Female; 65-74; USA)
- "*My disease progressed rapidly. I was on watch and wait for one year when my blood counts rapidly increased and my Fish tests indicated almost all 17p cells. According to my doctor I was about to feel very sick. I was tired, had shortness of breath, and my nodes were increasing in size. Within one month I was feeling better, nodes disappearing and by my 7 month check up my blood levels were normal and I felt like a normal, healthy individual. This is a miracle drug*." (Female; 65-74; USA)

3.3 Additional Information

According to LC, in Canada there is a need for access to targeted therapies that have proven to be effective at stopping disease progression and increasing quality of life. LC highlighted that an oral therapy is easier for patients and caregivers to follow, without the necessity to keep track of treatment cycles common to other treatments. An oral drug with mild side effects for most and proven efficacy will permit patients to regain a good quality of life, have fewer hospital visits and contribute to society. Specifically, patients and caregivers who live far from cancer treatment facilities and the elderly would particularly benefit from an oral medication.

CLLPAG also emphasized that ibrutinib is an oral medication and the patient is responsible for ensuring proper usage: proper education and support programs are needed to ensure patients understand they need to continue this medication unless advised by their hematologist to discontinue.

CLLPAG highlighted that the following question is not appropriate for patients who have used a drug regime for first-line indications: *"Which symptoms does the drug manage better than the existing therapy and which ones does it manage less effectively?"*

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of ibrutinib:

Clinical factors:

- Generalizability of results from the submitted trial to the Canadian context as chlorambucil monotherapy is not the current standard of care in Canada
- Sequential use of ibrutinib and other treatments available for CLL/SLL

Economic factors:

- Long duration of treatment
- Large prevalent number of patients potentially eligible for treatment

Please see below for more details.

4.1 Factors Related to Comparators

Current treatments available for newly diagnosed CLL/SLL patients include fludarabine/chlorambucil/rituximab (FCR), bendamustine and obinutuzumab/chlorambucil. PAG noted that chlorambucil monotherapy is rarely used, even for elderly patients and is no longer the appropriate comparator in Canadian practice, given the options currently available. PAG is seeking comparative data, if available, on ibrutinib compared to currently available treatments other than chlorambucil monotherapy.

4.2 Factors Related to Patient Population

PAG is seeking clarity on whether ibrutinib would be an option or a replacement of anti-CD20 therapies for patients based on the trial inclusion criteria (e.g. RESONATE-2 trial enrolled patients age 65 and over) or whether the results of the trial can be generalized to include patients who are not eligible for a fludarabine based treatment (e.g. <65 and with comorbidities). In addition, PAG is seeking clarity on the treatment of patients with 17p deletion.

PAG noted that patients would eventually be treated with ibrutinib in the second-line setting and this is moving the use of ibrutinib to early stage of disease to the first-line setting. PAG is seeking information on the use of anti-CD20 therapies after ibrutinib and guidance from provincial tumour groups on treatment options after use of ibrutinib in previously untreated CLL/SLL patients and the sequencing of therapy of all currently available treatments.

4.3 Factors Related to Dosing

The flat once daily dose of ibrutinib is convenient and there is one capsule strength for ease of dose adjustments. These are enablers to implementation.

4.4 Factors Related to Implementation Costs

PAG noted that there could be a potentially large budget impact given the high cost of ibrutinib, the long duration of treatment and the large prevalent population. In addition, there are a number of patients are currently treated with chemotherapy who would be eligible for ibrutinib in the second-line setting.

PAG indicated there may be an increase in number of newly diagnosed patients who would initially not be treated with chemotherapy but would now request treatment with an oral drug.

4.5 Factors Related to Health System

Ibrutinib is already funded for previously treated CLL/SLL patients and health care professionals are familiar with monitoring for adverse events. As an oral option, chemotherapy chair time and nursing time would not be required.

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.

4.6 Factors Related to Manufacturer

PAG noted the high cost of ibrutinib would be a barrier.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

One clinician input was provided on ibrutinib for previously untreated CLL/SLL. The input is summarized below.

Overall, it is felt that ibrutinib provides an oral treatment option, particularly for patients with 17p deletion and patients who are unable to receive intravenous chemotherapy/immunotherapy.

Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for this Chronic Lymphocytic Leukemia

The clinician providing input noted the oral chlorambucil alone, intravenous bendamustine alone, bendamustine with rituximab, FCR combination chemo/immunotherapy, or obinutuzumab/chlorambucil are the currently available treatments.

5.2 Eligible Patient Population

The clinician providing input indicated that many patients with CLL are treated with initial watchful waiting when asymptomatic. However, CLL is a common malignancy and given our aging demographics, more incident cases are expected. Given the alternative treatments have significant limitations (toxicity of FCR, limited benefits of oral chlorambucil, lack of funding in Ontario for rituximab with bendamustine which can also be toxic), and given that the median age at diagnosis is 72 where age and comorbidities may limit options, The clinician providing input identified that there may be a high incident patient population for whom first line ibrutinib will be considered a desirable option.

5.3 Identify Key Benefits and Harms with Ibrutinib

The clinician providing input identified the following benefits: oral route of administration (older patients, poor venous access), longer progression free survival (likely to mean significantly longer time until another line of therapy required or indicated, a clinically meaningful outcome), lack of infusion reactions, much less cytopenias, less expected resource utilization (e.g. hospital admissions, frequent visits for blood transfusion support).

As ibrutinib is a newer drug, the clinician providing input indicated that clinicians do have concerns about rare but concerning toxicities of bleeding (rarely grade 3-4) and atrial fibrillation. The oral route will require enhanced patient education (re toxicity reporting), team education (nursing, pharmacist) and compliance monitoring. As the drug is continued long term until disease progression, clinicians are concerned about the overall cost impact though the cost/benefit long term (compared with less effective or durable therapies reapplied or having salvage lines downstream) remains to be defined.

5.4 Advantages of Ibrutinib Over Current Treatments

The clinician providing input felt that ibrutinib is an important option in first-line treatment, especially where patient's age or comorbidities may preclude safe or effective use of other existing chemotherapy based treatments, as noted above.

5.5 Sequencing and Priority of Treatments with Ibrutinib

The clinician providing input noted that ibrutinib in the first-line treatment would displace previous first-line therapies to second and third-line use. The clinician providing input also noted that early experience suggests that progression on ibrutinib may however be associated with a more aggressive clinical course and the utility of FCR, bendamustine, or chlorambucil based therapies in salvage are not well defined and felt that for aggressive progression, novel therapies targeting different (non B-cell receptor mediated) pathways may be preferable.

5.6 Companion Diagnostic Testing

The clinician providing input felt that the presence of 17p deletion (or related Tp53 mutations) severely limits the value of other therapies and ibrutinib clearly would be the drug of choice for the first-line treatment for those patients.

5.7 Additional Information

No additional information provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

The objective of this review is to evaluate the safety and efficacy of ibrutinib (Imbruvica) for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate.

Note: Supplemental Questions most relevant to the PCODR review and to the Provincial Advisory Group have not been identified as of yet while developing the review protocol.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 4. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of ibrutinib should be included.	Adult patients with previously untreated CLL/SLL for whom fludarabine-based treatment is considered inappropriate	Ibrutinib	All appropriate multi-agent chemotherapy regimens including but not limited to: Chlorambucil Obinutuzumab + chlorambucil Bendamustine	• OS • PFS • ORR • HRQoL • AEs • SAEs • WDAE Adverse events of special interest: • hospitalization • atrial fibrillation • bleeding • other malignancies • infections - pneumonia
[Abbreviations] OS= overall survival; PFS= progression-free survival; ORR= overall response rate; HRQoL= health-related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events				

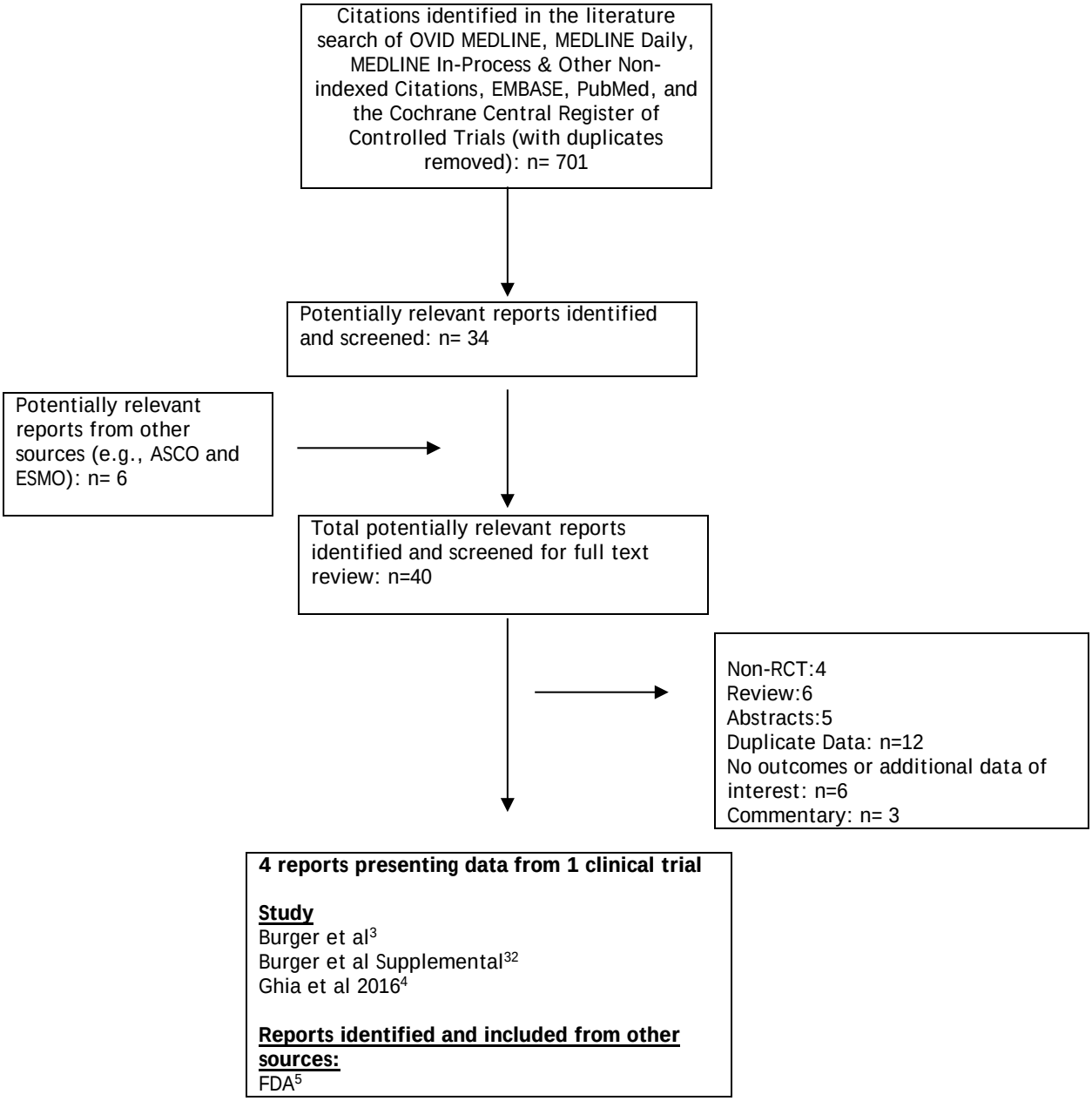
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 701 potentially relevant reports identified, 4 studies were included in the pCODR systematic review[3-5,32] and 697 studies were excluded. Studies were excluded because they were non-RCT, did not assess outcomes of interest, and had duplicate data.

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the RESONATE-2 study were also obtained through requests to the Submitter by pCODR[2]

6.3.2 Summary of Included Studies[3]

One clinical trial was identified that met the eligibility criteria of this review and was selected for inclusion (Please see Table 5). RESONATE™-2 was a randomized, multi-center, open-label phase 3 study to evaluate the safety and efficacy of ibrutinib versus chlorambucil in treatment naïve CLL patients who are ≥65 years of age. Please see table 5 below for further details.

Further information was also available from FDA reports, information that comes from the trial noted above but that is not found in the primary publication.

6.2.1.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Studies[33]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT01722487 RESONATE™-2 Other Study ID numbers: PCYC-1115, 2012-003967-23 Randomized, multicenter, open-label, phase 3 Enrollment: 269 Primary completion date: May 2015 (final data collection for primary outcome measure) Completion date: May 2015 Study Sponsor: Pharmacyclics Collaborators: Janssen Research & Development, LLC	**Key Inclusion Criteria:** • Adults (aged ≥65) • Diagnosis of CLL/SLL • Measurable nodal disease by computed tomography (CT) • ECOG performance status of 0-2 • Life expectancy > 4 months from randomization • Adequate hematologic, hepatic and renal function • Willingness to receive all outpatient treatment, all laboratory monitoring, and all radiological evaluations at the institution that administers study drug for the entire study • Ability to provide written informed consent and to understand and comply with the requirements of the study **Key Exclusion Criteria:** • Known involvement of the central nervous system by lymphoma or leukemia • History or current evidence of Richter's transformation or prolymphocytic leukemia • Documentation of deletion of the short arm of chromosome 17: del(17p13.1) in more than 20% of cells examined on any pre-treatment fluorescence in	**Intervention:** Ibrutinib as hard gelatin 420 mg (3 140 mg capsules) administered orally (PO) once daily First dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. **Comparator:** 0.5 mg/kg of body weight Chlorambucil for IV administration Chlorambucil is administered orally on Days 1 and 15 of each 28-day cycle.	**Primary:** PFS as assessed by IRC review **Secondary:** OS ORR Proportion of sustained hemoglobin improvement Proportion of sustained platelet improvement Safety AEs Event-free survival (EFS) - in response to EMA's recommendation, where PD, death and non-response at 3 months are defined as events. Patient reported outcomes

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	situ hybridization (FISH) or cytogenetic evaluation • Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura • Any previous treatment (chemotherapy, radiotherapy, and/or monoclonal antibodies) intended specifically to treat CLL/SLL • Received any immunotherapy, vaccine, or investigational drug within 4 weeks prior to randomization • Requirement for anticoagulation with warfarin • Requirement for treatment with a strong CYP3A4/5 and/or CYP2D6 inhibitor		
Abbreviations: OS= overall survival; AEs= adverse events; PO= per oso			

Table 6: Select quality characteristics of included studies of ibrutinib

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
RESONATE™-2	Ibrutinib vs. Chlomrabucil	PFS	81 PFS events (death/ disease progression) to have 85% power to detect HR of 0.50 at alpha of 0.025	Ibrutinib (n=136) Chlorambucil (n=133)	Randomly assigned in a 1:1 ratio	No	No	Yes	Yes	No	Yes

a) Trials[1,3,5,32]

RESONATE™-2 was a phase III randomized, multi-centre, open-label study to assess the safety and efficacy of ibrutinib versus chlorambucil in 269 patients with treatment naïve CLL or SLL who were 65 years of age or older.

Investigation sites for RESONATE™-2 were globally distributed across 16 countries including the United States, United Kingdom, Italy, Poland, Australia, Israel, New Zealand, Ukraine, Belgium, Spain, Canada, China, Czech Republic, Turkey, Ireland and Russia.

The primary endpoint of the study was to evaluate the efficacy of ibrutinib compared to chlorambucil based on the independent review committee (IRC) assessment of PFS according to 2008 IWCLL guidelines.

Secondary endpoints included ORR, defined as the proportion of patients who achieve CR, CRi, nPR, or PR as per IWCLL 2008 criteria over the course of the study as assessed by IRC, overall survival, FACiT-fatigue score, rate of hematological improvement, and safety events.[1]

The RESONATE-2 study protocol indicated that additional exploratory endpoints for patient reported outcomes were to be collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30) and EuroQoL Five-Dimension (EQ-5D-5L)instruments.

As pre-specified in the study protocol, the database was to be locked at the point when all enrolled patients have had the opportunity to complete at least 12 months of treatment and/or follow-up and either (a) 81 progression or death events have been observed or (b) 15 months have elapsed after the last patient is randomized - whichever occurs first. All safety and efficacy endpoints were to be analyzed using this locked database. No interim analyses were planned. As of the 28 May 2015 cut-off date, 15 months have elapsed after the last patient was randomized, for this reason the RESONATE-2 study is deemed complete and has been closed.

b) Populations[3,5,32]

Patient baseline characteristics in the RESONATE™-2 trial were mostly balanced between the two treatment groups, with the exception of a 10% difference between arms for the proportion of patients with bulky disease ≥5 cm (40% and 30% in the ibrutinib and chlorambucil groups, respectively). A larger proportion of patients enrolled were male in both arms (65% and 61%) and a small proportion of patients had SLL (10% and 5%) in the ibrutinib and chlorambucil groups, respectively. Median follow up was 18.4 months. At the time of the analysis 87% and 40% of patients were still on treatment in the ibrutinib and chlorambucil groups, respectively. Please see table 7 below for further details.

Table 7. Baseline Characteristics in the RESONATE-2 trial[3]

	Ibrutinib (n=136)	Chlorambucil (n=133)
Efficacy Analysis	136	133
Safety Analysis	135	132
Patient Characteristics		
Age, median in years **≥70 years**	**73 (65-89)** 96 (71)	**72 (65-90)** 93 (70)
Male, n (%)	88 (65)	81 (61)
ECOG PS, n (%)		
0	60 (44)	54 (41)

Table 7. Baseline Characteristics in the RESONATE-2 trial[3]		
	Ibrutinib (n=136)	Chlorambucil (n=133)
1	65 (48)	67 (50)
2	11 (8)	12 (9)
Rai stage III or IV, n (%)	60 (44)	62 (47)
Bulky disease ≥5 cm, n (%)	54 (40)	40 (30)
CIRS score >6, n (%)	42 (31)	44 (33)
Chromosome 11q22.3 deletion, n (%)	29 (21)	25 (19)
Cytopenia at baseline, n (%) Any cytopenia	72 (53)	73 (55)
Notes: CIRS= Cumulative Illness Rating Scale; ECOG PS= Eastern Cooperative Oncology Group Performance Status		

c) Interventions[3]

Patients in RESONATE™-2 were randomized 1:1 to receive either ibrutinib at a dose of 420 mg daily until disease progression or unacceptable toxicity, or chlorambucil at a starting dose of 0.5 mg/kg on days 1 and 15 of each 28 day cycle for a maximum of 12 cycles, disease progression, lack of efficacy (defined as a lack of complete or partial response as defined by the investigator) or the development of an unacceptable level of toxic effects. Dose increases were allowed up to 0.8 mg/kg based on tolerability. Following disease progression patients were entered into a separate extension study (PCYC-1116-CA) for follow up and second line treatment based on investigator's choice. Patients from the chlorambucil group could receive ibrutinib in the extension phase of the study.

d) Patient Disposition

A total of 269 patients were enrolled into RESONATE-2, all of whom provided informed consent. A total of 136 patients were randomized into the ibrutinib treatment arm and 133 patients were randomized into the chlorambucil comparator treatment arm.

Ibrutinib treatment arm[32]

Of the total 136 patients randomized, 1 patient did not receive study drug and withdrew consent. A total of 135 patients received oral ibrutinib at a dose of 420 mg daily until disease progression or unacceptable toxicity. Of these 135, 17 patients discontinued treatment due to 2 patients with IRC confirmed progressive disease, 14 patients who had unacceptable toxicity/adverse events/death, and 1 patient who withdrew treatment. An additional 4 patients withdrew from the study due to 3 experiencing death and 1 patient who withdrew consent. A total of 118 patients were continuing treatment at time of study closure, and 13 patients were on post-treatment follow up leading to 131 patients who were on study follow-up at the time of study closure.

Chlorambucil comparator arm[32]

Of the total 133 patients randomized, 1 patient did not receive study drug and withdrew consent. A total of 132 patients received oral chlorambucil at a dose of 0.5 mg/kg, with a maximum dose of 0/8 mg/kg, on days 1 and 15 every 28 days up to 12 cycles. Of these 132, 79 patients discontinued treatment due to 6 patients with IRC confirmed progressive disease, 30 patients who experienced unacceptable toxicity/adverse events/death, 6 patients who withdrew from treatment, 37 patients who withdrew due to an investigator decision involving new anticancer therapy (n=4), progressive disease (n=11), lack of efficacy (n=21) and other reasons (n=1). An additional 18 patients withdrew from study due to 12 experiencing death and 6 patients who withdrew consent. A total of 53 patients completed the maximum planned therapy of 12 cycles. There were 114 patients on study follow up at the time of study closure.

At the closure of the RESONATE-2 study, remaining patients in both treatment arms were transferred to an extension study for long-term follow-up and ibrutinib treatment, as appropriate.

e) Limitations/Sources of Bias

Trial Design

- The submitter noted that neither the study subjects nor the investigators were blinded to treatment. Due to the nature of the intervention used (oral administration versus IV), blinding of treatment arms was not possible. However, bias due to the open-label study design was minimized as data were analyzed by blinded assessors.

- The comparator chlorambucil used in the trial is not representative of clinical practice. Based on PAG input, chlorambucil is rarely used given the availability of effective treatment options. PAG noted that obinutuzumab + chlorambucil or bendamustine monotherapy are relevant comparators in this setting. Therefore, it is unclear what the magnitude and direction of benefit is with the use of ibrutinib as compared to currently available treatment options.

Patient Characteristics

- Baseline patient characteristics were somewhat balanced. However some differences were noted in the proportion of patients with bulky disease ≥5 cm (10% difference between arms) and proportion of male patients between arms (4% difference between arms). It is not clear what impact this imbalance may have had on the magnitude and direction of results.

- The proportion of patients with a cumulative illness rating scale (CIRS) of >6 were 31% and 33% in the ibrutinib and chlorambucil arms, respectively
  - Based on background clinical information from the Clinical Guidance Panel (CGP), the CIRS score is commonly used to identify patients who may not derive benefit from fludarabine and fludarabine-containing regimens due to higher rates of toxicity.
  - As the majority of patients in the trial did not have a CIRS score of > 6, it is unclear how representative the patient population within the RESONATE-2 trial is to patients in the clinical setting.

Results

- Given that the study was not powered to detect statistical differences in the PRO measures, results for the FACiT-fatigue score, EORTC QLQ-C30 and EQ-5D-5L need to be interpreted with caution.

6.2.1.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Table 8. Efficacy Outcomes for RESONATE-2		
Outcomes	**Ibrutinib (n=136)**	**Chlorambucil (n=133)**
Median follow up, months	**18.4**	
On treatment at analysis, n (%)	**87%**	**40%**
Median OS, months	NR	NR
OS rate at 24 months	98%	85%
HR	0.16 (95% CI 0.05-0.56, p=0.001)	
Median PFS, months	NE	18.9
PFS at 18-months	90%	52%
PFS (Hazard Ratio)	0.16 (95% CI 0.09-.028, p<0.001)	
RR	86%	35%
RR (Odds Ratio)	2.42 (95% CI 1.91-3.07, p<0.001)	
Notes: OS = overall survival; PFS = progression-free survival; RR = response rate; ECOG PS= Eastern Cooperative Oncology Group Performance Status		

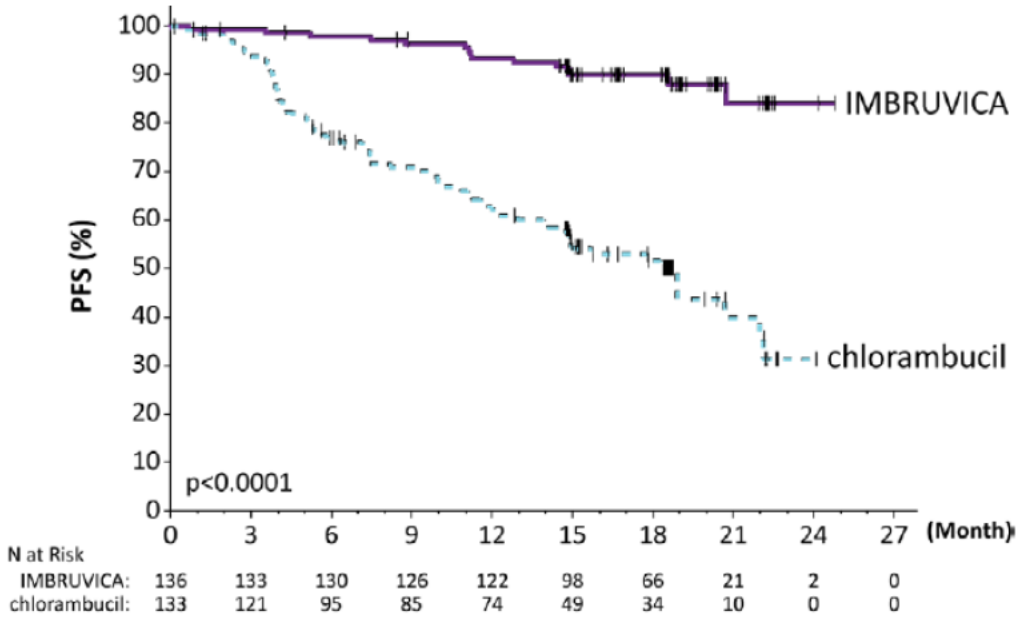
Primary Outcome

Progression-free survival (PFS)[3,5]

In the RESONATE-2 trial, during a median follow-up period of 18.4 months, treatment with ibrutinib resulted in significantly longer PFS compared to chlorambucil (median not reached vs. 18.9 months), as assessed by the independent review committee, with a relative risk of progression or death that was 84% lower than that with chlorambucil (HR: 0.16, 95% CI: 0.09 to 0.28; p<0.001).

The rate of PFS at 18 months was 90% in the ibrutinib treatment arm versus 52% in the chlorambucil comparator arm.

Figure 1. Kaplan-Meier Curve of Progression-Free Survival (ITT Population) in the RESONATE-2 trial[5]



Secondary Outcomes

Overall Survival (OS)

Although median OS was not reached in either treatment group, ibrutinib significantly prolonged OS in favour of the ibrutinib group. The overall survival rate at 24 months was 98% with ibrutinib versus 85% with chlorambucil, with a relative risk of death with ibrutinib that was 84% lower than that with chlorambucil (HR: 0.16, 95% CI: 0.05 to 056; p=0.001). Please see Table 9 below for further details. The OS results presented have not been adjusted for crossover. As of the May 28, 2015 cut-off date, 15 months had elapsed after the last patient was randomized, for this reason the RESONATE-2 study was deemed complete and was closed. At the study closure (May 28, 2015), 25% of patients in the chlorambucil group had crossed into the ibrutinib group.

Upon closure of RESONATE-2, the remaining study patients were transferred to a non-randomized observational study PCYC-1116 for follow-up and ibrutinib treatment, as appropriate. An interim analysis was provided for OS for study PCYC-1116. At 28.1 months, the OS rate for the ibrutinib and chlorambucil treatment arms were 94.7% (95% CI: 89.1 to 97.4), and 84.3% (95% CI: 76.7 to 89.6), respectively. The hazard ratio for the collective data set was 0.44 (95% CI: 0.21 to 0.92). At this time, 41% of patients had crossed over into the ibrutinib group.[2] At study closure, 25% of patients from the chlorambucil group had crossed over into the ibrutinib group.[67]

Hematologic Variables

Sustained hematologic improvement was defined as an increase in hematologic variables that was sustained continuously for at least 56 days without transfusion or growth factors, as measured by an increase in platelet count or absolute neutrophil count from baseline of at least 50%, or for hemoglobin, an increase from baseline of ≥2 g per deciliter; or for patients with baseline cytopenia, an increase to a hemoglobin level of more than 11 g per deciliter, a platelet count of more than 100,000 per cubic millimeter, or an absolute neutrophil count of more than 1500 per cubic millimeter.

The rates of sustained improvement in hematologic variables were significantly higher with ibrutinib than with chlorambucil. For patients with anemia at baseline, a higher proportion of patients in the ibrutinib treatment arm had sustained improvement in the hemoglobin level (84% versus 45% with chlorambucil, p<0.001). Also, for patients with thrombocytopenia at baseline, a higher proportion of patients in the ibrutinib treatment arm had sustained improvement in the platelet count (77% versus 43%, p=0.005).

Adverse Events and Safety

Deaths

Fatal treatment emergent adverse events were reported in 3 and 4 patients in the ibrutinib and chlorambucil groups, respectively.[2] Reasons for death in the ibrutinib arm included 1 klebsiella infection, and 2 general disorders and administration site conditions classified as death. In the chlorambucil arm, reasons for death included 1 stroke, 1 hepatitis toxic, 1 acute hepatitis B and 1 death due to CLL.[34] More patients in the chlorambucil group discontinued treatment due to an adverse event (9% and 23%) or had a dose reduction due to an adverse event (9.6% and 18.9%).

Any grade 3 or higher drug related adverse event (84.4 and 76.5%) and treatment emergent serious adverse event (33.3% and 20.5%) occurred more frequently in the ibrutinib group.[34] The most common grade 3 or higher AE was neutropenia (10% and 18% in the ibrutinib and chlorambucil

groups, respectively). Additionally, anemia occurred in 6% and 8% of patients in the ibrutinib and chlorambucil groups, respectively. Thrombocytopenia (2% and 6%) and fatigue (1% and 5%) occurred more in the chlorambucil group.[3] See table 8 for details.

Serious adverse events occurring in more than 2% of patients occurred more in the ibrutinib arm for pneumonia (4% and 2%), basal-cell carcinoma (4% and 0) and hyponatremia (2% and 0). Pyrexia as a serious adverse event occurred more in the chlorambucil group (1% and 4%).[3]

Table 9. Fatal treatment emergent adverse events[2]		
	Ibrutinib N=136	**Chlorambucil** N=133
Fatal treatment emergent adverse events, n (%)	3 (2.2%)	4 (3.0%)

Dose modifications and discontinuation

Table 10. Dose reduction and discontinuations[2,3]		
	Ibrutinib N=136	**Chlorambucil** N=133
Dose reductions due to adverse events, n (%)	13 (9.6)	25 (18.9)
Discontinued treatment due to Death, n (%)	2 (1.5)	0
Discontinued treatment due to Adverse Events/ Unacceptable toxicity, n (%)*	12 (9%)	30 (23%)

The most common adverse reactions occurring more frequently in the ibrutinib group were diarrhea (42% and 17%), cough (22% and 15%), peripheral edema (19% and 9%), dry eye (17% and 5%) and arthralgia (16% and 7%). The most common adverse reactions occurring more frequently in the chlorambucil group included fatigue (30% and 38%), nausea (22% and 39%), neutropenia (16% and 23%) and vomiting (13% and 20%).[3]

Adverse events of interest:

Atrial Fibrillation

Atrial fibrillation occurred in 8 patients in the ibrutinib arm (6 within the first 6 months) and in 1 patient in the chlorambucil group. In the ibrutinib group, atrial fibrillation events were mostly grade 1-2 in nature with 2 grade 3 events occurring. Atrial fibrillation was managed by discontinuation of drug in 2 patients and without dose modification in the remaining 6. No grade 3 or 4 atrial fibrillation occurred in the chlorambucil group. [2,3]

Major hemorrhage

Major Hemorrhage was observed in 6 vs. 2 patients in the ibrutinib and chlorambucil arms, respectively. In the ibrutinib arm, 2 major bleeding events occurred within first 6 months, 3 during months 6-12, and 1 during months 12-18. In the chlorambucil arm 1 major hemorrhage occurred each in first 6 months and 6-12 months.

Infections

Exposure-adjusted infection rate were also reported with 7.5 versus 10.1 per 100 patient-month in the ibrutinib and chlorambucil arms, respectively. Grade ≥3 infections decreased with time for ibrutinib.[4]

Pneumonia occurred in 11 (8.1%) and 5 (3.8%) of all patients in the ibrutinib and chlorambucil groups, respectively. Among patients experiencing all grades AE's of 10% or greater, infections and infestations occurred more frequently in the ibrutinib arm with all grades pneumonia occurring in 14% vs. 7% and grade 3/4 pneumonia occurring in 8% vs. 4% of patients in the ibrutinib vs chlorambucil arms, respectively.

Table 11. Serious Adverse Events related to Infections and infestations[33]

	Ibrutinib, n=135	Chlorambucil, n=132
Upper respiratory tract infection	1 (0.74%)	0 (0.00%)
Urinary tract infection	2 (1.48%)	0 (0.00%)
Cellulitis	1 (0.74%)	0 (0.00%)
Pneumonia	5 (3.70%)	2 (1.52%
Lower respiratory tract infection	2 (1.48%)	1 (0.76%)
Bronchopneumonia	2 (1.48%)	0 (0.00%)
Gastroenteritis viral	1 (0.74%)	0 (0.00%)
Escherichia sepsis	2 (1.48%)	0 (0.00%)
Klebsiella infection	1 (0.74%)	0 (0.00%)
Lobar pneumonia	1 (0.74%)	0 (0.00%)
Neutropenic sepsis	1 (0.74%)	1 (0.76%)
Pneumonia bacterial	1 (0.74%)	1 (0.76%)
Anal abscess	1 (0.74%)	0 (0.00%)
Arthritis bacterial	1 (0.74%)	0 (0.00%)
Clostridium difficile	1 (0.74%)	0 (0.00%)
Escherichia bacteremia	1 (0.74%)	0 (0.00%)
Escherichia infection	1 (0.74%)	0 (0.00%)
Gastrointestinal infection	1 (0.74%)	1 (0.76%)
Lung infection pseudomonal	1 (0.74%)	0 (0.00%)
Pneumonia legionella	1 (0.74%)	0 (0.00%)
Pneumonia viral	1 (0.74%)	0 (0.00%)
Viral infection	1 (0.74%)	0 (0.00%)
Pneumonia fungal	0 (0.00%)	1 (0.76%)

Hypertension

Some hypertension events were considered to be a treatment related adverse events as per investigator decision in RESONATE-2. Of the 19 (14%) ibrutinib patients who experienced a hypertension event (any grade), 5 were considered by the investigator as possibly related to ibrutinib. There were nine of 19 patients who had a medical history of hypertension prior to ibrutinib therapy. Events of hypertension appeared manageable, with none of the events leading to study drug discontinuation or dose reductions.[2]

Dose reductions due to adverse reactions occurred in approximately 6% of patients.[5] AEs leading to discontinuation of treatment were infrequent in the ibrutinib arm with most occurring during first 6 months. The majority of patients (87%) of continued ibrutinib treatment after a median follow up of 1.5 years.[4]

Hospitalizations[2]

Within the intent-to-treat (ITT) population, the mean number of hospitalizations and days of hospitalizations are similar between treatment arms. The ITT analysis has not been adjusted for the median duration of treatment exposure, which was 17.4 in the ibrutinib arm and 7.1 months in the chlorambucil arm.

Table 12. Number and days of hospitalizations[2]		
	Ibrutinib (N=136)	Chlorambucil (N=133)
Number of hospitalizations, n Mean (SD)	51 2.0 (1.27)	36 1.6 (0.84)
Days of hospitalizations, n Mean (SD)	51 17.2 (16.74)	36 14.0 (12.10)
Notes: 'n' = number of patients who had at least one hospitalization event; Mean number of hospitalizations = mean number of hospitalizations per person among patients who had a hospitalization event; Mean days of hospitalizations= mean number of days of hospitalizations per person among patients who had a hospitalization event		

Table 13. Adverse events of grade 3 or higher occurring in at least 2% of patients in either treatment arm in the RESONATE-2 trial[3]		
Median duration of treatment (range) - months	**17.4 (0.7-24.7)**	**7.1 (0.5-11.7)**
	Ibrutinib (n=135)	**Chlorambucil (n=132)**
Grade 3 or Higher Adverse event		
Neutropenia	14 (10)	24 (18)
Anemia	8 (6)	11 (8)
Hypertension	6 (4)	0
Pneumonia	5 (4)	2 (2)
Diarrhea	5 (4)	0
Maculopapular rash	4 (3)	2 (2)
Decreased platelet count	4 (3)	1 (1)
Abdominal pain	4 (3)	1 (1)
Hyponatremia	4 (3)	0
Thrombocytopenia	3 (2)	8 (6)
Febrile neutropenia	3 (2)	3 (2)
Upper respiratory tract infection	3 (2)	2 (2)
Pleural effusion	3 (2)	1 (1)
Cellulitis	3 (2)	0
Fatigue	1 (1)	7 (5)
Syncope	1 (1)	3 (2)
Hemolytic anemia	0	3 (2)

Patient Reported Outcomes[4]

The RESONATE-2 study protocol indicated that patient reported outcomes were to be collected using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires Core 30 (EORTC QLQ-C30), EuroQoL Five-Dimension (EQ-5D-5L), and FACiT-Fatigue instruments. The study was not powered to detect statistical differences in these PRO measures.

The FACiT-F measurement was a secondary endpoint in the RESONATE-2 trial. The questionnaire is a measure of fatigue-related quality of life in patients with Cancer and other chronic diseases. The 13-item FACiT-Fatigue Scale measures each item on a 5-point Likert scale. The FACiT-Fatigue Scale has been validated in the general population, as well as in patients with cancer or rheumatoid arthritis.[1]

The EORTC QLQ-C30 and EQ-5D-5L instruments were exploratory secondary endpoints. The EORTC QLQ-C30 has been widely used among cancer patients and includes 30 separate questions resulting

in 5 functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

The EQ-5D-5L is a standardized instrument used to measure of health outcome and consists of a 5-item questionnaire and a "thermometer" visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 dimensions are used to compute a single utility score ranging from 0 to 1, representing the general health status of the individual. The 5 dimensions evaluated are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

EORTC-QLQ-C30 Methodology[2]

Changes in EORTC QLQ C30 scores from baseline to each assessment for all scales were a pre-specified exploratory endpoint in RESONATE™-2, as evaluated in the (intent-to-treat) ITT population. This questionnaire was collected on day 1 of each cycle from cycle 1-12, every odd cycle thereafter (Cycles 13, 15, 17, 19, 21, 23, 25), then every 6 cycles (beginning Cycle 30) until progression or study closure.

A minimally important difference (MID) (or clinically meaningful improvement/worsening) was pre-defined as ≥10 points in either direction for all scales.

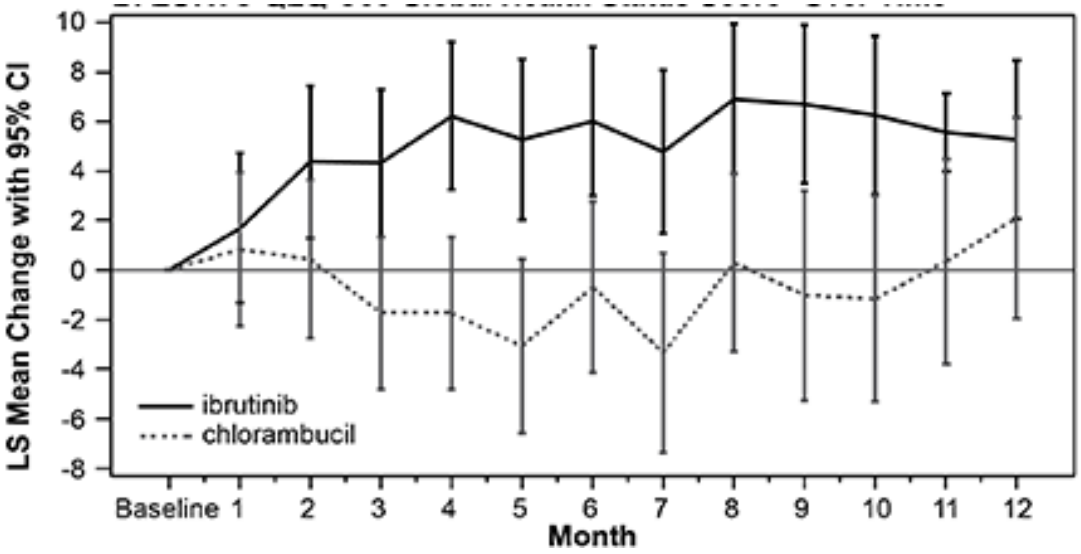
EORTC-QLQ-C30 Global Health Status Score results[2]

There were greater improvements in QOL which occurred with ibrutinib vs. chlorambucil in EORTC QLQ-C30 global health status scores by time-dependent mixed-models repeated measures analysis (P=0.0002). Higher rates of clinically meaningful improvement from baseline were also observed with ibrutinib vs. chlorambucil in EORTC QLQ-C30 global health status score (60% vs. 48%; P=0.045).

The median time to minimally important improvement was 1.92 months in the ibrutinib arm and 1.91 months in the chlorambucil arm. The median time to minimally important worsening of EORTC Global Health Status Score (deterioration of quality of life) was 2.79 months in the ibrutinib arm and 2.76 months in the chlorambucil arm.

Among patients with worse symptoms at baseline (patients with baseline score <67), a higher proportions of patients experienced clinically meaningful improvements in EORTC QLQ-C30 global health status score with ibrutinib (83% with ibrutinib vs. 73% with chlorambucil; P=0.121).

Figure 1. Change in EORTC QLQ-C30 Global Health Status Score* Over Time[4]



*Least mean square change from baseline

Other EORTC-QLQ-C30 subscales[2]

Improvements in EORTC QLQ-C30 physical, role, and social function scores were seen with ibrutinib regardless of the number of comorbidities at baseline. Reductions of ≥50% in lymph node SPD (sum of the product of perpendicular diameters of lymph node) was correlated with improvement in EORTC QLQ-C30 scores with ibrutinib.

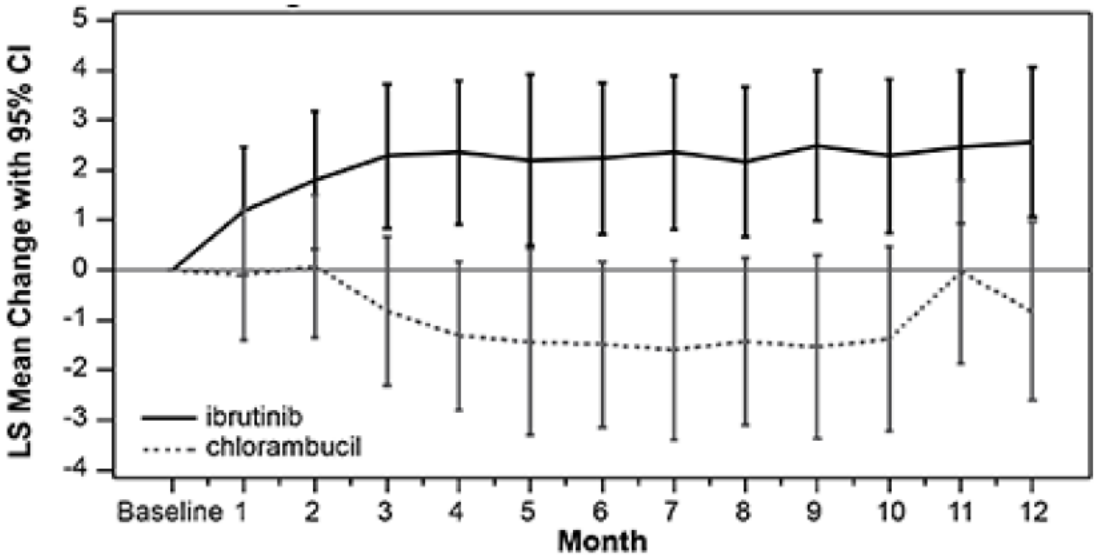
FACIT-fatigue Methodology[2]

Change from baseline FACIT-Fatigue score was a pre-specified secondary endpoint in the RESONATE-2 trial, as evaluated in the ITT population. This questionnaire was collected at screening, randomization, as well as through progressive disease and safety follow-up. A minimally important difference (MID) was pre-defined as ≥3 points in either direction for all scales.

Results

There were greater improvements in FACIT-Fatigue scale with ibrutinib vs. chlorambucil (P=0.0004) by time-dependent mixed-models repeated measures analysis. Higher rates of clinically meaningful improvement from baseline were observed with ibrutinib vs. chlorambucil in FACIT-Fatigue (62% vs. 53%; P=0.164). The median time to improvement was 3.98 months in the ibrutinib arm and 4.67 months in the chlorambucil arm (source: pg. 247 of CSR). No information on time to worsening (deterioration of quality of life) is available.

Figure 2. Change in FACIT-Fatigue Score* Over Time[4]



*Least mean square change from baseline

Among patients with worse symptoms at baseline (patients with baseline score <40), a higher proportions of patients experienced clinically meaningful improvements with ibrutinib (86% with ibrutinib vs. 77% with chlorambucil; P=0.230). An improvement in hemoglobin levels was associated with meaningful improvement in fatigue, as measured by FACIT-Fatigue score.

Both patients with and without anemia at baseline had clinically meaningful improvements in FACIT-Fatigue score, with patients having baseline anemia showing slightly higher proportion of meaningful improvement.

Questionnaire Completion

Questionnaire completion data for each cycle are available for EORTC-QLQ-C30 global health status score and EQ-5D-5L only. Completion rate for FACIT-Fatigue is available only for patients with baseline and any post baseline measurements. Table 14 below presents completion rates calculated using ITT population data unadjusted for drop-out.

Please see table 14 below for further details.

Table 14. Questionnaire completion for FACIT-Fatigue, EORTC QLQ-C30 and EQ-5D-5L[2]

	Ibrutinib, N=136	Chlorambucil, N=133
FACIT-Fatigue, patients with baseline and any post baseline measurements	94.9%	94.0%
EORTC-QLQ-C30 completion @ cycle :		
• Cycle 3	90.4%	84.2%
• Cycle 6	88.2%	73.7%
• Cycle 9	86.8%	56.4%
• Cycle 12	84.6%	42.9%
EQ-5D-5L completion @ cycle :		
• Cycle 3	89.7%	84.2%
• Cycle 6	89.7%	72.9%
• Cycle 9	86.8%	56.4%
• Cycle 12	85.3%	42.1%

6.3 Ongoing Trials

Table 15: Ongoing trials of ibrutinib for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NCT02315768[35] Other Study ID numbers: 141106 Open-label phase 1b/II Estimated enrollment: 32 Study Start date: November 2015 Estimated Primary Completion date: November 2017 Estimated Completion date: November 2018 Study Sponsor: University of California, San Diego Collaborators: Pharmacyclics	Key Inclusion Criteria: Diagnosis of CLL Indication for treatment as defined by the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) Guidelines No previous treatment for CLL Males and females 65 years of age and older Key Exclusion Criteria: Pregnant or nursing women Treatment with chemotherapy, monoclonal antibodies, or biological agents (e.g. lenalidomide) other than the investigational agents during the time of participation in the trial	Intervention: Ibrutinib Obinituzumab	Primary: Safety and tolerability Type, incidence and severity of AEs Secondary: PFS Treatment-free survival (TFS) OS
NCT01886872[36] Other study ID numbers: NCI-2013-01220, , ALLIANCE A041202, A041202, Phase III Randomized open-label Estimated enrollment: 523 Start Date: December 2013	Key Inclusion Criteria: Diagnosis of CLL Patients must be intermediate or high-risk Rai stage CLL Eastern Cooperative Oncology Group (ECOG) performance status 0-2 Key Exclusion Criteria: Patients who have had a myocardial infarction, intracranial bleed, or stroke within the past 6 months	Intervention: Ibrutinib Rituximab Comparator: Arm I (rituximab, bendamustine hydrochloride)	Primary: PFS Secondary: OS DOR Time to progression

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Estimated Primary Completion date: March 2018 Study Sponsor: National Cancer Institute (NCI) Collaborators: Not provided			
Abbreviations: OS= overall survival; PFS = progression free survival; HRQoL= health-related quality of life; AEs= adverse events			

7 SUPPLEMENTAL QUESTIONS

No supplemental question relevant to the review was identified.

7 COMPARISON WITH OTHER LITERATURE

Two separate studies[6,7] were identified by the Clinical Guidance Panel as relevant to the pCODR review of ibrutinib (Imbruvica) for adult patients with previously untreated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate. Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

Farooukі et al 2015[6]

The Farooukі study was an investigator-initiated phase II, single-arm trial of ibrutinib monotherapy prospectively conducted to address the safety and efficacy of ibrutinib in previously untreated and relapsed or refractory CLL with TP53 aberrations. The primary endpoint was overall response to treatment after six cycles of therapy at 24 weeks. Secondary endpoints included safety, overall survival, progression-free survival, best response and nodal response.

Between Dec 22 2011 and Jan 2014, 51 eligible patients were enrolled with CLL. Of these 35/51 patients had previously untreated CLL. Most patients had advanced Rai stage and IGHV-unmutated disease. There were 47/51 (92%) patients enrolled who had 17p13.1 deletion. At the time of analysis, the median follow-up for the previously untreated cohort was 15 months and for the relapsed or refractory cohort was 26 months.

Results:

Patient disposition: Median follow up for the previously untreated patient population was 15 months. Among all enrolled patients, 42/51 were still on treatment. Nine of 51 discontinued treatment due to disease progression (n=5, 10%) or death (n=3, 6%). One patient was found to have Hodgkin's lymphoma and was taken off the study and only included in the safety analysis. Progressive disease was caused by Richter's transformation in 3 patients.

Response: 32/33 (97%; 95% CI 86-100) previously untreated patients achieved an objective response, including a partial response in 18 patients (55%) and partial response with lymphocytosis in 14 (42%).

Overall Survival and PFS: The estimated overall survival in patients was 84% (95% CI 72-100) at 24 months. The estimated cumulative incidence of progression was 9% (1-27) in patients. In order to assess whether 17p13.1 deletion confers resistance to ibrutinib, the proportion of CLL cells carrying the 17p13.1 deletion were assessed at baseline and after 24 weeks on treatment. In 43 evaluable patients, the proportion of CLL cells with 17p13.1 deletion decreased in 20 (47%) patients, increased in 20 (47%) patients, and remained unchanged in three (6%) patients. In 20 patients who had a relative increase in the frequency of deletion 17p13.1, none progressed, 18 (90%) had a clinical response at 24 weeks, and two (10%) patients had stable disease.

Toxicities: Grade 3 treatment-related adverse events in this trial were neutropenia in 11 (24%), anaemia in 7 (14%), thrombocytopenia in 4 (10%), lung infection in 3(6%) and rash in 1 (2%). Grade 4 adverse events occurred for neutropenia and thrombocytopenia in 1 (2%) patient each.

Select Baseline Characteristics	Farooukі et al 2015[6] Previously untreated N=35	O'Brien et al 2014[7] N=31
Median Age, years	62 (33-82)	71 (65-84)
Sex		
Male, n (%)	23 (66%)	19 (61%)
Female, n (%)	12(34%)	12 (39%)
Rai Stage III/IV, n (%)	22 (63%)	17 (55%)
Deletion 17p13.1, n (%)	47 (92%)	2 (6%)

O'Brien et al 2014[7]

The second study was a phase 1b-2 multicenter study to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of ibrutinib in patients with relapsed or refractory CLL or small lymphocytic lymphoma. Patients included in the trial had symptomatic previously untreated CLL (94%) or SLL (6%), a median age of 71 (65-84) and ECOG PS of 0 (74%) or 1 (26%). Among n=31 patients enrolled, only 2 (6%) had the 17p13.1 deletion.

Patients received 28 day cycles of once-daily ibrutinib 420 mg (three 140 mg capsules) or once-daily ibrutinib 840 mg (six 140 mg capsules). The 840 mg per day cohort was closed before full accrual after comparable activity of the doses was shown elsewhere in relapsed or refractory patients with chronic lymphocytic leukaemia. Ibrutinib was to be given continuously, until disease progression or toxic effects led to discontinuation.

The primary endpoint was safety of the fixed-dose regimen assessed by the frequency and severity of adverse events after which point the study would be terminated. Patients were followed up for at least 12 cycles in the study, and then could continue ibrutinib treatment in a long-term extension study. Adverse events are reported from the first dose up to 30 days of the last dose of ibrutinib and not in the long term extension phase. Secondary endpoints included overall response (OR), progression free survival (PFS) and overall survival (OS).

Results:

Patient disposition: Two patients discontinued treatment due to adverse events (AE's), (one each of grade 3 fatigue and grade 2 viral infection) and 2 patients withdrew from the study to start a new treatment. Nine (29%) patients required treatment to be held due to grade 3 or higher toxicity. One patient with a 17p13.1 deletion, progressed and subsequently died due to progression. This patient had achieved an initial response but discontinued due to the development of Richter's transformation. The remaining patients (84%, 26/31) continued ibrutinib treatment in the long term extension phase of the study.

Safety: the most frequent grade 3 AE, occurring in 13% of patients was diarrhea. Other grade 3 AE's that occurred in patients include hypertension (6%) and 1 (3%) each of fatigue, dizziness, urinary tract infection, headaches, back pain, muscle spasms. Grade 4 thrombocytopenia occurred in 1 patient (3%).

OR: 71% (22/31) of patients achieved objective response (95%CI 52-85.8) with 4 (13%) achieving complete response, 4 (13%) partial response and 3 (10%) having stable disease.

PFS and OS: At 24 months, the Kaplan-Meir estimate for PFS was 96.3% (95%CI 76.5-99.5) and overall survival was 96.6% (77.9-99.5). Median PFS was not reached with only 1 patient progressing.

3-year follow-up[8]

Safety: the most frequent grade 3 AE, occurring in 7 (23%) patients was hypertension. Other grade 3 AE's that occurred in patients include diarrhea in 5 (16%) patients, pneumonia and atrial fibrillation occurring in 2 (6%) patients each, and neutropenia, thrombocytopenia, fatigue, hyperglycemia, hypokalemia, decreased lymphocyte count and syncope occurring in 1 (3%) patient each.

OR: 84% (26/31) of patients achieved objective response (95%CI 52-85.8) with 7 (23%) achieving complete response, 17 (56%) partial response and 3 (10%) having stable disease.

PFS and OS: With a median time on-study of 35.2 months, median PFS was not reached. The estimated PFS rate was 96% (95% CI, 76.5-99.5%) at 30 months. The only patient with progression at 8 months had a n= as previously described. Median OS was not reached at 3 years. The estimated OS rate was 97% (95%CI 78-99.5).

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia 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 Chronic Lymphocytic Leukemia. 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 CADTH website (www.cadth.ca/pcodr).

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 Leukemia Clinical Guidance Panel is comprised of three medical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). 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

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2016, **Embase** 1974 to 2016 May 2, **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Imbruvica* or ibrutinib* or CRA032765 or "CRA 032765" or "JNJ 02" or JNJ02 or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX or 936563-96-1).ti,ab,ot,kf,kw,hw,rn,nm.	2490
2	exp Leukemia, Lymphocytic, Chronic, B-Cell/ or (small-cell lymphoma* or lymphocytic lymphoma* or ((chronic or small or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or leukemia* or leukaemia*))).ti,ab,kf,kw.	131953
3	1 and 2	1315
4	3 use ppez,cctr	329
5	*ibrutinib/ or (Imbruvica* or ibrutinib* or CRA032765 or "CRA 032765" or "JNJ 02" or JNJ02 or PC32765 or PC 32765 or PCI32765 or PCI 32765 or 1X70OSD4VX).ti,ab,kw.	1835
6	exp Chronic Lymphatic Leukemia/ or (small-cell lymphoma* or lymphocytic lymphoma* or ((chronic or small or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or leukemia* or leukaemia*))).ti,ab,kw.	129402
7	5 and 6	953
8	7 use oemezd	668
9	4 or 8	997
10	limit 9 to English language	964

11	remove duplicates from 10	702

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#4	Search **#3 AND publisher[sb]**	20
#3	Search **#1 AND #2**	289
#2	Search **Exp Leukemia, Lymphocytic, Chronic, B-Cell[mh] OR small-cell lymphoma*[tiab] OR lymphocytic lymphoma*[tiab] OR ((chronic[tiab] OR small[tiab] OR well-differentiated[tiab]) AND (lymphocytic[tiab] OR lymphoplasmacytoid[tiab] OR lymphatic[tiab] OR lymphocyte*[tiab] OR lymphoid*[tiab] OR leukemia*[tiab] OR leukaemia*[tiab]))**	107113
#1	Search **PCI 32765 [Supplementary Concept] OR Imbruvica*[tiab] OR ibrutinib*[tiab] OR CRA032765[tiab] OR CRA 032765[tiab] OR JNJ 02[tiab] OR PC32765[tiab] OR PC 32765[tiab] OR PCI32765[tiab] OR PCI 32765[tiab] OR 936563-96-1[rn]**	600

3. **Cochrane Central Register of Controlled Trials (Central)**

   Searched via Ovid

4. **Grey Literature search via:**

   Clinical trial registries:

   U.S. NIH ClinicalTrials.gov
   http://www.clinicaltrials.gov/

   Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
   http://www.canadiancancertrials.ca/

   Search: Imbruvica/ibrutinib, chronic lymphocytic leukemia, small lymphocytic lymphoma

   Select international agencies including:

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

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

Search: Imbruvica/ibrutinib, chronic lymphocytic leukemia, small lymphocytic lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: Imbruvica/ibrutinib, chronic lymphocytic leukemia, small lymphocytic lymphoma

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

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-present) with in-process records & daily updates via Ovid; Embase (1974-May 2) via Ovid; The Cochrane Central Register of Controlled Trials (March 2016) via Ovid; 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 Imbruvica, ibrutinib, chronic lymphocytic leukemia and small lymphocytic lymphoma.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of August 4, 2016.

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 – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually, for conference years not available in Embase. 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 additional information as required by the pCODR Review Team.

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.

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. The SIGN-50 Checklist used in this review is included in Table X below.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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