

CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma: Recommendations

Service Line:	Optimal Use
Issue Number:	Volume 8, no. 3g
Publication Date:	January 2019
Report Length:	18 pages

Cite As: Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-cell Lymphoma: Recommendations. Ottawa: CADTH; 2019 Jan. (CADTH optimal use report, vol.8, no.3g).

ISSN: 1927-0127

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

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Abbreviations

AE	adverse event
ALL	acute lymphoblastic leukemia
CAR	chimeric antigen receptor
DLBCL	diffuse large B-cell lymphoma
FACT	Foundation for the Accreditation of Cellular Therapy
HTA	health technology assessment
HTERP	Health Technology Expert Review Panel
ICUR	incremental cost-utility ratio
QALY	quality-adjusted life-year
r/r	relapsed or refractory
SAE	serious adverse event
SCT	stem cell transplant
WTP	willingness to pay

Summary of Recommendation

Recommendations were developed by the Health Technology Expert Review Panel (HTERP) based on evidence reviewed in a CADTH Health technology Assessment (HTA). The HTA included a review of the clinical effectiveness of tisagenlecleucel,¹ an economic evaluation for each indication,^{2,3} an analysis of implementation issues, a review of ethical considerations, and a review of patient perspectives and experiences.⁴ The HTA was additionally informed by patient group and clinician input submissions.^{4,5}

HTERP deliberations and the information retrieved aimed to address the policy question: How should the provision of tisagenlecleucel for pediatric and young adults with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia (B-cell ALL) and adults with r/r diffuse large B-cell lymphoma (DLBCL) be structured? Separate recommendations have been developed for the two separate indications.

These recommendations are relevant for pediatric and young adult patients three to 25 years old with r/r B-cell ALL:

Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

On the condition that there is a reduction in price, HTERP recommends the provision of tisagenlecleucel to pediatric and young adult patients three to 25 years old with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogeneic stem cell transplant (SCT), or are 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.

These recommendations are relevant for adult patients with r/r DLBCL:

Relapsed or Refractory Diffuse Large B-Cell Lymphoma

On the condition that there is a substantial reduction in price, HTERP recommends the provision of tisagenlecleucel for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. 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.

Technology

Tisagenlecleucel is a second-generation chimeric antigen receptor (CAR) T-cell therapy that targets the CD19 antigen, expressed exclusively on B cells, including the cancer cells in ALL and DLBCL.^{6,7} Health Canada approved tisagenlecleucel in September of 2018 for: (1) pediatric and young adult patients three to 25 years of age with B-cell ALL who are refractory, have relapsed after allogeneic SCT, or are otherwise ineligible for SCT, or who have experienced a second or later relapse, and (2) adult patients (≥ 18 years) with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.⁷ Reports and recommendations from other countries are summarized in Appendix 2.

Methods

HTERP developed recommendations on the use of tisagenlecleucel based on information from a CADTH HTA of clinical evidence,¹ economic evaluations,^{2,3} an analysis of implementation considerations, and reviews of ethical issues and of patient and caregiver perspectives and experiences.⁴ The HTA was additionally informed by patient and clinician input submissions.^{4,5} HTERP members reviewed the evidence from these sources, discussed all elements of the [HTERP deliberative framework](#)⁸ and developed a consensus-based recommendation through discussion and deliberation. Additional information on the HTERP process is found on the [HTERP page](#) of the CADTH website.

Detailed Recommendation — Children and Young Adults With r/r B-cell ALL

The objective of these recommendations is to provide advice for Canadian health care decision-makers about the provision of tisagenlecleucel in pediatric and young adults with r/r B-cell ALL.

On the condition that there is a reduction in price, HTERP recommends the provision of tisagenlecleucel in pediatric and young adult patients three to 25 years old with B-cell acute lymphoblastic leukemia who are refractory, have relapsed after allogeneic stem cell transplant (SCT), or are 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.

Rationale

- HTERP was confident that there was a clinical benefit associated with tisagenlecleucel, considering the findings from the CADTH Clinical Review and the lack of treatment options for this population.
- CADTH's Clinical Review¹ reported that treatment with tisagenlecleucel results in an overall remission rate of 82.0% (██████████) after three months and 69% (98.95% confidence interval [CI], 43.6 – 88.1) after six months in children and young adults with r/r B-cell ALL.¹ The probability estimates for overall survival were reported to be ██████████ at 12 months.
- Although all patients experience adverse events (AEs), the events were generally manageable with supportive care. Serious adverse events (SAEs), such as cytokine release syndrome and neurotoxicity, are common complications of treatment with tisagenlecleucel and require management.
- Given the lack of long-term follow-up data, the single-arm study design of the pivotal trial, and the limited number of patients in the studies, there is uncertainty in the clinical and economic evidence. Reassessment using longer-term follow-up studies and registry data will be required.
- The CADTH reanalysis^{2,3} of the manufacturer's economic evaluation found that tisagenlecleucel had a 44.2% probability of being cost-effective at a willingness-to-pay (WTP) threshold of \$50,000 per quality-adjusted life-year (QALY) gained, and a 99.1% probability at a WTP threshold of \$100,000 per QALY gained. According to the CADTH reanalysis, at least a 10% price reduction would be required to ensure that the incremental cost-utility ratio (ICUR) is below \$50,000 per QALY. Results should be interpreted with caution in light of the uncertainty in the clinical evidence. The cost of tisagenlecleucel may affect the ability of jurisdictions to implement the therapy.

- Family caregivers view CAR T-cell therapies, including tisagenlecleucel, as easier than alternative treatments (such as SCT), and offer a hope for children and young adults with no other treatment options.⁴
- Models of access are likely to result in geographic inequities if not addressed by mechanisms that support out-of-province (or region) treatment, including travel.⁴ Interprovincial agreements on the appropriate eligibility criteria will be required to ensure equitable access.

Detailed Recommendation — Adults With Relapsed or Refractory Diffuse Large B-cell Lymphoma

The objective of these recommendations is to provide advice for Canadian health care decision-makers about the provision of tisagenlecleucel in adults with r/r DLBCL.

On the condition that there is a substantial reduction in price, HTERP recommends the provision of tisagenlecleucel for adult patients with r/r large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. 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.

Rationale

- HTERP was confident that there was a clinical benefit associated with tisagenlecleucel, considering the findings from the CADTH Clinical Review and the lack of treatment options for this population.
- The Clinical Review¹ reported that patients who received tisagenlecleucel and remained in the pivotal trials achieved an overall response rate of 51.6% (95% CI, 41.0 to 62.1) three months after infusion. The probability of survival was estimated at 49.0% at 12 months (95% CI, 39 to 59).
- Although all patients experienced AEs, the events were generally manageable with supportive care.¹ SAEs, such as cytokine release syndrome and neurotoxicity, are common complications of treatment with tisagenlecleucel and require management.
- Given the lack of long-term follow-up data, the single-arm study design of the pivotal trials, and the limited number of patients in the studies, there is uncertainty in the clinical and economic evidence. Reassessment using longer-term follow-up studies and registry data will be required.
- The CADTH reanalysis² found that tisagenlecleucel has a 0% probability of being cost-effective at a WTP threshold of \$50,000 per QALY gained, and a 1.8% probability at a

WTP threshold of \$100,000 per QALY gained. A substantial reduction in price is required for tisagenlecleucel to be considered cost-effective based on conventionally accepted thresholds.² According to the CADTH reanalysis, price reductions of at least 45% and at least 65% would be required to achieve an ICUR of \$100,000 and \$50,000 per QALY, respectively. Results should be interpreted with caution in light of the uncertainty in the clinical evidence. The cost of tisagenlecleucel may affect the ability of jurisdictions to implement the therapy.

- Models of access are likely to result in geographic inequities if not addressed by mechanisms that support out-of-province (or region) treatment, including travel.⁴ Interprovincial agreements on the appropriate eligibility criteria will be required to ensure equitable access.

Considerations

The pivotal study ELIANA⁹ reported an overall remission rate of 82.0% (██████████) at three months following infusion, and an estimated probability of overall survival of ██████████ at 12 months for r/r ALL. The reported results from the pivotal study for r/r DLBCL (JULIET)¹⁰ was lower, with an overall response of 51.6% (95% CI, 41.0 to 62.1) after three months, and an estimated overall survival of 49.0% (95% CI, 39 to 59) at 12 months.¹

All patients, for both indications, experienced AEs, but it was reported that these were generally manageable with supportive care. SAEs, such as cytokine release syndrome and neurotoxicity, are common complications of treatment with tisagenlecleucel and require management. The pivotal trials were single-arm studies, with a short follow-up period (median = 13.1 months for ELIANA and 13.9 months in JULIET) in a small number of patients (N = 79 in ELIANA and N = 111 in JULIET). There is a lack of long-term follow-up data and as such, evidentiary uncertainty for both the long-term benefits and harms of tisagenlecleucel for both r/r ALL and r/r DLBCL exists. Additional follow-up data were recently presented at the American Society of Hematology Annual Meeting.¹¹ After an additional 11 months of follow-up for ELIANA, the overall remission rate and the estimated probability of overall survival were similar to the data reported in the pivotal trial.¹² Updated analysis for an additional five months of follow-up for JULIET¹³ was also similar to the findings of the original publication included in the CADTH review.

There is a need to collect real-world data in registries to continue to monitor the long-term benefits and harms of this therapy. This information could also be used with additional evidence from ongoing trials for future reassessment of the therapy. The additional CAR T-cell therapies anticipated should be considered alongside tisagenlecleucel in future assessments.

Developing and maintaining a registry is resource intensive; therefore, it may be feasible to explore existing registries and other sources to standardize the outcomes and definition incorporated. These registries may have the potential to collect data for patients receiving tisagenlecleucel. The Foundation for the Accreditation of Cellular Therapy (FACT) maintains a database currently, and if a model of access includes FACT accreditation, building on this existing database may be an option. Standardized outcomes, including a defined set of outcomes and definitions, will be critical to ensuring the future usefulness of registry data in decision-making.

The high cost of the therapy may pose a challenge for the health care system, taking into account not only the cost of the treatment, but the additional associated costs. These

associated costs include pre-treatment, post-treatment monitoring, the likelihood of additional costs due to treating AEs, and hospitalization, in addition to the costs of travel and lodging for the patients to access treatment sites. Consideration must be given to the capacity to implement tisagenlecleucel due to its costs. With the uncertainty in the clinical evidence and the lack of long-term follow-up, confidence in the cost-effectiveness results is limited. Many other factors may affect the costs of treatment, including issues with manufacturing, capacity constraints, and long-term benefits and harms. Alternate payment or pricing models and risk-sharing agreements may address the limitations associated with the clinical and economic evidence.

The potentially limited number of initial treatment sites may affect capacity. Some consideration for increasing capacity may be needed as experience with and demand for the therapy grows; for example, by expanding either the number of or capacity of sites. The use of FACT-accredited sites may ensure necessary resources, experience, policies, and procedures to safely deliver tisagenlecleucel. However, not all provinces have FACT-accredited transplant centres, and FACT accreditation requires resources and time to obtain. Future expansion into other settings (sites that are not FACT-accredited, outpatient delivery) may be feasible. In addition to the setting for delivery of tisagenlecleucel, availability of treatments and intensive care facilities for the treatment of possible AEs is a consideration. The product monograph requires the availability of tocilizumab for the treatment of possible cytokine release syndrome following infusion with tisagenlecleucel.

The potentially limited number of treatment sites may also be a factor for equitable access for patients across the country. In addition, the costs, travel, and relocation to treatment sites may have social and psychological impacts. Support services for patients and caregivers may ease this burden and limit the potential issues with equity.

Other equity considerations include manufacturing and processing constraints, patient selection, and the age criterion for access. Issues of consent or assent involving pediatric patients should be sensitive to the child's capacity to make treatment decisions. Consent processes with continuous education may help alleviate the concerns related to possible patient vulnerability and autonomy. There is limited information available on other possible ethical or legal considerations due to the novelty of the therapy, but uncertainty of the long-term benefits and harms, and questions about ownership of cells and consent, may be raised.

Evidence

Clinical Evidence — B-cell Acute Lymphoblastic Leukemia

The clinical evidence was addressed in a systematic review incorporating published evidence and information provided by the manufacturer. The following questions addressed were:

- What are the beneficial and harmful effects of tisagenlecleucel in children and young adults with relapsed or refractory or B-cell acute lymphoblastic leukemia?
- What are the evidence-based clinical guidelines for the effective use of tisagenlecleucel for the treatment of children and young adults with relapsed and refractory B-cell acute lymphoblastic leukemia?

CADTH's clinical systematic review¹ reported that 82.0% (██████████) of patients in the pivotal ELIANA trial (N = 79) achieved overall remission within three months of infusion, and 69% (98.95% CI, 43.6 to 88.1) in the supporting ENSIGN trial (N = 58)

achieved overall remission within six months of infusion.^{9,14} The estimated probability of overall survival was ██████████ in ELIANA.⁹ There was uncertainty in the effect of tisagenlecleucel on health-related quality of life.

All patients in the trials experienced at least one AE following infusion, with cytokine release syndrome being the most common. Treatments that have SAEs or require long-term hospitalization may contribute to emotional and psychological harms for patients, caregivers, and families.

Economic Evidence — B-cell Acute Lymphoblastic Leukemia

The manufacturer-provided confidential price of tisagenlecleucel is ██████████ per patient.¹⁵ The manufacturer submitted an economic evaluation to assess tisagenlecleucel in pediatric and young adults with r/r B-cell ALL. The CADTH reanalysis found that tisagenlecleucel was associated with an additional 10.60 QALYs gained and an additional cost of \$565,624 compared with salvage chemotherapy, resulting in an ICUR of \$53,269 per QALY. Tisagenlecleucel had a 44.2% probability of being cost-effective at a WTP threshold of \$50,000 per QALY gained and a 99.1% probability at a WTP threshold of \$100,000 per QALY gained.

It is estimated ██████████ patients with r/r B-cell ALL will receive tisagenlecleucel in the first three consecutive years of funding in Canada. Based on CADTH's analysis, the three-year net budget impact of reimbursing tisagenlecleucel is expected to be \$25.6 million when adopting the perspective of the public health care payer.

Clinical Evidence — Diffuse Large B-cell Lymphoma

The clinical evidence was addressed in a systematic review incorporating published evidence and information provided by the manufacturer. The questions addressed were:

- What are the beneficial and harmful effects of tisagenlecleucel in adults with relapsed and refractory diffuse large B-cell lymphoma?
- What are the evidence-based clinical guidelines for the effective use of tisagenlecleucel for the treatment of adults with relapsed and refractory diffuse large B-cell lymphoma?

An overall response rate was reported to be 51.6% (95% CI, 41.0 to 62.1) three months after infusion with tisagenlecleucel in patients with DLBCL in the pivotal trial (JULIET).¹⁰ The estimated probability of overall survival was 49.0% (95% CI, 39 to 59) at 12 months among patients in the pivotal trial.¹⁰ There was uncertainty in the effect of tisagenlecleucel on health-related quality of life.

All patients experienced at least one AE following infusion, with cytokine release syndrome being the most common. Treatments that have SAEs or require long-term hospitalization may contribute to emotional and psychological harms for patients, caregivers, and families.

Economic Evidence — Diffuse Large B-cell Lymphoma

The manufacturer-provided confidential price of tisagenlecleucel is ██████████ per patient. The manufacturer submitted an economic evaluation to assess tisagenlecleucel in adults with r/r DLBCL. The CADTH reanalysis found that tisagenlecleucel was associated with an additional 1.97 QALYs gained and an additional cost of \$416,750 compared with salvage chemotherapy, resulting in an ICUR of \$211,870 per QALY. Tisagenlecleucel had a 0% probability being cost-effective at a WTP threshold of \$50,000 per QALY gained and a 1.8% probability of being cost-effective at a WTP threshold of \$100,000 per QALY gained. Price

reductions of 45% and 65% would be required to achieve an ICUR of \$100,000 and \$50,000 per QALY, respectively.

It is estimated [REDACTED] patients with r/r DLBCL will receive tisagenlecleucel in the first three consecutive years of funding in Canada. Based on CADTH's analysis, the three-year net budget impact of reimbursing tisagenlecleucel is expected to be \$387.4 million when adopting the perspective of the public health care payer.

Implementation Analysis — Both Indications

The Implementation Analysis had the following objectives:

- to provide a detailed description of potential pathways of care for patients to receive tisagenlecleucel, and the resources (e.g., health and human resources, training, organizational) needed to do so; and,
- to provide an overview of feasibility and capacity considerations relating to the provision of tisagenlecleucel at the level of the individual patient and provider (i.e., micro level); via hospital or health care organizations such as regional health authorities (i.e., meso level); and at the provincial, territorial, and federal levels (i.e., macro level).

The analysis described the proposed model of access within Canada and across jurisdictions. A centralized model of access with manufacturer-trained sites is required by the FDA and the European Medicines Agency to address key safety concerns about the management of potential AEs. Many stakeholders see accreditation by FACT as ensuring the necessary resources, experience, policies, and procedures to safely deliver CAR T-cell therapy and collect long-term data.

The ability to deliver effective therapy is dependent on timely access and provision. However, providing tisagenlecleucel may exacerbate existing capacity issues (such as treatment and clinical resources, space, and workforce) related to provision of hematopoietic SCT. Within Canada, a centralized model may create geographic inequities. Travel and relocation to receive treatment has economic, social, physical, and psychological impacts for patients and carers. Similar to other therapies delivered using a centralized model, consideration should be given to support services for patients, carers, and families, including travel support, lodging, and psychosocial support.

The analysis also found that developing and applying eligibility criteria is a key implementation challenge. Clear and transparent eligibility criteria that are based on approved indications and that are acceptable to clinicians and patients are needed. Interprovincial agreements on the appropriate eligibility criteria will be required to ensure equitable access.

Clinician judgment plays an important role in assessing suitability and likelihood of benefit.

Ethics Evidence — Both Indications

CADTH's Ethics Review addressed the research questions:

- What are the major ethical issues raised by the implementation of tisagenlecleucel for children and young adults with r/r ALL? How might these issues be addressed?
- What are the major ethical issues raised by the implementation of tisagenlecleucel for adults with r/r DLBCL? How might these issues be addressed?

The Ethics Review⁴ reported that given continuing evidentiary uncertainty concerning clinical and economic evidence, from an ethics perspective, similar considerations may be required as for experimental therapies. This means striking a balance between the protection of

vulnerable persons and the promotion of therapeutic benefit. Key ethical considerations include: (1) balancing safety and efficacy, both short and long term; (2) addressing barriers or limitations on equitable access, including geographic constraints, manufacturing and processing constraints, patient selection, and age as a criterion for access; and (3) considering the total cost of tisagenlecleucel, including its affordability at both the health system and patient levels. Considerations of safety and efficacy, including uncertainty, underline the importance of informed choice and consent in treatment decision-making as well as recognition of psychological and emotional benefits and burdens. There may also be legal questions associated with the ownership of the genetically modified T cells. The Ethics Review reported that the high cost of tisagenlecleucel poses a challenge for resource allocation; therefore, opportunity costs are an important consideration. Clinical and policy implications shed light on how some of these concerns may be addressed in practice and illuminate considerations for the implementation of tisagenlecleucel.

Limitations

There were no studies directly comparing tisagenlecleucel with other interventions as all included studies were single-arm, open-label trials. Long-term follow-up data are not available as studies are ongoing. Long-term data, data from comparative studies, and real-world evidence are needed; therefore, this therapy may require reassessment when additional evidence is available.

Uncertainty with respect to the clinical evidence (comparative information for tisagenlecleucel versus salvage chemotherapy, information on patient subgroups, long-term effects, need for re-treatment) limits confidence in the economic results. Issues with the manufacturing and administration (including capacity constraints) of tisagenlecleucel could impact the timing and effectiveness of treatment, and of expenditures associated with tisagenlecleucel. Consideration of outcome-based payment models (e.g., pay for performance) may provide greater certainty around the likely cost-effectiveness.

The novelty of the therapy created limitations for the Review of Ethical and Legal Considerations and the Analysis of Implementation Issues. Specifically, there was limited published information for the Ethics Review, particularly that which related to the pediatric population. Similarly, there was limited published information about legal considerations. The Implementation Analysis used available information on regulatory approvals and the implementation of tisagenlecleucel; as this is active and ongoing analyses regarding the optimal delivery of tisagenlecleucel, it may not reflect current practice.

Appendix 1: The Health Technology Expert Review Panel

The Health Technology Expert Review Panel (HTERP) consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, five expert members were appointed with expertise in pediatric and adult hematology and oncology. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available [here](#).

Health Technology Expert Review Panel Core Members

Dr. Hilary Jaeger (Chair)

Dr. Jenny Basran

Dr. Jeremy Petch

Dr. Lynette Reid

Ms. Tonya Somerton

Dr. Jean-Eric Tarride

Expert Members

Dr. Mark Bosch

Dr. Raewyn Broady

Dr. Natasha Kekre

Dr. Amanda Li

Dr. Maureen Trudeau

Conflict of Interest

Jean-Eric Tarride has received research funding from Amgen, Astra Zeneca, and Novo Nordisk; has acted as a consultant for Astra Zeneca and Novartis; and is a member of an advisory board for Novartis. Hilary Jaeger is the Chair of the Board of Directors of Osteoporosis Canada. Jenny Basran is a Senior Medical Information Officer for the Saskatchewan Health Authority. Lynette Reid has previously been engaged by CADTH to author reports relevant to her area of expertise.

Mark Bosch (Celgene, Roche), Natasha Kekre (Jazz, Jansen), and Raewyn Broady (Otsuka) have receiving travel funding for speaking engagements or lectures from Industry. Natasha Kekre (Jazz, Jansen, Sanofi, Gilead) and Raewyn Broady (Jazz, Janssen, Celgene, Gilead) are members of advisory boards for Industry, and Amanda Li has acted as a consultant for Novartis. Maureen Trudeau receives fellow funding support (Roche, Genomic Health, Novartis, Essai, Pfizer). Natasha Kekre is involved in clinical trials with Novartis (Rituximab) and Gilead; Maureen Trudeau with Astra Zeneca, Pfizer, Astellas, Novartis, Abbvie, Roche; and Raewyn Broady with Novartis and Pharmacyclics.

Jeremy Petch and Tonya Somerton have no conflicts of interest to declare.

[Conflict of Interest Guidelines](#) are posted on the CADTH website.

HTERP would like to acknowledge Dr. Avram Denburg, Staff Oncologist, Division of Haematology/Oncology, The Hospital for Sick Children, for his critical review and feedback on draft versions of these recommendations.

Appendix 2: Recommendations and Health Technology Assessments From Other Organizations

Organization, Country/Region	Recommendations
Regulatory Approvals	
Health Canada, Canada	<p><i>ALL</i>^a</p> <ul style="list-style-type: none"> Approved for the treatment of patients aged 3 to 25 with r/r B-cell ALL (September 5, 2018) <p><i>DLBCL</i>^b</p> <ul style="list-style-type: none"> Approved for the treatment of adult patients with r/r DLBCL (September 5, 2018)
Food and Drug Administration (FDA), US	<p><i>ALL</i>^c</p> <ul style="list-style-type: none"> Approved for the treatment of patients aged < 25 with r/r B-cell ALL with Risk Evaluation and Mitigation Strategy (August 30, 2017) <p><i>DLBCL</i>^d</p> <ul style="list-style-type: none"> Approved for the treatment of adult patients with r/r DLBCL with Risk Evaluation and Mitigation Strategy (May 1, 2018)
European Medicines Agency (EMA), European Union ^e	<p><i>ALL</i></p> <ul style="list-style-type: none"> Approved for treatment of patients aged < 25 with r/r B-cell ALL with Risk Management Plan (August 23, 2018) <p><i>DLBCL</i></p> <ul style="list-style-type: none"> Approved for the treatment of adult patients with r/r DLBCL with Risk Management Plan (August 23, 2018)
Ministry of Health, Labor and Welfare, Japan ^f	<i>ALL and DLBCL</i> — In-progress (April 2018)
In-Progress Health Technology Assessments for Reimbursement Decisions	
Institut national d'excellence en santé et services sociaux (INESSS), Quebec ^g	<i>ALL and DLBCL</i> — Decision made, review and recommendations to be posted January 15, 2019
National Institute for Health and Care Excellence (NICE), UK	<p><i>ALL</i>^h</p> <ul style="list-style-type: none"> NHS England announced coverage for tisagenlecleucel through the Cancer Drug Fund <i>prior</i> to NICE guidance being issued (Sept 2018) NICE guidance recommends tisagenlecleucel for r/r B-cell ALL in people up to 25 years of age if conditions in the managed access agreement (price and data collection) are followed (November 2018) <p><i>DLBCL</i>ⁱ</p> <ul style="list-style-type: none"> Draft guidance does not recommend tisagenlecleucel for reimbursement for r/r DLBCL (September 2018) NHS England announced coverage for tisagenlecleucel through the Cancer Drug Fund (November 2018) Full NICE guidance January 2019 — Expect positive NICE recommendation given price negotiations (January 2019)
National Centre for Pharmacoeconomics (NCPE), Ireland ^j	<i>ALL and DLBCL</i> — Full HTA recommended (in-progress)

Organization, Country/Region	Recommendations
Medical Services Advisory Committee, Australia ^k	<i>ALL and DLBCL</i> — In-progress

AL = acute lymphoblastic leukemia; DLBCL = diffuse large B-cell lymphoma; HTA = health technology assessment; NHS = National Health Service; r/r = relapsed or refractory.

^a <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00423>.

^b <https://hpr-rps.hres.ca/reg-content/regulatory-decision-summary-detail.php?lang=en&linkID=RDS00422>.

^c <https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm>.

^d <https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm606540.htm>.

^e https://www.ema.europa.eu/documents/assessment-report/kymriah-epar-public-assessment-report_en.pdf.

^f <https://www.thepharmaletter.com/in-brief/brief-novartis-files-for-japanese-approval-of-kymriah>.

^g <https://www.inesss.qc.ca/en/themes/sante/therapies-cellulaires.html>; and personal communication.

^h <https://www.nice.org.uk/guidance/ta554/documents/final-appraisal-determination-document>.

ⁱ <https://www.nice.org.uk/guidance/gid-ta10269/documents/appraisal-consultation-document>.

^j <http://www.ncpe.ie/drugs/tisagenlecleucel-kymriah-for-all/>.

^k <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1519-public>.

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