CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Negative and Positive

This report supersedes the CADTH Provisional funding algorithm report for Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Negative, dated February 2021.

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

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CADTH

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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:

- 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 Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Negative and Positive. 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

On February 2021, CADTH published its first provisional funding algorithm in Adult B-Cell Precursor Acute Lymphoblastic Leukemia. This provisional funding algorithm has incorporated the following CADTH recommendations: inotuzumab ozogamicin (Besponsa) and blinatumomab (Blincyto).

The purpose of this provisional funding algorithm is to incorporate the latest CADTH recommendation for brexucabtagene autoleucel (Tecartus) for the treatment of adult patients with released or refractory B-cell precursor acute lymphoblastic leukemia. This algorithm will also include treatment options for both B-cell ALL Ph- and Ph+.

CADTH has also published guidance on the use of tisagenlecleucel for acute lymphoblastic leukemia. Relevant implementation advice will also be incorporated in this provisional funding algorithm.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and Guidance on Treatment Sequencing
Brexucabtagene autoleucel (Tecartus)	April 27, 2023	pERC recommends that brexucabtagene autoleucel be reimbursed for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL) only if the following conditions are met: Initiation 1. Brexucabtagene autoleucel should be reimbursed in adult patients aged 18 years or older, with relapsed or refractory B-cell precursor ALL, defined as one of the following: 1.1. Primary refractory disease; 1.2. First relapse if first remission ≤ 12 months; 1.3. Relapsed or refractory disease after 2 or more lines of systemic therapy; or, 1.4. Relapsed or refractory disease after allo SCT. 2. Patients with Ph+ B-cell precursor ALL may receive brexucabtagene autoleucel if they are intolerant to TKI therapy, or have relapsed or refractory disease despite treatment with at least 2 different TKIs. 3. Patients must have good performance status. 4. Brexucabtagene autoleucel should not be initiated in patients with uncontrolled CNS disease. Renewal 5. Treatment with brexucabtagene autoleucel is a one-time therapy. Brexucabtagene autoleucel should not be reimbursed in patients who have had a previous CAR T-cell therapy. Prescribing 6. Brexucabtagene autoleucel should be prescribed by clinicians with expertise in the management of leukemia and cellular therapy or stem cell therapy. Brexucabtagene autoleucel should be administered in specialized centres with adequate infrastructure, resources, and expertise to facilitate treatment with CAR T-cell therapy. Pricing 7. A reduction in price. **Guidance on Treatment Sequencing**

		If brexucabtagene autoleucel is recommended for reimbursement, should patients be required to be ineligible for allo SCT and / or other therapies? • pERC and the clinical experts noted that the treatment selection in this patient population should be individualized, and flexibility should be allowed in providing the optimal treatment(s) to the patients. • The clinical experts indicated that patients with refractory or relapse Ph+ B-cell precursor ALL may be eligible to receive brexucabtagene autoleucel if they have not experienced failure on 2 different TKIs. • pERC and the clinical experts agreed that being ineligible for allo SCT and/or other therapies should not be included as a criterion for patients to be treated with brexucabtagene autoleucel. pERC and the clinical experts noted there is no evidence to support re-treatment with brexucabtagene autoleucel in the case of disease relapse in the future. Furthermore, pERC noted that there is no evidence to support the use of brexucabtagene autoleucel after prior treatment with tisagenlecleucel. If recommended for reimbursement, which exclusion criteria from ZUMA-3 should be applied in determining eligibility for brexucabtagene autoleucel? • The clinical experts indicated that patients with inadequate renal, hepatic, pulmonary or cardiac function should not be eligible for brexucabtagene autoleucel. • pERC and the clinical experts agreed it is reasonable for patients with HIV infection or Hepatitis B to be eligible if the viremia is undetectable and the patients can restart their antiviral therapy soon after or stay on antiviral therapy throughout the brexucabtagene autoleucel therapy. pERC and the experts also indicated that hepatitis C infection should not be considered an exclusion criterion because hepatitis C is potentially curable. • pERC agreed with the experts, who indicated that patients with prior non-cellular CD19-targeted therapy could be eligible for the treatment with brexucabtagene autoleucel. • pERC and the experts agreed that patients with uncontrolled or active CNS disease should be excluded. The clinical experts suggested that the added contribution to maintaining remission from the subsequent TKIs after brexucabtagene autoleucel infusion likely would have been small. The rationale to use subsequent TKIs for patients with Ph+ B-cell ALL is in line with the current guidance on the management of this subtype of B-cell precursor ALL. pERC agreed that the use of TKIs after brexucabtagene autoleucel infusion may be appropriate based on the knowledge of mutation status, prior TKI exposure, and tolerance. For patients between 18 and 25 years of age, under what clinical circumstances would brexucabtagene autoleucel be preferred over tisagenlecleucel and vice versa? • pERC and the clinical experts noted that there is a lack of evidence to answer this question and therefore could not recommend criteria for the choice of brexucabtagene autoleucel versus tisagenlecleucel.
Blinatumomab (Blincyto)	Oct 29, 2020	pERC conditionally recommends the reimbursement of blinatumomab for the treatment of Philadelphia chromosome-negative (Ph-), CD19 positive (CD19+), B-cell precursor acute lymphoblastic leukemia (BCP-ALL) adult and pediatric

		patients who are in first or second hematologic complete remission (CR) and are minimal residual disease positive (MRD+), if the following condition is met: - cost-effectiveness being improved to an acceptable level. Eligible patients include those with good performance status and those in first or second CR with MRD+ disease, defined as MRD detected at a level greater than or equal to 0.1% (i.e., ≥10^{-3}). Patients should have received, over the course of their treatment for BCP-ALL, a minimum of three intensive chemotherapy blocks of a treatment regimen that is age-appropriate and given with curative intent before proceeding to blinatumomab therapy. Treatment should be continued until unacceptable toxicity, hematologic relapse, MRD relapse, treatment with hematopoietic stem cell transplant (HSCT), or up to the completion of four cycles. **Guidance on Sequencing** pERC agrees with the CGP that re-treatment for adult patients should not be permitted as there is a lack of evidence to support this, and similarly, re-treatment of pediatric patients should not be permitted.
Blinatumomab (Blincyto)	April 4, 2019	pERC conditionally recommends the reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-positive B-cell precursor acute lymphoblastic leukemia (Ph+ BCP-ALL) who have been treated with at least two prior tyrosine kinase inhibitors (TKIs) and have relapsed or refractory (R/R) disease only if the following condition is met: - cost-effectiveness being improved to an acceptable level. **Guidance on Sequencing** pERC discussed PAG's request for guidance on the optimal sequencing and priority treatment with respect to inotuzumab ozogamicin and blinatumomab for relapsed or refractory Ph+ BCP-ALL. pERC noted that there is currently no clinical evidence to inform this and pERC concluded that the optimal sequencing of blinatumomab and inotuzumab in this setting is unknown.
Tisagenlecleucel	January 2019	On the condition that there is a reduction in price, HTERP recommends the provision of tisagenlecleucel to pediatric and young adult patients 3 to 25 years old with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogenic stem cell transplant (SCT), or otherwise ineligible for allogeneic SCT, or have experienced a second or later relapse. With regard to implementation of this therapy, HTERP recommends: • the creation of interprovincial agreements to ensure equitable access to eligible patients in all jurisdictions, including consideration of financial and logistic support for required travel and short-term relocation • the development of clear and transparent eligibility criteria that are acceptable to patients' and clinicians' needs, based on the approved indications • the collection of standardized outcomes data in a pan-Canadian registry of patients, which uses a defined set of outcomes and definitions to generate real-world evidence, for consideration in future reassessments to assess longer-term effectiveness, safety, and cost-effectiveness.
Inotuzumab ozogamicin (Besponsa)	July 6, 2018	pERC recommends the reimbursement of inotuzumab ozogamicin (Besponsa) for the treatment of relapsed or refractory BCP-ALL, only if the following condition is met: • cost-effectiveness is improved to an acceptable level.

		Optimal Sequencing of Inotuzumab Ozogamicin and Other Available Therapies pERC noted that the majority of the subgroups of patients in the INO-VATE ALL trial appeared to benefit from treatment with inotuzumab ozogamicin. Therefore, pERC agreed that patients with high-risk features and those with more advanced disease (e.g., first relapse, second relapse, primary refractory, and relapse after a stem cell transplant) should be eligible for treatment with inotuzumab ozogamicin. As per the eligibility criteria of INO-VATE ALL, patients with Ph-positive ALL must have failed treatment with at least one second-generation or third-generation tyrosine kinase inhibitor and standard multi-drug induction chemotherapy before treatment with inotuzumab ozogamicin. pERC noted that there is currently no clinical trial evidence to inform optimal sequencing of inotuzumab ozogamicin and other available treatments for relapse/refractory ALL. pERC agreed that treatment with inotuzumab ozogamicin will likely be used as a second-line option (first relapse) after upfront chemotherapy or second relapse. The Committee acknowledged that there is no direct evidence investigating the efficacy and safety or the appropriate sequence of inotuzumab ozogamicin with other available therapies (e.g., blinatumomab) for the treatment of relapsed/refractory ALL patients.
Blinatumomab (Blincyto)	January 2018	Withdrawn
Blinatumomab (Blincyto)	August 31, 2017	pERC recommends the reimbursement of blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-negative (Ph-_ relapsed/refractory B precursor acute lymphoblastic leukemia (conditional on the cost-effectiveness being improved to an acceptable level). Treatment should be for patients with a good performance status and should be continued until unacceptable toxicity or disease progression up to a maximum of 2 cycles for induction, 3 cycles for consolidation and 12 months for maintenance. **Time-Limited Need for Blinatumomab** At the time of implementing a funding recommendation for blinatumomab, jurisdictions may consider addressing the time-limited need of blinatumomab for those patients who are currently receiving treatment with combination chemotherapy as a second or later salvage therapy. pERC noted that this time-limited access should be for patients who would otherwise meet the reimbursement criteria.
Blinatumomab (Blincyto) – Pre NOC	April 1, 2016	pERC does not recommend funding blinatumomab (Blincyto) for the treatment of adult patients with Philadelphia chromosome-negative (Ph-) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who have had only one prior systemic chemotherapy.
Ponatinib (Iclusig)	October 1, 2015	pERC recommends funding ponatinib (Iclusig) conditional on cost-effectiveness being improved to an acceptable level. Funding should be for the treatment of patients with chronic phase, accelerated phase or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom other tyrosine kinase inhibitor (TKI) therapy is not appropriate, including CML or Ph+ ALL that is T315I mutation positive or where there is resistance or intolerance to prior TKI therapy. Funding should be for patients with ECOG performance status 0-2. Treatment should continue until unacceptable toxicity or disease progression.

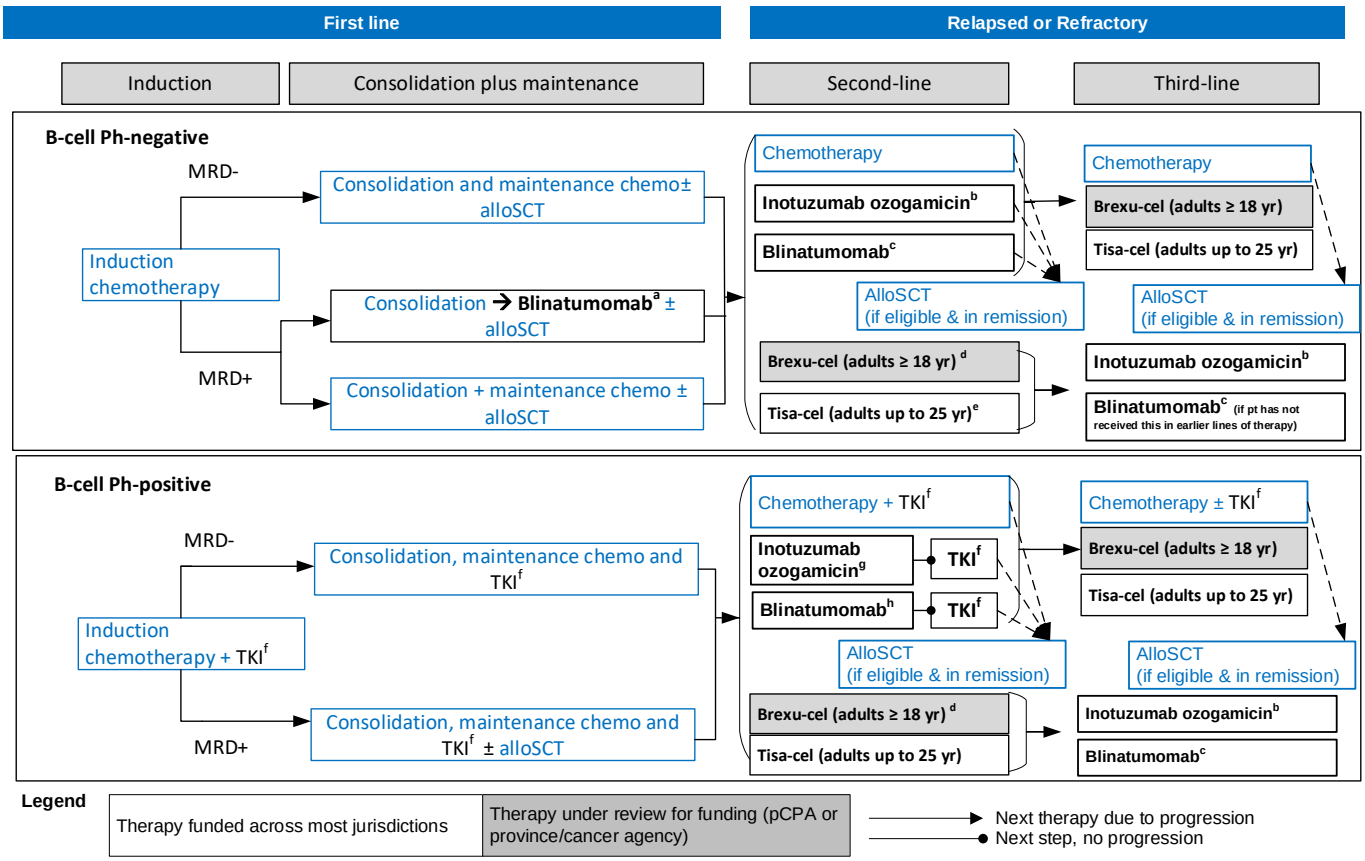
Table 2: CADTH Implementation Advice Panels on Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Negative

Date of publication	Implementation Advice
February 2021	The panel advises that inotuzumab ozogamicin should be used for adult patients with relapsed ALL who have been previously treated with blinatumomab in the setting of MRD+, Ph- ALL. The panel suggests that in this situation, inotuzumab ozogamicin should be used for curative intent therapy. The panel advises that for patients treated with fewer than 4 blinatumomab cycles in the relapsed setting, the preference would be to use inotuzumab ozogamicin; however, if this is not possible, blinatumomab could be used in patients with a beneficial first response to blinatumomab and who were in longer remission (≥ 6 months).

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Adult B-Cell Precursor Acute Lymphoblastic Leukemia, Philadelphia Chromosome Positive and Negative

Alt text: This figure depicts the funding options for first-line and relapse or refractory B-cell precursor acute lymphoblastic leukemia.



Note: CAR T-cellular therapies may be available in some jurisdictions.

[a] In first or second remission.

[b] Sequencing of inotuzumab ozogamicin and blinatumomab in any order is only allowed in patients treated with a curative intent.

[c] If not experienced previously.

[d] For first relapse if first remission ≤ 12 months, if primary refractory, relapsed after alloSCT

[e] If primary refractory, relapsed after alloSCT or ineligible for alloSCT

[f] TKI (Tyrosine Kinase Inhibitor) options include imatinib, dasatinib and ponatinib.

[g] Patients must have failed a 2nd or 3rd generation TKI or have failed imatinib and be in overt relapse.

[h] Patients must have failed at least 2 TKIs or be overt relapse.

Abbreviations

pCPA = pan-Canadian Pharmaceutical Alliance; Brexu-cel = Brexucabtagene autoleucel; Tisa-cel = Tisagenlecleucel

Figure 1 depicts the provisional funding algorithm. Note that this diagram is a summary representation of the drug funding options for the condition of interest. It is not a treatment algorithm and 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.

Description of the Provisional Funding Algorithm

B-cell Philadelphia negative ALL

Induction & Consolidation Plus Maintenance

Adult patients with BCP-ALL that is Ph- are first treated with induction chemotherapy. Following induction, hematologic response is assessed. Patients who do not show a CR, the MRD status is assessed. MRD- patients are offered consolidation and maintenance chemotherapy, whereas MRD+ patients can be offered consolidation chemotherapy followed by blinatumomab or maintenance chemotherapy. Patients may be considered for allogeneic stem cell transplantation. Note that patients should have received, over the course of their treatment for BCP-ALL, a minimum of three intensive chemotherapy blocks of a treatment regiment that is age-appropriate and given with curative intent before proceeding to blinatumomab therapy.

Relapsed or Refractory

For patients who experience relapsed or refractory ALL, their second-line options are as follow: chemotherapy, inotuzumab ozogamicin or blinatumomab if patient has not received this treatment previously. These patients may also be eligible for allogeneic stem cell transplantation if in remission. For adults 18 years or older, brexu-cel can be used for first relapse if first remission is 12 months or less, if primary refractory or if relapsed after alloSCT. Brexu-cel is under review for funding. Tisa-cel for adults up to 25 years may be available in some jurisdictions.

In the relapsed or refractory setting, the third-line options to patients who have received either chemotherapy, inotuzumab ozogamicin or blinatumomab are chemotherapy, brexu-cel for adults 18 years and older, or tisa-cel for adults up to 25 years.

Note that brexu-cel is for primary refractory disease, first release if first remission is 12 months or less, relapse or refractory disease after 2 or more lines of systemic therapy or relapsed or refractory disease after allo SCT.

For patients who have received brexu-cel or tisa-cel for primary as second-line (first relapse), they may be offered inotuzumab ozogamicin or blinatumomab if the patient has not previously received this option in the earlier lines of therapy.

B-cell Philadelphia positive ALL

Induction & Consolidation Plus Maintenance

Adult patients with BCP-ALL that is Ph+ are first treated with induction chemotherapy with TKI. TKI options include imatinib, dasatinib and ponatinib. Following induction, hematologic response is assessed. Patients who do not show a CR, the MRD status is assessed. MRD- patients are offered consolidation, maintenance chemotherapy and TKI, whereas MRD+ patients are offered consolidation, maintenance chemotherapy and TKI. Patients may be considered for allogenic stem cell transplantation.

Relapsed or Refractory

For patients who experience relapsed or refractory ALL, their second line options are as follow: chemotherapy with TKI, inotuzumab ozogamicin followed by TKI, or blinatumomab followed by TKI. These patients may also be eligible for allogenic stem cell transplantation if in remission. For adults 18 years or older, brexu-cel can be used for first relapse if first remission is 12 months or less, if primary refractory, relapsed after alloSCT. Brexu-cel is under review for funding. Tisa-cel for adults up to 25 years may be available in some jurisdictions.

In the relapse or refractory setting, the third line options for patients who have received either chemotherapy, inotuzumab ozogamicin or blinatumomab are chemotherapy, brexu-cel for adults 18 years and older, or tisa-cel for adults up to 25 years with or without TKI.

Note that brexu-cel is for primary refractory disease, first release if first remission is 12 months or less, relapse or refractory disease after 2 or more lines of systemic therapy or relapsed or refractory disease after allo SCT.

For patients who have received brexu-cel or tisa-cel for primary as second-line (first relapse), they may be offered inotuzumab ozogamicin or blinatumomab.

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