PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia

August 18, 2015

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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: requests@cadth.ca
Website: www.cadth.ca/pcodr

TABLE OF CONTENTS

DISCLAIMER AND FUNDING ii

INQUIRIES iii

TABLE OF CONTENTS iv

1 GUIDANCE IN BRIEF 1

1.1. Background 1
1.2. Key Results and Interpretation 1
1.3. Conclusions 3

2 CLINICAL GUIDANCE 4

2.1 Context for the Clinical Guidance 4
2.2 Interpretation and Guidance 9
2.3 Conclusions 11

3 BACKGROUND CLINICAL INFORMATION 12

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT 15

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT 33

6 SYSTEMATIC REVIEW 37

6.1 Objectives 37
6.2 Methods 37
6.3 Results 39
6.4 Ongoing Trials 52

7 SUPPLEMENTAL QUESTIONS 59

8 ABOUT THIS DOCUMENT 60

APPENDIX A: LITERATURE SEARCH STRATEGY 61

REFERENCES 63

1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of idelalisib (Zydelig) in combination with rituximab, as compared to an appropriate comparator for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Idelalisib is an oral, isoform-selective, small-molecular inhibitor of phosphatidylinositol 3-kinase p110δ (PI3Kδ). Idelalisib has a Health Canada indication which is the same as the indication under pCODR review as well as Health Canada indication with conditions for the treatment of patients with follicular lymphoma. Idelalisib is an oral tablet available as 100 and 150 mg; it has Health Canada approval without conditions for 150 mg twice daily in combination with rituximab (8 cycles of rituximab, first cycle at 375 mg/m^2, subsequent cycles at 500 mg/m^2).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one randomized, double-blind phase III study (GS US 312-0116) examining the use of idelalisib in combination with rituximab compared to rituximab in 220 patients with relapsed chronic lymphocytic leukemia (CLL). Patients had experienced CLL progression less than 24 months since the completion of the last prior therapy and were not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities. The median age of patients was 71 years. The median Cumulative Illness Rating Scale (CIRS) score was 8 and the median number of previous CLL drugs was 3.

Efficacy

Progression-free survival (PFS) was the primary outcome in the GS US 312-0116 study, this outcome was independently assessed by an Independent Review Committee. Secondary outcomes included overall response rate, lymph node response rate, complete response rate, and overall survival.

After a median follow-up of 13 months in the idelalisib group and 11 months in the placebo group, the median duration of PFS had not been reached for the idelalisib group and was 5.5 months in the placebo group (HR=0.18; 95%CI: 0.10-0.32; p<0.0001).[5] The rate of PFS at 24 weeks was 93% for the idelalisib group compared to 46% for the placebo group.[2]

The rate of overall survival at 12 months was 92% for the idelalisib group compared to 80% for the placebo group (HR=0.28; 95%CI: 0.09-0.86; p=0.02).[2] Overall response rate was 74.5% for the idelalisib group and 14.5% for the placebo group.[8]

Quality of life was assessed using the 44-item Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) scale measure. The mixed effects model demonstrated for physical, function, leukemia specific scale, trial outcome index, and FACT-Leu Total, the scores were significantly higher for the idelalisib group compared to placebo group, indicating improvement in quality of life for the idelalisib group. The scores for emotional and social subscales did not alter significantly over the trial period.

Harms

The most common grade 3 or 4 treatment emergent adverse events (AEs) were neutropenia (22% and 12% in the idelalisib and placebo groups, respectively) and pneumonia (13% and 10% in the idelalisib and placebo groups, respectively).[7]

Adverse events leading to death were mainly infectious in nature and occurred in 3 patients in the idelalisib group and 11 patients in the placebo group. Deaths occurred in 19 (8.7%) patients during or within 30 days of treatment, 5 were caused by disease progression (three in the idelalisib group and two in the placebo group).[7]

1.2.2 Additional Evidence

pCODR received input on idelalisib from three patient advocacy groups (Chronic Lymphocytic Leukemia Patient Advocacy Group, Leukemia and Lymphoma Society of Canada and Lymphoma Foundation Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies. The majority of people with CLL are asymptomatic at the time of diagnosis and the median survival of patients is more than 11 years; however for those with anemia and thrombocytopenia, survival is around 5 years. Treatment of CLL, with the exception of allogeneic stem cell transplant, is not curative, with patients undergoing many episodes of systemic therapies. For older patients or those with comorbidities, single agents with minimal toxicities are currently limited in the setting of relapsed or refractory CLL. Furthermore, the presence of mutations in the TP53 tumour suppressor gene or deletions of 17p is associated with resistance to standard chemoimmunotherapy and agents in this aggressive subgroup are needed.

Effectiveness

For the primary outcome progression-free survival (PFS), the median duration of PFS was not met in the idelalisib group and was 5.5 months in the placebo group. In pre-specified subset analyses, this benefit was seen in patients with a p53 mutation or 17p deletion, and in those with unmutated IGHV genes. Treatment with idelalisib improved overall survival with overall survival rates of 92% and 80% at 12 months for the idelalisib and placebo groups, respectively.[2] Quality of life was assessed and the minimally important differences were exceeded for the physical and leukemia specific subsets and FACT-Leu total, for the idelalisib group compared to the placebo group.

Safety

Overall, toxicities of grade 3 or 4 were uncommon with a slightly higher rate in the idelalisib group compared to the placebo group. Hepatotoxicity, pneumonitis and colitis of grade 3 or higher were uncommon. Adverse events (mainly infectious in nature) occurred in 3 patients in the idelalisib group and 11 patients in the placebo group. Rates of study discontinuation due to adverse events were similar (8% and 10% in the idelalisib and placebo groups, respectively).[7]

Limitations

There are limitations to the applicability of Study 116 given the very short median follow-up (13 and 11 months for the idelalisib and placebo groups, respectively), a population of patietns with CLL and a short duration of response to their most recent therapy (<24 months, the comparator of rituximab monotherapy is not commonly used in Canada, and the potential impact of cross over in Study 116.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be net overall clinical benefit to the use of idelalisib in the treatment of CLL, where duration of response to a previous regimen is less than two years, and when tolerance of cytotoxic chemotherapy would be expected to result in excessive toxicity due to poor renal function, residual neutropenia or thrombocytopenia from prior therapy, or the presence of multiple comorbidities. This recommendation is based on a single double blind placebo controlled trial that was of high quality, and demonstrated improvement in progression free survival and overall survival, as well as response rate and quality of life. These benefits were seen in older and younger patients, and in pre-defined subset analyses of patients with poor risk genetic features (p53 gene abnormalities and unmutated immunoglobulin variable region genes). The toxicity of idelalisib in this patient population was manageable, with few grade $\geq$3 toxicity or treatment discontinuation due to adverse events; side effects appear manageable with dose reduction after treatment interruption.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Single agent rituximab is not a common treatment of choice in this patient population in Canada; this is due to variable but generally restricted funding of rituximab in most provinces, as well as data that suggest efficacy is quite limited in CLL when rituximab is used alone. As noted by PAG, rituximab is given at higher doses and more frequently than current Canadian treatment protocols with rituximab.
- The follow-up of the GS US 312-0116 study was short at the time of reporting and the extent by which the results are influenced by the ability to cross over to idelalisib in the control arm is not known.
- Idelalisib has an acceptable toxicity profile, especially important in the patient population in the phase III trial who had limited therapeutic options because of comorbidities and organ function. Idelalisib does have the potential to cause significant toxicities (pneumonitis, hepatitis, colitis) that may not be encountered currently available agent used as palliative treatment of patients with relapsed and refractory CLL.
- Comparative data with ibrutinib, ofatumumab (a fully human CD20 antibody approved for the treatment of CLL as a single agent), rituximab-chlorambucil or chlorambucil are not available, and represent an area where additional research is needed. Idelalisib may be preferred to ibrutinib in patients who require anticoagulation with vitamin K antagonists or have experienced recent stroke or significant bleeding, for whom ibrutinib is contraindicated.
- Data on the sequencing of BTK inhibitors such as ibrutinib and PI3kinase inhibitors such as idelalisib in the treatment of CLL are not yet available.
- Similar response to idelalisib was seen regardless of cytogenic abnormalities, number of previous lines of therapies, and use of other anti-CD20 agents such as obinutuzumab or ofatumumab.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding Idelalisib (Zydelig) for Chronic Lymphocytic Leukemia. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth.ca/pcodr.

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

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

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies, with an incidence of 4.8 cases/100,000 persons. In 2010, 2,195 Canadians were diagnosed with CLL and 600 were expected to die from this disease in 2011, the most recent years for which there are Canadian statistics.[1]

For patients with CLL who require treatment and who are in good health and under the age of 65, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is standard treatment in most provinces in Canada. Patients over the age of 65, or those who are not considered fit enough to receive FCR may derive benefit from several less intensive regimens. Chlorambucil, is a standard agent for older patients or those with significant comorbidities, given on a number of schedules. However, complete response rates are low and progression-free survival with chlorambucil alone is approximately 12 months. Bendamustine has been compared to chlorambucil and resulted in a higher response rate and longer PFS, but no improvement in OS.[2,3]

The availability of newer CD20 antibodies for the treatment of CLL is currently limited in many provinces, including the ability to use rituximab, which has been tied to particular chemotherapy combinations.

For patients with CLL which has relapsed or is refractory to standard therapies including fludarabine, alkylating agents and rituximab—all current components of front-line therapy—there is no agreed-upon standard treatment, and there are few randomized trials to guide practice. Re-treatment with chlorambucil or fludarabine is common practice for patients with long initial response to these agents.

Particularly challenging is the management of patients with CLL that carries a del(17) mutation since fludarabine and alkylating agents are significantly less effective. Allogeneic transplantation is considered for younger patients, but there is currently no standard front-line or relapse therapy for this small subgroup. Alemtuzumab may result in a higher probability of response and better disease control, but this agent produces significant

toxicity and morbidity from infection, and availability is limited to special access programmes, as it is no longer approved for treatment of CLL.

Phase II studies of idelalisib have shown significant activity in patients with refractory CLL, as well as high response rates in combination with rituximab in previously untreated, symptomatic patients with advanced stage CLL. These results suggest that idelalisib may be a valuable agent in patients whose CLL has progressed during or after response to standard front-line treatments.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety of idelalisib in combination with rituximab in the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

2.1.3 Highlights of Evidence in the Systematic Review

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

One phase 3, randomized, double blind trial met the inclusion criteria for this systematic review. The GS US 312-0116 study by Furman et al. included patients with relapsed chronic lymphocytic leukemia. Patients were randomized in a 1:1 ratio to receive either idelalisib plus rituximab or placebo plus rituximab.[2] Detailed study characteristics can be seen in Table 18 in section 6.

The primary outcome in the Furman et al. trial was progression free survival (PFS). This outcome was independently assessed by an Independent Review Committee (IRC).[4] Secondary outcomes included overall response rate and complete response rate.[2] A total of 220 patients were included in the study with 110 patients randomized to each arm.

The rate of PFS at 24 weeks was 93% in the idelalisib arm, and 46% in the placebo arm (adjusted HR for progression or death in the idelalisib group of 0.15; 95% CI: 0.08-0.28; unadjusted P<0.001).[2] The pre-specified stopping boundary for efficacy at the significance level of 0.001 was crossed and this led to an early stop of the trial. The median PFS was not met in the idelalisib group and was 5.5 months in the placebo group (HR 0.18; 95%CI: 0.10-0.32; p<0.0001).[5] The rates of PFS at 12 months were 66% for patients in the idelalisib arm and 13% for patients in the placebo arm.[6] Disease progression was seen in 11 (10%) patients in the idelalisib arm and in 51 (46%) patients in the placebo arm.[7] The Kaplan-Meier figure for PFS can be seen in Figure 2.

In the idelalisib group, the rate of overall survival (OS) at 12 months was 92% compared to 80% in the placebo arm (adjusted HR for death 0.28; 95% CI: 0.09-0.86; P=0.02).[2] As of August 2013 the two groups have not yet reached the median duration of OS. The survival curve for the idelalisib group narrowly separates from the placebo group immediately after the start of the trial and then the curve widens at 2 months and widens again at 8 months and stays separate. There were 16 death while on treatment in the study, four (4%) in the idelalisib group and 12 (11%) in the placebo group.[2]

Overall response was evaluable in 176 patients with 88 patients in each group. The second interim analysis showed an overall response rate of 74.5% (95% CI: 65.4-82.4) for the idelalisib group and 14.5% (95% CI: 8.5-22.5) for the placebo group. The odds ratio for the overall response was 17.28 (95% CI: 8.66-34.46) which favoured the idelalisib group ($p=6.3x10^{-19}$).[8] The median time to response from the second interim analysis in the idelalisib group was 2.0 months and 3.6 months in the placebo group.[8]

Quality of Life was assessed using the 44-item Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale measure. The mixed effects model demonstrated that for physical (p=0.015), functional (p= 0.014), leukemia specific scale (p=0.001), TOI (p=0.002), and FACT-Leu Total (p=0.006), the scores were significantly higher for idelalisib, thereby showing improvement in quality of life when treated with idelalisib. The scores for emotional and social subscales did not alter significantly over a time period.

Adverse Events

Most grade 1 and 2 adverse events (AEs) were in-line with those expected for a relapsed CLL population. For the idelalisib group the top five grade 1 and 2 AEs were: pyrexia (29%), fatigue (24%), nausea (24%), chills (22%) and diarrhea (19%). For the placebo arm the top five grade 1 and 2 AEs were: infusion-related reaction (28%), fatigue (27%), cough (25%), nausea (21%) and dyspnea (19%).[2] Treatment emergent adverse events that were grade 3 or 4 that occurred in ≥ 2% of all subjects can be seen in Table 1 below. [7] The most common treatment emergent AEs in both groups were neutropenia, 22% in the idelalisib arm and 12% in the placebo arm and pneumonia, 13% in the idelalisib arm and 10% in the placebo arm.

Table 1: Grade 3 or 4 treatment emergent adverse events that occurred in ≥2% of all subjects[7]

Grade 3 or 4 event	Idelalisib + rituximab N=110; N (%)	Placebo + rituximab N=110; N (%)
Neutropenia	24 (21.8)	13 (12)
Pneumonia*	14 (12.7)	11 (10.2)
Sepsis¶	7 (6.4)	2 (1.9)
Fatigue	5 (4.5)	3 (2.8)
Febrile neutropenia	5 (4.5)	4 (3.7)
Anemia	5 (4.5)	7 (6.5)
Diarrhea	4 (3.6)	0
Pneumonitis	4 (3.6)	1 (0.9)
Rash §	4 (3.6)	1 (0.9)
Colitis	3 (2.7)	0
ALT increased	3 (2.7)	0
Pyrexia	3 (2.7)	1 (0.9)
Transaminases increased	3 (2.7)	1 (0.9)
Asthenia	1 (0.9)	4 (3.7)
Infusion related reaction	0	4 (3.7)

* Includes: pneumonia, lung infection, pneumocystis, jiroveci pneumonia, legionella pneumonia, lung infection pseudomonal and pneumonia fungal
¶ Includes: sepsis, septic shock, neutropenic sepsis and sepsis syndrome
§ Includes: rash, dermatitis exfoliative rash, rash macular, rash maculo-papular, rash popular, rash pruritis and skin disorder

Significant adverse events

There was one case of Hy's laws that was observed with the use of idelalisib in the study. This patient discontinued idelalisib permanently.[7] In addition there were 38 (34.5%) patients with ALT elevations that were treatment emergent in the idelalisib arm compared to 11 subjects (10.2%) in the placebo arm.[7]

In the idelalisib group, 21 patients (19.1%) patients developed diarrhea compared with 16 (14.8%) patients in the placebo group. The median grade for diarrhea was grade 2 (range 1-4) in the idelalisib arm and grade 1 (range 1-2) in the placebo arm. There were four

patients in the idelalisib arm who had grade 3 or 4 diarrhea.[7] Five patients in the idelalisib arm and one patient in the placebo arm developed colitis. The median grade for colitis was 3 in the idelalisib arm and 2 in the placebo arm. There were 3 patients in idelalisib arm with grade 3 colitis.[7] Colitis and/or diarrhea returned in some patients that were re-challenged with idelalisib. In addition biopsies needed to be performed in some of the patients with colitis, the pathologic findings showed acute cryptitis, crypt abscess formation, loss of surface epithelium, aggregates of inflammatory exudates.[7]

In the idelalisib arm, grade ≥3 pneumonitis occurred in 4 (3.6%) patients compared to one patient in the placebo arm. Prior respiratory conditions including: intermittent cough and dyspnea, COPD and history of pleurisy, baseline cough, and reactive airway disease, which were seen in 4 patients in the idelalisib arm. In addition one patient in the placebo arm that developed pneumonitis had a history of COPD.[7] In both the idelalisib and placebo arms, the median toxicity grade for the cases of pneumonitis was 3.

Rash

Rash had occurred in 11 (10%) patients in the idelalisib arm and in 5 (4.6%) patients in the placebo arm. When the term rash was expanded to include the following terms: dermatitis exfoliative, dermatosis, erythema, pruritis, pruritis generalized, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, skin disorder, and skin lesion, there were 24 subjects (21.8%) with events in the idelalisib and 18 (16.7%) in the placebo arm. In the idelalisib arm there were four grade 3 events and one grade 3 event in the placebo arm. [7]

Deaths

Deaths occurred in 19 (8.7%) patients during the study or within 30 days of treatment. Five deaths were caused by disease progression, three in the idelalisib arm and two in the placebo arm. [7] Another death took place in the follow-up period. This was in the placebo arm and was due to an adverse event.[7]

2.1.4 Comparison with Other Literature

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

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

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

Patient Advocacy Group Input

Three patient advocacy groups, (1) Chronic Lymphocytic Leukemia Patient Advocacy Group ("CLL PAG"), (2) the Leukemia and Lymphoma Society of Canada ("LLSC") and (3) Lymphoma Foundation Canada ("LC"), provided input on idelalisib in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia.

From a patient perspective, there is significant emotional and physical impact with their diagnosis of CLL. Fatigue was most commonly reported. Respondents described feeling a depletion of energy and stated that they needed to rest often in order perform their normal daily activities. Some respondents with CLL expressed difficulties with concentration, emotions, stress levels, insomnia and mood swings. Additional symptoms reported included enlarged lymph nodes, fever, night sweats, peripheral neuropathy and weight loss. Patient Advocacy Groups believes that treatment options currently available in Canada are not curative and tend to be associated with toxicity, short-lived remissions and unpleasant side effects. Respondents indicated they wanted longer remissions with less toxicity, having treatment choices and more knowledge on the treatments. Respondents who have experienced with idelalisib like the ease of use of idelalisib because it is an oral agent. There were no travel time and associated costs to visit clinic, and no chemo chair time. Most respondents to the LC, CLL PAG and LLSC surveys reported that their symptoms associated with CLL have improved with the use of idelalisib; however, a few respondents noted that idelalisib failed to manage their symptoms. Respondents reported the following side effects to idelalisib: diarrhea, elevated liver counts, swelling of the bowels, increased lymphocyte count, cough, pneumonia, gastric problems, nausea, vomiting, compromised immunity and skin rash. Respondents also reported experiencing more than one side effect. Some respondents indicated they had a dose reduction (from 150mg to 100mg, twice daily) due to diarrhea and/or elevated liver counts. One respondent discontinued idelalisib due to severe diarrhea, dehydration, vomiting, a skin rash and elevated liver counts. While there are side-effects with the drug under review, most respondents reported that idelalisib has changed their long-term health and well-being, and for the most part has provided improvement in the quality of life.

PAG Input

Input 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 idelalisib in combination with rituximab (idelalisib/rituximab):

Clinical factors:

- New class of drug with severe toxicities to monitor
- Generalizability of results from the submitted trial to the Canadian context as rituximab monotherapy is not a standard of care in Canada and is not funded for the re-treatment of CLL
- In the trial, rituximab is given at higher doses and more frequently than current treatment protocols with rituximab
- Sequential use of idelalisib/rituximab and other new treatments now available for CLL

Economic factors:

- Large prevalent patient population
- Additional drug and administration costs of rituximab

2.2 Interpretation and Guidance

Burden of Illness

Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies, with an incidence of 4.8 cases/100,000 persons. The median age of patients at diagnosis of CLL is 70 years, and the disease is rare in people <40 years of age. The lifetime risk of being diagnosed with CLL is about 1 in 200; the risk is elevated approximately two-fold**s** in first degree relatives of patients with CLL. In 2010, 2195 Canadians were diagnosed with CLL and in 2011, 600 were expected to die from this disease; this number is a reasonable estimate of the number of patient who may require second-line therapy in a given year.

The majority of persons with CLL are asymptomatic at time of diagnosis, which is most often made because of the finding of an elevated white blood cell (lymphocyte) count. Median survival of such patients is more than 11 years; for those with asymptomatic lymphadenopathy it is about 9 years; however, for those with anemia and thrombocytopenia, survival is only about 5 years. Treatment of CLL, with the exception of allogeneic stem cell transplant in highly selected, young patients, is not curative, and patients may expect to undergo one or more episodes of systemic therapy to control symptoms, reduce lymphadenopathy and improve bone marrow function, separated by periods of remission. For younger patients, such therapy includes fludarabine, cyclophosphamide and rituximab as initial treatment; for older patients, or those with comorbidities, single agent chlorambucil or bendamustine, with or without a CD20 antibody, is the standard of care. For the latter group, where both remission duration and overall survival is shorter compared to younger, fit patients, single agents with minimal toxicity currently represent desired treatment approaches in the setting of relapsed or refractory CLL. Such treatment options are currently quite limited.

Need

The delivery of therapy in patients with CLL, who are most frequently older and who usually have other comorbidities, is a significant challenge. In particular, patients with high CIRS scores who have relapsed or progressed on first line therapy have few non-toxic effective treatment options. The presence of mutations in the TP53 tumour suppressor gene or deletions of 17p is associated with resistance to standard chemoimmunotherapy, and agents with activity in this biologically aggressive subgroup are clearly needed. Ibrutinib, an orally available inhibitor of Bruton tyrosine kinase (BTK), is one such agent and has recently been approved by Health Canada and pCODR for patients with relapsed CLL after treatment with chemotherapy including fludarabine, and in the subgroup of patients with 17p deletion. Ibrutinib appears safe in patients with renal impairment but must be used with caution in patients receiving moderate or strong inducers of hepatic CYP3A, and may reduce efficacy when given with CYP3A inducers.

Effectiveness of idelalisib in CLL

The GS US 312-0116 study reported by Furman et al.[2] was a randomized double-blind phase III trial of the CD20 antibody rituximab combined with either idelalisib 150 mg twice daily or identical placebo in patients with relapsed CLL. Patients in the idelalisib arm could have their dose increased to 300mg twice daily at disease progression; those in the placebo arm who had progression were eligible to receive idelalisib therapy in a separate double-blind extension study.

One hundred and ten patients were randomized to each arm: the median age of participants was 71 years, and 22% were age <65. Approximately 90% of patients had previously received rituximab, and more than half in each arm had prior therapy with fludarabine and bendamustine. The median cumulative illness rating scale (CIRS) score in both groups was 8 (range 1-18); a CIRS score of 6 or less has been used to define CLL patients who are "fit" in previous studies.

Independently assessed PFS, the primary outcome measure, was 93% at 24 weeks in the idelalisib arm, and 46% in the placebo arm (adjusted HR for progression or death in the idelalisib group 0.15; 95% CI, 0.08-0.28; unadjusted P<0.001). The pre-specified stopping boundary for efficacy at the significance level of 0.001 was crossed and this led to an early stop of the trial. The median progression free survival was not met in the idelalisib group and was 5.5 months in the placebo group (HR 0.18; 95%CI 0.10-0.32; p<0.0001). In pre-specified subset analyses, this benefit was seen in patients with a p53 mutation or 17p deletion, and in those with unmutated IGHV genes. While the follow-up of the study was short at the time of reporting, treatment with idelalisib improved overall survival at 12 months: 92% vs 80% in the placebo arm (adjusted HR for death 0.28; 95% CI, 0.09 - 0.86; P=0.003). In the idelalisib group the overall response rate was 81% (95% CI, 71 to 88) compared to 13% (95% CI, 6 to 21) in the placebo group (odds ratio, 29.92; P<0.001). All of the responses were partial responses; response rates were all significantly higher in those receiving idelalisib in the previously defined genetic subgroups above. Quality of Life assessed using the 44-item Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) scale and leukemia-specific subscale improved in the idelalisib arm compared to placebo, and exceeded established minimally important difference (MID) change scores of 2, 4, 5 and 6 points for physical and leukemia specific subscales, and FACT-Leu total, in the idelalisib arm vs placebo.

Safety of idelalisib in CLL

Toxicities of grade 3 or higher were generally uncommon, and somewhat higher in the idelalisib arm compared to placebo. Treatment-emergent grade 3 or 4 neutropenia occurred in 22% of patients on active treatment compared to 12% of patients on placebo; thrombocytopenia did not appear to be increased compared to placebo. The incidence of pneumonia was 12.7% in patients receiving idelalisib compared to 10.2% in the placebo group.[7] Hepatotoxicity, pneumonitis and colitis grade $\geq$3 were uncommon. Adverse events leading to death (mainly infectious) occurred in 3/110 patients on idelalisib and 11/110 patients receiving placebo. The most common side effects reported in patients receiving idelalisib were fever, fatigue, nausea, chills and diarrhea. Elevated liver transaminases occurred more often in the idelalisib arm, but was grade ≥3 in 6 patients; onset was between 8 and 16 weeks from start of therapy and resolved upon holding drug in 4 patients. Rates of study drug discontinuation due to adverse events was similar in the idelalisib and placebo arms (8% and 10%, respectively).

Limitations of the evidence

The evidence in support of idelalisib in relapsed and refractory CLL compared to other available therapies is limited to a single phase III trial, with very short median follow-up, in a population of patients with short duration of response to their most recent therapy (<24 months). The comparator used as standard treatment was single agent rituximab, a treatment that is not commonly used in Canada, and, while potentially advantageous in the high-risk patient population enrolled in the GS US 312-0116 study, has limited efficacy with a low response rate and short PFS. The median number of prior lines of therapy was three, nearly all (90%) of patients had been previously treated with rituximab and more than 50% had received bendamustine and fludarabine, considered to be the most active drugs in the treatment of CLL. The extent to which the results are influenced by cross over is not clear. Eligible patients were considered unfit for further cytotoxic chemotherapy, and while it is clear that effective and non-toxic therapies are needed for this population, the relative benefit of idelalisib in other patient groups, with better functional status, kidney and bone marrow function or longer duration of response is not known. The rate of study drug discontinuation due to toxicity was similar to that observed in the phase II trial by Brown et al in patients who had received at least two prior lines of therapy, without eligibility restriction based on kidney function and comorbidities.[20]

2.3 Conclusions

The Clinical Guidance Panel concluded that there may be net overall clinical benefit to the use of idelalisib in the treatment of CLL, where duration of response to a previous regimen is less than two years, and when tolerance of cytotoxic chemotherapy would be expected to result in excessive toxicity due to poor renal function, residual neutropenia or thrombocytopenia from prior therapy, or the presence of multiple comorbidities. This recommendation is based on a single double blind placebo controlled trial that was of high quality, and demonstrated improvement in progression free survival and overall survival, as well as response rate and quality of life. These benefits were seen in older and younger patients, and in pre-defined subset analyses of patients with poor risk genetic features (p53 gene abnormalities and unmutated immunoglobulin variable region genes). The toxicity of idelalisib in this patient population was manageable, with few grade $\geq$3 toxicity or treatment discontinuation due to adverse events; side effects appear manageable with dose reduction after treatment interruption.

The Clinical Guidance Panel also considered that from a clinical perspective:

- Single agent rituximab is not a common treatment of choice in this patient population in Canada; this is due to variable but generally restricted funding of rituximab in most provinces, as well as data that suggest efficacy is quite limited in CLL when rituximab is used alone. As noted by PAG, rituximab is given at higher doses and more frequently than current Canadian treatment protocols with rituximab.
- The follow-up of the GS US 312-0116 study was short at the time of reporting and the extent by which the results are influenced by the ability to cross over to idelalisib in the control arm is not known.
- Idelalisib has an acceptable toxicity profile, especially important in the patient population in the phase III trial who had limited therapeutic options because of comorbidities and organ function Idelalisib does have the potential to cause significant toxicities (pneumonitis, hepatitis, colitis) that may not be encountered currently available agent used as palliative treatment of patients with relapsed and refractory CLL.
- Comparative data with ibrutinib, ofatumumab (a fully human CD20 antibody approved for the treatment of CLL as a single agent), rituximab-chlorambucil or chlorambucil are not available, and represent an area where additional research is needed. Idelalisib may be preferred to ibrutinib in patients who require anticoagulation with vitamin K antagonists or who have experienced recent stroke or significant bleeding, for whom ibrutinib is contraindicated.
- Data on the sequencing of BTK inhibitors such as ibrutinib and PI3kinase inhibitors such as idelalisib in the treatment of CLL are not yet available.
- Similar response to idelalisib was seen regardless of cytogenic abnormalities, number of previous lines of therapies, and use of other anti-CD20 agents such as obinutuzumab or ofatumumab.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Chronic lymphocytic leukemia (CLL) is one of the most common hematologic malignancies, with an incidence of 4.8 cases/100,000 persons: 2,195 Canadians were diagnosed with CLL in 2010 and 600 were expected to die from this disease in 2011, the most recent years for which there are Canadian statistics.[1]The majority of persons with CLL are asymptomatic, and diagnosed because of the finding of an elevated white blood cell count.

The diagnosis is usually made through flow cytometry of peripheral blood demonstrating the characteristic immunophenotype of CLL cells, which demonstrate kappa- or lambda immunoglobulin light-chain restriction, and CD19+, CD20+, CD5+, CD23+, CD10-, CD11cdim, with absent or dim expression of FMC-7 and CD79a.[9] 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; some patients present with lesser degrees of lymphocytosis and are designated as having monoclonal B cell lymphocytosis, which generally has a much longer natural history than CLL.[10] 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 are managed similarly, with a strategy of initial observation for patients who present with normal blood counts (hemoglobin, neutrophils and platelets) without extensive lymphadenopathy and enlarged liver or spleen. Patients who present with lymphocytosis (Rai stage 0) have progression-free survival of 75-80% after 3 years of follow-up (time to treatment).

Table 3: Staging

Staging System	Stage	Definition	Median OS (months) Original Report	Median OS (months) Mayo Clinic database
Rai [11]	0	Blood/marrow lymphocytosis	126	130
	1	Lymphadenopathy	92	106
	2	Splenomegaly	53	88
	3	Anemia (Hb < 110)	23	58
	4	Thrombocytopenia (Plt < 100)	20	69
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: unilateral or bilateral cervical, axillary or inguinal lymph nodes, liver and spleen.

A number of prognostic factors determine time to progression and overall survival, including age, lymphocyte doubling time and serum β2microglobulin. The four molecular/biologic features that have the best track record for use as clinical prognostic parameters are IGHV mutation status, recurrent cytogenetic abnormalities as identified by FISH testing, zeta-associated protein (ZAP) 70 expression and CD38 protein expression. Among these, only the presence of del17p has been used to direct therapy.

3.2 Accepted Clinical Practice

Common indications to initiate therapy for CLL include the development of anemia and thrombocytopenia (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< 3 months). Once a need for therapy is established, the choice of first line therapy depends on the age and overall health of the patient.

For patients 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) is standard in most provinces in Canada. 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. [12] Patients over the age of 65, or those who are not considered fit enough to receive FCR may derive benefit from several less intensive regimens. Chlorambucil, an alkylating agent that is well tolerated and has been in use for more than 30 years, is a standard agent for older patients or those with significant comorbidities, given on a number of schedules. It can be given in daily, weekly, biweekly and monthly schedules. Complete response rates are low and progression-free survival with chlorambucil alone is approximately 12 months. Fludarabine was compared to chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS.[13] [1414]Patients treated with fludarabine have a higher rate of severe infection and neutropenia; therapy requires close monitoring of renal function and the use of prophylaxis against PJP and herpes virus infection for up to one year after completion of therapy. Similarly, bendamustine has been compared to chlorambucil and resulted in a higher response rate and longer PFS, but no improvement in OS.[15]

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 obinutuzumab, have all demonstrated higher complete and overall response rates and progression-free survival without a significant increase in toxicity. A survival advantage was also demonstrated with the combination of obinutuzumab-chlorambucil compared to chlorambucil alone in a phase III trial in patients with high comorbidity scores or impaired renal function rather that age as the main eligibility criteria.[16,17]

The availability of newer CD20 antibodies for the treatment of CLL is currently limited in many provinces, and in some the ability to use rituximab, considered the global standard until recently, has been tied to particular chemotherapy combinations. In addition, while there is evidence in the setting of relapsed CLL from phase II and randomized phase III trials that the use of chemoimmunotherapy may be superior to chemotherapy alone, rituximab is often not funded by provincial cancer agencies, unlike other low grade CD20+ lymphomas.

For patients with CLL which has relapsed or is refractory to standard therapies including fludarabine, alkylating agents and rituximab—all current components of front-line therapy—there is no agreed-upon standard treatment, and there are few randomized trials to guide practice. Re-treatment with chlorambucil or fludarabine is common practice for patients with long initial response to these agents. Bendamustine alone or in combination with rituximab results in progression-free survival in patients previously treated with FC of about 15 months.[17] The addition of rituximab to BR chemotherapy improved the response rate and PFS in relapsed patients who were rituximab naïve, but this 10 month improvement (30.6 v 20.6 months) did not result in an improvement in overall survival.[18]

Particularly challenging is the management of patients with CLL that carries a del(17) mutation: fludarabine and alkylating agents are significantly less effective and response rates and PFS are uniformly poor; while allogeneic transplantation is considered for younger patients, there is currently no standard front-line or relapse therapy for this small subgroup. Alemtuzumab may result in a higher probability of response and better disease control, but this agent produces

significant toxicity and morbidity from infection[19], and availability is limited to special access programmes, as it is no longer approved for treatment of CLL.

CD20 antibody therapy for relapsed CLL may have less toxicity compared to cytotoxic chemotherapy, but reported response rates are low, and PFS is short; currently, rituximab is not approved as monotherapy for treatment of CLL as primary therapy or for relapse.

A number of cellular pathways have been identified that are responsible for the proliferation, migration and survival of CLL cells. One in particular is the presence of constitutive activation of the phosphoinositide-3 kinase (PI3K) family of proteins. The PI3Kδ isoform is restricted to hematopoietic cells, and CLL cells appear to be dependent on its expression for survival. Idelalisib is a selective inhibitor of the PI3Kδ isoform, and does not appear to inhibit normal T or NK cell function. Idelalisib reduces intracellular signaling via the B cell receptor (BCR), and reduces BCR and chemokine receptor activation of the AKT and MAPK/ERK pathways that are important for cell proliferation. Phase II studies of idelalisib have shown significant activity in patients with refractory CLL, as well as high response rates in combination with rituximab in previously untreated, symptomatic patients with advanced stage CLL.[20,21] These results suggest that idelalisib may be a valuable agent in patients whose CLL has progressed during or after response to standard front-line treatments.

3.3 Evidence-Based Considerations for a Funding Population

The prevalence of patients with relapsed or refractory CLL is difficult to estimate; taking the mortality rate from the most recent data reported in Canada, approximately 600 patients per year might be expected to need second-line therapy, a subset of which would meet the eligibility criteria for the randomized study by Furman et al.[2] The patient population who benefited from the combination of idelalisib were elderly (median age 70) and had significant comorbidities (median CIRS score 8) or impaired renal function, for whom fludarabine would pose a significant toxicity risk. In addition a high percentage had unmutated IGHV (85%) or 17p-/TP53 mutation (40%), which predict poor outcome with standard alkylator or fludarabine therapy as second-line treatment. Application of CIRS score, while somewhat cumbersome, is increasingly being used to stratify patients in clinical trials of CLL therapy, and is feasible in clinical practice to aid in decision making in older patients with CLL. Presence of the 17p- deletion is routinely available by FISH testing on peripheral blood lymphocytes in most centres; IGH mutation status is more difficult to come by and is not generally used outside of clinical trials to define patients at higher risk of treatment failure.

3.4 Other Patient Populations in Whom the Drug May Be Used

No other potential uses of the drug that may impact on its utilization were identified.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Three patient advocacy groups, (1) Chronic Lymphocytic Leukemia Patient Advocacy Group ("CLL PAG"), (2) the Leukemia and Lymphoma Society of Canada ("LLSC") and (3) Lymphoma Foundation Canada ("LC"), provided input on idelalisib in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia, and their input is summarized below.

CLL PAG and LLSC made a joint submission to pCODR. Information is gathered from four surveys. Surveys were distributed to patients by via social media; CLL list servers and directly emailed using databases from CLL PAG, LLSC and CLL Canada.

A general CLL survey was distributed in the summer of 2014 eliciting 212 responses from people with CLL. Of these respondents 54% were female and 46% male. It was reported that people with CLL are typically older, with an average age of diagnosis of ≈70 years. However, the average age at diagnosis indicated by respondents was 55 years, and 5 respondents had been diagnosed in their 30s. The following age breakdown were received at the time of filling out the survey: ≈10% of people were 40-49 yrs., ≈33% were 50-59 yrs., ≈40% were 60-69 yrs. and ≈17% were 70-79. One person was under 40 and another over 80 and ≈10% of people did not indicate their age. Two (2) respondents indicated having at least two other family members who were also diagnosed with CLL.

Of the 212 respondents surveyed, 43% of respondents indicated that they had received treatment for CLL and 57% were in a "watch & wait" phase. Respondents were diagnosed between 1988 and 2014, with over 52% being diagnosed within the last 5 years.

Respondents reported their geographical residence as follows: 60 from Canada, 104 from USA, 18 from the United Kingdom, 9 from Australia, 1 from France, 1 from Brazil and 19 people did not specify.

In addition to the above, two caregiver surveys were also conducted. There were 14 caregivers who responded to the CLL PAG caregiver survey, of which 13/14 (92.86%) were a spouse/partner and 1/14 was a child of a CLL patient. 50% of respondents had provided care during treatment and 50% of respondents were caring for patients in the watch & wait phase. It was reported that 92.31% of caregivers were female; 85% were ≥60 years.

Finally, a separate survey was distributed through the same channels for CLL patients who have used idelalisib as part of a drug regime. 11 respondents responded to the survey, but only seven (7) actually completed the survey and one (1) respondent partially answered the survey. One respondent was from Canada and 6 respondents were from the USA. The age range included the following: 1 person 50-59 years of age, four persons 60-69 years of age and two persons 70-79 years of age. Six respondents were male. One respondent did not indicate age, gender or country of residence.

LC conducted three online surveys of patients and caregivers to gather information about the impact of CLL on their lives and the effect of treatments on their disease. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into the surveys so respondents were asked questions only relevant to them. Open-ended responses to the surveys and quotes obtained from interviews are included verbatim to provide a deeper understanding of patient and caregiver perspectives. The surveys were sent via e-mail to patients and caregivers registered on the LC database, and were also made available via LC Twitter and Facebook accounts, as well as through CLL patient forums, a patient blog and the Lymphoma Research Foundation (USA) website.

LC reported on the number of respondents below (Table 4). LC obtained the perspectives from 35 patients with direct experience with idelalisib. It is important to note that five patients who completed an idelalisib experience survey also participated in an interview.

Table 4: Participants

Participants by Country	Canada	USA	Europe	Asia	Australia	Africa	Not Specified	Total (n)
Patients with Idelalisib Experience (Survey)	5	11	3	1	-	1	12	33
Patients with Idelalisib Experience (Interviews)	2	4	1	-	-	-	-	7*
Patients without Idelalisib Experience (Survey)	23	7	-	-	1	-	3	34
Caregivers (Survey)	9	1	1	-	-	-	-	11
***Please note: Telephone Interviews were conducted with five (5) CLL patients with direct experience with idelalisib. Two (2) online interviews of CLL patients with direct experience with idelalisib were also incorporated.**								

From a patient perspective, there is significant emotional and physical impact with their diagnosis of CLL. Fatigue was most commonly reported. Respondents described feeling a depletion of energy and stated that they needed to rest often in order perform their normal daily activities. Some respondents with CLL expressed difficulties with concentration, emotions, stress levels, insomnia and mood swings. Additional symptoms reported included enlarged lymph nodes, fever, night sweats, peripheral neuropathy and weight loss. Patient Advocacy Groups believes that treatment options currently available in Canada are not curative and tend to be associated with toxicity, short-lived remissions and unpleasant side effects. Respondents indicated they wanted longer remissions with less toxicity, having treatment choices and more knowledge on the treatments. Respondents who have experienced with idelalisib like the ease of use of idelalisib because it is an oral agent. There were no travel time and associated costs to visit clinic, and no chemo chair time. Most respondents to the LC, CLL PAG and LLSC surveys reported that their symptoms associated with CLL have improved with the use of idelalisib; however, a few respondents noted that idelalisib failed to manage their symptoms. Respondents reported the following side effects to idelalisib: diarrhea, elevated liver counts, swelling of the bowels, increased lymphocyte count, cough, pneumonia, gastric problems, nausea, vomiting, compromised immunity and skin rash. Respondents also reported experiencing more than one side effect. Some respondents indicated they had a dose reduction (from 150mg to 100mg, twice daily) due to diarrhea and/or elevated liver counts. One respondent discontinued idelalisib due to severe diarrhea, dehydration, vomiting, a skin rash and elevated liver counts. While there are side-effects with the drug under review, most respondents reported that idelalisib has changed their long-term health and well-being, and for the most part has provided improvement in the quality of life.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, 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.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with CLL

According to LC, patients with early stage CLL who participated in the survey reported minimal symptoms associated with their disease and noted a good quality of life. For those with more advanced disease, the respondents reported their quality of life being impacted more significantly. Fatigue was most commonly reported. Respondents described feeling a depletion of energy and stated that they needed to rest often in order perform their normal daily activities. Some respondents with CLL expressed difficulties with concentration, emotions, stress levels, insomnia and mood swings. Additional symptoms reported included enlarged lymph nodes, fever, night sweats, peripheral neuropathy and weight loss. Frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts) were also reported. LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day-activities. Many respondents also had relapsed from previous treatments. Below were some of the direct quotes from four (4) respondents.

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

CLL PAG and LLSC stated that while "watch & wait" is a common strategy at CLL diagnosis, it is often confusing for patients and comes with its own concerns. Respondents used "watch & worry" or "wait & worry" to describe a monitoring phase with uncertainty, fatigue, and other symptoms. The decisions of when to treat, the availability of new options and the potential drug side effects

also weigh heavily on them. One respondent said, "*I found the hardest part is 'watch & wait'. Watching the numbers go up & waiting for the other shoe to drop.*"

In addition to the above, respondents who have had treatment also worry about what will be available if current therapies fail or if future treatment is needed. One patient said, "I find it difficult to deal with the uncertainty about my future health and whether or not the new, less toxic drugs will be available when I next need treatment." Another stated, "I have become anxious about 'what next' and find it difficult to make any long term plans." Mortality is the latent or manifest theme in many patient responses.

CLL PAG and LLSC reported that respondents rated on the significance of the emotional impact of their diagnosis at levels 5-7, specifically for the following: stress (40%), anxiety (39%), and depression (28%) based on the survey featuring 7-point likert-type scales, where 1 indicated little impact and 7 indicated severe impact.

Respondents also rated on the significance of their physical disease symptom with ratings of 5-7 for the following: fatigue (46%), increased white blood count (38%) (leading to weakened immune systems and frequent infections), and enlarged lymph nodes (27%). Many respondents described debilitating levels of fatigue, and how immune suppression also limits daily routines and social engagements.

For those who are of working age, these respondents noted the impact of CLL on their ability to work, with one respondent stating, "*Fatigue and infections required I stop working in my forties. I could have been a more productive member of society - if the CLL effects were controlled.*"

4.1.2 Patients' Experiences with Current Therapy for CLL

CLL PAG and LLSC reported that patients' personal experience with CLL varies a great deal, with some patients going many years with 'watch and wait' management of the disease and others requiring treatment right away. Survival varies widely dependent on genetic mutation that triggers the disease, with some patients' disease being resistant to existing therapies. With age often comes comorbidities and this also impacts whether a patient can tolerate existing treatments.

93% (85/91) of respondents who have received treatment responded to questions asking about treatment type(s). The list of therapies as set out by CLL PAG and LLSC is in Table 5 below; this includes 2 respondents who are in clinical trials for non-marketed drugs:

Table 5: list of therapies as set out by CLL PAG and LLSC

Treatment Given	# Patients treated first-line	# Patients treated second-line	# Patients treated third-line
Bendamustine	0	3	2
BR - Bendamustine Rituxan	7	3	3
BR + idelalisib	0	2	1
Campath	1	0	0
Chlorambucil	5	0	0
CR - Chlorambucil Rituxan	1	0	0
CVP	1	0	0
CVP + R	0	2	11

Treatment Given	# Patients treated first-line	# Patients treated second-line	# Patients treated third-line
DHAP	0	0	1
Fludarabine	0	1	0
FC	0	1	0
FCR	35	4	1
FR	8	2	0
Idelalisib	6	4	4
Idelalisib Rituxan	2	1	0
Obinutuzumab	1	2	0
PCR	3	0	0
R-CHOP	0	1	0
Revlimid	2	0	0
Rituxan	13	0	0
TOTAL	85	28	14

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

According to LC, 25 respondents reported having experience with the following therapies:

Table 6: Respondents experience with therapies

Current Treatment	Response Count*	Current Treatment	Response Count*
FCR	7	FR	1
Rituximab alone	5	Radiation	3
CVP	3	Stem cell transplant	2
Ibrutinib	3	Blood transfusions	1
CHOP	2	Anti-nausea medication	1
Chlorambucil alone	1		
Fludarabine alone	1		
R-CHOP	1		
bendamustine	1		
ofatumumab	1		

Note: The total response count exceeded the total respondents (n=25) to this question because 8 patients indicated using multiple therapies to treat their CLL. Eight (27.6%) of the 29 patients indicated they have relapsed/refractory CLL.

According to CLL PAG and LLSC, 94% (84/89) of respondents that responded to the question on receiving treatment reported side effects. The most common side effects were fatigue (73%) and low blood counts (62%). 44% of respondents had nausea and about a third of respondents reported anemia, diarrhea, mouth sores and skin rashes.

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

> *"Short or no benefit from multiple therapies. Infusion reactions, rashes, joint pain, nausea and vomiting, diarrhea, hair loss, infections, insomnia, stomach pains, high blood*

pressure, liver inflammation, severe fatigue, isolation and prolonged hospitalization."(male; 55-64; USA)

"*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)

"*CHOP +R and two years rituximab maintenance. Did well. Then 2013 returned November. Bendamustine chemo 6 months very poor recovery and two months later back worse than in start tried. Rit/Flud/Cyclophophamide. No results needed weekly blood transfusions January 2015. Fludarabine chemo regime no help. Stopped after first dose to try steroid treatments which did no change. Now awaiting idelalisib approval.*" (male; 60; Canada)

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

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

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

LC also conducted a similar survey where respondents were asked how difficult it was to access their most current therapy(ies) (Table 7). According to LC, 38.5% of respondents who answered this question experienced difficulties. Difficulties expressed by patients and caregivers included the need to: travel great distances to receive treatments in Canada; meet specific provincial drug funding criteria; pay out-of- pocket costs for treatments and associated travel.

Table 7: Respondents difficulties to access their most current therapy(ies).

Level of Difficulty with Access	N (%)	Level of Difficulty with Access	N (%)
Not at all difficult	8 (30.8%)	Somewhat difficult	6 (23.1%)
Not very difficult	8 (30.8%)	Very difficult	4 (15.4%)
			Response Count: 26

Some notable comments from respondents include:

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

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

According to LC, treatments options currently available in Canada are not curative and tend to be associated with toxicity, short-lived remissions and unpleasant side effects. Respondents to the LC survey were asked to rate their level of agreement with how much their current therapy(ies) are able to manage symptoms associated with their CLL, on a scale of 1 (Strongly Disagree) to 10 (Strongly Agree). Those respondents who identified as having relapsed/refractory disease rated substantially lower (rating average 5.5, n= 4) than those patients without relapsed/refractory disease (rating average 7.5, n = 13).

When considering treatment, respondents to the LC survey were asked how important is it for them and their physician to have choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 (Not Important As Long There Is At Least One Treatment Choice) to 10 (Extremely Important To Have Choice of Treatment). 65.4% (17/26) of respondents who answered this question gave this a rating of 8 or higher. The rating average was 7.9, which according to LC means a large proportion felt that choice was very important based on the known side effects and expected outcomes of a drug. Respondents were also asked if they feel there is currently a need for more choice in drug therapy(ies) for patients with CLL. All 23 respondents who answered this question feel there is a definitive need for more therapies.

4.1.3 Impact of CLL and Current Therapy on Caregivers

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

Table 8: Impact on Caregivers

Impact on Day-to-Day Life of Retired Caregivers (N=5)*	Rating of 7 or Higher N (%)	Rating Average	Impact on Day-to-Day Life of Non-Retired Caregivers (N=6)*	Rating of 7 or Higher N (%)	Rating Average
Ability to travel	4 (80%)	7.2	Ability to volunteer	3 (50%)	6.2
Ability to volunteer	3 (60%)	5.8	Ability to exercise	2 (33.3%)	5.0
Ability to spend time with family and friends	2 (40%)	5.2	Ability to concentrate	2 (33.3%)	4.5
Ability to concentrate	2 (40%)	4.8	Ability to travel	1 (16.7%)	4.5
Ability to fulfill family obligations	2 (40%)	4.8	Ability to spend time with family and friends	1 (16.7%)	4.3
Ability to exercise	2 (40%)	4.4	Ability to contribute financially to household expenses	1 (16.7%)	4.2

Ability to attend household chores	1 (20%)	4.0	Ability to attend household chores	1 (16.7%)	4.0
Ability to contribute financially to household expenses	1 (20%)	2.2	Ability to fulfill family obligations	1 (16.7%)	4.0
***All 11 respondents answered questions relating to day-to-day life impact and retirement status**					

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

> *"Cancelled weekend away with friends due to anxiety about being out-of-town and too far away from mother. Have not taken time to workout…Sleep pattern is minimal since eating habit has changed and has affected my quality of sleep."* (child; female 45-54; not retired; Canada)

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

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

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

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

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

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

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

CLL PAG and LLSC reported the central focus of CLL on their family life was mentioned by most caregivers. CLL was identified as the dominant deciding factor for all of activities. Caregivers help patients manage physical symptoms of infections, fatigue, pain, neuropathy, impotence, and night sweats. Emotional and mental health issues are described as inadequately addressed by the health system, leaving family members to address the emotional responses. Caregivers worry about the physical exhaustion of household duties and the ability to meet increasing personal care needs.

Caregivers described negative impact of CLL diagnosis upon household responsibilities, career, financial status, socializing, and emotional well-being, as they assist family members with medical needs and provide physical and emotional support. Emotional responses as described in the LLSC caregiver survey included: depression (n=15/19), fear (n=8/19) and anxiety (n=13/19).

Caregivers also reported emotional impact as a constant "underlying tension" or "being on edge" and sense of functioning poorly. Caregiver respondents cited fear of recurrence (n=13/19) and that another family member would be diagnosed (n=6/19). Respondents also indicated the following: experienced financial difficulties (n=7/19), losing income (n=6/19), out-of-pocket drug costs (n=4/19), and burden of transportation costs (n=4/19). In addition to concerns for their family in managing this life-threatening condition, caregivers also relayed their stresses of treatments side-effect on their loved ones.

In addition to the above, the potential for exposing patients to infectious diseases was cited as a major reason for reduced social contacts with family and friends, sacrificing vacations and missing public events.

Caregivers also stated that they searched journal articles, and online postings to become informed about potential treatments, and the side effect profiles of various therapies as researching options can be too daunting for some patients. One respondent stated: "*He says reading too much information is depressing. He just wants to forget about it for now*." Many caregivers attend the medical appointments and ensure that patients followed physicians' instructions, "*The strain on him was such that he would sometimes forget or misunderstand what the physicians told him*." Another respondent stated, "*Case management is a big part of what I do for my husband. Medication management is another-research is one of the biggest things that I do*." Caregivers indicate the desire to do whatever is necessary to provide a better quality of life.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date Idelalisib

According to CLL PAG and LLSC, respondents indicated that the following factors are important in a new therapy: 95% of respondents indicated they wanted longer remissions with less toxicity, with the remainder 5% referencing having treatment choices and more knowledge on the treatments. Some of the comments included the following:

> "*Most important thing is to treat the CLL from the perspective that treatment is tailored to my version of the disease - better a scalpel than a chainsaw. Secondly, preserving quality of life while being treated is important…if the treatment is worse that the disease it makes it hard to be optimistic*."
>
> "*Currently available treatments put me at risk of further reductions in my already badly compromised immunity, both during treatment and after treatment*."

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

LC submits that as an oral therapy, idelalisib could be taken in the comfort of a patient's home, which may be a true benefit to patients and caregivers. An oral drug with proven efficacy may permit patients to regain a good quality of life, have fewer hospital visits and contribute to society.

Respondents to the CLL PAG and LLSC survey were also asked to rate what side effects were most important to control. Table 9 below summarized the key ranking to control side effects.

Table 9: Side effects that are important to control

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

According to LC, respondents were asked on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) and to rate the extent would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their CLL. 52.2% (n=12/23) of respondents gave a rating of 8 or higher (rating average 6.8). Many respondents described that they would be willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. The respondents reported the following:

> *"Because if I got my life back the side effects would be a reasonable trade off."* (female; 65-74; USA)
>
> *"To get a deep and long remission, I would put up with most side effects."*(female; 45-54; USA)
>
> *"Debilitating side effects are a major concern with any new drug and should be minimal with the use of any new drug."* (male; 75 or older; Canada)

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

Table 10: Level of Importance of a New Drug to be able to Control

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

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

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

LC reported that 35 respondents had direct experience with idelalisib. Nineteen (19) patients provided the length of time they have been taking idelalisib: 2 (since 2010: May; Oct); 1 (since 2011 - 4 years); 1 (since 2012 - Dec); 6 (since 2013 - June; July; July; Sept; 95 weeks; over 2 years); 5 (since 2014 - 8 months; 7 months; 7 months; 6 months; Dec) and 4 (since 2015 - 3 months; 6 weeks; 10 days; 2 weeks). The majority of respondents were male (15, 75.0%, n= 20). The age ranges of respondents were as follows:

Table 11: Age of respondents

Age (Yrs)	35-44	44-54	55-64	65-74	≥75	Response Count
n (%)	1 (5%)	4 (20%)	6 (30%)	7 (35%)	2 (10%)	20

CLL PAG and LLSC reported that 11 respondents responded to the survey on their experience with idelalisib, but only seven actually completed the survey and one person partially answered the survey. One respondent was from Canada and 6 respondents were from the USA. The age range included: 1 person 50-59 years of age, four persons 60-69 years of age and two persons 70-79 years of age. Six respondents were male. One person did not indicate age, gender or country of residence.

When asked what respondents knew about idelalisib with 1=know nothing, 3=information from my doctor and 5=well informed: 6 of 7 patients responded with 5 - well informed and one responded with 4.

Respondents were asked which symptoms of CLL that idelalisib managed for them. Please see the table below for a summary of managed symptoms.

Table 11: Summary of symptoms that idelalisib managed

CLL Symptom	# of respondents whose symptom was managed out of 7
Enlarged lymph nodes	5
Increasing white count	4
Fatigue, lack of energy	3
Enlarged spleen/discomfort on upper left side of stomach	3
Weight loss	2
Fever	1
Pain	1
Night sweats	1
Frequent infections	0
Did not manage any symptoms	0

Similarly, LC reported that since starting idelalisib, all respondents interviewed by LC emphasized their symptoms associated with CLL and their quality of life have improved dramatically. Respondents were asked to rate using a scale from 1 (No Improvement) to 10 (Very Significant Improvement) how much symptoms associated with CLL have improved with idelalisib.

It was reported that 33 of the 35 respondents (94.3%) with idelalisib experience noted an improvement in their CLL since taking idelalisib. These respondents reported that idelalisib brought their disease under control and makes them feel very similar to the way they did before their diagnosis.

Respondents were asked to rate how much each symptom has improved with idelalisib on a scale from 1 (No Improvement) to 10 (Very Significant Improvement). Table 12 below summarizes the responses of the 20 patients who answered this question. None of the patients reported a relapse of CLL.

Table 12: Symptom improvement

Improvement in symptoms	Rating of 10 N (%)	Rating of ≥8 N (%)	Rating Average	Response Count
Enlarged lymph nodes	9 (60.0%)	13 (86.7%)	9.1	15
Night sweats	3 (37.5%)	8 (100%)	9.1	8
Discomfort in left side of stomach (due to enlarged spleen)	4 (44.4%)	8 (88.9%)	8.9	9
Weight loss	2 (33.3%)	4 (66.7%)	8.2	6
Increase in white blood cell counts (leukopenia)	6 (54.5%)	7 (63.6%)	7.8	11
Fever	2 (33.3%)	5 (83.3%)	7.7	6
Shortness of breath during normal activities	1 (11.1%)	5 (55.6%)	7.6	9
Fatigue	5 (33.3%)	8 (53.3%)	7.5	15

Improvement in symptoms	Rating of 10 N (%)	Rating of ≥8 N (%)	Rating Average	Response Count
Infections	3 (27.3%)	6 (54.5%)	7.5	11
Chills	1 (20.0%)	4 (80.0%)	7.0	5
Low red blood cell counts (anemia)	1 (11.1%)	4 (44.4%)	6.9	9
Aches and pains	2 (28.6%)	2 (28.6%)	6.6	7
Low platelet counts (thrombocytopenia)	2 (18.2%)	5 (45.5%)	6.2	11
Skin rash	-	3 (37.5%)	5.5	8
Low immunoglobulin (Ig) levels	-	4 (44.4%)	5.3	9

> One respondent stated**: "***The biggest thing is the immediate benefit I had in shrinking lymph nodes, resolving my spleen size. I had an 80% reduction in the lymph burden within 6 weeks. Within 3-4 months all of my lymph nodes were back to normal size, my spleen was normal size in about 2-3 months. The fatigue was resolved immediately. My bloods were normal in about 2 months and the first time I did a MRD [minimal residual disease] test at about 6 months I was at 0.08% cancer cells in my blood. So it was like flipping an instantaneous switch that took away all of the problems and all of the symptoms of CLL and all of the blood test issues… So far, I have gotten 28 months out of idelalisib. So, I figure two wonderful years is worth it*." (male; 67: USA; on idelalisib since Dec 2012).

Respondents to the CLL PAG and LLSC surveys were also asked which symptoms of CLL that idelalisib did not manage for them. Two (2) respondents indicated fatigue, lack of energy and frequent infections were not controlled by idelalisib.

In addition, respondents were asked if idelalisib managed symptoms better than prior treatments. According to CLL PAG and LLSC, 3/7 responded "yes", 3/7 responded "no" and 1/7 received not prior treatment.

According to CLL PAG and LLSC, respondents reported the following side effects that they experienced with idelalisib:

Table 13: Side effects

Side effects of idelalisib treatment	Total respondents = 7
Cough	3
Mouth sores	3
Diarrhea	2
Fatigue	2
Infections	2
None of these	2
Abnormal liver function	1
Severe diarrhea or colitis	1
Lung infection or pneumonia	1
Thrombocytopenia (low platelets)	1
Nausea	1
Abdominal pain	1
Fever	0
Skin rashes	0

Side effects of idelalisib treatment	Total respondents = 7
Neutropenia	0
Severe rash	0

Based on the responses from the LC survey, when asked about the side effects experienced with idelalisib, 12 respondents attributed the following side effects to idelalisib:

- diarrhea (9)
- elevated liver counts (3)
- swelling of the bowels (1)
- increased lymphocyte count (1)
- cough (1)
- pneumonia (1)
- gastric problems (1)
- nausea (1)
- vomiting (1)
- compromised immunity (1)
- skin rash (1)

Five (5) respondents reported experiencing more than one side effect. Five (5) respondents indicated they had a dose reduction (from 150mg to 100mg, twice daily) due to diarrhea and/or elevated liver counts. Four (4) of these respondents remain at the lower dose and reported their CLL has not relapsed and that the side effects have subsided. One (1) of the 5 respondent discontinued idelalisib due to severe diarrhea, dehydration, vomiting, a skin rash and elevated liver counts.

Below were some notable comments gathered from respondents to the LC surveys:

> "*Complete remission of CLL, lymph nodes and spleen reduced in size by 90% in first 6 weeks of Zydelig + Rituxan. Bloods and nodes completely normal for 24 months. Minor diarrhea when Zydelig taken with Valacyclovir, no gastric problems when taken with Acyclovir or Valganciclovir*" (male; 65-74; USA; on idelalisib since December 2012)
>
> "*At the beginning I had very bad diarrhea. It has subsided now. The oncologist put me on a synthetic corticosteroid. I take 2 of those a day - 6mg a day. That stopped my diarrhea right away…They went from 150 mg to 100mg when I had the very bad diarrhea. I have been on the 100mg twice a day since August of 2013. I am getting wonderful results. I was just at the oncologist today and everything is at a 100% and my CT scan was at 100%. I really hope the drug will be funded soon because I think it is very, very good*." (male; 75; Canada; on idelalisib since July 2013)
>
> "*Severe diarrhea, severe abdominal pain, dehydration, chills, fevers, dizziness etc. Bloodwork indicates liver impairment. Had to suspend idelalisib until liver numbers come down*." (male; 55-64; USA; on idelalisib for 10 days)
>
> *The only side effect I have had up to now has been a very slight case of diarrhea when we first started the treatment and that was on the second day of starting to take the tablets. Literally it came and went within a day. It was over and done with immediately. The side effects have been far less with idelalisib. I certainly prefer to take tablets everyday as opposed to going to the hospital everyday for an infusion.* (male; 54; UK; on idelalisib since December 2014)
>
> *"Mild side effects far less of an issue than CLL symptoms."* (male; 65-74; USA; on idelalisib for nearly 2 years)
>
> *"It was just amazing, I had no side effects, my body responded to it immediately, my lymph nodes started to shrink, I felt my energy coming back and so it was just a God send*

and just a miracle drug for me." (male; 59; USA; on idelalisib since May 2010; online interview http://www.hcatodayblog.com/2015/01/22/hca-medical-breakthrough-how-clinical-trials-atsarah-cannon-are-leading-to-new-breakthroughs-in-cancer-therapies/)

CLL PAG and LLSC asked if it was necessary for respondents to interrupt treatment with idelalisib because of side effects?" 2/7 respondents replied "yes" and 5/7 respondents replied "no".

Respondents were asked as to which of the following side effects of idelalisib that they were willing to tolerate. Below is a summary of their responses.

Table 14: Side effects patients are willing to tolerate

Side effects of idelalisib treatment Patients are willing to tolerate	Total respondents = 7
Fatigue	5
Diarrhea	4
Thrombocytopenia (low platelets)	4
Cough	4
Neutropenia	3
Abnormal liver function	2
Nausea	2
Fever	1
Abdominal pain	1
Skin rashes	1
Chills	1
None of these	1
Severe diarrhea or colitis	0
Lung infection or pneumonia	0
Infections	0

Based on the survey from LC, 24 respondents who indicated they had received CLL treatment(s) previous to idelalisib were asked "how does idelalisib compare in terms of side effects to other treatments you have taken for your CLL on a scale of 1 - 10, with 1 being (Far Less Side Effects) and 10 being (Many More Side Effects)". According to LC, 19 respondents answered this question; rating average 3.4 with 12 (63.1%) of the respondents rating side effects as ≤3. Below is a summary of the findings:

Table 15: How idelalisib compares in terms of side effects with other treatments received

Rating	1	2	3	4	5	6	7	8	9	10
n (%) N = 19	8 (42.1%)	2 (10.5%)	2 (10.5%)	0 (0%)	4 (21.1%)	0 (0%)	0 (0%)	1 (5.3%)	1 (5.3%)	1 (5.3%)

CLL PAG and LLSC noted that 4/7 of respondents were able to access treatment in their own community. Of those unable to access treatment in their community, respondents stated: "*Don't think so, it's part of a clinical trial*", "*I get mine straight from the pharma company by Federal Express. It is too cost prohibitive to use a local pharmacy with a prescription from MD Anderson*", "*Was part of a clinical trial in Canada*".

It was also reported that 6/7 respondents indicated there were not financial implications other than drug costs, 1/7 respondents did not respond.

The LC survey also reported on respondents' opinion as to how idelalisib has changed or is expected to change their long-term health and well-being as follows:

Table 16: Change in Health from being on idelalisib

Long-Term Health or Well-Being (N = 18)	Survey & Interviews
Live longer	15 (83.3%)
Control disease and symptoms associated with the disease	15 (83.3%)
Improve quality of life	15 (83.3%)
Improve blood counts	14 (77.8%)
Bring about a remission	13 (72.2%)

One respondent stated: **"***I am very happy as it is working for me. I know it has side effects. Still overall no matter how it affects me with the side effects it is still controlling the cancer and that is what is the most important. I am really happy, I am coming to two years that I have been ok and that the cancer has been controlled with idelalisib."* (female; 42; Canada; on idelalisib since June 2013)

Respondents from CLL PAG and LLSC surveys also noted the following:

"It has been a great benefit, because even though it has not resolved all of my symptoms, it has helped me to avoid more toxic chemo treatments indefinitely."

"Controlling cancer cells greatly"

"It saved my life after running through all protocols. would still be using if it weren't for lung problem"

"Positive. Felt very well on this drug until I had a problem with Swollen lung tissue - 3 1/2 yrs after starting clinical trial".

"I have just started this protocol this past week. So far all is good."

"It has reduced my glands that were re enlarging with CLL again. It gives me peace of mind."

"*Almost killed me"*

Below were the overall experiences with idelalisib (both positive and negative) that were reported by respondents to the CLL PAG and LLSC surveys. It was reported that 6/7 respondents indicated that idelalisib improved their overall health and well-being.

"Very positive. My bulky lymph nodes shrank immediately after starting treatment (incredibly, within 3-4 days, baseball sized nodes in my armpits were no longer palpable)."

"Excellent response reducing spleen and per cent of cancer"

"At this point, it is working as well as imbruvica did for me before I relapsed. I suspect I will also relapse from Zydelig, but I have a very high quality of life using this drug. Nothing negative to report. The side effects are workable and much easier than the side effects of FCR and Revlimid".

"Terrible"

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

"We are very fortunate to be able to access all the new meds available to us CLLers"

"Diagnosed in 1989 at age 48. I have well tolerated lots of chemo plus a stem cell transplant. Given that, I was disappointed and surprised to have "hit the wall" with Ibrutinib. I got A-fib and a strain of Steven's Johnson Syndrome, forcing me to stop Ibrutinib at 6 months [June 2014]. In spite of all this, life is good. My lifestyle is active and enjoyable. My anecdotal observation is that Ibrutinib seems very well tolerated by patients with only one or two pre-treatments, but not so well by the heavily pre-treated. I hope my Zydelig/Rituxan journey is a good one."

"*My quality of life has improved massively. Before starting idelalisib, I literally could not get out and about. I was getting up in the morning and was having breakfast and would sit down in a chair and not do anything. I would go back to bed and sleep for a while and wake and go back to sleep… I had no life until I started on this idelalisib… It's unreal how I feel so much better now compared to how I felt 3 months ago. It's difficult to put into words actually. It's such an amazing difference. I would recommend idelalisib to other patients with CLL. It has been the quickest and most positive reaction I have had since taking treatment right at the beginning, when I was first diagnosed with CLL [in 2001]."* (male; 54; UK ; on idelalisib since December 2014)

"*Combination of rituximab & idelalisib reduced my disease and symptoms in 6 weeks and I returned to work & full life. Idelalisib has eliminated all symptoms for nearly 2 years. Prior to treatment with idelalisib & rituximab I was unable to work, drive a car, or travel and had frequent infections. Since starting idelalisib my life is entirely normal and I am working, traveling and have my life back."* (male, USA, 65-74; has been on idelalisib for nearly 2 years).

"Overall, I would say that idelalisib is working very well and that my quality of life is very good…Even if it only works for 2-3 years I would gladly take it… I think idelalisib is working perfectly fine and like I said before if I had to choose between the side effects and the drug then I would take the drug because I can live with the side effects. Overall my quality of life is good and I am happy… I would recommend idelalisib to other patients with CLL, big time, because it works." (female; 42; Canada; on idelalisib since June 2013)

4.3 Additional Information

CLL PAG and LLSC stated that it is important to note that the protocol for idelalisib includes the monoclonal antibody rituximab, which is not available in all provinces for more than one treatment. This could make the idelalisib protocol unavailable to patients who would benefit from it.

5 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 (www.cadth.ca/pcodr). 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 idelalisib in combination with rituximab (idelalisib/rituximab):

Clinical factors:

- New class of drug with severe toxicities to monitor
- Generalizability of results from the submitted trial to the Canadian context as rituximab monotherapy is not a standard of care in Canada and is not funded for the re-treatment of CLL
- In the trial, rituximab is given at higher doses and more frequently than current treatment protocols with rituximab
- Sequential use of idelalisib/rituximab and other new treatments now available for CLL

Economic factors:

- Large prevalent patient population
- Additional drug and administration costs of rituximab

Please see below for more details and other factors.

5.1 Factors Related to Comparators

For previously treated CLL patients, the treatment varies across the jurisdictions and there is no standard of care. In some provinces, rituximab in combination with chemotherapy is available for relapsed/refractory CLL patients who have not been previously treated with rituximab. Other treatments available for previously treated CLL patients include alemtuzumab, bendamustine, chlorambucil, cyclophosphamide/prednisone, or cyclophosphamide/vincristine/prednisone (CVP).

PAG noted that the pivotal trial submitted compared idelalisib/rituximab to rituximab monotherapy, which is not the current standard of care in Canada. In addition, PAG noted that ibrutinib may become available for the same patient population as idelalisib/rituximab in the relapse/refractory setting. PAG is seeking comparative data of idelalisib/rituximab to FCR, bendamustine, obinutuzumab/chlorambucil and ibrutinib, if available.

5.2 Factors Related to Patient Population

As hematologic malignancies tend to be less common than solid tumours overall, the number of patients diagnosed with CLL is small. However, given the course of the disease and the limited options for refractory disease, PAG noted that a large prevalent number of previously treated CLL patients would be eligible to receive treatment with idelalisib.

PAG noted that idelalisib is the first in a new class of drug that could fill the gap in therapy for previously treated CLL patients.

PAG is requesting information on the relative merits and sequencing of drugs for CLL based on clinical benefits and cost-effectiveness, if available. In particular, PAG is seeking information on

- whether specific cytogenic abnormalities respond better to treatment with idelalisib/rituximab
- the clinical efficacy of idelalisib/rituximab for patients who have been previously treated with other anti-CD20 drugs (e.g. obinutuzumab or ofatumumab)
- whether the use of idelalisib/rituximab in patients who have received only one prior therapy would be more beneficial
- the appropriate sequence of use of idelalisib/rituximab and other treatments.

Idelalisib is in combination with rituximab. Rituximab is given at higher doses and more frequently than current treatment protocols with rituximab. PAG noted that there will be patients who may not tolerate this dose of rituximab and is seeking any available information on the use of idelalisib as single agent in the treatment of CLL.

PAG noted that idelalisib for the treatment of refractory follicular lymphoma received a Notice of Compliance with conditions from Health Canada but this indication is not part of the pCODR funding request. Thus, PAG has concerns for indication creep with requests for treatment of these lymphomas.

5.3 Factors Related to Dosing

The dose of idelalisib is same for all patients and one dose reduction is supported. These are enablers to implementation.

PAG noted there are two tablet strengths available to accommodate for dose reductions. However, PAG has some concerns with drug wastage if dose reductions require change in tablet strength prior to the previously dispensed strength being all used.

5.4 Factors Related to Implementation Costs

Idelalisib is the first in a new class of drug. Health care professionals would need to become familiar with monitoring and managing toxicities and drug-drug interactions associated with idelalisib. At the time of the PAG input, the Health Canada approval for idelalisib has not yet been issued. However, PAG noted that the FDA approval contains several black box warnings for fatal and serious hepatotoxicities, severe diarrhea, colitis, pneumonitis, and intestinal perforation. These and other adverse events would require additional health care resources to monitor and treat.

The unknown number of patients who would be eligible and treatment duration are barriers to implementation as it is difficult to determine the budget impact.

In addition, PAG noted that rituximab monotherapy is not funded for the re-treatment of CLL in any of the provinces and rituximab is only funded for six cycles in first-line treatment of CLL in most provinces. Additional pharmacy and nursing resources and chair time will be required to prepare and administer the additional rituximab.

5.5 Factors Related to Health System

PAG noted that idelalisib is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings, where patients can take oral drugs at home. PAG identified the oral route of administration is an enabler to implementation. However, in some jurisdictions, oral medications are not funded in the same mechanism as intravenous cancer medications. This may limit accessibility of treatment for patients in these jurisdictions as they would first require an application to their pharmacare program and these programs can be associated with co-payments and deductibles, which may cause financial burden on patients and their families. The other coverage options in those jurisdictions which fund oral and intravenous cancer medications differently are: private insurance coverage or full out-of-pocket expenses.

5.6 Factors Related to Manufacturer

PAG noted the high cost of idelalisib would also be a barrier.

PAG noted that the tablets must be dispensed in its original container and thus, smaller quantities cannot be dispensed. There are some concerns for drug wastage if dose reductions occur.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of idelalisib in combination with rituximab in the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

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

Table 17: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Phase III Randomized control trials	Patients with relapsed chronic lymphocytic leukemia	Idelalisib 150 mg plus Rituximab 375 mg/m^2 followed by 500mg/m^2	• Placebo • Idelalisib • Chlorambucil plus an anti-CD20 monoclonal antibody • Rituximab • Obinutuzumab • Ofatumumab • Fludarabine plus rituximab (FR) • Bendamustine plus rituximab (BR) • Fludarabine, Cyclophosphamide and rituximab (FCR) • Ibrutinib • Alemtuzumab • Cyclophosphamide/ prednisone • Cyclophosphamide/ vincristine/prednisone (CVP)	-**Response rate** **-Overall survival** **-Progression free survival** -Adverse events including **fatigue**, **enlarged lymph nodes**, **infections,** severe diarrhea/colitis, hepatotoxicity, intestinal perforations, pneumonitis- -**Quality of life** -Subgroup analyses in patients with cytogenic abnormalities and in patients with other prior treatments - Which line of treatment/sequencing is most beneficial with Idelalisib/rituximab -Single agent idelalisib

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

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [idelalisib- Zydelig, CAL–101] and [chronic lymphocytic leukemia].

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

The search is considered up to date as of July 2, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicatrials.gov and Ontario Institute for Cancer Research – Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and [Include other conferences as per the guidance provided in S2 on tumour type, e.g. ESMO, ASH, SABCS] were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

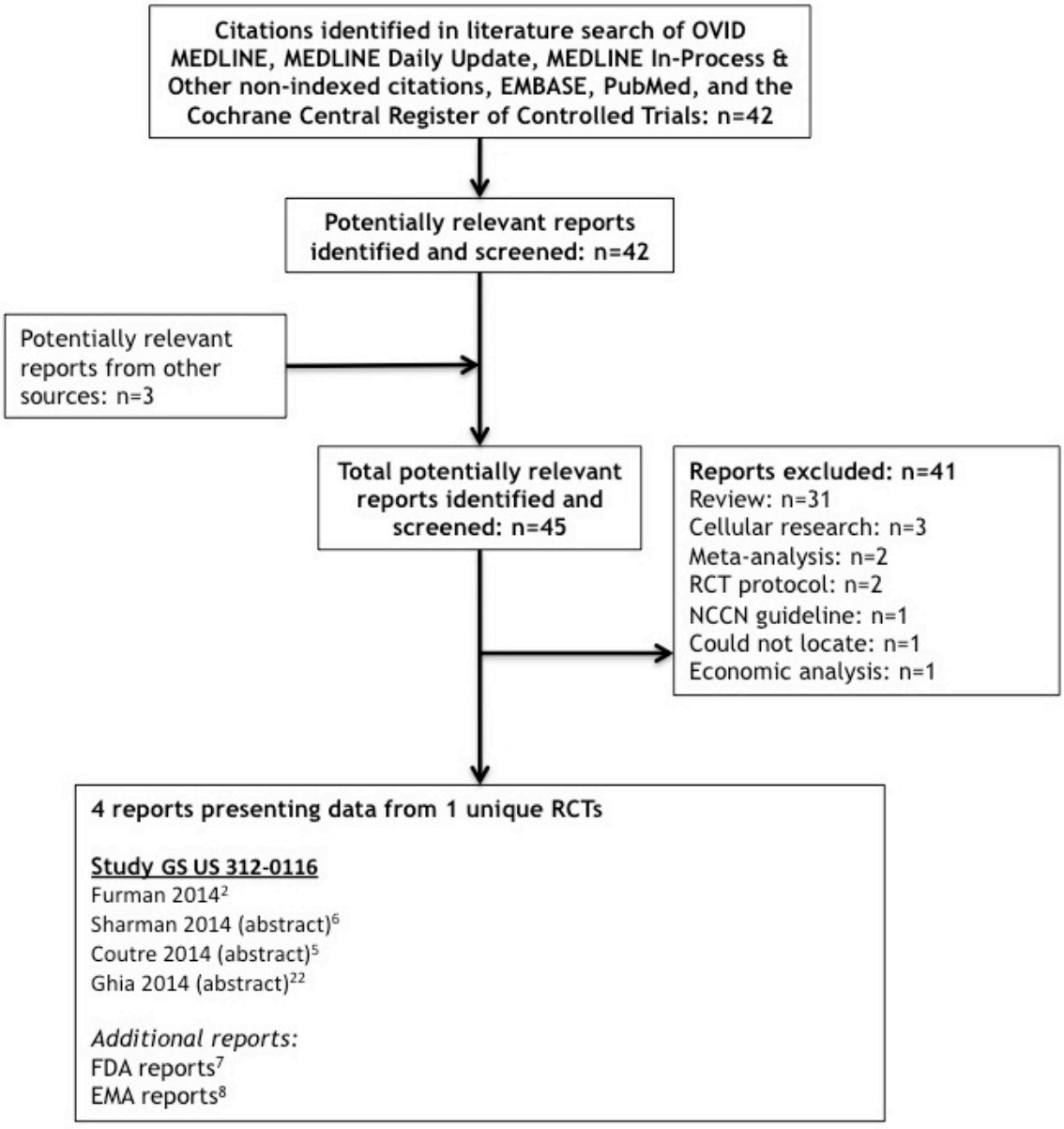
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 45 potentially relevant reports identified, 4 studies, representing one unique trial were included in the pCODR systematic review[2,5,6,22] and 45 studies were excluded. Studies were excluded because they were review,[23-53] cellular research,[54-56] meta-analysis,[57,58] RCT protocol,[59,60] guideline,[61] could not locate the study,[62] and economic analysis.[63]

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



Note: Additional data related to the study were also obtained through requests to the Submitter by pCODR

6.3.2 Summary of Included Studies

One phase 3, double blind, randomized controlled trial comparing idelalisib and rituximab to placebo and rituximab in relapsed CLL patients met the inclusion criteria for this review.

6.3.2.1 Detailed Trial Characteristics

Table 18. Summary of Trial characteristics of the included Study[2,64]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
NCT01539512 GS US 312-0116 Furman et al, 2014 Phase 3, randomized, double blind N=220 Study start date: April 2012 Primary Study completion date: October 2013 90 study locations in: France, Germany, Italy, the United Kingdom and the United States Funded by: Gilead Sciences	**Inclusion Criteria:** • Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy • Require therapy for CLL • Have experienced CLL progression < 24 months since the completion of the last prior therapy • Currently not sufficiently fit to receive cytotoxic therapy because of chemotherapy-induced bone marrow damage or comorbidities. **Exclusion criteria** • Known histological transformation from CLL to an aggressive lymphoma. • Presence of intermediate or high-grade myelodysplastic syndrome. • History of prior allogeneic bone marrow progenitor cell or solid organ transplantation. • Ongoing immunosuppressive therapy other than corticosteroids. • Prior therapy with any inhibitor of AKT, Bruton tyrosine kinase (BTK), Janus kinase (JAK), mammalian target of rapamycin (mTOR), phosphatidylinositol 3 kinase (PI3K: including IDELALISIB), or spleen tyrosine kinase (SYK). • History of anaphylaxis with previous use of monoclonal antibodies. • Prior or ongoing clinically significant illness or medical condition in the investigator's opinion, could adversely affect the safety of the subject or the assessment of study results.	idelalisib 150 mg tablet administered orally twice daily plus rituximab administered intravenously 8 times through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter vs. Placebo plus rituximab administered intravenously 8 times through Week 20: Day 1: 375 mg/m^2, and 500 mg/m^2 thereafter	**Primary Outcome:** • Progression-free survival **Secondary Outcomes:** • Overall response rate • Lymph node response rate • Overall survival • Complete response rate
CLL= Chronic lymphocytic leukemia			

a) Trials

One phase 3, randomized, double blind trial met the inclusion criteria for this systematic review.[2] The GS US 312-0116 study by Furman et al. included patients with relapsed chronic lymphocytic leukemia. Patients were randomized in a 1:1 ratio by an interactive web response system to receive idelalisib plus rituximab or placebo plus rituximab. Patients were stratified by 17p deletion and/or p53 mutation in CLL cells - either vs. neither, immunoglobulin heavy chain variable region (IgHV) mutation, un-mutated (or IgHV3-21) vs. mutated, and any prior therapy with an anti-CD20 therapeutic antibody - yes vs. no.[65] Patients along with their caregivers and study investigators were blinded to which treatment the patients were allocated. Un-blinding would occur only in emergencies. The study was multicentred and was conducted in 90 centres in Europe and the United States. Gilead Sciences funded the study.[64]

The primary outcome in the Furman et al. trial was progression free survival. This was defined as the first documentation of disease progression or death after the time of randomization. Disease progression was based on criteria defined by the 2008 update of the International Workshop on CLL guidelines (IWCLL). The criteria included; the appearance of any new lesion; increase by ≥ 50% in the sum of the products of the perpendicular diameters of measured lymph nodes (SPD); new or ≥ 50% enlargement of liver or spleen; transformation to a more aggressive histology (e.g., Richter's or prolymphocytic transformation); reduction in the number of blood cells (cytopenia) attributable to CLL.[64] Progression free survival was calculated using the Kaplan–Meier method and compared rates using a stratified log-rank test. Hazard ratios were calculated with a Cox model, which included adjustment for stratification. [2] The study size provided a power of more than 85% to detect a 75% improvement in the median progression free survival. There were two interim analyses that were pre-specified after 50% and 75% of 119 events had occurred, at alpha levels of 0.001 and 0.005, respectively. The results in the Furman et al. study are based on an August 30 2013 data cut off.[2] This outcome was independently assessed by an Independent Review Committee (IWC).[4]

Secondary outcomes included overall response rate and complete response rate. Overall response rate was described as the percentage of patients that had either a complete response or partial response. Complete response was defined as no lymphadenopathy, hepatomegaly, splenomegaly; normal complete blood count; confirmed by bone marrow aspirate & biopsy. Partial response was defined "as >1 of the following criteria: a 50% decrease in peripheral blood lymphocytes, lymphadenopathy, liver size, spleen size; plus ≥ 1 of the following: ≥ 1500/µL absolute neutrophil count, > 100000/µL platelets, > 11.0 g/dL hemoglobin or 50% improvement for either of these parameters without transfusions or growth factors".[64] Lymph node response rate was also a secondary outcome. This was described as the percentage of participants who achieved a ≥ 50% decrease from baseline in the SPD (sum of the products of the greatest perpendicular diameters) of index lymph nodes. The final secondary outcome was overall survival. This was calculated from the time of randomization to the time of death from any cause.[64] The rate of overall survival was 92% and 80% at 12 months for the idelalisib and placebo group, respectively. The median duration of overall survival had not been reached at the time of analysis.

b) Populations

A total of 220 patients were included in the Furman et al. study. There were 110 patients randomized to the idelalisib and rituximab arm and 110 to the rituximab and placebo arms. Patient characteristics can be seen in Table 19.

Table 19: Patient baseline characteristics[2]

Characteristic	Idelalisib + rituximab N=110	Rituximab + placebo N=110
Median age (range) - years	71 (48-90)	71 (47-92)
< 65 years (n)	21[64]	27[64]
Gender, males (%)	69[64]	62[64]
Ethnicity[64]		
Hispanic or Latino (n)	3	2
White (n)	100	98
Black or African American (n)	3	3
Other (n)	2	2
Rai stage -% of patients*		
0	0%	1%
1 or 2	31%	26%
3 or 4	64%	65%
Missing date	5%	7%
Binet Stage[64] (n)		
A+B	36	36
C	63	60
Extent of CLL - % of patients		
Splenomegaly§	79%	64%
Hepatomegaly§	54%	57%
Anemia (n)		
Any grade	75	72
Grade ≥3	6	11
Neutropenia (n)		
Any grade	34	35
Grade ≥3	17	16
Thrombocytopenia (n)		
Any grade	62	61
Grade ≥3	16	29
Median absolute lymphocyte count (range - per mm^3	31,960 (280-262,710)	30,880 (290-398,740)
Median estimated creatinine clearance (range) - ml/min	62 (32-161)	67 (23-199)
Genetic stratification factors - % of patients		
Unmutated IGHV	83%	85%
17p Deletion or TP53 mutation	42%	45%
Median CIRS score (range) ¶	8 (3-18)	8 (1-18)
Previous CLL treatment		
Median no. of drugs (range)	3(1-12)	3(1-9)
Drugs - % of patients		
Rituximab	91%	88%
Cyclophosphamide	64%	70%
Fludarabine	56%	64%
Bendamustine	58%	54%
Chlorambucil	31%	22%
Prior regimens, %		
BR	46%	43%
FCR	33%	36%
R monotherapy	32%	31%

Characteristic	Idelalisib + rituximab N=110	Rituximab + placebo N=110
FR	16%	18%
Chl monotherapy	18%	14%
*In the Rai staging system, stage 0 denotes low-risk disease, stage 1 or 2 intermediate risk and stage 3 and 4 high risk § Based on 91 patients in idelalisib + R arm and 90 patients in placebo + R arm with baseline assessment completed ¶ Scores on the cumulative illness rating scale (CIRS) range from 0-56, with higher scores indicating an increased number or severity of coexisting illnesses.		

c) *Interventions*

Patients randomized to the idelalisib and rituximab arm received idelalisib as a 150 mg tablet taken orally twice daily. Rituximab was administered intravenously. The starting dose was 375 mg/m^2, followed by 500 mg/m^2 every two weeks for four doses and then every four weeks for three doses for a total of eight infusions. Patients randomized to the placebo and rituximab arm received a placebo that looked identical to idelalisib and then the same dose and schedule of rituximab as in other arm.[2] Patients were treated with idelalisib or placebo until definitive disease progression until there was a valid reason for discontinuation.

Patients in the idelalisib arm could have their dose doubled to 300mg twice daily at disease progression. Patients in the placebo arm who had progression were eligible to receive idelalisib therapy in a double-blind extension study (Study 117).[2] In the placebo arm, of patients with progressive disease (n=51), 42 patients received idelalisib in Study 117, 7 died, and 2 discontinued the study. Of the patients without progressive disease prior to unblinding (n=59), 43 received idelalisib in Study 117, 9 died, and 7 discontinued the study.

Modifications and delays in dose were allowed in Study 116. If an adverse event occurred, the study drug was held until the adverse event resolved to grade ≤1. When the patients started treatment again the dose was to be reduced to dose level - 1 (100 mg/ twice a day).[4,7]

There were 16 (14.5%) patients in the idelalisib group and none in the placebo group who had a dose reduction. A dose interruption occurred in 39 (35.5%) of patients in the idelalisib arm and in 19 (17.6%) in the placebo arm.[7]

In the idelalisib group the median exposure duration was 5.0 months (range: 0.3-17.3) as of October 9, 2013.[7] The treatment duration was so short because of the recommendation of the data and safety monitoring board to stop the study. At the time that the study was terminated, 81% of patients in the idelalisib group were still receiving the drug contrasted to 52% of patients in the placebo group. Disease progression was the most common reason for study discontinuation.[7] The median cumulative dose of idelalisib was 20,925mg (range 1350-75,600mg).[7] The median number of doses of rituximab was 8 in the idelalisib arm and 6 in the placebo arm.[7] The median length of follow-up was 13 months in the idelalisib arm and 11 months in the placebo arm.[6]

d) *Patient Disposition*

The study included 220 patients. One hundred and ten patients were randomized to each arm. All patients randomized to the idelalisib and rituximab arm received treatment and 107 patients randomised to placebo and rituximab received treatment. Of the patients in this group who did not receive treatment, one patient had abnormal liver tests, one died

prior to randomization and one missed starting because of the data cut off.[8] Patient disposition can be seen in Table 20.

Table 20. Patient disposition[7]

	Idelalisib + rituximab N=110; N (%)	Placebo + rituximab N=110; N (%)	Total N=220; N (%)
Treatment ongoing	80 (72.7)	51 (46.4)	131 (59.5)
Discontinued	30 (27.3)	59 (53.6)	89 (40.4)
Reason for treatment discontinuation			
Progressive disease or lack of efficacy	7 (6.4)	42 (38.2)	49 (22.3)
Death	2 (1.8)	2(1.8)	4 (1.8)
Adverse event	12 (10.9)	12 (10.9)	24 (10.9)
Withdrawal by subject	8 (7.3)	2 (1.8)	10 (4.5)
Physician decision	1 (0.9)	1 (0.9)	2 (0.9)

Twelve patients (10.9%) in each arm discontinued the study due to adverse events.[7] The reasons for discontinuation can be seen in Table 21.

Table 21: Adverse events leading to study withdrawal[7]

	Idelalisib	Placebo
Arrhythmia	1	0
Bronchial carcinoma	1	0
Colitis	1	0
Exfoliative dermatitis	1	0
Diarrhea	1	0
Febrile Neutropenia	1	0
Heomolytic anemia	1	0
Pneumocystis jiroveci pneumonia	1	0
Fungal pneumonia	1	0
Pneumonitis	1	1
Rash maculo-papular	1	0
Sepsis	1	2
Transaminases increased	1	0
Acute Respiratory failure	0	1
Cardiac failure	0	1
Chronic obstructive pulmonary disease	0	1
Eczema	0	1
Gastroenteritis	0	1
Left ventricular failure	0	1
Mucosal infection	0	1
Multi-organ failure	0	1
Pancytopenia	0	1
Pneumonia	0	2
Pulmonary edema	0	1

e) Limitations/Sources of Bias

The study by Furman et al. was a well-conducted trial. Bias was evaluated using the SIGN-50 checklist and no bias could be found. The checklist is included in Table 22 below.[66] The

only issue found with the SIGN checklist was that the results were pooled and were not presented for each site or region independently and therefore cannot be compared.

Table 22: SIGN checklist for controlled trials

Section 1: Internal validity		
In a well conducted RCT study…		**Does this study do it?**
1.1	The study addresses an appropriate and clearly focused question.	Yes
1.2	The assignment of subjects to treatment groups is randomised.	Yes
1.3	*An adequate concealment method is used.*	Yes
1.4	Subjects and investigators are kept 'blind' about treatment allocation.	Yes
1.5	The treatment and control groups are similar at the start of the trial.	Yes
1.6	The only difference between groups is the treatment under investigation.	Yes
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	Yes
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	19.0% in the idelalisib group and 13.6% in the placebo arm.
1.9	All the subjects are analysed in the groups to which they were randomly allocated *(often referred to as intention to treat analysis)*.	Yes
1.10	Where the study is carried out at more than one site, results are comparable for all sites.	Can't say
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	*How well was the study done to minimise bias?*	High quality (++)
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	Yes
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

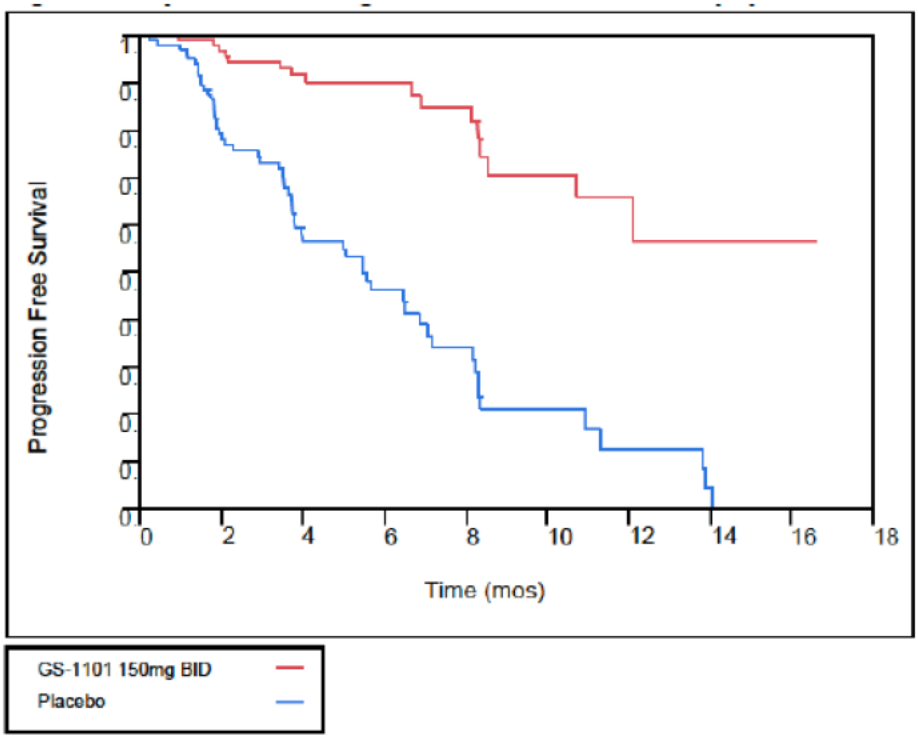
Efficacy Outcomes

Progression Free survival

Independently assessed progression free survival, which was the primary outcome, showed the rate of progression free survival at 24 weeks to be 93% in the idelalisib arm, and 46% in the placebo arm (adjusted HR for progression or death in the idelalisib group is 0.15; 95% CI: 0.08-0.28; unadjusted P<0.001).[2] The pre-specified stopping boundary for efficacy at

the significance level of 0.001 was crossed and this led to an early stop of the trial. At the second interim analysis, the median progression free survival was not met in the idelalisib group and was 5.5 months in the placebo group (HR 0.18; 95%CI: 0.10-0.32; p<0.0001).[5] The rates of progression free survival at 12 months were 66% for patients in the idelalisib arm and 13% for patients in the placebo arm.[6] Disease progression was seen in 11 (10%) patients in the idelalisib arm and in 51 (46%) patients in the placebo arm.[7] The Kaplan-Meier figure for progression free survival can be seen in Figure 2.

Figure 2: Kaplan-Meier figure for progression free survival in the ITT population[7]



Source: FDA reviewer's analysis

A pre-specified subgroup analysis showed that progression free survival strongly favoured the idelalisib arm for all subgroups, including those stratified according to the presence or absence of the 17p deletion or *TP53* mutation and *IGHV* mutational status. This can be seen in Table 23.

Table 23: subgroup analysis for progression free survival[6]

	Idelalisib - median months	Placebo - median months	Hazard Ratio	95% CI
Total N=220	NR	5.5	0.18	0.10-0.32
Del (17p) and/or TP53 mutation N=95*	NR	4.0	0.16	0.07-0.37
Del (17p) N=57	NR	3.7	0.11	0.03-0.38
TP53 mutation N=81	NR	3.8	0.17	0.07-0.39
IGHV unmutated N=184	NR	5.5	0.14	0.07-0.27
ZAP70 positive N=191	NR	5.5	0.16	0.09-0.29
Rai stage III/IV N=142	NR	4.0	0.16	0.08-0.31

	Idelalisib - median months	Placebo - median months	Hazard Ratio	95% CI
ß 2-microglobulin >4 mg/L N=177	NR	5.0	0.18	0.10-0.32
* Number of patients on both arms with respective test result. Distribution of risk features was balanced on both arms. NR = Not reached				

Overall survival

Data from the August 30 2013 cut-off showed that in the idelalisib group the rate of overall survival at 12 months was 92% compared to 80% in the placebo arm (adjusted HR for death 0.28; 95% CI, 0.09 to 0.86; P=0.02).[2] The two groups have not yet reached the median duration of overall survival. The survival curve for the idelalisib group narrowly separates from the placebo group immediately and then widens at 2 and again at 8 months and stays separate. There were 16 death while on treatment in the study, four (4%) in the idelalisib group and 12 patients (11%) in the placebo group.[2]

Overall Response

Overall response was evaluable in 176 patients with 88 patients in each group from the August 30 2013 cut-off. Patients were evaluable if they had at least one post-baseline assessment or had discontinued the study before the first assessment at the time of this analysis. In the first interim analysis, in the idelalisib group the overall response rate was 81% (95% CI: 71-88) compared to 13% (95% CI: 6-21) in the placebo group (odds ratio, 29.92; P<0.001). All of the responses were partial responses.[2] The second interim analysis (October 9, 2013) showed an overall response rate of 74.5 (95% CI: 65.4-82.4) for the idelalisib group and 14.5 (95% CI: 8.5-22.5) for the placebo group. The odds ratio for the overall response was 17.28 (95% CI: 8.66-34.46) which favoured the idelalisib group ($p=6.3x10^{-19}$).[8] The median time to response from the second interim analysis in the idelalisib group was 2.0 months and 3.6 months in the placebo group.[8] The overall response rate also favoured the idelalisib group in predefined subgroup analyses. This can be seen in Table 24.

Table 24. Overall response rate for subgroups[8]

Subgroup	Odds ratio (95% CI)
Either 17p deletion and/or TP53 mutation present	25.8 (8.55-77.88)
Neither 17p deletion and/or TP53 mutation present	13.03 (5.46-31.1)
Mutated IGHV	28.13 (4.46-177.46)
Unmutated IGHV	15.75 (7.55-32.86)
17p deletion	81.43 (9.27-715.08)
No 17p deletion	12.80 (6.06-27.05)
Males	19.64 (8.04-46.96)
Females	16.39 (5.28-50.91)
Age < 65 years	25.60 (5.35-122.42)
Age ≥ 65 years	15.45 (7.24-33.0)
Whites	16.22 (7.91-33.25)
Non-whites	45(3.47-584.34)

Lymph-Node Response

Lymph-node response was evaluated in 169 patients. These patients had at least one post-baseline imaging assessment of the lymph-node response to treatment. These independently assessed results showed that patients in the idelalisib group had a significantly higher proportion of patients with a reduction of 50% or more in lymphadenopathy 93%; 95% CI: 85-97 compared to 4%; 95% CI: 1-10, in the placebo group, with an odds ratio of 264 (P<0.001).[2]

Quality of Life

Quality of Life was assessed using the 44-item Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) scale measured. This scale measure physical, functional, social and emotional well-being and leukemia-specific concerns. The FACT-Leu Total score is the sum of all subscales and the Trial Outcome Index (TOI) is the sum of the physical, functional and leukemia specific subscales. The higher the score the better the health related quality of life.

A repeated measures mixed-effects model evaluated change from baseline and between-arms. The results (Table 25) indicate that idelalisib plus rituximab significantly improved leukemia-related symptoms (LeuS) by Week 8 compared to placebo plus rituximab and the improvement became clinically meaningful by Week 12. In the mixed-effects model analysis for overall treatment effect, physical (p=0.015), functional well-being (p=0.014), Leukemia specific subscale (p=0.001), TOI (p=0.002), and FACT-Leu total (p=0.006) scores were significantly higher for idelalisib plus rituximab compared with placebo plus rituximab. Emotional and social subscales scores did not change significantly over time.[22]

Table 25: A repeated measures mixed-effects model results[22]

Week	Physical	Functional	Leukemia Specific	TOI	FACT-Leu Total
2	-0.1 (0.65)	0.6 (0.80)	0.4 (1.31)	1.3 (2.38)	1.1 (2.96)
4	0.8 (0.66)	1.0 (0.81)	2.5 (1.33)	4.0 (2.41)	4.0 (3.01)
6	0.1 (0.68)	1.0 (0.84)	2.2 (1.37)	2.9 (2.48)	3.9 (3.09)
8	0.6 (0.71)	0.7 (0.87)	3.5 (1.43)*	4.6 (2.57)	5.2 (3.2)
12	1.1 (0.75)	1.5 (0.92)	4.7 (1.51 **	7.0 (2.72)**	6.5 (3.39)
16	1.9 (0.83)*	1.3 (1.01)	5.3 (1.66)**	8.4 (2.99)**	9.2 (3.72)**
20	1.6 (0.91)	1.4 (1.13)	5.4 (1.85)**	9.0 (3.33)**	9.0 (4.14)**
24	1.8 (1.02)	1.9 (1.26)	5.0 (2.06)**	9.1 (3.69)**	10.0 (4.58)**
30	2.1 (1.14)	2.6 (1.41)	3.0 (2.32)	7.7 (4.13)	9.6 (5.13)
36	1.5 (1.26)	2.8 (1.56)	5.1 (2.54)**	8.2 (4.59)	9.1 (5.69)
42	2.1 (1.57)	2.8 (1.93)	3.9 (3.16)	8.1 (5.57)	9.1 (6.92)
48	3.6 (1.79)**	3.6 (2.20)	5.5 (3.60)	12.4 (6.32)**	13.1 (7.85)

* p< 0.05;
** p<0.05 and exceeded established minimally important difference (MID) change scores of 2, 4, 5 and 6 points for physical, leukemia specific, TOI and FACT-Leu total, respectively, between arms.

Harms Outcomes

Adverse Events

Most grade 1 and 2 adverse events (AEs) were in-line with those expected for a relapsed CLL population. For the idelalisib group the top five grade 1 and 2 AEs were: pyrexia (29%), fatigue (24%), nausea (24%), chills (22%) and diarrhea (19%). For the placebo arm the top five grade 1 and 2 AEs were: infusion-related reaction (28%), fatigue (27%), cough (25%), nausea (21%) and dyspnea (19%).[2] Treatment emergent adverse events that were grade 3 or 4 that occurred in ≥ 2% of all subjects can be seen in Table 26 below.[7] The most common adverse events in both groups were neutropenia 22% in the idelalisib arm and 12% in the placebo arm and pneumonia 13% in the idelalisib arm and 10% in the placebo arm.

Table 26: Grade 3 or 4 treatment emergent adverse events that occurred in ≥ 2% of all subjects[7]

Event	Idelalisib + rituximab N=110; N (%)	Placebo + rituximab N=110; N (%)
Neutropenia	24 (21.8)	13 (12)
Pneumonia*	14 (12.7)	11 (10.2)
Sepsis¶	7 (6.4)	2 (1.9)
Fatigue	5 (4.5)	3 (2.8)
Febrile neutropenia	5 (4.5)	4 (3.7)
Anemia	5 (4.5)	7 (6.5)
Diarrhea	4 (3.6)	0
Pneumonitis	4 (3.6)	1 (0.9)
Rash §	4 (3.6)	1 (0.9)
Colitis	3 (2.7)	0
ALT increased	3 (2.7)	0
Pyrexia	3 (2.7)	1 (0.9)
Transaminases increased	3 (2.7)	1 (0.9)
Asthenia	1 (0.9)	4 (3.7)
Infusion related reaction	0	4 (3.7)

* Includes: pneumonia, lung infection, pneumocystis, jiroveci pneumonia, legionella pneumonia, lung infection pseudomonal and pneumonia fungal
¶ Includes: sepsis, septic shock, neutropenic sepsis and sepsis syndrome
§ Includes: rash, dermatitis exfoliative rash, rash macular, rash maculo-papular, rash popular, rash pruritus and skin disorder

Significant adverse events

Hepatotoxicity

There was one case of Hy's laws was observed with the use of idelalisib in the study. This patient discontinued idelalisib permanently.[7] In addition there were 38 (34.5%) patients with ALT elevations that were treatment emergent in the idelalisib arm compared to 11 subjects (10.2%) in the placebo arm. This was based on an analysis of the laboratory dataset. In the idelalisib arm the median time to onset was 93 days (range 15-308). In the idelalisib arm AST Elevations occurred in 27 (24.5%) patients compared to 16 (14.8%) patients in the placebo arm. The median time to onset in the idelalisib arm was 92 days (range 15-338). Additionally there were 11 patients in the idelalisib arm who had ALT elevations 3X ULN (CTCAE grade 2) compared to 2 patients in the placebo arm.[7]

Diarrhea/Colitis

In the idelalisib group 21 patients (19.1%) patients developed diarrhea compared with 16 (14.8%) patients in the placebo group. The median grade for diarrhea was grade 2 (range 1-4) in the idelalisib arm and grade 1(range 1-2) in the placebo arm. There were four patients in the idelalisib arm who had grade 3 or 4 diarrhea. Idelalisib was interrupted in the 3 patients with grade 3 diarrhea and withdrawn in the one patient with grade 4 diarrhea. The median time develop symptoms was 20 days in the idelalisib arm (range 1-220). Diarrhea usually lasted for a median of 7 days (range 0-98). However, two patients reported symptoms for longer than the median, ten patients required medication for symptom management and one patient required hospitalization.[7] One patient with intractable grade 3 diarrhea, was treated with loperamide, empiric flagyl, and empiric cholestyramine, and showed no improvement in symptoms. This patient was finally treated with intravenous high dose steroids and the symptoms resolved after 2 months.[7]

Five patients in the idelalisib arm and one patient in the placebo arm developed colitis. The median grade for colitis was 3 in the idelalisib arm and 2 in the placebo arm. There were 3 patients in idelalisib arm with grade 3 colitis, the study drug was interrupted or withdrawn for these patients.[7] Colitis and/or diarrhea returned in some patients that were re-challenged with idelalisib. In addition biopsies needed to be performed in some of the patients with colitis. The pathologic findings showed, acute cryptitis, crypt abscess formation, loss of surface epithelium, aggregates of inflammatory exudates.[7]

Pneumonitis

In the idelalisib arm grade ≥3 pneumonitis occurred in 4 (3.6%) patients compared to one patient in the placebo arm. Prior respiratory conditions including: intermittent cough and dyspnea, COPD and history of pleurisy, baseline cough, and reactive airway disease were seen in 4 patients in the idelalisib arm. In addition one patient in the placebo arm that developed pneumonitis had a history of COPD.[7] In both the idelalisib and placebo arms the median toxicity grade for the cases of pneumonitis was 3. Idelalisib was interrupted or withdrawn in 3 subjects. In all of the patients' medication, usually corticosteroids, was administered. Three patients were hospitalized for pneumonitis. This adverse event was not resolves in all cases. Some patients had residual sequela, such as new oxygen requirements. The FDA believes the incidence of pneumonitis may be under-reported, as the condition may be difficult to recognize in some cases.[7]

Rash

Rash had occurred in 11 (10%) patients in the idelalisib arm and in 5 (4.6%) patients in the placebo arm. When the term rash was expanded to include the following terms: dermatitis exfoliative, dermatosis, erythema, pruritis, pruritis generalized, rash, rash macular, rash maculo-papular, rash papular, rash pruritic, skin disorder, and skin lesion, there were 24 subjects (21.8%) with events in the idelalisib and 18 (16.7%) in the placebo arm. In the idelalisib arm there were four grade 3 events and one grade 3 event in the placebo arm. Patients were treated with steroids, either oral or topical. Hospitalisation was necessary in two patients and three patients discontinued the study due to rash in the idelalisib arm.[7]

Deaths

Deaths occurred in 19 (8.7%) of study patients during the study or within 30 days of treatment. Five deaths were caused by disease progression, three in the idelalisib arm and two in the placebo arm.[7] Another death took place in the follow-up period. This was in the placebo arm and was due to an adverse event.[7] Table 27. Shows the deaths on study outside of progressive disease. In both arms the most common cause of death was infection.

Table 27: Deaths[7]

Age/Gender	AE leading to death	Days on study when AE started
Idelalisib + rituximab		
82/F	Sepsis	57
67/F	Fungal pneumonia	53
69/M	Pneumocystis Jiroveci pneumonia	9
Placebo + rituximab		
74/F	Cardiac failure	37
77/M	Sepsis, septic shock	247
79/M	Chronic obstructive pulmonary disease	16
65/M	Acute respiratory failure	58
78/M	General physical health deterioration	101
69/M	Sepsis	166
53/F	Pneumonia	117
73/F	Pulmonary edema and left ventricular failure	5
66/M	Pneumonia	39
70/M	Bacteremia	43
71/F	Multi-organ failure	13

6.4 Ongoing Trials

Nine ongoing clinical trials were found by searching Clinicaltrials.gov. There were three ongoing randomized studies of idelalisib in previously treated patients. Two combined idelalisib with another agent and one compared two different doses of idelalisib. There were six studies of idelalisib in untreated patients. One study investigated single agent idelalisib and the other five examined it in combination with other agents.[67-75]

Table 28: Ongoing Trials

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Previously treated patients A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia [67]			
Study NCT01539291 Randomized, phase 3, double blind extension study Start date: May 2012 Expected completion date: December 2015 Active: Ongoing, but not recruiting patients Estimated enrolment: 160 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Subjects in the primary Phase 3 study (Study GS-US-312-0116) who are compliant • Tolerating primary study therapy	Idelalisib 300 mg twice daily (600 mg per day) Versus Idelalisib 150 mg twice daily (300 mg per day) plus placebo to match idelalisib.	**Primary outcome** Overall Safety **Secondary Outcome** • Tumour Control • Patient Well-Being • Pharmacodynamics
Previously treated patients A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia[68]			
Study NCT01569295 Randomized, phase 3, double blind Start date: June 2012 Expected completion date: December 2017 Active: Ongoing, but not recruiting patients Estimated enrolment: 390 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Previously treated recurrent CLL • Measurable lymphadenopathy • Requires therapy for CLL • Has experienced CLL progression <36 months since the completion of the last prior therapy **Exclusion criteria** • Recent history of a major non-CLL malignancy • Evidence of an ongoing infection • CLL refractory to bendamustine Concurrent participation in another therapeutic clinical trial	Idelalisib 150 mg administered orally twice daily + Rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a maximum of 6 infusions + Bendamustine 70 mg/mg^2/day on 2 consecutive days every 28 days administered intravenously for a maximum of 12 infusions Versus Rituximab 375 mg/m^2 on Day 1, then 500 mg/m^2 every 28 days administered intravenously for a maximum of 6 infusions + Bendamustine 70 mg/mg^2/day on 2 consecutive days every 28 days administered intravenously for a maximum of 12 infusions	**Primary outcome** Progression-free Survival (PFS) **Secondary Outcome** • Overall Response Rate • Lymph Node Response Rate • Overall Survival • Complete Response Rate
Single agent idelalisib			

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Previously treated patients An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects With Hematologic Malignancies[69]			
Study NCT01090414 Single arm, Open label, phase 1 Start date: Mar 2010 Expected completion date: Mar 2017 Active: By invitation only Estimated enrolment: 250 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Patients with hematologic malignancies completing a prior idelalisib study with a clinical benefit are eligible • Age ≥ 65 • Women of childbearing potential must have a negative pregnancy test to be eligible • Male patients, and female patients of childbearing potential, must agree to use method(s) of contraception specified in the protocol Exclusion Criteria: • Patients who are unwilling or unable to comply with the protocol are not eligible	300 mg of idelalisib once or twice daily until disease progression or unacceptable toxicity.	**Primary outcome** • Objective response rate • Safety as assessed by incidence of grade ≥ 3 adverse events according to the Common Terminology Criteria for Adverse Events **Secondary Outcome** • Overall survival • Progression-free survival • Duration of response • Time to response
Single agent idelalisib **Untreated patients** A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib Alone and in Combination With Rituximab in Elderly Subjects With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma[70]			
Study NCT01203930 Single arm, Open label Phase 2 Start date: Oct 2010 Expected completion date: Sept 2017 Active: Ongoing, but not recruiting patients Estimated enrolment: 105 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Confirmed CLL or SLL. • Age ≥ 65 • Presence of measurable lymphadenopathy • CLL - Binet Stage C or Rai Stage III or IV or has active disease defined by study criteria • World Health Organization Performance Status of ≤ 2 • Men of child-bearing potential, willing to use adequate methods of contraception for the study • Written informed consent **Exclusion Criteria:** • Prior therapy for CLL or SLL, except corticosteroids for symptom relief • Known active central nervous system involvement of the malignancy • Ongoing active, serious infection requiring systemic therapy. • Serum creatinine ≥ 2.0 mg/dL • Serum bilirubin ≥ 2 mg/dL or serum transaminases (ie, aspartate	This arm consists of 2 cohorts. Participants in Cohort 1 will receive idelalisib (150 mg tablets administered orally twice daily) for up to twelve 28-day cycles (or development of unacceptable toxicity) plus rituximab (375 mg/m^2 administered intravenously once weekly x 8 weeks through the end of Cycle 2). Participants in Cohort 2 will receive idelalisib (150 mg tablets administered orally twice daily) until disease progression or development of unacceptable toxicity.	**Primary outcome** • Overall Response Rate **Secondary Outcome** • Adverse events • Lymphadenopathy response rate • Overall Survival • Change from baseline in the sum of the perpendicular diameters of all measurable lesions • Progression-free survival • Duration of response • Trough and 1.5 hour post dose plasma concentrations of idelalisib • Changes in potential pharmacodynamic markers of drug activity in plasma and whole blood

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	aminotransferase, alanine aminotransferase) ≥ 2 x upper limit of normal • HIV positive • Active hepatitis B or C • History of a non-CLL malignancy		
Previously treated patients A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia[71]			
Study NCT01659021 Randomized, open label, phase 3 Start date: Dec 2012 Expected completion date: Nov 2016 Active: Ongoing, but not recruiting Estimated enrolment: 261 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Adult subjects with previously treated recurrent CLL who have measurable lymphadenopathy • Require therapy for CLL • Have experienced CLL progression <24 months since the completion of the last prior therapy • Have disease that is not refractory to ofatumumab	Idelalisib 150 mg tablets administered orally twice daily + ofatumumab administered intravenously weekly (300 mg on Day 1; thereafter 1000 mg Versus Ofatumumab administered intravenously weekly (300 mg on Day 1; thereafter 2000 mg	**Primary outcome** • Progression free survival **Secondary Outcome** • Overall response rate • Lymphadenopathy response rate • Overall survival • Complete response rate • PFS in participants with chromosome 17p deletion or TP53 mutation
Untreated patients A Phase II Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Leukemia (SLL) [72]			
Study NCT02135133 Phase 2, open label, single arm Start date: June 2014 Expected completion date: March 2021 Active: Recruiting Estimated enrolment: 50 Sponsor: Dana-Farber Cancer Institute Gilead Sciences GlaxoSmithKline	**Inclusion Criteria:** • Documented CLL / SLL with measurable disease • Must not have received prior systemic therapy for CLL and currently have an indication for treatment as defined by the IWCLL 2008 Guidelines: • ECOG performance status <2 • Age ≥ 18 years. • Participants must have normal organ and marrow function as defined in protocol • Written informed consent **Exclusion Criteria:** • Prior systemic therapy for CLL, or chemotherapy or radiotherapy within 4 weeks • History of severe allergic reactions attributed to compounds of similar chemical or biologic composition to ofatumumab or idelalisib.	Idelalisib will be given orally continuously at 150 mg BID. On day 57, ofatumumab will begin with the 300 mg dose, given after idelalisib is taken. Ofatumumab will then be administered at 1000 mg weekly to complete 8 weeks (days 64, 71, 78, 85, 92, 99, 106) throughout Cycles 3 and 4. This will be followed by monthly ofatumumab on weeks 20, 24, 28, 32 to complete 4 additional cycles (5-8). The overall induction treatment period will then be 8 months, comprised of two months of single agent idelalisib followed by 6 months of ofatumumab with idelalisib. After the completion of the induction treatment, idelalisib will continue indefinitely in	**Primary outcome** • Overall Response Rate **Secondary Outcome Measures:** • Complete response and progression free survival • Overall response rate and complete response rate of nodal partial response with lymphocytosis for idelalisib given alone for two months of therapy • Frequency of lymphocytosis with single agent idelalisib • Frequency of serious adverse events

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Current active hepatic or biliary disease • Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half lives or 4 weeks prior to enrolment, • Other past or current malignancy that could interfere with the interpretation of outcome. • Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment • History of significant cerebrovascular disease in the past 6 months or ongoing event with active symptoms or sequelae • Known HIV positive. • Clinically significant cardiac disease. • Significant concurrent, uncontrolled medical condition • Hepatitis B or C • Pregnant or lactating women. • Patients unable or unwilling to use adequate contraception methods from study start to 30 days after the last dose of protocol therapy. • Participants using concomitant corticosteroids are allowed as long as the subject is on the equivalent of 20mg/day or less of prednisone and has been on a stable dose for at least two weeks prior to initiating therapy.	arbitrarily defined 28 day cycles in all participants who have not had excessive toxicity and do not have progressive disease.	• Overall safety of idelalisib and in combination with ofatumumab, as measured by adverse events, and serious adverse events in particular • Correlation of clinical response with known CLL molecular prognostic factors including FISH, IGHV, ZAP-70 • Contribution of CT scans to response assessment • Correlation of serum ofatumumab and/or idelalisib levels in vivo with response • Cell surface marker phenotype of circulating CLL cells. • Impact of in vivo treatment with idelalisib on CLL cell sensitivity to therapy with antibodies or other kinase inhibitors. • Pharmacodynamic markers of PI3 kinase inhibition including AKT phosphorylation, production of T cell chemokines and response to CXCR 4/5. • Correlation of genetic alterations in PIK3CA or PIK3CD or other genes with response or resistance to idelalisib • Influence of idelalisib treatment on intrinsic innate immune suppression and on regulatory T cells • Prediction of response and resistance to

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
			idelalisib through biochemical and genetic analysis of the PI3K pathway.
Untreated patients A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia[73]			
Study NCT01980888 Randomized, double blind, phase 3 Start date: Feb 2014 Expected completion date: April 2024 Active: Ongoing, but not recruiting Estimated enrolment: 280 Sponsor: Gilead Sciences	**Inclusion Criteria:** • Documented diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) • No prior therapy for CLL other than corticosteroids for disease complications • CLL that warrants treatment • Presence of measurable lymphadenopathy • ECOG performance status of ≤ 2 **Exclusion Criteria:** • Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation) • Known presence of myelodysplastic syndrome • Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization • Ongoing liver injury • History of non-infectious pneumonitis • Ongoing inflammatory bowel disease • History of prior allogeneic bone marrow progenitor cell or solid organ transplantation • Ongoing immunosuppressive therapy other than corticosteroids • Received last dose of study drug on another therapeutic clinical trial within 30 days prior to randomization	idelalisib 150 mg tablet administered orally twice daily for 96 weeks + bendamustine administered intravenously at a starting dose of 90 mg/m^2. Dosing will be based on mg/m^2 of body surface area. + rituximab single-use vials administered intravenously weekly starting at 375 mg/m^2 on Day 1 (Week 0) and 500 mg/m^2 thereafter for 21 weeks. Versus Placebo to match idelalisib for 96 weeks + bendamustine administered intravenously at a starting dose of 90 mg/m^2. Dosing will be based on mg/m^2 of body surface area. + rituximab single-use vials administered intravenously weekly starting at 375 mg/m^2 on Day 1 (Week 0) and 500 mg/m^2 thereafter for 21 weeks.	**Primary outcome** • Progression free survival **Secondary outcomes** • Overall response rate • Nodal response rate • Complete response rate • Overall survival • Minimal residual disease negativity rate
Untreated patients A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Obinutuzumab Compared to Chlorambucil in Combination With Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia[74]			
Study NCT01980875	**Inclusion Criteria:** • Not a candidate for fludarabine therapy	Idelalisib 150 mg tablet administered orally twice daily	**Primary outcome** • Progression free survival

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Randomized, open label, phase 3 Start date: April 2015 Expected completion date: April 2025 Active: Currently recruiting Estimated enrolment: 306 Sponsor: Gilead Sciences	• Diagnosis of B-cell CLL, with diagnosis established according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) • No prior therapy for CLL other than corticosteroids for disease complications. • CLL that warrants treatment • Presence of measurable lymphadenopathy • ECOG performance status of ≤ 2 **Exclusion Criteria:** • Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation) • Known presence of myelodysplastic syndrome • Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of randomization • Ongoing liver injury • Ongoing drug-induced pneumonitis • Ongoing inflammatory bowel disease • History of prior allogeneic bone marrow progenitor cell or solid organ transplantation • Ongoing immunosuppressive therapy other than corticosteroids • Concurrent participation in another therapeutic clinical trial • Undergone major surgery within 30 days prior to randomization • Known hypersensitivity or intolerance to any of the active substances or excipients in the formulations for IDELA, obinutuzumab, or chlorambucil • History of non-infectious pneumonitis • Received last dose of study drug on another therapeutic clinical trial within 30 days prior to randomization	for 96 weeks + obinutuzumab in 1000 mg/40 mL single use vials administered intravenously for a total of 8 doses over 21 weeks Versus Chlorambucil 2 mg tablet administered orally every other week for a total of 12 doses + obinutuzumab in 1000 mg/40 mL single use vials administered intravenously for a total of 8 doses over 21 weeks	**Secondary outcomes** • Overall response rate • Nodal response rate • Complete response rate • Overall survival • Minimal residual disease negativity rate
Untreated patients A Phase 2, Single Arm Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia With 17p Deletion[75]			
Study NCT02044822	**Inclusion Criteria:** • Documented diagnosis of B-cell CLL, according to International	Participants will receive Rituximab 375 mg/m^2 administered intravenously once	**Primary outcome** • Overall Response Rate

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Single arm, open label, phase 2 Start date: July 2014 Expected completion date: Aug 2024 Active: Currently recruiting Estimated enrolment: 100 Sponsor: Gilead Sciences	Workshop on Chronic Lymphocytic Leukemia 2008 • Presence of 17p deletion in CLL cells as demonstrated by FISH testing • No prior therapy for CLL other than corticosteroids for disease complications. • CLL that warrants treatment • Presence of measurable lymphadenopathy • ECOG performance status of ≤ 2 **Exclusion Criteria:** • Known histological transformation from CLL to an aggressive lymphoma (ie, Richter transformation). • Known presence of myelodysplastic syndrome. • History of a non-CLL malignancy • Evidence of ongoing systemic bacterial, fungal, or viral infection at the time of enrolment • Ongoing liver injury • History of non-infectious pneumonitis. • Ongoing inflammatory bowel disease. • History of prior allogeneic bone marrow progenitor cell or solid organ transplantation. • Ongoing immunosuppressive therapy other than corticosteroids. • Received last dose of study drug on another therapeutic clinical trial within 30 days prior to enrollment. • Prior or ongoing clinically significant illness, medical condition, surgical history, physical finding, electrocardiogram (ECG) finding, or laboratory abnormality	weekly x 8 weeks and Idelalisib 150 mg tablets administered orally twice daily continuously throughout the study (up to 10 years).	**Secondary outcomes** •Duration of Response •Nodal response rate •Complete response rate •Overall survival •Progression-free survival •Minimal residual disease negativity rate

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Hematology Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Idelalisib (Zydelig) 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 pCODR 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 Hematology Clinical Guidance Panel is comprised of 3 hematologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.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

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily Update, Ovid EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL).

1. idelalisib.mp.
2. zydelig.mp.
3. CAL-101.mp.
4. CAL101.mp.
5. CAL 101.mp.
6. 1 or 2 or 3 or 4 or 5
7. chronic lymphocytic leukemia.mp.
8. cll.mp.
9. 7 or 8
10. 6 and 9
11. randomized controlled trial.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
12. 10 and 11
13. remove duplicates from 12
14. limit 13 to english language
15. limit 14 to humans

2. Literature Search via PubMed

1. (CLL) OR Chronic Lymphocytic Leukemia
2. ((((idelalisib) OR zydelig) OR CAL-101) OR CAL 101) OR CAL101
3. publisher[sb]
4. 1 and 2
5. 3 and 4

3. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: idelalisib, zydeligCAL-101, CAL 101, CAL101

Select International Agencies:

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

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

Search terms: idelalisib, zydeligCAL-101, CAL 101, CAL101

Conference Abstracts:

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

Search terms: idelalisib, zydeligCAL-101, CAL 101, CAL101

American Socety of Hematology (ASH)
Via Blood search portal: http://www.bloodjournal.org/ash-annual-meeting-abstracts?sso-checked=1

Search terms: idelalisib, zydeligCAL-101, CAL 101, CAL101

REFERENCES

1. Canadian Cancer Society's Steering Committee. Canadian cancer statistics 2015 [Internet]. Toronto: Canadian Cancer Society; 2011. [cited 2015 Jul 2]. Available from: http://www.cancer.ca/en/cancer-information/cancer-type/leukemia-chronic-lymphocytic-cll/statistics/?region=on.
2. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. New England Journal of Medicine. 2014;370(11):997-1007.
3. Zydelig (idelalisib) tablets: 150 and 100 mg [product monograph]. Mississauga (ON): Gilead Sciences Canada Inc; 2015 Mar 25.
4. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia; Protocol. New England Journal of Medicine. 2014;370(11):997-1007.
5. Coutre SE, Furman RR, Sharman JP, Cheson BD, Pagel JM, Hillmen P, et al. Second interim analysis of a phase 3 study of idelalisib (ZYDELIG) plus Rituximab for relapsed CLL. Journal of Clinical Oncology. 2014;32(5s):abstract 7012.
6. Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P, et al. Second interim analysis of a phase 3 study of idelalisib (ZYDELIG) plus Rituximab for relapsed chronic lymphocytic leukemia (CLL): Efficacy analysis in patient subpopulations with Del(17p) and other adverse prognostic factors. Blood. 2014;124(21):(abstract).
7. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical Review(s) [Internet]. In: Idelalisib (Zydelig). Company: Gilead Sciences, Inc. Application No.: 206545. Date: 6/12/2013. Rockville (MD): The Center; 2012 [cited 2015 July 2]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/206545Orig1s000MedR.pdf.
8. European Medicines Agency. Summary of Product Characteristics: Zydelig [Internet]. London" EMA; 2014 July 24. [cited 2015 July 2] avaliable from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003843/WC500175379.pdf.
9. Hallek M, Cheson BD, Catovsky D. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.
10. Morabito F, Mosca L, Cutrona G. Monoclonal B lymphocytosis versus Rai stage 0 chronic lymphocytic leukemia: A comparison of cellular, cytogenetic, molecular and clinical features. Clin Cancer Res. 2013;19(21):5890-900.
11. Rai KR, Sawitsky A, Cronkite EP. Clinical staging of chronic lymphocytic leukemia. Blood. 1975;46(2):219-34.
12. Hallek M, Fisher K, Fingerle-Rowson G. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: A randomised, open-label, phase 3 trial. Lancet. 2010;376:1164–74.
13. Rai KR, B.L. P, Appelbaum FR. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. New England Journal of Medicine. 2000;343(24):1750-7.
14. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, et al. Fludarabine Compared with Chlorambucil as Primary Therapy for Chronic Lymphocytic Leukemia. New England Journal of Medicine. 2000;343(24):1750-7.
15. Knauf WU, Lissichkov T, Alsaoud A. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. Journal of Clinical Oncology. 2009;27(26):4378-84.
16. Goede V, Fisher K, Busch R. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. New England Journal of Medicine. 2014;370(12):1101-10.

17. Fisher K, Cramer P, Busch R. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology. 2011;29(26):3559-66.
18. Robak T, Dmoszynska A, Solal-Céligny P. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. Journal of Clinical Oncology. 2010;28:1756-65.
19. Hillmen P, Stotnicki AB, Robak T. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. Journal of Clinical Oncology. 2007;25:5616-23.
20. Brown JR, Byrd JC, Coutre SE. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. Blood. 2014;123(22):3390-7.
21. O'Brien S, Lamanna N, Kipps TJ. Update on a Phase 2 Study of Idelalisib in Combination with Rituximab in Treatment-Naïve Patients ≥65 Years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Blood. 2014;124(21):(abstract).
22. Ghia P, O'Brien M, Hillmen P, Furman RR, Coutre SE, Sharman JP, et al. Health-related quality of Life (HRQL) impact of idelalisb (IDELA) in patients (pts) with relapsed chronic lymphocytic leukemia (CLL):Phase 3 results. Journal of Clinical Oncology. 2014;32(5s):abstract 7099.
23. Abdulla NE, Ninan MJ, Markowitz AB. Rituximab: Current status as therapy for malignant and Benign hematologic disorders. BioDrugs. 2012;26(2):71-82.
24. Best G, Thompson P, Tam CS. Diagnostic techniques and therapeutic challenges in patients with TP53 dysfunctional chronic lymphocytic leukemia. Leukemia and Lymphoma. 2012;53(11):2105-15.
25. Cheson BD. Bendamustine in CLL: How quickly will today's consensus become tomorrow's memory? Leukemia Research. 2014;38(11):1267-8.
26. Desai AV, El-Bakkar H, Abdul-Hay M. Novel Agents in the Treatment of Chronic Lymphocytic Leukemia: A Review About the Future. Clin Lymphoma Myeloma Leuk. 2014.
27. Ghia P, Hallek M. Management of chronic lymphocytic leukemia. Haematologica. 2014;99(6):965-72.
28. Hewamana S, Dearden C. Treatment options for high-risk chronic lymphocytic leukaemia. Therapeutic Advances in Hematology. 2011;2(3):147-59.
29. Hewett YG, Uprety D, Shah BK. Idelalisib- a PI3Kdelta targeting agent for B-cell malignancies. J Oncol Pharm Pract. 2015.
30. Jain P, Rai KR. Overview of recent developments in chronic lymphocytic leukemia. South Asian Journal of Cancer. 2012;1(2):84-9.
31. Kuznar W. Idelalisib improves outcomes in heavily pretreated patients with CLL. American Health and Drug Benefits. 2014;7(SPEC.ISSUE 1).
32. Lad DP, Malhotra P, Varma S. Chronic lymphocytic leukemia: Inception to cure: Are we there? Indian Journal of Hematology and Blood Transfusion. 2013;29(1):1-10.
33. Lu K, Wang X. Therapeutic advancement of chronic lymphocytic leukemia. Journal of Hematology and Oncology. 2012;5(55).
34. Markham A. Idelalisib: First global approval. Drugs. 2014;74(14):1701-7.
35. Molica S. Progress in the treatment of elderly/unfit chronic lymphocytic leukemia patients: Results of the German CLL-11 trial. Expert Review of Anticancer Therapy. 2014;15(1):9-15.
36. Molica S. Highlights in the treatment of chronic lymphocytic leukemia from the 2013 meeting of the American Society of Hematology. Expert Review of Hematology. 2014;7(2):187-90.
37. Molica S, Brugiatelli M, Morabito F, Ferrara F, Iannitto E, Di Renzo N, et al. Treatment of elderly patients with chronic lymphocytic leukemia: An unmet cinical need. Expert Review of Hematology. 2013;6(4):441-9.
38. Morabito F, Gentile M, Seymour JF, Polliack A. Ibrutinib, idelalisib and obinutuzumab for the treatment of patients with chronic lymphocytic leukemia: three new arrows aiming at the target. Leuk Lymphoma. 2015:1-20.
39. Nabhan C, Rosen ST. Chronic Lymphocytic Leukemia: A Clinical Review. JAMA - Journal of the American Medical Association. 2014;312(21):2265-76.
40. Niemann CU. [Targeted treatment of chronic lymphocytic leukaemia.]. Ugeskr Laeger. 2014;176(15).

41. Robak T. New horizons in the treatment of chronic lymphocytic leukemia. Acta Haematologica Polonica. 2014;45(2):122-31.
42. Sanford DS, Wierda WG, Burger JA, Keating MJ, O'Brien SM. Three Newly Approved Drugs for Chronic Lymphocytic Leukemia: Incorporating Ibrutinib, Idelalisib, and Obinutuzumab into Clinical Practice. Clin Lymphoma Myeloma Leuk. 2015.
43. Seymour J. ABT-199 for chronic lymphocytic leukemia. Clinical Advances in Hematology and Oncology. 2014;12(10):698-700.
44. Stephens DM, Byrd JC. Improving the Treatment Outcome of Patients with Chronic Lymphocytic Leukemia Through Targeted Antibody Therapy. Hematology/Oncology Clinics of North America. 2013;27(2):303-27.
45. Steurer M. ASH Update 2013: Chronic lymphocytic leukemia and indolent lymphoma. Memo - Magazine of European Medical Oncology. 2014;7(3):141-3.
46. Sun C, Wiestner A. Prognosis and therapy of chronic lymphocytic leukemia and small lymphocytic lymphoma. Kluwer Academic Publishers; 2015. p. 147-75.
47. Vanhaesebroeck B, Khwaja A. PI3Kdelta inhibition hits a sensitive spot in B cell malignancies. Cancer Cell. 2014;25(3):269-71.
48. Wei M, Wang X, Song Z, Jiao M, Ding J, Meng LH, et al. Targeting PI3Kdelta: Emerging Therapy for Chronic Lymphocytic Leukemia and Beyond. Med Res Rev. 2015.
49. Wiestner A. Emerging role of kinase-targeted strategies in chronic lymphocytic leukemia. Blood. 2012;120(24):4684-91.
50. Woyach JA, Johnson AJ. Targeted therapies in CLL: mechanisms of resistance and strategies for management. Blood. 2015.
51. Wu M, Akinleye A, Zhu X. Novel agents for chronic lymphocytic leukemia. Journal of Hematology and Oncology. 2013;6(1).
52. O'Brien SM. VIII. Treatment of chronic lymphocytic leukaemia, where are we heading? Hematological Oncology. 2015;33(S1):46-9.
53. Yang Q, Modi P, Newcomb T, Queva C, Gandhi V. Idelalisib: First-in-class PI3K delta inhibitor for the treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, and follicular lymphoma. Clinical Cancer Research. 2015;21(7):1537-42.
54. Balakrishnan K, Peluso M, Fu M, Rosin NY, Burger JA, Wierda WG, et al. The phosphoinositide-3-kinase (PI3K)-delta and gamma inhibitor, IPI-145 (Duvelisib), overcomes signals from the PI3K/AKT/S6 pathway and promotes apoptosis in CLL. Leukemia. 2015.
55. Cervantes-Gomez F, Lamothe B, Woyach JA, Wierda W, Keating MJ, Balakrishnan K, et al. Pharmacological and protein profiling suggest ABT-199 as optimal partner with ibrutinib in chronic lymphocytic leukemia. Clin Cancer Res. 2015.
56. Gockeritz E, Kerwien S, Baumann M, Wigger M, Vondey V, Neumann L, et al. Efficacy of phosphatidylinositol-3 kinase inhibitors with diverse isoform selectivity profiles for inhibiting the survival of chronic lymphocytic leukemia cells. Int J Cancer. 2015.
57. Police RL, Trask PC, Wang J, Olivares R, Khan S, Abbe A, et al. Randomized controlled trials in relapsed/refractory chronic lymphocytic leukemia: A systematic review and meta-analysis. Clinical Lymphoma, Myeloma and Leukemia. 2015;15(4):199-207.
58. Quigley JM, Thompson J, Barcena L, Mealing SJ, Leblond V. A systematic review and evidence synthesis of randomised controlled trials (RCT) for the treatment of relapased or refractory chronic lymphoctyic leukemia (CLL). Haematologica. 2014;99:60.
59. Kimby E, Flinn IW, Cotter FE, Giles FJ, Janssens A, Pulczynski EJ, et al. A phase iii, randomized, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with ofatumumab for previously treated chronic lymphocytic leukemia (CLL). Hematological Oncology. 2013;31:272-3.
60. Flinn I, Kimby E, Cotter FE, Giles FJ, Janssens A, Pulczynski EJ, et al. A phase III, randomized, controlled study evaluating the efficacy and safety of idelalisib (GS-1101) in combination with

ofatumumab for previously treated chronic lymphocytic leukemia (CLL). Journal of Clinical Oncology. 2013;1).
61. Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, Andreadis CB, et al. Chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2015. JNCCN Journal of the National Comprehensive Cancer Network. 2015;13(3):326-62.
62. Yamany T, Levender M, Silvers DN, Grossman ME. Erythema multiforme-like reaction with mucosal involvement following administration of idelalisib for relapse of chronic lymphocytic leukemia. Leuk Lymphoma. 2014:1-2.
63. Shanafelt TD, Borah BJ, Finnes HD, Chaffee KG, Ding W, Leis JF, et al. Impact of Ibrutinib and Idelalisib on the Pharmaceutical Cost of Treating Chronic Lymphocytic Leukemia at the Individual and Societal Levels. J Oncol Pract. 2015.
64. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01539512, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia; 2012 Feb 12[Last updated 2015 April 20; cited 2015 July 2]. Avaliable from: https://http://www.clinicaltrials.gov/ct2/show/NCT01539512?term=idelalisib&rank=4.
65. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia; Supplementary Appendix. New England Journal of Medicine. 2014;370(11):997-1007.
66. Sleith C. Methodology Checklist 2: Controlled Trials. 2012 [July 2, 2015]; Available from: http://www.sign.ac.uk/methodology/checklists.html.
67. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01539291, A Phase 3, Double-Blind Extension Study Evaluating the Efficacy and Safety of Two Different Dose Levels of Single-Agent Idelalisib (GS-1101) for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Feb 12[Last updated 2015 June 8; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01539291.
68. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01569295, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Mar 27[Last updated 2015 May 1; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01569295.
69. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01090414, An Extension Study to Investigate the Safety and Durability of Clinical Activity of Idelalisib in Subjects With Hematologic Malignancies; 2010 Mar 17[Last updated 2015 July 1; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01090414.
70. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01203930, A Phase 2 Single Arm Study to Investigate the Safety and Clinical Activity of Idelalisib Alone and in Combination With Rituximab in Elderly Subjects With Previously Untreated Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma; 2010 Sept 15[Last updated 2015 Mar; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01203930.
71. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01659021, A Phase 3, Randomized, Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination With Ofatumumab for Previously Treated Chronic Lymphocytic Leukemia ; 2012 Aug 3[Last updated 2015 Apr 30; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01659021.
72. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02135133, A Phase II Study of Idelalisib (GS1101, CAL101) + Ofatumumab in Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Leukemia

(SLL); 2014 Apr 24[Last updated 2015 Apr 13; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT02135133.
73. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01980888, A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Bendamustine and Rituximab for Previously Untreated Chronic Lymphocytic Leukemia; 2013 Nov 5[Last updated 2015 Mar; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01980888.
74. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT01980875, A Phase 3, Randomized, Open-Label Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Obinutuzumab Compared to Chlorambucil in Combination With Obinutuzumab for Previously Untreated Chronic Lymphocytic Leukemia; 2013 Nov 5[Last updated 2015 Jun 8; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT01980875.
75. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT02044822, A Phase 2, Single Arm Study Evaluating the Efficacy and Safety of Idelalisib in Combination With Rituximab in Patients With Previously Untreated Chronic Lymphocytic Leukemia With 17p Deletion; 2014 Jan 22[Last updated 2015 May 27; cited 2015 July 2]. Avaliable from: https://clinicaltrials.gov/show/NCT02044822.