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Reimbursement Recommendation

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)

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Venclexta?

Canada's Drug Agency (CDA-AMC) recommends that Venclexta be reimbursed by public drug plans, in combination with obinutuzumab, for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Venclexta in combination with obinutuzumab should only be covered to treat patients with previously untreated CLL who require treatment according to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria and are in good health (i.e., have a good performance status, as determined by a clinician).

What Are the Conditions for Reimbursement?

Venclexta in combination with obinutuzumab should only be reimbursed if prescribed by a clinician with expertise treating CLL and monitoring therapy, and if the cost of Venclexta is reduced. Patients who experience disease progression while taking Venclexta or who cannot tolerate the drug would not be eligible for continued coverage. Reimbursement of venetoclax should be discontinued after 12 months of therapy is completed.

Why Did CDA-AMC Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that treatment with Venclexta in combination with obinutuzumab improved progression-free survival (PFS) compared to chemotherapy (fludarabine, cyclophosphamide, and rituximab [FCR] and bendamustine and rituximab [BR]).
- Venclexta in combination with obinutuzumab meets some of the needs identified by patients, including prolonging disease remission and offering an additional treatment option. Based on the evidence from the clinical trial, it is uncertain whether Venclexta in combination with obinutuzumab prolongs survival or has fewer side effects, and it is unknown whether the drug improves health-related quality of life (HRQoL).
- Based on the CDA-AMC assessment of the health economic evidence, Venclexta does not represent good value to the health care system at the public list price when compared with FCR. A price reduction is therefore required when compared with FCR.

Summary

- Based on public list prices, Venclexta in combination with obinutuzumab may result in cost savings of approximately $8 million over the next 3 years for public drug plans.

Additional Information

What Is CLL?

CLL is a type of cancer that affects the blood. It is typically a slow-growing cancer that is characterized by a buildup of abnormal, ineffective B cells in various parts of the body, including the lymph nodes, bone marrow, and blood. While most patients do not show symptoms at the time of diagnosis, some patients may experience painless, swollen lymph nodes that wax and wane. CLL is the most common type of leukemia in adults living in Canada; in 2019, 1,700 people were diagnosed with CLL.

Unmet Needs in CLL

Patients identified a need for new treatments for CLL that prolong survival and remission, have fewer side effects, and improve HRQoL.

How Much Does Venclexta Cost?

Treatment with Venclexta in combination with obinutuzumab is expected to have a per-patient cost of $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.

Recommendation

This recommendation supersedes the pan-Canadian Oncology Drug Review 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 CLL only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from an ongoing phase III, 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 a 17p deletion (del[17p]) or *TP53* mutation compared with chemotherapy (FCR and BR). At the interim analysis (data cut-off date: January 20, 2022; median follow-up = 38.8 months; interquartile range [IQR], 32.7 to 46.1), the CLL13 trial demonstrated that venetoclax plus obinutuzumab results in an improvement in PFS compared to chemotherapy based on a hazard ratio (HR) of 0.42 (97.5% confidence interval [CI], 0.26 to 0.68; P < 0.001). Of note, the median PFS [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 and remission, have fewer side effects, and improve 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. 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 the sponsor's submission.

Using the sponsor-submitted price for venetoclax and the 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 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. Adults with previously untreated CLL who require treatment according to the iwCLL 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 iwCLL criteria.	Although patients with del(17p) and/or *TP53* mutations were excluded from the CLL13 trial, the clinical experts indicated that venetoclax plus obinutuzumab would be an appropriate option for the patients.
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 lasting 28 days. Patients in the CLL13 trial 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 6 months of venetoclax as a single drug.
Prescribing		
4. Venetoclax in combination with obinutuzumab should be prescribed by clinicians with expertise treating CLL and monitoring therapy.	This condition 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; BR = bendamustine and rituximab; ECOG = Eastern Cooperative Oncology Group; FCR = fludarabine, cyclophosphamide, and rituximab; ICER = incremental cost-effectiveness ratio; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; 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 1 of 2 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 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 may be an exception as it is subject to uncertainty because the interpretation relies on certain assumptions being made. Furthermore, the clinical experts advised that undetectable MRD is of limited applicability to practice in Canada 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 network meta-analysis (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 including the null and the small number of studies included. Additionally, the 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 by 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 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chronic Lymphocytic Leukemia 16 (EORTC QLQ-CLL16) in Study CLL13, the 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 a continuous Bruton tyrosine kinase inhibitor (BTKi) in patients who are younger and/or considered fit, 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 a del(17p) or *TP53* mutation. Although these patients were excluded from the CLL13 trial, 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 patients with a del(17p) and/or *TP53* mutation who are considered fit. 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 life-year benefits for venetoclax plus obinutuzumab were 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 a BTKi-based therapy, market shares, and market uptake.

Background

CLL 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 people 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 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 prenovel therapy era and estimated the median life expectancy for this subset of patients to be longer than 3 years from initial diagnosis.

In patients with previously untreated CLL with *TP53* aberrations (del[17p] and/or *TP53* mutations) who are symptomatic, the 2022 updated Canadian evidence-based guideline for the front-line treatment of CLL advised that continuous therapy with a BTKi (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 patients who are symptomatic and fit (per the guidelines, patients who are considered fit include those who are young and those who are eligible for treatment with FCR) and have previously untreated CLL without *TP53* aberrations, the guideline advises that FCR is preferred for *IGHV*-mutated CLL, while a BTKi 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 advises treatment with BR for patients who are considered fit and are older (65 years and older) and have 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 BCL2, a protein that inhibits cells from programmed cell death. 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 drug.

Submission History

Initial Submission

In 2020, venetoclax in combination with obinutuzumab was first reviewed by pERC for the treatment of adults 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 Cumulative Illness Rating Scale [CIRS] score greater than 6 or a creatinine clearance [CrCl] of less than 70 mL/min), require treatment according to the 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 publicly available on the project website.

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 who are 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 1 phase III, multicenter, randomized, prospective, open-label clinical trial in patients considered fit (defined in the trial by a CIRS score ≤ 6 and CrCl ≥ 70 mL/min) with previously untreated CLL and without a 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 CDA-AMC review process
- 2 clinical specialists with expertise diagnosing and treating patients with CLL

- input from 2 clinician groups, Lymphoma Canada and the 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 that responded to the call for input and from the 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 — 1 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 US, 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 17p, 13q, or 11q deletions; a *TP53* mutation; trisomy 12; and unmutated *IGHV*. The 2020 survey provided information on patients with CLL and SLL who had experience with front-line venetoclax in combination with obinutuzumab. Of the 33 survey respondents, 10 were aged between 40 and 59 years and 22 were aged between 60 and 79 years; 18 were male and 14 were female; 1 did not respond to either question. The survey respondents were from Canada (2 patients), the US (29 patients), and the 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 the 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 of the 2020 survey respondents 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 BTKi-free, and time-limited are needed for patients with previously untreated CLL who are considered fit. 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, molecular profile (*IGHV* and *TP53* mutation status) is the main criteria to inform discussions on selecting a treatment regimen. Other factors to consider when selecting a treatment regimen include accessibility to a local treatment centre and the 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 per the iwCLL response criteria. The clinical experts advised reassessing

for treatment response every 6 months in the first year after completing therapy and annually thereafter. The clinical experts identified the following factor to be considered for discontinuation of venetoclax in combination with obinutuzumab: patients continue to present with adverse events (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 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 the 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 that patients with high-risk genomic features (e.g., unmutated *IGHV*) who are younger 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 members 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 patients with lower-risk disease and the longest life expectancy who are youngest and/or fittest 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 Hematology Cancer 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 BTKi-based therapies 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 front-line, 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 a del(17p) or *TP53* mutation

(these patients will typically receive BTKi 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.

Per the OH-CCO Hematology Cancer Drug Advisory Committee, standard CLL response outcomes, improvement in PFS, 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 Hematology Cancer Drug Advisory Committee advised to consider treatment discontinuation in the setting of significant intolerance or disease progression, while Lymphoma Canada suggested considering treatment discontinuation if there is a lack of response or 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
- potential need for a provisional funding algorithm
- care provision issues
- system and economic issues.

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., BR, chlorambucil-rituximab).	This is a comment from the drug plans to inform pERC deliberations.

Implementation issues	Response
The comparators in the CLL13 trial were FCR or BR. Ibrutinib-venetoclax has received a positive recommendation for the treatment of adults with previously untreated CLL, including those with 17p deletion. This is currently being negotiated through pCPA.	
Considerations for initiation of therapy	
Venetoclax should be given for a total of 48 weeks as a finite treatment for six 28-day cycles in combination with obinutuzumab, followed by 6 months of venetoclax as a single drug. For those 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. In patients who had to stop or delay therapy for reasons other than disease progression, it may be clinically reasonable to restart treatment, based on clinical judgment, provided that the cumulative treatment duration does not exceed 48 weeks. 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 those 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 re-treatment upon progression that may provide guidance on venetoclax re-treatment are ongoing at the time of this review; however, the clinical experts do not foresee any concerns with re-treatment upon progression (i.e., the clinical experts suggested re-treatment is likely beneficial and safe based on the literature). pERC acknowledged that evidence to support re-treatment with venetoclax plus obinutuzumab upon progression was not available at the time of this submission; however, re-treatment at the discretion of the prescriber may be considered for patients who experience progression and have had at least 1 year of response following completion of the initial course of venetoclax plus obinutuzumab.
Considerations for prescribing of therapy	
If a patient experiences intolerance to venetoclax or obinutuzumab, can treatment with the other drug be continued as monotherapy?	The clinical experts advised that this scenario is reasonable and suggested that a 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 a time-limited switch to venetoclax plus obinutuzumab. pERC agreed with the clinical experts.

Implementation issues	Response
Should eligibility for venetoclax plus obinutuzumab be extended to fit patients with previously untreated SLL?	The clinical experts advised that patients with previously untreated SLL should be eligible for venetoclax plus obinutuzumab regardless of their fitness criteria (i.e., if they are considered fit or unfit) as SLL and CLL are different manifestations of the same disease. pERC agreed with the clinical experts.
Funding algorithm	
The drug under review may change the place in therapy of its relevant comparator drugs.	This is a comment from the drug plans to inform pERC deliberations.
Please clarify 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 17p deletions were designed for chemoimmunotherapy (the comparator in study CLL13) and are not used with novel drugs. pERC agreed with the clinical experts regarding the fitness criteria. pERC also indicated that, as noted in the initial recommendation, there is insufficient evidence to make an informed recommendation on the use of venetoclax plus obinutuzumab for patients with high-risk comorbidities such as Richter syndrome.
Under what clinical circumstances would venetoclax plus obinutuzumab be used instead of the existing first-line options?	The clinical experts advised that 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 of newly diagnosed CLL to relapsed and/or 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 the 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 III, 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 MRD in peripheral blood at month 15, and venetoclax plus obinutuzumab plus ibrutinib versus standard chemoimmunotherapy on PFS at predefined analysis time points in patients considered fit (defined in the trial by a CIRS score ≤ 6 and a CrCl ≥ 70 mL/min) with previously untreated CLL and without a 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, the 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 for a 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 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 mL/min to 180.2 mL/min) in the venetoclax plus obinutuzumab group and 86.3 mL/min (range = 39.5 mL/min 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 a 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 (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 was 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 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, 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 MRD 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 grade 1 to 5 Common Toxicity Criteria (CTC). The most common TEAE in

both groups was decreased neutropenia and/or neutrophil count based on Standardized MeDRA Queries — [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 grade 1 to 5 CTC. 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 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 grade 5 CTC AE, of which 1 had COVID-19 that was reported in the time frame between the treatment period and until day 84 after end of treatment (inclusive). The other 8 patients had a grade 5 CTC AE that was reported after day 84 (after end of treatment) — secondary neoplasia (excluding Richter transformation) in 3 patients; COVID-19 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 grade 5 CTC AE, of which 1 had an infection other than COVID-19 that was reported in the time frame between the treatment period and until day 84 after end of treatment (inclusive). The other 9 patients had a grade 5 CTC AE that was reported after day 84 (after end of treatment) — COVID-19; 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 were previously summarized.

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

At the 4-year follow-up, there were 45 cases of second cancers in the venetoclax plus obinutuzumab group, including 16 cases of nonmelanoma skin cancer, 15 cases of solid tumours, 7 cases of benign tumours, and 7 cases of Richter transformation. There were 69 cases of second cancers in the chemoimmunotherapy group, including 33 cases of nonmelanoma skin cancer, 19 cases of solid tumours, 7 cases of benign tumours, 6 cases of Richter 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 front-line setting, per the guideline. In consultation with the clinical experts, it was concluded that the subset of patients with unmutated *IGHV* randomized to receive chemoimmunotherapy were at a disadvantage compared to those randomized to venetoclax plus obinutuzumab, thereby introducing potential for bias in favour of venetoclax plus obinutuzumab. The clinical experts noted that as chemoimmunotherapy was the standard of therapy at the time the trial was conducted, this issue is considered reasonable; however, 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 after 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 MRD status data. 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 an 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. A 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. As the study was not designed nor powered to test specific hypotheses in all other secondary and exploratory analyses, these results are considered to be 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 — patients with previously untreated CLL without *TP53* aberrations who were considered fit (defined in the trial by a CIRS score ≤ 6 and CrCl ≥ 70 mL/min).

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 a del[17p] and *TP53* mutation). However, the clinical experts noted that some criteria are not applicable to practice in Canada 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 patients considered fit who were excluded from the trial, namely patients with SLL and a del(17p) and/or *TP53* mutation. Additionally, the baseline characteristics of the study population are generally representative of the patient population considered fit who are seen in practice and would be considered as candidates for venetoclax in combination with obinutuzumab, per the 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 practice in Canada due to limitations in accessing relevant tests (i.e., 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 the literature, from a clinical practice perspective, response to treatment and undetectable MRD are only relevant as supportive evidence for long-term outcomes.

According to the guidelines, FCR and BR are appropriate comparators in patients considered fit without *TP53* aberrations (del[17p] or *TP53* mutation) and with mutated *IGHV* in the front-line setting; albeit FCR is infrequently used and BR is not used in practice, per the clinician group and clinical expert input. As previously mentioned, patients without *TP53* aberrations and with unmutated *IGHV* who are considered fit do not typically receive chemoimmunotherapy in the front-line setting; instead, a BTKi would have been a more appropriate comparator in this subset of patients, per the guideline. Furthermore, based on the guideline, a BTKi would have been an appropriate comparator for patients with *TP53* aberrations who are considered fit — 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 NMA

The objective of the sponsor-submitted NMA was to estimate the comparative effectiveness of venetoclax plus obinutuzumab versus relevant comparators in the treatment of patients who are fit and have previously untreated CLL without a 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 a Hamiltonian Monte Carlo Markov chain.

The population of interest is adults aged 18 years and older who are considered 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 patients not considered fit was not feasible due to the limited evidence for patients who were solely fit. Hence, the base case included patients, both those considered fit and unfit, 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 III, multinational randomized controlled trials (except for FLAIR, which was conducted in the UK only) with a median follow-up ranging from 26.2 to 76.4 months. All studies included patients with CLL that was treatment naive, with the exception of the SEQUOIA trial, in which patients with SLL were also included.

Progression-Free Survival

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

Overall Survival

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

[redacted]

Time to Next Treatment

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

Undetectable MRD

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

Harms Results

Harms results were not assessed in the NMA.

Critical Appraisal

The 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 practice in Canada for the 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 the model results to the informative priors used in the random-effects model. Furthermore, assessment of consistency was not reported.

While the base-case analysis of mixed fit and unfit network was not conducted 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 patients considered fit, while 5 trials included only patients considered unfit or rather unfit according to 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 and 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 those who were FCR ineligible. These differences in eligibility criteria (i.e., fitness approximation) might have contributed to the difference observed in the direction of the results for the comparisons with the BTKis, 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 the literature, del(17p) and *TP53* mutations are predictive of worse clinical outcomes after treatment with chemoimmunotherapy, compared with targeted therapies, and an *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 a del(17p) and/or *TP53* mutation to align with the CLL13 trial population; however, these patients were included in the analyses when 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 the 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 BTKis 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 given that estimated HRs often wane with increased lengths of follow-up. Overall, these sources of clinical and methodological heterogeneity likely introduced bias in the NMA results.

Notably, the networks were sparse. The base-case and the sensitivity analyses included 4 or 8 studies that 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	Patients with previously untreated CLL, including those who are 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)
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 six 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 modelled OS and PFS for VEN + I and BTKi-based therapies. Additionally, because the sponsor's NMA included both patients considered fit and those considered unfit, while the CLL13 trial included only those considered fit, incorporating the sponsor's NMA results into the economic model may introduce an efficacy bias that favours VEN + O, BR, and FCR compared to VEN + I and BTKi-based therapies.

Component	Description
	• 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. The 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. • 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 modelling 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 into the submitted model. • In the CDA-AMC base case, the cost-effectiveness frontier comprised 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 (incremental costs = $82,007; incremental 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 to support 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 second-line therapy, VEN + O was extendedly dominated by a combination of FCR and VEN + I.

BR = bendamustine and rituximab; BTKi = Bruton tyrosine kinase inhibitor; CDA-AMC = Canada's Drug Agency; CLL = chronic lymphocytic leukemia; CrI = credible interval; FCR = fludarabine, cyclophosphamide, and rituximab; ICER = incremental cost-effectiveness ratio; 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 and ibrutinib; VEN + O = venetoclax and obinutuzumab; WTP = willingness to pay.

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

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the drug acquisition costs for BTKi-based therapies may be overestimated; the market shares in the reference scenario are uncertain; the uptake of venetoclax plus obinutuzumab is uncertain; the estimated proportion of patients who would be eligible for public coverage is uncertain; the Non-Insured Health Benefits population was inappropriately calculated; and there was a misalignment of model inputs between the sponsor-submitted cost-utility analysis (CUA) and budget impact analysis.

The CDA-AMC budget impact analysis base case corrected the prices of obinutuzumab, bendamustine, and cyclophosphamide; aligned the baseline characteristics for patient body weight and patient body surface area with the CUA; excluded drug wastage for all treatments; included annual costs for IV treatments in the Non-Insured Health Benefits 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 adults with previously untreated 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 Bruton tyrosine kinase inhibitor–based therapies before 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

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.