CADTH Provisional Funding Algorithm

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Indication: Chronic lymphocytic leukemia

This report supersedes the CADTH provisional funding algorithm report for chronic lymphocytic leukemia dated May 2021.

Please always check CADTH Provisional Funding Algorithms | CADTH to ensure you are reading the most recent algorithm report.

October 2023

Background

Following a request from jurisdictions, CADTH will update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed "provisional." Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the full clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., incident population). Time-limited funding of new options for previously or currently treated patients (i.e., prevalent population) is not detailed in the algorithm.

Provisional funding algorithms may contain drugs that are under consideration for funding. Algorithms will not be dynamically updated by CADTH following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm on chronic lymphocytic leukemia (CLL). However, no outstanding implementation issues were identified; therefore, no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

CADTH published the first provisional funding panel algorithm on CLL in May 2021 to address various outstanding implementation issues such as the alignment of funding criteria for different treatment options as well as sequencing guidance. Please refer to the previous provisional funding algorithm report for further details.

For this provisional funding rapid algorithm, the purpose is to incorporate the latest CADTH recommendation for zanubrutinib for CLL.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Zanubrutinib (Brukinsa)	September 20, 2023	CADTH pCODR Expert Review Committee (pERC) recommends that zanubrutinib be reimbursed for the treatment of adult patients with chronic lymphocytic leukemia (CLL) only if the following conditions are met: **Initiation** 1. Adult (≥ 18 years) patients with CLL who meet 1 of the following criteria: 1.1. previously untreated CLL for whom fludarabine-based treatment is inappropriate 1.2. relapsed or remitting CLL who have received at least 1 prior systemic therapy. 2. Patients must have a good ECOG performance status. 3. Patients must not have any of the following: 3.1. prior progression on a BTK inhibitor 3.2. prolymphocytic leukemia or Richter's transformation. **Renewal** 4. Renewal of zanubrutinib should be based on the following assessments: 4.1. Blood work and physical examination should be performed every 1 to 3 months at initiation then can be performed less frequently (i.e., 3 to 6 months) at the discretion of the treating physician. **Discontinuation** 5. Treatment with zanubrutinib should be discontinued upon the occurrence of any of the following: 5.1. progression of disease according to iwCLL response assessment criteria 5.2. unacceptable toxicity. **Prescribing** 6. Zanubrutinib should only be prescribed by a clinician with expertise and experience in the treatment of CLL and monitoring of therapy. **Pricing** 7. Zanubrutinib should provide cost savings for drug programs relative to the cost of treatment with either ibrutinib or acalabrutinib for the treatment of adult patients with CLL. **Guidance on sequencing** pERC agreed with the clinical expert consulted by CADTH that selection of a BTK inhibitor as a treatment option will be influenced by differences in patient populations and preferences such as dosing schedule and duration of therapy, side effect profile, and concomitant drug interactions. pERC also noted the lack of definitive clinical evidence and rationale that favours 1 BTK inhibitor option over another, and thus selection of the BTK inhibitor, would be for the treating clinician to determine in agreement with the patient.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		pERC agreed with the clinical expert consulted by CADTH that patients who have high-risk features or could not receive IV therapy should be able to obtain a BTK inhibitor. Although the clinical expert consulted by CADTH noted there should not be too many restrictions on the use of zanubrutinib because the drug may have certain benefits over the earlier BTK inhibitors, pERC recommended that reimbursement criteria for zanubrutinib be aligned with the eligibility criteria outlined under initiation. The clinical expert noted that patients who are doing well on current treatment (e.g., with ibrutinib or acalabrutinib) without disease progression should not be switched.
Acalabrutinib (Calquence)	November 17, 2020	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. Eligible patients must have received at least 1 prior systemic therapy, have active disease according to 1 or more of the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria, and good performance status. Treatment with acalabrutinib should be continued until disease progression or unacceptable toxicity.
Venetoclax (Venclexta) — Obinutuzumab	November 17, 2020	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. 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) less than 70 mL/min, require treatment according to the International Workshop on Chronic Lymphoma Leukemia criteria, and have good performance status. Treatment should be given for a total of 12 months as a finite treatment: for six 28-day cycles in combination with obinutuzumab (OBI) followed by 6 months of venetoclax (VEN) as a single agent.
Venetoclax (Venclexta) — Rituximab	May 31, 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. Patients should have a good performance status and treatment should be continued until disease progression or unacceptable toxicity up to a maximum of 2 years, whichever comes first.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		Guidance on sequencing pERC concluded that the optimal sequencing of venetoclax plus rituximab and other therapies, such as B-cell receptor inhibitors, in relapsed CLL is currently unknown, as there is insufficient evidence to inform this clinical situation. However, pERC recognized that provinces will need to address this issue upon implementation of reimbursement of venetoclax plus rituximab, and noted that a national approach to developing evidence-based clinical practice guidelines addressing the sequencing of treatments would be of value.
Venetoclax (Venclexta)	March 2, 2018	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.
Ibrutinib (Imbruvica)	November 3, 2016	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, conditional on the cost-effectiveness being improved to an acceptable level. Treatment should be for patients with a good performance status and until disease progression or unacceptable toxicity.
Idelalisib (Zydelig)	August 18, 2015	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). Treatment should continue until unacceptable toxicity or disease progression.

BCRi = B-cell receptor inhibitor; BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CrCl = creatinine clearance; ECOG = Eastern Cooperative Oncology Group; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; OBI = obinutuzumab; pERC = CADTH pCODR Expert Review Committee; SLL = small lymphocytic lymphoma; VEN = venetoclax.

Table 2: CADTH Implementation Advice Panels on Chronic Lymphocytic Leukemia

Date of publication	Implementation advice
May 2021 Chronic Lymphocytic Leukemia | CADTH	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. 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.

Date of publication	Implementation advice
	• Decisions concerning initiation of therapy should be individualized to patients balancing considerations around patient characteristics with the total cost of care. 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. 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. 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. • 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. 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. 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; BTKi = Bruton's tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; IBR = ibrutinib; VEN = venetoclax.

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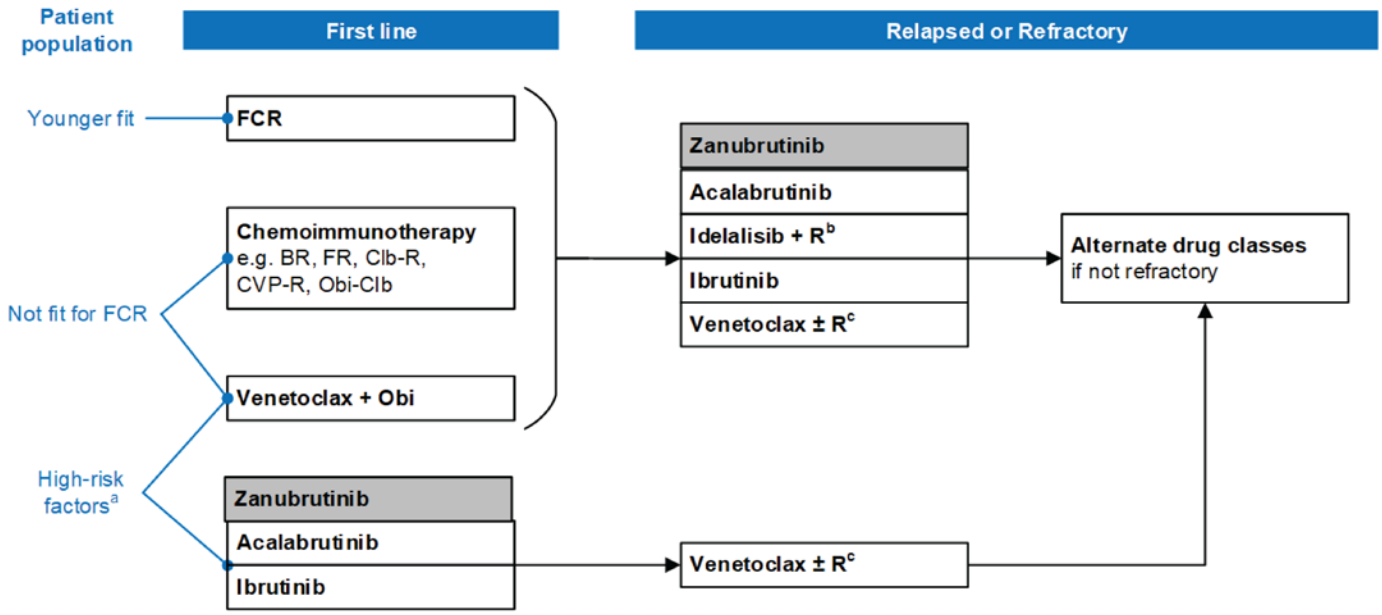
Figure 1: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia



BR = bendamustine-rituximab; Clb = chlorambucil; CVP = cyclophosphamide-vincristine-prednisone ; FCR = fludarabine-cyclophosphamide-rituximab; FR = fludarabine-rituximab; Obi = obinutuzumab; R = rituximab.

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 6 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.

Description of the Provisional Funding Algorithm

First Line

The standard first-line regimen for eligible CLL patients (e.g., younger and fit) is fludarabine-cyclophosphamide-rituximab (FCR). For individuals not fit for the FCR regimen, chemoimmunotherapies are available as well as venetoclax-obinutuzumab. For patients who have high-risk prognostic factors (e.g., *TP53* mutations, unmutated *IGHV*, or chromosomal deletion 17p), options include zanubrutinib, acalabrutinib, or ibrutinib as well as venetoclax-obinutuzumab. Zanubrutinib is under review for funding.

Relapsed or Refractory

Patients whose CLL is refractory to first-line therapies can be treated with a different drug class in the second-line setting. For example, for individuals who have received FCR, chemoimmunotherapies, or venetoclax-obinutuzumab, their second-line options include Bruton's tyrosine kinase inhibitors (zanubrutinib, acalabrutinib, ibrutinib), idelalisib with rituximab, or venetoclax with or without rituximab. Idelalisib with rituximab is available only in cases of intolerance to a Bruton's tyrosine kinase inhibitor or, on rare

occasions, as a bridge to transplant or other cellular therapy. Patients who relapse more than 12 months after completion of venetoclax-based therapy can be re-treated with venetoclax with or without rituximab. Venetoclax monotherapy is only funded after failure of a Bruton's tyrosine kinase inhibitor. Zanubrutinib is under review for funding.

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 progression, alternate classes can be offered to patients who meet the eligibility criteria.

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