CADTH

Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Project Protocol, Clinical Section

PROSPERO REGISTRATION NUMBER:
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CADTH

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Background and Rationale

Clinical Need and Target Population

Tisagenlecleucel is a chimeric antigen receptor (CAR) T-cell therapy for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (r/r-DLBCL) and children and young adults (25 years or younger) with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r-ALL).[1-3]

ALL is predominant in childhood and accounts for 80% of all leukemia cases in children.[4-7] About 300 children are diagnosed with leukemia each year in Canada.[5,6] Therefore, the estimated incidence of childhood ALL is 240 children per year. The overall cure rates with currently available therapies for newly diagnosed pediatric ALL is about 80% to 85%.[1,4,8] However, relapse occurs in 20% to 25% of children with ALL. With currently available second-line therapy, the long-term overall survival rates in patients with r/r-ALL range from 15% to 50%.[8]

DLBCL is an aggressive type of non-Hodgkin lymphoma (NHL). Although it can occur at any age, it is the most prevalent subtype of NHL in adults.[5,6,9,10] The estimated annual incidence of DLBCL is 10.2 per 100,000 adults, accounting for 30% to 40% of all lymphomas in adults.[5,6,11,12] The remission rate of DLBCL in patients who undergo first-line chemotherapy is approximately 50% to 70%.[10,13] However, 30% to 50% experience relapse and 10% have refractory disease.[10,13] If left untreated, the life expectancy of patients with r/r-DLBCL is three to four months.[13] The objective response rate to the salvage therapy is reported to be 26% (7% complete response rate) and the median overall survival is 6.3 months.[10] Currently, only palliative options are available for patients who do not respond to second-line therapy or with disease progression after stem-cell transplant.[1]

A Brief Overview of CAR T-cell Therapy and Tisagenlecleucel

CARs are artificial receptors that redirect antigen specificity, activate T cells, and further enhance T-cell function through their costimulatory component.[14] The CAR T-cell therapy involves leukapheresis to harvest the patient's peripheral blood mononuclear cells containing T cells, and the transfer of cells to a central facility where the DNA for the chimeric protein is inserted into the DNA of the patient's T cells using lentiviral vectors. The resulting CAR T cells are then frozen and shipped back to the treating institution for infusion into the patient's bloodstream to fight the cancer.[1,15] An overview of the CAR T-cell therapy procedure is provided in Figure 1.

Tisagenlecleucel is a second-generation CAR T-cell therapy that targets the CD19 antigen, which is expressed exclusively on B cells, including the malignant cells in ALL and DLBCL.[1] The CAR portion in tisagenlecleucel is composed of a murine single-chain antibody fragment, which recognizes CD19 and is fused to intracellular signalling domains from 4-1BB (CD137) and CD3 zeta. The CD3 zeta component is critical for initiating T-cell activation and antitumor activity, whereas 4-1BB enhances the expansion and persistence of tisagenlecleucel.[2,15,16] Upon infusion, the CAR binds to CD19-expressing cells and transmits a signal to promote T-cell expansion, activation, and target cell elimination and persistence of tisagenlecleucel in cells.[2,17] Thus, through its CAR activity, tisagenlecleucel may induce potent and durable responses.[17]

Currently, it takes a minimum of two to three weeks from leukapheresis to the time when CAR T cells are ready to be infused back into the patient. The majority of patients will require bridging chemotherapy to keep their cancer stable during this period.[1,2] In addition, lymphodepleting chemotherapy is administered prior to tisagenlecleucel to decrease the number of lymphocytes that antagonize CAR T cells. The lymphodepleting regimen is usually fludarabine 30 mg/m² intravenous (IV) infusion per day for four days and cyclophosphamide 500 mg/m² IV per day for two days starting with the first dose of fludarabine.[2,16] Tisagenlecleucel IV infusion is administered two to 14 days after completing lymphodepleting chemotherapy.[1,2]

Rationale for the Review

Tisagenlecleucel was approved by the FDA for the treatment of adult r/r-DLBCL in May of 2018, and for the treatment of pediatric r/r-ALL in August of 2017.[3] Prior to implementation in Canada, various stakeholders will need to evaluate the projected number of patients eligible for tisagenlecleucel, models of care, and the feasibility of an integrated work plan for identifying pediatric and adult populations with appropriate indications for tisagenlecleucel therapy. Questions about clinical effectiveness, cost-effectiveness, and implementation considerations (such as locations for treatment, system capacity, and clinical delivery protocols) will also need to be addressed. Contingency plans must be established if a scheduled tisagenlecleucel infusion cannot proceed because of manufacturing error, if the patient becomes too ill to receive the infusion, or dies during the waiting period after leukapheresis. Differences in the practice and use of CAR T-cell therapy between jurisdictions may result from variations in the availability or capacity to establish logistical and workforce requirements to deliver CAR T-cell therapies in the various provinces and territories.

Policy Question

This project will address the following policy question:

How should the provision of tisagenlecleucel for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r-ALL) and adults with relapsed or refractory diffuse large B-cell lymphoma (r/r-DLBCL) be structured?

Objectives

CADTH will conduct a health technology assessment (HTA) to assess the optimal use of tisagenlecleucel for:

1) Children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r-ALL), and

2) Adults with relapsed or refractory diffuse large B-cell lymphoma (r/r-DLBCL).

The assessment will include an analysis of the clinical effectiveness, cost-effectiveness, patient (and caregiver) perspectives and experiences, ethical issues, and implementation considerations.

Each component of the HTA will be conducted individually and collaboratively. This protocol describes the clinical review, which will assess the beneficial and harmful effects of tisagenlecleucel for r/r-ALL in children and young adults and for r/r-DLBCL in adults.

The purpose of this CADTH HTA is to provide evidence-based information in the areas of clinical impact, cost-effectiveness, funding, and locations for treatment; and eligibility and implementation considerations including, but not limited to, travel, hospital stay, and health care resource utilization costs; to support the jurisdictions to structure the provision of tisagenlecleucel therapy in Canada.

As tisagenlecleucel is a novel treatment, it may require reassessment once additional evidence is generated, including real-world evidence.

Research Questions

The following are proposed research questions for this HTA:

1. What are the beneficial and harmful effects of tisagenlecleucel in children and young adults with r/r-ALL?

2. What are the beneficial and harmful effects of tisagenlecleucel in adults with r/r-DLBCL?

3. What are the evidence-based clinical guidelines for the effective use of tisagenlecleucel, for the treatment of adults with r/r-DLBCL?

4. What are the evidence-based clinical guidelines for the effective use of tisagenlecleucel for the treatment of children and young adults with r/r-ALL?

Methods

The methodology adopted for this review is guided by the criteria outlined in the checklist described in AMSTAR II.[18] The clinical review will be published in accordance with CADTH standards for Optimal Use reviews and relevant reporting guidelines such as the PRISMA statement[19] and the PRISMA harms.[20]

The protocol for the systematic review (SR) was developed and written a priori based on information from an informal scoping review, from which we identified two completed HTAs, an SR, four non-randomized primary clinical studies, and two evidence-based practice guidelines. Given that tisagenlecleucel was first approved in the US for r/r-ALL in August 2017 and for r/r-DLBCL in May 2018, we anticipate that, if any other relevant HTAs or SRs have been conducted, they will be few in number and based on a small number of studies. Therefore, we will conduct a de novo SR of all relevant primary studies that permit an evaluation of different subgroups of interest, in a manner suitable to address our research questions. The protocol will be followed throughout the review process and, if any deviation occurs, the research registration with PROSPERO (registration number: CRD42018103201) will be updated and the final report will disclose any alterations.

Literature Search Strategy

The literature search will be performed by an Information Specialist using a peer-reviewed search strategy. See Appendix 4 for the detailed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–), Embase (1974–), the Cochrane Central Register of Controlled Trials via Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO, Scopus, and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept will be tisagenlecleucel (Kymriah).

No methodological filters will be applied to limit the retrieval by study type. The search will not be limited by language or publication date.

The search will be completed in July 2018. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies meeting the selection criteria of the review and identified in the alerts prior to the completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

An additional search will be conducted for clinical practice guidelines. The main search concepts will be leukemia, lymphoma, and CAR T-cell therapy. The search for lymphoma and leukemia guidelines will be limited to English- or French-language documents published between January 1, 2016 and July 2018. The search for CAR T-cell therapy guidelines will be limited to English- or French-language documents published between January 1, 2013 and July 2018. Conference abstracts will be removed from the search results.

Grey literature (literature that is not commercially published) will be identified by searching the websites of regulatory agencies (FDA and European Medicines Agency), clinical trial registries (US National Institutes of Health ClinicalTrials.gov and the Canadian Partnership Against Cancer CanadianCancerTrials.ca databases), and relevant conference abstracts. Conference abstracts will be retrieved through a search of the Embase database and will not be limited by publication date. Abstracts from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) will be searched manually for conference years not available in Embase.

Relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters) will also be searched, which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Study Design

This HTA is a de novo SR of published and unpublished primary clinical evidence to address the research question(s). The analytical framework is provided in Figure 2.

Study Eligibility

The eligibility criteria for the clinical research questions are listed in Table 1. Studies will be selected for inclusion in this SR if they are experimental or observational comparative or non-comparative primary studies of the following designs:

- randomized controlled trials (RCTs)
- non-randomized controlled clinical trials
- single-arm studies
- cohort studies
- case-control studies
- case series.

The reference lists of potentially relevant HTAs or SRs identified by the literature search for the project will be reviewed for primary studies that meet the inclusion criteria. The pivotal and supportive studies provided by the manufacturer will be included in the SR, as well as those meeting the selection criteria presented in Table 1.

Table 1: Eligibility Criteria for Clinical Research Questions

Indications	r/r-ALL	r/r-DLBCL
Population	• Pediatric and young adult patients 3 to 25 years 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	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
Intervention	Tisagenlecleucel cell suspension in infusion bag for intravenous use • For patients 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells/kg body weight • For patients more than 50 kg: 0.1 to 2.5x 10^8 CAR-positive viable T cells (non–weight- based)	Tisagenlecleucel cell dispersion for intravenous infusion 0.6 to 6.0 x 10^8 CAR-positive viable T cells (non–weight-based)
Comparator	• Blinatumomab • Inotuzumab ozogamicin • Clofarabine • Defined salvage chemotherapy for r/r-ALL • Allogenic HSCT • No comparator	• Axicabtagene ciloleucel • Defined salvage chemotherapy for r/r-DLBCL • Allogenic HSCT • No comparator
Main Outcomes	**Clinical effectiveness** • ORR, CR, PR, OS, RFS, PFS, EFS, HRQL, hospitalization/hospital readmission and relapse **Safety** (AEs, SAEs [Grade ≥ 3 AEs] and WDAEs) • CRS, neurological effects, prolonged cytopenia, infections and infestations, febrile neutropenia • Death	
Studies	Experimental and observational comparative or non-comparative primary studies (RCTs, NRCT, cohort, case-control and case-series studies) and clinical practice guidelines (including treatment recommendations for neurotoxicity and CRS)	

AEs = adverse events; CAR = chimeric antigen receptor; CR = complete remission; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; EFS = event-free survival; ECOG = Eastern Cooperative Oncology Group; HRQL = health-related quality of life; HSCT = hematopoietic stem cell transplant; NRCT = non-randomized controlled trial; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; PR = partial remission; RCT = randomized controlled trial; RFS = relapse-free survival; r/r-ALL = relapsed/refractory B-cell acute lymphoblastic leukemia; SAEs = serious adverse events; WDAEs = withdrawals due to adverse events.

Studies with mixed populations that include patients who do not meet the eligibility criteria will be included if separate results are reported for the eligible patients.

Where multiple publications are identified for the same study, the study which provides the most current and comprehensive information on the outcomes of interest will be selected over the others.

Literature Screening and Selection

Using the eligibility criteria, two reviewers will independently select potentially relevant citations by screening all titles and abstracts identified through comprehensive literature searches. The checklist for level 1 screening is available in Appendix 3, Table 2. Full-text articles of any abstracts and titles deemed potentially relevant by at least one reviewer will be retrieved for a second level screening. The same reviewers will independently examine all full-text articles to select studies for inclusion in the review. Disagreements between the

reviewers will be resolved through consensus or by a third reviewer, if needed. The checklist for level 2 screening is available in Appendix 3, Table 3.

The full texts of received titles will be retrieved and independently screened for inclusion by two reviewers using the previously described process.

The study selection process will be outlined in a PRISMA flow chart, and a list of excluded studies will be provided together with the reasons for exclusion.

Data Extraction

Data extraction will be performed by one reviewer for each indication (r/r-B-cell ALL or r/r-DLBCL) and independently checked for accuracy by a second reviewer. Data covering the following areas will be extracted, as well as other relevant information:

- study characteristics (e.g., first author's name, publication year, publication title, country where the study was conducted, funding sources)

- methodology (e.g., study design and objectives, inclusion and exclusion criteria, recruitment method, primary and secondary outcomes, definitions of outcomes, subgroup analyses of interest, and adjustment for confounders for non-randomized and observational studies)

- population (e.g., sample size, demographics and baseline characteristics, type of disease, Eastern Cooperative Oncology Group (ECOG) status, relapse or refractory status, prior treatment (e.g., chemotherapy or stem cell transplantation [SCT], details of bridging chemotherapy regimen, chemotherapy received prior to infusion)

- intervention (i.e., tisagenlecleucel [administered alone or with chemotherapy or SCT])

- comparator (i.e., another CAR T-cell therapy or a defined salvage treatment)

- outcomes following the therapy (i.e., measures of clinical effectiveness, quality of life and safety, need for additional treatment to manage side effects [e.g., administration of tocilizumab for cytokine release syndrome, or CRS]).

Quality Assessment of Studies

The risk of bias assessment will be conducted independently by two reviewers. Disagreements will be resolved by consensus, or through a third reviewer if needed. For RCTs, the methods described in the Cochrane Risk of Bias assessment tool[21] will be used. The Cochrane Risk of Bias assessment tool assesses seven sources of bias, assigning a "low," "high," or "unclear" rating for each item.[21] The Risk of Bias In Non-randomized Studies – Interventions (ROBINS-I) tool for non-randomized interventions and observational studies[22] will be used to evaluate non-randomized studies. The ROBINS-I tool assesses bias across 34 items in seven domains. Each item is answered as "yes," "probably yes," "probably no," "no," and "no information."[22] The "yes" signifies a judgment of low risk of bias and "no" indicates concern with the risk of bias. For each domain, the risk of bias can be graded as "low," "moderate," "serious," "critical," or "no information."[22] Information from the domain level will be used to assign an overall risk of bias in each study according to ROBINS-I guidance.[22] The quality of identified clinical practice guidelines will be assessed using the AGREE II instrument and the findings presented in a tabular form.

The results of the risk of bias assessment for the individual studies will be summarized in tabular form and reported narratively, along with a description of the strengths and limitations of each study. Any additional considerations not captured by the Cochrane Risk of Bias tool, the ROBINS-I, or the AGREE II instrument will be summarized narratively.

Data Analysis

The results of the scoping review show that the available literature is too heterogeneous to permit a meta-analysis. Therefore, a narrative synthesis will be conducted. A narrative synthesis is a SR approach, which relies primarily on the use of words and text to summarize and explain the findings from multiple sources when meta-analysis is not feasible because of excessive heterogeneity in the available studies. Relevant data will be extracted and summarized in tables for each study, and textual descriptions will be used to provide more details and clarity, where needed. Data tabulation will be performed by one reviewer for each indication (r/r-B-cell ALL or r/r-DLBCL) and independently checked for accuracy by a second reviewer. Within- and between-study relationships will be explored separately for studies on r/r-ALL and r/r-DLBCL. Observed trends and significant deviations will be noted and discussed. For the purpose of analysis, studies will be grouped by study design. For example, clinical trials (i.e., experimental design) will be analyzed separately from observational studies. The approaches used by the study authors to determine the efficacy and safety results will be analyzed and the likelihood of clinical benefit or harms will be reported separately for the individual studies. Subgroup analysis will be conducted depending on the availability of data. Factors that will be considered for subgroup analyses include age, disease status (relapse versus refractory), ECOG status, and the number of previous lines of therapies. The effectiveness and safety findings for tisagenlecleucel for r/r-B-cell ALL or r/r-DLBCL will be discussed in relation to reported findings for other salvage therapies, being mindful of the absence of any comparative study evaluating tisagenlecleucel and other interventions at this time.
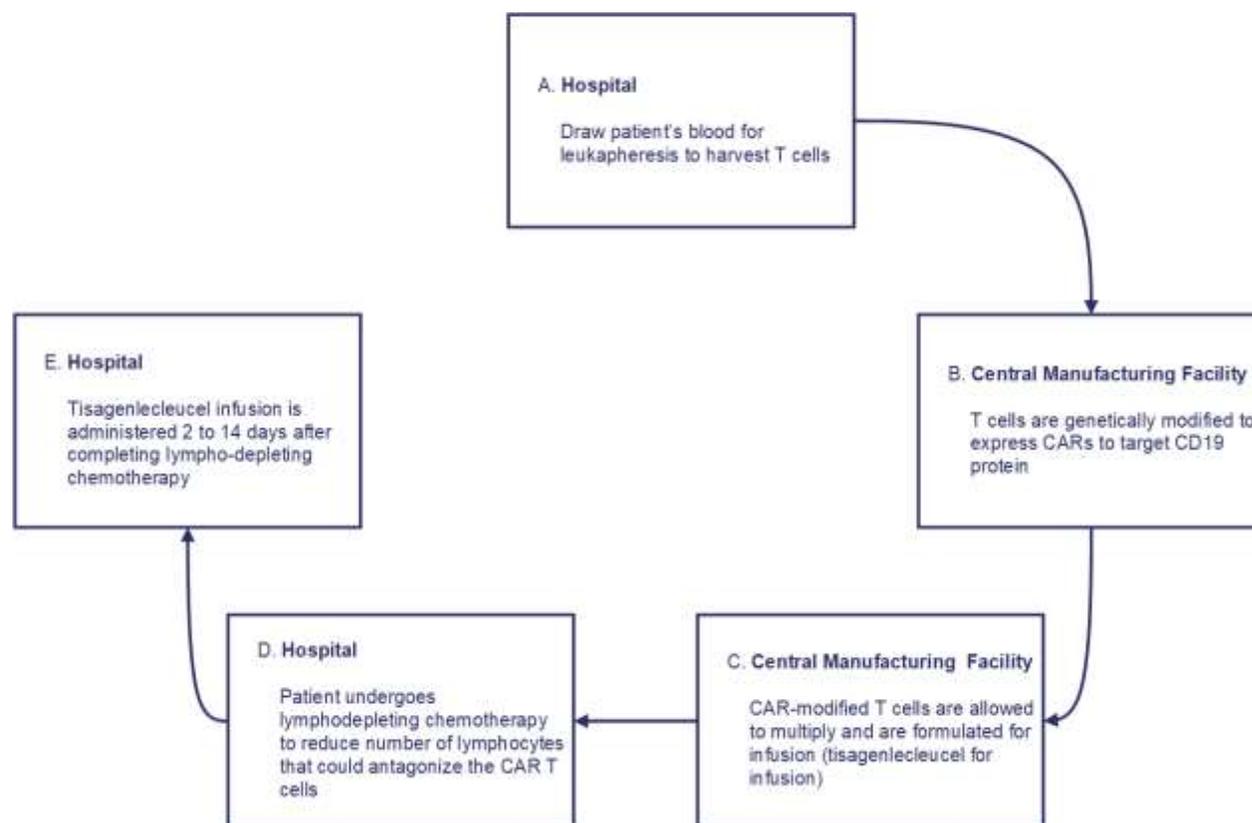
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Appendix 1: Therapy Procedure Overview

Figure 1: An Overview of Manufacturing and Administering CAR T-cell (Tisagenlecleucel) Therapy

A. Hospital

Draw patient's blood for leukapheresis to harvest T cells

B. Central Manufacturing Facility

T cells are genetically modified to express CARs to target CD19 protein

C. Central Manufacturing Facility

CAR-modified T cells are allowed to multiply and are formulated for infusion (tisagenlecleucel for infusion)

D. Hospital

Patient undergoes lymphodepleting chemotherapy to reduce number of lymphocytes that could antagonize the CAR T cells

E. Hospital

Tisagenlecleucel infusion is administered 2 to 14 days after completing lympho-depleting chemotherapy

CAR = chimeric antigen receptor.

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Appendix 2: Review Framework

Figure 2: Short- and Long-Term Review Framework After Tisagenlecleucel Infusion
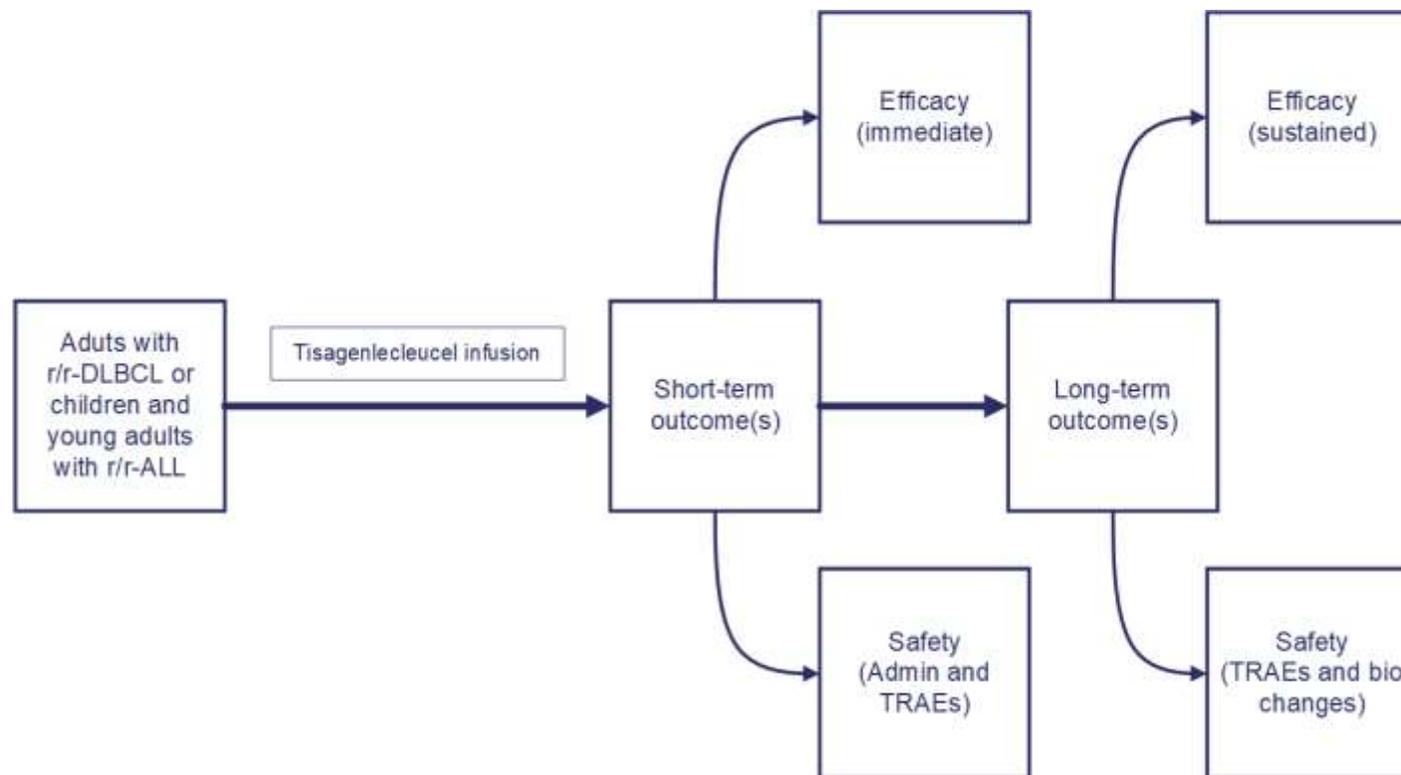
r/r-DLBCL = relapsed/refractory diffuse large B-cell lymphoma; r/r-ALL = relapsed/refractory B-cell acute lymphoblastic lymphoma; TRAEs = treatment-related adverse events.

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Appendix 3: Clinical Studies Screening Checklists

Table 2: Level 1 Checklist for Screening Titles and Abstracts

Reviewer: _____ Date: _____			
Ref ID:			
Author:			
Publication Year:			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
A. The population of interest:			
• Adults (mean age of ≥ 18 years) with r/r-DLBCL	☐	☐	☐
• Mixed, with ≥ 80% being adults with r/r-DLBCL	☐	☐	☐
• Pediatric or young adult (≤ 25 years) with r/r-ALL	☐	☐	☐
• Mixed, with ≥ 80% being pediatric or young adult (⩽25 years) with r/r-ALL	☐	☐	☐
B. The intervention of interest:			
• Tisagenlecleucel alone	☐	☐	☐
• Tisagenlecleucel together with drug interventions	☐	☐	☐
• Tisagenlecleucel together with HSCT	☐	☐	☐
C. The comparator(s) of interest:			
• Other Car T-cell therapies	☐	☐	☐
• Conventional salvage therapy • Allogenic HSCT	☐	☐	☐
• No Comparator	☐	☐	☐
D. The outcome(s) of interest:			
• Objective efficacy outcomes (e.g., CR, PR, OS, PFS, etc.)	☐	☐	☐
• Quality of life	☐	☐	☐
• Safety outcomes such as AEs (e.g., CRS, prolonged cytopenias, infections and infestations, febrile neutropenia, neurological effects including hallucination and dysphasia, etc.) SAEs (i.e., Grade ≥ 3 AEs), and WDAEs	☐	☐	☐
E. The study design(s) of interest:			
• RCTs	☐	☐	☐
• Non-randomized controlled trials • Single-arm studies	☐	☐	☐
• Cohort studies	☐	☐	☐
• Case-control studies	☐	☐	☐
F. Select for full-text review [b]	**Yes ☐**		**No ☐**

AE= adverse event; CAR = chimeric antigen receptor; CR = complete remission; CRS = cytokine release syndrome; HSCT = hematopoietic stem cell transplant;
OS = overall survival; PFS = progression-free survival; PR = partial remission; RCT = randomized controlled trial; WDAE = withdrawal due to adverse event.
[a] "Unclear" means that it cannot be ascertained from the title or abstract if the report is potentially relevant to the review.
[b] The full-text article of any title or abstract will be retrieved for further review if the response to all screening items above-noted are either "Yes" or "Unclear" by at least one of two independent reviewers.

Table 3: Level 2 Checklist for Screening Full-Text Articles and Study Reports

Reviewer: _____ Date: _____		
Ref ID:		
Author:		
Publication Year:		
Did the study include:	**Yes (Include)**	**No (Exclude)**
A. The population of interest:		
• Adults (mean age of ≥ 18 years) with r/r-DLBCL	☐	☐
• Mixed, with ≥ 80% being adults with r/r-DLBCL	☐	☐
• Pediatric or young adult (≤ 25 years) with r/r-ALL	☐	☐
• Mixed, with ≥ 80% being pediatric or young adult (≤ 25 years) with r/r-ALL	☐	☐
B. The intervention of interest:		
• Tisagenlecleucel alone	☐	☐
• Tisagenlecleucel together with drug interventions	☐	☐
• Tisagenlecleucel together with HSCT	☐	☐
C. A comparator of interest:		
• Other Car T-cell therapies	☐	☐
• Conventional salvage therapy	☐	☐
• No Comparator	☐	☐
D. Outcome(s) of interest:		
• Objective efficacy outcomes (e.g., CR, PR, OS, PFS, etc.)	☐	☐
• Quality of life	☐	☐
• Safety outcomes such as Grade ≥ 3 AEs (e.g., CRS, prolonged cytopenias, infections and infestations, febrile neutropenia, neurological effects including hallucination and dysphasia, etc.)	☐	☐
E. A study design of interest:		
• RCTs	☐	☐
• Non-randomized controlled trials • Single-arm studies	☐	☐
• Cohort studies	☐	☐
• Case-control studies	☐	☐
F. Notes:		
G. Selected for inclusion in the review [a]	**Yes ☐**	**No ☐**
H. Reason(s) for exclusion	☐ Irrelevant population ☐ Irrelevant intervention ☐ Irrelevant comparator ☐ Irrelevant outcomes ☐ Irrelevant study design ☐ Other (specify):	

AE= adverse event; CAR = chimeric antigen receptor; CR = complete remission; HSCT = hematopoietic stem cell transplant; OS = overall survival; PFS = progression-free survival; PR = partial remission; RCT = randomized controlled trial; r/r-DLBCL = relapsed/refractory diffuse large B-cell lymphoma; r/r-ALL = relapsed/refractory B-cell acute lymphoblastic lymphoma.

[a] Both reviewers must answer "Yes" to all questions for inclusion at the full-text level. If there is a discrepancy between the reviewers, disagreements will be resolved by discussion or with the involvement of a third reviewer, if necessary.

Appendix 4: Clinical Search Strategy

OVERVIEW

Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials
	Embase
	Ovid MEDLINE ALL
	Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 13, 2018
Alerts:	Monthly search updates
Study Types:	No filters used
Limits:	None

SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic;
	or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
oemezd	Embase database code
medal	MEDLINE database code
cctr	Cochrane CENTRAL database code

MUTLI-DATABASE STRATEGY

#	Searches
1	(tisagenlecleucel* or kymriah* or cart 19 or cart19 or "ctl 019" or ctl019 or Q6C9WHR03O).ti,ab,kf,kw,ot,hw,rn,nm.
2	1 use medall
3	1 use cctr
4	tisagenlecleucel T/
5	(tisagenlecleucel* or kymriah* or cart 19 or cart19 or "ctl 019" or ctl019).ti,ab,kw,dq.
6	4 or 5
7	6 use oemezd
8	2 or 3 or 7
9	remove duplicates from 8

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
CINAHL (EBSCO interface)	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.	
Scopus	Same keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Scopus platform.	

Grey Literature

Dates for Search:	June 2018
Keywords:	Included terms for tisagenlecleucel, Kymriah, ctl 019, ctl019, leukemia, lymphoma, chimeric antigen receptor T cell therapy
Limits:	None

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Clinical Trial Registries
- Regulatory Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals

Conferences and Meetings

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search terms: tisagenlecleucel, Kymriah, ctl 019, ctl019, cart 19, cart19