CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Initial Clinical Guidance Report

Venetoclax (Venclexta) for Chronic Lymphocytic Leukemia

December 1, 2016

DISCLAIMER

Not a Substitute for Professional Advice

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

Liability

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

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

FUNDING

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

INQUIRIES

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

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

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

TABLE OF CONTENTS

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 supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on 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 objective of this review is to evaluate the safety and efficacy of venetoclax (Venclexta) as monotherapy for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) with (chromosome 17p13.1 deletion: del(17p))del(17p) who have received at least one prior systemic regimen.

The appropriate comparators for venetoclax in this setting include ibrutinib or idelalisib plus rituximab. The patient population under review is narrower than the Health Canada approved indication in that market authorization has been granted by Health Canada for patients with chronic lymphocytic leukemia (CLL) with del(17p) who have received at least one prior therapy, or patients with CLL without the del(17p) who have received at least one prior therapy and for whom there are no other available treatment options. The pCODR review only focuses on patients with chronic lymphocytic leukemia (CLL) with del(17p) who have received at least one prior therapy.

Venetoclax is a potent orally bioavailable selective inhibitor of bcl-2. The recommended dose for venetoclax begins with 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 fully published non-randomized, non-comparative, open-label Phase II study (M13-982[26]) examining the use of venetoclax in patients with relapsed or refractory CLL harboring the del(17p). The study design required that 70 patients be enrolled to provide 90% or higher power (at two-sided alpha of 5%) to reject the null hypothesis of 40% of patients achieving an overall response. Overall, 107

patients were enrolled with an additional 51 patients who were later enrolled and included in the safety expansion of the study for a total of 158 patients.

Of the 107 patients enrolled in the M13-982 study, 106 had the del(17p) as verified by central laboratory. Patients were administered oral venetoclax once daily until disease progression, unacceptable toxicity, or other reason for discontinuation. A now standard stepwise weekly dose ramp-up schedule was followed until the final daily dose of 400mg was reached after 4-5 weeks. Within the additional 51 patients, as part of the safety expansion cohort, 42 harbored the del(17p). Therefore a combined total of 148 patients harbored the del(17p) mutation.

Key inclusion criteria specified that patients were age ≥ 18 years, diagnosed with relapsed or refractory CLL harbouring del(17p) in >7% of cells in peripheral blood, have an ECOG performance status of 0, 1 or 2, have creatinine clearance ≥50mL/min and adequate coagulation and hepatic function. Notably, patients were not excluded based on prior ibrutinib or idelalisib plus rituximab therapy. The protocol included prophylactic measures for tumour lysis syndrome (TLS).

The majority of patients entered into the trial were male (n=61.5%), Caucasian (97.3%) with a median age of 67. Patients entered into the trial also had and ECOG PS of 0 - 1(92.6%) or 2 (7.4%) and, from the within the main cohort, 5 patients had prior therapy with ibrutinib and 1had prior therapy with idelalisib. The median number of prior therapies was 2 (1-6 range). The primary outcome to be assessed was the overall response rate. Key secondary outcomes included proportion of patients achieving complete response and partial response, progression free survival (PFS), overall survival (OS), quality of life and safety.

Key Results

For the primary outcome, an overall response rate of 79% was detected in the main cohort (n=107), with 8 (7.5%) patients achieving a complete response. Medians were not reached for PFS, OS, duration of response (DOR) and number of other secondary outcomes at the time of the data analysis. The most frequent serious adverse events were neutropenia (41%), anemia (17%), and thrombocytopenia (16%).

Changes in quality of life were measured in the M13-982 trial using two questionnaires: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16 (QLQ-CLL16). Based on the minimum important difference (MID) of 5 points from baseline to Week 24,[1,2] significant improvements were observed in global health status, emotional, role, and social functioning of the QLQ-C30. There were no significant changes from baseline in cognitive functioning or the following items related to physical functioning: nausea, vomiting, pain, appetite loss, constipation or diarrhea. Scores from the QLQ-CLL16 demonstrated significant improvements in disease effects, social problems, and future health worries, which exceeded the MID at all time points up to 24 weeks and including weeks 36 and 48. Improvements in treatment side effects were reported as statistically significant, however, they did not exceed the MID in the first 24 weeks.

Table 10. Efficacy outcomes in patients with CLL harbouring del(17p) in the M13-982 study.[26]	
	Main cohort patients with 17p del in CLL treated with venetoclax (n=107)
ORR (%) (95% CI %)	85 (79.4) (70.5, 86.6)
CR rate, n (%) (CR/CRi)	8 (7.5) (6/2)
PR rate, n (%) (nPR)	74 (69.2) 3 (2.8)
No response	22 (20.6)
DOR, months (median, range)	Not reached
PFS (median, range) 12 month PFS rate	Not reached 72% (95% CI 61.8-79.8)
EFS	Not reached
TTP	Not reached
TTR, median (IQR), months	0.8 (0.7-1.7)
Time to 50% reduction in ALC	NR
% to HSCT	NR
Follow up, months (median, range)	NR
OS (median, range) 12 month OS rate	Not reached 86.7% 95% CI 78.6-91.9)
TTNT	NR
Rate of MRD negativity, n(%)	18 (16.8)
Abbreviations: ALC - absolute lymphocyte count; CI = confidence interval; CR = complete remission; CRi - complete remission with inadequate marrow recovery; DOR = duration of response; EFS - event-free survival; HSCT - stem cell transplant; MRD - minimal residual disease; nPR - nodular partial response; NR - not reported; ORR = overall 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	

Major limitations:

The results of the M13-982 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 harbour the del(17p) are lacking. Overall, the trial was well-conducted and made appropriate use of a blinded independent review committee for outcome assessment to mitigate the possibility of performance and selection biases, which Phase II non-comparative studies are inherently susceptible to. However, given that it has been reported that most chemotherapy regimens demonstrating positive results in single arm phase II trials do not translate into positive results in phase III RCTs,[3] it is unclear whether the outcomes observed with venetoclax will be consistent in a randomised controlled trial.

1.2.2 Additional Evidence

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, ibrutinib and ubilituximab, idelalisib, obinutuzumab, obinutuzumab and rituxan, obinutuzumab and bendamustine, obinutuzumab/venetoclax/ibrutinib, ofatumumab, lenalidomide, dexamethasone, among others. A minority of respondents have received fifth line and sixth line treatment. CLLPAG noted that although the current gold standard drug therapy for CLL is FCR, it is considered to be a toxic regimen that is known to be ineffective for certain genetic mutations of CLL such as del(17p).

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, 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.

Please see section 3 for details

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Lack of phase 3 comparative data
- Clarity of treatment population

Economic factors:

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

Please see section 4 for details

Registered Clinician Input

Overall, the clinicians providing input identified that venetoclax provides another treatment option for CLL patients with del(17p) and who have failed all other treatments or cannot tolerate or have contraindications other available treatments. They believe that venetoclax is superior to any other available therapy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del(17p), but noted that there are no direct comparison data to suggest whether venetoclax is superior or equivalent to the novel kinase inhibitors (ibrutinib and idelalisib). The clinicians providing

input indicated that adverse events are manageable but that incidence of adverse events in the real world are yet to be seen. It was also identified that patients with high risk for tumour lysis syndrome would need to be treated at tertiary care centres.

Please see section 5 for details

Summary of Supplemental Questions

Critical Appraisal of an Indirect Treatment Comparison between Venetoclax and Relevant Treatment Options

Given the absence of a comparative trials evaluating the safety and efficacy of venetoclax compared to relevant treatment options, an indirect treatment comparison was done for venetoclax (VEN) versus other relevant treatments in patients with chronic lymphocytic leukemic relapsed / refractory del(17p) setting (CLL R/R del(17p)). There was limited information available on the methodology and results of this indirect comparison and thus only a limited critical appraisal was done. This data is also pending peer-review and publication. Overall, although the point estimates of the analyses suggest that VEN is similarly efficacious as IBR in terms of progression-free survival and overall survival, great caution should be used in drawing conclusions based on these data.

Please see section 7 for details

Comparison with Other Literature

One study including 64 patients published as a poster (M14-032) for which interim data were obtained from the study investigators is being considered as an ongoing study. The study meets all eligibility criteria for the systematic review aside from the fact that it is not fully published. The M14-032 study is a non-randomized, non-comparative, open-label Phase II study in which the efficacy and safety of venetoclax is evaluated in patients with CLL who have relapsed after or are refractory to either ibrutinib or idelalisib. Since it was not a requirement for patients to have the del(17p) for eligibility, we are considering only those data pertaining to the 23 patients harbouring the del(17p). While very preliminary in a subset of 23 patients, the overall response rate was 65%.

In addition to the limitations that arise from study M14-032 being another Phase II non-comparative study, an important limitation that precluded this study from being formally included in the systematic review is that it has not yet been fully published. Rather, the information has been derived from interim results presented in poster form and results obtained directly from the submitter. Therefore the pCODR Review Team was unable to conduct a full critical appraisal on the study.

Please see section 8 for details

1.2.3 Factors Related to Generalizability of the Evidence

Table 2.2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for venetoclax in relapsed/refractory CLL patients with del(17p).

Domain	Factor	Evidence M13-982 Trial[26] M14-032 Trial[52, 53]	Generalizability Question	CGP Assessment of Generalizability
Population	Line of treatment	Patients who have had prior ibrutinib or idelalisib plus rituximab	Are the results of the M13-982 trial generalizable into patients who have previously failed ibrutinib or idelalisib plus rituximab or into patients who are resistant or intolerant to ibrutinib or idelalisib plus rituximab?	Based on the limited data from study M13-982 and study M14-032, the CGP agreed that the efficacy and safety outcomes observed with venetoclax in the M13-982 is generalizable in patients who have previously failed on ibrutinib or idelalisib plus rituximab or in patients who are resistant or intolerant to ibrutinib or idelalisib plus rituximab.
	Performance Status	Patient with ECOG 0, 1, or 2 were eligible. Most patients on study (91.5%) had ECOG 0 or 1. There are no data for patients with ECOG 3 or 4.	Does performance status limit the interpretation of trial results?	If treatment is indicated and poor PS is driven by disease progression, the CGP felt that treatment with venetoclax may be reasonable.
	Organ dysfunction	Patients with CrCl≥50ml/min were eligible. There are no data available for patients with CrCl < 50ml/min. Patients with renal impairment may be at higher risk for toxicity including tumour lysis syndrome.	Does the exclusion of patients with significant renal impairment limit interpretation of trial results?	In patients with baseline renal impairment, closer monitoring and consideration of hospitalization for patients at low or medium risk for TLS may be required to safely administer venetoclax. The CGP also agree that effective therapy, such as rasburicase, are available to treat or prevent TLS. The product monograph suggests dose adjustment is not required for mild-moderate renal dysfunction (CrCl≥30ml/min) however there are no dosing recommendations for patients with CrCl < 30ml/min or patients on dialysis.
	Organ dysfunction	Patients with significant hepatic dysfunction were excluded. There are no data available for patients with significant hepatic dysfunction. Patients with bilirubin greater than 1.5x the upper	Does the exclusion of patients with significant hepatic dysfunction limit interpretation of trial results?	The CGP agree with the precautions given in the product monograph, suggesting that venetoclax may be used with caution in patients with mild-moderate liver dysfunction without dose adjustment however the CGP agree that it should not be used for patients with severe hepatic dysfunction. The CGP therefore agree along with precautions outlined in the product monograph, an appropriate clinical

Domain	Factor	Evidence M13-982 Trial[26] M14-032 Trial[52, 53]	Generalizability Question	CGP Assessment of Generalizability
		limit of normal (ULN) or AST/ALT > 3xULN were excluded from M13-982.		judgment regarding risks/benefits need to be carefully considered when prescribing venetoclax.
	Prior therapy	Patients with at least one prior line of therapy were eligible. No evidence available to assess the efficacy and safety of venetoclax in the front line setting	Are the results generalizable to first line therapy?	The CGP felt venetoclax was appropriate for 2nd and subsequent lines of therapy. There were no data available for previously untreated patients.
	Prior allogeneic stem cell transplant	Patients with prior allogeneic transplant were excluded from the M13-982 trial.	Are the results generalizable to patients treated with prior allogeneic stem cell transplant?	There are no data evaluating venetoclax in this patient population. However, in this high risk group the CGP felt that treatment with venetoclax may be a reasonable treatment option. These patients are also generally treated similarly to relapsed/refractory patients that have not had transplant. Currently patients would generally be treated with ibrutinib (if not previously intolerant/refractory).
Setting	Supportive care medications, procedures, or care	Patients were treated at sites that had appropriate facilities to provide intensive in-patient and out-patient prevention and treatment of tumour lysis syndrome	Are the results generalizable to a treatment setting that is not able to access medications, laboratory monitoring, and in-patient care as required for the prevention and treatment of tumour lysis syndrome.	With appropriate risk assessment, prevention, monitoring and treatment as recommended in clinical trials and the product monograph (in addition to utilizing the standard dose ramp up phase) the incidence of clinical tumour lysis syndrome is low. The CGP felt that venetoclax should be administered in clinical settings that have medical expertise to assess and treat TLS and appropriate out-patient and in-patient resources to provide supportive care medications and intensive laboratory monitoring required to safely manage patients on venetoclax therapy.

1.2.4 Interpretation

Burden of Illness and Need

Chronic lymphocytic leukemia is an incurable B cell malignancy that is clinically and biologically heterogeneous. Interphase FISH cytogenetics is a useful prognostic test that helps define CLL risk groups and is available to most Canadian health care providers. Patients with a del17p abnormality are categorized as having high risk disease and a very poor prognosis. In the front line setting, median progression free survival (PFS) for patients with del17p is only 8-12 months with potent chemo-immunotherapeutic regimens (e.g. BR, FCR) compared with 3.5-5 years in previously untreated patients overall.[4,5] In the relapsed/refractory setting, outcomes have been even worse, characterized by responses in a minority of patients and brief progression free and overall survival (typically less than 6 months and 12 months respectively).[6-8] The incidence of del17p in previously untreated patients is approximately 5-10%.[4,9] Through a process of clonal evolution/selection the incidence increases through subsequent lines of therapy such that in the multiply relapsed/refractory setting the incidence is approximately 30-40%.[10,11]

Recently, the development of novel kinase inhibitors targeting the B cell receptor signalling pathway has improved outcomes. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, is approved for the treatment of previously treated CLL including patients with del17p. In a phase II study evaluating ibrutinib in relapsed/refractory patients with del17p, overall response rate was reported to be 83% and 2 year PFS was 63%. Idelalisib, a PI3Kδ inhibitor, in combination with rituximab was associated with a median PFS of approximately 17 months within the subset of relapsed/refractory patients with del17p in a phase III trial. However, neither of these regimens are considered curative and they are associated with a unique toxicity profile that includes arthralgias/myalgias, bleeding, atrial fibrillation, and hypertension (ibrutinib), and colitis, pneumonitis, transaminitis, and opportunistic infections (idelalisib plus rituximab). As a result some patients fail due to the development of resistance or intolerance. Patient outcomes after failure of B cell receptor pathway inhibitors are very poor and currently there are no effective therapies that predictably salvage such patients.

Effectiveness

The M13-982 trial is a large, non-randomized, multi-centre, open-label phase II trial evaluating venetoclax in patients with del17p relapsed or refractory after at least one prior therapy. The overall response rate, as determined by an independent review committee (the primary endpoint), was 79.4%; CR/CRi was reported in 8% of patients. Response rates were similar across all prognostic subgroups evaluated. Although only 5 patients were previously treated with ibrutinib or idelalisib (in the main cohort), 4 partial responses (80%) were reported. Estimated 12 month PFS was 72.0% (95%CI 61.8-79.8) and preliminary data reported significant improvement in several domains assessed with quality of life tools. Based on cross trial comparisons, these results are similar to outcomes reported for ibrutinib and idelalisib plus rituximab in this high risk patient population and are favourable in comparison to historical treatment options. In the absence of a comparator arm, it is not possible to determine whether there is a difference or what the magnitude of any difference in PFS, OS, or quality of life may be compared with alternative regimens. However, given the relatively small numbers of eligible patients, randomized controlled trials are unlikely to be feasible in this selected patient group and the members of the CGP are not aware of any currently accruing RCTs in this population.

The M14-032 trial is an ongoing non-randomized, two-arm, multi-centre, phase II, open-label study reported in abstract form evaluating venetoclax in patients intolerant or refractory to either ibrutinib (Arm A) or Idelalisib (Arm B); a subset of enrolled patients had a del17p. Although preliminary in nature, the members of the CGP felt these data were important to consider in this report because of: (1) the lack of comparative data to guide optimal sequencing of ibrutinib, Idelalisib plus rituximab, and venetoclax, and (2) the likelihood that venetoclax treatment would be considered an optimal approach in patients intolerant or resistant to ibrutinib or Idelalisib plus rituximab. Patients from Arm A (N=21) and Arm B (N=2) were combined in this preliminary assessment of response rate. Taken together, the overall response rate in this very high risk patient subset who have limited available treatment options for salvage was 65%. The data are immature with respect to PFS and OS.

Safety

Reported toxicity rates and severity were similar across the two phase II studies included in this systematic review. In general, venetoclax is well tolerated and toxicities are considered manageable. Grade ≥ 3 adverse events included neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%). Serious adverse events included autoimmune haemolytic anemia (7%), pneumonia (6%), and febrile neutropenia (5%). Venetoclax dosing is started at 20mg by mouth daily followed by weekly 'ramp up' over 4-5 weeks to a maximum of 400mg daily. With appropriate risk assessment (dividing patients into low, medium, and high risk for TLS), preventative measures, and intensive monitoring, the risk of laboratory tumour lysis syndrome (TLS) in the M13-982 trial was low (5%). Among the 5 patients that developed laboratory evidence of TLS, three continued treatment without interruption and the remaining 2 patients required a one-day dose interruption before resuming therapy. Laboratory TLS resolved in all cases without clinical sequelae. Determination of low, medium, and high risk was based upon now standard assessments of nodal size and degree of lymphocytosis. Prophylaxis with hydration and urate lowering agents and regular blood tests to monitor for laboratory evidence of tumour lysis were incorporated and hospitalization for high risk patients during the dose escalation phase was required.

Although the Clinician Input identified that patients at high risk for developing tumour lysis syndrome should be treated in tertiary care centres, the members of the CGP did not fully agree with this opinion. Rather than restrict treatment arbitrarily to specific clinical sites (academic/tertiary care centres), the CGP agreed that venetoclax should be administered by clinicians with experience in the prevention/management of TLS, within clinical settings appropriately resourced to provide the necessary prevention (hydration, urate lowering agents), frequent/timely laboratory monitoring, and treatment of TLS. The CGP felt that treatment outside of a tertiary care centre is reasonable if these parameters are satisfied. The CGP also noted that with appropriate management the incidence of TLS is low and are aware that venetoclax is already being administered in community cancer centres through compassionate access. The CGP also noted Clinician Input related to the lack of safety data with venetoclax in the 'real world' and their concern that toxicities may be underestimated in clinical trial populations. The CGP acknowledged this is common to many new cancer therapies and agree that careful long term follow-up of patients treated within and outside of clinical trials is important. However, existing data support the conclusion that with appropriate precautions venetoclax is generally well tolerated and has a manageable side effect profile.

1.3 Conclusions

The Clinical Guidance Panel concluded that there may be a net clinical benefit for treatment of CLL patients with del17p that are relapsed or refractory following one prior line of therapy. This is based primarily on the results from one large non-randomized phase II trial that reported high response rates, durable remissions, and a manageable toxicity profile in this high-risk patient population. Preliminary results from an ongoing second non-randomized phase II trial reported high response rates in the del17p subset that previously failed ibrutinib or idelalisib plus rituximab. As a consequence of the non-comparative trial designs, optimal sequencing of venetoclax in the context of ibrutinib and idelalisib plus rituximab remains uncertain. A careful, individualized approach to assessing risks, benefits and patient preferences will likely guide treatment decision-making between currently available treatment options and venetoclax. However, in previously treated patients for which treatment with ibrutinib or idelalisib is considered unsafe (due to toxicity concerns) or that develop intolerance/resistance, the CGP considers venetoclax to be the treatment of choice.

In making this conclusion the Clinical Guidance Panel considered that:

- Although typically well tolerated, some patients fail ibrutinib or idelalisib plus rituximab through the development of intolerance or resistance. Patients with relapsed CLL/SLL associated with a del17p and failure of ibrutinib represent an extremely high risk subset of patients with poor outcomes and limited treatment options.
- In the absence of comparative clinical trials the incremental benefit compared to alternative treatment options is uncertain however:
    - Based on clinical opinion, response rates, progression free survival, and health related quality of life are clinically relevant outcomes measures that are improved compared with historical patients treated prior to the introduction of B cell receptor pathway inhibitors (ibrutinib, idelalisib plus rituximab)
    - Most Canadian patients are currently being treated with ibrutinib and given the greater clinical experience and longer term follow-up it is likely ibrutinib will continue to be a preferred first option for most relapsed del17p CLL patients unless a specific safety concern exists.
    - The CGP acknowledge that although the M13-982 trial did not exclude patients previously treated with ibrutinib or idelalisib, the number of patients previously treated with these drugs and included in the trial was small. However, the overall response rate in patients treated with prior ibrutinib or idelalisib was similar to the overall study cohort. The M14-032 trial provides preliminary data to support the decision to generalize the data from M13-982 to patients previously treated with ibrutinib/idelalisib. In their deliberations, the CGP also considered the unique mechanism of action of venetoclax, the very poor prognosis of this patient group, and the lack of any reasonable alternative treatment options for patients with relapsed del17p that have failed prior ibrutinib or idelalisib.
- Median follow-up for patients enrolled on the phase II studies included in this systematic review is relatively short. Although preliminary results are consistent with important clinical benefit, longer term follow-up is necessary to more confidently estimate PFS, OS, and long term safety.
- Appropriate management requires that sufficient resources are available to prevent, monitor and manage the risk of tumour lysis syndrome including appropriate use of urate lowering agents and hydration, frequent and timely laboratory monitoring, the need for hospitalization of high risk patients, and appropriate management of patients that develop TLS. Clinicians should have appropriate comfort and expertise in the prevention and management of TLS.
- Venetoclax should be administered as monotherapy and continued indefinitely until intolerable toxicity or disease progression. The CGP noted Clinician Input that suggested

venetoclax can potentially be discontinued after a deep remission is obtained. However, there are no available data to support response adapted treatment discontinuation and the CGP concluded that this approach, while an important question to be addressed in ongoing studies, cannot be recommended currently in this high risk patient population.

- Based on information from the submitter, the dose titration and individual doses for venetoclax will be available as a blister pack in Canada.

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.[13] 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.[14,15] At diagnosis, patients are staged according to the Rai or Binet staging systems (see below).[16,17] 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).[18] 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) 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 or chlorambucil plus obinoutuzumab.[4,5,9,19] 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, and idelalisib) and bcl-2 (venetoclax). 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.[10,11] However, unique toxicities have been documented with B cell receptor pathway inhibitors and patients may be intolerant or develop resistance. 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 bcl-2, has also demonstrated excellent response rates, response duration, and survival in phase I/II trials evaluating

patients with relapsed/refractory CLL including patients including those with genetically high risk disease.[20] 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.[21] 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); 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.[4,14,21] 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%.[10,11] Most Canadian Cancer Centres have access to FISH testing and thus are able to identify patients with del17p. Few centres have routine access to TP53 gene mutation analyses; this represents an important gap that may adversely affect patient care. Since the approved indication for venetoclax is the treatment of relapsed/refractory patients with a del17p, and TP53 gene analysis is not widely available in Canada, this report will focus on the del17p population.

2.2 Accepted Clinical Practice

Patients with relapsed CLL/SLL and del17p have a particularly poor prognosis and chemoimmunotherapeutic regimens are largely ineffective. Based on clinical opinion, response rates, overall survival, progression free survival, and health related quality of life are clinically relevant outcomes in this patient population. Historically, attempts to improve outcomes have focused on drugs that do not require functional p53 in order to exert their effect. Examples included alemtuzumab +/- high dose corticosteroids and lenalidomide, neither of which are currently funded for Canadian patients. 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 [6,22] Allogeneic stem cell transplantation is a potentially curative treatment option and has been considered in a carefully selected subset of cases (young, fit patients with chemosensitive disease and a suitable donor).[23] 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 plus rituximab have demonstrated a marked improvement in outcomes compared to historical therapies with response rates of approximately 70-80%, and median PFS of approximately 16 months (idelalisib plus rituximab) and 28 months (ibrutinib) respectively.[10,24,25] These agents are now considered a standard of care in this very high risk population of CLL patients. Although typically well tolerated, some patients fail due to the development of intolerance or resistance. Patients with relapsed CLL/SLL associated with a del17p and failure of ibrutinib represent an extremely high risk subset of

patients with limited treatment options and a high unmet clinical need for new treatment approaches

Patients with Chronic Lymphocytic Leukemia		
Line of Therapy	Del17p	Non-del17p
1st-Line	Ibrutinib (if available) Chemo-immunotherapy (if ibrutinib not accessible)	FCR, FR, BR, chlorambucil-Obinutuzumab
Maintenance	Not applicable	Not applicable
2nd-Line	Ibrutinib, idelalisib plus rituximab versus venetoclax	Ibrutinib, idelalisib plus rituximab

2.3 Evidence-Based Considerations for a Funding Population

Based on the eligibility criteria from the M13-982 trial, patients with at least one prior therapy for CLL and with del17p would be eligible for treatment with venetoclax. Patients should have symptomatic disease requiring therapy. The number of patients in absolute terms is expected to be relatively small. Del17p is detected in approximately 5-10% of previously untreated patients and up to 30% in the heavily pretreated/refractory setting. There is a risk of developing tumour lysis syndrome (TLS) following treatment with venetoclax therefore adequate resources to manage this toxicity must be established prior to initiating therapy (regular laboratory monitoring for TLS including the potential need for hospitalization to manage patients at high risk). 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. The M14-032 trial is currently accruing patients to evaluate the safety and effectiveness of venetoclax in patients that have failed ibrutinib (Arm A) or idelalisib (Arm B). A proportion of patients enrolled in this trial have a del17p and results from this trial will be informative in the Canadian context given the availability of ibrutinib and idelalisib plus rituximab for the treatment of relapsed CLL with del17p. Patients that are intolerant or develop resistance to kinase inhibitor therapy (i.e. ibrutinib or idelalisib plus rituximab) have a particularly poor prognosis, limited treatment options and represent a high risk population that may be prioritized for treatment with venetoclax.

2.4 Other Patient Populations in Whom the Drug May Be Used

Venetoclax is also approved in Canada for treatment of relapsed/refractory non-del17p patients that do not have any available treatment options. It is currently being studied in patients with previously untreated and relapsed/refractory CLL (i.e. with or without del17p) including patients that have failed prior ibrutinib or idelalisib-based treatment. 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.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Two patient advocacy groups, Lymphoma Canada (LC) and CLL Patient Advocacy Group (CLLPAG), provided input on venetoclax for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; with a del(17p), and their input is summarized.

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

LC surveyed 20 patients who had direct experience with venetoclax in the relapsed setting. Of those surveyed, LC also conducted interviews with three patients on their experience with venetoclax. Nine respondents indicated they had del(17p).

Participants by Country	CAN	USA	UK	BE	AUS	Skipped	N
CLL Patients with Venetoclax Experience (Survey)	1*	10	4	1	1	1	18
SLL Patients with Venetoclax Experience (Survey)	-	2	-	-	-	-	2
CLL Patients with Venetoclax Experience (Interviews)	-	3	-	-	-	-	3**
CLL Patients without Venetoclax Experience (Survey)	23	7	-	-	1	3	34
SLL Patients without Venetoclax Experience (Survey)	10	-	-	-	-	2	12
Caregivers of CLL Patients (Survey)	9	1	1	-	-	-	11
Caregivers of SLL Patients (Survey)	1	-	-	-	-	-	1
The perspectives of 20 CLL/SLL patients with venetoclax experience in the relapsed setting; 46 CLL/SLL patients without venetoclax experience; and 12 caregivers are represented in this submission (Total participants: 78). *1 Canadian patient respondent did not indicate if he/she had CLL or SLL - this respondent was added to the table under CLL. **All patients with venetoclax experience who participated in an interview also completed surveys.							

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

CLLPAG received responses from 248 patients and 29 caregivers. CLLPAG reported that six patients have experience with venetoclax.

Respondents by Country	CAN	USA	UK	AUS	Other*	Skipped	Total
Total CLL/SLL patients	65	116	40	3	6	18	248
Patients with venetoclax experience	1	3	1			1	6
Caregivers	11	14	3		1		29
*Other includes 1 patient from each of the following: Belgium, Brazil, New Zealand, Norway, Scotland & Sweden and 1 caregiver from Ireland. **Note: del(17p) status unknown							

Respondents by Age	21-39	40-49	50-59	60-69	70-79	80-89	90+
Total CLL/SLL patients *18 persons skipped this question	3	18	57	98	51	2	1
Patients with venetoclax experience *1 person skipped question		1		2	2		
Caregivers	2	6	6	5	5	1	

Respondents by Gender	Male	Female
Total CLL/SLL patients *18 did not disclose gender	90 (39.1%)	140 (60.9%)
Patients with venetoclax experience * 1 did not disclose gender	1(20.0%)	4 (80.0%)
Caregivers	10 (34.5%)	19 (65.5%)

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, ibrutinib and ubilituximab, idelalisib, obinutuzumab, obinutuzumab and rituxan, obinutuzumab and bendamustine, obinutuzumab/venetoclax/ibrutinib, ofatumumab, lenalidomide, dexamethasone, among others. A minority of respondents have received fifth line and sixth line treatment. CLLPAG noted that although the current gold standard drug therapy for CLL is FCR, it is considered to be a toxic regimen that is known to be ineffective for certain genetic mutations of CLL such as del(17p).

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, 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.

CLLPAG respondents were asked to compare intravenous (IV) and oral drug treatment for CLL. CLLPAG reported that oral treatment resulted in less impact than IV treatment in all areas except ability to tolerate full dose. It was submitted that as an oral therapy, 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. It is worth noting that some respondents outside the survey have reported difficulty with swallowing these pills.

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 reported that patients with CLL were often diagnosed during investigation for another condition or during routine blood work. In a survey that was completed by patients diagnosed with CLL/SLL between 1989 and 2016, it was reported that 58% of respondents were diagnosed in the last five years. The results showed that 104 (41.94%) respondents were in watch and wait and 144 (58.06%) respondents had received treatment. Watch & wait management of the disease is often a difficult stage of the disease for patients to accept as noted by patients:

- *"That the secrecy of it needs to be addressed through public education. Because I am in watch and wait I feel like I don't really have cancer. But it affects my mental state and decisions every day"*
- *"My requests to be referred to specialist fobbed off as do not need treatment yet but I would like an expert opinion and to make myself known to him".*

LC noted that respondents with early stage CLL or SLL who participated in their survey reported minimal symptoms associated with their disease and tended to report a good quality of life. LC also noted that for those with more advanced disease, their quality of life was impacted more significantly.

CLLPAG reported that symptoms of CLL/SLL that affected the quality of life at diagnosis and on an ongoing basis were the following:

Symptom	At diagnosis	Ongoing
Fatigue/lack of energy	51.61% (128/248)	59.27% (147/248)
Increasing lymphocyte count	48.00% (119/248)	36.69% (91/248)
Enlarged lymph nodes	39.11% (97/248)	26.21% (65/248)
Frequent infections	21.00% (52/248)	19.00% (47/248)
Night sweats	19.40% (48/248)	12.10% (30/248)
Low platelet count	10.50% (26/248)	25.00% (62/248)
Low immunoglobulin levels	8.10% (20/248)	24.19% (60/248)
None of listed symptoms	22.60% (56/248)	14.50% (36/248)

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

Psycho-Social Condition	At diagnosis	Ongoing
Stress from diagnosis	75.8% (188/248)	29.0% (72/248)
Anxiety	53.9% (147/248)	40.3% (100/248)
Difficulty sleeping	38.7% (96/248)	34.7% (86/248)
Depression	30.6% (76/248)	22.6% (56/248)
None of these	16.5% (41/248)	34.3% (85/248)

To help provide context, the following comments were excerpted:

- *"Worry about how to cope with both CLL and RA."*
- *"I found that the diagnosis affected my relationships and I was in effect written off by some people."*

- *"Psychosocial support should be offered immediately upon diagnosis, which in my experience is not done."*
- *"Initially dealt with doctors who were not familiar with CLL - added to stress and anxiety. Mostly overwhelmed and very ill"*
- *"My ability to manage stressful situations appears to have reduced."*
- *"I feel unlucky to have been diagnosed with CLL and it is a struggle dealing with this incurable cancer on a daily basis. My overall survival is closely linked to having access to novel and proven drugs."*
- *"Not looking unwell has been a mixed blessing, particularly when feeling nauseous or very tired. Some refused to accept that I was/am ill and accused me of being negative when I avoid crowds, people with infections. Living alone I have felt very unsupported and lonely."*
- *"More information of what may happen next would have helped."*
- *"Its a long road to watch out for everything... your life style changes so much it's hard to handle, just glad there are people who understand out here."*
- *"I have had no support at all nor have I been given any information."*

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

Symptom	1	2	3	4	5	# of responses	% rated 4-5
Frequent infections	13	8	21	39	167	248	83.07
Fatigue/lack of energy	14	8	31	70	125	248	78.63
Viral reactivations	22	11	33	48	134	248	73.38
Low platelet count	16	13	44	65	110	248	70.56
Increasing lymphocyte count	13	13	48	58	116	248	70.16
Anemia	17	7	51	60	113	248	69.75
Neutropenia	16	11	53	43	125	248	67.74
Enlarged spleen	22	15	44	61	106	248	67.34
Shortness of breath	24	22	36	68	98	248	66.94
Low IgG levels	21	11	51	58	107	248	66.54
Enlarged lymph nodes	14	23	46	74	91	248	66.53
Pain	32	23	35	61	97	248	63.71
Fever	36	30	54	60	68	248	51.61
Night sweats	20	31	88	54	55	248	43.95
Weight loss	55	44	74	37	38	248	30.24

LC found that fatigue was commonly reported; respondents described themselves as being void of energy and stated that they needed to rest often in order perform their normal daily activities.

According to LC, some respondents with CLL or SLL expressed difficulties with concentration, emotions, stress levels, insomnia and mood swings. Additional symptoms reported included enlarged lymph nodes, fever, night sweats, peripheral neuropathy and weight loss. Frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts) were also reported. LC states that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day-activities.

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

- *"My main symptom initially was an inability to swallow and frequent choking due to enlarged nodes in the neck and throat…I experienced extreme fatigue, weakness and loss of taste, some hair loss... After my immunotherapy my major symptom was and remains peripheral neuropathy in my feet, upsetting my sense of balance and changes in my walking...I experienced loss of concentration and mood swings." (Male; 75 years or older; Canada)*
- *"In my daily life, I have learned to pace myself due to fatigue and shortness of breath experienced even when I am at rest…I alternate between rest and modest activity each day. There are times when I do not feel alert enough to drive the car and then my husband drives. …I estimate that my lifetime job earnings have been reduced by 25% due to my disease. I retired 10 years earlier than planned because I was unable to tolerate the demands of my job due to my disease and because I was not considered competent to continue in my job due to my disease."(Female; 55-64; Canada)*
- "My illness has robbed me of so many goals I had for my life and my family. I know I could have grown my business to a much greater level... I couldn't make it to work every day from the fatigue or was at another Cancer Clinic appointment. The illness plays on your mind and you are angry that it was me it picked. It has impacted my family life in ways that I must depend on my wife and children to help me out to do manual chores or submit paper work to get some reimbursement from insurance companies that structure themselves so that the forms are lengthy and multiple phone calls are required to obtain payment. I have cancelled holidays with family and friends because my platelet counts are too low and I might have a life threatening bleed. My wife and I plan our lives around my clinic appointments." (Male, 45-54; Canada)

3.1.2 Patients' Experiences with Current Therapy for Chronic Lymphocytic Leukemia

According to CLLPAG, respondents are currently receiving a variety of therapies to treat CLL/SLL as reported in the table below:

Treatment Given	# Patients treated first-line	#Patients treated second-line	#Patients treated third-line	# Patients treated fourth-line
ACP196 (acalabrutinib)	2	2	0	0
Bendamustine	2	2	1	1
BR - bendamustine rituxan	16	5	2	2
Campath	0	1	0	0
Chlorambucil	10	2	2	1
CVP	1	0	0	0
CVP + R	1	0	0	0
Cytoxan, pentostatin, rituxan	1	0	0	0
Fludarabine, rituxan, lenalidomide	1	0	0	0
Fludarabine	7	0	2	1
FC	2	0	0	0
FCR	37	7	1	0
FR	10	2	1	0
Fludarabine, cytotoxin, ofatumumab	1	0	0	0
GS-9973	0	0	1	0
Ibrutinib	15	22	13	4
Ibrutinib and rituxan	4	0	0	0
Ibrutinib and ubilituximab	0	2	0	0
Idelalisib	1	1	3	0
Obinutuzumab	3	0	0	1
Obinutuzumab and rituxan	1	0	0	0

Obinutuzumab and bendamustine	1	0	0	0
Obinutuzumab/venetoclax	1	0	0	0
Obinutuzumab/venetoclax/ibrutinib	0	1	0	0
Ofatumumab, lenalidomide, dexamethasone	1	0	0	0
PCR	3	1	0	0
R-CHOP	1	3	0	0
Revlimid	1	2	0	1
Rituxan/revlimid	1	2	0	0
Rituxan	6	15	3	2
Rituxan and HDMP	2	1	0	0
Venetoclax	1	0	1	1
Venetoclax/obinutuzumab	0	0	1	0
TOTAL	**144**	**71**	**31**	**14**

In addition to these therapies, seven respondents received fifth line therapy (revlimid, rituximab (n=2), FCR, ibrutinib (n=3)) and three respondents received sixth line treatment including Venetoclax, obinutuzumab and ibrutinib. CLLPAG indicated that response to current therapy is dependent on the genetic mutation(s) and IVGH mutation status of individual patients. Relapse or becoming refractory to a treatment requires retreatment and usually uses of a different therapy, as can be seen with individuals who have received up to six different treatments. CLLPAG submits that it is important for a knowledgeable hematologist to prescribe the appropriate treatment after relapse.

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

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

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

- *"I had hoped that the therapies would keep my red cell count up longer than it does. I am not able to maintain good nos. over a period of time. That means going on and off treatment often."* (Female; 65-74; Canada)
- *"All treatments wiped out my good blood components and made me tired. As treatment went on with each of these therapies I development more complications that made it unsafe for me to continue to receive treatment. Hence I endured the chemo treatments but had complications like low platelets; low neutrophils and was unable to finish the full treatment of each of these lines of therapy…My remissions were short before the leukemia came back..."* (Male; 45-54; Canada)

According to CLLPAG, 137 respondents reported the most common side effects experienced while undergoing treatment included: fatigue (70.80%), anemia or neutropenia (50.36%), nausea (48.91%), low platelets (39.42%), mouth sores (36.5%), skin rashes/severe itching (32.12%) and infections (32.12%).

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

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

Side effect	1	2	3	4	5	% rated 4-5
Fatigue	5.24%	15.31%	20.16%	27.42%	31.85%	59.27%
Cough	6.05%	13.31%	29.44%	24.29%	27.02%	51.21%
Diarrhea	10.89%	12.10%	27.42%	23.39%	26.21%	49.60%
Nausea	10.89%	14.52%	27.02%	20.56%	27.02%	47.58%
Fever	9.68%	14.52%	30.65%	20.97%	24.19%	45.16%
Back pain	14.52%	18.15%	34.75%	18.15%	14.92%	33.07%
Infusion reaction	23.39%	20.97%	24.60%	17.34%	13.71%	31.05%
Rash/severe itching	19.35%	20.16%	30.65%	16.53%	13.31%	29.84%
Low platelets	9.68%	24.19%	36.69%	16.94%	12.50%	29.$$%
Irregular heartbeat	26.61%	26.61%	22.58%	17.74%	6.45%	24.19%
Anemia or neutropenia	20.16%	26.61%	29.03%	12.90%	11.29%	24.19%
Tumour Lysis Syndrome	41.53%	15.73%	24.60%	8.87%	9.27%	18.14%
Breathing difficulties or pneumonia	42.74%	26.615	17.74%	6.45%	6.45%	12.90%

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

LC indicated that treatment options currently available in Canada tend to be associated with increased toxicity, reduced anti-tumour activity, unpleasant side effects and relapse. Respondents were asked to rate their level of agreement with how much their current therapy(ies) are able to manage symptoms associated with their CLL or SLL on a scale of 1 (Strongly Disagree) to 10 (Strongly Agree). Thirty four (34) patients answered this question. The rating average was 6.9.

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

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

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

- *"I live 130 Kilometers from Ottawa so I had to drive in order to get the treatments."* (Female, 75 years or older, Canada)
- *"This has been substantial. I have not been able to work since May 11, 2010. I have had assistance but have mounting medical bills due to my long stay in the hospital, surgery, stem cell transplant and monthly visits to the hospital and being unable to work. I was working and got sick within 6 weeks of getting medical coverage because of the 6 month waiting period and so I have had minimal coverage"* (Female; 45-54; Canada)

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

When considering treatment, respondents were asked how important it is for them and their physician to have choice in deciding which drug to take based on known side effects and expected outcomes with a rating scale of 1 (Not Important As Long There Is At Least One Treatment Choice) to 10 (Extremely Important To Have Choice of Treatment). Twenty-eight of the 38 patients (73.7%) who answered this question gave this a rating of 8 or higher. The rating average was 8.4 and according to LC, this means a large proportion felt that choice was very important based on the known side effects and expected outcomes of a drug. Patients were also asked if they feel there is currently a need for more choice in drug therapy(ies) for patients with CLL or SLL. All respondents (36, 100%) who answered this question feel there is a definite need for more therapies.

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

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

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

3.1.3 Impact of Chronic Lymphocytic Leukemia and Current Therapy on Caregivers

LC asked respondents to rate on a scale of 1 (No Impact) to 10 (Very Significant Impact) how caring for the person with CLL or SLL has impacted their "day-to-day life." LC noted differences in ratings were reported based on a caregiver's retirement status. Five (41.7%) respondents were retired at the time of completing the survey and seven (58.3%) were still working. For those factors with a rating average of 5 or more, LC indicated there was a greater than neutral impact on day-to-day life.

Impact on Day-to-Day Life of Retired Caregivers (N=5)*	Rating of 7 or Higher n (%)	Rating Average	Impact on Day-to-Day Life of Not Retired Caregivers (N=7)*	Rating of 7 or Higher n (%)	Rating Average
Ability to travel	4 (80.0%)	7.2	Ability to volunteer	4 (57.1%)	6.7
Ability to volunteer	3 (60.0%)	5.8	Ability to concentrate	3 (42.9%)	5.1
Ability to spend time with family and friends	2 (40.0%)	5.2	Ability to exercise	2 (28.6%)	4.7
Ability to concentrate	2 (40.0%)	4.8	Ability to attend to	2 (28.6%)	3.7
Ability to fulfill family obligations	2 (40.0%)	4.8	Ability to spend time with family and	2 (28.6%)	3.9
Ability to exercise	2 (40.0%)	4.4	Ability to contribute financially to	2 (28.6%)	3.7
Ability to attend to household chores	1 (20.0%)	4.0	Ability to travel	1 (14.3%)	4.3
Ability to contribute financially to household expenses	1 (20.0%)	2.2	Ability to fulfill family obligations	1 (14.3%)	3.6
**All 12 respondents answered questions relating to day-to-day life impact and retirement status.*					

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

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

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

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

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

- *"Cancelled weekend away with friends due to anxiety about being out-of-town and too far away from mother. Have not taken time to workout…Sleep pattern is minimal since eating habit has changed and has affected my quality of sleep."* (Child, Female 45-54, Not retired, Canada)
- *"The worst part is the stress and also "the unknown" about what will happen next, how long will the remission last...When treatment is underway, it takes over your life, always watching for bad side effects during the chemo and knowing how to best offer support...very emotionally and physically draining. Life sort of stops while all this is happening."* (Spouse/partner; Female; 65-74; retired; Canada)

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

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

- *"There were many days when my husband's mental state was such that I was subjected to shouting, being ignored and similar treatment, all due to drug side effects*." (Spouse/partner; Female; 65-74; Retired; Canada)
- *"No strength in mother's legs has presented safety and falling issues in house - strain to myself trying to assist lifting her"* (Child; Female; 45-54; Not retired, Canada)

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

LC noted that caregivers reported difficulties with "access" issues. The most commonly reported factors were financial burden and distance to drug. Some caregivers had to take time off work to assist in taking care of the patient (loss of income). Other caregivers reported the drug was difficult to access because they had to travel to a cancer centre far from home (travel to United States for a drug not available in Canada; travel to another province to receive drug; travel long distance from remote community). Below are quotes from caregiver respondents to illustrate the difficulties of accessing treatment:

- *"There were many additional expenses we had to cover: travel, sometimes accommodation, infusion charges, doctor and hospital fees, parking, etc…Since we are both retired and on pensions we suffered no loss of income but had a significant increase in costs, approximately $1,000 per month! Travel alone took an entire day when he had to be in the Buffalo clinic. The drug he was on is not available in Canada."* (Spouse/ partner; Female; 65-74; Retired; Canada)
- *"Have taken time off work - compassionate leave which has affected finances and ability to pay bills and going to declare bankruptcy."* (Child, Female 45-54, Not retired, Canada)

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

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Venetoclax

Expectations with Venetoclax

According LC, respondents seek access to new therapies that produce quick, favourable outcomes with relatively mild side effects compared to existing treatments. CLL and SLL patients want to transition from an era of chemotherapy to an era of targeted therapy with proven efficacy in treating a broad range of patients, including those who have the poorest prognostic factors and those who are of advanced age with existing co-morbidities.

CLLPAG indicated that chemotherapy is not without serious adverse effects. Venetoclax therapy carries risks of serious side effects as well, but patients who know they will not respond to other treatments because of their genetic profile are willing to tolerate those risks in the hope of having a treatment that extends their life. While the current gold standard drug therapy for CLL/SLL is fludarabine, cyclophosphamide, rituximab (FCR), CLLPAG submits that it is a toxic regimen that is known to be ineffective for certain genetic mutations of CLL such as del(17p). As such, venetoclax would provide a targeted therapy option for patients who have relapsed or are refractory to other therapies.

The following were key comments excerpted from the respondents:

- *"New and more targeted treatments bring patients hope that quality of life may be better while living with the disease and that life may be longer. Living with a Damocles sword hanging over life is very, very hard!"*
- *"More options provide more hope. Non-chemo treatments that lower the chances of a secondary fatal cancer are crucial to patients and their families."*
- *"Reduced side effects, greater tolerability ... chemo is like treating CLL with a tank, it takes out everything"*

LC respondents were asked on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) to rate the extent to which they would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their CLL or SLL. Twelve of the 29 respondents (41.4%) living in Canada who answered this question gave a rating of 8 or higher (rating average 6.3). Many 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. One respondent stated: "*"Because if I got my life back the side effects would be a reasonable trade off."* Another respondent indicated "*Debilitating side effects are a major concern with any new drug and should be minimal with the use of any new drug."*

LC respondents were asked to rate on a scale of 1 (Not important To Control) to 10 (Very Important To Control), how important it is for a new drug to be "able to control" specific aspects associated with their disease. The table below outlines the responses from the respondents.

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

CLLPAG respondents were asked to compare IV and oral drug treatment for CLL/SLL where 1 = little impact and 5 = severe impact.

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

CLLPAG found that oral treatment resulted in less impact than IV treatment in all areas except ability to tolerate full dose. CLLPAG noted that venetoclax is a daily oral medication; and therefore, a patient is responsible for ensuring proper usage. Proper education for haematologists for appropriate prophylactic medications and patient support programs would be needed.

Experience with Venetoclax

LC reported that 20 patient respondents had experience with venetoclax in the relapsed setting for CLL/SLL. Nine (45.0%) respondents indicated they had del(17p) and nine (45.0%) respondents indicated they did not. Two (10.0%) respondents did not know if they had del(17p). All respondents were asked: 1) when they began taking venetoclax, 2) are they still taking venetoclax, and 3) if they would recommend venetoclax to other patients with CLL/SLL based on their own personal experiences. Their responses appear in the table below. All of the 19 patient respondents who answered these questions recommend venetoclax (1 patient skipped question).

Start Date	Still Taking	Based on Your Personal Experience with Venetoclax Would You Recommend Venetoclax to Other Patients with CLL/SLL?
Feb 2012	Yes	*"Yes. It has stabilized my disease for over 4 years with few side effects. I have achieved better results on this drug than any other drug I have used."* (CLL; 17p deletion; Female; USA; 60; Previous treatments: rituxan single agent; rituxan + fenritinide; rituxan + HDMP; FCR)
Oct 2012	No	*"Yes. It has me in complete response now and have been that way after being off treatment for 10 months. It worked for me. I had to have surgery and chemo for lung cancer so I had to suspend taking venetoclax. I am currently CR for my CLL."* (CLL; 17p deletion; Male; 65-74; USA; Previous treatments: bendamustine; flubardine. Discontinued venetoclax in August 2015)
Nov 2013	No	*"Yes. It may control disease."* (CLL; Gender not specified; 65-74; USA; Previous treatments: FCR). Discontinued venetoclax in June 2015 due to disease progression.
Jan 2014	Yes	*"Yes. It has been beneficial without causing any bad side effects."* (CLL; Female; UK; ≥75 years; Previous treatment: camplan)
March 2014	Yes	*"Yes. No side effects, feel great, gave back my life."* (CLL; Female; 65-74; USA; Previous treatments: HDMP+R, campath subs, GS9973)
May 2014	Yes	*"Yes. It has extended my life. I thought it was quite possible that I wouldn't make it to the end of 2014 as my health was deteriorating fast. My QoL is now normal for a 56 year old. People who don't know my history are amazed when*

Start Date	Still Taking	Based on Your Personal Experience with Venetoclax Would You Recommend Venetoclax to Other Patients with CLL/SLL?
		I tell them I have advanced CLL. I have no idea what the future holds, but I have had over 2 years of very good quality of life that I would otherwise not have had." (CLL; 17p deletion; Male; 56; UK.; Previous treatments: FCR in 2004; BR in 2013)
June 2014	Yes	*"Yes. Virtually no side effects."* (CLL; 17p deletion; Male; 65-74; Australia; Previous treatments: FCR)
July 2014	Yes	*"Yes. I would recommend the treatment as the side effects are far less on this treatment than previous treatments that I have received."* (CLL; Male; 45-54; UK; Previous treatment: FCR)
Dec 2014	No	*"Yes, until I contracted pneumonia it seemed to be very successful."(*CLL; 17p deletion; Female; ≥75 years; USA; Previous treatment: R-CHOP; Discontinued venetoclax in June 2016 due to disease progression)
May 2015	Yes	*"Yes. No side effects. It works."* (CLL; 17p deletion; Male; 65-74; Belgium; Previous treatments: rituximab, chlorambucil)
June 2015	Yes	*"Yes. No side effects."* (CLL; Female; 55-64; USA; Previous treatments: FCR; ibrutinib)
Jan 2016	Yes	*"Yes. Feeling much better, sick less, improved energy. Excellent treatment option when others have failed"* (CLL; 17p deletion; Male; 55-64 USA; Previous treatments: FCR Lite, ofatumumab, ibrutinib)
Jan 2016	Yes	*"Yes. Low side effects and effective. More energy, able to fully engage in normal activity." (*SLL; Female; 55-64; USA; Previous treatments: bendamustine/rituxan for 6 cycles, ibrutinib)
Feb 2016	Yes	*"Yes. Venetoclax has prolonged my life expectancy and if patients with CLL can access this treatment before taking any other form of chemotherapy, then they will stand a better chance of survival I believe. It works and has no real side effects (thus far)."* (CLL; 17p deletion; Female; 55-64; UK; Previous treatments: chlorambucil; FCR; campath; ibrutinib)
March 2016	Yes	*"Yes. It caused a rapid marked decrease in the size of my abdomen which was dramatically enlarged because of bulky lymph nodes. The amount of CLL in my blood also rapidly decreased. There was a noticeable improvement in my fatigue level within a week of getting on the full 400 mg dose so that I could feel safe driving most of the time for the first time in several years. It is an amazing drug."* (SLL; Female; 55-64; USA; Previous treatments: Clinical trial of rituximab and Tru-016)
March 2016	Yes	*"Yes. Conventional chemotherapy is almost as bad as the disease in the way it hammers your immune system and causes---in many of us---peripheral neuropathy."* (CLL; Male; 65-74; USA; Previous treatments: FCR; ibrutinib)
June 2016	Yes	*"Yes. Better results less side effects."* (CLL; Male; 69; USA; Previous treatments: rituxan monotherapy; idelalisib + rituxan; ibrutinib)
June 2016	Yes	*"Yes. Most tolerable."* (CLL vs SLL status, gender and age not specified; Canada; Previous treatment: rituxan)
Oct 2015	Yes	*"It's a great drug. It goes right to the bone marrow. It may be the silver bullet. My only side effect that I have is a little constipation."* (CLL; Male; 66; Previous treatment: revlimid)

CLLPAG reported that six patients have experience with venetoclax.

CLLPAG respondents were asked "Which symptoms of CLL/SLL does venetoclax manage for you?"

The table below outline the responses from the respondents.

Symptom	% symptom was managed	# of respondents of 6
Increasing lymphocyte count	83.3	5
Enlarged lymph nodes	50.0	3
Night sweats	33.3	2
Enlarged spleen	66.7	4
Fatigue, lack of energy	50.0	3
Shortness of breath	16.7	1
Weight loss	16.7	1
Frequent infections	0.0	0
Fever	0.0	0
Did not manage any symptoms	16.7	1
Managed all of my symptoms	83.8	5

Similarly, LC respondents were asked on a scale from 1 (No Improvement) to 10 (Very Significant Improvement) to rate how much several symptoms associated with CLL/SLL have improved since starting treatment with venetoclax. Please refer to the table below for the responses.

Improvement in Symptoms	Rating ≥8 n (%)	Rating Average	Improvement in Symptoms	Rating ≥8 n (%)	Rating Average
Discomfort in left side (due to enlarged spleen) N=3	3 (100.0%)	9.67	Aches and pains, N=7	3 (42.9%)	7.57
Fever N=2	2 (100.0%)	9.50	Red blood cell counts (N=12)	6 (50.0%)	6.75
White blood cell counts N=13	10 (76.9%)	8.77	Infections N=9	4 (44.4%)	6.44
Enlarged lymph node(s) N=13	10 (76.9%)	8.46	Shortness of breath during normal activities N=10	5 (50.0%)	6.90
Night sweats N=7	6 (85.7%)	8.43	Platelet counts N=11	4 (36.4%)	6.09
Chills N=1	1 (100.0%)	8.00	Fatigue N=10	3 (30.0%)	6.30
Weight loss N=6	3 (50.0%)	7.83	Immunoglobulin levels N=10	2 (20.0%)	4.40
Not all patients experienced all symptoms. The number of patients who responded to each symptom is shown in the table as indicated by "N".					

LC respondents were asked on a scale of 1 - 10, with 1 being (Far Less Side Effects) and 10 being (Many More Effects), to rate how venetoclax compares, in terms of side effects, with other treatments they had taken for CLL/SLL. Eighteen (18) respondents answered this question; rating average was 1.4. 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 (n=7); neutropenia (n=2); low platelet counts (n=1); fatigue (n=1); acid reflux (n=1); cramps (n=1); constipation (n=1); mild headache (n=1). The side effect profile was easy to tolerate by most respondents. Five respondents reported they did not experience any side effects.

One respondent who has been taking venetoclax since May 2014 stated "*Neutropenia was a mild inconvenience as I needed filgrastim shots every 2 days initially, then less infrequently until I stopped after ~1 year.*" Another respondent who has been taking venetoclax since March 2016

stated "*Some fatigue during dose escalation.*"

CLLPAG also asked respondents on "Which of the following side effects of venetoclax have you experienced?" and "Which of the following side effects are you willing to tolerate?" The following were reported in the table below.

Venetoclax Side Effect	% (#) respondents who experienced side effect (6 total)	% (#) willing to tolerate side effect (6 total)
Fatigue	33.3% (2)	83.3% (5)
Diarrhea	33.3% (2)	83.3% (5)
Nausea	33.3% (2)	83.3% (5)
Respiratory Tract Infection/cough	16.7% (1)	83.3% (5)
Fever	00.0% (0)	83.3% (5)
Anemia or neutropenia	33.3% (2)	66.7% (4)
Tumour lysis syndrome	16.7% (1)	50.0% (3)
Viral reactivation	0% (0)	50.0% (3)
None of these	33.3% (2)	00.0% (0)

One respondent reported: "*Only side effect I get from taking ABT-199 was increased migraine activity, which has since been controlled and I have been migraine free for 4 months now. It probably would not have applied to anyone who did not normally get migraines.*"

Some respondents outside the survey have reported difficulty with swallowing pills.

LC respondents to the survey and interview were asked how venetoclax changed or is expected to change their long-term health and well-being. The table below outlines the responses from the respondents.

Long-Term Health or Well-Being (N=16; 4 skipped)	n(%)
Control my CLL/SLL and symptoms associated with CLL/SLL	15 (93.8%)
Improve my quality of life	13 (81.3%)
Allow me to live longer	12 (75.0%)
Improve my blood counts	12 (75.0%)
Bring about a remission	11 (68.8%)

Similarly, CLLPAG respondents were asked about their long-term health and well-being. Key comments from respondents included:

- "*Still early in trial but fatigue/energy has improved significantly. I have hope for a good future*"
- "*Kept me alive with hope that I may have a long remission so I can lead a normal life (apart from check ups at hospitals)*"
- "*I am optimistic it has the best chance of available drugs to save my life especially in combination with Ibrutinib and Gazyva*"
- "*Have my normal life back. No fatigue. Feel great*"
- "*if I did not have ABT-199 (venetoclax) I may not be here((p53 & 17p deletion).*"

LC respondents were asked, on a scale from 1 (Severely Negatively Impacted) to 10 (Normal Living), to rate their Quality of Life while having treatment with venetoclax. Fifteen respondents

answered this question. The rating average was 9.4. According to LC, venetoclax brought the majority of the respondents' disease under control and allowed them to have an improved quality of life. Below were the comments from the respondents:

- "*Immeasurably. Before taking ventoclax my bone marrow was >95% full of CLL. I was on regular transfusions for low haemoglobin, GCSF for low neutrophils and steroids for thrombocytopenia. My QoL was poor, working was difficult, walking any significant distance was problematic. Within 1 month of starting treatment these issues rapidly diminished and I feel that I now live a normal life*." (CLL; 17p deletion Male; 55-64; venetoclax since May 2014)
- "*I have aggressive CII. Most standard treatments I failed quickly. I was headed to a stem cell transplant when I was offered this drug in clinical trial. It has now been 4.5 years of taking 3 pills a day. I can't imagine where I'd be post SCT. I do know my QOL is far superior on this drug than any other option I had. I am 60 yoa. I hike, cycle, garden and live infection free*." (CLL; 17p deletion; Female; 60; USA; venetoclax since February 2012)
- "*No more night sweats, and energy level back to 100 percent. Can do anything I want now*." (CLL; Female; 65-74; USA; venetoclax since March 2014)

According to CLLPAG, 5/6 respondents indicated they needed to travel away from home as they could access venetoclax only through clinical trial. Length of time away from home ranged from one day to 3-6 months; as such, respondents are willing to travel to have access to this drug. It was reported that respondents have not paid for the drug itself but have incurred costs of tests and scans required by the trials, as well as travelling and accommodation, which could costs up to $10K.

3.3 Additional Information

N/A

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- Lack of phase 3 comparative data
- Clarity of treatment population

Economic factors:

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

Please see below for more details and other factors.

4.1 Factors Related to Comparators

The current treatments for CLL patients who have received at least one prior therapy is fludarabine/cyclophosphamide/rituximab (FCR) and ibrutinib. At the time of the PAG input, idelalisib/rituximab is not yet funded in any province for relapsed CLL.

PAG noted that this submission is based on a phase 2 single arm trial and is seeking information from phase 3 trials comparing venetoclax to ibrutinib or to idelalisib/rituximab.

4.2 Factors Related to Patient Population

PAG is seeking clarity on the patient population who would be eligible for treatment with venetoclax. It is unclear where the place of therapy venetoclax would fit – whether venetoclax would be an alternate for patients who are ineligible for ibrutinib and idelalisib/rituximab or whether it would be an additional line of therapy following relapse with ibrutinib or idelalisib/rituximab. PAG is seeking guidance on the sequencing of recently available therapies and upcoming therapies for CLL.

PAG indicated that as another oral option, there may be requests to use venetoclax upfront but there are ongoing trials for previously untreated CLL for future consideration.

PAG also indicated that there may be requests for use of venetoclax in combination with anti-CD20+ therapies, given the ongoing trials with combination therapy. PAG noted that combination therapy is out of scope of the current review for monotherapy.

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 if all strengths are dispensed concurrently. However, PAG

identified that the blister packaging for dose initiation available in the United States would be an enabler to implementation, if also available in Canada.

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 del(17p) 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.

There are some concerns for drug wastage if dose adjustments are required prior to patients finishing their existing supply of venetoclax. However, PAG noted that this could be minimized by dispensing smaller quantities.

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 and in some jurisdictions, 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

At the time of the PAG input, the packaging format was unknown. PAG noted that the starter package and the unit dose packaging available in the United States is convenient for patients while minimizing exposure to healthcare professionals and caregivers. This would be an enabler to implementation if the same packaging format is available in Canada.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Input from two clinicians on venetoclax for relapsed/refractory CLL with del(17p) was received: one submission from an individual oncologist and one joint submission from five oncologists.

Overall, the clinicians providing input identified that venetoclax provides another treatment option for CLL patients with (chromosome 17p13.1 deletion: del(17p))and who have failed all other treatments or cannot tolerate or have contraindications other available treatments. They believe that venetoclax is superior to any other available therapy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del(17p), but noted that there are no direct comparison data to suggest whether venetoclax is superior or equivalent to the novel kinase inhibitors (ibrutinib and idelalisib). The clinicians providing input indicated that adverse events are manageable but that incidence of adverse events in the real world are yet to be seen. It was also identified that patients with high risk for tumour lysis syndrome would need to be treated at tertiary care centres.

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

5.1 Current Treatment(s) for this Chronic Lymphocytic Leukemia

The clinicians providing input identified that there is no standard of care for this high risk population and that novel agents such as ibrutinib and idelalisib/rituximab are recently available and provide responses but are not curative. The clinicians providing input noted that allogeneic haematopoietic stem cell transplantation is recommended in younger patients (usually less than 65 years of age) though these are a small minority of patients, and allogeneic transplant is a highly toxic procedure.

5.2 Eligible Patient Population

The oncologist providing input stated that "novel therapeutics has clearly increased my capacity to treat patients and prolong their progression free survival and improve their quality of life. This novel agent is mechanistically different from any other class of agents. BCL2 remains an important target in CLL which has previously not been "druggable". These patients are functional elderly patients for the most part, with a few younger transplant eligible patients".

The clinician group input noted that "While CLL is a common hematological malignancy, those with a del(17p) are rare especially in patients who have few prior treatments. The frequency of del(17p) increases with multiple relapses/prior treatments where it can become more prevalent. The other novel agents (ibrutinib in particular), which is currently funded in most provinces, would generally be the first choice for CLL patients with del(17p) because of the greater experience with this drug."

5.3 Identify Key Benefits and Harms with Venetoclax

The oncologist providing input firmly believes this agent is an added benefit to patients with no other options and noted that "venetoclax is a BCL2 inhibitor that is given orally in a step-wise fashion. Excellent tumour lysis guides have been developed to identify high and low risk individuals that allow for outpatient and potential inpatient treatment. This drug will be essential for those were unable to tolerate tyrosine kinase inhibitors or progress. The sequencing may dependant on cost. It would also be of value to the 17p deleted patients as we do know that they will progress on treatment. In those that are ineligible for transplant this is another viable option. I currently have some young patients

that are in this situation, who would benefit from access to this agent. The data that has been provided supports the clinical benefit of a novel agent with a novel mechanism of action with an acceptable toxicity profile. From my experience the toxicities of the TKI were under estimated when applied to the general population outside of clinical trial and thus the real world toxicities of venetoclax are yet to be determined."

The clinician group input stated that "Venetoclax offers a treatment option for those patients that have RR CLL who have del(17p) or that have progressed or are unsuitable for BCR inhibition. The major benefit is the reported high response rates and durable responses in a patient population with few or no other effective treatment options. Venetoclax is a highly effective agent, leading to deep molecular remissions. The major advantage to this agent over other novel agents is that it can potentially be discontinued after a deep remission is obtained (whereas the kinase inhibitors need to be continued indefinitely). The toxicities are also generally very manageable for experienced hematologists (the most common being neutropenia and/or infections). However, tumour lysis syndrome (TLS), which is not typically seen in this patient population is a potential complication and provides an obstacle to the use of the therapy in non-academic centres where there is less experience managing and preventing TLS. Patients at high risk of TLS should be treated with venetoclax at a tertiary care centre or by an experienced hematologist."

5.4 Advantages of Venetoclax Over Current Treatments

The oncologist providing input noted that "relapsed/refractory patients on oral tyrosine kinase inhibitors experience a significant number of toxicities on treatment. It is also clear that those patients with high risk disease fludarabine resistance, 17p del and 11q loss, have a shorter progression free survival and currently do not have other good treatment options that have tolerable side effects".

The clinician group providing input indicated that "Venetoclax is superior to any other available therapy for patients who have failed a kinase inhibitor (ibrutinib or idelalisib), including patients with and without del(17p). For patients with del(17p) who have not previously been treated with a kinase inhibitor, it is unclear if this drug is superior or equivalent to the novel kinase inhibitors (ibrutinib and idelalisib). The results suggest superiority because of high complete remission rates and levels of minimal residual disease negativity, but no head to head studies have been performed or reported.

The recently reported infectious toxicity concerns with idelalisib and rituximab (and the limited responses and short durability of treatment with idelalisib after ibrutinib failure/discontinuation) suggest that venetoclax is superior to considering the use of the alternate kinase inhibitor after failure of a first kinase inhibitor (ibrutinib or idelalisib).

The highest unmet need would be for any patient with relapsed/refractory CLL who has progressed or is intolerant of a kinase inhibitor (most commonly, ibrutinib), though any patient with relapsed CLL and del(17p) would also greatly benefit"

5.5 Sequencing and Priority of Treatments with Venetoclax

The oncologist providing input indicated that venetoclax would be added as another line of therapy for those patients who fail other lines of therapy or who do not tolerate them.

The clinician group providing input noted that "Venetoclax is currently being investigated in all lines of therapy (including frontline) and appears to lead to more and deeper remissions in less refractory patients. Thus, the drug has great value at any line of

therapy. However, based on the currently published data, it would be appropriate to reserve this therapy for any patient with del(17p) CLL, AND any patient who has progressed on or been intolerant to a kinase inhibitor (because those patients are as high risk as del(17p) patients and have no other effective treatment options). Evidence is clear that TP53 mutation is as bad as del(17p), but this test is not available in Canada. Most patients with fludarabine-refractoriness without del(17p) have TP53 mutations and this population has a similar short survival and poor response to chemotherapy as del(17p) patients.

If venetoclax were accessible to any relapsed/refractory CLL patient or only in those with del(17p), I would see it replacing the use of ibrutinib in certain patients (those at greatest risk from atrial fibrillation or bleeding, which are the major toxicities with ibrutinib). However, most refractory patients and/or those with del(17p) would likely still be treated first with ibrutinib and only with venetoclax after failure or intolerance to ibrutinib (a population of patients who currently have NO treatment options and short expected survival of only 3 months)."

5.6 Companion Diagnostic Testing

No companion diagnostic test is required prior to starting treatment with venetoclax. However, the clinician group providing input indicated that CT scanning would be required to measure the largest lymph node size for determining tumour lysis syndrome risk and that CT scanning is not currently a routine test in CLL and would be a specific and special consideration for venetoclax.

5.7 Additional Information

No additional information provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of venetoclax (Venclexta) as monotherapy for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior systemic regimen.

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 7 and 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 relapsed or refractory CLL with (chromosome 17p13.1 deletion: del(17p))who have had at least one prior systemic regimen	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 Chemotherapies include: • Single agent Ibrutinib • Idelalisib + rituximab • Fludarabine + cyclophosphamide + rituximab (FCR) • Allogeneic stem cell transplantation • Fludarabine-based combination therapies • Bendamustine-based combination therapies	Primary • **HRQoL** • Overall survival • **Overall response rate (CR and PR)** • 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)*

[†]A mixed design was defined as a trial with a dose-escalation phase followed by an efficacy-determining phase in which the study intervention was administered at the same dose and schedule to all patients (generally the maximum tolerated dose determined in the dose-escalation phase).

6.2.2 Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (June 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was: Venetoclax.

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 were searched manually, limited to the past five years, for conference years not available in Embase at the time of the database search. 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.

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 3, 2016.

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

A data audit was conducted by another member of the pCODR Review Team.

6.2.5 Data Analysis

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

6.2.6 Writing of the Review Report

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

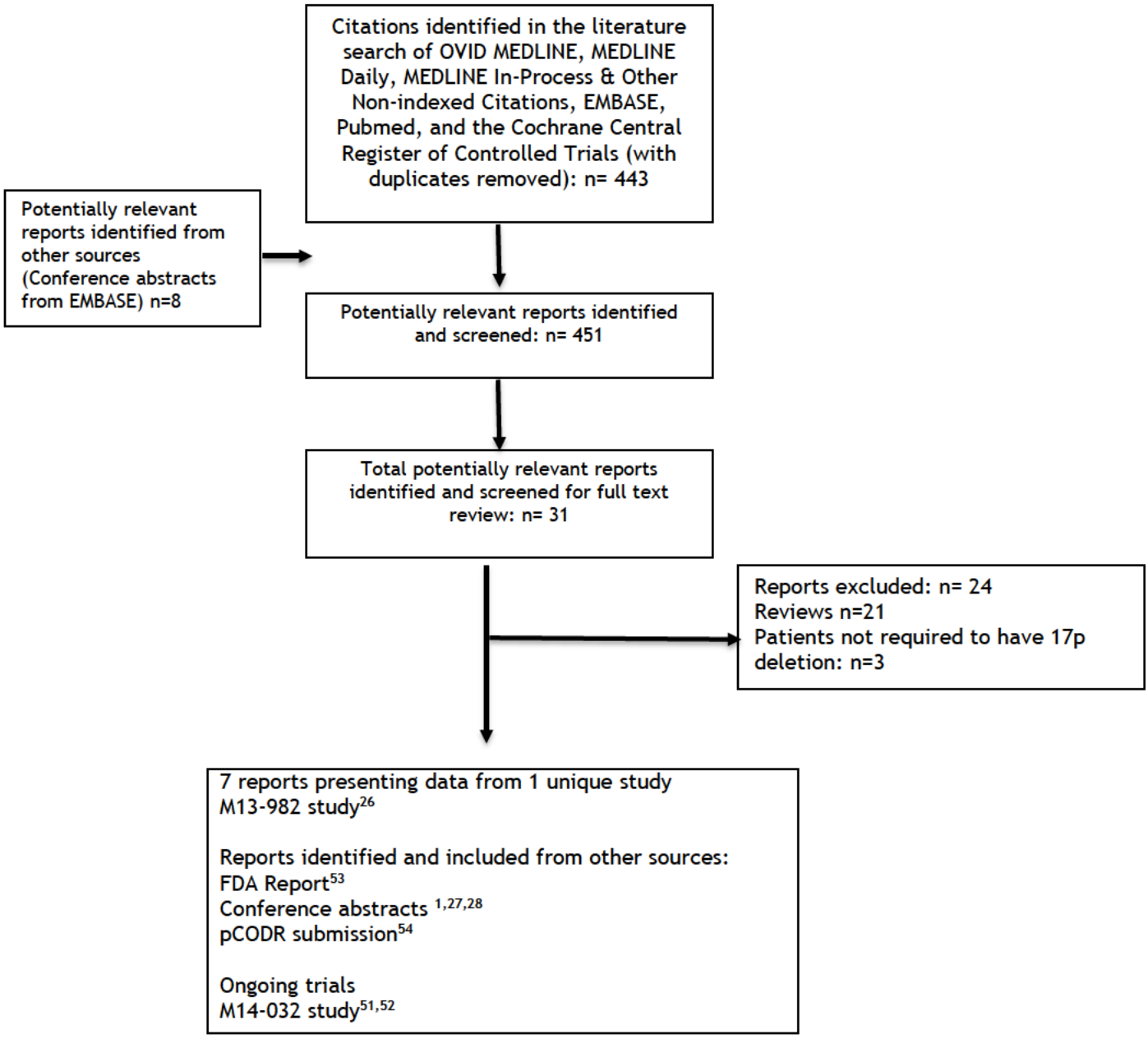
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 443 potentially relevant reports identified, 1 study[26] and 3 papers reporting results pertaining to said study were included in the pCODR systematic review. [1,27,28]. Studies were excluded because they did not require patients to have del(17p) as part of their eligibility criteria, they were review or opinion articles. [1,2,29-48] One Phase I study did not meet the eligibility criteria for this systematic review since patients were not all required to have del(17p).[20,49,50] While including the results of a post-hoc analysis of the subset of patients who had the del(17p) was considered, it was ultimately decided to exclude this study since patients did not receive the same dose escalation regime.[20,49,50] Due to the paucity of evidence in this specific patient population, interim results from an ongoing study, however, are being considered and included in this systematic review.[51,52]

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the Stilgenbauer et al.[26] study were also obtained through requests to the Submitter by pCODR[55]

6.3.2 Summary of Included Studies

One single-arm Phase II, multicenter study was identified that met the eligibility criteria for this systematic review. The key characteristics of this trial are summarized in Table 4 and specific features on trial quality are summarized in **Table 5**. Detailed Trial Characteristics

Table 4. Summary of trial characteristics of the included trial of venetoclax in patients with relapsed or refractory chronic lymphocytic leukemia with del(17p).

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Clinical Trial NCT01889186[56] Multicenter, international, single arm, open-label Phase II trial N= 107 pts were enrolled and included in the analysis Multicenter (38 sites in 7 countries) Patient Enrolment: May 2013-June 2014 N enrolled= 107 Data cut-off date: April 30, 2015 Final Analysis Date: August 2016 Funded by AbbVie and Genentech	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • Diagnosed with relapsed or refractory[1] CLL harbouring del(17p) in >7% of cells in peripheral blood[2] • ECOG of 0, 1 or 2 • Adequate bone marrow function[3] • Creatinine clearance ≥50mL/min • Adequate coagulation and hepatic function <u>Key Exclusion Criteria:</u> • Previous allogeneic stem cell transplantation • Richter's transformation • Uncontrolled autoimmune cytopenias or cancers • Systemic infection • Excluded drugs during venetoclax administration were CYP3A inhibitors, warfarin, potent CYP3A inducers, steroid treatment with anti-neoplastic intent, any anticancer treatments including chemotherapy, radiotherapy, or other investigational treatment (within 14d), and biological agents with anti-neoplastic intent (within 30d)	Venetoclax once daily, orally, via step-wise weekly dose ramp-up from starting dose of 20mg to final 400mg daily dose (20, 50, 100, 200, 400 mg) over 4-5 weeks Once at 400mg dose, pts were given daily continuous dosing until disease progression, unacceptable toxic effects, or discontinuation for any other reason No comparators were used in this study	<u>Primary:</u> • Activity of Venetoclax monotherapy as measured by OR[4] <u>Secondary:</u> • Proportion of patients with CR and PR • Safety • Time to first response[5] • Time to 50% reduction in absolute lymphocyte count[6] • Duration of overall response[7] • Progression-free survival[8] • Overall survival[9] • Event-free survival[10] • Time to progression[11] • Proportion of pts proceeding to allogeneic stem cell transplantation <u>Exploratory</u> • MRD • PK

<u>Abbreviations:</u> CLL - chronic lymphocytic leukemia; CR - complete remission; d - day(s); ECOG - Eastern Cooperative Oncology Group; MRD - minimal residual disease; n - number; OR - overall response; PK - pharmacokinetics; PR - partial remission; pts - patients; ref - refractory; rel - relapsed; del(17p): chromosome 17p13.1 deletion

<u>Notes:</u>

1 - defined as relapsed or refractory after receiving at least one previous line of treatment (defined as completing at least 2 cycles of treatment for a given treatment)

2 - assessed by a central laboratory with Vysis fluorescence in-situ hybridisation (FISH) kit

3 - defined as absolute neutrophil count ≥1000 cells/μL; platelet count ≥40000 cells/μL; haemoglobin ≥80g/L

4 - defined as partial remission or higher

5 - defined as time from first dose to first response

6 - defined as time from first dose to 50% reduction

7 - defined as the number of days from the date of first response to the earliest recurrence or disease progression per independent review committee assessment
8 - defined as the number of days from the date of first dose to the date of earliest disease progression or death
9 - defined as the number of days from the date of first dose to the date of death for all dosed patients
10 - defined as the number of days from the date of first dose to the date of earliest disease progression, death, or start of a new anti-leukaemic treatment
11 - defined as the number of days from the date of first dose to the date of earliest disease progression

Table 5: Select quality characteristics of the included M13-982 study of venetoclax in patients with chronic lymphocytic leukemia with del(17p).

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Blinding	ITT Analysis	Ethics Approval
NCT01889186 (M13-982)	Venetoclax No comparator	ORR	70 pts required to provide 90% or higher power (at two-sided alpha of 5%) to reject the null hypothesis of 40% of patients achieving an overall response[1]	107 pts enrolled and evaluated for efficacy outcomes in the main cohort 51 additional patients enrolled and evaluated in safety expansion of study (n=158 for safety evaluation)	Trial not randomized	Yes (IRC)	Yes	Yes

Abbreviations: IRC - independent review committee; NR - not reported; ORR - overall response rate; pts - patients;
Notes: 1 - The initial plan was to enrol 100 subjects in the main cohort to assess safety and efficacy albeit for the efficacy analysis, 70 subjects provided at least 90% power (at two-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favour of the alternative hypothesis of 60% ORR. While a ORR over a standard rate of 40% would be considered clinically meaningful, a suggestion by the FDA that a report containing final efficacy data on at least 100 patients would strengthen the submission led to a final sample size of 107 patients.
2 - sample size calculations are for the whole population, which was not limited to patients with del(17p)

a) Trials

One phase II study, M13-982, met the inclusion criteria of this systematic review. This study is no longer recruiting patients but follow up is ongoing with some patients still receiving treatment. M13-982 is a phase II, interventional, single-arm study in which patients with a confirmed diagnosis of chronic lymphocytic leukemia (CLL) harbouring the (chromosome 17p13.1 deletion: del(17p))who had relapsed or were refractory after receiving at least one previous line of treatment, were administered venetoclax monotherapy at an oral dose of 400mg daily. 17p status was evaluated by a central laboratory using Vysis fluorescence in-situ hybridisation (FISH). Patients were considered to have relapsed or been refractory after receiving at least one line of treatment, in which at least two cycles of treatment were administered for a given treatment. The focus was to evaluate the safety and efficacy of venetoclax in this patient population. The primary outcome to be assessed was the overall response rate.

The M13-982 study is sponsored by AbbVie and Genentech. It is a multi-centered trial taking place primarily at 38 sites across the United States and Europe. The study was designed to enroll approximately 100 patients in the main cohort (which was assessed for efficacy and safety) and 50 patients in the expansion cohort (which was assessed for safety only).

b) Populations

In the M13-982 study, a total of 107 patients were enrolled in the main study cohort and were evaluated for efficacy and safety. This group includes patients who have completed the scheduled 36-week assessment, have progressed prior to the 36-week disease assessment, or have discontinued the study drug for any reason. An expansion cohort of 51 patients was also assessed in the safety analysis, bringing the total number of patients to n=158. It should be noted, however, that there was a discrepancy in the number of patients in whom 17p del was detected by the investigator versus by a central laboratory. By central lab, the main cohort consisted of 106 patients with 17p del and 42 patients with 17p del comprised the safety expansion cohort bringing the total number of patients with 17p del to n=148. A greater proportion of men were enrolled in this study (65%) and most patients were Caucasian (97%) (Table 6). Patients remained on the study until disease progression or unacceptable toxicity, and patients could continue on venetoclax if they were still experiencing a benefit for up to two years.

The baseline disease status of patients with del(17p) in CLL in the M13-982 study and treatment history of these patients is presented in Tables 7 and 8.

b) Interventions

Details of the dosing and administration schedule of venetoclax in the M13-982 study can be found in Table 4. Based on data from the ongoing first-in-human study M12-175,[20] the dose of 400mg was selected. To mitigate the risk of tumour lysis syndrome (TLS), a 4-5-week dose-escalation design was used with patients starting on venetoclax at 20mg followed by weekly increases (20mg, 50mg, 100mg, 200mg, 400mg) until the target dose of 400mg was reached. Patients were carefully monitored during this phase for TLS, and any changes that increased risk were immediately addressed (2). A risk-based management plan was developed for TLS prophylaxis and additional prophylactic measures (such as Day 1 hospitalization, oral hydration, and use of uric acid reducers) were also employed as indicated by their risk category. Low, medium and high TLS risk categories were defined as follows:

- Low: requires all lymph nodes all <5cm AND ALC <25x10^9/L

- Medium: any LN ≥5cm to <10cm OR ALC ≥25x10^9/L
- High: any LN ≥10cm OR ALC ≥25x10^9/L AND any LN ≥5cm.

Patients were given continuous dosing of 400mg daily until disease progression or discontinuation for another reason to gradually reduce tumour bulk thereby reducing the risk of TLS. Dose reduction guidelines for neutropenia and discontinuation guidelines are described elsewhere.[53] Physical exams, vital signs, and ECOG performance status were assessed upon screening, on Day 1 of Weeks 1-5, Week 8, then every 4 weeks to week 36, and then every 12 weeks thereafter, at the final visit, and a safety check was conducted 30 days after the final visit. Laboratory tests included blood chemistry and hematology, a coagulation panel, urinalysis, quantitative immunoglobulins, and lymphocyte enumeration, which were evaluated according to the schedule outlined elsewhere.[53] Additional testing included electrocardiogram, left ventricular ejection fraction, and disease assessments, which comprised: clinical laboratory values (hematology) and physical exam, CT or MRI of the neck, chest, abdomen, and pelvis, bone marrow aspirate or biopsy, and MRD assessment by flow cytometry.

Patients were assessed for safety throughout the study with adverse event monitoring and laboratory assessments. Minimal residual disease (MRD) was measured in the peripheral blood and bone marrow using standardized procedures, with MRD negativity defined as fewer than one CLL cell in 10,000 nucleated cells. Efficacy was assessed at 2, 4, 6, 9, and 12 months and then every 3 months. Long term follow-up will be conducted for all patients at 6 to 12 month intervals until 5 years.

Table 6. Baseline demographics and characteristics of patients in the M13-982 study.

Characteristic	M13-982		
	Treatment Group n=148		Total N=148 n (%)
	Main Cohort n=106 n (%)	Safety Expansion n=42, n (%)	
Age			
Median (range) age, y	67.0 (37-83)	67.0 (29-83)	67 (29-83)
Mean (SD)	65.5 (9.7)	65.4 (10.6)	65.5 (10.0)
Groups			
< 65	46 (43.4)	17 (40.5)	63 (42.6)
≥ 65	60 (56.6)	25 (59.5)	85 (57.4)
Sex			
Male, n (%)	69 (65.1)	22 (52.4)	91 (61.5)
Female	37 (34.9)	20 (47.6)	57 (38.5)
Race			
Caucasian	102 (97.1)	40 (97.6)	142 (97.3)
Black or African American	3 (2.9)	1 (2.4)	4 (2.7)
Asian	0	0	0
Other[1]	1 (0.9)	1 (2.4)	2 (1.4)
Ethnicity			
Hispanic	0	1 (2.4)	1 (0.7)
No ethnicity	105 (99.1)	40 (97.6)	145 (99.3)
Missing	1 (0.9)	1 (2.4)	2 (1.4)
Region			
United States	17 (16.0)	18 (42.9)	35 (23.6)
Rest of the World[3]	89 (84.0)	29 (69.0)	118 (79.7)
Canada	1 (0.9)	4 (9.5)	5 (3.4)

Europe	79 (74.5)	20 (47.6)	99 (66.9)

Notes: 1 - race data missing in 2 patients, both enrolled in France.
2 - data on two patients were reported as Hispanic; all other patients were not reported.
3 - no patients were enrolled in South America, Asia, or Africa.
Abbreviations: n = number; SD - standard deviation; y = years

Table 7. Baseline disease status of patients in the M13-982 study.

Characteristic	Treatment Group n=148		Total n=148 n (%)
	Main Cohort n=106 n (%)	Safety Expansion n=42 n (%)	
ECOG performance status, n (%)			
0-1	97 (91.5)	40 (95.2)	137 (92.6)
2	9 (8.5)	2 (4.8)	11 (7.4)
Rai stage at study entry, n (%)			
Stage III	3 (2.8)	2 (4.8)	5 (3.4)
Stage IV	12 (11.3)	2 (4.8)	14 (9.5)
Other	32 (30.2)	18 (42.9)	50 (33.8)
Rai stage missing	59 (55.7)	20 (47.6)	79 (53.3)
Binet stage at study entry, n (%)			
Stage A-B	59 (55.7)	14 (33.3)	73 (49.3)
Stage C	18 (17.0)	3 (7.1)	21 (14.2)
Missing	29 (27.4)	25 (59.5)	54 (36.5)
Disease-related complications, n (%)			
Neutropenia	24 (22.4)		
Anaemia	22 (20.6)	NR	NR
Thrombocytopenia	16 (15.0)		
Absolute lymphocyte count, n (%)			
≥ 25 x 10^9 per L	54 (50.9)	20 (47.6)	74 (50.0)
< 25 x 10^9 per L	52 (49.1)	22 (52.4)	74 (50.0)
Median (x10^9)	25.8 (7.9-89.9)	NR	NR
Bulky disease, n (%)			
One or more nodes ≥ 5cm	56 (52.8)	14 (33.3)	70 (47.3)
Lymph nodes < 5cm	50 (47.2)	28 (66.7)	78 (52.7)
Tumour lysis syndrome risk category, n (%)			
Low	19 (17.9)	16 (38.1)	35 (23.6)
Medium	43 (40.6)	13 (31.0)	56 (37.8)
High	44 (41.5)	13 (31.0)	57 (38.5)
TP53 mutation, n (%)			
Yes	61 (57.5)	28 (66.7)	89 (60.1)
No	17 (16.0)	6 (14.3)	23 (15.5)
Indeterminate	6 (5.7)	1 (2.4)	7 (4.7)
Missing	22 (20.8)	7 (16.7)	29 (19.6)
IGHV mutation, n (%)			
Yes	8 (7.5)	5 (11.9)	13 (8.8)
No	28 (26.4)	14 (33.3)	42 (28.4)
Missing	70 (66.0)	23 (54.8)	93 (62.8)
Serum ß-2 microglobulin, n (%)			
< 3 mg/L	3 (2.8)	6 (14.3	9 (6.1)
≥ 3 mg/L	14 (13.2)	8 (19.0)	22 (14.9)
Missing	89 (84.0)	28 (66.7)	117 (79.1)
11q deletion, n (%)			

Deleted	20 (18.9)	3 (7.1)	23 (15.5)
Not deleted	36 (34.0)	27 (64.3)	63 (42.6)
Indeterminate	25 (23.6)	4 (9.5)	29 (19.6)
Missing	25 (23.6)	8 (19.0)	33(22.3)
Abbreviations: n = number			

Table 8. Treatment history of patients on venetoclax in the M13-982 study.		
Characteristic	***Main cohort (n=107)***	***Safety Expansion (n=38)***
Median (range) time since diagnosis, months	79.4 (1.2-385.6)	70.9 (5.6-222.8)
Median (range) n of previous treatments	2 (1-10)	2 (1-6)
Prior Therapies, n (%)		
Bendamustine	54 (50.5)	7 (18.4)
Fludarabine	78 (72.9)	13 (34.2)
Idelalisib	1 (0.9)	1 (2.6)
Ibrutinib	3 (2.8)	5 (13.2)
Other B-cell receptor inhibitors	1 (0.9)	NA
Prior Therapy to Which Disease was Refractory[1], n (%)		
Bendamustine	38 (35.5)	NA
Fludarabine	34 (31.8)	7 (18.4)
Bendamustine or Fludarabine	62 (57.9)	NA
Abbreviations: n = number; NA - not available; y - year(s) 1 - Refractory status was defined as no response or disease progression within 6 months of treatment; ten patients were refractory to both fludarabine and bendamustine.		

c) *Patient Disposition*

The M13-982 trial enrolled 145 patients with CLL harbouring the del(17p) (which affects the tumour suppressor gene TP53), in whom responses to chemoimmunotherapy are generally poor. The first 107 patients represented the main study cohort. It was determined after treatment initiation that one patient did not have the del(17p) by FISH, but all 107 patients were included in the analysis. An additional cohort of 51 patients were added to the safety analysis bringing the total number of patients to n=158.

As stated in the FDA report,[53] at the time of data cut-off 103 patients (71%), 65% from the main cohort, continued on treatment while 42 (30%) patients overall (34% in main cohort) had discontinued. The most frequent reason for discontinuation was due to progressive disease. It should be noted that the full report by Stilgenbauer states that 18 out of the 107 patients enrolled died (data cut-off April 30, 2015) and by the second interim analysis (August 2016) there were 34 and 6 deaths in the main and safety cohorts, respectively. The median duration of treatment was 12.1 months (IQR, 10.1-14.2 months). Further details on patient disposition can be seen in Table 9.

Table 9. Disposition of CLL patients in the M13-982 study.[1]			
Disposition	**Main cohort n=107**	**Safety expansion cohort n=51**	**Total n=158**
Ongoing treatment (n, %)	45 (42.1)	34 (66.7)	79 (50.0)

Discontinued treatment (n, %)[2]	62 (57.9)	17 (33.3)	79 (50.0)
Progressive disease	29 (27.1)	6 (11.8)	35 (22.2)
Adverse event(s) Death[3]	30 (28.0) 11 (10.3)	6 (11.8)	36 (22.8)
Withdrew consent	3 (2.8)	2 (3.9)	5 (3.2)
Noncompliance	1 (0.9)	0	1 (0.6)
Stem cell transplantation	3 (2.8)	1 (2.0)	4 (2.5)

Notes: [1] - table includes all treated subjects, which includes 1 patient in main cohort and 3 patients in safety expansion cohort who did not harbour 17p del
[2] - There were 18 deaths reported in the M13-982 study. Eleven patients died within 30 days of the last dose of venetoclax
[3] - seven patients died due to disease progression and 4 due to stroke, liver derangement, septic shock, and cardiorespiratory insufficiency. None of these deaths were considered treatment related. Seven additional patients died due to progressive disease beyond 30 days from discontinuation of venetoclax.

d) *Limitations/Sources of Bias*

The M13-982 trial by Stilgenbauer and colleagues[26] is single-arm non-randomized open-label trial in which neither participants nor investigators in the trial were blinded, and as such, are at risk for a number of different 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. To mitigate the impact of this bias however, the investigators used a blinded independent review committee (IRC) to evaluate responses using standardized criteria, in an unbiased manner. However, the study investigators also did their own assessments of efficacy and compared their assessments with those of the IRC in their publication of the results (21). To reduce the possibility of being influenced by a biased assessment, it may have been more appropriate to publish solely the assessments as per the IRC. Based on the FDA report, the discordance in the IRC and investigator assessments of response rates may be explained by differences in the interpretation of splenomegaly and hepatomegaly, which may have been affected by subjectivity in the assessment of the CT scans. The single-arm non-randomized design also makes interpreting the efficacy and safety events attributable to venetoclax challenging, since all patients received the same treatment.

The M13-982 study is a non-comparative study and as such the comparative efficacy of venetoclax cannot be determined compared to currently available treatment options.

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 these data reported by Wierda[1,28] are *interim* data that included assessments only up to Week 24 (Week 48 data were not reported) which may not present an accurate picture of patients' experiences with venetoclax for a prolonged period of time. Additionally, since study M13-982 was single arm, the comparative impact of venetoclax on patient's quality of life remains unknown.

For the safety evaluation, it is important to note that since the data come from a single-arm study (including aggregate data from the three trials), 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 would have been important.

Overall, the results of the M13-982 trial are limited by 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 harbour the del(17p) 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,[3], it is unclear whether or not the outcomes observed with venetoclax will be consistent in a randomised controlled trial.

Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Primary Outcome - Overall Response Rate

Relevant terms related to response (CR, CRi, nPR, PR, PD, and SD) were used as per the 2008 Modified IWCLL NCI-WG Guidelines for Tumour Response. In the M13-982 study, overall response rate was assessed both by independent review committee (IRC) and by the trial investigators. While there was some discordance between these assessments, the point estimate of ORR by both IRC and investigator assessments were both above 70% (79.4 and 73.8, respectively). Of the 85/107 patients who responded to venetoclax therapy, 8 (8%) achieved complete remission (CR) or complete remission with incomplete recovery of blood counts (CRi). There was a slight discrepancy between IRC and investigator assessment; with CRi achieved by 2 patients per IRC assessment and 3 patients per investigator assessment. Partial remissions were achieved by 69% (n=74) of patients with 3% achieving nodular partial remission (Table 10).

An additional analysis was performed to determine whether patients' age influenced efficacy. By independent review, in the 61 patients in the age ≥65 cohort, the ORR was 74% (45/61, 95% CI 60.9, 84.2). Compared with the <65 cohort, whose ORR was 87% (40/46, 95% CI 73.7, 95.1) it would seem that age is an important factor.

In an effort to determine whether Rai and Binet stage and age had an impact on efficacy an additional analysis combining patients with stage III/IV Rai and Binet stage and comparing those patients ≥65 years with those <65 years was conducted. In the ≥65 year cohort, an ORR of 73.8% (45/61, 95% CI 60.9, 84.2) was detected. The ORR was somewhat higher in the <65 year group with 81.0% (34/42, 95% CI 65.9, 91.4).

Secondary and Other Relevant Outcomes

Since patient follow-up is ongoing in the M13-982 study, a number of planned secondary outcomes, including progression-free survival, overall survival, median duration of response, and event-free survival are not yet evaluable. As per IRC assessment, an estimated durable response rate (Kaplan-Meier) at 12 months was 84.7% (95% CI: 74.5, 91.0). This measure was evaluated in 85 patients in the main cohort who had a recorded response (CR, CRi, nPR, or PR) (2). For the main cohort of patients, the median duration of exposure to venetoclax was 22.1 months (range, 0-34 months). Based on a 12.1 month follow up, as reported in

the main publication IRC assessment for PFS rate was 72% (95% CI 61.8-79.8) and the 12 month OS rate was 86.7% 95% CI 78.6-91.9).

Minimal Residual Disease (MRD) Negativity

Forty-five patients who achieved a CR, CRi, nPR, or PR with lymph nodes <2cm had an evaluable MRD assessment as per protocol by flow cytometry. Of the 45 evaluable MRD samples, 18 (40%) were MRD negative in the peripheral blood (7 CR/CRi as per investigator evaluation and the remaining were PR). Ten of the 18 patients also had bone marrow MRD assessments, of which 6 were MRD negative. Of note, the MRD negative rate based on the total enrolled patients in this study was 17% (18/107). The median time to achieve MRD negativity in peripheral blood was 8.8 months (IQR 4.4-10.8).

Table 10. Efficacy outcomes in patients with CLL harbouring del(17p) in the M13-982 study.[26]

	Main cohort patients with 17p del in CLL treated with venetoclax (n=107)
ORR (%) (95% CI %)	85 (79.4) (70.5, 86.6)
CR rate, n (%) (CR/CRi)	8 (7.5) (6/2)
PR rate, n (%) (nPR)	74 (69.2) 3 (2.8)
No response	22 (20.6)
DOR, months (median, range)	Not reached
PFS (median, range) 12 month PFS rate	Not reached 72% (95% CI 61.8-79.8)
EFS	Not reached
TTP	Not reached
TTR, median (IQR), months	0.8 (0.7-1.7)
Time to 50% reduction in ALC	NR
% to HSCT	NR
Follow up, months (median, range)	NR
OS (median, range) 12 month OS rate	Not reached 86.7% 95% CI 78.6-91.9)
TTNT	NR
Rate of MRD negativity, n(%)	18 (16.8)

Abbreviations: ALC - absolute lymphocyte count; CI = confidence interval; CR = complete remission; CRi - complete remission with inadequate marrow recovery; DOR = duration of response; EFS - event-free survival; HSCT - stem cell transplant; MRD - minimal residual disease; nPR - nodular partial response; NR - not reported; ORR = overall response rate; OS - overall survival; PFS = progression-free survivial; PR = partial response; TTNT - time to next treatment; TTP - time to progression; TTR - time to first response

Quality of Life

Changes in quality of life were measured in the M13-982 trial using two questionnaires: the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16 (QLQ-CLL16). The former is a 30-item cancer questionnaire assessing 5 functional scales (cognitive, emotional, social, physical, and role functioning). The QLQ-CLL16 is a questionnaire specific to CLL patients in which 5 domains (fatigue, treatment

side effects, disease symptoms, infection, and social activities/future health worries) are assessed in 16 questions.

Mean change scores from baseline to Weeks 4, 12, 24, 36, and 48 on both questionnaires were observed. Wierda and colleagues[28] conducted an interim analysis from baseline to Week 24 since there was a decline in the number of evaluable patients from approximately 80% at Week 24 to approximately 65% at Week 48. Clinical relevance was determined based on the minimum important difference (MID) of values from baseline to Week 24. A change score of 5 points was used for MID acceptance and the 95% confidence interval was used to determine whether the change was statistically significant (ref Wierda). Data on mean change scores from baseline to Weeks 36 and 48 were also requested and reviewed for this report. However, as noted by Wierda and colleagues (ref), since questionnaire completion rates were higher at Week 24, and since most data (unless otherwise reported below) trended in the same direction for Weeks 36 and 48, the data presented in this report are limited to scores from baseline to Week 24. Quality of life results including mean change scores are presented in Table 11.

Significant improvements were observed in 4 domains of the QLQ-C30, including global health status, emotional, role, and social functioning. There were no significant changes from baseline in cognitive functioning or the following items related to physical functioning: nausea, vomiting, pain, sleep (though significant changes observed at weeks 36 and 48), appetite loss, constipation or diarrhea. Results from both assessment scales demonstrated early and sustained statistically significant and clinically relevant improvements in fatigue. Large change scores from Weeks 4 (Δ = -16.9) and 24 (Δ = -21.9) were detected for the domain of future health worries with negative change scores representing improvement. Scores from the QLQ-CLL16 demonstrated significant improvements in disease effects, social problems, and future health worries, which exceeded the MID at all time points up to 24 weeks and including weeks 36 and 48. Improvements in treatment side effects were reported as statistically significant, however, they did not exceed the MID in the first 24 weeks. Further, improvements in infection were only significant at Week 4 (mean change from baseline -5.7, 95%CI -10.3 to -1.1).

Table 11. Clinically relevant changes in quality of life with venetoclax monotherapy treatment (Study 13-982).[28]				
EORTC-QLQ-C30 Parameter (n patients included in the analysis)	**BL Mean**	**Visit Mean**	**Mean change from BL (95% CI)**	**MID[1] Exceeded (yes/no)**
Global Health Status				
Week 4 (70)	55.2	64.4	9.2 (4.3, 14.1)	Yes
Week 24 (73)	58.6	67.9	9.4 (3.3, 15.5)	Yes
Emotional Functioning				
Week 4 (73)	72.0	81.2	9.2 (5.4, 12.9)	Yes
Week 24 (76)	74.6	82.4	7.9 (3.6, 12.1)	Yes
Physical Functioning[2]				
Week 4 (70)	75.3	76.3	1.0 (-2.6, 4.6)	No
Week 24 (74)	78.3	81.6	3.3 (-0.9, 7.6)	No
Role Functioning				
Week 4 (70)	64.3	73.6	9.3 (3.7, 14.8)	Yes
Week 24 (74)	68.0	79.1	11.0 (3.8, 18.2)	Yes
Social Functioning				
Week 4 (73)	64.6	71.5	6.8 (0.5, 13.2)	Yes
Week 24 (76)	69.1	80.9	11.8 (5.6, 18.1)	Yes
Cognitive Functioning				
Week 4 (73)	83.8	82.6	-1.1 (-5.6, 3.4)	No
Week 24 (76)	85.1	85.5	0.4 (-3.7, 4.6)	No
Fatigue				
Week 4 (74)	42.4	35.7	-6.7 (-11.7, -1.7)	Yes
Week 24 (77)	37.1	30.6	-6.5 (-11.6, -1.3)	Yes
EORTC-QLQ-CLL16 Parameter (n)	**BL Mean**	**Visit Mean**	**Mean change from BL (95% CI)**	
Treatment Side Effects				
Week 4 (75)	18.1	14.9	-3.3 (-6.4, -0.1)	No
Week 24 (78)	15.3	10.4	-4.9 (-7.9, -1.9)	No
Future Health				
Week 4 (73)	56.6	39.7	-16.9 (-23.4, -10.4)	Yes
Week 24 (73)	54.8	32.9	-21.9 (-30.1, -13.7)	Yes
Infection				
Week 4 (73)	23.1	17.4	-5.7 (-10.3, -1.1)	Yes
Week 24 (76)	20.0	15.0	-4.9 (-10.6, 0.7)	No[3]
Fatigue				
Week 4 (75)	34.0	24.0	-10.0 (-16.1, -3.9)	Yes
Week 24 (77)	29.7	21.2	-8.4 (-14.3, -2.6)	Yes
Notes: [1] MID = 5 points; [2] comprises fatigue, nausea, vomiting, pain, dyspnea, sleep, appetite, constipation, and diarrhea; [3] minimally important difference was exceeded at weeks 36 and 48 Abbreviations: BL - baseline; CI - confidence interval; MID - minimally important difference; n - number				

Adverse Events

The M13-982 study by Stilgenbauer and colleagues[26] limited their patient population to those with CLL *with* del(17p), and enrolled in the main cohort (n=107) plus the safety expansion (n=51) for a combined total of 158 patients all of whom received the target dose of 400mg. For the safety analysis, data from patients in the M14-032 trial were combined with those from the M13-982 trial. A total of 64 patients have received the 400mg dose and are currently evaluable for safety. Of these 64 patients, 23 had the del(17p). Upon study completion these

patients will also be evaluable for efficacy. Together, a total of 181 patients with the del(17p) were treated at the 400mg daily dose of venetoclax and are included in this safety analysis. Patients from the M13-982 trial comprised the majority harbouring the del(17p) and per protocol had their deletion status verified by central laboratory evaluation via Vysis fluorescence in-situ hybridisation (FISH) testing. The remaining patients from the M14-032 trial had their deletion status verified at their local laboratory. Table 12 presents adverse event data reported in >10% of CLL patients with del(17p) for the 107 patients in the M13-982 study, the 51 patients in the safety expansion cohort, as well as integrated data for the 181 CLL 17p deleted patients across the two Phase II studies (M13-982 and M14-032). On integration of these data, the rate of adverse events was found to be similar between the data sets (Table 12).

Grade 3 or 4 Adverse Events

The most common treatment-emergent adverse events of any grade in the M13-982 study when the main cohort data were combined with the safety expansion cohort data were neutropenia (42%), diarrhea (36%), nausea (37%), anemia (24%), and fatigue (22%). Severe (≥Grade 3) adverse events in the main study cohort included neutropenia (40%), infection (20%), anemia (18%), and thrombocytopenia (15%).

Neutropenia led to venetoclax interruption for 5 patients (5%) and dose reduction for 4 patients (4%).[26] All neutropenia-related events were managed through dose reduction or interruption, or with granulocyte-colony stimulating factor and antibiotics.

Serious adverse events were recorded in 59/107 (55%) patients with the most common being autoimmune hemolytic anemia (7%), pyrexia (7%), pneumonia (6%), and febrile neutropenia (5%).

While venetoclax was generally well tolerated and had an acceptable safety profile during the M13-982 trial, it should be noted that three protocol amendments were implemented, two of which were related to safety. The first amendment included all 107 patients enrolled in the main cohort and was issued to implement more stringent measures for prophylaxis and management of TLS, including modification to the dosing regimen with a starting dose of 20mg and ramp-up of 4-5 weeks, and to introduce TLS risk assessment with prophylaxis and monitoring according to the risk as well as intensive laboratory monitoring.[53] Thirty-six patients were enrolled under the second amendment, all of whom were in the safety expansion cohort. This amendment was introduced to revise prophylactic and management measures of TLS in response to extensive analysis among the CLL studies.[53] Laboratory TLS was reported in 5 patients during the dose escalation period (4 patients within the first 2 days of treatment; 1 patient at Week 3 of treatment) and resolved without clinical sequelae. While 2 patients had a one-day treatment interruption, no patients discontinued treatment due to TLS.

There were 18 deaths reported in the M13-982 study. Eleven patients died within 30 days of the last dose of venetoclax; seven due to disease progression and 4 due to one of the following adverse events: stroke, liver derangement, septic shock, and cardiorespiratory insufficiency. None of these deaths were considered treatment related. Seven additional patients died due to progressive disease beyond 30 days from discontinuation of venetoclax. At the time of the second interim analysis (August 2016), [redacted] and [redacted] deaths in the main and safety expansion cohorts were reported, respectively. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested the safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain*

redacted until May 31, 2017 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.)

In the M14-032 study, Coutre and colleagues[52] conducted an interim safety analysis which demonstrated that venetoclax monotherapy shows promising activity with the following adverse events reported in >20% of patients, albeit it should be noted that not all of these patients harboured the del(17p): neutropenia (48%), diarrhea (37%), nausea (35%), anemia (32%), fatigue (24%), and hyperphosphatemia (20%). Grade 3/4 adverse events in >10% of patients include: neutropenia (39%), thrombocytopenia (22%), anemia (20%), leukopenia (13%), pneumonia (13%). Severe adverse events reported in ≥2 patients include pneumonia (9%), febrile neutropenia (7%), increased potassium, multi-organ failure, septic shock (4% each). Two patients reportedly had TLS without clinical consequences. Again, it must be noted that only 35% of these patients harboured the del(17p). Adverse event data limited to patients with the del(17p) (n=23) are presented in Table 12.

Table 12. Adverse events reported in ≥10% of CLL patients with del(17p).

Event, n (%)	17p del treated at 400mg (M13-982) Main cohort n=107[55]	17p del treated at 400mg (M13-982) Safety expansion n=51[55]	17p del treated at 400mg (M14-032) n=23[55]	17p del treated at 400mg (Integrated data)[£] n=181
	[redacted]			
Any AE				
Anemia				
Neutropenia				
Thrombocytopenia				
Diarrhea				
Nausea				
Vomiting				
Constipation				
Fatigue				
Pyrexia				
Nasopharyngitis				
URTI				
Hyperphosphatemia				
Hypokalemia				
Back pain				
Headache				

Notes: £ - data integrated from M13-982 main cohort, M13-982 expansion cohort, and M14-032 studies

(*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested the safety information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until May 31, 2017 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier.*)

6.4 Ongoing Trials

The M14-032 phase II, open-label study of venetoclax monotherapy in patients with CLL relapsed after or refractory to ibrutinib or idelalisib is currently active and recruiting patients. In this non-randomized treatment study, patients enter one of two study arms: single daily doses of venetoclax starting at 20mg increasing weekly as tolerated to 400mg after Arm A) ibrutinib therapy or Arm B) idelalisib therapy. The primary outcomes of interest are efficacy and safety. Approximately 120 patients will be enrolled in the study, which is estimated to be complete by October 2017. Efficacy will be assessed by overall response rate, which will be evaluated by the investigator based on laboratory results, physical exams, CT scans, and bone marrow examinations. Secondary outcomes of interest include: duration of response, time to progression, progression-free survival, overall survival, time to next anti-CLL treatment, and rate of MRD negativity status.[51] Additional details including eligibility criteria are provided in Table 4.

While del(17p) is not a requirement for this trial, an interim analysis of 64 patients from the overall population (Arm A: 43, Arm B: 21) reported that 35% of patients had the del(17p) (23/64).[52] This includes 21 patients in Arm A harbouring the deletion and 2 patients in Arm B. A subgroup analysis of patients harbouring the del(17p) can therefore be done upon study completion. Final results of this study will strengthen the body of evidence for the efficacy and safety of venetoclax in this high risk, difficult to treat population.

Please see Section 8 of this document for details on this trial.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question were identified during development of the review protocol as relevant to the pCODR review of venetoclax for CLL:

- Critical Appraisal of an Indirect Treatment Comparison Between Venetoclax and Relevant Treatment Options

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of an Indirect Treatment Comparison Between Venetoclax and Relevant Treatment Options[54,55]

7.1.1 Objective

Given the absence of a comparative trial evaluating the safety and efficacy of venetoclax compared to relevant treatment options, an indirect treatment comparison was done for venetoclax (VEN) versus other relevant treatments in patients with chronic lymphocytic leukemic relapsed / refractory (chromosome 17p13.1 deletion: del(17p))setting (CLL R/R del(17p)). Based on input from the Clinical Guidance Panel, ibrutinib and idelalisib plus rituximab were considered to be relevant treatment options in this setting.

7.1.2 Findings

Results of a systematic literature review (i.e., extracted data of the studies) and simulated patient-level progression-free survival (PFS) and overall survival (OS) data were utilized as input parameters for the indirect treatment comparisons. The results pertaining to the comparison with the ibrutinib and idelalisib plus rituximab were considered to be relevant for the purpose of this pCODR Review. They are however not presented in this summary as they were made non-disclosable by the manufacturer pending a peer-reviewed publication of the results of this indirect comparison. The following information was made available on the methods, results and limitations of the indirect comparison.

Methods
Five relevant trials were identified in the systematic literature review that published Kaplan-Meier PFS and/or OS curves in the CLL R/R del(17p)setting providing input data for the indirect treatment comparisons for ibrutinib (IBR), ofatumumab (OFA), idelalisib + rituximab (IDE+R), fludarabine + cyclophosphamide + rituximab (FCR), and rituximab + bendamustine (BR). Outcomes considered for the indirect treatment comparisons were PFS, OS, overall response rate (ORR), and complete response (CR) rate. Hazard ratios (HR) and risk ratios (RR) were estimated for the time-to-event outcomes and binary outcomes, respectively.

Table 1. Inclusion and exclusion criteria of studies for systematic literature review for indirect comparison

	Inclusion criteria	Exclusion criteria
Population	Adult (≥18 years) Human Established R/R CLL with 17p deletion	Not Adult (<18 years) Not human Without established R/R CLL
Intervention	Treatment strategies for R/R CLL patients with 17p deletion such as: New strategies: Ibrutinib / Idelalisib / Venetoclax monotherapy Other treatment strategies: (high dose methylprednisolone / lenalidomide / oxaliplatin / fludarabin / cytarabine / rituximab/ ofatumumab / alemtuzumab / flavopiridol)	Treatment strategies not specific to R/R CLL
Comparator	Any comparator, including no treatment and any currently recommended treatments (e.g. Combination chemotherapy / biological therapies) Placebo Best supportive care (BSC)	No restrictions applied
Outcomes	Listed under the SLR outcome parameters	Clinical outcomes not recorded for 17p del R/R CLL patients.
Study Design	Randomized clinical trials(Phase 1-4) Follow up studies Prospective studies Case series Case-studies Non-randomized clinical controlled trials and studies Retrospective studies Chart Reviews	Studies not reporting clinical evidence. If Phase 2+ trial data is not published for a specific treatment regimen then Phase 1 trial data should be included.
Publication Type	In English Language Full text Articles Conference Abstracts	Non-English Notes Erratums Comments/Correspondence Editorials Reviews (not extracted but are reference checked)
Date	Conference abstracts/HTA studies / TA ≤ 3 years	HTA/Technological appraisals >3 years old Conference abstracts >3 years old

Based on materials submitted to pCODR (which has been made non-disclosable by the submitted), a total of 20 peer-reviewed articles and 38 conference abstracts were identified. Of these, 7 trials were selected for inclusion. Data made available to pCODR for critical appraisal however indicated that 5 trials were included, one per comparator, were used because they provided relevant input data (i.e., PFS and ORR) for the ITCs. The pCODR Review Team was unable to determine the reason for this discrepancy in the trials selected for inclusion.

Trials were selected for inclusion:

- 175 trial: venetoclax[31]
- RESONATE trial: ibrutinib (IBR), ofatumumab (OFA)[48, 63]
- RESONATE-17 trial: ibrutinib[64]
- Study 116: idelalisib in combination with rituximab (IDE+R)[50]
- FCR study: rituximab in combination with fludarabine and cyclophosphamide (FCR)[65]
- BR study: rituximab in combination with bendamustine (BR).[60]

Two indirect treatment comparison approaches were used:

1. Unadjusted for differences in trial design and patient selection and baseline population characteristics

For the unadjusted approach in the CLL R/R del(17p) setting, the five studies, one per comparator, were used because they provided relevant input data (i.e., PFS and ORR) for the ITCs. In this setting, matching-adjusted analysis was only possible for VEN versus IBR. At the time the analysis was conducted, only the RESONATE-17 trial provided baseline patient characteristics for the del(17p) population that allowed matching.

2. Match-adjusted for differences in trial design and patient population characteristics by matching patients of the venetoclax trials to trials of comparator treatments.
    a) The matching-adjusted analyses adjusted the VEN patient populations to the RESONATE-17 trial populations in terms of patient selection criteria and baseline disease characteristics. Three matching-adjusted indirect treatment comparison models of various levels of matching (i.e., number of included variables) were explored (See Table 2). Venetoclax 982 population to RESONATE-17 population, applying patient selection criteria of RESONATE-17 trial. This resulted in 11 patients excluded from the 982 trial population (n=96).
    b) Further adjustment of the 982 trial by matching on age, ALC level and number of prior treatments (n=90).
    c) Further adjustment of the 982 trial by matching on sex, bulky disease, LDH level and del(p17) cell rate (n=84).

The pCODR Clinical Guidance Panel noted that mutation status and chemotherapy resistance were important prognostic factors in this setting. Upon request made to the submitter, it was confirmed that the results were not matched for these factors because data in the M13-982 trial was available only for a small number of patients, with many missing values. This is an important limitation of the MAIC.

Table 2. Baseline patient characteristics before and after matching

Baseline characteristics	IBR (n=144)	VEN Unadjusted (n = 107)	VEN Adjusted for patient selection* (n =96)	VEN Adjusted for patient selection, age, ALC, prior treatments (n = 90)	VEN Adjusted for patient selection, and all available baseline characteristics (n=84)
Patients with age ≥65 years	48%	57%	55%	48%	48%
Male	67%	65%	67%	66%	67%
Bulky disease (≥5cm)	49%	53%	50%	48%	49%
Patients receiving 1 prior therapy	33%	27%	29%	33%	33%
Patients receiving 2 prior therapies	28%	23%	24%	28%	28%
Patients with 25*109 ALC count	57%	50%	51%	57%	57%
Patients with ≥258 LDH count	50%	49%	49%	49%	50%
Patients with ≥75% p17 deletion cells	27%	33%	35%	40%	27%

Results - Unadjusted comparison

For PFS and OS, hazard ratios were estimated using the observed data for venetoclax and the simulated data for the comparator. A hazard ratio lower than 1 indicated lower risk of progression or death for venetoclax than for the comparator treatment. When taking into account all patients of the main cohort of the M13-982 trial, estimated HRs indicate no significant difference between venetoclax and ibrutinib nor venetoclax and idelalisib plus rituximab for progression-free survival and overall survival. In terms of overall response rate, VEN was estimated to be similar to IDE+R (i.e., not statistically significantly different) however VEN was significantly better than IBR.

	Ven vs. Ibrutinib	Ven vs. Idelalisib + rituximab
	Unadjusted analyses	
PFS, HR	1.417, 95% CI 0.839-2.395	1.085, 95% CI 0.570-2.067
OS, HR	0.855, 95% CI 0.434-1.682	0.936, 95% CI 0.415-2.111
ORR, RR	0.983, 95% CI 0.863-1.121 not statistically significantly different	1.274, 95% CI 1.042-1.423

Results - Matching adjusted comparison

The matching-adjusted analyses indicated that matching the M13-982 patient population to the RESONATE-17 trial population improves all ITC outcomes (lower hazard ratio for PFS [HR=1.291] and OS [HR=0.727], higher risk ratio for ORR [RR=1.340] than in the unadjusted analyses) however the conclusions drawn from the results of the unadjusted analyses did not change. The 95% CI of the hazard ratios of each of the models comprised 1, suggested no difference between venetoclax and ibrutinib in terms of PFS.

Limitations:

- The submitter indicated that the results of the indirect comparison may be published in a peer-reviewed journal, therefore detailed information on this analysis were made non-disclosable. Therefore, the pCODR review team was only able to critically appraise very limited information while detailed information on the literature search, methodology and results of the indirect comparison were not considered as part of this summary. Therefore, given that the results of the ITC have not been peer- reviewed or published and that the pCODR review team was unable to fully do a critical appraisal, caution should be used in making any conclusions on the results of this analysis.
- For most trials included in the IDC, patient and disease characteristics were not provided for patients with del(17p); therefore, direct comparison of the trial (sub)populations was not possible. Thus, the unadjusted analyses implicitly assumed that the patient populations were comparable.
- Secondly, although the matching of the VEN trial population to the ibrutinib trial populations was done, a certain important variables could not be considered because data from the M13-982 trial was available only for a small number of patients at the time of the analysis. These variables included the stage of the disease (e.g. Rai stage), beta2-microglobulin level, IGVH mutation status, or whether patients were refractory to prior treatment(s).
- Thirdly, a drawback of the PFS and OS comparisons is that patient-level data were not available for the comparator trials and, as such, had to be simulated from the published Kaplan-Meier curves. Therefore uncertainty remains as to the results obtained from these indirect comparisons.

7.1.3 Summary

Given the absence of a comparative trials evaluating the safety and efficacy of venetoclax compared to relevant treatment options, an indirect treatment comparison was done for venetoclax (VEN) versus other relevant treatments in patients with chronic lymphocytic leukemic relapsed / refractory del(17p) setting (CLL R/R del(17p)). There was limited information available on the methodology and results of this indirect comparison and thus only a limited critical appraisal was done. This data is also pending peer-review and publication. Overall, although the point estimates of the analyses suggest that VEN is similarly efficacious as IBR and IDE+R in terms of progression-free survival and overall survival, great caution should be used in drawing conclusions based on these data.

8 COMPARISON WITH OTHER LITERATURE

The ongoing phase II multicenter study, M14-032, has published interim results, which are also being considered in this review. The key characteristics of this trial are summarized in Table 13 and specific features on trial quality are summarized in Table 14.

Table 13. Summary of trial characteristics for the M14-032 study.

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Clinical Trial NCT02141282[57] Phase II, open label, multicenter, single treatment arm trial Experimental Arm A: venetoclax after ibrutinib therapy Experimental Arm B: venetoclax after idelalisib therapy N= 120 estimated enrollment Study location: up to 15 US study sites Estimated final data collection date for primary outcome: October 2017 Estimated study completion date: October 2017 Funded by AbbVie	<u>Key Inclusion Criteria:</u> • Age ≥ 18 years • Diagnosed with rel or ref CLL with an indication for treatment • refractory disease or developed recurrence after therapy with a BCR PI • ECOG of 0, 1, or 2 • adequate bone marrow function • adequate coagulation profile, renal, and hepatic function, per laboratory reference range at screening Key Exclusion Criteria: • allogeneic stem cell transplant within the past year • development of Richter's transformation confirmed by biopsy • active/uncontrolled autoimmune cytopenia • malabsorption syndrome or other condition that precludes enteral route of administration • HIV positivity or chronic hepatitis B or C virus requiring treatment • known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase	Venetoclax once daily, orally, via step-wise weekly dose ramp-up from starting dose of 20mg to final 400mg daily dose (20, 50, 100, 200, 400 mg) over 4-5 weeks as tolerated No comparators were used in this study	<u>Primary</u> • ORR • Safety Secondary • Time to progression • Progression-free survival • Overall survival Exploratory • Duration of response • Time to next treatment • MRD negativity status
<u>Abbreviations:</u> BCR PI - B-cell receptor signaling pathway inhibitor; CLL - chronic lymphocytic leukemia; d - day(s); ECOG - Eastern Cooperative Oncology Group; MRD - minimal residual disease; n - number; ref - refractory; rel - relapsed			

Table 14: Select quality characteristics of the M14-032 study.

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Blinding	ITT Analysis	Ethics Approval
NCT02141282 (M14-032)	Venetoclax No comparator	ORR	A sample size of 20 subjects in each arm would ensure that the distance of true rate will be within 23% of the observed rate with 95% confidence[2]	Study is ongoing 64 patients currently enrolled 23 patients with del(17p)	Trial not randomized	NR	NR	Yes

Abbreviations: IRC - independent review committee; NR - not reported; ORR - overall response rate; pts - patients; del(17p): chromosome 17p13.1 deletion
Notes: 1 - The initial plan was to enrol 100 subjects in the main cohort to assess safety and efficacy albeit for the efficacy analysis, 70 subjects provided at least 90% power (at two-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favour of the alternative hypothesis of 60% ORR. While a ORR over a standard rate of 40% would be considered clinically meaningful, a suggestion by the FDA that a report containing final efficacy data on at least 100 patients would strengthen the submission led to a final sample size of 107 patients.
2 - sample size calculations are for the whole population, which was not limited to patients with del(17p)

The M14-032 study is an ongoing phase II study with a primary objective to evaluate the efficacy (by overall response rate) and safety of venetoclax monotherapy in patients with CLL who have relapsed after or are refractory to treatment with B-cell receptor signaling pathway inhibitors. This is an open-label, non-randomized, multicenter study in which approximately 40 patients were planned to be enrolled. Patients enter one of two study arms: Arm A is designed to enrol approximately 20 patients with relapsed or refractory CLL after ibrutinib treatment; Arm B is designed to enrol approximately 20 patients with relapsed or refractory CLL after idelalisib treatment. All patients will receive single daily doses of venetoclax starting with 20mg and increasing weekly to a target dose of 400mg. While (chromosome 17p13.1 deletion: del(17p)) is not an inclusion criterion for the study, it is anticipated that a sufficient number of patients will harbour the deletion given that patients have relapsed after or are refractory to either ibrutinib, idelalisib, or both and this will allow for a subgroup analysis of just those patients with a del(17p). At the first published interim analysis by Coutre et al.[52] 43 patients had been enrolled in Arm A and 21 in Arm B with 21 and 2 patients harbouring the del(17p) in each arm respectively.

As stated in the M14-032 study protocol, approximately 40 patients with relapsed or refractory CLL after receiving BCR signaling pathway inhibitors, were to be enrolled. To date however, a total of 64 patients have been enrolled, 43 in Arm A (prior ibrutinib) and 21 in Arm B (prior idelalisib). There is no statement or protocol amendment to describe why more than the originally planned 40 patients were enrolled. It is however stated on the Clinicaltrials.gov website that the estimated enrolment for this study is 120 patients. Among the 64 patients, 23 have been found to be harbouring the del(17p): 21 in Arm A and 2 in Arm B. As results for the M14-032 study are very preliminary, this section provides mainly descriptive results. However, safety data from both the M13-982 and the M14-032 studies have been integrated in Table 12.

The following description of the patients in the M14-032 study is limited to those 23 patients with del(17p) and apart from age, data from patients in Arm A and Arm B have been collapsed. The

majority of patients (70%) were ≥65 years with the median age in Arm A of 66 years (76 years in Arm B). Patients were primarily male (70%) and Caucasian (96%). In terms of performance status, 96% were in the ECOG Grade 0-1 range, while one patient was Grade 2. Three patients (13%) were Rai stage III, five (22%) were stage IV and the remainder were stage 0-2 (43%). These data were missing for 5 (22%) of patients. Data on Binet staging was missing for 96% of patients. Disease-related complications including anemia and thrombocytopenia were present in 6 (26%) and 8 (35%) patients, respectively. Ten out of the 23 patients had an absolute lymphocyte count ≥$25x10^9$ per L. None of the patients had nodes ≥10cm. Twelve patients were considered to be in the high risk category for TLS while 4 and 7 were medium and low risk, respectively. Sixteen patients harboured the TP53 mutation, 3 harboured the IGHV mutation, and 4 harboured the 11q deletion. Serum ß-2 microglobulin was ≥3mg/l in 12 patients but these data were missing for 8 patients.

Data on prior therapies to which the disease was refractory is not currently available. However, it is known that 19 patients had prior treatment with ibrutinib, 3 patients had been previously treated with idelalisib, 3 had received fludarabine, and 1 had received bendamustine therapy prior to venetoclax treatment in the study. The median number of months from diagnosis to the first dose of venetoclax in Arm A was 125.1 months (n=15) while the median in Arm B was 47.5 months, but the latter includes just two patients.

Interventions

Details of the dosing and administration schedule of venetoclax in the M14-032 study can be found in Table 13. Like the M13-982 study, patients enrolled in the M14-032 study followed a weekly venetoclax dose ramp-up schedule to mitigate the risk of TLS. Further, patients received prophylaxis with uric acid lowering agents and hydration starting at least 72 hours prior to the first venetoclax dose and patients with high tumour burden were hospitalized. Laboratories were monitored at scheduled time points at the first dose and at dose increases. Disease assessments were performed using standardized criteria modified to include partial nodular remission category for efficacy at weeks 8, 24, and every 12 weeks thereafter for up to 1 year. MRD and adverse events were monitored throughout the study.

Patient Disposition

Details on patient disposition for the M14-032 trial include the 21 patients in Arm A who were refractory to ibrutinib and the 2 patients in Arm B who were refractory to idelalisib. Of these 23 patients, 11 and 2 are receiving ongoing treatment in Arms A and B, respectively. Ten patients have discontinued treatment. Other treatment discontinuations were as follows: progressive disease (4), progressive disease/Richter's (2), adverse events not related to progression (1), adverse events related to progression (2), stem cell transplantation (2), and other reasons not defined (1).

Limitations/Sources of Bias

In addition to the limitations that arise from this being another Phase II non-comparative study, an important limitation that precluded this study from being formally included in the systematic review is that it has not yet been fully published. Rather, the information has been derived from interim results presented in poster form and results obtained directly from the submitter. Therefore the pCODR Review Team was unable to conduct a full critical appraisal on this study.

Efficacy Outcomes

Primary Outcome - Overall Response Rate

In the ongoing M14-032 study, an interim efficacy assessment in which 64 patients were evaluable, conferred a promising result in the overall population, with ORR of 70% by IRC in the ibrutinib arm and 48% by IRC in the idelalisib arm. However, it must be noted that only 35% of these patients had the del(17p).[52] When the analysis was limited to include only those patients with del(17p) (n=23, 21 in Arm A and 2 in Arm B) the ORR was 65% for the combined study arms (15/23). This number included 1 CR in Arm B, 1 CRi in Arm A, and 13 PR (12 in Arm A and 1 in Arm B).

Secondary and Other Relevant Outcomes

In the M14-032 study, the DOR estimate at 12 months for the 13 responders in Arm A was 83.3% (95% CI: 48.2, 95.6).). Five of the 21 patients in Arm A achieved MRD negative status (24%) while 9 were MRD positive. While none of the patients were deemed non-evaluable, seven patients were categorized as "other" in terms of the MRD status.

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 Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

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

See Appendix B for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials 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

APPENDIX B: DETAILED METHOLODGY OF LITERATURE REVIEW

Literature Search Methods

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

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with Epub ahead of print, in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (June 2016) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was: Venetoclax.

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 3, 2016.

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

Study Selection

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

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

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team. The SIGN-50 Checklist used in this review is included in Table X below.

[Table 7]: SIGN checklist for controlled trials

SECTION 1: INTERNAL VALIDITY

In a well conducted RCT study…		Does this study do it?
1.1	The study addresses an appropriate and clearly focused question.	
1.2	The assignment of subjects to treatment groups is randomised.	
1.3	*An adequate concealment method is used.*	
1.4	The design keeps subjects and investigators 'blind' about treatment allocation.	
1.5	The treatment and control groups are similar at the start of the trial.	
1.6	The only difference between groups is the treatment under investigation.	
1.7	All relevant outcomes are measured in a standard, valid and reliable way.	
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	
1.9	*All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).*	
1.1	Where the study is carried out at more than one site, results are comparable for all sites.	
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias?	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?	
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	
2.4	Notes:	

Data Analysis

Additional data analyses are not expected for pCODR reviews. If they are required, as determined in consultation with pCODR, provide details on any additional statistical analyses and details on software programs used. If additional data analyses are not conducted, insert the following:

[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.

REFERENCES

1. Wierda WG, Seymour JF, Roberts AW, Puvvada S, Davids MS, Wong S, et al. A phase 2 open-label study of the efficacy of ABT-199 (GDC-0199) in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL) harboring 17p deletion [abstract]. J Clin Oncol [Internet]. 2014 [cited 2016 Aug 10];32(15 suppl). Available from: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/TPS7121?sid=a2a4f314-382a-4527-b903-c2acec46afdb (Presented at 2014 Annual Meeting of the American Society of Clinical Oncology, ASCO; 2014 May 30-Apr 3; Chicago, IL).

2. Wierda WG. Updates to the management of chronic lymphocytic leukemia. J Natl Compr Canc Netw. 2015 May;13(5 Suppl):662-5.

3. Zia MI, Siu LL, Pond GR, Chen EX. Comparison of outcomes of phase II studies and subsequent randomized control studies using identical chemotherapeutic regimens. J Clin Oncol. 2005 Oct 1;23(28):6982-91.

4. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM, Busch R, Mayer J, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010 Oct 2;376(9747):1164-74.

5. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016 Jul;17(7):928-42.

6. Buhler A, Wendtner CM, Kipps TJ, Rassenti L, Fraser GA, Michallet AS, et al. Lenalidomide treatment and prognostic markers in relapsed or refractory chronic lymphocytic leukemia: data from the prospective, multicenter phase-II CLL-009 trial. Blood Cancer J [Internet]. 2016 Mar 11 [cited 2016 Nov 9];6:e404. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4817104

7. Fischer K, Cramer P, Busch R, Stilgenbauer S, Bahlo J, Schweighofer CD, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011 Sep 10;29(26):3559-66.

8. Stilgenbauer S, Dohner H. Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy. N Engl J Med. 2002 Aug 8;347(6):452-3.

9. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med. 2014 Mar 20;370(12):1101-10.

10. Furman RR, Sharman JP, Coutre SE, Cheson BD, Pagel JM, Hillmen P, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med [Internet]. 2014 Mar 13 [cited 2016 Nov 9];370(11):997-1007. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161365

11. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med [Internet]. 2014 Jul 17 [cited 2016 Nov 9];371(3):213-23. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4134521

12. Diehl LF, Karnell LH, Menck HR. The American College of Surgeons Commission on Cancer and the American Cancer Society. The National Cancer Data Base report on age, gender, treatment, and outcomes of patients with chronic lymphocytic leukemia. Cancer. 1999 Dec 15;86(12):2684-92.

13. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Dohner H, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood [Internet]. 2008 Jun 15 [cited 2016 Nov 9];111(12):5446-56. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2972576

14. Dohner H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000 Dec 28;343(26):1910-6.

15. Montserrat E, Vinolas N, Reverter JC, Rozman C. Natural history of chronic lymphocytic leukemia: on the progression and progression and prognosis of early clinical stages. Nouv Rev Fr Hematol. 1988;30(5-6):359-61.

16. Binet JL, Auquier A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer. 1981 Jul 1;48(1):198-206.

17. Rai KR, Sawitsky A, Cronkite EP, Chanana AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. Blood. 1975 Aug;46(2):219-34.

18. Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. CLL Trialists' Collaborative Group. J Natl Cancer Inst. 1999 May 19;91(10):861-8.

19. Michallet AS, Aktan M, Schuh A. Rituximab in combination with bendamustine or chlorambucil for the treatment of chronic lymphocytic leukaemia: primary results from the randomised phase IIIb MaBLe study [abstract]. Leuk Lymphoma. 2016;56(Suppl 1):abstract 88.

20. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016 Jan 28;374(4):311-22.

21. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. Lancet Oncol. 2016 Jun;17(6):779-90.

22. Pettitt AR, Jackson R, Carruthers S, Dodd J, Dodd S, Oates M, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the national cancer research institute CLL206 trial. J Clin Oncol. 2012 May 10;30(14):1647-55.

23. Kharfan-Dabaja MA, Kumar A, Hamadani M, Stilgenbauer S, Ghia P, Anasetti C, et al. Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2016 Sep 19.

24. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M, et al. Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. Blood [Internet]. 2015 Apr 16 [cited 2016 Nov 9];125(16):2497-506. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400288

25. O'Brien S, Jones JA, Coutre SE, Mato AR, Hillmen P, Tam C, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. Lancet Oncol. 2016 Oct;17(10):1409-18.

26. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol. 2016 Jun;17(6):768-78.

27. Stilgenbauer S, Eichhorst BF, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax (ABT-199/GDC-0199) monotherapy induces deep remissions, including complete remission and undetectable MRD, in ultra-high risk relapsed/refractory chronic lymphocytic leukemia with 17p deletion: Results of the pivotal international phase 2 study [abstract]. Blood [Internet]. 2015 [cited 2016 Aug 12];126(23):LBA6. Available from: http://www.bloodjournal.org/content/126/23/lba-6 (Presented at 57th Annual Meeting of the American Society of Hematology, ASH 2015; 2016 Dec 3-6; San Diego, CA).

28. Wierda W, Cifaldi M, Hsu L-I, Cerri E, Verdugo ME. Interim quality of life results with venetoclax (ABT-199/GDC-0199) monotherapy in patients with relapsed/refractory del(17p) chronic lymphocytic leukemia. Poster presented at: European Hematology Association. 21st Congress; 2016 Jun 9-12; Copenhagen, Denmark.

29. Cang S, Iragavarapu C, Savooji J, Song Y, Liu D. ABT-199 (venetoclax) and BCL-2 inhibitors in clinical development. Journal of Hematology and Oncology [Internet]. 2015 [cited 2016 Aug 10];8(1):129. Available from: https://jhoonline.biomedcentral.com/articles/10.1186/s13045-015-0224-3

30. Robak T. High-risk chronic lymphocytic leukemia. Acta Haematol Pol [Internet]. 2015 [cited 2016 Aug 10];46(2):68-74. Available from: http://ac.els-cdn.com/S000158141500033X/1-s2.0-S000158141500033X-main.pdf?_tid=81da8300-5f24-11e6-9259-00000aab0f6c&acdnat=1470852288_5c7cd302b66df31aeacd63e37777a507

31. Eichhorst B. Treatment of CLL: state of the art 2015 [abstract]. Oncology Research and Treatment [Internet]. 2015 [cited 2016 Aug 10];38:256. Available from: http://www.karger.com/Article/FullText/439070 (Presented at Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie; 2015 Oct 9-13; Basel, Switzerland).

32. Steurer M. Chronic lymphocytic leukemia: ASH update 2014. Memo - Magazine of European Medical Oncology. 2015;8(3):159-61.

33. Eichhorst B. Update CLL-state-of-the-art 2014 [abstract]. Oncology Research and Treatment [Internet]. 2014 [cited 2016 Aug 10];37(suppl 5):97. Available from: http://www.karger.com/Article/Pdf/368945 (Presented at Jahrestagung der Deutschen, Osterreichischen und Schweizerischen Gesellschaften fur Hamatologie und Medizinische Onkologie 2014; 2014 Oct 10-14; Hamburg, Germany).

34. Roberts A, Davids M, Mahadevan D, Anderson M, Kipps T, Pagel J, et al. Selective inhibition of BCL-2 is active against chronic lymphocytic leukemia (CLL): first clinical experience with the BH3-mimetic ABT-199 [abstract]. Haematologica [Internet]. 2012 [cited 2016 Aug 10];97(s1):219-20. Available from: http://www.haematologica.org/content/97/supplement_1/haematol_97_s1.full.pdf+html (Presented at 17th Congress of the European Hematology Association; 2012 Jun 14-17; Amsterdam, Netherlands).

35. Marini BL, Samanas L, Perissinotti AJ. Expanding the armamentarium for chronic lymphocytic leukemia: A review of novel agents in the management of chronic lymphocytic leukemia. J Oncol Pharm Pract. 2016 Jun 29.

36. Vitale C, Burger JA. Chronic lymphocytic leukemia therapy: new targeted therapies on the way. Expert Opin Pharmacother. 2016 Jun;17(8):1077-89.

37. Del Poeta G, Postorino M, Pupo L, Del Principe MI, Dal Bo M, Bittolo T, et al. Venetoclax: Bcl-2 inhibition for the treatment of chronic lymphocytic leukemia. Drugs Today (Barc). 2016 Apr;52(4):249-60.

38. Rossi D. Venetoclax: a new weapon to treat high-risk CLL. Lancet Oncol. 2016 Jun;17(6):690-1.

39. Deeks ED. Venetoclax: first global approval. Drugs. 2016 Jun;76(9):979-87.

40. Venetoclax approved for CLL. Cancer Discov. 2016 Jun;6(6):564.

41. Venetoclax yields strong responses in CLL. Cancer Discov. 2016 Feb;6(2):113-4.

42. Brown JR, Hallek MJ, Pagel JM. Chemoimmunotherapy versus targeted treatment in chronic lymphocytic leukemia: when, how long, how much, and in which combination? Am Soc Clin Oncol educ book. 2016;35:e387-98.

43. Starr P. Venetoclax shows strong activity in CLL. Am Health Drug Benefits [Internet]. 2016 Feb [cited 2016 Aug 10];9(Spec Issue):21. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4782240

44. Stilgenbauer S. Prognostic markers and standard management of chronic lymphocytic leukemia. Hematology. 2015;2015:368-77.

45. Owen C, Assouline S, Kuruvilla J, Uchida C, Bellingham C, Sehn L. Novel therapies for chronic lymphocytic leukemia: a Canadian perspective. Clin Lymphoma Myeloma Leuk. 2015 Nov;15(11):627-34.

46. ABT-199 shows effectiveness in CLL. Cancer Discov [Internet]. 2014 Sep [cited 2016 Aug 10];4(9). Available from: http://cancerdiscovery.aacrjournals.org/content/4/9/OF7.long

47. Brower V. Venetoclax targets BCL2 in chronic lymphocytic leukaemia. Lancet Oncol. 2016 Jan;17(1):e11.

48. Molica S. Highlights in the treatment of chronic lymphocytic leukemia from the 2014 meeting of the American Society of Hematology. Expert Rev Hematol. 2015 Jun;8(3):277-81.

49. Seymour JF, Davids MS, Pagel JM, Kahl BS, Wierda WG, Puvvada S, et al. ABT-199 (GDC-0199) in relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma: High response rates among patients with high risk disease features including unmutated IGHV [abstract]. Haematologica [Internet]. 2014 [cited 2016 Sep 10];99:249. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4060398/pdf/haematol_99_s1.pdf (Presented at 19th Congress of the European Hematology Association; 2014 Jun 12-5; Milan, Italy).

50. Seymour JF, Davids MS, Pagel JM, Kahl BS, Wierda WG, Miller TP, et al. Bcl-2 inhibitor ABT-199 (GDC-0199) monotherapy shows anti-tumor activity including complete remissions in high-risk relapsed/refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) [abstract]. Blood [Internet]. 2013 [cited 2016 Aug 10];122(21). Available from: https://ash.confex.com/ash/2013/webprogram/Paper64686.html (Presented at 55th Annual Meeting of the American Society of Hematology, ASH 2013; 2013 Dec 7-10; New Orleans, LA).

51. Jones J, Mato AR, Coutre S, Wierda W, Choi MY, Davids MS, et al. Preliminary results of a phase 2, open-label study of venetoclax (ABT-199/GDC-0199) monotherapy in patients with chronic lymphocytic leukemia relapsed after or refractory to ibrutinib or idelalisib therapy [abstract]. Blood [Internet]. 2015 [cited 2016 Aug 12];126(23):715. Available from:

http://www.bloodjournal.org/content/126/23/715 (Presented at 57th Annual Meeting of the American Society of Hematology, ASH 2015; 2016 Dec 3-6; San Diego, CA).

52. Coutre S, Wierda W, Choi M, Davids MS, Chesom.B.D., Furman RR, et al. Venetoclax is active in CLL patients who have relapsed after or are refractory to ibrutinib or idelalisib. Poster presented at: European Hematology Association. 21st Congress; 2016 Jun 9-12; Copenhagen, Denmark.

53. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s) / Statistical review(s). In: Venetoclax (Venclexta). AbbVie Corporation. Application no.: 208573. Approval date: 04/11/2016 [Internet]. Rockville (MD): FDA; 2016 Jun 25 [cited 2016 Nov 7]. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208573Orig1s000MedR.pdf

54. pan-Canadian Oncology Drug Review manufacturer submission: Venetoclax, tablets (10mg, 50mg, 100mg). AbbVie Corporation. Pointe-Claire (QC): AbbVie Corporation; 2016 Aug 7.

55. AbbVie response to pCDOR checkpoint meeting questions on venetoclax (Venclexta) for chronic lymphocytic leukemia [additional manufacturer's information]. Point Claire (QC): AbbVie; 2016 Sep 14.

56. AbbVie. A study of the efficacy of ABT-199 in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia with the 17p deletion. 2013 Jun 26 [cited 2016 Nov 8]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01889186 Identifier: NCT01889186.

57. AbbVie. A phase 2 open-label study of the efficacy and safety of ABT-199 (GDC-0199) in chronic lymphocytic leukemia (CLL) subjects with relapse or refractory to B-cell receptor signaling pathway inhibitor therapy. 2014 May 12 [cited 2016 Nov 8]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT02141282?term=NCT02141282 Identifier: NCT02141282.