CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia

March 2, 2018

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INQUIRIES

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

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

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

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding venetoclax (Venclexta) 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 CADTH website (www.cadth.ca/pcodr).

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

The systematic review and comparison with other relevant literature are fully reported in Sections 6 and 8. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on venetoclax (Venclexta) for chronic lymphocytic leukemia, a summary of submitted Provincial Advisory Group Input on venetoclax (Venclexta) for chronic lymphocytic leukemia, and a summary of submitted Registered Clinician Input on venetoclax (Venclexta) for chronic lymphocytic leukemia, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The reimbursement request for venetoclax, and therefore the objective of this review is to assess the efficacy and safety of venetoclax monotherapy in the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi). The Health Canada regulatory approval is for the use of venetoclax as monotherapy for the treatment of patients with CLL with 17p deletion who have received at least one prior therapy, or patients with CLL without 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options.

Venetoclax, a potent orally bioavailable selective inhibitor of BCL2. The recommended dose of venetoclax includes a 5-week ramp-up dosing schedule starting at 20 mg per day, and then increasing each week to 50 mg, 100 mg, 200 mg and finally 400 mg. Patients continue to receive 400 mg of venetoclax once daily until disease progression or unacceptable toxicity.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review includes one non-randomized, non-comparative, open-label, Phase II trial (M14-032) examining the efficacy and safety of venetoclax in patients with CLL who have previously received treatment with ibrutinib and/or idelalisib, have relapsed on treatment, or experienced progression after discontinuation of either of these agents. As of the interim analysis data cut-off date of January 2017, 127 patients were enrolled in the study. Patients were enrolled in one of two study arms and an expansion cohort: 43 into Arm A (patients with relapsed or refractory CLL after ibrutinib treatment), 21 into Arm B (patients with relapsed or refractory CLL after idelalisib treatment), and 63 into the expansion cohort (patients previously treated with either ibrutinib (n=53) or idelalisib (n=22). A total of 22/127 patients received both ibrutinib and idelalisib as a prior line of therapy: 4 in Arm A (ibrutinib failure), 6 in Arm B (idelalisib failure), and 12 in the

expansion cohort. The study was conducted entirely in the United States. There were no Canadian sites. No blinding methods were used in this non-randomized study.

Screening included PET/CT scans, bone marrow aspirate, and biopsy performed within 28 days of the administration of the study drug. To meet the eligibility criteria, patients must have had a diagnosis of CLL that met published International Workshop on Chronic Lymphocytic Leukemia (IWCLL NCI-WG) criteria. Restaging CT/MRI scans were performed at prespecified time points. The primary efficacy outcome was objective response rate (ORR), which was evaluated by the investigator and by an independent review committee (IRC) based on analysis of clinical laboratory tests, complete physical exam, CT/MRI scan of involved anatomic regions, bone marrow aspirate, and biopsy. Minimal residual disease was also assessed as an exploratory outcome in this study. Safety evaluations were ongoing and intense prophylaxis and monitoring for tumour lysis syndrome took place.

The majority of patients enrolled in the study were white males between 65-75 years of age. Venetoclax administration followed a weekly dose ramp-up schedule to mitigate the risk of tumour lysis syndrome, starting at 20mg until the target dose of 400mg was reached. Disease assessments were performed at each visit and once a complete remission (CR) was determined by clinical and radiographic criteria, a bone marrow aspirate and biopsy were performed for confirmation.

As per investigator assessment (which included the expansion cohort up to the January 2017 data cut-off), the ORR for patients in Arm A (ibrutinib failure) was 72.1% (31/43), with partial remission (PR) in 58.1% (25/43) of patients. The majority of responses were partial responses while complete remission was reported in 9.3% (4/43) and nodular partial remission in 4.7% (2/43) of patients. In study Arm B (idelalisib failure), as per investigator assessment, the ORR for patients was 66.7% (14/21), of whom 47.6% (10/21) of patients achieved a PR and 19.0% (4/21) patients achieved a complete remission and complete remission with incomplete marrow recovery (CR/Cri). As per investigator assessment, the ORR for the 63 patients in the expansion cohort was 42.9% (27/63), with PR observed in 38.1% (24/63) and CR/CRi in 4.8% (3/63) of patients.

Grade 3 or 4 adverse events (AEs) were reported in 93.0% of patients in Arm A, 81.0% of patients in Arm B, and 71.4% of patients in the expansion cohort. The most common AEs by study arm were anemia, decreased neutrophil count, and neutropenia in Arm A, neutropenia, thrombocytopenia, and anemia in Arm B, and neutropenia, anemia, and decreased neutrophil count in the expansion cohort. Some symptoms deemed, by the patient input, to be important to have controlled, such as lymph node size, viral reactivation, and IgG levels were not reported. Electrolyte abnormalities (hyperphosphatemia and hyperuricemia or hyperkalemia, respectively) meeting Howard criteria for laboratory TLS were observed in 2 patients with high tumour burden; both cases occurred during the 200mg dose of the standard ramp-up period. Key efficacy and harm data are summarized in Table 1 below.

Table 1. Highlights of key outcomes of the M14-032 study of venetoclax in patients with CLL refractory to a BCRi. [5]

	Arm A Ibrutinib Failure N=43		Arm B Idelalisib Failure N=21		Expansion Cohort N=63	All Patients N=127
	IRC Assessed	Investigator Assessed	IRC Assessed	Investigator Assessed	Investigator Assessed	Investigator Assessed
Efficacy Outcomes						
ORR N (%) [95% CI]	30 (69.8) [53.9. 82.8]	31 (72.1) [56.3, 84.7]	13 (61.9) [38.4, 81.9]	14 (66.7 [43.0, 85.4]	27 (42.9) [30.5, 56.0]	72 (56.7) [47.6, 65.5]
CR Rate, n (%) (CR/CRi) [95% CI]	1 (2.3) [0.1, 12.3]	4 (9.3) [2.6, 22.1]	0 [0, 0]	4 (19.0) [5.4, 41.9]	3 (4.8) [1.0, 13.3]	11 (8.7) [4.4, 15.0]

Table 1. Highlights of key outcomes of the M14-032 study of venetoclax in patients with CLL refractory to a BCRi. [5]						
PR Rate, n (%) (nPR+PR) [95% CI]	29 (67.4) [51.5, 80.9]	27 (62.8) [46.7, 77.0]	13 (61.9) [38.4, 81.9]	10 (47.6) [25.7, 70.2]	24 (38.1) [26.1, 51.2]	61 (48.0) [39.1, 57.1]
12-month Estimated PFS Rate (95% CI)	77.7% (61.4, 97.9)	71.0% (54.6, 82.4)	NA	85.7% (62.0, 95.2)	74.2% (57.0, 85.3)	74.2% (64.3, 81.8)
12-month OS Estimate (95% CI)	88.2% (73.9, 94.9)		95.2% (70.7, 99.3)		96.2% (85.3, 99.1)	93.1% (86.6, 96.5)
DoR at 12 months (95% CI)	79.7 (60.3, 90.3)		84.4 (50.4, 95.9)		NA	84.7 (71.2, 92.2)
Harms Outcomes (Any Grade 3 or 4 Adverse Event)						
Anemia, n (%)	14 (32.6)		3 (14.3)		15 (23.8)	32 (25.2)
Neutropenia, n (%)	12 (27.9)		9 (42.9)		21 (33.3)	42 (33.1)
Thrombocytopenia, n (%)	7 (16.3)		5 (23.8)		10 (15.9)	22 (17.3)
Abdominal Pain, n (%)	2 (4.7)		0		2 (3.2)	4 (3.1)
Fatigue, n (%)	5 (11.6)		2 (9.5)		1 (1.6)	8 (6.3)
Infections, n (%)	14 (32.6)		5 (23.8)		9 (14.3)	28 (22.0)
Abbreviations: BCRi - B cell receptor inhibitor; CI - confidence interval; IRC - independent review committee; ORR - objective response rate; PFS - progression-free survival; PR - partial response; CR = complete remission; CRi - complete remission with incomplete marrow recovery						

Updated June 2017 Results Based on the 2017 Lancet Oncology Publication[7]

As per investigator assessment, the ORR for all patients who failed ibrutinib therapy (n=91) was 64.8%. The majority of responses were partial with 56% of all patients achieving a nodular partial remission or partial remission (51/91). A total of 8 (8.8%) complete remissions were reported (4 in the main cohort and 4 in the expansion cohort).

While not reported by study cohort, the most common overall grade 3 or 4 adverse events were anemia, neutropenia, thrombocytopenia, abdominal pain, fatigue, diarrhea, and pneumonia. Key efficacy and harm data for the updated June 2017 cut-off date are outlined in Table 2 below.

Table 2. Key efficacy outcomes at the June 2017 data cut-off in patients with CLL in the M14-032 study.[7]			
	Main cohort N=43	Expansion Cohort N=48	All Patients N=91
Outcome	Investigator Assessed		
ORR N (%) [95% CI %]	30 (69.8) [54-83]	29 (60.4) [43-72]	59 (64.8%) [53-74]
CR rate, n (%) (CR/CRi)	4 (9.3)	4 (8.3)	8 (8.8)
PR rate, n [%] (nPR+PR)	26 (2+24) [60.5]	25 (1+24) [52.1]	51 (3+48) [56.0]
12 month estimated DOR (95% CI)	NR	NR	88% (76-95)
12 month Estimated PFS rate (95% CI)	NR	NR	75% (64-83)
12 month OS estimate (95% CI)	NR	NR	91% (83-95)
Harms Outcomes (Any Grade 3 or 4 Adverse Event)			
Anemia, n (%)	NR	NR	26 (29%)
Neutropenia, n (%)	NR	NR	46 (51%)
Thrombocytopenia, n (%)	NR	NR	26 (32%)
Abdominal Pain, n (%)	NR	NR	4 (4%)

Table 2. Key efficacy outcomes at the June 2017 data cut-off in patients with CLL in the M14-032 study.[7]			
	Main cohort N=43	Expansion Cohort N=48	All Patients N=91
Outcome	Investigator Assessed		
Fatigue, n (%)	NR	NR	6 (7%)
Diarrhea, n (%)	NR	NR	6 (7%)
Pneumonia, n (%)	NR	NR	6 (7%)
Notes: CI - confidence interval; DOR - duration of response; NR - not reported; OS - overall survival; PFS - progression-free survival; TTP - time to progression; TTR - time to response			

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

From a patient's perspective, symptoms of CLL that affect the quality of life at diagnosis and on an ongoing basis include the following: fatigue/lack of energy, increasing lymphocyte count, enlarged lymph nodes, frequent infections, night sweats, low platelet count and low immunoglobulin levels. Respondents also reported on the psychosocial aspects of a CLL diagnosis, which includes stress from diagnosis, anxiety, difficulty sleeping and depression. Respondents with early stage CLL reported minimal symptoms associated with their disease and tended to report a good quality of life. The impact affect those with more advanced disease. Respondents receive a variety of therapies including fludarabine/cyclophosphamide and rituximab (FCR), bendamustine and rituximab (BR), chlorambucil, fludarabine and rituximab (FR), and rituximab alone, ibrutinib, ibrutinib and rituxan, idelalisib, among others.

Respondents seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. Many respondents reported 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.

Respondents who have experience with venetoclax found that it managed a number of their symptoms, including lymphocyte count, fatigue/lack of energy, enlarged lymph nodes, night sweats, enlarged spleen, among others. When asked about the side effects experienced with venetoclax, the majority of respondents stated the side effects were mild and quickly dissipated. Side effects reported by respondents included diarrhea, neutropenia, low platelet counts, fatigue, acid reflux, cramps, constipation and mild headache.

Respondents also noted that venetoclax is not administered in a hospital or cancer care setting which will lower the risk of patients developing hospital acquired infections. Moreover, it can be taken in the comfort of a patient's home, which could be a benefit to patients and caregivers.

Please see Section 3 for more details.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Clarity of treatment population
- Sequencing of treatments

Economic factors:

- Monitoring for and treatment of adverse effects, such as tumour lysis syndrome and neutropenia

Please see Section 4 for more details.

Registered Clinician Input

The clinicians providing input noted that venetoclax offers a treatment option for patients with relapsed or refractory chronic lymphocytic leukemia (CLL), where tyrosine kinase inhibitors (TKIs) and/or other treatment options (including B-Cell receptor inhibitors (BCRi)) are not effective or not tolerated. After TKI failure, venetolax has shown to result in higher response rates, when compared with the use of an alternate kinase inhibitor (e.g., ibrutinib or idelalisib). Venetoclax would be used as a third or greater lines of therapy in the majority of CLL patients. It may be considered as a second-line treatment, if funding for first-line ibrutinib becomes available. It was also noted that CT scanning would be required, as an accompanying test, for the purpose of tumour lysis syndrome (TLS) risk stratification.

Please see Section 5 for more details.

Summary of Supplemental Questions

There were no supplemental questions identified for this review.

Comparison with Other Literature

One single-arm, open-label multicenter study partially meets the eligibility criteria for this systematic review and is being considered as an ongoing study. The study is aimed at evaluating the efficacy of venetoclax in relapsed or refractory patients with CLL including those with 17p deletion or TP53 mutation OR those who have received prior treatment with a B-cell receptor inhibitor. The estimated enrolment for this study is 250 patients from 56 locations in 20 countries including 5 centers in Canada. The study began in March 2016 and is estimated to be complete in October 2022. Interim results are expected by June 2018. Complete response rate data in the BCRi-treated patients will be reported as part of the secondary efficacy endpoints thereby making this study relevant to the current review.

With optimal sequencing of BCRis and venetoclax being of interest to clinicians managing patients with CLL, in the absence of clinical trial data, we identified two multicenter retrospective studies that may be helpful to clinicians facing this decision.

The first of the two studies by Mato et al.,[9] published in 2016, was a retrospective review that included 178 patients with CLL, 143 of which received prior ibrutinib and 35 of which received prior idelalisib. The aim of the review was to investigate reasons for BCRi discontinuation, outcomes after stopping therapy, and the impact that BCRi sequencing

had on outcomes. Of note, the ORR was 50% for patient treated with an alternate BCRi (ie, ibrutinib followed by idelalisib and idelalisib followed by ibrutinib), with an additional 30% of patients having stable disease. The median PFS and OS for the entire cohort of 178 patients from the time of BCRi initiation was 10.5 months and 29 months. Interestingly, initial BCRi choice (ibrutinib vs. idelalisib) did not impact PFS or OS. When PFS was stratified for patients with CLL treated with an alternate BCRi by reason for discontinuation of the first BCRi, it was found that alternate BCRi therapy following BCRi discontinuation, especially if the first BCRi was discontinued due to intolerance, could be effective. This is in contrast to the observation that if the initial BCRi was discontinued due to disease progression, PFS was considerably shorter as compared to those with BCRi intolerance, and therefore other therapies, such as novel agents like venetoclax, should be considered over switching to an alternate BCRi. It is also important to note that outcomes did not appear to differ whether ibrutinib or idelalisib was the first or second BCRi, suggesting that either sequence may be appropriate.[9]

In the 2017 study by Mato et al.,[10] 683 patients with CLL treated first with BCRis (n=621 ibrutinib first, n=62 idelalisib first) were identified in a retrospective cohort study of 9 US-based centers. The primary outcome was PFS and secondary outcomes included OS, ORR, and reasons for novel agent discontinuation. It was determined that patients who received ibrutinib-based therapy as their first BCRi experienced a significantly better PFS as compared to those who first received idelalisib-based therapy. This was true in the front-line, relapsed, refractory, and complex karyotype setting. The most common reasons for discontinuation was toxicity, and was similar between the two agents. At the time of publication, 167 patients had received a subsequent therapy after their first treatment with a BCRi. The ORRs (CR rate) to KI-based therapy, venetoclax, and chemoimmunotherapy (CIT) combinations were 58.5% (4.1%), 73.6% (31.5%), and 49.9% (2.1%), respectively. In patients treated with an alternate BCRi (after an initial BCRi) (ibrutinib followed by idelalisib or idelalisib followed by ibrutinib), those that were intolerant to the initial BCRi had a superior PFS as compared to those for whom disease progression was the reason for discontinuation.[10] Further, those patients who discontinued ibrutinib for any reason had both a better ORR when treated with venetoclax (ORR 79%) when compared with idelalisib (ORR 46%), and a trend to improvement in PFS (HR 0.6, 95% CI 0.3-1.0, p=0.06). Mato et al. concluded that ibrutinib appears superior to idelalisib as the first BCRi and, in the setting of BCRi failure, alternate BCRis or venetoclax appear superior to chemoimmunotherapy combinations. Further, the use of venetoclax might be superior to idelalisib upon ibrutinib failure. Confirmation from comparative clinical trials however, remains a gap in the evidence.

1.2.3 Factors Related to Generalizability of the Evidence

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

Table 2: Assessment of generalizability of evidence for venetoclax (Venclexta) for chronic lymphocytic leukemia

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Population	SLL	No data available	Are the result from the trial generalizable to patients with SLL	Because SLL is biologically equivalent to CLL patients with SLL are typically treated the same way as CLL therefore the results of the trial are generalizable to this group of patients.
	Intolerant to a BCRI	According to the description of patients in the M14-032 trial, as reported in the manuscript yet to be published, patients that discontinued ibrutinib due to adverse events were included[11] Mato et al report an ORR of 79% in patients who discontinued ibrutinib due to progression or toxicity and then received venetoclax versus those that subsequently received idelalisib, ORR 46% (PFS HR 0.6, 95% CI 0.3-1.0, p=0.06	Are the result from the trial generalizable to patients with intolerance to a BCRI	Based on clinical opinion and results from the Mato et al 2017 data, the CGP agree that patients who are intolerant to a BCRi should qualify for venetoclax treatment. Although patients could switch from ibrutinib to idelalisib this choice is seen by Canadian clinicians as strongly undesirable because of the more frequent and more serious toxicity seen with idelalisib compared to venetoclax and because a variety of funding rules have made idelalisib much less frequently available for the treatment of CLL in Canada. This is echoed by the registered clinician input. The experience reported by Mato et al also makes clear that the durability of response seen when venetoclax follows ibrutinib is superior to that seen when idelalisib follows ibrutinib.
Intervention	None			
Comparator	None			
Outcomes	None			
Setting	Results from real world evidence in Mato trial	See section 8 for detailed description of outcomes from Mato study	Are the results from the Mato study, based on retrospective analysis of patients in the US generalizable to the Canadian clinical setting?	The CGP agree that the real world experience reported by Mato is applicable to the Canadian setting. Basic CLL management in the US and Canada consists of primary chemoimmunotherapy and second line BCRi. The Mato results can be generalized to Canada.

1.2.4 Interpretation

Burden of illness and need

Chronic lymphocytic leukemia (CLL) is an incurable malignancy of B lymphocytes. With an incidence of approximately 4-5/100,000 in the general population, it is the most common adult leukemia in the western hemisphere. Approximately 2400 Canadians are diagnosed and 650 die from CLL each year. Median age at diagnosis is 72 years, and within incident cases there is a male predominance.[12] Based on clinical opinion, it is reasonable to anticipate that if venetoclax becomes available for patients with CLL that can no longer be adequately controlled by chemoimmunotherapy and BCRi treatment approximately 500 patients will be treated with this new agent per year in Canada for this indication. Based on clinical opinion, if venetoclax performs as well as it has in phase 1 and 2 trials, these 500 patients will have their median overall survival expectation increased from < 6 months to > 2 years.

Initial treatment for patients typically includes a chemoimmunotherapy. Second line treatment usually includes a B-cell receptor inhibitor (BCRi) either ibrutinib or, much less frequently, idelalisib and rituximab. Those with del17p skip initial chemoimmunotherapy and begin treatment with a BCRi, ibrutinib or, again much less frequently, idelalisib. Unprecedented response rates, prolonged progression free survival, and improved survival have been demonstrated in randomized controlled trials evaluating ibrutinib or idelalisib plus rituximab in heavily pretreated, high risk patients.[13-17] The two BCRi pathway inhibitors ibrutinib and idelalisib have different specific molecular targets, Bruton's tyrosine kinase and PI3 kinase, respectively, and, therefore can at least potentially be used in sequence if resistance to or intolerance for one or the other develops. However, unique toxicities have been documented with B cell receptor pathway inhibitors and patients may be intolerant or disease resistance may emerge. Patients with CLL whose symptomatic leukemia cannot any longer be adequately controlled by standard chemoimmunotherapy regimens or at least one B-cell receptor pathway inhibitors (BCRi) either because of treatment resistance or intolerance have a marked clinical need for effective, acceptably tolerated intervention. Venetoclax, an oral BCL2-targeted agent, is sufficiently effective and well-tolerated to fill that need.

Effectiveness

In this phase 2 single arm open label clinical trial, M14-032, for the treatment of patients with symptomatic CLL that can no longer be adequately controlled by chemoimmunotherapy and a BCRi, venetoclax induces overall response rates of approximately 60%, complete response rates of 9% and progression free survival of at least 74% at 12 months of follow-up. These data are supported by the Mato et al 2017 study which reported ORR of approximately 74% in this patient population.[10] This establishes venetoclax as the most effective agent yet discovered for the treatment of such patients and demonstrates that venetoclax provides better disease control than any currently available chemotherapy or immunotherapy, including possible use of alternative BCRi treatments. These results have been achieved in a population that currently has no well-defined treatment options and an expected median overall survival of less than 6 to 12 months. An effective, well-tolerated agent can be expected to have a major health impact in this population.

Although not demonstrated in the trial, the CGP anticipate that a major OS advantage is likely to be present with more follow up. Without more mature data, it is difficult to determine the magnitude of OS benefit anticipated. Given that venetoclax is being compared to minimally effective treatment options and has demonstrated substantial

improvements in important outcomes, the CGP consider it reasonable to expect that at least a 1-2 year OS benefit is likely to be observed. This is based on clinical opinion.

Safety: The major toxicity of venetoclax seen in early trials was tumor lysis syndrome secondary to rapid lysis of large numbers of leukemic cells with resultant electrolyte imbalance, renal failure and, at worst, death. Use of a gradual ramp up approach in which the dose is increased over 4-6 weeks has almost completely eliminated severe episodes of tumor lysis syndrome, which is now seen in < 2% of patients treated with venetoclax. Appropriate management of tumor lysis syndrome will require identification of patients at high risk, which can be accomplished with standard laboratory and imaging tests, and detection of early laboratory evidence of incipient but as yet asymptomatic tumor lysis, which also can be detected with standard blood tests. Patients at high risk or with evidence of incipient tumor lysis (lymph node ≥10 cm or lymph node ≥5 cm and absolute lymphocyte count ≥25 x 10^9/L and elevated baseline uric acid) will require monitoring in hospital for up to several days during the initial treatment of the CLL and standard interventions with intravenous hydration, anti-hyperuricemics and fluid balance monitoring. This was also remarked upon by the registered clinician input. Such enhanced measures to prevent clinically significant tumor lysis syndrome will be necessary for at most 5% to 10% of patients. Other adverse events of grade 3 or greater intensity seen in more than 5% of patients include neutropenia (~40%), febrile neutropenia (~5%), anemia (~15%), thrombocytopenia (~15%) and hyperglycemia (~10%). The CGP agree that these other AE's are typically associated with treatment in this disease and clinicians would know how to manage them. Given the life-threatening nature of BCRi-resistant CLL, venetoclax provides potentially effective treatment at an acceptable level of toxicity.

Other considerations

In the early trials of ibrutinib and idelalisib patients only started the BCRi very late in overall treatment after many different agents and regimens were tried. In those trials the BCRi was usually stopped because of treatment resistance. As the BCRi's were moved into earlier rounds of treatment patients began the BCRi while more fit, with less treatment resistance present in their CLL and, therefore with a greater likelihood the BCRi would be used for a longer time. As a result there was more time for intolerance to emerge, leading to the higher rates of reported intolerance. The CGP therefore agree that a substantial portion of the patients who switch from a BCRi to venetoclax will do so because of BCRi intolerance; however, such patients will have an even higher response rate and longer durability of response than those patients who make the switch because of disease progression. That is both clinical opinion and what was seen in the Mato studies.[9,10] Since use of venetoclax is likely to produce even better outcomes in the patients with BCRi intolerance than in those with BCRi resistance, it remains appropriate to use venetoclax for both sets of patients.

The CGP agree that an RCT would have been very difficult to conduct and quite unlikely to be successfully concluded in the target population. The main challenge is that there is no established or attractive standard arm for such a trial. It would be very difficult to reach any consensus that clinicians would accept for such an arm. One could propose a venetoclax versus clinician's choice randomization but even that would be unattractive because potential investigators would object that equipoise would be lacking. The phase 1-2 data on venetoclax are so compelling that most clinicians would find the possibility of a patient being randomly assigned to any treatment other than venetoclax ethically unacceptable. One could try to meet that objection by allowing cross-over from the standard treatment arm to venetoclax but the objection remains that allowing a potentially preventable progression, which would be necessary for cross-over, would unethically jeopardize the patient since additional disease progression could easily make

the patient ineligible for venetoclax due to progressive organ compromise or infectious complications.

Following the posting of the pERC initial recommendation, the CGP noted a number of questions raised by pERC on the clinical effectiveness of venetoclax. To address these questions and concerns, the CGP provided the comments below.

Feasibility of a RCT:

The CGP re-iterate that there are no appropriate comparators in this setting. Currently, best supportive care (BSC) is equivalent to palliative care and would be appropriate in the absence of other effective therapies. The CGP also note that ibrutinib is currently available for reimbursement in jurisdictions and is the preferred option. For patients with CLL that is progressive despite treatment with primary treatment and later ibrutinib, there is currently no effective treatment. Thus, a randomized trial would have to be conducted with venetoclax versus palliative care (no CLL treatment); however, such a trial would violate the need for equipoise. In this situation, given no CLL treatment, >50% of patients would be expected to have died by 20 months as demonstrated in the Jain et al 2017 paper.[18] Notably in the Jain 2017 paper, a minority of patients received venetoclax toward the end of treatment therefore the outcomes of patients in this trial may be an overestimate because it already reflects the early use of venetoclax. Based on the Jones et al 2017 publication of the M14-032 trial results, less than 20% of patients will have died by 20 months if given venetoclax [7]. The CGP further note that their research ethics boards would not allow the randomization of patients to treatment options with such a large difference in 20-month overall survival, <50% vs >80%. The CGP therefore re-iterate that an RCT is unethical. Given the difficulty in ignoring such an ethical objection, that level of asymmetry would make it very unlikely that treating doctors would support such a trial or that patients would consent to enrollment unless coerced by the lack of availability of venetoclax.

Historical responses in this setting and magnitude of clinical benefit:

The CGP also note the following related to the results observed in the M14-032 trial. In Canada, patients with CLL that can no longer be controlled by chemoimmunotherapy or ibrutinib typically experience worsening of their leukemia very quickly because there are no effective treatments currently available. This is reflective of the patient population treated with venetoclax on the M14-032 trial. In addition, the publication by Jones 2017 specifically addresses the subset of patients treated with chemoimmunotherapy and ibrutinib, which thus describes Canadian experience where BCRi other than ibrutinib is very seldom used or available (as previously mentioned, a second BCRi is not reimbursed by jurisdictions).[7] Although median OS has not been reached, the CGP feel that the available data are meaningful. In the report by Jones the median follow-up is 14 months, and the median overall survival is estimated to exceed 28 months, considerably longer than the median overall survival observed in the literature for patients in this setting. As previously mentioned, the best available data is based on the Jain 2017 study which reported a median OS of 20.6 months in this subgroup of patients.[18] However, it is important to note this experience is an overestimate because some of the included patients actually received venetoclax toward the end of the study period. Based on this historical information and the results of the M14-032 trial, a 1 year OS of 93% is remarkably better than that seen in CLL that has progressed despite ibrutinib. [7] Furthermore, based on the Kaplan-Meir curves for OS in the Jones 2017 publication, the predicted 2 year OS is >70%.[7] The CGP therefore re-iterate that at least a 1-2 year OS benefit is expected with the use of venetoclax in this patient population.

The CGP also note that treatment in this setting is not for curative intent. Therefore the use of response rate for the assessment of non-curative life-extending treatment, as was done in the M14-032 trial, is appropriate as it is indicative of what proportion of patients have a meaningful clinical response. With regards to concerns related to tumour lysis syndrome, the CGP notes that with appropriate measures including gradual escalation of initial dosing and planned monitoring during treatment initiation the rate of clinically significant TLS is 1% to 2%, a very low and acceptable rate in this patient population.

Overall, the CGP re-iterate their conclusion that there is a net overall clinical benefit of venetoclax in patients and the importance of making venetoclax available to patients in this setting. Presently there is no effective or clinically useful treatment for such patients available in Canada. The CGP note that venetoclax is remarkably effective at safe levels of administration (ORR 65%; 12-month OS 91%; 24-month OS ~70%; 12-month PFS ~75%; 24-month PFS >50%; 7% venetoclax discontinuation rate due to toxicity; <2% clinically significant tumour lysis syndrome).

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit from the use of venetoclax in the treatment of patients with symptomatic chronic lymphocytic leukemia whose leukemia has proven resistant to at least one B-cell receptor pathway inhibitor. This conclusion is based on data from the phase 2 clinical trial of venetoclax (MT 14-032) for patients with CLL with or without the presence of del17p demonstrating that venetoclax induces overall response rates of approximately 60%, complete response rates of approximately 9% and progression free survival of at least 74% at 12 months of follow-up.

In making this conclusions, the CGP also considered that:

- These data from the M14-032 trial are supported by real world evidence presented in the Mato et al 2017 study which demonstrated ORR of 74%, CR 32% and PFS of at least 75%-80% after 2 years.
- These outcome improvements are not seen with any other therapeutic agents available in Canada at this time and are achievable with acceptable moderate levels of major toxicity.
- The CGP anticipate that venetoclax will be used subsequent to ibrutinib as third line option for patients without a prognostic biomarker del17p mutation and as second line in those with the mutation.
- Based on clinical opinion and results from the Mato et al 2017 data, the CGP agree that patients who are intolerant to a BCRi should qualify for venetoclax treatment. Although, in theory, a patient whose CLL is no longer adequately controlled by ibrutinib could switch to idelalisib this choice will be seen by Canadian clinicians as strongly undesirable because of the more frequent and more serious toxicity seen with idelalisib compared to venetoclax and because a variety of funding rules have made idelalisib much less frequently available for the treatment of CLL in Canada. This is echoed by the registered clinician input. The experience reported by Mato et al also makes clear that the durability of response seen when venetoclax follows ibrutinib is superior to that seen when idelalisib follows ibrutinib (estimated 2-y PFS 75% vs 37%, respectively).
- The Clinician input speaks to venetoclax potentially allowing patients to achieve deep molecular remission and the possibility of treatment discontinuation. Deep molecular remission usually speaks to MRD status. Given that there were not sufficient data from

M14-032 trial to evaluate MRD, it is difficult to determine if patients have achieved deep molecular remission. At present MRD detection is an investigational technique and has not reached the point of established clinical utility.

- The CGP agreed that there are insufficient data to determine the efficacy and safety of venetoclax in the following patient populations
    - Patients who have not previously been treated with a chemoimmunotherapy, except in patients with the del17p mutation who would not be treated with a chemoimmunotherapy at any point.
    - Patients who have not been treated with a BCRi
    - Intolerance to front line ibrutinib treatment, except in patients with the del17p mutation who would be treated with a BCRi upfront.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Chronic lymphocytic leukemia (CLL) is an incurable malignancy of B lymphocytes. With an incidence of approximately 4-5/100,000 in the general population, it is the most common adult leukemia in the western hemisphere. Approximately 2400 Canadians are diagnosed and 650 die from CLL each year. Median age at diagnosis is 72 years, and within incident cases there is a male predominance.[12] Diagnosis requires detection of elevated peripheral blood monoclonal B cells (≥ 5.0x109/L) that have a characteristic immunophenotype. The nodal counterpart, small lymphocytic lymphoma (SLL), is considered the same disease and is treated according to the same principles as CLL.[19] The clinical presentation is variable and includes lymphadenopathy, hepato-splenomegaly, cytopenias (anemia, thrombocytopenia, neutropenia due to marrow infiltration or autoimmunity), fatigue, and B symptoms (disease related fevers, drenching sweats, weight loss). Although it is often described as an indolent malignancy, the disease is characterized by substantial clinical and biologic heterogeneity and a variable disease course. Some newly diagnosed patients with 'low risk' asymptomatic disease may have survival similar to age-matched controls from the general population while others may have an aggressive clinical course characterized by the rapid development of severe symptoms, resistance to available chemotherapies, and short survival.[20,21] At diagnosis, patients are staged according to the Rai or Binet staging systems (see below).[22,23] Asymptomatic, early stage patients are recommended for clinical surveillance because early treatment with chemotherapy is not associated with improvement in overall survival (or quality of life).[24] In the setting of symptomatic disease progression, in accordance with established internationally endorsed indications for treatment, chemotherapy is recommended. Choice of first line therapy is dictated by patient and disease related characteristics however current standard options in Canada include one of several standard 'chemo-immunotherapy' regimens depending on patient age and fitness; young fit patients (< 65-70 years) are generally treated with fludarabine, cyclophosphamide, and rituximab (FCR)[25-27] for up to 6 monthly cycles while older patients with comorbid illnesses are usually treated with effective, less toxic regimens such as bendamustine and rituximab (BR)[28] or chlorambucil plus obinutuzumab (CO).[29]

Although the usual endpoint for measuring the effectiveness of treatment for CLL is based on clinical assessment of symptoms, organ function, peripheral blood counts, resolution of lymphadenopathy and organomegaly and clearance of bone marrow involvement there has been a recent focus on determining persistence of minimal numbers of malignant cells either in the peripheral blood or bone marrow, a process entitled detection of minimal residual disease (MRD). MRD has been defined in several ways but most consistently on the basis of multi-parameter flow cytometry of peripheral blood.[27,30,31] Increasing evidence has been accumulated indicating that achievement of a state in which there is no detectable MRD, also sometimes referred to as a "deep molecular remission" is a strong predictor of excellent long term remission and may possibly identify a subpopulation of patients with CLL that have been cured. However, at present MRD detection is an investigational technique and has not reached the point of established clinical utility.

The management of CLL/SLL, particularly in the relapsed setting, is in the midst of dramatic change due to the development of several highly active, orally administered novel targeted therapies. These include drugs that target the B cell receptor signalling

pathway (ibrutinib, which targets Bruton's tyrosine kinase,[13,32,33] idelalisib,[14,15] which targets PI3 kinase) and venetoclax,[34-37] which targets BCL2. Unprecedented response rates, prolonged progression free survival, and improved survival have been demonstrated in randomized controlled trials evaluating ibrutinib or idelalisib plus rituximab in heavily pretreated, high risk patients.[13-17] However, unique toxicities have been documented with B cell receptor pathway inhibitors and patients may be intolerant or disease resistance may emerge. Examples of specific adverse events associated with ibrutinib include increased bleeding, hypertension, atrial fibrillation, and joint/muscle pain; colitis, pneumonitis, transaminitis, and opportunistic infections have been reported with idelalisib. Although a major step forward in the treatment of CLL/SLL, these novel agents are not expected to cure patients as monotherapies. Thus, there remains an urgent need for continued drug development and testing in rigorously conducted prospective comparative clinical trials.

Venetoclax, a potent orally bioavailable selective inhibitor of BCL2, has also demonstrated excellent response rates, response duration, and survival in phase I/II trials evaluating patients with relapsed/refractory CLL including patients with genetically high risk disease.[34,36,37] Although severe cases of tumour lysis syndrome were reported in early phase clinical trials, with modifications to the dosing schedule (a now standard 'ramp up' phase) and careful attention to prevention/lab monitoring, clinically significant tumour lysis syndrome is now rarely reported.

Over the past 15 to 20 years, substantial progress has been made in understanding the underpinnings of disease heterogeneity through the development of several new prognostic biomarkers that are associated with treatment failure and poor survival. More recently, known prognostic variables have been incorporated into validated, powerful prognostic models that reliably identify patients with different risks of progression or death.[38] The most important prognostic markers currently in clinical practice are those that detect a defective TP53 gene (either by interphase FISH cytogenetics as del17p, or sequencing to assess for gene mutations);[39-42] a functioning p53 is an essential cofactor for programmed cell death and patients with this abnormality are generally resistant to chemotherapy and radiotherapy. Del17p is associated with shortened time to first treatment (in asymptomatic patients on clinical surveillance), and shortened progression free and overall survival despite treatment with highly active chemoimmunotherapeutic regimens.[20,38,43] In previously untreated patients the incidence of TP53 abnormalities is approximately 10-12% (5-7% del17p by interphase FISH cytogenetics, 3-5% gene mutations). In the relapsed/refractory setting, through the process of clonal evolution, the incidence of TP53 abnormalities can increase up to approximately 30%.[14,16]

Presently in Canada patients with symptomatic or threatening CLL but without del17p are initially treated with the regimens described above (fit patients, FCR; less fit patients, BR or CO). When relapse occurs, patients are then treated with a B-cell receptor inhibitor (BCRi) either ibrutinib or, much less frequently, idelalisib and rituximab. Those with del17p skip chemoimmunotherapy and begin treatment with a BCRi, ibrutinib or, again much less frequently, idelalisib. This particular pCODR/pERC request addresses patients whose CLL once again progresses and becomes symptomatic or threatening and a BCRi can no longer control the disease because of progression despite the BCRi or intolerance for the BCRi.

The two BCRi pathway inhibitors ibrutinib and idelalisib have different specific molecular targets, Bruton's tyrosine kinase and PI3 kinase, respectively, and, therefore can at least potentially be used in sequence if resistance to or intolerance for one or the other develops. The modest available data on the potential effectiveness of a second alternative

BCRi have been summarized in two publications from Mato, *et al*[9,10] in which pooled results from several US centers are reported. A detailed summary of these data is presented in the section on Comparison with Other Literature. The following table summarizes the important cross-over outcomes and a comparison to use of venetoclax after a BCRi.

Outcome	Sequence		
	Ibrutinib => idelalisib	Idelalisib => ibrutinib	BCRi => venetoclax
ORR %	46	75	74
CR %	0	5	32
PR/PR with lymphocytosis %	46	70	32
Stable %	39	15	16
Progression %	15	10	10

The most relevant comparison is between the group switching from ibrutinib to idelalisib and the group switching from ibrutinib to venetoclax because by far the most commonly used BCRi in Canada is ibrutinib. Although, in theory, a patient whose CLL is no longer adequately controlled by ibrutinib could switch to idelalisib this choice will be seen by Canadian clinicians as strongly undesirable because of the more frequent and more serious toxicity seen with idelalisib compared to venetoclax and because a variety of funding rules have made idelalisib much less frequently available for the treatment of CLL in Canada. Finally, the experience reported by Mato et al also makes clear that the durability of response seen when venetoclax follows ibrutinib is superior to that seen when idelalisib follows ibrutinib (estimated 2-y PFS 75% vs 37%, respectively).

The best estimate of incidence of failure of a BCRi to control CLL and, therefore, a need for another effective agent is based on the annual Canadian death rate from CLL. Essentially, every Canadian now dying of progressive CLL no longer has leukemia that can be controlled by chemoimmunotherapy and BCRis and, as such, will be a candidate for venetoclax. If one arbitrarily discounts that number by 20% to allow for a subgroup that has grown too frail for active anticancer treatment, a reasonable estimate of the annual use of venetoclax for CLL, once it becomes available, is approximately 520 patients. The goal of treatment with venetoclax will be to prolong overall and progression free survival within acceptable limits of toxicity.

2.2 Accepted Clinical Practice

Patients with relapsed CLL/SLL after failure of initial chemoimmunotherapy and at least one BCRi have a particularly poor prognosis and currently available chemoimmunotherapeutic regimens are largely ineffective. Clinicians infrequently recommend a variety of agents such as alemtuzumab, high dose corticosteroids, high dose corticosteroids + rituximab, lenalidomide or single agent rituximab; however, this use of these agents, with the exception of corticosteroids, is not currently funded for Canadian patients and even when they are employed their impact is minimal. Median overall response rates are poor (20-50%) and progression free survival (PFS) in this setting has typically been less than 6 months. Furthermore, these agents can be associated with extensive toxicity (e.g. myelosupression, infection, tumour flare/tumour lysis syndrome).[44,45] Allogeneic stem cell transplantation is a potentially curative treatment option and is considered in a carefully selected subset of cases (young, fit patients with chemosensitive disease and a suitable donor) and is offered to less than 5% of the population with CLL.[46] Toxicity (infection and graft versus host disease) and transplant related mortality (approximately 20%) represent additional limitations to transplant. The B cell receptor pathway inhibitors ibrutinib and idelalisib+rituximab have demonstrated a

marked improvement in outcomes compared to historical therapies with response rates of approximately 70-80%, and median PFS of approximately 28 months (ibrutinib) and 16 months (idelalisib+rituximab), respectively.[14,17,32] These agents are now considered a standard of care for the population of relapsed CLL patients or as initial treatment for those with del17p. Although typically well tolerated, these agents fail to control the CLL in a substantial portion of such patients due to the development of intolerance or resistance. Patients with relapsed CLL/SLL after failure of a BCRi represent an extremely high risk subset of patients with limited treatment options and a high unmet clinical need for new treatment approaches.

The current and proposed treatment algorithm for the integration of venetoclax for Canadian patients with symptomatic CLL is shown in the following table.

Patients with Symptomatic or Health-threatening Chronic Lymphocytic Leukemia		
Line of Therapy	**non-del17p**	**del17p**
1st-Line		
Fit, age <70	Fludarabine+cyclophosphamide+ rituximab (FCR)	Ibrutinib
Frail, age >70	Bendamustine+rituximab (BR)or Chlorambucil+obinotuxumab (CO)	Ibrutinib
Maintenance	Not applicable	Not applicable
2nd-Line	Ibrutinib or idelalisib+rituximab	Venetoclax
3rd line	Venetoclax	No established therapy

2.3 Evidence-Based Considerations for a Funding Population

The pooled results from phase 1 and 2 clinical trials for patients with at least one prior therapy for CLL and failure to control the leukemia due to symptomatic progression despite or intolerance for a BCRi (ibrutinib or idelalisib +/- rituximab) indicate that venetoclax can be expected to induce an overall response rate of approximately 70%-80%, complete responses in 5%-20% and 2-y progression free survival of 50%-60%.[10,34,36,37] There is a risk of developing tumour lysis syndrome (TLS) following treatment with venetoclax therefore adequate resources to screen for the risk of this toxicity and to manage it, if necessary, must be established prior to initiating therapy (regular laboratory monitoring for TLS including the potential need for hospitalization to manage patients at high risk). Such screening will require resources already in place at Canadian centers where CLL is managed and will include standard blood tests and imaging assessments to determine tumor bulk, usually CT scanning. Although CT scanning is not ordinarily required for initial assessment and primary management of patients with CLL it is a standard evaluation for management of patients in need of treatment for recurrent leukemia and, therefore, will not require extra resources beyond standard care. There are no published reports that clearly demonstrate improved outcomes with venetoclax in combination with other agents compared with venetoclax monotherapy, therefore, venetoclax should be administered as a single agent outside of clinical trials. Patients with CLL and failure of control of the leukemia due to symptomatic progression despite or intolerance for a BCRi (ibrutinib or idelalisib +/- rituximab) have a particularly poor prognosis, limited treatment options and represent a high risk population that will be prioritized for treatment with venetoclax.

2.4 Other Patient Populations in Whom the Drug May Be Used

Venetoclax is also being studied in several other diseases including subtypes of non-Hodgkin Lymphoma (diffuse large B cell lymphoma, follicular lymphoma, Waldenström's macroglobulinemia, mantle cell lymphoma), multiple myeloma, and acute myeloid leukemia. All such uses of venetoclax remain investigational in Canada at this time.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG), provided joint input on venetoclax for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi).

LC & CLLPAG conducted online surveys of chronic lymphocytic leukemia and small lymphocytic lymphoma patients and caregivers (as noted in the table below) in June 2017. Links to the surveys were sent via e-mail to CLL Patient Advocacy Group members and patients and caregivers registered on the LC database. The links were also made available via LC Twitter and Facebook accounts as well as through the CLL Support Association, online patient forums and blogs. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was also built into the surveys so that respondents were asked questions only relevant to them.

A total of 320 patients responded to the survey, of which 21 patients had direct experience with venetoclax. Also, a total of 41 caregivers responded to the survey. Of the 320 patients, 279 (87.2%) were diagnosed with CLL, 11 (3.44%) were diagnosed with SLL and 30 (9.38%) were diagnosed with CLL & SLL.

Respondents by Country	CAN	USA	UK	AUS	Other*	Skipped	Total
CLL/SLL patients	102	127	51	2	4	34	320
Patients with venetoclax experience	4	13	4	-	-	0	21
Caregivers	20	16	1	-	-	4	41
**Other includes 1 patient from each of the following: Brazil, France, India, Israel*							

As a note, the surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into the surveys so respondents were only asked questions relevant to them. The table below outlines the baseline patient characteristics, age and gender, for survey respondents.

	Age								Gender		
Category	21-39	40-49	50-59	60-69	70-79	80-89	90+	N/A	Male	Female	N/A
CLL/SLL patients	2	9	59	108	92	14	0	18	142	145	33
Patients with venetoclax exp.	0	0	1	14	5	1	0	1	13	8	
Caregivers	1	2	10	15	8	1	0	4	8	29	4

From a patient's perspective, symptoms of CLL that affect the quality of life at diagnosis and on an ongoing basis include the following: fatigue/lack of energy, increasing lymphocyte count, enlarged lymph nodes, frequent infections, night sweats, low platelet count and low immunoglobulin levels. Respondents also reported on the psychosocial aspects of a CLL diagnosis, which includes stress from diagnosis, anxiety, difficulty sleeping and depression. Respondents with early stage CLL reported minimal symptoms associated with their disease and tended to report a good quality of life. The impact affect those with more advanced disease. Respondents receive a variety of therapies including fludarabine/cyclophosphamide and rituximab (FCR), bendamustine and rituximab (BR), chlorambucil, fludarabine and rituximab (FR), and rituximab alone, ibrutinib, ibrutinib and rituxan, idelalisib, among others.

Respondents seek individualized choice in treatment that will offer disease control and improve quality of life while offering ease of use relative to other treatments. Many respondents reported 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.

Respondents who have experience with venetoclax found that it managed a number of their symptoms, including lymphocyte count, fatigue/lack of energy, enlarged lymph nodes, night sweats, enlarged spleen, among others. When asked about the side effects experienced with venetoclax, the majority of respondents stated the side effects were mild and quickly dissipated. Side effects reported by respondents included diarrhea, neutropenia, low platelet counts, fatigue, acid reflux, cramps, constipation and mild headache.

Respondents also noted that venetoclax is not administered in a hospital or cancer care setting which will lower the risk of patients developing hospital acquired infections. Moreover, it can be taken in the comfort of a patient's home, which could be a benefit to patients and caregivers.

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

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with chronic lymphocytic leukemia

CLLPAG and LC reported that patients with CLL were often diagnosed during investigation for another condition or during routine blood work.

Patients were asked what treatment phase they were currently in, of the 301 respondents, 115 patients (38.2%) are in active surveillance (watch and wait), 80 patients (26.6%) are in treatment currently and 106 (35.2%) respondents had received treatment and are now in remission or relapsed (with 13 indicating a remission under 6 months, 26 a remission of 6 months-2 years, 27indicating a remission of 2-5 years and 19 have been in remission for 5+ years; 13 have relapsed and 8 have relapsed after new treatment).

Watch & wait management of the disease is often a difficult stage of the disease for patients to accept as noted by patients:

- *"I am 70 years old in July and I do not want to spend the rest of my life being afraid and that is what it is like. I just want to die when I am supposed to and not spend what is left of my life Waiting....just waiting for the other shoe to drop. I hate this so much!"*
- *"Diagnosis is life - changing for all concerned. In many ways the most difficult part is 'watch and wait'. The stress of having regular blood tests and trying not to anticipate bad results is almost overwhelming and has a great impact on quality of life."*
- *"Watching a loved one deteriorate over time is extremely stressful. Watch and wait, changes to watch and worry as blood work changes"*

CLLPAG & LC asked which CLL symptoms affected patient quality of life at diagnosis and on an ongoing basis. The following were provided by patients:

Symptom	At diagnosis	Ongoing
Fatigue/lack of energy	47.5% (152/320)	83.07% (260/313)
Increasing lymphocyte count	33.4% (107/320)	30.35% (95/313)
Enlarged lymph nodes	30.3% (97/320)	22.68% (71/313)

Symptom	At diagnosis	Ongoing
Frequent infections *(due to compromised immunity)*	19.1% (61/320)	27.16% (85/313)
Night sweats	20.6% (66/320)	18.53% (58/313)
Shortness of breath *(attributed to anemia)*	12.8% (41/320)	19.81% (62/313)
Anemia	11.3% (36/320)	19.17% (60/313)
None of the listed symptoms	29.7% (95/320)	23.64% (74/313)

Respondents to the survey also reported on the psychosocial aspects of a CLL/SLL diagnosis and the ongoing issues they continue to experience were the following:

	Patients		
Psycho-Social Condition	At diagnosis	Ongoing	Caregivers
Stress of diagnosis	63.8% (204/320)	26.2% (82/313)	78.05% (32/41)
Anxiety/worry	65.3% (209/320)	44.4% (139/313)	80.49% (33/41)
Difficulty sleeping	32.5% (104/320)	30.8% (96/313)	60.99% (25/41)
Depression	26.9% (86/320)	17.9% (56/313)	34.15% (14/41)
None of these	20.0% (64/320)	31.3% (98/313)	4.88% (2/41)

Some patients also expressed difficulties with concentration, emotions and mood swings. The symptoms also interfered with a patient's performance, ability to work, travel and day-to-day activities. The survey respondents noted that of the 307 patients, the disease affected work for 120 (39.9%), family for 117 (38.11%) patients, personal image for 84 (27.36 patients), intimate relations for 69 (22.48%) and friendships for 56 (18.4%) of patients. To help provide context, the following comments were excerpted:

- *"My husband has recently died and I have no family was unable to have children I suffer badly with loneliness and depression life has no meaning now."*
- *"can not do everything I used to…worried about colds and infection with low neutrophils thus stay away from crowds and family events...not worth the risk."*
- *"I have lost my job, my relationship with my coworkers, and my career."*
- *"My husband was 24 when diagnosed. I was 8 months pregnant and we had just purchased our first home. He received chemotherapy the first time and then when it came back again in less than a year, Rituximab (which was an amazing drug for him) and then shortly after a stem cell transplant…I feel that we have never been able to live our life fully since his diagnosis. We hesitate purchasing big items or planning anything in the future because we're never sure how he will be feeling that far in advance. He has not worked in 2 years and receives significantly less while on disability."*

Survey respondents were also asked to rate which symptoms of CLL are the most important for treatment to control with 1 = not important and 10 = very important.

Symptom, n=301	1	2	3	4	5	6	7	8	9	10	% rated 8, 9 or 10
Infections	4	1	2	2	9	8	9	31	60	175	88.4%
Thrombocytopenia	8	0	2	3	23	13	27	57	67	101	74.8%
Neutropenia	8	3	3	4	16	15	29	50	58	115	74.1%
Viral reactivation	12	7	2	4	24	10	21	54	48	119	73.4%
Anemia	8	4	4	5	23	10	28	64	49	106	72.8%
Fatigue, lack of energy	7	3	5	5	31	18	30	57	49	96	67.1%
White blood cell counts	7	8	8	10	31	24	20	38	25	130	64.1%
Fever	14	2	7	12	27	17	29	61	46	86	64.1%

Symptom, n=301	1	2	3	4	5	6	7	8	9	10	% rated 8, 9 or 10
Lymph node size	9	10	8	11	33	13	30	52	34	101	62.1%
Enlarged spleen or abdominal discomfort	13	4	5	10	31	13	41	51	50	83	61.1%
IgG levels	11	3	8	6	40	24	29	48	49	83	59.8%
Pain	14	4	13	9	32	22	33	57	45	72	57.8%
Psychological issues	15	7	19	16	44	24	34	57	28	57	47.2%
Stress levels	13	11	10	21	39	25	40	57	36	49	47.2%
Night sweats	20	10	21	6	38	31	47	67	31	30	42.5%
Weight loss	23	14	14	15	53	34	43	45	28	32	34.9%

In addition to the above, approximately one third, 110/301 (36.54) of patients reported having a comorbidity, with 41/110 having another cancer (37.27%), 23 (20.91%) having cardiovascular issues and 20 (18.8%) having diabetes.

3.1.2 Patients' Experiences with Current Therapy for chronic lymphocytic leukemia

According to CLLPAG & LC, respondents are currently receiving a variety of therapies to treat CLL as reported in the table below. CLLPAG & LC noted that 'n' represents the total number of patients who answered a specific question in the table below; however, the numbers will not add to 'n' as one patient may have had multiple therapies. They have only listed the numbers for patients who have received each therapy. Even though responders may have indicated they received a treatment, they did not always answer which line of therapy their completion status.

Conventional Therapy n=165	Overall Use n (%)	Line of Treatment						Completed Tx	
		1st	2nd	3rd	4th	5th	6+	Yes	No
FCR [1]	76 (61.8%)	58	11	2	3	0	3	50	11
BR [2]	26 (28%)	11	8	3	1	0	1	17	4
Chlorambucil	22 (26.8%)	16	1	1	0	0	0	10	6
FR [3]	20 (23.3%)	15	2	2	0	0	0	14	2
R CHOP [4]	9 (11.5%)	2	3	0	0	0	1	6	0
Bendamustine	8 (11.3%)	2	1	3	0	0	0	4	2
CVP [5]	5 (6.8%)	3	1	0	0	0	0	1	3
PCR	3 (4.1%)	3	0	0	0	0	0	2	0
FCM	1 (1.4%)	0	1	0	0	0	0	1	1
CHOP	1 (1.4%)	1	0	0	0	0	0	1	0

[1]FCR - fludarabine, cyclophosphamide, rituximab; [2]BR - bendamustine, rituximab; [3]FR - fludarabine, rituximab; [4]R CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; [5]CVP - cyclophosphamide, vincristine and prednisone.

Other Drug Therapy n=142	Overall Use n (%)	Line of Therapy						Able to Complete Treatment?		
		1st	2nd	3rd	4th	5th	6+	Yes	Ongoing	No
Ibrutinib	86 (67.2%)	25	35	12	4	1	3	7	48	13

Other Drug Therapy n=142	Overall Use n (%)	Line of Therapy						Able to Complete Treatment?		
		1st	2nd	3rd	4th	5th	6+	Yes	Ongoing	No
Venetoclax	21 (25.3%)	7	3	8	3	0	0	5	9	1
Other	18 (27.3%)	5	4	2	1	0	1	6	3	1
Idelalisib	9 (11.4%)	2	4	1	0	1	2	0	4	4

Other Treatment n=110	Overall Use n (%)	Line of Treatment					
		1st	2nd	3rd	4th	5th	6+
Surgery	7 (7.1%)	4	2	0	0	0	0
Radiation	5 (5.2%)	1	1	1	0	0	1
Stem Cell Transplant	5 (5.2%)	0	0	2	1	1	0
Other	5 (5.2%)	3	0	1	0	0	0

Survey respondents were asked to rate if their current therapy could manage their symptoms on a scale of 1 (strongly agree) to 10 (strongly disagree). Of the patients who respondents to the survey, 179 respondents gave a weighted average response of 6.04, with 86 people (48.04%) rating an 8, 9, or 10. Of the total respondents, less than one third, 56 or 31.28% rated this question as a 1, 2, 3 and strongly agreed that their therapy managed their symptoms. The following quotes provide additional context:

- *"It seems they can only manage for limited time..."*
- *"I think it will; the question is what the QOL will be."*

CLLPAG & LC noted the following for side effects of current treatments, of the respondents, 126 of patients reported fatigue, 77 patients had diarrhea, 59 had problems with infections. Patients indicated that the most difficult to tolerate side effect was fatigue, nausea and frequency of infections. The following quotations were provided by the patient respondents:

- *"I am still weak from all the problems I had from FR chemo. Life has lost its lustre."*
- *"I have chronic ITP because of having CLL and having treatment/chemo in the pasts. Currently, I am very mindful of avoiding any infections or viruses as well as avoiding high risk situations where I could bleed, especially internal bleeding from falls."*

Patient respondents also rated on a scale of 1 (little impact) to 10 (significant impact) how their treatment experience impacted their quality of life. The results are noted below. Of the 186 patients who received treatment for CLL/SLL and responded (179), 42 or 23.5% could not access treatment in their own community. Of these 42, 25 could not access treatment as there isn't a local cancer centre, 13 as their treatment was unavailable in their province/state and 3 had to travel out of the country.

	IV Administered Therapies			Oral Therapies		
Experience	6 or 7 N=148	8, 9 or 10 N=148	Total 6-10	6 or 7 N=136	8, 9 or 10 N=136	Total 6-10
Number of clinic visits	32 (21.62%)	49 (33.11%)	81 (54.73%)	15 (11.03%)	22 (16.18%)	37 (27.21%)
Treatment-related fatigue	20 (13.51%)	56 (37.84%)	76 (51.35%)	14 (10.29%)	31 (22.79%)	45 (33.09%)
Infusion time	30 (20.27%)	42	72 (48.65%)	N/A	N/A	N/A

Experience	IV Administered Therapies			Oral Therapies		
	6 or 7 N=148	8, 9 or 10 N=148	Total 6-10	6 or 7 N=136	8, 9 or 10 N=136	Total 6-10
		(28.38%				
Activity level	25 (16.89%)	43 (29.05%)	68 (45.95%)	18 (13.24%)	27 (19.85%)	45 (33.09%)
Toleration of treatment	21 (14.19%)	39 (26.35%)	60 (40.54%)	11 (8.09%)	33 (24.26%)	44 (32.35%)
Infusion reaction	17 (11.49%)	39 (26.35%)	56 (37.84%)	N/A	N/A	N/A
Number of infections	18 (12.16%)	27 (18.24%)	45 (30.41%)	10 (7.35%)	17 (12.50%)	27 (19.85%)
Frequency of infections	11 (7.43%)	28 (18.92%)	39 (26.35%)	10 (7.35%)	18 (13.24%)	28 (20.59%)

In addition to the above, 60 of the total 301 patient respondents (19.93%) have required immunoglobulin therapy, 50 (16.61%) have received blood growth factors and 49/301 have received transfusions of blood products. As a note, respondents were not asked if the blood products were received for managing the disease or treatment adverse events

3.1.3 Impact of chronic lymphocytic leukemia and Current Therapy on Caregivers

CLLPAG & LC asked caregivers to rate on a scale of 1 to 1 how caring for the person with cLL has impacted or limited their own day-to-day activities and quality of life. Below were the results of the responses:

Activity	1-5 (no to little impact)	6-10 (significant impact)
Ability to perform household chores	75.00% (30/40)	25.00% (10/40)
Ability to concentrate	55.00% (26/40)	45.00% (14/40)
Ability to contribute financially to household finances	75.00% (30/40)	25.00% (10/40)
Ability to exercise	80.58% (33/41)	19.52% (8/41)
Ability to fulfill family obligations	67.50% (29/40)	27.50% (11/40)
Ability to spend time with family & frien	65.00% (26/40)	35.00% (14/40)
Ability to travel	55.00% (26/40)	45.00% (14/40)
Ability to volunteer	87.50% (31/40)	22.50% (9/40)

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with venetoclax

Expectations with Venetoclax

CLLPAG & LC noted that, for patients with CLL who have received at least one prior therapy and who have failed a B-cell Receptor Inhibitor (BCRI), there are few treatment options.

CLLPAG & LC asked respondents to rate important of choice in therapy, 286 (95.02%) of the 301 patient respondents rated this as a 8,9, or 10 on a scale of 1-10, with 1 as not important and 10 as very important. The weighted average for this question was 9.6.

Similarly, when respondents were asked if they would take a drug with known side-effects, potentially serious, if their doctor recommended it was the best choice for them, 133/301 (44.19%) replied “yes”, 25 (8.31%) said “no” , and 143 (47.51%) answered “I don’t know”. It was

noted that more relapsed patients said "yes" to this question (12/21), with 1 (4.76%) person answering "no" and 8 (37.09%) as "I don't know".

CLLPAG & LC noted that patients seek individualized choice in treatment which will offer disease control and improve quality of life while offering ease of use relative to other available treatments. When respondents were asked "what was most important about a new therapy", A total of 162 patients respondents, of which 72 (44.44%) prioritized increase effectiveness, 40 (24.69%) rated decreased toxicity as most important, 12 (7.41%) prioritized remission, 12 (7.41%) wanted accessible and affordable treatments, 11 (6.79%) wanted an improved quality of life and 9 (5.56%) stressed the important of an oral therapy. The patient respondents also provided the following quotes for this question:

- *"That it is tried and tested with minimal side effects. On a personal level I would probably accept anything if there were no more options."*
- *"Because as my CLL will return at some point i would hope new and better drugs are available."*
- *"I am 75, and will probably not take drugs that likely have severe side effects. I also have a signed DNR and am committed to quality not quantity of years left."*

CLLPAG & LC noted that patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a range of patients, including those with poor prognostic factors and those with advanced age and exciting co-morbidities. They also noted that new targeted therapies will change the management of CLL from life/death situation to one of chronic disease management.

In addition, CLLPAG & LC added that as an oral therapy, venetoclax would not be administered in a hospital of cancer care setting which will lower the risk of patients developing hospital acquired infections. The oral drug can be taken in the comfort of a patient's home. Also, patients and caregivers who live far from cancer treatment facilities and the elderly would benefit from an oral medication.

Experience with Venetoclax

There were 21 patient respondents who had experience with venetoclax, 4 from Canada, 4 from the UK, and 13 from USA. One patient had just started taking venetoclax and the longest anyone had been on the drug was 3.5 years.

Of the 21 respondents, four (4) received venetoclax as first-line therapy. Out of the seventeen (17) who had received prior therapies, six (6) had one previous therapy; eight (8) had 2 previous line of therapy; two (2) had 3 previous therapies; one (1) participant had received 4 previous lines of treatment. Six (6) were resistant or intolerant or failed ibrutinib, one (1) failed idelalisib and one (1) respondent failed both ibrutinib and idelalisib. Five (5) patients reported a 17p deletion. Four (4) did not know if they had this deletion or not. Four (4) reported knowing they were IgVH unmutated; four (4) were mutated; the rest did not report their mutational status.

Of the 21 respondents, fifteen (15) participants are still taking venetoclax. For the six (6) who are not, four (4) are in remission; one (1) is intolerant to the ibrutinib they were taking with the venetoclax so is waiting further direction from their physician; one (1) could not tolerate the full dose of venetoclax and is taking a half-dose while waiting for a stem cell transplant as they are also ibrutinib intolerant.

Thirteen respondents are receiving venetoclax as part of a clinical trial: 8 venetoclax as a monotherapy; 3 venetoclax and ibrutinib, 1 venetoclax and obinutuzumab; 1 venetoclax, obinutuzumab and ibrutinib. For the eight (8) respondents not part of a venetoclax clinical trial, for six (6) venetoclax is a monotherapy, one (1) receives venetoclax and Rituxan, and one is

receiving ibrutinib and venetoclax. Out of this non-clinical trial group, one is receiving the drug through a pharma-sponsored drug access program, the others had private or public insurance to cover the cost. Five (5) have been on previous clinical trials for other therapies.

Respondents were asked which of their symptoms were managed by taking venetoclax.

Answer Choices (n=21)	Managed		Did Not Manage	
Managed all my symptoms	61.90%	13	N/A	N/A
Enlarged lymph nodes	23.81%	5	4.76%	1
Increasing lymphocyte count	19.05%	4	0.00%	0
Fatigue, lack of energy	19.05%	4	28.57%	6
Enlarged spleen	9.52%	2	0.00%	0
Night sweats	4.76%	1	4.76%	1
Weight loss	9.52%	2	0.00%	0
Frequent infections	4.76%	1	9.52%	2
Shortness of breath	4.76%	1	4.76%	1
Pain	0.00%	0	0.00%	0
Did not manage any of my symptoms*	N/A	N/A	4.76%	1*

**This person just started taking venetoclax and indicated it is too soon to tell.*

CLLPAG and LC noted the following regarding side effects experienced with venetoclax, 15 (71.43%) patients stated the side effects were mild and quickly dissipated or were effectively treated with medication, 3 participants did not indicate the intensity of the side effects and 1 person just started the medication and was not able to provide input.

Side effects reported by participants included diarrhea (8), neutropenia (7), fatigue (6), nausea (5), thrombocytopenia (2), upper respiratory tract infection (1), tumour lysis syndrome (1). Five (5) respondents did not experience side effects. The person with tumour lysis syndrome had the condition successfully managed as it was detected early and they are still taking ventoclax, with the only continuing side effect being diarrhea.

Participants were asked if they would take this drug again if their doctor thought it was the best choice, knowing the potential side effects. Twenty (20) responded positively. As expressed by patients:

- *"I have had the least side effects with Venetoclax of any treatment. I feel great!"*
- *"Frequent respiratory and urinary infections while on Venetoclax (one year). It controls my CLL while apparently making me more vulnerable to respiratory & urinary infections . . . not a happy trade-off."*
- *"It is an incredible drug. I have been on it for over a year. My blood counts are all good. It has saved my life. I had nausea for 8 months but it has gone away."*
- *"It is saving my life at moment so few complaints. Side effect profile so far better than Imbruvica."*

CLLPAG & LC asked respondents how venetoclax changed their long-term health and well-being. As depicted in the table, most respondents report positive experiences with venetoclax.

Long-Term Health or Well-Being (N=21)	N (%)
Improved my blood counts	9 (42.86%)
Improved my quality of life	5 (23.81%)
Brought about a remission or minimal residual disease	5 (23.81%)
Reduced lymph node size *(person could not tolerate full dose)*	1 (4.76%)
Too soon to tell	1 (4.76%)

The following quotes are from patients who answered this question:

- *"Benefits of Ibrutinib began to wain. Venetoclax started and numbers started and continue to improve. 4 horse pills a day is a pain but the effects of CLL is worse."*
- *"It probably saved my life after Ibrutinib began to fail (and had already failed FCR)"*
- *"I was MRD neg in blood when tested at 6 months and MRD neg in marrow when tested at 9 months. I finally have confidence I can stop treatment without progressing if I choose."*
- *"Complete miracle. I am my old self again. Able to work, go out socially, go on vacation. All the things I had forgotten how much I missed! Regained weight as I had poor appetite previous to treatment. My zest for life and optimism have returned."*

Of the caregivers who responded to the survey, they reported that their patients had tried numerous treatments (up to 6) before trying Venclexta and 2/3 patients have responded well to Venclexta. As with other treatments, Venclexta is not effective for every patient. The following are quotes that the caregivers provided:

- *"She was on ibrutinib and now is on venetoclax with rituximab (which was given in the beginning). She now is MRD neg complete! "*
- *"My husband was put on Ibrutinib but because of side effects (joint pain and atrial fibrillation), was taken off it after about 2 years. He is now on Venetoclax which he has been on for about 7 months."*
- *"CLL dominates our lives. My wife was in a clinical trial for Ibrutinib at NIH for 3.5 years. We live in California and had to travel regularly to Bethesda, Maryland. My wife relapsed off Ibrutinib in the fall of 2015. She was then in a trial for Venetoclax at Stanford. We made 13 trips to Stanford in 9 months time. She relapsed off Venetoclax in October of 2016. She underwent CAR-T therapy at Seattle Cancer Care Alliance this winter. We had to live there for three months. She is now relapsing again."*

3.3 Additional Information

CLLPAG & LC noted the following as additional information from a patient: "*PLEASE APPROVE THIS DRUG! When I achieve MRD negativity the plan is to eventually stop this drug. So long term cost, consider all the second cancers and other issues caused by chemo, is ultimately going to be lower with this drug than chemo. I regret that the people I meet from other countries on line do not have this same wonderful treatment available to them that I do. They have to deal with FCR with all its side effects and second cancers. So sad."*

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

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

Clinical factors:

- Clarity of treatment population
- Sequencing of treatments

Economic factors:

- Monitoring for and treatment of adverse effects, such as tumour lysis syndrome and neutropenia

Please see below for more details.

4.1 Factors Related to Comparators

Ibrutinib, bendamustine/rituximab or idelalisib/rituximab would be considered for patients who have relapsed after first-line treatment. However, PAG noted that there are limited treatment options for patients who have been previously treated with ibrutinib or idelalisib, particularly patients with del (17p).

4.2 Factors Related to Patient Population

PAG is seeking clarity on the patient population who would be eligible for treatment with venetoclax and its place in therapy. PAG noted that this review is for patients who have relapsed or are refractory to ibrutinib or idelalisib/rituximab. However, the Health Canada approval is for a broader patient population. PAG is also seeking clarity on the use of venetoclax in patients who have not been previously treated with chemotherapy, as the M14-032 trial included patients who have refractory disease or developed recurrence after therapy with a BCR inhibitor.

PAG identified that there may be requests to use venetoclax for patients who have intolerance to treatment with ibrutinib in the front-line setting. There may also be interest to use venetoclax in patients who have been treated with chemotherapy or chlorambucil monotherapy and not been previously treated with ibrutinib or idelalisib/rituximab.

4.3 Factors Related to Dosing

Venetoclax is once daily dosing schedule, which is an enabler to implementation. PAG noted that the initiation of therapy involves ramp-up dosing schedule, which may lead to confusion for some patients. However, the packaging of venetoclax identifies the ramp up dosing schedule.

4.4 Factors Related to Implementation Costs

PAG noted that there would be a potentially large budget impact given the prevalent number of patients with relapsed/refractory CLL who have received at least one prior therapy. However, if venetoclax is recommended only for patients with 17p deletion CLL, the budget impact would be smaller.

PAG noted that the high incidence of neutropenia requiring supportive therapy would be additional costs associated with venetoclax therapy.

4.5 Factors Related to Health System

PAG noted that prior to initiating therapy with venetoclax, patients should be assessed for risk of tumour lysis syndrome. Prophylactic intravenous hydration and anti-hyperuricemics are required prior to first dose of venetoclax to reduce risk of tumour lysis syndrome and regular monitoring of blood chemistries after the first dose is required. Additional health care resources are required for monitoring. The initiation of treatment may require hospitalization to monitor and treat tumour lysis syndrome.

As such, PAG noted that venetoclax may need to be restricted to dispensing from pharmacies in cancer centres with the expertise and resources to monitor and treat the severe adverse effects associated with venetoclax.

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

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician input was received, one from an individual oncologist and one as a joint submission from a total of 11 oncologists.

The clinicians providing input noted that venetoclax offers a treatment option for patients with relapsed or refractory chronic lymphocytic leukemia (CLL), where tyrosine kinase inhibitors (TKIs) and/or other treatment options (including B-Cell receptor inhibitors (BCRi)) are not effective or not tolerated. After TKI failure, venetolax has shown to result in higher response rates, when compared with the use of an alternate kinase inhibitor (e.g., ibrutinib or idelalisib). Venetoclax would be used as a third or greater lines of therapy in the majority of CLL patients. It may be considered as a second-line treatment,if funding for first-line ibrutinib becomes available. It was also noted that CT scanning would be required, as an accompanying test, for the purpose of tumour lysis syndrome (TLS) risk stratification.

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

5.1 Current Treatment(s) for Chronic Lymphocytic Leukemia

In their joint input, a group of clinicians identified that there is no standard of care for high-risk CLL patients (i.e., those with del(17p) and TP53 mutations). Conventional chemotherapies are ineffective in these patients, and the only funded and available option is treatment with TKIs (including ibrutinib and rarely, idelalisib + rituximab). Patients in whom TKIs fail have a very short life expectancy (approximately three months based on prior studies) and no other viable treatment options. Allogeneic haematopoietic stem cell transplantation is recommended in younger patients (usually less than 65 years of age), which accounts for a small minority of patients. In addition, allogeneic transplant is a highly toxic procedure. Due to the relatively long response to TKIs, standard of care has currently shifted towards deferring allogenic transplant until after failure of TKIs. However, these patients often progress very quickly after TKI failure and, hence, require an alternative treatment to bridge to successful transplant (e.g., venetoclax).

One clinician providing input noted that in CLL patients are currently treated with chemo-immunotherapy in the first-line setting, and BCRi as a second-line therapy. Venetoclax would be used as a third-line treatment in most patients. If funding for first-line ibrutinib becomes available, venetoclax may be considered as a second-line treatment in patients with CLL.

5.2 Eligible Patient Population

The clinicians providing input indicated that the incidence of CLL is slowly increasing over time. Acknowledging that CLL is a common hematological malignancy, the clinicians noted that the proportion of patients who have failed a TKI, and have exhausted all other treatment options, is currently small. The duration of response for ibrutinib is more than 5 years for many patients without a del(17p) mutation. In addition, in an aged population, a number of patients might succumb to unrelated diseases before requiring a subsequent therapy. Therefore, not all patients receiving TKIs would qualify for venetoclax in their lifetime. Only patients with very high-risk CLL (e.g., those with del(17p)] currently receive TKIs as primary therapy, and the venetoclax would be considered as third-line (or higher level) of therapy for the majority of CLL patients.

5.3 Identify Key Benefits and Harms with Venetoclax

Venetoclax is a treatment option for patients with relapsed/refractory CLL who have progressed or are unable to tolerate TKIs. A group of clinicians providing input identified key benefits as follows:

- High response rates and durable responses in a patient population with no other effective treatment options
- Highly effective agent, leading to deep molecular remissions
- Possibility of being discontinued after a deep remission is obtained
- Considerably higher response rates after TKI failure when compared with alternate TKIs. For example responses to venetoclax after ibrutinib failure are higher than responses to idelalisib in patients who have failed on ibrutinib.
- Convenient administration (oral cancer drug)

The clinicians also identified the following key harms:

- Common toxicities are generally manageable by experienced hematologists (e.g., neutropenia and/or infections).
- Risk of TLS which provides an obstacle to the use of the therapy in non-academic centres where there is less experience managing and preventing TLS
- Potential need for hospitalization during drug initiation for TLS monitoring

5.4 Advantages of Venetoclax Over Current Treatments

One clinician providing input indicated that venetoclax could be considered as a response to an unmet need, because once CLL patients fail first-line chemo-immunotherapy, and a subsequent BCRi, there are no other treatment options.

The group of clinicians providing joint input also stated that venetoclax is the only agent with documented efficacy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del (17p), and that there are no other treatments available for this particular patient population. They suggested that due to the reported infectious toxicity concerns with idelalisib and rituximab, limited response to idelalisib, and short durability of treatment with this agent after ibrutinib failure/discontinuation, venetoclax would be superior to the potential use of an alternate kinase inhibitor after failure of a first TKI (e.g., ibrutinib or idelalisib).

5.5 Sequencing and Priority of Treatments with venetoclax

The joint clinician input indicated that venetoclax is currently being investigated in all lines of therapy (including first-line). In less refractory CLL patients, the drug has resulted in more and deeper remissions. However, the agent is being requested purely for refractory CLL patients (i.e., those who have failed or been intolerant to TKIs). Thus, there is no sequencing to consider as this would be the only, and last possible, effective therapy available to such patients.

One clinician providing input identified that venetoclax would mostly be used as a third-line therapy. The drug might be administered as a second-line treatment in some circumstances, if first-line ibrutinib becomes available. However, it is not expected to replace any existing agents in the treatment of CLL.

5.6 Companion Diagnostic Testing

The clinicians providing input identified no specific testing that would be necessary prior to considering the use of venetoclax, except for CT scanning to measure the largest lymph node size (for TLS risk stratification). They acknowledged that CT scanning is not currently a routine test for CLL and, thus, its use in CLL patients would be a specific and special consideration for venetoclax.

5.7 Additional Information

None

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of venetoclax (Venclexta) as monotherapy for the treatment patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi).

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in Section 8.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below (Table 3). Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

[Table 3]. Systematic Review Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs In the absence of RCT data, fully published non-comparative clinical trials investigating the efficacy of Venetoclax were to be included. Exclude reports of trials with only a dose-escalation design. Reports of trials with a mixed design† were to be included only if separate data were reported for the cohort of patients who received the study intervention.	Patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy and who have failed a B-Cell Receptor Inhibitor (BCRi)	Venetoclax monotherapy at a starting dose of 20mg administered orally as a single tablet once daily, then increasing weekly to 50mg, 100mg, 200mg, to a target dose of 400mg per day	No consensus on current standard of care Comparators include: • Allogeneic stem cell transplantation • Rituximab monotherapy • Rituximab + HDMP	Primary • **Objective response rate (CR and PR)** Secondary • **HRQoL** • Overall survival • Progression free survival • Duration of response • Toxicity (≥Grade 3 and <Grade 3) Additional Outcomes of Interest: • Minimal residual disease (MRD)

CLL = chronic lymphocytic leukemia; CR = complete response; HRQoL = health related quality of life; PR = partial response; MRD = minimal residual disease; RCT = randomized controlled trial

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

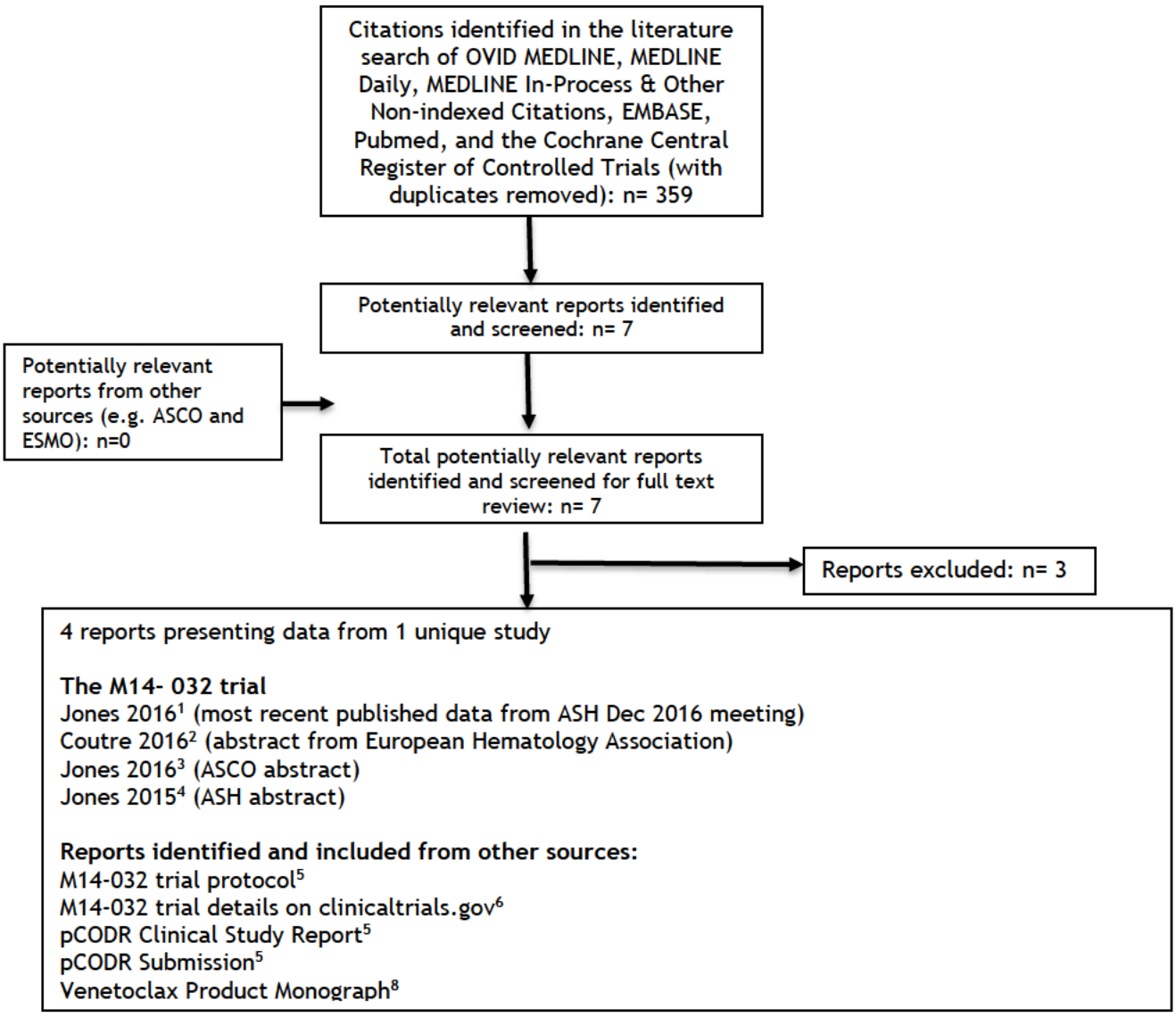
The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

6.3 Results

6.3.1 Literature Search Results

Of the 359 potentially relevant reports identified 1 ongoing study was included in the pCODR systematic review[1-5] and three studies were excluded. Studies were excluded because they did not require that patients had relapsed or were refractory to a B-Cell receptor inhibitor (BCRi).[36,47,48]

QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the M14-032 study were also obtained through requests to the Submitter by pCODR[48]

6.3.2 Summary of Included Studies

One ongoing Phase II non-randomized, open-label, multicenter trial published in abstract form was identified and met the eligibility criteria of this systematic review. Characteristics of the trial are summarized in Table 3 and specific features of trial quality are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of Trial Characteristics of the Included M14-032 Study

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
Clinical Trial NCT02141282 Open-label, non-randomized, non-comparative Phase II trial Patient enrolment: September 2014-January 2017 Interim analysis data cut-off date: January 31, 2017 N enrolled = 127 (study is ongoing, but not recruiting patients) Multicenter (15 sites in the USA) Estimated study completion date: December 6, 2018 Funded by Abbvie	<u>Key Inclusion Criteria:</u> • Diagnosis of CLL that meets iwCLL NCI-WG criteria • Relapsed or refractory disease and indication for treatment • Refractory disease or recurrence after therapy with a BCR PI (either ibrutinib or idelalisib) • ECOG PS ≤2 • Adequate bone marrow function at screening • Adequate coagulation profile, renal and hepatic function, per laboratory reference range at screening <u>Key Exclusion Criteria:</u> • Prior treatment with venetoclax • Allogeneic stem cell transplantation within past year • Development of Richter's transformation confirmed by biopsy • Active or uncontrolled autoimmune cytopenia • Malabsorption syndrome or other condition that precludes enteral route of administration • HIV positive or has chronic hepatitis B or C virus requiring treatment • Known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase	<u>Intervention:</u> Venetoclax once daily, orally via step-wise weekly dose ramp-up from starting dose of 20mg (Week 1) to final 400mg daily dose (20, 50, 100, 200, 400mg) over 4-5 weeks as tolerated No comparators were used in this study	<u>Primary:</u> • Objective response rate • Adverse events <u>Secondary:</u> • Duration of response • Time to disease progression • Progression-free survival • Overall survival • Quality of life <u>Exploratory:</u> • time to subsequent anti-CLL treatment • Rate of MRD negativity

Abbreviations: BCR PI - B-cell receptor signaling pathway inhibitors; CLL - chronic lymphocytic leukemia; ECOG - Eastern Cooperative Oncology Group; HIV - Human immunodeficiency virus; iwCLL - International Workshop on Chronic Lymphocytic Leukemia; MRD - minimal residual disease; N - number; NCI-WG - National Cancer Institute- Working Group; PS - performance status

Notes:

a) Trials

One non-randomized, non-comparative, open-label, Phase II trial, referred to as M14-032, met the inclusion criteria of this systematic review.

The M14-032 study is an ongoing study (no longer recruiting patients) with a primary objective to evaluate the efficacy (by objective response rate) and safety of venetoclax monotherapy in patients with CLL who have previously received treatment with ibrutinib and/or idelalisib, have relapsed on treatment, or experienced progression after

discontinuation of either of these agents. As of the data cut-off date of January 31, 2017 for the interim clinical study report,[5] 127 patients were enrolled in the study. Patients were enrolled in one of two study arms and an expansion cohort: 43 into Arm A (patients with relapsed or refractory CLL after ibrutinib treatment), 21 into Arm B (patients with relapsed or refractory CLL after idelalisib treatment), and 63 into the expansion cohort (patients previously treated with either ibrutinib (n=53) or idelalisib (n=22). All patients received single daily oral doses of venetoclax starting with 20mg and increasing weekly to a target dose of 400mg over 4-5 weeks.

M14-032 is a multicenter trial being conducted at 15 centers across the United States. There are no Canadian sites. Randomization did not occur in this non-comparative study nor did any blinding methods. Select quality characteristics of the trial are described in Table 4.

Screening, which included positron emission tomography/computed tomography (PET/CT) scans, bone marrow aspirate, and biopsy was performed within 28 days of study drug administration. For patients enrolled in either Arm A or Arm B, restaging CT/magnetic resonance imaging (MRI) scans were performed at Week 8, Week 24, and every 12 weeks thereafter for a period of 1 year and at the patient's final visit. For patients enrolled in the Expansion cohort, restaging CT/MRI scans were performed at Week 12, Week 36, and at the patient's final visit. Study visits were conducted on Day 1 of each week (Weeks 1-5), Week 8, Week 12, Week 16, Week 24 and then every 12 weeks thereafter.

When an investigator has determined that a patient should discontinue the study, a final visit is conducted as well as a 30-day safety follow-up. If the patient discontinued due to toxicity attributable to venetoclax, additional follow-up visits are conducted as clinically appropriate until a satisfactory clinical resolution of the adverse event (AE) is achieved and progression is documented.

The primary efficacy outcome in the M14-032 trial was objective response rate (ORR), which was calculated for all patients based on 2008 International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-sponsored Working Group (IWCLL NCI-WG) criteria. The assessment of response was performed by the investigator and by an independent review committee (IRC) based on analysis of clinical laboratory tests (hematology laboratory values), complete physical examination, CT or MRI scan of involved anatomic regions, bone marrow aspirate and biopsy. Details on tumour response criteria can be found in Appendix A.

The assessment of minimal residual disease (MRD) was considered an exploratory outcome in this study. A baseline specimen was collected and follow-up samples at Week 24 and after a confirmed complete response (CR), CR with incomplete marrow recovery (CRi), or partial remission (PR) for analysis of MRD levels. Safety evaluations were ongoing and included adverse event monitoring, vital signs, physical examination, electrocardiogram, and laboratory assessments. Intense monitoring for signs of tumour lysis syndrome (TLS) also took place.

b) Populations

For inclusion in the trial, patients must have had a diagnosis of CLL that met published IWCLL NCI-WG criteria. Patients must have had relapsed or refractory disease with an indication for treatment. Refractory disease or recurrence must have occurred after treatment with either one of the B-cell receptor signalling pathway inhibitors (BCRi), ibrutinib or idelalisib and met one of the following: 1) treatment failure with either of these agents or 2) progression during treatment or after discontinuation or either of these agents. It was not indicated that there is a requirement that patients must have refractory disease or recurrence following treatment with both BCRi's (ibrutinib and

idelalisib). Additional inclusion and exclusion criteria are outlined in the trial characteristics summary provided in Table 3.

Since the data cutoff date of January 31, 2017, a total 127 patients were enrolled in the M14-032 trial; 43 into Arm A (previously treated with ibrutinib), 21 into Arm B (previously treated with idelalisib), and 63 into the Expansion cohort (previously treated with either ibrutinib (n=53) or idelalisib (n=22)). A total of 22/127 patients (17.3%) received both ibrutinib and idelalisib as a prior line of therapy: 4 in Arm A (ibrutinib failure), 6 in Arm B (idelalisib failure), and 12 in the Expansion cohort.

The majority of patients enrolled in the study were white (92.1%) males (70.1%), between 65-75 years of age. Most patients were in the ECOG Stage 0 (32.3%) or 1 (59.1%) in terms of performance status, and [redacted]. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). For tumour lysis syndrome (TLS) prophylaxis, all patients were classified into 3 risk categories based on their tumour burden prior to venetoclax administration. The tumour burden assessed by the nodal disease and absolute lymphocyte count (ALC) at screening that was used to define each category are described in Appendix A. There were more patients in the low risk category for TLS in Group A (ibrutinib failure) compared with Group B (idelalisib failure) (35% versus 24%) while fewer patients in Arm A were of medium risk as compared to Arm B (26% versus 43%, respectively). In the Expansion cohort low medium and high risk category for TLS occurred in 38%, 44% and 17.5% of patients. Overall, 35/127 patients (28%) were of high risk for TLS in the total patient population.

The median time to the first dose of venetoclax since the initial diagnosis of CLL for all patients was 100.0 months (range, 3.7-222.5). Within the different cohorts, the median time to first dose of venetoclax was 107.4 months (range, 6.9-222.5) in Arm A, 84.2 months (3.7-211.4) in Arm B, and 95.0 months (7.6-215.9) in the Expansion cohort. The arms were similar in terms of the median number of previous lines of therapy with 4 (1-13) in Arm A, 3 (1-11) in Arm B, and 4 (1-15) in the Expansion cohort.

A total of 57 (44.9%) patients harboured the 17p deletion and/or TP53 mutation as assessed by the investigators local laboratory. Additional baseline characteristics are outlined in Tables 5-8.

c) Interventions

Details of the dosing and administration schedule of venetoclax in the M14-032 study can be found in Table 3. Patients enrolled in the study followed a weekly venetoclax dose ramp-up schedule to mitigate the risk of TLS. Patients started on venetoclax at 20mg followed by weekly increases (20mg, 50mg, 100mg, 200mg, 400mg) until the target dose of 400mg was reached. To further reduce the risk of TLS, patients received prophylaxis with uric acid lowering agents starting at least 72 hours prior to the first venetoclax dose and patients with high tumour burden were hospitalized. Patients also received oral hydration irrespective of TLS risk category starting at least 48 hours prior to each dose. Patients unable to maintain adequate oral hydration or those with medium or high risk for TLS were also given intravenous hydration. Laboratories were monitored at scheduled time points at the first dose and at dose increases. Patients were carefully monitored during this phase for TLS, and any changes that increased risk were immediately addressed.

Disease assessments were performed at each visit by physical examination and laboratory testing and took place at baseline, on Week 5 Day 1 (or Day 1 of initiation of 400mg dose of venetoclax), Week 8, Week 12, Week 16, Week 24 and then every 12 weeks thereafter

until disease progression, death, discontinuation from the study, or study completion. Radiographic studies were performed and analyzed in conjunction with bone marrow, which were both required to be free of disease for the determination of complete remission (CR). Once a CR was determined by clinical and radiographic criteria, a bone marrow aspiration and biopsy was performed for confirmation. MRD was assessed using flow cytometry and MRD negativity was defined as the presence of less than one CLL cell per 10,000 leukocytes in either peripheral blood and/or bone marrow.

By the data cutoff date (January 31, 2017), a total of 127 patients were enrolled and received at least one dose of venetoclax. The median time between the end of B-cell receptor (BCR) inhibitor therapy to the first dose of venetoclax in all patients was 1.4 months (Table 7). The median duration of study treatment in all patients was 10.2 months (range, 0.1-25.6). Within the treatment cohorts, median duration of treatment in Arm A (ibrutinib failure) was 18.5 months (range, 0.1-25.6), in Arm B (idelalisib failure) was 16.3 months (range, 1.3-24), and 7.9 months for the Expansion Arm (range, 0.1-13.2). Patients were able to continue receiving venetoclax for up to 2 years provided they continued to tolerate the drug, had no evidence of disease progression, and did not meet any of the criteria for discontinuation. The anticipated median duration of treatment is approximately 1 year.

Whether or not dose modifications were allowed for venetoclax is not clear.

All 127 subjects received at least 6 concomitant medications. The most common protocol specified concomitant medications were allopurinol, which was to be initiated at least 72 hours prior to dosing; sodium chloride, furosemide and rasburicase. Other common concomitant medications were paracetamol acyclovir, valaciclovir, Bactrim, acetylsalicylic acid, filgrastim, ondansetron, docusate, immunoglobulin human normal, levofloxacin, azithromycin, potassium, fluticasone and senna alexandrina.

Table 4: Select quality characteristics of the included M14-032 study of venetoclax in patients with CLL refractory to a BCRi.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
NCT02141282 (M14-032)	Venetoclax No comparator	ORR	No formal a-priori statistical hypothesis plan on the primary endpoint ORR; a sample size of 60 patients ensured that the distance of the true rate will be within 14% of the observed rate with 95% confidence	Study is ongoing but no longer recruiting patients 127 patients currently enrolled	Trial not randomized	No	No	Yes	No	No	Yes

Abbreviations: BCRi - B cell receptor inhibitor; CLL - chronic lymphocytic leukemia; ITT - intention to treat; ORR - overall response rate

Table 5. Baseline demographics and characteristics of patients in the M14-032 study.[5]				
	Arm A (n=43)	Arm B (n=21)	Expansion (n=63)	Total (n=127)
Age (years)				
< 65	17 (39.5)	6 (28.6)	30 (47.6)	53 (41.7)
≥ 65	26 (60.5)	15 (71.4)	33 (52.4)	74 (58.3)
< 75	35 (81.4)	18 (85.7)	50 (79.4)	103 (81.1)
≥ 75	8 (18.6)	3 (14.3)	13 (20.6)	24 (18.9)
Sex				
Male, n (%)	33 (76.7)	15 (71.4)	41 (65.1)	89 (70.1)
Female	10 (23.3)	6 (28.6)	22 (34.9)	38 (29.9)
Race				
White	40 (93.0)	19 (90.5)	58 (92.1)	117 (92.1)
Black	2 (4.7)	2 (9.5)	4 (6.3)	8 (6.3)
Asian	1 (2.3)	0	1 (1.6)	2 (1.6)
Ethnicity				
Hispanic or Latino	1 (2.3)	0	8 (12.7)	9 (7.1)
No ethnicity	42 (97.7)	21 (100)	55 (87.3)	118 (92.9)

Table 6. Baseline disease status of patients in the M14-032 study.[5]				
Characteristic	Venetoclax 400mg			Total n=127
	Arm A n=43	Arm B N=21	Expansion n=63	
ECOG performance status, n (%)				
Grade 0	13 (30.2)	5 (23.8)	23 (36.5)	41 (32.3)
Grade 1	27 (62.8)	14 (66.7)	34 (54.0)	75 (59.1)
Grade 2	3 (7.0)	2 (9.5)	6 (9.5)	11 (8.7)
Absolute lymphocyte count, n (%)				
≥ 25 x 10^9 per L	17 (39.5)	7 (33.3)	15 (24.2)	39 (30.7)
< 25 x 10^9 per L	26 (60.5)	14 (66.7)	47 (75.8)	87 (68.5)
≥ 100 x 10^9 per L	7 (16.3)	4 (19.0)	10 (16.1)	21 (16.5)
< 100 x 10^9 per L	36 (83.7)	17 (81.0)	52 (83.9)	105 (82.7)
Bulky disease, n (%)				
One or more nodes ≥ 5cm	15 (34.9)	11 (52.4)	27 (42.9)	53 (41.7)
Lymph nodes < 5cm	28 (65.1)	10 (47.6)	36 (57.1)	74 (58.3)
One or more nodes ≥10cm	7 (16.3)	5 (23.8)	2 (3.2)	14 (11.0)
Lymph nodes <10	36 (83.7)	16 (76.2)	61 (96.8)	113 (89.0)
Tumour lysis syndrome risk category, n (%)				
Low	15 (34.9)	5 (23.8)	24 (38.1)	44 (34.6)
Medium	11 (25.6)	9 (42.9)	28 (44.4)	48 (37.8)
High	17 (39.5)	7 (33.3)	11 (17.5)	35 (27.6)
17p deletion and or TP53 mutation, n (%)				
Yes[b]	24 (55.8)	5 (23.8)	28 (44.4)	57 (44.9)
IGHV mutation, n (%)				
Yes	4 (13.8)	2 (15.4)	14 (28.0)	20 (21.7)
No	25 (86.2)	11 (84.6)	36 (72.0)	72 (78.3)
Missing	14	8	13	35
11q deletion, n (%)				
Deleted	13 (30.2)	6 (28.6)	23 (36.5)	42 (33.1)
Not deleted	29 (67.4)	14 (66.7)	34 (54.0)	77 (60.6)
Indeterminate	1 (2.3)	1 (4.8)	6 (9.5)	8 (6.3)

Table 6. Baseline disease status of patients in the M14-032 study.[5]				
Characteristic	Venetoclax 400mg			Total n=127
	Arm A n=43	Arm B N=21	Expansion n=63	
Notes: [b] Reporting only for subjects with known positive 17p deletion or *TP53* mutation; the remaining subjects includes those that had missing, indeterminate, or negative status.				

Table 7. Time (months) between end of Ibrutinib or Idelalisib therapy to first dose of venetoclax.[5]				
Baseline Characteristics	Arm A (Ibrutinib R/R)	Arm B (Idelalisib R/R)	Expansion	Total
N	43	21	63	127
Median	0.9	3.9	1.9	1.4
Range	0.0-13.3	1.1-26.3	0.1-21.5	0.0-26.3
Mean (SD)	1.9 (2.57)	6.7 (7.18)	4.7 (5.68)	4.1 (5.40)
Abbreviations: R/R - relapsed/refractory; SD - standard deviation				

Table 8. Duration of Ibrutinib and Idelalisib use prior to study entry.[5]						
Baseline Characteristics	Arm A (Ibrutinib R/R) N=43		Arm B (Idelalisib R/R) N=21		Expansion (N=63)	
	Prior Ibrutinib Use (Most Recent Prior Therapy) (N=43)	Prior Idelalisib Use (Any Prior Therapy) (N=4)[a]	Prior Ibrutinib Use (Any Prior Therapy) (N=6)[b]	Prior Idelalisib Use (Most Recent Prior Therapy) (N=21)	Prior Ibrutinib Use (Any Prior Therapy) (N=53)[c]	Prior Idelalisib Use (Any Prior Therapy) (N=22)[c]
Months of Prior Ibrutinib Use						
Mean (SD)	21.6 (15.92)	-	12.1 (14.20)	-	22.8 (16.13)	-
Median	17.6	-	7.8	-	22.4	-
Range	1.0-56.3	-	2.0-40.3	-	1.0-60.8	-
Months of Prior Idelalisib Use						
Mean (SD)	-	16.1 (16.02)	-	9.6 (8.01)	-	14.4 (12.63)
Median	-	15.9	-	9.0	-	9.6
Range	-	1.7-31.0	-	0.9-26.9	-	1.9-44.9

Abbreviations: SD - standard deviation

Notes: a - A total of 4 patients in Arm A (ibrutinib failure) also had received idelalisib as a prior therapy
b - A total of 6 patients in Arm B (idelalisib failure) also had received ibrutinib as a prior therapy
c - Patients in the Expansion cohort are listed by ibrutinib or idelalisib use as any prior therapy. A total of 12 patients had received both ibrutinib and idelalisib as a prior therapy.

d) Patient Disposition

The disposition of patients at the January 31, 2017 cutoff date is outlined in Table 9 below. A total of 127 patients received at least one dose of treatment with venetoclax (43 patients in Arm A (previously treated with ibrutinib), 21 in Arm B (previously treated with idelalisib) and 63 in the Expansion Cohort (previously treated with either ibrutinib (n=53) or idelalisib (n=22). Of those that received treatment, there were a total of 50 (39.4) treatment discontinuations (25 in Arm A, 8 in Arm B, and 17 in the Expansion arm).[5] The main reason for treatment discontinuation was disease progression, which occurred in 25/127 (19.7%) of patients. Twelve patients discontinued due to adverse events (6 related and 6 not related to progression). Six patients underwent stem cell transplantation, 5 progressed to Richter's, 2 withdrew consent (1 at the investigator's request), and 10 discontinued for other reasons.

A total of 14 patients died during the study: 10 in Arm A, 2 in Arm B, and 2 in the Expansion Arm. Seven patients died within 30 days of the last dose of venetoclax and experienced fatal adverse events: 1 death not otherwise specified, 1 septic shock, 1 multiple organ dysfunction syndrome, 1 asphyxia, 1 of malignant neoplasm progression, 1 of corynebacterium sepsis and 1 of cytokine release syndrome. Seven other patients died more than 30 days after the last dose of venetoclax and information was collected during survival follow-up. All reasons for death in these seven patients were listed as unknown.

Table 9. Patient disposition in the M14-032 study.[5]

Disposition	Number of Subjects
Screened	167
Enrolled and received treatment	127
Ongoing treatment (n, %)	77 (60.6)
Discontinued treatment (n, %)[a]	50 (39.4))
Progressive disease	25 (19.7)
Richter's transformation	5 (3.9)
Adverse event	6 (4.7)
Adverse event not related to progression	6 (4.7)
Withdrew consent	2 (1.6)
Investigator request	1 (0.8)
Stem cell transplantation	6 (4.7)
Other	10 (7.9)
Death	14 (11.0)

Notes:
[a] - For subjects who discontinued venetoclax, post-treatment follow-up visits were to be performed every 3 months until discontinuation from the study due to disease progression requiring alternative therapy or a subject's refusal of the post-treatment visits.

e) Limitations/Sources of Bias

A summary of key quality indicators for the M14-032 trial is provided in Table 4. The M14-032 trial was sponsored by AbbVie to evaluate the efficacy and safety of venetoclax monotherapy in patients with CLL relapsed after or refractory to treatment with B-cell receptor signalling pathway inhibitors. This is a single-arm, non-randomized, non-comparative, open-label trial in which neither participants nor investigators were blinded, and as such, are at risk for several biases that can affect the internal validity. Two such biases include patient selection as part of the inclusion criteria for eligibility and performance bias due to knowledge of the study treatment. It is important to note that investigators, study personnel, clinicians and patients involved in the trial were aware of the study drug assigned, which can introduce the

potential to bias results and outcomes in favour of venetoclax if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results.

The M14-032 trial was well conducted but the risk of bias was not absent. No formal statistical hypothesis testing on the primary endpoint of ORR was planned but appropriate sample sizes calculations were conducted. The current interim efficacy analyses were appropriately performed by the total number of patients enrolled according to intention-to-treat. However, the following limitations and biases associated with the trials should be considered when reviewing the results:

- With respect to reporting of outcomes, it should be emphasized that all the evidence from the M14-032 trial is coming from an interim analysis that has only been published in abstract form (with a less mature data cutoff). None of the data currently presented in this report has been peer reviewed and published and as such, estimates of ORR data and other efficacy and safety outcomes are immature and should therefore be interpreted with a fair degree of caution.
- The single-arm non-randomized design makes interpreting the efficacy and safety events attributable to venetoclax challenging, since all patients received the same treatment.
- To mitigate the impact of bias, the investigators could have used a blinded independent review committee (IRC) to evaluate responses using standardized criteria. However, no blinding methods were used, and the study investigators did their own assessments of efficacy and compared their assessments with those of the IRC. Discordance between the two outcome assessors was observed and explained to be due to a difference in data cut-off dates used for assessment, (June 2016 for IRC versus January 2017 for investigator assessment).
- The M14-032 study is a non-comparative study and as such the efficacy of venetoclax cannot be determined compared to current standard(s) of care. However, there is no consensus on the optimal current standard of care in patients with relapsed or refractory CLL who have received treatment with either ibrutinib or idelalisib.
- Patient reported outcomes (PROs) were collected in the form of measurement of health-related quality of life (HRQL) using the validated 30-item EORTC QLQ-C30 questionnaire and the validated 16-item scale specific to CLL patients (QLQ-CLL16). The effect of pharmacological treatments on HRQL is an important consideration when making treatment decisions. It should be noted however, that the current HRQoL data are *interim* data that do not include assessments up to the final visit for all patients, and this may not present an accurate picture of patients' experiences with venetoclax throughout the entire treatment period. Further, the HRQL data should be interpreted with caution due to the relatively small number of patients and because this was an exploratory outcome in an open-label, single arm study.
- For the safety evaluation, it is important to note that since the data come from a single-arm study, it is difficult to estimate the contribution of the underlying disease on adverse reactions. Furthermore, patients with relapsed or refractory CLL are generally elderly and may have significant comorbidities and concomitant medications, therefore data on the comparative safety of venetoclax with other available treatments is an important consideration.

- The trial was funded by AbbVie and sponsor employees were involved in all aspects of their conduct including design, data collection, analyses, and interpretation, as well as writing the final manuscript. While the use of an independent data safety and monitoring committee minimizes bias, other measures such as central review of radiographic scans and biopsies and blinding of sponsor staff to treatment assignment were not employed. The extent to which the use of blinded independent investigators, outcome assessors, and data analysts would have influenced the results and reporting of the trial is unknown.
- The utility of MRD status is gaining greater importance in determining depth of response to therapy and is being used in more trials as a predictor of PFS and OS. While this is promising, and meta-analyses have shown a strong association between MRD negativity and improved PFS and OS,[49] the effect of the intervention on a surrogate outcome cannot predict the actual effect of treatment on important clinical outcomes such as PFS and OS. Further, MRD status was an exploratory outcome and therefore the results should be interpreted with caution.
- Overall, the results of the M14-032 trial are limited by the level of evidence (Phase II) and the fact that it is a non-comparative single arm study. Further, comparative studies assessing efficacy and safety of an appropriate comparator drug in the specific population of CLL patients who are resistant/refractory to B-cell receptor pathway inhibitors are lacking. Given that it has been reported that the majority of chemotherapy regimens demonstrating positive results in single arm phase II trials do not translate into positive results in phase III RCTs (Zia et al. J Clin Oncol 2005;23:6982-91), it is unclear whether or not the outcomes observed with venetoclax will be consistent in a randomised controlled trial.

Overall, while it is important to point out the various possible sources of bias in each trial, whether these limitations have an impact on the treatment effect is unknown. The most notable limitation comes from the fact that these are interim, and not fully mature data published only in abstract form.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

On November 30, 2017, the submitter provided a manuscript accepted for publication reporting updated data from a June 30, 2017 cut-off.[48] This manuscript had been accepted for publication and was subsequently published on December 12, 2017.[7] The data within this accepted manuscript was different from a draft manuscript (January 31, 2017 data cut) provided to the pCODR Program earlier in the review. Given that the accepted manuscript with a new data cut was provided to the pCODR reviewers less than 2 weeks prior to the finalization of the pERC Brief, the reviewers were not able to revise the report with the updated data cut of June 2017 in time for the first pERC Meeting and deliberations. At that time, the pCODR reviewers compared the manuscript and the clinical report to ensure consistency among findings.

One main difference between the manuscript and the data within this report (from the CSR) was related to the patient population. In the manuscript, only patients that received prior ibrutinib were included. This is true of Cohort A and the expansion cohort. Cohort B and those patients in the Expansion cohort who had received idelalisib were excluded from the analysis and the results were described

in a separate manuscript. This second manuscript has yet to be published. The pCODR review, based on data from the CSR, included CLL patients who relapsed or were refractory to prior ibrutinib (Arm A), idelalisib (Arm B), and those in the Expansion cohort that received prior ibrutinib or idelalisib. Further, the manuscript was limited to efficacy and safety data, indicating that patient-reported outcomes, which were exploratory, were not fully analysed yet and would be reported at a later date.

In general, the efficacy and safety data were reasonably consistent between the clinical study report and the manuscript. Minor inconsistencies were noted but likely due to the small total number of patients included. Of note, in the manuscript it was reported that 91 patients (n=43 in the main cohort, n=48 in the expansion cohort) who previously received ibrutinib were included in the analysis. However, in the January 2017 data cut, 96 patients had previously received ibrutinib (n=43 in Arm A, n=53 in the Expansion cohort). There is no further discussion within the manuscript related to this discrepancy and the pCODR review team is unable to account for the 5 patients who are missing from the analysis in the manuscript.[48]

After the posting of the pERC initial recommendation, the review team updated the clinical guidance report with the results of the Jones et al. 2017 Lancet Oncology publication. [7] Please see the bottom of Section 6.3.2.2 for further details on the results of this publication.

Objective Response Rate

The proportion of patients with objective response (per the investigator assessment) was calculated for all patients based on IWCLL NCI-WG criteria. A 95% confidence interval based on the binomial distribution was constructed for the calculated objective response rate (ORR). The assessment of ORR was conducted independently for Arm A, Arm B, and the Expansion cohort.

Investigator assessed responses were available for all 127 patients enrolled in the study. All patients in Arms A and B completed more than 24 weeks whereas 36 of the 63 patients in the Expansion cohort completed a 2nd assessment between 24 and 36 weeks of study treatment as of the January 31, 2017 cutoff. The independent review committee (IRC) only assessed efficacy for the 64 patients who were enrolled in Arms A and B and completed at least 24 weeks of treatment as a previous cutoff of June 10, 2016. IRC analyses for subjects in the Expansion Cohort who have reached the 36 week time point have not been performed as of the 31 January 2017 data cut. The ORR by investigator and IRC assessment for all treatment arms is presented in Table 10.

Study Arm A (ibrutinib failure)

As per investigator assessment, the ORR for patients in Arm A (ibrutinib failure) was 72.1% (31/43), with partial remission (PR) in 58.1% (25/43) of patients. The majority of responses were partial responses (58.1%, 25/43) while complete remission (CR/CRi rate) was reported in 9.3% (4/43) and nodular partial remission (nPR) in 4.7% (2/43) patients. As per IRC assessment (June 10, 2016 evaluation), the ORR for patients in Arm A was 69.8% (30/43) patients, with CR/CRi+nPR+PR seen in 2.3% (1/43) and 67.4% (29/43) of patients, respectively.

Deep responses (CR/CRi+nPR) were reported in 14.0% (6/43) of patients. This included 3 CR, 1 CRi, and 2 nPR based on the investigator's assessment.

Study Arm B (idelalisib failure)

As per investigator assessment, the ORR for patients in Arm B (idelalisib failure) was 66.7% (14/21), of whom 47.6% (10/21) of patients achieved a PR and 19.0% (4/21) patients achieving CR/CRi. As per IRC assessment (June 2016 evaluation), 61.9% (13/21) of patients in Arm B achieved an objective response, with PR seen in all 13 patients.

Expansion Cohort

As per investigator assessment, the ORR for the 63 patients in the Expansion cohort was 42.9% (27/63), with PR observed in 38.1% (24/63) and CR/CRi in 4.8% (3/63) of patients. Approximately half (36/63) of the patients in the Expansion cohort completed a second assessment between 24 and 36 weeks of venetoclax treatment; the other 27 patients only completed the 12-week assessment. The ORR for those 36 patients with a second assessment between 24-36 weeks of treatment was 86.1%, including 3 patients with CR/CRi and 28 patients achieving PR. As previously noted, IRC analyses for subjects in the Expansion Cohort who have reached the 36-week time point have not been performed as of the 31 January 2017 data cut.

For comparison, the ORR as assessed by the investigator in the subgroup of patients with either 17p deletion or p53 mutation was 16 (66.7%, 95% CI: 44.7, 84.4), 4 (80.0%, 95% CI: 28.4, 99.5), and 14 (50.0%, 95% CI: 30.6, 69.4), in Arms A (n=24), B (n=5), and the Expansion cohort (n=28, total N=57), respectively.

Duration of Response

Duration of response was evaluated per investigator assessment at the January 31, 2017 data cutoff for 72 patients (n=31 in Arm A, n=14 in Arm B, and n=27 in the Expansion Cohort) who had a record of first response (CR, CRi, PR, or nPR). Median duration of response was not reached. The median DoR has not been reached. The Kaplan-Meier estimate of DoR at 12 months for patients in Arm A and Arm B were 79.7% (60.3%, 92.7%) and 84.4% (50.4%, 95.9%), respectively, and not available for patients in the Expansion cohort.

Progression-free Survival

Progression-free survival (PFS) is defined as the number of months from the day the patient started the study drug to either an event of disease progression or death.[5] To date, the median PFS has not been reached. The Kaplan-Meier estimates of PFS at 12 months are presented as investigator assessments (with January 31, 2017 data cutoff) in Table 10. For comparison, the investigator-assessed 12-month rate of PFS (and 95% CI) in the subgroup of patients with either 17p deletion or p53 mutation was 65.4% (42.4%, 81.1%), 80.0% (20.4%, 96.9%), and 72.8% (47.9%, 87.2%) in Arms A (n=24), B (n=5), and the Expansion cohort, respectively.

Table 10. Key efficacy outcomes in patients with CLL in the M4-032 study.[5]

	Arm A Ibrutinib Failure N=43		Arm B Idelalisib Failure N=21		Expansion Cohort N=63	All Patients N=127
Outcome	**IRC Assessed[a]**	**Investigator Assessed[b]**	**IRC Assessed[a]**	**Investigator Assessed[b]**	**Investigator Assessed[b]**	**Investigator Assessed[b]**
ORR[c] N (%) [95% CI %]	30 (69.8) [53.9, 82.8]	31 (72.1) [56.3, 84.7]	13 (61.9) [38.4, 81.9}	14 (66.7) [43.0, 85.4]	27 (42.9) [30.5, 56.0]	72 (56.7%) [47.6, 65.5]
CR rate, n (%) (CR/CRi) [95% CI]	1 (2.3) [0.1, 12.3]	4 (9.3) [2.6, 22.1]	0 [0, 0]	4 (19.0) [5.4, 41.9]	3 (4.8) [1.0, 13.3]	11 (8.7) [4.4, 15.0]
PR rate, n (%) (nPR+PR) [95% CI]	29 (67.4) [51.5, 80.9]	27 (62.8) [46.7, 77.0]	13 (61.9) [38.4, 81.9]	10 (47.6) [25.7, 70.2]	24 (38.1) [26.1, 51.2]	61 (48.0) [39.1, 57.1]

Table 10. Key efficacy outcomes in patients with CLL in the M4-032 study.[5]

	Arm A Ibrutinib Failure N=43		Arm B Idelalisib Failure N=21		Expansion Cohort N=63	All Patients N=127
Outcome	IRC Assessed[a]	Investigator Assessed[b]	IRC Assessed[a]	Investigator Assessed[b]	Investigator Assessed[b]	Investigator Assessed[b]
Nodular Partial Remission	0	2 (4.7)	0	0	0	2 (1.6)
Partial Remission	29 (67.4)	25 (58.1)	13 (61.9)	10 (47.6)	24 (38.1)	59 (46.5)
Non responder[d]	13 (30.2)	NR	8 (38.1)	NR	NR	??
Stable Disease	NR[d]	7 (16.3)	NR[d]	6 (28.6)	28 (44.4)	41 (32.3)
Progressive Disease	NR[d]	1 (2.3)	NR[d]	1 (4.8)	5 (7.9)	7 (5.5)
Incomplete Data	NR[d]	4 (9.3)	NR[d]	0	3 (4.8)	7 (5.5)
DOR, months (median, 95% CI)	NR [16.6, --]		NR [14.5, --]		NR	NR [17.6, --]
DOR at 12 months (95% CI)	79.7 (60.3, 90.3)		84.4 (50.4, 95.9)		NA	84.7 (71.2, 92.2)
12 month Estimated PFS rate (95% CI) (investigator assessed)	71.0% (54.6, 82.4)		85.7% (62.0, 95.2)		74.2% (57.0, 85.3)	74.2% (64.3, 81.8)
12 month Estimated PFS rate (95% CI) (IRC assessed)	77.7% (61.4, 97.9)		NA		Not measured	81.0% (68.0, 89.1)[e]
TTP (median, 95%CI) (IRC assessed)	83.6 (66.9, 92.3) (n=43)		NA (n=21)		NR	86.5 (73.4, 93.4) (n=64)
TTR[f] (median, range) (IRC assessed)	1.6 (1.0, 5.5) (n=30)		1.6 (1.3, 5.3) (n=13)		NR	1.6 (1.0, 5.5) (n=43)
12 month OS estimate (95% CI)[g]	88.2% (73.9, 94.9)		95.2 (70.7, 99.3)		96.2% (85.3, 99.1)	93.1% (86.6, 96.5)

Notes: [a] - Data are as of June 10, 2016
[b] - Data are as of January 31, 2017
[c] - ORR includes CR + CRi + nPR + PR
[d] - Patients with progressive disease, stable disease, or incomplete data were considered non-responders by the IRC.
[e] - As IRC assessment was not conducted on the Expansion cohort, the total number of patients in the 'All Patients" category are n=64
[f] - First response could be CR or PR
[g] - It was not reported whether the data on OS estimates are investigator or IRC assessed
Abbreviations: CI = confidence interval; CR = complete remission; CRi - complete remission with incomplete marrow recovery; DOR = duration of response; IRC - Independent review committee; MRD - minimal residual disease; NA - not assessed; nPR - nodular partial response; NR - not reported; ORR = objective response rate; OS - overall survival; PFS = progression-free survival; PR = partial response; TTNT - time to next treatment; TTP - time to progression; TTR - time to first response

Time to Disease Progression

Time to disease progression (TTP) was defined as the number of days from the date of the first venetoclax dose or enrollment (if not dosed) to the date of earliest disease progression. All disease progression was included regardless of whether the event occurred while the patient was taking the study drug or had previously discontinued the study drug. If the patient did not experience disease progression, then the data were censored at the date of the last available disease assessment. TTP was analyzed by Kaplan-Meier estimates using data for all patients enrolled. The median and 95% confidence intervals for TTP were calculated.

Clinical response was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scan. If the CT scan demonstrated a complete response (CR) based on investigator assessment, then a bone marrow biopsy was performed to confirm the CR. Confirmation of a CR was made when both the CT scan and the bone marrow biopsy were negative. Data on the IRC's assessment of TTP are presented in Table 10.

Time to First Response

Clinical response was to be confirmed by CT/MRI for each patient, which, if found to be a CR based on the investigator assessment, was followed by a bone marrow biopsy to confirm the CR. For determination of CR, both tests were required to be negative. As per investigator assessment (January 31, 2017 cutoff), the median time to first response for the 31 patients in Arm A with an objective response was 1.6 months (range, 1.6-16.4).[5] For the 14 patients in Arm B with an objective response, the median time to first response was 1.8 months (range, 1.6 to 8.1), and for the 27 patients in the Expansion cohort, the median was 2.6 months (range, 2.3-3.5) (Table 10).

Overall Survival

Overall survival (OS) was defined as the number of months from the date of the first dose of venetoclax to the date of death. At the time of this analysis with the January 31, 2017 data cut-off, 14 out of 127 (11.0%) deaths had occurred. This included 10 deaths (23.3%) in Arm A (ibrutinib failure), 2 (9.5%) in Arm B (idelalisib failure), and 2 (3.2%) in the Expansion arm. Kaplan-Meier estimates for overall survival along with 95% confidence intervals were calculated at 6, 9, and 12 months. At 12 months, the estimate for overall survival in Arm A, Arm B, and the Expansion cohort were 88.2% (95% CI: 73.9, 94.9), 95.2% (70.7, 99.3), and 96.2% (85.3, 99.1), respectively (Table 10).

The 12-month overall survival estimates were also calculated for the subgroup of patients harbouring the 17p deletion and/or TP53 mutation in Arms A (n=24), B (n=5), and the Expansion cohort (n=28, total N=57). They were as follows: 87.5% (95% CI: 66.1, 95.8), 80.0% (95% CI: 20.4, 96.9), and 95.7% (95% CI: 72.9, 99.4), respectively. Follow-up for long-term survival is ongoing.

Other Key Secondary Outcomes

Minimal Residual Disease (MRD)

As a measure of remaining tumour load after treatment and therefore, MRD status is an indicator of the depth of response to treatment in CLL. MRD negativity status at the end of treatment, independent of clinical response, is associated with improved PFS and OS compared with patients with a positive MRD status.[5] Notably, MRD status was an exploratory endpoint in the trial.

A central laboratory was used to assess MRD status in all patients using multicolour flow cytometry. This was assessed via blood sample collected at Week 24. In patients achieving a CR/CRi, MRD was reassessed every 12 weeks thereafter until MRD negativity was reached. An MRD negative status was defined as a negative bone marrow assessment with or without two consecutive negative blood assessments.

At the January 31, 2017 data cut-off date, 73/127 patients had at least one peripheral blood MRD assessment performed at their regional laboratory. Thirty-three patients had at least one MRD negative assessment, while 40 patients were MRD positive (as they had residual CLL cells detected as assessment). It should be noted however, that 14 of the 73 patients (10 of the 40 MRD positive and 4 of the 33 MRD negative) reportedly had CLL cells expressing an atypical phenotype (i.e., either strong expression of CD20/CD79b or weak expression of CD5/CD43). As such, the true MRD level may be underestimated and may result in a false MRD assessment. Therefore, all MRD results from these 14 patients were excluded from the analysis. Consequently, the blood MRD negative rate was 29 out of 59 (42%) evaluable patients or 29/127 (22.8%) of all subjects enrolled (intention to treat, ITT).

Nineteen of the 29 patients that achieved MRD negativity underwent additional assessments, whereas 10 patients did not have an additional assessment within the data cut-off period of the current report. Eighteen of the 19 patients (15 after ibrutinib failure, 3 after idelalisib failure) achieved sustained MRD negativity in the peripheral blood, and the remaining patient was MRD positive at a subsequent assessment. At the time of current data cut-off, 8/28 patients achieving a negative MRD status in the blood had a bone marrow aspirate in which it was detected that 5 patients were MRD negative in the bone marrow, while 3 patients had low, detectable MRD levels (0.011%, 0.015%, and 0.035%).

Quality of Life

According to patient input received from two patient advocacy groups that included 320 patients, 279 of whom were diagnosed with CLL and 21 of which had direct experience with venetoclax, symptoms of CLL that affect the quality of life at diagnosis and on an ongoing basis include: fatigue/lack of energy, increasing lymphocyte count, enlarged lymph nodes, frequent infections, night sweats, low platelet count and low immunoglobulin levels. Patient input indicated that the side effects that were the most difficult to tolerate were fatigue, nausea, and frequency of infection.

Health related quality of life (HRQoL) measures were considered exploratory efficacy endpoints in the M14-032 trial. Functional status and well-being was assessed using the EORTC-QLQ-C30, which has been widely used among cancer patients, the EQ-5D-5L, which is a generic measure of health status, the EORTC QLQ-CLL16 (more specific to CLL patients), and the EQ VAS. The EORTC QLQ-C30 consists of a Global Health Status/QoL (GHS/QoL) scale, and financial difficulties scale, 5 functional scales (Cognitive, Social, Physical, Emotional, and Role Functioning), and 8 symptom scales (Fatigue, Insomnia, Appetite Loss, Pain Constipation, Diarrhea, Dyspnea, and Nausea and Vomiting. A positive change on the functioning and global QoL scales indicates an improvement in functioning or QoL, while a negative change on the symptom or financial difficulties scales indicates an improvement in symptoms. Changes of 5-10 points are considered small changes (and the lower bound of 5 was used for minimum important difference (MID) acceptance. Changes of 10-20 points are considered moderate changes, and changes over 20 points are considered large changes to patients.

Quality of life data were assessed by treatment arm (Arm A, Arm B, or Expansion cohort) as well as in aggregate form. Results are presented below.

Key changes from baseline at each time point are summarized descriptively by treatment group. In Arm A, patients experienced clinically relevant improvements in GHS/QoL and several functioning scores, including role, social, emotional, physical and cognitive functioning. Improvements were reported in seven out of the eight symptoms scales, including fatigue, appetite loss, nausea and vomiting, pain, insomnia, dyspnea, and constipation with fatigue, pain, and appetite loss being clinically meaningful improvements. Improvements were greater than 5 points (minimally important) at all measurement time points for GHS, role functioning and social functioning. Clinically meaningful worsening with venetoclax treatment was measured for diarrhea. Financial difficulties had also improved.

Patients in Arm B also experienced clinically relevant improvements in GHS/QoL and several functioning scores, including social, role, and physical functioning. There were no improvements in emotional functioning and a moderate worsening of cognitive functioning at Week 72. In terms of symptoms, improvements were reported for insomnia, dyspnea, fatigue, and a small improvement for pain at Week 60, while there was a small worsening

of nausea at Week 72. The clinically meaningful observations included a worsening of diarrhea, pain, and cognitive functioning between baseline and the final observation. Some of the measured quality of life scales demonstrated changes greater than 5 points (both minimally important improvement and decline) at different measurement time points.

Looking at the aggregate data from all 3 treatment arms, both the EORTC QLQ-CLL16 and the EORTC QLQC30 scales demonstrated clinically important improvement of fatigue, with negative mean change from baseline scores at all but one time point (Weeks 24, 36, 48, 60, 72, 84, and 96). The highest mean change in fatigue from baseline, at -17.3 (95% CI, -36.4 to 1.9), was reported at the Week 96 visit. On the CLL16 scale, patients also demonstrated concern for their future health, as this domain showed moderate worsening at all time points except Week 96, where large changes from baseline were reported (-29.6, 95% CI, -53.4 to -5.9). Moderate to large changes from baseline scores were also reported for social problems, with minimal clinically important differences ranging from -15.0 at Week 84 to -29.6 at Week 96 indicating a worsening at all time periods.[5]

Harms Outcomes

Grade 3 or 4 Adverse Events

Treatment-related grade 3 or 4 adverse events are presented in Table 11. Most patients (126/127, 99.2%) experienced at least one treatment-emergent adverse event (TEAE). The most common TEAEs in patients who had failed on ibrutinib therapy (Arm A), regardless of severity, were anemia (53.5%), diarrhea and nausea (51.2% each), and fatigue (44.2%). In patients who had failed on idelalisib therapy (Arm B), the most common TEAEs were neutropenia (47.6%), diarrhea (42.9%), thrombocytopenia, nausea, fatigue, hyperphosphatemia, and rash (28.6% each). For patients in the Expansion cohort, the most common TEAEs were nausea (50.8%, anemia, diarrhea (42.9% each), and neutropenia (39.7%).

Grade 3 or 4 adverse events (AEs) were reported in 93.0% of patients in Arm A, 81.0% of patients in Arm B, and 71.4% of patients in the Expansion cohort. The following were the 3 most common grade 3 or 4 AEs by study arm: Arm A, anemia (32.6%, decreased neutrophil count and neutropenia (27.9% each); Arm B, neutropenia (42.9%), thrombocytopenia (23.8%), anemia (14.3%), and Expansion cohort, neutropenia (33.3%), anemia (23.8%), and decreased neutrophil count (17.5%). The most important symptoms and adverse events for patients to have controlled, which include white blood cell count, fever, anemia, neutropenia, thrombocytopenia, abdominal pain, fatigue and infections, were generally well reported; however, no data on viral reactivation, lymph node size, or IgG levels were provided.

Treatment-related AEs (TRAE) (those considered being related to venetoclax, regardless of severity) were reported in 72.1%, 81.0%, and 90.5% of patients in Arms A, B, and the Expansion cohort, respectively. The most common TRAEs by study arm were: Arm A, decreased neutrophil count (30.2%), diarrhea (27.9%) and neutropenia and nausea (20.9% each); Arm B, diarrhea (28.6%), neutropenia (23.8%), and hyperphosphatemia, nausea, and thrombocytopenia (19.0% each); Expansion cohort, neutropenia (38.1%), nausea (31.7%) and anemia and diarrhea (25.4% each).

Treatment-emergent serious adverse events (SAE) were reported in 46.5% of all patients. In Arm A, 67.4% of patients experienced a treatment related SAE. The most common SAEs in this arm were febrile neutropenia (16.3%), pneumonia (9.3%), and increased blood potassium (4.7%). Nine (42.9%) patients in Arm B reported SAEs, which included pneumonia (9.5%) (This was the only SAE reported in ≥2 patients in this arm). In the

Expansion cohort, 33.3% of patients reported treatment-related SAEs, with the most common being febrile neutropenia, pyrexia, cytokine release syndrome, and hypercalcemia (3.2% each).

In Arm A, a total of 28 patients (65.1%) experienced at least one AE of neutropenia or related terms (neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis). Among these, 21 patients (48.8%) reported neutropenia events ≥grade 3. Neutropenia events that led to venetoclax interruption were reported for 5 patients (11.6%). In Arm B, 11 patients (52.4%) experienced at least one AE of neutropenia or related terms and 10 patients (47.6%) reported neutropenia events ≥grade 3. Neutropenia events that led to venetoclax interruption occurred in one patient. In the Expansion cohort, a total of 36 patients (57.1%) experienced at least one neutropenia-related AE, with 31 patients (49.2%) reporting ≥ grade 3 neutropenia-related AEs. Two patients in this cohort experienced neutropenia events that led to venetoclax interruption.

The total number of patients that reported infections in Arms A, B, and the Expansion cohort was 30 (69.8%), 14 (66.7%), and 35 (55.6%), respectively. This included 14 patients (32.6%) in Arm A, 5 patients (23.8%) in Arm B, and 9 patients (14.3%) in the Expansion cohort reporting ≥ grade 3 infections.[5] Infections leading to venetoclax interruption occurred in 7 patients (16.3%) in Arm A, 3 (14.3%) in Arm B, and 4 (6.3%) patients in the Expansion cohort.

Tumour Lysis Syndrome

All patients were categorized as low, medium, or high risk for tumour lysis syndrome (TLS) based on their tumour burden at screening. To minimize the risk of TLS, all patients received prophylaxis with oral and/or intravenous hydration, a uric acid reducer, and patients in the medium or high risk category with bulky nodal disease were closely monitored in hospital during the weekly ramp-up of venetoclax. Most patients received concomitant oral uric acid reducers for TLS prophylaxis prior to and during the venetoclax ramp-up period. With this prophylaxis regimen, clinical TLS does not typically occur.

Electrolyte abnormalities (hyperphosphatemia and hyperuricemia or hyperkalemia, respectively) meeting Howard criteria for laboratory TLS were only observed in two patients with high tumour burden; both cases occurred during the 200mg dose of the standard ramp-up period.[5] Other occurrences of LTLS were deemed to not be related to venetoclax treatment and were not made disclosable by the submitter.

Adverse Events Leading to Withdrawals or Death

Treatment-emergent adverse events leading to discontinuation of venetoclax in the M14-032 trial occurred in 12 patients (9.4%). Six patients discontinued due to progressive disease while 6 discontinued due to other adverse events. Adverse events leading to discontinuation due to progressive disease included febrile neutropenia, fatigue, multiple organ dysfunction, CLL, malignant neoplasm progression and Richter's syndrome. Other adverse events leading to withdrawal were gastrointestinal disorders, death, sepsis, and other malignancy (salivary gland cancer).[5] (ref).

Treatment-emergent adverse events leading to dose interruption were reported in 44 patients (34.6%). This included 21 patients in Arm A in whom diarrhea, pneumonia, febrile neutropenia, neutropenia, dyspepsia, and increased blood potassium were the causes of dose interruption. For the 10 patients in Arm B, the causes included thrombocytopenia

and hyperphosphatemia for ≥ 2 patients. Causes for dose interruption for the 13 patients in the Expansion cohort included diarrhea, nausea, and hyperkalemia.

As of the data cut-off date of January 31, 2017, fourteen patient deaths were reported. Seven patients died within 30 days of the last dose of venetoclax and experienced fatal adverse events while 7 deaths were reported during survival follow-up. In Arm A, causes of death in the 4 patients that died within 30 days of taking venetoclax included septic shock, multiple organ dysfunction syndrome, and asphyxia. One of these deaths, based on the investigator's assessment, resulted from disease progression. In Arm B, one patient died within 30 days of the last venetoclax dose of progression of a malignant neoplasm, which was attributed to disease progression. In the Expansion cohort, 2 patients died within the 30-day period of venetoclax administration; one of Corynebacterium sepsis (not related to venetoclax) and the other due to cytokine release syndrome - also not related to disease progression based on the investigator's assessment.[5]

Seven patients (6 in Arm A, 1 in Arm B) died more than 30 days after the last dose of venetoclax.

Table 11: Number of patients with Grade 3/4 adverse events occurring in ≥2 patients in any study arm.

Venetoclax 400mg				
Treatment Arm	**Arm A (N=43) N (%)**	**Arm B (N=21) N (%)**	**Expansion (N=63) N (%)**	**Total[5] (N=127) N (%)**
Any Grade 3 o4 4 Adverse Event	40 (93.0)	17 (81.0)	45 (71.4)	102 (80.3)
Blood and Lymphatic System Disorders	**23 (53.5)**	**10 (47.6)**	**30 (47.6)**	**63 (49.6)**
Anemia	14 (32.6)	3 (14.3)	15 (23.8)	32 (25.2)
Febrile Neutropenia	8 (18.6)	0	2 (3.2)	10 (7.9)
Neutropenia	12 (27.9)	9 (42.9)	21 (33.3)	42 (33.1)
Thrombocytopenia	7 (16.3)	5 (23.8)	10 (15.9)	22 (17.3)
Gastrointestinal Disorders	**6 (14.0)**	**0**	**8 (12.7)**	**14 (11.0)**
Abdominal Pain	2 (4.7)	0	2 (3.2)	4 (3.1)
Diarrhea	3 (7.0)	0	3 (4.8)	6 (4.7)
General Disorders and Administration Site Conditions	**5 (11.6)**	**3 (14.3)**	**6 (9.5)**	**14 (11.0)**
Fatigue	5 (11.6)	2 (9.5)	1 (1.6)	8 (6.3)
Infections	**14 (32.6)**	**5 (23.8)**	**9 (14.3)**	**28 (22.0)**
Lung Infection	2 (4.7)	0	0	2 (1.6)
Pneumonia	5 (11.6)	2 (9.5)	1 (1.6)	8 (6.3)
Injury, Poisoning, Procedural Complications	**3 (7.0)**	**0**	**1 (1.6)**	**4 (3.1)**
Fall	2 (4.7)	0	1 (1.6)	3 (2.4)
Investigations[1]	**24 (55.8)**	**6 (28.6)**	**15 (23.8)**	**45 (35.4)**
White Blood Cell Count Decreased	8 (18.6)	1 (4.8)	9 (14.3)	18 (14.2)

Table 11: Number of patients with Grade 3/4 adverse events occurring in ≥2 patients in any study arm.				
Venetoclax 400mg				
Treatment Arm	**Arm A (N=43) N (%)**	**Arm B (N=21) N (%)**	**Expansion (N=63) N (%)**	**Total[5] (N=127) N (%)**
Metabolism and Nutrition Disorders[2]	**11 (25.6)**	**5 (23.8)**	**15 (23.8)**	**31 (24.4)**
Respiratory, Thoracic, Mediastinal Disorders	**5 (11.6)**	**2 (9.5)**	**5 (7.9)**	**12 (9.4)**
Dyspnea	0	1 (4.8)	3 (4.8)	4 (3.1)
Hypoxia	3 (7.0)	0	1 (1.6)	4 (3.1)
Vascular Disorders	**3 (7.0)**	**2 (9.5)**	**6 (9.5)**	**11 (8.7)**
Hypertension	3 (7.0)	1 (4.8)	5 (7.9)	9 (7.1)

Abbreviations: N- number
[1] - Investigations included: alanine aminotransferase increases, aspartate aminotransferase increases, lymphocyte count decreases, lymphocyte count increases, neutrophil count decreases, platelet count decreases, white blood cell count decreases
[2] - Metabolism and Nutrition Disorders included: dehydration, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcaemia, hypokalemia, hyponatremia, hypophosphatemia

Symptoms considered to be important to control with treatment included anemia, neutropenia, thrombocytopenia, abdominal pain, fatigue, infections, viral reactivation, white blood cell count, fever, lymph node size and IgG levels were highlighted as important aspect of disease for patients to control. The trial provided data on the impact of venetoclax on anemia, neutropenia, white blood cell count, thrombocytopenia, abdominal pain, fatigue and infections.

Updated June 2017 Results based on the Jones et al 2017 Lancet Oncology Publication.[7]

Detailed trial characteristics, as outlined in Table 3, are largely the same with the exception of the data cut-off date and the number of patients analyzed, as the Lancet publication [7] focused solely on patients who were refractory to or relapsed during or after ibrutinib therapy. The following data correspond to the 91 patients that had received ibrutinib as the last BCRi therapy before study enrolment. Of those 91 patients, 43 were enrolled in the main cohort and 48 in the expansion cohort (who were recruited after the protocol amendment). Baseline patient demographics, characteristics, and disease status are outlined in Table 12 and 13 below.

Table 12. Baseline demographics and characteristics of patients in the June 2017 cut-off of the M14-032 study.[7]			
	Main Cohort (n=43)	**Expansion Cohort (n=48)**	**Total (n=91)**
Age (years) median (IQR)	66 (48-80)	65 (28-81)	66 (28-81)
Sex			
Male, n (%)	33 (77)	31 (65)	64 (70)
Female	10 (23)	17 (35)	27 (30)
Race			
White	40 (93)	44 (92)	84 (92)
Black	2 (5)	4 (8)	6 (7)
Asian	1 (2)	0	1 (1)

Table 13. Baseline disease status and clinical characteristics of patients in the June 2017 cut-off of the M14-032 study.[7]			
Characteristic	**Venetoclax 400mg**		
	Main Cohort (n=43)	**Expansion Cohort (n=48)**	**Total (n=91)**
ECOG performance status, n (%)			
Grade 0	13 (30)	16 (33)	29 (32)
Grade 1	27 (63)	27 (56)	54 (59)
Grade 2	3 (7)	5 (10)	8 (9)
Absolute Lymphocyte count, n (%)			
≥ 25 x 10^9 per L	17 (40)	10 (22)	27 (30)
≥ 100 x 10^9 per L	7 (16)	5 (11)	12 (13)
Bulky disease, n (%)			
One or more nodes ≥ 5cm	15 (35)	21 (44)	36 (40)
One or more nodes ≥10cm	7 (16)	2 (4)	9 (10)
Tumour lysis syndrome risk category[1], n (%)			
Low	15 (35)	19 (40)	34 (37)
Medium	11 (26)	20 (41)	31 (34)
High	17 (39)	9 (19)	26 (29)
Prognostic factors based on site-reported data, n (%)			
Non-mutated IGHV	25/29 (86)	25/38 (66)	50/67 (75)
17p deletion	21/43 (49)	21/47 (40)	42/90 (47)
11q deletion	13/43 (30)	17/48 (33)	30/91 (33)
TP53 mutation	15/41 (37)	14/46 (30)	29/87 (33)
CD38 positive	21/42 (50)	16/44 (36)	37/86 (43)
ZAP-70 positive	12/24 (50)	17/40 (43)	29/64 (45)
Treatment history			
Number of previous therapies	5 (1-12)	4 (1-15)	4 (1-15)
Previous ibrutinib use	43 (100%)	48 (100%)	91 (100%)
Months of prior ibrutinib use, median (range)	18 (1-56)	21 (1-61)	20 (1-61)
Relapsed during or after ibrutinib	11 (26%)	17 (35%)	28 (31%)
Refractory to ibrutinib	32 (74%)	30 (63%)	62 (68%)
Previous idelalisib use[2]	4 (9%)	7 (15%)	11 (12%)
Months of prior idelalisib use, median (range)	16 (2-31)	9 (2-33)	9 (2-33)
Notes: 1 - Low was defined as all lymph nodes smaller than 5cm with an absolute lymphocyte count of less than 25 x 10^9/L; medium was defined as any lymph node 5cm or larger but smaller than 10cm with an absolute lymphocyte count of 25 x 10^9/L or higher; high was defined as any lymph node 10cm or larger or 5cm or larger and with an absolute lymphocyte count of 25 x 10^9/L or higher. 2 - 11 patients had previously received idelalisib followed by ibrutinib during their previous course of treatment			

The disposition of patients at the June 2017 cutoff date is outlined in Table 14 below. A total of 91 patients received venetoclax for CLL after progressing on ibrutinib therapy. There was a total of 45 (49.5%) treatment discontinuations, 27 in the main cohort and 18 in the expansion cohort, with the main reason for discontinuation being disease progression, which occurred in 22/91 (24.2%) of patients. Six patients discontinued due to the following adverse events: multi-organ failure (n=1), dysphagia (n=1), stomach ulcers (n=1), Corynebacterium sepsis (n=1), salivary gland cancer (n=1), and mechanical asphyxia (n=1). Laboratory tumour lysis syndrome was observed in 2 patients with high tumour burden, with both cases occurring during administration of the 200mg dose of venetoclax. [7]

A reported 17 out of 91 patients died (18.7%). Six patients died within 30 days of the last dose of venetoclax and experienced fatal adverse events: 1 from Corynebacterium sepsis, 1 multi-organ failure, 1 septic shock, 1 possible cytokine release syndrome on subsequent therapy, 1 mechanical asphyxia, and 1 for unknown reasons. Seven died due to disease progression, and four deaths occurred more than 30 days after the last dose of venetoclax for unknown reasons. The authors indicated that no treatment-related deaths were reported.

Table 14. Patient disposition at the June 2017 cut-off in the M14-032 study. [7]	
Disposition	**Number of Subjects (%)**
Screened	167
Enrolled and received treatment	127
Received ibrutinib as the last BCRi therapy before enrolment	91 (71.7)
Ongoing treatment (n, %)	46 (50.5)
Discontinued treatment (n, %)[a]	45 (49.5)
Progressive disease	22 (24.2)
Richter's transformation	5 (5.5)
Adverse event	6 (6.6)
Withdrew consent	1 (1.1)
Investigator request	1 (1.1)
Stem cell transplantation	5 (5.5)
Other	5 (5.5)
Death	17 (18.7)
Notes: [a] - For subjects who discontinued venetoclax, post-treatment follow-up visits were to be performed every 3 months until discontinuation from the study due to disease progression requiring alternative therapy or a subject's refusal of the post-treatment visits.	

Results:

Key efficacy outcomes are outlined in Table 15 below. The median follow-up as of the June 30, 2017 cut-off was 14 months (interquartile range (IQR) 8-18) for all 91 patients, 19 months (9-27) for the main cohort, and 12 months (8-15) for the expansion cohort. [7] As per investigator assessment, the ORR for patients in the main cohort was 69.8% (30/43), with a complete remission rate of 9.3% (4/43) and partial response rate of 60.5% (26/43). After including patients in the expansion cohort, the rates of overall response, complete remission and partial response among the 91 patients were 64.8% (59/91), 8.8% (8/91), and 56.0% (51/91), respectively. The median follow-up to first response was 2.5 months (IQR 1.6-2.6) and median follow-up to best response was 7.9 months (5.3-8.1). Median follow-up to the first partial response or nodular partial response was 2.6 months (1.7-2.7). Median time to complete response or complete response with incomplete bone marrow recovery was 8.2 months (4.9-9.0). Twenty two (24.0%) of 91 patients had stable disease and five had disease progression. Nineteen (59%) of 32 patients with B symptoms at baseline had reportedly resolved their symptoms by week 8.

Objective response rate: There was good concordance between overall response assessments made by the investigators and those made by the independent review committee (70% and 67%, respectively). [7] There were discrepancies in response assessments for 10 patients, which were primarily due to differences in interpretation of splenomegaly by CT scans, timing of CT scans, and the sum product of the lymph nodes by radiographic assessment given different selection of nodes. [7] For patients with high-risk chromosomal abnormalities, the proportion of those achieving a response was similar compared to patients without these risk factors. Twenty eight og 46 patients (61%, 95% CI 45-75) with a known 17p deletion or TP53 mutation had an overall response, including 4 patients who had a CR or CRi and 24 patients who had a nPR or a PR. Thirty of 45

patients (67%, 95% CI 51-80) without 17p and TP53 mutations had an overall response, including 4 patients who had a CR and 26 patients who had a nPR or a PR. [7]

Progression free survival: Median time to progression as assessed by the investigator for all patients was 24.7 months (95% CI 19.6 - not reached). An estimated 80% of patients had not progressed at 12 months. Median PFS was 24.7 months (95% CI 19.2 - not reached) and an estimated 12-month PFS was 75%. For patients with high-risk chromosomal abnormalities, no difference in PFS was seen in patients with mutations versus those without (median PFS was 21.9 months for patients with mutations and 15.4 months for patients without; HR 1.04, 95% CI 0.22-4.80; p=0.96).

Overall survival: Median OS was not reached and an estimated 12-month OS was 91%.

Duration of response: Median duration of response was not reached and an estimated 88% of patients were still responding at 12 months.

Minimal residual disease: As of the June 2017 data cut-off, 57 patients were assessed for minimal residual disease in peripheral blood, which was collected at Week 24. Twenty four of 57 patients (42%) were negative for MRD (24/91=26% by ITT analysis), with 5 of 13 patients subsequently assessed for MRD in the bone marrow being negative. Median PFS was not reached for patients who were negative for MRD in peripheral blood and was 24.7 months (15.4 - not reached) for patients who were positive for MRD.

Table 15. Key efficacy outcomes at the June 2017 data cut-off in patients with CLL in the M14-032 study. [7]

	Main cohort N=43	Expansion Cohort N=48	All Patients N=91
Outcome	**Investigator Assessed**		
ORR N (%) [95% CI %]	30 (69.8) [54-83]	29 (60.4) [43-72]	59 (64.8%) [53-74]
CR rate, n (%) (CR/CRi)	4 (9.3)	4 (8.3)	8 (8.8)
PR rate, n [%] (nPR+PR)	26 (2+24) [60.5]	25 (1+24) [52.1]	51 (3+48) [56.0]
Nodular Partial Remission	NR	NR	NR
Partial Remission	NR	NR	NR
Stable Disease, n (%)	8 (18.6)	14 (29.2)	22 (24.2)
Progressive Disease	1 (2.3)	4 (8.3)	5 (5.5)
Discontinued before response assessment	4 (9.3)	2 (4.2)	6 (6.6)
DOR, months (median, 95% CI) 12 month estimated DOR (95% CI)	NR	NR	Not reached [17.6, not reached] 88% (76-95)
PFS (median, 95% CI)	NR	NR	24.7 (19.2, not reached) (n=33)
12 month Estimated PFS rate (95% CI) (investigator assessed)	NR	NR	75% (64-83)
TTP (median, 95%CI)	NR	NR	24.7 (19.6, not reached) (n=26)
TTR (median, range) (IRC assessed)	1.6 (1.0, 5.5) (n=30)	NR	1.6 (1.0, 5.5) (n=43)
OS (median, 95% CI)	NR	NR	Not reached (27.8, not reached)

Table 15. Key efficacy outcomes at the June 2017 data cut-off in patients with CLL in the M14-032 study. [7]			
	Main cohort N=43	Expansion Cohort N=48	All Patients N=91
Outcome	Investigator Assessed		
12 month OS estimate (95% CI)	NR	NR	91% (83-95)
Notes: CI - confidence interval; DOR - duration of response; NR - not reported; OS - overall survival; PFS - progression-free survival; TTP - time to progression; TTR - time to response			

Table 16: Number of patients with Grade 3 or 4 adverse events. [7]	
Venetoclax 400mg	
Adverse Event	Total (N=91) N (%)
Blood and Lymphatic System Disorders	
Anemia	26 (29)
Autoimmune hemolytic anemia	2 (2)
Febrile Neutropenia	12 (13)
Neutropenia	46 (51)
Thrombocytopenia	26 (29)
Gastrointestinal Disorders	
Abdominal Pain	4 (4)
Diarrhea	6 (7)
Nausea	1 (1)
Vomiting	1 (1)
General Disorders & Administration Site Conditions	
Fatigue	6 (6)
Chills	1 (1)
Pyrexia	1 (1)
Infections	
Cellulitis	3 (3)
Lung Infection	2 (2)
Pneumonia	6 (6)
Urinary Tract Infection	2 (2)
Injury, Poisoning, Procedural Complications	
Fall	3 (3)
Investigations	
Decreased white blood cell count	17 (18)
Increased alanine aminotransferase	3 (3)
Increased aspartate aminotransferase	2 (2)
Increased blood bilirubin	1 (1)
Decreased lymphocyte count	14 (15)
Increased lymphocyte count	4 (4)
Metabolism and Nutrition Disorders	

Table 16: Number of patients with Grade 3 or 4 adverse events. [7]	
Venetoclax 400mg	
Adverse Event	**Total (N=91) N (%)**
Dehydration	2 (2)
Hypercalcemia	2 (2)
Hyperglycemia	5 (5)
Hyperkalemia	1 (1)
Hypoalbuminemia	2 (2)
Hypocalcemia	3 (3)
Hypokalemia	5 (5)
Hyponatremia	6 (7)
Hypophosphatemia	12 (13)
Respiratory, Thoracic, Mediastinal Disorders	
Dyspnea	2 (2)
Hypoxia	4 (4)
Vascular Disorders	
Hypertension	6 (7)
Abbreviations: N- number [1] - Investigations included: alanine aminotransferase increases, aspartate aminotransferase increases, lymphocyte count decreases, lymphocyte count increases, neutrophil count decreases, platelet count decreases, white blood cell count decreases [2] - Metabolism and Nutrition Disorders included: dehydration, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcaemia, hypokalemia, hyponatremia, hypophosphatemia	

Safety: The most common adverse events of any grade were neutropenia (56/91 [62%]), nausea (52/91 [57%]), anemia (48/91 [53%]), diarrhea (47/91 [52%]), and thrombocytopenia (43/91 [47%]). Common grade 3 or 4 adverse events are outlined in Table 16. The rate of adverse events was similar in the main and expansion cohorts [7]. Treatment-emergent grade 3 or 4 adverse events were mainly hematological, with the median time to the first grade 3 or 4 event being 21 days for neutropenia and 21 days for thrombocytopenia. Fifty percent of patients (45/91) experienced a serious adverse event, the most frequent being febrile neutropenia in 10 (11%) of patients and pneumonia in 5 (6%) of 91 patients.

Serious adverse events possibly related to venetoclax treatment were febrile neutropenia (n=2), pneumonia (n=1), increased potassium levels (n=1), hyperphosphatemia (n=1), and hyperkalemia (n=1). Thirty five percent of patients (32/91) had a treatment interruption because of adverse events, with neutropenia (n=9) being the most common reason. [7]

A total of 15 (16%) patients required a dose reduction, with the most common reasons being nausea (n=12), neutropenia (n=11), and diarrhea (n=9). There was a total of 45 treatment discontinuations, 27 in the main cohort and 18 in the expansion cohort. The main reason for discontinuation was disease progression in 22 (24%) of 91 patients and Richter's transformation in 5 (5%) of patients. Six additional patients (7%) discontinued due to the following grade 5 adverse events (one patient per event): multi-organ failure, dyshphagia, stomach ulcers, Corynebacterium sepsis, salivary gland cancer, or mechanical asphyxia.

Howard criteria for laboratory tumour lysis syndrome were observed in 2 patients with high tumour burden.

6.4 Ongoing Trials

One phase 3b, single-arm, open-label multicenter study partially meets the eligibility criteria for the current systematic review. The purpose of the study is to evaluate the efficacy of venetoclax in relapsed or refractory patients with CLL including those with 17p deletion or TP53 mutation OR those who have received prior treatment with a B-cell receptor inhibitor. The inclusion criteria are such that patients must have a confirmed diagnosis of CLL with an indication for treatment and clinically measurable disease and in addition, patients MAY harbour 17p deletion or TP53 mutation AND/OR they MAY have been previously treated with a B-cell receptor inhibitor. As this trial is also being sponsored by the current submitter, we are able to report that there are currently no interim data available since the trial is still recruiting patients. The first interim data are expected by the end of 2018. Complete response rate in the BCRi-treated patients will be reported as part of the secondary efficacy end-points, which would make the study relevant to the current review. Details of this trial can be found in Table 17 below.

Table 17. Ongoing M15-550 trial of venetoclax in patients with relapsed/refractory CLL.			
Trial Design	**Inclusion Criteria**	**Intervention and comparator**	**Trial Outcomes**
NCT02756611 Phase 3b, open-label, non-comparative, multicenter study Estimated Enrolment: N=250 Status: currently recruiting Study Locations: 56 locations in 20 countries including 5 Canadian centers Study Start Date: March 2016 Estimated Study Completion Date: October 2022 Study Sponsor: AbbVie	Key Inclusion Criteria: Diagnosis of CLL that meets IWCLL NCI-WG guidelines with an indication for treatment and clinically measurable disease Participants MAY harbour 17p deletion or TP53 mutation, assessed by local laboratory in bone marrow or peripheral blood AND/OR patients MAY have been previously treated with a prior B-cell receptor inhibitor Relapsed or refractory disease (received at least 1 prior therapy) ECOG PS of ≤2 Adequate bone marrow function, coagulation profile, renal and hepatic function at screening Key Exclusion Criteria: Development of Richter's transformation or Prolymphocytic leukemia Prior treatment with venetoclax History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax1 Active and uncontrolled autoimmune cytopenias Patient has undergone ASCT grade 2, any anti-cancer therapy including chemotherapy, or radiotherapy, investigational therapy, including targeted small molecule agents HIV positive Known allergy to xanthine oxidase inhibitors and rasburicase	Intervention: Venetoclax 20mg orally, once daily gradually increasing dose over 5 weeks to final daily dose of 400mg Patients may continue receiving venetoclax for up to 2 years No active comparator	Primary: Complete remission rate (CR + CRi) as assessed by investigator Proportion of patients achieving a CR or CRi as their best response Secondary: ORR DoR TTP PFS OS CR rate Rate of MRD Other Outcomes: HRQoL
Abbreviations: ASCT - autologous stem cell transplantation, CLL - chronic lymphocytic leukemia, CR - complete response, CRi - complete remission with incomplete marrow recovery, DoR - duration of response, ECOG - Eastern Cooperative Oncology Group, HIV - human immunodeficiency virus, HRQoL - health-related quality of life, IWCLL NCI-WG - International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute-Working Group, MRD - minimal residual disease, ORR - objective response rate, OS - overall survival, PFS - progression free survival, PS - performance status, TTP - time to treatment progression, Notes: 1 - with the exception of adequately treated in situ carcinoma of the cervix uteri, adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin, or previous malignancy confined and surgically resected (or treated with other modalities) with curative intent			

7 SUPPLEMENTAL QUESTIONS

None identified

8 COMPARISON WITH OTHER LITERATURE

This section describes how the evidence and results summarized in the pCODR systematic review compare with published literature or other findings.

While the pCODR review team is not aware of any clinical trials aimed at identifying optimal sequencing of BCRis and venetoclax, two studies may be helpful in assisting with this decision.[9,10] Both studies were multicenter, retrospective cohort studies.

Mato et al. 2016

In the 2016 study by Mato and colleagues,[9] eligible patients were identified from 10 U.S. academic cancer centers via retrospective chart review and included all patients with CLL who discontinued ibrutinib- or idelalisib-based therapies. The aim of the study was to determine the reasons for BCRi discontinuation, outcomes after stopping therapy, and the impact that BCRi sequencing had on outcomes. A total of 178 patients with CLL who had discontinued BCRi therapy were identified: 80.3% (143/178) discontinued ibrutinib-based and 19.7% (35/178) discontinued idelalisib-based therapy. The most common reasons for BCRi discontinuation in both ibrutinib and idelalisib-based therapy groups were toxicity (Ibrutinib, 51%; Idelalisib, 52%) and CLL progression (Ibrutinib, 28%; Idelalisib 31%). The most common toxicity-related reasons for discontinuation of ibrutinib were atrial fibrillation (20%), infection (12%) and cytopenias (9%) while those reasons for idelalisib discontinuation were pneumonitis (33%), colitis (28%), and rash (17%).

The ORR in the ibrutinib cohort was 58% while the ORR in the idelalisib cohort was 76%. Interestingly, for patients treated with alternate subsequent BCRi therapies (eg. ibrutinib → idelalisib and idelalisib → ibrutinib) the ORR was 50%. A notable outcome reported by Mato et al. is that when stratified by the initial choice of BCRi (ibrutinib vs. idelalisib), there was no impact on PFS (HR 1.2, 95% confidence interval [CI] 0.8-1.8) or OS (HR 0.8, 95% CI 0.4-1.5). In terms of treatment following ibrutinib or idelalisib discontinuation, the most common choice of treatment was an alternate BCRi (39%, 44/114). The rate of PFS for patients with CLL treated with an alternate BCRi was also stratified by the reason for discontinuation and it was determined that alternate BCRi therapy following initial BCRi therapy discontinuation could be effective, especially when the first BCRi was stopped due to intolerance. It was also observed that patients who discontinue BCRi therapy due to disease progression achieve less durable responses when treated with an alternate BCRi. Mato et al. add that the outcomes did not differ according to which agent was used first, and they suggest that either sequence should be considered appropriate (ref Mato 2016).

Mato et al. also mention the FDA approval of venetoclax, which occurred in close proximity in time to their report, and that this newer agent should be considered instead of another BCRi inhibitor if the reason for discontinuation of the first BCRi was due to progressive disease, since shorter PFS was observed in this patient cohort. In contrast, if the discontinuation of the initial BCRi was due to intolerance, considerably longer PFS was observed and therefore switching to another BCRi might be appropriate.

Mato et al. 2017

In a subsequent paper published in 2017, Mato et al. aimed to identify rates and causes of discontinuation of ibrutinib, idelalisib, or venetoclax-based therapies, to assess outcomes after discontinuation, and to define the best sequencing strategy using BCRis and venetoclax.[10] In another retrospective cohort study of CLL patients treated with one of the three aforementioned therapies, 9 U.S.-based academic centers were included from which 683 CLL patients were identified. Investigators were asked to utilize resources such as institutional clinical/pathological databases, chart review, electronic medical records at each respective institution to identify the

complete cohort of CLL patients treated with KI or venetoclax. A total of 621 (91%) patients were first treated with ibrutinib-based therapy and 62 (9%) patients were first treated with idelalisib-based therapy. Most patients received BCRi-based therapy in the relapsed setting with 14% of patients (n=80 ibrutinib, n=14 idelalisib) receiving BCRi-based therapy in the front-line setting. Baseline characteristics were similar between the ibrutinib and idelalisib groups.

In the relapsed setting, the ORR to ibrutinib as the first BCRi was 68% (n=357) as compared to the front line setting, where the ORR to ibrutinib was 71% (n=80).[10] In the relapse setting, the ORR to idelalisib was 80% (n=47) and was 85% (n=14) in the front-line setting. After stratifying outcomes by first BCRi choice, patients who received ibrutinib-based therapy (versus idelalisib) as their first BCRi experienced a significantly better median PFS in all settings including front line (not reached vs. 16 months), relapsed/refractory (36 vs. 11 months), 17p deletion (36 vs. 12 months), or complex karyotype (29 vs. 9 months). Notably, there were more patients contributing to the data in the ibrutinib cohort (n=357) compared to idelalisib (n=80) likely due to the fact that idelalisib has become available more recently.

Among the 683 enrolled patients 316 (46%) discontinued treatment (258 ibrutinib treated and 58 idelalisib treated). The reasons for treatment discontinuation were similar between the two agents. Of note, BCRi toxicity was the most common reason for discontinuation of either ibrutinib (51.2%) or idelalisib (44.8%), which accounted for almost 50% of the discontinuation events. Discontinuation due to disease progression was the second most common reason with 20.5% and 27.6% in the ibrutinib and idelalisib groups, respectively. The authors noted that this was inconsistent with what had been reported in the clinical trials evaluating the efficacy of ibrutinib and idelalisib as those studies had reported disease progression as the main reason for treatment discontinuation. The most common toxicities to discontinue ibrutinib were: atrial fibrillation, infection, pneumonitis, bleeding, and arthralgia whereas the most common reasons to discontinue idelalisib were: pneumonitis, colitis, rash, transaminitis, and infection. The median time to BCRi discontinuation due to toxicity was 6 months (0-28 months).

At the time of reporting, 24% (n=167) of patients received another line of therapy after their first treatment with a BCRi containing regimen. The median time to the next therapy following BCRi discontinuation was 1 month (0-28 months). Subsequent therapies were grouped as BCRi-based, venetoclax, or chemoimmunotherapy combinations. The ORRs for each of the three subsequent therapies were 58.5%, 73.6%, and 49.9%, respectively. In patients treated with alternate BCRis (eg. ibrutinib → idelalisib or idelalisib → ibrutinib), those that did not tolerate the initial BCRi had a better rate of PFS compared with those who had progressive disease on the initial BCRi (median PFS not reached vs. 9 months). Further, patients who discontinued ibrutinib for any reason had both a better ORR (when treated with venetoclax, ORR 79%) and a trend to improvement in PFS, when compared with idelalisib (ORR 46%).

Response to subsequent therapy following initial kinase therapy			
	Ibrutinib → Idelalisib	Idelalisib → Ibrutinib	Kinase inhibitor → Venetoclax
ORR (%)	46	75	74
CR (%)	0	5	32
PR//PR with lymphocytosis (%)	16	70	42
SD (%)	39	15	16
PD (%)	15	10	10
ORR: objective response rate; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.			

The overall result of this study demonstrates that ibrutinib appears to be superior to idelalisib as a first-line BCRi. Further, after initial BCRi failure, the use of an alternate BCRi or venetoclax have a superior PFS compared with chemoimmunotherapy. While this is a useful finding, there remains a paucity of evidence on the sequencing of venetoclax, which might be superior to idelalisib upon ibrutinib failure but again, comparative studies on sequencing strategies are needed.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of 3 Medical Oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials June 2016, Embase 1974 to 2016 July 15, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

#	Searches	Results
1	(venetoclax* or venclexta* or 1257044-40-8 or N54AIC43PW or ABT-199 or (ABT adj2 "199") or (GDC adj2 "0199") or ABT199 or GDC0199 or rg-7601 or rg7601).ti,ab,ot,kf,kw,hw,rn,nm.	847
2	1 use ppez	195
3	1 use cctr	5
4	*venetoclax/	132
5	(venetoclax* or venclexta* or 1257044-40-8 or N54AIC43PW or ABT-199 or (ABT adj2 "199") or (GDC adj2 "0199") or ABT199 or GDC0199 or rg-7601 or rg7601).ti,ab,kw.	619
6	4 or 5	630
7	6 use oemezd	433
8	conference abstract.pt.	2301967
9	7 not 8	182
10	2 or 3 or 9	382
11	7 and 8	251
12	limit 11 to yr="2011 -Current"	251
13	10 or 12	633
14	limit 13 to english language	618
15	remove duplicates from 14	478

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#10	Search #8 AND #9	21
#9	Search publisher[sb]	502314
#8	Search #6 OR #7	191
#7	Search venetoclax*[tiab] OR venclexta*[tiab] OR 1257044-40-8[rn] OR 1257044-40-8[tiab] OR N54AIC43PW[tiab] OR ABT-199[tiab] OR ABT199[tiab] OR GDC 0199[tiab] OR GDC0199[tiab] OR rg-7601[tiab] OR rg7601[tiab]	180
#6	Search "4-(4-((2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl)methyl)piperazin-1-yl)-N-((3-nitro-4-((tetrahydro-2H-pyran-4-ylmethyl)amino)phenyl)sulfonyl)-2-(1H-pyrrolo(2,3-b)pyridin-5-yloxy)benzamide"[Supplementary Concept]	59

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

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

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

Search: Venetoclax

Select international agencies including:

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

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

Search: Venetoclax

Conference abstracts:

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

American Society of Hematology
http://www.hematology.org/

Search: Search: Venetoclax - last 5 years

Literature Search Methods

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were venetoclax (Venclexta) and chronic lymphocytic leukemia.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of November 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

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

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

Quality Assessment

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

Data Analysis

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

Writing of the Review Report

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

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

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

Tumour response criteria.
Complete Remission (CR)

Requires <u>all</u> the following criteria:
• Peripheral blood lymphocytes (evaluated by blood and differential count) below $4x10^9$/L (4000/μL)
• Absence of lymphadenopathy (nodes >15mm in longest diameter or any extra nodal disease) by physical examination and CT scan
• No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)
• Absence of disease or constitutional symptoms (B symptoms: unexplained fevers >38°C or 100.4°F, drenching night sweats, >10% body mass weight loss in the preceding 6 months)
• Blood counts above thee following laboratory values
  ○ Neutrophils >$1.5x10^9$/L [1500/μL] (without the need for exogenous growth factors
  ○ Platelets >$100x10^9$/L [100,000/μL] (without the need for platelet transfusion or exogenous growth factors)
  ○ Hemoglobin >110g/L [11g/dL] (without the need for blood transfusions or exogenous erythropoietin)
• Bone marrow at least normocellular for age, <30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone marrow aspirate and biopsy was to be performed after CR/CR with incomplete marrow recovery (CRi) had been achieved. If the bone marrow was hypocellular, a repeat determination was to be made in 4 weeks or when peripheral blood counts had recovered. A marrow biopsy was to be compared to a pre-treatment marrow if available. Subjects who were otherwise in a CR, but bone marrow nodules could be identified histologically were to be considered to be nodular PR (nPR). Immunohistochemistry was to be performed to define whether these nodules were composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Complete Remission with Incomplete Marrow Recovery (CRi)
• Subjects who fulfilled criteria for CR (including bone marrow) but who had persistent cytopenia (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug toxicity were considered CRi. The marrow evaluation described above was to be performed with scrutiny and not show any clonal infiltrate.
Partial Remission (PR)
To be considered a PR, <u>at least 2</u> of the following must have been met: • ≥50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value • ≥50% reduction in lymphadenopathy • ≥50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy) In addition, <u>at least one</u> of the following criteria must be met: • Neutrophils >1,500/μL or ≥50% improvement over baseline • Platelets >100,000/μL or ≥50% improvement over baseline • Hemoglobin >11.0 g/dL or ≥50% improvement over baseline without transfusions or exogenous growth factors
Progressive Disease (PD)

Disease progression according to 2008 Modified IWCLL NCI-WG Criteria for Tumour Response was characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (>1.5cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site
- An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter. The increase was to be assessed against the best response while on study
- Transformation to a more aggressive histology (eg. Richter's Syndrome). Whenever possible, this diagnosis was to be established by lymph node biopsy.
- Occurrence of cytopenia (neutropenia, anemia, or thrombocytopenia) attributable to CLL

Risk Categories for Developing Tumour Lysis Syndrome (TLS)

TLS Risk Category	Criteria
Low	All measurable lymph nodes with the largest diameter <5cm AND absolute lymphocyte count (ALC) $<25x10^9/L$
Medium	Any measurable lymph node with the largest diameter ≥5cm and <10 cm OR ALC $\geq 25x10^9/L$
High	Any measurable lymph node with the largest diameter ≥10cm OR ALC $\geq 25x10^9/L$ AND any measurable lymph node with the largest diameter ≥5cm but <10cm

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