Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Venetoclax (Venclexta)

Indication: Venetoclax (Venclexta), in combination with obinutuzumab, is indicated for the treatment of patients with previously untreated chronic lymphocytic leukemia.

Sponsor: AbbVie Corporation (AbbVie)

Recommendation: Reimburse with Conditions

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Recommendation

This recommendation supersedes the pCODR Expert Review Committee (pERC) recommendation for this drug and indication dated November 2020.

pERC recommends that venetoclax, in combination with obinutuzumab, be reimbursed for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

Evidence from an ongoing phase 3, multicenter, randomized, prospective, open-label clinical trial (CLL13) demonstrated that treatment with venetoclax in combination with obinutuzumab resulted in added clinical benefit for patients with previously untreated CLL without del(17p) or *TP53* mutation compared with chemotherapy [fludarabine, cyclophosphamide, and rituximab (FCR) and bendamustine and rituximab (BR)]. At the interim analysis (data cut-off date: January 20, 2022, median follow-up 38.8 months, IQR = 32.7 to 46.1), the CLL13 trial demonstrated that venetoclax plus obinutuzumab results in an improvement in progression-free survival (PFS) compared to chemotherapy based on a hazard ratio (HR) of 0.42 (97.5% CI, 0.26 to 0.68; P < 0.001). Of note, the median PFS was [redacted] in the venetoclax plus obinutuzumab group and was [redacted] in the chemoimmunotherapy group. At the 4-year follow-up, the PFS rate was 81.8% (97.5% CI, 75.8% to 87.8%) in the venetoclax plus obinutuzumab group, and 62.0% (97.5% CI, 54.4% to 69.7%) in the chemoimmunotherapy group (HR = 0.47, 97.5% CI, 0.32 to 0.69; P value < 0.0001). pERC also noted that venetoclax plus obinutuzumab was favoured over chemoimmunotherapy based on the undetectable minimal residual disease (MRD) rate at month 15, which was 86.5% (97.5% CI, 80.6% to 91.1%) in the venetoclax plus obinutuzumab group, compared with 52.0% (97.5% CI, 44.4% to 59.5%) in the chemoimmunotherapy group (P value < 0.0001). Median overall survival (OS) was not reached in either treatment group at the interim analysis or the 4-year follow-up.

Patients identified a need for new treatments for CLL that prolong survival, prolong remission, have fewer side effects, and improve health-related quality of life (HRQoL). pERC concluded that venetoclax plus obinutuzumab met some of the needs identified by patients because it prolongs disease remission (PFS) and offers an additional treatment option for patients with CLL. Whether venetoclax plus obinutuzumab prolongs survival or has fewer side effects was considered uncertain. Improvement in HRQoL is also unknown as the results of these assessments during the trial were unavailable at the time of sponsor submission.

Using the sponsor submitted price for venetoclax and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for venetoclax plus obinutuzumab was $167,257 per quality-adjusted life-year (QALY) gained compared with FCR. At this ICER, venetoclax is not cost-effective compared with FCR at a willingness to pay (WTP) threshold of $50,000 per QALY gained for the treatment of patients with previously untreated CLL. A price reduction for venetoclax is required for venetoclax plus obinutuzumab to be considered cost-effective at a $50,000 per QALY gained threshold compared with FCR.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with previously untreated CLL who require treatment according to the International Workshop on CLL criteria.	Evidence from the CLL13 trial demonstrated that treatment with venetoclax plus obinutuzumab has a beneficial effect compared to standard chemotherapy (FCR or BR) in adults with previously untreated CLL who require treatment according to the International Workshop on CLL criteria.	Although excluded from the CLL13 trial, clinical experts indicated that venetoclax plus obinutuzumab would be an appropriate option for patients with del(17p) and/or *TP53* mutation.
2. Patients must have a good ECOG performance status.	Patients with an ECOG performance status of 0 to 2 were included in the CLL13 trial.	—
Discontinuation		
3. Reimbursement of venetoclax should be discontinued upon occurrence of any of the following: 3.1. Disease progression 3.2. Unacceptable toxicity 3.3. Completion of 12 months of therapy	In the CLL13 trial, treatment with venetoclax plus obinutuzumab was administered for 6 cycles, followed by 6 additional cycles of venetoclax alone, each cycle with a duration of 28 days. Patients in CLL13 discontinued treatment if they experienced disease progression or unacceptable toxicity.	Treatment should be given for a total of 12 months as a finite treatment: for six 28-day cycles in combination with obinutuzumab followed by six months of venetoclax as a single agent.
Prescribing		
4. Venetoclax in combination with obinutuzumab should be prescribed by clinicians with expertise in treating CLL and monitoring therapy.	This is meant to ensure that venetoclax is prescribed appropriately and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
5. A reduction in price	The ICER for venetoclax plus obinutuzumab is $167,257 per QALY gained when compared with FCR. A price reduction of 75% for venetoclax would be required for venetoclax plus obinutuzumab to achieve an ICER of $50,000 per QALY gained compared to FCR.	—

CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; iwCLL = International Workshop on chronic lymphocytic leukemia; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- **Relevance of MRD and time-to-event outcomes**: pERC discussed the MRD rate at 15 months from start of therapy, which was one of two primary end points in the CLL13 trial, and acknowledged that venetoclax plus obinutuzumab was favoured over chemoimmunotherapy based on this outcome. pERC also discussed the relevance of this outcome, and while treatment response and undetectable MRD are standard outcome measures in clinical trials of CLL and recognized as surrogate outcome for long-term outcomes such as OS, patient and clinician input indicated that time-to-event outcomes, namely PFS and OS, are most meaningful. pERC noted that other time-to-event outcomes such as time to next treatment (TTNT) may be an exception as it is subject to uncertainty because the interpretation relies on certain assumptions being made. Further, the clinical experts advised that undetectable MRD is of limited applicability to Canadian practice due to limitations in access to MRD measurements in many centres and lack of data as to how it should inform treatment.

- **Indirect evidence**: The NMA results showed a [redacted] treatment effect with venetoclax plus obinutuzumab compared with venetoclax plus ibrutinib on undetectable MRD in peripheral blood. For all other indirect comparisons assessed in the NMA, there was uncertainty in the results primarily due to the 95% credible interval (CrI) including the null and the small number of studies included. Additionally, heterogeneity identified in population fitness and mutational status, and the differential follow-up times likely introduced bias in the NMA results. No safety end point was evaluated in the NMA; therefore, no conclusions on safety can be drawn on the indirect comparison of venetoclax plus obinutuzumab versus other relevant comparators.

- **HRQoL:** HRQoL was identified as an outcome of importance in the patient and clinician group input as well as input from the clinical experts. pERC noted that patient input for this submission described some of the negative impacts that their current CLL treatment had on their HRQoL, which included side effects, ability to travel, and ability to go to work, school, or volunteer. Although HRQoL was measured by EORTC QLQ-C30 and EORTC QLQ-CLL16 in Study CLL13, results were unavailable at the time of the sponsor's submission therefore the effect of treatment with venetoclax plus obinutuzumab on HRQoL in patients with CLL when compared with relevant comparators is unknown. Input submitted by patients and clinicians also noted there may be added value of an oral therapy that is well-tolerated. pERC also noted that venetoclax plus obinutuzumab provides a finite duration or time limited therapy relative to continuous BTKi in younger and/or fit patients, and that time off treatment may be preferred by some patients based on their values and comorbidities.

- **Patients with del(17p) or TP53 mutation**: pERC discussed the use of venetoclax plus obinutuzumab in patients with del(17p) or TP53 mutation. Although these patients were excluded from CLL13, given the clinical experience of venetoclax in those patients and the potential benefit of a time-limited treatment to patients and the health care system, pERC indicated that it would be appropriate to consider treatment with venetoclax plus obinutuzumab as an option for fit patients with del(17p) and/or TP53 mutation. In addition, in consultation with the clinical experts consulted for this submission, pERC noted that it is important to consider the toxicity profile of venetoclax plus obinutuzumab compared to other options when making this treatment decision.

- **Economic considerations:** The CDA-AMC base case assumes a sustained OS benefit for venetoclax plus obinutuzumab compared to FCR; however, pERC emphasized that the extent of this survival benefit remains highly uncertain without robust long-term clinical evidence. If the long-term effectiveness of venetoclax plus obinutuzumab is lower than predicted, the ICER would exceed the CDA-AMC base case estimate, requiring larger price reductions to achieve cost-effectiveness. pERC also noted that most of the QALY and LY benefit for venetoclax plus obinutuzumab was derived from extrapolation in the post-trial period, reflecting model-based outcomes rather than direct trial evidence. Additionally, pERC noted that the estimated budget impact, which suggests that reimbursing venetoclax plus obinutuzumab would result in cost savings, is subject to uncertainty due to assumptions regarding discontinuation of BTKi-based therapy, market shares, and market uptake.

Background

Chronic lymphocytic leukemia is a lymphoid neoplasm that is characterized by a progressive accumulation of monoclonal, mature, functionally impaired B lymphocytes. The pathologic and immunophenotypic features of the malignant cells are identical in CLL and small lymphocytic lymphoma (SLL). Although some patients might present with painless, swollen lymph nodes that wax and wane, most patients with CLL do not present with symptoms at the time of diagnosis.

CLL is the most common leukemia in adults living in Canada — in 2019, 1,700 patients were diagnosed with CLL and in 2020 and 2022, 222 and 554 deaths due to CLL were reported, respectively. CLL is considered incurable; the 5-year net survival for CLL is estimated to be 83%. The estimated median life expectancy for patients with 17p deletion (del[17p]) or *TP53* mutation is less than 2 to 3 years from the time of initial diagnosis; however, the clinical experts advised that this statistic likely reflects the pre-novel therapy era and estimated the median life expectancy for this subset of patients to be longer than 3 years from initial diagnosis.

In symptomatic patients with previously untreated CLL with *TP53* aberrations (del[17p] and/or *TP53* mutation), the 2022 updated Canadian evidence-based guideline for frontline treatment of CLL advised that continuous therapy with a Bruton tyrosine kinase (BTK) inhibitor (namely, ibrutinib and acalabrutinib) is the preferred therapy, while venetoclax, in combination with obinutuzumab, would be preferred in patients who would benefit from a time-limited therapy, if funded.

In symptomatic fit patients (as per the guidelines, patients who are considered fit include those who are young and those who are eligible for treatment with fludarabine, cyclophosphamide, and rituximab [FCR]) with previously untreated CLL without *TP53* aberrations, the guideline advised that FCR is preferred for immunoglobin heavy chain variable (*IGHV*) mutated CLL, while a BTK inhibitor is an option for *IGHV* mutated CLL and is the preferred option for *IGHV* unmutated CLL. The guideline further advised that venetoclax, in combination with obinutuzumab, would become the preferred therapy in this subset of patients, regardless of *IGHV* mutation, if funded across Canada. Of note, the 2018 guideline had advised on bendamustine and rituximab (BR) for fit, older (65 years and older) patients with previously untreated CLL without *TP53* aberrations but with mutated *IGHV* due to less toxicity concerns.

Venetoclax, in combination with obinutuzumab, has been approved by Health Canada for the treatment of patients with previously untreated CLL. Venetoclax is a selective small molecule inhibitor of B-cell lymphoma-2. It is available as 10 mg, 50 mg, and 100 mg oral tablets and the dosage recommended in the product monograph is that venetoclax should be given for a total of 12 months as finite treatment: for six 28-day cycles in combination with obinutuzumab, followed by 6 months of venetoclax as a single agent.

Submission History

Initial Submission

In 2020, venetoclax in combination with obinutuzumab was first reviewed by pERC for the treatment of adult patients with previously untreated CLL who are fludarabine ineligible. pERC issued a recommendation that venetoclax in combination with obinutuzumab be listed for the indication under review in the reimbursement request, if the specified clinical criteria and conditions are met. Patients should have previously untreated CLL, be fludarabine ineligible as indicated by either a CIRS score greater than 6 or a CrCl less than 70 ml/min, require treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria, and have good performance status.

The final recommendation issued by pERC and the clinical review report for the previous review of venetoclax, in combination with obinutuzumab, which contains the summary and appraisal of Study CLL14 that was used to inform the recommendation, are available on the project website, publicly accessible here.

Basis of Present Reassessment

Since the previous recommendation for venetoclax in combination with obinutuzumab, new clinical evidence is available for the first-line treatment of patients with CLL considered fit and potentially fludarabine-eligible — the CLL13 trial.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of one phase 3, multicenter, randomized, prospective, open-label clinical trial in in fit patients (defined in the trial by CIRS score ≤ 6 and CrCl ≥ 70 ml/min) with previously untreated CLL and without del(17p) or *TP53* mutation; and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups, Lymphoma Canada and Chronic Lymphocytic Leukemia Canada
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with CLL
- input from 2 clinician groups, Lymphoma Canada and Ontario Health Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to the call for input and from clinical experts consulted for the purpose of this review.

Patient Input

Two patient groups, Lymphoma Canada and Chronic Lymphocytic Leukemia Canada submitted a joint input for the current review. The input includes results from 2 surveys conducted for past drug reimbursement reviews in CLL — one was for the original submission for venetoclax, in combination with obinutuzumab, reviewed in 2020, and a recent CLL survey conducted in 2023. For the 2023 survey, Lymphoma Canada collected information through an online survey that was distributed throughout Canada and international locations from March 22 to May 2, 2023. A total of 87 people (49 from Canada, 12 from the United States, 1 from Australia, and 25 from unknown locations) responded to the survey. Among the 87 respondents, 32 were female, 30 were male, and 25 skipped the question. Of the 87 respondents, most (36 respondents) were diagnosed with CLL 9 to 10 years ago, while other respondents were diagnosed with CLL 3 to 5 years ago (15), 1 to 2 years ago (10), 5 to 8 years ago (8), and less than a year ago (4); 14 skipped the question. The respondents reported various subtypes of CLL, including deletion 17p, 13q, or 11q; *TP53* mutation; trisomy 12; and unmutated *IGHV*. The 2020 survey provided information on patients with CLL and SLL who had experience with frontline venetoclax, in combination with obinutuzumab. Of the 33 survey respondents, 10 were between the ages of 40 to 59 years and 22 were between the ages 60 to 79 years, and 18 were male and 14 were female; 1 did not respond to either question. Survey respondents were from Canada (2 patients), USA (29 patients), and UK (1 patient) (and 1 did not respond).

Based on the 2023 survey, most patients with CLL are diagnosed through routine bloodwork and experience minor to no symptoms at the time of diagnosis. According to the 64 respondents who reported high negative impact at the time of diagnosis, fatigue (47%), high white blood cell counts (leukocytosis) (26%), body aches and pains (25%), enlarged lymph nodes (23%), and night sweats (20%) were the most frequent symptoms. Of the 71 respondents who reported on the psychosocial impact of CLL at the time of diagnosis, anxiety and worry (61%), stress of diagnosis (59%), and difficulty sleeping (28%) were the most common concerns. According to the 70 respondents who reported high negative impact on their current HRQoL, fatigue (44%); body aches and pains (27%); and indigestion, abdominal pain, or bloating (17%) were the most frequently reported symptoms. Of the 87 respondents who reported on the psychosocial impact of CLL on their current HRQoL, anxiety and worry (42%), difficulty sleeping (31%), and stress of diagnosis (28%) were the most common concerns. Of 87 respondents who indicated that CLL has a negative impact on their daily activities, fulfilling family obligations (51%) and spending time with family and friends (45%) were the most frequently affected activities.

Of the 68 respondents to the 2023 survey who provided information on their experience with CLL treatments, 21 indicated they have not received therapy, 26 received 1 line of treatment, and 19 completed 2 or more lines of treatments. According to the respondents, the most difficult to tolerate side effects include nausea, fatigue, joint pain, skin issues and bleeding, atrial fibrillation, diarrhea,

inflammation, bodily aches and pain, headache, muscle weakness, heartburn, indigestion, night sweats, neuropathy, and frequent infections. Additionally, 26% of patient respondents indicated their CLL treatment had a negative impact on their HRQoL (due to side effects) (76%), ability to travel (26%), and ability to go to work, school, or volunteer (19%). Based on patient respondent input, the most important considerations for a novel CLL treatment are longer survival (81%), control of disease symptoms (75%), longer remission (71%), better HRQoL (66%), and fewer side effects (35%). Approximately half of all survey respondents emphasized the importance of having a choice in their treatment plan and having increased treatment options available to choose from. While some respondents to the 2023 survey indicated preference for a fixed duration therapy (24%), others indicated preference for a continuous therapy (10%); 66% indicated they were uncertain.

A total of 33 patient respondents from the 2020 survey reported experience with the current drug under review (i.e., either currently receiving venetoclax or completed the treatment regimen). Among these patients, 2 reported not being able to complete the full course of obinutuzumab infusions due to side effects. While most respondents in the 2020 survey noted that side effects from this treatment had “no” or “some” impact on their HRQoL, 15% to 18% of respondents reported “significant” or “very significant” impact on their HRQoL due to side effects. Most patient respondents (20 out of 33; 61%) reported that treatment managed all their symptoms. Symptoms that were not managed by treatment in more than 10% of respondents included fatigue or lack of energy (10 out of 33; 30%), and shortness of breath (4 out of 33; 12%). Overall, most respondents (31 out of 33; 90%) reported a positive experience with the drug under review, and 85% described their experience with treatment as “very good” or “excellent”.

Clinician Input

Input From Clinical Experts Consulted For the Present Review

The clinical experts indicated that alternative treatment options that are targeted, chemoimmunotherapy-free and/or BTK inhibitor-free, and time-limited are needed for fit patients with previously untreated CLL. Additionally, the clinical experts highlighted the importance of having alternative treatment regimens for patients to choose from (i.e., improving access and equity to care) to align with their values, needs, and lifestyle. The clinical experts indicated that venetoclax, in combination with obinutuzumab, would be considered as an option for front line therapy in patients regardless of fitness, age, and high-risk cytogenetic markers. According to the clinical experts, the molecular profile (*IGHV* and *TP53* mutation status) are the main criteria that inform discussions on selecting a treatment regimen. Other factors to consider when selecting a treatment regimen include accessibility to a local treatment center and availability of resources to implement the therapy and monitor for tumour lysis syndrome.

The clinical experts identified the following outcomes that are used to determine treatment response in practice: time to next treatment, clinical improvement in nodal burden or splenomegaly, and improvement in symptoms, HRQoL, and bloodwork as per iwCLL response criteria. The clinical experts advised on reassessing for treatment response every 6 months in the first year after completing therapy and annually thereafter. The clinical experts identified the following factors that would be considered for discontinuation of venetoclax, in combination with obinutuzumab: patients continue to present with AEs despite dose reductions and disease progression while on therapy. The clinical experts also presented a scenario where treatment response was demonstrated but treatment was discontinued due to AEs — the clinical experts advised on switching to an alternative treatment when there is disease progression.

The clinical experts advised that hematologists and hematologist oncologists should diagnose, treat, and monitor patients who might receive venetoclax, in combination with obinutuzumab. In consideration of the infusion-related reactions and tumour lysis syndrome, the clinical experts advised that a clinic with the resources to enable appropriate monitoring for laboratory abnormalities and access to advanced, complex care if needed are the most appropriate settings for treatment with venetoclax, in combination with obinutuzumab.

Clinician Group Input

Two clinician groups provided input on the current review of venetoclax (in combination with obinutuzumab): Lymphoma Canada (represented by 6 clinicians) and OH-CCO Hematology Cancer Drug Advisory Committee (represented by 1 clinician). Note that Lymphoma Canada is a patient advocacy group that helped to facilitate their clinician group input submission by hematologists. The OH-CCO Hematology Cancer Drug Advisory Committee provides evidence-based, clinical and health system guidance on drug-

related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program.

In consideration of the unmet needs, Lymphoma Canada highlighted the younger patients with high-risk genomic features (e.g., unmutated *IGHV*) are only able to access the treatment under review by justifying that the poor-risk genomic features meet the definition for fludarabine-ineligibility. The group felt that the current requested change in funding may reduce confusion and ensure fairness and equitable access across Canada for this subset of patients with CLL. Lymphoma Canada further suggested that an expanded funding may allow the youngest and/or fittest patients with lower risk disease and the longest life expectancy to benefit from targeted therapy and avoid the use of FCR and its associated risk of short- and long-term bone marrow toxicities. The OH-CCO's Drug Advisory Committee indicated that the treatment under review provides an immunotherapy option that is not combined with chemotherapy.

Both clinician groups indicated that venetoclax, in combination with obinutuzumab, would be considered for first line therapy in all patients with previously untreated CLL. Lymphoma Canada highlighted that the option of venetoclax, in combination with obinutuzumab, may encourage deferring BTK inhibitor-based therapy to the relapsed or refractory setting for most patients. Lymphoma Canada anticipates this may reduce the budget impact of CLL therapy and would be in keeping with patient preference for frontline fixed-duration, targeted therapy. Both clinician groups indicated that all patients with CLL who require a first line therapy would benefit from treatment with venetoclax, in combination with obinutuzumab. Lymphoma Canada suggested that the least suitable patients for the treatment under review are patients with del(17p) or *TP53* mutation (these patients will typically receive BTK inhibitor monotherapy). Regardless, the group suggested that fixed duration therapies should still be made available to this subset of patients on the rare occasion that a fixed duration therapy is desired.

As per the OH-CCO's Drug Advisory Committee, standard CLL response outcomes, improvement in progression free survival, reduction in symptoms, and improvement in HRQoL outcomes are used to determine whether a patient is responding to the treatment under review in clinical practice.

The OH-CCO Drug Advisory Committee advised to consider treatment discontinuation in the setting of significant intolerance or disease progression, while Lymphoma Canada suggested to consider treatment discontinuation if there is a lack of response or consider an abbreviated therapy in the setting of significant toxicity.

The clinician groups advised that any specialist physician who treats CLL or any prescribers familiar with CLL treatment should be able to provide and supervise therapy with the treatment under review. The OH-CCO Hematology Cancer Drug Advisory Committee also indicated that additional lab monitoring may be required during venetoclax ramp-up. Lymphoma Canada added that a physical exam and review of blood work are part of routine practice in response assessment.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CDA-AMC recommendation for venetoclax:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues
- potential need for a provisional funding algorithm

The clinical experts consulted by CDA-AMC provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
Relevant funded comparators include acalabrutinib, ibrutinib, zanubrutinib, fludarabine-based therapy, obinutuzumab plus chlorambucil, and other rituximab-based chemotherapy combinations (e.g. bendamustine-rituximab, chlorambucil-rituximab). The comparators in the CLL13 trial were FCR or BR. Ibrutinib-venetoclax has received a positive recommendation for the treatment of adult patients with previously untreated CLL including those with 17p deletion. This is currently being negotiated through pCPA.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for initiation of therapy	
Venetoclax should be given for a total of 48 weeks as finite treatment for six 28-day cycles in combination with obinutuzumab, followed by 6 months of venetoclax as a single drug. For patients who do not experience progression, are there instances where these patients should be treated beyond the 48 weeks of treatment?	The clinical experts indicated that treatment with venetoclax, in combination with obinutuzumab, should be finite and advised that treatment beyond 48 weeks in patients who do not experience progression should be based on clinical judgement. For example, patients may be considered for treatment beyond 48 weeks if there was a delay in their therapy due to tumour lysis syndrome, difficulty in ramping up the dose, or potential cytopenia. pERC agreed with the clinical experts.
For patients who have completed the 48 weeks of treatment, should these patients be re-treated with venetoclax plus obinutuzumab upon progression?	The clinical experts acknowledged that clinical trials on retreatment upon progression that may provide guidance on venetoclax retreatment are ongoing at the time of this review; however, the clinical experts do not foresee any concerns with retreatment upon progression (i.e., the clinical experts suggested retreatment is likely beneficial and safe based on literature). pERC acknowledged that evidence to support retreatment with venetoclax plus obinutuzumab upon progression was not available at the time of this submission; however, retreatment at the discretion of the prescriber may be considered for patients who experience progression after one year following completion of prior treatment.
Considerations for prescribing of therapy	
If a patient experiences intolerance to venetoclax or obinutuzumab, can treatment with the other agent be continued as monotherapy?	The clinical experts advised that this scenario is reasonable and suggested dose adjustment is also possible and reasonable in this setting. The clinical experts advised that it is important to recognize that this may result in shorter remission. pERC agreed with the clinical experts.
Venetoclax (oral) and obinutuzumab (IV) will be reimbursed through different programs.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
Should patients currently on existing treatments (e.g., chemoimmunotherapy) be offered a time-limited switch to venetoclax plus obinutuzumab?	The clinical experts acknowledged that there is a lack of evidence for this scenario; however, in the setting of toxicity or progression with their current treatment, or if treatment decisions were previously based on access to existing treatments (in particular, to FCR), the clinical experts suggested it is reasonable to offer these patients with a time-limited switch to venetoclax plus obinutuzumab.

Implementation issues	Response
	pERC agreed with the clinical experts.
Should eligibility for venetoclax plus obinutuzumab be extended to fit patients with previously untreated small lymphocytic leukemia?	The clinical experts advised that eligibility for venetoclax plus obinutuzumab should be extended to fit patients with previously untreated SLL as SLL and CLL are different manifestations of the same disease. pERC agreed with the clinical experts.
Funding algorithm	
Drug under review may change place in therapy of relevant comparator drugs.	This is a comment from the drug plans to inform pERC deliberations.
Please clarify on the eligible patient population for the drug under review (i.e., in reference to the fitness criteria used in Study CLL13).	The clinical experts advised that all patients should be eligible for venetoclax, in combination with obinutuzumab, regardless of fitness, age, and high-risk cytogenetic markers. The clinical experts noted that fitness and age criteria and exclusion of del(17p) were designed for chemoimmunotherapy (the comparator in Study CLL13) and are not used with novel drugs. pERC agreed with the clinical experts.
Under what clinical circumstances would venetoclax plus obinutuzumab be used over existing first-line options?	The clinical experts advised that the molecular profile, access to certain treatments, and patient values are considerations when selecting first-line treatment with venetoclax, in combination with obinutuzumab. pERC agreed with the clinical experts.
What will be the impact of the drug under review on the downstream sequencing from newly diagnosed CLL to relapsed/refractory CLL?	The clinical experts advised referring to the sequencing of treatment in the older adult population for which venetoclax, in combination with obinutuzumab, is already approved and funded. pERC agreed with the clinical experts.
Care provision issues	
Venetoclax has potential for drug-drug, drug-food, and drug-herb interactions.	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
There would be a budget impact for obinutuzumab given the increase in the venetoclax population.	This is a comment from the drug plans to inform pERC deliberations.

BR = bendamustine and rituximab; CLL = chronic lymphocytic leukemia; FCR = fludarabine, cyclophosphamide, and rituximab; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; SLL = small lymphocytic leukemia.

Clinical Evidence

Systematic Review

Description of Study

Study CLL13 is an ongoing phase 3, multicenter, randomized, prospective, open-label clinical trial (N = 926). The primary objective of the study is to assess the efficacy of venetoclax plus obinutuzumab versus standard chemoimmunotherapy (BR or FCR) on the negativity rate of minimal residual disease (MRD) in peripheral blood at month 15, and venetoclax plus obinutuzumab plus ibrutinib versus standard chemoimmunotherapy on progression-free survival (PFS) at pre-defined analysis time points in fit patients (defined in the trial by CIRS score ≤ 6 and creatinine clearance [CrCl] ≥ 70 ml/min) with previously untreated CLL and without del(17p) or *TP53* mutation. Eligible patients were randomized in a 1:1:1:1 ratio to receive chemoimmunotherapy, venetoclax plus obinutuzumab, venetoclax plus obinutuzumab plus ibrutinib, and venetoclax plus rituximab. Randomization was stratified by Binet stage, age (with a cut-off of 65 years), and region study group. In the chemoimmunotherapy group, patients aged 65 years and younger received FCR, while patients aged older than 65 years received BR. The end of the trial was defined as the time point when 213 PFS events are

reached which may take place approximately 73 months after the first patient was randomized. At the time of sponsor submission, results from the primary analysis of undetectable MRD; results from the interim analysis, which was also the primary analysis, of PFS; and results from a post-hoc, exploratory 4-year follow-up analysis were available of prespecified end points with all patients off treatment.

Note that venetoclax plus rituximab is not approved by Health Canada for the population under review and venetoclax plus obinutuzumab plus ibrutinib is also not approved by Health Canada. Therefore, data for these treatment groups from Study CLL13 are not presented in this Clinical Review Report for the purposes of this review.

The median age of patients was 62 years (range = 31 to 83 years) in the venetoclax plus obinutuzumab group and 61 years (range = 29 to 84 years) in the chemoimmunotherapy group. All patients in both groups had a CIRS score of 6 or less. The median CrCl was 86.3 ml/min (range = 41.5 to 180.2 ml/min) in the venetoclax plus obinutuzumab group and 86.3 ml/min (range = 39.5 to 223.6 ml/min) in the chemoimmunotherapy group. The distribution of patients by Rai staging was generally well balanced between groups, with most patients presenting with Rai stages I to IV. The median Eastern Cooperative Oncology Group (ECOG) performance status was 0 (range = 0 to 2) in both groups. No patients in either group had del(17p) and all patients in both groups had unmutated *TP53*. The distribution of patients by *IGHV* mutation status was generally well balanced between groups, with most patients presenting with unmutated *IGHV* (approximately 57% of patients in each group).

Efficacy Results

The median duration of follow-up in the full study population at the interim analysis (including safety), based on a data cut-off date of January 20, 2022, was 38.8 months (interquartile range [IQR] = 32.7 to 46.1 months). The median duration of follow-up in the full study population at the post-hoc, exploratory 4-year follow up analysis, based on a data cut-off date of January 31, 2023, was 50.7 months (IQR = 44.6 to 57.9 months).

Progression-free Survival

At the time of the interim analysis, the proportion of observed events (first occurrence of progression or relapse or death) was 14.4% (33 events) in the venetoclax plus obinutuzumab group and 29.3% (67 events) in the chemoimmunotherapy group. The median PFS was [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group [redacted]. Venetoclax plus obinutuzumab was favoured over chemoimmunotherapy (HR = 0.42; 97.5% CI, 0.26 to 0.68). The PFS rates at 1, 2, 3, and 4 years were [redacted] 87.7%, and [redacted], respectively, in the venetoclax plus obinutuzumab group, and [redacted], 75.5%, and [redacted], respectively, in the chemoimmunotherapy group.

At the 4-year follow-up, the proportion of observed events was 24% (55 events) in the venetoclax plus obinutuzumab group and 39% (90 events) in the chemoimmunotherapy group. The median PFS was still not reached in the venetoclax plus obinutuzumab group and 59.4 months (95% CI not reported) in the chemoimmunotherapy group. The HR was 0.47 (97.5% CI, 0.32 to 0.69) following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The PFS survival rate at 4 years was 81.8% (97.5% CI, 75.8% to 87.8%) in the venetoclax plus obinutuzumab group, and 62.0% (97.5% CI, 54.4% to 69.7%) in the chemoimmunotherapy group.

Overall Survival

At the time of the interim analysis, the proportion of observed events (death due to any cause) was [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group. The median overall survival (OS) was not reached in either group. The HR was [redacted] following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The OS rates at 1, 2, 3, and 4 years were [redacted], 96.3%, and [redacted], respectively, in the venetoclax plus obinutuzumab group, and [redacted], 95.0%, and [redacted], respectively, in the chemoimmunotherapy group.

At the 4-year follow-up, the proportion of observed events was 5% (11 events) in the venetoclax plus obinutuzumab group and 7% (17 events) in the chemoimmunotherapy group. The median OS was still not reached in either group. The HR was 0.58 (97.5% CI, 0.24 to 1.38) following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The OS survival rate at 4 years was 95.1% (97.5% CI, 91.9% to 98.3%) in the venetoclax plus obinutuzumab group, and 93.5% (97.5% CI, 89.6% to 97.4%) in the chemoimmunotherapy group.

Duration of Response

At the time of the interim analysis, the proportion of observed events (first occurrence of progression or relapse or death after the first documented response) was [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group. The median duration of response was [redacted] in either group. The HR was [redacted] following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The event-free survival rates at 1, 2, 3, and 4 years were [redacted] respectively, in the venetoclax plus obinutuzumab group, and [redacted] respectively, in the chemoimmunotherapy group.

Time to Next Treatment (From Randomization)

At the time of the interim analysis, the proportion of observed events (initiation of the first subsequent treatment for CLL) was [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group. The median time to next treatment was [redacted] in either group. The HR was [redacted] following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The event-free survival rates at 1, 2, 3, and 4 years were [redacted] respectively, in the venetoclax plus obinutuzumab group, and [redacted] respectively, in the chemoimmunotherapy group.

At the 4-year follow-up, the proportion of observed events was 10.0% (23 events) in the venetoclax plus obinutuzumab group and 23.6% (54 events) in the chemoimmunotherapy group. The median time to next treatment was still not reached in either group. The HR was 0.34 (97.5% CI, 0.20 to 0.60) following treatment with venetoclax plus obinutuzumab versus chemoimmunotherapy. The event-free survival rate at 4 years was 90.4% (97.5% CI, 85.7% to 95.0%) in the venetoclax plus obinutuzumab group, and 77.2% (97.5% CI, 70.2% to 84.1%) in the chemoimmunotherapy group.

Undetectable Minimal Residual Disease in Peripheral Blood

Venetoclax plus obinutuzumab was favoured over chemoimmunotherapy — at month 15, the undetectable MRD rate was 86.5% (97.5% CI, 80.6% to 91.1%) (198 of 229 patients) in the venetoclax plus obinutuzumab group, compared with 52.0% (97.5% CI, 44.4% to 59.5%) (119 of 229 patients) in the chemoimmunotherapy group (P value < 0.0001). A total of 4.4% (10 patients) in the venetoclax plus obinutuzumab group and 14.8% (34 patients) in the chemoimmunotherapy group had a missing MRD status.

Complete Response to Treatment

The median duration of follow-up in the full study population at month 15, based on a data cut-off date of February 28, 2021, was 27.9 months (IQR = 22.1 to 35.3 months).

At month 15, the complete response rate was 56.8% (130 of 229 patients) in the venetoclax plus obinutuzumab group, compared with 31.0% (71 of 229 patients) in the chemoimmunotherapy group. A total of 3.1% (7 patients) in the venetoclax plus obinutuzumab group and 14.8% (34 patients) in the chemoimmunotherapy group had missing data for this parameter.

Harms Results

The harms results from Study CLL13 are based on a data cut-off date of January 20, 2022 (interim analysis).

Adverse Events

A total of [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group had at least 1 treatment emergent adverse event (TEAE) of any Common Toxicity Criteria (CTC) grade 1 to 5. The most common TEAE in both groups was neutropenia and/or neutrophil count decreased based on Standardized Medical Query — [redacted] in the intervention group and [redacted] in the comparator group. A total of [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group had an infusion related reaction. A total of [redacted] in the venetoclax plus obinutuzumab group and [redacted] in the chemoimmunotherapy group had febrile neutropenia.

Serious Adverse Events

A total of 44.7% (102 patients) in the venetoclax plus obinutuzumab group and 47.7% (103 patients) in the chemoimmunotherapy group had at least 1 serious TEAE of any CTC grade 1 to 5. The most common serious TEAEs in both groups were infections and infestations — [redacted] in the intervention group and [redacted] in the comparator group.

Withdrawals Due to Adverse Events

A total of 5.7% (13 patients) in the venetoclax plus obinutuzumab group and 15.3% (33 patients) in the chemoimmunotherapy group had at least 1 TEAE leading to early treatment discontinuation. In the venetoclax plus obinutuzumab group, the most common TEAE leading to early treatment discontinuation was Richter's syndrome — [redacted] in the intervention group and [redacted] in the comparator group. In the chemoimmunotherapy group, the most common TEAE leading to early treatment discontinuation was neutropenia — [redacted] in the intervention group and [redacted] in the comparator group.

Treatment-Emergent Lethal Adverse Events

In the venetoclax plus obinutuzumab group, a total of 9 patients had a CTC grade 5 adverse event (AE), of which 1 had COVID19 that was reported in the timeframe between treatment period and until day 84 after end of treatment, inclusive. The other 8 patients had a CTC grade 5 AE that was reported after day 84 after end of treatment — secondary neoplasia (excluding Richter transformation) in 3 patients, COVID19 in 2 patients, and cardiac arrest or failure, Richter transformation, and pneumonia in 1 patient each.

In the chemoimmunotherapy group, a total of 10 patients had a CTC grade 5 AE, of which 1 had an infection other than COVID19 that was reported in the timeframe between treatment period and until day 84 after end of treatment, inclusive. The other 9 patients had a CTC grade 5 AE that was reported after day 84 after end of treatment — COVID19; Richter transformation; and bronchial obstruction, stroke, and respiratory failure in 2 patients each, and secondary neoplasia (excluding Richter transformation), cardiac arrest or failure, and pneumonia in 1 patient each.

Notable Harms

Serious infections and infestations are summarized above.

At the interim analysis, there was a total of 27 cases of second primary malignances in the venetoclax plus obinutuzumab group, including 14 cases of non-melanoma skin cancer and 13 cases of solid tumours. There was a total of 49 cases of second primary malignancies in the chemoimmunotherapy group, including 27 cases of non-melanoma skin cancer, 18 cases of solid tumours, and 4 cases of hematological malignancies.

At the 4-year follow-up, there was a total of 45 cases of second cancers in the venetoclax plus obinutuzumab group, including 16 cases of non-melanoma skin cancer, 15 cases of solid tumours, 7 cases of benign tumours, and 7 cases of Richter's transformation. There was a total of 69 cases of second cancers in the chemoimmunotherapy group, including 33 cases of non-melanoma skin cancer, 19 cases of solid tumours, 7 cases of benign tumours, 6 cases of Richter's transformation, and 4 cases of hematological malignancies (2 cases of plasma cell myeloma and 1 case each of myelodysplastic syndrome and cutaneous T-cell lymphoma).

In the venetoclax plus obinutuzumab group, 1 case of cardiac arrest and 1 case of arrythmia was reported. In the chemoimmunotherapy group, 1 case of arrythmia was reported.

Critical Appraisal

Internal Validity

Study CLL13 was generally appropriately designed and powered to evaluate the efficacy of venetoclax plus obinutuzumab relative to chemoimmunotherapy. Although the trial was open label and therefore susceptible to reporting and performance bias, this was considered justifiable in the context of CLL and the requirement of different study drug formulations and administration routes.

Relevant baseline characteristics were generally well balanced between the venetoclax plus obinutuzumab and chemoimmunotherapy groups. As such, it was concluded that the risk of bias arising from the randomization process is unlikely. While patients with unmutated *IGHV* was balanced between the treatment groups, this subset of patients would not typically receive chemoimmunotherapy in the frontline setting, as per the guideline. In consultation with the clinical experts, it was concluded that this

subset of patients with unmutated *IGHV* randomized to receive chemoimmunotherapy were at a disadvantage when compared to venetoclax plus obinutuzumab, thereby introducing potential for bias in favour of venetoclax plus obinutuzumab. However, the clinical experts noted that since chemoimmunotherapy was the standard of therapy at the time of when the trial was conducted, this issue is considered reasonable but specific bias remains.

In consultation with the clinical experts, it was concluded that a median follow-up of 38 months at the interim analysis is appropriate for evaluating the safety and efficacy of the study drugs and that the assessment time point at 15 months for MRD and response to treatment is standard in trials (i.e., 3 months post-treatment).

A total of 4.4% of patients in the venetoclax plus obinutuzumab group and 14.8% of patients in the chemoimmunotherapy group had missing data on MRD status. It was concluded that the imbalance observed in missing data and the relatively high rate of missing data in the chemoimmunotherapy group is a concern for the potential for biased results. Although patients without MRD sample at month 15 were kept and indicated as non-negative in the analysis, missing data were not replaced or imputed in the primary efficacy analysis of undetectable MRD in peripheral blood at month 15. However, in consideration of the results (i.e., most patients had a negative MRD status in both treatment groups and the imbalance observed in missing data), there is a concern for the potential for biased results, likely in favour of venetoclax plus obinutuzumab, due to the approach for handling missing data.

Type I error was controlled only in the analyses of undetectable MRD and PFS, using a hierarchical testing sequence. Sensitivity analysis was not performed for the comparison of venetoclax plus obinutuzumab versus chemoimmunotherapy; therefore, no conclusions can be drawn on the robustness (or lack thereof) of the results. Since the study was not designed nor powered to test specific hypotheses in all other secondary and exploratory analyses, these results are considered as supportive evidence only.

External Validity

Study CLL13 included a subset of the population of interest identified in the indication for venetoclax, in combination with obinutuzumab, that was not considered in the previous review — fit (defined in the trial by CIRS score ≤ 6 and CrCl ≥ 70 ml/min) patients with previously untreated CLL without *TP53* aberrations.

In consultation with the clinical experts, it was concluded that the inclusion and exclusion criteria are standard in trials of CLL and are justifiable in the context of minimizing confounders and to avoid placing chemoimmunotherapy at a disadvantage in the comparisons made (i.e., excluded patients with del[17p] and *TP53* mutation). However, the clinical experts noted that some criteria are not applicable to Canadian practice and are narrow when compared with patients with CLL seen in practice. Most of the patients excluded from the trial may still be considered as candidates for venetoclax, in combination with obinutuzumab, in practice by the clinical experts by working with the multidisciplinary team to resolve drug-drug interactions, control other preexisting conditions, and dose adjust accordingly. Overall, despite the narrow inclusion and exclusion criteria, the clinical experts had no concerns with generalizing the results to fit patients who were excluded from the trial, namely patients with SLL and with del(17p) and *TP53* mutation. Additionally, the baseline characteristics of the study population are generally representative of fit patient population seen in practice who would be considered as candidates for venetoclax, in combination with obinutuzumab, as per clinical expert input.

Based on patient and clinician group input and in consultation with the clinical experts, it was concluded that the time-to-event outcomes are most meaningful to patients and clinicians. While treatment response and undetectable MRD are standard outcome measures in clinical trials of CLL, the clinical experts advised that they are of limited applicability to Canadian practice due to limitations in accessing relevant tests (MRD measurements, bone marrow biopsies and scans for treatment response). Thus, while MRD levels might serve as a surrogate marker for OS and PFS in CLL according to literature, from a clinical practice perspective, response to treatment and undetectable MRD are relevant as supportive evidence for long-term outcomes.

According to the guidelines, FCR and BR are appropriate comparators in fit patients without *TP53* aberrations (del[17p] and *TP53* mutation) and with mutated *IGHV* in the frontline setting; albeit FCR is infrequently used, and BR is not used in practice as per clinician group and clinical expert input. As mentioned above, fit patients without *TP53* aberrations and with unmutated *IGHV* do not typically receive chemoimmunotherapy in the frontline setting; instead, a BTK inhibitor would have been a more appropriate comparator in this subset of patients, as per the guideline. Further, based on the guideline, a BTK inhibitor would have been an appropriate comparator for fit patients with *TP53* aberrations — a gap in the present systematic review evidence.

Long-Term Extension Study

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Sponsor Submitted Network Meta-Analysis

The objective of the sponsor submitted network meta-analysis (NMA) was to estimate the comparative effectiveness of venetoclax plus obinutuzumab versus relevant comparators in the treatment of patients who are fit, with previously untreated CLL and without del(17p) or *TP53* mutation in terms of PFS, OS, time to next treatment, and undetectable MRD. Indirect comparisons of venetoclax plus obinutuzumab, venetoclax plus ibrutinib, FCR, BR, obinutuzumab plus chlorambucil, acalabrutinib, zanubrutinib, and ibrutinib were made using a Bayesian NMA with Hamiltonian Monte Carlo Markov Chain.

The population of interest is adult patients aged 18 years and older who are fit (defined in the trials by a CIRS score ≤ 6 and CrCl ≥ 70 ml/min), with previously untreated CLL and without del(17p) or *TP53* mutations. According to the authors of the NMA, an NMA that excludes all studies with unfit patients was not feasible due to the limited evidence for solely fit patients. Hence, the base case included both fit and unfit patients without del(17p) or *TP53* mutations (and based on blood sampling for undetectable MRD).

Efficacy Results

The evidence informing the NMA was based on the February 2024 literature search. After applying the more restrictive inclusion criteria used for the NMA, a total of 9 unique clinical trials were included in the feasibility assessment: CLL13, CLL10, CLL14, ELEVATE-TN, SEQUOIA, GLOW, ALLIANCE, FLAIR, and Filo. The authors of the NMA indicated that the Filo trial was excluded from the analysis due to unclear reporting of outcomes as only conference abstracts were available at the time of the latest search; albeit the interventions are relevant to the NMA. All studies were open-label, phase 3, multinational randomized controlled trials (RCTs) (except for FLAIR which was conducted in the United Kingdom only) with a median follow-up ranging from 26.2 to 76.4 months. All studies included treatment-naïve patients with CLL, the exception was SEQUOIA in which patients with SLL were also included.

Progression-free Survival

Venetoclax plus obinutuzumab was favoured over [redacted]. [redacted] was favoured between [redacted].

Overall Survival

[redacted] was favoured based on comparisons between [redacted].

Time to Next Treatment

Venetoclax plus obinutuzumab was favoured over [redacted]. [redacted] was favoured between [redacted].

Undetectable Minimal Residual Disease

Venetoclax plus obinutuzumab was favoured between comparators: [redacted].

Harms Results

Not assessed in the NMA.

Critical Appraisal

Studies included in the NMA were selected from those identified by the systematic literature review. The systematic literature review was conducted using standard methods, a defined research question was specified a priori, and multiple databases were searched with the last literature search conducted in February 2024. A narrowed set of criteria for the inclusion of studies for the NMA were provided and are consistent with the objective, including further restricting the eligible interventions to those that are relevant to Canadian practice for first-line treatment of CLL in the population of interest based on the CLL13 trial population.

A Bayesian NMA was conducted, which according to the authors, was consistent with the NICE DSU Technical Support Document 2. No major concerns with the statistical methods used were identified by the review team. Notably, no sensitivity analysis was performed to assess the sensitivity of model results to the informative priors used in the RE model. Further, assessment of consistency was not reported.

While the base case analysis of mixed fit and unfit network was not according to protocol, the clinical experts had no concern with generalizing the NMA results that are based on the broader population to the fit population, regardless of del(17p) or *TP53* mutation, as there are fewer concerns with comorbidities in the fit population. Nonetheless, it is important to note the differences in population fitness across the network that would represent a potential source of bias in the network. Notably, 3 trials included only fit patients, while 5 trials included only unfit or rather unfit patients according to criteria based on CIRS, CrCl, and age. While exploring areas of uncertainty in the NMA results, the review team noted that the ELEVATE-TN trial evaluated acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab in patients aged 65 years and older, or older than 18 years and younger than 65 years with comorbidities (CrCl of 30 to 69 mL/min CIRS for Geriatrics score > 6). This contrasts with the ALLIANCE trial, which evaluated ibrutinib versus ibrutinib with rituximab and BR in patients aged 65 years and older, and the SEQUOIA trial, which assessed zanubrutinib versus BR in patients aged 65 years and older or FCR-ineligible. These differences in eligibility criteria (i.e., fitness approximation) might have contributed to the difference observed in direction of the results for the comparisons with the BTK inhibitors, suggesting fitness is an effect modifier, and as such, raises concerns for comparing the studies included in the NMA.

Heterogeneity in patient baseline characteristics was reported by the authors of the NMA as part of their feasibility assessment. Based on literature, del(17p) and *TP53* mutation are predictive of worse clinical outcomes after treatment with chemoimmunotherapy, compared with targeted therapies, and *IGHV* mutation is associated with prolonged durable remission after chemoimmunotherapy treatment, which was not observed in patients with *IGHV* unmutated CLL or SLL; the clinical experts were in agreement. The base case excluded patients with del(17p) and *TP53* mutation to align with the CLL13 trial population; however, these patients were included in the analyses where not possible to exclude by the investigators. Therefore, differences in these treatment effect modifiers across the network would introduce bias in the NMA results.

Heterogeneity in study methodology was also reported by the authors of the NMA as part of their feasibility assessment. Across the included studies, the median follow-up ranged from 26.2 to 76.4 months. The clinical experts advised that a median follow-up of 26 months is likely too short to evaluate treatment effect; the exception is upfront toxicities as CLL is not expected to progress until later. In contrast, a median follow-up of 76 months is likely appropriate for assessing the treatment effect of time limited therapies. The clinical experts further advised that a longer follow up is likely advantageous for continuous therapies (i.e., potential for biased results favouring BTK inhibitors with long follow-up) as disease progression is expected to occur later with chronic therapy. Differential follow-up can also lead to bias when specifically comparing time to event outcomes such as PFS and OS since estimated HR often wane with increased lengths of follow-up. Overall, these sources of clinical and methodological heterogeneity likely introduced bias in the results of the NMA.

Notably, the networks were sparse. The base case and the sensitivity analyses included 4 or 8 studies which likely introduced uncertainty about the results. Due to the small number of studies included in the NMA, the authors deemed it was infeasible to account for heterogeneity using meta-regression.

Study Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted by the sponsor.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target population	Previously untreated patients with CLL, including fludarabine-eligible (i.e., ≤65 years who received FCR in the CLL13 trial) and fludarabine-ineligible (i.e., >65 years who received BR in the CLL13 trial) patients.
Treatments	VEN+O
Dose regimen	The recommended dose of venetoclax is 400 mg daily. This dose is achieved according to a weekly ramp-up schedule over a period of 5 weeks: 20 mg daily during Week 1, 50 mg daily during Week 2, 100 mg daily during Week 3, 200 mg daily during Week 4, and 400 mg daily during Week 5. Venetoclax is started on Day 22 of the first cycle and should be given for 6 28-day cycles in combination with obinutuzumab, followed by 6 months of venetoclax as monotherapy. The recommended dose for obinutuzumab is 1,000 mg on Days 1, 8, and 15 of the first 28-day cycle, followed by 1,000 mg on Day 1 of the 5 subsequent cycles (total of 6 cycles, 28 days each).
Submitted price	Venetoclax: $7.08 per 10 mg oral tablet Venetoclax: $35.40 per 50 mg oral tablet Venetoclax: $70.80 per 100 mg oral tablet
Submitted treatment cost	$17,354 in cycle 1, $9,469 in cycle 2, $13,681 in cycles 3 to 6, and $7,930 in cycles 7 to 12[a]
Comparators	• Acalabrutinib • BR • FCR • Ibrutinib • VEN+I • Zanubrutinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	• Efficacy inputs for VEN+O, BR, and FCR were informed by the CLL13 trial (i.e., GAIA-CLL13; NCT02950051) (data cut-off date: January 31, 2023). • Efficacy inputs for acalabrutinib, ibrutinib, VEN+I, and zanubrutinib were derived from a sponsor-submitted NMA.
Key limitations	• The comparative clinical efficacy of VEN+O, VEN+I, and BTKi-based therapies is uncertain due to the lack of head-to-head evidence and limitations with the sponsor's NMA. Factors such as 95% CrI including the null and heterogeneity in population fitness introduce uncertainty in the modeled OS and PFS for VEN+I and BTKi-based therapies. Additionally, because the sponsor's NMA included both fit and unfit patients, while the CLL13 trial included only fit patients, incorporating the sponsor's NMA results into the economic model may introduce an efficacy bias favoring VEN+O, BR, and FCR compared to VEN+I and BTKi-based therapies. • The long-term efficacy of VEN+O, FCR, and BR in the economic model is uncertain due to the reliance on extrapolated OS and PFS data, with most of the predicted benefits of VEN+O occurring beyond the observed trial period. Clinical experts noted that the sponsor's OS extrapolation for BR likely underestimated survival and that PFS estimates are inconsistent with what is expected in clinical practice.

Component	Description
	• The impact of VEN+O on TTNT is uncertain, as the sponsor's chosen parametric extrapolation suggests a 14.6-year lag between median PFS and median TTNT, which contrasts sharply with clinical expectations of a 4 to 8-year difference. This discrepancy suggests that the sponsor's assumptions may not accurately reflect real-world clinical practice. • The economic model submitted by the sponsor exhibited poor modeling practices, including failure to execute probabilistically and errors in wastage calculations, which compromised the model's accuracy and auditing.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by adopting alternative parametric distributions to extrapolate OS for BR; adopting alternative parametric distributions to extrapolate PFS for BR and FCR; and, adopting alternative parametric distributions to extrapolate TTNT for VEN+O. CDA-AMC additionally corrected the sponsor's submitted base case by revising the unit prices for obinutuzumab, bendamustine, and cyclophosphamide, which were incorrectly programmed in the submitted model. • In the CDA-AMC base case, the cost-effectiveness frontier was comprised of BR, FCR, VEN+O, and VEN+I, representing the optimal treatment strategies. In sequential analysis, VEN+O was associated with an ICER of $167,257 per QALY gained compared to FCR (incr. costs = $82,007; incr. QALYs = 0.49). A price reduction of 75% for venetoclax would be required for VEN+O to be cost-effective compared with FCR at a WTP threshold of $50,000 per QALY gained. • The cost-effectiveness of VEN+O was sensitive to assumptions concerning TTNT and subsequent therapy costs. When assuming a Weibull distribution for the TTNT extrapolation for VEN+O, the ICER for VEN+O decreased to $88,275 per QALY gained compared to FCR. This led to the relative risk of TTNT between VEN+O and BR or FCR remaining constant for 25 years, which is considered optimistic given the lack of evidence supporting a prolonged benefit of VEN+O in delaying TTNT. When excluding subsequent therapy costs to capture the cost-effectiveness of VEN+O among the small subset of patients who may not receive 2L therapy, VEN+O was extendedly dominated by a combination of FCR and VEN+I.

2L = second-line; BR = bendamustine, in combination with rituximab; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; CrI = credible intervals; FCR = fludarabine-cyclophosphamide-rituximab; ICER = incremental cost-effectiveness ratio; incr. = incremental; ITT = intention-to-treat; LY = life-year; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; TTNT = time to next treatment; VEN+I = venetoclax, in combination with ibrutinib; VEN+O = venetoclax, in combination with obinutuzumab; vs = versus; WTP = willingness-to-pay.

[a] Submitted treatment cost with the price of obinutuzumab corrected from $5,477.84 to $5,751.73 per 1,000 mg vial.

Budget Impact

The review team identified the following key limitations with the sponsor's analysis: drug acquisition costs for BTKi-based therapies may be overestimate; market shares in the reference scenario are uncertain; uptake of venetoclax plus obinutuzumab is uncertain; the estimated proportion of patients that would be eligible for public coverage is uncertain; the NIHB population was inappropriately calculated; there is a misalignment of model inputs between the sponsor-submitted CUA and BIA.

The CDA-AMC BIA base case corrected the price of obinutuzumab, bendamustine, and cyclophosphamide, aligned the baseline characteristics for patient body weight and patient BSA with the CUA, excluded drug wastage for all treatments, included annual costs for IV treatments in the NIHB population, and adjusted the duration of BTKi-based therapies to align with the CUA. The CDA-AMC base case suggests that the 3-year budget impact of reimbursing venetoclax plus obinutuzumab for previously untreated adult patients with CLL considered fit and potentially fludarabine-eligible is expected to result in cost savings of $8,371,343 (Year 1 costs: $1,158,251; Year 2 savings: $2,535,407; Year 3 savings: $6,994,187).

The estimated budget impact is sensitive to the proportion of patients who discontinue BTKi-based therapies prior to progression.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villneuve, and Danica Wasney.

Meeting date: October 9, 2024

Regrets:

None

Conflicts of interest:

None