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.

Publication date: June 2023

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

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

In February 2021, CADTH published its first provisional funding algorithm for adult B-cell precursor acute lymphoblastic leukemia (ALL). 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 relapsed or refractory B-cell precursor ALL. This algorithm will also include treatment options for both B-cell ALL Philadelphia chromosome negative and positive (Ph– and Ph+).

CADTH has also published guidance on the use of tisagenlecleucel for ALL. 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 1 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 1.4. Relapsed or refractory disease after allogenic stem cell transplant (alloSCT). 2. Patients with Philadelphia chromosome positive (Ph+) B-cell precursor ALL may receive brexucabtagene autoleucel if they are intolerant to tyrosine kinase inhibitor (TKI) therapy, or have relapsed or refractory

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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 central nervous system (CNS) disease. **Renewal:** 5. Treatment with brexucabtagene autoleucel is a 1-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 alloSCT 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 relapsed Ph+ B-cell precursor ALL may be eligible to receive brexucabtagene autoleucel if they have not experienced failure on 2 different TKIs.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• pERC and the clinical experts agreed that being ineligible for alloSCT 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 the ZUMA-3 trial 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 noncellular 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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		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 3 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,

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		MRD relapse, treatment with hematopoietic stem cell transplant (HSCT), or up to the completion of 4 cycles. **Guidance on sequencing:** pERC agrees with the Clinical Guidance Panel (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 2 prior tyrosine kinase inhibitors (TKIs) and have relapsed or refractory disease only if the following condition is met: • cost-effectiveness being improved to an acceptable level. **Guidance on sequencing:** pERC discussed the Provincial Advisory Group (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 aged 3 to 25 years with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogenic stem cell transplant (alloSCT), or otherwise ineligible for allogeneic SCT, or have experienced a second or later relapse. With regard to implementation of this therapy, HTERP recommends:

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• 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 B-cell precursor acute lymphoblastic leukemia (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 1 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

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		inotuzumab ozogamicin and other available treatments for relapsed or 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 or 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 or 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

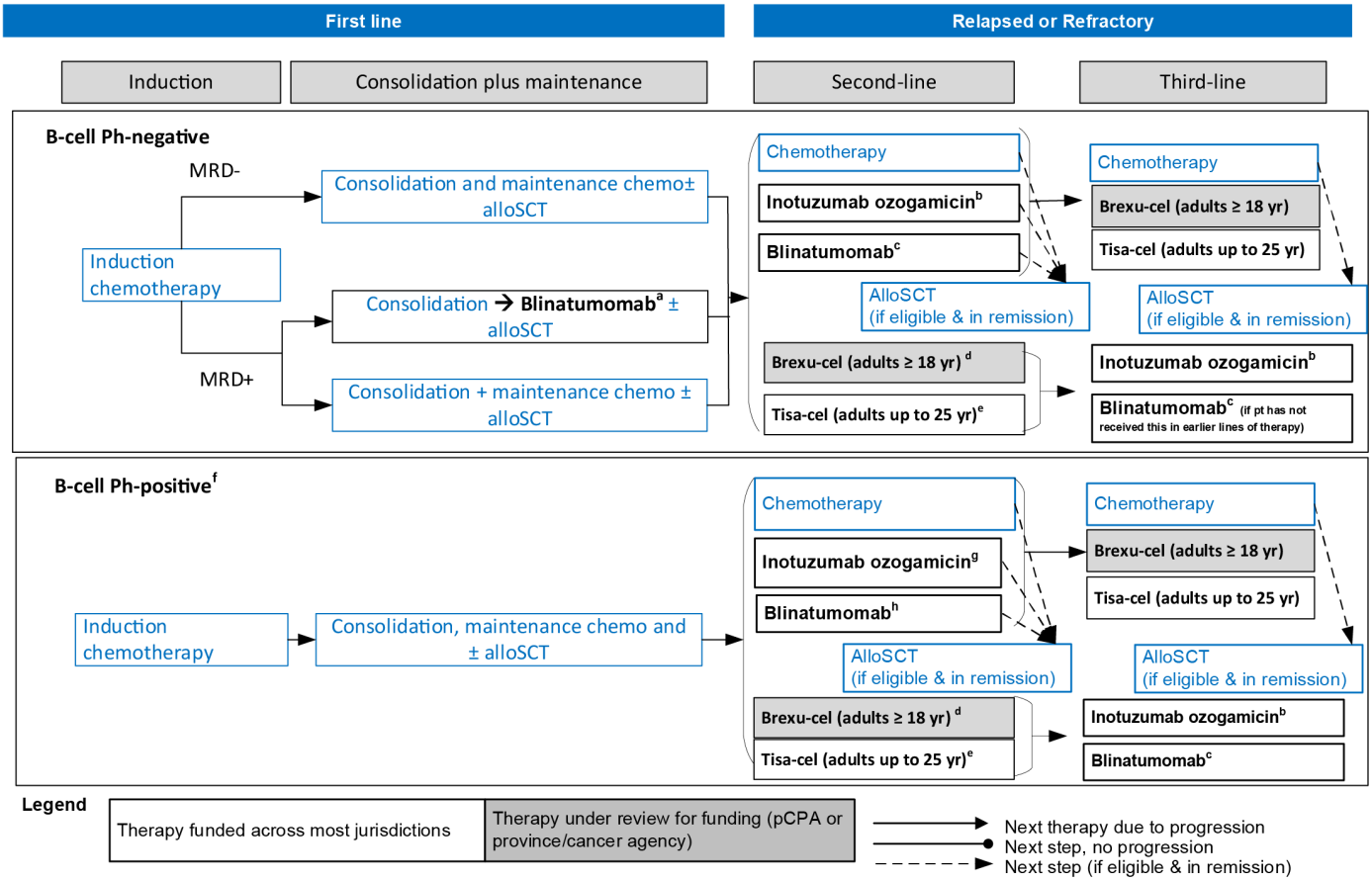
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		negative (Ph−) relapsed or refractory B precursor acute lymphoblastic leukemia (ALL) and who have had only 1 prior systemic chemotherapy.
Ponatinib (Iclusig)	October 1, 2015	pERC recommends funding 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 to 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 acute lymphoblastic leukemia (ALL) who have been previously treated with blinatumomab in the setting of minimal residual disease positive (MRD+), Philadelphia chromosome negative (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 ALL, Ph+ and Ph-



ALL = acute lymphoblastic leukemia; alloSCT = allogeneic stem cell transplant; Brexu-cel = brexucabtagene autoleucel; MRD = minimal residual disease; pCPA = pan-Canadian Pharmaceutical Alliance; Ph+ = Philadelphia positive; Ph- = Philadelphia negative; Tisa-cel = tisagenlecleucel; TKI = tyrosine kinase inhibitor.

Note: CAR T-cell 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 or if primary refractory or relapsed after alloSCT; 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.

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

[f] Note that the use of a TKI is a standard of care in B-cell Ph+ ALL. TKI options include imatinib, dasatinib, and ponatinib. Refer to jurisdictional drug funding criteria for more details.

[g] Patients must have failed a second or third generation TKI or have failed imatinib and be in overt relapse.

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

Description of the Provisional Funding Algorithm

B-Cell Ph– ALL

Induction and Consolidation Plus Maintenance

Adult patients with BCP-ALL that is Ph– are first treated with induction chemotherapy. Following induction, hematologic response is assessed. In patients who achieve a complete response (CR), the minimal residual disease (MRD) status is assessed. MRD-negative (MRD–) patients are offered consolidation and maintenance chemotherapy, whereas MRD-positive (MRD+) patients can be offered consolidation chemotherapy followed by blinatumomab or maintenance chemotherapy. Patients may be considered for alloSCT. Note that patients should have received, over the course of their treatment for BCP-ALL, a minimum of 3 intensive chemotherapy blocks of a treatment regimen 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 follows: chemotherapy, inotuzumab ozogamicin, or blinatumomab, if the patient has not received this treatment previously. Patients who receive chemotherapy and achieve CR who are MRD+ may receive blinatumomab as maintenance therapy, if not previously treated. For adults aged 18 years or older, brexucabtagene autoleucel can be used for first relapse in primary refractory disease, or first relapse, if the duration of first remission is 12 months or less, or in relapsed or refractory disease following alloSCT. Brexucabtagene autoleucel is under review for funding. Tisagenlecleucel for adults up to 25 years may be available in some jurisdictions.

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

Note that brexucabtagene autoleucel is for primary refractory disease, first relapse, if the duration of first remission is 12 months or less, or for relapsed or refractory disease after 2 or more lines of systemic therapy, or for relapsed or refractory disease after alloSCT, as outlined in the pERC recommendations.

For patients who have received brexucabtagene autoleucel or tisagenlecleucel as second-line therapy (i.e., for first relapse), they may be offered inotuzumab ozogamicin or blinatumomab, if they have not previously received this option in the earlier lines of therapy.

B-Cell Ph+ ALL

Induction and Consolidation Plus Maintenance

Adult patients with BCP-ALL that is Ph+ are first treated with induction chemotherapy. Note that TKI is a standard of care in this population. TKI options include imatinib, dasatinib, and ponatinib. Refer to jurisdictional funding criteria for more details. Following induction, hematologic response is assessed. Patients who achieve first complete response (CR1) are further assessed for MRD status. For both MRD+ and MRD– patients, they are offered consolidation followed by maintenance chemotherapy. Patients may be considered for alloSCT.

Relapsed or Refractory

For patients who experience relapsed or refractory ALL, their second-line options are as follows: chemotherapy, inotuzumab ozogamicin, or blinatumomab. These patients may also be eligible for alloSCT if in remission. For adults aged 18 years or older, brexucabtagene autoleucel can be used for first relapse if the duration of first remission is 12 months or less, or in primary refractory disease, or in relapsed or refractory disease after alloSCT, as described in the initiation funding criteria in the pERC report. Brexucabtagene autoleucel is under review for funding. Tisagenlecleucel for young adults up to 25 years may be available in some jurisdictions.

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

Note that brexucabtagene autoleucel is for primary refractory disease, first relapse, if the duration of first remission is 12 months or less; relapsed or refractory disease after 2 or more lines of systemic therapy; or relapsed or refractory disease after alloSCT.

For patients who have received brexucabtagene autoleucel or tisagenlecleucel as second-line therapy (i.e., for first relapse), they may be offered inotuzumab ozogamicin or blinatumomab.