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CADTH PCODR FINAL CLINICAL GUIDANCE REPORT

Clinical Report

Venetoclax (VENCLEXTA)

(AbbVie Corporation)

Indication: In combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible.

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Abbreviations

AE	adverse event
BEN-RIT	bendamustine plus rituximab
CGP	Clinical Guidance Panel
CI	confidence interval
CIRS	Cumulative Illness Rating Score
CHL	chlorambucil
CHL-OBI	chlorambucil in combination with obinutuzumab
CHL-OFA	chlorambucil plus ofatumumab
CHL-RIT	chlorambucil plus rituximab
CLL	chronic lymphocytic leukemia
CLLPAG	Chronic Lymphocytic Leukemia Patient Advocacy Group
CR	complete response
CrCl	creatine clearance
CRi	complete response and incomplete bone marrow recovery
CRR	complete response rate
DOR	duration of response
EFS	event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FCR	fludarabine plus cyclophosphamide plus rituximab
GHS-QoL	global health status-quality of life
HR	hazard ratio
IBR	ibrutinib
IBR-OBI	ibrutinib plus obinutuzumab
IBR-RIT	ibrutinib plus rituximab
iDMC	Independent Data Monitoring Center
IGVH	immunoglobulin heavy chain variable region gene
IRC	independent review board
ITC	indirect treatment comparison
ITT	intention-to-treat
iwCLL	International Workshop on chronic lymphocytic leukemia
KM	Kaplan-Meier
LC	Lymphoma Canada
MAIC	matching-adjusted indirect comparison
MDASI	M.D. Anderson Symptom Inventory

MID	minimal important difference
MRD	minimal residual disease
NE	not estimable
NMA	network meta-analysis
OBI	obinutuzumab
ORR	overall response rate
OS	overall survival
PAG	Provincial Advisory Group
PD	progressive disease
pERC	pCODR Expert Review Committee
PFS	progression-free survival
PR	partial response
PRO	patient reported outcomes
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse events
SD	stable disease
SLL	small lymphocytic leukemia
SLR	systematic literature review
TLS	tumour lysis syndrome
VEN	venetoclax
VEN-OBI	venetoclax in combination with obinutuzumab
VEN-RIT	venetoclax plus rituximab

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 (excluding Quebec) regarding venetoclax (Venclexta) in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible. 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 conducted by the Clinical Guidance Panel (CGP) and the CADTH 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. Background clinical information provided by the CGP, a summary of submitted Patient Advocacy Group input, a summary of submitted Provincial Advisory Group input, and a summary of submitted Registered Clinician input 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 obinutuzumab for the treatment of patients with previously untreated CLL who are fludarabine ineligible.

Venetoclax is a potent orally bioavailable selective inhibitor of the anti-apoptotic B-cell lymphoma-2 Bcl-2 protein; thus, its mechanism of action results in programmed cell death of CLL cells. The reimbursement request is for the treatment of patients with previously untreated CLL who are fludarabine ineligible. Venetoclax in combination with obinutuzumab has been issued marketing authorization without conditions for the treatment of patients with previously untreated CLL. Note that the Health Canada indication differs from the reimbursement request as it does not specify patients 'who are fludarabine ineligible'.

On Cycle 1 Day 1, start obinutuzumab administration at 100 mg, followed by 900 mg which may be administered on Day 1 or Day 2. Administer 1000 mg on Days 8 and 15 of Cycle 1, and on Day 1 of five subsequent cycles (total of 6 cycles, 28 days each).

On Cycle 1 Day 22, start venetoclax according to a weekly ramp-up schedule to the daily dose of 400 mg over a period of 5 weeks, continuing through Cycle 2 Day 28. 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 completing the ramp-up schedule, patients should continue venetoclax 400 mg once daily from Cycle 3 Day 1 of obinutuzumab to the end of Cycle 12.

Venetoclax should be given for a total of 12 months as finite treatment: for six 28-day cycles in combination with obinutuzumab, followed by six months of venetoclax as a single agent.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The CADTH systematic review included one randomized controlled trial (RCT), the CLL14 trial (n=432).[1]

CLL14

CLL14 is an international, open-label, phase III, randomized, active-controlled superiority trial that evaluated the efficacy and safety of venetoclax (VEN) in combination with obinutuzumab (OBI) (VEN-OBI) compared to chlorambucil (CHL) in combination with obinutuzumab (CHL-OBI) for first-line treatment of CLL patients with co-existing conditions.[1] Eligible patients were ≥18 years of age, had previously untreated CLL that required treatment, and either a Cumulative Illness Rating Score (CIRS) >6 or a creatine clearance (CrCl) <70 mL/min. Patients who met the eligibility criteria were randomized in a 1:1 ratio to receive either VEN-OBI or

CHL-OBI for 12 cycles of 28 days as described under Section 6.3.2.1 *Detailed Trial Characteristics* in the c) *Intervention* section. No crossover was permitted between treatment groups. The trial was open-label; however, the sponsor and an independent review committee (IRC) were blinded to the treatment arms.[2]

The primary endpoint of the trial was investigator-assessed progression-free survival (PFS) defined as the time from randomization to the first occurrence of progression or relapse (defined from the International Workshop on chronic lymphocytic leukemia (iwCLL) guidelines) or death from any cause.[3] Pre-specified subgroup analyses were conducted for the following groups: Binet stage at screening (A, B, C), age (<75 years, ≥75 years), gender (male, female), cytogenetic factors (deletion 17p, 11q and 13q, and trisomy 12), *TP53* status (deletion and/or mutation, none), and immunoglobulin heavy chain variable region gene (IGVH) mutational status (unmutated, mutated).[1]

The secondary efficacy outcomes included IRC-assessed PFS, overall survival (OS), and the following outcomes evaluated three months after treatment completion: minimal residual disease (MRD) in bone marrow, complete response rate (CRR), MRD in peripheral blood, MRD in bone marrow of patients with a complete response (CR), MRD in peripheral blood in patients with a CR, and overall response rate (ORR).[1,3]

Patient reported outcomes (PROs) were assessed with the M.D. Anderson Symptom Inventory (MDASI)-CLL and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30).[2] PROs were analyzed in the intention-to-treat (ITT) population for all randomized patients who completed the baseline assessment and at least one post-baseline assessment for the scales.[2] Paper PRO questionnaires were administered at each treatment cycle and every three months during the follow-up period.[4] All PRO scores were given as mean ± standard deviation (SD) values for all patients per study group.[2] Clinically relevant differences reported were based on the minimal important differences (MIDs) derived from the Cocks et al., 2012[5] for the EORTC QLQ-C30 scales.[6]

Safety outcomes were analyzed in the safety population according to the study drug actually consumed by the patient.[2] Adverse events (AEs) of any grade were reported up until 28 days after the last dose of any study treatment. Grade 3/4 AEs and major infections were reported for up to six months and two years after the last dose of study drug, respectively or until the next anti-leukemia treatment. Serious adverse events (SAEs) and secondary malignancies were reported indefinitely after study drug completion.

Overall, the baseline characteristics in the trial arms were well-balanced. A total of 432 patients were randomly assigned to receive either VEN-OBI (n=216) or CHL-OBI (n=216).[1] Overall, the median age was 72 years (range: 41 to 89), with 33.3% and 36.1% of patients ≥75 years in the VEN-OBI group in the CHL-OBI group, respectively. Most patients were male (67.6% in VEN-OBI group versus 66.2% in CHL-OBI group), and most were categorized as 'Intermediate' risk of TLS (64.4% in VEN-OBI group versus 68.1% in CHL-OBI group). The median CIRS score for all trial participants was 8 (range: 0 to 28). Median CIRS scores were slightly higher in the VEN-OBI group compared to the CHL-OBI group (9 versus 8), with 86.1% and 81.9% of patients having a CIRS score of >6 in the VEN-OBI group in the CHL-OBI group, respectively.[3] The proportion of patients with CrCl <70ml/min was slightly higher in the VEN-OBI group compared to the CHL-OBI group (59.5% versus 55.4%). The percentage of patients in the cytogenetic subgroups were balanced for the VEN-OBI group compared to the CHL-OBI group: deletion in 17p – 8.5% versus 7.3%, deletion in 11q – 18.0% versus 19.7%, trisomy 12 – 18.0% versus 20.7%, no abnormalities – 25.0% versus 21.8%, and deletion in 13q alone – 30.5% versus 30.6%. Most patients in both groups had unmutated IGHV (VEN-OBI – 60.5%; CHL-OBI – 59.1%), and unmutated TP53 (VEN-OBI – 88.9%; CHL-OBI – 91.7%).

At the time of the primary data cut-off on August 17, 2018, a similar proportion of patients between the two groups had received treatment (VEN-OBI: 98.1% versus CHL-OBI: 99.1%).[1] Additionally, a similar proportion of patients between the VEN-OBI group versus the CHL-OBI group had completed treatment (76.4% versus 74.1%), discontinued at least one treatment component (21.8% versus 25.0%), been lost to follow-up (13.9% versus 12.0%), and/or remained in the trial at the data cut-off (86.1% versus 88.0%). The most common reason for treatment discontinuation in both groups was due to AEs (14.4% versus 15.7%). At the time of the updated analysis, 177 (81.9%) patients in the VEN-OBI group, and 178 (82.4%) patients in the CHL-OBI group remained in the post-treatment follow-up.[7]

Efficacy

The results of the primary and secondary outcomes of the CLL14 trial are summarized in Table 1. As of the August 17, 2018 primary data cut-off, median follow-up was 28.1 months (range: 0.0 to 35.9 months).[1] All patients had stopped treatment for a median of 17.1 months (range: 0.0 to 30.4 months) in the VEN-OBI group and 17.9 months (range: 0.0 to 30.2 months) in the CHL-OBI group. As of an updated data cut-off on August 23, 2019, median follow up was 39.6 months (range: 0.0 to 47.3 months).[7] The results of the analyses from the August 17, 2018 primary data cut-off are reported below unless otherwise noted. Overall, efficacy results from the updated data cut-off were consistent with those from the primary data cut-off.

As of the primary data cut-off, a statistically significant longer duration of investigator-assessed PFS in the VEN-OBI group compared to the CHL-OBI group was demonstrated ($p<0.0001$).[1] Although median PFS had not been reached in either group, results of the primary analyses demonstrated a hazard ratio (HR) of 0.35 [95% confidence interval (CI): 0.23 to 0.53; $p<0.0001$]. The PFS benefit for VEN-OBI was consistently demonstrated at the updated data cut-off, at which time the HR was 0.31 [95% CI: 0.22, 0.44; $p<0.0001$].[7]

The results of pre-specified subgroup analyses at the primary data cut-off were consistent with the overall PFS results in the ITT population, showing a statistically significant longer PFS in the VEN-OBI group compared to the CHL-OBI group, except for the following subgroups: Binet stage at screening *'C'*, cytogenetic factors *'no abnormalities'* and *'deletion 13q'*, and IGHV status *'mutated'*.[1] In these subgroups, the treatment effect estimate CI included the null value of 1, suggesting no difference in PFS between the treatment groups. Additionally, the HR in the cytogenetic factor subgroup 'Trisomy 12' was not estimable. These subgroup analyses were not powered to detect statistically significant differences between treatment groups and may have been limited by small sample sizes in some subgroups.

Overall, the results of the secondary efficacy outcomes were consistent with the primary outcome; whereby, the results demonstrated an improvement on VEN-OBI compared to the CHL-OBI group.[1] At the time of both the August 17, 2018 and the August 23, 2019 data cut-offs, the OS data were immature and median OS was not estimable for either treatment group.[1,7] As of the primary data cut-off, a total 37 patients had died (VEN-OBI group: 20 patients and CHL-OBI group: 17 patients) corresponding to an HR of 1.24 (95% CI: 0.64 to 2.40; $p=0.5216$). At 24 months, the Kaplan-Meier (KM) estimate of the percentage of patients still alive was 91.8% (95% CI: 88.1 to 95.5) in the VEN-OBI group and 93.3% (95% CI: 90.0 to 96.7) in the CHL-OBI group. At the time of the August 23, 2019 data cut-off, 54 patients had died (27 patients in each treatment group) corresponding to an HR of 1.03 (95% CI: 0.60 to 1.75; $p=0.9210$).[7]

Patient Reported Outcomes

Completion rates for the MDASI-CLL and the EORTC QLC-C30 were 100% at baseline, over 90% throughout treatment, and above 85% throughout 18 months of follow-up.[4] Overall, results of the analyses of the MDASI-CLL and the EORTC QLQ-C30 did not show a clinically meaningful difference based on the MIDs between treatment with VEN-OBI or CHL-OBI.[3]

For the MDASI-CLL, baseline scores were comparable for the VEN-OBI group versus the CHL-OBI group: CLL symptoms (1.6 ± 1.3 versus 1.5 ± 1.2), core cancer symptoms (1.8 ± 1.7 versus 1.5 ± 1.4), and symptom interference (2.3 ± 2.3 versus 2.1 ± 2.3).[4] No significant improvement or deterioration to the score was demonstrated throughout treatment and the follow-up period. For the EORTC QLQ-C30, baseline scores were comparable for the VEN-OBI group versus the CHL-OBI group: physical functioning (76.9 ± 19.4 versus 75.9 ± 20.1), role functioning (72.6 ± 26.9 versus 73.6 ± 27.86), and global health status-quality of life (GHS-QoL) (60.3 ± 20.5 versus 63.6 ± 21.0). The most severe symptoms at baseline were (listed as VEN-OBI versus CHL-OBI) dyspnea (24.8 ± 27.76 versus 21.3 ± 25.6), fatigue (39.2 ± 24.7 versus 35.8 ± 23.3), insomnia (30.8 ± 30.5 versus 26.9 ± 29.0), pain (18.4 ± 25.6 versus 16.8 ± 22.1), appetite loss (15.6 ± 26.7 versus 14.7 ± 23.6), and constipation (12.8 ± 23.7 versus 10.9 ± 20.9). Baseline physical and role functioning were maintained throughout treatment and the follow-up period with no clinically meaningful improvement or deterioration to the scores. Patients showed an improvement of the GHS-QoL score by at least eight points at cycle 3 in the VEN-OBI group and at cycle 8 in the CHL-OBI group. Insomnia and fatigue scores also showed an improvement starting at cycle 3 in the VEN-OBI group and at cycle 4 and cycle 6, respectively in the CHL-OBI group.

Harms

At least one AE of any grade was reported in 94.3% of patients in the VEN-OBI group and in 99.5% of patients in the CHL-OBI group.[1] Most AEs were blood and lymphatic system disorders. The most common AEs of any grade that occurred in the VEN-OBI group versus the CHL-OBI group were neutropenia (57.5% versus 57.0%), infusion-related reactions (44.8% versus 51.4%), diarrhea (27.8% versus 15.0%), and pyrexia (22.6% versus 15.4%). The most common grade 3 or 4 AE in the VEN-OBI group versus the CHL-OBI group were neutropenia (52.8% versus 48.1%), thrombocytopenia (13.7% versus 15.0%), and anemia (8.0% versus 6.5%). The incidence of an SAE of TLS was lower in the VEN-OBI group compared to the CHL-OBI group (0.5% versus 1.9%). All occurrences of TLS in the VEN-OBI group (three patients) occurred during the administration of OBI - prior to starting VEN.

During treatment, five fatal AEs occurred in the VEN-OBI group and four occurred in the CHL-OBI group.[1] Two of the fatal AEs in the VEN-OBI group occurred in patients who received only OBI (i.e. no VEN). After treatment, 11 fatal AEs occurred in the VEN-OBI group and four occurred in the CHL-OBI group. As of the updated data cut-off, 30 patients (19 (9.0%) in the VEN-OBI group and 11 (5.1%) in the CHL-OBI group) had died due to AEs.[7]

At the primary data cut-off, second primary cancers were reported in 13.7% of patients in the VEN-OBI group and in 10.3% of patients in the CHL-OBI group.[1] Additionally, Richter's transformation was reported in two patients in the VEN-OBI group and in one patient in the CHL-OBI group. As of the updated data cut-off, second primary malignancies had been reported in an additional seven patients in the VEN-OBI group, and an additional Richter's transformation was reported in the CHL-OBI group.[7]

AEs leading to a dose interruption or dose reduction of VEN occurred in 57.1% (n=121) and 20.3% (n=43) of patients respectively.[3] AEs leading to a dose interruption or dose reduction of CHL occurred in 56.5% (n=121) and 7.9% (n=17) of patients, respectively. The most common AE that led to either a dose interruption or reduction for both VEB and for CHL was neutropenia. AEs leading to a dose interruption of OBI occurred in 56.1% (n=119) of patients in the VEN-OBI group and in 52.3% (n=112) of patients in the CHL-OBI group. The most common AEs leading to a dose interruption of OBI were infusion-related reactions and neutropenia. Dose reductions of OBI were not allowed according to the protocol; however, reductions of OBI were reported in 1.4% (n=3) of patients in the VEN-OBI group and in 0.9% (n=2) of patients in the CHL-OBI group.

Limitations and Potential Sources of Bias

The major limitations and potential sources of bias associated with the CLL14 trial, based on the CADTH Methods Team's critical appraisal of the evidence, are summarized below. The complete list is available in Section 6.

- The study design was open-label, which is susceptible to reporting and performance biases. Patients and investigators were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of VEN-OBI if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results. However, the sponsor and the IRC were blinded to treatment arms, and an Independent Data Monitoring Center (iDMC) reviewed unblinded safety data by treatment arm for the safety reviews and the planned interim analysis of efficacy. The sponsor and study team did not have access to the unblinded information reviewed by the iDMC. This would therefore reduce some potential for bias in the study analyses. Due to the different modes of administration of study treatments, the open-label design of the trial was considered justified.
- At the time of both the August 17, 2018 and the August 23, 2019 data cut-offs, the OS data were immature and median OS was not estimable for either treatment group, therefore the magnitude of long-term survival benefit is currently unknown. Although patient crossover upon disease progression was not permitted in the trial, survival data will be confounded by the use of post-trial treatments. Of note, OS was listed last in the hierarchical order, which may potentially limit the power to analyze this outcome.
- The comparator of the CLL14 trial was CHL-OBI; however, the CGP noted that ibrutinib (IBR) is considered the standard of care for the subgroup of patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. Although ITCs were conducted to investigate the comparison of VEN-OBI to IBR in these patients (see Section 7.2), many limitations of these analyses were identified; thus, results were interpreted with caution.
- Several other secondary efficacy analyses were conducted (i.e. DOR, EFS, and time to new anti-leukemic treatment) as were multiple subgroup analyses. The results of these analyses should be interpreted as exploratory and hypothesis generating because the CLL14 trial was not designed nor powered to test specific hypotheses in these analyses.

Table 1: Highlights of Key Outcomes in the CLL14 Trial at the Primary Data Cut-Off (August 17, 2018)

	CLL14	
	VEN-OBI (n=216)	**CHL-OBI (n=216)**
Median follow-up time (range) months	**28.1 (0.0 to 35.9)**	
Primary Outcome		
PFS (investigator-assessed)		
Median (95% CI) months	NE (NE to NE)	NE (31.1 to NE)
HR (95%CI)	0.35 (0.23 to 0.53)	
p-value [b]	p<0.0001	
Key Secondary Outcomes		
PFS (IRC-assessed)		
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)
Hazard ratio (95% CI) [a]	0.33 (0.22 to 0.51)	
p-value [b]	p<0.0001	
MRD-Negativity Rate – Bone Marrow (three months after treatment completion)		
MRD negative patients, n (%)	123 (56.9)	37 (17.1)
Difference in response rate (95% CI)	39.8 (31.3 to 48.4)	
Odds ratio (95% CI)	6.4 (4.1 to 10.0)	
p-value [c]	p<0.0001	
CRR (three months after treatment completion)		
Responders, n (%)	107 (49.5)	50 (23.1)
Difference in response rate (95% CI)	26.4 (17.4 to 35.4)	
Odds ratio (95% CI)	3.3 (2.2 to 5.1)	
p-value [c]	p<0.0001	
MRD-Negativity Rate – Peripheral Blood (three months after treatment completion)		
MRD negative patients, n (%)	163 (75.5)	76 (35.2)
Difference in response rate (95% CI)	40.3 (31.5 to 49.1)	
Odds ratio (95% CI)	5.7 (3.7 to 8.6)	
p-value [c]	p<0.0001	
MRD-Negativity Rate in Complete Responders – Bone Marrow (three months after treatment completion)		
MRD negative patients, n (%)	73 (33.8)	23 (10.6)
Difference in response rate (95% CI)	23.2 (15.4 to 30.9)	
Odds ratio (95% CI)	4.3 (2.6 to 7.2)	
p-value [c]	p<0.0001	
MRD-Negativity Rate in Complete Responders – Peripheral Blood (three months after treatment completion)		
MRD negative patients, n (%)	94 (42.1)	31 (14.4)

	CLL14	
Difference in response rate (95% CI)	27.8 (19.5 to 36.1)	
Odds ratio (95% CI)	4.3 (2.7 to 6.9)	
p-value [c]	p<0.0001	
ORR (three months after treatment completion)		
Responders, n (%)	183 (84.7)	154 (71.3)
Difference in response rate (95% CI)	13.4 (5.5 to 21.4)	
Odds ratio (95% CI)	2.3 (1.4 to 3.6)	
p-value [c]	p=0.0007	
OS		
Median (95% CI) (months)	NE (NE to NE)	NE (NE to NE)
Event rate, n (%)	20 (9.3)	17 (7.9)
Hazard ratio (95% CI) [a]	1.24 (0.64 to 2.40)	
p-value [b]	p=0.5216	
Harms Outcome, n (%)	**VEN-OBI (n=212)**	**CHL-OBI (n=214)**
AE (any grade)	200 (94.3)	213 (99.5)
Grade 3/4 SAE	167 (78.8)	164 (76.6)
SAE	104 (49.1)	90 (42.1)
AE leading to dose interruption (of VEN or CHL)	121 (57.1)	121 (56.5)
AE leading to dose reduction (of VEN or CHL)	43 (20.3)	17 (7.9)

AE = adverse event, CI = confidence interval; CHL = Chlorambucil; CHL-OBI = Chlorambucil plus Obinutuzumab; CLL = chronic lymphocytic leukemia; CRR = complete response rate; GHS-QoL = global health status quality of life; IRC = independent review committee; MDASI = the M.D. Anderson Symptom Inventory; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient-reported outcome; SAE = serious adverse event; SD = standard deviation; VEN = Venetoclax: VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] Stratified by Binet stage at screening and geographic region

[b] From log-rank test stratified by Binet stage at screening and geographic region

[c] From Cochran–Mantel–Haenszel tests stratified by Binet stage and geographic region

*HR < 1 favours VEN-OBI

Data Source: Fischer et al. 2019[1], Al-Sawarf 2019 et al. 2019[4], EPAR 2020[3], Clinical Study Report[8]

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

One joint input was provided by Lymphoma Canada (LC) and Chronic Lymphocytic Leukemia Patient Advocacy Group (CLLPAG) for the review of VEN-OBI for patients with previously untreated CLL who are fludarabine ineligible. LC and CLLPAG gathered data from three online surveys distributed from June 2017 to January 2020 to the following groups (total respondents, n = 394): 1) patients with CLL/ small lymphocytic leukemia (SLL) who did not have experience with VEN-OBI (n=320), 2) caregivers (n=41), and 3) patients with CLL/SLL who had experience with VEN-OBI (n=33).

Quality of life (QoL) was reported to be more severely impacted for patients with advanced disease compared to patients with early stage disease who reported minimal disease symptoms. Fatigue (83%), frequent infections (27%), enlarged lymph nodes (23%), and shortness of breath due to anemia (20%) were commonly reported disease symptoms affecting patients' QoL on an ongoing basis.

IBR was the most commonly reported therapy patients previously reported being treated with (67%). Commonly reported side effects related to treatments included fatigue, nausea, reduced blood counts, diarrhea, and frequent infections; these were also reported to be difficult to tolerate. Oral treatments were reported to negatively impact patients' QoL less so compared to IV therapies. Many patients (48%) reported a need for treatments with better disease symptom management.

A total of 33 patients reported having experience with VEN-OBI as frontline treatment. At the time of survey completion, most patients either completed or were still receiving VEN-OBI treatment. Enlarged lymph nodes (82%), fatigue (76%), and an enlarged spleen (58%) were the most commonly managed disease symptoms as a result of VEN-OBI. Almost two-thirds of patients (61%) indicated that VEN-OBI was able to manage all of their CLL/SLL disease symptoms. Fatigue (30%) and shortness of breath (12%) were symptoms patients reported that VEN-OBI were not able to manage. Commonly reported side effects from VEN-OBI included muscle or joint pain (45%), neutropenia (42%), and thrombocytopenia (30%). The side effects experienced from VEN-OBI were reported to have little impact on patients' QoL, and that aspects of daily activities were mostly unchanged or improved due to treatment. Patient comments tended to view VEN-OBI positively, *"Treatment has improved my quality of life significantly both physically and mentally."*

From a patient's perspective, having a choice in treatment option was considered very important. Overall, patients value treatments with minimal side effects, are able to better manage disease symptoms, have increased effectiveness resulting in delayed disease progression and increased survival, and improve QoL.

Provincial Advisory Group 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 with other therapies for CLL
- Use in CLL with high risk cytogenetic features

Economic factors:
- Management of adverse reactions

Registered Clinician Input

A total of two registered clinician inputs were provided for the review of VEN-OBI for patients with previously untreated CLL: one from an individual oncologist from Ontario and one joint input from clinicians from Cancer Care Ontario. Currently available treatments for patients with CLL who are ineligible for fludarabine-based regimens were stated to be CHL-OBI, bendamustine ± rituximab, or IBR monotherapy; the funding of these treatments was stated to vary across jurisdictions in Canada. Essentially all patients who are ineligible for fludarabine-based regimens, and who are currently eligible for CHL-OBI, were considered to be eligible for VEN-OBI by clinicians; most eligible patients were acknowledged to be those who are elderly and with significant comorbidities. Eligibility criteria from the CLL14 trial were considered reasonable for implementation in practice, and the use of a CIRS score of >6 or CrCl <70 mL/min to categorize "unfit" CLL patients was stated to be standard in clinical trials as well as in clinical practice.

Both clinician inputs acknowledged that trial data showed that treatment with VEN-OBI is superior to CHL-OBI and may replace CHL-OBI as frontline therapy for eligible patients. The individual clinician noted that IBR may place some patients at high risk for cardiac/bleeding complications, and that these patients who are high risk with 17p or TP53 mutations may benefit from treatment with VEN-OBI instead of IBR. However, the clinicians from the joint input expressed that VEN-OBI would likely not replace IBR for subgroups of patients with del17p, TP53, and IGHV mutation status. While the CLL14 trial did not address the possibility of re-treatment with VEN-OBI or venetoclax plus rituximab, the individual clinician highlighted the MURANO trial, which may suggest that patients can continue to respond to venetoclax as re-treatment was permitted in the trial. If VEN-OBI were to receive funding, IBR was suggested as a possible therapy in the second line or beyond. The individual clinician also suggested acalabrutinib as another treatment option for patients in the second line. Of note, acalabrutinib in a similar indication is currently under pCODR review. Upon relapse, idelalisib plus rituximab, chemoimmunotherapy, or entry into a clinical trial were suggested as possible treatment options.

Currently, diagnostic testing is used to help guide treatment decisions by stratifying patients by disease risk, aside from this testing, no additional testing is expected to be required. However, it was noted that there is differential coverage for testing of mutation status across jurisdictions in Canada.

Summary of Supplemental Questions

The following supplemental questions were identified during development of the review protocol as relevant to the CADTH review of VEN-OBI compared to standard care for the treatment of patients with previously untreated CLL who are fludarabine ineligible:

- Summary and critical appraisal of sponsor-submitted network meta-analysis (NMA) comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL

In the absence of head-to-head trial data comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL the sponsor submitted an NMA to estimate the relative effectiveness of VEN-OBI compared to CHL-OBI, ibrutinib plus rituximab (IBR-RIT), ibrutinib plus obinutuzumab (IBR-OBI), IBR monotherapy, bendamustine plus rituximab (BEN-RIT), chlorambucil plus ofatumumab (CHL-OFA), chlorambucil plus rituximab (CHL-RIT), CHL monotherapy, and fludarabine plus cyclophosphamide plus rituximab (FCR). Two NMAs were conducted based on the 'fitness' of the patient populations: 1) an 'unfit' network, and 2) an 'overall' network (both 'unfit' and 'fit' patients). A systematic literature review (SLR) identified nine RCTs that met the inclusion criteria for the NMA. Seven trials contributed data to the 'unfit' network and two additional trials (nine total) contributed data to the 'overall' network. Results for PFS in the 'unfit' network suggested that VEN-OBI was favoured over all competing interventions except for IBR-OBI. For the 'overall' network, the results suggested that VEN-OBI was favoured over all competing interventions except for over IBR-OBI and IBR-RIT. Results for OS in both the 'unfit' and the 'overall' networks suggested that VEN-OBI was favoured over CHL, but not over any other competing treatments, for which the credible intervals included 1. The NMA did not consider potentially relevant comparators (i.e. acalabrutinib) and did not evaluate outcomes related to safety and HRQoL. The key limitations of the NMA included the potential sources of heterogeneity across the trials related to differences in patient and study characteristics and the limited evidence (one trial per network arm), which precluded the use of random-effects models. The proportional hazards assumption was not tested; therefore, it was not possible to determine whether the assumption was violated. Results of the NMA should be interpreted with consideration of these limitations.

See Section 7.1 for more information.

- Summary and critical appraisal of sponsor-submitted ITC and matching-adjusted indirect comparison (MAIC) comparing VEN-OBI to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation

In the absence of head-to-head trial data comparing the effectiveness of VEN-OBI to IBR in terms of PFS and OS for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation, the sponsor submitted naïve ITCs and a MAIC. Three naïve ITCs were conducted, comparing VEN-OBI data from CLL14 to IBR data from three separate studies using the following patient populations: Ahn et al. – TP53 mutation, Mato et al. – del17p, and CORE study – del17p/TP53 mutation and ≥65 years. Although it was determined that it was not feasible to conduct a MAIC, one was conducted following a specific request for the data from CLL14 compared to Ahn et al. Results from all the comparisons for PFS and OS demonstrated no statistically significant differences between the two treatments except for the PFS HR calculated with the naïve ITCs using IBR data from Ahn et. al, which suggested that IBR led to statistically longer PFS compared to VEN-OBI. Important limitations of the analyses included very small sample sizes and a large amount of identified clinical heterogeneity. Additionally, the study designs varied, including phase II trials, phase III trials, and retrospective cohort studies (real-world evidence), which further lead to challenges in comparing the results of the studies. The results of these analyses should therefore be interpreted with extreme caution in light of the limitations.

See Section 7.2 for more information.

Comparison with Other Literature

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

Table 2: Assessment of Generalizability of Evidence for VEN-OBI for the Treatment of Adult Patients with Previously Untreated CLL who are Fludarabine Ineligible

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
Intervention	Administration of intervention	Patients assigned to VEN-OBI were treated for 12 cycles of 28 days as described: • Obi administered IV for six months starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. • Ven administered orally starting on day 22 of cycle 1, with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week), thereafter continuing at 400 mg daily until completion of cycle 12.	Is the intervention administered differently (e.g., dose or schedule) in clinical practice than in the trial?	The ramp-up method for administration will be necessary to minimize the risk for AEs. In current clinical practice, the administration of Obi is generally not split in the first cycle (i.e. with 100 mg on day 1 and 900 mg on day 2) and is instead given at the full dose (i.e. 1000 mg on day 1). The CGP felt the dosing schedule for VEN-OBI from CLL14 was applicable to clinical practice.
Comparator	Standard of care	In the CLL14 trial, the comparator was Chlorambucil plus Obinutuzumab. In order to assess the comparative efficacy of VEN-OBI compared with Chlorambucil plus Obinutuzumab, Ibrutinib plus Rituximab, Ibrutinib plus Obinutuzumab, Ibrutinib, Bendamustine plus Rituximab, Chlorambucil plus Ofatumumab, Rituximab plus Chlorambucil, Chlorambucil, and *Fludarabine plus Cyclophosphamide plus Rituximab* the CADTH Methods Team reviewed one submitter-provided ITC. Refer to section 7 for more details.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	There is a lack of direct evidence indicating the preferred treatment between VEN-OBI and other treatments. Although ITCs were conducted to investigate the comparison of VEN-OBI to other treatments for these patients, many limitations of these analyses were identified, and no confirmative conclusions could be made. For the comparison to Fludarabine plus Cyclophosphamide plus Rituximab, there is currently no evidence to support the generalizability of results to patients who are eligible to receive fludarabine.
Outcomes	Appropriateness of primary and secondary outcomes	The primary outcome was PFS (investigator-assessed). Secondary outcomes included PFS (IRC assessed), MRD, CRR, ORR, OS, and PROs.	Were the selection of endpoints appropriate and of clinical relevance to this indication and therapeutic setting?	The selection of endpoints in the CLL14 trial were appropriate and of clinical relevance.
Settings	Countries participating in the trial	The CLL14 trial was conducted in 196 sites in 21 countries (Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Italy, Mexico, New Zealand, Poland, Romania, Russia,	Are there any known differences in the practice patterns between Canada and other countries that the trial was conduced in?	The included countries have practice patterns similar to those of Canada. The trial results may be applied to Canadian patients.

Domain	Factor	Evidence	Generalizability Question	CGP Assessment of Generalizability
		Spain, Switzerland, United Kingdom, and United States).	Can the results be applied to Canadian patients?	

CHL = chlorambucil; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CrCl = creatine clearance; CRR = complete response rate; IRC = independent review committee; MRD = minimal residual disease; OBI = obinutuzumab; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; VEN = venetoclax.

1.2.4 Interpretation

Burden of Illness and Need

Chronic lymphocytic leukemia is one of the most common hematologic malignancies, with an incidence of 4.8 cases/100,000 persons:[9] 1745 Canadians were diagnosed with CLL in 2016 and 611 died from this disease in 2017 according to the most recent available Canadian statistics.[10] The majority of persons with CLL are asymptomatic, and diagnosed because of the finding of an elevated white blood cell count.

For first line treatment of patients with CLL who require treatment and who are in good health and under the age of 65 years, FCR is standard in most provinces in Canada. However, patients treated with fludarabine have a higher rate of severe infection and neutropenia and therefore, patients over the age of 65, or those who are not considered fit enough to receive FCR may derive benefit from several less intensive regimens. CHL-OBI is a standard agent for older patients or those with significant comorbidities. A survival advantage was demonstrated with the combination of CHL-OBI compared to CHL alone in patients with high comorbidity scores or impaired renal function.[11] Additionally, in a trial comparing FCR to bendamustine-rituximab, in a subset of patients who were older than 65 years or who had a CIRS score 4-6, while there was no difference in PFS, bendamustine-rituximab resulted in less hematologic toxicity, suggesting that this regimen may be appropriate for older patients or those with limited comorbidities.[12] Particularly challenging is the management of patients with CLL that have abnormalities in del17p/TP53. Del17p, which is associated with shorter PFS, shorter time to progression, a lower response rate, and shorter OS following chemoimmunotherapy regimens such as FCR.[13] In these patients, IBR is approved as initial therapy for patients with del17p CLL and is publicly funded in almost all provinces.[14]

Acalabrutinib is also currently under review by CADTH for a similar indication, “with or without obinutuzumab, for the treatment of patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate”.

Effectiveness

CLL14 is an international, open-label, phase III, randomized, active-controlled superiority trial that evaluated the efficacy and safety of VEN-OBI compared to CHL-OBI for first-line treatment of CLL patients with co-existing conditions.[1] Eligible patients must have had previously untreated CLL which required treatment, and either a CIRS >6 or a CrCl <70 mL/min.

Overall, the median age was 72 years, with 33.3% and 36.1% of patients ≥75 years in the VEN-OBI group and in the CHL-OBI group respectively. Most patients were categorized as ‘Intermediate’ risk of TLS (64.4% in VEN-OBI group versus 68.1% in CHL-OBI group). The median CIRS score for all trial participants was 8 (range: 0 to 28), with 86.1% and 81.9% of patients having a CIRS score of >6 in the VEN-OBI group in the CHL-OBI group respectively.[3] The proportion of patients with CrCl <70ml/min was 59.5% in the VEN-OBI group and 55.4% in the CHL-OBI group. The percentage of patients for the cytogenetic subgroups in the VEN-OBI group compared to the CHL-OBI group were: deletion in 17p – 8.5% versus 7.3%, deletion in 11q – 18% versus 19.7%, trisomy 12 – 18% versus 20.7%, no abnormalities – 25% versus 21.8%, and deletion in 13q alone – 30.5% versus 30.6%. Most patients in both groups had unmutated *IGHV* (VEN-OBI – 60.5%; CHL-OBI – 59.1%), and unmutated TP53 (VEN-OBI – 88.9%; CHL-OBI – 91.7%).

The primary outcome in the CLL14 trial was investigator-assessed PFS. At the time of primary data cut-off on August 17, 2018, median follow-up was 28.1 months (range: 0.0 to 35.9 months).[1] Although median PFS had not been reached in either group, results of the primary analyses demonstrated a longer PFS for the VEN-OBI group compared to the CHL-OBI group, with an HR of 0.35 [95% CI: 0.23, 0.53; p<0.0001). Results were consistent at the updated data cut-off of August 23, 2019, with a median follow up of

39.6 months (range: 0.0 to 47.4 months).[7] At the time of both the August 17, 2018 and the August 23, 2019 data cut-offs, the OS data were immature and median OS was not estimable for either treatment group.[1,7]

The sponsor also submitted an ITC to estimate the relative effectiveness of VEN-OBI, with other relevant treatments for this patient population. Separate analyses were conducted based on the 'fitness' of the patient populations: 1) an 'unfit' network, and 2) an 'overall' network (both 'unfit' and 'fit' patients). Results for PFS in the 'unfit' network suggested that VEN-OBI was favoured over all competing interventions except for IBR-OBI. For the 'overall' network, the results suggested that VEN-OBI was favoured over all competing interventions except for over IBR-OBI and IBR-RIT. Results for OS in both the 'unfit' and the 'overall' networks suggested that VEN-OBI was only favoured over CHL. The NMA did not consider all potentially relevant comparators (i.e. acalabrutinib) and did not evaluate outcomes related to safety and HRQoL. Key limitations of the NMA included the potential sources of heterogeneity across the trials related to differences in patient and study characteristics, and the limited evidence (one trial per network arm). The sponsor also submitted naïve indirect treatment comparisons and a MAIC comparing the effectiveness of VEN-OBI to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. Results from all the comparisons (naïve and MAIC) for PFS and OS demonstrated no statistically significant differences between the two treatments, except for the PFS HR calculated with the naïve indirect treatment comparisons using data from one of the included trials, which suggested that IBR led to statistically longer PFS compared to VEN-OBI. Important limitations of the analyses included very small sample sizes and a large amount of identified clinical heterogeneity. Additionally, the study designs varied, including phase II trials, phase III trials, and retrospective cohort studies (real-world evidence), which further leads to challenges in comparing the results of the studies. Due to the important limitations of all the indirect treatment comparisons, the results of these analyses were interpreted with extreme caution and no conclusion could be made.

In terms of PROs, overall, results of the analyses of the MDASI-CLL and the EORTC QLQ-C30 did not show a difference between treatments during treatment or follow-up.[3] Baseline scores were comparable between the two groups for both questionnaires.[4] For the MDASI-CLL, there was no significant improvement or deterioration to the score throughout treatment and the follow-up period for either treatment group. For the EORTC QLQ-C30, baseline physical and role functioning were maintained throughout treatment and the follow-up period, with no significant improvement or deterioration to the scores. Patients showed an improvement of the GHS-QOL score by at least eight points starting at cycle 3 in the VEN-OBI group and starting at cycle 8 in the CHL-OBI group. Insomnia and fatigue scores also showed an improvement starting at cycle 3 in the VEN-OBI group, and at cycle 4 and 6 respectively in the CHL-OBI group. The differences in scores between the two treatments did not meet the pre-specified MIDs for any of the PRO measurements.

Safety

Although at least one AE of any grade was reported in 94.3% of patients in the VEN-OBI group and in 99.5% of patients in the CHL-OBI group, with most AEs being blood and lymphatic system disorders, [1] the safety profile of VEN-OBI was manageable and comparable to that of CHL-OBI. A ramp-up dosing for VEN-OBI was necessary to obtain this safety profile. The most common grade 3 or 4 AEs in the VEN-OBI group versus the CHL-OBI group were neutropenia (52.8% versus 48.1%), thrombocytopenia (13.7% versus 15.0%), and anemia (8.0% versus 6.5%). The incidence of TLS was lower in the VEN-OBI group compared to the CHL-OBI group (0.5% versus 1.9%), and all the occurrences of TLS in the VEN-OBI group occurred during the Obi only period, prior to starting Ven. During treatment, five fatal AEs occurred in the VEN-OBI group and four occurred in the CHL-OBI group. Two of the fatal AEs in the VEN-OBI group occurred in patients who received only O. After treatment, eleven fatal AEs occurred in the VEN-OBI group, and four occurred in the CHL-OBI group. As of the primary data cut-off, Richter's transformation was reported in two patients in the VEN-OBI group and in one patient in the CHL-OBI group,[1] with one additional transformation reported in the CHL-OBI group at the updated data cut-off.[7] Second primary cancers were reported in 13.7% of patients in the VEN-OBI group and in 10.3% of patients in the CHL-OBI group as of the primary data cut-off,[1] as well as an additional seven patients experiencing second primary malignancies in the VEN-OBI group at the time of the updated data cut-off.[7] Although a higher percentage of patients in the VEN-OBI group experienced second primary malignancies, the majority of occurrences were squamous cell carcinomas. This type of cancer is not unexpected in CLL patients, and there is no evidence to suspect a higher frequency of treatment related malignancies in either study group.

1.3 Conclusions

The CGP concluded that there is a net clinical benefit of VEN-OBI compared to CHL-OBI for first-line treatment of CLL patients with multiple comorbidities as indicated by an elevated CIRS score or abnormal renal function. The CGP based this conclusion on a well conducted randomized, open-label, phase III trial which demonstrated a statistically significant improvement for VEN-OBI compared to CHL-OBI in the efficacy outcomes of PFS, MRD-negativity in both bone marrow and peripheral blood, CRR, ORR, a manageable safety profile, and no apparent detriment to quality of life. VEN-OBI is a valid treatment option for first-line treatment of CLL patients who are fludarabine ineligible, that provides a more durable response compared to CHL-OBI.

In making this conclusion, the CGP also considered the following:

- As long as the per study protocol ramp-up dosing scheme for venetoclax is followed, the safety profile of VEN-OBI is considered similar to that of CHL-OBI, with no unexpected AEs.
- The eligibility criteria and patient demographics of the trial align with clinical practice of patients that would be considered fludarabine ineligible.
- Treatment with VEN-OBI should be restricted to patients who are fludarabine ineligible as there is a lack of data to support the use outside of this indication.
- A BTK inhibitor (e.g., IBR) would be the standard of care for the subgroup of patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation, and not CHL-OBI, which was the comparator in the CLL14 trial. While the exploratory subgroup analyses of these patients did show a PFS improvement with VEN-OBI compared to CHL-OBI, it is unclear what the relative efficacy would be compared to a BTK inhibitor. Although ITCs were conducted to investigate the comparison of VEN-OBI to IBR in these patients, many limitations of these analyses were identified, and no confirmative conclusions could be made.

Table 3: CADTH Clinical Guidance Panel Response to Provincial Advisory Group Implementation Questions

PAG Implementation Questions	CGP Response
Currently Funded Treatments	
The standard of care for non-high risk CLL patients who cannot tolerate FCR combination is CHL-OBI. In some provinces, bendamustine monotherapy or in combination with rituximab is available for this population. For treatment-naive CLL patients with high-risk genetic factors in whom fludarabine is unsuitable, IBR is available in some provinces. The comparator of the CLL-14 trial is CHL-OBI. PAG notes that acalabrutinib is currently under review at CADTH for the same indication. PAG is seeking information comparing VEN-OBI to acalabrutinib ± OBI, bendamustine + rituximab, IBR, and CHL-OBI.	Currently, except for compared to CHL-OBI, only indirect comparisons can be made between VEN-OBI and other treatments for CLL (refer to Section 7 for a summary and critical appraisal of the ITC/MAIC included in this submission). Although ITCs were conducted to investigate the comparison of VEN-OBI to other treatments for these patients, many limitations of these analyses were identified, and no confirmative conclusions could be made.
Currently Funded Treatments	
The standard of care for non-high risk CLL patients who cannot tolerate FCR combination is CHL-OBI. In some provinces, bendamustine monotherapy or in combination with rituximab is available for this population. For treatment-naive CLL patients with high-risk genetic factors in whom fludarabine is unsuitable, IBR is available in some provinces. The comparator of the CLL-14 trial is CHL-OBI.	Currently, except for compared to CHL-OBI, only indirect comparisons can be made between VEN-OBI and other treatments for CLL (refer to Section 7 for a summary and critical appraisal of the ITC/MAIC included in this submission). Although ITCs were conducted to investigate the comparison of VEN-OBI to other treatments for these patients, many limitations of these analyses were identified, and no confirmative conclusions could be made.

PAG Implementation Questions	CGP Response
PAG notes that acalabrutinib is currently under review at CADTH for the same indication. PAG is seeking information comparing VEN-OBI to acalabrutinib ± obi, BEN-RIT, IBR, and CHL-OBI.	
Eligible Patient Population	
PAG is seeking clarity on whether the following patients would be eligible for treatment with Ven+O in the first line setting:	
• Patients with a score lower than 6 on the Cumulative Illness Rating Scale	• As the eligibility criteria for the trial CLL14 specified patients with a CIRS score of > 6 OR a CrCl of < 70 ml/min, there would have been patients enrolled with CIRS score ≤6 (as long as their CrCl of < 70 ml/min). The CGP agreed that patients with a CIRS score <6 would be eligible for VEN-OBI as long as they were considered fludarabine ineligible.
• CD20-negative CLL	• The trial publication indicated that the trial included patients who had CD20+ CLL, however the sponsor indicated that this was not part of the patient eligibility requirements. The CGP felt that it would be reasonable for these patients to be eligible for VEN-OBI, although they would be unlikely to respond to the Obi portion of the treatment.
• Known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.	• Patients with these high-risk comorbidities were excluded from the CLL14 trial and therefore the potential survival benefit from VEN-OBI in these patients is unknown.
• Patients with or without high risk cytogenetic or mutational features (e.g., 17p deletion, TP53 mutation).	• Patients with and without high risk cytogenetic or mutational features were included in the CLL14 trial. Prolonged PFS for patients treated with VEN-OBI compared to CHL-OBI was demonstrated in the exploratory subgroup analyses for these patients. The CGP therefore felt it was reasonable for these patients to be eligible for treatment.
• Patient with SLL	• The CLL14 trial did not include patients with SLL. There is no direct evidence to support the use of VEN-OBI in SLL patients, however treatments for CLL and SLL are often considered the same disease; therefore, results would be applicable to patients with SLL.
Implementation Factors	
The dosing schedule for Ven+O is for a fixed duration of 48 weeks. 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 48 weeks of treatment.	• The CGP noted that there is no evidence to support the use of VEN-OBI beyond the 48 weeks of treatment in patients who do not experience progression. They did note that patients should be treated for the equivalent of 48 weeks (i.e. if treatment was paused and then resumed, the total time of treatment should equal to 48 weeks).
• For patients who have completed the 48 weeks of treatment, whether these patients should be re-treated with Ven+O upon progression.	• The CGP noted that there is no evidence to support retreatment with VEN-OBI upon progression. Second line treatment would need to take into account how quickly the patient relapsed and how the patient responded to initial treatment.

PAG Implementation Questions	CGP Response
Sequencing and Priority of Treatment	
PAG is seeking guidance on the appropriate place in therapy of Ven+O and overall sequencing of all treatments available for CLL/SLL. In particular, PAG would need information on the following aspects:	
• Clinical scenarios justifying preferential use of VEN-OBI, acalabrutinib or IBR in high-risk [del17p] patients, and of VEN-OBI, acalabrutinib, or CHL-OBI in FCR-ineligible patients.	• The CGP noted that there is currently no evidence to justify preferential use of the outlined treatments in either patient population.
• Use of venetoclax with rituximab (including subcutaneous formulation) for first-line treatment, given that this combination can be used in the RR CLL space.	• The CGP noted that there is currently no evidence to support the use of venetoclax with rituximab for first-line treatment. However, the CGP did note that physicians would be unlikely to use venetoclax in first-line and then again in the RR setting.
• Sequencing of VEN-OBI, BEN-RIT, CHL-OBI, IBR, idelalisib plus rituximab, and acalabrutinib, from newly diagnosed CLL to RR CLL.	• The CGP noted that there is currently no evidence to determine the appropriate sequencing of treatments for CLL.
• Since venetoclax treatment has a fixed duration, PAG seeks guidance on the appropriateness and timing of re-treatment with venetoclax (either Ven, VEN-OBI or Ven+R) after prior VEN-OBI.	• The CGP noted that there is currently no evidence to determine the appropriateness and timing of re-treatment with venetoclax after prior VEN-OBI use. As stated above, the CGP noted that physicians would be unlikely to retreat with venetoclax after prior VEN-OBI use.

BEN-RIT = Bendamustine plus Rituximab; CGP = Clinical Guidance Panel; CHL-OBI = Chlorambucil plus Obinutuzumab; CLL = chronic lymphocytic leukemia; CNS = central nervous system; FCR = fludarabine plus cyclophosphamide plus Rituximab; PAG = Provincial Advisory Group; RR = relapsed/refractory; SLL = small lymphocytic lymphoma; VEN-OBI = Venetoclax plus Obinutuzumab

2 Background Clinical Information

2.1 Description of the Condition

Chronic lymphocytic leukemia is one of the most common hematologic malignancies with an incidence of 4.8 cases/100,000 persons:[9] 1,745 Canadians were diagnosed with CLL and 611 died from this disease in 2016 and 2017, respectively, according to the most recent available Canadian statistics. [10] The majority of persons with CLL are asymptomatic and diagnosed because of the finding of an elevated white blood cell count.

The diagnosis usually consists 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.[15] Additionally, 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. Moreover, 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.[16] 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. At three years follow-up, 75-80% of patients who present with lymphocytosis (Rai stage 0) were free of progression.[17] Outcome of patients according to the two accepted staging systems is summarized in the Table 4.[17,18]

Table 4: Staging Systems for CLL

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	

Hb = hemoglobin; OS = overall survival; Plt = platelet.

* 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 OS in patients with CLL including age, lymphocyte doubling time, and serum β_2-microglobulin. The four molecular/biologic features that have the best track record for use as clinical prognostic parameters are IGHV mutation status and 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 guide treatment options; however, increasingly the identification of unmutated IGHV associated with shorter PFS and OS with standard immunochemotherapy has been suggested as an indication for primary therapy with IBR.[19] A prognostic index incorporating the following molecular and clinical factors: *TP53* status (no abnormalities versus *del17p*, *TP53* mutation, or both), *IGHV* mutational status (mutated versus unmutated), serum β_2-microglobulin concentration (≤3.5 mg/L versus >3.5 mg/L), clinical stage (Binet A or

Rai 0 versus Binet B–C or Rai I–IV), and age (≤65 years versus >65 years) has recently been published, which refines the ability to identify patients who could benefit from targeted therapies.[20]

2.2 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, and B-symptoms or rapid lymphocyte doubling (<3 months).[15] 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. The currently accepted clinical practice is summarized in Table 5.

Table 5: Accepted Clinical Practice

Patients with symptomatic Chronic Lymphocytic Leukemia		
Line of Therapy	**Non-del17p**	**del17p**
1st-Line: Fit, age 65-70 Less fit, frail; age>70	 FCR BEN-RIT CO acalabrutinib[a]	 IBR IBR
Maintenance	not indicated	not indicated
2nd-Line	BR IBR idelalisib + rituximab	idelalisib + rituximab venetoclax

BEN-RIT = bendamustine, rituximab; CHL-OBI = chlorambucil, obinutuzumab; FCR = fludarabine, cyclophosphamide, rituximab; IBR = ibrutinib.
Note:
[a] Treatment has received Notice of Compliance from Health Canada and is currently under review at CADTH.

First-line

For patients with CLL who require treatment, who are in good health, and under the age of 65-70 years, the combination of FCR is standard in most provinces in Canada. The German CLL Study Group study showed improvement in PFS in the chemoimmunotherapy arm compared to the chemotherapy arm (median PFS: 51.8 versus 32.8 months, p<0.0001) and OS (percentage of patients being alive at three years after randomization: 87% in the chemoimmunotherapy arm versus 83% in the chemotherapy arm, p=0.012) with the addition of rituximab to FC.[13] 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; accordingly, fludarabine therapy requires close monitoring of renal function and the use of prophylaxis against pneumocystis jiroveci pneumonia and herpes virus infection for up to one year after completion of therapy.

Chlorambucil, an alkylating agent that is well tolerated, has been in use for more than 30 years and 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 PFS without a significant increase in toxicity.[11,21] 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.[11]

In a randomized phase III trial comparing FCR to bendamustine-rituximab 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; however, bendamustine-rituximab resulted in less hematologic toxicity suggesting that this regimen may be appropriate for older patients or those with limited comorbidities.[12]

Particularly challenging is the management of patients with CLL that have 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, a lower response rate, and shorter PFS and OS following chemoimmunotherapy regimens such as FCR.[13] Agents that interfere with B cell receptor signaling are the hallmark of CLL such as the BTK inhibitor IBR and the PI3-kinase δ inhibitor idelalisib, which have resulted in superior response rates in patients with TP53 abnormalities. Namely, IBR is approved as initial therapy for patients with 17p deletion CLL and is publicly funded in almost all provinces.[14]

3 Summary of Patient Advocacy Group Input

One joint input was provided by Lymphoma Canada (LC) and Chronic Lymphocytic Leukemia Patient Advocacy Group (CLLPAG) for the review for VEN-OBI for patients with previously untreated CLL.

LC and CLLPAG gathered data from three online surveys, summarized here:

- Survey 1: Distributed in June 2017 to patients with CLL/SLL who did not have experience with VEN-OBI (n=320)
- Survey 2: Distributed in June 2017 to caregivers (n=41)
- Survey 3: Distributed in January 2020 specifically to patients with CLL/SLL who had experience with VEN-OBI (n=33).

In total, 394 respondents provided information through these online surveys. Information gathered from Survey 1 and Survey 2 were used to inform sections 3.1, Condition and Current Therapy Information, and 3.2.1, Patient Expectations for Current Therapy, of this summary. Survey 3was used to inform sections pertaining specifically to VEN-OBI.

The surveys were distributed via email to CLLPAG members and the LC database, website posts on the organizations' websites (cllpag.ca, lymphoma.ca, cllcanada.ca, cllsupport.org.uk), social media pages and groups, blog posts and online CLL forums. The online surveys included multiple choice, rating and open-ended questions; surveys incorporated skipping logic so respondents could answer questions only relevant to them. Table 6 and Table 7 include a demographic breakdown of respondents; most respondents were from Canada or the US, and between the ages of 60 and 79. Roughly equal proportions of males and females responded to the surveys.

Table 6: Geographic Distribution of Survey Respondents

Respondents	CAN	USA	UK	AUS	Other*	Skipped	Total
Survey 1: CLL/SLL patients WITHOUT VEN-OBI experience	102	127	51	2	4	34	320
Survey 2: Caregivers	20	16	1	0	0	4	41
Survey 3: CLL/SLL patients WITH VEN-OBI experience	2	29	1	0	0	1	33

AUS = Australia; CAN = Canada; CLL= chronic lymphocytic leukemia; SLL= small lymphocytic leukemia; UK = United Kingdom; USA = United States of America; VEN-OBI = venetoclax plus obinutuzumab.
Note:
*Other includes 1 patient from each of the following: Brazil, France, India, Israel.

Table 7: Age and Gender Distribution of Survey Respondents

Respondents	Age					Gender		
	21-39	40-59	60-79	80-89	N/A	M	F	N/A
Survey 1: CLL/SLL patients WITHOUT VEN-OBI experience	2	68	200	14	18	142	145	33
Survey 2: Caregivers	1	12	23	1	4	8	29	4
Survey 3: CLL/SLL patients WITH VEN-OBI experience	0	10	22	0	1	18	14	1

CLL= chronic lymphocytic leukemia; F = female; M = male; N/A = not available; SLL= small lymphocytic leukemia; VEN-OBI = venetoclax plus obinutuzumab.

Based on information from Survey 1, quality of life (QoL) was reported to be more severely impacted for patients with advanced disease compared to patients with early stage disease who reported minimal disease symptoms. Fatigue (83%), frequent infections (27%), enlarged lymph nodes (23%) and shortness of breath due to anemia (20%) were commonly reported disease symptoms affecting patients' QoL on an ongoing basis. Comorbidities were reported in 37% of patients, with patients also reporting another

cancer, cardiovascular disease, and diabetes. Many patients reported receiving at least two or more therapies, with 54% previously receiving two, and 28% previously receiving three or more. IBR was the most commonly reported therapy patients previously reported being treated with (67%). Commonly reported side effects related to treatments included fatigue, nausea, reduced blood counts, diarrhea and frequent infections; these were also reported to be difficult to tolerate. Oral treatments were reported to negatively impact patient's QoL less so compared to intravenous therapies. Many patients (48%) reported a need for treatments with better disease symptom management.

A total of 33 patients reported having experience with VEN-OBI as frontline treatment, most having received VEN-OBI within the past year (52%) or between one to two years ago (40%); few patients (9%) reported receiving VEN-OBI between two and five years ago. At the time of survey completion, most patients either completed or were still receiving VEN-OBI treatment. Enlarged lymph nodes (82%), fatigue (76%) and an enlarged spleen (58%) were the most commonly managed disease symptoms as a result of VEN-OBI. Almost two-thirds of patients (61%) indicated that VEN-OBI was able to manage all of their CLL/SLL disease symptoms; fatigue (30%) and shortness of breath (12%) were symptoms patients reported that VEN-OBI were not able to manage. Commonly reported side effects from VEN-OBI included muscle or joint pain (45%), neutropenia (42%), and thrombocytopenia (30%). The side effects experienced from VEN-OBI were reported to have little impact on patient's QoL, and that aspects of daily activities were mostly unchanged or improved due to treatment. Patient comments tended to view VEN-OBI positively, *"Treatment has improved my quality of life significantly both physically and mentally."*

From a patient's perspective, having a choice in treatment option was considered very important. Overall, patients value treatments with minimal side effects which are able to better manage disease symptoms, have increased effectiveness resulting in delayed disease progression and increased survival, and improve QoL.

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

3.1 Condition and Current Therapy Information

3.1.1 Patients Experiences

CL and CLLPAG noted that the information gathered from Survey 1 and Survey 2 distributed to patients and caregivers in June of 2017 were used to inform this section related to patient experiences with CLL.

Of the 320 patient respondents, 279 (87%) were diagnosed with CLL; the remaining were diagnosed with SLL (3%, n=11) or had both CLL and SLL (9%, n=30). Patients reported that receiving their diagnosis was often a complete shock to them, as often patients were diagnosed during an investigation for another condition or during routine blood work. At the time of the survey, 301 patients indicated what treatment they were currently receiving to treat their condition; 38% (n=115) were under active surveillance/watch and wait, 27% (n=80) were receiving treatment, 28% (n=85) were in remission, and 7% (n=21) reported having recently relapsed following one or more lines of therapy. Table 8 reports the length of time patients reported being in remission, with the greatest proportion of patients reporting being in remission between six months and five years (63%).

Table 8: Length of Remission for Treated Patients

Length of time in remission	N=85 n (%)
<6 months	13 (15)
6 months – 2 years	26 (31)
2-5 years	27 (32)
>5 years	19 (22)

LC and CLLPAG reported that the watch and wait stage was a very difficult stage of the disease to accept for both patients and caregivers. Two quotes provided by LC and CLLPAG describe the difficulty patients experience during this stage of their disease:

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

LC and CLLPAG highlighted that patients with early stage disease and who experienced minimal symptoms tended to report good QoL. Patients with more advanced disease reported greater impact on their QoL. Table 9 reports the symptoms of CLL affecting the QoL of patients at diagnosis and on an ongoing basis. Fatigue and lack of energy was the most commonly reported symptom to affect QoL of patients at diagnosis; fatigue and lack of energy was also reported by over 80% of patient respondents to negatively affect QoL throughout the course of patient's disease. LC and CLLPAG reported that patients described being void of energy and that in order to perform daily activities they needed to rest often. Frequent infections, anemia, and shortness of breath were other commonly reported symptoms of disease to affect QoL on an ongoing basis.

Table 9: Disease Symptoms Affecting Patients' Quality of Life

Symptom	At diagnosis (N=320)	Ongoing (N=313)
Fatigue/lack of energy	152 (48%)	260 (83%)
Enlarged lymph nodes	97 (30%)	71 (23%)
None of the listed symptoms	95 (30%)	74 (24%)
Night sweats	66 (21%)	58 (19%)
Frequent infections *(due to compromised immunity)*	61 (19%)	85 (27%)
Shortness of breath *(attributed to anemia)*	41 (13%)	62 (20%)

When asked to report on the psychosocial aspects of their disease experienced at diagnosis, many patients reported experiencing feelings of anxiety/worry and stress related to their diagnosis (Table 10). Common psychosocial issues experienced by patients on an ongoing basis included anxiety/worry and difficulty sleeping. LC and CLLPAG also highlighted that some patients experienced difficulties with concentration, emotions, and mood swings; these symptoms were noted to interfere with a patient's performance, ability to work, travel, and day-to-day activities. Disease symptoms were reported to affect 39% (n=117/307) of patient's work, resulting in working fewer hours, changing careers, or retiring early. Out of the 307 patient respondents, disease symptoms were also reported to affect family (38%, n=117), personal image (27%, n=84), intimate relations (23%, n=69,), and friendships (18%, n=56). The following were quotes provided from respondents and reflect the impact patients' condition has had on their work life, friendships, and families:

- *"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."*

Table 10: Psychosocial Aspects of Disease Affecting Patients

	Patients	
Psycho-Social Condition	At diagnosis (N=320)	Ongoing (N=313)
Anxiety/worry	209 (65%)	139 (44%)
Stress of diagnosis	204 (64%)	82 (26%)
Difficulty sleeping	104 (33%)	96 (31%)
Depression	86 (27%)	56 (18%)
None of these	64 (20%)	98 (31%)

Over one-third of patients reported having another comorbidity (37%, n=110/301); of these 110 patients, 37% (n=41) reported also having another cancer, 21% (n=23) had cardiovascular issues, and 18% (n=20) had diabetes. In order to help manage CLL/SLL symptoms, some patients also reported needing supportive therapies, such as immunoglobulin therapy (20%, n=60/301), blood growth factors (17%, n=50/301), and transfusions of blood products (16%, n=49/301).

3.1.2 Patients' Experiences with Current Therapy

Of 320 respondents, 179 patients reported having experience with one or more therapies to treat their CLL/SLL. Treatments reported by patients are included in Table 11; the most commonly reported treatments were fludarabine plus cyclophosphamide plus rituximab (FCR) (62%, n=76/165,), BEN-RIT (28%, n=26), chlorambucil (27%, n=22) and fludarabine plus rituximab (FR) (23%, n=23%). LC and CLLPAG also reported that most respondents reported receiving one or more conventional intravenous therapies, including chemotherapy or chemoimmunotherapy (92%, n=165/179); the use of one or more oral therapies were reported by 79% of patients (n=142/179), and 61% of patients reported receiving one or more other types of therapies (n=110/179). Respondents indicated using an average of two different therapies (range: 1-8) to treat their CLL/SLL; more than half of respondents reported receiving two therapies (54%, n=97/179), and 28% (n=50/179) reported receiving three or more therapies.

Table 11: Previously Received Therapies

Conventional IV Therapy	Responses N=165	Conventional IV Therapy	Responses N=165
FCR	76 (62%)	Bendamustine	8 (11%)
BEN-RIT	26 (28%)	CVP	5 (7%)
Chlorambucil	22 (27%)	PCR	3 (4%)
FR	20 (23%)	FCM	1 (1%)
R CHOP	9 (12%)	CHOP	1 (1%)

BEN-RIT = bendamustine, rituximab; CVP = cyclophosphamide, vincristine, prednisone; FCR = fludarabine, cyclophosphamide, rituximab; FR = fludarabine, rituximab; R CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

Table 12 and Table 13 report other treatments received by 142 patient respondents. IBR was the most commonly reported target therapy (67%, n=86), with venetoclax reported by a quarter of respondents (25%, n=21). Other reported therapies by less than 10% of patients included surgery, radiation, stem cell transplant as well as others. LC and CLLPAG highlighted that many patients will require more than one line of therapy throughout the course of their disease.

Table 12: Other Targeted Therapies Received by Patients

Other Drug Therapy	Responses N=142
Ibrutinib	86 (67%)
Venetoclax	21 (25%)
Other*	18 (27%)
Idelalisib	9 (11%)

Note:*Additional information about 'other' therapies patients received was not available

Table 13: Other Non-targeted Therapies Received by Patients

Other Therapy	Responses N=110
Surgery	7 (7%)
Radiation	5 (5%)
Stem Cell Transplant	5 (5%)
Other	5 (5%)

Respondents were asked to rate on a scale from 1 (strongly agree) to 10 (strongly disagree) how effective they thought their current therapy was able to manage their disease symptoms. A score of 3 or less, indicating effective symptom management from treatment, was reported by 31% of respondents (n=56). A score of 8 or higher, indicating poor symptom management from current treatment, was reported by 48% of respondents (n=86). Among 179 respondents, a weighted average of 6.0 was reported regarding the effectiveness of respondent's current treatments on their symptom management; which indicated a better need for symptom management from treatments for CLL/SLL.

Side effects of current treatments are reported in Table 14. Fatigue was the most commonly reported side effect from current treatments. LC and CLLPAG also highlighted that patients noted fatigue, nausea, reduced blood counts, diarrhea, and frequency of infections as the most concerning and difficult side effects to tolerate.

Table 14: Side Effects of Current Treatments

Side effect	n (%) N=179
Fatigue	126 (70)
Anemia or neutropenia	77 (43)
Nausea	70 (39)
Diarrhea	63 (35)
Low platelet counts	62 (35)
Infections	59 (33)

The following quotes were provided by patients/caregivers and illustrate the difficulties they experience due to side effects from their treatments:

- *"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."*
- *"I am on Imbruvica and have a few side effects such as fatigue, mouth sores, and joint pain. It is difficult for me because I am raising my grandchild who is now nine. I do not have enough energy to do the things they would like to."*
- *"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."*

Respondents were asked to rate on a scale from 1 (little impact) to 10 (significant impact) how their experiences with treatment for CLL, both administered orally and intravenously, had impacted their QoL (Table 15). Regarding therapies administered intravenously, between 30%-55% of patients rated aspects of their treatment experience impacting their QoL with a score of 6 or higher. Aspects of treatment that most negatively impacted patient's QoL due to intravenously administered therapies included treatment-related fatigue, number of clinic visits, activity level, and infusion time.

Regarding orally administered therapies, between 20%-33% of patients rated aspects of their treatment experience as impacting their QoL with a score of 6 or higher. Most patients receiving oral therapies reported scores of 5 or lower, indicating that orally administered therapies had relatively little negative impact on patient's QoL. Overall, based on patient's responses orally administered therapies impacted patient's QoL negatively less so compared to treatments which were administered intravenously.

Table 15: Patient Experiences with Previously Received Intravenous and Oral Therapies

Experience	IV Therapies n=148			Oral Therapies n=136		
	6 or 7*	8, 9 or 10*	Total 6-10	6 or 7*	8, 9 or 10*	Total 6-10
Number of clinic visits	32 (22%)	49 (33%)	**81 (55%)**	15 (11%)	22 (16%)	**37 (27%)**
Treatment-related fatigue	20 (14%)	56 (38%)	**76 (51%)**	14 (10%)	31 (23%)	**45 (33%)**
Infusion time	30 (20%)	42 (28%)	**72 (49%)**	N/A	N/A	**N/A**
Activity level	25 (17%)	43 (29%)	**68 (46%)**	18 (13%)	27 (20%)	**45 (33%)**
Toleration of treatment	21 (14%)	39 (26%)	**60 (41%)**	11 (8%)	33 (24%)	**44 (32%)**
Infusion reaction	17 (11%)	39 (26%)	**56 (38%)**	N/A	N/A	**N/A**
Number of infections	18 (12%)	27 (18%)	**45 (30%)**	10 (7%)	17 (13%)	**27 (20%)**

N/A = not applicable.
Note: *Respondents rated their experiences with therapies on a 10-point scale: 1=little impact to 10=significant impact

3.1.3 Impact on Caregivers

LC and CLLPAG asked respondents to rate on a scale from 1 (little to no impact) to 10 (significant impact) how caring for a person with CLL has impacted or limited their own day-to-day activities and QoL (Table 16). Most respondents indicated that caring for a person with CLL had little impact on their day-to-day activities. However, over one-third of respondents reported a significant impact on their ability to spend time with family and friends, ability to travel, and ability to concentrate.

Table 16: Impact of CLL Caregiving on Caregiver's Daily Activities and Quality of Life

Activity (Caregivers)	6-10 (significant impact) n=40	1-5 (no to little impact) n=40
Ability to spend time with family & friends	14 (35%)	26 (65%)
Ability to travel	14 (35%)	26 (65%)
Ability to concentrate	14 (35%)	26 (55%)
Ability to fulfill family obligations	11 (28%)	29 (68%)
Ability to perform household chores	10 (25%)	30 (75%)
Ability to contribute financially to household finances	10 (25%)	30 (75%)
Ability to volunteer	9 (23%)	31 (88%)
Ability to exercise	8 (20%)	33 (83%)

Caregivers (N=41) were also asked to report psychosocial aspects of CLL/SLL that affected them. Caregivers mostly reported feelings of anxiety/worry (n=33, 80%), stress related to their loved one's diagnosis (n=32, 8%) and difficulty sleeping (n=25, 61%); other psychosocial effects included depression (n=14, 35%) and other (n=2, 5%).

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for New Therapies

Patients were asked to rate on a scale from 1 (not important) to 10 (very important) which symptoms they thought were the most important for treatments to control. The most commonly reported symptoms patients expected their treatment to control were infections (88%, n=266/301), reduced blood counts, or thrombocytopenia (75%, n=225), neutropenia (74%, n=223), anemia (73%, n=219), and fatigue (67%, n=202); all of these symptoms were rated a score of 8 or higher. Ongoing fatigue, frequent infections, and reduced blood counts were highlighted by LC and CLLPAG to be frequent concerns for patients. In addition, as patients' disease progress, patients experience increasing symptoms.

LC and CLLPAG asked patients to rate on a scale from 1 (not important) to 10 (very important) how important it was for them and their physicians to have choice in their therapy. Almost all respondents (95%, n=286/301) provided a score of 8 or higher, with a weighted average score of 9.5. Respondents were also asked to indicate what was most important to them about a new therapy; it was noted that this question was only asked to respondents who were currently, or who had previously received treatments, and that respondents could only choose one option. Increased effectiveness and decreased toxicity were the most common responses as expectations of new therapies; other expectations for new therapies are included in Table 17; after follow-up with the patient groups, it was confirmed that when discussing increased effectiveness for new therapies, patients value delayed disease progression and increased survival.

Table 17: Respondent's Expectations for New Therapies

Expectations for new therapies	n (%) N=163
Increased effectiveness	72 (44)
Decreased toxicity	40 (25)
Remission	12 (7)
Accessible and affordable treatments	12 (7)
Improved quality of life	11 (7)
Oral therapy	9 (6)

LC and CLLPAG emphasized that CLL is currently incurable, and that patients live with the knowledge that their disease may progress at any time. The following two quotes indicate that patients are hoping for new and effective treatments to treat their CLL:

- *"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."*

There was also a focus on improved QoL: *"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."*

LC and CLLPAG stated that patients seek individualized choice in treatment that will offer disease control and improve QoL while offering ease of use relative to other treatments. In addition, it was stated that patients prefer transitioning away from treatment with chemotherapy and would prefer targeted therapies with proven efficacy in treating a range of patients, including those with poor prognostic factors, advanced age, and existing co-morbidities.

3.2.2 Patient Experiences to Date

A total of 33 patients indicated having received VEN-OBI as frontline treatment to treat their CLL/SLL. Of these patients, most received VEN-OBI fairly recently, with 52% having received it within the past year, and 40% having received it between one to two years ago (Table 18). Most patients were able to access VEN-OBI through a clinical trial (45%) or through their private insurance (30%), with few patients receiving it through the public drug plain (9%) or other sources (9%).

Table 18: Treatment Information of Patients Treated with Venetoclax plus Obinutuzumab

Frontline treatment	Started treatment N=33				Access to treatment N=33			
	< 1 year ago	1-2 years ago	2-5 years ago	> 5 years ago	Clinical trial	Private insurance	Public Drug Plan	Other
VEN-OBI	17 (52%)	13 (40%)	3 (9%)	0	15 (45%)	10 (30%)	4 (12%)	4 (12%)

VEN-OBI = venetoclax plus obinutuzumab.

Table 19 indicates whether patients had completed a full course of treatment with VEN-OBI. All patients were either still receiving, or had already completed their treatment with venetoclax (100%, n=33/33). Most patients were also either still receiving or had already completed their treatment with obinutuzumab (94%, n=31); however, 6% of patients had to stop treatment with obinutuzumab due to side effects (n=2).

Table 19: Treatment Status of Patients Treated with Venetoclax plus Obinutuzumab

Completed treatment?	Venetoclax (N = 33)	Obinutuzumab (N = 33)
Yes	9 (27%)	18 (55%)
Still receiving treatment	24 (73%)	13 (39%)
No, due to side effects	0 (0%)	2 (6%)
No, because CLL/SLL progressed	0 (0%)	0 (0%)

CLL = chronic lymphocytic leukemia; SLL= small lymphocytic leukemia.

Respondents were asked to indicate which symptoms of CLL were managed with treatment with VEN-OBI. The most commonly managed disease symptoms were reported to be enlarged lymph nodes, fatigue, and an enlarged spleen; other managed symptoms from treatment with VEN-OBI are included in Table 20. Only one patient reported that they were not experiencing any disease symptoms prior to receiving VEN-OBI.

Table 20: Disease Symptoms Managed by Venetoclax plus Obinutuzumab

Disease symptom	Responses (N = 33)
Enlarged lymph nodes	27 (82%)
Fatigue, lack of energy	25 (76%)
Enlarged spleen	19 (58%)
Night sweats	14 (42%)
Frequent infections	13 (39%)
Pain	11 (33%)
Weight loss	6 (18%)
Shortness of breath	5 (15%)
Fever	1 (3%)
I was not experiencing symptoms before treatment	1 (3%)

LC and CLLPAG also asked respondents to indicate any CLL symptoms which were not able to be managed by treatment with VEN-OBI. Sixty-one percent of patients (n=20/33) reported that treatment with VEN-OBI was able to manage all of their disease symptoms. Symptoms that were not able to be managed with VEN-OBI that were reported by more than 10% of respondents included fatigue/lack of energy (30%, n=10) and shortness of breath (12%, n=4).

Table 21 reports side effects from treatment with VEN-OBI experienced by respondents. Muscle or joint pain (45%), neutropenia (42%), and thrombocytopenia (30%) were the most commonly reported treatment related side effects.

Table 21: Side Effects Experienced by Patients Treated with Venetoclax plus Obinutuzumab

Treatment side effect	Responses (N = 33)	Treatment side effect	Responses (N = 33)
Muscle or joint pain	15 (45%)	Anemia	6 (18%)
Neutropenia	14 (42%)	Headache	6 (18%)
Thrombocytopenia	10 (30%)	Constipation	5 (15%)
Diarrhea	9 (27%)	Infections	5 (15%)
Nausea	9 (27%)	Abdominal pain	5 (15%)
Fatigue	9 (27%)	Fever	4 (12%)
Cough	8 (24%)	Tumor lysis syndrome	0 (0%)
Infusion reaction	7 (21%)		

Table 22 illustrates the impact of the treatment related side effects on respondent's QoL; respondents were asked to rate the impact on a scale from 1 (no impact) to 4 (very significant impact). Most respondents indicated that side effects from VEN-OBI had very little impact on their QoL (55%-76%); a greater proportion of respondents reported low scores for impact of treatment related side effects on their QoL, and the weighted average for treatment related side effects were between 1.5 and 1.8.

One patient reported that *"all symptoms were very mild, intermittent, and I recovered quickly" and another reported that they "had no symptoms before starting therapy and happy to say I am still symptom free!" Another patient stated that their treatment related symptoms "appeared during the venetoclax ramp up. Once they added Gazyva [obinutuzumab] and decreased the venetoclax to 100mg, they all went away."*

Table 22: Impact on Quality of Life of Treatment Related Symptoms Related to Venetoclax plus Obinutuzumab

Treatment factor	No or some impact (score = 1-2)	Significant or Very Significant impact (score = 3-4)	Not Applicable	Weighted Average (N=33)
Treatment-related fatigue	25 (76%)	5 (15%)	3 (9%)	1.8
Infusion reaction	22 (67%)	6 (18%)	5 (15%)	1.8
Other side effects	18 (55%)	6 (18%)	9 (27%)	1.5

Respondents were asked to rate on a scale from 1 (much worse off) to 5 (greatly improved) how VEN-OBI changed aspects of their day-to-day life (Table 23). The weighted averages for various aspects of daily living affected by treatment with VEN-OBI were between 3.1-3.6, indicating that most aspects of day-to-day life were relatively unchanged or were improved due to treatment with VEN-OBI.

One patient stated that treatment with VEN-OBI helped to improve their physical condition *"mostly because of the absence of pain and fatigue." Another patient stated, "Treatment has improved my quality of life significantly both physically and mentally."*

Table 23: Impact of Venetoclax plus Obinutuzumab on Patient's Daily Living

Aspect of daily living	Worse off (score = 1-2)	Unchanged (score = 3)	Improved (score = 4-5)	Not Applicable	Weighted Average (N=33)
Travel	10 (30%)	9 (27%)	14 (42%)	0 (0%)	3.4
Spend time with family & friends	8 (24%)	11 (33%)	14 (42%)	0 (0%)	3.5
Fulfill family obligations	7 (21%)	13 (39%)	13 (39%)	0 (0%)	3.5
Perform household chores	6 (18%)	12 (36%)	15 (45%)	0 (0%)	3.6
Contribute to household finances	10 (30%)	12 (36%)	9 (27%)	2 (6%)	3.1

Aspect of daily living	Worse off (score = 1-2)	Unchanged (score = 3)	Improved (score = 4-5)	Not Applicable	Weighted Average (N=33)
Volunteer	3 (9%)	16 (48%)	8 (24%)	6 (18%)	3.3
Exercise	10 (30%)	8 (24%)	15 (45%)	0 (0%)	3.4

Table 24 reports how respondents thought treatment with VEN-OBI changed their health and well-being. Most patients reported that their health and well-being were improved (88%, n=29/33) due to treatment with VEN-OBI; further, almost two-thirds of patients reported that their health and well-being were greatly improved (64%, n=21). The following quotes from patients were provided by LC and CLLPAG, illustrating the overall positive experiences of patients with VEN-OBI:

- *"I have my life back better than expected by a high degree of measure."*
- *"For me this treatment was efficacious, tolerable, expedient, and appealing because it allowed the possibility for discontinuation as compared to the BTK's. I discontinued treatment December 12, 2019. I am very satisfied with the immediate response from obinutuzumab plus venclexta, and I hope to experience a reasonable durability of at least five years."*
- *"I am on a maintenance dose of Venetoclax now. As time goes on after the 1 year mark, I'm getting much stronger."*
- *"Essentially no side effects for me. Very easy ride so far and my CBC numbers are looking very good."*

Table 24: Impact of Venetoclax plus Obinutuzumab on Patient's Health and Wellbeing

Much worse off (1)	Somewhat worse off (2)	Unchanged (3)	Somewhat improved (4)	Greatly improved (5)	Weighted Average (N=33)
0 (0%)	2 (6%)	2 (6%)	8 (24%)	21 (64%)	4.5

Respondents were also asked to rate their experience with VEN-OBI (Table 25); most patients reported that they had either a very good or excellent experience with their treatment (84%, n=28/33).

Table 25: Overall Patient Experience with Venetoclax plus Obinutuzumab

Poor (1)	Satisfactory (2)	Good (3)	Very good (4)	Excellent (5)	Weighted Average (N = 33)
0 (0%)	2 (6%)	3 (9%)	15 (45%)	13 (39%)	4.2

Overall, LC and CLLPAG stated that VEN-OBI provided patients with an effective treatment option with limited treatment duration and mild side effects; further, treatment with VEN-OBI allowed for patients to maintain or regain good QoL, have fewer hospital visits and contribute to society.

3.3 Companion Diagnostic Testing

No additional information provided.

3.4 Additional Information

No additional information provided.

4 Summary of Provincial Advisory Group Input

The PAG 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 CADTH 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 with other therapies for CLL
- Use in CLL with high risk cytogenetic features

Economic factors:

- Management of adverse reactions

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care for non-high risk CLL patients who cannot tolerate fludarabine, cyclophosphamide, and rituximab (FCR) combination is chlorambucil in combination with obinutuzumab (CHL-OBI). In some provinces, bendamustine monotherapy or in combination with rituximab is available for this population. For treatment-naive CLL patients with high-risk genetic factors in whom fludarabine is unsuitable, IBR is available in some provinces. The comparator of the CLL-14 trial is CHL-OBI.

PAG notes that acalabrutinib is currently under review at pCODR for the same indication. PAG is seeking information comparing VEN-OBI to acalabrutinib ± obi, BEN-RIT, IBR, and CHL-OBI.

4.2 Eligible Patient Population

The reimbursement request is in combination with obinutuzumab for the treatment of adult patients with previously untreated lymphocytic leukemia (CLL) who are fludarabine ineligible. In view of the inclusion and exclusion criteria and subgroups of the CLL-14 trial, PAG is seeking clarity on whether the following patients would be eligible for treatment with VEN-OBI in the first line setting:

- Patients with a score lower than 6 on the Cumulative Illness Rating Scale
- CD20-negative CLL
- Known CNS lymphoma or leukemia, or known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
- Patients with or without high risk cytogenetic or mutational features (e.g., 17p deletion, TP53 mutation).
- Patient with small lymphocytic lymphoma (SLL)

If recommended for reimbursement, CLL patients having initiated CHL-OBI, bendamustine, BEN-RIT, acalabrutinib or IBR would need to be addressed on a time-limited basis. PAG identified risk of indication creep from the use of first line venetoclax monotherapy, or combination with rituximab instead of obinutuzumab (i.e., as used in RR CLL), or use of VEN-OBI (instead of venetoclax plus rituximab (VEN-RIT)) in the RR setting. There was also concern of creep to other patients excluded from the trial or the reimbursement request, including those who can tolerate fludarabine-based regimens and those who don’t have significant comorbidities.

4.3 Implementation Factors

Venetoclax is available as 10 mg, 50 mg and 100 mg tablets. The recommended dose of venetoclax for CLL is 400 mg (four 100 mg tablets) daily. The treatment duration in the trial consisted of 12 cycles lasting 28 days each. Venetoclax dosing is ramped up for 5 weeks. Obinutuzumab is administered intravenously for the first 6 cycles (3000 mg for cycle 1, 1000 mg per subsequent cycles). PAG identified the once daily dosing schedule and the finite treatment duration as enablers 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 details the ramp up dosing schedule. With regard to obinutuzumab, the option of splitting the first 1000 mg between 2 days (100 mg on day 1, on 900 mg day 2) may lead to some drug wastage as the vials come in 1000 mg sizes.

The dosing schedule for VEN-OBI is for a fixed duration of 48 weeks. 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 48 weeks of treatment. For patients who have completed the 48 weeks of treatment, whether these patients should be re-treated with VEN-OBI upon progression.

PAG noted that prior to initiating therapy with VEN-OBI, patients should be assessed for risk of tumour lysis syndrome. During the 5-week ramp-up period, 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 VEN-OBI therapy. G-CSF may be needed to manage neutropenia. All of these considerations entail the allocation of additional laboratory, nursing and pharmacy resources. Given these concerns and real-life experience with venetoclax, PAG noted that the latter is a time-consuming and resource-intensive therapy.

PAG observed that VEN-OBI would be a replacement of an existing therapy. Should it displace IBR monotherapy, the presence of obinutuzumab would require additional pharmacy and nursing resources for outpatient IV therapy. Obinutuzumab is associated with longer infusions than rituximab, which may entail more chair time when compared with BEN-RIT treatment. Clinicians are familiar with venetoclax and obinutuzumab as they are both used for other indications.

PAG noted that venetoclax is an oral drug that can be delivered to patients more easily than intravenous therapy in both rural and urban settings. As such, PAG identified the oral route of administration, in which patients could easily use in the community, as an enabler. 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 place in therapy of VEN-OBI and overall sequencing of all treatments available for CLL/SLL. In particular, PAG would need information on the following aspects:

- Clinical scenarios justifying preferential use of VEN-OBI, acalabrutinib or IBR in high-risk [del17p] patients, and of VEN-OBI, acalabrutinib, or CHL-OBI in FCR-ineligible patients.
- Use of venetoclax with rituximab (VEN-RIT) (including subcutaneous formulation) for first-line treatment, given that this combination can be used in the RR CLL space.
- Sequencing of VEN-OBI, BEN-RIT, CHL-OBI, IBR, idelalisib plus rituximab, and acalabrutinib, from newly diagnosed CLL to relapsed/refractory CLL.

Since venetoclax treatment has a fixed duration, PAG seeks guidance on the appropriateness and timing of re-treatment with venetoclax (either VEN, VEN-OBI, or VEN-RIT) after prior VEN-OBI.

4.5 Companion Diagnostic Testing

Should there be a recommendation to use VEN-OBI differently in high-risk CLL populations, genetic markers (IGVH mutation, *TP53* mutation, 17p deletion) would need to be identified. Such tests are available in most but not all jurisdictions, and turnaround of results may vary across provinces. CD20 testing is routinely performed by flow cytometry.

4.6 Additional Information

None provided.

5 Summary of Registered Clinician Input

A total of two registered clinician inputs were provided: one from an individual oncologist from Ontario and one joint input from clinicians from Cancer Care Ontario.

Currently available treatments for patients with CLL who are ineligible for fludarabine-based regimens were stated to be CHL-OBI, bendamustine ± rituximab, or IBR monotherapy; the funding of these treatments was stated to vary across jurisdictions in Canada. Essentially all patients who are ineligible for fludarabine-based regimens, and who are currently eligible for CHL-OBI, were considered to be eligible for VEN-OBI by clinicians; most eligible patients were acknowledged to be those who are elderly and with significant comorbidities. Eligibility criteria from the CLL14 trial were considered reasonable for implementation in practice, and the use of a CIRS score of >6 or CrCl <70 mL/min to categorize "unfit" CLL patients was stated to be standard in clinical trials as well as in clinical practice.

Both clinician inputs acknowledged that trial data showed that treatment with VEN-OBI is superior to CHL-OBI and may replace CHL-OBI as frontline therapy for eligible patients. The individual clinician noted that IBR may place some patients at high risk for cardiac/bleeding complications, and that these patients who are high risk with 17p or TP53 mutations may benefit from treatment with VEN-OBI instead of IBR. However, the clinicians from the joint input expressed that VEN-OBI would likely not replace IBR for subgroups of patients with del17p, TP53, IGHV mutation status. While the CLL14 trial did not address the possibility of re-treatment with VEN-OBI or venetoclax plus rituximab, the individual clinician highlighted the MURANO trial which may suggest that patients can continue to respond to venetoclax as re-treatment was permitted in the trial. If VEN-OBI were to receive funding, IBR was suggested as a possible therapy in the second line or beyond. The individual clinician also suggested acalabrutinib as another treatment option for patients in the second line. Of note, acalabrutinib in a similar indication is currently under pCODR review. Upon relapse, idelalisib plus rituximab, chemoimmunotherapy or entry into a clinical trial were suggested as possible treatment options.

Currently, diagnostic testing is used to help guide treatment decisions by stratifying patients by disease risk; aside from this testing, no additional testing is expected to be required. However, it was noted that there is differential coverage for testing of mutation status across jurisdictions in Canada.

Please see below for details from the clinician inputs.

5.1 Current Treatments

The individual clinician input stated that patients with CLL who are currently not eligible for fludarabine-based therapies as front-line treatment may instead be treated with CHL-OBI, bendamustine ± rituximab, or IBR monotherapy. The clinician stated that IBR is funded for patients with high risk features; however, this treatment is not funded in all provinces. The clinician highlighted that the funding criteria for bendamustine ± rituximab, and IBR vary across the provinces; approximately half of patients are not eligible for fludarabine-based therapies and are receiving IBR monotherapy in Canada.

5.2 Eligible Patient Population

The individual clinician stated that patients with CLL are generally elderly with significant comorbidities. As most CLL patients are not candidates for fludarabine-based treatments, they would fit the patient population under consideration. The clinician also stated that using a CIRS score of >6 or CrCl <70 mL/min has become a standard way of categorizing the "unfit" CLL population in clinical trials which is also practically and clinically applicable. The individual clinician stated they would use VEN-OBI among patients with CLL who meet iwCLL criteria for treatment initiation and who meet study criteria for entry. Essentially, the clinician stated that any patient who would presently be a candidate for CHL-OBI would be a candidate for VEN-OBI.

The individual oncologist further elaborated that IBR, which is currently being prescribed to some patients, places patients at risk of cardiac and bleeding complications. Unmet need was highlighted for a subgroup of patients for whom novel frontline therapies are preferred, including those who are considered high risk with 17p or TP53 mutations who have cardiac comorbidities and/or require anticoagulation; these patients would be at particularly high risk of significant cardiac or bleeding toxicity with frontline IBR

monotherapy, and would benefit from treatment with VEN-OBI. The clinician also highlighted patients who are intolerant to frontline treatment with IBR as being another group of patients who would benefit from treatment with VEN-OBI. The clinician also stated that the time-limited nature of the VEN-OBI regimen is favourable to the regimen of IBR which is given indefinitely.

No additional information was provided from the joint clinician input.

5.3 Relevance to Clinical Practice

None of the clinicians providing input declared having experience with the combination of VEN-OBI, although the individual clinician stated having experience with using each therapy individually.

The individual clinician stated that given the PFS advantage of VEN-OBI over CHL-OBI, as observed in the CLL14 Trial, VEN-OBI should be applied in clinical practice and given to the majority of patients currently receiving CHL-OBI. The clinician stated that VEN-OBI is superior to CHL-OBI in terms of both PFS and CR rate. The safety and tolerability profile of VEN-OBI was considered to be comparable to CHL-OBI. the clinician stated that there were no clear contraindications to VEN-OBI treatment in patients who met the CLL14 study criteria. However, the clinician stated that a relative contraindication to current treatment would be patients on frontline IBR with intolerance, or with significant bleeding complications or cardiac risk, for whom VEN-OBI would be a preferred treatment.

No additional information was provided from the joint clinician input.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The individual clinician stated that, should VEN-OBI be funded in their jurisdiction in Ontario, they would use VEN-OBI as frontline therapy, and that due to its superior PFS and comparable toxicity, it would replace the current standard of care of CHL-OBI. In some cases, VEN-OBI was stated by the individual clinician to replace IBR, particularly for patients with high risk features. However, the joint clinician input stated that VEN-OBI would not replace IBR for some subgroups (e.g., cytogenetics/del17p, TP53, IGHV mutation status; see sub-section 5.4.1).

5.4.1 Is there any evidence to inform the preferred use of venetoclax plus obinutuzumab vs. other treatment options in all patients and in defined subgroups (e.g., cytogenetics/del17p, TP53, IGHV mutation status)?

Both clinician inputs stated that the CLL14 trial included high risk CLL patients, including unmutated IGHV status, 17p deletion, and TP53 mutation. Both clinician inputs acknowledged that these high-risk patients showed superior PFS with VEN-OBI compared to CHL-OBI. The joint clinician input stated that this subgroup of patients would receive IBR as frontline treatment in Ontario. Further, they stated that although VEN-OBI is superior to CHL-OBI, that it would not replace IBR in these subgroups of patients. The individual clinician stated that there is currently no RCT data to compare frontline ibrutinib to CHL-OBI.

5.4.2 What evidence is available to support re-treatment with VEN-OBI (or with VEN-RIT) after prior treatment with VEN-OBI, including information on the appropriate progression-free interval for re-treatment?

The joint clinician input highlighted that the CLL14 trial did not address re-treatment with VEN-OBI or VEN-RIT. However, the individual clinician pointed to the MURANO trial comparing VEN-RIT and BEN-RIT, which has been amended to allow for re-treatment in the relapsed/refractory setting. The individual clinician also stated that patients can continue to respond to venetoclax and highlighted a phase 1b trial showing that venetoclax re-treatment can result in continued response in patients who have responded and discontinued therapy.

5.4.3 Should VEN-OBI be selected as initial treatment, what are the treatment options in the 2nd/3rd line?

The individual clinician suggested that IBR may be given as a second line treatment. The joint clinician input agreed that patients who receive VEN-OBI in the first line may receive IBR in the second line and beyond. The individual clinician also suggested acalabrutinib, which is currently available only through patient support programs, as another option for second line treatment. For patients who relapse following a completed regimen of VEN-OBI, venetoclax may be re-initiated in select patients. The clinician suggested that the timing of response duration would need to be of clinical significance, likely at least one year since discontinuation; however, clear data on the retreatment response rate, efficacy, and optimal timing of retreatment is pending. Regarding data to support retreatment of patients, the clinician referred to the MURANO trial which allowed for retreatment of patients. Upon relapse, the clinician stated that patients may be given idelalisib plus rituximab, chemoimmunotherapy, or enter a clinical trial.

5.5 Companion Diagnostic Testing

Both clinician inputs agreed that, with the adoption of VEN-OBI, no additional companion testing will be required beyond testing to stratify patients by risk, which is already in place to guide decisions around the use of IBR as frontline therapy for high risk patients. The individual clinician from Ontario stated that standard FISH testing is currently already in place in their jurisdiction to test for 17p deletion status; however, this clinician stated that uniform access to TP53 mutation and IGHV mutational status testing does not exist in all jurisdictions across Canada.

5.5.1 Is there evidence on substituting rituximab (including the subcutaneous formulation) for obinutuzumab in the first-line combination treatment, given that VEN-RIT is used in the relapsed/refractory CLL space?

Both clinician inputs agreed that they would not use rituximab in place of obinutuzumab, and that the treatments should not be considered interchangeable. Both clinician inputs stated that evidence from clinical trial show that frontline CHL-OBI is superior to rituximab plus obinutuzumab; the joint clinician input stated that this evidence suggests a difference between the two antibodies.

5.7 Additional Information

No additional information provided.

6 Systematic Review

6.1 Objectives

The primary objective of this systematic review is to evaluate the efficacy and safety of VEN-OBI compared to standard care for the treatment of patients with previously untreated CLL who are fludarabine ineligible.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the PAG were identified while developing the review protocol and are outlined in Section 7.

- Summary and critical appraisal of sponsor-submitted NMA comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL
- Summary and critical appraisal of sponsor-submitted ITC and MAIC comparing VEN-OBI to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the CADTH Methods Team. Studies were chosen for inclusion in the review based on the criteria in Table 26. The literature search strategy and detailed methodology used by the CADTH Methods Team are provided in Appendix A.

Table 26: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of venetoclax in combination with obinutuzumab should be included	Patients with previously untreated CLL who are fludarabine ineligible Subgroups: – patients with molecular high-risk factors/status	Venetoclax plus obinutuzumab	– Chlorambucil plus obinutuzumab – Ibrutinib plus obinutuzumab – Ibrutinib plus rituximab – Ibrutinib monotherapy – Bendamustine plus rituximab – Chlorambucil plus rituximab – Chlorambucil plus ofatumumab – Chlorambucil monotherapy – Bendamustine monotherapy – Alemtuzumab plus rituximab – Acalabrutinib	– PFS (investigator assessed and IRC assessed) – MRD – CRR – ORR – OS – PRO – AEs (including specifically Grade 5 AEs and compliance)

AE = adverse event; CLL = chronic lymphocytic leukemia; CRR = complete response rate; IRC = independent review committee; MRD = minimal residual disease; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; RCT = randomized controlled trial

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

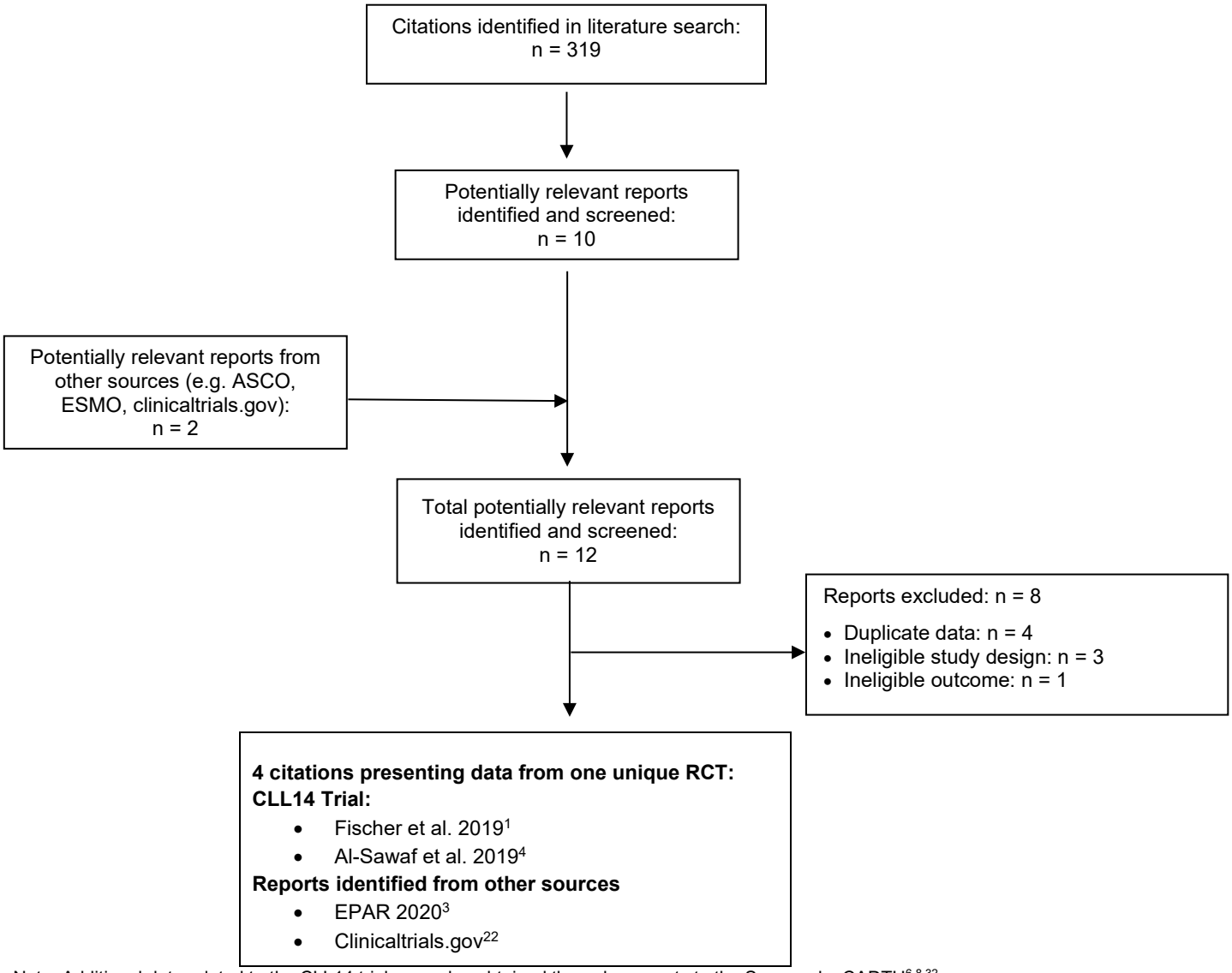
6.3 Results

6.3.1 Literature Search Results

Of the 12 potentially relevant reports identified, four studies were included in the pCODR systematic review[1,3,4,22] and eight studies were excluded (Figure 1). Studies were excluded because they reported duplicate data,[23-26] data from an ineligible study design,[27-29] or data for an ineligible outcome.[30]

No ongoing trials were identified that would have met the review protocol of the systematic review. Of note, CLL13 is a phase III, investigator-initiated clinical trial currently being conducted in a 'fit' patient population to support the registrational CLL14 trial.[31] Primary completion is estimated to occur in January 2023.

Figure 1: Flow Diagram for Study Selection



Note: Additional data related to the CLL14 trial were also obtained through requests to the Sponsor by CADTH[6-8,32]

6.3.2 Summary of Included Studies

One RCT, the CLL14 trial, met the selection criteria of the systematic review. Key characteristics of the CLL14 trial including study design, eligibility criteria, interventions, and trial outcomes are summarized in Table 27.

6.3.2.1 Detailed Trial Characteristics

Table 27: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
CLL14 **NCT02242942** **Characteristics:** Phase III, superiority, open-label, randomized (1:1), active-controlled • n randomized = 432 (VEN-OBI: n=216; CHL-OBI: n=216) • n treated = 426 (VEN-OBI: n=212; CHL-OBI: n=214) **Settings:** 196 sites in 21 countries (Argentina, Australia, Austria, Brazil, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Italy, Mexico, New Zealand, Poland, Romania, Russia, Spain, Switzerland, UK, and US) **Patient Enrolment Dates:** August 7, 2015 to August 4, 2016 **Primary Data cut-off:** August 17, 2018 **Database lock:** October 12, 2018 **Updated Data cut-off:** August 23, 2019 [7] **Final Analysis Date:** [redacted] 32 **Funding:** F. Hoffmann-La Roche and AbbVie	**Key Inclusion Criteria:** • Adults ≥ 18 years • Untreated CD20+ CLL[1a] that requires therapy according to iwCLL criteria • CIRS score >6 or CrCl <70mL/min • Adequate marrow function (independent of growth factor or transfusion support) within two weeks of screening and adequate liver function • Historical data to confirm a lymphocyte count of ≥5000 cells/μL at time of diagnosis if lymphocyte count was <5000 cells/μL at time of screening • Life expectancy >6 months **Key Exclusion Criteria:** • Transformation of CLL to aggressive non-Hodgkin lymphoma • CNS involvement • History of progressive multifocal leukoencephalopathy • Individual organ/system impairment score of 4 as assessed by CIRS (exception of eyes, ears, nose, and throat organ system) • Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia • Inadequate renal function (creatinine clearance <30 mL/min) • History of prior malignancy (except for the following if patients have recovered from the acute side effects incurred from the previous therapy: malignancies surgically treated with curative intent and with no known active disease present for ≥3 years before randomization; Adequately (or surgical where appropriate) treated nonmelanoma skin cancer, lentigo	**Intervention:** VEN-OBI (12 cycles of 28 days as follows): • OBI administered IV for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6 • VEN administered orally starting on day 22 of cycle 1 with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg then 400 mg daily for 1 week); thereafter, continuing at 400 mg daily until completion of cycle 12. **Comparator:** CHL-OBI (12 cycles of 28 days as follows): OBI administered IV for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8, and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6. CHL administered orally at 0.5 mg/kg of body weight on days 1	**Primary:** • PFS (investigator assessed) **Secondary:** • PFS (IRC assessed) • MRD • CRR • ORR • OS • PRO • DOR • EFS • Time to next anti-CLL treatment

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	maligna, cervical carcinoma in situ, or low-grade, early-stage, localized prostate without evidence of disease) • Grade 3/4 infections requiring IV treatment within two months of enrollment • History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products • Hypersensitivity to trial drugs or any of the excipients (e.g. trehalose) • Pregnant women and nursing mothers	and 15 of each cycle until completion of 12 cycles.	

(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)

CIRS = Cumulative Illness Rating Scale; CHL = chlorambucil; CHL-OBI = chlorambucil plus obinutuzumab; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CrCl = creatine clearance; CRR = complete response rate; DOR = duration of response; EFS = event-free survival; iwCLL = International Workshop on chronic lymphocytic leukemia; IRC = independent review committee; MRD = minimal residual disease; OBI = obinutuzumab; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; VEN = venetoclax; VEN-OBI = venetoclax plus obinutuzumab.

Note:

[a] The trial publication indicated the trial included patients who had CD20+ CLL, however the sponsor indicated that this was not part of the patient eligibility requirements

Data Sources: Fischer et al. 2019 [1], Clinical Study Report Supplementary[7], AbbVie Corporation Checkpoint Responses 2020[32]

a) Trial

CLL14 is an international, open-label, phase III, randomized, active-controlled superiority trial that evaluated the efficacy and safety of VEN-OBI compared to CHL-OBI for first-line treatment of CLL patients with co-existing conditions.[1] The trial was conducted at 196 sites across 21 countries, which included thirteen patients from Canada (refer to Table 27 for a list of participating studies).

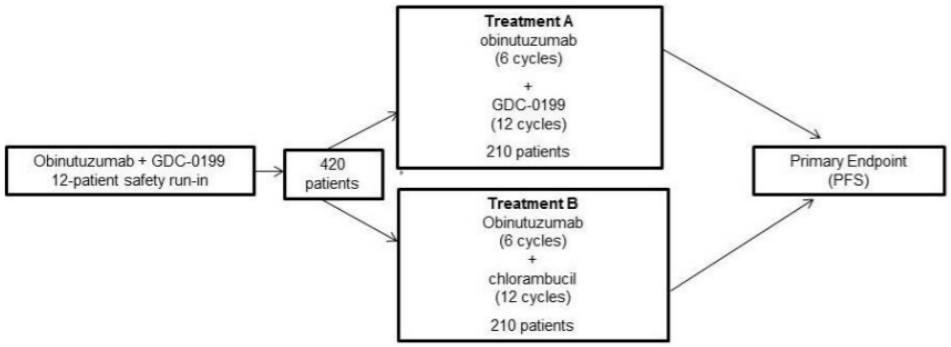
Trial Design

Screening, Eligibility Criteria, and Randomization

The CLL14 study design is depicted in Figure 2.[3] The trial was conducted following a safety run-in population with 13 patients receiving VEN-OBI (these patients were not included as part of the trial analyses).[3] After the twelfth patient had completed the third cycle, the randomized portion of the trial was initiated. Key inclusion and exclusion criteria for the trial are outlined in Table 27.[1] In brief, patients must have had previously untreated CLL that required treatment and either a CIRS score[33] >6 or a CrCl <70 mL/min. The CIRS score was determined based on the guidelines from the modified CIRS; a cumulative score was calculated from scores rated on a scale from 0 to 4 to assess disease burden categorized by organ system. The CIRS score is correlated with mortality, rate and duration of hospitalization, need for medication, functional impairment, and psychological status.[2] A CIRS score of six or higher is reached when multiple coexisting medical conditions are present; CLL patients with coexisting medical conditions are reported to have inferior outcomes compared to CLL patients who do not have coexisting conditions.

Eligible patients were randomized in a 1:1 ratio by an interactive voice/web-based system (based on a computer-generated randomization schedule) to receive either VEN-OBI or CHL-OBI.[1,2] Randomization was balanced using a block size of six and patients were stratified according to Binet stage (A, B, or C) and geographic region (US/Canada/Central America, Australia/New Zealand, Western Europe, Central/Eastern Europe, or Latin America).

Figure 2: CLL14 Study Design Flow Chart



Data Source: EPAR 2020[3]

The trial was open-label; however, the sponsor and an independent review committee (IRC) were blinded to the treatment arms.[2] An Independent Data Monitoring Center (iDMC) reviewed unblinded safety data by treatment arm for the safety reviews and the planned interim analysis of efficacy. The sponsor and study team did not have access to the unblinded information reviewed by the iDMC.

Patients were screened with the following baseline assessments: immunophenotyping of circulating lymphocytes, central analysis of genomic aberrations with fluorescence in situ hybridization, mutational analysis of the IGHV and TP53 by DNA sequencing, and evaluation of lymph-node size by physical assessment and CT scanning or MRI.[1] Baseline tumour assessments were conducted a maximum of four weeks prior to randomization. In patients with signs of rapidly progressing disease at screening, a CT scan was required within four weeks prior to randomization. Patients were also assessed at baseline for risk of tumor lysis syndrome (TLS) and were assigned to a TLS risk category (low, medium, or high risk) according to the risk criteria listed below. TLS risk assessments were made based on measurement of nodal disease burden based on radiological assessments during screening. Different monitoring/prophylaxis guidance was followed depending on the assigned risk category (further described in *Treatment Modifications* section below).

- Low TLS risk - All measurable lymph nodes with the largest diameter less than 5 cm and less than $25x10^9$/L absolute lymphocyte count.
- Medium TLS risk - Any measurable lymph nodes with the largest diameter equal to or greater than 5 cm but less than 10 cm OR equal to or greater than $25x10^9$/L absolute lymphocyte count.
- High TLS risk - Any measurable lymph nodes with the largest diameter equal to or greater than 10 cm OR both an equal to or greater than $25x10^9$/L absolute lymphocyte count AND any measurable lymph nodes with the largest diameter equal to or greater than 5 cm but less than 10 cm.

Study Assessments

Disease assessments were conducted at baseline and during the trial on day one of Cycles 4, 7, and 9.[1] The end of treatment assessment was performed three months (no earlier than two months) after the last study treatment. After treatment completion, patients were assessed for progression and safety every three months (± 14 days) for two years; thereafter, patients were assessed every six months (± one month) for five years.[1,2] If disease progression was suspected before a scheduled visit, an additional assessment could be performed.[1]

Treatment response during the treatment period was determined by physical examination and laboratory tests.[1] The end of treatment response assessment was based on full iwCLL guidelines as imaging and bone-marrow aspirate were available at this assessment time point. When disease progression was detected by physical examination in the absence of any objective hematological progression, CT scans of the nodes with disease involvement were performed. Patients with a treatment response confirmed by

laboratory and physical examination and by CT scan also had a bone marrow aspirate and biopsy performed at the three-month post-treatment assessment.

Minimal residual disease (MRD) was analyzed centrally according to international guidelines with the use of an allele-specific oligonucleotide polymerase-chain-reaction assay.[1] MRD was assessed in peripheral-blood at baseline and at cycles 7, 9, and 12, then, following treatment completion, every three months. In patients with a treatment response, MRD was assessed in bone marrow at Cycle 9 and three months after completion of treatment.

Patients could also be reassessed throughout treatment for the risk of TLS and could be reassigned to a lower risk category if the higher risk criteria were no longer met. If the patient's risk category was lowered, the prophylaxis guidance for the lower risk group was followed.[1] Patients classified at baseline as high risk due to the presence of a measurable lymph node with the largest diameter of ≥10 cm could not be reassessed for TLS risk and were continuously followed by the prophylaxis plan for the high-risk category. Patients who developed signs or symptoms of TLS, regardless of the risk group, may have received additional monitoring at subsequent visits at the investigator's discretion.

Study Endpoints and Statistical Analyses

Response Definitions:

Response was assessed according to iwCLL guidelines and were defined as follows:[1]

- **Complete response (CR)** – all of the following criteria must be met, as assessed no earlier than two months after completion of therapy: peripheral blood lymphocytes <4x10^9/L; absence of significant lymphadenopathy (nodes ≤15mm in longest diameter or any extra nodal disease); no hepatomegaly; no splenomegaly; absence of disease or constitutional symptoms; blood counts with levels of neutrophils >1.5x10^9/L, platelets >100x10^9/L, and hemoglobin >110g/L; bone marrow at least normocellular for age (<30% of nucleated cells being lymphocytes); and lymphoid nodules should be absent.
- **Complete response and incomplete bone marrow recovery (CRi)** – fulfilling all criteria for a CR, but have persistent cytopenia, anemia, thrombocytopenia, or neutropenia.
- **Partial response (PR)** – the following criteria must be met for at least two months following end of treatment: ≥50% reduction in peripheral blood lymphocyte count from the pre-treatment value; and either ≥50% reduction in lymphadenopathy, no increase in any node, and no new enlarged lymph nodes; or ≥50% reduction of liver enlargement if enlarged at baseline; or ≥50% reduction of spleen enlargement if enlarged at baseline; and at least one of the following: neutrophils >1.5x10^9/L or ≥50% increase of pre-treatment value; platelets >100x10^9/L or ≥50% increase of pre-treatment value; hemoglobin >110g/L or ≥50% increase of pre-treatment value.
- **Progressive disease (PD)** – at least one of the following criteria: ≥50% increase in the absolute number of circulating lymphocytes to at least 5x10^9/L; appearance of new palpable lymph nodes or any extra nodal lesions; ≥50% increase in the longest diameter of any lymphadenopathy classified as clinically significant at baseline (any lesion >10mm); ≥50% increase in enlargement of the liver and/or spleen; transformation to a more aggressive histology; after treatment, the progression of any cytopenia unrelated to autoimmune cytopenia.
- **Stable disease (SD)** – patients not achieving a CR or PR or who do not have PD; additionally, patients without CT evaluation who would have otherwise met the criteria for CR or PR.

Efficacy Outcomes

Efficacy outcomes were analyzed in the intention-to-treat (ITT) population.[3] Key efficacy outcomes are listed below.

Primary efficacy endpoint:[1,3]

- PFS (investigator-assessed) – time from randomization to the first occurrence of progression or relapse (determined from iwCLL guidelines) or death from any cause for patients who did not progress, relapse, or die at the timing of analysis. PFS was censored on the date of the last disease assessment; if no disease assessments were performed after the baseline visit, PFS was censored at the time of randomization plus one day.

Key secondary efficacy outcomes (in the following hierarchical order to adjust for multiple testing):[1,3]

- PFS (IRC-assessed)
- MRD rate in bone marrow three months after treatment completion
- CR rate (investigator-assessed) three months after treatment completion
- MRD rate in peripheral blood three months after treatment completion
- MRD rate in bone marrow of patients with a CR three months after treatment completion
- MRD rate in peripheral blood of patients with a CR three months after treatment completion
- Overall response rate (ORR) (investigator-assessed) three months after treatment completion
- Overall survival (OS) – time from randomization to death due to any cause; patients alive at time of analysis (including those lost to follow-up) were censored at the date they were last known to be alive

Additionally, the following other secondary outcomes were analyzed; however, they were not included as part of the hierarchical testing procedure:[1,3]

- Duration of response (DOR) – time from first occurrence of either CR, CRi, or PR (all investigator-assessed) to the first occurrence of progression, relapse, or death from any cause. For patients without an event at the time of analysis, DOR was censored on the date of the last disease assessment.
- Event-free survival (EFS) – time from randomization to first occurrence of progression, relapse, death from any cause, or start of new anti-leukemic therapy. For patients without an event at the time of analysis, event-free survival was censored on the date of the last disease assessment.
- Time to new anti-leukemic treatment – time from randomization to first start of new anti-leukemic therapy. For patients without an event at the time of analysis, time to new anti-leukemic treatment was censored on the date of the last disease assessment or the date of death if they have not yet started a new anti-leukemic treatment at time of analysis.

To control for multiplicity for multiple testing, the key secondary efficacy endpoints were tested in the order listed above (i.e. starting with PFS [IRC-assessed] and ending with OS) according to the Fallback Procedure[34] in which the α is split for the endpoints in the pre-specified order.[1] P-values were not reported for the endpoints that were not listed in the hierarchical testing procedure.

Analyses for the time-to-event outcomes were performed using two-sided log-rank test at 0.05 significance level.[1] Analyses were stratified by Binet stage and geographical region. Median PFS and 95% confidence intervals (CIs) were estimated using the Brookmeyer-Crowley method with the Kaplan-Meier (KM) survival curves also presented for visual inspection. Treatment effects were expressed as the HR with 95% CIs estimated through a Cox proportional hazards analysis stratified by Binet stage and geographical region.

Analyses for the response rate outcomes were compared using the Cochran–Mantel–Haenszel tests, stratified by Binet stage and geographical region.[1] Rates and 95% CI were reported for each treatment group. For the response rate endpoints, patients without an evaluable response at the three months post-treatment completion study assessment were counted as 'non-responder'. For the MRD rate endpoints, patients without an evaluable sample at the three months post-treatment completion study assessment were counted as 'non-negative'.

Subgroup Analyses

The following pre-specified subgroups analyses were conducted for investigator-assessed PFS and MRD negativity in peripheral blood three months after treatment completion.[1] The subgroup analyses were exploratory; therefore, p-values were not reported.

- Binet stage at screening (A, B, C)
- Age (<75 years, ≥75 years)
- Gender (male, female)
- Cytogenetic factors (deletion 17p, 11q and 13q, and trisomy 12)
- *TP53* status (deletion and/or mutation, none)
- IGVH mutational status (unmutated, mutated)

Sensitivity Analyses

The following sensitivity analyses were planned for the primary outcome of PFS (both investigator and IRC-assessed) to explore the potential impact of differences in modelling or censoring:[1,2]

- Analysis with a unstratified log-rank test
- Analysis with censoring at initiation of non-protocol specified anti-CLL therapy before meeting disease progression or relapse criteria (to assess potential confounding of treatment effect estimates by subsequent therapy); stopping one component only of the study treatment was not considered as meeting criteria for censoring
- Analysis with censoring of death or disease progression after more than one missed response assessment at the date of last adequate response assessment

Safety Outcomes

All-cause mortality was reported in the ITT population,[22] and all other safety outcomes were assessed in the safety population, defined as all patients who had received at least one dose of the study drug.[1] The following outcomes were analyzed in the safety population according to the study drug actually consumed by the patient (note: patients randomized to VEN-OBI who received only Obi treatment were analyzed with the VEN-OBI group rather than the CHL-OBI group—i.e. patients were analyzed under the treatment group to which they were randomized for safety analyses of patients who only received obinutuzumab):[2,35]

- Nature, frequency, and severity of AEs and serious adverse events (SAEs)
- Changed in vital signs, physical findings, and clinical laboratory results
- Lymphocyte immunophenotyping and incidence of human-anti-human antibodies
- Premature withdrawals

AE of any grade were reported up until 28 days after the last dose of any study treatment.[2] Grade 3/4 AEs and major infections were reported for up to six months and two years after the last dose of study drug, respectively or until the next anti-leukemia treatment. SAEs and secondary malignancies were reported indefinitely after study drug completion.

Patient Reported Outcomes

PROs were analyzed in the ITT population for all randomized patients who completed baseline and at least one post-baseline assessment for the PRO scales.[2] Paper PRO questionnaires were administered at each treatment cycle and every three months during the follow-up period.[4]

To compare disease and treatment-related symptoms between study groups, the MDASI-CLL was used.[2] Scores in the inventory range from 0 to 10 with lower scores indicating lower symptom severity or interference.[4] The EORTC QLQ-C30 was used to evaluate changes in physical functioning, role functioning, and global health status quality of life (GHS-QoL) and to compare differences between the treatment groups. Scores for this scale range from 0 to 100: higher scores for the functioning scales and global health status indicate a better level of functioning; alternatively, higher scores on the symptom and single-item scales indicate a higher level of symptoms. All PRO scores were reported as the mean ± standard deviation for all patients per study group. Clinically relevant differences were based on the minimal important differences (MIDs) derived from the Cocks et al., 2012[5] for the EORTC QLQ-C30.[6]

Sample Size

The required sample size was calculated to provide a power of 80% to determine statistical superiority for the primary endpoint (investigator-assessed PFS) using two-side log-rank test at 0.05 level of significance.[1] A targeted sample size of 170 PFS events required to calculate the final analysis was based on the following assumptions:

- Median PFS for CHL-OBI being 27 months
- Power to detect HR of 0.65 for the comparison of VEN-OBI versus CHL-OBI, with median PFS for VEN-OBI increased to 41.5 months
- Exponential distribution of PFS
- Annual dropout rate of 10%

Interim Analyses

The sample size was also calculated to account for an interim analysis for the efficacy outcomes after 75% of PFS events, using a stopping boundary according to the γ family error spending function with parameter γ = 9.21.[1] Following a protocol amendment, the interim analysis was subsequently changed to be performed after a minimum of 65% of events (110 events) had occurred.

While the final analysis for PFS was designed to occur after 170 IRC-assessed PFS events, the interim analysis that occurred after the 110 events (data cut-off: August 17, 2018) crossed the pre-specified boundary for the primary endpoint ($\alpha = 0.0019$); therefore, this analysis was considered the primary analysis.[8] Although it was stated that no further PFS analyses would be performed,[8] an updated data analysis was conducted on August 23, 2019.[7] Final OS analysis will be conducted at the end of the study.[8]

Protocol Amendments

A total of six protocol amendments occurred, which have been summarized in Table 28.[2]

Table 28: Summary of Amendments in the CLL14 trial

Amendment Number (Date)	Amendment summary
Amendment 1 (October 21, 2014)	– Correction of trial inclusion criteria; namely, the removal of criteria related to previously treated patients that were incorrectly listed in the original protocol – Clarification of the AE reporting period
Amendment 2 (November 7, 2014)	– Modification of the time window for contraception/abstinence after final dose of study treatment to align with the product information for obinutuzumab
Amendment 3 (May 21, 2015)	– Correction/modification of TLS assessments post-Ven and post-CHL administration – Correction to exclusion criteria regarding immunization – Modification to the collection of AEs and SAEs during the study and follow-up period – Update of contraception and pregnancy testing requirements to comply with International Conference on Harmonisation and health authority guidance
Amendment 4 (November 2, 2015)	– Inclusion of new safety data for obinutuzumab relating to patients with history of gastrointestinal bleeding – Modification of moving cytogenetic sampling to screening visits to allow investigators to decide prior to randomization whether alternative treatment should be considered (particularly for patients with 17p deletion and/or TP53 mutation) – Clarification for eligibility criteria regarding previous infections – Clarification for eligibility criteria for patients who have history of deep venous thrombosis or pulmonary embolism that these patients do not have to discontinue study treatment if they do not revert to >Grade 1
Amendment 5 (March 29, 2017)	– Modification of interim analysis timing to mitigate the potential for delay in study readout – PFS analysis assumptions modified with a change in alpha-spending at the interim analysis; namely, the 2-sided significance level was modified to 0.005 with 75% information fraction, which corresponds to a gamma function of 9.21 – Clarification that all response assessments to be made according to iwCLL criteria

Amendment Number (Date)	Amendment summary
	– Clarification of response criteria for stable disease – Clarification of post-treatment follow-up visits have to specify that bone marrow aspirate and biopsy assessments are required at follow-up Month 3 for patients with CR Cri, or PR confirm response and for MRD assessment – Modification to the Ven administration instructions regarding food requirements to align with the Investigator's Brochure
Amendment 6 (February 12, 2018)	– Addition of the option to add an earlier interim efficacy analysis to mitigate the potential for delay in study readout – Extension of the blood sample collection for MRD duration from 18 months after treatment to five years after last patient enrollment – Addition of CR as a secondary endpoint to explore the potential depth of response – Clarification of time windows for study assessments; namely, all assessments during the treatment period and follow-up day 28 visit must be performed within seven days of the scheduled visit unless otherwise specified

AE = adverse event; CHL = chlorambucil; CLL = chronic lymphocytic leukemia; CR = complete response; CRi = complete response and incomplete bone marrow recovery; iwCLL = International Workshop on chronic lymphocytic leukemia; IRC = independent review committee; MRD = minimal residual disease; Obi = obinutuzumab; PFS = progression-free survival; PR = partial response; SAE = serious adverse event; TLS = tumour lysis syndrome; Ven = venetoclax.

Data Source: Clinical Study Protocol[2]

Funding

The trial was sponsored and funded by F. Hoffmann-La Roche Ltd. (Roche) and AbbVie Inc.[1] The sponsors and the German CLL Study Group designed the study. Study sites in Germany were considered German CLL Study Group sites and were selected based on feasibility criteria of both the German CLL Study Group and Roche. Feasibility criteria established by Roche for sites external to Germany were used for site selection and these sites were reviewed by the German CLL Study Group. The selected sites were contracted either directly through Roche or through a clinical research organization (Covance Inc.). Data analyses were performed by the sponsor in conjunction with the German CLL Study Group according to the statistical analysis plan.

b) Populations

Demographic Characteristics

The baseline demographic characteristics of the CLL14 trial population are summarized in Table 30.[1] A total of 432 patients were randomly assigned to receive either VEN-OBI (n=216) or CHL-OBI (n=216). Overall, the median age was 72 years (range: 41 to 89), with 33.3% and 36.1% of patients ≥75 years in the VEN-OBI group in the CHL-OBI group, respectively. Most patients were male (67.6% in VEN-OBI group versus 66.2% in CHL-OBI group), and most were categorized as 'Intermediate' risk of TLS (64.4% in VEN-OBI group versus 68.1% in CHL-OBI group). The median CIRS score for all trial participants was 8 (range: 0 to 28). Median CIRS scores were slightly higher in the VEN-OBI group compared to the CHL-OBI group (9 versus 8), with 86.1% and 81.9% of patients having a CIRS score of >6 in the VEN-OBI group in the CHL-OBI group, respectively.[3] The proportion of patients with CrCl <70ml/min was slightly higher in the VEN-OBI group compared to the CHL-OBI group (59.5% versus 55.4%).

Disease Characteristics

Disease characteristics of the CLL14 trial population are summarized in Table 29.[1] The percentage of patients in the cytogenetic subgroups were balanced for the VEN-OBI group compared to the CHL-OBI group: deletion in 17p – 8.5% versus 7.3%, deletion in

11q – 18.0% versus 19.7%, trisomy 12 – 18.0% versus 20.7%, no abnormalities – 25.0% versus 21.8%, and deletion in 13q alone – 30.5% versus 30.6%. Most patients in both groups had unmutated IGHV (VEN-OBI – 60.5%; CHL-OBI – 59.1%), and unmutated TP53 (VEN-OBI – 88.9%; CHL-OBI – 91.7%).

Table 29: Demographic and Disease Characteristics in the CLL14 trial

Characteristic	Venetoclax–Obinutuzumab (N=216)	Chlorambucil–Obinutuzumab (N=216)
Age ≥75 yr — no. (%)	72 (33.3)	78 (36.1)
Male sex — no. (%)	146 (67.6)	143 (66.2)
Binet stage — no. (%)†		
A	46 (21.3)	44 (20.4)
B	77 (35.6)	80 (37.0)
C	93 (43.1)	92 (42.6)
Tumor lysis syndrome risk category — no. (%)		
Low	29 (13.4)	26 (12.0)
Intermediate	139 (64.4)	147 (68.1)
High	48 (22.2)	43 (19.9)
Total CIRS score >6 — no. (%)‡	186 (86.1)	177 (81.9)
Calculated creatinine clearance <70 ml/min — no./total no. (%)	128/215 (59.5)	118/213 (55.4)
Cytogenetic subgroup — no./total no. (%)§		
Deletion in 17p	17/200 (8.5)	14/193 (7.3)
Deletion in 11q	36/200 (18.0)	38/193 (19.7)
Trisomy 12	36/200 (18.0)	40/193 (20.7)
No abnormalities	50/200 (25.0)	42/193 (21.8)
Deletion in 13q alone	61/200 (30.5)	59/193 (30.6)
IGHV mutational status — no./total no. (%)		
Mutated	76/200 (38.0)	83/208 (39.9)
Unmutated	121/200 (60.5)	123/208 (59.1)
Could not be evaluated	3/200 (1.5)	2/208 (1.0)
TP53 mutational status — no./total no. (%)		
Mutated	19/171 (11.1)	13/157 (8.3)
Unmutated	152/171 (88.9)	144/157 (91.7)

Notes:
† Binet stages indicate the degree of advancement of chronic lymphocytic leukemia and are based on organ and lymph-node involvement, hemoglobin levels, and platelet counts.
‡ Scores on the Cumulative Illness Rating Scale (CIRS) range from 0 to 56, with higher scores indicating more impaired function of organ systems.
§ Cytogenetic subgroups were determined according to the hierarchical model of Döhner at al.[36]

From New England Journal of Medicine, Venetoclax and obinutuzumab in patients with CLL and coexisting conditions, volume 380, number 23, page no.2229. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

c) Intervention

Treatment

Patients assigned to VEN-OBI were treated for 12 cycles of 28 days as described below.[1] No crossover was permitted between treatment groups. Patients were to permanently discontinue treatment if they experienced pregnancy, patient non-compliance, disease progression, Grade 4 infusion-related reactions, or Grade 4 TLS.[2]

- OBI administered IV for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6.
- VEN administered orally and daily starting on day 22 of cycle 1, with a 5-week dose ramp-up (1 week each of 20, 50, 100, and 200 mg, then 400 mg daily for 1 week); thereafter, continuing at 400 mg daily until completion of cycle 12.

Patients assigned to CHL-OBI were treated for 12 cycles of 28 days as follows:

- OBI administered IV for six cycles starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, and subsequently 1000 mg on day 1 of cycles 2 through 6.
- CHL administered orally at 0.5 mg/kg of body weight on days 1 and 15 of each cycle until completion of 12 cycles.

Treatment Modification

A summary of TLS prophylaxis for venetoclax and monitoring measures are listed in Table 30.[1] Modifications for prophylactic medication, hospitalization, hydration, and laboratory assessments were made for patients depending on their TLS risk category and on the dose level of day 1.

Table 30: Summary of TLS Prophylaxis for Venetoclax and Monitoring Measures in the CLL14 Trial

TLS risk category	Day 1 of dose level	Prophylaxis medication	Hospita-lization	Hydration [a]	Laboratory assessments [b,e]
Low	20, 50, 100, 200, 400 mg	Oral uric acid reducer (e.g. allopurinol 300 mg/day) beginning ≥72 hr before dose and continued until end of ramp-up period with venetoclax is completed (C3D1)	No	Oral hydration of 1.5-2 L/day beginning ≥48 hr before dose and continuing for ≥24 hr after dose.	▪ Hematology and chemistry samples will be taken pre-dose and 8 and 24 hr after dosing. ▪ Pre-dose is defined as up to 4 hr before venetoclax administration, and results must be reviewed before dosing; if it is not possible to review results from a sample taken up to 4 hr pre-dose, then it is acceptable to take a pre-dose hematology and chemistry sample within 24 hr before dosing. The results of these samples must be reviewed before dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration before dosing are not required to be reviewed before dose administration. However, these pre-dose (0–4 hr before dosing) laboratory samples should still be drawn, and will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hr postdosing time points. ▪ The 8-hr chemistry results must be reviewed before the patient leaves the outpatient clinic that day. ▪ The investigator or sub-investigator must review the 24-hr laboratory results before dosing on the next day.
Medium	20 and 50 mg	Oral uric acid reducer (e.g. allopurinol 300 mg/day) beginning ≥72 hr before dose and	No [c,d]	Oral hydration of 1.5-2 L/day beginning ≥48 hr before dose and	▪ Hematology and chemistry samples will be taken pre-dose and at 8 and 24 hr postdosing time points. ▪ Pre-dose is defined as up to 4 hr before venetoclax administration, and results must be reviewed before dosing; if

TLS risk category	Day 1 of dose level	Prophylaxis medication	Hospitalization	Hydration [a]	Laboratory assessments [b,e]
		continued until the end of the ramp-up period with venetoclax is completed (C3D1).		continuing for ≥24 hr after dose. In addition to oral hydration, IV hydration (1.5-2 L) will be given in the outpatient setting during the clinic stay.	it is not possible to review results from a sample taken up to 4 hr pre-dose, then it is acceptable to take a pre-dose hematology and chemistry sample within 24 hr before dosing. The results of these samples must be reviewed before dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration before dosing are not required to be reviewed before dose administration. However, these pre-dose (0–4 hr before dosing) laboratory samples should still be drawn, and will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hr postdosing time points. ▪ The 8-hr chemistry results must be reviewed before the patient leaves the outpatient clinic that day. ▪ The investigator or sub-investigator must review the 24-hr laboratory results before dosing on the next day.
	100, 200, 400 mg	Continue oral uric acid reducer as above.		Oral hydration of 1.5-2 L/day beginning ≥48 hr before dose and continuing for ≥24 hr after dose.	
High	20 and 50 mg	Oral uric acid reducer (e.g. allopurinol 300 mg/day) beginning ≥72 hr before dose and continued until the first week of combination therapy with venetoclax is completed. Rasburicase must be administered per regional standards/ institutional guidelines as prophylaxis before first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above local laboratory ULN or the Howard et al. (2011) threshold of 8 mg/dL (475.8 µmol/L)). For patients with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase deficiency), the TLS risk-mitigation plan must be reviewed with the Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed.	Yes [d]	Oral hydration of 1.5-2 L/day beginning ≥48 hr before dose and continuing for ≥24 hr after dose. Upon hospital admission, IV hydration should be started with a target of ~2–3 L/day or as clinically appropriate.	▪ Hematology and chemistry samples will be taken pre-dose and 8, 12, and 24 hr after dosing. ▪ Pre-dose is defined as up to 4 hr before venetoclax administration, and results must be reviewed before dosing; if it is not possible to review results from a sample taken up to 4 hr pre-dose, then it is acceptable to take a pre-dose hematology and chemistry sample within 24 hr before dosing. The results of these samples must be reviewed before dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration before dosing are not required to be reviewed before dose administration. However, these pre-dose (0–4 hr before dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS. ▪ The investigator or sub-investigator must review the 24-hr laboratory results before dosing on the next day.
	100, 200, 400 mg	Continue oral uric acid reducer as above.	No [c,d]	Oral hydration of 1.5–2 L/day beginning ≥48 hr before dose and	▪ Patients who are not hospitalized at these time points will have hematology and chemistry samples taken pre-dose and 8 and 24 hr after dosing.

TLS risk category	Day 1 of dose level	Prophylaxis medication	Hospita-lization	Hydration [a]	Laboratory assessments [b,e]
				continuing for ≥24 hr after dose. In addition to oral hydration, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay.	▪ Pre-dose is defined as up to 4 hr before venetoclax administration, and results must be reviewed before dosing; if it is not possible to review results from a sample taken up to 4 hr pre-dose, then it is acceptable to take a pre-dose hematology and chemistry sample within 24 hr before dosing. The results of these samples must be reviewed before dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration before dosing are not required to be reviewed before dose administration. However, these pre-dose (0–4 hr before dosing) laboratory samples should still be drawn and will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS. ▪ The investigator or sub-investigator must review the 24-hr laboratory results before dosing on the next day. ▪ Patients who are hospitalized at these time points will have chemistry and hematology samples obtained pre-dose, 8, 12, and 24 hr post-dose. These results must be reviewed promptly by the investigator or sub-investigator. The 24-hr post-dose laboratory results must be reviewed by the investigator or sub-investigator before the patient leaves the hospital or receives any additional study drug.

C = cycle; CrCl = creatinine clearance; D = day; TLS = tumor lysis syndrome; ULN = upper limit of normal.

Notes:

[a] For patients unable to maintain oral hydration at 1.5-2 L/day starting ≥48 hr before the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended (unless being hospitalized) to ensure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

[b] For laboratory samples drawn on days of study treatment, "pre-dose" laboratory samples should be drawn within 0-4 hr before the dose. Other laboratory samples occurring on the same day should be obtained within a ±15-min window of any exact scheduled time. Any laboratory tests occurring at time intervals ≥24 hr after dose should be obtained within a ±2-hr window of the scheduled time. If it is not possible to review a sample taken up to 4 hr pre-dose, then it is acceptable to take a pre-dose hematology and chemistry sample within 24 hr before dosing. The results of these samples must be reviewed before dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and chemistry samples drawn on the day of venetoclax administration before dosing are not required to be reviewed before dose administration. However, these pre-dose (0-4 hr before dosing) laboratory samples should still be drawn, and these will serve a baseline for later laboratory values when assessing for laboratory evidence of TLS.

[c] Patients with CrCl <80 mL/min and/or who have a higher tumour burden (defined per the discretion of the investigator) may be handled as TLS high-risk patients. Currently, limited clinical experience has been gained with venetoclax in patients with CrCl 30–50 mL/min. Therefore, these patients should receive additional consideration by the investigator with regard to their management, including the decision on whether to administer IV hydration and to hospitalize the patient to facilitate monitoring and expedite response to electrolyte changes at initial dosing as well as at each first dose during the ramp-up period.

[d] Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

[e] Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose withheld until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per protocol. At any time during the ramp-up period, if venetoclax was withheld for ≤7 days, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). The dose must be resumed at one lower dose level if dose was withheld >7 days, with the exception of initial dose level of 20 mg (400 mg → 200 mg, 200mg →100 mg, 100 mg →50 mg, 50 mg→20 mg).

From New England Journal of Medicine, Venetoclax and obinutuzumab in patients with CLL and coexisting conditions, volume 380, number 23, Supplementary material: appendix, page no.15. Copyright ©2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society[1]

Drug Exposure

Patient exposure to study drug was reported in the safety population (defined as all randomized patients who received at least one dose of study treatment (Ven, O, and/or CHL), with patients analyzed according to the treatment they actually received).[2]

Of the 198 patients who started the single agent period for VEN, 166 completed treatment. Median duration of exposure was 315 days (10.5 months) from first VEN dose. Median dose intensity for Ven was 97.5% (range: 14% to 100%). Of the 203 patients who started Ven, 189 reached the target dose of 400mg.[8] The target dose was not reached in the remaining 14 patients for various reasons, including AEs leading to withdrawal and withdrawal of consent to participate in the study. After reaching the target dose, 88 patients (44.3%) had a dose modification (interruption or reduction), of which 81 patients (39.9%) had an AE which led to the dose modification. Fifteen patients had a dose reduction to 50 mg. Of the 85 patients who had a dose reduction at the 400 mg dose, 14 (16.5) withdrew from treatment, 29 (34.1%) returned to the 400 mg dose, and 42 (49.4) stayed at the reduced level. For the patients who reached the 400 mg dose and subsequently had a dose reduction, the median duration treatment below 400 mg was 77 days.

The median dose intensity for CHL was 95.4% (range: 4% to 111%). Median number of cycles was 12.00 cycles (range: 4% to 111%).[8] Dose modifications (interruption or reduction) for CHL occurred in 57 (26.9%) of patients, of which 29 patients (13.7%) had an AE which led to the dose modification.

In patients from both study groups, median dose intensity for OBI was 100% (range 0 -111%), median number of cycles was 6.00 (range: 1.0 to 6.0), and the median cumulative dose was 8000.0 (range in VEN-OBI group: 31 to 8900 versus range in CHL-OBI group: 25 to 8900).[8] The percentage of patients with a dose modification for OBI was lower in the VEN-OBI group compared to the CHL-OBI group (33.5% versus 43.0%). Dose modifications resulting from AEs occurred in 69 patients (32.5%) in the VEN-OBI group, compared to 89 (41.6%) in the CHL-OBI group. Of the 203 patients who received both VEN and OBI in the VEN-OBI group, 159 completed treatment.[3]

d) Patient Disposition

The disposition of patients through the CLL14 trial are summarized in Table 31. Of the 514 patients who were assessed for trial eligibility, 432 underwent randomization (216 patients randomized to each group).[1] Patients were excluded prior to randomization for the following reasons: 51 – did not meet inclusion criteria or met exclusion criteria, 14 – withdrew consent, 11 – had wrong diagnosis, and 6 – did not have treatment indication. All patients randomized to each group were included in the efficacy analysis. In the VEN-OBI group, four patients did not receive treatment (three had a worsening medical condition leading to ineligibility and one was withdrawn by investigator) and were excluded from the safety analysis.[1]

At the time of the primary data cut-off on August 17, 2018, a similar proportion of patients between the two groups had received treatment (VEN-OBI: 98.1% versus CHL-OBI: 99.1%).[1] Additionally, a similar proportion of patients between the VEN-OBI group versus the CHL-OBI group had completed treatment (76.4% versus 74.1%), discontinued at least one treatment component (21.8% versus 25.0%), been lost to follow-up (13.9% versus 12.0%), and/or remained in the trial at the data cut-off (86.1% versus 88.0%).At the time of the updated analysis, 177 (81.9%) patients in the VEN-OBI group, and 178 (82.4%) patients in the CHL-OBI group remained in the post-treatment follow-up.[7]

Table 31: Participant Disposition in CLL14 Trial at the Primary Data Cut-Off

Patient Disposition, n (%)	VEN-OBI	CHL-OBI
Patients randomized	216 (100.0)	216 (100.0)
Did not receive treatment	4 (1.9)	2 (0.9)
Worsening medical condition leading to ineligibility	3 (1.4)	0
Withdrawn by investigator	1 (0.5)	0
Died	0	1 (0.5)
Withdrew consent	0	1 (0.5)
Received treatment	212 (98.1)	214 (99.1)
Completed Treatment	165 (76.4)	160 (74.1)

Patient Disposition, n (%)	VEN-OBI	CHL-OBI
Discontinued at least one treatment component	47 (21.8)	54 (25.0)
Adverse events	31 (14.4)	34 (15.7)
Withdrew consent	9 (4.2)	11 (5.1)
Had progressive disease	1 (0.5)	5 (2.3)
Died	4 (1.9)	3 (1.4)
Non-adherent	1 (0.5)	0
Withdrawn by investigator	0	1 (0.5)
Unknown reason	1 (0.5)	0
Loss to follow-up	30 (13.9)	26 (12.0)
Died	20 (9.3)	17 (7.9)
Withdrew consent	10 (4.6)	8 (3.7)
Withdrawn by investigator	0	1 (0.5)
Remained in trial at data cut-off	186 (86.1)	190 (88.0)

CHL-OBI= Chlorambucil plus Obinutuzumab; VEN-OBI = Venetoclax plus Obinutuzumab.

Data Source: Fischer et al. 2019[1]

Protocol Deviations

In the VEN-OBI group, a total of 296 major protocol deviations occurred and 122 (56.5%) patients had at least one major protocol deviation.[8] In the CHL-OBI group, a total of 306 major protocol deviations occurred and 124 (57.4%) patients had at least one major protocol deviation. Most protocol deviations in both groups were related to deviations with study conduct/procedures including deviations with study assessments, screening, dose formulation/dose administration, sample collections, study restrictions/withdrawal criteria, inclusion/exclusion criteria, and sample processing/storage. Details of the major protocol deviations are listed in Table 32.

Table 32: Major Protocol Deviations in the CLL14 trial

Category	GClb (N=216)	VEN+G (N=216)
Total number of patients with at least one major protocol deviation	124 (57.4%)	122 (56.5%)
Total number of major protocol deviations	306	296
Study Conduct/Procedures		
Subjects with at least one major protocol deviation	98 (45.4%)	98 (45.4%)
Total number of major protocol deviations	178	204
Study Assessment	37 (17.1%)	44 (20.4%)
Screening	38 (17.6%)	37 (17.1%)
Dose Formulation/Dose Administration	17 (7.9%)	25 (11.6%)
Sample Collection	24 (11.1%)	18 (8.3%)
Study Restrictions/Withdrawal Criteria	15 (6.9%)	18 (8.3%)
Inclusion/Exclusion Criteria	6 (2.8%)	2 (0.9%)
Sample Processing/Storage	1 (0.5%)	2 (0.9%)
Investigational Product		
Subjects with at least one major protocol deviation	37 (17.1%)	21 (9.7%)
Total number of major protocol deviations	73	35
Dispensing/Accountability	37 (17.1%)	21 (9.7%)
Supply	0	1 (0.5%)
Safety		
Subjects with at least one major protocol deviation	23 (10.6%)	27 (12.5%)
Total number of major protocol deviations	27	34
Reporting/Follow-up	16 (7.4%)	21 (9.7%)
Recording	8 (3.7%)	6 (2.8%)
Informed Consent		
Subjects with at least one major protocol deviation	26 (12.0%)	23 (10.6%)
Total number of major protocol deviations	28	23
Presence/Absence	12 (5.6%)	12 (5.6%)
Version	6 (2.8%)	5 (2.3%)
Signature/Date	5 (2.3%)	4 (1.9%)
Process	5 (2.3%)	2 (0.9%)

CHL-OBI= chlorambucil plus obinutuzumab; VEN-OBI = Venetoclax plus obinutuzumab.

Data source: Clinical Study Report[8]

e) Critical Appraisal: Limitations and Potential Sources of Bias

Overall, the CLL14 trial was well conducted. The primary objective of the trial was to compare the investigator-assessed PFS between VEN-OBI and CHL-OBI, which was appropriately conducted. The randomization and allocation concealment methods were appropriately performed. Protocol defined criteria for treatment interruption, dose reductions, and administration of concomitant medications were followed, unless otherwise reported. The procedures employed in the CLL14 trial included appropriate methods for randomization, overall study methodology, and adequate statistical power. Overall, patients at baseline in both study groups had similar demographics and disease characteristics; therefore, the two groups were comparable.

The CADTH Methods Team identified the following limitations and potential sources of bias that should be considered when interpreting the trial results:

- The study design was open-label, which is susceptible to reporting and performance biases. Patients and investigators were aware of the study drug assigned, which can introduce the potential to bias results and outcomes in favour of VEN-OBI if the assessor (investigator or patient) believes the study drug is likely to provide a benefit. This limits the robustness of the efficacy results. However, the sponsor and the IRC were blinded to treatment arms and an iDMC reviewed unblinded safety data by treatment arm for the safety analysis and the planned interim efficacy analysis. The sponsor and study team did not have access to the unblinded information reviewed by the iDMC, which reduces some potential for bias in the study analyses. Due to the different modes of administration of study treatments, the open-label design of the trial was considered justified.
- There were multiple secondary efficacy outcomes in this trial. To control for multiplicity for multiple testing, the secondary efficacy endpoints were tested in a hierarchical order according to the Fallback Procedure, in which the α was split for the endpoints in the pre-specified order. Of note, OS was listed last in the hierarchical order, which may potentially limit the power to analyze this outcome.
- Several other secondary efficacy analyses were conducted (i.e. DOR, EFS, and time to new anti-leukemic treatment) as were multiple subgroup analyses. The results of these analyses should be interpreted as exploratory and hypothesis generating because the CLL14 trial was not designed nor powered to test specific hypotheses in these analyses.
- At the time of both the August 17, 2018 and the August 23, 2019 data cut-offs, the OS data were immature and median OS was not estimable for either treatment group; therefore, the magnitude of long-term survival benefit is currently unknown. Although patient crossover upon disease progression was not permitted in the trial, survival data may be confounded by the use of post-trial treatments.
- The comparator of the CLL14 trial was CHL-OBI; however, the CGP noted that IBR is considered the standard of care for the subgroup of patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. Although ITCs were conducted to investigate the comparison of VEN-OBI to IBR in these patients (see section 7.2), many limitations of these analyses were identified; thus, results were interpreted with caution.
- Protocol Amendment 4 (November 2, 2015) modified the procedure to move cytogenetic sampling to screening visits to allow investigators to decide prior to randomization whether alternative treatment should be considered (particularly for patients with del17p and/or TP53 mutation). There may have been a potential for selection bias after this amendment that would elicit differences in the selection of patients enrolled prior to this date as patients may have been considered for alternative treatments with the knowledge of the cytogenetic status. Therefore, this could affect the external validity of the trial results to patients with a higher-risk cytogenetic status if they were more likely to be excluded from this trial (as they could have been considered for an alternative treatment) based on this amendment.
- Major protocol deviations occurred in over half of the patients in both treatment groups (56.5% in VEN-OBI versus 57.4% in CHL-OBI).[8] Most protocol deviations in both groups were related to deviations with study conduct/procedures including deviations with study assessments, screening, dose formulation/dose administration, sample collections, study restrictions/withdrawal criteria, inclusion/exclusion criteria, and sample processing/storage. According to the sponsor, few of the protocol deviations classified as major would have impacted the data integrity, patient safety, or study results or conclusions. The effect of these protocol deviations on the results of the trial and the validity of the analyses can not be determined.
- Study sites in Germany were considered German CLL Study Group sites and were selected based on feasibility criteria of both the German CLL Study Group and Roche; however, sites external to Germany were selected based on feasibility criteria established by Roche and these sites were reviewed by the German CLL Study Group. 54 patients (12.5%) were enrolled in Germany. While unlikely, if there was a variance in the selection criteria for German patients, this could limit the generalizability of the results to non-German patients.
- The utility of MRD status is gaining greater importance in determining depth of response to therapy and is being used in more trials as a predictor of PFS and OS. Namely, meta-analyses have shown a strong association between MRD negativity and improved PFS and OS[37]; however, the effect of the intervention on a surrogate outcome cannot predict the actual effect of treatment on important clinical outcomes such as PFS and OS.

- The trial was a global study; however, based on location of the sites, it doesn't appear as though there was a wide range of ethnic diversity. Few details were provided as to the ethnic demographics of the patients in included trials (e.g. White versus Black versus Asian).
- The sponsors F. Hoffmann-La Roche Ltd. (Roche) and AbbVie Inc. funded the trial and were involved in all aspects of its conduct including design of the study, data collection, and data analysis including interpretation. The extent to which the sponsors' involvement may have influenced the results and reporting of the trial is unknown.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The results for the primary and secondary efficacy outcomes (listed in order of their hierarchical testing) of the CLL14 trial are summarized in Table 33.[1] The results of the analyses from the August 17, 2018 primary data cut-off are reported below unless otherwise noted. At the time of data cut-off, median follow-up was 28.1 months (range: 0.0 to 35.9 months).[1] All patients had stopped treatment for a median of 17.1 months (range: 0.0 to 30.4 months) in the VEN-OBI group and 17.9 months (range: 0.0 to 30.2 months) in the CHL-OBI group.

Table 33: Summary of Efficacy Outcomes for the Primary Data Cut-Off of the CLL14 Trial (August 17, 2018)

Efficacy Outcome	VEN-OBI (n=216)	CHL-OBI (n=216)
PFS (investigator-assessed)		
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)
Event rate, n (%)	30 (13.9)	77 (35.6)
Hazard ratio (95% CI) [a]	0.35 (0.23 to 0.53)	
p-value [b]	p<0.0001	
Estimate of 1-year PFS rate, % (95% CI)	94.62 (91.53 to 97.71)	92.11 (88.40 to 95.82)
Estimate of 2-year PFS rate, % (95% CI)	88.15 (83.69 to 92.60)	64.10 (57.39 to 70.81)
PFS (IRC-assessed)		
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)
Event rate, n (%)	29 (13.4)	79 (36.6)
Hazard ratio (95% CI) [a]	0.33 (0.22 to 0.51)	
p-value [b]	p<0.0001	
MRD-Negativity Rate – Bone Marrow (three months after treatment completion)		
MRD negative patients, n (%)	123 (56.9)	37 (17.1)

Efficacy Outcome	VEN-OBI (n=216)	CHL-OBI (n=216)
Difference in response rate (95% CI)	39.8 (31.3 to 48.4)	
Odds ratio (95% CI)	6.4 (4.1 to 10.0)	
p-value [c]	p<0.0001	
CRR (three months after treatment completion)		
Responders, n (%)	107 (49.5)	50 (23.1)
Difference in response rate (95% CI)	26.4 (17.4 to 35.4)	
Odds ratio (95% CI)	3.3 (2.2 to 5.1)	
p-value [c]	p<0.0001	
MRD-Negativity Rate – Peripheral Blood (three months after treatment completion)		
MRD negative patients, n (%)	163 (75.5)	76 (35.2)
Difference in response rate (95% CI)	40.3 (31.5 to 49.1)	
Odds ratio (95% CI)	5.7 (3.7 to 8.6)	
p-value [c]	p<0.0001	
MRD-Negativity Rate in Complete Responders – Bone Marrow (three months after treatment completion)		
MRD negative patients, n (%)	73 (33.8)	23 (10.6)
Difference in response rate (95% CI)	23.2 (15.4 to 30.9)	
Odds ratio (95% CI)	4.3 (2.6 to 7.2)	
p-value [c]	p<0.0001	
MRD-Negativity Rate in Complete Responders – Peripheral Blood (three months after treatment completion)		
MRD negative patients, n (%)	94 (42.1)	31 (14.4)
Difference in response rate (95% CI)	27.8 (19.5 to 36.1)	
Odds ratio (95% CI)	4.3 (2.7 to 6.9)	
p-value [c]	p<0.0001	
ORR (three months after treatment completion)		
Responders, n (%)	183 (84.7)	154 (71.3)

Efficacy Outcome	VEN-OBI (n=216)	CHL-OBI (n=216)
Difference in response rate (95% CI)	13.4 (5.5 to 21.4)	
Odds ratio (95% CI)	2.3 (1.4 to 3.6)	
p-value [c]	p=0.0007	
OS		
Median (95% CI) (months)	NE (NE to NE)	NE (NE to NE)
Event rate, n (%)	20 (9.3)	17 (7.9)
Hazard ratio (95% CI) [a]	1.24 (0.64 to 2.40)	
p-value [b]	p=0.5216	

CI = confidence interval; CHL-OBI = Chlorambucil plus Obinutuzumab; CRR = complete response rate; IRC = independent review committee; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.
Notes:
[a] Stratified by Binet stage at screening and geographic region
[b] From log-rank test stratified by Binet stage at screening and geographic region
[c] From Cochran–Mantel–Haenszel tests stratified by Binet stage and geographic region

Data Source: Fischer et al. 2019,[1] EPAR 2020,[3] Clinical Study Report[8]

At the time of the August 23, 2019 data cut-off, median follow up was 39.6 months (range: 0.0 to 47.3 months).[7] Efficacy results for the updated data cut-off were reported for investigator-assessed PFS, off-treatment PFS, MRD-negativity in bone marrow three months after treatment completion, MRD-negativity in peripheral blood three months after treatment completion, and OS (Table 34). Overall, efficacy results from these analyses were consistent with those from the primary data cut-off.[7]

Table 34: Summary of Efficacy Outcomes for the Updated Data Cut-Off of the CLL14 Trial (August 23, 2019)

Efficacy Outcome	VEN-OBI (n=216)	CHL-OBI (n=216)
PFS (investigator-assessed)		
Median (95% CI) (months) [a,b]	NE (NE to NE)	35.6 (33.7 to 40.7)
Event rate, n (%)	42 (19.4)	113 (52.3)
Hazard ratio (95% CI) [b,c]	0.31 (0.22 to 0.44)	
p-value	p<0.0001	
Off-Treatment PFS (investigator-assessed)		
Median (95% CI) (months) [a,b]	NE (0.0 to 41.0)	25.3 (0.0 to 39.3)

Efficacy Outcome	VEN-OBI (n=216)	CHL-OBI (n=216)
Event rate, n (%)	42 (19.4)	110 (50.9)
Hazard ratio (95% CI) [b,c]	0.33 (0.23 to 0.47)	
p-value	p<0.0001	
MRD-Negativity Rate – Bone Marrow (three months after treatment completion)		
MRD negative patients, n (%)	124 (57.4)	37 (17.1)
Difference in response rate (95% CI)	40.28 (31.74 to 48.82)	
Odds ratio (95% CI)	6.52 (4.18 to 10.17)	
p-value	p<0.0001	
MRD-Negativity Rate – Peripheral Blood (three months after treatment completion)		
MRD negative patients, n (%)	155 (71.8)	74 (34.3)
Difference in response rate (95% CI)	37.50 (28.52 to 46.48)	
Odds ratio (95% CI)	4.88 (3.24 to 7.33)	
p-value	p<0.0001	
OS		
Median (95% CI) (months) [a,b]	NE (NE to NE)	NE (NE to NE)
Event rate, n (%)	27 (12.5)	27 (12.5)
Hazard ratio (95% CI) [b,c]	1.03 (0.60 to 1.75)	
p-value	p=0.9210	

CI = confidence interval; CHL-OBI = Chlorambucil plus Obinutuzumab; CRR = complete response rate; NE = not estimable; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] HR estimated by Cox regression model.

[b] 95% CI median was computed using the method of Brookmeyer and Crowley.

[c] From log-rank test stratified by Binet stage at screening and geographic region

Data Source: Clinical Study Report Supplement[7]

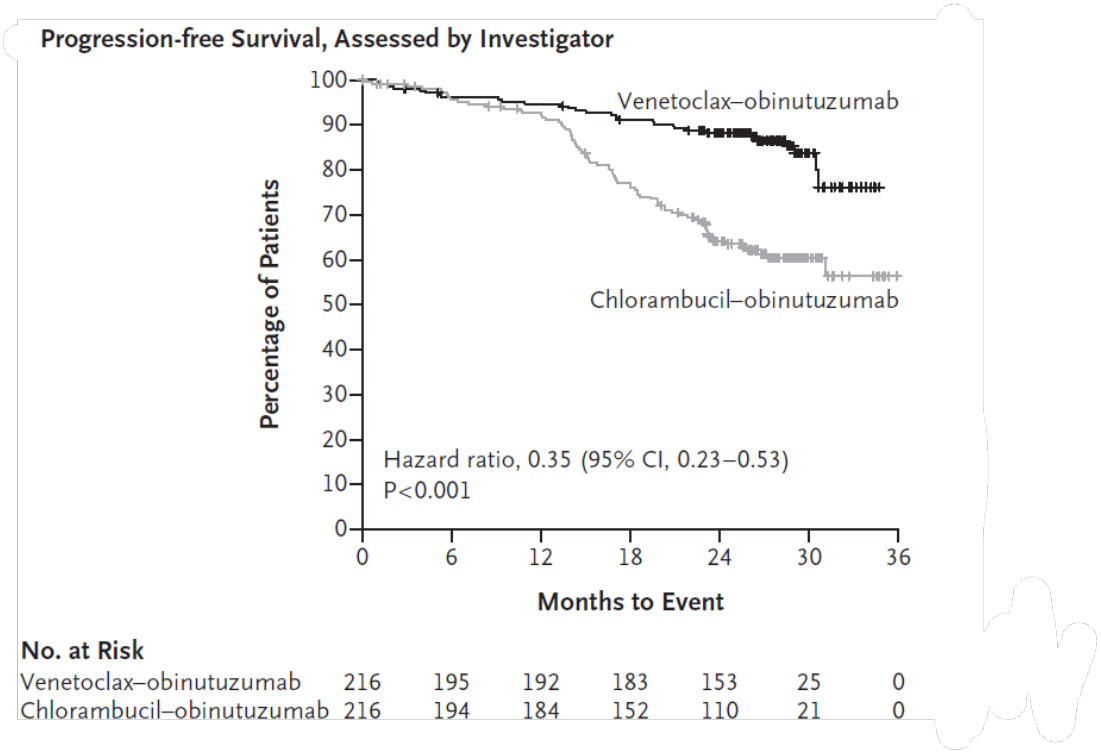
Primary Efficacy Outcome: Progression Free Survival – Investigator-Assessed

The PFS KM curves for the primary analysis are displayed in Figure 3.[1] At the time of the data cut-off, 30 PFS events had occurred in the VEN-OBI group (14 events of disease progression and 16 events of death) and 77 PFS events had occurred in the CHL-OBI

group (69 events of disease progression and eight events of death). Although median PFS had not been reached in either group, results of the primary analyses demonstrated an HR of 0.35 (95% CI: 0.23, 0.53; p<0.0001). Estimates for the PFS rate were similar between the two groups at one year and higher for the VEN-OBI group at two years (Table 33).

At the updated data cut-off, 42 PFS events had occurred in the VEN-OBI group (21 events of disease progression and 21 events of death), 113 PFS events had occurred in the CHL-OBI group (102 events of disease progression and 11 events of death), the HR was 0.31 [95% CI: 0.22, 0.44; p<0.0001].[7] [redacted][32][redacted] *(Non-disclosable information was used in this CADTH Guidance Report and the sponsor requested this clinical information not be disclosed pursuant to the CADTH Disclosure of Information Guidelines. This information will remain redacted until notification by the sponsor that it can be publicly disclosed.)*

Figure 3: Kaplan–Meier Estimates of Investigator-Assessed Progression-Free Survival in the CLL14 Trial



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PFS in subgroups

The results of prespecified subgroup investigator-assessed PFS analyses are shown in Figure 4 and the KM curves according to TP53 and IGVH are shown in Figure 5 and Figure 6, respectively.[1] The results of these analyses were consistent with the overall PFS results in the ITT population; a statistically significant longer PFS in the VEN-OBI group compared to the CHL-OBI group was found except in the following subgroups: Binet stage at screening '*C*', cytogenetic factors '*no abnormalities*' and '*deletion 13q*', and IGHV mutational status '*mutated*'. In these subgroups, the treatment effect estimate CI included the null value of 1, which suggests no difference in PFS between the treatment groups. Additionally, the HR in the cytogenetic factors' subgroup '*trisomy 12*' was not

estimable. These subgroup analyses were not powered to detect statistically significant differences between treatment groups and may have been limited by the small sample sizes of some subgroups.

Figure 4: Subgroup Analyses of Investigator-Assessed Progression-Free Survival in the CLL14 Trial

			Chlorambucil–obinutuzumab			Venetoclax–obinutuzumab				
Category	Subgroup	Total n	n	Events	PFS rate month 24 (%)	n	Events	PFS rate month 24 (%)	Hazard ratio	95% Wald CI
All		432	216	77	64.1	216	30	88.1	0.34	0.23–0.53
Binet stage at screening	A	90	44	18	56.6	46	3	95.7	0.13	0.04–0.42
	B	157	80	30	62.5	77	9	88.9	0.26	0.12–0.55
	C	185	92	29	69.1	93	18	83.4	0.58	0.32–1.05
Age groups (years)	<75	282	138	49	63.5	144	17	89.7	0.28	0.16–0.48
	≥75	150	78	28	65.1	72	13	84.9	0.48	0.25–0.93
Gender	Male	289	143	49	65.4	146	21	87.7	0.37	0.22–0.61
	Female	143	73	28	61.4	70	9	89.1	0.29	0.13–0.60
Cytogenetic subgroups as per hierarchy	del(17p)	31	14	10	23.1	17	7	64.7	0.33	0.12–0.89
	del(11q)	74	38	20	41.3	36	4	91.2	0.11	0.03–0.38
	Trisomy 12	76	40	17	55.6	36	0	100.0	NE	NE
	No abnormalities	92	42	8	82.1	50	9	87.2	0.93	0.36–2.41
	del(13q)	120	59	16	78.3	61	8	88.1	0.45	0.19–1.05
TP53 deletion and/or mutation	Present	46	22	15	32.7	24	7	73.9	0.31	0.13–0.76
	Not present	287	139	49	65.0	148	14	92.1	0.23	0.13–0.42
IGHV mutational status	Unmutated	244	123	57	51.0	121	16	89.4	0.22	0.12–0.38
	Mutated	159	83	15	85.6	76	9	90.3	0.64	0.28–1.46

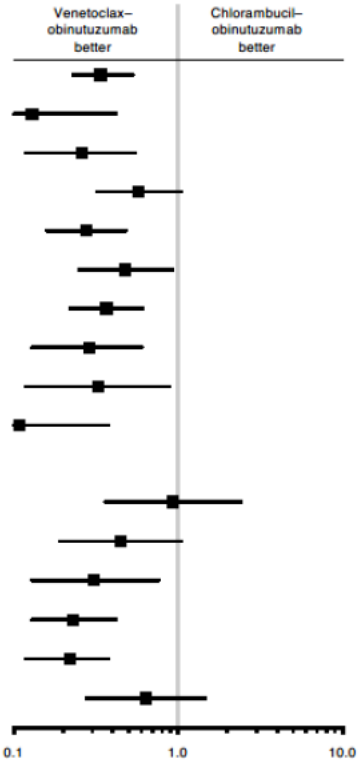

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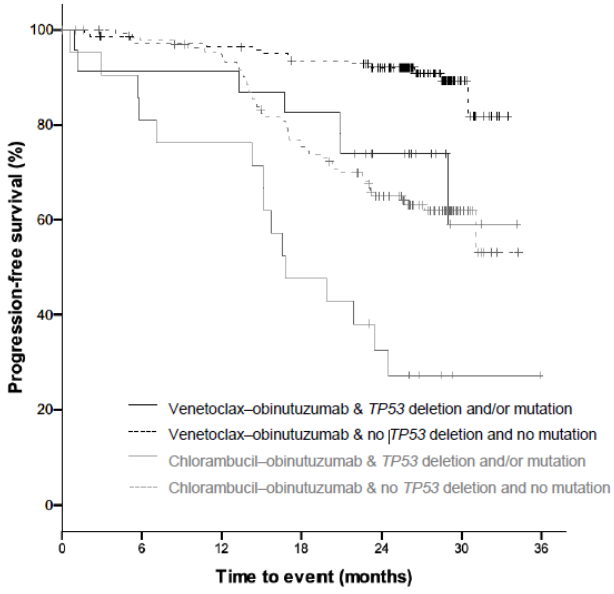
Figure 5: Kaplan–Meier Estimates of Investigator-Assessed Progression-Free Survival According to TP53 Mutational Status in the CLL14 Trial



Patients at risk							
Venetoclax–obinutuzumab & no *TP53* deletion and no mutation	148	135	134	128	113	15	0
Venetoclax–obinutuzumab & *TP53* deletion and/or mutation	24	21	21	19	12	2	0
Chlorambucil–obinutuzumab & no *TP53* deletion and no mutation	139	129	123	98	77	13	0
Chlorambucil–obinutuzumab & *TP53* deletion and/or mutation	22	17	16	10	6	1	0

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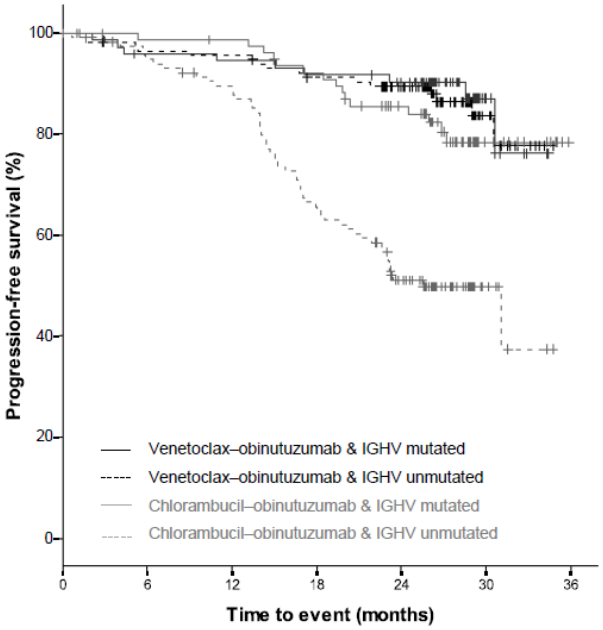
Figure 6: Kaplan–Meier Estimates of Investigator-Assessed Progression-Free Survival According to IGVH Mutational Status in the CLL14 Trial



Patients at risk							
Venetoclax–obinutuzumab & IGHV mutated	76	69	68	66	62	9	0
Venetoclax–obinutuzumab & IGHV unmutated	121	110	109	102	87	16	0
Chlorambucil–obinutuzumab & IGHV mutated	83	77	76	70	56	12	0
Chlorambucil–obinutuzumab & IGHV unmutated	123	109	100	74	50	8	0

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Sensitivity Analyses for PFS

Results of the sensitivity analyses for both investigator-assessed PFS and IRC-assessed PFS were consistent with the primary analysis; whereby, there was a statistically significant longer PFS in the VEN-OBI group compared to the CHL-OBI group (Table 35).[3]

Table 35: Results of the Sensitivity Analyses for PFS in the CLL14 Trial

Efficacy Outcome	PFS (investigator-assessed)		PFS (IRC-assessed)	
	VEN-OBI	CHL-OBI	VEN-OBI	CHL-OBI
Censoring for more than one missed response assessment				
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)	NE (NE to NE)	NE (31.1 to NE)

Efficacy Outcome	PFS (investigator-assessed)		PFS (IRC-assessed)	
	VEN-OBI	CHL-OBI	VEN-OBI	CHL-OBI
Event rate, n (%)	28 (13.0)	75 (34.7)	27 (12.5)	77 (35.6)
Stratified HR (95% CI)	0.33 (0.22 to 0.52)		0.32 (0.21 to 0.50)	
Stratified p-value	p<0.0001		p<0.0001	
Unstratified HR (95% CI)	0.32 (0.21 to 0.50)		0.30 (0.20 to 0.47)	
Unstratified p-value	p<0.0001		p<0.0001	
Censoring for new anti-CLL treatment				
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)	NE (NE to NE)	NE (31.1 to NE)
Event rate, n (%)	29 (13.4)	77 (35.6)	28 (13.0)	78 (36.1)
Stratified HR (95% CI)	0.34 (0.22 to 0.52)		0.33 (0.21 to 0.50)	
Stratified p-value	p<0.0001		p<0.0001	
Unstratified HR (95% CI)	0.33 (0.21 to 0.50)		0.31 (0.20 to 0.48)	
Unstratified p-value	p<0.0001		p<0.0001	

CI = confidence interval; CHL-OBI = Chlorambucil plus Obinutuzumab; CLL = chronic lymphocytic leukemia; IRC = independent review committee; NE = not estimable; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Data Source: EPAR 2020[3]

Key Secondary Efficacy Outcomes

Detailed results for the secondary efficacy outcomes (IRC-assessed PFS, MRD rate in bone marrow, CRR rate, MRD rate in peripheral blood, MRD rate in bone marrow of patients with a CR, MRD rate in peripheral blood of patients with a CR, ORR, and OS) are summarized in Table 33.[1] Overall, the results for these outcomes showed an improvement with VEN-OBI compared to CHL-OBI.

At the time of both the August 17, 2018 and the August 23, 2019 data cut-offs, the OS data were immature and median OS was not estimable for either treatment group. [1,7] As of the primary data cat-off, a total of 37 patients had died (VEN-OBI group: 20 patients and CHL-OBI group: 17 patients), corresponding to an HR of 1.24 (95% CI: 0.64, 2.40; p=0.5216) (Table 33).[1] At 24 months, the KM estimate of the percentage of patients still alive was 91.8% (95% CI: 88.1 to 95.5) in the VEN-OBI group and 93.3% (95% CI: 90.0 to 96.7) in the CHL-OBI group. At the time of the August 23, 2019 data cut-off, 54 patients had died (27 patients in each treatment group), corresponding to an HR of 1.03 (95% CI: 0.60, 1.75; p=0.9210].[7]

Other Secondary Efficacy Outcomes

The analyses for DOR, EFS, and time to next anti-CLL treatment are summarized in Table 36. Overall, the results for these outcomes showed an improvement with VEN-OBI compared to CHL-OBI. The results from the updated data cut-off were consistent

with the primary analyses. The trial was not powered to detect differences between groups; therefore, the results should be interpreted with caution.

Table 36: Results of the Other Secondary Outcome Analyses in the CLL14 Trial

Efficacy Outcome	August 17, 2018 Data Cut-Off		August 23, 2019 Data Cut-Off	
	VEN-OBI (n=216)	CHL-OBI (n=216)	VEN-OBI (n=216)	CHL-OBI (n=216)
Duration of response				
Patients included in analysis	200 (100.0)	197 (100.0)	200 (100.0)	197 (100.0)
Median (95% CI) (months)	NE (NE to NE)	NE (28.1 to NE)	NE (NE to NE)	34.7 (31.8 to 38.0)
Event rate, n (%)	24 (12.0)	67 (34.0)	36 (18.0)	103 (52.3)
Stratified hazard ratio (95% CI) [a]	0.31 (0.20 to 0.50)		0.29 (0.20 to 0.42)	
Stratified analysis p-value [b,c]	p<0.0001		p<0.0001	
Event-free survival				
Median (95% CI) (months)	NE (NE to NE)	NE (31.1 to NE)	NE (NE to NE)	35.5 (31.1 to 40.5)
Event rate, n (%)	32 (14.8)	80 (37.0)	44 (20.4)	118 (54.6)
Stratified hazard ratio (95% CI) [a]	0.36 (0.24 to 0.54)		0.31 (0.22 to 0.44)	
Stratified analysis p-value [b,c]	p<0.0001		p<0.0001	
Time to next anti-CLL treatment				
Median (95% CI) (months)	NE (NE to NE)	NE (34.6 to NE)	NE (NE to NE)	NE (NE to NE)
Event rate, n (%)	27 (12.5)	45 (20.8)	35 (16.2)	66 (30.6)
Stratified hazard ratio (95% CI) [a]	0.60 (0.37 to 0.97)		0.51 (0.34 to 0.78)	
Stratified analysis p-value [b,c]	p=0.0340		p=0.0012	

CI = confidence interval; CHL-OBI = Chlorambucil plus Obinutuzumab; CRR = complete response rate; IRC = independent review committee; MRD = minimal residual disease; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] Stratified by Binet stage at screening and geographic region

[b] From log-rank test stratified by Binet stage at screening and geographic region

[c] Provided for descriptive purposes only and do not represent statistical significance.

Data Sources: Clinical Study Report,[8] Clinical Study Report Supplement[7]

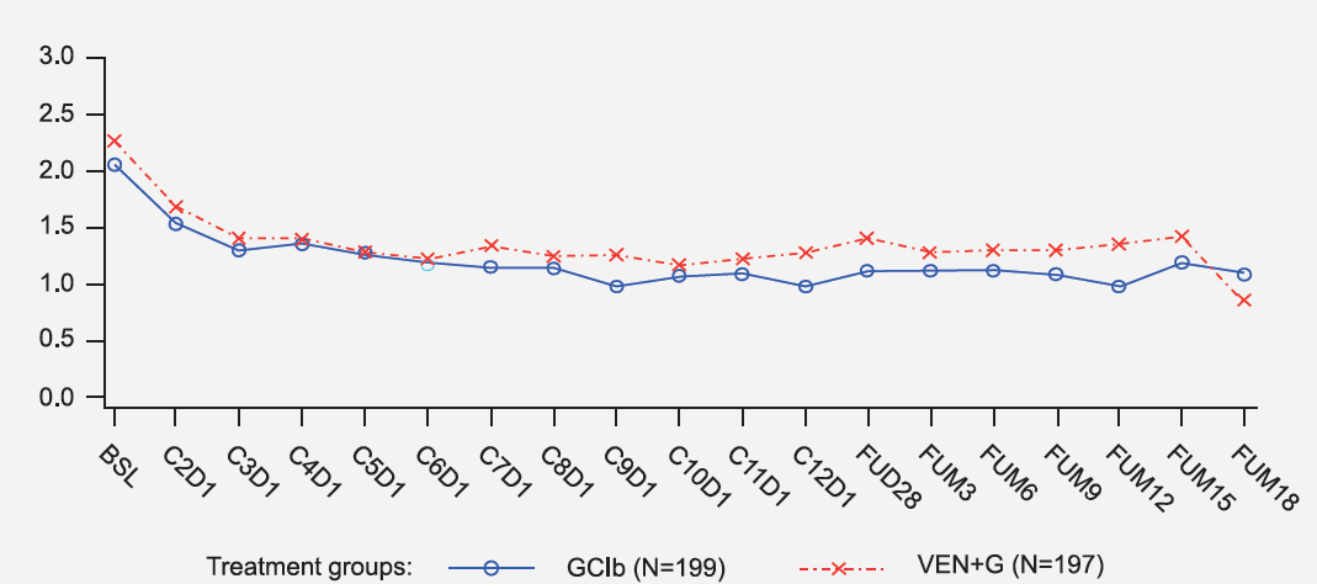
Patient Reported Outcomes

Overall, results of the analyses of the MDASI-CLL and the EORTC QLQ-C30 did not show a statistically significant difference between treatments.[3] Completion rates for the MDASI-CLL and the EORTC QLC-C30 were 100% at baseline, over 90% throughout treatment, and above 85% throughout 18 months of follow-up.[4] Median observation time was 28.1 months. PRO analyses at the August 23, 2019 data-cut off were consistent with the results reported below.[7]

MDASI-CLL

Baseline scores (mean ± SD) were comparable for the VEN-OBI group versus the CHL-OBI group: CLL symptoms (1.6 ± 1.3 versus 1.5 ± 1.2), core cancer symptoms (1.8 ± 1.7 versus 1.5 ± 1.4), and symptom interference (2.3 ± 2.3 versus 2.1 ± 2.3).[4] No clinically meaningful improvement or deterioration to the score throughout treatment and the follow-up period (Figure 7).

Figure 7: Mean Change Over Time in Symptom Interference Subscale of MDASI-CLL in the CLL14 Trial

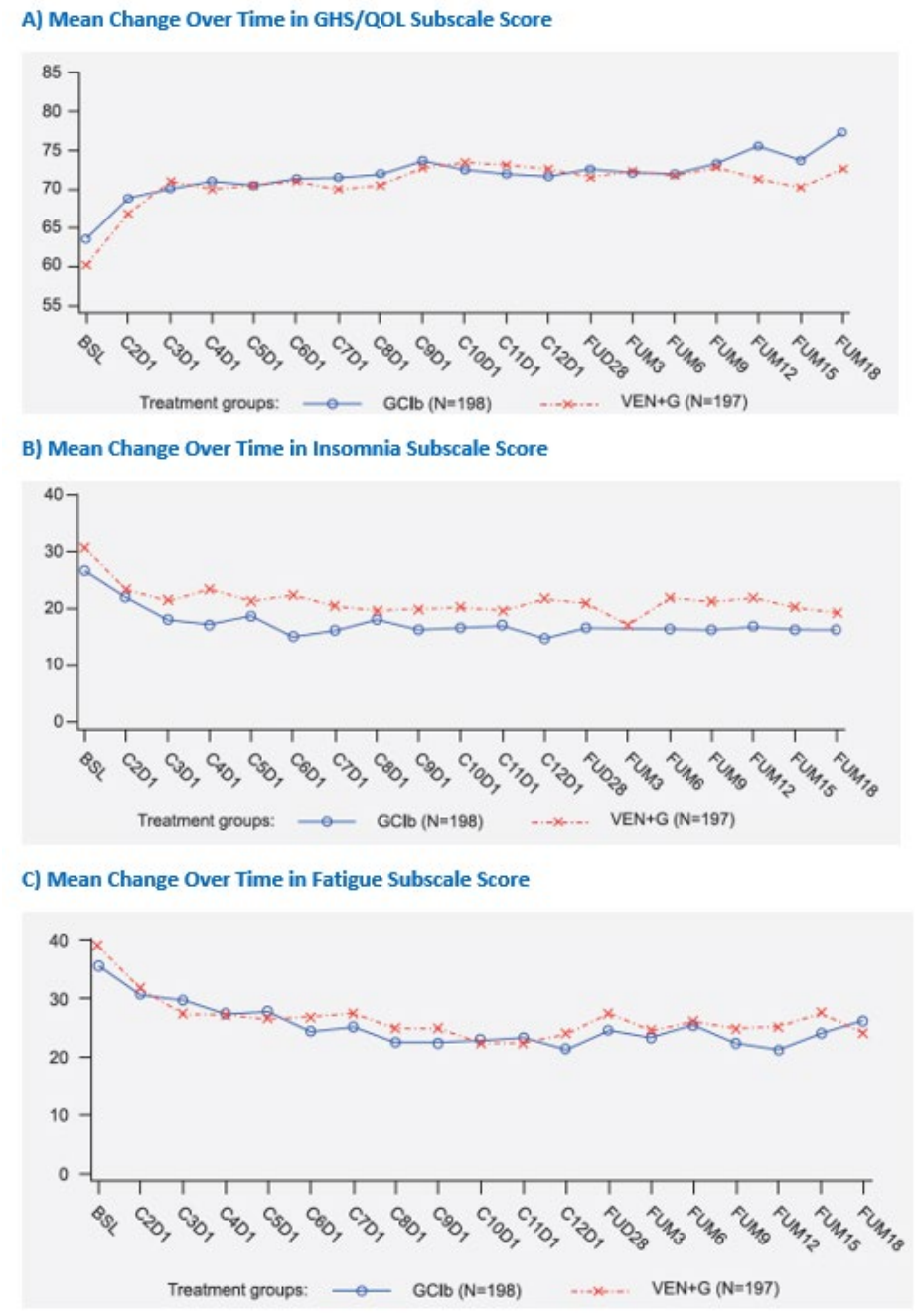


From Al-Sawaf O, Gentile B, Devine J, et al. Rapid improvement of patient-reported outcomes with venetoclax plus obinutuzumab in patients with previously untreated CLL and coexisting conditions: a prospective analysis from the CLL14 trial. Blood. 2019;134. Copyright © 2019 American Society of Hematology. Reprinted with permission from the American Society of Hematology[4]

EORTC QLQ-C30

Baseline scores (mean ± SD) were comparable for the VEN-OBI group versus the CHL-OBI group: physical functioning (76.9 ± 19.4 versus 75.9 ± 20.1), role functioning (72.6 ± 26.9 versus 73.6 ± 27.86), and GHS-QoL (60.3 ± 20.5 versus 63.6 ± 21.0).[4] The most severe symptoms at baseline were (listed as VEN-OBI versus CHL-OBI) dyspnea (24.8 ± 27.76 versus 21.3 ± 25.6), fatigue (39.2 ± 24.7 versus 35.8 ± 23.3), insomnia (30.8 ± 30.5 versus 26.9 ± 29.0), pain (18.4 ± 25.6 versus 16.8 ± 22.1), appetite loss (15.6 ± 26.7 versus 14.7 ± 23.6), and constipation (12.8 ± 23.7 versus 10.9 ± 20.9). Baseline physical and role functioning were maintained throughout treatment and the follow-up period with no clinically meaningful improvement or deterioration to the scores. Patients showed an improvement of the GHS-QOL score by at least eight points at cycle 3 in the VEN-OBI group; whereas, less pronounced but consistent improvement was found at cycle 8 in the CHL-OBI group (Figure 8A). Insomnia (Figure 8B) and fatigue (Figure 8C) scores also showed an improvement starting at cycle 3 in the VEN-OBI group and at cycle 4 and cycle 6, respectively in the CHL-OBI group.

Figure 8: Mean Change Over Time in Subscales from EORTC QLQ-C30 in the CLL14 Trial



From Al-Sawaf O, Gentile B, Devine J, et al. Rapid improvement of patient-reported outcomes with venetoclax plus obinutuzumab in patients with previously untreated CLL and coexisting conditions: a prospective analysis from the CLL14 trial. Blood. 2019;134. Copyright © 2019 American Society of Hematology. Reprinted with permission from the American Society of Hematology[4]

Harms Outcomes

Adverse Events

Table 37 provides a summary of the AEs of any grade, grade 3/4 AEs, and SAEs occurring in ≥10%, ≥3%, and ≥1% of patients, respectively in either treatment group.[1] At least one AE of any grade was reported in 94.3% of patients in the VEN-OBI group and in 99.5% of patients in the CHL-OBI group. Most AEs were blood and lymphatic system disorders. The most common AEs of any grade that occurred in the VEN-OBI group versus the CHL-OBI group were neutropenia (57.5% versus 57.0%), infusion-related reactions (44.8% versus 51.4%), diarrhea (27.8% versus 15.0%), and pyrexia (22.6% versus 15.4%). The most common grade 3 or 4 AEs in the VEN-OBI group versus the CHL-OBI group were neutropenia (52.8% versus 48.1%), thrombocytopenia (13.7% versus 15.0%), and anemia (8.0% versus 6.5%). The incidence of TLS (SAE) was lower in the VEN-OBI group compared to the CHL-OBI group (0.5% versus 1.9%). All occurrences of TLS in the VEN-OBI group (three patients) occurred during the administration of OBI only period, prior to starting VEN. None of the TLS events met the Howard criteria for clinical TLS.

Table 37: Summary of Any Grade AEs, Grade 3/4 AEs, and SAEs Occurring in ≥10%, ≥3%, and ≥1% of Patients, Respectively in Either Treatment Group in the CLL14 trial

Adverse event	Any Grade AE		Grade 3/4 AE		SAE	
	VEN-OBI (n=212)	CHL-OBI (n=214)	VEN-OBI [a] (n=212)	CHL-OBI (n=214)	VEN-OBI (n=212)	CHL-OBI (n=214)
At least one of the AE category – no. of patients (%)	200 (94.3)	213 (99.5)	167 (78.8)	164 (76.6)	104 (49.1%)	90 (42.1%)
Blood and lymphatic disorders	**145 (68.4)**	**137 (64.0)**	**128 (60.4)**	**118 (55.1)**	-	-
Neutropenia	122 (57.5)	122 (57.0)	112 (52.8)	103 (48.1)	3 (1.4)	1 (0.5)
Thrombocytopenia	51 (24.1)	50 (23.4)	29 (13.7)	32 (15.0)	2 (0.9)	5 (2.3)
Anemia	35 (16.5)	40 (18.7)	17 (8.0)	14 (6.5)	-	-
Febrile neutropenia	-	-	11 (5.2)	8 (3.7)	11 (5.2)	8 (3.7)
Leukopenia	-	-	5 (2.4)	10 (4.7)	-	-
Infections and infestations	-	-	**37 (17.5)**	**32 (15.0)**	-	-
Pneumonia	-	-	9 (4.2)	8 (3.7)	10 (4.7)	9 (4.2)
Sepsis	-	-	-	-	6 (2.8)	2 (0.9)
Cellulitis	-	-	-	-	3 (1.4)	0
Infusion-related reactions	**95 (44.8)**	**110 (51.4)**	**19 (9.0)**	**22 (10.3)**	**9 (4.2)**	**13 (6.1)**
Investigations	-	-	**32 (15.1)**	**23 (10.7)**	-	-
Neutrophil count decreased	-	-	9 (4.2)	10 (4.7)	-	-
Aspartate aminotransferase increased	-	-	5 (2.4)	7 (3.3)	0	4 (1.9)
Alanine aminotransferase increased	-	-	4 (1.9)	7 (3.3)	0	3 (1.4)
Metabolism and nutrition disorders	-	-	**25 (11.8)** [b]	**12 (5.6)** [b]	-	-
Hyperglycemia	-	-	8 (3.8)	3 (1.4)	-	-
Tumour lysis syndrome	-	-	-	-	1 (0.5)	4 (1.9)
Gastrointestinal disorders	**89 (42.0)**	**74 (34.6)**	**17 (8.0)**	**7 (3.3)**	-	-
Diarrhea	59 (27.8)	32 (15.0)	9 (4.2)	1 (0.5)	-	-
Nausea	40 (18.9)	46 (21.5)	-	-	-	-
Constipation	28 (13.2)	19 (8.9)	-	-	-	-
General disorders and administration-site conditions	**68 (32.1)**	**60 (28.0)**	**14 (6.6)** [c]	**6 (2.8)** [c]	-	-
Pyrexia	48 (22.6)	33 (15.4)	-	-	8 (3.8)	7 (3.3)
Fatigue	32 (15.1)	30 (14.0)	-	-	-	-
Respiratory, thoracic, and mediastinal disorders	**34 (16.0)**	**25 (11.7)**	**10 (4.7)**	**6 (2.8)**	-	-
Cough	34 (16.0)	25 (11.7)	-	-	-	-
Chronic obstructive pulmonary disease	-	-	-	-	3 (1.4)	2 (0.9)
Nervous system disorders	**24 (11.3)**	**21 (9.8)**	**10 (4.7)**	**7 (3.3)**	-	-
Headache	24 (11.3)	21 (9.8)	-	-	-	-
Cardiac disorders	-	-	**10 (4.7)**	**12 (5.6)**	-	-
Atrial fibrillation	-	-	-	-	1 (0.5)	3 (1.4)
Cardiac failure	-	-	-	-	3 (1.4)	1 (0.5)
Myocardial infarction	-	-	-	-	1 (0.5)	3 (1.4)
Vascular disorders *	-	-	**14 (6.6)** [d]	**7 (3.3)** [d]	-	-

Adverse event	Any Grade AE		Grade 3/4 AE		SAE	
	VEN-OBI (n=212)	CHL-OBI (n=214)	VEN-OBI [a] (n=212)	CHL-OBI (n=214)	VEN-OBI (n=212)	CHL-OBI (n=214)
Musculoskeletal and connective-tissue disorders	-	-	**6 (2.8)**	**7 (3.3)**	-	-
Skin and subcutaneous tissue disorder ‡‡	-	-	**2 (0.9)** [e]	**8 (3.7)**	-	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	**13 (6.1)**	**8 (3.7)**	**2 (0.9)**	**3 (1.4)**

AE = adverse event; CHL-OBI = Chlorambucil plus Obinutuzumab; SAE = serious adverse event; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] Nine patients received obinutuzumab only.

[b] Category includes tumor lysis syndrome and changes in electrolyte levels, each occurring in less than 3% of patients in each group.

[c] Category includes asthenia, pyrexia, fatigue, and chest pain, each occurring in less than 3% of patients in each group.

[d] Category includes hypertension and hypotension, each occurring in less than 3% of patients in each group.

[e] Category includes different types of rash, each occurring in less than 3% of patients in each group.

Data Source: Fischer et al. 2019[1]

Table 38 provides a summary of the fatal (Grade 5) AEs at the primary data cut-off.[1] During treatment, five fatal AEs occurred in the VEN-OBI group and four occurred in the CHL-OBI group. Two of the fatal AEs in the VEN-OBI group occurred in patients who received only OBI (i.e. no VEN). After treatment completion, 11 fatal AEs occurred in the VEN-OBI group and four occurred in the CHL-OBI group. As of the updated data cut-off, 30 patients (19 (9.0%) in the VEN-OBI group and 11 (5.1%) in the CHL-OBI group) had died due to AEs.[7]

Table 38: Fatal (Grade 5) Adverse Events in the CLL14 Trial

Adverse Event	Venetoclax–Obinutuzumab (N = 212)†	Chlorambucil–Obinutuzumab (N = 214)
	number of patients (percent)	
Grade 5 adverse event during treatment	5 (2.4)‡	4 (1.9)
Infections and infestations	4 (1.9)	3 (1.4)
Neoplasms benign, malignant, and unspecified, including cysts and polyps	1 (0.5)	1 (0.5)
Grade 5 adverse event after completion of treatment	11 (5.2)	4 (1.9)
Cardiac disorders	3 (1.4)	1 (0.5)
Infections and infestations	4 (1.9)	0
Neoplasms benign, malignant, and unspecified, including cysts and polyps	2 (0.9)	2 (0.9)
Other event	2 (0.9)	1 (0.5)

Note:

† Nine patients received obinutuzumab only.

‡ Two patients received obinutuzumab only.

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Table 39 provides an overview of second primary malignancies as of the primary data cut-off.[1] Second primary cancers were reported in 13.7% of patients in the VEN-OBI group and in 10.3% of patients in the CHL-OBI group. Additionally, Richter's transformation was reported in two patients in the VEN-OBI group and in one patient in the CHL-OBI group. As of the updated data

cut-off, second primary malignancies had been reported in an additional seven patients in the VEN-OBI group and an additional Richter's transformation was reported in the CHL-OBI group.[7]

Table 39: Overview of Second Primary Malignancies in the CLL14 Trial

Second primary malignancies	Venetoclax–obinutuzumab (N=212)	Chlorambucil–obinutuzumab (N=214)
At least one second primary malignancies – no. of patients (%)	29 (13.7)	22 (10.3)
Second primary malignancies – no. of patients (%)		
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	28 (13.2)	22 (10.3)
Squamous cell carcinoma of skin	7 (3.3)	8 (3.7)
Basal cell carcinoma	6 (2.8)	6 (2.8)
Malignant melanoma	2 (0.9)	1 (0.5)
Malignant melanoma in situ	2 (0.9)	1 (0.5)
Bowen's disease	2 (0.9)	0
Keratoacanthoma	1 (0.5)	1 (0.5)
Prostate cancer	2 (0.9)	0
Acute myeloid leukemia	0	1 (0.5)
Adenocarcinoma of colon	0	1 (0.5)
Anal squamous cell carcinoma	0	1 (0.5)
Bladder cancer	1 (0.5)	0
Bladder cancer recurrent	1 (0.5)	0
Invasive breast carcinoma	1 (0.5)	0
Invasive ductal breast carcinoma	1 (0.5)	0
Lung adenocarcinoma	0	1 (0.5)
Lung adenocarcinoma stage IV	1 (0.5)	0
Metastatic malignant melanoma	1 (0.5)	0
Myelodysplastic syndrome	1 (0.5)	0
Pancreatic carcinoma metastatic	0	1 (0.5)
Penile cancer	1 (0.5)	0
Prostate cancer metastatic	1 (0.5)	0
Sarcoma of skin	0	1 (0.5)
Skin squamous cell carcinoma metastatic	0	1 (0.5)
T-cell lymphoma	1 (0.5)	0
Blood and lymphatic system disorders	1 (0.5)	0
Myeloid maturation arrest	1 (0.5)	0

Second primary malignancies are reported by *Medical Dictionary for Regulatory Activities* (MedDRA) superclass and preferred terms.

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An overview of the AEs reported from the August 23, 2019 data cut-off is reported in Table 40.[7] New fatal AEs between the two analyses were cerebrovascular accident, encephalitis, renal failure, and sepsis in one patient each in the VEN-OBI group and metastatic pancreatic carcinoma, septic shock, and metastatic skin squamous cell carcinoma in one patient each in the CHL-OBI group.

Table 40: Overview of AEs Reported in the Updated Data Cut-off in the CLL14 Trial

Category, n (%)	Primary Data Cut-Off (August 17, 2018)		Updated Data Cut-Off (August 23, 2019)	
	VEN-OBI (n=212)	CHL-OBI (n=214)	VEN-OBI (n=212)	CHL-OBI (n=214)
Total number of patients with at least 1 AE	200 (94.3)	213 (99.5)	201 (94.8)	213 (99.5)
Total number of deaths (all deaths)	20 (9.4)	16 (7.5)	27 (12.7)	26 (12.1)
AE with fatal outcome	16 (7.5)	8 (3.7)	19 (9.0)	11 (5.1)
Serious AE	104 (49.1)	90 (42.1)	115 (54.2)	95 (44.4)
Related SAE	56 (26.4)	56 (26.2)	56 (26.4)	57 (26.6)
Grade 3/4 AE (at greatest intensity)	151 (71.2)	157 (73.4)	150 (70.8)	155 (72.4)

AE = adverse event; CHL-OBI = Chlorambucil plus Obinutuzumab; SAE = serious adverse event; VEN-OBI = Venetoclax plus Obinutuzumab.

Data Source: Clinical Study Report Supplement[7]

Dose interruptions or reductions due to AEs

AEs leading to a dose interruption or dose reduction of VEN occurred in 57.1% (n=121) and 20.3% (n=43) of patients, respectively.[3] AEs leading to a dose interruption or dose reduction of CHL occurred in 56.5% (n=121) and 7.9% (n=17) of patients, respectively. The most common AE that led to either a dose interruption or reduction for both VEN and for CHL was neutropenia. AEs leading to a dose interruption of OBI occurred in 56.1% (n=119) of patients in the VEN-OBI group and in 52.3% (n=112) of patients in the CHL-OBI group. The most common AEs leading to a dose interruption of OBI were infusion-related reactions and neutropenia. Dose reductions of OBI were not allowed according to the protocol; however, reductions of OBI were reported in 1.4% (n=3) of patients in the VEN-OBI group and in 0.9% (n=2) of patients in the CHL-OBI group.

Subsequent Cancer Therapies

A summary of the subsequent anti-cancer treatments that patients received is provided in Table 41.[7] The proportion of patients who received subsequent anti-cancer treatments was lower in the VEN-OBI group (6.0%) compared to the CHL-OBI group (22.7%). One patient in the CHL-OBI group received additional treatment with CHL-OBI off-protocol.

Table 41: Subsequent Anti-Cancer Treatments in the CLL14 Trial

Treatment, n (%)	VEN-OBI (n=216)	CHL-OBI (n=216)
Total number of patients with at least one treatment	*13 (6.0)*	*49 (22.7)*
Total number of treatments	*14*	*65*
BEFORE Disease Progression		

Treatment, n (%)	VEN-OBI (n=216)	CHL-OBI (n=216)
Total number of patients with at least one treatment	*4 (1.9)*	*5 (2.3)*
Total number of treatments	*5*	*5*
Ibrutinib	2 (0.9)	4 (1.9)
Bendamustine plus Rituximab	3 (1.4)	0
Chlorambucil plus Obinutuzumab [a]	0	1 (0.5)
AFTER Disease Progression		
Total number of patients with at least one treatment	*9 (4.2)*	*44 (20.4)*
Total number of treatments	*9*	*60*
Ibrutinib	5 (2.3)	26 (12.0)
Bendamustine plus Rituximab	1 (0.5)	7 (3.2)
Venetoclax	0	6 (2.8)
Rituximab plus Cyclophosphamide plus Doxorubicin plus Vincristine plus Prednisone	1 (0.5)	3 (1.4)
Rituximab	0	3 (1.4)
Bendamustine	0	2 (0.9)
BGB-3111	0	1 (0.5)
Chlorambucil	1 (0.5)	0
Cyclophosphamide plus Vincristine plus Prednisone	0	1 (0.5)
Cyclophosphamide plus Prednisone	0	1 (0.5)
Durvalumab plus Ibrutinib	0	1 (0.5)
Fludarabine plus Cyclophosphamide plus Rituximab	0	1 (0.5)
Fludarabine plus Cyclophosphamide plus Rituximab - Lite	0	1 (0.5)
Idelalisib	0	1 (0.5)
Idelalisib plus Rituximab	0	1 (0.5)
Rituximab plus Cyclophosphamide plus Vincristine plus Prednisone	0	1 (0.5)
Rituximab plus Cyclophosphamide plus Dexamethasone	1 (0.5)	0
Study Hovon 141	0	1 (0.5)

CHL-OBI = Chlorambucil plus Obinutuzumab; VEN-OBI = Venetoclax plus Obinutuzumab.
Notes:
[a] Out of protocol

Data Source: Clinical Study Report Supplement[7]

6.4 Ongoing Trials

No ongoing trials were identified as being relevant to this review.

7 Supplemental Questions

The following supplemental questions were identified during development of the review protocol as relevant to the CADTH review of VEN-OBI compared to standard care for the treatment of patients with previously untreated CLL who are fludarabine ineligible:

- Summary and critical appraisal of sponsor-submitted NMA comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL
- Summary and critical appraisal of sponsor-submitted ITC and MAIC comparing VEN-OBI to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation

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

7.1 Summary and critical appraisal of sponsor-submitted NMA comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL

7.1.1 Objective

To summarize and critically appraise the methods and findings of the sponsor-submitted NMA comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL.

7.1.2 Findings

Methods

Systematic Review

The primary objective of the sponsor-submitted NMA was to estimate the comparative effectiveness of VEN-OBI for PFS and OS as first-line therapy in unfit patients with CLL compared to CHL-OBI, IBR-RIT, IBR-OBI, IBR monotherapy, BEN-RIT, CHL-OFA, CHL-RIT, CHL monotherapy, and FCR (FCR only included for the secondary objective of the NMA evaluating both 'unfit' and 'fit' patients as further described below). The NMA was based on a systematic literature review (SLR) in which the following databases were searched on December 12, 2018: EMBASE, MEDLINE (including MEDLINE In-Process), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Center for Reviews and Dissemination database (including Database of Abstracts of Reviews of Effects and HTA). Additionally, the following conference proceedings were searched for the years from 2016 to 2018: American Society of Clinical Oncology, American Society of Haematology, British Society of Haematology, European Haematology Association, European Society for Medical Oncology, International Society of Pharmacoeconomics and Outcomes Research, and iwCLL. The search was updated on July 8, 2019 to include literature published since the initial search date.

Full text articles published in English that met the eligibility criteria described in Table 42 were considered for inclusion in the SLR. Titles and abstracts of all literature identified by the search were screened for eligibility followed by full-text article screening. All screening was performed by two independent screeners who came to consensus on any conflicts. Data from the included full-text publications were extracted into a pre-specified template by one researcher and a second reviewer checked all the extracted data. A single researcher performed a critical appraisal of the quality of the selected studies using the quality assessment checklist presented in the National Institute for Health and Care Excellence (NICE) single technology assessment manufacturer submission template for randomized controlled trials (RCTs).

Table 42: Inclusion Criteria for the Systematic Literature Review

Criteria	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients (≥18 years) • Human • Established first-line CLL (CLL, B-CLL, or SLL) • With or without del(17p) or TP53 mutation • ± including fit and unfit patients	• Patients without established first-line CLL • Paediatric patients (<18 years) • Animal studies • In vitro studies • Patients with aggressive Non-Hodgkin's lymphoma (Richter's transformation or pro-lymphocytic leukaemia)
Interventions	• Venetoclax + obinutuzumab • Obinutuzumab + chlorambucil • Ibrutinib • Ofatumumab+ chlorambucil • Rituximab + chlorambucil • Obinutuzumab • High-dose methylprednisolone + rituximab • Chlorambucil • Fludarabine + cyclophosphamide + rituximab • Fludarabine + rituximab • Bendamustine ± CD20 monoclonal antibody (rituximab, ofatumumab. or obinutuzumab) • Pentostatin + cyclophosphamide + rituximab • Rituximab • Alemtuzumab ± rituximab • Idelalisib + rituximab • Ibrutinib + obinutuzumab • Ibrutinib + rituximab • Cladribine • Umbralisib/TGR-1202 • Acalabrutinib	• Any interventions not specified under inclusion criteria
Comparators	• Any comparator • No treatment • Placebo	• N/A
Outcomes	**Efficacy & safety parameters:** • PFS • ORR • CRR • Non-complete response • Partially complete response • PR • Non-partial response • Partial response with lymphocytosis • Complete remission with incomplete hematologic recovery • Stable disease • Progressive disease • Percentage of participants with MRD negativity • OS • Duration of (objective) response • EFS • Time to next treatment	• Any outcome not specified under inclusion criteria

Criteria	Inclusion Criteria	Exclusion Criteria
	• Time on treatment • AEs (Frequency, any grade, grade ≥3/4) • Haematological AEs • Non-haematological AEs • Tolerability	
Study Design	• Clinical trials • Observational studies	• Any study design not described under inclusion criteria

AE = adverse events; B-CLL = B-cell chronic lymphocytic leukemia; CLL = chronic Lymphocytic Leukemia; CRR = complete response rate; EFS = event-free survival; MRD = minimal residual disease; N/A = not applicable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SLL = small lymphocytic lymphoma.

Network Meta-Analysis

Feasibility Assessment

An assessment was conducted to determine the comparability of the included trials. Potential treatment effect modifiers assessed from the studies included in the NMA were determined based on a review of included trials and the clinical significance was determined during an advisory board meeting. The baseline patient characteristics that were assessed for heterogeneity were based on the selection criteria for the unfit and the overall networks and included the following: median age, CIRS scores (including timeframe of measurement of CIRS scores), ECOG scores, del17p/ TP53 mutation status, IGVH mutation status, and creatinine clearance. Heterogeneity in comparators was assessed in terms of treatment dose and dosing regimen. The outcomes (PFS and OS) were assessed for heterogeneity in reporting based on type of assessment, method of assessment, and the type of analyses presented. Additionally, the median duration of follow up was assessed for heterogeneity.

The report stated that the 'fitness' of patients was identified as an important prognostic factor and effect modifier. The classification of patients in the trials as 'fit' or 'unfit' was based on criteria derived from the National Comprehensive Cancer Network guidelines (Table 43). To reduce heterogeneity in the network, a base case analysis was performed as the primary objective of the NMA, which included only trials with 'unfit' patients. To assess the effect of heterogeneity between the trials with 'unfit' patients versus trials with 'fit' patients, a scenario analysis ('overall' network) was conducted as the secondary analysis of the NMA. The scenario analysis included trials with both 'fit' and 'unfit' patients. The heterogeneity assessment was performed by visual comparison of the point estimate results from the base case analyses compared to the scenario analyses.

Table 43: Criteria for Categorizing Patients as Fit or Unfit Based on Trial Inclusion Criteria

Category	Definition
Fit patients	– Patients aged <65 years with CIRS score <6 – Fludarabine eligible patients
Unfit patients	– Patients aged ≥65 years – Patients aged <65 years with CIRS score ≥6 – Patients that are specified to be fludarabine ineligible

CIRS = Cumulative illness rating scale.

Analysis

The analyses were conducted according to a Bayesian framework. The outcomes assessed were OS and PFS and comparisons were reported as HRs and 95% credible intervals (CrI) for comparing any two treatments (pairwise) in the network. Fixed-effect models were used for the analyses, which were conducted in WinBUGS. The report stated that the network was formed by only one trial per arm, which precluded the use of random-effect models.

A non-informative prior was used for the Bayesian analyses. To estimate the treatment effects (logHR in this NMA) a normal distribution with mean 0 and precision 0.0001 was used. In the Monte Carlo simulation, three simulation chains were used with 60,000 iterations, 20,000 burn-ins, and one thinning simulation chain. The Gelman-Rubin statistics, the size of the Monte Carlo error, auto-correlation function, trace plots, and Kernel density plots were checked to assess the convergence. The report stated that all analyses converged.

For trial publications that did not report HRs, HRs and their CIs were calculated from Kaplan-Meier (KM) curves using the methodology from Guyot, et al.,[38] which allows the simulation of patient-level data from KM curves. Once individual patient data were simulated, HRs and CIs were calculated assuming that the simulated data were equal to the observed data. This analysis was conducted using a Cox proportional hazard model with the R package *survival*.[39] This procedure for obtaining HRs from KM curves was only applied to the Alliance trial.

For the multi-arm trials (CLL11 and Alliance trials), an adjustment was made to account for the correlation between treatment relative effects from the same trials. This adjustment was performed using a vector of random effects for each trial, which was calculated using the distribution of one treatment effect conditional on the one of the other treatment effects from the same trial. The report stated that the calculation took the between-arm correlation into account, which is the approach recommended by the NICE Decision Support Unit Technical Support Document 2.[39]

The generalized linear model from Dias et al., 2011[39] was used to analyze the treatment differences. To mitigate the issue of the HRs not being normally distributed (which violates an assumption from the Dias model), the natural logarithm was applied to the HRs from the trials. To calculate the standard error (SE), the natural logarithm was applied to the CrIs of the HRs first and then a formula to transform CrIs to SE was applied.

Results

Systematic Review

The SLR identified 151 relevant publications based on the search strategy. Of these, 56 were RCT publications representing 36 unique RCTs. Nine RCTs met the inclusion criteria for the NMA. Although more recent evidence for five of the nine included RCTs was identified in the SLR, the report stated that the main reasons for not including newer evidence in the NMA were incompleteness of the reported results, or longer median follow-up times for either PFS or OS, but not for both. The classification of trials included in the network for patients defined as 'fit' or 'unfit' based on the criteria outlined in Table 43 are outlined in Table 44. Seven trials contributed data to the 'unfit' network (base case analysis) and two additional trials (nine total) contributed data to the 'overall' (scenario analysis) network.

Table 44: Classification of Trials Included in the Network as Fit or Unfit

Trial name	Age (years)		CIRS score ≥6	Fludarabine eligibility status	Fitness category
	<65	≥65			
CLL14	+	+	+	N/A	Unfit
CLL11	+	+	+	N/A	Unfit
MaBLe	+	+	NR	+	Unfit
CLL10 [a]	+	+	-	N/A	Fit
Resonate-2 [b]	-	+	NR	N/A	Unfit
iLLUMINATE	+	+	+	N/A	Unfit
COMPLEMENT1	+	+	NR	+	Unfit
ECOG [a]	+	+	NR	-	Fit

Trial name	Age (years)		CIRS score ≥6	Fludarabine eligibility status	Fitness category
	<65	≥65			
Alliance	-	+	NR	N/A	Unfit

CIRS = Cumulative illness rating scale; N/A = not applicable; NR = not reported.

Notes:

[a] Only included in the overall network only.

[b] Inputs from the Tedeschi et al., 2019 used in the NMA analyses for PFS and OS. Patient characteristics from Barr et al., 2018 were used for the feasibility assessment as this information was not available in the conference slides of Tedeschi et al., 2019.[6]

All the included trials were phase III trials; namely, the MaBLe trial was a phase IIIb study. Additionally, all included trials except the ECOG trial were multi-centre studies conducted internationally. Canada was a participating country in all the trials except for the MaBLe trial. Detailed baseline patient characteristics are reported in Table 45 and Table 46. Most studies had an open-label design; the Alliance and ECOG trials did not report whether they had an open-label design. Median age in the trials included in the 'unfit' network was consistent (69 to 74 years) and median CIRS scores ranged from 4-9. For the two additional trials included in the 'overall' network, CLL10 had a younger median age of patients (61 and 62.1 years in each arm) and a lower median CIRS score of 2 while the ECOG trial did not report either of these characteristics. Most patients had an ECOG PS of either 0 or 1 (not reported in CLL11 or ECOG). Median CrCl from the trials reporting this characteristic ranged from <60 mL/min to 87 mL/min. This characteristic was not reported in ECOG, and the MaBLe trial reported that all patients (both front-line and second-line) had normal CrCl levels (i.e. did not report a numerical value) but did not provide a breakdown by treatment line. From the studies reporting on the genetic abnormalities, 5 to 14% had del17p (reported in six studies), 7 to 13% had TP53 mutations (reported in three studies), and 43 to 61% had IGVH-unmutated (reported in eight studies) (Table 46). MRD negativity ranged from 1 to 58%. The method for measuring MRD in each study was not reported.

Table 45: Baseline Patient Characteristics of the Included Trials

Trial name	Treatment	Patients (n)	Median age (range) in years	Gender (% male)	ECOG score = 0 (%)	ECOG score = 1 (%)	ECOG score = 2 (%)	Median CIRS score	Median CrCl in mL/min
CLL14	VEN-OBI	216	72 (43-89)	67.6	41.2	45.8	12.5	9	65.16
	CHL-OBI	216	71 (41-89)	66.2	47.9	40.5	11.6	8	67.52
COMPLEMENT1	CHL-OFA	221	69 (35-92)	64	39	53	8	9	<70 [b]
	CHL	226	70 (36-91)	62	38	54	8	8	<70 [b]
iLLUMINATE	IBR-OBI	116	70 (66-75)[a]	59	50	46	4	4	72
	CHL-OBI	113	72 (66-77)[a]	68	46	48	6	4	69.6
Resonate-2	IBR	136	73 (65-89)	65	44	48	8	-	<60
	CHL	133	72 (65-90)	61	41	50	9	-	<60
Alliance	IBR	182	71 (65-89)	68	48	49	3	NR	69
	IBR-RIT	182	71 (65-86)	69	47	52	1	NR	67
	BEN-RIT	183	70 (65-86)	65	54	41	5	NR	67
MaBLe	BEN-RIT	121	72 (41-86)	58	51	41	7	NR	Normal CrCl
	CHL-RIT	120	72 (38-91)	67	49	43	7	NR	Normal CrCl
CLL11	CHL-RIT	330	73 (40-90)	62	-[c]	-[c]	-[c]	8	62.6
	CHL-OBI	333	74 (39-88)	59	-[c]	-[c]	-[c]	8	62.5
	CHL	118	72 (43-87)	64	-[c]	-[c]	-[c]	8	63.8
CLL10 [b]	BR	279	61 (54-69)[a]	74	64	36	0	2	86.4

Trial name	Treatment	Patients (n)	Median age (range) in years	Gender (% male)	ECOG score = 0 (%)	ECOG score = 1 (%)	ECOG score = 2 (%)	Median CIRS score	Median CrCl in mL/min
	FCR	282	62.1 (55-67)[a]	71	64	34	2	2	87
ECOG [b]	IBR-RIT	354	NR	NR	NR	NR	NR	NR	NR
	FCR	175	NR	NR	NR	NR	NR	NR	NR

BEN-RIT = Bendamustine plus Rituximab; CIRS = Cumulative Illness Rating Scale; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; ECOG PS = Eastern Cooperative Oncology Group performance status; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NR = not reported; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] Range represents inter-quartile range.

[b] 48% patients in the trial had a CrCL or <70mL/min

[c] Median ECOG score reported as <1.

Table 46: Genetic Abnormalities and MRD Status in Patients from the Trials

Trial name	Mutation type and status (%)			Treatment	Patients with MRD negativity		
	Del17p	TP53 mutation	IGVH unmutated		%	Measurement site	Measurement timing [b]
CLL14	8	7	56	VEN-OBI	56.9	Bone marrow	Three months after end of treatment
				CHL-OBI	17.1	Bone marrow	
COMPLEMENT1	6	NR	56	CHL-OFA	NR	NR	NR
				CHL	NR	NR	
iLLUMINATE	14	13	57	IBR-OBI	20	Bone marrow	samples collected before initiation of subsequent antineoplastic treatment[40]
				CHL-OBI	17	Bone marrow	
Resonate-2	NR	NR	43	IBR	NR	NR	NR
				CHL	NR	NR	
Alliance	6	10	61	IBR	1	Bone marrow	Cycle 9
				IBR-RIT	4	Bone marrow	
				BEN-RIT	8	NR	NR
MaBLe	5	NR	55	BEN-RIT	41	Bone marrow	12 weeks after the end of disease response assessment at cycle 6
				CHL-RIT	13	Bone marrow	
CLL11	8	NR	61	CHL-RIT	2.6	Bone marrow	Three months after end of treatment
				CHL-OBI	19.5	Bone marrow	
				CHL	NR	NR	NR
CLL10 [a]	NR	NR	61	BEN-RIT	32	Bone marrow	At the final re-staging
				FCR	58	Bone marrow	
ECOG [a]	NR	NR	NR	IBR-RIT	NR	NR	NR
				FCR	NR	NR	

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CrI = credible interval; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; IBR = Ibrutinib monotherapy; IBR-OBI =

Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NR = not reported; VEN-OBI = Venetoclax plus Obinutuzumab.
Notes:
[a] Include only fit patients.
[b] Timing of measurement according to trial publications. 12 weeks after the end of disease response assessment at cycle 6.
[c] Measurement for MRD at the final re-staging.

Heterogeneity between trials in dosing for both chlorambucil and rituximab was observed (Table 47). For the chlorambucil containing trials, the report states that while there was a difference in dosing regimens and cumulative dose, the difference in dosing was considered acceptable in a previous NICE submission (TA344).[41] For the rituximab containing trials, dosing regimens were different and the median cumulative doses were not comparable due to lack of information regarding treatment duration in the ECOG trial.

Table 47: Heterogeneity in Dosing Regimen for Comparators in the Trials

Trial name	Dosing Regimen	Cumulative Dose
Chlorambucil dosing (oral)		
COMPLEMENT1	10 mg/m² on days 1-7 of each 28-day cycle	728mg
RESONATE-2	0.5 mg/kg on days 1 and 15 of each 28-day cycle	454mg[a]
CLL11	0.5 mg/kg on days 1 and 15 of each 28-day cycle	384mg
Rituximab dosing (IV)		
Alliance	375mg/m^2 every one week for 4 weeks beginning on day 1 of the 2nd cycle, followed by 375mg/m^2 on day 1 of cycles 3-6	N/A
ECOG	50mg/m^2 on day 1 and 325mg/m^2 on day 2 of the 2nd cycle, followed by 500mg/m^2 on day 1 of subsequent cycles	N/A

N/A = not applicable
Notes:
[a] Median cumulative dose was calculated as a product of dose and median treatment duration when cumulative dose was not reported.

The efficacy results for both PFS and OS are presented in Table 48. For PFS, some trials reported HRs for PFS that were investigator-assessed and some reported IRC-assessed PFS. The ECOG trial did not report how PFS was assessed. Some trials also performed stratified Cox models while others used unstratified models. The stratification factors used in the individual trials were not reported. Preferentially, unstratified, IRC-assessed HRs were used in the NMA; however, when these were unavailable, stratified HRs or investigator-assessed endpoints were used as inputs in the networks. Heterogeneity was also observed in the method of assessment of progression. In the COMPLEMENT1 and iLLUMINATE trials, progression was mainly measured by CT scan while the Alliance and MaBLe trials reported other techniques of measuring progression. The median follow-up duration for the included trials ranged from 18.4 months to 38 months. Median follow up was not reported for ECOG. The report noted that updated estimates for RESONATE-2 were used with a follow-up time of over 60 months.

Table 48: Efficacy Results from the Trial

Trial name	Intervention	Comparator	PFS			OS	
			Assessment IRC/INV	Cox model	HR (95% CI; p-value)	Cox model	HR (95% CI; p-value)
CLL14	VEN-OBI	CHL-OBI	INV	Unstratified	0.295 (0.207 to 0.421; <0.0001)	Unstratified	1.023 (0.600 to 1.744; 0.933)
COMPLEMENT1	CHL-OFA	CHL	IRC	Stratified[a]	0.570 (0.450 to 0.720; <0.0001)	Unstratified	0.910 (0.570 to 1.430; 0.666)
iLLUMINATE	IBR-OBI	CHL-OBI	INV	Unstratified	0.260 (0.160 to 0.420; <0.0001)	NR	0.921 (0.479 to 1.772; 0.810)
Resonate-2	IBR	CHL	IRC	Stratified[a]	0.146 (0.098 to 0.218; NR)	Stratified[a]	0.450 (0.266 to 0.761; NR)

Trial name	Intervention	Comparator	PFS			OS	
			Assessment IRC/INV	Cox model	HR (95% CI; p-value)	Cox model	HR (95% CI; p-value)
Alliance [b]	IBR	BEN-RIT	IRC	Unstratified	0.370 (0.250 to 0.560; <0.001)	Unstratified	1.115 (0.610 to 2.030; 0.720)
	IBR-RIT	BEN-RIT	IRC	Unstratified	0.400 (0.270 to 0.600; <0.001)	Unstratified	1.072 (0.580 to 1.960; 0.820
MaBLe	BEN-RIT	CHL-RIT	IRC or INV	Stratified[a]	0.523 (0.339 to 0.806; 0.0030)	Stratified[a]	0.975 (0.505 to 1.880; 0.939)
CLL11	CHL-OBI	CHL-RIT	INV	Stratified[a]	0.400 (0.330 to 0.500; <0.0010)	Stratified[a]	0.700 (0.470 to 1.020; 0.063)
	CHL-OBI	CHL	INV	Stratified[a]	0.180 (0.140 to 0.240; <0.0001)	Stratified[a]	0.470 (0.290 to 0.760; 0.0001
	CHL-RIT	CHL	INV	Stratified[a]	0.440 (0.340 to 0.560; <0.0001)	Stratified[a]	0.600 (0.380 to 0.940; 0.024)
CLL10 [c]	BEN-RIT	FCR	IRC or INV	Unstratified	1.626 (1.244 to 2.125; 0.0003)	Unstratified	1.034 (0.620 to 1.724; 0.897)
ECOG [c]	IBR-RIT	FCR	NR	Stratified[a]	0.352 (0.223 to 0.558; <0.0001)	Stratified[a]	0.168 (0.053 to 0.538; <0.0001)

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CI = confidence interval; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazard ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; IRC = independent review committee; INV = investigator; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] Adjusted HRs presented

[b] The HR (± 95% CI) for OS were estimated based on digitized KM curves from Woyach, et al. 2018.

[c] Only included in the overall network (scenario analyses).

The quality assessments of the included studies performed by the authors showed mixed ratings of the trials (Table 49). The ECOG trial was not assessed for quality as the data was only available as a published conference abstract.

Table 49: Quality Assessment of RCTs

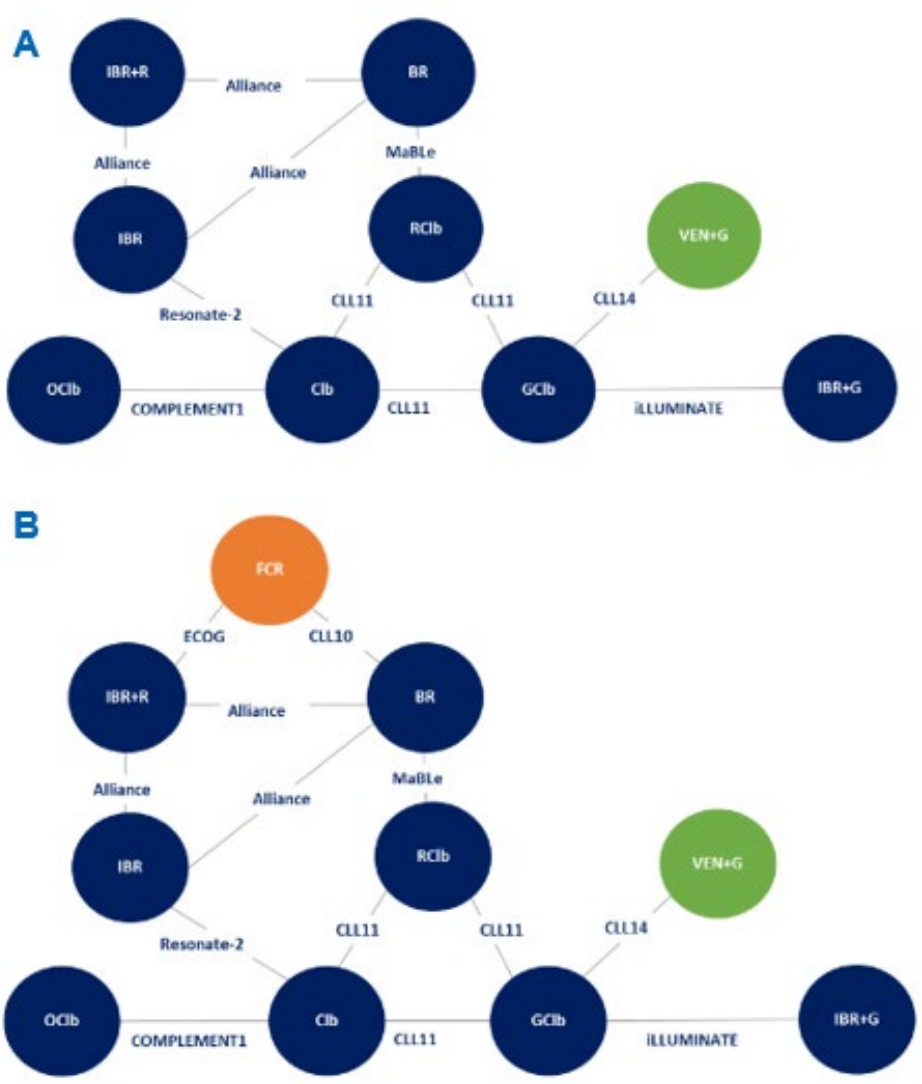
Publication	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants, and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missingness?
CLL14	Yes	Yes	Yes	No	Unclear (NR)	No	Unclear (NR)
COMPLEMENT1	Yes	Yes	Yes	No	Unclear (NR)	No	ITT yes, Unclear (NR)
iLLUMINATE	Yes	Yes	Yes	No	Unclear (NR)	No	Unclear (NR)
Resonate-2	Unclear (NR)	Unclear (NR)	Yes	No	Unclear (NR)	No	ITT yes, Unclear (NR)
Alliance	Unclear	Yes	Yes	Unclear (NR)	Unclear (NR)	No	ITT yes, Unclear (NR)
MaBLe	Unclear (NR)	Unclear (NR)	Yes	No	Unclear (NR)	No	ITT yes, Unclear (NR)
CLL11	Yes	Yes	Yes	No	Unclear (NR)	No	ITT yes, Unclear (NR)
CLL10	Yes	Yes	Yes	No	Unclear (NR)	No	ITT yes, Unclear (NR)
ECOG	The ECOG-ACRIN data has been published as a conference abstract, hence trial methods have not been assessed for quality.						

ITT = intention-to-treat; NR = not reported.

Network Meta-Analysis

The network of evidence for trials included in ‘unfit’ and the ‘overall’ networks are displayed in Figure 9.

Figure 9: Evidence Network for Trials Included in A) the ‘Unfit’ Network and B) the ‘Overall’ Network



BR = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; GCHL = Chlorambucil plus Obinutuzumab; IBR = Ibrutinib monotherapy; IBR+G = Ibrutinib plus Obinutuzumab; IBR+R = Ibrutinib plus Rituximab; OCHL = Chlorambucil plus Ofatumumab; RCHL = Chlorambucil plus Rituximab; VEN+G = Venetoclax plus Obinutuzumab.

Progression-Free Survival

The results of the analysis of the ‘unfit’ network for PFS are displayed in Table 50. VEN-OBI was favoured over all competing interventions [HR range: 2.51 to 16.83] except for IBR-OBI [HR=0.92; 95% CrI, 0.49 to 1.61].

Table 50: Pairwise Hazard Ratios with 95% CrIs for the NMA of PFS in the Unfit Network

Reference \ Comparator [HR (95% CrI)]	VEN-OBI	CHL	CHL-OBI	CHL-RIT	IBR	IBR-OBI	IBR-RIT	BEN-RIT	CHL-OFA
VEN-OBI	1	16.83 (10.70 to 25.17)	3.44 (2.37 to 4.82)	8.97 (5.86 to 13.11)	2.51 (1.33 to 4.31)	0.92 (0.49 to 1.61)	2.79 (1.21 to 5.5)	6.92 (3.17 to 13.11)	8.18 (5.02 to 12.59)
CHL		1	0.21 (0.16 to 0.26)	0.54 (0.43 to 0.67)	0.15 (0.10 to 0.22)	0.06 (0.03 to 0.09)	0.17 (0.08 to 0.29)	0.41 (0.22 to 0.69)	0.49 (0.39 to 0.60)
CHL-OBI			1	2.60 (2.15 to 3.13)	0.73 (0.44 to 1.13)	0.27 (0.16 to 0.42)	0.81 (0.39 to 1.49)	2.01 (1.04 to 3.52)	2.37 (1.75 to 3.14)
CHL-RIT				1	0.28 (0.17 to 0.43)	0.10 (0.06 to 0.17)	0.31 (0.15 to 0.57)	0.77 (0.40 to 1.36)	0.91 (0.69 to 1.19)
IBR					1	0.39 (0.19 to 0.72)	1.11 (0.67 to 1.74)	2.76 (1.82 to 4.00)	3.41 (2.11 to 5.23)
IBR-OBI						1	3.22 (1.29 to 6.70)	7.96 (3.38 to 16.00)	9.42 (5.11 to 15.89)
IBR-RIT							1	2.55 (1.69 to 3.71)	3.25 (1.60 to 5.95)
BEN-RIT								1	1.29 (0.67 to 2.25)
CHL-OFA									1

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CrI = credible interval; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazard ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NMA = network meta-analysis; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

The results of the analysis of the 'overall' network for PFS are displayed in Table 51. VEN-OBI was favoured over all competing interventions [HR range: 2.29 to 18.34] except for IBR-OBI [HR=0.92; 95% CrI, 0.48 to 1.61], and IBR-RIT [HR=1.88; 95% CrI, 0.98 to 3.27].

Table 51: Pairwise Hazard Ratios with 95% CrIs for the NMA of PFS in the Overall Network

Reference \ Comparator [HR (95% CrI)]	VEN-OBI	CHL	CHL-OBI	CHL-RIT	IBR	IBR-OBI	IBR-RIT	FCR	BEN-RIT	CHL-OFA
VEN-OBI	1	18.34 (11.68 to 27.53)	3.44 (2.38 to 4.83)	8.64 (5.66 to 12.69)	2.29 (1.31 to 3.73)	0.92 (0.48 to 1.61)	1.88 (0.98 to 3.27)	3.87 (2.08 to 6.61)	5.61 (3.20 to 9.19)	10.54 (6.28 to 16.66)
CHL		1	0.19 (0.15 to 0.24)	0.48 (0.37 to 0.60)	0.13 (0.09 to 0.17)	0.05 (0.03 to 0.08)	0.10 (0.06 to 0.16)	0.21 (0.13 to 0.32)	0.31 (0.21 to 0.44)	0.57 (0.45 to 0.72)
CHL-OBI			1	2.51 (2.06 to 3.02)	0.67 (0.44 to 0.96)	0.27 (0.16 to 0.42)	0.54 (0.33 to 0.85)	1.13 (0.70 to 1.72)	1.63 (1.08 to 2.35)	3.06 (2.15 to 4.24)
CHL-RIT				1	0.27 (0.18 to 0.38)	0.11 (0.06 to 0.18)	0.22 (0.13 to 0.33)	0.45 (0.29 to 0.67)	0.65 (0.45 to 0.91)	1.23 (0.86 to 1.69)
IBR					1	0.42 (0.21 to 0.74)	0.83 (0.54 to 1.22)	1.71 (1.12 to 2.50)	2.48 (1.76 to 3.41)	4.73 (3.06 to 6.98)

		Comparator [HR (95% CrI)]									
	IBR-OBI						1	2.16 (1.03 to 4.01)	4.46 (2.17 to 8.17)	6.46 (3.29 to 11.40)	12.15 (6.42 to 20.91)
	IBR-RIT							1	2.10 (1.49 to 2.88)	3.06 (2.21 to 4.13)	5.91 (3.39 to 9.62)
	FCR								1	1.47 (1.14 to 1.86)	2.85 (1.67 to 4.54)
	BEN-RIT									1	1.94 (1.21 to 2.94)
	CHL-OFA										1

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CrI = credible interval; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazard ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NMA = network meta-analysis; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Overall Survival

The results of the analysis of the 'unfit' network for OS are displayed in Table 52. VEN-OBI was favoured over CHL [HR=2.31; 95% CrI, 1.06 to 4.41] but not over any other competing treatments, for which the CrIs included 1.

Table 52: Pairwise Hazard Ratios with 95% CrIs for the NMA of OS in the Unfit Network

		Comparator [HR (95% CrI)]								
		VEN-OBI	CHL	CHL-OBI	CHL-RIT	IBR	IBR-OBI	IBR-RIT	BEN-RIT	CHL-OFA
Reference	VEN-OBI	1	2.31 (1.06 to 4.41)	1.01 (0.57 to 1.67)	1.30 (0.63 to 2.37)	1.15 (0.47 to 2.38)	0.99 (0.39 to 2.10)	1.16 (0.42 to 2.57)	1.15 (0.46 to 2.40)	2.16 (0.84 to 4.63)
	CHL		1	0.46 (0.28 to 0.72)	0.58 (0.37 to 0.86)	0.50 (0.31 to 0.78)	0.45 (0.19 to 0.93)	0.51 (0.26 to 0.90)	0.51 (0.28 to 0.86)	0.94 (0.57 to 1.45)
	CHL-OBI			1	1.28 (0.84 to 1.85)	1.13 (0.59 to 1.99)	0.97 (0.48 to 1.77)	1.15 (0.52 to 2.20)	1.13 (0.57 to 2.02)	2.13 (1.04 to 3.90)
	CHL-RIT				1	0.90 (0.50 to 1.49)	0.79 (0.34 to 1.58)	0.91 (0.44 to 1.66)	0.89 (0.50 to 1.47)	1.70 (0.86 to 3.02)
	IBR					1	0.95 (0.35 to 2.10)	1.02 (0.62 to 1.58)	1.03 (0.60 to 1.66)	1.97 (0.96 to 3.60)
	IBR-OBI						1	1.32 (0.44 to 3.09)	1.30 (0.47 to 2.89)	2.45 (0.86 to 5.55)
	IBR-RIT							1	1.05 (0.57 to 1.77)	2.04 (0.87 to 4.09)
	BEN-RIT								1	2.01 (0.90 to 3.89)
	CHL-OFA									1

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CrI = credible interval; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazards ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NMA = network meta-analysis; OS = overall survival; VEN-OBI = Venetoclax plus Obinutuzumab.

The results of the analysis of the 'overall' network are displayed in Table 53. VEN-OBI was favoured over CHL [HR=2.25; 95% CrI, 1.04 to 4.29] but not over any other competing treatments, for which the credible intervals included 1.

Table 53: Pairwise Hazard Ratios with 95% CrIs for the NMA of OS in the Overall Network

Reference	Comparator [HR (95% CrI)]									
	VEN-OBI	CHL	CHL-OBI	CHL-RIT	IBR	IBR-OBI	IBR-RIT	FCR	BEN-RIT	CHL-OFA
VEN-OBI	1	2.25 (1.04 to 4.29)	1.01 (0.57 to 1.67)	1.31 (0.64 to 2.41)	1.07 (0.44 to 2.21)	0.99 (0.38 to 2.10)	0.94 (0.35 to 2.07)	1.61 (0.56 to 3.67)	1.26 (0.51 to 2.65)	2.11 (0.83 to 4.50)
CHL		1	0.48 (0.29 to 0.74)	0.60 (0.39 to 0.89)	0.48 (0.29 to 0.74)	0.46 (0.19 to 0.95)	0.42 (0.22 to 0.74)	0.73 (0.33 to 1.38)	0.57 (0.31 to 0.96)	0.94 (0.57 to 1.46)
CHL-OBI			1	1.29 (0.85 to 1.88)	1.05 (0.54 to 1.84)	0.97 (0.48 to 1.78)	0.93 (0.43 to 1.77)	1.59 (0.68 to 3.17)	1.25 (0.63 to 2.22)	2.08 (1.02 to 3.81)
CHL-RIT				1	0.82 (0.46 to 1.36)	0.78 (0.34 to 1.56)	0.73 (0.36 to 1.30)	1.23 (0.57 to 2.32)	0.97 (0.55 to 1.59)	1.63 (0.83 to 2.90)
IBR					1	1.02 (0.38 to 2.24)	0.90 (0.55 to 1.36)	1.55 (0.77 to 2.79)	1.22 (0.72 to 1.93)	2.08 (1.02 to 3.80)
IBR-OBI						1	1.07 (0.36 to 2.47)	1.82 (0.58 to 4.36)	1.43 (0.52 to 3.16)	2.39 (0.84 to 5.38)
IBR-RIT							1	1.77 (0.89 to 3.17)	1.40 (0.81 to 2.26)	2.43 (1.05 to 4.84)
FCR								1	0.83 (0.50 to 1.30)	1.47 (0.57 to 3.13)
BEN-RIT									1	1.78 (0.80 to 3.43)
CHL-OFA										1

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; CrI = credible interval; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazard ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NMA = network meta-analysis; OS = overall survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Evaluation of Consistency

To evaluate the consistency of the NMA results, the indirect comparison HRs derived from the NMA were compared to the direct comparison HRs obtained from the trial publications for both PFS and OS (Table 54). The report stated that overall, the consistency between the evidence was good but major inconsistencies were identified that relate to the scenario analysis ('overall' network), which includes data from the ECOG trial and the CLL10 trial. The ECOG trial and the CLL10 trial both included fit patients; whereas, the other trials included unfit patients resulting in clinical heterogeneity. The authors noted that the heterogeneity associated with the ECOG and CLL10 trials would be expected to have an impact on the pairwise HRs and that the results from the consistency check are in line with earlier findings on heterogeneity.

Table 54: Comparison of Results from the NMA (Indirect HRs in the Loops of the Networks) Compared to the Direct HRs for both PFS and OS

Trial	Outcome	Intervention	Comparator	Direct HR	Inverse direct HR	Indirect HR ('unfit' network)	Difference	Indirect HR ('overall' network)	Difference
CLL10	PFS	BEN-RIT	FCR	1.626	0.615	NA	NA	1.470	111%
	OS	BEN-RIT	FCR	1.034	0.967	NA	NA	0.831	124%
MaBLe	PFS	BEN-RIT	CHL-RIT	0.523	1.912	1.423	134%	0.650	80%

Trial	Outcome	Intervention	Comparator	Direct HR	Inverse direct HR	Indirect HR ('unfit' network)	Difference	Indirect HR ('overall' network)	Difference
	OS	BEN-RIT	CHL-RIT	0.975	1.026	0.902	108%	0.967	101%
Resonate-2	PFS	IBR	CHL	0.146	8.264	0.149	98%	0.266	55%
	OS	IBR	CHL	0.450	2.315	0.520	87%	0.480	94%
ECOG	PFS	IBR-RIT	FCR	0.352	2.841	NA	NA	2.100	135% [a]
	OS	IBR-RIT	FCR	0.168	5.952	NA	NA	1.776	335% [a]
Alliance	PFS	IBR	BEN-RIT	0.370	2.703	2.756	98%[a]	2.483	109% [a]
	PFS	IBR-RIT	BEN-RIT	0.400	2.500	2.550	98% [a]	3.059	82% [a]
	OS	IBR	BEN-RIT	1.115	0.897	1.024	88% [a]	1.226	73% [a]
	OS	IBR-RIT	BEN-RIT	1.072	0.933	1.042	90% [a]	1.408	66% [a]
CLL14	PFS	CHL-OBI	CHL	0.180	5.556	0.208	87%	0.191	94%
	PFS	CHL-RIT	CHL	0.440	2.273	0.538	82%	0.476	92%
	OS	CHL-OBI	CHL	0.470	2.128	0.466	101%	0.476	99%
	OS	CHL-RIT	CHL	0.600	1.667	0.581	103%	0.600	100%

BEN-RIT = Bendamustine plus Rituximab; CHL = Chlorambucil monotherapy; CHL-OFA= Chlorambucil plus Ofatumumab; CHL-RIT = Chlorambucil plus Rituximab; FCR = Fludarabine plus Cyclophosphamide plus Rituximab; CHL-OBI = Chlorambucil plus Obinutuzumab; HR = hazard ratio; IBR = Ibrutinib monotherapy; IBR-OBI = Ibrutinib plus Obinutuzumab; IBR-RIT = Ibrutinib plus Rituximab; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.

Notes:

[a] The inverse of the direct HR was used to calculate the difference, since the inverse indirect HR was presented in the pairwise table only.

Critical Appraisal of NMA

The sponsor submitted NMA was critically appraised according to recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons and Network Meta-Analyses.[42] Details of the quality appraisal are provided in Table 55.

The NMA was based on a SLR that identified studies according to pre-specified inclusion criteria. The literature search appeared comprehensive. The search was last updated in July of 2019; therefore, there is a possibility that recent eligible evidence may not be included in the NMA. While the report was unclear in their summary of why publications were excluded ("*Main reasons for not including newer evidence were incompleteness of the reported results, or longer median follow-up times for either PFS or OS, but not for both*." (pg.16)), a list of the publications excluded in the full-text screening phase with the reason for exclusion was provided in the SLR report. More recent evidence indicated that some trials were excluded as only investigator-assessed PFS data was available and the preference in this NMA was to use IRC-assessed PFS. Some data was also excluded as only PFS or OS updated data was available for a trial. The authors stated that this updated evidence was excluded to keep the follow up length consistent for both OS and PFS. No sensitivity analyses were provided to determine whether the exclusion of the newer evidence impacted the NMA results.

Some limitations of the NMA methodology should be considered. The proportional hazards assumption was not tested; therefore, it is not possible to determine whether the assumption was violated. The report also does not mention whether alternative models than the generalized linear model by Dias were tested to determine the best fit. Furthermore, given that only one study per comparison arm was available, only fixed-effect models were used in the analysis. However, it must be noted that effect modifiers were different across studies, particularly in the scenario analysis where the CLL10 and ECOG studies were included in the model. Therefore, it is unlikely that the assumptions of a fixed-effect model were met. As a result, the precision of the estimates in the NMA may be overestimated. The authors also acknowledged limitations to the estimation of HRs from KM curves: "*Firstly, the estimation of HRs*

considers the simulated individual patient data as if they are observed data. In other words, it ignores the uncertainty coming from the simulation of individual patient data. Secondly, the extraction process of coordinates from the KM curves may introduce small deviations due to resolution of the KM chart, though the size of the error is usually small. (pg. 36)"

The authors did however perform a consistency check of the NMA results. The HRs derived from the NMA (indirect HRs in the loops of the networks) were compared to the HRs obtained directly from the trial publications for both PFS and OS. The report stated that overall, the consistency between the evidence was good but major inconsistencies were identified that related to the scenario analysis ('overall' network), which included data from the ECOG and CLL10 studies. The ECOG trial and the CLL10 trial showed more clinical heterogeneity compared to the other trials, mainly because of inclusion of 'fit' patients instead of just 'unfit' patients. The authors noted that this would be expected to have an impact on the pairwise HRs and that the results from the consistency check are in line with earlier findings on heterogeneity.

The authors performed quality assessments of the included studies using the quality assessment checklist presented in the NICE single technology assessment manufacturer submission template for RCTs. Several categories for each of the trials were rated as 'unclear' or 'not reported' and the implications of these ratings were not discussed. Additionally, the ECOG trial was not assessed for quality as the data was only available as a published trial conference.

As the 'fitness' of patients had been identified by the authors as an important prognostic factor and effect modifier, separate analyses were conducted for the 'unfit' network and for the 'overall' network. This would account for some of the heterogeneity of the patient characteristics contributing to the 'fitness' of the patients. Several other sources of clinical heterogeneity were acknowledged, however the authors stated that not enough variability was observed to exclude the trials from the network. For the 'unfit' network, heterogeneity was observed in the baseline patient characteristics for CIRS scores, and mutation status for genetic abnormalities (Del17p, TP53, and IGVH). The median age and creatinine clearance were similar across the trials included in this network. For the 'overall' network, heterogeneity was observed in the baseline patient characteristics for median age, CIRS scores, ECOG scores, creatinine clearance, mutation status for genetic abnormalities (Del17p, TP53, and IGVH), and MRD negativity at baseline. For both networks, heterogeneity between trials in dosing for both Chlorambucil and Rituximab was observed. The report stated that the difference in dosing for Chlorambucil was considered acceptable in a previous NICE submission. For the Rituximab containing trials, dosing regimens were different, and the median cumulative doses was not comparable due to lack of information on treatment duration in the ECOG trial. The authors also reported that heterogeneity was observed in median duration of follow-up (e.g. RESONATE-2 trial with 60 months of follow-up) and in some trials for outcome assessments (investigator-assessed versus IRC-assessed, and method of assessing disease progression). Additionally, some study and patient characteristics were missing from the included trials, and it was therefore not possible to determine whether there were additional imbalances between trials. No information was provided on the treatment exposure of patients in any of the trials.

Overall, the results can be considered generalizable to the Canadian context. The base case analysis ('unfit' network) is in line with the patient population under review (patients with previously untreated CLL who are fludarabine ineligible). Most of the included treatments are approved for use in Canada for the same patient population. However, the NMA did not consider acalabrutinib, which is currently under review by CADTH for the same patient population and would have been relevant to include in these analyses. Additionally, outcomes related to safety and HRQoL were not analyzed; therefore, no conclusions can be drawn comparing the treatment for these outcomes.

Table 55: Appraisal of the NMA using ISPOR criteria

ISPOR Questions	Details and Comments
1. Is the population relevant?	The population was relevant to the patient population under CADTH review for the base case analyses ('unfit' network). The scenario analyses ('overall' network) included a patient population that was broader than the population under CADTH review.
2. Are any critical interventions missing?	The NMA did not consider acalabrutinib. Acalabrutinib is under review by CADTH for the same patient population and would have been relevant to include in these analyses.
3. Are any relevant outcomes missing?	The NMA report only included analyses for efficacy outcomes. Outcomes related to safety and HRQoL were not included in the NMA.

ISPOR Questions	Details and Comments
4. Is the context (e.g., settings and circumstances) applicable to your population?	Overall, the results can be considered generalizable to the Canadian context. The base case analysis ('unfit' network) is in line with the patient population under review (patients with previously untreated CLL who are fludarabine ineligible). Most of the included treatments are approved for use in Canada for the same patient population.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	The researchers performed a SLR with pre-specified PICOS criteria to identify relevant trials. The NMA report described the information sources searched and the search strategies used. However, the literature search was performed in July 2019; therefore, the results may be outdated and recent trials may not have been included.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	The trials in the analysis for each outcome formed a connected network.
7. Is it apparent that poor quality studies were included thereby leading to bias?	The authors performed quality assessments of the included studies using the quality assessment checklist presented in the NICE single technology assessment manufacturer submission template for RCTs. Several categories for each of the trials were rated as 'unclear' or 'not reported' and the implications of these ratings were not discussed. Additionally, the ECOG trial was not assessed for quality as the data was only available as a published trial conference.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Selective outcome reporting was evaluated as part of the quality assessments of the trials. No selective outcome reporting was suspected for any of the trials.
9. 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?	For the 'unfit' network, heterogeneity was observed in the baseline patient characteristics for CIRS scores, and mutation status for genetic abnormalities (del17p, TP53, and IGVH). The median age and creatinine clearance were similar across the trials included in this network. For the unfit plus fit network, heterogeneity was observed in the baseline patient characteristics for median age, CIRS scores, ECOG scores, creatinine clearance, and mutation status for genetic abnormalities (del17p, TP53, and IGVH). For both networks, heterogeneity between trials in dosing for both chlorambucil and rituximab was observed. The authors also reported that heterogeneity was observed in the median duration of follow up (RESONATE-2 trial) and in some trials for outcome assessments (investigator-assessed versus IRC-assessed and method of assessing disease progression). Additionally, some study and patient characteristics were missing from the included trials; therefore, it was not possible to determine whether there were additional imbalances between trials. No information was provided on the treatment exposure of patients in any of the trials.
10. 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?	Potential treatment effect modifiers were identified prior to comparing the studies; they were identified based on a review of the included trials and the potential clinical significance was determined based on an advisory board meeting.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	It appeared that methods were used to preserve within-study randomization.
12. 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?	The results from the indirect HRs in the loops of the networks were compared to the direct HRs retrieved directly from the trial publications for both PFS and OS.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	It appears that both the direct and indirect comparisons were included in the NMA.
14. 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 with the analysis?	The authors performed two separate NMAs based on the 'fitness' of the patients to account for heterogeneity in this treatment effect modifier. Other inconsistences in treatment effect modifiers were not accounted for, and it was not possible to use random-effects models as each arm of the network was formed by only one trial.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	The report stated that random-effects models were not considered as each arm of the network was formed by only one trial. Given that fixed-effect models were used, precision of the estimates may be overestimated.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.

ISPOR Questions	Details and Comments
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	As the 'fitness' of patients had been identified by the authors as an important prognostic factor and effect modifier, separate analyses were conducted for the 'unfit' network and for the 'overall' network NMAs. The separate analyses could account for heterogeneity of the patient characteristics contributing to the 'fitness' (for the base case analysis). Several other sources of clinical heterogeneity were acknowledged (as discussed in Question 14); however, the authors stated that not enough variability was observed to exclude the trials from the network. Meta-regression was not performed.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Graphical representation of the networks and the number of trials per arm were provided for both outcomes analyzed.
19. Are the individual study results reported?	Individual study results were reported.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	The results of direct comparisons are reported separately from results of the NMA.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	All pairwise point estimates and CrIs were provided.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	No rankings were provided of the reported treatment effects and its uncertainty by outcome.
23. Is the impact of important patient characteristics on treatment effects reported?	While potential treatment effect modifiers were identified prior to performing the analyses, the impact of important patient characteristics on treatment effects was not reported.
24. Are the conclusions fair and balanced?	The conclusions appeared to be fair and balanced. Some limitations of the NMA were recognized and reported.
25. Were there any potential conflicts of interest?	No conflict of interest information was reported; however, the ITC/NMA was commissioned by the sponsor.
26. If yes, were steps taken to address these?	No.

7.1.3 Summary

In the absence of head-to-head trial data comparing VEN-OBI with other relevant treatments for patients with previously untreated CLL, the sponsor submitted an NMA to estimate the relative effectiveness of VEN-OBI compared to CHL-OBI, IbrB, IBR-OBI, IBR, BEN-RIT, CHL-OFA, CHL, CHL-RIT, and FCR. Two NMAs were conducted based on the 'fitness' of the patient populations: 1) an 'unfit' network and 2) an 'overall' network (both 'unfit' and 'fit' patients). A SLR identified nine RCTs that met the inclusion criteria for the NMA. Seven trials contributed data to the 'unfit' network and two additional trials (nine total) contributed data to the 'overall' network.

Results for PFS in the 'unfit' network suggested that VEN-OBI was favoured over all competing interventions except for IBR-OBI. For the 'overall' network, the results suggested that VEN-OBI was favoured over all competing interventions except for over IBR-OBI and IBR-RIT. Results for OS in both the 'unfit' and the 'overall' networks suggested that VEN-OBI was favoured over CHL but not over any other competing treatments, for which the credible intervals included 1.

The NMA did not consider potentially relevant comparators (i.e., acalabrutinib) and did not evaluate outcomes related to safety and HRQoL. The key limitations of the NMA include the potential sources of heterogeneity across the trials related to differences in patient and study characteristics and the limited evidence (one trial per network arm), which precluded the use of random-effects models. Additionally, the proportional hazards assumption was not tested; therefore, it was not possible to determine whether the assumption was violated. Results of the NMA should be interpreted with consideration of these limitations.

7.2 Summary and critical appraisal of sponsor-submitted ITCs comparing venetoclax in combination with obinutuzumab to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation

7.2.1 Objective

To summarize and critically appraise the sponsor-submitted ITCs comparing venetoclax in combination with obinutuzumab to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation.

7.2.2 Findings

Methods

Systematic Review

The objective of the sponsor-submitted analyses was to estimate the relative effectiveness of VEN-OBI compared to IBR for PFS and OS in patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. These analyses were conducted as no direct head-to-head evidence or evidence evaluating the effectiveness of VEN-OBI to IBR that included common comparators in previously untreated and unfit CLL patients with del17p/TP53 mutation were identified.

The ITCs were based on the SLR described in Section 7.1. Data sources for IBR were considered for inclusion if they met the following criteria: 1) included the population of previously untreated and unfit CLL patients with del17p/TP53 and treated with IBR; 2) reported PFS and/or OS or reported outcomes similarly defined (i.e., a KM PFS and/or OS graph clearly displaying the survival and progression events and numbers at risk); and 3) reported baseline clinical characteristics for the population of interest.

Feasibility Assessment

An assessment was conducted to evaluate the available efficacy data obtained from the CLL14 trial for VEN-OBI and the comparator data from identified studies for IBR to determine the suitability of conducting a MAIC of VEN-OBI versus IBR for the patient population (unfit and untreated patients with CLL who have del17p/TP53 mutation). Data on trial design, inclusion criteria, outcomes, and patient characteristics were reviewed to identify whether there were important differences between studies that would impact the likelihood of bias associated with MAIC estimates and to identify potential prognostic variables and effect modifiers for PFS and OS. The feasibility of conducting a MAIC was determined with an assessment of potentially overlapping variables based on the selection criteria for the 'unfit and 'overall' network (Table 43 of Section 7.1 for more details). These baseline characteristics included age, gender, CIRS scores, ECOG scores, IGVH mutational status, and CrCl. If it was determined that a MAIC was not suitable, unadjusted naïve indirect comparisons were conducted.

Results of the Feasibility Assessment

Four data sources were identified from the SLR for potential inclusion in the analyses: Ahn et al., Farooqui et al., Mato et al., and the Alliance trial (Woyach et al., 2018). The Alliance trial was subsequently excluded as the results for only nine patients in the relevant patient population were reported and the report authors stated that they considered this data source unsuitable. Additionally, an unpublished data source (CORE, a real-world evidence study in the United States) was identified for inclusion.

Details of the identified studies are summarized in Table 56. The CLL14 trial was an open-label multi-centre phase III RCT that compared VEN-OBI to CIbO. Ahn et al. and Farooqui et al. reported on the same trial; however, Ahn et al. reported on a later data cut-off of the single-arm, single-centre, open-label phase II trial that evaluated IBR. The CORE data and Mato et al. were multi-centre, retrospective, observational cohort studies (real-world evidence studies) that also evaluated IBR. Neither the dosage scheme (of both VEN-OBI and IBR) nor the length of follow-up in the studies were indicated.

Table 56: Overview of Trial Designs

Trial Characteristic	CLL14	Ahn et al.	Farooqui et al.	CORE data (unpublished)	Mato et al.
Study description	Open-label, multi-centre, randomized phase III study to compare the efficacy and safety of a combined regimen of VEN-OBI versus CHL-OBI in participants with CLL and coexisting medical conditions.	Phase 2, single-arm, open-label, single-centre study to evaluate safety and efficacy of IBR in CLL patients (NCT01500733).	Phase 2, open-label, single-centre, investigator-initiated study to investigate the safety and activity of IBR in previously untreated and relapsed or refractory CLL with TP53 aberrations (NCT01500733).	Multi-centre, retrospective, observational cohort study. A site-based chart review will be conducted to collect information on patients with CLL treated in a real-world setting.	Multi-centre, retrospective cohort study.
Total number of study participants	432	86	51	747	391
Key inclusion criteria	• ≥18 years • Documented previously untreated CLL according to the iwCLL criteria • CLL requiring treatment according to iwCLL criteria • CIRS score >6 or CrCl <70 mL/min • Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as per protocol, unless cytopenia is due to marrow involvement of CLL • Adequate liver function • Life expectancy >6 months • Agreement to use highly effective contraceptive methods per protocol	• Active CLL or SLL requiring therapy, and del17p by fluorescence in situ hybridization (FISH) in ≥10% of nuclei or TP53 mutation for the TP53 cohort; or age ≥65 years for the elderly cohort • ECOG performance status ≤ 2 • Neutrophil count ≥500/µl • Platelet count≥30,000/µl • All patients provided written informed consent	• Previously untreated patients with CLL and patients with relapsed or refractory disease • Diagnosis of CLL, including SLL according to WHO criteria, with deletion 17p13.1 identified by interphase fluorescence in-situ hybridization in at least 10% of nuclei scored or presence of TP53 mutation in the absence of deletion 17p13.1 • Active disease requiring therapy according to the iwCLL criteria • ≥18 years • ECOG performance status of ≤ 2 • Neutrophil count ≥500/µl	• Adult patients who initiated a first-line therapy for the treatment of CLL on or after January 1, 2012	• Patients were categorized based on key inclusion criteria for the RESONATE-2 trial: ○ Younger than 65 years of age at time of starting IBR (<65) versus ≥ 65 ○ Chromosome del(17p13) present versus del(17p13) absent.
Population of interest: previously untreated and unfit CLL with del17p/TP53	• Previously untreated and unfit CLL with del17p/ TP53 and treated with VEN-OBI (n=25) • Previously untreated CLL (age≥65) with del17p/ TP53 and treated with VEN-OBI (n=18)	• TP53 cohort (n=51) • Elderly cohort (n=35) • Subgroup for the untreated patients, TP53 (n=35) Elderly (n=18) • No subgroup for the unfit patients with TP53	• TP53 cohort (n=51) • Del17p cohort (n=47) • Subgroup for the previously untreated patients (n=35) • No subgroup for the unfit patients	• Previously untreated CLL patients with del17p/TP53 and treated with IBR (n=63) • For IBR, no subgroup for the unfit patients as CIRS was not captured, subgroup for age ≥65 (n=36)	• CLL patients treated with IBR in the front-line setting with del(17p13) mutation (N=110)
Efficacy endpoint	• PFS for previously untreated and unfit CLL with del17p/ TP53 ○ Investigator-assessed: median not reached ○ IRC-assessed: median not reached • OS for previously untreated and unfit CLL with del17p/ TP53: median not reached	• PFS: KM curve for previously untreated patients with TP53 • OS: KM curve for previously untreated patients with TP53	• PFS: KM curve for previously untreated patients with TP53 • OS: KM curve for previously untreated patients	• PFS for previously untreated CLL with del17p/ TP53 (age≥65, investigator-assessed): median not reached • OS for previously untreated CLL with del17p/ TP53 (age≥65): median not reached	• PFS stratified by age at IBR initiation and del(17p13) status (both categorical variables): median not reached • OS stratified by age at IBR initiation and del(17p13) status (both categorical variables): median not reached

CIRS = Cumulative Illness Rating Scale; CHL-OBI = Chlorambucil plus Obinutuzumab; CLL = chronic lymphocytic leukemia; CrCl = creatine clearance; IBR = Ibrutinib; IRC = independent review committee; iwCLL = International Workshop on chronic lymphocytic leukemia; KM = Kaplan=Meier; OS = overall survival; PFS = progression-free survival; PRO = patient reported outcomes; Ven = venetoclax; VEN-OBI = Venetoclax plus Obinutuzumab.

All the included studies had broader patient populations than the patient population of interest of the indirect comparisons (previously untreated and unfit CLL patients with del17p/ TP53); however, subgroup data specific to the population of interest were available from these studies. Details of the relevant subgroup of patients are displayed in Table 56. The CLL14 trial included previously untreated and unfit CLL patients but only patients with del17p/ TP53 mutation were included in these analyses (n=25). The CORE study and Mato et al. included previously untreated patients. Namely, patients in the CORE study with the del17p/TP53 mutation who were treatment naïve, treated with IBR, and were ≥ 65 years were included in these analyses (n=36) and patients in Mato et al. who had the del17p mutation were included (n=110). The report stated that is was unknown how many patients in the Mato et al. trial were ≥ 65 years but based on the total population included in the trial, it was assumed about 59% were ≥ 65 years old. Ahn et al. and Farooqui et al. (both reported on the same trial) included both patients with previously untreated CLL and patients with relapsed/refractory CLL; however, only subgroup data for the previously untreated patients were available (n=35).

Subgroup analyses for the outcomes based on the unfit patients were not reported in any of the IBR data sources. However, the CORE study reported the subgroup analyses for PFS and OS for patients that were ≥65 years and Mato et al. reported KM curves of PFS and OS, stratified for del17p status and age. Farooqui et al. reported the KM estimates of PFS and OS for the for previously untreated patients with TP53 mutation and del17p and Ahn et al. provided updated KM estimate of PFS and OS with 5-year median follow-up. In the CLL14 trial, the CORE study, and Mato et al. neither the median PFS nor the median OS for the relevant population were reached.

Details of the baseline patient characteristics of the studies are displayed in Table 57. All four studies contributing data for IBR reported on populations with TP53 mutations; however, the studies did not collect information about CIRS scores and no subgroup data were available for the unfit patients with del17p/TP53 mutation (as 'fitness' level is based partially on the CIRS scores). The CORE study reported data on age, gender, ECOG, IGVH mutation status, and CrCl in elderly patients (≥65 years)—including subgroup data for patients with del17p/TP53 mutations. Mato et al. reported PFS and OS stratified for del17p status and for age but not the combination of these two characteristics (i.e. del17p stratified by age). While Farooqui et al. reported data for patients with previously untreated CLL with TP53 mutations and del17p, they did not report on the required matching variables including age, gender, and IGVH mutation status. Ahn et al. did not report on the required baseline matching variables for the subgroup (treatment-naïve patients) but after correspondence with the author some baseline characteristics were obtained for treatment-naïve patients. Therefore, data was obtained for patients with TP53 mutations and for the categorical variable of age (65 years threshold); however, a subgroup analysis based on elderly patients was not available.

Table 57: Characteristics of the included trials

Characteristic	CLL14 (n=25)	Ahn et al. [a] (n=35)	Farooqui et al. (n=35)	CORE Data (n=36)	Mato et al (n=10)
Age, median (range)	70 (60-80)	62 (33 – 82)	62 (33-82)	NR	NR
Age, n (%)					
≥65 years	19 (76.0)	14 (40.0)	NR	36 (100)	NR
<65 years	6 (24.0)	NR	NR	0 (0)	NR
Gender, n (%) male	21 (84.0)	23 (65.7)	23 (65.7)	24 (66.7)	NR
CIRS score, n (%)					
≤6	5 (20.0)	NR	NR	NR	NR
>6	20 (80.0)	NR	NR	NR	NR
ECOG, n (%)					
0	10 (40.0)	NR	NR	12 (33.3)	NR
1	11 (44.0)	NR	NR	13 (36.1)	NR
2	4 (16)	NR	NR	7 (19.4)	NR
unknown/not measured	0 (0)	NR	NR	4 (11.1)	NR

Characteristic	CLL14 (n=25)	Ahn et al. [a] (n=35)	Farooqui et al. (n=35)	CORE Data (n=36)	Mato et al (n=10)
IGVH mutation, n (%)					
unmutated	5 (20.0)	22 (62.9)	22 (62.9)	14 (38.9)	NR
mutated	16 (64.0)	13 (37.1)	NR	4 (11.1)	NR
unknown	4 (16.0)	0 (0)	NR	NR	NR
Creatinine clearance, n (%)					
<70 mL/min	14 (56.0)	NR	NR	22 (61.1) [b]	NR
≥70 mL/min	11 (44.0)	NR	NR	13 (36.1) [b]	NR
unknown/not measured	0 (0)	NR	NR	1 (2.8) [b]	NR

NR = not reported.
[a] Data on treatment-naïve patients retrieved after correspondence with the author.
[b] Data reported is for the categories of <80 mL/min or ≥80 mL/min.

The patient inclusion and sample size for the naïve indirect comparisons are displayed in Table 58. Due to the limitations in data identified, the report concluded that it was not feasible to perform an unanchored MAIC to estimate the relative effectiveness for PFS and OS of VEN-OBI compared to IBR for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. Therefore, an unadjusted naïve indirect comparison was performed using data from Ahn et al. (for patients with TP53 mutations), the CORE data (for patients with del17p/TP53 mutation and who were ≥65 years), and Mato et al. (for patients with del17p). The authors also reported that Farooqui et al. was not used in these analyses due to the small sample size available (n=35).

Results of the Analyses

While IPD was available for the CLL14 trial, simulation of the patient level data (as described in the Methods section) was performed for Ahn et al., Mato et al., and the CORE study by digitizing the available KM curves in WebPlotDigitizer11 using the methodology from Guyot, et al.[38] The datasets were then merged and unstratified Cox regression models were used to calculate the HRs for PFS and OS to compare between VEN-OBI and IBR. Patients from the CLL14 trial were removed for these analyses if they did not meet the inclusion criteria from the IBR trials.

Table 58: Sample Sizes for the Naïve Indirect Comparisons

Source data for IBR	Inclusion	VEN-OBI sample size (from CLL14)	IBR source sample size
Ahn et al.	TP53	25	35
Core	del17p/TP53 mutation, age ≥65 years	19 [a]	36
Mato et al.	del17p	25	PFS - 108; OS - 103

IBR = Ibrutinib; OS = overall survival; PFS = progression-free survival; VEN-OBI = Venetoclax plus Obinutuzumab.
[a] Patients under the age of 65 are excluded from the CLL14 trial to match the inclusion criteria of the CORE study.

Furthermore, as per a specific request, a MAIC of VEN-OBI compared to IBR was performed using data from Ahn et al. The MAIC was carried out according to the NICE technical support document on population adjustments.[39] Four variables were available, which could be considered as potential matching variables (age <65 years, median age, sex, and IGVH mutation status). The authors reported that due to the small sample size in the patient-level dataset, statistical tests for confounders or effect modifiers were unlikely to yield reliable results; therefore, matching variables were based on scientific literature on prognostic variables. The following variables were considered for matching and adjustment: proportion of patients with age <65, proportion of patients with age ≤62 (median age in Ahn et al.), sex (female versus male), proportion of patients with unmutated IGVH (mutated versus unmutated or missing), and proportion of patients with mutated IGVH (unmutated versus mutated or missing).

Adjusting for these variables resulted in an effective sample size of 7.7 patients in the CLL14 dataset; namely, weights varied from 0 to >6, nine patients were at risk at t=0, and four patients were at risk at 30 months for PFS. The report stated that this limited sample size was caused by matching on IGVH mutational status of which, 4 (16%) records for this variable were missing. Accordingly, IGVH

mutational status was removed from the matching variables. Matching based on age and sex yielded an effective sample size of 14.6 patients in the CLL14 dataset; namely, weights varied between 0.4 to 1.8, 19 patients were at risk at t=0, and two and five patients were at risk at 40 months for PFS and OS, respectively. The patient characteristics before and after matching are displayed in Table 59.

Table 59: Patient Characteristics Before and After Adjusting for Age and Sex

Characteristic (%)	CLL14 before adjusting n = 25	CLL14 after adjusting ESS n = 14.5	Ahn et al. n = 35
Age =< 65	24.0	60.0	60.0
Age >= 62	80.0	50.0	50.0
Sex (male)	64.0	62.8	62.8
IGVH unmutated [a]	64.0	68.1	62.9
IGVH mutated [a]	20.0	9.5	37.1

ESS = effective sample size
Note:
[a] IGVH was not used as matching variable but effects of reweighting the population are shown in this table

Efficacy Results

Results for the unadjusted naïve comparisons for both PFS and OS are displayed in Table 60. None of the comparisons for either PFS or OS were statistically significant except for the PFS calculated from the Ahn et al. IBR data, which suggested that IBR leads to a statistically longer PFS compared to VEN-OBI (HR: 0.318; 95% CI, 0.112 to 0.903; p=0.031).

Table 60: HR Estimates of IBR versus VEN-OBI from the Unadjusted Naïve Indirect Comparisons

Treatment (IBR versus VEN-OBI)	PFS	OS
Ahn et al.		
HR (95% CI)	0.318 (0.112 to 0.903)	0.401 (0.123 to 1.315)
SE ln(HR)	0.533	0.606
p-value	0.031	0.132
CORE data		
HR (95% CI)	0.500 (0.140 to 1.792)	0.536 (0.120 to 2.399)
SE ln(HR)	0.651	0.764
p-value	0.287	0.415
Mato et al.		
HR (95% CI)	0.660 (0.270 to 1.615)	0.841 (0.301 to 2.352)
SE ln(HR)	0.457	0.525
p-value	0.363	0.741

CI = confidence interval; HR = hazards ratio; IBR = Ibrutinib; OS = overall survival; PFS = progression-free survival; SE = standard error; VEN-OBI = Venetoclax plus Obinutuzumab.

Results for the MAIC for both PFS and OS are displayed in Table 61. The comparison for PFS displayed a statistically significant difference between the two treatments, which suggested that IBR leads to a longer PFS compared to VEN-OBI (HR: 0.280; 95% CI, 0.093 to 0.842; p=0.024). The comparison for OS did not display a statistically significant difference between the two treatments.

Table 61: HR Estimates of IBR versus VEN-OBI from the MAIC

Treatment (IBR versus VEN-OBI)	PFS	OS
Ahn et al.		
HR (95% CI)	0.280 (0.093 to 0.842)	0.497 (0.128 to 1.926)
SE ln(HR)	0.562	0.691
p-value	0.024	0.312

CI = confidence interval; HR = hazards ratio; IBR = Ibrutinib; OS = overall survival; PFS = progression-free survival; SE = standard error; VEN-OBI = Venetoclax plus Obinutuzumab.

Critical Appraisal of Indirect Treatment Comparisons

The SLR was used to identify studies that could be evaluated in a feasibility assessment to conduct ITCs. The literature search appeared comprehensive. The search was last updated in July of 2019; therefore, it is possible that recent eligible evidence may not have been included in the ITCs. While specific methods for identifying and including literature for these analyses were not provided, a list of publications excluded during the full-text screening phase with the exclusion reason was provided in the SLR report. Therefore, it was possible to refer to the respective publication for reasons of exclusion. However, it was not clear how the CORE study was identified as this data was unpublished. Farooqui et al. reported on the same trial as Ahn et al.; however, it was not clear why the data was excluded. The report stated that it was excluded due to the small sample size but the available sample size from that trial (n=35) was comparable to other sample sizes used in these analyses. Additionally, the report did not provide quality assessments of the included studies.

Several limitations of the methodology of the analyses should be considered. The comparisons were unanchored because no common comparator was identified between the CLL14 study and other identified studies for this patient population. The authors stated that the feasibility assessment demonstrated that a MAIC should not be undertaken and that naïve comparisons were preferred. The identified sample sizes for the eligible patients from each of the trials were small; thus, there is concern that randomization would not have been upheld when only subgroups from the trials were included in these analyses. The report also noted that in examining the KM curves, the curves crossed in each of the analyses, indicating that the proportional hazards assumption did not hold, which increases the unreliability of long-term results. The resulting CIs were wide; therefore, conclusions about the results should be interpreted with extreme caution.

Although the authors concluded a MAIC was not feasible, a MAIC was still performed as per a specific request for CLL14 compared to Ahn et al. Limited details were provided as to the methodology that was used; although, the authors stated that the analysis was "*carried out according to the NICE technical support document (TSD) on population adjustment*". The authors stated that given the small sample size available for the specific patient population for the CLL 14 trial, weighting was only performed for age and sex as weighting of all known prognostic variables in the dataset would have reduced the effective sample size to an unacceptable size (i.e. too small). Nevertheless, this still resulted in a small effective sample size (14.6 patients) and IGVH mutations were not matched for between the two trials.

Additionally, several sources of clinical heterogeneity must be considered. As previously stated, matching even on the known/potential prognostic variables and effect modifiers was not feasible due to the small sample sizes. The inclusion/exclusion criteria for the patients varied substantially between the studies. For example, Mato et al. included patients of all ages and did not provide detail on the number of patients ≥ 65 years; whereas, the CLL14 trial included patients mostly ≥ 65 years. The median age for Ahn et al. was also eight years younger than the median age from the included patients from the CLL14 trial (62 versus 70). Furthermore, several patient characteristics that may impact disease prognosis were not available from most of the trials (i.e. gender, CIRS score, ECOG PS, IGVH mutation status, and CrCl). The length of follow up was also not provided for the included studies.

Moreover, several study types were included in these analyses including phase II trials, phase III trials, and retrospective cohort studies (real-world evidence), which further leads to challenges in comparing the results of the studies. In addition, differences in when (i.e. calendar year) the studies were conducted could have had important implications regarding clinical standards that are susceptible to differences in timing (i.e. may change over time) such as disease testing, treatment sequencing, etc. Furthermore, length of follow-up and medication dosing (both VEN-OBI and IBR) may also have had important implications on the results of the trials. In light of these important limitations, the results of both the unadjusted naïve comparisons and the MAIC must be interpreted with caution as there is a high risk of residual bias in these estimates.

Overall, the results can be considered generalizable to the Canadian context for the population of patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation. The treatment analyzed as the comparator (IBR) is the standard of care in Canada for these patients; therefore, the comparison was relevant. However, outcomes related to safety and HRQoL were not analyzed; thus, no conclusions can be drawn comparing the treatment for these outcomes.

7.2.3 Summary

In the absence of head-to-head trial data comparing the effectiveness of VEN-OBI to IBR in terms of PFS and OS for patients with previously untreated CLL who are unfit and have a del17p/TP53 mutation, the sponsor submitted ITCs and a MAIC. Three naïve indirect treatment comparisons were conducted, comparing VEN-OBI data from CLL14 to IBR data from three separate studies using the following patient populations: Ahn et al. – TP53 mutation, Mato et al. – del17p, and CORE study – del17p/TP53 mutation and ≥65 years. Although it was determined that it was not feasible to conduct a MAIC, one was conducted following a specific request for the data from CLL14 compared to Ahn et al.

Results from all the comparisons for PFS and OS demonstrated no statistically significant differences between the two treatments except for the PFS HR calculated with both the ITC and the MAICs using IBR data from Ahn et. al, which suggested that IBR led to a statistically longer PFS compared to VEN-OBI.

Important limitations of the analyses included very small sample sizes and a large amount of identified clinical heterogeneity. Additionally, the study designs varied including phase II trials, phase III trials, and retrospective cohort studies (real-world evidence), which further leads to challenges in comparing the results of the studies. Therefore, the results of these analyses should be interpreted with extreme caution in light of the limitations.

8 Comparison with Other Literature

The CADTH CGP and the CADTH Method Team did not identify other relevant literature as supporting information for this review.

9 About this Document

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

CADTH 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 Procedures for the CADTH pan-Canadian Oncology Drug Review. The sponsor, as the primary data owner, did not agree to the disclosure of some clinical information which was provided to pERC for their deliberations, and this information has been redacted in this publicly posted Guidance Report.

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

Appendix 1: Literature Search Strategy and Detailed Methodology

1. Literature search via Ovid platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** March 2020**, Embase** 1974 to 2020 April 28**, Ovid MEDLINE(R)**

ALL 1946 to April 28, 2020

Search Strategy:

#	Search Strategy	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,nm,rn.	4773
2	Leukemia, Lymphocytic, Chronic, B-Cell/	39232
3	(small-cell adj3 lymphoma*).ti,ab,kf,kw.	1207
4	(lymphocytic lymphoma* or lymphocytic leuk?emia* or lymphoncytic leuc?emia* or lymphoplasmacytoid lymphoma* or b-cell malignan*).ti,ab,kf,kw.	76808
5	((chronic or small or smallcell or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or lymphoblastic or leuk?emia* or leuc?emia* or lymphoma*)).ti,ab,kf,kw.	150571
6	(CLL or SLL or BCLL).ti,ab,kf,kw.	44246
7	2 or 3 or 4 or 5 or 6	186187
8	1 and 7	1992
9	8 use medall	462
10	limit 9 to english language	446
11	8 use cctr	134
12	*Venetoclax/	1157
13	(venetoclax* or venclexta* or venclyxto* or ABT-199 or ABT199 or GDC-0199 or GDC0199 or RG-7601 or RG7601).ti,ab,kw,dq.	3721
14	12 or 13	3758
15	exp Chronic Lymphatic Leukemia/ or Lymphocytic lymphoma/	60368
16	(small-cell adj3 lymphoma*).ti,ab,dq,kw.	1212
17	(lymphocytic lymphoma* or lymphocytic leuk?emia* or lymphoncytic leuc?emia* or lymphoplasmacytoid lymphoma* or b-cell malignan*).ti,ab,dq,kw.	76778
18	((chronic or small or smallcell or well-differentiated) adj3 (lymphocytic or lymphoplasmacytoid or lymphatic or lymphocyte* or lymphoid* or lymphoblastic or leuk?emia* or leuc?emia* or lymphoma*)).ti,ab,dq,kw.	150544
19	(CLL or SLL or BCLL).ti,ab,dq,kw.	44175
20	15 or 16 or 17 or 18 or 19	194601
21	14 and 20	1711

#	Search Strategy	Results
22	21 use oemezd	1140
23	limit 22 to english language	1108
24	23 and conference abstract.pt.	598
25	limit 24 to yr="2015 -Current"	543
26	23 not conference abstract.pt.	510
27	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.	1176246
28	Randomized Controlled Trial/	1105402
29	exp Randomized Controlled Trials as Topic/	320925
30	"Randomized Controlled Trial (topic)"/	177800
31	Controlled Clinical Trial/	557774
32	exp Controlled Clinical Trials as Topic/	333436
33	"Controlled Clinical Trial (topic)"/	10678
34	Randomization/	189275
35	Random Allocation/	206127
36	Double-Blind Method/	440572
37	Double Blind Procedure/	171787
38	Double-Blind Studies/	286685
39	Single-Blind Method/	85516
40	Single Blind Procedure/	38698
41	Single-Blind Studies/	87510
42	Placebos/	351761
43	Placebo/	349365
44	Control Groups/	112242
45	Control Group/	112145
46	(random* or sham or placebo*).ti,ab,hw,kf,kw.	4611294
47	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	879204
48	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	4042
49	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	3110126
50	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	108184
51	allocated.ti,ab,hw.	206773

#	Search Strategy	Results
52	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	138979
53	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	32906
54	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	1248
55	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	14924
56	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	22274
57	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.	158613
58	or/27-57	6500493
59	(10 or 26) and 58	169
60	11 or 59	303
61	remove duplicates from 60	247
62	25 and 58	144
63	61 or 62	391

2. **Literature search via PubMed**

A limited PubMed search was performed to retrieve citations not found in the MEDLINE search.

#	Query	Results
23	Search: **#21 AND publisher[sb]** Filters: **English**	4
22	Search: **#21 AND publisher[sb]**	4
21	Search: **#7 AND #20**	62
20	Search: **#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19**	2,988,538
19	Search: **(phase III[tiab] OR phase 3[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])**	49,468
18	Search: **quasiexperimental study[tiab] OR quasi-experimental study[tiab] OR quasiexperimental studies[tiab] OR quasi-experimental studies[tiab] OR quasiexperimental trial*[tiab] OR quasi-experimental trial*[tiab]**	5,300
17	Search: **pragmatic study[tiab] OR pragmatic studies[tiab] OR pragmatic trial*[tiab] OR practical trial*[tiab]**	1,662
16	Search: **(equivalence[tiab] OR superiority[tiab] OR non-inferiority[tiab] OR noninferiority[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab)**	37,336
15	Search: **open-label[tiab] AND (study[tiab] OR studies[tiab] or trial*[tiab])**	41,272
14	Search: **random allocation[tiab] OR randomly allocated[tiab]**	29,788

#	Query	Results
13	Search: **nonrandom*[tiab] OR non-random*[tiab] OR quasi-random*[tiab] OR quasirandom*[tiab]**	42,908
12	Search: **control group*[tiab]**	451,031
11	Search: **(control[tiab] OR controlled[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])**	1,809,066
10	Search: **(singl*[tiab] OR doubl*[tiab] OR tripl*[tiab] OR trebl*[tiab]) AND (blind*[tiab] OR dumm*[tiab] OR mask*[tiab])**	192,800
9	Search: **random*[tiab] OR sham[tiab] OR placebo*[tiab]**	1,265,025
8	Search: **Randomized Controlled Trial[pt] OR Randomized Controlled Trials as Topic[mh] OR Controlled Clinical Trial[pt] OR Controlled Clinical Trials as Topic[mh] OR Random Allocation[mh] OR Double-Blind Method[mh] OR Single-Blind Method[mh] OR Placebos[mh] OR Control Groups[mh]**	836,896
7	Search: **#1 AND #6**	480
6	Search: **#2 OR #3 OR #4 OR #5**	160,472
5	Search: **CLL[tiab] OR SLL[tiab] OR BCLL[tiab]**	15,131
4	Search: **(chronic[tiab] OR small[tiab] OR smallcell[tiab] OR well-differentiated[tiab]) AND (lymphocytic[tiab] OR lymphoplasmacytoid[tiab] OR lymphatic or lymphocyte*[tiab] OR lymphoid*[tiab] OR lymphoblastic[tiab] OR leukemia*[tiab] OR leukaemia* OR leucemia*[tiab] OR leukaemia*[tiab])**	148,719
3	Search: **small-cell lymphoma*[tiab] OR lymphocytic lymphoma*[tiab] OR lymphoplasmacytoid lymphoma*[tiab] or b-cell malignan*[tiab] OR lymphocytic leukemia*[tiab]**	26,284
2	Search: **Leukemia, Lymphocytic, Chronic, B-Cell[mh]**	15,970
1	Search: **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[tiab] OR N54AIC43PW[rn] OR venetoclax[Supplementary Concept]**	1,043

3. Cochrane Central Register of Controlled Trials (CENTRAL)
(searched via Ovid)

4. Grey literature search via:

Clinical trial registries:
US National Library of Medicine. ClinicalTrials.gov
https://clinicaltrials.gov/

World Health Organization
http://apps.who.int/trialsearch/

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

The European Clinical Trial Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Search: Venclexta/venetoclax, chronic lymphocytic leukemia (CLL)

Select international agencies including:

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

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

Search: Venclexta/venetoclax, chronic lymphocytic leukemia (CLL)

Conference abstracts:

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

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

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

Search: Venclexta/venetoclax, chronic lymphocytic leukemia (CLL) – last five years

Literature Search Methods

The literature search for clinical studies was performed by an information specialist from the pCODR Methods Team using the abovementioned search strategy, which was peer-reviewed according to the *PRESS Peer Review of Electronic Search Strategies* checklist (https://www.cadth.ca/resources/finding-evidence/press).[43]

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials (CENTRAL) 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 (venetoclax) and chronic lymphocytic leukemia.

Search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. The search was also limited to English-language documents but not limited by publication year.

The search is considered up to date as of September 17, 2020.

Grey literature (literature that is not commercially published) was identified by searching websites from relevant sections of the *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature* checklist (https://www.cadth.ca/grey-matters).[44]

Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency), clinical trial registries (US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry, and Canadian Partnership Against Cancer Corporation's 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), the European Society for Medical Oncology (ESMO), and American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by through contacts with the CADTH Clinical Guidance Panel. As well, the manufacturer of the drug was contacted for additional information, as required by the pCODR Review Team.

Study Selection

One member of the CADTH 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 made the final selection of studies to be included in the review.

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

Quality Assessment

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

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

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