CADTH

CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma: Clinical Report

PROSPERO REGISTRATION NUMBER: CRD42018103201

Service Line:	Optimal Use
Version:	Volume 8, Issue 3c
Publication Date:	January 2019
Report Length:	158 Pages

CADTH

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

ISSN: 1927-0127 (English only)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

CADTH

Table of Contents

Tables

Figures

Abbreviations

ABC	activated B-cell
AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
BOR	best overall response
CAR	chimeric antigen receptor
CARTOX	CAR T-cell-therapy-associated TOXicity (Working Group)
CI	confidence interval
CNS	central nervous system
CR	complete response
CR_i	complete remission with incomplete blood count recovery
CRS	cytokine release syndrome
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
EAS	efficacy analysis set
EFS	event-free survival
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels questionnaire
EQ VAS	EuroQol Visual Analogue Scale
FACT-G	Functional Assessment of Cancer Therapy–General
FAS	full analysis set
GCB	germinal centre B-cell
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICU	intensive care unit
IPI	International Prognostic Index
IRC	Independent Review Committee
ISRT	involved-site radiation therapy
MAIC	matching-adjusted indirect comparison
MedDRA	Medical Dictionary for Regulatory Activities
MCID	minimal clinically important difference
MCS	Mental Component Summary (of the SF-36)

MRD	minimum residual disease
NCCN	National Comprehensive Cancer Network
NHL	non-Hodgkin lymphoma
ORR	overall remission rate
ORsR	overall response rate
OS	overall survival
PCS	Physical Component Summary (of the SF-36)
PD	progressive disease
PedsQL	Pediatric Quality of Life Inventory
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
r/r B-cell ALL	relapsed or refractory B-cell acute lymphoblastic leukemia
r/r DLBCL	relapsed or refractory diffuse large B-cell lymphoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
RFS	relapse-free survival
SAE	serious adverse event
SCT	stem cell transplant
SD	stable disease
SF-36	Short Form Health Survey
SR	systematic review
TOI	Trial Outcome Index
WBC	white blood cell

Executive Summary

Introduction

Acute lymphoblastic leukemia (ALL) is a hematological malignancy leading to the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. It is predominant in childhood and accounts for 80% of all leukemia cases in children and young adults. Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of non-Hodgkin lymphoma (NHL), and the most common NHL. The estimated annual incidence of DLBCL is 10.2 per 100,000. It accounts for 30% to 40% of all lymphomas in adult patients in Canada and internationally.

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. Health Canada approved tisagenlecleucel in September 2018 for: pediatric and young adult patients three to 25 years of age with B-cell acute ALL who are refractory, have relapsed after allogeneic stem cell transplant (SCT) or are otherwise ineligible for SCT, or who have experienced a second or later relapse; and for adult patients (≥ 18 years) with relapsed or refractory (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.

Objective

The objectives of this clinical review were to systematically evaluate the benefits and harms of tisagenlecleucel in: (1) children and young adults with r/r B-cell ALL; and (2) adults with r/r DLBCL. This project is a component of a larger CADTH Health Technology Assessment (HTA) to assess clinical effectiveness, cost-effectiveness, patient and caregiver perspectives and experiences, ethical issues, and implementation.

Results and Interpretation

Search and Screening

A total of 12 reports were included that described one pivotal and two supporting studies for r/r B-cell ALL, one pivotal study and one supporting study for r/r DLBCL, and three evidence-based clinical practice guidelines (two guidelines for ALL and one for DLBCL). All studies were prospective, single-arm designs with no comparator groups.

Included Studies

r/r B-Cell ALL

For r/r B-cell ALL, a pivotal study (ELIANA), two supporting studies (ENSIGN and B2101J), and two clinical practice guidelines met the inclusion criteria. ELIANA and ENSIGN determined the efficacy and safety of tisagenlecleucel in pediatric and young adult patients (age ≤ 25) with r/r B-cell ALL. Study B2101J determined the safety, tolerability, and persistence of tisagenlecleucel in pediatric and young adult patients with r/r CD19-positive leukemia and lymphoma.

ELIANA is an ongoing, phase II, multi-centre, single-arm, open-label global study with 25 study sites across 11 countries, including Canada, with two sites. ENSIGN is an ongoing, phase II, single-arm, open-label study with nine centres, all in the US. Study B2101J is an

ongoing, phase I/IIa single-arm, open-label, single-centre study in the US. Two clinical practice guidelines — one from the collaboration between the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) and MD Anderson Cancer Center CAR T-cell-therapy-associated TOXicity (CARTOX) Working Group and one from the National Comprehensive Cancer Network (NCCN) — addressed patient selection and evaluation, leukapheresis, lymphodepletion treatment, bridging chemotherapy, cell infusion, in-patient and outpatient management, and monitoring, grading, and management of cytokine release syndrome (CRS).

r/r DLBCL

The evidence for DLBCL consisted of one pivotal study (JULIET), one supporting study (A2101J), and one clinical practice guideline. JULIET is a phase II, single-arm, open-label, multi-centre study conducted in 27 centres across 10 countries. Study A2101J is a phase IIa, single-arm, open-label, single-centre study in patients with DLBCL or follicular lymphoma, conducted in the US. The clinical practice guideline was developed by the NCCN and covered aspects of patient selection for CAR T-cell therapy and management of toxicities.

Outcomes Assessed

r/r B-Cell ALL

The outcomes evaluated in the pivotal ELIANA study and the two supporting studies, ENSIGN and B2101J, were overall remission rate (ORR), duration of remission (DOR), relapse-free survival (RFS), event-free survival (EFS), overall survival (OS), and harms.

r/r DLBCL

The outcomes evaluated in JULIET were overall response rate (ORsR), progression-free survival (PFS), EFS, OS, and harms. In the supporting study, A2101J, outcomes evaluated in patients with DLBCL were ORsR, PFS, OS, and harms.

Conclusion

The efficacy findings from ELIANA, ENSIGN, and B2101J suggest that in pediatric and young adults with r/r B-cell ALL, treatment with tisagenlecleucel results in significant ORR in the majority of patients. JULIET also demonstrated tisagenlecleucel responses on ORsR and secondary outcomes in adults with r/r DLBCL. However, long-term and direct comparative data were not available. Tisagenlecleucel has the potential to exert severe adverse events and is resource-intensive, requiring an established infrastructure to ensure patients receive the treatment safely and according to protocol standards. Thus, more long-term follow-up and comparator data will be required to fully understand the benefit-risk profile of tisagenlecleucel and its place in therapy in these hematological malignancies.

Introduction

Disease Prevalence and Incidence

Acute lymphoblastic leukemia (ALL) is a hematological malignancy leading to the proliferation of immature, non-functional lymphoid cells in the bone marrow, peripheral blood, and other organs.[1] It is predominant in childhood and accounts for 80% of all leukemia cases in children.[2-5] About 300 children are diagnosed with leukemia each year in Canada.[3,4] Therefore, the estimated incidence of childhood ALL is 240 children per year. The overall cure rate with currently available therapies for newly diagnosed pediatric ALL is about 80% to 85%.[2,6,7] The IMPACT cohort (N = 2,963) of adolescents and young adults (15 years to 21 years) with a malignancy from 1992 to 2011 in Ontario included 271 patients with ALL.[8] The five-year overall survival (OS) was 82% in patients treated at pediatric centres and 64% in patients treated at adult centres.[8] However, relapse occurs in 20% to 25% of children. With currently available second-line therapy, the long-term OS rate in patients with relapsed or refractory B-cell ALL (r/r B-cell ALL) ranges from 15% to 50%.[7]

Diffuse large B-cell lymphoma (DLBCL) is an aggressive type of non-Hodgkin lymphoma (NHL) in adults, and is the most common type. Subtypes of DLBCL include germinal centre B-cell (GCB), activated B-cell (ABC), and primary mediastinal large B-cell lymphoma. The GCB subtype is associated with better outcomes compared with non-GCB in patients treated with standard first-line therapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). The estimated annual incidence of DLBCL is 10.2 per 100,000, accounting for 30% to 40% of all lymphomas in adults.[3,4,9,10] The remission rate of DLBCL in patients who undergo first-line chemotherapy is approximately 50% to 70%.[11,12] However, 30% to 50% experience relapse and 10% have primary refractory disease.[11,12] If left untreated, the life expectancy of patients with high-risk relapsed or refractory DLBCL (r/r DLBCL) after an autologous stem cell transplant (SCT) is three to four months. Based on the largest meta-analysis available for r/r DLBCL (defined as progressive disease [PD] or stable disease [SD] as best response at any point during chemotherapy or relapsed ≤ 12 months after autologous SCT), the objective response rate to salvage therapy is reported to be 26% (7% complete response rate) and the median OS is 6.3 months.[11] Currently, only palliative options are available for patients who do not respond to second-line therapy or have disease progression after SCT.

Standards of Therapy

ALL treatment is categorized into the phases of induction, consolidation, and maintenance.[13] The induction phase is meant to reduce tumour burden by clearing leukemic cells in the blood and bone marrow with combination chemotherapy regimens that may include vincristine, an anthracycline (i.e., daunorubicin or doxorubicin), and corticosteroids, with or without L-asparaginase and/or cyclophosphamide. Consolidation eliminates leukemic cells that remain after induction and may include high-dose methotrexate (MTX), cytarabine, 6-mercaptopurine (6-MP), cyclophosphamide, vincristine, corticosteroids, and L-asparaginase. Maintenance therapy is administered to prevent disease relapse; most regimens include daily 6-MP and weekly MTX, with periodic vincristine and corticosteroids, for two to three years.[13] Tyrosine kinase inhibitors, such as imatinib and dasatinib, or the anti-CD20 antibody, rituximab (in adults), may be used for certain ALL subtypes.[13] ALL treatment also includes central nervous system (CNS) prophylaxis and/or treatment with chemotherapy instilled into the cerebrospinal fluid or radiation therapy directed to the brain.[13]

Patients with r/r B-cell ALL may be treated with blinatumomab, inotuzumab, chemotherapy alone, or chemotherapy followed by allogeneic hematopoietic SCT in a subset of patients. According to a clinical expert consulted for this review, after first relapse, the majority of patients will undergo re-induction therapy and may proceed to hematopoietic SCT, depending on risk classification and response to therapy. If disease relapses after the first allogeneic SCT, a second allogeneic SCT or donor lymphocyte infusion may be attempted.[13]

Although current salvage therapy for r/r B-cell ALL patients includes multi-drug chemotherapy, the increased toxicity of multi-drug chemotherapy protocols makes this an unfeasible option for many patients. Moreover, the majority of patients who achieve complete remission on these protocols eventually relapse.[14,15] Thus, consolidation of remission from chemotherapy with allogeneic SCT is the standard of care during second- and subsequent-line therapy. However, up to 50% of patients with r/r B-cell ALL do not qualify for SCT.[16]

The treatment regimen for patients with DLBCL depends on disease stage. For patients with non-bulky (< 7.5 cm) stage I or II disease, the National Comprehensive Cancer Network (NCCN) recommends three cycles of R-CHOP with involved-site radiation therapy (ISRT) or six cycles of R-CHOP with or without ISRT.[17] Bulky disease (≥ 7.5 cm) is treated with six cycles of R-CHOP with or without locoregional radiation therapy. If patients are not candidates for chemotherapy, ISRT may be administered alone. For patients with stage III or IV disease, R-CHOP 21 (i.e., R-CHOP administered every three weeks) for six cycles is recommended. Some patients may also receive radiation therapy to bulky sites. An alternative chemotherapy regimen for stage III or IV disease is dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R).[17] Patients with other considerations, such as frailty or poor left ventricular function, may be initiated on other treatment regimens.[17] Patients with first relapse or refractory DLBCL may be treated with salvage combination chemotherapy and, if their lymphoma can be controlled (i.e., if they achieve a partial response or better), they would proceed to high-dose chemotherapy (HDT) followed by autologous SCT, or allogeneic hematopoietic SCT if there is response to HDT. Patients who experience disease progression after three or more successive regimens are unlikely to benefit from further chemotherapy.[17]

Description of Intervention

Chimeric antigen receptors (CARs) are artificial receptors that redirect antigen specificity, activate T cells, and further enhance T-cell function through their costimulatory component.[18] The CAR T-cell therapy involves applying leukapheresis to harvest the patient's peripheral blood mononuclear cells containing T cells and sending them to a central facility where the DNA for the chimeric protein is inserted into the DNA of the patient's T cells using viral vectors, such as lentivirus (CAR = chimeric antigen receptor.). The resulting CAR T-cells are then shipped back to the treating institution for infusion into the patient's bloodstream to fight the malignancy.[6,19] Currently, it takes a minimum of two to three weeks from leukapheresis to the time the CAR T cells are ready to be infused back into the patient.[6] Many patients require some form of bridging chemotherapy to keep their cancer stable during this period. In addition, before infusion of the CAR T-cells, patients must undergo lymphodepleting chemotherapy to decrease the number of competing lymphocytes that could result in reduced efficacy of the CAR T-cell product.[6,20]

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

CAR = chimeric antigen receptor.

Tisagenlecleucel (formerly known as CTL019) is a second-generation CAR T-cell therapy that targets the CD19 antigen, expressed exclusively on B cells, including the cancer cells in ALL and DLBCL. The CAR portion in tisagenlecleucel is composed of a murine single-chain antibody fragment that 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 antitumour activity, while 4-1BB enhances the expansion and persistence of tisagenlecleucel.[19-21] Upon infusion, the CAR binds to CD19-expressing cells and transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the tisagenlecleucel in cells.[20,22] According to the Health Canada product monograph, lymphodepleting chemotherapy is recommended prior to tisagenlecleucel infusion unless white blood cell (WBC) count one week prior to infusion is less than or equal to 1,000 cell/µL.[23] Tisagenlecleucel is administered as an IV infusion two to 14 days after completing lymphodepleting chemotherapy.[23] The recommended lymphodepleting chemotherapy regimen for B-cell ALL is fludarabine 30 mg/m² IV per day for four days and cyclophosphamide 500 mg/m² IV per day for two days starting with the first dose of fludarabine.[23] If a patient previously experienced grade 4 hemorrhagic cystitis with cyclophosphamide, or was chemorefractory to a cyclophosphamide-containing regimen, then an alternative regimen of cytarabine (500 mg/m^2 IV daily for two days) and etoposide (150 mg/m^2 IV daily for three days starting with the first dose of cytarabine) is

administered.[23] For adults with DLBCL, the recommended lymphodepleting therapy is fludarabine (25 mg/m^2 IV daily for three days) and cyclophosphamide (250 mg/m^2 IV daily for three days starting with the first dose of fludarabine) or, as an alternative, bendamustine (90 mg/m^2 IV daily for two days).[23]

Tisagenlecleucel is intended for the treatment of a subset of CD19 positive malignancies. Tisagenlecleucel was approved by the FDA (August 2017 for ALL and April 2018 for DLBCL), the European Medicines Agency (for both pediatric r/r B-cell ALL and adult r/r DLBCL),[24] and more recently by Health Canada (in September 2018) for (1) pediatric and young adult patients three years to 25 years of age with B-cell acute ALL who are refractory, have relapsed after allogeneic SCT, are otherwise ineligible for SCT, or have experienced a second or later relapse, and for (2) adult patients (≥ 18 years) with relapsed or refractory 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. For children and young adults with ALL, the recommended dosing is 0.2 to 5.0 × 10^6 CAR-positive viable T cells/kg body weight for patients 50 kg and below and 0.1 to 2.5 × 10^8 CAR-positive viable T cells (non–weight-based) for patients above 50 kg.[23] For adults with DLBCL, the recommended dosing is 0.6 to 6.0 × 10^8 CAR-positive viable T cells (non–weight-based).[23].

In general, there is a need for an intervention that will durably improve remission rates in children and young adults with r/r B-cell ALL and in adults with r/r DLBCL.[25] Given the associated high costs, the infrastructure required to safely administer treatment to patients, and the risk of adverse events (AEs), a critical evaluation of the benefits and risks of tisagenlecleucel is needed for informed decision-making about this therapy.

Policy Question

This Health Technology Assessment (HTA) will address the following policy question:

How should the provision of tisagenlecleucel for children and young adults with r/r B-cell ALL and adults with r/r DLBCL be structured?

Objectives

The objectives of this clinical review are to systematically evaluate the benefits and harms of tisagenlecleucel in: (1) children and young adults with r/r B-cell ALL; and (2) adults with r/r DLBCL. This project is a component of a larger CADTH HTA to assess clinical effectiveness, cost-effectiveness, patient and caregiver perspectives and experiences, ethical issues, and implementation considerations. Each component of the HTA is being conducted individually and collaboratively. It is anticipated that this work will support the jurisdictions involved in the organization and provision of tisagenlecleucel therapy in Canada.

The goal of the clinical review is to provide clinical evidence about the beneficial and harmful effects of tisagenlecleucel in children and young adults with r/r B-cell ALL and adults with r/r DLBCL to help answer the policy question.

Research Questions

The following clinical research questions were addressed in this review:

1. What are the beneficial and harmful effects of tisagenlecleucel in children and young adults with r/r B-cell 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 children and young adults with r/r B-cell ALL?
4. What are the evidence-based clinical guidelines for the effective use of tisagenlecleucel for the treatment of adults with r/r DLBCL?

Methods

The methodology adopted for this review is guided by the criteria outlined in the checklist described in AMSTAR II.[26] The clinical review was conducted in accordance with CADTH standards for Optimal Use reviews and relevant reporting guidelines, such as the PRISMA statement and the PRISMA harms.[27,28]

The protocol[29] for the systematic review (SR) was developed and written a priori based on information from an informal scoping review, from which two completed HTAs, an SR, four non-randomized primary clinical studies, and two evidence-based practice guidelines were identified. The protocol was followed throughout the review process.

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy. See Appendix 1: Literature Search Strategy for the detailed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–), Embase (1974–), the Cochrane Central Register of Controlled Trials through Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) through EBSCO, Scopus, and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was tisagenlecleucel (Kymriah). No methodological filters were applied to limit the retrieval by study type. The search was not limited by language or publication date.

The search was completed on July 12, 2018. Regular alerts were established to update the searches until the publication of the final report. Regular search updates were 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 were incorporated into the analysis of the final report. Any studies that were identified after the stakeholder feedback period were 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 was conducted for clinical practice guidelines. The main search concepts were leukemia, lymphoma, and CAR T-cell therapy. The search for lymphoma and leukemia guidelines was limited to English- or French-language documents published

between January 1, 2016 and July 12, 2018. The search for CAR T-cell therapy guidelines was limited to English- or French-language documents published between January 1, 2013 and July 12, 2018. Conference abstracts were removed from the search results.

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

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

Study Eligibility

Studies were selected for inclusion in the SR based on the selection criteria in Table 1. Studies were classified as pivotal or supporting according to the terminology used by the manufacturer.

The reference lists of potentially relevant HTAs or SRs identified by the literature search for the project were reviewed for primary studies that met the inclusion criteria.

Table 1: Eligibility Criteria for Clinical Research Questions

Indications	r/r B-Cell ALL	r/r DLBCL
Population	Pediatric and young adult patients 3 years to 25 years with B-cell ALL who are refractory, have relapsed after allogeneic SCT, are otherwise ineligible for SCT, or have experienced second or later relapse Subgroups according to age, disease status (refractory vs. relapsed), ECOG status, previous lines of therapy	Adult patients with relapsed or refractory 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
Intervention	Tisagenlecleucel cell suspension in infusion bag for IV use:[a] • For patients 50 kg or less: 0.2 to 5.0 × 10^6 CAR-positive viable T cells/kg body weight • For patients more than 50 kg: 0.1 to 2.5 × 10^8 CAR-positive viable T cells (non–weight- based)	Tisagenlecleucel cell dispersion for IV infusion[a] 0.6 to 6.0 × 10^8 CAR-positive viable T cells (non–weight-based)
Comparator	• Blinatumomab • Inotuzumab ozogamicin • Clofarabine • Defined salvage chemotherapy for r/r- B-cell ALL • Allogeneic SCT • No comparator	• Axicabtagene ciloleucel • Defined salvage chemotherapy for r/r DLBCL • Allogeneic SCT • No comparator

Indications	r/r B-Cell ALL	r/r DLBCL
Main outcomes	**Clinical effectiveness** • ORR/ORsR, CR, PR, OS, RFS, PFS, EFS, HRQoL, 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, single-arm studies, cohort, case-control and case series studies) and clinical practice guidelines (including treatment recommendations for neurotoxicity and CRS)	

AE = adverse event; ALL = acute lymphoblastic leukemia; CAR = chimeric antigen receptor; CR = complete remission; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; HRQoL = health-related quality of life; NRCT = non-randomized controlled trial; ORR = overall remission rate; ORsR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial remission; RCT = randomized controlled trial; RFS = relapse-free survival; r/r B-cell ALL = relapsed or refractory B-cell acute lymphoblastic leukemia; r/r DLBCL = relapsed or refractory diffuse large B-cell lymphoma; SAE = serious adverse event; SCT = stem cell transplant; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Lymphodepleting chemotherapy is recommended before tisagenlecleucel infusion unless the white blood cell count within one week prior to tisagenlecleucel infusion is ≤ 1,000 cells/microlitre.[23]

Studies with mixed populations were included if separate results were reported for the eligible patients.

The SR used the most current published or unpublished data available at the time of data extraction. Studies were excluded if they did not meet the criteria in Table 1. For instance, HTAs, SRs, and meta-analyses (MAs) were not included because the clinical review is intended to be a de novo SR of published and unpublished primary clinical evidence to address the research questions. Rather, the reference lists of potentially relevant HTAs, SRs, and MAs identified by the literature search were reviewed for primary studies that met the inclusion criteria.

Literature Screening and Selection

Using the eligibility criteria, two reviewers independently selected potentially relevant citations by screening all titles and abstracts identified through the literature searches (Level 1 screening). Full-text articles of titles/abstracts deemed potentially relevant by at least one reviewer were retrieved for a second-level (full-text) screening. The same reviewers independently examined full-text articles to select studies for inclusion in the review. Disagreements between the reviewers were resolved through consensus or by a third reviewer, if needed. The screening checklists for Level 1 and Level 2 are available in Appendix 2. The materials submitted by the manufacturer were examined by one reviewer for each indication (r/r B-cell ALL and r/r DLBCL) to ensure that eligibility criteria were met.

The study selection process is outlined in a PRISMA flow chart (Appendix 3). A list of included and excluded studies, with the reasons for exclusion, is provided in Appendix 4 and Appendix 5, respectively.

Data Extraction

Data extraction was performed by one reviewer for each indication (r/r B-cell ALL and r/r DLBCL) and independently checked for accuracy by a second reviewer. Data covering the following areas were extracted if available:

- Study characteristics (e.g., first author's name, publication year, publication title, countries where the study was conducted, funding sources, number of centres or sites)
- 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 potential 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 SCT, details of bridging chemotherapy regimen, chemotherapy received prior to infusion])
- Intervention (i.e., tisagenlecleucel including dose, details of conditioning regimen used)
- Comparator (i.e., another CAR T-cell therapy or a defined salvage treatment)
- Outcomes (e.g., measures of clinical effectiveness, quality of life and safety, need for additional treatment to manage side effects — for example, administration of tocilizumab for cytokine release syndrome [CRS]).

Quality Assessment of Studies

The risk of bias assessment was conducted independently by two reviewers. Disagreements were resolved by consensus, or through a third reviewer if needed. The Risk of Bias In Non-randomized Studies – Interventions (ROBINS-I) tool for non-randomized interventions and observational studies was used as a guide to evaluate non-randomized studies.[30] The ROBINS-I tool assesses bias across 34 items in seven domains. The quality of identified clinical practice guidelines was assessed using the AGREE II instrument.[31] The findings were presented in a tabular format.

Data Analysis

A narrative synthesis was conducted, relying primarily on the use of words and text to summarize and explain the findings from the included studies. The relevant data for the narrative synthesis were extracted and summarized in tables for each study, and textual descriptions were used to provide more details and clarity, where needed. Within- and between-study relationships were explored for studies in r/r B-cell ALL and also for studies in r/r DLBCL, noting any significant trends and deviations for discussion. The study authors' approach to determine the efficacy and safety results was analyzed for its appropriateness and applicability in the Canadian context through consultation with clinical experts engaged by CADTH for this review. The findings regarding the effectiveness and safety of tisagenlecleucel for the treatment of r/r-B-cell ALL or r/r DLBCL were discussed, referencing reported findings of other salvage therapies as appropriate, and being mindful of the absence of any comparative study evaluating tisagenlecleucel and other interventions at the time of review.

Clinical Review Results

Selection of Primary Studies

Studies selected for inclusion in the SR were pivotal and supportive trials provided by the manufacturer, as well as those identified by comprehensive literature searches that met the selection criteria in Table 1.

Information provided by the manufacturer for r/r B-cell ALL included three clinical study reports (CSRs) — one each for the pivotal (ELIANA)[32] and two supporting studies (ENSIGN[33] and B2101J[34]), as well as a clinical summary.[35] There was one CSR[36] for the pivotal study in r/r DLBCL.

The electronic database searches identified a total of 362 citations. Following screening of the titles and abstracts, 305 citations were excluded and 57 full-text articles were retrieved. An additional 19 reports were identified from other sources. Three published papers[37-39] describing two unique studies addressing r/r B-cell ALL were retrieved and used for data extraction — one for ELIANA[37] and two for B2101J.[38,39] For ENSIGN, no full-text publication was identified.[33] One unique study[40] published in full for r/r DLBCL was retrieved and used for data extraction. Additional reports were identified from eligible studies, but were not relevant to data extraction as they contained either duplicate or less recent data. The grey literature search identified three relevant clinical practice guidelines for CAR T-cell therapies; two were for patients with ALL[13,41] and one was for patients with DLBCL.[42]

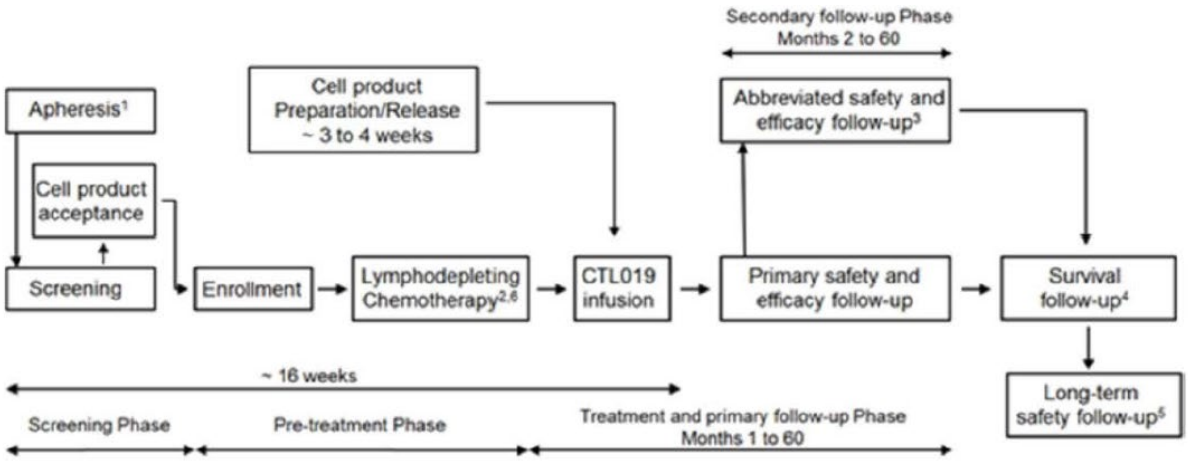
Thus, in all, 12 reports[13,32-42] comprising four CSRs, one clinical summary, four full-text published articles, and three clinical practice guidelines were included in this clinical review. For r/r B-cell ALL, there were three CSRs (one each for three primary studies), a clinical summary of three primary studies, three articles published in full, and two clinical practice guidelines. For r/r DLBCL, there was one CSR for one primary study, one full-text article published in full, and one clinical practice guideline.

Study Characteristics

Acute Lymphoblastic Leukemia

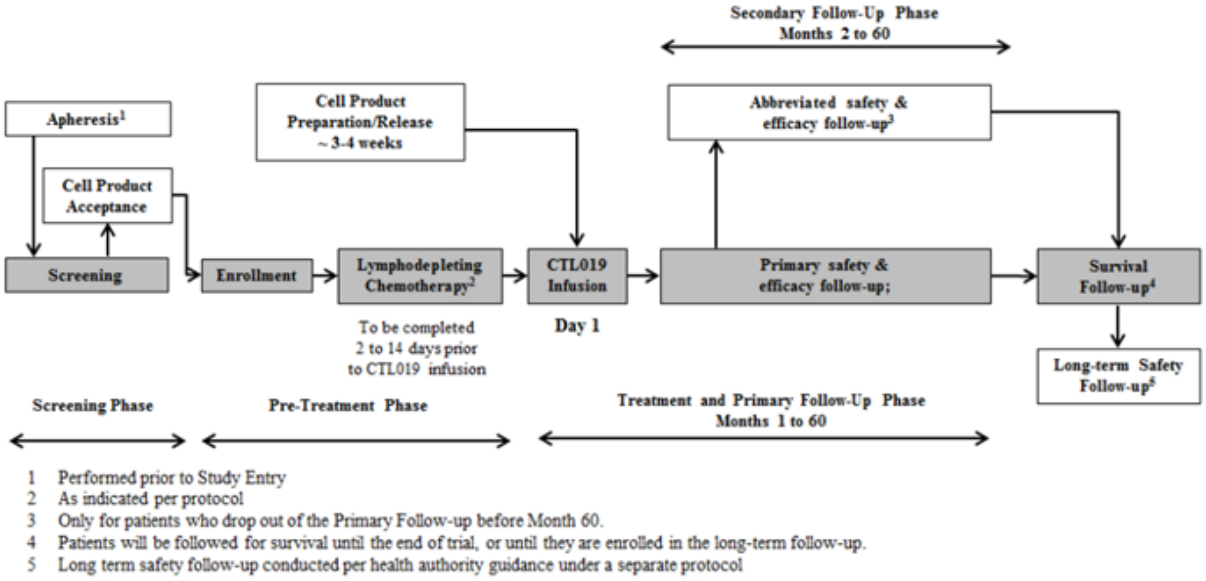
One pivotal study (ELIANA) and two supporting studies (ENSIGN and Study B2101J) were identified that examined the efficacy and safety of tisagenlecleucel in children and young adults with r/r B-cell ALL. ELIANA and ENSIGN are ongoing phase II, multi-centre, single-arm, open-label studies. ELIANA is a global study with 25 study sites across 11 countries (including Canada, with two sites); whereas, ENSIGN has nine study sites, all in the US. Study B2101J is an ongoing, phase I/IIa, single-centre study conducted in the US. The literature search identified several full-text articles and/or abstracts for all the studies, with publication years ranging from 2013 to 2018. However, the information submitted by manufacturer was the primary source of information for this HTA because it contained unpublished, updated data and details that were not available in the published articles and abstract. The study designs are shown in Figure 2.

Figure 2: Study Design of the Phase II ELIANA Trial



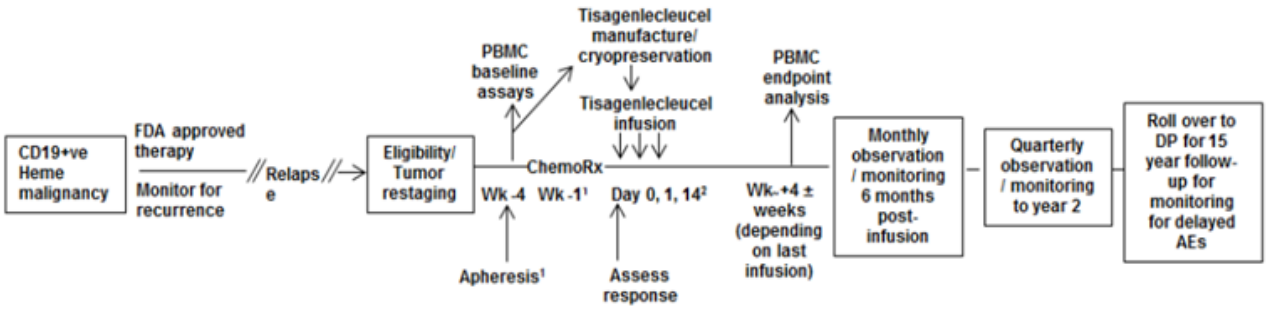
CTL019 = tisagenlecleucel.
[1] Performed prior to study entry.
[2] As indicated per protocol.
[3] Only for patients who drop out of the primary follow-up before month 60.
[4] Long-term safety follow-up conducted per health authority guidance, under a separate protocol.
[5] To be completed 2 to 14 days prior to tisagenlecleucel infusion.
Source: FDA Statistical Review (p. 9).[43]

Figure 3: Study Design of the Phase II ENSIGN Trial



CTL019 = tisagenlecleucel.
[a] Performed prior to study entry.
[b] As indicated per protocol.
[c] Only for patients who drop out of the primary follow-up before month 60.
[d] Patients will be followed for survival until the end of the trial or until enrolled in the long-term follow-up.
[e] Long-term safety follow-up conducted per health authority guidance under a separate protocol.
Source: European Medicines Agency.[24]

Figure 4: Study Design of the Phase I/IIa B2101J Trial



AEs: Adverse events; DP: Destination protocol; FDA: Food and Drug Administration; PBMC: Peripheral blood mononuclear cells; Wk: Week.
[1] If required
[2] Day 14 is tentative based on response to prior infusions

AE = adverse event; DP = destination protocol; PBMC = peripheral blood mononuclear cells; wk = week.
[a] If required.
[b] Day 14 is tentative based on response to prior infusions.
Source: FDA Oncologic Drugs Advisory Committee Briefing Document.[44]

Table 2: Characteristics of Included Studies

		ELIANA (N = 79)	ENSIGN (N = 58)	B2101J (N = 56)[a]
Designs and Populations	**Study design**	A phase II, single-arm, open-label, multi-centre, global trial	A phase II, single-arm, open-label, multi-centre trial	A phase I/IIa, single-arm, open-label, single-centre trial
	Locations	11 countries (Australia, Austria, Belgium, Canada, France, Germany Italy, Norway, Japan, Spain, US)	US	US
	Inclusion criteria	To be eligible for participation in the study, patients had to be ≥ 3 years of age at screening and ≤ 21 years of age at diagnosis and have ≥ 5% lymphoblasts in BM at screening. Other criteria included, but were not limited to: • Life expectancy > 12 weeks • Adequate organ function • Karnofsky or Lansky (for age ≥ 16 years or < 16 years, respectively) performance status ≥ 50 at screening • ≥ Second BM relapse or any BM relapse after SCT and ≥ 6 months from SCT at the time of infusion • Primary refractory as defined by not achieving a CR after two cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after one cycle of standard chemotherapy for relapsed leukemia • For relapse patients, documentation of CD19 tumour expression in BM or peripheral blood by flow cytometry within three months of study entry		• Eligible diseases: CD19 + leukemia or lymphoma • Age 1 year to 24 years. Patients aged 22 to 24 were enrolled only if they were treated at CHOP or another pediatric facility/oncologist at the time of enrolment. • Expected survival > 12 weeks • Patients with CNS3 disease were eligible if CNS disease was responsive to therapy.
	Exclusion criteria	Patients were excluded if they had: • Previously received anti-CD19 therapy or treatment with any gene therapy product • Isolated extra-medullary disease relapse • A concomitant genetic syndrome, such as Faconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known BM failure syndrome • Presence of grade 2 to grade 4 extensive chronic GVHD • Active or latent HBV, HCV, or any uncontrolled infection at screening		• Pregnant or lactating women • Female study participants of reproductive potential must have had a negative serum or urine pregnancy test performed within 48 hours of infusion • Uncontrolled active infection • Active hepatitis B or hepatitis C infection • CNS3 disease that is progressive on therapy, or with CNS parenchymal lesions that might increase the risk of CNS toxicity
Intervention	Intervention	Tisagenlecleucel administered as a single infusion of transduced viable T cells per kg body weight at a dose of 2.0 to 5.0 × 10^6 cells/kg for patients ≤ 50 kg and 1.0 to 2.5 × 10^8 cells for those > 50 kg. Median (range) weight-adjusted dose was 3.1 × 10^6 (0.2 to 5.4 ×10^6).	Tisagenlecleucel administered as a single infusion at a target dose of 2.0 to 5.0 ×10^6 cells/kg for ≤ 50 kg and 1.0 to 2.5 × 10^8 cells for > 50 kg. The median weight-adjusted dose was 1.20 × 10^8 (range was not reported).	Tisagenlecleucel administered as a total dose of 1.5 × 10^7 to 5 × 10^9 (0.3 × 10^6 to 1.0 × 10^8/kg) CAR-positive viable T cells was infused. 10% dose on day 0, 30% dose on day 14, possibly followed by 60% dose on day 28.

		ELIANA (N = 79)	ENSIGN (N = 58)	B2101J (N = 56)[a]
Duration	**Phase**			
	Run-in, for safety observation and stabilizing chemotherapy, if needed, median (range), weeks	[redacted]	[redacted]	[redacted]
	Time (months) from infusion to data cut-off date, median (range)	13.1 (2.1 to 23.5)	19.6 (NR)	NR
	Follow-up (months), median (range)	[redacted]	[redacted]	[redacted]
Outcome	**Primary end point**	ORR (defined as CR + CRi) > 20% by three months after tisagenlecleucel infusion as assessed by IRC	ORR (defined as CR + CRi) by six months after infusion (maintained at two evaluations ≥ 28 days apart post-CTL019 infusion) as determined by IRC	The safety and feasibility of tisagenlecleucel administration
	Other end points	Key secondary end points: • ORR during the three months after infusion in patients treated with tisagenlecleucel from the US manufacturing facility • BOR of CR or CRi with MRD-negative BM among all patients infused with tisagenlecleucel from both the US and German facilities • Percentage of patients who achieve a BOR of CR or CRi with an MRD-negative BM among all patients who receive tisagenlecleucel from the US manufacturing facility Other secondary (exploratory) end points: • CR and CRi as determined by IRC assessment • Percentage of patients who achieve CR or CRi at month 6 without SCT between the tisagenlecleucel infusion and month 6 response assessment • Percentage of patients who achieve CR or CRi and then proceed to SCT while in remission before the month 6 response assessment • DOR, RFS, EFS, OS • HRQoL • Safety results: all-cause mortality, AEs, SAEs, and WDAEs	• Remission with MRD-negative bone marrow in patients infused with tisagenlecleucel • CR or CRi at month 6 without allogeneic SCT between tisagenlecleucel infusion and month 6 response assessment • CR or CRi, then proceed to allogeneic SCT while in remission before month 6 response assessment; DOR, EFS, OS, and day 28 disease response	• Antitumour response • Assessment of cellular or humoral host immunity against the murine anti-CD29 • Safety and efficacy in the CNS3 group

		ELIANA (N = 79)	ENSIGN (N = 58)	B2101J (N = 56)[a]
NOTES	**Publications**	• Maude et al. 2018[37]	• Maude et al. 2016 (abstract)[45] • Maude at al. 2018 (abstract)[46]	• Fitzgerald et al. 2017[39] • Maude et al. 2014[38]

AE = adverse event; ALL = acute lymphoblastic leukemia; BM = bone marrow; BOR = best overall response; CHOP = Children's Hospital of Philadelphia; CNS = central nervous system; CNS3 = active CNS involvement by malignancy; CR = complete remission; CRi = complete remission with incomplete blood count recovery; DOR = duration of remission; EFS = event-free survival; GVHD = graft versus host disease, HRQoL = health-related quality of life; HVB = hepatitis B infection; HVC = hepatitis C infection; IRC = independent review committee; MRD = minimal residual disease; NR = not reported; ORR = overall remission rate; OS = overall survival; RFS = relapse-free survival; SAE serious adverse event; SCT = stem cell transplant; WDAE = withdrawal due to adverse event.

[a] 62 of 73 enrolled patients were treated with tisagenlecleucel at the data cut-off date (January 30, 2017). Of the 62 treated patients, 56 were non-CNS3 ALL patients, four had CNS3 ALL, and two had lymphoma.[24] However, the reported analysis and study outcomes were based only on the 56 non-CNS3 patients.

Sources: Manufacturer Clinical Summary and CSRs B2202, B2205J, and B2101J); European Medicines Agency.[24,32-34]

Population

The inclusion criteria for ELIANA and ENSIGN were similar. The age of eligibility to participate in ELIANA and ENSIGN ranged between three years and 25 years; patients had to have one of the following inclusion criteria: refractory disease, relapsed disease after two or more lines of therapy, relapsed after allogeneic SCT, or ineligible for allogeneic SCT.

Patients with r/r B-cell ALL were considered ineligible for allogeneic SCT if they:

- Had comorbidities or other contraindications (such as failing to achieve complete response [CR] or relapsing before being able to proceed to allogeneic SCT)
- Had prior allogeneic SCT or lack of suitable donor
- Chose not to have allogeneic SCT

Other eligibility criteria included bone marrow with ≥ 5% lymphoblasts by morphologic assessment, evaluable CD19 tumour expression (in relapsed patients), adequate organ function, Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status scores ≥ 50, and life expectancy of more than 12 weeks.

Patients were excluded from ELIANA and ENSIGN if they had isolated extra-medullar disease relapse, concomitant genetic syndromes associated with bone marrow failure, Burkitt lymphoma or leukemia, prior malignancy (excluding carcinoma in situ of the skin or cervix treated with curative intent and with no evidence of active disease), or if they had previously received treatment with any anti-CD19 or gene therapy.

For the most part, the inclusion and exclusion criteria of the B2101J study were similar to those of ELIANA and ENSIGN. The key exceptions were that patients with prior CD19 targeted therapy, patients positive or negative for minimum residual disease (MRD), and patients with either CNS3 (CNS involvement in malignancy) or non-CNS3 disease were permitted to participate in the B2101J study. [redacted]

At baseline, the median age of patients in ELIANA was 11 years (range: 3.0 years to 24.0 years). The majority were white (73.4%) and male (57%). Most of the patients (92.4%) had

relapsed B-cell ALL with no detectable blast cells in cerebrospinal fluid samples (i.e., CNS-1 patients = 84%) and no extramedullary disease (85.3%). The Karnofsky/Lansky performance status for the majority ([redacted]) was ≥ 80%, indicating that at worst, patients could engage in normal activity with effort (Karnofsky)[47] or were restricted in strenuous play and tired more easily, but were otherwise active (Lansky).[47] The patients had a median of three previous lines of therapy; 60.8% received hematopoietic SCT.

ENSIGN had more female (53.4%) than male (46.6%) patients at baseline, but otherwise had demographics similar to ELIANA, with a median patient age of 12.0 years (range: 3.0 years to 25.0 years) and a majority of white patients ([redacted]). The disease condition of patients in ENSIGN was similar to those in ELIANA, with most being relapsed B-cell ALL (91.4%), CNS-1 patients (87.9%), [redacted] Patients in ENSIGN also had a treatment history similar to those in ELIANA, with a median of three previous lines of therapy and 44.8% of patients with prior SCT.

The median age of patients in Study B2101J was 10.5 years (range: 1.0 years to 24.0 years); the majority were white ([redacted]) and male ([redacted]). [redacted]; most had relapsed B-cell ALL ([redacted]), [redacted]. [redacted] The baseline characteristics of patients enrolled in the three studies are reported in Appendix 6: Additional Data – Relapsed or Refractory B-Cell .

Patient Disposition

In all three studies, the investigators were obligated to withdraw any patient about whom they had reason to believe continuation would be detrimental. Patients could voluntarily withdraw from the study for any reason at any time, and could be considered withdrawn if they stated an intention to withdraw or became lost to follow-up for any other reason. The proportions of enrolled patients who discontinued or withdrew before treatment with tisagenlecleucel were [redacted], [redacted], and [redacted] in ELIANA, ENSIGN, and B2101J, respectively. The overall patient disposition of enrolled patients is summarized in Table 3.

Table 3: Patient Disposition – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

	ELIANA[a] n (%)	ENSIGN[b] n (%)	B2101J[c] n (%)	ELIANA (Data Cut-Off Date: April 25, 2017)
Patients enrolled	[redacted]	[redacted]	[redacted]	92 (100)
Discontinued before infusion				
Overall	[redacted]	[redacted]	[redacted]	17 (18.5)
Reasons for discontinuation				
• Production failure	[redacted]	[redacted]	[redacted]	7 (7.6)
• Progressive disease	[redacted]	[redacted]	[redacted]	NA
• Death	[redacted]	[redacted]	[redacted]	7 (7.6)
• AEs	[redacted]	[redacted]	[redacted]	3 (3.3)
• Others	[redacted]	[redacted]	[redacted]	NA
Patients treated	[redacted]	[redacted]	[redacted]	75 (81.5)
Tisagenlecleucel infusion pending	[redacted]	[redacted]	[redacted]	0 (0)

	ELIANA[a] n (%)	ENSIGN[b] n (%)	B2101J[c] n (%)	ELIANA (Data Cut-Off Date: April 25, 2017)
Discontinued treatment and primary follow-up phase				
Overall	[redacted]	[redacted]	[redacted]	27 (29.3)
Reasons for discontinuation				
• Lack of efficacy	[redacted]	[redacted]	[redacted]	9 (9.8)
• New therapy	[redacted]	[redacted]	[redacted]	5 (5.4)
• Death	[redacted]	[redacted]	[redacted]	11 (12.0)
• Patient or guardian decision	[redacted]	[redacted]	[redacted]	2 (2.2)
Analyses sets				
Enrolment set	[redacted]	[redacted]	[redacted]	92
EAS	[redacted]	[redacted]	[redacted]	NR
FAS	[redacted]	[redacted]	[redacted]	75
PPS	[redacted]	[redacted]	[redacted]	68
Safety set	[redacted]	[redacted]	[redacted]	75

AEs = adverse events; ALL = acute lymphoblastic leukemia; EAS = efficacy analysis set; FAS = full analysis set; N = number of patients as of the data cut-off dates when the discontinuation assessments were done; NR = none reported; PPS = per-protocol set; NA = not applicable.

Notes:

- In ENSIGN, the updated results at the data cut-off date of October 6, 2017 were based on EAS, defined as all patients treated with tisagenlecleucel at least 6 months prior to the clinical data cut-off.
- The enrolled set comprised all patients who were enrolled in the study. The enrolment date was defined as the point at which the patient met all inclusion or exclusion criteria and the patients' leukapheresis product was received and accepted by the manufacturing facility.
- The FAS comprised all patients who received infusion of tisagenlecleucel.
- The PPS consisted of a subset of the patients in the FAS who were compliant with the major requirements of the clinical study protocol.
- The safety set comprised all patients who received infusion of tisagenlecleucel.

[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]

[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]

[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Source: European Medicines Agency.[24]

Intervention

In all three r/r B-cell ALL studies (ELIANA, ENSIGN, B2101J), tisagenlecleucel was the only intervention; there were no comparator arms.[35] In ELIANA, cells were manufactured at the Morris Plains Facility in the US and at the Fraunhofer-Institut für Zelltherapie und Immunologie, Leipzig in Germany. In ENSIGN, cells were manufactured at the University of Pennsylvania and the Morris Plains facility; in Study B2101J, they were manufactured at the University of Pennsylvania. It was recommended that the time between thawing the cryopreserved tisagenlecleucel received from the manufacturing facility and completing the infusion not exceed 30 minutes in order to maintain maximum product viability. In both the ELIANA and ENSIGN studies, tisagenlecleucel was administered as a single IV infusion, whereas Study B2101J allowed multiple infusions. Most of the patients treated with tisagenlecleucel in all three studies underwent lymphodepleting chemotherapy before treatment.

In ELIANA, [redacted] of patients in the full analysis set (FAS) as of the December 31, 2017 data cut-off date of received lymphodepleting chemotherapy with cyclophosphamide and fludarabine.[35] Each tisagenlecleucel infusion bag contained a cell dose of 0.2 to 5.0 × 10^6 CAR-positive viable T cells per kilogram (kg) body weight for patients ≤ 50 kg, or 0.1 to 2.5 × 10^8 CAR-positive viable T cells for patients > 50 kg, with volume ranging from 10 mL to

50 mL. The total median dose was 1.0 × 10^8 cells; the median weight-based dose was 3.0 × 10^6 cells/kg body weight.[35] The treatment was administered as either an IV infusion at approximately 10 mL to 20 mL per minute or as an IV push for smaller volumes using a syringe. Appropriate adjustments were made in the rate of infusion for smaller children and smaller volumes. A study physician evaluated patients just prior to infusion to ensure they met the tisagenlecleucel pre-infusion criteria. The patients' vital signs were taken before, during, and immediately after the infusion, then approximately every 15 minutes for one hour, and repeated at two hours. If vital signs were unsatisfactory and unstable, the patient was further monitored until vital sign stabilization. Patients had protective isolation based on institutional standards and policies. Emergency medical equipment was available during each infusion in case the patient had a significant reaction to the infusion, such as anaphylaxis or severe hypotension.

In ENSIGN, [redacted] of patients in the FAS had received pre-treatment with lymphodepleting chemotherapy at the interim data cut-off date of February 1, 2016. The most commonly used lymphodepleting chemotherapeutic drugs were cyclophosphamide and fludarabine, received by [redacted] patients.[33] The other lymphodepleting chemotherapy drugs included etoposide and cytarabine.[33] [redacted]

In B2101J, [redacted] of patients in the FAS received pre-treatment lymphodepleting chemotherapy as at the data cut-off date of January 30, 2017. The most commonly used chemotherapeutic drugs were cyclophosphamide ([redacted]), fludarabine ([redacted]), and etoposide ([redacted]). [redacted] The maximum total dose of tisagenlecleucel infused was 1.5 × 10^7 to 5 × 10^9 (0.3 × 10^6 to 1.0 × 10^8/kg) total cells using intra-patient dose escalations of 10%, 30%, and 60% aliquots.[34] The dose distribution in the three studies is summarized in Table 4.

Table 4: Tisagenlecleucel Dose Administration (Safety Set) – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

	ELIANA[a] N = 75	ENSIGN[b] N = 29	B2101J[c] (Non-CNS3 ALL Patients) N = 56	
			Within first 28 days	At any time
Total number of tisagenlecleucel infusion – n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
• 1	75 (100.0)	[redacted]	[redacted]	[redacted]
• 2	NA	[redacted]	[redacted]	[redacted]
• 3			[redacted]	[redacted]
• > 3			[redacted]	[redacted]
Tisagenlecleucel dose categorized*	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Below target dose range	6 (8.0)	[redacted]	[redacted]	[redacted]
Within target dose range	[redacted]	[redacted]		
Above target dose range	[redacted]	[redacted]		
Tisagenlecleucel dose infused (× 10^8 CAR-positive viable T cells)				
Mean (SD)	1.14 (0.60)	[redacted]	[redacted]	[redacted]
Median	1.00	[redacted]	[redacted]	[redacted]
Range	0.03 to 2.60	[redacted]	[redacted]	[redacted]
Weight-adjusted tisagenlecleucel dose infused (10^6 CAR-positive viable T cells/kg)				
Mean (SD)	2.90 (1.17)	[redacted]	[redacted]	[redacted]
Median	3.06	[redacted]	[redacted]	[redacted]
Range	0.2 to 5.4	[redacted]	[redacted]	[redacted]
Total viable cell dose infused (10^8 cells)				
Mean (SD)	5.50 (3.952)	[redacted]	[redacted]	[redacted]
Median	4.65	[redacted]	[redacted]	[redacted]
Range	0.2 to 20.0	[redacted]	[redacted]	[redacted]

CAR = chimeric antigen receptor; CNS3 = CNS involvement in malignancy; N = number of patients evaluated; NA = not applicable; NR = not reported; SD = standard deviation.
Note: The target dose range is 2 to 5 × 10^6 CAR-positive viable T cells/kg for patients ≤ 50 kg, and 1 to 2.5 × 10^8 CAR-positive viable T cells for patients > 50 kg in ELIANA and ENSIGN.
Sources: Maude 2018;[37] European Medicines Agency;[24] information submitted by manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

A list of the most common clinically significant concurrent medications in all three studies taken by patients during tisagenlecleucel therapy, excluding vitamins, herbs, and nutritional supplements, is compared with those in ENSIGN and B2101J in Table 5. A list of therapies that were restricted during the treatment is available in Table 6.

Table 5: Concomitant Medications – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Drug Class	Most Common	ELIANA[a] (%)	ENSIGN[b] (%)	B2101J[c] (%)
Antineoplastic medications used before tisagenlecleucel infusion				
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Concomitant medications by ATC class used post-tisagenlecleucel infusion				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ATC = anatomical therapeutic chemical.

Sources: The manufacturer.

[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]

[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]

[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Table 6: Restricted Therapy in ELIANA, ENSIGN, and B2101J – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Therapy	Time to Complete/Stop Before Tisagenlecleucel Infusion	Comments
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]

CNS = central nervous system; GVHD = graft versus host disease; LD = lymphodepleting.
Sources: The manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Outcome Measures

In ELIANA and ENSIGN, the efficacy of tisagenlecleucel infusion was assessed monthly for the first six months, and will continue quarterly for up to two years and semi-annually for up to five years or until the patient relapses. In addition, semi-annual and annual evaluations will be performed for up to 15 years on all patients under a separate destination protocol, as recommended by health authority guidance for patients treated with gene therapies.

For B2101J, tumour response assessments were done on day 28 after the last infusion of tisagenlecleucel. Monthly evaluations were done for up to six months after tisagenlecleucel

infusions, and will continue quarterly for up to two years after infusion, or until the patient requires alternative therapy. Patients will continue to be followed and evaluated annually for up to 15 years as recommended by the FDA for protocols utilizing integrating viral vectors.

The outcomes of interest for this review are specified in Table 1. Efficacy outcome measures include the overall remission rate (ORR), CR, OS, relapse-free survival (RFS), event-free survival (EFS), and health-related quality of life (HRQoL). Other efficacy outcomes, such as best overall response (BOR) and MRD, which were not listed in the SR protocol but may provide useful insight, are reported in Appendix 6: Additional Data – Relapsed or Refractory B-Cell .

Overall Remission Rate

The ORR is defined as the sum of CR and CR with incomplete blood recovery (CRi).

Time-to-Event End Points

The time-to-event end points (duration of response [DOR]/RFS, EFS, and OS) were analyzed using the Kaplan–Meier method. The EFS refers to the time from the date of first tisagenlecleucel infusion to the earliest date of death due to any cause after remission, relapse, or treatment failure. The RFS was measured as the time from when a patient achieved CR or CRi, whatever occurred first, to relapse or death due to any cause during CR or CRi. The OS was the time from the date of first tisagenlecleucel infusion to the date of death due to any reason. In case a patient did not have an event or death due to any cause prior to data cut-off, the data were censored at the date of the last adequate disease assessment on or before the earliest censoring event (except for SCT). The censoring rules for the EFS and RFS end points were:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- New anticancer therapy
- Adequate assessment no longer available
- Event after at least two missing scheduled disease assessments

For OS, patients not known to have died at the data cut-off date were censored at their last contact date, which was defined as the latest date they were known to be alive. Patients were also followed up for survival if they had received an SCT. As a sensitivity analysis, the OS Kaplan–Meier analysis was censored for SCT.

The definitions of outcome measures are summarized in Table 7.

Table 7: Definition of Selected Efficacy Measures in ELIANA, ENSIGN, and B2101J – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Outcome Measure	Assessment Criteria
Overall remission rate	CR + CRi
Event-free survival	The time from the date of first tisagenlecleucel infusion to the earliest date of death due to any cause after remission, relapse, or treatment failure
Relapse-free survival	The time from when a patient achieved CR or CRi, whatever occurred first, to relapse or death due to any cause during CR or CRi
Complete remission	1. Bone marrow < 5% blasts 2. Peripheral blood • Neutrophils > 1.0 × 10^9/L • Platelets > 100 × 10^9/L • Circulating blasts < 1% 3. Extramedullary disease • No clinical evidence of extramedullary disease (by physical exam and central nervous system symptom assessment), and • If additional assessments (e.g., cerebrospinal fluid assessment by lumbar puncture, nervous system symptom imaging, biopsy) are performed, results must show remission status 4. Transfusion independency • No platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment
Complete remission with incomplete blood count recovery	All criteria for CR as defined above are met, except that the following exist • Neutrophils ≤ 1.0 × 10^9/L, and/or • Platelets ≤ 100 × 10^9/L, and/or • Platelet and/or neutrophil transfusions less than or equal to 7 days before peripheral blood sample for disease assessment
Relapsed disease	Applies only in patients with a CR or CRi and who have • Reappearance of blasts in the blood (≥ 1%), • Reappearance of blasts in bone marrow (≥ 5%), or • Appearance/reappearance of any extramedullary disease after CR or CRi
Health-related quality of life	As measured by • PedsQL • EQ VAS
The following were not in the systematic review protocol, but may provide additional useful information	
Best overall response	CR or CRi
MRD-negative	MRD in bone marrow as assessed by flow cytometry < 0.01%
No response	Failure to attain the criteria needed for any response categories or relapse

CR = complete remission; CRi = complete remission with incomplete blood count recovery; EQ VAS = EuroQol Visual Analogue Scale; MRD = minimal residual disease; PedsQL = Pediatric Quality of Life Inventory.
Sources: The manufacturer:
[a] ELIANA—CSR; (data cut-off August 7, 2016).[32]
[b] ENSIGN—CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

The primary efficacy outcome in the ELIANA and ENSIGN studies was ORR as assessed by an independent review committee (IRC) within three months and six months of tisagenlecleucel infusion, respectively. In Study B2101J, the safety, feasibility of administering tisagenlecleucel, and persistence of tisagenlecleucel after infusion were the primary end points. Efficacy outcomes, including ORR at day 28 as assessed by local

investigator, were secondary end points. The feasibility of administering tisagenlecleucel and persistence of tisagenlecleucel after infusion were not included in our protocol and were not extracted. Other secondary outcomes of interest in ELIANA, ENSIGN, and B2101J included EFS, RFS, and OS. ELIANA also reported HRQoL and hospitalization outcomes.

Health-Related Quality of Life

The pivotal ELIANA study was the only one of the three included studies that evaluated patient-reported HRQoL. The results of the Pediatric Quality of Life Inventory (PedsQL) and EuroQol Visual Analogue Scale (EQ VAS) questionnaires were reported for the subgroup of patients eight years or older at baseline that achieved CR or CRi within three months of tisagenlecleucel infusion and remained evaluable for post-baseline HRQoL assessments from three months onwards. Most patients who did not achieve CR or CRi had discontinued at an earlier date; thus, they did not qualify for HRQoL assessment. Thus, the HRQoL is reported only for a subgroup of patients aged eight years and older at baseline who achieved CR or CRi within three months (n = 50) of tisagenlecleucel infusion. The number of evaluable patients declined progressively over the evaluation time points and was lowest at the 12-month assessments at the time of the data cut-off for both the PedsQL and EQ-5D. The investigators did not provide a reason for the smaller number of patients at the successive HRQoL assessments. Therefore, it is unknown whether the numbers decreased because patients were lost to follow-up or because they had not yet been followed long enough at the time of assessment (for instance, patients who had not been followed for 12 months yet would not have 12-month HRQoL scores). Descriptions of the PedsQL and EQ VAS and their psychometric properties are provided in Appendix 8: Validity of HRQoL Instruments.

Resource Utilization

The pivotal ELIANA study was the only one among the three included studies that assessed resource utilization data regarding hospitalization. Issues of interest included the length of hospital stay, hospital ward facilities used (e.g., emergency department, intensive care unit [ICU], general ward), and reasons for hospitalization as they related to the tisagenlecleucel treatment regimen. Hospitalizations were not reported if they were for any of the following reasons:

- Elective or preplanned treatment for a pre-existing condition that was unrelated to the indication under study and had not worsened since signing the informed consent form.
- Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Treatments occurring on an emergency outpatient basis that did not result in hospital admission and involved an event not fulfilling any of the definitions of a serious adverse event (SAE) in the study.

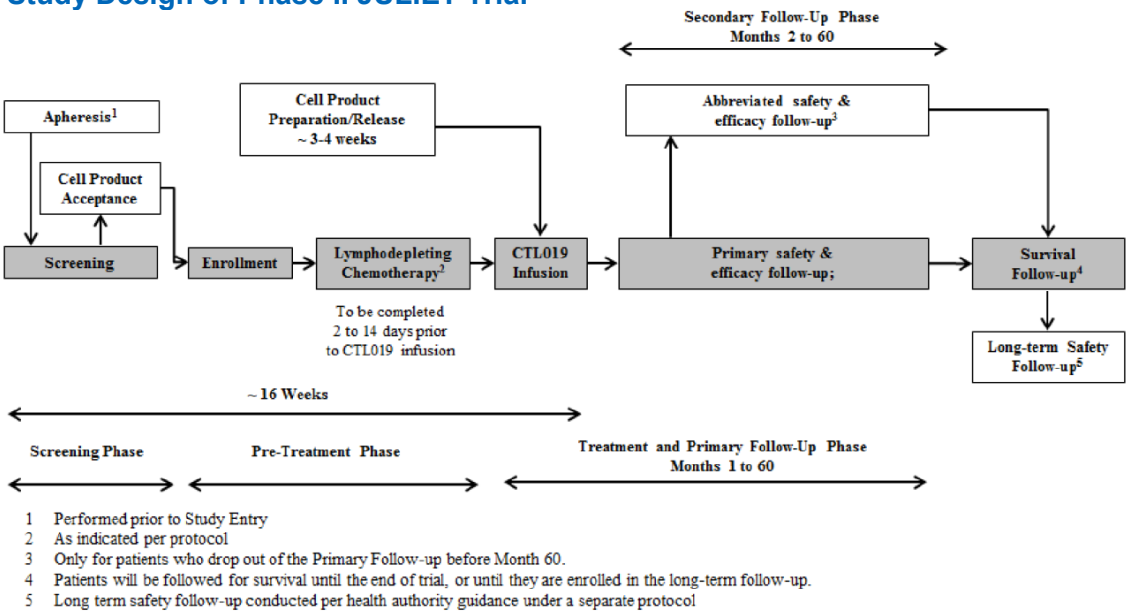
Safety

The included studies reported AEs using the Medical Dictionary for Regulatory Activities (MedDRA) and the Common Terminology Criteria for Adverse Events (CTCAE), except for CRS, which was graded by a protocol-defined scoring scheme. ELIANA and ENSIGN used MedDRA version 20.0 and CTCAE version 4.03, whereas B2101J used MedDRA version 19.1 and CTCAE version 3.0. Safety was assessed as the proportion of patients reporting AEs, SAEs, CRS and deaths. Treatment-emergent adverse events (TEAEs) were reported for lymphodepleting chemotherapy and after tisagenlecleucel infusion. The investigators in the three included studies also reported AEs of special interest (AESIs), many of which align with the AEs specified in the protocol for this SR. The criteria for AESIs were based on limited experience from ongoing clinical studies without an accurate assessment of causality. AESIs included CRS, febrile neutropenia, hematopoietic cytopenias not resolved by day 28, infections, neurological events, and tumour lysis syndrome.

Diffuse Large B-Cell Lymphoma

JULIET was the pivotal study that examined the efficacy and safety of tisagenlecleucel (CTL019) in adults with r/r DLBCL (Table 8).[36] This study was a phase II, single-arm, open-label, multi-centre investigation conducted in 27 centres across 10 countries (i.e., US, Canada, Austria, Germany, Italy, France, the Netherlands, Australia, Norway, and Japan). The tisagenlecleucel cells were manufactured in two sites: a US manufacturing facility in Morris Plains, New Jersey and the Fraunhofer-Institut für Zelltherapie und Immunologie, a manufacturing facility in Leipzig, Germany. Patients who were infused with cells manufactured in the US are referred to as the Main Cohort (N = 95) and comprise the primary study population for efficacy outcomes. Patients who were infused with cells manufactured in Germany are referred to as Cohort A (N = 16) and are included in the secondary efficacy analyses. The Main Cohort and Cohort A were combined in safety analyses. Follow-up is ongoing for up to five years post-tisagenlecleucel infusion (with a median follow-up of 13.9 months completed at the last data cut-off of December 8, 2017). Based on the recommendation of the FDA for gene therapies that utilize integrating viral vectors, patients will be followed through semi-annual and annual safety assessments in a separate long-term extension follow-up protocol for 15 years post-infusion (Study CCTL019B2401).[36] Patients who discontinued the study before month 60 will continue to be followed for safety assessments. The study design of JULIET is depicted in Figure 5.

Figure 5: Study Design of Phase II JULIET Trial



CTL019 = tisagenlecleucel.
[a] Performed prior to study entry.
[b] As indicated per protocol.
[c] Only for patients who drop out of the primary follow-up before month 60.
[d] Patients will be followed for survival until the end of trial or until enrolled in the long-term follow-up.
[e] Long-term safety follow-up conducted per health authority guidance under a separate protocol.
Source: European Medicines Agency.[24]

The supporting study for patients with r/r DLBCL was A2101J, a phase IIa, single-arm, open-label, single-centre study conducted at the University of Pennsylvania in the US.[40] This study enrolled adult patients with DLBCL and follicular lymphoma (N = 28 infused); 14 infused patients had DLBCL. The primary efficacy end point and selected secondary end points were provided separately for patients with DLBCL; however, safety analyses were reported for DLBCL and follicular lymphoma combined. The study included a screening phase, an intervention phase of apheresis, chemotherapy, and infusion of CTL019 cells followed by tumour collection and follow-up. Patients were followed for a median of 28.6 months until the last data cut-off of May 7, 2017. Follow-up will continue with twice yearly assessments from years two to five years, then annually for up to 15 years post-infusion.

Table 8: Characteristics of Included Studies – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

		JULIET: C2201 (N = 111)	A2101J (N = 28, 14 DLBCL + 14 FL)
Designs and Populations	**Study design**	Single-arm, multi-centre, open-label, prospective study (phase II)	Single-arm, single-centre, open-label, prospective study (phase IIa)
	Locations	27 study centres in 10 countries: US (12 centres), Canada (2 centres), Austria (1 centre), Germany (2 centres), Italy (1 centre), France (1 centre), Netherlands (1 centre), Australia (2 centres), Norway (1 centre), Japan (2 centres) Tisagenlecleucel cells were manufactured at 2 sites, one in the US (Main Cohort) and one in Germany (Cohort A).	US (University of Pennsylvania)
	Inclusion criteria	• ≥ 18 years with r/r DLBCL that had progressed after receiving 2 or more lines of chemotherapy (including rituximab and anthracycline) • Histologically confirmed DLBCL at last relapse (by central pathology review before enrolment) • Ineligible for, failed, or not consenting to autologous SCT • Measurable disease at time of enrolment • Life expectancy ≥ 12 weeks • ECOG performance status of 0 or 1 at screening • Adequate organ function (renal and liver) • Minimum level of pulmonary reserve defined as ≤ grade 1 dyspnea and pulse oxygenation > 91% on room air • Hemodynamically stable and LVEF ≥ 45% • Adequate bone marrow reserve without transfusions • An apheresis product of non-mobilized cells accepted for manufacturing	• Adults (≥ 18 years) with CD19+ B-cell lymphomas with no curative treatment options • Limited prognosis (< 2 years survival); however, expected survival > 12 weeks • Creatinine < 1.6 mg/dL; ALT/AST < 3 x upper limit of normal; bilirubin < 2.0 mg/dL, unless patient has Gilbert's Syndrome (< 3.0 mg/dL) • Any relapse after prior autologous SCT • Relapsed disease after prior allogeneic SCT if: experienced graft rejection, no active GVHD, and requires no immunosuppression; > 6 months from transplant • Measurable or assessable disease • ECOG performance status of 0 or 1 DLBCL-specific inclusion criteria: • Residual disease after primary therapy and not eligible for autologous SCT • Relapsed or persistent disease after prior autologous SCT • Beyond first CR with relapsed or persistent disease and not eligible or appropriate for conventional allogeneic or autologous SCT
	Exclusion criteria	• T-cell rich or histiocyte-rich large B-cell lymphoma, primary cutaneous large B-cell lymphoma, primary mediastinal B-cell lymphoma, Epstein-Barr virus-positive, DLBCL of the elderly, Richter's transformation, and Burkitt lymphoma • Previous or concurrent malignancy (except for adequately treated basal cell or squamous cell carcinoma, in situ carcinoma of the cervix or breast treated curatively, or a primary malignancy that has been completely resected and in complete remission for ≥ 5 years) • Active CNS involvement by malignancy • Active neurological autoimmune or inflammatory disorders (e.g., Guillain-Barré	• Complete remission with no evidence of disease • Active CNS involvement by malignancy; prior CNS disease effectively treated was eligible provided that treatment was > 4 weeks before enrolment • Concurrent use of systemic steroids (not including inhaled corticosteroids) • Active hepatitis B or hepatitis C infection • HIV infection • Uncontrolled active infection • Any uncontrolled active medical disorder that precluded participation • Pregnant or lactating women

		JULIET: C2201 (N = 111)	A2101J (N = 28, 14 DLBCL + 14 FL)
		Syndrome, AML) • Prior treatment with any anti-CD19/anti-CD3 therapy or any other anti-CD19 therapy • Prior treatment with any gene therapy product • Prior treatment with any adoptive T-cell therapy • Prior allogeneic SCT • Prior radiation therapy within 2 weeks of infusion • Investigational medicinal product within the last 30 days prior to screening • Use of the following medications: therapeutic doses of steroids stopped > 72 hours prior to leukapheresis and tisagenlecleucel infusion; immunosuppressive medications (including check point inhibitors) stopped ≥ 2 weeks prior to leukapheresis and tisagenlecleucel infusion; antiproliferative therapies other than LD chemotherapy within 2 weeks of leukapheresis and 2 weeks prior to infusion; antibody use (including anti-CD20) within 4 weeks prior to infusion or 5 half-lives of the antibody, whichever is longer; CNS disease prophylaxis (e.g., intrathecal MTX) stopped > 1 week prior to tisagenlecleucel infusion • Eligible for and consenting to autologous SCT • Active replication of or prior infection with hepatitis B or active hepatitis C • HIV-positive • Uncontrolled, acute, life-threatening bacterial, viral, or fungal infection • Unstable angina and/or MI within 6 months prior to screening; uncontrolled cardiac arrhythmia • Pregnant or lactating women • Intolerance to excipients of tisagenlecleucel cell product	
INTERVENTION	**Intervention[a]**	Tisagenlecleucel (CTL019): single IV infusion Administered: median (range) × 10^8 cells; 3.1 (0.1 to 6.0)	Tisagenlecleucel (CTL019): single IV infusion Administered: median (range) × 10^8 cells; 5.0 (1.79 to 5.0) Administered (per kg body weight): median (range) × 10^6 cells; 5.79 (3.08 to 8.87)
	Comparator(s)	NA	NA

		JULIET: C2201 (N = 111)	A2101J (N = 28, 14 DLBCL + 14 FL)
Duration	**Follow-up**	Median (months): 13.9	Median (months): 28.6
Outcomes	**Primary end point**	ORsR (CR + PR) at 3 months (90 days) per IRC in the EAS of the Main Cohort[b]	ORsR at 3 months and response rate according to NHL subtype[c]
	Other end points	Duration of response Time to response PFS EFS Overall survival HRQoL Safety	CR PFS Duration of response Median survival time Probability of survival Safety
Notes	**Publications**	Maziarz RT et al. Blood 2017; 130:5215 (abstract) Borchmann P. et al. EHA 2018;214521 (abstract)	Schuster SJ et al. NEJM 2017; 377;26:2545-54

ALT = alanine aminotransferase; AML = amyotrophic lateral sclerosis; AST = aspartate aminotransferase; CNS = central nervous system; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EAS = efficacy analysis set; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EHA = European Hematology Association; FL = follicular lymphoma; GVHD = graft versus host disease; HRQoL = health-related quality of life; IRC = independent review committee; LD = lymphodepleting; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MTX = methotrexate; NA = not applicable; NHL = non-Hodgkin lymphoma; NR = not reported; ORsR = overall response rate; PFS = progression-free survival; PR = partial response; r/r DLBCL = relapsed/refractory diffuse large B-cell lymphoma; SCT = stem cell transplant.

[a] Lymphodepleting chemotherapy was administered within one week prior to tisagenlecleucel infusion unless WBC count was ≤ 1,000 cells /µL. The lymphodepleting regimen consisted of fludarabine and cyclophosphamide, or bendamustine.

[b] The Main Cohort included patients treated with tisagenlecleucel from the US manufacturing facility in Morris Plains, New Jersey. The FAS included all patients who received an infusion of tisagenlecleucel (95 patients in the Main Cohort).

[c] In this review, results for DLBCL have been presented separately, wherever available.

Sources: The manufacturer (CSRs, JULIET – March 8, 2017 and December 8, 2017 data cut-off dates); Schuster SJ et al. NEJM 2017; 377;26:2545-54; European Medicines Agency.[24,36,40,48]

Population

The inclusion and exclusion criteria for JULIET and A2101J are detailed in Table 8. Baseline characteristics are in Table 9.

JULIET included adults 18 years of age or older with r/r DLBCL who had progressed after receiving two or more lines of chemotherapy, including rituximab and an anthracycline. The Main Cohort (N = 95) included patients who were infused with cells manufactured from the US manufacturing facility. Cohort A (N = 16) included patients infused with cells from Germany. The primary efficacy outcome was based on patients in the Main Cohort who had been followed for at least three months after infusion (i.e., the efficacy analysis set [EAS] of the Main Cohort, N = 93). Safety analyses included all infused patients (i.e., the FAS, N = 111). Patients were required to have failed, to have been ineligible for, to have not consented to autologous SCT. JULIET excluded DLBCL among the elderly, those with active CNS involvement by malignancy, those with prior treatment with any anti-CD19 therapy or gene therapy, and those with prior allogeneic SCT. Patients in the EAS of the Main Cohort ranged from [redacted] and the majority were male ([redacted]), white ([redacted]), with stage IV disease ([redacted]), and an International Prognostic Index (IPI) of 2 or more ([redacted]). The molecular subtype was GCB in [redacted] patients and ABC in [redacted]. Most patients ([redacted]) did not have bone marrow involvement at baseline.

Triple-hit gene mutations (CMYC, BCL2, and BCL6) were present in [redacted] patients, and double-hit mutations (CMYC+BCL2 or CMYC+BCL6) in [redacted]. Prior hematopoietic SCT was administered in [redacted] patients and [redacted] received two to four previous therapies. Baseline characteristics of the FAS of Cohort A and all infused patients are provided Table 47.

The supporting study, A2101J, included adults 18 years of age or older with CD19 + B-cell lymphomas with no curative treatment options and limited prognosis (N = 14 DLBCL patients infused). Patients with any relapse after autologous SCT were considered. In addition, patients who had relapsed after allogeneic SCT were included if there was graft rejection, no active graft versus host disease (GVHD), and no requirement for immunosuppression, and if the transplant occurred more than six months prior to enrolment. The DLBCL-specific inclusion criteria included residual disease after primary therapy and ineligibility for autologous SCT. Patients with active CNS involvement by malignancy were excluded. Tisagenlecleucel was infused in 14 of 23 enrolled patients (60.9%) with DLBCL.

The patient characteristics presented in Table 9 from Study A2101J are for patients with DLBCL who received tisagenlecleucel infusion. Patients ranged in age from 25 years to 77 years (median 58) and the majority were male (78.6%) (Table 9).

Table 9: Baseline Characteristics – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201 (N = 93)[a]	A2101J (N = 14 DLBCL)
Age, median (range), years	57 (22 to 75)	58 (25 to 77)
Male, n (%)	[redacted]	11 (78.6)
Race, n (%)		
White	[redacted]	NR
Asian	[redacted]	NR
Black	[redacted]	NR
Other	[redacted]	NR
Stage (at Study Entry), n (%)		
Stage I	[redacted]	NR
Stage II	[redacted]	NR
Stage III	[redacted]	9 (64.3)[b]
Stage IV	[redacted]	
IPI (at Study Entry)[c], n (%)		
< 2	25 (26.9)	NR
≥ 2	68 (73.1)	NR
Predominant Histology/Cytology, n (%)		
DLBCL	74 (79.6)	NR
Transformed FL	18 (19.4)	NR
Other	1 (1.1)	NR
BM Involvement (at Study Entry), n (%)		
No	[redacted]	11 (78.6)
Yes	[redacted]	3 (21.4)
ECOG Performance Status		
Score, median (range)	NR	1 (0 to 1)
0, n (%)	49 (52.7)	NR
1, n (%)	44 (47.3)	NR

	JULIET: C2201 (N = 93)[a]	A2101J (N = 14 DLBCL)
Molecular Subtype (Cell of Origin)		
GCB, n (%)	50 (53.8)	7 (50.0)
ABC, n (%)	40 (43.0)	NR
Non-germinal centre phenotype	NR	5 (35.7)
Missing/not assessed, n (%)	3 (3.2)	2 (14.3)
Double/Triple Hits in MYC/BCL2/BCL6 genes, n (%)		
CMYC + BCL2 + BCL6	[redacted]	NR
CMYC + BCL2	[redacted]	3 (21.4)[d]
CMYC + BCL6	[redacted]	
Negative	[redacted]	NR
Not done	[redacted]	9 (64.3)
Missing	[redacted]	NA
Treatment History		
Number of previous therapies, median (range)	[redacted]	3 (1 to 8)
• 1 • 2 • 3 • 4 • 5 • 6	[redacted]	NR
Patients with prior HSCT, n (%)	41 (44.1)	7 (50)
Disease Response Status, n (%)		
Refractory to last line	48 (51.6)	12 (86%)
Relapsed to last line	45 (48.4)	NR
Time Since Most Recent Relapse/Progression to Tisagenlecleucel Infusion		
Median (range), months	[redacted]	NR

ABC = activated B-cell type; BM = bone marrow; DLBCL = diffuse large B-cell lymphoma; EAS = efficacy analysis set; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; FL = follicular lymphoma; GCB = germinal centre B-cell type; HSCT = hematopoietic stem cell transplant; IPI = International Prognostic Index; NA = not applicable; NR = not reported.
[a] Patients in the EAS of the Main Cohort.
[b] Stage III or IV.
[c] IPI: (1) Age > 60 years; (2) ECOG performance status ≥ 2; (3) More than one site of extranodal disease; 4) elevated lactate dehydrogenase > upper limit of normal; and 5) stage III/IV disease. IPI factors were summarized by category based on number of questions with "yes" and number of questions with "no."
[d] Classified as double-hit lymphoma; however, genes not specified.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off); Schuster SJ et al. NEJM 2017; 377;26:2545-54.[36,40]

Patient Disposition

In JULIET, a total of 238 patients were screened up to the last data cut-off date of December 8, 2017, of which 165 (69.3%) were enrolled (Table 10). Of those enrolled, 50 (30.3%) did not receive an infusion of tisagenlecleucel; for most of these patients, this occurred due to death ([redacted]), physician decision ([redacted]), or product-related issues (i.e., manufacturing failures) (N = 12). Tisagenlecleucel infusion was administered to 111 (67.3%) patients, 95 in the Main Cohort and 16 in Cohort A. Follow-up is ongoing for [redacted] of these patients, while [redacted] have discontinued follow-up, primarily due to death ([redacted]) or progressive disease ([redacted]). The FAS and safety set consisted of all patients infused (N = 111 in Main

Cohort + Cohort A, N = 95 Main Cohort, and N = 16 Cohort A). The EAS included all patients who received an infusion of tisagenlecleucel at least three months prior to the data cut-off date of December 8, 2017 (N = 93 Main Cohort and 13 Cohort A). [redacted]

In Study A2101J, until the last data cut-off date of May 7, 2017, 23 patients with DLBCL were enrolled (Table 10) and 14 received tisagenlecleucel infusion. Nine patients (39.1%) discontinued before receiving tisagenlecleucel infusion due to product-related issues (i.e., insufficient T-cell count for the CTL019 cell manufacturer) (N = 5), progressive disease (N = 3), and patient decision (N = 1).

Table 10: Patient Disposition – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201	A2101J	JULIET: C2201 (Data Cut-Off Date: March 8, 2017)
Screened, N	238 (100)	NR	217
Enrolled, n (%)	165 (69.3)	DLBCL: 23	147 (67.7)
Not enrolled, n (%)	[redacted]	NR	70 (32.3)
• **Ineligible (not meeting any inclusion criteria)**	[redacted]	NR	52
• **Patient or guardian decision**	[redacted]	NR	8
• **Screen failure**	[redacted]	NR	NA
• **Adverse event**	[redacted]	NR	2
• **Death**	[redacted]	NR	1
• **Physician decision**	[redacted]	NR	2
• **Other**	[redacted]	NR	5
Discontinued before infusion, n/N-enrolled (%)	50/165 (30.3)	9/23 (39.1)	43/147 (29.3)
• **Progressive disease**	[redacted]	3 (13.0)	0
• **Physician decision**	[redacted]	0 (0)	12
• **Patient decision**	[redacted]	1 (4.3)	3
• **Product-related issues**	12 (7.3)	5 (21.7)	9
• **Adverse event**	[redacted]	0 (0)	2
• **Death**	[redacted]	0 (0)	16
• **Protocol deviation**	[redacted]	0 (0)	1
Tisagenlecleucel-infused patients, n/N-enrolled (%)	111/165 (67.3)	14/23 (60.9)	99/147 (67.3)
Tisagenlecleucel infusion pending	4/165 (2.4)	NA	5
Study follow-up completed	[redacted]	NR	0
Follow-up ongoing, n/N-infused	[redacted]	NR	64
Discontinued follow-up, n/N-infused	[redacted]	NR	35/99 (35.4)
• **Progressive disease**	[redacted]	NR	10
• **Physician decision**	[redacted]	NR	1
• **Patient decision**	[redacted]	NR	3
• **Adverse event**	[redacted]	NR	1
• **Death**	[redacted]	NR	20
Analyses sets, N			
FAS[a]			
• **All patients**	111	14	99
• **Main Cohort**	95	NA	NR
• **Cohort A**	16	NA	NR

	JULIET: C2201	A2101J	JULIET: C2201 (Data Cut-Off Date: March 8, 2017)
Safety set			
• **All patients**	[redacted]	NA	99
• **Main Cohort**		NA	NR
• **Cohort A**		NA	NR
EAS[b]			
• **Main Cohort**	93	NA	81
• **Cohort A**	13	NA	2
PPS[c]			
• **Main Cohort**	[redacted]	NA	80

DLBCL = diffuse large B-cell lymphoma; EAS = efficacy analysis set; FAS = full analysis set; NA = not applicable; NR = not reported; PPS = per-protocol set.
[a] The FAS includes all patients who received an infusion of tisagenlecleucel.
[b] The EAS includes all patients who received an infusion of tisagenlecleucel at least 3 months prior to the data cut-off date.
[c] The PPS is a subset of the EAS who were compliant with major requirements of the protocol. Patients were not included in the PPS in the following circumstances: diagnosis of disease other than DLBCL at baseline; missing or incomplete documentation of disease at baseline; or received less than the minimum target dose of 1×10^8 tisagenlecleucel transduced cells.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off); Schuster SJ et al. NEJM 2017; 377;26:2545-54;[36,40] European Medicines Agency;[24] Schuster SJ et al. NEJM 2018; December 1. [49]

Intervention

In JULIET, a single IV infusion of tisagenlecleucel (CTL019) was administered as 0.1 to 6.0 $\times 10^8$ (median: 3.1 $\times 10^8$) cells (Table 11). The target dose was 1.0 to 5.0 $\times 10^8$ cells: most patients were within this target range (93.5%). One patient received a lower dose and five patients received higher doses. The doses administered to Cohort A and all infused patients are provided in Appendix 7: Additional Data – Relapsed or Refractory Diffuse Large B-Cell Lymphoma (Table 48).

T cells were harvested from patients by leukapheresis. [redacted].[48] The tisagenlecleucel cells were depleted of magnetic beads, washed, concentrated, and cryopreserved. To induce lymphopenia and facilitate engraftment and expansion of cells, patients received lymphodepleting chemotherapy one week prior to tisagenlecleucel infusion unless their WBC count was less than or equal to 1,000 cells/µL. The lymphodepleting regimen of choice was fludarabine (25 mg/m^2 IV daily for three doses) and cyclophosphamide (250 mg/m^2 IV daily for three doses, starting with the first dose of fludarabine). Bendamustine 90 mg/m^2 IV daily for two days was used as an alternative if patients had previously experienced grade 4 hemorrhagic cystitis with cyclophosphamide or had resistance to a previous cyclophosphamide regimen. Of all infused patients (N = 111), 103 (92.8%) received lymphodepleting chemotherapy; [redacted] patients received a fludarabine-cyclophosphamide regimen and [redacted] received bendamustine. Patients may have also received bridging chemotherapy prior to lymphodepleting therapy for disease stabilization while waiting for tisagenlecleucel infusion. At the time of tisagenlecleucel administration, the cryopreserved cell product was thawed; to preserve maximum cell viability, the time between thawing and completion of the infusion was not to exceed 30 minutes. Vital signs were monitored prior to, during, and after the infusion.

In Study A2101J, patients received 1.8 to 5.0 × 10^8 (median: 5.0 × 10^8) cells. Patients completed a lymphodepleting chemotherapy regimen (cyclophosphamide, fludarabine, bendamustine, or any other appropriate combination chemotherapy) one to four days before tisagenlecleucel infusion.[40] Prior to infusion, patients received premedication with 650 mg acetaminophen and 25 mg to 50 mg diphenhydramine hydrochloride, which could be repeated every six hours if needed. Patients may have received bridging chemotherapy to stabilize disease while waiting for tisagenlecleucel infusion.

Table 11: Tisagenlecleucel Dose Administration – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201 (N = 93)[a]	A2101J (N = 14 DLBCL)
Total tisagenlecleucel dose infused (× 10^8 transduced viable T cells)		
Mean (SD)	[redacted]	NR
Median	3.00	5.00
Range	0.10 to 6.00	1.79 to 5.00
Dose categorization, n (%)		
Below target dose[b] range	[redacted]	NR
Within target dose range	[redacted]	NR
Above target dose range	[redacted]	NR

NR = not reported; EAS = efficacy analysis set; SD = standard deviation.
[a] Patients in the EAS of the Main Cohort.
[b] The target dose range was 1 to 5 × 10^8 tisagenlecleucel transduced cells.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off); Schuster SJ et al. NEJM 2018; December 1[49]; Schuster SJ et al. NEJM 2017; 377;26:2545-54.[36,40]

Outcomes

In JULIET, disease status was and will be evaluated at one, three, six, nine, 12, 18, 24, 36, 48, and 60 months by computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET)-CT. After five years, patients will be followed semi-annually and annually for safety assessment until 15 years post-infusion in a separate extension safety protocol (Study B2401). [redacted]. Outcomes related to disease response were reviewed by an IRC, [redacted].[48]

In the supporting study, A2101J, patients were assessed on a monthly basis from months two to six post-tisagenlecleucel infusion.[40] After month six, patients were assessed quarterly up to two years post-infusion. After the second year, patients will be followed twice yearly until five years after infusion. Subsequently, patients will be followed annually for up to 15 years post-infusion in a separate protocol (Study CCTL019B2401).

The definitions of the outcomes evaluated in JULIET are provided in Table 12.

Table 12: Definitions of Selected Efficacy Measures in JULIET – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Outcome	Definition
ORsR	BOR of CR or PR
BOR	Best disease response from tisagenlecleucel infusion to progressive disease or start of new anticancer therapy, including SCT, whichever came first Classified as CR, PR, SD, PD, or unknown See Appendix 9 for more details about how BOR was clinically assessed.
PFS	The time from tisagenlecleucel infusion to the earliest of death due to any cause or progression
EFS	The time from tisagenlecleucel infusion to the earliest of death from any cause, disease progression or relapse, or new anticancer therapy for lymphoma, excluding SCT
OS	The time from tisagenlecleucel infusion to the date of death due to any reason among all treated patients
HRQoL	SF-36 and FACT-Lym

BOR = best overall response; CR = complete response; EFS = event-free survival; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; HRQoL = health-related quality of life; ORsR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; r/r DBLCL = relapsed or refractory diffuse large B-cell lymphoma; SCT = stem cell transplant; SD = stable disease; SF-36 = Short Form (36) Health Survey.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off).[36]

Overall Response Rate and Best Overall Remission

The primary outcome in JULIET was ORsR in the EAS of the Main Cohort (i.e., at three months in patients who received tisagenlecleucel cells from the US manufacturing facility). The ORsR was based on the Lugano classification, which uses information from radiological imaging (i.e., CT, MRI) and metabolic activity (i.e., PET, PET-CT), and assessed by the IRC.[48] The ORsR was defined as the proportion of patients with a BOR of CR or partial response (PR), as defined in Table 12. The BOR could be classified as either CR, PR, SD, PD, or unknown. A patient was classified as CR if that was the overall disease response for at least one of the assessments; as PR if at least one overall disease response was PR and the patient did not quality for CR; as SD if that was the overall response on one assessment at least four weeks after tisagenlecleucel infusion and the patient did not quality for CR or PR; and as PD if that was observed less than 14 weeks after tisagenlecleucel infusion and the patient did not quality for CR, PR, or SD. The BOR was unknown if the patient did not qualify for CR, PR, SD, or PD.

In Study A2101J, the primary outcome was ORsR at three months in NHL (i.e., DLBCL, follicular lymphoma, and mantle cell lymphoma combined), defined as CR, complete remission unconfirmed (CRu), or PR. A secondary objective was to evaluate ORsR separately for each type of lymphoma in an exploratory analysis. Patients qualified for CR, CRu, or PR according to the following criteria:

- CR: complete disappearance of all detectable clinical and radiographic evidence of disease; disappearance of all disease-related symptoms; normalization of biochemical abnormalities; all lymph nodes and nodal masses regressed to normal size; spleen or other organs regressed in size if enlarged before therapy due to lymphoma; no detectable macroscopic nodules in any organs; and clearing on bone marrow aspirate and biopsy if the bone marrow was involved by lymphoma prior to treatment.

- CRu: qualification for CR criteria (aside from bone marrow involvement) with one or more of the following: a residual lymph node mass or indeterminate bone marrow.
- PR: More than 50% decrease in the sum of the product of the longest perpendicular dimensions (SPD) of the six largest dominant nodes or nodal masses; no increase in the size of other nodes, liver, or spleen; regression of splenic and hepatic nodules by at least 50% in the SPD; involvement of other organs assessable and with no measurable disease; and no new sites of disease.

Time-to-Event End Points

Secondary outcomes in JULIET were DOR, time to response, progression-free survival (PFS), EFS, OS, and HRQoL as defined in Table 12. Other outcomes reported in A2101J were DOR, PFS, and OS.

Health-Related Quality of Life

HRQoL was a secondary outcome in JULIET. It was measured using the Short Form (36) Health Survey (SF-36), version 2 and the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) scale. A description of these scales, as well as an appraisal of their measurement properties, is in Appendix 8: Validity of HRQoL Instruments.

Resource Utilization

JULIET reported data on hospitalization during tisagenlecleucel infusion, hospitalization within three days of infusion, number of hospitalizations, duration of hospital stay, and duration of ICU stay.

Safety

In JULIET, AEs aside from CRS were reported based on MedDRA version 20.0 and CTCAE version 4.03 for the safety set. The grading of CRS was based on a protocol-specific scale. AESIs were CRS or macrophage activation syndrome, tumour lysis syndrome (TLS), febrile neutropenia, infection, neurological events, and hematopoietic cytopenias not resolved by day 28 post-tisagenlecleucel infusion. The AESIs were reported within eight weeks of infusion. Deaths and SAEs were also recorded.

In Study A2101J, reported safety outcomes were combined for patients with DLBCL and follicular lymphoma. At each study visit, AEs were recorded using the CTCAE version 4.0.[50] CRS was graded based on a protocol-specific scale.

Statistical Analysis Plan

Acute Lymphoblastic Leukemia

The statistical analysis approach used by the study investigators is described below.

Power Calculation

The Pivotal ELIANA Trial

The primary efficacy analysis for ELIANA tested if the ORR within three months was greater than 20% at an overall one-sided 0.025 level of significance. The value of 20% was selected for comparison based on a previous study of clofarabine in patients with r/r B -cell ALL who had had two or more prior regimens in which the reported ORR was 20% (95% confidence

interval [CI], 10 to 34).[51] The investigators determined that, based on the null hypothesis of ORR ≤ 20% and alternative hypothesis of ORR > 20%, 76 patients in the FAS would provide > 95% power to demonstrate statistical significance at a one-sided, cumulative 0.025 level of significance if the underlying ORR was 45%. Under these assumptions, an ORR of 30% (23 of 76) would be needed to claim success. Thus, in patients with r/r B -cell ALL, an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy. Assuming a 20% to 25% pre-infusion dropout rate, it was estimated that approximately 95 patients needed to be enrolled to reach the number of patients required.

Power calculations were also performed for the three key secondary end points. Common assumptions for all calculations were that the tisagenlecleucel efficacy was the same regardless of where it was manufactured (i.e., the US or Germany); an ORR of 45% that excludes a 20% ORR at the 0.025 significance level would indicate meaningful efficacy; and the interim analysis involved the first 50 patients. In the first key secondary end point of ORR during three months in patients infused with tisagenlecleucel from the US manufacturing facility, it was estimated that provided the primary end point was statistically significant, 50 patients in an interim analysis up to 66 patients in the final analysis infused with tisagenlecleucel would be needed for > 95% overall power.

For the second key secondary outcome of remission with MRD-negative bone marrow in patients who received tisagenlecleucel from all manufacturing facilities, the power calculation was based on previous studies in the r/r B-cell ALL setting, which found that 67% to 82% of patients who achieved CR or CRi also achieved MRD-negative status.[52,53] The investigators estimated that up to 76 patients in the FAS would provide greater than 95% power to demonstrate statistical significance at one-sided 0.025 level of significance, if the underlying percentage of patients who achieve BOR or CR or CRi with MRD-negative bone marrow was 34%.

For the third key secondary outcome of remission with MRD-negative bone marrow in patients who received tisagenlecleucel from a US manufacturing facility, it was estimated that up to 66 patients in the final analysis infused with tisagenlecleucel from a US manufacturing facility would provide 94% power.

Supportive Studies

The primary efficacy analysis for ENSIGN tested if the ORR within six months was greater than 20% at an overall one-sided 0.025 level of significance. [redacted]. The investigators determined that, based on the null hypothesis of ORR ≤ 20% and the alternative hypothesis of ORR > 20%, [redacted] ALL patients in the FAS provided [redacted] power to demonstrate statistical significance using a two-look Lan–DeMets group sequential design with O'Brien–Fleming type boundary at a one-sided overall 0.025 level of significance if the underlying ORR is 45%. [redacted]. Power analyses were not applied to secondary end points in the ENSIGN study.

In Study B2101J, the antitumour activity of tisagenlecleucel was assessed as a secondary trial end point without a power calculation.

Statistical Method

The Pivotal ELIANA trial

The results in the ELIANA study were based on analysis using the IRC-assessed data observed in the interim efficacy analysis set (IEAS) and the current updated analysis using the FAS. The primary efficacy end point, ORR, was summarized along with the two-sided 98.9% exact Clopper–Pearson CIs with coverage level determined by the O'Brien–Fleming[54] type alpha-spending approach, according to Lan and DeMets (1983).[55] The null hypothesis was that ORR would be ≤ 20%; the alternative hypothesis was that the ORR would be > 20% at an overall one-sided 2.5% level of significance. The study met its primary objective if the lower bound of the two-sided 98.9% exact CI for ORR was > 20%, or equivalently, if the nominal exact *P* value was less than the interim analysis adjusted threshold of 0.0057.

The ELIANA study had three key secondary efficacy end points, which were analyzed following a hierarchical model. Thus, the first key secondary end point assessment was performed when the primary objective was met; the second key secondary end point was assessed if the primary end point and first key secondary end points were met; and the third key secondary end point was evaluated if the primary end point and the first and second key secondary end points were met. At each step, starting with the first key secondary end point, the family-wise type I error rate was controlled at a one-sided 2.5% level under the hierarchical testing scheme.

The focus of the first key secondary end point was all patients who received tisagenlecleucel from the US manufacturing facility. It tested the same null hypothesis and alternative as the primary end point among this subgroup of patients. The first key secondary objective was considered successfully met if the lower bound of the two-sided 98.0% exact CI was > 20%, or equivalently, the nominal exact *P* value was less than 0.01.

The second key secondary end point tested the null hypothesis that the percentage of MRD-negative responders among all patients who received tisagenlecleucel infusion was ≤ 15% against the alternative hypothesis that it was > 15% at an overall one-sided 2.5% level of significance. The second key secondary objective was considered successfully met if the lower bound of the two-sided 98.9% exact CI was > 15%, or equivalently, if the nominal exact *P* value was less than 0.0057.

The third key secondary end point was also based on data from all patients who received tisagenlecleucel from the manufacturing facility in the US. It tested the null hypothesis that the percentage of patients in this group who achieved a BOR of CR or CRi with an MRD-negative bone marrow during the three months after tisagenlecleucel administration would be ≤ 15% against the alternative that it would be > 15%. The third key secondary objective was considered successfully met if the lower bound of the two-sided 98.0% exact CI was > 15%, or equivalently, the nominal exact *P* value was less than 0.01.

Analysis of other secondary or exploratory end points was descriptive and included summary statistics, such as means, standard deviations, and 95% CIs. For the time-to-event end points (DOR, RFS, EFS, and OS), cumulative incidence functions, Kaplan–Meier curves, and median time-to event were presented if appropriate.

Handling Missing Data and Censoring — ELIANA

Missing data were recorded in appropriate tables as missing. When a full outcome evaluation was not possible because of missing data, the overall evaluation was assigned

"unknown" unless at least one observation was made, which qualified for relapse. Patients with unknown clinical response were considered as non-responders in the analysis. EFS and RFS were censored after at least two missing scheduled disease assessments. Specific information about imputation for other variables was not provided.

Subgroup Analyses — ELIANA

A number of subgroup analyses were preplanned for efficacy outcomes, including, but not limited to, baseline bone marrow tumour burden, baseline extramedullary disease presence, and Down syndrome. A minimum of five patients were required for a subgroup analysis. The results of subgroup analyses were considered exploratory. Appendix 6: Additional Data – Relapsed or Refractory B-Cell (Table 43) provides additional details of subgroup analyses.

Sensitivity Analyses — ELIANA

The robustness of the primary analysis of ORR was evaluated using a series of predefined sensitivity analyses. Sensitivity analyses were performed on various analysis populations, including the FAS, the enrolled set, the PPS, and all patients who satisfied all clinical eligibility. Table 13 summarizes the various analysis sets used in the preplanned sensitivity analyses. Also, results of the IRC assessment were compared with the results of the local investigator assessments in sensitivity analyses of selected efficacy end points.

Table 13: Analysis Sets – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA[a]	ENSIGN[b]	B2101J[c]
	n (%)	n (%)	n (%)
Enrolment set	[redacted]	[redacted]	[redacted]
EAS	[redacted]	[redacted]	[redacted]
FAS	[redacted]	[redacted]	[redacted]
PPS	[redacted]	[redacted]	[redacted]
Safety set	[redacted]	[redacted]	[redacted]

EAS = efficacy analysis set; FAS = full analysis set; NR = none reported; PPS = per-protocol set.
Note: In ENSIGN, the updated results at data cut-off date October 6, 2017 was based on efficacy analysis set (EAS), defined as all patients treated with tisagenlecleucel at least 6 months prior to the clinical data cut-off.

- The enrolment set comprised all patients who were enrolled in the study. Enrolment date was defined as the point at which the patient met all inclusion or exclusion criteria and the patients' leukapheresis product was received and accepted by the manufacturing facility.
- The FAS comprised all patients who received infusion of tisagenlecleucel.
- The PPS consisted of a subset of the patients in the FAS who were compliant with the major requirements of the clinical study protocol.
- The safety set comprised all patients who received infusion of tisagenlecleucel.

Sources: The manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Supporting studies

[redacted]. The null hypothesis that the ORR was ≤ 20% could be rejected if the lower bound of the two-sided 98.95% exact CI for ORR was > 20%, or equivalently, if the nominal exact *P* value is less than [redacted]. [redacted]. The lower bound of the 95% CI of ORR was > 20% in all sensitivity analyses. It was unclear if the subgroup and sensitivity analyses in ENSIGN were preplanned.

Descriptive analyses were reported for all end points in Study B2101J. The study did not describe how missing data were handled; a sensitivity analysis was not reported. The subgroup analyses for the primary end point in B2101J were performed on similar patients' baseline statuses, as was done in ELIANA and ENSIGN. It was unclear if the subgroup analyses in B2101J were preplanned.

Diffuse Large B-Cell Lymphoma

The latest data cut-off for JULIET was December 8, 2017. Three previous analyses were performed: an interim analyses (data cut-off December 20, 2016) when the first 51 patients treated with tisagenlecleucel from the Main Cohort had been followed for at least three months or discontinued earlier and the primary objective had been met; a primary analysis (data cut-off March 8, 2017), when the first 81 patients from the Main Cohort had been followed for at least three months or discontinued earlier; [redacted]. The results reported in this review are from the latest data cut-off of December 8, 2017. The latest data cut-off available for the supporting study, A2101J, is May 7, 2017.

The analysis sets in JULIET are provided in Table 14.

Table 14: Analysis Sets in JULIET – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Analysis Set	Definition	Main Cohort[a] n (%)	All Patients n (%)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

EAS = efficacy analysis set; FAS = full analysis set; PPS = per-protocol set.
[a] The Main Cohort included patients who received tisagenlecleucel cells from the US manufacturing facility.

Power Calculation

In JULIET, the primary end point of ORsR at three months was based on testing the null hypothesis of ORsR being less than or equal to 20% and the alternative hypothesis that ORsR is greater than 20% at a one-sided 2.5% level of significance. The primary objective was met if the lower bound of the two-sided 95.28% exact Clopper–Pearson CI was greater than 20%. [redacted]. Based on the 20% threshold, 80 patients were calculated to provide 94% cumulative power to demonstrate statistical significance using a two-look Lan–DeMets group sequential design with O'Brien–Fleming type boundary and an exact CI at a one-sided cumulative 0.025 level of significance if the underlying ORsR was 38%. [redacted].

In Study A2101J, at least eight patients of each NHL subtype, with a maximum of 14 patients, were planned for recruitment.

Statistical Method

ORsR was presented as the number of patients who achieved CR or PR (JULIET) or who achieved CR, CR_u, or PR (A2101J). DOR, time to response, EFS, PFS, and OS were analyzed using the Kaplan–Meier method. In JULIET, a one-sided 2.5% level of significance was used to interpret ORsR. Estimates for all other outcomes in JULIET and the supporting study were presented with 95% CIs at a two-sided 5% level of significance.

The HRQoL scales in JULIET were scored by summing the item responses for each domain and following scoring procedures provided by scale developers. The mean changes from baseline were provided for each domain for each post-baseline assessment.

Handling Missing Data and Censoring

In JULIET, patients with unknown clinical responses were treated as non-responders.

The censoring rules for the time-to-event end points in JULIET were according to the following:

- **DOR:** Patients were censored at the date of last adequate assessment if they had not experienced an event, were lost to follow-up, withdrew consent, died due to DLBCL, initiated new anticancer therapy, had an event documented after at least two missing tumour assessments, or did not have adequate assessments available. Additionally, if responding patients received SCT, they were censored at the date of SCT.
- **EFS:** Patients were censored at the date of last adequate assessment if they had not experienced an event, were lost to follow-up, withdrew consent, received SCT, had an event documented after at least two missing tumour assessments, or did not have adequate assessments available. In sensitivity analysis, patients were not censored for SCT.
- **PFS:** Patients were censored at the date of last adequate assessment if they had not experienced an event, were lost to follow-up, withdrew consent, initiated new anticancer therapy, had an event documented after at least two missing tumour assessments, or did not have adequate assessments available. If responding patients received SCT, they

were censored at the date of SCT. In sensitivity analysis, patients were not censored for SCT.

- **OS:** Patients were censored at the last contact date if they were not known to have died.

Subgroup Analyses

In JULIET, exploratory, preplanned subgroup analyses for ORsR were conducted for histological and molecular subgroups if there were at least five patients in each group. The histological subgroups were DLBCL not otherwise specified, transformed lymphoma, and other. The molecular subgroups were GCB ABC, and other. Additional planned subgroup analyses for ORsR, if there were at least five patients in each group, were age (< 40, ≥ 40 to < 65, and ≥ 65), gender, race (white, Asian, black, and other), ethnicity (Hispanic or Latino and other), prior response status (refractory and relapsed), IPI at enrolment (< 2 and ≥ 2 risk factors), number of prior lines of antineoplastic therapy (≤ two lines, three to four lines, and ≥ four lines), stage of disease at baseline (I/II and III/IV), and double-hit/triple-hit status (i.e., genetic rearrangement of MYC, BCL2, BCL6).

Sensitivity Analyses

In JULIET, ORR was analyzed in the following sets: per-protocol (PPS); EAS plus enrolled but not infused (Main Cohort); EAS plus those who satisfied all clinical eligibility criteria and discontinued prior to infusion; and EAS excluding those who achieved CR at baseline after bridging therapy and who remained in CR post-baseline.

Critical Appraisal

Acute Lymphoblastic Leukemia

The Pivotal ELIANA Trial

Internal Validity

Bias due to confounding was considered moderate for the ELIANA study because of its non-randomized design and lack of a comparison group. Selection of patients was also rated to have moderate risk of bias, since there was no information about how participants were selected to be screened for study eligibility, and a large proportion ([redacted]) of patients discontinued before treatment with the tisagenlecleucel, due mainly to death, physician decision, or production failure. Another limitation is the absence of a comparator or control group against which the treatment benefits of tisagenlecleucel can be compared. The investigators justified the single-arm study design by citing the high medical need of patients with r/r B-cell ALL, the lack of effective therapies in this population, and the preliminary positive results observed in the supporting Study B2101J. The intervention (tisagenlecleucel or CTL019) was well-defined, with clear descriptions of the processes leading to its production at a central laboratory, the doses suitable for individuals based on weight, and the preparation of patients before the administration of the intervention, among others.

The study is ongoing, with [redacted] of enrolled patients already treated. There were no issues with adherence or deviations from the intended intervention, since tisagenlecleucel was administered as a single-dose infusion. However, as at the data cut-off date of August 7, 2017, [redacted] of enrolled patients had discontinued the study after tisagenlecleucel infusion. The discontinuation rate was driven primarily by [redacted] of all enrolled patients who discontinued the study and [redacted] of total discontinuations

at the data cut-off date. Overall, the risk of bias due to the classification of or deviations from the intervention was low.

The study met its primary end point with a high three-month ORR; and the lower bound of the 95% exceeding the preset 20% limit for clinical relevance as at the data cut-off date of December 31, 2017 was high ([redacted]). However, long-term data are lacking and [redacted] ([redacted]). Therefore, at the time of review, there is no conclusive evidence of durable remission over the long-term.

In general, open-label studies such as ELIANA, in which assessors are aware of the intervention, have increased risk of outcome measure bias due to assessor judgment. However, an IRC performed the outcome assessments using standard objective measures that were recognized as reliable, accurate, and relevant for the targeted patient population by the clinical experts engaged by CADTH for this project, thereby limiting the potential for bias. Although the main analysis was based on the FAS, which may not be as rigorous as an intent-to-treat population, several preplanned sensitivity analyses using different analysis sets were performed to evaluate the consistency and robustness of the findings. The FAS was defined as the number of enrolled patients infused with tisagenlecleucel. The FAS had [redacted] patients as at the data cut-off date of December 31, 2017. The results of all the analyses were reported with CI, standard deviation, or range, as appropriate. Thus, the overall risk of bias in the measurement of outcomes was considered low. Patients' HRQoL was assessed using the PedsQL and EQ-5D scales. The HRQoL outcomes are patient-reported; therefore, they are subjective. Given the open-label designs of the studies and lack of a comparator group, there is a high risk of bias for these outcomes. Also, the HRQoL is reported only for a subgroup of patients aged ≥ 8 at baseline who achieved CR/CRi within three months of tisagenlecleucel infusion, as most of the patients who did not achieve CR/CRi had discontinued before they were due for evaluation. Further, the number of available patients decreased progressively with each subsequent assessment, with only [redacted] patients available for assessment at 12 months. The investigators did not provide a reason for the smaller number of patients at the successive HRQoL assessments. Therefore, it is unknown whether the numbers decreased because patients were lost to follow-up or because they had not yet been followed long enough at the time of assessment (for instance, patients who had not been followed for 12 months yet would not have 12-month HRQoL scores). Thus, there is a high potential for bias in the reported HRQoL outcomes dues to patients' subjectivity, and the progressive reductions in available data for assessment over time weakens the robustness of the findings.

The methods of statistical analysis were appropriate. A sample-size calculation was performed to determine the number of patients needed to show a meaningful difference in efficacy outcomes based on a previous clofarabine study in patients with r/r B-cell ALL. The sample-size analysis was performed for the primary end point as well as three key secondary end points. The calculation assumed a lower-bound ORR threshold of 20% for clinical relevance, which seems reasonable because it was based on an ORR of 20% and median OS of three months reported for clofarabine, a currently approved therapy for r/r B-cell ALL.[51]

The study used a group sequential design, which typically conducts a number of interim statistical analyses as the number of patients enrolled and or treated increases over time. Performing repeated analysis of accumulating data with conventional statistical testing can lead to substantially increased type I or false-positive error rates. The O'Brien–Fleming[54]

type alpha-spending function approach, which was used to analyze the data in ELIANA and the supporting studies, controls the type I error while allowing the IRC to review the data as needed without having to specify a priori when and how many such interim analyses will be conducted. A hierarchical testing scheme was used to analyze the three key secondary end points. The first key secondary end point (ORR during the three months after infusion in patients treated with tisagenlecleucel from the US manufacturing facility) was evaluated when the primary objective was met. The second key secondary end point (BOR of CR or CRi with MRD-negative bone marrow [BM] among all patient infused with tisagenlecleucel from both the US and German facilities) was assessed only when both the primary objective and the first key secondary end point were met. The third key secondary end point (the percentage of patients who achieved a BOR of CR or CRi with a MRD-negative BM among all patients who received tisagenlecleucel from the US manufacturing facility) was assessed when the primary end point and both the first and second key secondary end points were met. The family-wise type I error rate (FWER) was used to adjust for multiplicity and control type I error rate at each step, with the FWER controlled at the one-sided 2.5% level of significance. The other outcomes (i.e., time-to-event outcomes, HRQoL, hospitalization, and safety), as well as subgroup analyses, were not adjusted for multiplicity. Therefore, they are prone to type I error.

Missing data were to be recorded in appropriate tables as missing. Although there were no data categorically described as missing, [redacted] were not included in the per-protocol analysis for missing or incomplete baseline data. When a full outcome evaluation was not possible because of missing data, the overall evaluation was assigned “unknown” unless at least one observation was made that qualified for relapse.

A series of preplanned subgroup analyses with at least five patients in the subgroup were performed by the IRC. Thus, the sizes of the individual subgroups were smaller, and no power calculation was performed to assess the ability of these subgroups to detect clinically relevant differences. Also, the subgroup analyses were exploratory — intended to evaluate the robustness and consistency of any treatment effects found overall, but not for clinical decision-making.

External Validity

Patients were screened for their eligibility to participate in the study using predefined inclusion and exclusion criteria. The clinical experts consulted for the review agreed that the study eligibility criteria were likely to select children and young adults with r/r B-cell ALL who were representative of the population for whom tisagenlecleucel is indicated. However, they questioned whether one of the inclusion criteria — BM with ≥ 5% lymphoblasts by morphologic assessment — could cause some attending physicians to wait too long before considering switching patients to tisagenlecleucel, placing patients at risk of disease relapse and extramedullary non-CNS disease. It was explained that r/r B-cell ALL patients with ≥ 3% BM lymphoblasts on conventional salvage therapy had poor prognoses and a better chance of remission if their intervention was changed at this point instead of waiting for them to deteriorate to ≥ 5% BM lymphoblasts.

The clinical experts consulted for the review agreed that the definition of the outcome measures (ORR, BOR, CR, CRi, EFS, RFS, and OS) were standard and generalizable to the Canadian context. The outcomes of the study were consistent for all subgroups, including patients treated with tisagenlecleucel from either the US or German facility. Thus, the effects of the tisagenlecleucel product appear to be uniform between the two facilities and across the subgroups of patients with r/r B-cell ALL specified in the protocol.

The clinical experts consulted for the review agreed that other medications used during tisagenlecleucel therapy were within standard clinical practice in children and young adults with r/r B-cell ALL, and unlikely to confound the effect of the intervention. The clinical experts consulted for the review agreed that the co-interventions during the tisagenlecleucel therapy (including antineoplastic medications used for lymphodepleting chemotherapy before infusion and medications used after tisagenlecleucel infusion) were standard and generalizable to the Canadian context.

Taking all of the above together and considering that the ELIANA study was global, with 25 centres in 11 countries including Canada, the generalizability of the study findings appears to be acceptable. However, the generalizability of the HRQoL findings is unknown because it is reported only for a subgroup of patients aged ≥ 8 at baseline who achieved CR or CRi within three months of tisagenlecleucel infusion, as most of the patients who did not achieve CR or CRi had discontinued before evaluations were available. Also, because the number of responders who participated in the HRQoL evaluations decreased progressively with each subsequent assessment, it is unclear if the findings from the latter assessments would be representative of the patient population.

The information provided about resource utilization was limited to hospitalization and ICU admissions. It is insufficient for evaluating the impact of tisagenlecleucel use on overall health care resources.

Supporting Studies

The ENSIGN study was similar to the ELIANA study in terms of design, participating patients, outcome measures, methods of assessment, and approach to statistical analysis. Therefore, the two studies have commonalities in strengths and limitations. However, one difference between the two studies is the fact that although ENSIGN was a multi-centre study with nine centres, all of the sites were in the US, which might limit its generalizability compared with ELIANA, a global study. Also, in ELIANA, power calculations were made for the primary and three key secondary efficacy end points, whereas they were limited to the primary end point in ENSIGN, which treated all secondary end points as exploratory. Another limitation of the ENSIGN study is that it did not explore HRQoL or resource utilization of the study patients.

Study B2101J was a single-centre study that accepted MRD-negative patients and patients who had prior anti-CD19 therapy. Thus, in addition to a potentially reduced generalizability compared with either ELIANA or ENSIGN, the study population could confound the interpretation of its findings. Further, unlike ELIANA or ENSIGN, Study B2101J allowed multiple tisagenlecleucel infusions, which is not consistent with the Health Canada–approved dosing, and the local investigator, not the IRC, performed the outcome assessment instead. Also, many patients received doses that varied outside the indicated tisagenlecleucel dose range. Therefore, in addition to the limitations described for ELIANA and ENSIGN, the potential for biases are high in Study B2101J due to the classification of and deviation from intervention as well as the measurement of outcomes.

Diffuse Large B-Cell Lymphoma

JULIET

Internal Validity

The primary limitation is the absence of a comparator or control group against which the treatment benefits of tisagenlecleucel can be compared. The single-arm study design for JULIET was justified by the manufacturer based on the high medical need in this clinical area, the lack of effective therapies in patients with r/r DLBCL, and the preliminary positive results observed in the supporting study, A2101J.[36] In addition, patients with DLBCL who have failed two or more lines of systemic therapy have only palliative options available, and a randomized trial in this context would be unethical. Another major limitation was the large percentage of patient drop-outs. Of the 165 patients enrolled in JULIET, [redacted] discontinued the study before even receiving an infusion of tisagenlecleucel. An additional [redacted] discontinued follow-up after receiving infusion, primarily due to death ([redacted]). Given the large percentage of drop-outs at the pre-infusion stage, the sample who did receive tisagenlecleucel may have been prone to selection bias and resulting biases in assessment of some outcomes.

Patients were enrolled in JULIET if they had a leukapheresis product received and accepted by the manufacturing facility; therefore, these patients were eligible to receive treatment, and should be included in analyses based on the intention-to-treat principal. However, the primary and secondary analyses were restricted to patients who received tisagenlecleucel infusion, rather than including all enrolled patients. This concern was addressed by two sensitivity analyses for ORsR [redacted]

The FDA and Health Canada noted the potential for interference of the clinical effect of tisagenlecleucel by bridging chemotherapy.[25,56] In their reviews, the analyzed set consisted of 68 of 92 patients in the EAS of the Main Cohort (from an earlier data cut-off date of September 6, 2017) who had documented measurable disease after bridging therapy. The current review examined an updated cohort of the EAS of the Main Cohort (i.e., data cut-off date of December 8, 2017), and reported a sensitivity analysis for the ORsR outcome that included patients in the EAS and excluded those who achieved CR at baseline after bridging chemotherapy and remained in CR post-baseline. The ORsR excluding patients with a potential response to bridging chemotherapy [[redacted]] was slightly lower, but consistent with the ORsR that included these patients [51.6% (95% CI, 41.0 to 62.1)].

The CTL019 cell product was released by the manufacturing facility to the study site [redacted] after the start of manufacturing, and only if all safety and quality criteria were satisfied. During this waiting period, a large number of patients were lost from the trial ([redacted]), with nearly [redacted] of patients who died. A physician evaluated patients prior to infusion to ensure that all criteria for tisagenlecleucel were met. These measures indicate that study procedures and protocols were followed and that the intervention was delivered in a

controlled environment with oversight and monitoring. However, there were a total of 12 tisagenlecleucel product manufacturing failures. These patients were not able to receive treatment and were excluded from analyses, thereby increasing the chance of bias.

A comprehensive and clinically relevant set of efficacy outcomes was assessed in JULIET, including ORsR as the primary end point and BORs of CR, PR, SD, and PD. These end points were assessed based on the published Lugano classification, which includes PET- and CT-based assessment criteria. Secondary outcomes were DOR, time to response, PFS, EFS, OS, resource utilization, and HRQoL. Preplanned subgroup analyses were also conducted for the primary end point if there were at least five patients in the subgroup. However, none of the outcomes or subgroup analyses were adjusted for multiple testing; therefore, type I error is a possibility. The subgroups were exploratory; some groups had small sample sizes. The outcomes related to disease response were reviewed by an IRC consisting of one radiologist and one oncologist appointed by Novartis. Radiological imaging and clinical data, such as physical exam and BM results, were transmitted by study sites to an imaging contract research organization designated by Novartis, where quality checks and the IRC review took place. The IRC carried out the assessment in a blinded fashion with respect to patient name, date of birth, and initials as well as investigator site identifiers, limited clinical information, site lesion selection for tumour assessments, site determination of tumour response, exam dates, and reason for exams. The data quality checks and assessment of outcomes by an IRC increase confidence in the validity of reported outcomes. However, the HRQoL data contained a large number of missing observations at month three and onwards. These data are prone to significant selection bias because the majority of responses post-infusion were among patients who achieved a status of CR or PR. In addition, the minimal clinically important differences (MCIDs) for the FACT-Lym total (6.5 to 11.2), FACT–Trial Outcome Index (TOI) (5.5 to 11), and lymphoma subscale (2.9 to 5.4) were developed based on patients with r/r mantle cell lymphoma rather than on those with r/r DLBCL;[57] and the MCID for the FACT–General total (3 to 7) was based on cancer patients but was not specific to DLBCL.[58] The SF-36 MCIDs (range: 2 to 4) were also not specific to patients with DLBCL.[59] JULIET conducted a comprehensive evaluation of safety outcomes, including those that occurred during lymphodepleting chemotherapy (i.e., prior to tisagenlecleucel infusion) and after tisagenlecleucel infusion, with a special emphasis on AESI within eight weeks of infusion.

In JULIET, the primary ORsR end point was tested for the null hypothesis of ORsR ≤ 20% and the alternative hypothesis of ORsR > 20%. The threshold of 20% was based on two retrospective studies in patients with r/r DLBCL who received second- or third-line therapies and had ORsRs of 14% and 20%, and on a prospective clinical trial with ibrutinib that found an ORsR of 40% in patients with ABC-type lymphoma and 5% in patients with germinal centre-like lymphoma, for an overall ORsR of 21.7%. A clinical expert for this review advised that the 20% threshold was appropriate for comparison, as this threshold was derived from key studies. However, limitations of these studies were noted. In particular, the two retrospective studies were single-centre, with high risk of bias. Although the studies that defined the threshold were prone to bias, the clinical expert indicated that they were key studies, with results generalizable to the patient population in JULIET. A power analysis conducted by the manufacturer found that 80 patients were needed to provide 94% cumulative power to show statistical significance using an exact one-sided CI of 0.025, if the underlying ORsR was 38%. Kaplan–Meier analyses were conducted for DOR, time to response, EFS, PFS, and OS, with specified rules for censoring. Patients with unknown clinical response were treated as non-responders.

Study A2101J

As with JULIET, Study A2101J was a single-arm, open-label study with ORsR as the primary end point. ORsR by B-cell lymphoma type was a secondary analysis. Tumour response assessments were conducted by a dedicated independent radiologist. However, fewer secondary outcomes were available for patients with DLBCL (i.e., PFS and OS only). The supporting study also evaluated safety outcomes; however, a limitation was that the reported data were combined for DLBCL and follicular lymphoma.

External Validity

JULIET was conducted in 27 centres across 10 countries and included a relatively large number of patients with r/r DLBCL who received tisagenlecleucel (N = 93, Main Cohort). The median age in the Main Cohort was [redacted] years; the majority of patients were male ([redacted]) and white ([redacted]). Most had advanced (i.e., stage IV) disease. Although both GCB and ABC subtypes were represented, there were few patients with double- or triple-hit DLBCL ([redacted] and [redacted], respectively); in about [redacted] of patients, genotyping was not conducted. Most patients ([redacted]) did not have BM involvement at study entry. A clinical expert for this review indicated that the characteristics of patients in JULIET were generalizable to patients seen in Canadian practice. Patients received a single IV infusion of tisagenlecleucel at a target dose range of 1×10^8 to 5×10^8 cells based on previous clinical experience. The majority ([redacted]) were within the target range. To prevent infusion-related reactions, patients were premedicated with acetaminophen and diphenhydramine or another antihistamine; this could be repeated every six as hours as needed. Other appropriate co-interventions included bridging chemotherapy to maintain disease stability between leukapheresis and infusion, and lymphodepleting chemotherapy prior to infusion to induce lymphopenia and promote cell engraftment.

Study A2101J was conducted at only one site and evaluated a smaller number of patients with the indication of interest (N = 14). The median age of patients was 58 years. As with JULIET, the majority of patients were male (79%). Additionally, most patients had stage III or IV disease (64%). Other characteristics — such as race, IPI, predominant histology and cytology, and triple-hit lymphoma — were not reported. Study A2101J allowed for the inclusion of patients with prior allogeneic SCT if certain criteria were met, such as no active GVHD, whereas JULIET excluded patients with prior allogeneic SCT. However, none of the A2101J patients who were infused with tisagenlecleucel had received a prior allogenic SCT.[40] Patients were administered a single IV infusion of tisagenlecleucel, although a target dose range was not specified. As with JULIET, patients received premedication (with acetaminophen and diphenhydramine, bridging chemotherapy, and lymphodepleting chemotherapy) before infusion.

Summary of Efficacy and Safety Findings

Research Question #1:

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

At the current data cut-off date (December 31, 2017) for the pivotal ELIANA study, a median of [redacted] months of efficacy and safety follow-up data were available for [redacted] treated patients; [redacted]

Efficacy

Overall Remission Rate

At the interim analysis (data cut-off date of August 7, 2016) of the pivotal ELIANA study, the ORR three months after tisagenlecleucel infusion, as assessed by the IRC, was 82.0% ([redacted]). The lower bound of the 98.9% exact CI exceeded the pre-specified threshold of 20% for clinical relevance; therefore, the study met its primary end point. The result is consistent with the current IRC-assessed ORR finding [[redacted]] using the FAS at the data cut-off date of December 31, 2017 (Table 15).

Table 15: Overall Remission Rate Within Three Months of Post-Tisagenlecleucel Infusion – ELIANA

		Analysis Set	N	Cut-Off Date
Updated ORR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
95% CI (*P* value)	[redacted]			
Updated ORR, n (%)	61 (81)	FAS	75	April 25, 2017
95% CI (*P* value)	71 to 89			
ORR, n (%)	41 (82.0)	FAS (IEAS)	50	[redacted]
98.9% CI (*P* value)	[redacted]			

CI = confidence interval; FAS = full analysis set; IEAS = interim efficacy analysis set; N = number of patients; ORR = overall remission rate.
[a] All treated patients with ≥ 3 months of follow-up (or who discontinued earlier) at the time of the December 31, 2017 data cut-off.
Sources: The Manufacturer: ELIANA Clinical Summaries (data cut-off December 31, 2017);[35] CSR (data cut-off August 7, 2016);[32] Maude 2018.[37]

At the data cut-off date of February 1, 2016 for the ENSIGN study, the IRC-assessed ORR for six months post-tisagenlecleucel infusion was 69.0% (98.95% CI, 43.6 to 88.1; $P < 0.0001$). The lower bound of the 98.95% exact CI exceeded the pre-specified threshold of 20% for clinical relevance. Therefore, the study met its primary objective. The results of the updated IRC-assessed ORR using the EAS were consistent with the findings from the interim analysis (Table 16). In Study B2101J, the local investigator-assessed ORR at 28 days was 94.6% (95% CI, 85.1 to 98.9) at the data cut-off date of January 30, 2017 (Table 16). Thus, the results of the primary analysis of ORR in the pivotal ELIANA study were confirmed by the results from the two supporting studies, although the time limits for end point analysis were different for the different studies.

Table 16: Overall Remission Rate Post-Tisagenlecleucel Infusion – ENSIGN and Study B2101J

		Analysis Set	N	Cut-Off Date
ENSIGN—six months after infusion				
Updated ORR, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
• 95% CI (*P* value)	[redacted]			
ORR, n (%)	20 (69.0)	FAS (IEAS)[b]	29	February 1, 2016
• 98.95% CI (*P* value)	43.6 to 88.1; (*P* < 0.0001)			
Study B2101J—At 28 Days after infusion				
ORR, n (%)	53 (94.6)	FAS[c]	56	January 20, 2017
95% CI (*P* value)	(85.1 to 98.9) (NR)			

CI = confidence interval; EAS = efficacy analysis set; FAS = full analysis set, IEAS = interim efficacy analysis set; N = number of patients; NR = not reported; ORR = overall remission rate.
Sources: Information submitted by manufacturer:
[a] ENSIGN—Clinical Summaries (data cut-off October 6, 2017).[35]
[b] ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]
European Medicines Agency.[24]

A series of preplanned subgroup analyses with at least five patients in the subgroup were performed by IRC. The protocol-specified subgroups included age, disease status, and previous lines of therapy. The results of the analysis showed that ORR was consistently above 20% across all subgroups evaluated (Appendix 6: Additional Data – Relapsed or Refractory B-Cell).

Sensitivity Analyses: A series of predefined sensitivity analyses of ORR were performed by IRC in the ELIANA and ENSIGN studies to determine the rigour of the results of the primary analysis ORR in both studies. [redacted] However, the lower bounds of the 95% CIs for each of the analyses was > the 20% threshold for clinical relevance and consistent with the main results. In Study B2101J, the results of the preplanned sensitivity analyses of ORR as assessed by the local investigator in the enrolled set were consistent with the result of the primary analysis (Table 17).

Table 17: Results of Sensitivity Analyses – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA[a]		ENSIGN		B2101J[c]		ELIANA (Data Cut-Off April 25, 2017)	
	n/N (%)	95% CI	n (%)	95 % CI	n (%)	95 % CI	n/N (%)	95% CI
Enrolment set	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61/92 (66.3)	55.7 to 75.8
FAS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	61/75 (81.3)	70.7 to 89.4
PPS	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	56/68 (82.4)	71.2 to 90.5
All patients who met eligibility criteria	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	61/96 (63.5)	53.1 to 73.1

CI = confidence interval; FAS = full analysis set; N = number of patients; NR = not reported; ORR = overall remission rate; PPS per-protocol set.
Sources: Maude 2018;[37] European Medicines Agency;[24] information submitted by manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

The ELIANA study met all three predefined key secondary objectives. These were not protocol-specified outcomes; the results are not reported in tables. Among the first 50 patients who were treated with tisagenlecleucel from the US manufacturing facility as of the August 17, 2016 data cut-off, (82.0% [95% CI, 68.6 to 91.4; $P < 0.0001$]) had achieved an IRC-assessed BOR of CR or CRi with MRD-negative BM three months after tisagenlecleucel infusion. Among all 75 patients infused with tisagenlecleucel from both the US and German facilities, 61 (81.3% [95% CI, 71 to 89]) had achieved a BOR of CR or CRi with MRD-negative BM as of the April 25, 2017 data cut-off date.

Best Overall Remission Rate

All the treated patients in the ELIANA study who had achieved a BOR of CR or CRi as per IRC assessment three months after tisagenlecleucel infusion also achieved BM MRD (i.e., MRD < 0.01%) as of the April 25, 2017 cut-off date. A summary of the proportion of patients who had a BOR of CR or CRi with MRD-negative BM is presented in Table 18.

Table 18: Best Response Rate – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA (FAS by IRC)[a] N = 75		ENSIGN (EAS by IRC)[b] N = 42		B2101J (FAS by LI)[c] N = 56	
BOR	**n (%)**	**95% CI**	**n (%)**	**95 % CI**	**n (%)**	**95 % CI**
With BM MRD < 0.01% (MRD-negative)	61 (81)	71 to 89	[redacted]	[redacted]	[redacted]	[redacted]
(*P* value)	[redacted]		[redacted]		[redacted]	
With BM MRD > 0.01% (MRD-positive)	[redacted]		[redacted]		[redacted]	[redacted]

BM = bone marrow; BOR = best overall response; CI = confidence interval; EAS = efficacy analysis set; FAS = full analysis set; IRC = Independent Review Committee, LI = local investigator; MRD = minimal residual disease.
Notes: EAS includes all patients treated with tisagenlecleucel at least 6 months prior to the clinical data cut-off.
Sources: Maude 2018;[37] information submitted by manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017).[35]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Time-to-Event End Points

[redacted] The estimated probability for 12-month RFS, EFS, and OS as assessed by IRC for ELIANA was [redacted] respectively (Table 19). The estimated probability for 12-month RFS, EFS, and OS as assessed by IRC for ENSIGN was [redacted], respectively. For Study B2101J, 12-month estimated probabilities for RFS, EFS, and OS were [redacted] respectively. The assessments in B2101J were done by the local investigator.

Table 19: Probability Estimates for Time-to-Event Outcomes – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA (FAS)[a]		ENSIGN (EAS)[b]		B2101J[c]		ELIANA (FAS) (Data Cut-Off: April 25, 2017)	
Relapsed after onset of CR, n/N (%)	[redacted]		[redacted]		[redacted])		17/61 (27.9)	
	%	**95% CI**	**%**	**95% CI**	**%**	**95% CI**	**%**	**95% CI**
RFS	[redacted]		[redacted]		[redacted]		**N = 75**	
• 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	80	65 to 89
• 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59	41 to 73
EFS	[redacted]		[redacted]		**N = 56**		**N = 75**	
• 6 months	[redacted]	[redacted]	[redacted]	[redacted]	73.9	59.9 to 83.7	73	60 to 82
• 9 months	[redacted]	[redacted]	[redacted]		[redacted]			

	ELIANA (FAS)[a]		ENSIGN (EAS)[b]		B2101J[c]		ELIANA (FAS) (Data Cut-Off: April 25, 2017)	
• 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50	35 to 64
OS	[redacted]		[redacted]		[redacted]		**N = 75**	
• 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	90	81 to 95
• 9 months	[redacted]	[redacted]	[redacted]		[redacted]			
• 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76	63 to 86

CI = confidence intervals; EAS = efficacy analysis set EFS = event-free survival; NR = reported; OS = overall survival; RFS = relapse-free survival.
Note: The EAS was defined as all patients treated with tisagenlecleucel at least 6 months prior to the clinical data cut-off.
Sources: European Medicines Agency;[24] Maude 2018;[37] information submitted by manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017).[35]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017).[35]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Health-Related Quality of Life

Data for HRQoL were available only from patients who achieved responses from the tisagenlecleucel treatment. Most of the patients who did not achieve CR or CRi had discontinued before the HRQoL assessment was due, and the investigators presented HRQoL results for only the subgroup of patients who achieved CR or CRi. For PedsQL, the responding patients had clinically meaningful improvements in the total score ([redacted]) at three months after tisagenlecleucel treatment, and maintained them through month 6 and month 9 (Table 20). The MCID of PedsQL has been estimated to be ± 4.4 in pediatric patients.[60] The PedsQL subscale scores also showed clinically meaningful improvements at three months after tisagenlecleucel treatment ([redacted]) and appeared to be well maintained at six and nine months in responding patients. A summary of the PedsQL subscale scores is available in Table 20.

For EQ-5D, the responding patients achieved a clinically meaningful improvement in total EQ VAS scores ([redacted]) for three months after treatment with tisagenlecleucel (Table 21). The MCID ranges from ± 7 to ± 10 in cancer patients.[61] The mean EQ VAS scores approached or exceeded those from normative young adult populations from six months onwards. The EQ-5D dimensions results show a decrease in the number of patients in Level 2 and Level 3 from three months, which indicates a reduction in the severity of patients' HRQoL issues. However, the level of impairment at six months was higher than at three months for the mobility, usual activities, and pain/discomfort dimensions, whereas improvements were observed in the self-care and anxiety and depression dimensions at six months compared with three months.

Table 20: Mean PedsQL Scores Among Patients With CR/CRi, ELIANA

Table redacted

Sources: The manufacturer; ELIANA—Clinical Summaries (data cut-off December 31, 2017).[35]

Table 21: Mean EQ VAS Scores Among Patients With CR/CRi, ELIANA

Table redacted

Sources: The manufacturer; ELIANA—Clinical Summaries (data cut-off December 31, 2017).[35]

Hospitalization

The pivotal ELIANA study was the only one among the three included studies that assessed resource utilization data regarding hospitalization. Areas of interest included the length of stay, the use of hospital ward facilities, and reasons for hospitalization as they related to the study treatment regimen. Summarized hospitalization data for data cut-off date of April 25, 2017 are presented in Table 22.

Table 22: Tisagenlecleucel-Related Hospitalization – ELIANA

Number of patients with ≥ 1 hospitalization, n (%)	[redacted]
Patients infused during hospitalization, n (%)	[redacted]
Patients hospitalized within 3 days infusion, n (%)	[redacted]
Number of hospitalizations, n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
≥ 4	[redacted]
Duration of hospitalization (days)	
• Total duration, median (range)	[redacted]
• Average duration of each hospitalization, median (range)	[redacted]
Number of patients admitted to the ICU	[redacted]
Total duration of ICU stay (days)	
• Median (range)	[redacted]

ICU = intensive care unit.
Source: The manufacturer; ELIANA—Clinical Summaries (data cut-off December 31, 2017).[35]

Safety

Adverse Events During Lymphodepleting Chemotherapy

AEs during lymphodepleting chemotherapy were reported for ELIANA and ENSIGN, but not for Study B2101J. The most commonly occurring AE in ELIANA was nausea ([redacted]); in ENSIGN, it was febrile neutropenia ([redacted]). The incidence of SAEs was generally low ([redacted]) in ELIANA, with the highest reported being [redacted] infections and infestation. In ENSIGN, the highest incidence of SAEs occurred with febrile neutropenia as well as infections and

infestations, with a rate of [redacted] for each. [redacted] Safety outcomes during lymphodepleting chemotherapy are summarized in Table 23.

Table 23: Adverse Events During Lymphodepleting Chemotherapy – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA[a] (N = 73)			ENSIGN[b] (N = 28)		
	All Grades, n (%)	**Grade 3, n (%)**	**Grade 4, n (%)**	**All Grades, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**
Any AE						
Patients with ≥ 1 AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most frequently reported AE (cut-off ≥ 10% all grade), n (%)						
• Nausea	[redacted]	[redacted]	[redacted]		[redacted]	
• Decreased white blood cell count (%)	[redacted]	[redacted]	[redacted]			
• Infections and infestations	[redacted]	[redacted]	[redacted]			
• Anemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Febrile neutropenia		[redacted]		[redacted]	[redacted]	[redacted]
• Neutropenia				[redacted]	[redacted]	[redacted]
SAE						
Patients with ≥ 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most frequently reported SAE (≥ 2%), n (%)						
• Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death		[redacted]			[redacted]	
Cause of death	[redacted]			[redacted]		

AE = adverse event; SAE = serious adverse event; NA = not applicable (i.e., below the cut-off for the applicable category).
Sources: The manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—CSR (data cut-off February 1, 2017).[33]

Post-Tisagenlecleucel Infusion

All Adverse Events

All treated patients across the three included studies reported at least one AE during follow-up. The most commonly reported TEAEs included CRS, pyrexia, decreased appetite, hypogammaglobulinemia, febrile neutropenia, headache, anemia, decreased WBC count, and decreased platelet count. According to the investigators, AEs were reported primarily within eight weeks of tisagenlecleucel infusion, with the incidence decreasing substantially after this period. No CRS AEs were reported eight weeks after tisagenlecleucel infusion. The median time to CRS onset was three days, with a median duration of eight days. Overall, the incidence of AEs was similar across all subgroups evaluated and consistent for patients treated with tisagenlecleucel from the US or German production facilities. The most frequently reported AEs (cut-off ≥ 10 for grades 3 or 4 AEs) are listed in Table 24.

Table 24: Adverse Events Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

TEAEs	ELIANA (N = 79)			ENSIGN (N = 58)			B2101J (N = 56)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Patients with ≥ 1 AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most commonly reported AE (cut-off: ≥ 15% grade 3 or grade 4)									
CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	50 (89.3)	12 (21.4)	14 (25.0)
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44 (78.6)	36 (64.3)	8 (14.3)
Anemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	
Platelet count decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
WBC count decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; CRS = cytokine release syndrome; NR = not reported; TEAE = treatment-emergent adverse event; WBC = white blood cell.
Sources: European Medicines Agency;[24] information submitted by manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

The following published data were available from an earlier data cut-off (April 25, 2017).

Table 25: Adverse Events Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA (N = 75)		
	All Grades, n (%)	**Grade 3, n (%)**	**Grade 4, n (%)**
Patients with ≥ 1 AE	75 (100)		
Most commonly reported AE (cut-off: ≥ 10% grade 3 or grade 4)			
CRS	58 (77)	16 (21)	19 (25)
Pyrexia	30 (40)	8 (11)	2 (3)
Decreased appetite	29 (39)	10 (13)	1 (1)
Hypotension	22 (29)	8 (11)	7 (9)
AST increase	20 (27)	8 (11)	3 (4)
Hypokalemia	20 (27)	9 (12)	2 (3)
Hypoxia	18 (24)	10 (13)	4 (5)
Hypophosphatemia	18 (24)	8 (11)	1 (1)
Blood bilirubin increase	13 (17)	9 (12)	0 (0)

AE = adverse event; AST = aspartate aminotransferase; CRS = cytokine release syndrome.
Source: Maude 2018.[37]

Serious Adverse Events

Reported SAEs ranged from [redacted] to [redacted] across the three studies. The most frequently reported SAE was CRS, ranging from [redacted] to [redacted] across the studies. The proportions of patients who died after tisagenlecleucel treatment were [redacted] in ELIANA, ENSIGN, and Study B2101J, respectively. The most common cause of death was progression of the underlying disease, accounting for [redacted] of all deaths after tisagenlecleucel infusion in ELIANA, ENSIGN, and Study B2101J, respectively (Table 26).

Table 26: Serious Adverse Events Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-cell Acute Lymphoblastic Leukemia

	ELIANA[a] (N = 75)			ENSIGN[b] (N = 29)			B2101J[c] (N = 56)			ELIANA (FAS) (Data Cut-Off: April 25, 2017) (N = 75)
SAE, N (%)	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade3**	**Grade 4**	
Patients with ≥ 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Most common SAE (cut-off: ≥ 10% grade 3 or 4)										
• CRS	47 (62.7)	15 (20)	19 (25.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
• Febrile neutropenia	15 (20)	14 (18.7)	1 (1.3)	[redacted]	[redacted]	[redacted]	40 (71.4)		[redacted]	
• Hypotension	8 (10.7)	1 (1.3)	7 (9.3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
• Encephalopathy	[redacted]			[redacted]			[redacted]	[redacted]	[redacted]	
• Infections and infestations	25 (33.3)	15 (20)	10 (13.3)	[redacted]	[redacted]	[redacted]	12 (21.4)	[redacted]	[redacted]	
Death after treatment	[redacted]			[redacted]			[redacted]			
Overall, n (%)	[redacted]			[redacted]			[redacted]			19 (25.3)
Cause of death,	**n/N (%)**			**n/N (%)**			[redacted]			**Within 30 days of infusion**
[redacted]	[redacted]			[redacted]						Cerebral hemorrhage: 1 (1.3)
[redacted]	[redacted]			[redacted]						Progressive B-cell ALL: 1 (1.3)
										> 30 days of infusion
										Progression or relapse of B-cell ALL: 12 (16.0)
										Other: 5 (6.7)

ALL = acute lymphoblastic leukemia; CRS = cytokine release syndrome; SAE = serious adverse event.
Sources: Maude 2018;[37] European Medicines Agency;[24] information submitted by manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Adverse Events of Special Interest

CRS was the most commonly reported AESI. The incidence of AESIs is summarized in Table 27.

Table 27: Adverse Events of Special Interest Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Treatment-emergent AESIs	ELIANA (N = 75)			ENSIGN (N=58)			B2101J (N = 30)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Patients with ≥ 1 AESI	67 (89.3)	26 (34.7)	30 (40.0)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
CRS	58 (77)	16 (21.3)	19 (25.3)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Infections	32 (42.7)	16 (21.3)	2 (2.7)		[redacted]		[redacted]	[redacted]	[redacted]
Neurological AEs	30 (40.0)	9 (12.0)	1 (1.3)		[redacted]		[redacted]	[redacted]	[redacted]
Cytopenia not resolved by day 28	28 (37.3)	12 (16.0)	12 (16.0)		[redacted]		[redacted]		[redacted]
Febrile neutropenia	26 (34.7)	24 (32.0)	2 (2.7)		[redacted]		[redacted]	[redacted]	[redacted]
TLS	3 (4)	3 (4.0)	0		[redacted]		[redacted]	[redacted]	[redacted]

AE = adverse event; AESI = adverse event of special interest; CRS = cytokine release syndrome; NA = not applicable; NR = none reported; TLS = tumour lysis syndrome.
Sources: Maude 2018;[37] information submitted by manufacturer:
[a] ELIANA—CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017).[35]
[c] B2101J—CSR (data cut-off January 30, 2017):[34]

Research Question #2:

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

Efficacy

Overall Response Rate and Best Overall Response

The cut-off dates for the presented efficacy data are December 8, 2017 for JULIET and May 7, 2017 for Study A2101J. The primary efficacy outcome, ORsR at three months, and the breakdown of BOR for JULIET and Study A2101J, are shown in Table 28. Among the EAS of the Main Cohort in JULIET, 51.6% achieved ORsR (95% CI, 41.0 to 62.1); among DLBCL patients in Study A2101J, 50% achieved ORsR (95% CI, 23 to 77). The ORsRs by subgroups of age, sex, race, prior response status, IPI at enrolment, number of prior lines of chemotherapy, prior SCT, stage of disease, cell of origin, double- or triple-hit (CMYC/BCL2/BCL6), and time from most recent relapse to infusion in JULIET are shown in Appendix 7: Additional Data – Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Results were generally consistent across subgroups. Among the 16 patients of the FAS in Cohort A, the ORsR was [redacted] (Table 50).

Table 28: Primary Efficacy Outcomes – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201 (N = 93)	A2101J (N = 14 DLBCL)	JULIET: C2201 (Data Cut-Off Mar. 8, 2017) (N = 81)
Primary end point			
ORsR (CR + PR), n/N, • % (95% CI)	48/93 51.6 (41.0 to 62.1)	7/14[a] 50 (23 to 77)	43/81 53.1 (41.7 to 64.3)
Breakdown of BOR			
CR, n (%)	37 (39.8)	6 (43)[b]	32 (39.5)
PR, n (%)	11 (11.8)	NR	11 (13.6)
SD, n (%)	14 (15.1)	NR	11 (13.6)
PD, n (%)	24 (25.8)	NR	18 (22.2)
Unknown, n (%)	7 (7.5)	NR	9 (11.1)
Sensitivity Analyses for ORR (n/N) (%, 95% CI)			
Main Cohort – PPS [redacted]	[redacted]	NR	43/80 (53.8, 42.2 to 65.0)
Main Cohort patients in EAS plus patients who satisfied all clinical eligibility criteria and discontinued prior to tisagenlecleucel infusion [redacted]	[redacted]	NR	NR
Main Cohort patients in EAS plus enrolled patients who discontinued prior to tisagenlecleucel infusion [redacted]	[redacted]	NR	43/125 (34.4, 26.1 to 43.4)
Main Cohort EAS, excluding patients with no evidence of disease at baseline prior to tisagenlecleucel infusion and who remain CR after infusion [redacted]	[redacted]	NR	37/75 (49.3, 37.6 to 61.1)

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; EAS = efficacy analysis set; NR = not reported; ORsR = overall response rate; PD = progressive disease; PPS = per-protocol set; PR = partial response; SD = stable disease.

[a] 86% (95% CI, 33% to 98%) of DLBCL patients who achieved ORR maintained this response at the end of the follow-up period. (Manufacturer Clinical Summary, p.45).[62]

[b] At six months.

Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off);[36] European Medicines Agency;[24] Schuster SJ et al. NEJM 2018; December 1.[49]

Time-to-Event End Points

The secondary efficacy outcomes for the EAS of the Main Cohort in JULIET are provided in Table 29. Secondary outcomes for the FAS of Cohort A and all infused patients in JULIET are provided in Appendix 7: Additional Data – Relapsed or Refractory Diffuse Large B-Cell Lymphoma (Table 51). The reported outcomes for DOR, EFS, and PFS in JULIET were censored for SCT. At the time of data cut-off, the median DOR had not yet been reached. The six- and 12-month event-free probabilities (i.e., free of progression or death due to DLBCL) were 68.2% (95% CI, 52.2 to 79.8) and 65.1% (95% CI, 48.7 to 77.5), respectively. The median time to response (i.e., achievement of CR or PR) among responders was [redacted]. The median PFS (i.e., time from infusion to progression or death due to any cause) was [redacted]. The median EFS (i.e., time from infusion to disease progression or relapse, new anticancer therapy excluding SCT, or death from any cause) was [redacted] among all infused patients in the FAS. The median OS (i.e., time from infusion to death due to any cause) was 12 months in the EAS of Main Cohort, [redacted] in the FAS of Cohort A, and [redacted] in the FAS of all infused patients. The probability of survival at 12 months was 49.0% (95% CI, 39 to 59) among the Main Cohort. In the supporting study (A2101J), the median PFS among patients with DLBCL was 3.2 months; the median OS was 22.2 months (Table 29).

Table 29: Secondary Efficacy Outcomes – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201 (N = 93)[a]	A2101J (N = 14 DLBCL)	JULIET: C2201 (Data Cut-Off March 8, 2017) (N = 81 or N = 99)
Secondary end points			
Duration of response, median months (95% CI)	NE (10.0 to NE)	NE	NE
• Event-free probability at month 6, % (95% CI)	68.2 (52.2 to 79.8)	NR	73.5 (52.0, 86.6)
• Event-free probability at month 12, % (95% CI)	65.1 (48.7 to 77.5)	NR	NE
Time to response, median months (95% CI)	[redacted]	NR	0.9 (0.9 to 1.0)
PFS, median months (95% CI)	[redacted]	3.2 (0.9 to NE)	2.9 (2.2 to 6.2)
• Event-free probability at month 12, % (95% CI)[c]	[redacted]	NR	37.0 (25.0 to 48.9)
EFS, median months (95% CI)	[redacted]	NR	2.8 (2.1 to 3.5)
• Event-free probability of month 9, % (95% CI)[c]	[redacted]	NR	32.2 (20.9 to 44.0)
OS, median months (95% CI)	12 (7 to NE)	22.2 (NR)	NE (6.5 to NE)
• Probability of survival at month 12, % (95% CI)	49.0 (39 to 59)	NR	54.1 (38.5 to 67.3)

CI = confidence interval; EFS = event-free survival; NE = not estimated; NR = not reported; OS = overall survival; PFS = progression-free survival; SCT = stem cell transplant.
[a] N = 93 unless otherwise specified
[b] Censoring for hematopoietic SCT.
[c] Data based on an earlier data cut-off of September 6, 2017 (9-month follow-up) in Main Cohort + Cohort A. By that time, 106 patients had been infused.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off; Clinical Summary of Efficacy – September 7, 2017 data cut-off); Schuster SJ et al. NEJM 2017; 377;26:2545-54;[36,40,62] European Medicines Agency;[24] Schuster SJ et al. NEJM 2018; December 1.[49]

Health-Related Quality of Life

Table 30 and Table 31 show FACT-Lym and SF-36 scores, respectively, at baseline, month 3, month 12, and month 18 in the Main Cohort of JULIET. The changes from baseline scores for the FACT-Lym scales were within or above the estimated MCIDs, which are provided in Table 29. The SF-36 subscales of general health, [redacted], and vitality [redacted]) were above estimated MCIDs. [redacted]

Table 30: FACT-Lym Scores in Efficacy Analysis Set of Main Cohort – JULIET

	FACT-Lym							Data Cut-Off (March 8, 2017)		
Component	**Baseline** [redacted]	**Month 3** [redacted]	**Change From Baseline** [redacted]	**Month 12** [redacted]	**Change From Baseline** [redacted]	**Month 18** [redacted]	**Change From Baseline** [redacted]	**Baseline (N = 76)**	**Month 3 (N = 34)**	**Change From Baseline**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean**	**Mean**	**Mean**
Emotional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Functional	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Physical	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Social/family	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Lym subscale Estimated MCID: 2.9 to 5.4[57]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	44.2	NR	2.4
FACT-Lym TOI Estimated MCID: 5.5 to 11[57]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	81.4	NR	6.3
FACT-Lym Total Score Estimated: MCID: 6.5 to 11.2[57]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	121.2	NR	8.8
FACT-G total score Estimated: MCID: 3 to 7[58]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	77.4	NR	5.8

FACT-G = Functional Assessment of Cancer–General; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; MCID = minimal clinically important difference; SD = standard deviation; TOI = trial outcome index.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off); Maziarz RT et al. Blood 2017; 130:5215 (abstract).[36,63]

Table 31: Short Form (36) Health Survey Scores in Efficacy Analysis Set of Main Cohort – JULIET

	SF-36							Data Cut-Off (March 8, 2017)		
Component	**Baseline** [redacted]	**Month 3** [redacted]	**Change From Baseline** [redacted]	**Month 12** [redacted]	**Change From Baseline** [redacted]	**Month 18** [redacted]	**Change From Baseline** [redacted]	**Baseline (N = 76)**	**Month 3 (N = 34)**	**Change From Baseline**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean**	**Mean**	**Mean**
Bodily Pain Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
General Health Estimated MCID: 2[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	9.6
Mental Health Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Physical Functioning Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	3.3
Role Emotional Estimated MCID: 4[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Role Physical Estimated MCID: 4[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	4.0
Social Functioning Estimated MCID: 4[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	NR	NR	NR
Vitality Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52.6	NR	4.9
PCS Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	43.9	NR	NR

SF-36								Data Cut-Off (March 8, 2017)		
Component	**Baseline** [redacted]	**Month 3** [redacted]	**Change From Baseline** [redacted]	**Month 12** [redacted]	**Change From Baseline** [redacted]	**Month 18** [redacted]	**Change From Baseline** [redacted]	**Baseline (N = 76)**	**Month 3 (N = 34)**	**Change From Baseline**
MCS Estimated MCID: 3[59,63]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	48.6	NR	NR

MCID = minimal clinically important difference; MCS = Mental Component Summary; NR = not reported; PCS = Physical Component Summary; SD = standard deviation; SF-36 = Short Form 36 Health Survey version 2.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off); Maziarz RT et al. Blood 2017; 130:5215 (abstract).[36,63]

Hospitalization

Table 32 shows the number of patients who received tisagenlecleucel infusion during hospitalization, the number hospitalized within three days of infusion, the number of hospitalizations, and duration of hospital and ICU stay.

Table 32: JULIET – Health Care Resource Utilization in All Infused Patients

	JULIET: C2201 (N = 111)
Tisagenlecleucel infusion during hospitalization, n (%)	
• No	[redacted]
• Yes	[redacted]
Hospitalization within 3 days of CTL019 infusion, n (%)	
• No	[redacted]
• Yes	[redacted]
Number of hospitalizations, n (%)	
• 0	[redacted]
• 1	[redacted]
• 2	[redacted]
• 3	[redacted]
• 4	[redacted]
• 5	[redacted]
• 6	[redacted]
• 7	[redacted]
Total duration of hospitalization, days (N = 104)	
• Mean	[redacted]
• Median	[redacted]
• Range	[redacted]
Average duration of each hospitalization, days (N = 104)	
• Mean	[redacted]
• Median	[redacted]
• Range	[redacted]
Total duration of ICU stay, days (N = 28)	
• Mean	[redacted]
• Median	[redacted]
• Range	[redacted]

ICU = intensive care unit.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off).[36]

Harms

The cut-off dates for the presented safety data are December 8, 2017 for JULIET and May 7, 2017 for Study A2101J. In JULIET, [redacted] of 111 patients who received tisagenlecleucel (Main Cohort and Cohort A) also received lymphodepleting therapy prior to infusion. Harms (AEs and SAEs) that occurred during the lymphodepleting therapy phase are provided in Table 33. AEs that occurred post-tisagenlecleucel infusion in 10% or more of all infused patients, regardless of relationship to treatment, are provided in Table 34. [redacted] patients experienced at least one AE. The most common were AESIs within eight weeks of infusion

([redacted]), which included CRS ([redacted]), hematopoietic cytopenias not resolved by day 28 ([redacted]), infections (34.2%), neurological events ([redacted]), febrile neutropenia ([redacted]), and TLS ([redacted]). [redacted] patients experienced hypogammaglobulinemia. In Table 35, SAEs with at least two patients in all grades are listed for all infused patients. The majority (64.9%) experienced at least one event. There were [redacted] deaths post-infusion, three (2.7%) that occurred within 30 days of infusion (cause of death: DLBCL progression), and [redacted] that occurred after 30 days post infusion ([redacted]). CRS classified as an SAE was experienced by 27% of patients; among them, 9.9% were grade 3 and 7.2% grade 4.Table 36 provides data on the characteristics of CRS and how it was managed among the 64 patients in JULIET who experienced CRS. Tocilizumab was administered as one or two doses in patients with grade 3 or 4 CRS. No patient received siltuximab. Corticosteroids were given to [redacted] patients. A management algorithm for CRS is provided in Appendix 10.

In Appendix 7: Additional Data – Relapsed or Refractory Diffuse Large B-Cell Lymphoma, Table 52 provides selected safety data for the supporting study, which reported the number of events in patients with DLBCL and with follicular lymphoma (14 patients in each case). CRS occurred 16 times; among them, four instances were grade 3 and one was grade 4.

Table 33: Selected Harms During Lymphodepleting Chemotherapy – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

	JULIET: C2201 (N = 103)[a]		
	All Grades	Grade 3	Grade 4
Adverse Events			
At least one event, n (%)	[redacted]	[redacted]	[redacted]
Anemia	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
WBC count decrease	[redacted]	[redacted]	[redacted]
Neutrophil count decrease	[redacted]	[redacted]	[redacted]
Infection or infestation	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Platelet count decrease	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Nervous system	[redacted]	[redacted]	[redacted]
Lymphocyte count decrease	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Weight decrease	[redacted]	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Leukopenia	[redacted]	[redacted]	[redacted]
Pancytopenia	[redacted]	[redacted]	[redacted]
Serious Adverse Events			
At least one event, n (%)	[redacted]	[redacted]	[redacted]

	JULIET: C2201 (N = 103)[a]		
	All Grades	Grade 3	Grade 4
Febrile neutropenia	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]
Atrial flutter	[redacted]	[redacted]	[redacted]
Tachycardia	[redacted]	[redacted]	[redacted]

WBC = white blood cell.
[a] All patients who received tisagenlecleucel infusion (Main Cohort + Cohort A) and lymphodepleting chemotherapy,
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off).[36]

Table 34: Adverse Events Post-Tisagenlecleucel Infusion, Regardless of Relationship to Tisagenlecleucel – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Adverse Event (≥ 10% all grade)	JULIET: C2201 (N = 111)[a]			JULIET: C2201 (Data Cut-Off March 8, 2017) (N = 99)		
	All Grades	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
At least one event, n (%)	111 (100)	31 (27.9)	68 (61.3)	98 (99.0)	28 (28.3)	57 (57.6)
AESIs (within 8 weeks of infusion)[b]	[redacted]	[redacted]	[redacted]			
• CRS	64 (57.7)	15 (13.5)	9 (8.1)			
• Hematopoietic cytopenias not resolved by day 28	49 (44.1)	18 (16.2)	18 (16.2)	36 (36.4)	15 (15.2)	12 (12.1)
• Infections	38 (34.2)	20 (18.0)	2 (1.8)			
• Neurological event	23 (20.7)	8 (7.2)	5 (4.5)	21 (21.2)	8 (8.1)	4 (4.0)
• Febrile neutropenia	17 (15.3)	14 (12.6)	2 (1.8)			
• TLS	1 (0.9)	1 (0.9)	0 (0)			
CRS	64 (57.7)	15 (13.5)	9 (8.1)	57 (57.6)	15 (15.2)	8 (8.1)
Infections or infestations	60 (54.1)	[redacted]	[redacted]	52 (52.5)	25 (25.3)	4 (4.0)
Anemia	53 (47.7)	41 (36.9)	2 (1.8)	NR	NR	NR
Pyrexia	39 (35.1)	6 (5.4)	0 (0)	NR	NR	NR
Neutrophil count decrease	38 (34.2)	9 (8.1)	28 (25.2)	NR	NR	NR
Platelet count decreased	37 (33.3)	6 (5.4)	25 (22.5)	NR	NR	NR
WBC count decreased	37 (33.3)	15 (13.5)	19 (17.1)	NR	NR	NR
Diarrhea	35 (31.5)	1 (0.9)	0 (0)	NR	NR	NR
Nausea	32 (28.8)	1 (0.9)	0 (0)	NR	NR	NR
Hypotension	29 (26.1)	7 (6.3)	3 (2.7)	NR	NR	NR
Fatigue	28 (25.2)	7 (6.3)	0 (0)	NR	NR	NR
Headache	25 (22.5)	1 (0.9)	0 (0)	NR	NR	NR
Hypokalemia	25 (22.5)	9 (8.1)	0 (0)	NR	NR	NR
Neutropenia	22 (19.8)	7 (6.3)	15 (13.5)	NR	NR	NR
Cough	19 (17.1)	0 (0)	0 (0)	NR	NR	NR
Dyspnea	19 (17.1)	5 (4.5)	0 (0)	NR	NR	NR
Hypomagnesemia	19 (17.1)	0 (0)	0 (0)	NR	NR	NR
Hypophosphatemia	19 (17.1)	15 (13.5)	0 (0)	NR	NR	NR
Febrile neutropenia	18 (16.2)	14 (12.6)	3 (2.7)	13 (13.1)	11 (11.1)	2 (2.0)
Constipation	18 (16.2)	1 (0.9)	0 (0)	NR	NR	NR
Peripheral edema	17 (15.3)	0 (0)	0 (0)	NR	NR	NR

Adverse Event (≥ 10% all grade)	JULIET: C2201 (N = 111)[a]			JULIET: C2201 (Data Cut-Off March 8, 2017) (N = 99)		
	All Grades	Grade 3	Grade 4	All Grade	Grade 3	Grade 4
Chills	14 (12.6)	0 (0)	0 (0)	NR	NR	NR
Thrombocytopenia	14 (12.6)	3 (2.7)	10 (9.0)	NR	NR	NR
Decreased appetite	13 (11.7)	4 (3.6)	0 (0)	NR	NR	NR
Dizziness	13 (11.7)	0 (0)	0 (0)	NR	NR	NR
URTI	13 (11.7)	2 (1.8)	0 (0)	NR	NR	NR
Anxiety	12 (10.8)	1 (0.9)	0 (0)	NR	NR	NR
Blood creatinine increase	12 (10.8)	4 (3.6)	0 (0)	NR	NR	NR
Tachycardia	12 (10.8)	3 (2.7)	0 (0)	NR	NR	NR
Weight decrease	12 (10.8)	3 (2.7)	0 (0)	NR	NR	NR

AEs = adverse events; AESI = adverse events of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; NR = not reported; TLS = tumour lysis syndrome; URTI = upper respiratory tract infection; WBC = white blood cell.
[a] All patients who received tisagenlecleucel infusion (Main Cohort + Cohort A).
[b] AESI = CRS, tumour lysis syndrome, neutropenic fever, cytopenia > 28 days (that is, cytopenias not resolving by day 28 post-tisagenlecleucel infusion); drop in cardiac ejection fraction, neurological events, hepatic events, and infections.
Sources: The manufacturer. (CSR, JULIET – December 8, 2017 data cut-off);[36] European Medicines Agency;[24] Schuster SJ et al. NEJM 2018; December 1.[49]

Table 35: Serious Adverse Events Post-Tisagenlecleucel Infusion, Regardless of Relationship to Tisagenlecleucel – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Serious Adverse Events (at least two patients in all grades)	JULIET: C2201 (N = 111)		
	All Grades	Grade 3	Grade 4
At least one event, n (%)	72 (64.9)	31 (27.9)	31 (27.9)
Death		N/A	N/A
• Within 30 days infusion	3 (2.7)		
• > 30 days post-infusion	[redacted]		
CRS	30 (27.0)	11 (9.9)	8 (7.2)
Febrile neutropenia	9 (8.1)	6 (5.4)	3 (2.7)
Pyrexia	8 (7.2)	5 (4.5)	0 (0)
Acute kidney injury	4 (3.6)	1 (0.9)	2 (1.8)
Encephalopathy	4 (3.6)	1 (0.9)	3 (2.7)
Fatigue	4 (3.6)	4 (3.6)	0 (0)
Clostridium difficile infection	3 (2.7)	3 (2.7)	0 (0)
Confusional state	3 (2.7)	3 (2.7)	0 (0)
Dyspnea	3 (2.7)	2 (1.8)	0 (0)
Multiple organ dysfunction syndrome	3 (2.7)	0 (0)	3 (2.7)
Neutropenia	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	3 (2.7)	1 (0.9)	2 (1.8)
Pneumonia	3 (2.7)	3 (2.7)	0 (0)
Bone marrow failure	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]
GI hemorrhage	[redacted]	[redacted]	[redacted]
Hypotension	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]

Serious Adverse Events (at least two patients in all grades)	JULIET: C2201 (N = 111)		
	All Grades	Grade 3	Grade 4
Pancytopenia	[redacted]	[redacted]	[redacted]
Pneumocystis jirovecii pneumonia	[redacted]	[redacted]	[redacted]
Prostate cancer	[redacted]	[redacted]	[redacted]
Pulmonary embolism	[redacted]	[redacted]	[redacted]
Sepsis	[redacted]	[redacted]	[redacted]

CRS = cytokine release syndrome; GI = gastrointestinal.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off);[36] European Medicines Agency.[24]

Table 36: Cytokine Release Syndrome Post-Tisagenlecleucel Infusion - r/r DLBCL

	JULIET: C2201 (N_{CRS}= 64)	JULIET: C2201 (Data Cut-Off March 8, 2017) (N_{CRS} = 57)
Time to onset (days)		
Median (range)	3.0 [redacted]	3.0
Duration (days)		
Median (range)	7.0 (2-30)	7.0
Concurrent infection		
n (%)	[redacted]	NR
Admitted to ICU		
n (%)	[redacted]	NR
Duration of ICU stay (days)		
Median (range)	[redacted]	NR
Hypotension that required intervention		
n (%)	[redacted]	28 (49.1)
Dialysis required		
n (%)	[redacted]	NR
Pulmonary abnormalities		
n (%)	[redacted]	NR
DIC observed		
n (%)	[redacted]	3 (5.3)
Bleeding observed		
n (%)	[redacted]	NR
Blood product given for bleeding		
n (%)	[redacted]	NR
Tocilizumab		
1 dose, n (%)	[redacted]	6 (10.5)
2 doses, n (%)	[redacted]	9 (15.8)
Corticosteroids		
n (%)	[redacted]	11 (19.3)

CRS = cytokine release syndrome; DIC = disseminated intravascular coagulation; ICU = intensive care unit.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off);[36] European Medicines Agency;[24] Schuster SJ et al. NEJM 2018; December 1.[49]

Research Question #3:

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

The comprehensive consensus guidelines on the care of children receiving CAR T-cell therapy were developed by an expert panel formed by a collaboration between the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network Hematopoietic Stem Cell Transplantation Subgroup and the MD Anderson Cancer Center CAR-T-Cell-Therapy-Associated TOXicity (CARTOX) Program. The characteristics of the guidelines are summarized in Table 37.

Table 37: Characteristics of Evidence-Based Clinical Practice Guidelines for CAR T-Cell Therapy in r/r B-Cell ALL

Guideline			Methodology			
Intended Users/ Target Population, Country of Development	**Intervention**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality Assessment**	**Recommendations Development and Evaluation**	**Guidelines Validation**
Mahadeo, 2018[41] (PALISI-CATOX Consensus guidelines on the care of children receiving CAR T-cell therapy)						
Health care practitioners (physicians, nurses, pharmacists) Pediatric patients receiving CAR T-cell therapy US	CAR T Cell therapies (including tisagenlecleucel)	• Patients selection, evaluation, and monitoring • Bridging chemotherapy • Lymphodepleting chemotherapy • CAR T-cell infusion • CRS grading and management • Algorithms for the management of other safety issues related to CAR T-cell therapy	NR	Performed using modified Delphi method Definitions of the levels and grades assigned to the evidence are in Appendix 11: Clinical Practice Guideline Recommendations.	Recommendations were formulated through expert consensus, within a multidisciplinary guideline development team.	NR
NCCN Clinical Practice Guidelines in Oncology – ALL (March 12, 2018)[13]						
Health care practitioners (physicians, nurses, managed care organizations, pharmacists) Patients (adults and children) with ALL US	Treatment induction and consolidation therapies (including tisagenlecleucel)	• Diagnosis • Work-up and risk stratification • Relapsed/refractory disease, treatment • Supportive care • Response assessment	English language publications only: clinical trials (phases II to IV), guidelines, meta-analyses, RCTs, SRs, and validation studies.	NR	Multidisciplinary panel of NHL experts – critical review of evidence integrated with clinical expertise and consensus Recommendations are categorized based on evidence and consensus: Category 1: Based on high-level evidence, uniform NCCN consensus that the intervention is appropriate	NR

Guideline			Methodology			
Intended Users/ Target Population, Country of Development	**Intervention**	**Major Outcomes Considered**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality Assessment**	**Recommendations Development and Evaluation**	**Guidelines Validation**
					Category 2A: Based on lower-level evidence, uniform NCCN consensus that the intervention is appropriate Category 2B: Based on lower-level evidence, NCCN consensus that the intervention is appropriate Category 3: Based on any level of evidence, major NCCN disagreement that the intervention is appropriate	

ALL = acute lymphoblastic leukemia; CAR = chimeric antigen receptor; CARTOX = CAR-T-Cell-Therapy-Associated TOXicity (Working Group); CRS = cytokine release syndrome; HSCT = hematopoietic stem cell transplantation; PALISI = Pediatric Acute Lung Injury and Sepsis Investigators.

The guidelines cover a wide variety of issues and propose recommendations for many aspects of therapy considerations, such as patient selection and evaluation, leukapheresis for CAR T-cell production, preparative lymphodepletion treatment, bridging chemotherapy, cell infusion, in-patient and outpatient management, and monitoring, grading, and management CRS. A summary of selected recommendations is provided in Table 55 of Appendix 11.

The quality of the consensus guidelines[41] on the care of children receiving CAR T-cell therapy is high based on the AGREE II assessment criteria.[31] The objectives and applicable population are clearly stated. The methods for formulating recommendations are well-described and the rigour of the recommendations is linked with the level and grade of the supporting evidence. The recommendations are presented with clarity. The authors disclose potential competing interests. There is no indication of financial or other factors influencing the editorial independence of the expert panel that formulated the recommendations. The main limitation is that the methods of evidence collection, selection, and synthesis are not adequately described. Also, there is no indication of patient input; and it is unknown if the guidelines were externally peer-reviewed before publication.

The NCCN guideline in ALL[13] is comprehensive and addresses several aspects of care, including diagnosis, treatment by disease stage, and management of r/r disease. However, specific information on tisagenlecleucel for r/r B-cell ALL patients is scanty, and the recommendations for its use in this patient population are not rated or linked to supporting evidence.

Research Question #4:

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

The NCCN has formulated updated recommendations for the treatment of patients with B-cell lymphomas, including DLBCL (Table 38). In the most recent version, recommendations are provided for two CAR T-cell therapies: axicabtagene ciloleucel and tisagenlecleucel. The development of the guideline followed the NCCN process,[64] which includes a critical review of evidence and consensus by a multidisciplinary panel of NHL experts. The guideline provides recommendations on the appropriate patient candidates for tisagenlecleucel therapy and management of CRS (Appendix 11, Table 59).

Based on the AGREE II assessment criteria,[31] the NCCN guideline is of high quality overall. The guideline is comprehensive and addresses several aspects of care, including diagnosis, treatment by disease stage, and management of r/r disease. Its main limitation is that the quality of the underlying evidence base is not specifically described.

Table 38: Characteristics of Evidence-Based Clinical Practice Guidelines for CAR T-Cell Therapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Guideline		Methodology			
Name	**Intervention**	**Evidence Collection, Selection, and Synthesis**	**Evidence Quality Assessment**	**Guideline Validation**	**Recommendations, Development, and Evaluation**
NCCN Clinical Practice Guidelines – B-Cell Lymphomas (Oct. 2 2018)[42] Section for patients with DLBCL	Tisagenlecleucel	English language publications only: clinical trials (phases II to IV), guidelines, meta-analyses, RCTs, SRs, and validation studies	NR	NR	Multidisciplinary panel of NHL experts – critical review of evidence integrated with clinical expertise and consensus Recommendations are categorized based on evidence and consensus: Category 1: Based on high-level evidence, uniform NCCN consensus that the intervention is appropriate Category 2A: Based on lower-level evidence, uniform NCCN consensus that the intervention is appropriate Category 2B: Based on lower-level evidence, NCCN consensus that the intervention is appropriate Category 3: Based on any level of evidence, major NCCN disagreement that the intervention is appropriate

DLBCL = diffuse large B-cell lymphoma; NCCN = National Comprehensive Cancer Network; NHL = non-Hodgkin lymphoma; NR = not reported; RCT = randomized controlled trial; SR = systematic review.

Discussion

Children and young adult patients with r/r B-cell ALL, and adult patients with r/r DLBCL, currently have few treatment options available, aside from salvage chemotherapies and SCT. A high clinical need exists in these patient populations for effective therapies. Tisagenlecleucel has a potentially important place in the treatment of patients with r/r B-cell ALL and r/r DLBCL who have failed two previous lines of treatment. The FDA approved tisagenlecleucel for the treatment of pediatric r/r B-cell ALL in August 2017 and for the treatment of adult r/r DLBCL in May 2018. Health Canada approved tisagenlecleucel for these indications in September 2018.

The pivotal ELIANA study and two supporting studies (ENSIGN and B2101J) demonstrated clinical benefits of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL. ELIANA met its primary and key secondary end points by demonstrating that the lower-bound CI of the ORR, as assessed by the IRC, exceeded the pre-specified 20% threshold within three months of follow-up. Similarly, the supporting study, ENSIGN, met its primary end point, with the lower bound of the IRC-assessed ORR at six months exceeding the pre-specified 20% threshold. Overall, the results of the ENSIGN study were consistent with those of ELIANA. While the estimated probabilities of OS at six and 12 months were high, a large proportion of patients discontinued the study after tisagenlecleucel infusion primarily due to lack of efficacy at the data cut-off dates, with their data censored at the date of the last adequate disease assessment on or before the earliest censoring event. This high discontinuation rate limits the strength of the evidence for durable remissions in the long term. Additionally, the results of the HRQoL assessments in the pivotal ELIANA study, using both PedsQL and EQ-5D tools, showed that the remission was accompanied by clinically meaningful improvements in patients' quality of life. However, the HRQoL findings have potential for bias since the analyses were based on patient-reported data and were limited to patients who responded to tisagenlecleucel. Given the potential for bias and limited generalizability, the HRQoL findings should be interpreted with caution.

In the pivotal study of adults with r/r DLBCL, JULIET demonstrated that the primary outcome of ORsR threshold ≥ 20% after three months was met. In secondary outcome analyses, high event-free probabilities were observed among responders, and a statistically significant probability of survival at 12 months, with a point estimate of 49%, was shown. Study A2101J supported the results of the pivotal study, with an ORsR of 50% at three months. One evidence-based guideline for tisagenlecleucel in r/r DLBCL was identified that provided recommendations about appropriate patient selection and management of associated toxicities.[17] Neelapu et al. also provided recommendations for the assessment and management of toxicities of CAR T-cell therapy, based on the consensus of the CARTOX Working Group; however, while providing useful information, this guideline was not formally included, as no mention was made that recommendations were based on an evidence review.[65] Aside from matching-adjusted indirect comparisons of tisagenlecleucel with salvage chemotherapies or pixantrone (as described in Appendix 12: Indirect Comparisons), no direct comparative data were available for tisagenlecleucel in patients with r/r DLBCL.

AEs associated with tisagenlecleucel were common in both ALL and DLBCL. In the pivotal studies, ELIANA and JULIET, all patients experienced at least one AE, with CRS being the most frequent. Among patients with ALL, [redacted] experienced CRS; a large percentage of cases were grade 3 or 4 in severity ([redacted]). Among patients with DLBCL, 58% experienced CRS and [redacted]

[redacted]. Other AESIs, such as infections and neurological events, were also experienced by many patients. Although the incidence of AEs was consistently high across all studies, they were generally manageable with supportive care. The management of CRS was based on the clinical presentation and in accordance with the CRS management algorithm available in the product monograph[23] and presented in Appendix 10.

The manufacturer has established a Risk Management Plan to monitor and safely deliver tisagenlecleucel treatment to patients in Canada.[25] The Risk Management Plan will consist of controlled distribution and education programs, a long-term follow-up study for the collection of ongoing safety data, and patient enrolment into a registry for cellular therapy managed by the Center for International Blood and Marrow Transplant Research.

The inclusion and exclusion criteria helped to ensure that study populations across the three studies were representative of children and young adults with r/r B-cell ALL, and across the two studies for adult patients with DLBCL. Considering that the pivotal ELIANA study was conducted in 25 countries including Canada, and that the results of its primary and preplanned subgroups analyses were consistent within the study and with the supporting studies, the potential generalizability of the reported findings in the Canadian context is high. Overall, the consistencies in outcomes across the studies and within the individual studies demonstrate the robustness of the reported clinical efficacy and safety of tisagenlecleucel for the treatment of r/r B-cell ALL in children and young adults.

The main limitations of the included studies were the open-label, single-arm, non-randomized designs. Non-randomized studies are inherently weaker and the results prone to multiple biases. The single-arm design, which excluded comparators, cannot be used to directly evaluate the efficacy and safety of tisagenlecleucel compared with other interventions, such as allogeneic SCT, clofarabine, inotuzumab, and blinatumomab for r/r B-cell ALL or for salvage treatments for r/r DLBCL. In addition, studies that compare tisagenlecleucel with other CAR T-cell therapies, such as axicabtagene ciloleucel for DLBCL, are needed.

The reliance on an IRC to assess outcomes likely reduced outcome-assessment bias in ELIANA, ENSIGN, and JULIET. Unlike ELIANA and ENSIGN, which were multi-centre studies of single-infusion tisagenlecleucel, study B2101 was a single-centre study that allowed for multiple, non-standardized infusion doses with outcomes evaluated by a local investigator. Similarly, Study A2101J — the supporting study for DLBCL — was conducted at a single centre with few patients. Other limitations in the available data were the lack of long-term follow-up and the large number of discontinuations pre- and post-infusion. In addition, in the ALL studies, the assessment of efficacy was not referenced to a set time, but rather to a broad period, such as “within three months” or “during six months” after tisagenlecleucel infusion.

The primary gaps in the evidence for tisagenlecleucel are the absence of data that directly compare tisagenlecleucel with other treatments used in r/r disease (commonly encountered in oncology trials) and the absence of long-term efficacy and safety data for this new therapy (however, note that the studies are ongoing up to five years). Indirect comparisons with historical cohorts were generated for ALL and DLBCL (Appendix 12: Indirect Comparisons). Long-term safety data will be collected in a separate study protocol for up to 15 years post-infusion. Appendix 13: Ongoing Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy lists CAR T-cell therapy trials that have been registered in Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform for ALL and NHL. In addition, the Health Canada indication for adults with NHL includes those with DLBCL,

DLBCL arising from transformed follicular lymphoma, and high-grade lymphoma. There are limited data for the latter two groups. In JULIET, about 19% of patients had DLBCL arising from transformed follicular lymphoma; however, outcomes were not available specifically for this group. No data were identified for the administration of tisagenlecleucel for high-grade lymphoma, which may be a distinct entity. Another area of uncertainty is how tisagenlecleucel manufacturing failures will be handled and whether improvements will be observed after implementation and accumulation of experience with the intervention. In the ALL and DLBCL trials, the incidence of failures ranged from [redacted] and [redacted], respectively.

The Institute for Clinical and Economic Review (ICER) conducted an assessment of CAR T-cell therapies for pediatric ALL and adult DLBCL.[6] The three tisagenlecleucel trials (ELIANA, ENSIGN, and B2101J) for ALL and the two trials (JULIET, A2101J) for DLBCL were reviewed. ICER concluded that tisagenlecleucel has higher rates of CR, OS, and disease-free survival compared with other therapies for ALL, and higher rates of CR compared with salvage therapies for DLBCL, in naive comparisons. However, the review also highlighted the high frequency of important harms observed with tisagenlecleucel, the uncertainties of the evidence base (i.e., single-arm, short follow-up), and the lack of long-term data. From a payer perspective, the National Institute for Health and Care Excellence (NICE) did not recommend tisagenlecleucel for r/r DLBCL because the cost-effectiveness estimates were above the range considered acceptable.[66] NICE also highlighted the absence of data to compare tisagenlecleucel with salvage therapy and long-term follow-up.[66]

The efficacy findings from ELIANA, ENSIGN, and B2101J suggest that in pediatric and young adults with r/r B-cell ALL, treatment with tisagenlecleucel results in significant ORR in the majority of patients. [redacted] The HRQoL results from ELIANA were inconclusive because data were available only for patients who had BOR of CR or CRi, and the number of patients with data for analysis decreased progressively at each successive time of assessment. JULIET also demonstrated tisagenlecleucel responses on ORsR and OS in adults with r/r DLBCL. However, tisagenlecleucel has the potential to cause severe AEs and is resource-intensive, requiring an established infrastructure to ensure patients receive the treatment safely and according to protocol standards. Unresolved therapeutic issues, such as treatment of patients outside of the indicated age range and rationale for repeated infusions, must also be addressed. Thus, more long-term follow-up and comparator data, as well as further clinical experience, are required to fully understand the benefit-risk profile of tisagenlecleucel and its place in therapy in hematological malignancies. Upon the availability of additional data from trials, registries, and long-term follow-up, a reassessment of the efficacy and safety of tisagenlecleucel will be warranted.

References

1. Brown PA, Shah B, Fathi A, et al. NCCN guidelines insights: Acute lymphoblastic leukemia, version 1.2017. *J Natl Compr Canc Netw.* 2017;15(9):1091-1102.
2. National Cancer Institute. Childhood acute lymphoblastic leukemia treatment (PDQ®)–health professional version. 2018; https://www.cancer.gov/types/leukemia/hp/child-all-treatment-pdq. Accessed 2018 May 1.
3. Canadian Cancer Society. Non-Hodgkin lymphoma: diffuse large B-cell lymphoma. 2018; http://www.cancer.ca/en/cancer-information/cancer-type/non-hodgkin-lymphoma/non-hodgkin-lymphoma/diffuse-large-b-cell-lymphoma/?region=on. Accessed 2018 Jul 4.
4. Lymphoma Canada. Understanding diffuse large B cell lymphoma (DLBCL). 2018; https://www.lymphoma.ca/DLBCL. Accessed 2018 Jul 4.
5. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. A systematic literature review of the clinical and epidemiological burden of acute lymphoblastic leukaemia (ALL). *Eur J Cancer Care.* 2005;14(1):53-62.
6. Chimeric antigen receptor T-cell therapy for B-cell cancers: Effectiveness and value. Boston (MA): Institute for Clinical and Economic Review; 2018 Mar 23: https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Accessed 2018 Jul 4.
7. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. *Leukemia.* 2008;22(12):2142-2150.
8. Lau C, Nagamuthu C, Pole J, et al. Survival outcomes of a population-based cohort of adolescent and young adult (AYA), acute lymphoblastic leukemia (ALL) patients in Ontario, Canada: The IMPACT Cohort. *International Journal of Population Data Science.* 2018;3(3):232.
9. Kochenderfer JN, Dudley ME, Kassim SH, et al. Chemotherapy-refractory diffuse large B-cell lymphoma and indolent B-cell malignancies can be effectively treated with autologous T cells expressing an anti-CD19 chimeric antigen receptor. *J Clin Oncol.* 2015;33(6):540-549.
10. Wang HI, Smith A, Aas E, et al. Treatment cost and life expectancy of diffuse large B-cell lymphoma (DLBCL): a discrete event simulation model on a UK population-based observational cohort. *Eur J Health Econ.* 2017;18(2):255-267.
11. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. *Blood.* 2017;130(16):1800-1808.
12. Raut LS, Chakrabarti PP. Management of relapsed-refractory diffuse large B cell lymphoma. *South Asian J Cancer.* 2014;3(1):66-70.
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute lymphoblastic leukemia Version I.2018 - March 12, 2018. Fort Washington (PA): National Comprehensive Cancer Network; 2018: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2018 Aug 31.
14. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. *J Clin Oncol.* 2010;28(14):2339-2347.
15. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. *Blood Cancer J.* 2017;7(6):e577.
16. Crotta A, Keir C, Cleret J, Thomas S, Armstrong L. Disease characteristics and overall survival in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia after stem cell transplantation. *Biol Blood Marrow Transplant.* 2016;23(3):S50.
17. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas Version 4.2018 - June 25, 2018. Fort Washington (PA): National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2018 Aug 31.
18. Davila ML, Riviere I, Wang X, et al. Efficacy and toxicity management of 19-28z CAR T cell therapy in B cell acute lymphoblastic leukemia. *Sci Transl Med.* 2014;6(224):224ra225.
19. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: An exploration of methods for review, economic evaluation and appraisal. *Health Technology Assessment.* 2017;21(7):1-204.
20. Medscape. Tisagenlecleucel (Rx): Dosing & uses. 2018; https://reference.medscape.com/drug/kymriah-tisagenlecleucel-1000169. Accessed 2018 Jul 4.
21. U.S. Food and Drug Administration. FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome. 2017 Sep 7; https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm574154.htm. Accessed 2018 Jul 4.
22. Grupp S, Frey N, Aplenc R, et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019 cells) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory all. *Bone Marrow Transplant.* 2014;49(Suppl 1):S1.
23. PrKymriah™ (tisagenlecleucel) cell suspension in infusion bag, 2.0 x 10^6 to 6.0 x 10^8 CAR-positive viable T-cells, for intravenous use [product monograph]. Dorval (QC): Novartis Pharma Canada Inc; 2018 Sept 5.
24. Committee for Medicinal Products for Human Use. Assessment report (EPAR): Kymriah (tisagenlecleucel). *(European public assessment report)*. London (GB): European Medicines Agency; 2018: https://www.ema.europa.eu/documents/assessment-report/kymriah-epar-public-assessment-report_en.pdf.
25. Biologics and Genetic Therapies Directorate. Biologics Safety and Efficacy Assessment Report (BSEAR) - KYMRIAH (tisagenlecleucel). **[CONFIDENTIAL manufacturer's submission]**. Ottawa (ON): Health Canada; 2018 Sep 4.
26. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol.* 2007;7(1):10.

27. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-34.

28. Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ.* 2016;352:i157.

29. CADTH. Tisagenlecleucel (Kymriah) for pediatric acute lymphoblastic leukemia and diffuse large B-cell lymphoma. 2018; https://cadth.ca/tisagenlecleucel-kymriah-pediatric-acute-lymphoblastic-leukemia-and-diffuse-large-b-cell-lymphoma. Accessed 2018 Oct 24.

30. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ.* 2016;355.

31. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ.* 2010;182(18):E839-842.

32. Clinical Study Report: B2202. A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Sep 22.

33. Clinical Study Report: B2205J. A Phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2016 Nov 23.

34. Clinical Study Report: B2101J. A phase I/IIA study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR zeta and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Sep 27.

35. Clinical Summary: KYMRIAH (tisagenlecleucel) for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 May 28.

36. Clinical Study Report: C2201 data cutoff Dec 8 2017. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL): Final Analysis Results (FAR) **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Apr 17.

37. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448.

38. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371(16):1507-1517.

39. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med.* 2017;45(2):e124-e131.

40. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017;377(26):2545-2554.

41. Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nat Rev Clin Oncol.* 2018.

42. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas Version 5.2018 - October 2, 2018. Fort Washington (PA): National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2018 Oct 29.

43. Center for Drug Evaluation and Research. Statistical review(s). Kymriah (tisagenlecleucel). Company: Novartis Pharmaceutical Corporation. Application No.: 125646. Approval date: August 30, 2017 (FDA drug approval package). Rockville (MD): U.S. Food and Drug Administration (FDA); 2018: https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm. Accessed 2018 Oct 24.

44. Novartis Pharmaceuticals Corporation. Oncologic Drugs Advisory Committee briefing document: Tisagenlecleucel (CTL019) for the treatment of pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia. Rockville (MD): U. S. Food and Drug Administration; 2017: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM566168.pdf. Accessed 2018 Oct 25.

45. Maude SL, Pulsipher MA, Boyer MW, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis. *Blood Conference: 58th annual meeting of the american society of hematology, ASH.* 2016;128(22).

46. Maude SL, Grupp SA, Mody R, et al. An updated analysis of tisagenlecleusel in pediatric/young adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) in a US multicenter clinical trial (ENSIGN). The Hague (NL): European Hematology Association Learning Center 2018: https://learningcenter.ehaweb.org/eha/2018/stockholm/214670/shannon.maude.an.updated.analysis.of.tisagenlecleucel.in.pediatric.young.adult.html?f=menu=6*ce_id=1346*ot_id=19044*media=3. Accessed 2018 Sep 27.

47. Form manual appendix L: Larnofsky/Lansky performance status. *(A00428 revision 1)*. Milwaukee (WI): Center for International Blood & Marrow Transplant Research; 2009: http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/appendix-l.pdf. Accessed 2018 Sep 27.

48. Clinical Study Report: C2201 data cutoff Mar 8 2017. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc; 2017 Oc 10.

49. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* December 1, 2018.

50. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) *(Version 4.0)*. Bethesda (MD): National Cancer Institute; 2010: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed 2018 Oct 24.

51. Jeha S, Gaynon PS, Razzouk BI, et al. Phase II study of clofarabine in pediatric patients with refractory or relapsed acute lymphoblastic leukemia. *J Clin Oncol.* 2006;24(12):1917-1923.

52. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2015;16(1):57-66.

53. O'Brien S, Schiller G, Lister J, et al. High-dose vincristine sulfate liposome injection for advanced, relapsed, and refractory adult Philadelphia chromosome-negative acute lymphoblastic leukemia. *J Clin Oncol.* 2013;31(6):676-683.

54. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics.* 1979;35(3):549-556.

55. Lan GKK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70(3):659-663.

56. U. S. Food and Drug Administration. KYMRIAH (tisagenlecleucel). 2018 Apr 13; https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm. Accessed 2018 Sep 27.

57. Carter GC, Liepa AM, Zimmermann AH, Morschhauser F. Validation of the Functional Assessment of Cancer Therapy –Lymphoma (FACT-LYM) in patients with relapsed/refractory mantle cell lymphoma. *Blood.* 2008;112:2376.

58. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: Properties, applications, and interpretation. *Health Qual Life Outcomes.* 2003;1:79.

59. Swigris JJ, Brown KK, Behr J, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respir Med.* 2010;104(2):296-304.

60. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr.* 2003;3(6):329-341.

61. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes.* 2007;5:70.

62. Manufacturer submission: Kymriah (tisagenlecleucel) **[CONFIDENTIAL manufacturer's submission]**. Dorval (QC): Novartis Pharma Canada Inc; 2018 Jun 15.

63. Maziarz RT, Bishop MR, Tam CS, et al. Patient-reported quality of life (QoL) following CTL019 infusion in adult patients (pts) with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).

64. National Comprehensive Cancer Network. About the NCCN clinical practice guidelines in oncology (NCCN Guidelines®). 2018; https://www.nccn.org/professionals/default.aspx. Accessed August 27, 2018.

65. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

66. Appraisal consultation document: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. London (GB): National Institute for Health and Care Excellence (NICE); 2018: https://www.nice.org.uk/guidance/gid-ta10269/documents/appraisal-consultation-document. Accessed 2018 Nov 13.

67. Ewing JE, King MT, Smith NF. Validation of modified forms of the PedsQL generic core scales and cancer module scales for adolescents and young adults (AYA) with cancer or a blood disorder. *Qual Life Res.* 2009;18(2):231-244.

68. Eiser C, Vance YH, Horne B, Glaser A, Galvin H. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. *Child Care Health Dev.* 2003;29(2):95-102.

69. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800-812.

70. Varni JW, Burwinkle TM, Katz ER. The PedsQL in pediatric cancer pain: a prospective longitudinal analysis of pain and emotional distress. *J Dev Behav Pediatr.* 2004;25(4):239-246.

71. Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. *Diabetes Care.* 2003;26(3):631-637.

72. Uzark K, et al. The pediatric quality of life inventory in children with heart disease. *Prog Pediatr Cardiol.* 2003;18(2): 141–149.

73. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy.* 1990;16(3):199-208.

74. van Dongen-Leunis A, Redekop WK, Uyl-de Groot CA. Which questionnaire should be used to measure quality-of-life utilities in patients with acute leukemia? An evaluation of the validity and interpretability of the EQ-5D-5L and preference-based questionnaires derived from the EORTC QLQ-C30. *Value Health.* 2016;19(6):834-843.

75. Hlubocky FJ, Webster K, Cashy J, Beaumont J, Cella D. The Development and Validation of a Measure of Health-Related Quality of Life for Non-Hodgkin's Lymphoma: The Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym). *Lymphoma.* 2013;2013:1-9.

76. Yost KJ, Thompson CA, Eton DT, et al. The Functional Assessment of Cancer Therapy - General (FACT-G) is valid for monitoring quality of life in patients with non-Hodgkin lymphoma. *Leukemia & Lymphoma.* 2013;54(2):290-297.

77. Cheson BD, Trask PC, Gribben JG, et al. Health-related quality of life and symptoms in patients with rituximab-refractory indolent non-Hodgkin lymphoma treated in the phase III GADOLIN study with obinutuzumab plus bendamustine versus bendamustine alone. *Ann Hematol.* 2017;96(2):253-259.

78. Ware JE, Kosinski MA, Keller SD. *SF-36 physical and mental health summary scales: A user's manual.* Boston (MA): The Health Institute, New England Medical Center; 1994.

79. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care.* 1993;31(3):247-263.

80. Jordan-Marsh M. The SF-36 quality-of-life instrument: updates and strategies for critical care research. *Crit Care Nurse.* 2002;22(6):35-43.

81. Hamilton AS, Miller MF, Arora NK, Bellizzi KM, Rowland JH. Predictors of use of complementary and alternative medicine by non-hodgkin lymphoma survivors and relationship to quality of life. *Integ Cancer Ther.* 2013;12(3):225-235.

82. Novartis Pharmaceuticals Corporation. Prescribing information: KymriahTM (tisagenlecleucel) suspension for intravenous infusion. Silver Spring (MD): U.S. Food and Drug Administration; 2018: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf. Accessed 2018 Sep 27.

83. Seattle Children's Hospital. NCT02028455: A pediatric and young adult trial of genetically modified T cells directed against CD19 for relapsed/refractory CD19+ leukemia. *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine; 2018: https://clinicaltrials.gov/ct2/show/NCT02028455. Accessed 2018 Sep 27.

84. Informed consent, parental permission, and assent in pediatric practice. Committee on Bioethics, American Academy of Pediatrics. *Pediatrics*. 1995;95(2):314-317.

85. Crookston KP, Simon TL. Physiology of apheresis. In: McLeod BC, Price, T. H., & Weinstein R, eds. *Apheresis: Principles and practice*. 2nd ed2003.

86. Goldstein SL. Therapeutic apheresis in children: special considerations. *Semin Dial* 2012;25:165-170.

87. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. *Blood.* 2017;129(25):3322-3331.

88. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *J Clin Invest.* 2016;126(6):2123-2138.

89. Turtle CJ, Hanafi LA, Berger C, et al. Addition of fludarabine to cyclophosphamide lymphodepletion improves in vivo expansion of CD19 chimeric antigen receptor- modified T cells and clinical outcome in adults with B cell acute lymphoblastic leukemia. *Blood* 2015;126:3773

90. Heczey A, Louis CU, Savoldo B, et al. CAR T cells administered in combination with lymphodepletion and PD-1 inhibition to patients with neuroblastoma. *Mol Ther.* 2017;25(9):2214-2224.

91. Shank BR, Do B, Sevin A, Chen SE, Neelapu SS, Horowitz SB. Chimeric antigen receptor T cells in hematologic malignancies. *Pharmacotherapy.* 2017;37(3):334-345.

92. Brentjens RJ, Riviere I, Park JH, et al. Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias. *Blood.* 2011;118(18):4817-4828.

93. Power N, Franck L. Parent participation in the care of hospitalized children: a systematic review. *J Adv Nurs.* 2008;62(6):622-641.

94. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) *(Version 5.0)*. Bethesda (MD): National Cancer Institute; 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed 2018 Sep 27.

95. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood.* 2016;127(26):3321-3330.

96. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.

97. Chong SL, Ong GY, Chin WYW, et al. A retrospective review of vital signs and clinical outcomes of febrile infants younger than 3 months old presenting to the emergency department. *PLoS One.* 2018;13(1):e0190649.

98. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet.* 2011;377(9770):1011-1018.

99. Rowan CM, Loomis A, McArthur J, et al. High-frequency oscillatory ventilation use and severe pediatric ARDS in the pediatric hematopoietic cell transplant recipient. *Respir Care.* 2018;63(4):404-411.

100. Rowan CM, Smith LS, Loomis A, et al. Pediatric acute respiratory distress syndrome in pediatric allogeneic hematopoietic stem cell transplants: A multicenter study. *Pediatr Crit Care Med.* 2017;18(4):304-309.

101. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med.* 2015;16(5):428-439.

102. Kidney Disease Improving Global Outcomes (KDIGO). Clinical practice guideline for acute kidney injury. *Kidney Int.* 2012;2(Supp 1):1–138

103. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int.* 2007;71(10):1028-1035.

104. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124-131.

105. Frey NV, Levine BL, Lacey SF, et al. Refractory cytokine release syndromein recipients of chimeric antigen receptor (CAR) T cells. *Blood* 2014;124:2296.

106. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J.* 2014;20(2):119-122.

107. Yanni Hao LK. Cost- effectiveness analysis of CTL019 for the treatment of pediatric and young adult patients with relapsed or refractory B- cell acute lymphoblastic leukemia in the United States. *Blood* 2017;130 609.

108. LaMattina J. Pharma's paradox: cure a deadly childhood disease and then get attacked on price. 2017; https://www.forbes.com/sites/johnlamattina/2017/11/28/cure-a-deadly-childhood-disease-and-then-get-attacked-on-price/#56664ef6479a. Accessed 2018 Sep 27.

109. Prasad V. Immunotherapy: Tisagenlecleucel - the first approved CAR-T-cell therapy: implications for payers and policy makers. *Nat Rev Clin Oncol.* 2018;15(1):11-12.

110. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA.* 2016;316(10):1093-1103.

111. Gold M. Panel on cost-effectiveness in health and medicine. *Med Care.* 1996;34(12 Suppl):Ds197-199.

112. FACT Standards for immune effector cells. 1st ed. Omaha (NE): Foundation for the Accreditation of Cellular Therapy; 2017: http://www.factweb.org/forms/store/ProductFormPublic/first-edition-v1-1-fact-standards-for-immune-effector-cells-free-download. Accessed 2018 Oct 24.

113. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. *West J Med.* 1999;170(6):348-351.

114. Signorovitch JE, Sikirica V, Erder MH, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value Health.* 2012;15(6):940-947.

115. Austin PC. Primer on statistical interpretation or methods report card on propensity-score matching in the cardiology literature from 2004 to 2006: a systematic review. *Circ Cardiovasc Qual Outcomes.* 2008;1(1):62-67.

116. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. *Med Decis Making.* 2018;38(2):200-211.

Appendix 1: Literature 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 12, 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

MULTI-DATABASE STRATEGY	
Search 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:	August 2018
Keywords:	Included terms for tisagenlecleucel, 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: tisagenlecleucel, Kymriah, ctl 019, ctl019

Appendix 2: Checklist for Level 1 and Level 2 Screening

Table 39: 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 B-cell ALL	☐	☐	☐
• Mixed, with ≥ 80% being pediatric or young adult (≤ 25 years) with r/r B-cell 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)	☐	☐	☐
• 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; r/r B-cell ALL = relapsed or refractory acute lymphoblastic leukemia; r/r DLBCL = relapsed or refractory diffuse large B-cell lymphoma; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] "Unclear" means 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 of the above-noted screening items is either "Yes" or "Unclear" by at least one of two independent reviewers.

Table 40: Level 2 Checklist for Screening Full-Text Articles and Study Reports

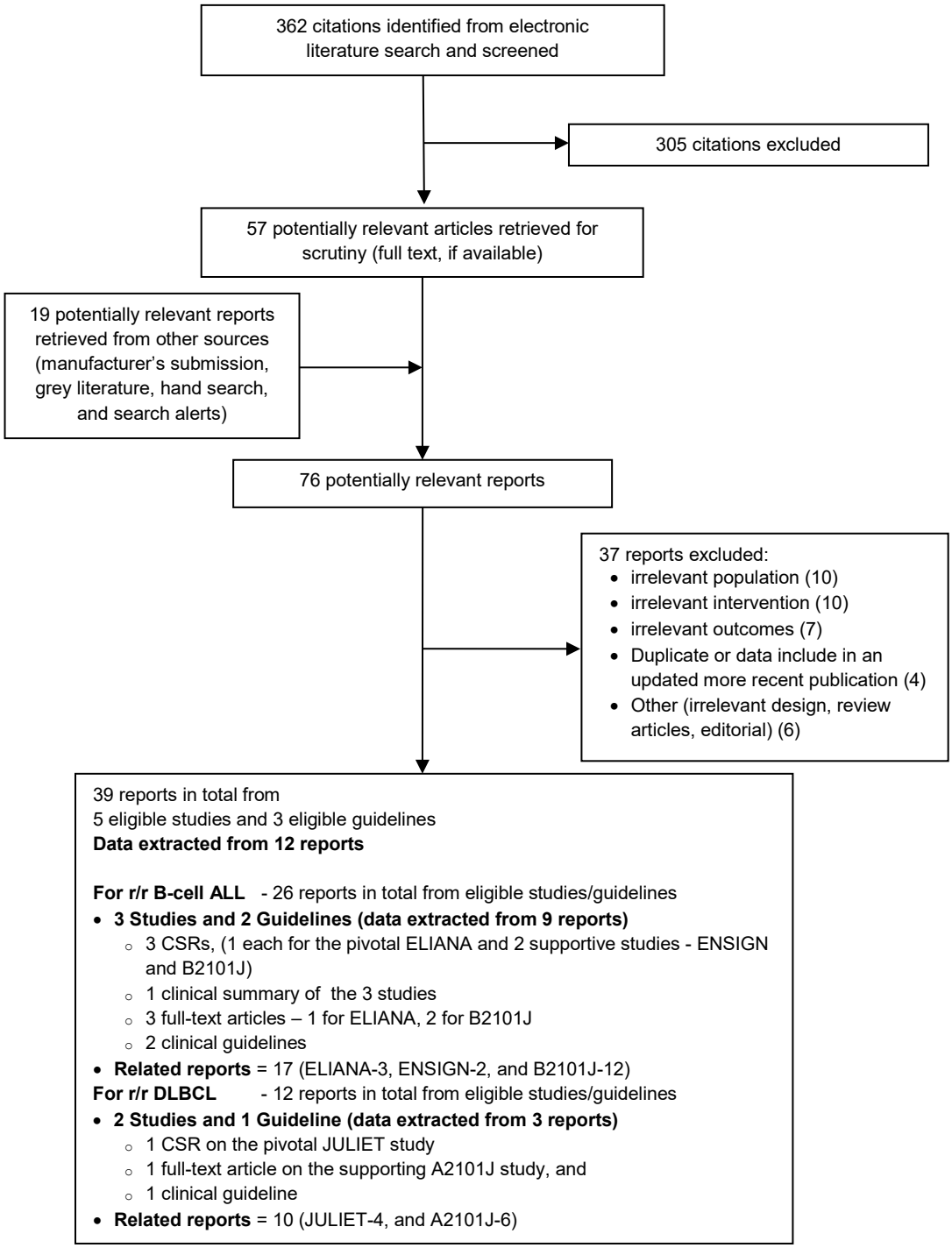
Reviewer: _____ Date: _____		
Ref ID: **Author:** **Publication Year:**		
Did the study include:	**Yes (Include)**	**No (Exclude)**
A. The population of interest:		
• Adults (mean age of ≥ 18 years) with r/r DLBCL	☐	☐
• Mixed, with ≥ 80% being adults with r/r DLBCL	☐	☐
• Pediatric or young adult (≤ 25 years) with r/r B-cell ALL	☐	☐
• Mixed, with ≥ 80% being pediatric or young adult (≤ 25 years) with r/r B-cell 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, and 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 B-cell ALL = relapsed/refractory B-cell acute lymphoblastic leukemia; r/r DLBCL = relapsed/refractory diffuse large B-cell 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 3: PRISMA Flow Diagram

Figure 6: PRISMA Flow Diagram — Selection of Included Studies/Reports



Appendix 4: List of Included Studies/Reports

r/r B-cell ALL

Reports from which data were extracted, per eligible study/guidelines

ELIANA

Clinical Study Report: B2202. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc.; 2017 Sep 22.

Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448.

ENSIGN

Clinical Study Report: B2205J. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell acute lymphoblastic leukemia. **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc.; 2016 Nov 23.

Study B2101J

Clinical Study Report: B2101J. A phase I/IIA study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR zeta and 4-1BB signaling domains in patients with chemotherapy resistant or refractory CD19+ leukemia and lymphoma **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc.; 2017 Sep 27.

Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. *Crit Care Med.* 2017;45(2):e124-e131.

Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371(16):1507-1517.

ELIANA, ENSIGN and B2101J (data describing 3 studies)

Clinical Summary: KYMRIAH (tisagenlecleucel) for the treatment of pediatric and young adult patients with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc.; 2018 May 28.

Clinical Guidelines

Mahadeo KM, Khazal SJ, Abdel-Azim H, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nat Rev Clin Oncol.* 2018.

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Acute lymphoblastic leukemia Version I.2018 - March 12, 2018. Fort Washington (PA): National Comprehensive Cancer Network; 2018: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2018 Aug 31.

Related reports from which data were not extracted, per eligible study

ELIANA

Buechner J, Grupp SA, Maude SL, Boyer M, Bittencourt H, Laetsch TW, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): Update to the interim analysis. *Clin Lymphoma Myeloma Leuk.* 2017;17:S263-S264.

Grupp SA, Laetsch TW, Buechner J, Bittencourt H, Maude SL, Verneris MR, et al. Analysis of a global registration trial of the efficacy and safety of CTL019 in pediatric and young adults with relapsed/refractory acute lymphoblastic leukemia (ALL). *Blood Conference: 58th annual meeting of the American society of hematology, ASH.* 2016;128(22).

Dietz AC, Grupp SA, Laetsch TW, Stefanski H, Myers GD, Bittencourt H, et al. Patient-reported quality of life (QoL) following CTL019 in pediatric and young adult patients (pts) with relapsed/refractory (r/r) b-cell acute lymphoblastic leukemia (B-ALL). *Journal of Clinical Oncology Conference.* 2017;35(15 Supplement 1).

ENSIGN

Maude SL, Grupp SA, Mody R, Driscoll T, Laetsch TW, Qayed M, et al. An updated analysis of tisagenlecleucel in pediatric/young adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) in a US multicenter clinical trial (ENSIGN). The Hague (NL): European Hematology Association Learning Center 2018: https://learningcenter.ehaweb.org/eha/2018/stockholm/214670/shannon.maude.an.updated.analysis.of.tisagenlecleucel.in.pediatric.young.adult.html?f=menu=6*ce_id=1346*ot_id=19044*media=3. Accessed 2018 Sep 27.

Maude SL, Pulsipher MA, Boyer MW, Grupp SA, Davies SM, Phillips CL, et al. Efficacy and safety of CTL019 in the first US phase II multicenter trial in pediatric relapsed/refractory acute lymphoblastic leukemia: results of an interim analysis. *Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH.* 2016;128(22).

Study B2101J

Gofshteyn JS, Shaw PA, Teachey DT, Grupp SA, Maude S, Banwell B, et al. Neurotoxicity after CTL019 in a pediatric and young adult cohort. *Ann Neurol.* 2018;84(4):537-546.

Grupp S, Frey N, Aplenc R, Levine B, Maude S, Rheingold S, et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019 cells) produce significant in vivo proliferation, complete responses and long-term persistence without GVHD in children and adults with relapsed, refractory all. *Bone Marrow Transplant.* 2014;49(Suppl 1):S1.

Grupp S, Maude S, Shaw PA, Aplenc R, Barker C, Barrett DM, et al. Durable remissions, with control and prediction of cytokine release syndrome (CRS), using T cells expressing a CD19-targeted chimeric antigen receptor (CTL019) to treat relapsed/refractory (r/r) pediatric ALL. *Bone Marrow Transplant.* 2016;1):S321-S322.

Grupp SA, Maude SL, Shaw PA, Aplenc R, Barrett DM, Callahan C, et al. Durable remissions in children with relapsed/refractory all treated with t cells engineered with a CD19-targeted chimeric antigen receptor (CTL019). *Blood.* 2015;126 (23):681.

Grupp SA, Maude SL, Shaw P, Aplenc R, Barrett DM, Callahan C, et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) have long term persistence and induce durable remissions in children with relapsed, refractory ALL. *Blood Conference: 56th Annual Meeting of the American Society of Hematology, ASH.* 2014;124(21).

Grupp SA, Frey NV, Aplenc R, Barrett DM, Chew A, Kalos M, et al. T Cells engineered with a Chimeric Antigen Receptor (CAR) targeting CD19 (CTL019) produce significant in vivo proliferation, complete responses and long-term persistence without Gvhd in children and adults with relapsed, refractory ALL. *Blood Conference: 55th Annual Meeting of the American Society of Hematology, ASH.* 2013;122(21).

Grupp SA, Maude S, Aplenc R, Barrett DM, Kalos M, Levine B, et al. T cells engineered with a chimeric antigen receptor (CAR) targeting CD19 (CTL019) produce complete responses and long-term persistence without GVHD in children with relapsed, refractory ALL. *Cancer Research Conference: AACR Special Conference: Pediatric Cancer at the Crossroads: Translating Discovery into Improved Outcomes.* 2013;74(20 SUPPL. 1).

Levine BL, Maude S, Zheng Z, Shaw P, Ambrose D, Aplenc R, et al. Durable remissions with control of cytokine release syndrome (CRS) using T cells expressing CD19 targeted chimeric antigen receptor (CAR) CTL019 to treat relapsed/refractory (R/R) acute lymphoid leukemia (ALL). *Cytotherapy.* 2016;1):S14-S15.

Maude S, Shaw P, Aplenc R, Barrett D, Barker C, Callahan C, et al. Chimeric antigen receptor (CAR)-modified t cells targeting CD19 induce sustained remissions in children and young adults with relapsed/refractory all. *Haematologica.* 2015;1:6.

Maude S, Shaw P, Aplenc R, Barrett D, Barker C, Callahan C, et al. Chimeric antigen receptor (CAR)-modified T cells induce durable remissions in children with relapsed/refractory all. *Pediatr Blood Cancer.* 2015;62 (Supplement 2):S21.

Maude S, Teachey D, Rheingold S, Shaw P, Aplenc R, Barrett D, et al. Durable remissions after monotherapy with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children and young adults with relapsed/refractory all. *Haematologica.* 2016;101 (Supplement 1):183-184.

Maude SL, Teachey DT, Rheingold SR, Shaw PA, Aplenc R, Barrett DM, et al. Sustained remissions with CD19-specific chimeric antigen receptor (CAR)-modified T cells in children with relapsed/refractory ALL. *Journal of Clinical Oncology Conference.* 2016;34(Supplement 15).

r/r DLBCL

Reports from which data were extracted, per eligible study/clinical guidelines

JULIET

Clinical Study Report: C2201 data cutoff Dec 8 2017. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL): Final Analysis Results (FAR) **[CONFIDENTIAL internal manufacturer's report]**. Dorval (QC): Novartis Pharma Canada Inc.; 2018 Apr 17.

A2101J

Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017;377(26):2545-2554.

Clinical Guideline

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): B-Cell Lymphomas Version 5.2018 – Oct. 2, 2018. Fort Washington (PA): National Comprehensive Cancer Network: https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 2018 Oct 29.

Related reports from which data were not extracted, per eligible study

JULIET

Maziarz RT, Bishop MR, Tam CS, Borchmann P, Jaeger U, McGuirk JP, et al. Patient-reported quality of life (QoL) following CTL019 infusion in adult patients (pts) with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).

Schuster SJ, Bishop R, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Primary analysis of JULIET: A global, pivotal, phase II trial of CTL019 in adult patients with relapsed or refractory diffuse large b-cell lymphoma. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).

Schuster S, Bishop MR, Tam C, Waller EK, Borchmann P, McGuirk J, et al. Global pivotal phase II trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)—An interim analysis. *Clin Lymphoma Myeloma Leuk.* 2017;17:S373-S374.

Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med*. December 1, 2018.

A2101J

Levine B, Svoboda J, Nasta SD, Porter D, Chong E, Lacey S, et al. Chimeric antigen receptor modified T cells directed against CD19 (CTL019) induce clinical responses in patients with relapsed or refractory CD19+ lymphomas. *Cytotherapy.* 2015;1:S13.

Schuster SJ, Svoboda J, Nasta S, Chong EA, Porter DL, Landsburg DJ, et al. Recovery of humoral immunity in patients with durable complete responses following chimeric antigen receptor modified t cells directed against CD19 (CTL019). *Journal of Clinical Oncology Conference.* 2016;34(Supplement 15).

Schuster SJ, Svoboda J, Nasta SD, Chong EA, Winchell N, Landsburg DJ, et al. Treatment with chimeric antigen receptor modified T cells directed against CD1 9 (CTL019) result in durable remissions in patients with relapsed or refractory diffuse large B cell lymphomas of germinal center and non-germinal center origin, "double hit" diffuse large B cell lymphomas, and transformed follicular to diffuse large B cell lymphomas. *Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH.* 2016;128(22).

Schuster SJ, Svoboda J, Nasta SD, Porter DL, Chong EA, Thvedt RE, et al. Phase II trial of chimeric antigen receptor modified T cells directed against CD19 in relapsed/refractory diffuse large B cell, follicular, and mantle cell lymphomas. *Hematol Oncol.* 2015;1):175-176.

Schuster SJ, Svoboda J, Nasta SD, Porter DL, Chong EA, Landsburg DJ, et al. Sustained remissions following chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. *Blood.* 2015;126 (23):183.

Schuster SJ, Svoboda J, Nasta SD, Porter DL, Chong EA, Mahnke Y, et al. Phase II a trial of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed or refractory CD19+ lymphomas. *Blood Conference: 56th Annual Meeting of the American Society of Hematology, ASH.* 2014;124(21).

Appendix 5: List of Excluded Studies/Reports

Table 41: Excluded studies

Citation	Reason for Exclusion
Anonymous. American Society of Pediatric Hematology/Oncology, ASPHO 26th annual meeting. *Pediatric Blood and Cancer Conference: 26th Annual Meeting of the American Society of Pediatric Hematology/Oncology, ASPHO.* 2013;60(SUPPL. 2).	Other (News)
Arnold DE, Callahan CA, Maude SL, Grupp SA, Heimall J. Subcutaneous immunoglobulin replacement following CD19-specific chimeric antigen receptor-T cell therapy for B-cell acute lymphoblastic leukemia. *Biol Blood Marrow Transplant.* 2018;24 (3 Supplement 1):S171-S172.	Intervention
Awasthi R, Lee C, Bittencourt H, Rives S, Boyer M, Pulsipher M, et al. Pharmacokinetics and pharmacodynamics of tocilizumab for the management of Cytokine Release Syndrome (CRS) in pediatric and young-adult patients with Relapsed/Refractory (R/R) b-cell Acute Lymphoblastic Leukemia (B-All) treated with Chimeric Antigen Receptor (CAR) t-cell therapy tisagenlecleucel (CTL019). *Pediatr Blood Cancer.* 2018;65 (Supplement 1):S212-S213.	Intervention
Awasthi R, Tam CS, Jaeger U, Jaglowski S, Foley SR, Van Besien K, et al. Clinical pharmacology of CTL019 in patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL). *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Outcome
Barrett D, Kalos M, Teachey D, Levine B, Rheingold S, Aplenc R, et al. CD19-targeted chimeric antigen receptor (CAR)-modified t (CTL019) cells in pediatric all: Immune activation syndromes and durable response. *Pediatr Blood Cancer.* 2013;2):S1.	Other (Study design)
Buchner J, Grupp SA, Maude SL, Hiramatsu H, Teachey DT, Wood PA, et al. Management of coagulopathy associated with CTL019 car T-cell therapy. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Outcome
Buechner J, Grupp SA, Maude SL, Boyer M, Bittencourt H, Laetsch TW, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL): update to the interim analysis. *Haematologica Conference: 22th congress of the European Hematology Association Spain.* 2017;102(178).	Duplicate
Buechner J, Grupp SA, Maude SL, Hiramatsu H, Teachey D, Wood P, et al. Management of coagulopathy associated with tisagenlecleucel Chimeric Antigen Receptor (CAR) t-cell therapy. *Pediatr Blood Cancer.* 2018;65 (Supplement 1):S237.	Outcome
Callahan C, Baniewicz D, Ely B. CAR T-cell therapy: Pediatric patients with relapsed and refractory acute lymphoblastic leukemia. *Clin J Oncol Nurs.* 2017;21(2 Suppl):22-28.	Intervention
Cope S, Ayers D, Shih T, Zhang J, Jansen J, Batt K. Expert elicitation of long-term survival for pediatric acute lymphoblastic leukemia patients receiving CTL019 in eliana phase II study. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Outcome
Grupp SA, Kalos M, Barrett D, Aplenc R, Porter DL, Rheingold SR, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368(16):1509-1518.	Other (Study design)
Grupp SA, Kalos M, Barrett DM, Teachey DT, Levine B, Milone M, et al. Use of CD19-targeted Chimeric Antigen Receptor-modified T (CART19) cells in ALL and CLL produce transient cytokine release syndrome (CRS), macrophage activation syndrome (MAS) and durable responses. *Cancer Research Conference: 104th Annual Meeting of the American Association for Cancer Research, AACR.* 2013;73(8 SUPPL. 1).	Population
Grupp SA, Porter DL, Levine B, Kalos M, Strait C, Rheingold SR, et al. Pilot study of redirected autologous T cells engineered to contain anti-CD19 attached to TCR and 4-1BB signaling domains in patients with chemotherapy-resistant or -refractory CD19+ leukemia and lymphoma. *Journal of Clinical Oncology Conference.* 2013;31(15 SUPPL. 1).	Other (Study design)
Grupp SA, Porter DL, Teachey DT, Barrett DM, Chew A, Suppa E, et al. CD19-redirected chimeric antigen receptor t (CART19) cells induce a cytokine release syndrome (CRS) and induction of treatable macrophage activation syndrome (MAS) that can be managed by the IL-6 antagonist tocilizumab (TOC). *Blood Conference: 54th Annual Meeting of the American Society of*	Population

Citation	Reason for Exclusion
Hematology, ASH. 2012;120(21).	
Hu Y, Wu Z, Luo Y, Shi J, Yu J, Pu C, et al. Potent anti-leukemia activities of chimeric antigen receptor-modified T cells against CD19 in Chinese patients with relapsed/refractory acute lymphocytic leukemia. *Clin Cancer Res.* 2017;23(13):3297-3306.	Population
Hu Y, Wu Z, Yu J, Wang J, Wei G, Wu W, et al. Efficacy of CD19-targeted chimeric antigen receptor T cells in the treatment of relapsed extramedullary B-cell acute lymphoblastic leukemia (B-ALL) and diffuse large B-cell lymphoma (DLBCL). *Journal of Clinical Oncology Conference.* 2017;35(15 Supplement 1).	Other (Study design)
Hu Y, Yu J, Luo Y, Shi J, Wu Z, Wei G, et al. Superior therapeutic efficacy of chimeric antigen receptor modified T cells against CD19 over chemotherapy in relapsed/refractory acute lymphocytic leukemia. *Blood Conference: 58th Annual Meeting of the American Society of Hematology, ASH.* 2016;128(22).	Population
June CH. Engineered T cell therapies for cancer. *Cancer Research Conference: AACR Special Conference on Tumor Immunology: Multidisciplinary Science Driving Basic and Clinical Advances.* 2012;73(1 SUPPL. 1).	Intervention
Kalos M, Nazimuddin F, Finklestein JM, Gupta M, Kulikovskaya I, Ambrose DE, et al. Long-term functional persistence, B cell aplasia and anti-Leukemia efficacy in refractory B cell malignancies following T cell immunotherapy using CAR-redirected T Cells targeting CD19. *Blood Conference: 55th Annual Meeting of the American Society of Hematology, ASH.* 2013;122(21).	Outcome
Laetsch TW, Maude SL, Grupp SA, Boyer MW, Harris AC, Qayed M, et al. CTL019 therapy appears safe and effective in pediatric patients with down syndrome with relapsed/refractory (R/R) acute lymphoblastic leukemia. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Outcome
Lee C, Bittencourt H, Rives S, Boyer MW, Pulsipher MA, Verneris MR, et al. Pharmacokinetics and pharmacodynamics of tocilizumab for the management of cytokine release syndrome (CRS) in pediatric and young adult patients with relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-all) treated with car T-cell therapy, CTL019. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Intervention
Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med.* 2018;378(5):439-448.	Duplicate (127812140)
Maude SL, Hucks GE, Seif AE, Talekar MK, Teachey DT, Baniewicz D, et al. Pembrolizumab to augment response to CD19-targeted chimeric antigen receptor (CAR) T cells in relapsed acute lymphoblastic leukemia (ALL). *Journal of Clinical Oncology Conference.* 2017;35(15 Supplement 1).	Intervention
Maude S, Barrett D, Rheingold S, Aplenc R, Teachey D, Callahan C, et al. Efficacy of retreatment with humanized CD19-targeted chimeric antigen receptor (CAR)-modified t cells in children with relapsed all. *Pediatr Blood Cancer.* 2016;63 (Supplement 3):S37.	Population
Maude SL, Barrett DM, Rheingold SR, Aplenc R, Teachey DT, Callahan C, et al. Efficacy of humanized CD19-targeted chimeric antigen receptor (CAR)-modified T cells in children and young adults with relapsed/refractory acute lymphoblastic leukemia. *Blood Conference: 58th annual meeting of the american society of hematology, ASH.* 2016;128(22).	Population
Maude SL, Barrett DM, Rheingold SR, Aplenc R, Teachey DT, Callahan C, et al. Efficacy of humanized CD19-targeted chimeric antigen receptor (CAR)-modified T cells in children with relapsed ALL. *Journal of Clinical Oncology Conference.* 2016;34(Supplement 15).	Population
Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med.* 2014;371(16):1507-1517.	Other (Study design)
Maude SL, Hucks GE, Callahan C, Baniewicz D, Fasano C, Barker C, et al. Durable remissions with humanized CD19-targeted chimeric antigen receptor (car)-modified T cells in car-naive and car-exposed children and young adults with relapsed/refractory acute lymphoblastic leukemia. *Blood Conference: 59th Annual Meeting of the American Society of Hematology, ASH.* 2017;130(Supplement 1).	Intervention

Citation	Reason for Exclusion
Maude SL, Barrett DM, Ambrose DE, Rheingold SR, Aplenc R, Teachey DT, et al. Efficacy and safety of humanized chimeric antigen receptor (CAR)-modified t cells targeting CD19 in children with relapsed/refractory all. *Blood.* 2015;126(23):683.	Population
Schuster SJ, Bishop MR, Tam C, Waller EK, Borchmann P, McGuirk J, et al. Global pivotal phase II trial of the CD19-targeted therapy CTL019 in adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL)-an interim analysis. *Hematol Oncol.* 2017;35 (Supplement 2):27.	Duplicate
Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak O, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017;377(26):2545-2554.	Duplicate
Talekar MK, Maude SL, Hucks GE, Motley LS, Callahan C, White CM, et al. Effect of chimeric antigen receptor-modified T (CAR-T) cells on responses in children with non-CNS extramedullary relapse of CD19+ acute lymphoblastic leukemia (ALL). *Journal of Clinical Oncology Conference.* 2017;35(15 Supplement 1).	Intervention (and combined data for CTL019 and CTL119)
Teachey DT, Lacey S, Shaw PA, Melenhorst J, Frey N, Barrett D, et al. Clinical and biologic characterization of cytokine release syndrome after Chimeric Antigen Receptor (CAR) T cell therapy for acute Lymphoblastic Leukemia (ALL). *Inflamm Res.* 2015;64(Suppl 2):S237.	Outcome
Teachey DT, Lacey SF, Shaw PA, Melenhorst JJ, Frey NV, Maude SL, et al. Biomarkers accurately predict cytokine release syndrome (CRS) after chimeric antigen receptor (CAR) T cell therapy for acute lymphoblastic leukemia (ALL). *Blood.* 2015;126 (23):1334.	Population
Wei G, Hu Y, Pu C, Yu J, Luo Y, Shi J, et al. CD19 targeted CAR-T therapy versus chemotherapy in re-induction treatment of refractory/relapsed acute lymphoblastic leukemia: results of a case-controlled study. *Ann Hematol.* 2018;97(5):781-789.	Population
Xiao L, Tang Y, Zhu X, Chen J, Wu Z. CD19 targeted chimeric antigen receptor T (CAR-T) cell immunotherapy has demonstrated significant anti-leukemia activity in pediatric patients with relapsed/refractory acute lymphocytic leukemia: a multicentre study in China. *Journal of clinical oncology Conference.* 2017;35(15 Supplement 1).	Intervention
Yongxian H, Yi L, Jimin S, Jian Y, Guoqing W, Wenjun W, et al. CD19 targeted CAR-T therapy followed by haploidentical HSCT for refractory/relapsed acute leukemia: Superior therapeutic efficacy. *Biol Blood Marrow Transplant.* 2018;24 (3 Supplement 1):S231.	Intervention

Appendix 6: Additional Data – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Table 42: Summary of Baseline Characteristics – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Title	ELIANA – FAS[a] (N = 79)	ENSIGN – FAS[b] (Interim) (N = 58)	Study B2101J – FAS[c] (N = 56)*	ELIANA – FAS (Data Cut-Off April 25, 2017) (N = 75)
Age, years				
• Median (range)	[redacted]	[redacted]	[redacted]	11.0 (3.0 to 23.0)
Sex, n (%)				
• Male	[redacted]	[redacted]	[redacted]	43 (57.0)
• Female	[redacted]	[redacted]	[redacted]	32 (43.0)
Race, n (%)				
• White	[redacted]	[redacted]	[redacted]	58 (77.3)
• Asian	[redacted]	[redacted]	[redacted]	6 (8.0)
• Other	[redacted]	[redacted]	[redacted]	11 (14.7)
Treatment history				
Previous lines of therapy				
• Median (range)	[redacted]	[redacted]	[redacted]	3 (1 - 8)
• 1	[redacted]	[redacted]	[redacted]	NR
• 2	[redacted]	[redacted]	[redacted]	NR
• 3	[redacted]	[redacted]	[redacted]	NR
• 4	[redacted]	[redacted]	[redacted]	NR
• 5	[redacted]	[redacted]	[redacted]	NR
• 6	[redacted]	[redacted]	[redacted]	NR
• 7	[redacted]	[redacted]	[redacted]	NR
• 8	[redacted]	[redacted]	[redacted]	NR
• 9	[redacted]	[redacted]	[redacted]	NR
Patients with prior SCT, n (%)	[redacted]	[redacted]	[redacted]	46 (61.0)

Title	ELIANA – FAS[a] (N = 79)	ENSIGN – FAS[b] (Interim) (N = 58)	Study B2101J – FAS[c] (N = 56)*	ELIANA – FAS (Data Cut-Off April 25, 2017) (N = 75)
Disease response status				
• Relapsed disease, n (%)	[redacted]	[redacted]	[redacted]	Chemorefractory or relapsed: 69 (92.0)
• Primary refractory, n (%)	[redacted]	[redacted]	[redacted]	6 (8.0)
Karnofsky/Lansky performance status, n (%)				
• 100	[redacted]	[redacted]	[redacted]	26 (34.7)
• 90	[redacted]	[redacted]	[redacted]	23 (30.7)
• 80	[redacted]	[redacted]	[redacted]	13 (17.3)
• 70	[redacted]	[redacted]	[redacted]	8 (10.7)
• 60	[redacted]	[redacted]	[redacted]	2 (2.7)
• 50	[redacted]	[redacted]	[redacted]	3 (4.0)
• Missing	[redacted]	[redacted]	[redacted]	0 (0)

FAS = full analysis set; MAIC = matching-adjusted indirect comparison; SCT = stem cell transplant.
* A total of 62 patients comprising 56 non-CNS3 ALL patients, four CNS3 ALL patients, and two lymphoma patients received ≥ 1 tisagenlecleucel infusions. However, the analysis was based on only the 56 non-CNS3 ALL patients.
Sources: Maude 2018;37 European Medicines Agency;24 Manufacturer's Submission:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017).35
[b] ENSIGN—Manufacturer submission (MAIC); data cut-off October 6, 2017.[62]
[c] B2101J—CSR (data cut-off January 1, 2017).

Table 43: Key Efficacy Outcome By Subgroups – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

ORR WITHIN ≥ 3 MONTHS FOLLOW-UP	ELIANA[a]	ENSIGN[b]	B2101J[c]
By age, years, n (%)			
< 10	**N = 31**	[redacted]	[redacted]
Overall ORR	24 (77.4)	[redacted]	[redacted]
95% CI	58.9 to 90.4		[redacted]
• CR	16 (51.6)		
• Cri	8 (25.8)		[redacted]
• No response	3 (9.7)		
• Unknown	4 (12.9)		
≥ 10 to < 18	**N = 31**		[redacted]
Overall ORR	27 (87.1)		[redacted]
95% CI	70.2 to 96.4		[redacted]
• CR	22 (71.0)		
• CRi	5 (16.1)		[redacted]
• No response	1 (3.2)		
• Unknown	3 (9.7)		
≥ 18	**N = 13**	[redacted]	[redacted]
Overall ORR	10 (76.9)	[redacted]	[redacted]
95% CI	46.2 to 95.0	[redacted]	[redacted]
• CR	7 (53.8)	[redacted]	
• CRi	3 (23.1)	[redacted]	[redacted]
• No response	2 (15.4)	[redacted]	
• Unknown	1 (7.7)	[redacted]	
By sex, n (%)			
Male	**N = 43**	[redacted]	[redacted]
Overall ORR	33 (76.7)	[redacted]	[redacted]
95% CI	61.4 to 88.2	[redacted]	[redacted]
• CR	26 (60.5)	[redacted]	
• CRi	7 (16.3)	[redacted]	[redacted]
• No response	5 (11.6)	[redacted]	
• Unknown	5 (11.6)	[redacted]	
Female	**N = 32**	[redacted]	[redacted]
Overall ORR	28 (87.5)	[redacted]	[redacted]
95% CI	71.0 to 96.5	[redacted]	[redacted]
• CR	19 (59.4)	[redacted]	
• CRi	9 (28.1)	[redacted]	[redacted]
• No response	1(3.1)	[redacted]	

ORR WITHIN ≥ 3 MONTHS FOLLOW-UP	ELIANA[a]	ENSIGN[b]	B2101J[c]
• Unknown	3 (9.4)		
By baseline bone marrow tumour burden, n (%)			
Low (< 50%)	**N = 24**		
Overall ORR	22 (91.7)		
95% CI	73.0 to 99.0		
• CR	15 (62.5)		
• CRi	7 (29.2)		
• Unknown	2 (8.3)		
High (≥ 50%)	**N = 51**		
Overall ORR	39 (76.5)		
95% CI	62.5 to 87.2		
• CR, n (%)	30 (58.8)		
• CRi, n (%)	9 (17.6)		
• No response	6 (11.8)		
• Unknown	6 (11.8)		
By baseline extramedullary disease, n (%)			
Yes	**N = 11**		
Overall ORR	10 (90.9)		
95% CI	58.7 to 99.8)		
• CR	7 (63.6)		
• CRi	3 (27.3)		
• Unknown	1 (9.1)		
No	**N = 64**		
Overall ORR	51 (79.7)		
95% CI	67.8 to 88.7		
• CR	38 (59.4)		
• CRi	13 (20.3)		
• No response	6 (9.4)		
• Unknown	7 (10.9)		
By baseline disease status, n (%)			
Primary refractory	**N = 6**		
Overall ORR	5 (83.3)		
95% CI	35.9 to 99.6		
• CR	5 (83.3)		
• Unknown	1 (16.7)		
Chemorefractory	**N = 0**		
Overall ORR	N/A		
95% CI	N/A		
• CR	N/A		

ORR WITHIN ≥ 3 MONTHS FOLLOW-UP	ELIANA[a]	ENSIGN[b]	B2101J[c]
• No response	N/A	[redacted]	
• Unknown	N/A	[redacted]	
Relapsed disease	**N = 69**	[redacted]	[redacted]
Overall ORR	56 (81.2)	[redacted]	[redacted]
95% CI	69.9 to 89.6	[redacted]	[redacted]
• CR	40 (58.0)	[redacted]	
• CRi	16 (23.2)	[redacted]	[redacted]
• No response	6 (8.7)	[redacted]	
• Unknown	7 (10.1)	[redacted]	
By prior SCT, n (%)			
Yes	**N = 46**	[redacted]	[redacted]
Overall ORR	38 (82.6)	[redacted]	[redacted]
95% CI	68.6 to 92.2	[redacted]	[redacted]
• CR	26 (56.5)	[redacted]	
• CRi	12 (26.1)	[redacted]	[redacted]
• No response	4 (8.7)	[redacted]	
• Unknown	4 (8.7)	[redacted]	
No	**N = 29**	[redacted]	[redacted]
Overall ORR	23 (79.3)	[redacted]	[redacted]
95% CI	60.3 to 92.0	[redacted]	[redacted]
• CR	19 (65.5)	[redacted]	
• CRi	4 (13.8)	[redacted]	[redacted]
• No response	2 (6.9)	[redacted]	
• Unknown	4 (13.8)	[redacted]	
By eligibility for SCT, n (%)			
Eligible	**N = 12**	[redacted]	
Overall ORR	10 (83.3)	[redacted]	
95% CI	51.6 to 97.9	[redacted]	
• CR	8 (66.7)	[redacted]	
• CRi	2 (16.7)	[redacted]	
• No response	1 (8.3)	[redacted]	
• Unknown	1 (8.3)	[redacted]	[redacted]
Ineligible	**N = 63**	[redacted]	
Overall ORR	51 (81.0)	[redacted]	
95% CI	69.1 to 89.8	[redacted]	
• CR	37 (58.7)	[redacted]	
• CRi	14 (22.2)	[redacted]	
• No response	5 (7.9)	[redacted]	
• Unknown	7 (11.1)	[redacted]	

ORR WITHIN ≥ 3 MONTHS FOLLOW-UP	ELIANA[a]	ENSIGN[b]	B2101J[c]
By any high-risk mutations, n (%)			
Yes	**N = 28**	[redacted]	[redacted]
Overall ORR	22 (78.6)	[redacted]	
95% CI	59.0 to 91.7	[redacted]	
• CR	19 (67.9)	[redacted]	
• CRi	3 (10.7)	[redacted]	
• No response	2 (7.1)	[redacted]	
• Unknown	4 (14.3)	[redacted]	
No	**N = 47**	[redacted]	
Overall ORR	39 (83.0)	[redacted]	
95% CI	69.2 to 92.4	[redacted]	
• CR	26 (55.3)	[redacted]	
• CRi	13 (27.7)	[redacted]	
• No response	4 (8.5)	[redacted]	
• Unknown	4 (8.5)	[redacted]	
By Down syndrome, n (%)			
Yes	**N = 6**	[redacted]	[redacted]
Overall ORR	5 (83.3)		
95% CI	35.9 to 99.6		
• CR	1 (16.7)		
• CRi	4 (66.7)		
• Unknown	1 (16.7)		
No	**N = 69**		
Overall ORR	56 (81.2)		
95% CI	69.9 to 89.6		
• CR	44 (63.8)		
• CRi	12 (17.4)		
• No response	6 (8.7)		
• Unknown	7 (10.1)		

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; ORR = overall remission rate; SCT = stem cell transplant.
Sources: European Medicines Agency;[24] information submitted by manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Table 44: Details of Other Efficacy Outcomes – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

	ELIANA[a] – FAS (N = 77)		ENSIGN[b] – EAS (N = 42)		B2101J[c] – FAS (N = 56)	
BOR (defined as CR or CRi)	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At day 28 ± 4 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Within 3 months post-tisagenlecleucel infusion	[redacted]	[redacted]		[redacted]	[redacted]	
Within 6 months post-tisagenlecleucel infusion	[redacted]		[redacted]	[redacted]	[redacted]	
BOR with MRD-negative, n (%)	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
At day 28 ± 4 days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Within 3 months post-tisagenlecleucel infusion, n/N (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Within 6 months post-tisagenlecleucel infusion, n/N (%)	[redacted]		[redacted]	[redacted]		
Allogeneic SCT therapy while in remission						
Without allogeneic SCT at month 6		[redacted]		[redacted]	[redacted]	
Allogeneic SCT before month 6		[redacted]		[redacted]	[redacted]	
Duration of remission, months	**Median (n = 75)**	**95% CI**	**Median**	**95% CI**	**Median**	**95% CI**
• RFS	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
• EFS	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
• OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Relapsed after onset of CR, n/N (%)	[redacted]		[redacted]	[redacted]	[redacted]	
RFS probability estimates at a median follow-up of 8.6 months, % (95% CI)	**N = 77**					
• 3 months	[redacted]	[redacted]	[redacted]	[redacted]		
• 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• 9 months to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• 15 months to 21 months	[redacted]	[redacted]	[redacted]	[redacted]		
• 24 months					[redacted]	[redacted]
• 36 months					[redacted]	[redacted]
EFS probability estimates at a median follow-up of 8.6 months, % (95% CI)	[redacted]					
• 3 months	[redacted]	[redacted]	[redacted]	[redacted]		
• 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• 9 months	[redacted]	[redacted]	[redacted]	[redacted]		
• 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• 15 months to 24 months	[redacted]	[redacted]	[redacted]	[redacted]		

	ELIANA[a] – FAS (N = 77)		ENSIGN[b] – EAS (N = 42)		B2101J[c] – FAS (N = 56)	
• 24 months						
• 36 months						
OS probability estimates at a median follow-up of 17.6 months, % (95% CI)						
• 3 months						
• 6 months						
• 9 months						
• 12 months						
• 18 months						
• 21 months to 30 months						
• 36 months						

BOR = best overall response; CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete blood count recovery; EAS = efficacy analysis set; EFS = event-free survival; FAS = full analysis set; MRD = minimal residual disease; NE = not evaluated; OS = overall survival; RFS = relapse-free survival; SCT = stem cell transplant.
* For best response rate at any time.
Sources: Information submitted by the manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Table 45: Detailed Adverse Events Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Treatment-emergent Adverse Events*	ELIANA[a] (N = 79)			ENSIGN[b] (N = 58)			B2101J[c] (N = 56)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Patients with ≥ 1 AE									
Most commonly reported AEs (cut-off: ≥ 10% grade 3 or grade 4 in ELIANA)									
CRS									
Anemia									
Pyrexia									
Platelet count decrease									
WBC count decrease									
Decreased appetite									

Treatment-emergent Adverse Events*	ELIANA[a] (N = 79)			ENSIGN[b] (N = 58)			B2101J[c] (N = 56)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutrophil count decrease									
Febrile neutropenia									
Hypotension									
AST increase									
Hypokalemia									
Hypophosphatemia									
Hypoxia									
Lymphocyte count decrease									
Blood bilirubin increase									
Infections and infestations (N = 75)									
Other commonly reported AEs (cut-off: ≥ 10% all grades)									
Nausea									
Acute kidney injury									
Neutropenia									
Hypogammaglobulinemia									
Headache									
Vomiting									
Diarrhea									
Cough									
ALT									
Tachycardia									
Fatigue									
Hypocalcemia									

Treatment-emergent Adverse Events*	ELIANA[a] (N = 79)			ENSIGN[b] (N = 58)			B2101J[c] (N = 56)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
Hypertension									
Pain in extremity									
Constipation									
Anxiety									
Pulmonary edema									
URTI									
Abdominal pain									
Hypoalbuminemia									
Back pain									
Myalgia									
Hyperuricemia									
INR increased									
Nasal congestion									
Thrombocytopenia									
Arthralgia									
Delirium									
Disseminated intravascular coagulation									
Encephalopathy									
Hyperglycemia									
Pleural effusion									
Rhinovirus infection									
Serum ferritin increased									
Tachypnea									
AEs requiring dose adjustment or interruption (no cut-off)									
• Febrile neutropenia									
• CSR									
• Fatigue									

Treatment-emergent Adverse Events*	ELIANA[a] (N = 79)			ENSIGN[b] (N = 58)			B2101J[c] (N = 56)		
	All Grades, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)	All Grade, n (%)	Grade 3, n (%)	Grade 4, n (%)
• Streptococcal infection							[redacted]	[redacted]	[redacted]

AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; INR = international normalized ratio; LRTI = lower respiratory tract infection; URTI = upper respiratory tract infection; WBC = white blood cell.
* AEs were reported primarily within eight weeks post-infusion; the incidence of AEs decreased substantially after this period. No CRS AEs were reported after eight weeks post-infusion. The median time to CRS onset was three days; the median duration was eight days.
Sources: The manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Table 46: Detailed Serious Adverse Events Post-Tisagenlecleucel Infusion – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Treatment-emergent Serious Adverse Events	ELIANA[a] (N = 75)			ENSIGN[b] (N = 29)			B2101J[c] (N = 56)		
SAE, n (%)	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Patients with ≥ 1 SAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Most common SAE (cut-off: all-grade rate ≥ 5%)									
• CRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Febrile neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Disseminated intravascular coagulation		[redacted]			[redacted]		[redacted]	[redacted]	[redacted]
• Hypotension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Encephalopathy							[redacted]	[redacted]	[redacted]
• Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Capillary leak syndrome	[redacted]				[redacted]		[redacted]	[redacted]	[redacted]
• Acute kidney injury	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
• Hypoxia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Respiratory failure/distress	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
• Acute respiratory distress syndrome			[redacted]				[redacted]	[redacted]	[redacted]
• Dehydration							[redacted]	[redacted]	[redacted]

Treatment-emergent Serious Adverse Events	ELIANA[a] (N = 75)			ENSIGN[b] (N = 29)			B2101J[c] (N = 56)		
SAE, n (%)	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**	**All Grades**	**Grade 3**	**Grade 4**
• Left ventricular dysfunction									
• Coagulopathy									
• Seizure									
• Nervous system disorders									
AE leading to study drug discontinuation (no cut-off)									
AE requiring hospitalization									
Death after treatment									
Overall, n (%)									
• Cause of death, n (%)									
○ Underlying leukemia									
○ Cerebral hemorrhage									
○ Encephalitis									
○ Systemic mycosis									
○ Embolic stroke									
○ LRTI									
○ Hepatobiliary disease									
○ Unknown causes									
○ Complication of transplant									
○ Respiratory failure									

AE = adverse event; CRS = cytokine release syndrome; LRTI = lower respiratory tract infection; SAE = serious adverse event.
Sources: Information submitted by the manufacturer:
[a] ELIANA—Clinical Summaries (data cut-off December 31, 2017)[35] and CSR (data cut-off August 7, 2016).[32]
[b] ENSIGN—Clinical Summaries (data cut-off October 6, 2017)[35] and ENSIGN CSR (data cut-off February 1, 2017).[33]
[c] B2101J—CSR (data cut-off January 30, 2017).[34]

Appendix 7: Additional Data – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Table 47: JULIET – Baseline Characteristics (Cohort A and All Infused Patients)

	Cohort A (N = 16)	Main Cohort + Cohort A (FAS, N = 111)[a]
Age, median (range), years	[redacted]	56 (22 to 76)
Male, n (%)	[redacted]	68 (61.3)
Race, n (%)		
White	[redacted]	98 (88.3)
Asian	[redacted]	6 (5.4)
Black	[redacted]	4 (3.6)
Other	[redacted]	3 (2.7)
Stage (at study entry), n (%)		
Stage I	[redacted]	8 (7.2)
Stage II	[redacted]	19 (17.1)
Stage III	[redacted]	22 (19.8)
Stage IV	[redacted]	62 (55.9)
IPI (at study entry), n (%)		
< 2	[redacted]	31 (27.9)
≥ 2	[redacted]	80 (72.1)
Predominant histology/cytology, n (%)		
DLBCL	[redacted]	88 (79.3)
Transformed FL	[redacted]	21 (18.9)
Transformed lymphoma – other	[redacted]	1 (0.9)
Other	[redacted]	1 (0.9)
BM Involvement (at study entry), n (%)		
No	[redacted]	103 (92.8)
Yes	[redacted]	8 (7.2)
ECOG performance status		
0, n (%)	[redacted]	61 (55.0)
1, n (%)	[redacted]	50 (45.0)
Molecular subtype (cell of origin)		
GCB, n (%)	[redacted]	63 (56.8)
ABC, n (%)	[redacted]	45 (40.5)
Missing, n (%)	[redacted]	3 (2.7)
Double/triple hits in MYC/BCL2/BCL6 genes, n (%)		
CMYC +BCL2 + BCL6	[redacted]	5 (4.5)
CMYC + BCL2	[redacted]	10 (9.0)
CMYC + BCL6	[redacted]	4 (3.6)
Negative	[redacted]	51 (45.9)
Not done	[redacted]	38 (34.2)
Missing	[redacted]	3 (2.7)
Treatment history		
Number of previous therapies, n (%) • 1 • 2	[redacted] [redacted] [redacted]	 5 (4.5) 49 (44.1) 34 (30.6)

	Cohort A (N = 16)	Main Cohort + Cohort A (FAS, N = 111)[a]
• 3 • 4 • 5 • 6	[redacted]	15 (13.5) 7 (6.3) 1 (0.9)
Patients with prior HSCT, n (%)	[redacted]	54 (48.6)
Disease response status, n (%)		
Refractory to last line	[redacted]	61 (55.0)
Relapsed to last line	[redacted]	50 (45.0)
Time since most recent relapse/progression to tisagenlecleucel infusion		
Median (range), months	[redacted]	5.4 (1.6 to 21.5)

ABC = activated B-cell type; BM = bone marrow; DLBCL = diffuse large B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; FL = follicular lymphoma; GCB = germinal centre B-cell type; HSCT = hematopoietic stem cell transplant; IPI = International Prognostic Index.
[a] The FAS for Cohort A (N = 16) included patients infused with tisagenlecleucel from the German manufacturing facility, Fraunhofer-Institut für Zelltherapie und Immunologie, Leipzig. The FAS for Main Cohort + Cohort A (N = 111) included patients infused with tisagenlecleucel from the US manufacturing facility in Morris Plains, New Jersey or from the German manufacturing facility.
Sources: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off);[36] European Medicines Agency.[24]

Table 48: JULIET – Tisagenlecleucel Dose Administration (Cohort A and All Infused Patients)

	Cohort A (N = 16)	Main Cohort + Cohort A (N = 111)
Total tisagenlecleucel dose infused ($\times 10^8$ transduced viable T cells)		
Mean (SD)	[redacted]	[redacted]
Median	[redacted]	[redacted]
Range	[redacted]	[redacted]
Target dose categorization,[a] n (%)		
Below target dose range	[redacted]	[redacted]
Within target dose range	[redacted]	[redacted]
Above target dose range	[redacted]	[redacted]

NR = not reported; SD = standard deviation.
[a] The target dose range was 1 to 5 × 10^8 tisagenlecleucel transduced cells.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off).[36]

Table 49: JULIET – Overall Response Rate in DLBCL Subgroups

JULIET: C2201 (N = 93)	n/N[a]	ORsR, % (95% CI)
Age (years)		
< 40	[redacted]	[redacted]
≥ 40 to < 65	[redacted]	[redacted]
≥ 65	13/22	59 (36 to 79)
Sex		
Female	19/33	58 (39 to 74)
Male	29/60	48 (35 to 62)
Race		
White	[redacted]	[redacted]
Prior Response Status		
Refractory to last line	19/48	40 (26 to 55)
Relapsed to last line	29/45	64 (49 to 78)
IPI at Enrolment		
< 2 risk factors	14/25	56 (35 to 76)
≥ 2 risk factors	34/68	50 (38 to 62)
Prior lines of chemotherapy		
≤ 2	26/49	53 (38 to 68)
> 2	22/44	50 (35 to 65)
Prior SCT		
No	26/52	50 (36 to 64)
Yes	22/41	54 (37 to 69)
Stage of Disease at Baseline		
Stage I/II	[redacted]	[redacted]
Stage III/IV	[redacted]	[redacted]
Cell of Origin		
ABC	21/40	52 (36 to 69)
GCB	24/50	48 (34 to 63)
High-Risk Genomic Lesions		
Double- or triple-hit lymphoma in MYC/BCL2/BCL6 genes	8/16	50 (25 to 75)
Time From Most Recent Relapse to Infusion		
≤ median	23/48	48 (33 to 63)
> median	25/45	56 (40 to 70)

ABC = activated B-cell type; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; GCB = germinal centre B-cell type; IPI = International Prognostic Index; ORsR = overall response rate; SCT = stem cell transplant.
[a] Efficacy analysis set of Main Cohort.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off);[36] Schuster SJ et al. NEJM 2018; December 1.[49]

Table 50: JULIET – Primary Efficacy Outcome (Cohort A)

	Cohort A (N = 16)[a]
Primary end point	
ORsR (CR + PR), n/N, • % (95% CI)	[redacted]
Breakdown of BOR	
CR, n (%)	[redacted]
PR, n (%)	[redacted]
SD, n (%)	[redacted]
PD, n (%)	[redacted]
Unknown, n (%)	[redacted]

BOR = best overall response; CI = confidence interval; CR = complete response; FAS = full analysis set; ORsR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.
[a] FAS of Cohort A.
Source: The manufacturer (CSR, JULIET – December 8, 2017 data cut-off).[36]

Table 51: JULIET – Secondary Efficacy Outcomes (Cohort A and All Infused Patients)

	Cohort A (N = 16)	Main Cohort + Cohort A (N = 111)
Secondary end points		
Duration of response, median months (95% CI)	[redacted]	[redacted]
PFS, median months (95% CI)	[redacted]	[redacted]
EFS, median months (95% CI)	[redacted]	[redacted]
OS, median months (95% CI)	[redacted]	[redacted]

CI = confidence interval; EFS = event-free survival; NE = not estimated; NR = not reported; OS = overall survival; PFS = progression-free survival; SCT = stem cell transplant.
[a] Censoring for hematopoietic SCT.
[b] Sensitivity analysis: without censoring for hematopoietic SCT.
Source: The manufacturer. (CSR, JULIET – December 8, 2017 data cut-off).[36]

Table 52: A2101J – Safety Data Combined for DLBCL and Follicular Lymphoma

Selected Adverse Events	A2101J (N = 28 DLBCL + FL) No. Events		
	All Grades	Grade 3	Grade 4
Infections and infestations	44	7	1
Neutrophil count decrease	22	10	8
Hyperglycemia	18	0	0
Fatigue	18	1	0
CRS	16	4	1
Hyponatremia	15	2	0
WBC count decrease	14	4	1
Hypocalcemia	12	1	0
Anemia	11	3	0
Neurological event	11[a]	1	1
Headache	11	0	0
Hypokalemia	10	0	0
ALT increase	10	0	0
Hypomagnesemia	9	0	0
Constipation	9	0	0
Pyrexia	7	1	0
Hypophosphatemia	7	4	1
AST increase	6	1	0
Diarrhea	6	0	0
Nausea	8	0	0
Hypotension	4	2	1
Tachycardia	4	0	0
Febrile neutropenia	3	3	0
Dyspnea	2	1	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; WBC = white blood cell.
[a] 11% were ≥ grade 3.
Sources: Schuster, SJ et al. NEJM 2017; 377;26:2545-54.[40]

Appendix 8: Validity of HRQoL Instruments

Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) instrument is designed to measure health-related quality of life (HRQoL) in children and in adolescents aged 13 years to 18 years using a 30-day recall period.[67] There are parallel child self-report and parent proxy-report formats as well as age-specific forms in developmentally appropriate language for children ages two years to four years (toddler, proxy-report only), five years to seven years (young child), eight years to 12 years (child), and 13 years to 18 years (adolescent).[68]

The validity and reliability of the PedsQL has been demonstrated in healthy and general patient populations[69] as well as in specific pediatric patient populations for diseases including cancer,[68,70] diabetes,[71] and heart disease.[72] A modified PedsQL generic core and cancer forms have also been validated and reported to be reliable to evaluate HRQoL in adolescents and young adults with cancer or blood disorders.[67]

The PedsQL generic core has four domains with a total of 23 items. The domains are Physical Functioning (eight items), Emotional Functioning (five items), Social Functioning (five items), and School Functioning (five items). Composite quality of life scores can be calculated for the total scale score (sum of all 23 items) and a psychosocial health summary score (the sum of 15 items from emotional, social, and school or work functioning). The cancer module has eight domains with a total of 27 items: Pain and Hurt (two items); Nausea (five items); Procedural Anxiety (three items); Treatment Anxiety (three items); Worry (three items); Cognitive Problems (five items); Perceived Physical Appearance (three items); and Communication (three items).[67]

Scoring involves asking the patients to rank how much of a problem they have experienced over the last 30 days as a result of their condition on five-point Likert scales, from 0 (never a problem) to 4 (almost always a problem). Each domain is then scored as the sum of the individual item scores and linearly transformed to scores ranging from 0 to 100, with higher scores representing better quality of health.[67,68]

The minimal clinically important difference (MCID) for the PedsQL scale scores was estimated to ± 4.4 in pediatric patients. [60]

EuroQol 5-Dimensions Questionnaire

The EuroQol Group developed the EuroQol 5-Dimensions questionnaire (EQ-5D), a generic, self-reported health status assessment tool that can be applied in a wide range of health conditions and treatments to measure the respondent's immediate HRQoL.[73] The EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) was introduced in 1990 and consists of two parts: the EQ-5D descriptive system and the EuroQol Visual Analogue Scale (EQ VAS). The descriptive system contains five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression; each dimension has three levels ranked as 1 (no problems), 2 (some problems), or 3 (extreme problems). Each state is referred to in terms of a five-digit code such that a patient's condition — e.g., no problems with mobility or self-care, some problems with performing usual activities, moderate pain or discomfort, and extreme anxiety or depression — will be designated as 112233. Descriptively defined EQ-5D health states can be converted into a single summary index using a formula that applies weights to the levels in each dimension. This index value can be used to calculate qualify-adjusted life-years (QALYs), an important outcome in economic evaluations of health care

interventions. The EQ VAS records the respondent's self-rated health on a vertical analogue scale ranging from 0 for "worst imaginable health state" to 100 for "best imaginable health state."

One of the limitations of EQ-5D-3L is that it has a relatively high ceiling effect (reporting full health for a large proportion of patients) and therefore small changes in health are difficult to identify. The EuroQol Group developed the EQ-5D 5-levels questionnaire (EQ-5D-5L) in 2005. It has five levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems) instead of three. It has been shown that the additional two levels reduces the ceiling effect of the EQ-5D-5L questionnaire and improves its discriminative power.[74]

The EQ-5D-5L has been validated in a diverse patient population, including patient groups with acute leukemia.[74] However, a 2016 study found that the discriminatory power of the EQ-5D-5L instrument was lower than that of the disease-specific, preference-based questionnaires derived from the European Organisation for Research and Treatment of Cancer — Quality of Life C30 questionnaire (EORTC QLQ-C30).[74] Nonetheless, the investigators concluded that there was no strong evidence against the use of the EQ-5D-5L to evaluate quality of life utilities in acute leukemia.[74]

The MCID for the EQ VAS scores was estimated to range from eight to 12 based on performance status in cancer patients.[61]

Functional Assessment of Cancer Therapy–Lym

The Functional Assessment of Cancer Therapy (FACT)–Lym is an HRQoL scale that was designed to evaluate patient-reported outcomes specifically relevant to non-Hodgkin lymphoma (NHL).[75] It is part of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system and consists of the lymphoma subscale, and the Functional Assessment of Cancer Therapy–General (FACT-G) scale. The lymphoma subscale consists of 15 items, generated from health care provider interviews and the published literature, with supplemental content validity from patient interviews. Initial evidence of validity was available in a sample of 84 patients with NHL from a medical centre in the US.[75] The Functional Assessment of Cancer Therapy–General (FACT-G) is a 27-item scale to measure physical, social/family, emotional, and functional well-being in patients with cancer who are receiving therapy. It has a possible score range of 0 to 108.[75,76] The validity of FACT-G for NHL was demonstrated in a sample of 611 newly diagnosed patients.[76] However, certain items of the scale, such as "I have nausea," "I am bothered by side effects of treatment," and "I am losing hope in the fight against my illness," were found to be less relevant to patients at later assessments.[76] Higher scores on FACT-Lym reflect better HRQoL. Components of FACT-G and FACT-Lym may be combined into a summary index of physical, functional, and lymphoma-specific concerns known as the Trial Outcome Index (TOI).[75] The MCIDs for the FACT-Lym total (6.5 to 11.2), FACT-TOI (5.5 to 11), and lymphoma subscale (2.9 to 5.4) were developed based on patients with relapsed or refractory mantle cell lymphoma.[57] The MCID for the FACT-G total (3 to 7) was based on cancer patients, but not specifically for diffuse large B-cell lymphoma (DLBCL).[58] A literature search identified one study that described the application of FACT-Lym to evaluate HRQoL in patients with rituximab-refractory NHL in the GADOLIN trial.[77]

Short Form (36) Health Survey

The Short Form (36) Health Survey (SF-36) survey was developed by Ware et al. to measure patients' perceived health status.[78] It consists of eight health domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries: the physical component summary (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from 0 to 100, with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population.[78] The MCIDs for SF-36, which range from two to four, are not specific to patients with DLBCL.[59]

The validity of the SF-36 was demonstrated among a cross-sectional sample of 3,445 patients in the US using clinical and psychometric criteria.[79] The patients were English-speaking adults (18 years of age or older) and were categorized into one of four groups: minor chronic medical condition only, serious chronic medical condition only, psychiatric condition only, and both serious medical and psychiatric conditions. The PF scale of the SF-36 had the highest validity in differentiating between patients with minor and serious medical conditions. This was followed by the general health perceptions scale, the role physical scale, and the vitality scale. The bodily pain scale did not perform well, which may have been due to the inclusion of serious medical conditions not characterized by pain (i.e., heart-related conditions and diabetes). The presence of a psychiatric condition was best identified with the mental health scale of the SF-36, followed by the role emotional scale and social functioning scale. The general health perceptions scale was most valid for identifying combined medical and psychiatric conditions. In addition, the SF-36 was found to contain two main components through principal component analysis. The physical functioning, role physical, and bodily pain scales were highly correlated with one component, whereas the mental health, role emotional, and social functioning scales were highly correlated with the second; the former component was identified as the physical dimension of health and the latter as the mental dimension. The SF-36 has been administered to diverse patient populations across many countries.[80] One study was identified that evaluated HRQoL with the SF-36, version 2 in adult patients with intermediate or high-grade NHL from the Surveillance, Epidemiology, and End Results cancer registry for Los Angeles County.[81]

Summary

The measurement of patient-reported outcomes in JULIET with the SF-36 and FACT-Lym was appropriate. The SF-36 is a widely used scale to evaluate quality of life in diverse patient populations, whereas the FACT-Lym is an HRQoL scale specific to NHL. Both scales have been tested for validity and have been applied to patients with NHL in previous studies.

Appendix 9: Best Overall Response Definition (Complete Response and Partial Response) – Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The following tables were extracted from the Clinical Study Report using the March 8, 2017 data cut-off date.[48]

Table 53: Best Overall Response Definition – Complete Response in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

		PET-based response	CT-based response
		Complete Metabolic Response (All of the Following)	Complete Radiologic Response (All of the Following)
Complete response	[redacted]	[redacted]	[redacted]
	[redacted]		[redacted]
	[redacted]		[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

CT = computed tomography; PET = positron emission tomography.

Table 54: Best Overall Response Definition – Partial Response in Relapsed or Refractory Diffuse Large B-Cell Lymphoma

		PET-Based Response	CT-Based Response
		Partial Metabolic Response (All of the Following)	**Partial Remission** (All of the Following)
Partial response	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

CT = computed tomography; PET = positron emission tomography.

Appendix 10: Cytokine Release Syndrome Management Algorithm

The following table was extracted from the tisagenlecleucel product monograph (KYMRIAH PM September 5, 2018.[23]

Table 55: Cytokine Release Syndrome Management Algorithm

Pre-treatment	Acetaminophen/paracetamol and diphenhydramine /H_1 antihistamine and prophylaxis for complications of tumour lysis syndrome as appropriate
KYMRIAH Infusion	
Prodromal syndrome (hours to days): • low-grade fever • fatigue • anorexia	
Prodromal syndrome management	• Observation, rule out infection (surveillance cultures), rule out TLS • Antibiotics per local guidelines (febrile neutropenia); symptomatic support
Symptom progression: • high fever • hypoxia • mild hypotension	
First-line management TLS	• Oxygen, fluids, vasopressor support, antipyretics • Monitor/manage complications
Further symptom progression (one or more of the following): • Hemodynamic instability despite IV fluids and vasopressor support • Worsening respiratory distress, including pulmonary infiltrates; increasing oxygen requirement, including high-flow oxygen and/or need for mechanical ventilation • Rapid clinical deterioration	

Second-line management	• Tocilizumab: IV infusion
	  ○ Patient weight < 30 kg: 12 mg/kg IV over 1 hour
	  ○ Patient weight ≥ 30 kg: 8 mg/kg IV over 1 hour (max dose 800 mg)
	• Hemodynamic and respiratory support

Lack of clinical improvement: if lack of clinical improvement despite prior management, the following management sequence is recommended. At all times, provide hemodynamic and respiratory support, and consider other diagnoses that might cause clinical deterioration (e.g., TLS, sepsis, adrenal insufficiency):	
Third-line management	*If no improvement with first dose of tocilizumab within 12 hours to 18 hours, consider corticosteroids*: • 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg per day Plan rapid taper only after hemodynamic normalization. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement. *If no response to steroids within 24 hours, consider* • Second dose of tocilizumab (dosed as above)
Fourth-line management	*If no response to steroids and second dose of tocilizumab within 24 hours or further clinical deterioration, consider* • a third dose of tocilizumab • or pursue alternative measures for treatment of CRS
Fifth-line management	*In ongoing CRS despite prior therapy, consider* • anti-T-cell therapies, such as cyclophosphamide, anti-thymocyte globulin, or alemtuzumab

CRS = cytokine release syndrome; H_1 = histamine receptor; TLS = tumour lysis syndrome.

Appendix 11: Clinical Practice Guideline Recommendations

Acute Lymphoblastic Leukemia

Table 56: Summary of Key Recommendations for CAR T-Cell Therapy – Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Recommendation	Level of Evidence	Grade
Providers are encouraged to adhere to product information labels and guidance from REMS programs, as they are approved by the FDA.[82]	IV	D
Patient selection should be based upon the indications approved by the FDA and the criteria used in pivotal studies and can be tailored on the basis of emerging information from each new product[38,82,83]	IV	D
Consent should include descriptions of the risks and benefits associated with leukapheresis, lymphodepletion, CRS, CRES, bridging chemotherapy, intensive care support (mechanical ventilation, dialysis, and inotropic support), and anti-IL-6 therapy.[37]	IIA	B
When appropriate, child assent should also be obtained; age-appropriate advance directives should be considered. Incorporation of child life and psychological services in assent discussions can be helpful.[84]	IV	D
Pediatric patients can require a leukapheresis catheter for cell collection. Close monitoring for hypotension, hypocalcemia, and catheter-related pain is imperative during pediatric leukapheresis, particularly among infants and younger children who might not verbalize symptoms.[85,86]	IIA	B
We recommend the selection of cyclophosphamide–fludarabine regimens for lymphodepletion, with exceptions considered in cases of hemorrhagic cystitis and/or resistance to a prior cyclophosphamide-based regimen.[38,87-92]	IIA	B
Given the potential for rapid clinical deterioration, if CAR T-cell therapy is administered in an outpatient setting, a low threshold should be set for patient admission upon the development of a fever and/or signs or symptoms that are suggestive of CRS and/or CRES.[37]	IIA	B
On the basis of the published experience for tisagenlecleucel in pediatric and young adult patients with CD19+ relapsed and/or refractory B-cell acute lymphoblastic leukemia, considering in-patient admission for a minimum of 3 to 7 days following infusion is reasonable.[37,82]	IIA	B
CRS grading should be performed as outlined in Table 2 at least once every 12 hours and more often if a change is noted and/or concerns exist.[65]	IIA	B
Parent and/or caregiver concerns should be addressed because early signs or symptoms of CRS can be subtle and best recognized by those who know the child best.[93]	III	C
CRS should be suspected if at least one of the following four symptoms or signs is present during the CRS risk period within the first 2 weeks following CAR T-cell infusion: fever ≥ 38 °C; hypotension — defined as systolic blood pressure < [70 + (2 × age in years)] mm Hg for patients aged 1 year to 10 years or < 90 mm Hg for those > 10 years; a change from baseline and/or reduced requirements for chronic antihypertensive medications; hypoxia with an arterial oxygen saturation of < 90% on room air; or evidence of organ toxicity as determined by the most recent CTCAE grading system (version 5.0)[94] and pediatric considerations.[65,95,96]	IIA	C
High vigilance for sinus tachycardia as an early sign of CRS is recommended (on the basis of age-specific normal range or baseline values).[97,98]	IIA	B
We recommend application of the PALICC at-risk P-ARDS criteria for the CRS grading of hypoxia. [99-101]	IIA	B
Acute kidney injury in children can be graded according to CTCAE using pRIFLE and KDIGO definitions of Oliguria.[102,103]	IIA	B
Tocilizumab pediatric dosing: patients weighing < 30 kg are dosed at 12 mg/kg; those weighing ≥ 3 0 kg are dosed at 8 mg/kg.[21]	IIA	B

Recommendation	Level of Evidence	Grade
CAR T cell-related HLH and/or MAS have been shown to resolve following administration of anti-IL-6 therapy and corticosteroids, although refractory cases can require further therapy, including consideration of systemic and/or intrathecal therapy on the basis of HLH-2004 management guidelines or use of the IL-1 receptor antagonist anakinra; further research is needed in this area.[104-106]	IIA	C
We recommend that delirium screening using the CAPD tool 116 (or the CARTOX-10 grading system[65] for patients aged ≥ 12 years who have sufficient cognitive abilities) be performed at least twice per 24-hour period among admitted patients and at least daily among outpatients during the high-risk periods for CRES.	IIA	C
Consideration should be given to a prospective collaboration with intensive care registries, such as VPS, which could allow accurate data entry of cell-therapy variables into the CIBMTR registry (by cell-therapy programs) with concurrent entry of intensive care variables into an appropriate registry by pediatric critical care teams.	IV	D
We strongly encourage consideration of QALYs for pediatric patients who might achieve long-term remission through this therapy and encourage all efforts to reduce the cost of care.[107-111]	IV	D
We recommend that CAR T-cell programs seek FACT IEC accreditation as a voluntary means of ensuring adherence to quality standards.[112]	IV	D

CAPD = Cornell Assessment of Pediatric Delirium; CAR = chimeric antigen receptor; CARTOX-10 = CAR-T-Cell-Therapy-Associated TOXicity 10-point assessment scale; CIBMTR = Center for International Blood and Marrow Transplant Research; CRES = CAR T cell-related encephalopathy syndrome; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; FACT = Foundation for the Accreditation of Cellular Therapy; HLH = hemophagocytic lymphohistiocytosis; IEC = immune effector cell; IL = interleukin; KDIGO = Kidney Disease: Improving Global Outcomes; MAS = macrophage activation syndrome; P-ARDS = pediatric acute respiratory distress syndrome; PALICC = Pediatric Acute Lung Injury Consensus Conference; pRIFLE = Pediatric Risk, Injury, Failure, Loss, End-Stage Renal Disease; QALY = quality-adjusted life-year; REMS = risk evaluation and mitigation strategy; SBP = systolic blood pressure; VPS = virtual pediatric intensive care unit systems.
Note: Levels and grades of evidence have been assigned on the basis of the definitions proposed by Shekelle et al.[113]
Sources: Mahadeo et al.[41] (Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for pediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol. 2018. https://creativecommons.org/licenses/by/4.0/).

Table 57: Levels of Evidence for CAR T-Cell Therapy in Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Level of Evidence	
Level	**Definition**
Ia	Evidence from a meta-analysis of randomized controlled trials
Ib	Evidence from at least one randomized controlled trial
IIa	Evidence from at least one controlled study without randomization
IIb	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Source: Mahadeo et al.[41] (Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for pediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol. 2018. https://creativecommons.org/licenses/by/4.0/)

Table 58: Grades of Evidence for CAR T-Cell Therapy in Relapsed or Refractory B-Cell Acute Lymphoblastic Leukemia

Grades of Evidence			
Grade	**Descriptor**	**Level of Evidence**	**Implication for Clinical Practice**
A	Strong recommendation	Directly based on category I evidence	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
B	Recommendation	Directly based on category II evidence, or extrapolated recommendation from category I evidence	Generally, clinicians should follow a recommendation, but should remain alert to new information.
C	Optional	Directly based on category III evidence, or extrapolated recommendation from category I or II evidence	Clinicians should be flexible in their decision-making regarding appropriate practice, although they may set bounds on alternatives.
D	Optional	Directly based on category IV evidence, or extrapolated recommendation from category I, II, or III evidence	Clinicians should consider all options in their decision-making and be alert to new published evidence that clarifies the balance of benefit versus harm.

Source: Mahadeo et al.[41] (Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for pediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol. 2018. https://creativecommons.org/licenses/by/4.0/)

Diffuse Large B-Cell Lymphoma

Table 59: Summary of Key Recommendations for Tisagenlecleucel – Relapsed or Refractory DLBCL

Therapeutic Area	Recommendation
Patient selection	Adult patients with r/r large B-cell lymphomas (DLBCL, NOS, high-grade B-cell lymphoma, DLBCL arising from FL) after ≥ 2 lines of systemic therapy, with adequate organ and marrow function Exclusion of patients with ECOG ≥ 2, CNS involvement, or serious infections
Management of CRS	
Prodromal syndrome: low-grade fever, fatigue, anorexia	Observation; antibiotics if neutropenic; symptomatic support
Mild intervention: high fever, hypoxia, mild hypotension	Antipyretics, oxygen, IV fluids, and/or low-dose vasopressors
Moderate to aggressive intervention: hemodynamic instability, worsening respiratory distress, rapid clinical deterioration	High-dose or multiple vasopressors, oxygen, mechanical ventilation, and/or other supportive care. Administer tocilizumab. Repeat tocilizumab if no clinical improvement (minimum interval of 8 hours); maximum 4 doses. Methylprednisolone if no clinical improvement within 12 hours to 18 hours of first tocilizumab dose, or worsening at any time.

CNS = central nervous system; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma, ECOG = Eastern Cooperative Oncology Group; FL = follicular lymphoma; NCCN = National Comprehensive Cancer Network; NOS = not otherwise specified; r/r = relapsed or refractory.
Source: NCCN guidelines for B-cell lymphomas.[17]

Appendix 12: Indirect Comparisons

Background

The studies in the primary clinical review of tisagenlecleucel (CTL019) are all single-arm, providing no comparative data with other treatments. The aim of this section was to provide an overview and critical appraisal of the indirect evidence available for the assessment of the comparative efficacy and harms of tisagenlecleucel compared with other treatments for children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r B-cell ALL) and adults with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL).

Methods

This section was compiled based on the information submitted by manufacturer; i.e., material for both indications.

Acute Lymphoblastic Leukemia

[redacted].

[redacted].

The three tisagenlecleucel trials are:

- B2202 (ELIANA), a multi-centre, single-arm, phase II trial in pediatric and young adult patients (up to 25 years) with r/r B-cell ALL
- B2205J (ENSIGN), a multi-centre, single-arm, phase II trial in pediatric and young adult patients with r/r B-cell ALL
- B2101J, a single-centre, single-arm phase I/II trial in pediatric and young adult patients with CD19 + B-cell malignancies, no available curative treatment options, and limited prognosis with currently available therapies. In this analysis, data were included for patients with non-CNS3 ALL only, while data from patients with CNS3 and lymphoma were excluded.

[redacted]

- [redacted]

[redacted]

- [redacted]
  - [redacted]
    - [redacted]
  - [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Results

Table 60 shows a comparison of key study characteristics.

Table 60: Key Study Characteristics – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	Study Design	Age	Characteristics	Blasts	Prior Treatment	Refractory Status	KPS
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]					
[redacted]	[redacted]		[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]				

ALL = acute lymphocytic lymphoblastic leukemia; ALL-REZ BFM = acute lymphoblastic leukemia relapse Berlin–Frankfurt–Münster; CR = complete response; DLCL = diffuse large-cell lymphoma; FL = follicular lymphoma; HSCT = hematopoietic stem cell transplant; KPS = Karnofsky Performance Score; MCL = mantle cell lymphoma; NHL = non-Hodgkin lymphoma; Ph+ = Philadelphia chromosome positive; r/r = relapsed or refractory; SCT = stem cell transplant.

[a] Only briefly reported; generally similar to tisagenlecleucel studies.

Table 61: Baseline Patient Characteristics – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	N	Baseline Characteristics						
		Age (Years)	Gender	Relapses	Number of Prior Lines of Therapy	Prior HSCT/SCT	Months Since Last Relapse	Blast Count
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	

ALL = acute lymphocytic lymphoblastic leukemia; F = female; HSCT = hematopoietic stem cell transplant; M = male; SCT = stem cell transplant.
[a] Variable in sensitivity analyses.
[b] Variable included in primary analysis.

[redacted]

[redacted]

[redacted]

[redacted]

Table 62: Overall Survival – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	MAIC Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	MAIC Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.
[a] Adjusted for number of previous relapses and prior HSCT.
[b] Adjusted for number of previous relapses and prior HSCT.
[c] Adjusted for prior HSCT.
[d] Adjusted for number of prior lines of therapy and prior HSCT.
[e] Adjusted for number of prior lines of therapy.
[f] Adjusted for number of previous relapses, prior SCT, and time to relapse from most recent SCT.

Table 63: Sensitivity Analyses for Overall Survival – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	MAIC Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.
[a] Adjusted for number of previous relapses, blast count, and prior HSCT. Median months since last relapse removed from model due to linear relationship with number of previous relapses.
[b] Adjusted for number of previous relapses, months since last relapse, blast count, and prior HSCT.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 64: Relapse-Free Survival – Relapsed or Refractory B-Cell ALL Indirect Comparisons

Comparison	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	Adjusted Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.
[a] Adjusted for number of previous relapses and prior HSCT.
[b] Adjusted for number of previous relapses and prior HSCT.

Table 65: Sensitivity Analyses for Relapse-Free Survival – Relapsed or Refractory B-Cell ALL Indirect Comparisons

Comparison	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	Adjusted Comparison
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.
[a] Adjusted for number of previous relapses, blast count, and prior HSCT. Median months since last relapse removed from model due to linear relationship with number of previous relapses.
[b] Adjusted for number of previous relapses, months since last relapse, blast count, and prior HSCT.

[redacted]

[redacted]

[redacted]

[redacted]

Table 66: Event-Free Survival – Relapsed or Refractory B-Cell ALL Indirect Comparisons

Comparison	Unadjusted Comparison HR (95% CI)	Effective Sample Size MAIC	Adjusted Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; SCT = stem cell transplant.
[a] Adjusted for number of previous relapses, prior SCT, and time to relapse from most recent SCT.
[b] Adjusted for prior SCT.

[redacted]

[redacted]

[redacted]

[redacted]

Table 67: Overall Remission Rate – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	Unadjusted Comparison OR (95% CI)	Effective Sample Size MAIC	Adjusted Comparison OR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.

[a] Adjusted for number of previous relapses and prior HSCT.

[b] Adjusted for number of previous relapses and prior HSCT.

[c] Adjusted for prior HSCT.

[d] Adjusted for number of prior lines of therapy and prior HSCT.

[e] Adjusted for number of prior lines of therapy.

Table 68: Sensitivity Analyses for Overall Remission Rate – Relapsed or Refractory B-Cell ALL Indirect Comparisons

	Unadjusted Comparison OR (95% CI)	Effective Sample Size MAIC	Adjusted Comparison HR (95% CI)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

ALL = acute lymphocytic/lymphoblastic leukemia; CI = confidence interval; HR = hazard ratio; HSCT = hematopoietic stem cell transplant; MAIC = matching-adjusted indirect comparison.
[a] Adjusted for number of previous relapses, blast count, and prior HSCT. Median months since last relapse removed from model due to linear relationship with number of previous relapses.
[b] Adjusted for number of previous relapses, months since last relapse, blast count, and prior HSCT.

Critical Appraisal

The methods for conducting the matching-adjusted indirect comparison (MAIC) were appraised with reference to the best practice principles for MAIC as described by Signorovitch et al., 2012,[114] and to the application of propensity scoring as described by Austin, 2008. [115]

All applicable data for tisagenlecleucel were included; [redacted]

Data were available in the form of individual patient data from tisagenlecleucel trials, excluding patients from one trial with CNS3 leukemia or lymphoma. [redacted]

Detailed comparisons of study characteristics and baseline patient information were presented, limited by incomplete reporting in several studies.

Traditional tests of fit and balance are not usable with summary data (Signorovitch 2012).[114]

the number of adjustments had to be balanced against a reduced sample size due to unmatched patients. Not all variables identified as high priority could be adjusted for in all comparisons. There was good baseline balance for matched variables following adjustment, but continued mismatch on unmatched variables. Some studies were missing important prognostic baseline data, such as refractory status and the number of prior treatments. Residual confounding from unmatched variables is highly likely. It is difficult to anticipate the direction of overall bias.

Duration of follow-up varied, There was some variability in the definition of the index time, which was the start of infusion for the tisagenlecleucel trials, and in the relapse after first stem cell transplant (SCT) for salvage chemotherapy.

The end points were generally standard cancer trial end points, with some variation in definition. Overall survival (OS) was a standard, objective end point, consistently defined across trials. [redacted] Details of definition of response were not provided.

No data were available on adverse events (AEs).

Overall, there is uncertainty as to whether all appropriate comparators were included. Tisagenlecleucel and comparators were both represented by single-arm studies, either alone or pooled. Only paired comparisons were available, with no comparisons through the network. The method used to adjust for potential confounding was limited by the lack of common comparators, the lack of consistently reported information on important prognostic baseline variables, and the limited number of covariates that could be fitted in each model. The approach that the primary confounders are patient-level variables, and does not include an adjustment for differences in study-level factors, advances in supportive care over time, or other non-baseline factors, could influence outcomes.

Conclusion

[redacted] The absence of long-term data for analysis and lack of head-to-head trials between tisagenlecleucel and any comparators are limitations to the interpretation of the results.

Diffuse Large B-Cell Lymphoma

The following is from the Study Report: Efficacy of Tisagenlecleucel versus Historical Control Groups for Relapsed/Refractory Diffuse Large B-Cell Lymphoma, the clinical summary provided by the manufacturer, and a report by the European Medicines Agency.[24,62]

1. JULIET Versus SCHOLAR-1

This was a MAIC that compared individual patient-level data in JULIET with the meta-analysis of SCHOLAR-1, which is the largest meta-analysis for patients with relapsed or refractory DLBCL.[11] [redacted] The comparators were tisagenlecleucel versus salvage chemotherapy; the outcomes examined were ORsR, complete response (CR), and OS. [redacted] SCHOLAR-1 had a total of 636 pooled patients; however, in the current analysis, 523 were analyzed for ORsR and CR and 603 for OS due to missing data

(imputation of missing data was not done for SCHOLAR-1). The analyses of SCHOLAR-1 for the indirect comparison involved the use of aggregate data on patient characteristics, [redacted] Patients in JULIET who met the criteria of SCHOLAR-1 (i.e., progressive disease or stable disease as best response to chemotherapy or relapse ≤ 12 months post-autologous SCT) were included in the analysis ([redacted]). Patients in JULIET and SCHOLAR-1 were matched with propensity score weighting on the following factors: gender, primary diagnosis, International Prognostic Index (IPI) classification, and refractory category. The weighting was applied to the individual patient-level data of JULIET.

The following results were extracted from *Study Report: Efficacy of Tisagenlecleucel versus Historical Control Groups for Relapsed/Refractory Diffuse Large B-Cell Lymphoma* and a report by the European Medicines Agency.[24,62]

Table 69: JULIET Versus SCHOLAR-1 – Relapsed or Refractory DLBCL Indirect Comparisons

	Before Matching				After Matching			
	JULIET Infused	**SCHOLAR-1**	**Response Difference (95% CI)**	***P* Value**	**JULIET Infused**	**SCHOLAR-1**	**Response Difference (95% CI)**	***P* Value**
	[A]	**[B]**	**[A] – [B]**		**[A]**	**[B]**	**[A] – [B]**	
Response Rates	[redacted]	**N = 523**			[redacted]	**N = 523**		
CR	[redacted]	7.0%	[redacted]	[redacted]	[redacted]	7.0%	30.8% (19.9% to 41.8%)	< 0.01
ORsR (CR + PR)	[redacted]	26.0%	[redacted]	[redacted]	[redacted]	26.0%	20.5% (8.9% to 32.0%)	< 0.01
OS	[redacted]	[redacted]			[redacted]	[redacted]		
Median, 95% CI (month)	[redacted]	[redacted]			[redacted]	[redacted]		
Log-rank test				[redacted]				[redacted]
HR, 95% CI ([A] vs. [B])	[redacted]			[redacted]	0.68 (0.48 to 0.96)			< 0.05

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; HR = hazard ratio; ORsR = overall response rate; OS = overall survival; PR = partial response; vs. = versus.

Table 70: JULIET Versus SCHOLAR-1 (Overall Survival is Subset Who Achieved Complete Response) – Relapsed or Refractory DLBCL Indirect Comparisons

	Unadjusted Comparison		
	JULIET CR Subset, FAS, Both Cohorts[1]	SCHOLAR-1 CR Subset[2]	*P* Value[3]
	[redacted]	[redacted]	
[redacted]			
[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]
[redacted]	[redacted]		[redacted]

CR = complete response; DLBCL = diffuse large B-cell lymphoma; FAS = full analysis set.

Although patients in JULIET and SCHOLAR-1 were matched for certain characteristics, not all factors were considered, such as number of prior lines of therapy, which may have led to residual imbalances among groups. [redacted]. There was no common comparator as an anchor in the indirect comparison, which increases the risk for prognostic differences.[116] The study designs in the indirect comparison were also different (i.e., single-arm for JULIET versus pooled randomized controlled trials and observational cohorts in SCHOLAR-1). In SCHOLAR-1, 113 of 636 patients were excluded from analyses due to missing responses, which introduces the possibility of selection bias.

[redacted]

2. JULIET Versus Pooled CORAL Extension Studies

The CORAL extensions included pooled data from two studies among patients who received salvage chemotherapy upon relapsing after autologous SCT or failing to proceed to autologous SCT after second-line treatment. [redacted] The comparators were tisagenlecleucel versus salvage chemotherapy; the outcomes examined were ORsR, CR, and OS. Aggregate data were obtained from the CORAL studies [redacted] The definition of OS in JULIET was modified to align with that of CORAL (i.e., time from relapse after the most therapy, the last dose of the most recent therapy, or the most recent autologous SCT, whichever occurred latest before enrolment, to death from any cause). [redacted] Patients in JULIET and CORAL were matched with propensity score weighting on the following factors: gender, IPI classification, autologous SCT as the most recent therapy, and relapsed after

autologous SCT. [redacted]

The following results were extracted from *Study Report: Efficacy of Tisagenlecleucel versus Historical Control Groups for Relapsed/Refractory Diffuse Large B-Cell Lymphoma* and a report by the European Medicines Agency.[24,62]

Table 71: JULIET Versus Pooled CORAL Extension Studies – Relapsed or Refractory DLBCL Indirect Comparisons

	Before Matching				After Matching			
	JULIET Infused	CORAL Extension Studies	Response Difference (95% CI)	*P* Value	JULIET Infused	CORAL Extension Studies	Response Difference (95% CI)	*P* Value
	[A]	[B]	[A] – [B]		[A]	[B]	[A] – [B]	
Response rates	[redacted]	[redacted]			[redacted]	[redacted]		
CR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.2% (1.1% to 23.3%)	< 0.05
ORsR (CR + PR)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	12.2% (0.6% to 23.7%)	< 0.05
OS	[redacted]	[redacted]			[redacted]	[redacted]		
Median, 95% CI (month)	[redacted]	[redacted]			[redacted]	[redacted]		
Log-rank test				[redacted]				[redacted]
HR, 95% CI ([A] vs. [B])	[redacted]			[redacted]	0.41 (0.31 to 0.54)			< 0.01

CI = confidence interval; CR = complete response; DLBCL = diffuse large B-cell lymphoma; HR = hazard ratio; ORsR = overall response rate; OS = overall survival; PR = partial response; vs. = versus.

Table 72: JULIET Versus Pooled CORAL Extension Studies (Overall Survival in Subset Who Achieved Complete Response) – Relapsed or Refractory DLBCL Indirect Comparisons

	Unadjusted Comparison		
	JULIET CR Subset, FAS, Both Cohorts[1]	CORAL Extension Studies CR/CRu Subset[2]	*P* Value[3]
	[redacted]	[redacted]	
OS from most recent relapse			
Median (month), 95% CI	[redacted]	[redacted]	
Log-rank test			[redacted]
HR (tisagenlecleucel vs. salvage therapies), 95% CI	[redacted]		[redacted]

CI = confidence interval; CR = complete response; CRu = complete remission unconfirmed; DLBCL = diffuse large B-cell lymphoma; FAS = full analysis set; HR = hazard ratio; OS = overall survival; vs. = versus.

Many of the same considerations described above for JULIET versus SCHOLAR-1 apply to JULIET versus CORAL. All patients in JULIET were included in the analysis, regardless of the number of prior lines of therapy. This may have introduced heterogeneity because in JULIET, patients failed two or more lines of therapy; whereas in CORAL, patients failed only two lines of therapy. However, this difference would be expected to bias the results against tisagenlecleucel (due to the inclusion of patients with more severe disease in JULIET). [redacted]

[redacted]. There was no common comparator as an anchor in the indirect comparison, which increases the risk for prognostic differences.[116] The CORAL studies were randomized trials, whereas JULIET was a single-arm trial; comparisons across different study designs introduces additional uncertainty about the comparability of effect estimates.

3. JULIET Versus PIX301

PIX301 is a randomized trial that compared pixantrone to physician's choice of drug among adults with multiple relapsed or refractory aggressive non-Hodgkin lymphoma (NHL). In the analysis, [redacted] patients with aggressive B-cell NHL who had received prior rituximab and then pixantrone as third-line or higher treatment were included. In JULIET, all efficacy analysis set (EAS) patients in the Main Cohort (N = 93) were included. The comparator was tisagenlecleucel versus pixantrone; the outcomes evaluated were ORsR and CR. [redacted] Pixantrone is not marketed in Canada, so the relevance of this comparison to the Canadian context is limited.

The following results were extracted from *Study Report: Efficacy of Tisagenlecleucel versus Historical Control Groups for Relapsed/Refractory Diffuse Large B-Cell Lymphoma* and a report by the European Medicines Agency.[24,62]

Table 73: JULIET Versus PIX301 – Relapsed or Refractory DLBCL Indirect Comparisons

	Unadjusted Comparison			
	JULIET Infused EAS Main Cohort	**PIX30**	**Response Difference (95% CI)**	***P* Value**
	[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]	
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; EAS = efficacy analysis set.
[redacted]

[redacted]

[redacted]

[redacted]

Conclusion

Given the absence of any direct comparative data to evaluate tisagenlecleucel with other interventions in patients with r/r DLBCL, the indirect comparisons are instructive in providing some preliminary data regarding how tisagenlecleucel may fare against salvage treatments. These data, however, must be interpreted cautiously, as the potential for residual confounding in baseline patient characteristics remains, despite the attempts at matching on certain characteristics. In addition, the indirect comparisons addressed only a few efficacy outcomes, and there are currently no data to evaluate the safety profile of tisagenlecleucel versus other treatments.

Appendix 13: Ongoing Clinical Trials of Chimeric Antigen Receptor T-Cell Therapy

The following trials were identified from ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform.

Table 74: Ongoing Clinical Trials

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
ALL								
EUCTR2017-002116-14-ES	A phase II trial of tisagenlecleucel in first-line, high-risk pediatric and young adult patients with B-cell ALL who are MRD-positive at the end of consolidation therapy	Sept. 2018 to NR	Phase II, single-arm, open-label; multiple countries (Europe, UK, US, Canada)	140	B-cell ALL (1 year to 25 years)	Biological: tisagenlecleucel	Disease-free survival (5 years)	Disease-free without allogeneic SCT (1 year) OS MRD-negative CR or CRi (month 3) PedsQL 4.0 and EQ-5D Cogstate computerized cognitive battery age standardized scores Safety
ChiCTR 1800018211	One-arm, single-centre, open, phase II clinical study of CAR T-19 cells in the treatment of	Sept. 2018 to Dec. 2019	Phase II, single-arm, open-label; China	10	r/r B-cell ALL (4 years to 70 years)	Biological: CAR T-19 cells	Efficacy Safety	DOR PFS

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
	relapsed/refractory B-cell leukemia or lymphoma							
NCT03676504	Treatment of patients with relapsed or refractory CD19+ lymphoid disease with T cells expressing a third-generation CAR	Sept. 2018 to Oct. 2020	Phase I/II; parallel assignment; Germany	NR (child/adolescent ALL)	r/r B-cell ALL (children and adolescents) (3+ years)	Biological: CAR T-19 cells	Safety (3 months) Number of transduced T cells (45 days)	NR
NCT03599375	Immunotherapy with CD19 CAR T-cells for B-cell acute lymphoblastic leukemia	Sept. 2018 to Dec. 2021	Phase I, single-arm, open-label; China	20	r/r B-cell ALL (14 years to 75 years)	Biological: CAR T-19 cells	ORR (3 months)	PFS (15 years) OS (15 years)
NCT03671460	CD19 CAR T cells for patients with relapsed and refractory CD19+ B-cell ALL	Sept. 2018 to Jan. 2021	Phase I, single-arm, open-label; China	18	r/r B-cell ALL (1+ years)	Biological: CAR T-19 cells	AEs (6 months)	CR (6 months) Objective remission rate (6 months)
NCT03573700	Evaluation of CD19-specific CAR engineered autologous T cells for treatment of relapsed or refractory CD19+ acute lymphoblastic leukemia	July 2018 to July 2024	Phase I/II, single-arm, open-label; US	35	r/r B-cell ALL (up to 21 years)	Biological: CAR T-19 cells	Maximum tolerated dose and dose-limiting toxicities (28 days) CR (28 days)	NR

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
NCT03574168	CD19-CAR T cells in patients with r/r B-ALL	July 2018 to Dec. 2019	Phase I, single-arm, open-label; China	40	r/r B-cell ALL (3 years to 70 years)	Biological: CAR T-19 cells	Objective response rate (3 months)	Amount of CAR T cells remaining in vivo (2 years) Lifetime of CAR T cells remaining in vivo (2 years)
NCT03467256	CD19 CAR T-cell therapy for treatment of children and young adults with r/r B-ALL	May 2018 to March 2023	Phase I/II, single-arm, open-label	18	r/r B-cell ALL (3 months to 25 years)	Biological: CAR T-19 cells	Toxicity (1 month) MRD-negative remission (1 month) Hematologic remission (1 month)	Duration of MRD-negative remission (2 years) Persistence/ frequency of CAR T cells (2 years) Duration of B-cell aplasia (5 years) OS (5 years)
NCT03544021	CAR T-19 for relapsed or refractory ALL	March 2018 to March 2020	Phase I/II, single-arm, open-label; China	10	r/r B-cell ALL (14 years to 75 years)	Biological: CAR T-19 cells	Dose-limiting toxicity (28 days) AEs (3 months) CR and CRi (3 months)	Engraftment of cells (28 days) CAR T-19 antibody (6 months) DOR (1 year) PFS (1 year) Survival (1 year)
NCT02435849	Determine efficacy and safety of CTL019l in pediatric patients	Apr. 2015 to Nov. 2021	Phase II, single-arm, open-label, multi-centre;	81	Lymphoblastic leukemia • Acute • Childhood	Biological: a single dose of tisagenlecleucel	ORR (CR and CRi)	CR or CRi (6 months)

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
	with relapsed and refractory B-cell ALL		US				Assessment: independent review committee Time frame: 6 months	Without SCT between CTL019 infusion and month 6 CR or CRi and proceed to SCT while in remission (prior to month 6) Duration of remission (60 months) CR or CRi with MRD-negative bone marrow (60 months) RFS (60 months) EFS (60 months) OS (60 months) In vivo cellular PK profile of CTL019 cells (60 months) Immunogenicity to CTL019 (60 months)
NCT02028455 (PLAT-02)	A pediatric and young adult trial of genetically modified T cells directed against CD19 for relapsed or	Jan. 2014 to Jan. 2032	PhaseI/II, single-arm, open-label, multi-centre; US	80	CD19+ acute leukemia	Biological: • Auto CD19 CAR+ EGFTt + T cells	Safety (30 days) MRD-negative CR (63 days)	CD19 CAR+ T-cell persistence (63 days) Recrudescence or development of acute GVHD

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
	refractory CD19+ leukemia						Releasable cell product (28 days)	(63 days) T cells ablated with cetuximab (3 years)
NCT02228096	Study of efficacy and safety of CTL019 in pediatric ALL patients	Aug. 2014 to Oct. 2024	Phase II, single-arm, open-label, multi-centre; US	67	B-cell ALL Relapsed B-cell ALL Refractory B-cell ALL	Biological: tisagenlecleucel	ORR (CR and CRi) Assessment: peripheral blood, bone marrow, and CNS symptoms, physical examination and CSF Time frame: 1 year	Adverse events Laboratory abnormalities (type, frequency and severity) Time frame: 1 year
NCT01683279 (PLAT-01)	A pediatric trial of genetically modified autologous T cells directed against CD19 for relapsed CD19+ ALL	Dec. 2012 to Jan. 2031	Phase I, single-arm, open-label, single-centre; US	18	B-cell leukemia	Biological: • Auto CD19 CAR+ EGFTt + T cells	Adverse events Time frame: 42 days	CD19 CAR+ T-cell persistence Anti-leukemic activity of CD19 CAR+ T cells Time frame: 42 days
NHL								
NCT03570892	Tisagenlecleucel in adult patients with aggressive B-cell non-Hodgkin lymphoma (BELINDA)	Oct. 2018 to June 2025	Phase III, RCT, open-label; NR	318	Aggressive B-cell NHL (adults ≥ 18 years)	Biological: tisagenlecleucel vs. standard of care	EFS (5 years) assessed by BIRC	EFS assessed by local investigator OS ORR

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
								DOR SF-36 FACT-Lym EQ VAS Immunogenicity Time frame: 5 years
NCT03630159	Study of tisagenlecleucel in combination with pembrolizumab in r/r DLBCL patients (PORTIA)	Sept. 2018 to Feb. 2023	Phase Ib, single-arm, open-label; US	32	DLBCL (adults ≥ 18 years)	Biological: tisagenlecleucel + pembrolizumab	ORR (3 months post-infusion) Dose-limiting toxicities	DOR PFS OS In vivo cellular kinetics Immunogenicity Time frame: 24 months
NCT03484702	Trial to determine the efficacy and safety of JCAR017 in adult patients with aggressive B-cell non-Hodgkin lymphoma	June 2018 to Aug. 2022	Phase II, single-arm, open-label	124	NHL (18+ years)	Biological: CAR T-19 cells	ORR (2 years)	AEs (2 years) CR (2 years) EFS (2 years) PFS (2 years) OS (2 years) DOR (2 years) EORTC QLQ-C30 (2 years) EQ-5D-5L (2 years) FACT-Lym (2 years)

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
NCT03483688	A phase Ib study evaluating the safety and efficacy of C-CAR011 treatment in B-NHL patients	March 2018 to Dec. 2019	Phase I, single-arm, open-label; China	10	NHL (18 years to 70 years)	Biological: CAR T-19 cells	Safety (12 weeks)	ORR (12 months) DOR (12 months) PFS (12 months) OS (12 months)
NCT01840566	High-dose therapy and autologous stem cell transplant followed by infusion of CAR-modified T cells directed against CD19+ B cells for relapsed and refractory aggressive B-cell non-Hodgkin lymphoma	Apr. 2013 to Apr. 2019	Phase I, single-arm, open-label, single-centre; US	17	NHL	Auto stem cell transplant **Biological:** • 19-28z T dells • Pegfilgras-tim **Drug:** • Carmustine • Etoposide • Cytarabine • Melphalan	Maximum tolerated dose Safety Time frame: 2 years	PFS OS Time frame: 2 years
ALL/NHL								
NCT03642626	CAR T-cell therapy for heme malignancies	Nov. 2018 to June 2028	Phase II, parallel assignment; US	120	ALL Large B-cell lymphoma (Child, adult, older adult)	Biological: tisagenlecleucel, axicabtagene ciloleucel	CR and CR_i (28 days) ORR (56 days)	MRD-negative CR or CR_i (28 days) Alive but not in remission (28 days) Treatment-related mortality (1 year) RFS EFS (1 year)

Identifier	Study Description	Start Date to Estimated End Date	Design/ Country	Sample Size	Conditions	Interventions	Primary Outcome(s) and Time Frame	Secondary Outcome(s) and Time Frame
								OS Toxicity

AE = adverse event; ALL = acute lymphoblastic leukemia; BIRC = blinded independent review committee; CAR = chimeric antigen receptor; CNS = central nervous system; CR = complete response; CR_i = complete remission with incomplete blood count recovery; CSF = cerebrospinal fluid; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; EFS = event-free survival; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer — Quality of Life C30 questionnaire; EQ-5D = EuroQol 5 Dimensions questionnaire; EQ VAS = EuroQol Visual Analogue Scale; FACT-Lym = Functional Assessment of Cancer Therapy–Lymphoma; GVHD = graft versus host disease; MRD = minimum residual disease; NHL = non-Hodgkin lymphoma; NR = not reported; ORR = overall response rate; OS = overall survival; PedsQL = Pediatric Quality of Life Inventory; PFS = progression-free survival; PK = pharmacokinetic; RCT = randomized controlled trial; RFS = relapse-free survival; r/r = relapsed or refractory; SCT = stem cell transplant; SF-36 = Short Form Health Survey; vs. = versus.