CADTH

CADTH Reimbursement Review

Provisional Funding Algorithm

Chronic Lymphocytic Leukemia

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Key Messages

- As members of the same drug class indicated for the same populations, acalabrutinib and ibrutinib should be reimbursed in a similar manner.
- There currently is no clinical rationale for prioritizing, ibrutinib, acalabrutinib, or venetoclax plus obinutuzumab for first-line treatment in adult patients with chronic lymphocytic leukemia who are fludarabine ineligible; therefore, affordability and total cost of care will be important considerations.
- Re-treatment with venetoclax may be considered if the patient's disease did not progress during treatment or within 12 months after cessation of a venetoclax-based regimen.
- Alternate drug classes should be prioritized for subsequent treatments upon cancer progression.

Background

CADTH has reviewed and issued recommendations for drugs that can be used in adults with chronic lymphocytic leukemia (CLL) who are either untreated or have received at least 1 prior therapy.

pERC Recommendations for Acalabrutinib (Calquence)

Based on the 2020 and 2021 reviews[1,2] of acalabrutinib for the treatment of patients with CLL for whom a fludarabine-based regimen is inappropriate or have received at least 1 prior therapy, through the CADTH pan-Canadian Oncology Drug Review (pCODR), the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) issued the following reimbursement recommendations:

- pERC conditionally recommends reimbursement of acalabrutinib as monotherapy in adult patients with previously untreated CLL for whom a fludarabine-based regimen is inappropriate, if the following conditions are met:
  - cost-effectiveness improved to an acceptable level
  - feasibility of adoption (budget impact) is addressed
- pERC conditionally recommends reimbursement of acalabrutinib as monotherapy in adult patients with relapsed or refractory CLL who have received at least 1 prior therapy, if the following condition is met:
  - cost-effectiveness being improved to an acceptable level

pERC Recommendations for Venetoclax (Venclexta)

Based on the 2018, 2019, and 2020 reviews[3-5] of venetoclax for the treatment of patients with CLL who are fludarabine ineligible or have received at least 1 prior therapy, through the CADTH pCODR, pERC issued the following reimbursement recommendations:

- pERC conditionally recommends reimbursement of venetoclax (Venclexta) in combination with obinutuzumab (VEN-OBI) for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) who are fludarabine ineligible if the following condition is met:
  - cost-effectiveness improves to an acceptable level
- 2019: pERC conditionally recommends reimbursement of venetoclax (Venclexta) in combination with rituximab for the treatment of adult patients with chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy, irrespective of their 17p deletion status, only if the following condition is met:
  - cost-effectiveness being improved to an acceptable level.

- pERC conditionally recommends the reimbursement of venetoclax (Venclexta) for patients with chronic lymphocytic leukemia (CLL) who have received at least 1 prior therapy and who have failed a B-cell receptor inhibitor (BCRi) only if the following condition is met:
  - an improvement of cost-effectiveness in the form of a substantial price reduction until more robust clinical data are made available for a future reassessment.

pERC Recommendations for Ibrutinib (Imbruvica)

Based on the 2015 and 2016 reviews[6,7] of ibrutinib for the treatment of patients with CLL (previously untreated and patients who had received at least 1 previous therapy), through the CADTH pCODR, pERC issued the following reimbursement recommendations:

- pERC recommends reimbursement of ibrutinib (Imbruvica) as an option for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) for whom fludarabine-based treatment is considered inappropriate, condition on:
  - cost-effectiveness being improved to an acceptable level
- pERC recommends funding ibrutinib (Imbruvica) conditional on:
  - the cost-effectiveness being improved to an acceptable level
  - funding should be for patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) who have received at least 1 prior therapy and are considered inappropriate for treatment or re-treatment with a fludarabine-based regimen.

pERC Recommendations for Idelalisib (Zydelig)

Based on the 2015 review[8] of idelalisib for the treatment of patients with relapsed chronic CLL in combination with rituximab through the CADTH pCODR, pERC issued the following reimbursement recommendation:

- pERC recommends funding idelalisib (Zydelig), conditional on cost-effectiveness being improved to an acceptable level, when used in combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Implementation Issues

At the request of the participating drug programs, CADTH convened a panel of Canadian clinical experts to provide advice for addressing the outstanding implementation issues as follows:

- alignment of funding criteria for acalabrutinib and ibrutinib
- relative place in therapy and target patient populations for ibrutinib (IBR), acalabrutinib (ACA), and venetoclax in combination with obinutuzumab (VEN-OBI) in the first-line setting
- appropriateness and timing of re-treatment with VEN in subsequent lines of therapy
- use of idelalisib-rituximab after treatment with ACA
- sequencing of treatments for patients with CLL who received a Bruton's tyrosine kinase (BTK) inhibitor in the first-line setting
- sequencing of treatments for patients with CLL who received a B-cell lymphoma 2 (BCL-2) inhibitor in the first-line setting
- sequencing of treatments for patients with CLL who received chemoimmunotherapy in the first-line setting.

Consultation Process and Objectives

The implementation advice panel comprised 6 Canadian specialists with expertise in the diagnosis and management of patients with CLL, a representative from a public drug program, and a panel chair. The objective of the panel was to provide advice to the participating drug programs regarding the implementation issues noted the Background section. A consensus-based approach was used, and input from stakeholders was solicited using questionnaires. Stakeholders including patient and clinician groups and pharmaceutical manufacturers, and public drug programs were invited to provide input in advance of the meeting.

The advice presented in this report is not necessarily evidence-based but has been developed based on the experience and expertise of the implementation advice panel members and, as such, represents experience-informed opinion.

Advice on Funding Algorithm

Summary of Implementation Advice

Implementation advice regarding the optimal sequencing of treatments is summarized in Table 1. For each implementation issue, a summary of the relevant panel discussion is provided for additional context.

Table 1: Summary of Advice for Addressing Implementation Issues

Issue	Advice
Alignment of funding criteria for ACA and IBR	The panel advises that both ACA and IBR should be reimbursed in the same manner, with decisions concerning initiation of therapy being individualized to patients, balancing considerations around patient characteristics with the total cost of care.
Relative place in therapy and target patient populations for IBR, ACA, and VEN in the first-line setting	The panel advises that: • Contingent on affordability challenges being addressed, options should remain available between IBR, ACA, and VEN-OBI in the first-line setting for all patients with CLL who are not eligible for fludarabine-based therapy. • If the provinces cannot afford BTKi for their full indication, then they should be prioritized in patients with high-risk factors. • Decisions concerning initiation of therapy should be individualized to patients, balancing considerations around patient characteristics with the total cost of care.
Appropriateness and timing of re-treatment with VEN in subsequent lines of therapy	The panel advises that re-treatment with a VEN-based regimen should be available for patients with CLL who relapse, unless relapse occurs while receiving, or within 12 months of completing, a VEN-based regimen.
Use of idelalisib-rituximab after treatment with ACA	The panel advises that: • Idelalisib should not be available following disease progression on ACA or other BTKi. • Idelalisib should only be available on a case-by-case basis following intolerance and/or relapse after previous lines of therapy, due to its poor tolerability and safety concerns relative to BTKi.
Sequencing of treatments for CLL patients who received a BTKi in the first-line setting	The panel advises that: • Patients who are refractory to a BTKi in the first-line setting should next be treated with a VEN-based regimen.

Issue	Advice
	• Patients who are intolerant, but not refractory, to a BTKi in the first-line setting may be treated with another BTKi or a VEN-based regimen.
Sequencing of treatments for CLL patients who received a BCL-2 inhibitor in the first-line setting	The panel advises that: • Patients who experience a shorter duration of remission (less than 12 months) following treatment with a VEN-based regimen may be offered next-line therapy with a BTKi. • Patients who experience a longer duration of remission (12 months or more) following treatment with a VEN-based regimen may be offered next-line therapy with either a VEN-based regimen or a BTKi.
Sequencing of treatments for CLL patients who received chemoimmunotherapy in the first-line setting	The panel advises that: • Options should remain available for IBR, ACA, and a VEN-based regimen as next-line therapy for CLL patients following chemoimmunotherapy. • Sequencing decisions should be individualized to each patient, balancing considerations around patient characteristics with the total cost of care.

ACA = acalabrutinib; BCL-2 = B-cell lymphoma 2; BTK = Bruton's tyrosine kinase; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; IBR = ibrutinib; VEN = venetoclax.

In addition to the preceding advice, the panel indicated that all reimbursement recommendations were contingent upon ensuring improved cost-effectiveness so that the relevant treatments are affordable to public payers.

Panel Discussion

Alignment of Funding Criteria for ACA and IBR

Panellists were asked to consider available evidence addressing the extent to which ACA and IBR provide comparable clinical outcomes in CLL patients. Given the current scarcity of available published data directly comparing the drugs, the panel collectively acknowledged that there is neither a plausible biological nor demonstrated evidentiary basis upon which to establish that ACA or IBR would be preferential in the treatment of CLL patients. Nonetheless, it was acknowledged that there may be patient preference for one drug over the other drug (e.g., once-daily IBR may be preferred to twice-daily ACA by some patients) or that tolerability may vary across patients and drive a preference for one drug or the other drug.

Notably, the panel did highlight the ongoing ELEVATE-RR trial[9] which is currently undertaking a head-to-head comparison of ACA and IBR in previously treated CLL patients — including those with high-risk features. While the panellists acknowledged that a full report of data from this trial will remain embargoed until the summer of 2021, it has been reported, at 40 months of follow-up in 553 patients, that the primary end point of noninferior progression-free survival in ACA has been achieved.[9] Further, the manufacturer has reported an early signal in the preliminary safety data suggesting a lower incidence of atrial fibrillation in patients treated with ACA compared to those treated with IBR.[9] Panellists agreed that these early direct comparative data could suggest that although efficacy is likely comparable between the 2 therapies, some relative benefit in terms of reduced toxicity may occur with ACA.

Given early evidence suggesting the potential for superior tolerability of ACA, the panellists agreed that there may not be a clinical rationale to favour IBR over ACA. Consequently, cost considerations could feature importantly in decision-making. Specifically, if the pricing of ACA renders it significantly more costly than IBR, it may be optimal to prioritize IBR in the treatment of CLL patients and assess tolerability using ACA as an alternate therapy if

toxicity becomes a concern. Nonetheless, cost-effectiveness — as opposed to cost alone — was highlighted as a key consideration for decision-making concerning the use of the drugs (e.g., avoidance of excess cardiac events in patients treated with ACA could reduce overall costs of care).

Relative Place in Therapy and Target Patient Populations for IBR, ACA, and VEN in the First-Line Setting

The panellists discussed sequencing and eligibility for first-line therapy for fludarabine-ineligible patients among IBR, ACA, and VEN-OBI therapies. Sequencing and prioritization of 1 drug over another was also discussed in the context of CLL patients across various risk strata.

The panellists agreed that patient characteristics, both clinical and personal, including proximity to a care facility and/or patient preference for avoidance of IV therapy, are key features that must inform decisions around sequencing in the first-line setting. In addition, cost considerations were acknowledged as having an important bearing on how to position IBR, ACA, and VEN in the first-line and second-line settings. However, the panel emphasized that cost considerations should not be limited to the cost of the drugs themselves but should include associated costs of administering therapy (e.g., for VEN-OBI, the costs of travel and accommodation for rural and/or remote patients during the ramp-up period, which may involve hospitalization for some patients, when treatment is initiated).

Ultimately, the panellists agreed that these drugs have shown efficacy and safety in their target populations and that currently there is no definitive clinical rationale, per se, to favour 1 drug over another of the 3 drug therapies as a first-line intervention in either high-risk or other CLL patients. The panellists emphasized the importance of balancing available options for individualizing patient therapy in all settings, including first-line; the cost of care in its entirety required for a particular patient (including travel and/or accommodation as necessary) as opposed to the cost of the drug alone; and equitable access across the jurisdictions.

The panellists acknowledged that the decision made by the provinces to fund IBR only for high-risk patients was motivated by economic considerations. The panel received input from the jurisdictions indicating that BTK inhibitor therapies are not time-limited which, combined with the high cost of the drugs, makes them very expensive treatments for most CLL patients compared with VEN-OBI or more conventional therapies. Some jurisdictions have decided to restrict access to IBR due to these affordability concerns. The panel agreed that if affordability cannot be improved to allow broader funding, BTKi should be prioritized for high-risk patients, who typically have poorer prognosis, fewer therapeutic options, and are likely to obtain the greatest relative clinical benefits over other therapies. This advice may be reconsidered should economic factors change. Additionally, the panel felt that CLL patients who experience challenges accessing injectable therapies should be considered for BTKi access on a case-by-case basis.

Appropriateness and Timing of Re-Treatment With VEN in Subsequent Lines of Therapy

The panellists indicated that there are limited data available to inform decisions concerning re-treatment with VEN, and virtually no data informing re-treatment following VEN-OBI, largely due to low rates of relapse in these patients. As it concerns re-treatment with a VEN-based regimen following VEN plus rituximab (VEN-rituximab), 4-year follow-up from the MURANO trial has generated some relevant data describing response to subsequent therapies in relapsed or refractory CLL.[10] Notably, 100% of a small subset of trial patients (n = 10) re-treated with IBR following relapse after VEN-rituximab experienced a response, but 55% of patients (n = 6 of 11) re-treated with a VEN-based therapy following VEN-rituximab experienced a response.

Apropos of this limited evidence, 1 panellist highlighted that the likelihood of re-treating a patient with a VEN-based regimen following relapse after VEN-rituximab is low, as a BTKi (i.e., ACA or IBR) would more likely be considered as the next best option. Nonetheless, panellists agreed that disallowing re-treatment with VEN is not supported by the available data and that re-treatment should therefore remain an available option to clinicians and patients. Re-treatment after VEN-OBI should be with VEN-rituximab because this is the funded therapy for relapsed disease. Importantly, panellists reiterated the necessity of ensuring equitable access for this and other therapeutic options across the provinces.

Regarding timing, the panellists agreed that patients who relapse while on a VEN-based therapy, or within 12 months of completing treatment, should not be eligible for re-treatment with VEN; otherwise, there would be no justifiable basis upon which to refuse re-treatment.

Use of Idelalisib-Rituximab After Treatment With Acalabrutinib

The panellists agreed that idelalisib would be an unlikely treatment option given its relatively poor clinical effectiveness compared with other available drugs (e.g., VEN, IBR, ACA) and a mechanism of action similar to BTKi; therefore, its use in patients refractory to BTKi would be similarly unlikely to produce a benefit.

In general, there was consensus among the panel that the use of idelalisib is very infrequent and would likely be reserved only for relapsed or refractory CLL patients who experience intolerance of a BTKi or relapse following several previous lines of therapy. Nonetheless, it was suggested that there may be residual value in allowing idelalisib on a case-by-case basis for patients who experience intolerance and/or disease progression following several previous lines of therapy, and/or as a “last resort” while bridging patients to allogenic transplant or cellular therapy, for instance.

Sequencing of Treatments for CLL Patients Who Received a BTKi in the First-Line Setting

Panellist feedback and discussion demonstrated a general consensus that patient relapse on a BTKi should indicate next-line therapy with a different class of therapy (e.g., VEN-based regimen) and that there are data to support this approach.[11] One prospective study investigated the clinical effectiveness of venetoclax in patients with CLL who were refractory to, or had relapsed following, therapy with IBR. Researchers reported that 59 of 91 patients (65%) achieved an objective response, with 8 of 91 patients (9%) achieving complete remission.[11] Panellists also indicated that patient intolerance to 1 drug should not preclude a patient from being offered another drug within the same class (e.g., ACA and IBR).

Sequencing of Treatments for CLL Patients Who Received a BCL-2 Inhibitor in the First-Line Setting

Most panellists agreed that there are little to no data available to inform an answer to this question, but that it is reasonable to follow first-line BCL-2 inhibitor therapy with a BTKi (e.g., ACA or IBR) following a VEN-based regimen.

Feedback from the panellists also indicated that re-treatment with a BCL-2 inhibitor may be beneficial when the duration of remission has been relatively long. However, if the time to relapse was relatively short, switching to a BTKi would far more likely lead to a durable remission.

Sequencing of Treatments for CLL Patients Who Received Chemoimmunotherapy in the First-Line Setting

There was consensus among the panellists concerning a lack of direct, comparative evidence to inform optimal sequencing of therapies following chemoimmunotherapy; however, panellists agreed that decisions concerning the sequencing of treatments following chemoimmunotherapy should be driven by similar principles as those when considering these treatments in the first-line setting.

As newer drugs become candidates for first-line therapy, the panellists acknowledged that chemoimmunotherapy could become an option for the treatment of patients with relapsed and/or refractory disease if they are not considered refractory to chemoimmunotherapy. Panellists agreed that there currently is no evidence on the use of chemoimmunotherapy after newer therapies, and new evidence is unlikely to develop. Nevertheless, panellists agreed that although this scenario may be unlikely, chemoimmunotherapy could be considered in subsequent lines of therapy.

The 12-month interval to relapse for rituximab-containing therapy (currently specified within the relevant pERC recommendation[4] to be eligible for VEN-rituximab) was considered by the panellists to be inconsistent with current clinical practice. The panellists suggested that a 6-month interval would be more appropriate given that 6 months is an accepted rituximab "refractory" definition.[12,13]

For all the treatments discussed, the panellists agreed that ensuring options remain available to clinicians and patients should be a guiding principle, with patient characteristics, broad cost considerations (including care costs and not only drug costs), and equitable access across the provincial jurisdictions informing clinical decisions.

Provisional Funding Algorithm

Figure 1 depicts the provisional funding algorithm proposed by the panel. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm; it is neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagram may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain provinces. All drugs are subject to explicit funding criteria, which may also vary between provinces. Readers are invited to refer to the individual drug entries on the CADTH website for more details.

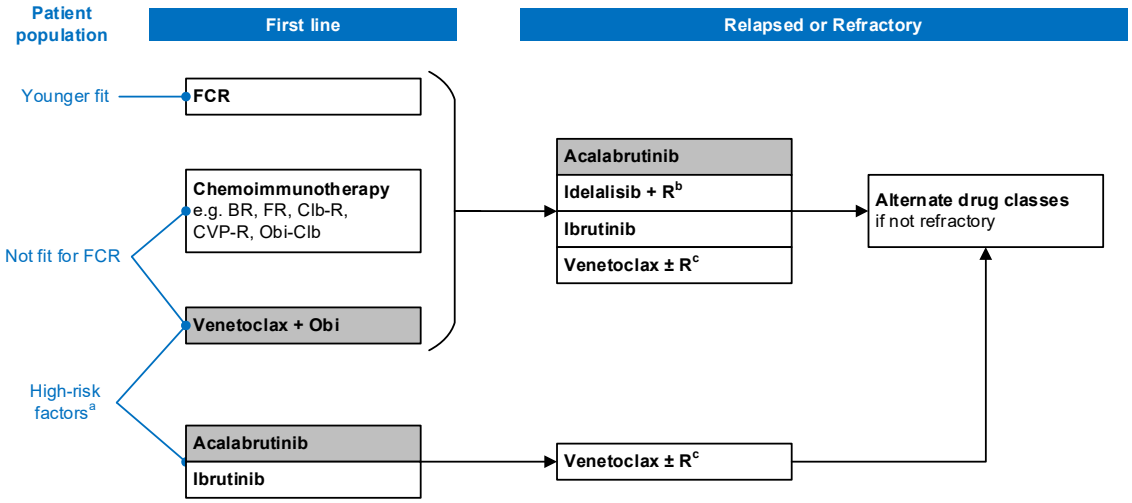
First-Line Setting

The standard first-line regimen for eligible CLL patients (i.e., younger and fit) is fludarabine-cyclophosphamide-rituximab. This therapy may be inappropriate for older, less fit patients or those exhibiting high-risk prognostic factors (e.g., *TP53* mutations, unmutated *IGHV*, or chromosomal deletion 17p). For the former, chemoimmunotherapies are available and VEN-OBI is under consideration for funding; BTKi are not prioritized in this population although they may be available in some provinces. For the latter, IBR and ACA as well as VEN-OBI are funded or under consideration.

Relapsed or Refractory

Patients who are refractory to first-line therapies can be treated with a different drug class in the second-line setting, such as a BTKi or VEN with or without rituximab. Idelalisib combined with rituximab is available for patients who show intolerance of a BTKi and may be used on rare occasions as a bridge to transplant or other cellular therapy. Patients who relapse more than 12 months after completion of VEN-based therapy can be re-treated with VEN with or without rituximab. Alternate chemoimmunotherapies are not depicted in the algorithm but may be given in rare circumstances contingent on a progression-free interval of at least 6 months after prior CD20-targeting therapy. Upon further progression, alternate classes can be offered to patients who meet the eligibility criteria.

Figure 1: Provisional Funding Algorithm Diagram for CLL



Note: Re-treatment with venetoclax is allowed at the time of relapse if the progression-free interval was at least 12 months after completion of previous therapy. Rituximab-containing therapy may be offered at time of relapse contingent on a progression-free interval of at least six months from prior anti-CD20 therapy or if no prior anti-CD20 therapy.

[a] Including del(17p) alteration, TP53 mutation and unmutated IGHV
[b] Idelalisib-rituximab available only in cases of intolerance of a BTKi or for bridging to cellular therapy
[c] Venetoclax monotherapy only funded after failure of a BTKi

Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)

B = bendamustine; BTKi = Bruton's tyrosine kinase inhibitor; C = cyclophosphamide; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; F = fludarabine; IGHV = immunoglobin heavy-chain variable region gene; Obi = obinutuzumab; R= rituximab; V = vincristine.

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