



CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Chronic lymphocytic leukemia

This report supersedes the CADTH Provisional Funding Algorithm report for chronic lymphocytic leukemia dated October 2023.

Please always check [CADTH Provisional Funding Algorithms | CADTH](#) to ensure you are reading the most recent algorithm report.

March 2024

Background

Following a request from jurisdictions, CADTH may design or 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:

- pan-Canadian Oncology Drug Review 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, and 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 convened an implementation advice panel and published the first provisional funding 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.

The provisional funding rapid algorithm was then updated in October 2023 to incorporate CADTH recommendation for zanubrutinib for CLL.

This current update in the provisional funding rapid algorithm incorporates the latest CADTH recommendation for ibrutinib (Imbruvica) in combination with venetoclax (Venclexta).

Details of the relevant CADTH recommendations are outlined in [Table 1](#), while [Table 2](#) summarizes conclusions from the implementation advice panel.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
First-line setting		
Ibrutinib (Imbruvica) in combination with venetoclax (Venclexta)	November 22, 2023	<p>The CADTH pCODR Expert Review Committee (pERC) recommends that ibrutinib in combination with venetoclax be reimbursed for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL), including those with 17p deletion only if the following conditions are met:</p> <ol style="list-style-type: none"> 1. Adult (≥ 18 years) patients with previously untreated CLL, including those with 17p deletion. 2. Patients must have a good ECOG performance status. 3. Patients must not have any of the following: <ol style="list-style-type: none"> 3.1. major surgery within 4 weeks of first dose of study treatment 3.2. bleeding disorder 3.3. CNS involvement 3.4. Richter syndrome 3.5. uncontrolled autoimmune hemolytic anemia or thrombocytopenia. 4. Renewal of I+V should be based on assessments as per clinical standard of care to be performed every 1 to 3 months. 5. Treatment with I+V should be discontinued upon the occurrence of any of the following: <ol style="list-style-type: none"> 5.1. progression of disease according to iwCLL response assessment criteria 5.2. unacceptable toxicity. 6. I+V should only be prescribed by hematologists/oncologists with expertise and experience in the treatment of CLL and monitoring of therapy. 7. I+V should be negotiated so that it does not exceed the drug program cost of treatment with the least costly comparator reimbursed for the treatment of CLL. 8. The feasibility of adoption of I+V must be addressed. <p>Guidance on sequencing:</p> <ul style="list-style-type: none"> • pERC discussed the potential of I+V meeting patients' needs and to be cost saving with I+V being a fixed duration and completely oral regimen. According to clinical expert opinion, patients exhibiting good response will likely be offered the same treatment again as those patients are not necessarily resistant, which could be an advantage over continuous BTK inhibitor treatments. Overall, the clinical expert commented to pERC that a fixed duration treatment (i.e., I+V) might be attractive and used for older or higher-risk patients who have impaired renal function and/or atrial fibrillation, as those patients are more likely to experience adverse events if they have been exposed to BTK inhibitors for a long time.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<ul style="list-style-type: none"> • Evidence to support re-treatment with single-drug ibrutinib: The clinical expert consulted by CADTH stated that there is no evidence yet. However, if patients have a durable response to first treatment (e.g., at least 3 years DOR) then the clinical expert would speculate that re-treatment with I+V would be considered. pERC acknowledged the clinical expert's recommendation but determined that a 1-year DOR to first treatment would suffice for re-treatment with I+V to be considered. pERC also noted that the reassessment of single-drug ibrutinib as re-treatment was beyond the scope of this review. • Intolerance to ibrutinib: The clinical expert consulted by CADTH confirmed that treatment with venetoclax monotherapy should be continued if a patient experiences intolerance to ibrutinib because venetoclax monotherapy is an active therapy in treating patients with CLL. The clinical expert noted that patients receiving venetoclax monotherapy may have an elevated risk of tumour lysis syndrome at the beginning of the treatment. pERC agreed with the clinical expert that administering ibrutinib in combination with venetoclax would reduce the risk of tumour lysis syndrome in patients with CLL. If patients have to stop ibrutinib due to intolerance, it is safe to continue venetoclax as monotherapy. • Should patients currently receiving ibrutinib monotherapy and have not experienced disease progression be eligible for the addition of venetoclax? pERC cannot comment on this specific enquiry as no data are available. However, pERC asserts that, as a general rule, patients who are already responding to therapy and are not experiencing toxicity should remain on the current therapy without adding a new treatment. <p>pERC agreed with the clinical expert consulted by CADTH that several treatments are currently available for first-line treatment. pERC also noted that use of I+V as a first-line treatment for CLL would impact subsequent treatment sequencing. Further, it is unclear how BTK inhibitors compare to venetoclax-based combination therapies as first-line treatment.</p>
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: <ol style="list-style-type: none"> 1. Adult (≥ 18 years) patients with CLL who meet 1 of the following criteria: <ol style="list-style-type: none"> 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: <ol style="list-style-type: none"> 3.1. prior progression on a BTK inhibitor 3.2. polymphocytic leukemia or Richter's transformation. 4. Renewal of zanubrutinib should be based on the following assessments: <ol style="list-style-type: none"> 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. 5. Treatment with zanubrutinib should be discontinued upon the occurrence of any of the following:

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		<p>5.1. progression of disease according to iwCLL response assessment criteria</p> <p>5.2. unacceptable toxicity.</p> <p>6. Zanubrutinib should only be prescribed by a clinician with expertise and experience in the treatment of CLL and monitoring of therapy.</p> <p>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.</p> <p>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. 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.</p>
Venetoclax (Venclexta) in combination with obinutuzumab (Gazyva)	<p>November 17, 2020</p>	<p>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:</p> <ul style="list-style-type: none"> • Cost-effectiveness improves to an acceptable level. <p>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.</p> <p>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.</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Acalabrutinib (Calquence)	January 8, 2020	<p>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:</p> <ul style="list-style-type: none"> • cost-effectiveness improved to an acceptable level • feasibility of adoption (budget impact) is addressed. <p>Eligible patients include those who are 65 years of age or older, or between 18 and 65 years of age with comorbidities (defined as creatinine clearance between 30 mL/min to 69 mL/min or a cumulative Illness Rating Scale (CIRS) for geriatric score > 6), who 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.</p>
Ibrutinib (Imbruvica)	November 3, 2016	<p>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.</p>
Second-line setting		
Acalabrutinib (Calquence)	November 17, 2020	<p>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:</p> <ul style="list-style-type: none"> • Cost-effectiveness being improved to an acceptable level. <p>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.</p>
Venetoclax (Venclexta) in combination with rituximab (bioequivalents)	May 31, 2019	<p>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:</p> <ul style="list-style-type: none"> • Cost-effectiveness being improved to an acceptable level. <p>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.</p> <p>Guidance on sequencing:</p> <p>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.</p>

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
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: <ul style="list-style-type: none"> 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.
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.

BTK = Bruton tyrosine kinase; CLL = chronic lymphocytic leukemia; CNS = central nervous system; C+O = chlorambucil plus obinutuzumab; del(17p) = deletion of 17p; ECOG = Eastern Cooperative Oncology Group; I+V = ibrutinib plus venetoclax; iwCLL = International Workshop on Chronic Lymphocytic Leukemia.

Table 2: CADTH Implementation Advice Panels on Chronic Lymphocytic Leukemia

Publication and date of publication	Implementation advice
Provisional Funding Algorithm – Panel: May 2021	<p>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.</p> <p>The panel advises that:</p> <ul style="list-style-type: none"> 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. <p>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.</p> <p>The panel advises that:</p> <ul style="list-style-type: none"> 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. <p>The panel advises that:</p> <ul style="list-style-type: none"> 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. <p>The panel advises that:</p> <ul style="list-style-type: none"> 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

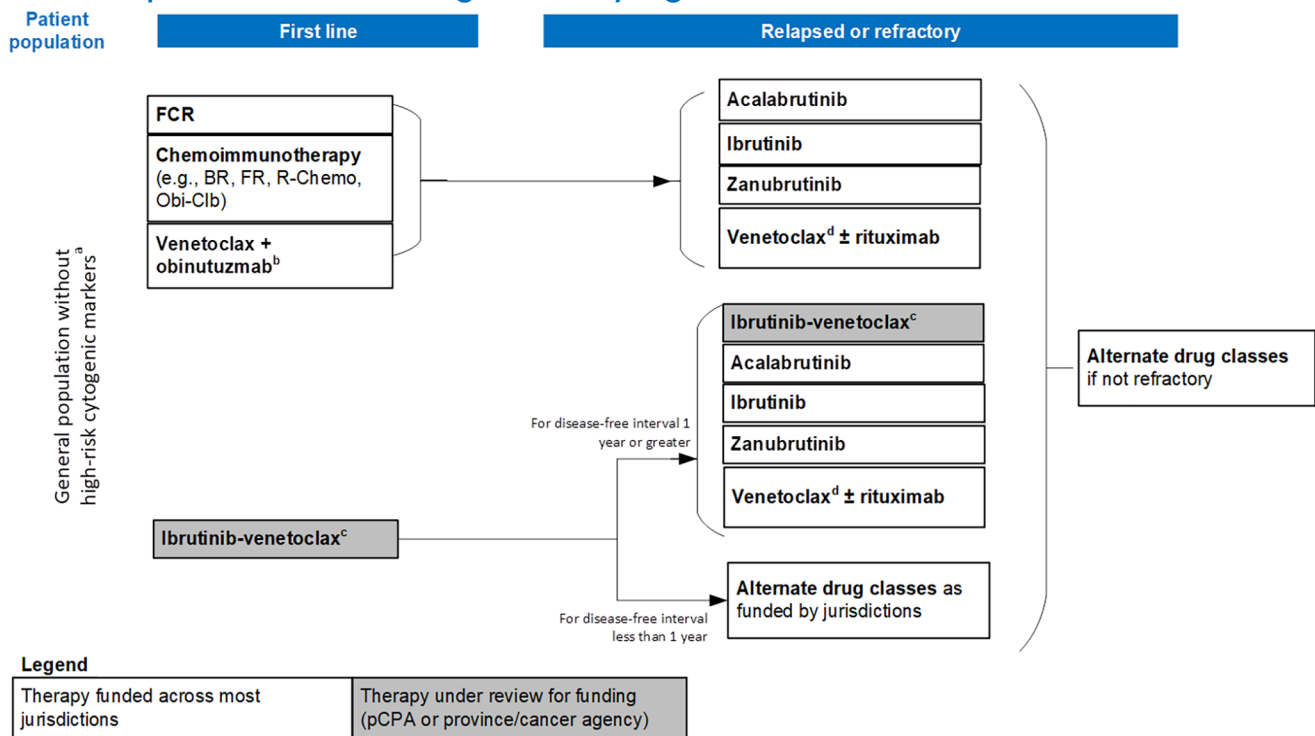


Publication and date of publication	Implementation advice
	<p>a VEN-based regimen may be offered next-line therapy with either a VEN-based regimen or a BTKi.</p> <p>The panel advises that:</p> <ul style="list-style-type: none">• Options should remain available for IBR, ACA, and a VEN-based regimen as next-line therapy for CLL patients following chemoimmunotherapy. <p>Sequencing decisions should be individualized to each patient, balancing considerations around patient characteristics with the total cost of care.</p>

ACA = acalabrutinib; BTKi = Bruton tyrosine kinase inhibitor; CLL = chronic lymphocytic leukemia; IBR = ibrutinib; VEN = venetoclax.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (General Population Without High-Risk Cytogenetic Markers)



BR = bendamustine-rituximab; Chemo = chemotherapy; Clb = chlorambucil; CVP = cyclophosphamide-vincristine-prednisone; FCR = fludarabine-cyclophosphamide-rituximab; FR = fludarabine-rituximab; Obi = obinutuzumab; pCPA = pan-Canadian Pharmaceutical Alliance; R = rituximab.

Note: Idelalisib-rituximab is available only in cases of intolerance of a Bruton tyrosine kinase inhibitor or for bridging to cellular therapy.

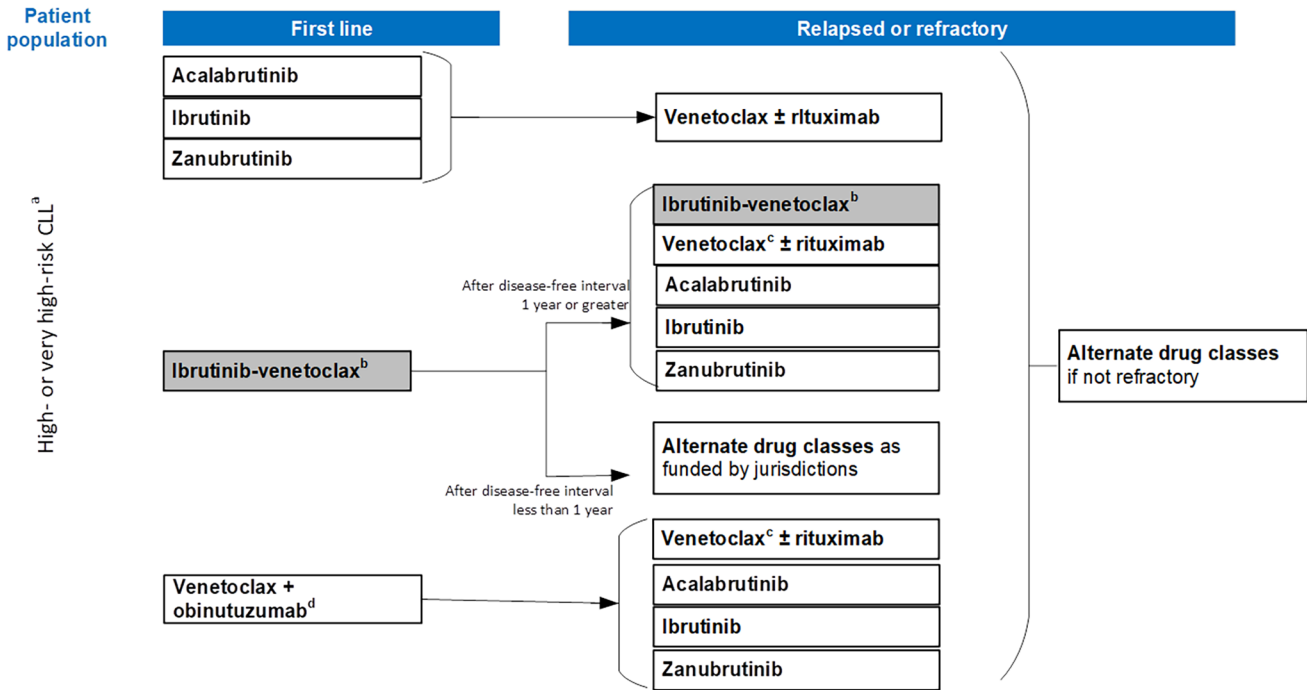
^a For the general population with CLL. (For patients with high-risk cytogenetic risk factors, such as those with del(17p) alteration, TP53 mutation, and unmutated IGHV, refer to the funding algorithm for patients with high- or very high-risk CLL.)

^b Venetoclax-obinutuzumab is for treatment of adult patients with previously untreated chronic lymphocytic leukemia who are ineligible for fludarabine-based regimens. The dosing schedule for venetoclax-obinutuzumab is for a fixed duration of 48 weeks.

^c Ibrutinib-venetoclax should be given for a fixed duration, as a single drug at a dose of 420 mg once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg daily for twelve 28-day cycles. Venetoclax should be initiated at cycle 4 with dose ramp-up over 5 weeks. If patients have a durable response to first-line ibrutinib-venetoclax (i.e., duration of response ≥ 1 year), then re-treatment with I+V would be considered.

^d 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. Re-treatment with venetoclax is for a fixed duration of 24 months.

Figure 2: Provisional Funding Algorithm Diagram for Chronic Lymphocytic Leukemia (High or Very High Risk)



Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)
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CLL = chronic lymphocytic leukemia; pCPA = pan-Canadian Pharmaceutical Alliance.

Note: Idelalisib-rituximab is available only in cases of intolerance of a BTKi or for bridging to cellular therapy.

^a High- or very high-risk CLL includes del(17p) alteration, TP53 mutation, and unmutated IGHV.

^b Ibrutinib-venetoclax should be given for a fixed duration as a single drug at a dose of 420 mg once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg daily for twelve 28-day cycles. Venetoclax should be initiated at cycle 4 with dose ramp-up over 5 weeks. If patients have a durable response to first-line ibrutinib-venetoclax (i.e., duration of response ≥ 1 year) then re-treatment with I+V would be considered.

^c 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. Re-treatment with venetoclax is for a fixed duration of 24 months.

^d Venetoclax-obinutuzumab is for treatment of adult patients with previously untreated CLL who are fludarabine ineligible. The dosing schedule for venetoclax-obinutuzumab is for a fixed duration of 48 weeks.

Description of the Provisional Funding Algorithms

General Population Without High-Risk Cytogenetic Markers

Figure 1 depicts the funded options for patients with CLL who do not have any high-risk cytogenetic markers.

First-Line Setting

For these individuals, the first-line options include fludarabine-cyclophosphamide-rituximab (FCR), chemoimmunotherapy, venetoclax-obinutuzumab, or ibrutinib-venetoclax. Ibrutinib-venetoclax is under review for funding. Venetoclax-obinutuzumab is for adult patients with previously untreated CLL who are ineligible for fludarabine-based regimens. The dosing schedule is for a fixed duration of 46 weeks. Ibrutinib-

venetoclax is also given for a fixed duration as a single drug at a dose of 420 mg once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg daily for twelve 28-day cycles.

Relapsed or Refractory Setting

For patients whose CLL is refractory to first-line therapies, including FCR, chemoimmunotherapy, or venetoclax-obinutuzumab, their subsequent options include acalabrutinib, ibrutinib, zanubrutinib, or venetoclax with or without rituximab. Venetoclax re-treatment is allowed at the time of relapse if the progression-free interval was at least 12 months after completion of previous therapy. Re-treatment with venetoclax is for a fixed duration of 24 months.

For patients who have received ibrutinib-venetoclax in the first-line setting with a disease-free interval of 1 year or greater, they may be re-treated with ibrutinib-venetoclax, any of the Bruton tyrosine kinase (BTK) inhibitors (acalabrutinib, ibrutinib, zanubrutinib), or venetoclax with or without rituximab. If the disease-free interval is less than 1 year, other alternate drug classes as funded by jurisdictions would be considered.

Note that in all cases, idelalisib-rituximab would be available only in cases of intolerance of a BTK inhibitor or for bridging to cellular therapy.

High- or Very High-Risk CLL

[Figure 2](#) depicts the funded options for patients with high- or very high-risk CLL, including those with del(17p) alteration, TP53 mutation, and unmuted IGHV.

First-Line Setting

For patients with high- or very high-risk CLL, their first-line options include BTK inhibitors (acalabrutinib, ibrutinib, and zanubrutinib), ibrutinib-venetoclax, or venetoclax-obinutuzumab. Ibrutinib-venetoclax are under review for funding. Ibrutinib-venetoclax is given for a fixed duration as a single drug at a dose of 420 mg once daily for three 28-day cycles, followed by ibrutinib 420 mg plus venetoclax 400 mg daily for twelve 28-day cycles. Venetoclax should be initiated at cycle 4 with dose ramp-up over 5 weeks. Note that venetoclax-obinutuzumab treatment is for a fixed duration of 48 weeks.

Relapsed or Refractory Setting

For patients in the high- or very high-risk CLL setting who have received a BTK inhibitor (acalabrutinib, ibrutinib, zanubrutinib) in the first-line setting, the relapsed or refractory treatment funded option is venetoclax with or without rituximab.

For patients in the high- or very high-risk CLL setting who have received ibrutinib-venetoclax in the first-line setting with a disease-free interval of 1 year or greater, the relapsed or refractory treatment funded options include ibrutinib-venetoclax, venetoclax with or without rituximab, or BTK inhibitors (acalabrutinib, ibrutinib, or zanubrutinib). If the disease-free interval is less than 1 year, these patients may be considered for alternate drug classes as funded by jurisdictions.

For patients in the high- or very high-risk CLL setting who have received venetoclax-obinutuzumab, the relapse or refractory funded options include venetoclax with or without rituximab or a BTK inhibitor (acalabrutinib, ibrutinib, zanubrutinib).

For all relapsed or refractory funded options, the following notes apply:

- 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. Re-treatment with venetoclax is for a fixed duration of 24 months.

Note that in all cases, idelalisib-rituximab would be available only in cases of intolerance of a BTK inhibitor or for bridging to cellular therapy.



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