CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Venetoclax (Venclexta) Rituximab for Chronic Lymphocytic Leukemia

May 31, 2019

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding venetoclax (Venclexta) in combination with rituximab for chronic lymphocytic leukemia (CLL). 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) in combination with rituximab for CLL 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) in combination with rituximab for CLL, a summary of submitted Provincial Advisory Group Input on venetoclax (Venclexta) in combination with rituximab for CLL, and a summary of submitted Registered Clinician Input on venetoclax (Venclexta) in combination with rituximab for CLL, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of venetoclax in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Venetoclax is potent orally bioavailable selective inhibitor of the anti-apoptotic B-cell lymphoma-2 (Bcl-2) protein, leading to programmed cell death of CLL cells. Venetoclax has been issued a Health Canada marketing authorization without conditions that reflects the requested patient population for reimbursement; venetoclax in combination with rituximab is indicated for the treatment of patients with CLL who have received at least one prior therapy. Note that the Health Canada indication differs slightly from the reimbursement criteria, in that it does not specify 'irrespective of their 17p deletion status' in its indication.

Venetoclax should be administered according to a weekly ramp-up schedule to the daily dose of 400 mg over a period of 5 weeks. The 5-week ramp-up dosing schedule is designed to gradually reduce tumour burden (debulk) and decrease the risk of tumour lysis syndrome (TLS). The starting dose of venetoclax is 20 mg once daily for 7 days followed by 50 mg daily in the second week, 100 mg daily in the third week, and 200 mg daily in the fourth week.

After completion of the dose ramp-up period for venetoclax and after the patient has received the 400 mg dose of VENCLEXTA for 7 days, administration of rituximab (375 mg per square meter of body-surface area intravenously for the first dose [day 1 of cycle 1] and 500 mg per square meter intravenously thereafter [day 1 of cycles 2 through 6]) should be initiated. A total of six infusions of rituximab should be administered. Venetoclax should be taken at least 30 minutes prior to administering the rituximab infusion.

Patients should continue venetoclax 400 mg orally once daily for 24 months from Cycle 1 Day 1 of rituximab.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multicenter, open-label, randomized phase 3 trial (the MURANO study)[1] met the inclusion criteria and was included in the systematic review for venetoclax in combination with rituximab. The study enrolled 389 adult patients with CLL who have received at least one prior therapy. Enrolment was done in 20 countries and the patients were randomized in a 1:1 ratio to receive venetoclax-rituximab (n=194) or the bendamustine-rituximab (n=195) across 109 study sites. The study population was predominantly male (>70% in each group), and the median age was 64.5 and 66 years in the venetoclax-rituximab and bendamustine-rituximab arms, respectively. In each treatment group, the majority of patients had ECOG performance status score of either 0 or 1 (>90%), a single previous anti-CLL therapy (≥57%), and no chromosome 17p deletion (73%). Overall, the demographic and medical characteristics were balanced across both study arms.

Patients in the venetoclax-rituximab arm started treatment with oral venetoclax at an initial dose of 20 mg per day. The dose was gradually ramped-up to 400 mg per day over five weeks. After completion of the dose ramp-up period, intravenous (IV) rituximab was initiated in 28-day treatment cycles for six cycles while continuing the daily oral venetoclax. The first dose of rituximab, given on day one of cycle-1, was 375 mg per square meter (m^2) of body-surface area. The remaining five doses were 500 mg/m^2 each, administered on day one of cycle-2 through cycle-6. Patient continued oral venetoclax treatment for a total of 24 months from the time rituximab is started. For patient in the bendamustine-rituximab arm, IV bendamustine was administered at a dose of 70 mg m^2 body-surface area on days one and two of each 28-day cycle for six cycles. The patients received the accompanying IV rituximab using the same dosing schedule as previously described for the venetoclax-rituximab arm.

The primary efficacy endpoint was investigator-assessed progression-free survival (PFS), which was defined as the time from random assignment to the first occurrence of progression, relapse, or death, whichever occurred first. Secondary endpoints included overall survival (OS), overall response rate (ORR), and safety. The assessment of minimal residual disease (MRD) was a pre-specified exploratory endpoint. Patient-reported outcomes, including health-related quality of life (HRQoL), were included as secondary endpoints, and assessed with the MD Anderson Symptom Inventory (MDASI), the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), the EORTC QLQ-CLL16, and the 3-level EuroQol 5 Dimension (EQ-5D-3L) questionnaire. Efficacy analysis was based on the intention-to-treat (ITT) population which comprised all randomized patients. The safety analysis included all patients who received at least one dose of study medication.

Selected key outcomes have been summarized in Table 1.1. At the time of the primary analysis, the median PFS was 17 months in the bendamustine–rituximab group but was not reached in the venetoclax–rituximab group. However, the hazard ratio (HR) indicated a significantly longer PFS with venetoclax–rituximab than with bendamustine–rituximab (HR = 0.17; 95% confidence interval [CI]: 0.12 to 0.26). An

updated analysis performed with one more year of follow-up after the primary analysis (a median follow-up period of 36 months), showed that the PFS with venetoclax-rituximab remained superior to bendamustine-rituximab (HR = 0.16; 95% CI: 0.12 to 0.23). As of the 8 May 2017 data cut (primary analysis), median OS was not reached in either treatment arm. The Kaplan-Meier estimates of 24-month OS were higher in the venetoclax–rituximab arm than the bendamustine–rituximab arm (24-month OS: 91.9% versus 86.6%, respectively). The incidence of adverse events (AEs) was high in both treatment groups (Table 1.1). The proportion of patients who experienced grade ≥3 AEs was 82.0% with venetoclax-rituximab and 70.2% with bendamustine–rituximab. The percentage of patients with at least one AE leading to treatment discontinuation was 12.9% with venetoclax and 9.0% with bendamustine. The treatment discontinuation rate due to AEs with rituximab was 5.2% in the venetoclax-rituximab arm compared with 6.9% in the bendamustine-rituximab arm.

Quality of life

The patient-reported outcomes (PRO) were included as secondary outcome in the MURANO[1] trial. The analyses centered on changes from baseline (pretreatment) scores for the different instruments (i.e., MDASI, QLQ-C30, and QLQ-cLL16). Day 1 of ramp-up with venetoclax was established as baseline for the V + R arm when patients were pre-treatment. For the bendamustine-rituximab arm, baseline was Cycle 1 Day 1, before the start of combination therapy. A mixed effects model for repeated measures (MMRM) was used to estimate the mean of change from baseline. A ten-point change (or higher) in mean scores indicated a clinically meaningful difference on the QLQ-c30 and QLQ-cLL16. For the MDASI a clinically meaningful difference was defined as a change of 1.2 points or more. Due to administrative errors the baseline PRO assessments (EORTC-QLQ -c30 and CLL16) were partially collected. Additionally the MD Anderson Symptom Inventory (MDASI) was only administered until the end of Cycle 3, also due to administrative error. In the evaluable sample there was no clinically meaningful difference observed between venetoclax-rituximab and bendamustine-rituximab in any of the QOL domains during treatment and through follow-up. However, the health related quality of life results collected in the MURANO[1] trial were inconclusive. Due to administrative errors the baseline scores (EORTC-QLQ -c30 and CLL16) were partially collected which resulted in a significant extent of missing patient reported outcomes data.[2] Although EQ-5D data were collected in the trial, they were not analysed. As a result of these limitations, the health related quality of life results from the MURANO trial were inconclusive.

Limitations

The open-label design of the MURANO trial increases the potential theoretical risk for bias.[1] Aspects of the study that minimise this risk include the use of standard objective measures to evaluate outcomes at pre-specified time points and the involvement of an independent review committee (IRC) in the assessments. Other limitations include

- The median OS was not reached in either treatment arm at the time of primary analysis.
- The pre-specified hierarchical testing of the three key secondary efficacy endpoints failed; therefore, the differences in the complete response (CR)/CR

with incomplete hematologic recovery (CRi), overall response rate (ORR) and OS were descriptive and not statistically significant.
- The assessment of minimal residual disease (MRD) was a pre-specified exploratory endpoint.
- The health-related quality of life (HRQoL) findings were inconclusive due to administrative errors in data collection, which led to a significant extent of missing patient reported outcomes data.
- There was no statistical provision to account for multiple testing of endpoints in the updated analysis. Therefore, all reported p-values were for descriptive purposes only without indicating statistical significance.
- There was no direct comparison with ibrutinib or idelalisib-rituximab which have been approved for treatment in patients with relapsed or refractory (R/R) CLL.

The available data suggest that in general, the study was well-conducted.

Table 1.1: Highlights of Key Outcomes of the MURANO[1] Trial

	Venetoclax-Rituximab (N=194)		Bendamustine-Rituximab (N=195)	
Primary Outcome – PFS by investigator assessment				
Primary analysis at 08 May 2017 (median follow-up 2 years)				
Median PFS [a]	Not reached		17.1 months (15.7, 21.6)	
	HR* 0.17; (95% CI: 0.12, 0.26) p-value <0.0001			
PFS rate, %	84.9 (95% CI: 91.9, 90.6)		36.3 (95% CI: 28.5, 44.0)	
PFS from updated analysis at 08 May 2018* (at 3 years)				
Median PFS [b]	Not reached		17.1 months	
	HR* 0.16 (95%CI: 0.12, 0.23) p-value [c] <0.001			
Key Secondary Outcome				
Primary analysis at 08 May 2017 (median follow-up 2 years)				
Median OS	Not reached		Not reached	
OS rate, %	91.9		86.6	
	HR* 0.48 (95% CI: 0.25, 90) p-value: 0.0186			
ORR (CR/CRi + PR/nPR), %	93.3		67.7	
	Difference: 25.6% (95% CI: 17.9, 33.3)			
MRD-negativity [d] in peripheral blood	162 (83.5%)		45 (23.1%)	
	Difference: 60.4% (95% CI: 52.3, 68.6%)			
Updated analysis at 08 May 2018* (median follow-up 3 years)				
Median OS, months (95%CI)	Not reached		Not reached	
OS rate, %	87.9		79.5	
	HR* 0.50 (95%CI: 0.30, 0.85) p-value [c] = 0.0093			
Harms Outcome, n (%)	Venetoclax–Rituximab (N=194)		Bendamustine–Rituximab (N=188)	
Grade ≥3	159 (82.0)		132 (70.2)	
Patients with ≥1 AE (any grade)	194 (100.0)		185 (98.4)	
WDAE	Venetoclax	Rituximab	Bendamustine	Rituximab
	25 (12.9)	10 (5.2)	17 (9.0)	13 (6.9)

AE = adverse event, CI = confidence interval, HR = hazard ratio, MRD = minimal residual disease; NR = not reported, SD = standard deviation, TRAE = treatment-related adverse event, WDAE = withdrawal due to adverse event

Table 1.1: Highlights of Key Outcomes of the MURANO[1] Trial		
	Venetoclax-Rituximab (N=194)	**Bendamustine-Rituximab (N=195)**
*HR < 1 favours the Venetoclax–Rituximab arm.		

[a] = for primary analysis, data cut-off date May 8th 2017, median follow-up 24 months
[b] = for updated analysis, data cut-off date May 8th 2018, median follow-up 36 months
[c] = p value is only descriptive
[d] = for all times during the 2-year treatment period
* Updated results are only descriptive.

Source: Seymour et al.;[1,3] Kater et al.;[4] Seymour et al.;[5]

1.2.2 Additional Evidence

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

Patient Advocacy Group Input

Patient input on venetoclax (Venclexta) in combination with rituximab (VR) for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy was provided as a joint submission from two patient advocacy groups: Lymphoma Canada (LC) and the CLL Patient Advocacy Group (CLLPAG).

From a patient's perspective, fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to CLL affecting quality of life. Specifically, fatigue and frequent infections were highlighted as greatly impacting patients on an ongoing basis. Respondents also indicated experiencing emotional and mental distress due to their condition; patients felt stress, anxiety and difficulty sleeping, and depression.

Patients had experience with a wide range of therapies (up to six for some patients), including several chemotherapy regimens and various other pharmacological and non-drug therapies. Two-thirds of the patients who responded to the surveys had some experience with ibrutinib therapy. Fatigue, anemia or neutropenia, nausea, thrombocytopenia, diarrhea and infections were side effects of current therapies most frequently cited by patients. Patients reported that the most difficult side effects to tolerate were fatigue, nausea and frequency of infections. Patients viewed intravenous (IV) therapy as having a larger impact on quality of life than oral therapy (see Table 9). Caregivers consistently reported some interruption in their ability to perform various life activities, however the impact was generally small.

In terms of expectations for alternative treatment options, focus was placed on individualized treatment options, delaying disease progression, reducing side effects, improving quality of life, having accessible and affordable treatments, and an oral route of administration.

A total of 14 patients had experience with venetoclax-rituximab. Overall, patients had a favourable experience. Most patients saw a reduction in commonly reported symptoms with CLL. The majority of patients

experienced improvement in lymph node size, lymphocyte counts, and fatigue. Treatment with VR led to various side effects; most commonly reported were neutropenia, fatigue, and diarrhea. The majority of respondents indicated that they were willing to tolerate potentially serious or significant side effects. Overall, treatment did not have a significant negative impact on quality of life and daily living, although patients noted that clinician visits and infusions were burdensome. In that regard, patient groups remarked that the potential availability of subcutaneous rituximab would reduce the need for visits to the clinic. The opportunity of VR discontinuation after reaching MRD status was an important advantage over other treatments according to the patient groups.

Provincial Advisory Group (PAG) Input

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

Clinical factors:

- Sequencing of treatments

Economic factors:

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

Registered Clinician Input

pCODR received three clinician input submissions (representing fifteen clinicians) on the combination of venetoclax and rituximab (VR) in patients with chronic lymphocytic leukemia (CLL) who have received and failed at least one prior therapy. The submissions from Cancer Care Manitoba and Cancer Care Ontario (CCO) provided the perspective of an oncologist and a hematologist, respectively. Alberta Health Services submitted a joint input from thirteen clinicians comprising nine hematologists, three medical oncologists, and one hematology nurse practitioner.

The clinicians mentioned that for the specified indication, the most relevant comparator for VR would be ibrutinib. However, evidence comparing the two regimens is lacking. Clinicians have a positive experience with VR and view the time-limited treatment of two years as more attractive to patients and payers, although IV administration of rituximab remains a challenge. The fewer contraindications of VR compared with ibrutinib also make it an attractive option for patients with cardiovascular conditions.

The use of minimal residual disease (MRD) testing was mentioned by some but not all clinicians as a metric to inform treatment decisions and discontinuation. Sequencing of alternative therapies before and after VR remains theoretical with little supporting data, but most clinicians would prefer VR as first-line/second-line and use ibrutinib after VR has failed.

Summary of Supplemental Questions

The submitted ITC evaluated the relative effectiveness of the venetoclax-rituximab combination versus ibrutinib single-agent and idelalisib-rituximab combination in adult patients with R/R-CLL by estimating hazard ratios (HR) for survival and relative risk ratios (RR) for tumour responses. However, given that PFS and OS were the outcomes required for the submitter's economic model, they are the only outcomes discussed in this section. The unanchored ITC estimates suggest a higher OS rate for venetoclax-rituximab than ibrutinib single agent (HR 0.297, 95% CI: 0.129 to 0.684). However, the PFS difference between the two treatments did not reach the level of statistical significance (HR 0.696, 95% CI: 0.412 to 1.178). The unanchored ITC estimates suggest higher PFS and OS rates for venetoclax-rituximab than idelalisib-rituximab (HR 0.178, 95% CI: 0.086 to 0.368; and HR 0.223, 95% CI: 0.084 to 0.593, respectively). The findings must be interpreted with caution given that the assumptions of the unanchored ITC are difficulty to meet and there is an unknown amount of bias in the unanchored estimate.

See section 7.1 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 1.2 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 1.2: Assessment of generalizability of evidence for venetoclax-rituximab for CLL				
Domain	**Factor**	**Evidence** **MURANO Trial by Seymour et a., 2018[1]**	**Generalizability Question**	**CGP Assessment of Generalizability**
Population	Line of treatment	The MURANO trial included patients who had received one to three previous treatments (including at least one chemotherapy containing regimen). The majority of patients in both treatment arms had a single previous anti-CLL therapy (57.2% in the venetoclax-rituximab arm and 60% in the bendamustine-rituximab arm). The majority of patients in both treatment arms had prior anti-CLL therapy with: (venetoclax–rituximab vs. bendamustine–rituximab) alkylating agent (93.3% vs. 95.4%), purine analog (80.5% vs. 81.4%), and anti-CD20 antibody 78.5% vs. 76.3%). The proportion of patients with prior B-cell receptor inhibitors was less than three percent in both arms (2.6% vs. 1.5%). No evidence available to assess the efficacy and safety of venetoclax in the front line setting.	• Does the proportions of prior CLL treatments received by patients in the trial limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice patients)	There may be a difference in the proportions of prior CLL treatments received by patients between the MURANO trial and Canadian clinical practice (e.g., currently approximately 30-50% of patients, based on the age distribution of CLL, will have received chloramubucil-obinutuzumab, and 20-30% may have received bendamustine-rituximab), but this does not limit the interpretation of the trial results. CGP notes that an increasing number of patients will have received a BCR pathway inhibitor such as ibutinib which has become available for high risk cytogenetic subtypes as primary therapy, and for treatment beyond first-line for other patients, but the results from the Murano trial are applicable to this patient population as well.
			Are the results of the MURANO trial generalizable to patients for whom fludarabine-based treatment is considered inappropriate and who	As above, generalization is felt to be appropriate to this population, based on biological plausibility and phase I and phase II data from

Table 1.2: Assessment of generalizability of evidence for venetoclax-rituximab for CLL				
Domain	**Factor**	**Evidence MURANO Trial by Seymour et a., 2018[1]**	**Generalizability Question**	**CGP Assessment of Generalizability**
			have been previously treated with first-line ibrutinib.	other trials including post BCRi failure [6,7]
			Are the results of the MURANO trial generalizable to patients who currently receive monotherapy venetoclax for previously treated CLL (i.e., who have received at least one prior therapy and who have failed a BCRi)? Should rituximab be added to their treatment? If so, at what point in their treatment?	There are no data specifically addressing the addition of rituximab to patients who are responding to venetoclax. However, CGP considers that it would be reasonable to add rituximab at any point at the discretion of the treating physician. The CGP does not recommend additon of rituximab to those patients who are progresssing on venetoclax, as there are no data that doing so would result in response; this clinical scenario was not addressed in the Murano trial.
			Are the results of the MURANO trial generalizable to patients who have received obinutuzumab or chlorambucil, as obinutuzumab has been associated with greater efficacy and potency than rituximab in CLL.	The Murano trial are applicable to this patient population, based on biological plausibility.
	Performance Status	Patient with ECOG PS of 0 or 1 were eligible. There are no data for patients with ECOG 3 or 4.	Does performance status limit the interpretation of trial results?	Most patients in clinical practice will have an ECOG PS of 0 or 1. The benefit for patients with ECOG 2 cannot be concluded, however, it would be

Table 1.2: Assessment of generalizability of evidence for venetoclax-rituximab for CLL				
Domain	**Factor**	**Evidence** **MURANO Trial by Seymour et a., 2018[1]**	**Generalizability Question**	**CGP Assessment of Generalizability**
				reasonable to expand combination therapy to patients with a good performance status, based on clinical experience and the manageable side-effect profile. Consideration of whether therapy for patients with poor performance status will provide benefit is a clinical decision that should be left to the treating physician.
	Organ dysfunction	The trial limited eligibility to patient's with adequate bone marrow, renal, and hepatic function	Does the exclusion of patients with significant renal impairment limit interpretation of trial results?	Treatment of patients with impaired organ function should be based on a clinical decision weighing risks and benefits of therapy.
Intervention	Treatment intent	The intent of treatment in the trial was curative and/or palliative?	Are the results of the treatment generalizable to an alternative treatment intent? (i.e., if the trial is palliative in intent, could the therapy also be used in the adjuvant setting or vice versa?)	There is no other relevant treatment intent for CLL: treatment is symptomatic and palliative.
	Administration of intervention	Venetoclax was administered according to a 5-week schedule of a gradual increase in the dose (ramp-up) from 20 mg per day to 400 mg per day. After completion of the dose ramp-up period for venetoclax, administration of rituximab (375 mg per square meter of body-surface area intravenously for the first dose [day 1 of cycle 1] and 500 mg per square meter	Is the intervention administered differently (e.g., dose or schedule) in clinical practice than in the trial ?	The dose and schedule including ramp-up phase are familiar to clinicians and considered standard.

Table 1.2: Assessment of generalizability of evidence for venetoclax-rituximab for CLL				
Domain	**Factor**	**Evidence** **MURANO Trial by Seymour et a., 2018[1]**	**Generalizability Question**	**CGP Assessment of Generalizability**
		intravenously thereafter [day 1 of cycles 2 through 6]) was initiated in 28-day treatment cycles, while daily administration of venetoclax was continued. Administration of venetoclax at a dose of 400 mg per day was continued for 2 years (which was calculated from day 1 of cycle 1) unless disease progression or unacceptable toxic effects occurred sooner.		
Comparator	Brendamustine in combination with rituximab	The comparator in the MURANO trial was bendamustine in combination with rituximab. Bendamustine was administered at a dose of 70 mg per square meter was administered intravenously on days 1 and 2 of each 28-day cycle for six cycles in combination with rituximab. Rituximab was administered according to the same dosing schedule as in combination with venetoclax (see above). Currently funded treatments for patients who have received at least one prior therapy are ibrutinib or idelalisib in combination with rituximab. In order to assess the comparative efficacy of venetoclax plus rituximab compared with ibrutinib or idelalisib plus rituximab, the pCODR Methods Team reviewed one submitter-provided ITC. Refer to section 7 for more details.	Are the findings of the MURANO trial generalizable to patients who may receive ibrutinib or idelalisib in combination with rituximab instead of bendamustine and rituximab?	Due to the lack of randomized comparative data, there is no reliable estimate of the comparative efficacy of venetoclax plus rituximab to ibrutinib or idelalisib plus rituximab. The CGP suggests that, patient values and preferences, co-morbidities, treatment toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection in clinical practice. Refer to section 7 for the complete critical appraisals of the submitter-provided ITC.
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcome of the trial was investigator assessed PFS. The secondary outcomes were PFS by IRF, PFS among patients with chromosome 17p	Were the primary and secondary outcomes appropriate for the trial design?	PFS as a primary endpoint is considered appropriate in an indolent neoplasm like CLL, where both heterogeneous

Table 1.2: Assessment of generalizability of evidence for venetoclax-rituximab for CLL

Domain	Factor	Evidence MURANO Trial by Seymour et a., 2018[1]	Generalizability Question	CGP Assessment of Generalizability
		deletion, ORR and CRR, OS, rates of clearance of MRD (to below the threshold of 1 tumor cell per 104 white cells), the DOR, event-free survival, and the time to the next treatment for CLL.		disease biology and application of further therapies after progression may influence overall survival. Large improvements in PFS, especially when accompanied by a favourable toxicity profile, may change practice, without demonstrating an improvement in OS.
Setting	Supportive care medications, procedures, or care	Prophylactic and monitoring measures were instituted to mitigate the potential for development of the tumor 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.	Treatment should only be provided in settings able to provide appropriate supportive care to prevent and manage TLS.

BCR = B-cell receptor; CLL = Chronic lymphocytic leukemia; CGP = pCODR Clinical Guidance Panel; CRR = complete response rate; ECOG PS = Eastern Cooperative Oncology Group (ECOG) Performance Status; ITC = Indirect treatment comparison; MRD = Minimal residual disease; TLS = tumor lysis syndrome; ORR = objective response rate; OS = overall survival; PFS = progression free survival.

1.2.4 Interpretation

Burden of Illness and Need

Chronic lymphocytic leukemia (CLL) is an incurable malignancy of B lymphocytes. With an incidence of approximately 4-5/100,000 in the general population, it is the most common adult leukemia in the western hemisphere. Approximately 2,400 Canadians are diagnosed and 650 die from CLL each year.[8] Median age at diagnosis is 72 years, and within incident cases there is a male predominance. Current front-line therapy for symptomatic patients is selected on the basis of age and comorbidities, in order to minimize toxicities and maximize disease control. Treatments include conventional chemotherapy drugs (fludarabine + cyclophosphamide, bendamustine or chlorambucil) combined with a CD20 antibody (rituximab or obinutuzumab). Disease control as reflected in progression-free survival ranges from 36-60 months with current front-line combination therapy depending on risk factors at the time of therapy (including cytogenetic assessment of CLL cells by FISH); duration of response in second or third line is usually much shorter, 12-24 months.

Bendamustine-rituximab represents a frequent second-line regimen (for those patients who are bendamustine-naïve or who experienced prolonged benefit from primary therapy with chemo immunotherapy and 2 year treatment-free interval since last dose of anti-CD20 antibody); however this option is not available in all provinces due to funding limitations. The CGP noticed that obinutuzumab in combination with chlorambucil was mentioned as comparator in the registered clinician input (see section 5). However, CGP noted that obinutuzumab-chlorambucil does not have Health Canada approval and is not funded currently for second-line therapy, therefore, this combination would not be a relevant comparator to venetoclax-rituximab. Increasingly, B cell receptor (BCR) pathway inhibitors—ibrutinib and much less frequently idelalisib—are becoming the most common second-line treatments in Canada, supported by previous pCODR and Provincial Cancer Agency funding decisions. In addition, ibrutinib is standard therapy for the minority of patients identified to have aberrations in TP53 (usually 17p deletion detected by FISH) because of the relative lack of efficacy of chemoimmunotherapy in this patient population. The BCL2 antagonist venetoclax has become available as third-line therapy, due to its activity in heavily pre-treated patients, relatively favourable toxicity profile (including oral bioavailability) and activity that is independent of TP53 status.

Based on clinical opinion, it is reasonable to anticipate that if venetoclax plus rituximab becomes available for patients with CLL that can no longer be adequately controlled by chemoimmunotherapy approximately 500 patients will be treated with this new agent per year in Canada for this indication.

Venetoclax-rituximab represents an important new treatment option for patients needing second- or third-line therapy for CLL, because of the prolonged PFS observed with this regimen with a finite duration of therapy. Bendamustine-rituximab remains a relevant comparator for many patients, and venetoclax-rituximab is clearly a superior treatment for such patients. There are no data regarding the use of standard chemoimmunotherapy after failure of a BCR inhibitor (mostly ibrutinib in the current Canadian environment) as first or second-line therapy, and CGP feels that venetoclax-rituximab represents an important new treatment option for those patients.

Effectiveness

In the phase III Murano trial, patients who had progressive CLL following chemoimmunotherapy were randomized to receive bendamustine-rituximab or venetoclax-rituximab. Patients in the bendamustine-rituximab arm received up to six 28-day cycles, while those in the experimental arm received longer duration of treatment, with rituximab monthly for six doses, and daily dosing of venetoclax continued until progression or for up to 2 years. Most patients were treated after one line of therapy (~60%), and 25% after 2 lines of therapy; notably, very few patients had previously received a BCR inhibitor. Two-year PFS rates were significantly different: 84.9% vs 36.3% (HR 0.17, p<0.001 by stratified log rank test). In all pre-specified patient subset analyses, venetoclax rituximab resulted in superior PFS, notably in those with TP53 abnormalities (17p-, TP53 mutation or both), which comprised 40% of the study population. Significantly more patients were found to have negative peripheral blood testing for minimal residual disease (MRD; < 1 tumor cell in 10^4 WBC), 62.4% vs 13.3%, an important surrogate for progression-free survival.[9] This response was maintained during venetoclax therapy, though the duration of MRD response after cessation of treatment is not described. Taken together, these results represent an important advance in the management of relapsed CLL and provide another treatment option in this patient population, especially those who have TP53 abnormalities, some of which arise at the time of relapse as part of clonal evolution. Follow-up is still short. However, this study showed a trend towards better OS at 2 years in favour of the venetoclax-rituximab group (HR 0.48), despite the fact that 20% of patients assigned to bendamustine + rituximab received a BCR or BCL2 inhibitor after progression.

It is not possible to conclude the benefit of venetoclax-rituximab in a patient population that would be more reflective of the current use of BCR pathway inhibitors—largely ibrutinib—for both front-line therapy and at first progression. However, it would be reasonable to expand the venetoclax combination with rituximab to patients, who have been previously treated with first-line ibrutinib based on biological plausibility and phase I and phase II data from other trials including post BCRi failure (M14-032).[6,7]

The CGP noted that B cell receptor (BCR) pathway inhibitors—ibrutinib and much less frequently idelalisib—are rapidly becoming the most common second-line treatments in Canada. The CGP acknowledged that in order to assess the comparative efficacy of venetoclax and rituximab to ibrutinib and idelalisib plus rituximab in patients with CLL who have received at least one prior therapy, irrespective of their 17p deletion status, the pCODR Methods Team reviewed an unanchored matched adjusted indirect comparison (MAIC). The unanchored ITC estimates suggest a significantly higher OS rate for venetoclax-rituximab than ibrutinib single agent (HR 0.297, 95% CI: 0.129 to 0.684). However, the PFS difference between the two treatments did not reach the level of statistical significance (HR 0.696, 95% CI: 0.412 to 1.178). The unanchored ITC estimates suggest significantly higher PFS and OS rates for venetoclax-rituximab than idelalisib-rituximab (HR 0.178, 95% CI: 0.086 to 0.368; and HR 0.223, 95% CI: 0.084 to 0.593, respectively). The quality assessment performed by the pCODR Methods Team determined that no decisive conclusion can be drawn from the manufacturer-submitted ITC for how the effectiveness of venetoclax-rituximab compares with that of ibrutinib monotherapy or with that of idelalisib-rituximab in patients with r/r CLL. The unanchored ITC between the two treatments assumed that absolute outcomes can be predicted from the covariates, accounting for all effect modifiers and prognostic factors. This assumption is mostly considered impossible to meet,

leading to an unknown amount of bias in the unanchored estimate. Also, since the median PFS and OS had not been reached in the studies, there is uncertainty about how the intervention will compare using matured data. The CGP agreed with the Methods Team and cautioned against drawing conclusions from the ITC on the magnitude of effect of venetoclax-rituximab compared with either one of the BCR pathway inhibitors given the absence of more robust direct evidence from a randomized trial and lack of long term outcomes such as OS and safety. The CGP noted that it seemed likely that in clinical practice similar PFS benefits would be observed between venetoclax-rituximab and ibrutinib monotherapy and possibly better tolerability and efficacy compared to idelalisib-rituximab. However, the CGP concluded that there is insufficient evidence to determine the comparative effectiveness of venetoclax-rituximab compared to ibrutinib monotherapy or compared to idelalisib-rituximab and therefore patient values and preferences, co-morbidities, individual toxicity profiles, and treatment availability (provincial reimbursement) should guide treatment selection. Refer to section 7 for the complete critical appraisal of the ITC.

Safety

The principal toxicity in both arms of the MURANO trial, was neutropenia, with grade 3 or 4 neutropenia reported in 57.7% of patients receiving venetoclax and 38.8% of patient receiving bendamustine. This may in part reflect the longer duration of therapy for those on the venetoclax arm; notably the incidence of grade 3 or 4 febrile neutropenia or infections was higher with bendamustine-rituximab. Approximately one-half of patients in both arms received growth factor support (48 and 43%). Myelosuppression requiring supportive measures is common in therapies for hematologic malignancies and can be successfully managed and prevented by clinicians who treat CLL.

The use of a ramp-up dosing strategy for initiation of venetoclax has been shown to reduce or eliminate the development of tumor lysis syndrome (TLS), and identification of those patients who are at high risk because of bulky nodal masses or high lymphocyte counts and who should be managed with brief hospital admission for hydration and monitoring, has become standard practice. In this study, with appropriate supportive measures, laboratory evidence of TLS was seen in only 6 patients (3.1%) on the venetoclax arm compared to 2 patients (1.1%) receiving bendamustine-rituximab; only one patient on each arm had additional clinical evidence of TLS. Adverse events resulting in death were similar in both arms (5.2 % and 5.9%) and there were four fatal infections in each arm.

Overall, the combination of venetoclax-rituximab has a toxicity profile that is manageable by clinicians and similar to that of a common second line chemoimmunotherapy regimen.

Several questions have been raised regarding the applicability of these results to certain patient populations:

1) Patients in the MURANO trial were eligible for venetoclax-rituximab if they were previously treated with 1-3 lines of therapy, including at least one standard chemotherapy-containing regimen. PAG is seeking guidance on, for patients treated with a first-line rituximab-containing regimen (e.g., fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine-rituximab), the appropriate minimum treatment-free interval for these

patients and their treatment with venetoclax-rituximab.

   a. It should be noted that patients who had no response to a front-line chemotherapy-containing regimen, or who progressed within 24 months of chemoimmunotherapy were considered high risk, but were eligible for the Murano trial. Clinical trials in CLL which have included a CD20 antibody second line have not specified a treatment-free interval as an eligibility criterion (see for example Furman R, NEJM 2014).[10] Patients who have responded to rituximab-containing therapy such as FCR or obinutuzumab-containing therapy would be considered to have CLL that is sensitive to a CD20 antibody if the treatment-free interval is 12 months or longer; however it should be noted that benefit was seen for venetoclax over bendamustine in those patients with CLL refractory to prior therapy (i.e., a treatment-free interval shorter than 12 months).

2) Venetoclax is a 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 and require additional pharmacy resources. PAG noted that the multiple tablet strengths as well as fills during the ramp up dose schedule can lead to an increased risk for medication error, where appropriate patient education and monitoring will be required for implementation. However, the packaging of venetoclax identifies the ramp up dosing schedule.

   a. There will be need to educate patients on toxicities and need for adherence to ramp up dosing, but this will not require additional resources to be in place; patients will have ongoing monitoring for TLS during this time and dosing can be reviewed at their regular clinic visits with medical staff; additional resources are not in place for bendamustine which is IV or oral idelalisib.

3) The dosing schedule for venetoclax-rituximab is for a fixed duration of 24 months. PAG is seeking clarity on treatment duration. For patients who do not experience progression, whether there are instances where these patients should be treated beyond the 24 months of treatment.

   a. There are no data regarding the benefits of continuing venetoclax beyond the 24 month duration post-ramp-up; in light of the observation that there are higher rates of neutropenia with venetoclax-rituximab compared to bendamustin-rituximab, in part due to duration of therapy, treatment beyond 24 months would not be recommended.

4) For patients who have completed the 24 months of treatment, whether these patients should be re-treated with venetoclax-rituximab upon progression.

   a. Re-treatment with venetoclax upon progression, for those who showed benefit and were able to tolerate the drug during the initial 24 months, should be an option. It is not possible to identify a minimum duration of response off therapy that would predict response to re-treatment; progression-free survival duration of 12 months or more would be reasonable.

      In their feedback on the initial recommendation, PAG had the

following questions regarding re-treatment with venetoclax-rituximab.

- Did the trial allow re-treatment with rituximab? If yes, what criteria were applied? What proportion of patients would require re-treatment?

  In response to PAG's questions the pCODR Methods Team stated that the MURANO study protocol did not specify a retreatment strategy, and therapy after the occurrence of disease progression was at the investigators' discretion (Seymour et al., 2017; page 3). Further, the venetoclax–rituximab combination was not used for retreatment in any patient enrolled in the MURANO trial.

  Over a median follow-up of 3 years (updated analysis; data cut-off May 8, 2018) a total of ten patients (three in the venetoclax-rituximab arm and seven in the bendamustine-rituximab arm) were treated with venetoclax monotherapy as subsequent CLL therapy.

  The time between initial treatment with the venetoclax–rituximab combination and the commencement of subsequent therapy for CLL with venetoclax monotherapy was not reported. Therefore, it is unclear whether the retreatment occurred during or after the 2-year treatment duration. Also, the median time to the next anti-CLL treatment (defined as the time from randomization to start of new, non-protocol, anti-CLL therapy or death from any cause) had not been reached in the venetoclax-rituximab arm, even at the updated analysis.(Kater et al., 2018 page 3).

  There is no evidence from the MURANO trial regarding the proportion of patients requiring re-treatment with venetoclax-rituximab. In response to PAG's question the CGP Lead noted that since there are other treatments that could be offered in the setting of progression after venetoclax-rituximab therapy, it is difficult to be precise in estimating the number who would be retreated with this combination. Conservatively, since the drug is well tolerated, up to 50% could be retreated.

5) Prophylactic intravenous hydration and anti-hyperuricemics are required prior to first dose of venetoclax to reduce risk of TLS and regular monitoring of blood chemistries after the first dose is required. The initiation of treatment may require hospitalization to monitor and treat tumour lysis syndrome. Rasburicase may be required to treat TLS which would be additional costs associated with venetoclax-rituximab therapy

   a. The measures outlined to reduce the risk of TLS align with Canadian practice. The proportion of patients who would require hospitalization for hydration or monitoring (based on high-risk features of bulky adenopathy and elevated lymphocyte count) is hard to predict in general practice, but likely to be less than half of

patients. In the Murano trial, 28% of patients were at high risk of TLS and 55% at medium risk; therefore about 1 in 4 patients would need admission for hydration and monitoring, but this is usually brief (one or two days for the first admission, one day for the second admission if needed); it is not possible to estimate the proportion who would require rasburicase but in clinical experience it is low.

6) PAG noted that pharmacy resources and weekly clinic visits would be required with venetoclax-rituximab. Venetoclax is associated with drug-drug interactions and neutropenia. These adverse events would require additional health care resources compared to other second-line therapy options.
    a. Beyond the first month of therapy, the frequency of visits to clinic would not be expected to be different between those who receiving venetoclax-rituximab vs. those receiving bendamustine-rituximab (in the latter case, it is 3 visits/month for assessment and treatment, not counting visits to manage toxicities). While the incidence of neutropenia is slightly higher, febrile neutropenia was lower with venetoclax, and persistent neutropenia would be managed with dose reduction, as it would for bendamustine. There are significant toxicities associated with idelalisib (pneumonitis, enteritis) that require monitoring, dose adjustment and treatment. Drug interactions are possible with many new targeted agents; patient and practitioner awareness of this will be required and reinforced during clinic assessments, but should not consume additional resources.
7) In clinical practice if available, would subcutaneous rituximab be used in combination with venetoclax?
    a. There are no published data on the use of subcutaneous rituximab in the management of CLL; the use of this preparation in patients who tolerate an initial IV rituximab infusion may be adopted as standard practice in the future, and this route of administration would be considered appropriate in combination with venetoclax as given in the Murano trial.

Sequencing questions:

8) PAG noted that other second-line treatments may be available (e.g., ibrutinib, idelalisib plus rituximab). For patients who have received one prior therapy, what would be the best treatment?
    a. The optimum sequencing of therapies in CLL is evolving and current data do not inform this decision directly. For those who commenced therapy with standard chemoimmunotherapy (e.g., FCR or FR, as was the case for most patients in the Murano trial), venetoclax-rituximab would be an option. However, there are data that would also support single agent ibrutinib in this patient population, especially for CLL with unmutated IGH genes or who have acquired a TP53 derangement. The choice between a fixed duration of therapy (venetoclax-rituximab) and treatment until progression (ibrutinib or other BTK inhibitor) would be influenced by discussions of patient values and (indirect) comparative toxicities.

For the increasing number of patients who will have commenced a BTK inhibitor as primary therapy and experienced progression or intolerance, venetoclax-rituximab would be an attractive first choice based on the Murano trial, under the assumption that those results obtained in the BTKi-naïve population would be similar in patients previously treated with ibrutinib. Bendamustin-rituximab or FCR could also be considered for those without high-risk genetic abnormalities, following discussion of toxicities and duration of therapy (24 months for venetoclax-rituximab, 6 months for chemoimmunotherapy).

Currently in Ontario, idelalisib-rituximab is funded for patients with relapsed CLL/SLL in combination with rituximab. Patients whose disease has progressed on ibrutinib therapy in the relapsed setting are not eligible to receive idelalisib. Patients who have experienced intolerance but not disease progression to ibrutinib in the relapsed setting may switch to idelalisib. Idelalisib was studied in patients with poor renal function and/or high levels of comorbidity (median CIRS score 8).[10] The proportion of patients in the Murano trial who would have been eligible for the study by Furman et al.[10] is not known, but either regimen (venetoclax-rituximab or bendamustine-rituximab) could be used after initial chemoimmunotherapy, or, as discussed above, following front-line ibrutinib (or in the future, acalabrutinib), in patients with comorbidities. A number of real-world and phase II studies suggest venetoclax is active after treatment with a BCR pathway inhibitor (either BTK or PI3Kinase),[11-13] although the Murano data suggest that use of venetoclax prior to treatment with these agents produces excellent disease control with manageable toxicities.

9) Ibrutinib was recently reviewed at pCODR, for the treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy and are not considered appropriate for treatment or re-treatment with a purine analog (e.g., fludarabine). In what clinical scenarios would ibrutinib or venetoclax-rituximab be the preferred treatment for patients with CLL that have received at least one prior therapy? Please comment on the preference considering patient preference, efficacy, safety, and administration.
    a. The scenario above—patients with relapsed CLL not appropriate for purine analog-based therapy—would include some patients eligible for the Murano trial, and others who were ineligible, on basis of organ function or performance status. As previously mentioned, decisions as to the appropriateness of ibrutinib vs venetoclax are complex, and, with the currently available safety data for both of these agents, should be left to the discretion of the treating physician. Patients, for example, who might be at high risk of morbidity from TLS and/or the supportive therapy required to administer venetoclax because of cardiac or renal impairment, may be better treated with ibrutinib.

10) What is the optimal sequencing for patients with del(17p) who have received first-line ibrutinib (e.g. venetoclax monotherapy, venetoclax-

rituximab)?

a. Venetoclax-rituximab should be used second-line after progression of disease on ibrutinib (in the absence of known transformation to large B cell lymphoma, an exclusion criterion of the Murano trial), in light of the lack of efficacy of chemoimmunotherapy in this patient population, and the benefit seen in patients with TP53 deletion or mutation over bendamustine-rituximab in this trial.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to venetoclax in combination with rituximab over standard chemoimmunotherapy (bendamustine-rituximab) for patients with CLL who have received at least one prior therapy. This is based on a single high quality randomized controlled trial (MURANO), which showed a significant improvement in progression-free survival and a clinically meaningful improvement in MRD negative rate with an acceptable degree of treatment-related toxicity in the venetoclax-rituximab group compared to patients receiving bendamustine-rituximab. The trial data on OS remain immature at the primary and updated analyses, however, it should be noted that the three-year update shows a consistently higher improvement in OS rate with venetoclax-rituximab.

Benefit was seen among patients with a number of risk factors for treatment failure, including those with TP53 abnormalities, where standard chemotherapy has been shown to be much less effective. Hematologic toxicities were manageable and TLS preventable with standard supportive treatments. Venetoclax-rituximab represents an important new treatment option for patients with relapsed or refractory CLL.

In making this conclusion, the Clinical Guidance Panel also considered:

- The study population in the Murano trial was BCRi naïve (<3% of patients in in both arms received BCR inhibitors), and there is increasing use of ibrutinib in first line therapy for patients with TP53 aberrations and other high risk features such as unmutated immunoglobulin genes.
- The CGP is aware of recent presentation and publication of studies of ibrutinib as front-line therapy for CLL which show significant advantages in PFS and OS over standard chemoimmunotherapy, which will change the nature of patients who require second or third line therapy in the future.[14,15] These trials employed treatment with ibrutinib until progression or intolerance (ie, indefinite therapy) and other trials evaluating strategies of fixed duration of treatment are ongoing.
- The optimum sequencing of agents targeting the BCR pathway (ibrutinib, acalabrutinib, idelalisib) and BCL2 inhibitors is unknown and data on this important area are evolving.
- The durability of MRD response upon cessation of venetoclax therapy is unknown, and whether a continuous dosing strategy is superior to the 24 month treatment has not been tested directly.

2 BACKGROUND CLINICAL INFORMATION

Chronic lymphocytic leukemia is one of the most common hematologic malignancies, with an incidence of 4.8 cases/100,000 persons: 2,465 Canadians were diagnosed with CLL and 608 died from this disease in 2013 according to the most recent available Canadian statistics.[8] The majority of persons with CLL are asymptomatic, and diagnosed because of the finding of an elevated white blood cell count.

The diagnosis is usually made of flow cytometry of peripheral blood demonstrating the characteristic immunophenotype of CLL cells, which demonstrate kappa- or lambda immunoglobulin light-chain restriction, and CD19+, CD20+, CD5+, CD23+, CD10-, with absent or dim expression of FMC-7 and CD79a.[16] There must be $\geq$ 5 x 10^9 cells/L in the peripheral blood with this phenotype for a diagnosis of CLL to be made; some patients present with lesser degrees of lymphocytosis and are designated as having monoclonal B cell lymphocytosis, which generally has a much longer natural history than CLL.[17] Lymph node infiltration by B-lymphocytes with a CLL immunophenotype may occur in the absence of peripheral lymphocytosis; when this occurs, a diagnosis of small lymphocytic lymphoma (SLL) is made. CLL and SLL are generally considered to be manifestations of the same indolent lymphoma and are managed similarly, with a strategy of initial observation for patients who present with normal blood counts (hemoglobin, neutrophils and platelets) without extensive lymphadenopathy and enlarged liver or spleen. At 3 years follow-up, 75-80% of patients who present with lymphocytosis (Rai stage 0) were free of progression.[18] Outcome of patients according to the two accepted staging systems is summarized in the table below[18,19].

Staging System	Stage	Definition	Median OS (mo) Original Report	Median OS (mo) Mayo Clinic database
Rai	0	Blood/marrow lymphocytosis	126	130
	1	Lymphadenopathy	92	106
	2	Splenomegaly	53	88
	3	Anemia (Hb < 110)	23	58
	4	Thrombocytopenia (Plt < 100)	20	69
Binet	A	< 3 lymph node areas*	128	
	B	$\geq$ 3 lymph node areas	47	
	C	Anemia (Hb < 100) or thrombocytopenia (Plt < 100)	24	

* Lymph node areas for Binet staging: unilateral or bilateral cervical, axillary or inguinal lymph nodes, liver and spleen.

Several prognostic factors determine time to progression and overall survival in patients with CLL, including age, lymphocyte doubling time and serum ß2microglobulin. The four molecular/biologic features that have the best track

record for use as clinical prognostic parameters are IGHV mutation status, recurrent cytogenetic abnormalities as identified by FISH testing, zeta-associated protein (ZAP) 70 expression and CD38 protein expression. Among these, at the present time, only the presence of del17p has been used to direct therapy, although increasingly the presence of identification of unmutated IGHV, associated with shorter progression-free and overall survival with standard immunochemotherapy, has been suggested as an indication for primary therapy with ibrutinib.[20] A prognostic index incorporating these molecular and clinical factors (*TP53* status (no abnormalities *vs* del17p or *TP53* mutation or both), *IGHV* mutational status (mutated *vs* unmutated), serum ß $_2$-microglobulin concentration (≤3·5 mg/L *vs* >3·5 mg/L), clinical stage (Binet A or Rai 0 *vs* Binet B–C or Rai I–IV), and age (≤65 years *vs* >65 years) has recently been published that refines the ability to identify patients who could benefit from targeted therapies.[21]

2.1 Accepted Clinical Practice

Common indications to initiate therapy for CLL include the development of anemia and thrombocytopenia (Rai stage 3 or 4 disease, or Binet stage B or C), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< 3 months).[16] Once a need for therapy is established, the choice of first line therapy depends on the age and overall health of the patient, as well as knowledge of specific risk factors determined by cytogenetic or molecular testing.

Patients with symptomatic Chronic Lymphocytic Leukemia		
Line of Therapy	Non-del17p	del17p
1st-Line: Fit, age 65-70	FCR (fludarabine, cyclophosphamide,rituximab)	Ibrutinib
Less fit, frail; age>70	BR (bendamustine, rituximab) CO (chlorambucil, obinutuzumab)	ibrutinib
Maintenance	not indicated	not indicated
2nd-Line	BR Ibrutinib Idelalisib + rituximab	Idelalisib + rituximab venetoclax

First-line

For patients with CLL who require treatment and who are in good health and under the age of 65-70 years, the combination of fludarabine, cyclophosphamide and rituximab (FCR) is standard in most provinces in Canada. The German CLL Study Group study showed improvement in PFS (median PFS: 51.8 vs. 32.8 months, p<0.0001) and OS (percentage of patients being alive at 3 years after randomization: 87% vs. 83%, p=0.012) with the addition of rituximab to FC.[22] Patients over the age of 65-70, or those who are not considered fit enough to receive FCR may derive benefit from several less intensive regimens. Patients treated with fludarabine have a higher rate of severe infection and neutropenia; therapy requires close monitoring of renal function and the use of prophlyaxis

against pneumocystis jiroveci pneumonia (PJP) and herpes virus infection for up to one year after completion of therapy.

Chlorambucil, an alkylating agent that is well tolerated and has been in use for more than 30 years, is a standard agent for older patients or those with significant comorbidities, given on a number of schedules. The addition of a CD20 monoclonal antibody to first-line chlorambucil and bendamustine has been attempted to improve response rates without significantly increasing toxicity. In phase III studies, the CD20 monoclonal antibodies rituximab, ofatumumab, and obinutuzumab, have all demonstrated higher complete and overall response rates and progression-free survival without a significant increase in toxicity.[23,24] A survival advantage was also demonstrated with the combination of obinutuzumab-chlorambucil compared to chlorambucil alone in a phase III trial in patients with high comorbidity scores or impaired renal function rather than age as the main eligibility criteria.[24]

In a randomized phase III trial comparing fludarabine, cyclophosphamide and rituximab (FCR) to bendamustine-rituximab, conducted in fit patients (CIRS score <6) with CLL without 17p deletion, PFS was superior among patients treated with FCR (median 55.2 months) compared to bendamustine-rituximab (median 41.7 months). In a subset analysis of patients who were older than 65 years or who had a CIRS score 4-6, there was no difference in PFS, but bendamustine-rituximab resulted in less hematologic toxicity, suggesting that this regimen may be appropriate for older patients or those with limited comorbidities.[25]

Particularly challenging is the management of patients with CLL that has abnormalities in TP53, either arising from deletion (detected by FISH as del17p) or mutation (detected as a mutation by direct sequencing). Del17p is associated with shorter time to progression from diagnosis and a lower response rate, and shorter PFS and overall survival following chemoimmunotherapy regimens such as FCR.[22] Agents which interfere with B cell receptor signaling that is the hallmark of CLL, such as the BTK inhibitor ibrutinib and the PI3kinase δ inhibitor idelalisb, have resulted in superior response rates in patients with TP53 abnormalities, and ibrutinib is approved as initial therapy for patients with 17p deletion CLL and is publicly funded in almost all provinces.[26]

Second-line

For patients with CLL which has relapsed or is refractory to standard therapies including fludarabine, alkylating agents and rituximab—all current components of front-line therapy—there is no agreed-upon standard treatment, and there are few randomized trials to guide practice. Bendamustine alone or in combination with rituximab results in progression-free survival in patients previously treated with FC of about 15 months.[27] The addition of rituximab to FC chemotherapy significantly improved the response rate and PFS (median 30.6 v 20.6 months) in relapsed patients who were rituximab naïve, but did not result in improved overall survival.[28] Ibrutinib has demonstrated activity in the second line setting with the phase III trial, RESONATE,[29] for patients with CLL/SLL who had relapsed or refractory disease, had received at least one previous therapy, and for whom treatment or retreatment with purine analog based therapy was considered inappropriate. Patients were randomized to receive either ibrutinib (420 mg once daily) or ofatumumab. Ibrutinib demonstrated a statistically significant improvement in PFS compared to ofatumumab (hazard ratio (HR) 0.22, 95%CI: 0.15-0.32, p<0.001). The improvement in PFS was seen in all subgroups examined, including patients with del(17)p of whom 83% were alive and progression-free at six months, compared with 49% with this deletion in the ofatumumab group. Ibrutinib

also significantly improved overall survival (HR=0.43, 95%CI: 0.24-0.79, p=0.005). Ibrutinib received a conditional final pERC recommendation in 2015 for the treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy and are not considered appropriate for treatment with a purine analog (e.g., fludarabine). It is currently publicly available across Canada.

Idelalisib plus rituximab has also demonstrated activity as second line treatment. In a phase III study, Furman et al randomized patients with relapsed CLL to receive rituximab plus idelalisib (n=110) or rituximab plus placebo (n=110).[10] At 24 weeks, 93% of patients in the idelalisib plus rituximab arm were free of progression compared with 46% of patients in the rituximab plus placebo arm. The median PFS was not met in the idelalisib group but was 5.5 months in the placebo group (HR 0.18; CI: 0.10-0.32; p<0.0001). Pre-specified sub-group analysis showed that PFS favoured the idelalisib arm for all subgroups, including those with CLL bearing a 17p deletion or TP53 mutation or unmutated IgHV gene. Median OS was not reached in either group. Idelalisib in combination with rituximab received a conditional final pERC recommendation in 2015 for the treatment of patients with relapsed CLL. It is currently publicly available across Canada, although this combination is less commonly used than single agent ibrutinib because of greater toxicity with the combination, and relative ease of administration of the single agent.

While increasingly chemoimmunotherapy is being replaced by BCR signaling antagonists as second-line therapy, there are still instances where the former may be selected, based on disease-free interval with primary therapy (longer being associated with a greater likelihood of response to second-line chemoimmunotherapy), favourable cytogenetics and patient preference for treatment of finite duration (e.g., bendamustine-rituximab for 6 months) versus indefinite therapy with a BTK inhibitor.

Venetoclax is an orally bioavailable inhibitor of the anti-apotosis protein BCL2 which has demonstrated significant activity in relapsed and refractory CLL. In a large phase I/II trial in heavily pre-treated patients (median number of prior regimens 3, range 1-11), the overall response rate was 79%, and response rates were similar among patients with high-risk disease features, specifically fludarabine resistant CLL (79%), del17p (71%), del11q (82%) and unmutated IGHV (76%).[7] The most common dose-limiting toxicity was tumor lysis syndrome (10/56 patients during dose-escalation), which can be mitigated by gradual intra-patient dose escalation (ramp-up), along with hospitalization for hydration and monitoring for patients at high risk. These results have been confirmed in a large phase II study enrolling 158 patients with R/R CLL and del17p (73 with accompanying TP53 mutation) treated with venetoclax 400mg/day: response rate was 77% (122/158), with a complete response rate of 20%. Progression-free survival at 24 months was 54% (95%CI 45-62%).[30] Most non-hematologic toxicities from venetoclax are grade 1 or 2 (nausea, diarrhea); neutropenia is generally the most common grade 3-4 event, with grade 4 neutropenia occurring in 28% of patients. In 2018 venetoclax monotherapy received a conditional final pERC recommendation for patients who have received at least one prior therapy and who have failed a B-cell receptor inhibitor. It is not yet publicly reimbursed in Canada.

In a phase Ib trial of venetoclax 200-600mg/day with rituximab in standard doses for treatment of CLL, the overall response rate was observed to be 86% (42/49) with and complete response rate 51%, which appeared higher than with other agents together CD20 antibody. Nineteen percent of patients had del17p, 70% had

unmutated IGHV and 31% of those tested had TP53 mutation. Of the 25 patients with complete response, bone marrow testing for MRD by flow cytometry was negative ($<10^{-4}$) in 20 patients, and in 28/49 overall. Eight patients who had MRD-negative bone marrow biopsies remained in remission median of 8 months after stopping venetoclax, suggesting that patients with deep responses to this combination may be able to discontinue therapy. Most grade 3-4 toxicity was hematologic and was manageable with supportive care; there were two cases of TLS, one of which was fatal. No MTD was defined in this study, and the recommended phase II dose of venetoclax for further testing in randomized trials was 400 mg daily.[31]

There is still a need to identify therapy that is active in second or third line treatment of CLL, which has both a favourable toxicity profile and activity that is independent of genetic and other mechanisms of treatment resistance, as well as intolerance to currently available molecularly targeted agents such as ibrutinib and idealisib. The possibility of continued remission without continuing therapy is also an attractive feature of newer regimens, to patients, their physicians and the health care systems that provides these promising therapies.This submission is seeking reimbursement approval for venetoclax plus rituximab for the treatment of patients with CLL who have received at least one prior therapy.

2.2 Evidence-Based Considerations for a Funding Population

Venetoclax and rituximab is appropriate therapy for patients with relapsed or progressive CLL after at least one prior line of chemoimmunotherapy. In the trial reported by Seymour et al, patients were randomized in a 1:1 ratio to receive venetoclax-rituximab (n=194) or the bendamustine-rituximab (n=195) after one (58.6%), two (25.7%) or three or more (15.7%) lines of prior therapy.[1] In total, 92 of 342 patients (26.9%) who were assessed for chromosome 17p deletion status had chromosome 17p deletion, 99 of 376 patients (26.3%) who were tested for TP53 mutation status had TP53 mutations, and 246 of 360 patients (68.3%) tested for IGHV mutational status had unmutated IGHV. Eighty-one percent had prior therapy with a purine analogue, 77.4% with a CD20 antibody and 54.8% with FCR; 15% were fludarabine refractory. Median age was 65 years (range 22-85), and ECOG performance status was 0 or 1. Two year investigator-assessed progression-free survival was 84.9% for venetoclax-rituximab compared to 36.3% bendamustine-rituximab (HR 0.17 for progression or death, p<0.001). The 2-year rate of investigator-assessed progression-free survival was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group among patients with or without chromosome 17p deletion, TP53 mutations or unmutated IGVH genes, as well as in patients with one, two or three or more lines of prior therapy, and in those refractory to most recent treatment. Of the patients in the venetoclax arm, 67% completed the prescribed 2 years of venetoclax therapy, and 62% were MRD negative (<10-4), vs 13% after bendamustine-rituximab. After a median follow-up post-therapy, only 16/130 patients (12%) who completed fixed duration venetoclax therapy had disease progression, and only 2 had been MRD negative.[4] Toxicity in this study was mild and manageable with standard supportive measures: Neutropenia was the most common grade 3-4 adverse event, with a higher incidence in the venetoclax– rituximab group than in the bendamustine– rituximab group (57.7% vs. 38.8%). The incidence of grade 3 or 4 febrile neutropenia and of grade 3 or 4 infections was lower in the venetoclax–rituximab group.

2.3 Other Patient Populations in Whom the Drug May Be Used

As recently published trials demonstrate, first line therapy of CLL will consist of agents targeting the BCR signaling pathway, in particular ibrutinib, and ibrutinib is already established as standard of care for patients with TP53 abnormalities as initial therapy, and increasingly after relapse from chemoimmunotherapy. Venetoclax-rituximab is also appropriate therapy for patients requiring treatment for second, third and fourth line therapy following treatment with a BCR inhibitor, based on the activity seen with single agent venetoclax following ibrutinib failure. While only a small number of patients (1%) in the MURANO trial had been previously treated with ibrutinib, data summarized above support the use of venetoclax + rituximab in the post-BCR inhibitor failure setting. It is very unlikely that a randomized trial such as MURANO would be conducted in patients previously treated with a BCR inhibitor, given the single agent activity demonstrated in phase II trials as described above.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

Patient input on venetoclax (Venclexta) in combination with rituximab (VR) for patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy was provided as a joint submission from two patient advocacy groups: Lymphoma Canada (LC) and the CLL Patient Advocacy Group (CLLPAG). Their methods and input are summarized below.

Data were gathered from three online surveys: 1) a survey for patients; 2) a survey for caregivers (both distributed in June 2017); and 3) a survey for patients with CLL who have treatment experience with VR, distributed in September 2018. Surveys were promoted by the CLLPAG and LC via email to CLLPAG members and the LC database; website posts (cllpag.ca, lymphoma.ca, cllcanada.ca, cllsupport.org.uk); posts on various social media pages and groups; blog posts; and online CLL forums.

All of the surveys had a combination of multiple-choice questions, as well as rating and open-ended questions. Skipping logic was built into the surveys so that respondents were only asked questions relevant to them. The demographic and geographic distribution of all survey respondents is presented in Tables 1 and 2.

Table 2: Survey Respondent Geographic Distribution

Respondents by Country	CAN	USA	UK	AUS	Other	Skipped	Total
CLL/SLL patients	102	127	51	2	4*	34	320
Patients with VR experience	4	9	0	0	1**	0	14
Caregivers	20	16	1	0	0	4	41
**Other includes 1 patient from each of the following: Brazil, France, India, Israel* ***1 from France*							

Table 3: Survey Respondent Age/Gender Distribution

	Age								Gender		
Category	21-39	40-49	50-59	60-69	70-79	80-89	90+	N/A	Male	Female	N/A
CLL/SLL patients	2	9	59	108	92	14	0	18	142	145	33
Patients with VR exp.	0	0	1	7	6	0	0	0	7	7	0
Caregivers	1	2	10	15	8	1	0	4	8	29	4

Of the 320 patient respondents to the surveys, 279 (87.19%) were diagnosed with CLL, 11 (3.44%) were diagnosed with small cell lymphocytic lymphoma (SLL) and 30 (9.38%) were diagnosed with CLL & SLL.

From a patient's perspective, fatigue or lack of energy and enlarged lymph nodes were the most commonly reported symptoms related to CLL affecting quality of life. Specifically, fatigue and frequent infections were highlighted as greatly impacting patients on an ongoing basis. Respondents also indicated experiencing emotional and mental distress due to their condition; patients felt stress, anxiety and difficulty sleeping, and depression.

Patients had experience with a wide range of therapies (up to six for some patients), including several chemotherapy regimens and various other pharmacological and non-drug therapies. Two-thirds of the patients who responded to the surveys had some experience with ibrutinib therapy. Fatigue, anemia or neutropenia, nausea, thrombocytopenia, diarrhea and infections were side effects of current therapies most frequently cited by patients. Patients reported that the most difficult side effects to tolerate were fatigue, nausea and frequency of infections. Patients viewed intravenous (IV) therapy as having a larger impact on quality of life than oral therapy (see Table 9). Caregivers consistently reported some interruption in their ability to perform various life activities, however, the impact was generally small.

In terms of expectations for alternative treatment options, focus was placed on individualized treatment options, delaying disease progression, reducing side effects, improving quality of life, having accessible and affordable treatments, and an oral route of administration.

A total of 14 patients had experience with VR. Overall, patients had a favourable experience. Most patients saw a reduction in commonly reported symptoms with CLL. The majority of patients experienced improvement in lymph node size, lymphocyte counts, and fatigue. Treatment with VR led to various side effects; most commonly reported were neutropenia, fatigue, and diarrhea. The majority of respondents indicated that they were willing to tolerate potentially serious or significant side effects. Overall, treatment did not have a significant negative impact on quality of life and daily living, although patients noted that clinician visits and infusions were burdensome. In that regard, patient groups remarked that the potential availability of subcutaneous rituximab would reduce the need for visits to the clinic. The opportunity of VR discontinuation after reaching MRD status was an important advantage over other treatments according to the patient groups.

A summary of some unedited quotes from the patients input received from LC and CLLPAG have been provided in various parts of this report. The statistical data that are reported have also been reproduced according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients Have with CLL

Patients who answered the CLLPAG and LC surveys reported that CLL was often diagnosed during investigation for another condition or during routine blood work. The diagnosis was often a complete surprise and shock to them.

Responding patients reported their current treatment phase. Of 301 patient respondents, 115 (38%) were in the active surveillance or watch-and-wait phase, 80 (27%) were continuing treatment, and 106 (35%) were in remission after receiving treatment. Of those in remission, 13 had been in remission for less than six months, 26 for six months to two years, 27 for two to five years, and 19 for more than five years. Thirteen responders had relapsed and eight relapsed after subsequent therapy.

CLL symptoms that affected patient quality of life at diagnosis and on an ongoing basis were reported by survey respondents and their respective proportions are listed below.

Table 4: Symptoms Experienced by CLL Patients

Symptom	At diagnosis (n=320)	Ongoing (n=313)
Fatigue/lack of energy, n (%)	152 (48)	260 (83)
Increasing lymphocyte count, n (%)	107 (33)	95 (30)
Enlarged lymph nodes, n (%)	97 (30)	71 (23)
Frequent infections, n (%)	61 (19)	85 (2)
Night sweats, n (%)	66 (21)	58 (19)
Shortness of breath, n (%)	41 (13)	62 (20)
Anemia, n (%)	36 (11)	60 (19)
None of the listed symptoms, n (%)	95 (30)	74 (24)

According to LC and CLLPAG, patients with early stage CLL reported few symptoms associated with their disease and tended to report a good quality of life. Quality of life was impacted more significantly in patients with more advanced disease. Fatigue was commonly reported, with patients reporting that they were "void of energy" and stated that they needed to rest often in order to perform their normal daily activities. Frequent infections on an ongoing basis were noted by more than 25% of respondents. Approximately one-third of patients reported having a comorbidity, (36.54 %) or having another cancer (37%), whereas 21% had cardiovascular issues and 18% had diabetes.

Respondents reported on the psychosocial responses to diagnosis and the ongoing issues they continue to experience, as displayed in Table 4.

Table 5: Psychosocial Responses to Diagnosis

Psychosocial condition	Patients		Caregivers (n=41)
	At diagnosis (n=320)	Ongoing (n=313)	
Stress of diagnosis, n (%)	204 (64)	82 (26)	32 (78)
Anxiety/worry, n (%)	209 (65)	139 (44)	33 (80)
Difficulty sleeping, n (%)	104 (33)	96 (31)	25 (61)
Depression, n (%)	86 (27)	56 (18)	14 (34)
None of these, n (%)	64 (20)	98 (31)	2 (5)

Some patients also expressed difficulties with concentration, emotions and mood swings. It was noted that these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day-activities. For example, impact of the disease was reported in the following areas: work (39%) (either working fewer hours, changing careers or retiring early), family (38%), personal image (27%), intimate relations (22%) and friendships (18%).

Patients shared the following unedited comments:

- *My husband has recently died and I have no family was unable to have children I suffer badly with loneliness and depression life has no meaning now.*

- *can not do everything I used to…worried about colds and infection with low neutrophils thus stay away from crowds and family events...not worth the risk.*
- *I have lost my job, my relationship with my coworkers, and my career.*
- *My husband was 24 when diagnosed. I was 8 months pregnant and we had just purchased our first home. He received chemotherapy the first time and then when it came back again in less than a year, Rituximab (which was an amazing drug for him) and then shortly after a stem cell transplant…I feel that we have never been able to live our life fully since his diagnosis… He has not worked in 2 years and receives significantly less while on disability.*

Survey respondents rated the importance of treatment-induced control of CLL symptoms on a scale of 1 to 10, with 1 = not important and 10 = very important. More than 70% of respondents rated infections (including viral reactivation) and low blood counts (thrombocytopenia, neutropenia and anemia) as most important for treatment to control.

Table 6: Important Symptoms to Control

Symptom (n=301)	% who rated 8, 9 or 10	Rating									
		1	2	3	4	5	6	7	8	9	10
Infections	**88**	4	1	2	2	9	8	9	31	60	175
Thrombocytopenia	**75**	8	0	2	3	23	13	27	57	67	101
Neutropenia	**74**	8	3	3	4	16	15	29	50	58	115
Viral reactivation	**73**	12	7	2	4	24	10	21	54	48	119
Anemia	**73**	8	4	4	5	23	10	28	64	49	106
Fatigue, lack of energy	**67**	7	3	5	5	31	18	30	57	49	96
White blood cell counts	**64**	7	8	8	10	31	24	20	38	25	130
Fever	**6**	14	2	7	12	27	17	29	61	46	86
Lymph node size	**62**	9	10	8	11	33	13	30	52	34	101
Enlarged spleen or abdominal discomfort	**61**	13	4	5	10	31	13	41	51	50	83
IgG levels	**60**	11	3	8	6	40	24	29	48	49	83
Pain	**58**	14	4	13	9	32	22	33	57	45	72
Psychological issues	**47**	15	7	19	16	44	24	34	57	28	57
Stress levels	**47**	13	11	10	21	39	25	40	57	36	49
Night sweats	**43**	20	10	21	6	38	31	47	67	31	30
Weight loss	**35**	23	14	14	15	53	34	43	45	28	32

3.1.2 Patient's Experience With Current Therapies

Respondents' use of CLL therapies are listed in the tables below. Note that not all respondents who answered questions on specific therapies provided further details on line of therapy or treatment completion status.

Table 7: Conventional Therapies Experienced by Patients

Conventional Therapy (n=165)	Overall Use n (%)	Line of Treatment						Completed Tx	
		1st	2nd	3rd	4th	5th	6+	Yes	No
FCR	76 (46)	58	11	2	3	0	3	50	11

Conventional Therapy (n=165)	Overall Use n (%)	Line of Treatment						Completed Tx	
		1st	2nd	3rd	4th	5th	6+	Yes	No
BR	26 (16)	11	8	3	1	0	1	17	4
Chlorambucil	22 (13)	16	1	1	0	0	0	10	6
FR	20 (12)	15	2	2	0	0	0	14	2
R CHOP	9 (5)	2	3	0	0	0	1	6	0
Bendamustine	8 (5)	2	1	3	0	0	0	4	2
CVP	5 (3)	3	1	0	0	0	0	1	3
PCR	3 (2)	3	0	0	0	0	0	2	0
FCM	1 (1)	0	1	0	0	0	0	1	1
CHOP	1 (1)	1	0	0	0	0	0	1	0

Abbreviations: BR = bendamustine, rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CVP = cyclophosphamide, vincristine and prednisone; FCR = fludarabine, cyclophosphamide, rituximab; FCM = fludarabine, cyclophosphamide, mitoxantrone; FR = fludarabine, rituximab; PCR = pentostatin, cyclophosphamide, rituximab; R CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 8: Other Drug Therapies Experienced by Patients

Other Drug Therapy (n=142)	Overall Use n (%)	Line of Therapy						Able to Complete Treatment		
		1st	2nd	3rd	4th	5th	6+	Yes	Ongoing	No
Ibrutinib	86 (67)	25	35	12	4	1	3	7	48	13
Venetoclax	21 (25)	7	3	8	3	0	0	5	9	1
Other	18 (27)	5	4	2	1	0	1	6	3	1
Idelalisib	9 (11)	2	4	1	0	1	2	0	4	4

Table 9: Other Treatments Experienced by Patients

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

The survey participants rated their agreement with how well their current therapy could manage their symptoms on a scale of 1 (strongly agree) to 10 (strongly disagree). One hundred and seventy-nine respondents gave a weighted average response of 6.04, with 86 respondents (48%) giving a rating of 8, 9, or 10. Fifty six patient (31%) responded with a rating of 1, 2, or 3 indicating that they strongly agreed that their therapy managed their symptoms.

According to the survey responses, the most commonly reported side effects of current therapies were fatigue (70%), anemia or neutropenia (43%), nausea (39%), thrombocytopenia (35%), diarrhea (35%), and infections (33%). Patients reported

that the most difficult side effects to tolerate were fatigue, nausea and frequency of infections.

Patients and caregivers expressed the following thoughts in regard to current therapies:

- *I am still weak from all the problems I had from FR chemo. Life has lost its lustre.*
- *I have chronic ITP because of having CLL and having treatment/chemo in the pasts. Currently, I am very mindful of avoiding any infections or viruses as well as avoiding high risk situations where I could bleed, especially internal bleeding from falls.*
- *My husband has been on Imbruvica for a year now and suffers harsh bone pain, difficulty breathing and massive bruising with bleeding on arms. His illness has become our life. His blood counts have improved but the side effects are difficult. We wish there was an alternative therapy*
- *He was initially started on Ibrutinib, but had to discontinue due to toxicity, which has left him with permanent joint damage which impacts his function in his hands. The ibrutinib was horrible, but now on Acalabrutinib trial.*

Patients rated on a scale of 1 (little impact) to 10 (significant impact) how their treatment experience affected their quality of life. The results presented in the table below show a larger impact on quality of life for those who received IV therapies.

Table 10: Impact of Treatment on Quality of Life

Experience	IV therapies (n=147) n (%)			Oral therapies (n=136) n (%)		
	Significant impact (8, 9 or 10)	Moderate impact (6 or 7)	Total (6-10)	Significant impact (8, 9 or 10)	Moderate impact (6 or 7)	Total 6-10
Treatment-related fatigue	56 (38)	20 (14)	76 (51)	31 (23)	14 (10)	45 (33)
Number of clinic visits	49 (33)	32 (22)	81 (55)	22 (16)	15 (11)	37 (27)
Activity level	43 (29)	25 (17)	68 (46)	27 (20)	18 (13)	45 (33)
Infusion time	42 (28)	30 (20)	72 (49)	N/A	N/A	N/A
Toleration of treatment	39 (26)	21 (14)	60 (40)	33 (24)	11 (8)	44 (32)
Infusion reaction	39 (26)	17 (11)	56 (38)	N/A	N/A	N/A
Frequency of infections	28 (19)	11 (7)	39 26)	18 (13)	10 (7)	28 (21)
Number of infections	27 (18)	18 (12)	45 (30)	17 (13)	10 (7)	27 (20)

3.1.3 Impact on Caregivers

Caregivers who responded to the surveys rated on a scale of 1 (no impact) to 10 significant impact how caring for the person with CLL has impacted their own day-

to-day activities and quality of life. Results of this assessment are found in the table below.

Table 11: Impact of Caregiver Activities

Activity	6-10 (significant impact) n (%)	1-5 (no to little impact) n (%)	Number of responses
Ability to concentrate	14 (35)	26 (65)	40
Ability to travel	14 (35)	26 (65)	40
Ability to spend time with family & friends	14 (35)	26 (65)	40
Ability to fulfill family obligations	11 (28)	29 (73)	40
Ability to perform household chores	10 (25)	30 (75)	40
Ability to contribute financially to household finances	10 (25)	30 (75)	40
Ability to volunteer	9 (23)	31 (78)	40
Ability to exercise	8 (20)	33 (81)	41

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Experiences with Venetoclax and Rituximab

A total of 14 patient who responded the surveys had experience with venetoclax-rituximab. Their basic characteristics (gender, age, location, etc.) are listed in Table 11.

Table 12: Patient Characteristics

Patient	Gender	Age	Location	Date of diagnosis	VR start date	Access to drug
1	Female	70-79	Canada	2010	2018	Compassionate access
3	Female	60-69	Canada	2011	2016	Compassionate access
9	Male	50-59	Canada	2010	2017	Compassionate access (paid for rituximab)
13	Male	70-79	Canada	2009	2014	Clinical trial
11	Male	70-79	France	2000	2012	Did not disclose
2	Female	60-69	USA	2012	2018	Medicare + compassionate access
5	Female	70-79	USA	2001	2018	Private insurance
7	Female	60-69	USA	2015	2018	Medicare
12	Female	60-69	USA	2012	2018	Private insurance
14	Female	60-69	USA	2005	2018	Clinical trial
4	Male	60-69	USA	2007	2018	Clinical trial
6	Male	70-79	USA	2002	2018	Medicare
8	Male	60-69	USA	2013	2018	Private insurance
10	Male	70-79	USA	2006	2018	Medicare

Twelve respondents received chemotherapy as first-line therapy and two received ibrutinib as their first-line treatment. Four participants received chemotherapy second-line, two third-line, one fourth-line and one sixth-line. Three respondents received ibrutinib as second-line treatment, two third-line, one fourth line and one fifth-line. One received idelalisib fourth-line but discontinued due to intolerance.

The nine respondents who had previously received ibrutinib therapy became resistant or intolerant to this drug.

Of 14 respondents, three completed treatment and discontinued VR after 2 years, eight participants were on continued treatment with VR (< 2 years on drug), one discontinued due to side effects (is now using venetoclax single agent), one used VR to prepare for an allogeneic stem cell transplant, and one achieved minimal residual disease (MRD) negative status, but relapsed and re-started venetoclax therapy.

Respondents reported which of their CLL symptoms were managed by VR treatment. The following table lists the proportion of patients for each managed symptom. Note that not all respondents experienced each of the listed symptoms.

Table 13: Symptoms Managed by VR

Symptom	Number of respondents (n=13) n (%)	Symptom	Number of respondents (n=13) n (%)
Enlarged lymph nodes	11 (85)	Shortness of breath	2 (15)
Fatigue, lack of energy	7 (54)	Frequent infections	1 (8)
Increasing lymphocyte count	7 (54)	Pain	1 (8)
Weight loss	4 (31)	Fever	0 (0)
Night sweats	4 (31)	I was not experiencing any symptoms before treatment	0 (0)
Other (please specify)[a]	3 (23)	VR did not manage any of my symptoms	0 (0)
Enlarged spleen	2 (15)		

[a] Just started treatment- too soon to know (2), joint pain (1)

Survey respondents also reported CLL symptoms which were not adequately managed by VR (Table 13).

Table 14: Symptoms Not Managed by VR

Symptom	Number of respondents (n=10) n (%)	Symptom	Number of respondents (n=10) n (%)
Managed all symptoms	7 (70)	Night sweats	1 (10)
Fatigue, lack of energy	3 (30)	Increasing lymphocyte count	0 (0)
Enlarged lymph nodes	0 (0)	Shortness of breath	0 (0)
Enlarged spleen	0 (0)	Fever	1 (10)
Frequent infections	1 (10)	Pain	1 (10)
Weight loss	1 (10)	Other (please specify)[a]	2 (2)

[a] Just started treatment - too soon to know (2)

Respondents reported the extent to which they would be willing to tolerate potential VR side effects on a scale of 1(will not tolerate any side effects) to 5 (willing to tolerate significant side effects). All patients responded with ratings ranging from 3 to 5, and indicated that they would be willing to tolerate some side

effects of VR, with the majority (74%) willing to tolerate potentially serious or significant side effects (rating = 4 or 5).

Respondents reported which side effects they had experienced during treatment with VR, as presented in Table 14.

Table 15: Experienced Side Effect

Treatment side effect	Number of respondents (n=13) n (%)	Treatment side effect	Number of respondents (n=13) n (%)
Neutropenia	6 (46)	Anemia	1 (8)
Fatigue	4 (31)	Tumour lysis syndrome[a]	1 (8)
I did not experience side effects	3 (23)	Fever	1 (8)
Diarrhea	3 (23)	Upper respiratory tract infection	0 (0)
Thrombocytopenia	3 (23)	Autoimmune haemolytic anemia (AIHA)	0 (0)
Infusion reaction	2 (15)	Other (please specify)	0 (0)
Nausea	1 (8)		

[a] Patient in the early trial before protocols were initiated to reduce the risk of tumour lysis syndrome[a]

Other aspects of the respondent ratings of the impact of treatment with VR are presented in the Table 15.

Table 16: Impact of Treatment on Daily Living

Aspect of treatment	Impact of VR treatment on daily living and quality of life (n=13) n (%)					
	1 Little Negative impact	2	3	4	5 Significant Negative impact	N/A
Number of clinic visits	10 (71)	1 (7)	3 (21)	0 (0)	0 (0)	0 (0)
Infusion time	6 (43)	5 (36)	3 (21)	0 (0)	0 (0)	0 (0)
Infusion reaction	10 (71)	1 (7)	1 (7)	0 (0)	0 (0)	2 (14)
Side effects of treatment	5 (36)	5 (36)	1 (7)	1 (7)	1 (7)	1 (7)
Number of infections	6 (43)	2 (14)	1 (7)	0 (0)	0 (0)	5 (36)
Frequency of infections	6 (43)	2 (14)	1 (7)	0 (0)	0 (0)	5 (36)

According to CLLPAG and LC, a major benefit of the VR treatment regimen, compared to other currently available oral drug treatments, is the ability to discontinue the drug regimen once negative MRD status has been achieved (up to a maximum of two years of therapy). The patient groups maintained that this drug regimen is also effective and well-tolerated in patients over 65 years of age, which typically can be a more difficult group to treat. The patient groups added that since sub-cutaneous rituximab is currently approved by Heath Canada for, hospital

visits for patients being treated with VR will be reduced upon funding of sub-cutaneous rituximab.

Respondents described their experience with VR treatment, as both positive and negative:

- *I have not had any negative experience. Since completing the 2 years of the medication, my blood numbers are normal and physicals excellent (just completing 4th year of trial)*
- *at this point, my absolute lymphocyte count is normal as is the rest of my blood work. Negative is the intensity of the build up and now Rituxan infusions*
- *[lab work] daily for 1 week then every other day, then every two weeks. She also had to stay twice for IV hydration*
- *frequent travel to trial site*
- *intensity of the build up and Rituxan infusions*
- *negatives are similar to other treatments in past (fatigue, chronic sinus infections, trips to clinic, etc.) Positive is that it is working!*
- *Feel great – positive. Low platelets – negative*
- *All positive. Emerged from the trial MRD Negative.*

In view of responses regarding previous treatment, the submitting organizations suggested that the VR drug regimen benefits those who have failed chemotherapy and/or B-cell inhibitors such as ibrutinib and idelalisib. It also appears to be well-tolerated by older patients, as indicated by the seven respondents in the 60-69 age group and the six respondents in the 70-79 age group.

3.2.2 Patient Expectations for Venetoclax and Rituximab

The CLLPAG and LC emphasized that CLL is currently incurable and patients live with the knowledge that their disease may progress at any time. The surveys of CLLPAG and LC asked respondents to rate how important it was for patients and their physicians to have choice in their therapy on a scale of 1 (not important) to 10 (extremely important). Ninety-five percent (286/301) of respondents rated choice of treatment as very important (8, 9, or 10), with the weighted average for response to this question being 9.6. Patients reported seeking individualized choice in treatment that will offer disease control and improve quality of life, while offering ease of use relative to other treatments. . The response of patients with previous CLL treatment who were asked to indicate the most important quality they expect of a new therapy are presented in Table 16.

Table 17: Importance of Outcomes

Priority for a new therapy	Responses (n=162) n (%)
Increased effectiveness or remission	84 (52)
Decreased toxicity	40 (25)
Accessible & affordable treatments	12 (7)
Improved quality of life	11 (7)
Oral therapy.	9 (6)

The following unedited patient quotes related to their expectations were provided in the input submission:

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

3.3 Additional Information

No other relevant information was included in the patient input submission.

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

Clinical factors:

- Sequencing of treatments

Economic factors:

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

Please see below for more details.

4.1 Currently Funded Treatments

PAG identified that there is no standard of care for adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. Ibrutinib and idelalisib/rituximab would be considered for patients who have relapsed after first-line treatment. PAG noted that venetoclax as monotherapy was recently reviewed at pCODR, for the treatment of patients with CLL who have received at least one prior therapy and who have failed a BCRi. However, PAG noted that there are limited treatment options for patients who have been previously treated with ibrutinib or idelalisib.

PAG noted that the comparator in the MURANO trial was bendamustine/rituximab, PAG is seeking information on data comparing venetoclax/rituximab with ibrutinib and idelalisib/rituximab.

4.2 Eligible Patient Population

The MURANO trial excluded patients with an ECOG PS of 2, PAG is seeking guidance on whether venetoclax/rituximab would be limited to patients with an ECOG PS of 0-1.

PAG noted that ibrutinib is available in some jurisdictions for patients with previously untreated CLL/SLL for whom fludarabine-based treatment is considered inappropriate. PAG is seeking guidance on the use of venetoclax/rituximab in these patients previously treated with first-line ibrutinib.

Patients in the MURANO trial were eligible for venetoclax/rituximab if they were previously treated with 1-3 lines of therapy, including at least one standard chemotherapy-containing regimen. PAG is seeking guidance on, for patients treated with a first-line rituximab-containing regimen (e.g., fludarabine, cyclophosphamide, and rituximab (FCR) or

bendamustine/rituximab), the appropriate minimum treatment-free interval for these patients and their treatment with venetoclax/rituximab.

If recommended for reimbursement, PAG noted that patients currently on an alternative second-line therapy for CLL would need to be addressed on a time-limited basis. PAG is also seeking guidance for patients currently on venetoclax for previously treated CLL, the appropriateness (and if so, the appropriate time frame) of adding rituximab.

PAG identified that there may be requests to use venetoclax/rituximab for patients in the first-line setting, particularly patients with del(17p) or for those who have intolerance to treatment with ibrutinib (i.e., increased cardiac risk profile). These requests are out of scope of this current pCODR review.

4.3 Implementation Factors

Venetoclax is a 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 and require additional pharmacy resources. PAG noted that the multiple tablet strengths as well as fills during the ramp up dose schedule can lead to an increased risk for medication error, where appropriate patient education and monitoring will be required for implementation. However, the packaging of venetoclax identifies the ramp up dosing schedule.

PAG also noted that additional pharmacy and nursing resources and chair time will be required to prepare and administer the additional rituximab. PAG noted that additional chair time as well as wastage could be reduced with implementation of subcutaneous rituximab for cycles 2 to 6.

The dosing schedule for venetoclax/rituximab is for a fixed duration of 24 months. PAG is seeking clarity on treatment duration. For patients who do not experience progression, whether there are instances where these patients should be treated beyond the 24 months of treatment. For patients who have completed the 24 months of treatment, whether these patients should be re-treated with venetoclax/rituximab upon progression.

After the completion of dose ramp-up period for venetoclax, rituximab is administered intravenously in the first dose. Given the increased risk of tumor lysis syndrome, rituximab administration is started after the ramp-up schedule for venetoclax is completed. PAG noted that prior to initiating therapy with venetoclax/rituximab, 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. The initiation of treatment may require hospitalization to monitor and treat tumour lysis syndrome. Rasburicase may be required to treat tumor lysis syndrome which would be additional costs associated with venetoclax/rituximab therapy.

PAG noted that pharmacy resources and weekly clinic visits would be required with venetoclax/rituximab. Venetoclax is associated with drug-drug interactions, tumor lysis syndrome, and neutropenia. These adverse events would require additional health care resources compared to other second-line therapy options.

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.

4.4 Sequencing and Priority of Treatments

PAG is seeking guidance on the appropriate treatment options in the first-line and relapsed/refractory CLL setting,

- PAG noted that other second-line treatments may be available (e.g., ibrutinib, idelalisib/rituximab). For patients who have received one prior therapy, what would be the best treatment?
- What is the optimal sequencing of relapsed/refractory venetoclax/rituximab treatment with other treatments (e.g., first-line chemo-immunotherapy, ibrutinib, idelalisib/rituximab)?
- What is the optimal sequencing for patients with del(17p) who have received first-line ibrutinib?

4.5 Companion Diagnostic Testing

None identified.

4.6 Additional Information

PAG noted that currently venetoclax is only available through specialty pharmacies and/or retail oncology pharmacies that are part of AbbVie's managed distribution program distribution program.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

pCODR received three clinician input submissions (representing fifteen clinicians) on the combination of venetoclax and rituximab (VR) in patients with chronic lymphocytic leukemia (CLL) who have received and failed at least one prior therapy. The submissions from Cancer Care Manitoba and Cancer Care Ontario (CCO) provided the perspective of an oncologist and a hematologist, respectively. Alberta Health Services submitted a joint input from thirteen clinicians comprising nine hematologists, three medical oncologists, and one hematology nurse practitioner.

The clinicians mentioned that for the specified indication, the most relevant comparator for VR would be ibrutinib. However, evidence comparing the two regimens is lacking. Clinicians have a positive experience with VR and view the time-limited treatment of two years as more attractive to patients and payers, although IV administration of rituximab remains a challenge. The fewer contraindications of VR compared with ibrutinib also make it an attractive option for patients with cardiovascular conditions.

The use of minimal residual disease (MRD) testing was mentioned by some but not all clinicians as a metric to inform treatment decisions and discontinuation. Sequencing of alternative therapies before and after VR remains theoretical with little supporting data, but many clinicians would prefer VR as first-line/second-line and use ibrutinib after VR has failed.

5.1 Current Treatment(s) for This Type of Cancer

According to clinicians providing input, ibrutinib is given to adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy, with idelalisib/rituximab being a less common option. According to the clinician from CCO, the comparator used in the main study (bendamustine/rituximab) is not funded in Ontario and thus not relevant in this particular context.

5.2 Eligible Patient Population

Clinicians providing input explained that relapsed/refractory CLL is a very common disease that is treated by hematologists. Clinicians believed that the study population in the MURANO trial was representative of the R/R CLL patients they see in practice. It was noted that the trial did not include patients who have received three or more previous lines of therapy, for whom some clinicians may want to use venetoclax/rituximab (VR). One clinician noted that the MURANO trial included patients who had previously received bendamustine, provided that the duration of response after the treatment was at least 24 months. Another clinician was of the view that treatment with VR should be reserved for R/R CLL patients who have failed at least one line of therapy and who are not eligible for or progressed on a (Bruton's tyrosine kinase) BTK inhibitor.

One oncologist believed that a more appropriate comparator in the MURANO trial would have been chlorambucil/obinutuzumab instead of bendamustine/rituximab given the former has a Health Canada approval for this indication and is used in clinical practice. According to this oncologist,

a head-to-head comparison of VR versus ibrutinib in the second line setting is needed to assess the place of therapy for VR.

Some clinicians providing input observed that since patients in the MURANO trial were enrolled before ibrutinib became available, the study did not include patients who had previously been treated with a B-cell receptor inhibitor. However, given the favourable data from the study, they would be comfortable to treat such patients with VR.

One clinician indicated that rituximab could be used for debulking in patients with bulky disease to reduce admissions and promote outpatient-based treatment. The clinician added that the high clinical response rate and minimal residual disease (MRD) negativity suggest that treatment with VR could lead to treatment-free period for patients and prevent repeated use of chemotherapy.

5.3 Relevance to Clinical Practice

All clinicians submitting input had experience with using VR for CLL. Clinicians would use the treatment as the standard option for relapsed CLL. In their experience, the therapy is effective, safe, tolerable, and associated with an excellent durability of response. One clinician added that they would use this combination mainly to get a response in the setting of progression with a goal of MRD negativity. Clinicians see the defined treatment period (2 years) as an advantage over the indefinite use of a B-cell receptor inhibitor (ibrutinib). According to clinicians, time-limited therapy is more attractive to patients and also less costly. Given the perceived better tolerability of venetoclax relative to ibrutinib, clinicians foresee higher patient compliance with the new treatment plan. However, a clinician observed that some patients may still prefer ibrutinib since it is administered orally, as opposed to VR which requires intravenous rituximab.

Clinicians submitting input could not identify specific R/R CLL subpopulations for whom they would not use VR as therapy. This contrasts with contraindications associated with the use of ibrutinib (patients with a bleeding history, unstable cardiac disease or those who require anticoagulant therapy). Therefore, the treatment may be a good option for someone on warfarin, for example.

5.4 Sequencing and Priority of Treatments With New Drug Under Review

Clinicians providing input highlighted that there is currently no data to inform sequencing of treatments. In theory, VR would be the preferred choice for first relapse of CLL and would thus displace the current standard (ibrutinib) for most patients, moving it to next line. Clinicians would also use this therapy in patients who progress on ibrutinib or discontinue due to intolerance. One clinician added that should novel targeted agents informed by IGVH mutation testing be given upfront, VR would be an option for any relapsing patients.

5.5 Companion Diagnostic Testing

Clinicians indicated that FISH, TP53 and IGVH are tests which are conducted routinely as part of workup in oncology, these are generally standard of care for any patient undergoing pre-treatment workup and they are not specifically reserved for this indication. A clinician suggested that MRD testing would be required for drug discontinuation and should be considered a companion test. CT scans are recommended to assessing the risk of tumour lysis syndrome (TLS) with venetoclax, this would not always be required as part of standard of care and when required, CT scans are readily accessible for these patients.

5.6 Additional Information

A clinician noted that there may be resource implications for using this therapy, such as patient monitoring and treating TLS.

5.7 Implementation Questions

5.7.1 In regards to question 3.4 above, please consider the optimal sequencing of treatments in CLL specifically: chemo-immunotherapy, ibrutinib, idelalisib/rituximab

5.7.1.1 Ibrutinib was recently reviewed at pCODR, for the treatment of patients with CLL/SLL with or without deletion 17p who have received at least one prior therapy and are not considered appropriate for treatment or re-treatment with a purine analog (e.g., fludarabine). In what clinical scenarios would ibrutinib or venetoclax/rituximab be the preferred treatment for patients with CLL that have received at least one prior therapy? Please comment on the preference considering patient preference, efficacy, safety, and administration.

According to clinicians, it is difficult to determine optimal sequencing due to limited data. For patients who have relapsed after first-line therapy, the preferred treatment option would be VR. In patients who have relapsed beyond first-line therapy and have had prior treatment with a B-cell receptor inhibitor (i.e., either ibrutinib or idelalisib), VR would be the best option.

Clinicians contended that, until further data is made available, patients with 17p deletion should be treated with ibrutinib in the frontline setting, but this should not prevent them from receiving VR at relapse. Patients who receive ibrutinib upfront are unlikely to be eligible for chemo-immunotherapy. Patients who receive ibrutinib for un-mutated IgVH would likely receive VR in second line as they cannot receive chemo-immunotherapy.

A clinician indicated that they would prefer VR in patients with recent cardiac events, on stable anticoagulation, with skin issues, or poor tolerance to ibrutinib. In the absence of data on BTK inhibitors after venetoclax, there is hesitance to sequence the latter ahead of ibrutinib.

It was mentioned that from the perspective of the patients and clinicians, there could be a preference for ibrutinib because it does not include an IV therapy component (rituximab) and does not require TLS monitoring at the initiation of

therapy. However, clinicians believe that improved tolerability of VR and the defined treatment duration are strong incentives to compensate for the inconvenience that may be associated with IV rituximab.

5.7.2 Obinutuzumab has been associated with greater efficacy and potency than rituximab in CLL. In clinical practice, would you consider subsequent venetoclax/rituximab for patients who receive obinutuzumab/chlorambucil?

All clinicians submitting input agreed that the results of the MURANO trial could be generalized to patients who have received obinutuzumab/chlorambucil. Clinicians noted that re-treatment with anti-CD20 therapy is commonly used in the treatment of B-cell malignancies, therefore prior obinutuzumab exposure would not exclude usage of venetoclax-rituximab. However, it was cautioned that the exception could be for patients who progress within 6 months of obinutuzumab therapy (but this would only apply to very few patients).

5.7.2.1 For patients who do not experience progression, are there instances where these patients should be treated beyond the 24 months of treatment?

5.7.2.2 For patients who have completed the 24 months of treatment, are there instances where these patients should be retreated with venetoclax/rituximab upon progression?

Answers to these questions varied. One clinician answered that they would test MRD at 24 months and stop treatment if negative; otherwise they would be continued. In case of a relapse after stopping the drug, the clinician would restart and would not consider it a drug failure. Another clinician agreed that clinicians will want to treat beyond 24 months unless there is data indicating it is not effective.

The joint clinician input cautioned that the use of MRD is unclear in clinical practice and that answering the above questions is an area of active research. Their position is to discontinue treatment at the two-year mark for all patients.

5.7.3 In clinical practice if available, would subcutaneous (SC) rituximab be used in combination with venetoclax?

All clinicians answered “yes” to this question. They were interested in SC rituximab and understood that the efficacy of this formulation was equivalent to IV rituximab. Clinicians were comfortable extrapolating this equivalence to the rituximab component of VR. They observed that there is a significant decrease in reactions with the SC form of rituximab and this formulation leads to time saved in the cancer centre treatment areas. Thus they felt that many centres and physicians/patients will opt to replace IV rituximab with SC rituximab for this regimen once the latter is incorporated into other CLL regimens.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety of venetoclax in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy.

Supplemental Questions relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Critical appraisal of the submitter-provided unanchored indirect treatment comparison (ITC) between venetoclax-rituximab and ibrutinib or idelalisib-rituximab to support their economic evaluation.

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 6.1. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 6.1: Study Selection Criteria for Systematic Review

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators**	Outcomes
• Published or unpublished RCTs. Fully published non-comparative clinical trials investigating the efficacy of venetoclax in combination with rituximab will be considered for inclusion in the absence of RCT data. Reports of trials with a mixed	Adult patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy **Subgroups of interest**: • Age (<65 vs. ≥65 years • Number of previous lines of therapy • ECOG performance status • Mutation status (deletion of chromosome 17p [del17p], or somatic	Venetoclax in combination with rituximab. The starting dose of venetoclax is 20 mg once daily for seven days and then titrated upwards on a weekly schedule to the daily dose of 400 mg over five weeks. Rituximab * should be started after the patient has received the 400 mg dose of	• Venetoclax as monotherapy • B-cell receptor inhibitors (Ibrutinib or Idelalisib) as monotherapy or in combination with rituximab. • Chemoimmunotherapy *** • None (i.e., single-arm studies of the index intervention are eligible)	***Efficacy*** • PFS • OS • ORR (CR + PR) • DOR • HRQoL **EOSI** • MRD ***Safety*** • AE (≥Grade 3) • SAEs • WDAEs **AESI** • TLS

Table 6.1: Study Selection Criteria for Systematic Review				
Clinical Trial Design	**Patient Population**	**Intervention**	**Appropriate Comparators****	**Outcomes**
design will be included only if separate data were reported for the cohort of patients who received the study intervention. Trials designed solely to assess dose-escalation, or intended as proof of concept, mechanistic, or pilot studies will be considered for inclusion only if the primary endpoint included efficacy outcomes.	mutations in TP53	venetoclax for seven days.		
AE = adverse even; AESI = adverse event of special interest; CR = complete response; DOR = duration of response; HRQoL = health related quality of life; EOSI = efficacy outcome of special interest; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; MRD = minimal residual disease; RCT = randomized controlled trial; TLS = tumour lysing syndrome				

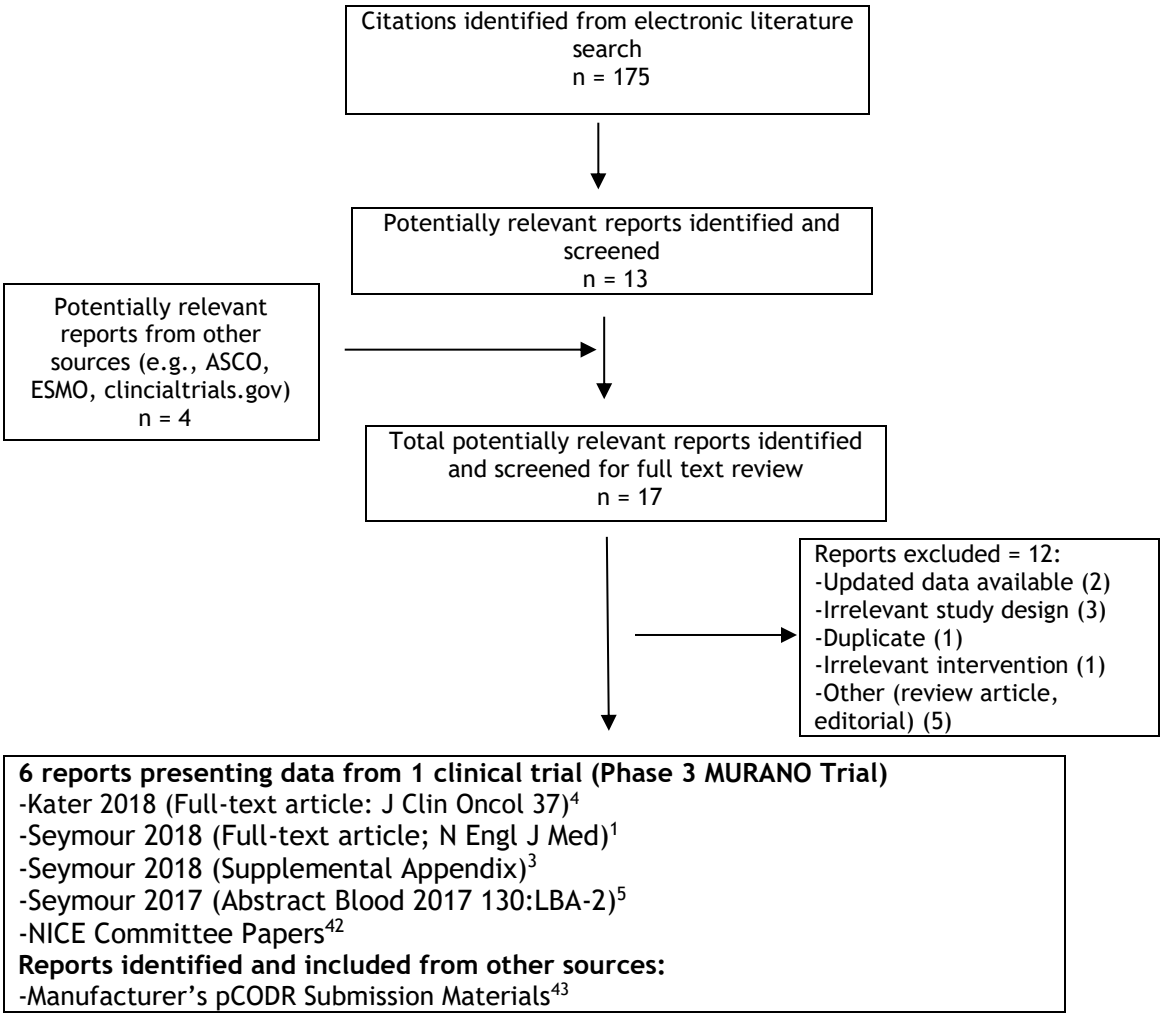
* In the pivotal MURANO[1] trial, intravenous (IV) rituximab was administered to patients at 375 mg/m2 on Day 1 of Cycle 1 followed by 500 mg/m2 on Day 1 of Cycles 2 through cycle 6 for a total of six infusions of rituximab. Each cycle was 28 days.
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)
*** Chemoimmunotherapy, the combination of chemotherapy with an anti-CD20 monoclonal antibody

6.3 Results

6.3.1 Literature Search Results

Seventeen titles and abstracts were retrieved from a total of 175 citations in the first level of screening and assessed for potentially relevant studies. Of these, five reports (two articles published in full text, one supplemental appendix, one abstract, and a paper from a committee of a regulatory agency) presenting data from a single trial (the Phase 3 MURANO study)[1] were included in this pCODR systematic review. Twelve papers were excluded[4,31-41] because they did not meet the selection criteria outlined in Table 6.1,[31-41] or were duplicate of already selected article.[4] Where more than one publication was available for the same study, the one with the most comprehensive or updated data was selected over the others. Figure 6.1 presents the flowchart of the study selection process.

Figure 6.1. PRISMA Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

6.3.2.1 Detailed Trial Characteristics

One randomized controlled trial, MURANO[1] was identified that met the eligibility criteria of this review. The key characteristics of the MURANO study are summarized in Table 6.2.

Table 6.2: Summary of Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Clinical Trials NCT02005471 (the MURANO study)[1] An international, randomized, open-label, phase 3 trial. Patients were randomly assigned to either of the interventions in a 1:1 ratio. Randomization was stratified by the presence or absence of chromosome 17p deletion, responsiveness to previous therapy, and geographic region. N Enrolled = 389 at 109 sites in 20 countries; N Randomized = 389; Patient Enrolment Dates: March 31, 2014, to September 23, 2015	<u>Key Inclusion Criteria:</u> • 18 years of age or older, • Diagnosis of R/R CLL that required therapy, • Had received one to three previous treatments (including at least one chemotherapy-containing regimen), • ECOG performance status score of 0 or 1 • Had adequate bone marrow, as well as renal, and hepatic function <u>Key Exclusion Criteria:</u> • Richter's transformation or CNS involvement • History of an allogeneic or autologous SCT • Major organ dysfunction • Significant uncontrolled conditions including, but not limited to, systemic infection • Other active malignancy • Current pregnancy or breastfeeding • Positive test results for chronic HBV or HCV serology, or HIV; and	• Venetoclax, given once daily orally at a starting dose of 20 mg and ramped-up to 400mg per day final dose over 5 weeks. *versus* • Bendamustine at standard dosage of 70mg/m^2 administered on days 1 and 2 of a 28 day cycle for six cycles. In both arms, rituximab infusions were given on day 1 of each 28-day cycle for 6 cycles (375mg/m^2 cycle 1; followed by 500mg/m^2 cycles 2–6), with cycle 1 beginning after the initial ramp-up period in the venetoclax arm.	<u>Primary:</u> Investigator-assessed PFS <u>Secondary:</u> Investigator-assessed and/or IRC-assessed CR, ORR, OS, PFS, and MRD-negativity, and safety

Table 6.2: Summary of Characteristics of the Included Study			
Trial Design	**Inclusion Criteria**	**Intervention and Comparator**	**Trial Outcomes**
Data cut-off for primary analysis: May 8, 2017 Funding: AbbVie and Genentech	• Receipt of warfarin (during venetoclax dose ramp-up) or strong CYP3A4 inhibitors/inducers.		
CR = complete response rate; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IRC = independent review committee; iwCLL = International Workshop for Chronic Lymphocytic Leukaemia; MRD = minimal residual; N = number of patients; ORR = overall response rate; OS = overall survival, PFS = progression-free survival;			

Source: Seymour et al.[1,3]

Quality characteristics of the MURANO[1] study have been summarized in Table 6.3

Table 6.3: Select quality characteristics of MURANO[1] trial of venetoclax-rituximab in patients with R/R CLL

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
The MURANO[1] study(NCT02005471)	Venetoclax + Rituximab Versus Bendamustine + Rituximab	Investigator-assessed PFS	370	389	1:1	No	No	Yes	Yes	No	Yes
CLL = chronic lymphocytic leukemia; PFS = progression-free survival; R/R = relapsed or refractory											

a) Trials

One ongoing, international, multicenter, open-label, randomized phase 3 trial, the MURANO[1] study, met the inclusion criteria and was included in this systematic review.

The MURANO[1] trial evaluated the efficacy and safety of venetoclax in combination with rituximab (venetoclax-rituximab) compared to the combination of bendamustine and rituximab (bendamustine-rituximab) in patients with relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL). The key inclusion criteria have been summarized in Table 6.2 and included adult patients (age ≥18 years) with diagnosis of R/R CLL that required therapy, prior treatment with one to three lines of treatment (including at least one chemo-containing regimen), and a response duration of at least 24 months if prior treatment included bendamustine. The exclusion criteria

included transformation of CLL to aggressive or central nervous system involvement, previous allogeneic or autologous stem-cell transplant, major organ dysfunction, active infection, other active malignancy, current pregnancy or breastfeeding, and treatment with warfarin (during venetoclax dose ramp-up) or strong CYP3A4 inhibitors or inducers.

Eligible patients were randomly assigned in a 1:1 ratio to receive either of the combination treatments. The study was funded by Genentech and AbbVie and conducted at 109 sites in 20 countries.

The primary endpoint in the MURANO[1] trial was investigator-assessed progression-free survival (PFS), defined as the time from randomization to the first occurrence of disease progression or relapse using the International Workshop on Chronic Lymphoid Leukemia (iwCLL) guidelines (2008), or death from any cause, whichever occurred first. The secondary endpoints include an independent review committee (IRC)-assessed PFS, complete response rate (CR), the overall response rate (ORR) and overall survival (OS), as well as patients' minimal residual disease (MRD) status, and the safety profile of the treatments. Patient-reported outcomes were included as secondary end points [assessed with the MD Anderson Symptom Inventory (MDASI), the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), the EORTC QLQ-CLL16, and the 3-level EuroQol 5 Dimension (EQ-5D-3L) questionnaire].

Statistical Analyses

The investigators estimated that a sample of 370 patients with a total of 186 events of disease progression or relapse or death would provide the trial with 80% power to detect a risk of disease progression or relapse or death that was lower by 34% (hazard ratio, 0.66) with venetoclax-rituximab than with bendamustine plus rituximab, at a two-sided alpha level of 0.05.[1]

The efficacy analyses were based on the intention-to-treat (ITT) population defined as all randomized patients. The distributions of time-to-event endpoints, including PFS, OS, event-free survival (EFS) and time to next anti-CLL treatment (TTNT) were estimated by the Kaplan–Meier method.[3] Three sensitivity analyses of the primary efficacy outcome (investigator- and IRC-assessed PFS) were conducted to test for the potential impact of differences in modeling or censoring approaches:[3]

- An unstratified log-rank test
- PFS analyses with censoring at initiation of non-protocol–specified anti-CLL therapy before meeting disease progression criteria to assess potential confounding of treatment effect estimates by subsequent therapy
- PFS analyses with censoring of death or disease progression after more than one missed response assessment at the date of last adequate response assessment.[3]

Formal statistical testing of key secondary efficacy endpoints was performed to adjust for multiple testing using a pre-specified hierarchical approach in the following order: IRC-assessed CR or CR with incomplete hematologic recovery (CRi); IRC-assessed ORR; and OS. Statistical analysis applied a stratified Cochran–Mantel–Haenszel test with a two-sided significance level of 0.05.

All randomized patients who received at least one dose of study drug were included in the safety analyses.[3]

b) Populations

A total of 389 patients were randomized in the MURANO[1] trial at 109 sites in 20 countries. Randomization assigned 194 patients to receive venetoclax plus rituximab, and 195 to receive bendamustine plus rituximab. The study population was predominantly male (>70% in each group), and the median age was 64.5 and 66.0 years in the venetoclax-rituximab and bendamustine-rituximab groups, respectively (Table 6.4). The majority of patients in each group had ECOG performance status score of 0 (>55%) or 1 (>42%), and chromosome 17p deletion was absent in 73% of patients in both treatment groups (Table 6.4). Most patients (≥85%) in each group, had lymph nodes with largest diameter <10 cm and the proportion of patients with a single previous anti-CLL therapy was 57% and 60% in the venetoclax-rituximab and bendamustine-rituximab groups, respectively (Table 6.4). Overall, the baseline demographic and disease characteristics were similar across the two treatment groups. The majority of patients in both treatment arms had prior anti-CLL therapy with alkylating agent, purine analog, and anti-CD20 antibody (Table 6.4). The proportion of patients with prior B-cell receptor inhibitors was less than three percent in both arms.

Table 6.4: Demographic and baseline disease characteristics[3]		
Characteristic	**Venetoclax plus rituximab n=194**	**Bendamustine plus rituximab n=195**
Sex, n (%)	N=194	N=195
Male	136 (70.1)	151 (77.4)
Female	58 (29.9)	44 (22.6)
Age, years		
Median	64.5	66.0
Min–Max	28–83	22–85
ECOG performance status, n (%)		
N	194	194
0	111 (57.2)	108 (55.7)
1	82 (42.3)	84 (43.3)
2	1 (0.5)	2 (1.0)
Rai staging at diagnosis[a], n (%)		
N	130	140
Stage 0–II	88 (67.7)	103 (73.6)
Stage III–IV	30 (23.1)	18 (12.9)
Fludarabine refractory[b], n (%)		
N	191	194
Yes	27 (14.1)	30 (15.5)
No	164 (85.9)	164 (84.5)
Creatinine clearance[c], n (%)		
N	194	195
<50 mL/min	6 (3.1)	10 (5.1)
≥50 mL/min	188 (96.9)	185 (94.9)
Baseline tumor lysis syndrome risk, n (%)		
N	194	195
High	54 (27.8)	55 (28.2)
Medium	106 (54.6)	104 (53.3)
Low	34 (17.5)	36 (18.5)
Absolute lymphocyte count, × 10^9/L		
<25	65 (33.5)	61 (31.3)
Platelets, × 10^9/L		
Median (min–max)	113.0 (13.0–419.0)	123.5 (11.0–457.0)
<100 × 10^9/L, %	42.8	33.5
Hemoglobin, g/dL		
Median (min–max)	11.4 (5.5–16.7)	12.0 (6.8–16.1)
<10 g/dL, %	31.4	19. 1
del(17p) status, n (%)		
N	173	169
Absent	127 (73.4)	123 (72.8)
Present	46 (26.6)	46 (27.2)
TP53 mutation status, n (%)		
N	192	184
Mutated	48 (25.0)	51(27.7)
Unmutated	144 (75.0)	133 (72.3)
del(17p) vs. TP53 mutation status, n/N (%)	171	158
Only del(17p)	24 (14.0)	18 (11.4)
TP53 mutation only	19 (11.1)	23 (14.6)
del(17p) and TP53 mutated	22 (12.9)	22 (13.9)
IGHV mutational status[d], n (%)	180	180
N		
Mutated	53 (29.4)	51 (28.3)
Unmutated	123 (68.3)	123 (68.3)
Stratification factor: risk status (derived), n (%)[e]		
N	194	195
High	109 (56.2)	118 (60.5)
Low	84 (43.3)	75 (38.5)

Number of prior CLL therapies, n (%)		
N	194 195	
1	111 (57.2)	117 (60.0)
2	57 (29.4)	43 (22.1)
3	22 (11.3)	34 (17.4)
>3	4 (2.1)	1 (0.5)
Type of prior CLL therapies, n (%)		
Alkylating agent	182 (93.3)	185 (95.4)
Purine analog	157 (80.5)	158 (81.4)
Anti-CD20 antibody)	153 (78.5	148 (76.3)
B-cell receptor inhibitors	5 (2.6)	3 (1.5)

[a] Unknown Rai stage at diagnosis: 12 (9.2%) patients in the venetoclax plus rituximab arm and 19 (13.6%) patients in the bendamustine plus rituximab arm.
[b] Per investigator assessment. Indicating not fludarabine refractory did not mean patients were exposed to fludarabine.
[c] Based on Cockcroft–Gault formula.
[d] Unknown IGHV mutational status: 4 (2.2%) patients in the venetoclax plus rituximab arm and 6 (3.3%) patients in the bendamustine plus rituximab arm.
[e] High-risk status was defined as having ANY of the following features: 17p deletion, or no response to front-line chemotherapy-containing regimen, or relapsed disease within 12 months after chemotherapy alone or within 24 months after chemoimmunotherapy. All others were considered to be of low-risk status. One patient in the venetoclax plus rituximab arm and two patients in the bendamustine plus rituximab arm had an unknown or missing risk status.
ECOG, Eastern Cooperative Oncology Group; Max, maximum; Min, minimum.

c) Interventions

In the venetoclax-rituximab arm, patients were given oral venetoclax at an initial dose of 20 mg per day, which was gradually increased to 400 mg per day according to a 5-week schedule. Prophylactic and monitoring measures, including administering oral uric acid reducer beginning ≥72 hours before dosing, were instituted to mitigate the potential for developing tumor lysis syndrome (TLS). After completion of the dose ramp-up period for venetoclax, IV rituximab was initiated in a 28-day treatment cycle for six cycles while the daily oral venetoclax continued. The first dose of rituximab, given on day one of cycle-1, was 375 mg per square meter (m^2) of body-surface area. The remaining five doses were 500 mg/m^2 each, administered on day one of subsequent cycles – thus, cycle-2 through cycle-6. For patient in the bendamustine-rituximab arm, IV bendamustine was administered at a dose of 70 mg m^2 body-surface area on days one and two of each 28-day cycle for six cycles, alongside IV rituximab using the same dosing schedule as described for the venetoclax-rituximab group. After the six cycles of combination, patients in the venetoclax-rituximab arm were expected to continue venetoclax monotherapy for a total treatment duration of two years. In line with standard practice recommended in its product monograph,[44] the treatment with bendamustine was not continued after the six-cycle combination therapy ended. The trial design did not include crossover to venetoclax-rituximab for patients in the bendamustine–rituximab group in whom progression occurred.

At the time of the data cut-off for primary analysis, the median duration of exposure to venetoclax was 22.1 months (range; 0.1 to 27.9). The median duration of exposure with bendamustine was not specified, although it was expected to be shorter since the drug was not continued after the sixth cycle ended. The exposure to rituximab was similar in the two treatment groups, with patients in either group receiving rituximab for a median of six cycles, at 100% median relative dose intensity.[1] The number of patients reported to have received at least one anti-cancer follow-up therapy was 8 (4.1%) in the venetoclax-rituximab group compared with 54 (27.7%) in the bendamustine-venetoclax group. Table 6.5 shows the subsequent therapies received.

Table 6.5: Follow-up anticancer therapy use (intent-to-treat population).

Treatment, n (%)	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=195
Patients with ≥ 1 treatment	8 (4.1)	54 (27.7)
Total number of treatments	14	95
Selected therapies of interest		
Ibrutinib monotherapy	1 (0.5)	33 (16.9)
BTK inhibitor BGB 3111	0	2 (1.0)
R-CHOP	1 (0.5)	4 (2.1)
Venetoclax monotherapy	1 (0.5)	3 (1.5)
Allogenic stem cell Transplantation	0	3 (1.5)
CHOP	0	3 (1.5)
Idelalisib and rituximab	1 (0.5)	2 (1.0)

BTK, Bruton's tyrosine kinase; R-CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab.

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d) Patient Disposition

The disposition of patients is outlined in Table 6.6. One hundred and ninety-four (194) and 195 patients were randomised to the venetoclax-rituximab and the bendamustine-rituximab arms, respectively. Seven patients in the bendamustine-rituximab group did not receive any treatment. However, the efficacy analysis was based on the intent-to-treat (ITT) population which included all randomised patients. Safety analysis included all patients who received at least one dose of study medication. At the time of primary analysis (data cut at May 2017), the proportions of patients who discontinued treatment were 32.0% and 17.4% in the venetoclax–rituximab and bendamustine–rituximab groups, respectively. The main reason for treatment discontinuation was adverse events (AEs). According to the published patients' disposition chart, 24 (12.37%) patients in the venetoclax-rituximab arm discontinued venetoclax due to AEs and 10 (5.15%) patients in

the group discontinued rituximab for the same reason. Eleven patients (5.6%) discontinued bendamustine plus rituximab due to AEs.

Table 6.6: Patient disposition in the Phase 3 MURANO[1] study

	Venetoclax-Rituximab	Bendamustine-Rituximab
Screened	489	
Enrolled	389	
Randomized, n (%)	194 (100)	195 (100)
Patients receiving combination, n (%)	187 (96.4)	188 (96.4)
Patients with no treatment, n (%)	0	7 (3.6)
Completed Combination, n (%)	174 (89.7)	154 (79.0)
Completed 2 years of venetoclax, n (%)	130 (67)	N/A [1]
Discontinued treatment, n (%)	62 (32.0)	34 (17.4)
- Progressive disease or relapse, n (%)	10 (5.2)	6 (3.1)
- Adverse event, n (%)	34* (17.5)	11 (5.6)
- Patient withdrew consent, n (%)	0	6 (3.1)
- Other reasons, n (%)	16 (8.2)	8 (4.1)
- Death, n (%)	2 (1.0)	3 (1.5)
Analysis Sets		
ITT population[2]	194	195
Safety population [3]	194	188

Abbreviation: ITT = intent-to-treat; N/A = not applicable;
Notes:
[1]– Bendamustine is administered on days 1 and 2 of each 28-day cycle, for up to 6 cycles (https://pdf.hres.ca/dpd_pm/00043152.PDF).[44] Accessed March 8, 2019)
[2]– The ITT population included all randomized patients
[3]– The safety population included all patients that have received at least one dose of study medication

* 24 patients discontinued venetoclax and 10 discontinued rituximab due to AEs

Source: Seymour et al.;[1] Kater et al.[4]

e) Limitations/Sources of Bias

- The open-label design in which neither participants nor investigators were blinded to treatment assignment increases the potential theoretical risk for bias in the trial. However, the impact of this on the reported outcomes may be small since most outcomes were objectively evaluated using measures which the clinical experts consulted on this review accept as standard in the Canadian context. Additional factors that mitigate the risk of bias were the use of the IRC, pre-specification of endpoints to measure, and assessing outcomes at pre-specified time points.
- The inclusion criteria specified ECOG performance status score of 0 or 1, and most patients in the study population had lymph nodes with largest diameter <10 cm and had had a single previous therapy. Therefore, it is uncertain if the results can be replicated in heavily treated R/R CLL patients with worse disease burden and higher ECOG score which indicate greater disability.
- The health-related quality of life (HRQoL) findings were inconclusive due to administrative errors in data collection, which resulted in a significant extent of missing data.

- MURANO[1] is an industry-funded trial in which the staff of the sponsors were involved in all aspects of conducting the study including design, data collection, analyses, interpretation, and the preparation of the final manuscript. Thus a high potential for conflict of interest exists which could risk the objectivity in the conduct of study as well as the reporting and interpretation of findings. However, the IRC involvement in data analysis seems to be a mitigating factor for the risk.
- Assessment of MRD was a pre-specified exploratory endpoint. Given the limited number of patients in whom MRD-negativity was evaluated, there is uncertainty about the use of this metric to promote treatment-free intervals for R/R CLL patients treated with venetoclax-rituximab. Larger randomized trials are required to explore the concept further before confirmation and adoption.
- The median OS was not reached in either treatment arm at the time of primary analysis
- The pre-specified hierarchical testing of the three key secondary efficacy endpoints failed; therefore, the differences in the complete response (CR)/CR with incomplete hematologic recovery (CRi), overall response rate (ORR) and OS were descriptive and not statistically significant.
- There was no statistical provision to account for multiple testing of endpoints in the updated analysis. Therefore, all reported p-values were for descriptive purposes only without indicating statistical significance.
- There was no direct comparisons with ibrutinib or idelalisib-rituximab which have been approved for treatment in patients with relapsed or refractory (R/R) CLL.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The following paragraphs summarize the efficacy outcomes of the MURANO[1] trial. The efficacy outcomes data from the primary and updated analyses (data cuts of May 2017 and May 2018) have been summarized in Table 6.7.

Although an updated analysis, performed with one more year of follow-up after the primary analysis (data cut at May 2018), has been published,[4] the investigators reported that there was no statistical provision to account for multiple testing of the endpoints of the updated analysis. Therefore, all reported p-values were for descriptive purposes only without indicating statistical significance.

Progression-free survival

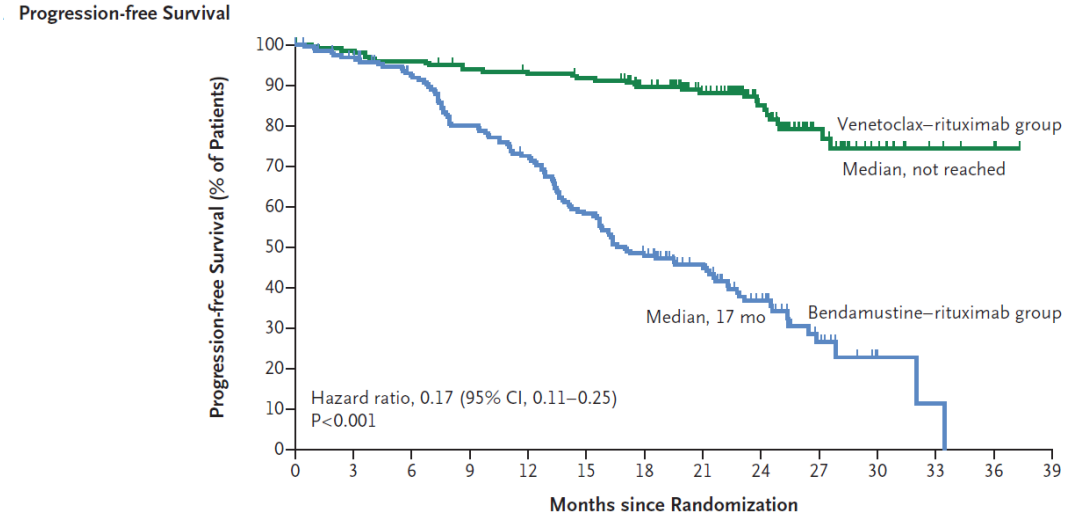
Investigator-assessed progression-free survival (PFS), which was defined as the time from randomization to the first occurrence of disease progression or relapse or death from any cause, whichever occurred first was the primary endpoint of the phase 3 MURANO[1] study. After a median follow-up period of 23.8 months (range: 0.0 to 37.4), the primary analysis showed that the median PFS was 17

months in the bendamustine–rituximab group but was not reached in the venetoclax–rituximab group. However, the median investigator-assessed PFS was significantly longer in the venetoclax–rituximab group than in the bendamustine–rituximab group (Figure 6.2).

Similarly, the two-year rate of investigator-assessed PFS was higher for the venetoclax–rituximab group (84.9%; 95% CI: 79.1 to 90.6) than the bendamustine–rituximab group (36.3%; (95% CI: 28.5 to 44.0). The risk of disease progression or death was estimated to be significantly higher for patients in the bendamustine–rituximab group (HR = 0.17; 95% CI: 0.11 to 0.25; P<0.001 by the stratified log-rank test) (Table 6.7).

The result of the IRC assessment of the risk of disease progression or relapse or death was consistent in magnitude to the investigator-reported PFS outcome (Table 6.7). Also, consistently more significant improvements in PFS were observed for venetoclax-rituximab than for bendamustine–rituximab in all subgroups evaluated (Figure 6.6).

Figure 6.2: Kaplan-Meier estimates of investigator-assessed PFS in the MURANO[1] trial at the primary analysis (data cut-off date May, 2017) for Venetoclax-rituximab compared with Bendamustine-rituximab



Key: CI =confidence interval

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An updated analysis in May 2018, when all patients had completed therapy with a median follow-up period of 36 months, shows that the PFS with venetoclax-rituximab remained superior to bendamustine-rituximab (HR = 0.16; 95% CI: 0.12 to 0.23), although

events in the venetoclax-rituximab arm were not enough to determine the median PFS. The three-year PFS estimates were 71.4% (95% CI, 64.8% to 78.1%) for the venetoclax–rituximab group compared with 15.2% (95% CI, 9.1% to 21.4%) for the bendamustine–rituximab group.[4] The results of the updated analysis were descriptive and not statistically significant.[4]

Table 6.7: Key efficacy outcomes at the primary analysis- Data Cut dates of May 8, 2017 and May 8, 2018.

	Investigator Assessed		IRC-Assessed	
Outcome	**Venetoclax-Rituximab (n=194)**	**Bendamustine-Rituximab (n=195)**	**Venetoclax-Rituximab (n=194)**	**Bendamustine-Rituximab (n=195)**
Progression-free survival				
Median PFS, months (95% CI)	Not reached	17.1 (15.7, 21.6)	Not reached	18.1 (15.8, 22.3)
HR (95% CI)	0.17 (0.11, 0.25)		0.19 (0.13, 0.28)	
p-value (log-rank)	<0.0001		<0.0001	
PFS rate in 2-years, % (95% CI)	84.9 (91.9, 90.6)	36,3 (28.5, 44.0)	NR	NR
PFS from updated analysis at 08 May 2018				
Median PFS at 3 years, months	Not reached	17.1 months	NR	
- HR (95%CI)	0.16 (0.12, 0.23)			
- p-value[6]	<0.001			
Overall survival				
Median OS, months (95%CI)	**Not reached**	**Not reached**		
OS rate at 24 months, %	91.9	86.6	NR	NR
HR of OS (95% CI)	0.49 (0.25, 90)		NR	NR
- p-value[6]	0.0186			
OS from updated analysis at 08 May 2018			NR	
Median OS, months (95%CI)	Not reached	Not reached		
OS rate at 36 months, %	87.9	79.5		
- HR (95%CI)	0.50 (0.30, 0.85]			
- p-value[6]	0.0093			
Response				
ORR (CR/CRi + PR/nPR), %	93.3	67.7	92.3	72.3
Difference, % (95% CI)	25.6 (17.9, 33.3)		20 (12.4, 27.6)	
CR/CRi rate, n (%)	26.8	8.2	8.2	3.6
PR/nPR	66.5	59.5	84.0	68.7
Duration of Response				
Median DOR, Months[2]	Not reached	19.6	NR	NR
EFS [2] rate in 2 years	84.9	34.8	NR	NR

Table 6.7: Key efficacy outcomes at the primary analysis- Data Cut dates of May 8, 2017 and May 8, 2018.

	Investigator Assessed		IRC-Assessed	
Outcome	**Venetoclax-Rituximab (n=194)**	**Bendamustine-Rituximab (n=195)**	**Venetoclax-Rituximab (n=194)**	**Bendamustine-Rituximab (n=195)**
HR for EFS (95% CI)	0.17 (0.11, 0.25)			
TTNT[3]- Patients with no anti-CLL treatment within 2 years, %	90.0	52.1	NR	NR
HR of next anti-CLL treatment or death (95% CI)	0.19 (0.12, 0.31)			
MRD negativity[4] in peripheral blood			NR	NR
- **At 9 months assessment,[5] n (%)**	121 (62.4)	26 (13.3)	NR	NR
- **At any time, n (%)**	162 (83.5)	45 (23.1)	NR	NR
- **Difference % (95% CI)**	60.4 (52.3, 68.6%)		NR	NR
MRD negativity [4] in BM (time of assessment not stated)	53 (27.3)	3 (1.5)	NR	NR
Difference of MRD negativity in BM (95% CI)	25.8% (19.0, 32.6)		NR	NR
P-value[6]	<0.0001		NR	NR

Abbreviations: CI = confidence interval; CR = complete remission; CRi – complete remission with incomplete marrow recovery; DOR = duration of response; EFS = event-free survival; IRC – Independent review committee; MRD – minimal residual disease; NR – not reported; ORR = objective response rate; OS – overall survival; PFS = progression-free survival; PR = partial response; TTNT = time to next anti-CLL treatment

Notes:

[1] – Duration of response was defined for patients with a best overall response as the time from first occurrence of a documented complete response or partial response to disease progression/relapse, as assessed by the investigator, or death from any cause.

[2] – EFS was defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-CLL treatment.

[3]- Time to next anti-CLL treatment was defined as the time from randomization to start of new, non-protocol, anti-CLL therapy or death from any cause.

[4] – MRD negativity was defined as blood or marrow with less than one CLL cell per 10,000 white blood cells (10^{-4}).

[5] – Corresponding with the time of the combination-treatment response assessment visit

[6] – Descriptive P-value

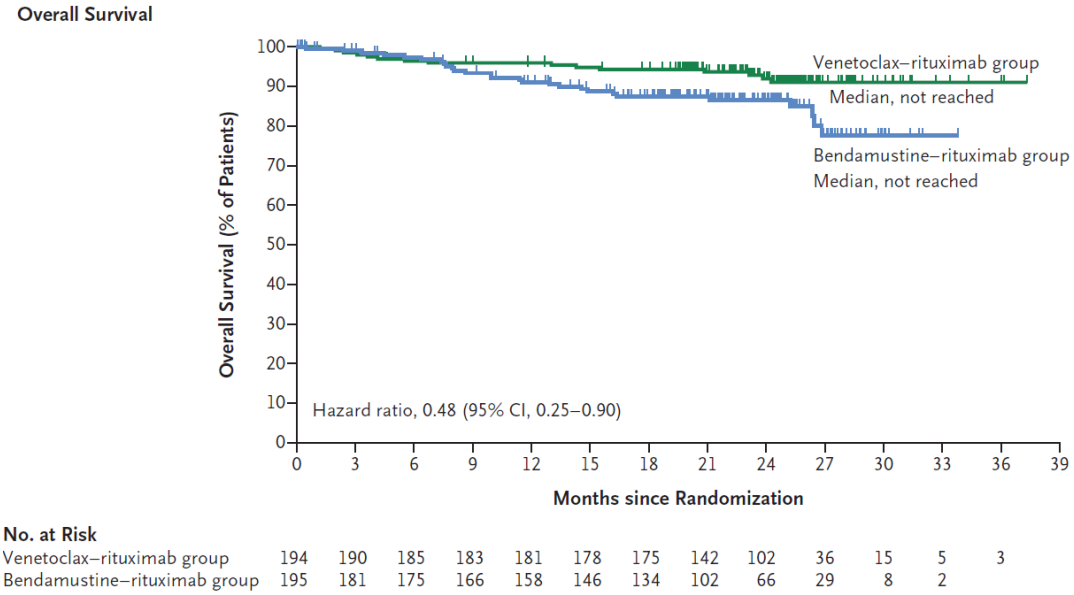
Source: Seymour et al.;[1,3] Kater et al.;[4] Submitter-Provided Clinical Study Report[2]

Overall survival

Overall survival (OS), defined as the time from the date of randomization to the date of death from any cause, was a secondary endpoint in the MURANO[1] trial. The median OS was not reached in either treatment arm at the time of primary analysis. The OS rate

was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group (Figure 6.3).

Figure 6.3: Kaplan-Meier estimates of investigator-assessed overall survival in the MURANO[1] trial at the primary analysis (data cut-off date May, 2017) for Venetoclax-rituximab compared with Bendamustine- rituximab



Key: CI = confidence interval
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The 24-month OS rates was 91.9% and 86.6% with venetoclax-rituximab and bendamustine-rituximab, respectively (HR = 0.48; 95% CI, 0.25 to 0.90) (Table 6.7). However, this OS difference between the treatment groups was only descriptive since the first formal statistical test in a pre-specified hierarchical testing to adjust for multiple testing of the key secondary efficacy endpoints was not statistically significant.

The median OS was not reached in either treatment arm at the time of the updated analysis (data cut-off May 2018)[4]. However, the 3-year estimates showed a consistent higher improvement in OS rate with venetoclax-rituximab (87.9%) than with bendamustine-rituximab (79.5%), with HR = 0.50 (95% CI: 0.30 to 0.85; P = .0093)

Overall response rate

The overall response rate (ORR) was a secondary outcome in the MURANO[1] study and include CR or CRi, nodular partial response (nPR), or partial response (PR). The ORR was consistently higher in

the venetoclax–rituximab group than in the bendamustine–rituximab group in both the investigator-assessed and the IRC-assessed analysis (Table 6.7). However, because the hierarchical testing failed as described under OS, the difference between the two treatment groups is only descriptive and without indication of the level of statistical significance.

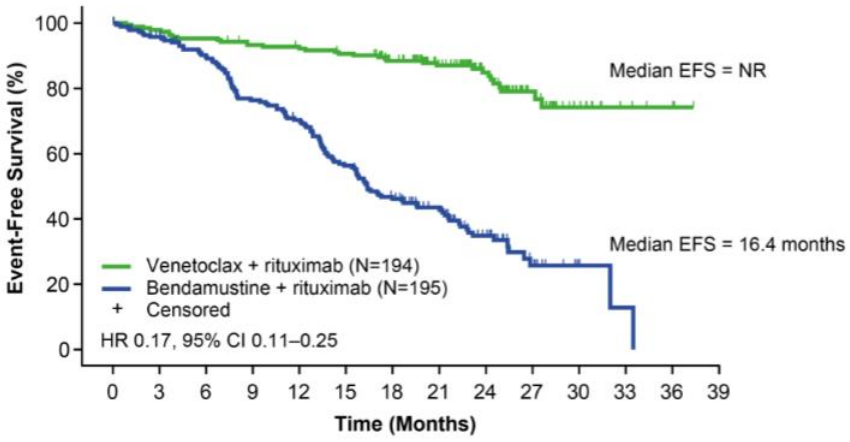
Duration of response

Duration of response (DOR) was a secondary outcome in the MURANO[1] study and it was defined as the time from first occurrence of a documented CR or partial response (PR) to disease progression or relapse, as assessed by the investigator, or death from any cause. DOR was evaluated in patients with a best overall response and was censored on the date of last adequate response assessment for patients achieving a response who did not die or had definite disease progression or relapse at the time of analysis. The median DOR was 19.4 months in the bendamustine–rituximab group but was not reached in the venetoclax–rituximab group.[45] Although they were not stated in the systematic review protocol (Table 6.1), the event-free survival (EFS) and time to the next treatment for R/R CLL (TTNT) outcomes are reported below as additional measures of duration of response.

Event-free survival

The EFS was a secondary outcome defined as the time between date of randomization and the date of disease progression, relapse, death, or start of a new anti-CLL treatment. At the time of the primary analysis, the EFS was longer in the venetoclax–rituximab group than in the bendamustine–rituximab group (Figure 6.4), with two-year EFS rates of 84.9% versus 34.8% for the venetoclax–rituximab and bendamustine–rituximab groups, respectively.

Figure 6.4: Kaplan-Meier estimates of investigator-assessed event-free survival for Venetoclax-rituximab compared with Bendamustine- rituximab



No. of patients at risk													
Venetoclax + rituximab	194	189	184	178	175	171	155	113	75	33	14	5	3
Bendamustine + rituximab	195	177	162	138	126	101	80	56	34	11	3	1	

Key: CI = confidence interval, EFS = event-free survival; HR = hazard ratio, NR = not reached
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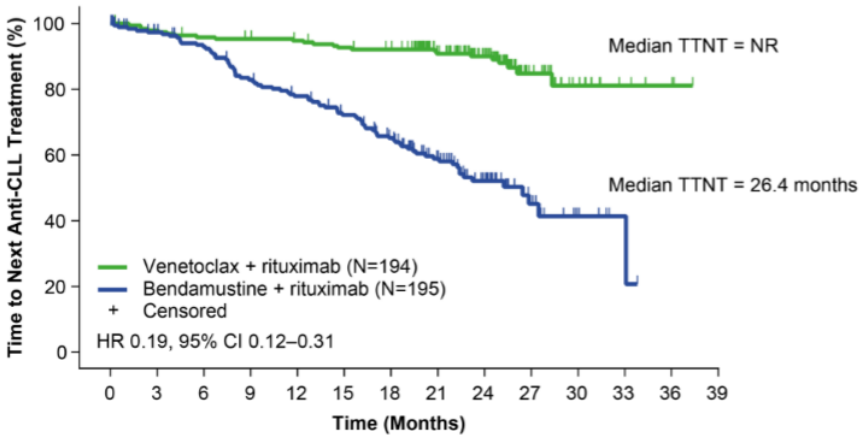
Time to next anti-CLL treatment (TTNT)

The TTNT was a secondary outcome defined as the time from randomization to start of new, non-protocol, anti-CLL therapy or death from any cause. At the time of the primary analysis, 90.0% of patients in the venetoclax–rituximab group compared with 52.1% of patients in the bendamustine–rituximab group had not received a subsequent CLL treatment for two years (Figure 6.5).The Kaplan-Meier curve in Figure 6. show that it took longer for patients treated with venetoclax-rituximab to require next anti-CLL treatment than those treated with bendamustine-rituximab.

Figure 6.5: Kaplan-Meier estimates of investigator-assessed time to next anti-CLL treatment for Venetoclax-rituximab compared with Bendamustine-rituximab



No. of patients at risk													
Venetoclax + rituximab	194	189	184	182	179	174	171	137	98	34	14	5	3
Bendamustine + rituximab	195	179	168	149	138	125	106	73	44	15	6	2	

Key: CI = confidence interval, HR = hazard ratio, NR = not reached, TTNT = time to next anti-CLL treatment

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At the updated analysis in the May 2018, the median TTNT or death was 23.9 months (range: 0.0 to 43.7 months) in the bendamustine-rituximab arm.[4] The median TTNT in the venetoclax-rituximab arm could not be estimated because there were too few patients at risk in that group for a reliably assessment. Anti-CLL treatment had been administered to 91 patients in the bendamustine-rituximab arm after disease progression compared with 27 patients in the venetoclax-rituximab arm. Thus, overall, patients in the venetoclax–rituximab group had a longer TTNT for CLL than those in the bendamustine–rituximab group and were less likely to receive subsequent therapy.

Quality of Life

The patient-reported outcomes (PRO) were included as secondary outcome in the MURANO[1] trial. The analyses centered on changes from baseline (pretreatment) scores for the different instruments (i.e., MDASI, QLQ-C30, and QLQ-cLL16). Day 1 of ramp-up with venetoclax was established as baseline for the venetoclax-rituximab arm when patients were pre-treatment. For the bendamustine-rituximab arm, baseline was Cycle 1 Day 1, before the start of combination therapy. A mixed effects model for repeated measures (MMRM) was used to estimate the mean of change from baseline. A ten-point change (or higher) in mean scores indicated a clinically meaningful difference on the QLQ-c30 and QLQ-cLL16. For the MDASI a clinically meaningful difference was defined as a change of 1.2 points or more. Due to administrative errors the baseline PRO assessments (EORTC-QLQ -c30 and CLL16) were partially collected. Additionally the MD Anderson Symptom Inventory (MDASI) was only administered until the end of Cycle 3, also due to administrative error. In the evaluable sample there was no clinically meaningful

difference observed between venetoclax-rituximab and bendamustine-rituximab in any of the QOL domains during treatment and through follow-up. However, the health related quality of life results collected in the MURANO[1] trial were inconclusive. Due to administrative errors the baseline scores (EORTC-QLQ -c30 and CLL16) were partially collected which resulted in a significant extent of missing patient reported outcomes data.[2]

Minimal residual disease status

The assessment of minimal residual disease (MRD) was a pre-specified exploratory endpoint. Undetectable MRD (MRD-negativity) was defined as less than one CLL cell in 10,000 leukocytes (i.e., MRD value less than 10-4). Among patients with detectable MRD, the MRD status was further categorized into low-level MRD (10^{-4} to less than 10^{-2}) and high-level MRD ($\geq 10^{-2}$).

As shown in Table 6.7 the assessments at the primary analysis demonstrated that the peripheral blood MRD-negativity rate was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group at the end of the combination treatment period (the 9-month time point) (62.4% versus 13.3%), and at any time during the trial (83.5% versus. 23.1%). The assessment of MRD in bone marrow aspirate also showed higher rate of clearance of MRD in the venetoclax–rituximab group than in the bendamustine–rituximab group (27.3% vs.1.5%), although the time of the bone marrow MRD assessment was not specified. At the end of the combination therapy, patients with low-level MRD had a longer duration of PFS compared with those with high-level MRD in both the venetoclax-rituximab arm (HR = 0.24; 95% CI: 0.08 to 0.72), and the bendamustine-rituximab arm (HR = 0.22; 95% CI: 0.13 to 0.38).[4]

As at the May 2018 updated analysis, the overall MRD-negativity rate was 82.5% with venetoclax-rituximab compared with 23.1% with bendamustine-rituximab.[4] Analysis using paired samples from 47 patients who received venetoclax-rituximab found that 44 (90%) of undetectable MRD in peripheral blood was confirmed in bone marrow, demonstrating a high concordance for MRD status between peripheral blood and bone marrow samples.

Of 130 (67%) patients who completed two years of venetoclax, 83 (64%) achieved MRD-negativity status. After a median of 9.9 months off venetoclax, 58 (70%) of these patients retained their MRD-negative status, whereas two (2.4%) patients developed progressive disease. Twenty-five (30%) of the 83 patients developed detectable MRD, classified as low-level MRD in 21 patients, and high-level MRD in four patients.[4] At the updated analysis, in May 2018, these 25 patients had been off venetoclax for a median 11.1 months, and all the 21 low-level MRD patients remained progression-free and event free, whereas one of the four patients with high-level MRD status had developed progressive disease.[4]

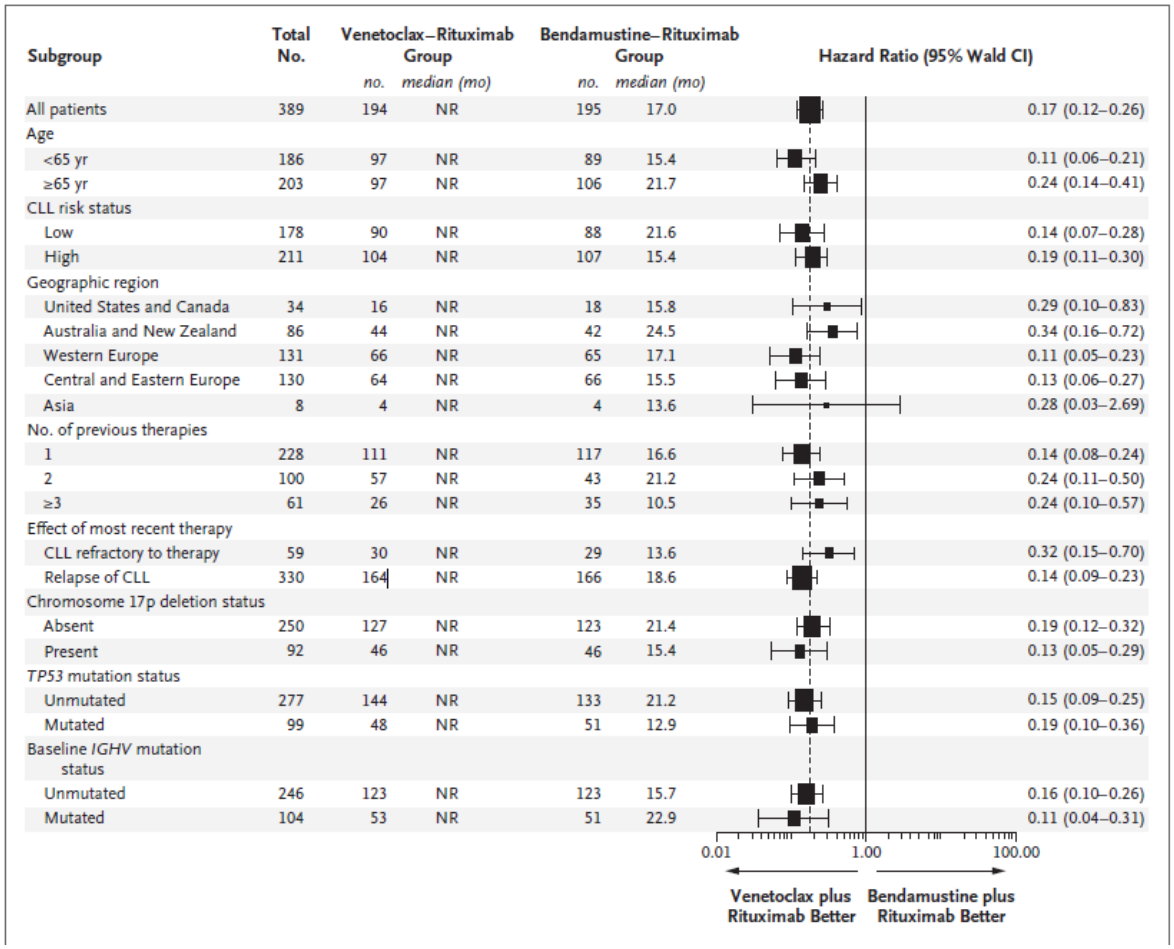

Figure 6.6: Prespecified Subgroup Analysis of Investigator-Assessed Progression-free Survival.
A hazard ratio of less than 1.00 indicates a lower risk of disease progression or relapse or death with venetoclax plus rituximab than with bendamustine plus rituximab. The size of each square is proportional to the amount of data available. CLL denotes chronic lymphocytic leukemia, IGHV immunoglobulin heavy-chain variable, and NR not reached.

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Harms Outcomes

Adverse events (overall)

The safety analysis population was defined as all patients that have received at least one dose of study medication and included 194 patients in the venetoclax–rituximab arm and 188 in the bendamustine–rituximab arm. At the time of the data cut-off for safety analysis (May 8, 2017), the median duration of exposure to venetoclax was 22.1 months (range, 0.1 to 27.9). All the patients (100.0%) in the venetoclax–rituximab group and 98.4% in the bendamustine–rituximab group had at least one adverse event (AE) of any grade (in at least 10% of the safety population). Neutropenia was the most common AE of any grade in both treatment groups. It was reported in 60.8% of the patients in the venetoclax–rituximab group and 44.1% of the patients in the bendamustine–rituximab

group (Table 6.8). Other AEs reported commonly in the venetoclax–rituximab group (vs. bendamustine–rituximab) included diarrhea (39.7% vs. 16.5%), infections and infestations (34.0% vs. 42.3%),[2] upper respiratory tract infection (URTI) (22.2% vs. 15.4%), nausea (21.1% vs. 34.0%), and fatigue (17.5% vs. 20.7%).

Adverse events ≥grade 3

Grade 3 or 4 AEs were reported in 82.0% of patients in the venetoclax–rituximab group and in 70.2% in the bendamustine–rituximab group, with neutropenia being the most common Table 6.9. The incidence of grade 3 or 4 neutropenia was higher in the venetoclax–rituximab group than in the bendamustine–rituximab group (57.7% vs. 38.8%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the venetoclax–rituximab group.[1]

Serious adverse events

The incidence of serious adverse events (SAEs) was similar in the two groups (Table 6.9). Adverse events that resulted in death were reported in 5.2% of the patients in the venetoclax–rituximab group and in 5.9% of the patients in the bendamustine–rituximab group. Infections or infestations were the most common AEs that resulted in death, accounting for four fatalities in each group.

Withdrawal due to adverse events

The percentage of patients with at least one AE leading to treatment discontinuation was 12.9% with venetoclax and 9.0% with bendamustine. The treatment discontinuation rate due to AEs with rituximab was 5.2% in the venetoclax-rituximab arm compared with 6.9% in the bendamustine-rituximab arm.

The percentage of patients with at least one AE leading to dose interruption was 69.6% with venetoclax and 28.2% with bendamustine. The dose interruption rate due to AEs with rituximab was 20.1% in the venetoclax-rituximab arm compared with 36.7% in the bendamustine-rituximab arm.

The percentage of patients with at least one AE leading to dose reduction was 13.9% with venetoclax and 13.8% with bendamustine. The dose reduction rate due to AEs with rituximab was 1.0% in the venetoclax-rituximab arm compared with 1.1% in the bendamustine-rituximab arm.

Adverse event of special interest

Tumor lysis syndrome

Grade 3 or 4 tumor lysis syndrome (TLS) was reported in six patients (3.1%) in the venetoclax–rituximab group and in two patients (1.1%) in the bendamustine–rituximab group. One patient in each treatment group had clinical TLS. All other cases of TLS syndrome were based on changes in laboratory values only.

Table 6.8. Incidence of adverse events (all grades)

	Venetoclax plus rituximab N=194	Bendamustine plus rituximab N=188
Patients with ≥1 adverse event, n (%)	194 (100.0)	185 (98.4)
Total number of adverse events	978	907
Adverse events occurring in >10% of patients in either arm, n (%)		
Neutropenia	118 (60.8)	83 (44.1)
Diarrhea	77 (39.7)	31 (16.5)
Nausea	41 (21.1)	64 (34)
Anemia	30 (15.5)	43 (22.9)
Fatigue	34 (17.5)	39 (20.7)
Upper respiratory tract infection	43 (22.2)	29 (15.4)
Thrombocytopenia	26 (13.4)	42 (22.3)
Pyrexia	29 (14.9)	38 (20.2)
Cough	35 (18)	31 (16.5)
Constipation	27 (13.9)	39 (20.7)
Infusion-related reaction	16 (8.2)	45 (23.9)
Pneumonia	18 (9.3)	22 (11.7)
Headache	21 (10.8)	19 (10.1)
Vomiting	16 (8.2)	23 (12.2)
Rash	14 (7.2)	24 (12.8)
Bronchitis	20 (10.3)	13 (6.9)
Insomnia	21 (10.8)	12 (6.4)
Nasopharyngitis	22 (11.3)	10 (5.3)
Febrile neutropenia	7 (3.6)	19 (10.1)

Adverse event reporting period: Prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention were reported (e.g. serious adverse events related to invasive procedures, such as biopsies). After initiation of study drug, all adverse events, regardless of relationship to study drug, were reported until 28 days after the last dose of study drug (maximum 2 years for venetoclax), or 90 days after last dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern believed to be related to prior study drug treatment.

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Table 6.9. Adverse Events.*

Event	Venetoclax–Rituximab Group (N=194)	Bendamustine–Rituximab Group (N=188)
Grade 3 or 4 adverse event — no. of patients (%)	159 (82.0)	132 (70.2)
Total no. of events	335	255
Grade 3 or 4 adverse events with at least 2% difference in incidence between groups — no. of patients (%)	130 (67.0)	104 (55.3)
Neutropenia†	112 (57.7)	73 (38.8)
Infections and infestations	34 (17.5)	41 (21.8)
Anemia	21 (10.8)	26 (13.8)
Thrombocytopenia	11 (5.7)	19 (10.1)
Febrile neutropenia	7 (3.6)	18 (9.6)
Pneumonia	10 (5.2)	15 (8.0)
Infusion-related reaction	3 (1.5)	10 (5.3)
Tumor lysis syndrome‡	6 (3.1)	2 (1.1)
Hypotension	0	5 (2.7)
Hyperglycemia	4 (2.1)	0
Hypogammaglobulinemia	4 (2.1)	0
Serious adverse events with at least 2% incidence in either group — no. of patients (%)	90 (46.4)	81 (43.1)
Pneumonia	16 (8.2)§	15 (8.0)
Febrile neutropenia	7 (3.6)	16 (8.5)
Pyrexia	5 (2.6)	13 (6.9)
Anemia	3 (1.5)	5 (2.7)
Infusion-related reaction	1 (0.5)	6 (3.2)
Sepsis	1 (0.5)	4 (2.1)
Tumor lysis syndrome	4 (2.1)	1 (0.5)
Hypotension	0	5 (2.7)
Fatal adverse events — no. of patients (%)	10 (5.2)§	11 (5.9)

* Before the initiation of a trial drug, only serious adverse events that were considered to have been caused by a protocol-mandated intervention were reported (e.g., serious adverse events related to invasive procedures, such as biopsies). After the initiation of a trial drug, all adverse events, regardless of the relationship to the trial drug, were reported through 28 days after the last dose of trial drug (a maximum of 2 years for the venetoclax–rituximab group) or through 90 days after the last dose of rituximab, whichever was longer. After this period, investigators were to report any deaths, serious adverse events, or other adverse events of concern that were believed to be related to previous treatment with the trial drug.

† A higher percentage of new-onset events of neutropenia occurred during the combination-treatment period than during the venetoclax monotherapy phase (54.1% vs. 11.1%). Protocol-mandated dose interruption for all grade 3 or 4 events of neutropenia occurred in 43.3% of the patients in the venetoclax–rituximab group. In total, 47.9% of the patients in the venetoclax–rituximab group and 43.1% of the patients in the bendamustine–rituximab group received growth factor.

‡ Additional information on the events of the tumor lysis syndrome can be found in Table S12 in the Supplementary Appendix.

§ Two serious adverse events of pneumonia that resulted in death occurred in patients who had both disease progression and confirmed Richter's transformation (i.e., conversion into an aggressive lymphoma, typically diffuse large B-cell lymphoma).

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6.4 Ongoing Trials

No ongoing and/or unreported trials were identified that would have been included in this systematic review if they were completed.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of venetoclax-rituximab for relapsed or refractory (R/R) chronic lymphocytic leukemia (CLL):

- Summarise and critically appraise the indirect treatment comparison submitted by the manufacturer as part of materials supporting their economic evaluation.

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

7.1 Summary of Indirect Treatment Comparison

7.1.1 Objective

In the absence of head-to-head randomized controlled trial evidence of the comparative efficacy and harms, the submitter presented results from indirect treatment comparison (ITC)[46] between the venetoclax-rituximab combination and comparator treatments for adult patients with R/R CLL. This section aims to summarize and critically appraise the manufacturer-provided ITC,[46] as it applies to the comparators ibrutinib monotherapy or idelalisib-rituximab combination therapy.

7.1.2 Methods

One reviewer reviewed and summarized the ITC provided by the submitter,[46] and evaluated its methodological quality using the ISPOR Questionnaire as a guide. A literature search to identify additional relevant published information for independent indirect comparison was not undertaken. The submitted ITC evaluated the relative effectiveness of the venetoclax-rituximab combination versus ibrutinib single-agent and versus idelalisib-rituximab in adult patients with R/R-CLL by estimating hazard ratios (HR) for survival and relative risk ratios (RR) for tumour responses. However, given that progression-free survival (PFS) and overall survival (OS) were the outcomes required for the submitter's economic model, they are the only outcomes discussed in this section.

7.1.3 Objectives and rationale of the manufacturer-submitted ITC

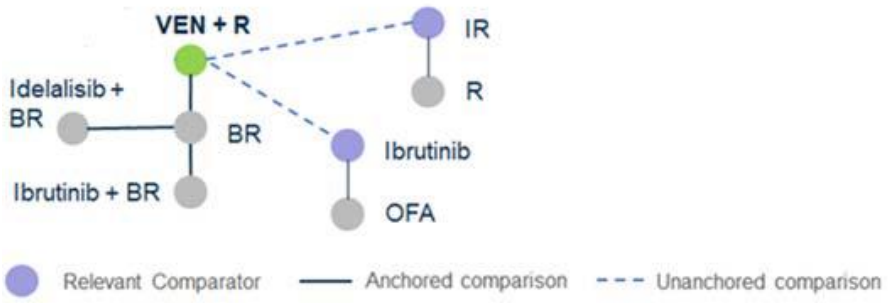
The specific objective of the manufacturer-submitted ITC[46] was to estimate the relative effectiveness of the venetoclax-rituximab combination versus relevant comparators concerning PFS, OS, overall response rates (ORRs), complete response (CR) and partial response (PR) to support launch activities. In the absence of head-to-head RCT evidence of comparative efficacy, the manufacturer presented the ITC[46] results to support economic evaluation as part of materials submitted to request listing approval of the venetoclax-rituximab combination in Canada.

7.1.4 Description of the Manufacturer-submitted ITC

The manufacture-submitted ITC[46] followed the NICE guidance on "Methods for population-adjusted indirect comparisons in submissions to NICE."[47] Since there

is no common comparator between venetoclax-rituximab and ibrutinib single-agent or idelalisib-rituximab, the investigators performed an unanchored matched adjusted indirect comparison (MAIC) to calculate the relative efficacy estimates for the comparators. The MAIC followed the methodology outlined in Signorovitch et al.[48] Prognostic and effect modifier variables were matched to balance patient characteristics between MURANO[1] and its comparator trials to minimize any bias in relative treatment effect estimates. The status of each variable as prognostic or effect modifier was determined using information obtained from the literature and confirmed by expert opinion, as well as a quantitative assessment of data in the MURANO[1] trial. Figure shows the evidence network for the ITC.[46] The doted lines signify that no connections were identified for ibrutinib single-agent or idelalisib-rituximab which are relevant to clinical practice in Canada.

Figure 7.1: Evidence network of the included comparator trials



Key: BR, bendamustine + rituximab; IR, idelalisib + rituximab; OFA, ofatumumab; R, rituximab; VEN, venetoclax
Source: Manufacturer-submitted ITC[46]

The unanchored indirect comparisons for PFS or OS were formed by calculating the logarithm of the HRs and 95% CIs of the reweighted venetoclax-rituximab relative to data derived from the comparator's digitized survival curve using the following model:

- Log HR venetoclax-rituximab vs. Comparator = log HR (reweighted venetoclax- rituximab survival curve) vs. Comparator (digitized survival curve)

A weighted Cox model with standard errors was used to analyse the MURANO[1] data and the simulated patient-level outcomes data for comparators. Statistical analyses were conduct with the R software to derive the HR of PFS and OS for venetoclax-rituximab relative to the comparators, such that an HR<1 indicates lower risk of progression or death for venetoclax-rituximab than for the comparator treatment.

7.1.5 Data sources for the manufacturer-submitted ITC

Patient-level data from the MURANO[1] study were reweighted using propensity score reweighting methods to match common patient characteristics across the comparator trials. The comparator data for all the comparisons were taken from the literature,[49,50] identified through a systematic literature review covering published studies from 2014 until April 2018. Randomized controlled

trials and observational studies were eligible for inclusion in the ITC[46] if they met the following criteria:

- Reported baseline clinical characteristics
- Included a Kaplan-Meier PFS and OS graph displaying the survival and progression events and numbers at risk
- Reported outcomes were defined similarly as the MURANO[1] trial, and
- Had comparator survival data that most closely matched the follow-up availability in MURANO.[1]

A two-step process was used to derive patient-level OS and PFS data for the comparator trials from the published Kaplan-Meier graphs. In the first step, the numerical values of the survival curves were obtained through graphical digitization software at dozens of time points. In the second step, a "simulated" trial population was derived using values from the initial step based on the algorithm described by Guyot et al.[51] The simulated patient-level data sets were then used in the ITC analyses.[46]

7.1.6 Results

Two studies were selected from the RCTs and observational studies identified by the literature search for the unanchored ITC.[46] One study was on ibrutinib single-agent (long-term efficacy update of phase 3 RESONATE trial)[49] and the other was on idelalisib-rituximab (second interim analysis of a Phase 3 ZYDELIG trial).[50] They provided data on their respect interventions for comparison with venetoclax-rituximab with data from the post-treatment follow-up of the phase 3 MURANO trial[4].

Unanchored ITC of Venetoclax-rituximab versus Ibrutinib single-agent

The effect modifiers and prognostic variables reweighted for MURANO[1] versus ibrutinib unanchored ITC[46] have been listed in Table 7.1.

After adjustments to minimize bias due to imbalance across all observed effect modifiers and prognostic covariates, 169 patients (87% of initially 194) in the venetoclax-rituximab arm of MURANO[1] and 195 patients in the ibrutinib arm of the RESONATE[49] trial were compared in the unanchored ITC analyses.[46] The adjusted HR for the investigator-assessed PFS and OS of venetoclax-rituximab versus ibrutinib was 0.797 (95% CI: 0.505 to 1.258) and 0.445 (95% CI: 0.218 to 0.909), respectively (Table 7.2). The unanchored estimates suggest a higher OS rate for venetoclax-rituximab than ibrutinib single agent. However, the PFS difference between the two treatments did not reach the level of statistical significance. The findings must be interpreted with caution given that the assumptions of the unanchored ITC[46] are difficulty to meet and there is an unknown amount of bias in the unanchored estimate. Also, since the median PFS and OS had not been reached in the studies, there is uncertainty about how the intervention will compare using matured data.

Table 7.1: Effect Modifier and Prognostic Variables Applied in the Unanchored Indirect Comparison[46]		
Effect modifier / prognostic characteristics	IBR RESONATE (N=195)	IDE+R STUDY 116 (N=110)
AGE ≥65 Years	Yes	Yes
RAI Stage III-IV	Yes	Yes
Bulky Disease ≥5 cm	Yes	No
Prior therapy >1	Yes	Yes
Chromosome 11Q Deletion	Yes	Yes
Chromosome 17p Deletion	Yes	Yes
ECOG = 1	Yes	No
IGVH Mutation	Yes	No
Beta-2 Microglobulin >3.5 mg/L	Yes	No
Prior Purine Analog	Yes	No
Prior Anti-CD20 Antibodies	Yes	No

Notes: Yes= MURANO[1] patients data were adjusted for the comparison with the published data of the comparator study
No = ITC did not report that MURANO[1] patients data were adjusted for the comparison with the published data of the comparator study

Source: Manufacturer-submitted ITC[46]

Table 7.2: Relative treatment effectiveness for survival – venetoclax-rituximab versus ibrutinib						
Outcome- Investigator-assessed	VEN+R vs. BR- MURANO[1]	IBR vs. OFA- RESONATE (Ref)	ITC- VEN+R vs. IBR	VEN+R vs. BR- MURANO[1]	IBR- RESONATE (Ref)	ITC- VEN+R vs. IBR
	Adjusted- May 2018 for Murano[1] Data Cut			**Adjusted- Previous Murano[1] Data Cut**		
PFS, HR (95% CI)	0.212 (0.128 to 0.351)	0.133 (0.099 to 0.178)	0.797 (0.505 to 1.258)	0.196 (0.111 to 0.345)	0.133 (0.099 to 0.178)	0.696 (0.412 to 1.178)
OS, HR (95% CI)	0.332 (0.170 to 0.649)	0.361 (0.208 to 0.628)	0.445 (0.218 to 0.909)	0.219 (0.087 to 0.552)	0.361 (0.208 to 0.628)	0.297 (0.129 to 0.684)
BR = bendamustine-rituximab; CI = confidence interval; HR = hazard ratio; IBR = ibrutinib; ITC = indirect treatment comparison; OFA = ofatumumab; VEN+R = venetoclax-rituximab						

Source: Manufacturer-submitted ITC[46]

Unanchored ITC of Venetoclax-rituximab versus Idelalisib-rituximab combination

The effect modifiers and prognostic variables reweighted for MURANO[1] versus ibrutinib unanchored ITC[46] have been listed in Table 7.1.

After adjustments to minimize bias due to imbalance across all observed effect modifiers and prognostic covariates, data from 170 patients (88% of initially 194) in the venetoclax-rituximab arm of MURANO[1] and 110 patients in the

Idelalisib-rituximab arm of STUDY 116[50] were compared in unanchored ITC analyses. The adjusted investigator-assessed HR was 0.171 (95% CI: 0.089 to 0.329) for the PFS and 0.193 (0.075 to 0.494) for OS (Table 7.3). The unanchored estimates suggest higher PFS and OS rates for venetoclax-rituximab than idelalisib-rituximab. The findings must be interpreted with caution given that the assumptions of the unanchored ITC[46] are difficulty to meet and there is an unknown amount of bias in the unanchored estimate. Also, since the median PFS and OS had not been reached in the studies, there is uncertainty about how the intervention will compare using matured data.

Table 7.3: Relative treatment effectiveness for survival – venetoclax-rituximab versus idelalisib-rituximab

Outcome	VEN+R vs. BR- MURANO[1]	IDE+R vs. OFA- STUDY 116 (Ref)	ITC- VEN+R vs. IDE+R	VEN+R vs. BR- MURANO[1]	IDE+R vs. OFA – STUDY 116 (Ref)	ITC- VEN+R vs. IDE+R
	Adjusted- May 2018 for Murano[1] Data Cut			Adjusted- Previous Murano[1] Data Cut		
PFS, HR (95% CI)	0.229 (0.144 to 0.365)	0.250 (0.160 to 0.390)	0.171 (0.089 to 0.329)	0.272 (0.155 to 0.475)	0.250 (0.160 to 0.390)	0.178 (0.086 to 0.368)
OS	0.381 (0.191 to 0.758)	0.340 (0.190 to 0.600)	0.193 (0.075 to 0.494)	0.299 (0.124 to 0.726)	0.340 (0.190 to 0.600)	0.223 (0.084 to 0.593)

BR = bendamustine-rituximab; CI = confidence interval; HR = hazard ratio; IDE+R = Idelalisib-rituximab; ITC = indirect treatment comparison; OFA = ofatumumab; VEN+R = venetoclax-rituximab

Note: The updated analysis used investigator-assessed data in MURANO[1] compared with IRC-assessed data in STUDY 116

Source: Manufacturer-submitted ITC[46]

7.1.7 Critical appraisal

The authors stated the rationale for conducting an indirect comparison analysis and the study objectives. Details regarding literature search and the eligibility criteria for individual studies to include in the ITC[46] were described. However, methods of study selection and data extraction were not provided, and the quality of included studies, heterogeneity, and publication bias were not examined.

The ITC[46] assessed PFS, OS, and tumour response outcomes. However, improvement in HRQoL, which is one of the important expectations of patients groups that provided input to this review, and adverse event outcomes were not evaluated.

Overall, the reporting of the ITC[46] was good. The characteristics of all included studies and patient at baseline were summarized in tabular form, and the evidence network of the comparator trials was presented in Figure 7.1. The results of the analysis, including point estimates and a measure of uncertainty, were clearly reported for each outcome measure.

A significant limitation of the ITC[46] is that there was no anchored analysis between venetoclax-rituximab and ibrutinib, which is the most relevant comparator for the indication in the Canadian context. The unanchored ITC[46] between the two treatments assumed that absolute outcomes can be predicted

from the covariates, accounting for all effect modifiers and prognostic factors. This assumption is mostly considered impossible to meet, leading to an unknown amount of bias in the unanchored estimate. To compensate for this drawback, the investigators compared outcomes of the MURANO[1] and HELIOS[52] studies in an exploratory anchored ITC between venetoclax-rituximab and ibrutinib plus bendamustine-rituximab which found no significant difference in PFS and OS between the two treatments. Based on these findings, the authors inferred equivalence in effectiveness between venetoclax-rituximab and ibrutinib single-agent by referring to a published indirect comparison[53] of the RESONATE[49] and HELIOS[52] trials which concluded that the addition of bendamustine-rituximab to ibrutinib did not improve PFS or OS compared with single-agent ibrutinib. For the weakness of this naïve comparison and the previously mentioned limitations of the unanchored ITC,[46] no decisive conclusion can be drawn from the manufacturer-submitted ITC for how the effectiveness of venetoclax-rituximab compares with that ibrutinib monotherapy in patients with R/R CLL. The median PFS and OS had not been reached in the venetoclax- rituximab arm in the MURANO[1] trial. The PFS and OS data were also not matured in the publications of the RESONATE[49] and the STUDY 116[50] trials that were used in the unanchored comparisons.[46] Thus the comparisons may be premature and there is uncertainty about how the intervention will compare using matured data. The unanchored ITC was performed by a consultancy group hired by the submitter and has not been peer reviewed. These limitations are additional sources of uncertainty about the reported ITC[46] results. Also, adjustment for covariates resulted in a smaller sample size of MURANO[1] patients matched to the comparator trial. However, the impact of this on the outcomes is unclear.

Table 7.4: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

IPSOR Questions	Details and Comments
Is the population relevant?	Yes. Major criteria of the systematic literature search for studies to include in the ITC were randomized and non-randomized clinical trials reporting survival and/or response outcomes of R/R CLL treatments. Thus the population in the MURANO[1] and comparator trials comprised patients with R/R CLL.
Are any critical interventions missing?	Unclear. For the purposes of clinical practice in Canada, other potential interventions include ibrutinib single agent and idelalisib–rituximab combination. The authors reported that one study for each comparator of interest was selected from the identified RCTs and observational studies from systematic literature search for inclusion in the ITC. It is unclear whether for each comparator there were more than one eligible studies but one was selected.
Are any critical outcomes missing?	Yes; some patients-specified relevant outcomes including HRQoL and safety were not covered in the ITC. However, PFS and OS, which were the outcomes used in the economic model, were reported in the ITC
Is the context (e.g., settings and circumstances) applicable to your population?	Unclear. Details of settings and circumstances were not provided
Did the researchers attempt to identify and include all relevant randomized controlled trials?	Unclear. Although a systematic literature review was conducted for relevant studies to include in the ITC, details regarding how studies were selected for inclusion were not provided

IPSOR Questions	Details and Comments
Do the trials for the interventions of interest form one connected network of randomized controlled trials?	No. There were no connections identified between either ibrutinib single agent or idelalisib-rituximab and venetoclax-rituximab. Therefore, the ITC performed was unanchored.
Is it apparent that poor quality studies were included leading to bias?	Unclear. It is unknown if the trials included in the ITC were assessed for risk of bias as part of the systematic review performed.
Is it likely that bias was introduced by selective reporting of outcomes in the studies?	Unclear. There was no indication that publication bias was assessed in the included studies. Also, the authors reported that one study for each comparator of interest was selected for inclusion in the ITC from the identified RCTs and observational studies from systematic literature search. It is unclear whether for each comparator there were more than one eligible studies from which one study for each comparator was selected.
Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Likely so. The unanchored ITC was based on MAIC data with propensity score-matched prognostic variables and effect modifiers. Although potential prognostic variables and effect modifiers were identified through empirically evaluation of the MURANO[39] trial and published comparator data with confirmation by clinical experts, some covariates could be unobserved. Thus the adjustment model did not include undetected effect modifiers leading to an unknown amount of bias in the unanchored estimates.
If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Not Applicable
Were statistical methods used that preserve within-study randomization? (i.e. no naïve comparisons)	No. Unanchored ITC between two treatments do not rely on the presence of a common comparator, and do not respect any randomization within studies.
If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops, was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable. Unanchored ITC based on MAIC.
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable. Unanchored ITC based on MAIC.
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias in the analysis?	Yes. The unanchored ITC was based on MAIC data with propensity score-matched prognostic variables and effect modifiers.

IPSOR Questions	Details and Comments
Was a valid rationale provided for the use of random effects or fixed effect models?	Not applicable. Unanchored ITC based on MAIC.
If random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable. Unanchored ITC based on MAIC.
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Not applicable. An unanchored ITC based on MAIC was performed, and heterogeneity was not assessed.
Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
Are the individual study results reported?	Yes. Results for ITC between venetoclax-rituximab and ibrutinib single agent was reported separately from venetoclax-rituximab versus idelalisib-rituximab.
Are the results of direct comparisons reported separately from results of the indirect comparisons or NMA?	Not applicable. There was no direct comparison or a common comparator arm for the MURANO[1] study and the comparator trials. Therefore, an unanchored ITC based on MAIC was performed.
Are all pairwise contrasts between interventions as obtained with the NMA reported along with measures of uncertainty?	Not applicable. An unanchored ITC based on MAIC was performed
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No.
Is the impact of important patient characteristics on treatment effects reported?	No.
Are the conclusions fair and balanced?	Yes, The authors acknowledged the limitations of the unanchored ITCs and stated that the results should be interpreted with high degree of caution given the high possibility of unaccounted unobserved residual bias.
Were there any potential conflicts of interest?	Not reported.
If yes, were steps taken to address these?	Not applicable.
Abbreviations: CLL = chronic lymphocytic leukemia; HR = hazard ratio; HRQoL – Health-related quality of life. ITC – indirect treatment comparison; MAIC = Matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; R/R = relapsed or refractory	

Source: Manufacturer-submitted ITC[46], † Adapted from Jansen et al., 2014[54]

7.1.8 Summary

In the absence of head-to-head randomized controlled trial evidence of comparative efficacy and harms, the submitter conducted indirect treatment comparisons (ITCs) between the venetoclax-rituximab and comparator treatments for adult patients with R/R CLL. Two treatments, ibrutinib-bendamustine-rituximab and Idelalisib-bendamustine-rituximab, were compared with venetoclax in anchored ITC with a common bendamustine-

rituximab anchor. Unanchored ITCs were performed between venetoclax-rituximab and four other treatments, venetoclax monotherapy, ibrutinib as single-agent, idelalisib-rituximab, and fludarabine-cyclophosphamide-rituximab combination therapies.

For this review, the most relevant comparators for the indication in the Canadian context are single-agent ibrutinib and idelalisib-rituximab combination, given their similar place in therapy as what the submitter is seeking for venetoclax-rituximab. The findings from the manufacturer-submitted unanchored ITC[46] for both venetoclax-rituximab versus ibrutinib and venetoclax-rituximab versus idelalisib-rituximab were inconclusive because the assumptions used for the unanchored analyses are impossible to meet and present an unknown amount of bias in the unanchored estimate. The median PFS and OS had not been reached in the venetoclax-rituximab arm in the MURANO[1] trial. The PFS and OS data were also not matured in the publications of the RESONATE[49] and the STUDY 116[50] trials that were used in the unanchored comparisons.[46] Thus the comparisons may be premature and there is uncertainty about how the intervention will compare using matured data. The unanchored ITC[46] was performed by a consultancy group hired by the submitter and has not been peer reviewed.[46] These limitations are additional sources of uncertainty about the reported ITC results. Also, adjustment for covariates resulted in a smaller sample size of MURANO[1] patients matched to the comparator trial. However, the impact of this on the outcomes is unclear.

8 COMPARISON WITH OTHER LITERATURE

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

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) in combination with rituximab for chronic lymphocytic leukemia (CLL). 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.

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2018**, Embase** 1974 to 2018 November 16**, Ovid MEDLINE(R) ALL** 1946 to November 16, 2018
Search Strategy:

#	Searches	Results
1	(venetoclax* or venclexta* or venclyxto* or ABT 199 or ABT199 or "GDC 0199" or GDC0199 or rg 7601 or rg7601 or N54AIC43PW).ti,ab,ot,kf,kw,hw,rn,nm.	2634
2	Leukemia, Lymphocytic, Chronic, B-Cell/	35913
3	CLL.ti,ab,kf,kw.	38677
4	((Lymphocytic or lymphoblastic) adj5 (Lymphoma* or lymphosarcoma*)).ti,ab,kf,kw.	19118
5	((chronic or CLL or well differentiated or disrupted or low grade) adj5 (b cell or cell or B Lymphocytic or Lymphoblastic or lymphatic or lymphocyte or Lymphocytic or lymphoid or lymphoplasmacytoid) adj5 (leukemia* or leukaemia* or lymphoma* or malignan* or leucemia* or leucaemia*)).ti,ab,kf,kw.	65079
6	or/2-5	89329
7	1 and 6	1098
8	7 use medall	268
9	7 use cctr	57
10	*venetoclax/ or (venetoclax* or venclexta* or venclyxto* or ABT 199 or ABT199 or "GDC 0199" or GDC0199 or rg 7601 or rg7601).ti,ab,kw,dq.	2033
11	chronic lymphatic leukemia/	34208
12	CLL.ti,ab,kw,dq.	38625
13	((Lymphocytic or lymphoblastic) adj5 (Lymphoma* or lymphosarcoma*)).ti,ab,kw,dq.	19501
14	((chronic or CLL or well differentiated or disrupted or low grade) adj5 (b cell or cell or B Lymphocytic or Lymphoblastic or lymphatic or lymphocyte or Lymphocytic or lymphoid or lymphoplasmacytoid) adj5	65024

	(leukemia* or leukaemia* or lymphoma* or malignan* or leucemia* or leucaemia*)).ti,ab,kw,dq.	
15	or/11-14	90806
16	10 and 15	928
17	16 use oemezd	619
18	17 and conference abstract.pt.	292
19	limit 18 to yr=2013-current	289
20	17 not conference abstract.pt.	327
21	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1108357
22	Randomized Controlled Trial/	994783
23	exp Randomized Controlled Trials as Topic/	282171
24	"Randomized Controlled Trial (topic)"/	152890
25	Controlled Clinical Trial/	551267
26	exp Controlled Clinical Trials as Topic/	293512
27	"Controlled Clinical Trial (topic)"/	9757
28	Randomization/	176609
29	Random Allocation/	193434
30	Double-Blind Method/	397962
31	Double Blind Procedure/	155275
32	Double-Blind Studies/	261092
33	Single-Blind Method/	75547
34	Single Blind Procedure/	33059
35	Single-Blind Studies/	77494
36	Placebos/	327616
37	Placebo/	326546
38	Control Groups/	111308
39	Control Group/	111216
40	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3986569
41	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	778258
42	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	3001
43	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2603561

44	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	94520
45	allocated.ti,ab,hw.	176536
46	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	114195
47	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	24850
48	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	943
49	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	11079
50	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	17387
51	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	127385
52	or/21-51	5704478
53	19 and 52	76
54	8 or 20	595
55	52 and 54	105
56	9 or 55	162
57	remove duplicates from 56	136
58	53 or 57	212
59	limit 58 to english	206
60	59 and conference abstract.pt.	98
61	59 not conference abstract.pt.	108

2. Literature search via PubMed

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

Search	Query	Items found
#9	Search (#7 AND publisher[sb]) Filters: English	11
#8	Search (#7 AND publisher[sb])	11
#7	Search (#1 AND #6)	278
#6	Search (#2 OR #3 OR #4 OR #5)	66530

Search	Query	Items found
#5	Search ((chronic[tiab] OR CLL[tiab] OR well differentiated[tiab] OR disrupted[tiab] OR low grade[tiab]) AND (b cell[tiab] OR cell[tiab] OR B Lymphocytic[tiab] OR Lymphoblastic[tiab] OR lymphatic[tiab] OR lymphocyte[tiab] OR Lymphocytic[tiab] OR lymphoid[tiab] OR lymphoplasmacytoid[tiab]) AND (leukemia*[tiab] OR leukaemia*[tiab] OR lymphoma*[tiab] OR malignan*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab]))	55913
#4	Search ((Lymphocytic[tiab] OR lymphoblastic[tiab]) AND (Lymphoma*[tiab] OR lymphosarcoma*[tiab]))	14151
#3	Search CLL[tiab]	13498
#2	Search "Leukemia, Lymphocytic, Chronic, B-Cell"[Mesh]	14903
#1	Search "venetoclax" [Supplementary Concept] OR (venetoclax*[tiab] OR venclexta*[tiab] OR venclyxto*[tiab] OR ABT 199[tiab] OR ABT199[tiab] OR GDC 0199[tiab] OR GDC0199[tiab] OR rg 7601[tiab] OR rg7601[tiab] OR N54AIC43PW[rn])	589

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: Venclexta or Venclyxto /venetoclax, CLL

Select international agencies including:

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

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

Search: Venclexta or Venclyxto /venetoclax, CLL

Conference abstracts:

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

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

Search: Venclexta or Venclyxto /venetoclax, CLL – last 5 years

Detailed Methodology

The literature search was performed by the pCODR Methods Team using the search strategy above.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (Ocotber 2018) via Ovid and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were venclexta, venclyxto, and venetoclax and chronic lymphatic leukemia.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of March 07, 2019.

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

Study Selection

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

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

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of

the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

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

Writing of the Review Report

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

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

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