

Immune Effector Cell Therapy for Adult Patients in Canada: Consensus Statement

Background and Purpose:

Chimeric antigen receptor (CAR) T-cell therapy is a type of immune effector cell (IEC) therapy, that harnesses a person's own immune cells to fight cancer. Since 2018, multiple CAR T-cell therapy products have been approved for use in Canada, with anticipated approvals for additional products, and indications, in the years ahead. For products that are publicly funded (e.g., Kymriah, Yescarta, Tecartus, Breyanzi), Health Canada approved indications for use are detailed in the manufacturer's product monographs.^{i,ii,iii,iv}

As a new and expensive health technology, the implementation of CAR T-cell therapy presents various clinical and health system planning challenges including the impact of age-related co-morbidities, long term effectiveness and variability of clinical course for the adult population. While Canada's Drug Agency (CDA-AMC) (formerly known as the Canadian Agency for Drugs and Technologies in Health (CADTH)) has evaluated the clinical and cost-effectiveness of CAR T-cell therapy for specific leukemia and lymphoma indications, the evidence on long-term outcomes are currently limited, with an evolving knowledge basis.^{v,vi,vii,viii}

The purpose of this document is to provide guidance on the application of Health Canada Notice of Compliance (NOC) indications, which are publicly funded, and clarify criteria that were not covered in CADTH's recommended reimbursement criteria for adult patients being considered for CAR T-cell therapy. This guidance is intended to support standardized use of this therapy in Canada. This will assist clinicians, policy makers, and payers responsible for treatment and funding decisions. Consensus on the use of CAR T-cell therapy will also support alignment in access between the provinces.

This guidance covers the following products and specific indications that have been authorized for use by Health Canada in adults, and are publicly funded:

- Axicabtagene ciloleucel (under the brand name Yescarta® from Gilead) for the treatment of:
 - Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), HGBL, and DLBCL arising from follicular lymphoma.
- Brexucabtagene autoleucel (brand name Tecartus® from Gilead) for the treatment of:
 - Adult patients with relapsed or refractory (r/r) mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.
 - Adult patients with CD19+ relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).
- Tisagenlecleucel (under the brand name Kymriah® from Novartis) for the treatment of:
 - Adult patients with relapsed or refractory LBCL after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B lymphoma and DLBCL arising from follicular lymphoma.

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- Pediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (ALL) who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or have experienced second or later relapse.
- Lisocabtagene maraleucel (under the brand name Breyanzi® from Bristol Myers Squibb) for the treatment of:
 - Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

Development of these Recommendations:

These recommendations are the result of discussions at the National Immune Effector Cell (IEC) Therapy Consensus Advisory Committee, including expert clinicians in the field from across Canada (see **Appendix A**). The Advisory Committee has been established to:

- Develop clinical consensus guidance on patient selection criteria for Health Canada approved indications/products for immune effector cell (IEC) therapy, to support standardized referral and recommendations for care of adult patients.
- Provide clinical perspective and participate in consensus building activities to ensure an evidence-informed approach to service delivery which is responsive to a rapidly evolving knowledge base.
- Work collaboratively to ensure consensus recommendations remain current with emerging products, new indications, and evolving evidence.
- Review available evidence and emerging product information, and incorporate into recommendations, as appropriate.
 1. Maintaining *Immune Effector Cell Therapy for Adult Patients in Canada: Consensus Statement* through semi-annual review and updating document, as needed.
 2. As needed, establish and oversee Working Groups (WGs) to develop consensus on new indications. Consensus from these WGs will be brought back to this Committee for documentation and communication.
- Support inter-provincial alignment through liaising with local ministries and policy decision makers.

The Consensus Statement was first drafted in 2019 after a fulsome discussion considering various factors such as approved Health Canada indications, patient-specific clinical presentation and age, the role of multiple infusions, and the use of “out-of-spec” products. In addition to addressing clinical topics, the group also discussed challenges and opportunities for standardized implementation across the country. This included provincial readiness, capacity and inter-provincial collaborative networks, the role of clinical trials, data collection and an ethical framework for equitable access.

The Consensus Statement will be subject to a semi-annual review as part of the National IEC Therapy Consensus Advisory Committee's meetings. It will be updated as needed to ensure that its content remains accurate and reflects the most up-to-date evidence and clinical experience. This review process will enable the Advisory Committee to incorporate new findings, adjust the Statement's recommendations and to keep pace with the developments in terms of evidence and clinical practice with this therapy.

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General Consensus Recommendations applicable to all publicly funded CAR T-cell Therapy Products:

- Health Canada approved indications for use and CDA-AMC's recommended reimbursement criteria provide a sound basis for clinical decision making with regard to patient selection.
- To ensure the suitability of patients for CAR T-cell therapy, it is recommended to review their performance status (e.g., Karnofsky performance status score), organ function, adherence to local Standard Operating Procedures, and recommendations from Multidisciplinary Cancer Conference (or Tumour Board). In addition to age, factors such as disease behavior and comorbidities should also be taken into account to determine the patient's suitability for the therapy. This approach is the accepted standard practice for selecting patients for CAR T-cell therapy.
 - It is advisable for provinces to ensure that their provincial eligibility criteria are publicly available.
- Current evidence does not support the retreatment of patients with the same CAR T-cell product or another CAR T-cell product targeting the same target (e.g., CD19). Based on this, a life-time limit of one infusion is recommended.
 - Infusion of residual, previously manufactured cells may be considered in certain circumstances.
- Nothing has been stipulated by Health Canada regarding the use of products that do not meet the manufacturer's specifications (i.e., out-of-spec). No guidance is required at this time, but it may need to be addressed in the future.
- The ethical framework developed in 2018 should guide decision-making. The framework addresses substantive and process principles, which was developed by the Joint Centre of Bioethics with support from Cancer Care Ontario (now a part of Ontario Health), and proposes a precautionary approach is useful for new and emerging technologies such as this and should be adopted.

Recommendations specific to relapsed or refractory large B cell lymphoma (LBCL):

- Patients who have undergone allogeneic stem cell transplant but have no active graft versus host disease (GvHD) and are not on immunosuppressive therapy may be eligible for CAR T-cell therapy.^{ix}
 - It is recommended that provinces track and monitor outcomes of patients previously treated with allogeneic stem cell transplant prior to CAR T-cell therapy.
- Patients who received prior non-cellular anti-CD19 treatment (e.g., tafasitamab) can be considered for CAR T-cell therapy.^{ix}
 - It is recommended that provinces track and monitor outcomes of patients previously treated with non-cellular anti-CD19 treatment prior to CAR T-cell therapy.
- Patients with secondary central nervous system (CNS) lymphoma may be eligible for CAR T-cell therapy.^{x,xi}
 - It is recommended that provinces track and monitor outcomes of patients with secondary CNS lymphoma who are treated with CAR T-cell therapy.
- Patients with active primary CNS disease are not suitable candidates for CAR T-cell therapy.^x

- Patients with follicular large B-cell lymphoma (FLBL) may be eligible for CAR T-cell therapy.^{x,xii,xiii}
- Patients with transformations of indolent B-cell lymphoma (e.g., marginal zone, follicular lymphoma) to LBCL may be suitable for CAR-T cell therapy.^x
 - This recommendation excludes patients with Richter’s transformation from chronic lymphocytic leukemia/small lymphocytic leukemia to DLBCL.^{xiv}
- Patients with other sub-types of LBCL^{xii} may be suitable for CAR T-cell therapy.^{x,xiv}

Recommendations specific to mantle cell lymphoma (MCL):

- Patients who have undergone allogeneic stem cell transplant but have no active graft versus host disease (GvHD) and are not on immunosuppressive therapy may be eligible for CAR T-cell therapy.^{ix}
 - It is recommended that provinces track and monitor outcomes of patients previously treated with allogeneic stem cell transplant prior to CAR T-cell therapy.
- Patients who received prior non-cellular anti-CD19 treatment (e.g., tafasitamab) can be considered for CAR T-cell therapy.^{ix}
 - It is recommended that provinces track and monitor outcomes of patients previously treated with non-cellular anti-CD19 treatment prior to CAR T-cell therapy.
- Patients with controlled secondary central nervous system (CNS) lymphoma may be eligible for CAR T-cell therapy.^{xi,xv}
 - The above recommendation is applicable to patients with previous or controlled CNS disease at time of treatment. Patients with persistent or active or actively progressive CNS disease are not suitable candidates for CAR T-cell therapy.^{xv}
 - It is recommended that provinces track and monitor outcomes of patients with secondary CNS lymphoma who are treated with CAR T-cell therapy.
- Patients with primary CNS disease are not suitable candidates for CAR T-cell therapy.^{xv}

Recommendations specific to relapsed or refractory B-cell acute lymphoblastic leukemia (B-cell ALL).

- Patients with controlled secondary central nervous system (CNS) leukemia may be eligible for CAR T-cell therapy.^{xi,xv}
 - The above recommendation is applicable to patients with previous or controlled CNS disease, or CNS-1 or CNS-2 disease (as defined by NCCN Guidelines for acute lymphoblastic leukemia version 4.2023)^{xvi} at time of treatment. Patients with persistent or active or actively progressive CNS disease or CNS-3 disease (as defined by NCCN Guidelines for acute lymphoblastic leukemia version 4.2023)^{xvi} are not suitable candidates for CAR T-cell therapy.^{xv}
 - It is recommended that provinces track and monitor outcomes of patients with secondary CNS acute lymphoblastic leukemia who are treated with CAR T-cell therapy.

Next Steps:

A pan-Canadian model for uniform data collection is suggested for all patients who may be eligible for treatment.

To ensure that the recommendations in this Consensus Statement remain current, it is essential to review and update them regularly. The Advisory Committee should convene twice annually to review available evidence, evaluate the clinical experience gained thus far, and update recommendations accordingly. As new products and indications are approved by Health Canada and implemented in Canada, they should be discussed and incorporated into this Consensus Statement. Additional experts in specific disease sites should be included on the Advisory Committee, or as sub-committee members, when indications expand beyond hematology and/or oncology.

Appendix A: National Immune Effector Cell Therapy Consensus Advisory Committee Membership (as of May 2024):

Province/Organization	Participants
British Columbia	Tammy Currie, Kevin Song
Alberta	Donna Rose, Mona Shafey, Kevin Hay
Saskatchewan	Mark Bosch, Denise Budz
Manitoba	David Szwajcer
Ontario	Chris Bredeson, Ronan Foley, Michael Kennah, Tom Kouroukis, John Kuruvilla
Quebec	Annie Charbonneau, Isabelle Fleury
Nova Scotia	Mahmoud Elsayy, Josee Rioux
New Brunswick	Terrance Comeau
Newfoundland	Jeannine Herritt, Kirsty Tompkins
Prince Edward Island	Philip Champion

National Immune Effector Cell Therapy Consensus Advisory Committee Secretariat Support (as of May 2024):

Organization	Individuals
Ontario Health (Cancer Care Ontario)	Jessica Arias, Colleen Fox, Mitali Garg, Scott Gavura, Cassandra McKay, Elaine Meertens, Arthur Manzon, Lisa Milgram
CAPCA	Kristi MacKenzie

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- ⁱⁱ Gilead Sciences Canada, Inc. Yescarta™ (axicabtagene ciloleucel) Product Monograph. February 13, 2019. Revised: December 6, 2022. Available at: https://pdf.hres.ca/dpd_pm/00068693.PDF.
- ⁱⁱⁱ Gilead Sciences Canada, Inc. Tecartus™ (brexucabtagene autoleucel) Product Monograph. June 8, 2021. Revised: November 16, 2022. Available at: https://pdf.hres.ca/dpd_pm/00068268.PDF.
- ^{iv} Celgene, Inc., a Bristol Myers Squibb company. Breyanzi™ (lisocabtagene maraleucel). May 6, 2022. Available at: https://pdf.hres.ca/dpd_pm/00066444.PDF
- ^v Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma: Recommendations. Canadian Agency for Drugs and Technologies in Health. January 2019. Available at <https://cadth.ca/tisagenlecleucel-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma-recommendations>
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