HTA Austria
Austrian Institute for
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GmbH

CAR-T cell therapy: Contrasting the evidence from pivotal trials with the real world evidence (RWE)

Systematic Review

Final report

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Project Team

Project leader: Priv.-Doz. Dr. phil. Claudia Wild

Authors: Dr. med. Andrea Titieni-Schuhmann
Anja Panhuber, MSc
Gregor Goetz, MSSc MPH

Project Support

Systematic literature search: Tarquin Mittermayr, BA(Hons), MA

Hand search: Dr. med. Andrea Titieni-Schuhmann
Anja Panhuber, MSc

External Review: Ao. Univ. Prof. Dr. Ulrich Jäger, Univ. Prof of Haematology, Medical Unviersity of Vienna, Dept. of Internal Medicine I, Head of Division of Haematology and Hemostaseology

Internal Review: PD Dr. phil. Claudia Wild

Correspondence: Claudia Wild, claudia.wild@aihta.at; anja.panhuber@aihta.at

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List of abbreviations

AE ..... adverse event
AIEOP ..... Associazione Italiana di Ematologia e Oncologia
ALL ..... acute lymphoblastic leukaemia
(allo)HSCT ..... (allogenic) stem cell transplantation
AML ..... acute myeloblastic leukaemia
ASTCT ..... American Society for Transplantation and Cellular Therapy
ASCTR ..... Austrian Stem Cell Transplantation Registry
ATMP ..... advanced therapy medicinal product
autoHSCT ..... autologous stem cell transplantation
axi-cel ..... axicabtagene ciloleucel (Yescarta®)
BCA ..... B-cell aplasia
BCMA ..... B-cell maturation antigen
CAPD ..... Cornell Assessment of Pediatric Dellirium
CAR-T ..... chimeric antigen receptor T-cells
CARTOX-10 ..... CAR-T associated toxicity 10-point
CAYAs ..... children, adolescents, and young adults
CHOP ..... Cyclophosphamide – Hydroxydaunorubicin – Oncovin – Prednisone chemotherapy
CI ..... confidence interval
CIBMTR ..... Center for International Blood and Marrow Transplant Research Registry
CNS ..... central nervous system
CR ..... complete remission
CRi ..... complete remission with incomplete haematologic recovery
CRS ..... cytokine release syndrome
CTCAE ..... National Cancer Institute Common Terminology Criteria for Adverse Events
DLBCL ..... diffuse large B-cell lymphoma
DOR ..... duration of remission
DRST ..... Deutsches Register für Stammzelltranspantation
EBMT ..... European Society for Blood and Marrow Transplantation
EFS ..... event-free survival
EMA ..... European Medicines Agency
EORTC QLQ-C30 ... European Organisation for Research and Treatment of Cancer quality of life of cancer patients questionnaire
EQ-5D ..... European Quality of Life-5 Dimensions questionnaire
EU ..... European Union
FDA ..... Food and Drug Administration
GRADE ..... Grading of Recommendations, Assessment, Development and Evaluation
GTMP ..... gene therapy medicinal product
GVHD ..... graft-versus-host disease
HLH ..... haemophagocytic lymphohistiocytosis
HR ..... hazard ratio
HRQoL ..... Health-related Quality of Life
HTA ..... health technology assessment

ICANS..... immune effector cell-associated neurotoxicity syndrome
LFS..... leukaemia-free survival
MCID..... minimally clinically important difference
MRD ..... Minimal Residual Disease
NCI..... National Cancer Institute
NE ..... not evaluable
NHL ..... Non-Hodgkin lymphoma
NICE..... National Institute for Health and Care Excellence
NIH ..... National Institutes of Health
NOS..... not otherwise specified
NR ..... not reported
NR* ..... not reached
nRCT ..... non-randomized controlled trial
ORR ..... overall response rate
OS ..... overall survival
OOS..... out of specification
PCR..... polymerase chain reaction
PD ..... progressive disease
PedsQL ..... Pediatric Quality of Life Inventory
PET/CT ..... positron emission tomography-computed tomography
PFS..... progression-free survival
PICO ..... Framework for research questions of Population, Intervention, Comparators and Outcomes
PICU ..... Paediatric Intensive Care Unit
PMBCL..... primary mediastinal B-cell lymphoma
Pola-BR..... Polatuzumab-Rituximab-Bendamustin
pts..... patients
PR..... partial remission
PRISMA..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRST..... Pädiatrischen Register für Stammzelltransplantation
PRWCC ..... Paediatric Real World CAR Consortium
r/r ..... refractory/relapsed
RoB..... risk of bias
RWE..... real-world evidence
SAE..... serious adverse event
SD..... stable disease
SD*..... standard deviation
SOC ..... standard of care
tDLBCL..... transformed DLBCL
tFL ..... transformed follicular lymphoma
tisa-cel..... tisagenlecleucel (Kymriah®)
VAS ..... visual analogue scale
WHO..... World Health Organisation

Executive Summary

Introduction

Different types of blood cancers such as B-cell acute lymphoblastic leukaemia (B-ALL) and large B-cell lymphoma (LBCL: diffuse large B-cell lymphoma/ DLBCL and primary mediastinal B-cell lymphoma/PMBCL) arise from B-cells. While B-ALL often occurs in children, adolescents and young adults (CAYAs), LBCL mainly affects adults over 65 years. Current treatments for these diseases involve chemotherapy and stem cell transplantation. New immunological treatments such as chimeric antigen receptor T-cell (CAR-T) therapy have recently emerged, raising expectations in patients and practitioners.

blood cancers from B-cells: acute lymphoblastic leukaemia (B-ALL) and large B-cell lymphoma (LCBL)

current treatment: chemotherapy, stem cell transplantation

This report aimed to synthesize the results of international health technology assessments (HTAs) regarding the available evidence and their critical evaluation of CAR-T cell therapies and to contrast the results from the pivotal studies ELIANA, ZUMA-1 and JULIET with real-world evidence (RWE) studies on patient characteristics, clinical effectiveness and safety of Kymriah® and Yescarta® for B-ALL in CAYAs and LBCL (DLBCL and PMBCL) in adults.

aim of report: synthesize results from HTAs, contrast pivotal trials with real-world evidence

CAR-T cells are genetically modified T-cells targeting cancer antigens, thereby specifically eliminating tumour cells. Two CAR-T cell therapies were approved by the FDA and EMA 2017 and 2018 for cancer patients after two or more lines of systemic therapy: Kymriah® (for B-ALL and DLBCL) and Yescarta® (for DLBCL and PMBCL). The corresponding pivotal trials for the approval were ELIANA for Kymriah® (B-ALL), ZUMA-1 (Yescarta®) and JULIET (Kymriah®) for LBCL.

CAR-T therapies as new treatment option

pivotal trials: ELIANA, ZUMA-1 and JULIET

Methods

To summarise the results of HTAs, a recent review covering five HTA institutions was consulted, the table of results controlled, revised and expanded. For the systematic review a systematic search was conducted in Medline, Embase, the Cochrane Library to evaluate the effectiveness and safety of real-world evidence of B-ALL and LBCL. Two independent researchers performed study selection, risk of bias assessment and data extraction. RWE results were then compared with pivotal studies. For LBCL, a systematic review by Cochrane covering the evidence on the pivotal studies was identified. For clinical effectiveness, crucial outcomes included overall survival, event-free survival, progression-free survival, response rates, relapse and health-related quality of life. For safety, crucial outcomes included (serious) adverse events and (treatment-related) mortality.

overview on HTA results + SR on RWE of B-ALL and LBCL

outcomes for effectiveness and safety: OS, EFS, PFS, ORR, CR, relapse, HRQoL, AE, mortality

Results

Available evidence: To summarise the HTA results, the assessments of ten HTA institutions from nine countries were used: In summary, the pivotal studies were found to have extensive limitations. However, a possible clinical benefit of Kymriah® or Yescarta® was acknowledged by some institutions.

HTAs from 10 institutions: evidence gaps

For the assessment of the RWE on B-ALL, 12 observational studies (with a total of 641 patients) were identified. All (except of three studies) were conducted retrospectively. The length of follow-up ranged from 7.6-24 months (RWE) and was 13.1 in the pivotal trial. For the RWE assessment of LBCL,

12 observational studies for B-ALL; 15 observational studies + 2 nRCTs for LBCL

15 observational studies and two nRCTs were identified. A total of 2,105 patients were analysed. All (except of two studies) were conducted retrospectively. The length of follow-up ranged from 4-19.8 months (real-world) and 19.3-27.1 (pivotal trials).

large differences in patient characteristics between pivotal trials and RWE:

less strict eligibility criteria in RWE

Patients' characteristics: Patients' characteristics differed between pivotal and real-world studies, as eligibility criteria were more restrictive in the pivotal trials. In ELIANA, only patients with ≥5% lymphoblasts were included, and patients with relapse, CNS involvement or extramedullary disease were excluded. Patients with prior anti-CD19/CD3 immunological therapies were also excluded from ELIANA. Prior allogenic stem cell transplantation was not allowed in ZUMA-1 and JULIET, as well as bridging therapy in ZUMA-1. Other differences in ZUMA-1 and JULIET included the number of prior therapies or the ECOG performance status. Patients in all pivotal trials were slightly younger.

moderate to high RoB

The *risk of bias* of included studies (B-ALL and LBCL) was moderate to high.

effectiveness results B-ALL: OS 76% vs. 38.5-100%

LBCL: OS 12, n.r vs. 10.7-19.3 months

Clinical effectiveness and safety: For B-ALL, overall survival (OS) rate at 12 months was 76% in ELIANA and ranged from 38.5%-100% in real-world studies. Event-free survival (EFS) rate at 12 months was 50% in ELIANA and ranged from 31%-72% in the RWE. Relapse rate ranged from 28%-100% in RWE and occurred in 36% of ELIANA's patients. For LBCL, median OS ranged from 10.7-19.3 months in RWE and was 12 months in JULIET and not reached in ZUMA-1. The progression-free survival rate after 12 months ranged from 29.3-55.7% (RWE) and was 44% in ZUMA-1.

safety results mortality: B-ALL: 25% vs. 0-42% LBCL: 50%, 61% vs. 25-48%

The most common adverse events in B-ALL and LBCL patients were cytokine release syndrome (CRS), neurotoxicity, infections and cytopenias. Mortality in ELIANA was 25%, compared with 0-42% in RWE. Mortality in ZUMA-1 and JULIET was 50% and 61%, respectively. In contrast, between 25%-48% of the patients died in RWE.

2 ongoing RCTs

Two RCTs are currently ongoing and investigating Kymriah® and Yescarta® in LBCL patients as second-line treatment compared with standard therapies. No RCTs are currently ongoing for Kymriah® in B-ALL patients.

Discussion

limitations of the evidence: uncontrolled, unblinded, restrospective, small sample size, short FU, heterogeneity of pts.

The evidence on effectiveness and safety of Kymriah® and Yescarta® for B-ALL and LBCL patients is uncertain. According to other HTA institutions and Cochrane, limitations of pivotal trials were uncontrolled study design, short follow-up, small patient cohort and lack of safety data. Uncertainties in the RWE studies remain due to lack of a control arm, an unblinded, retrospective study design, heterogeneous cohorts and heterogeneity in the grading systems for adverse events.

Conclusion

evidence remains uncertain

The differences between pivotal studies and RWE are analysed in this report. The assessed real-world studies could not close the evidence gaps due to limitations in study quality, design and heterogeneity of data and the lack of RCTs. The superiority of CAR-T cell therapies compared to standard therapies remains uncertain.

Zusammenfassung

Einleitung

Leukämie und Lymphom – Grundlagen und Behandlungsoptionen

Blutkrebsarten ausgehend von B-Zellen: akute lymphoblastische Leukämie (B-ALL) und großzelliges B-Zell Lymphom (LBCL)

Das menschliche Blut besteht aus verschiedenen Zellarten, welche verschiedene Aufgaben erfüllen. Die weißen Blutkörperchen, auch Leukozyten genannt, sind Teil unseres Immunsystems und bekämpfen Krankheitserreger. Zu ihnen gehören die B-Zellen und T-Zellen. Diese Blutzellen entstehen im Knochenmark und können anschließend über den Blut- und Lymphkreislauf in Lymphknoten gelangen, wo sie sich weiterentwickeln. Durch spontane Veränderungen, welche im Erbgut der B-Zellen passieren, können – abhängig vom Entwicklungsstadium der Zelle – verschiedene B-Zell Krebsarten entstehen. Bei der akuten lymphatischen B-Zell Leukämie (B-ALL) findet die Veränderung der Zellen im Knochenmark statt. Das diffus großzellige B-Zell Lymphom (DLBCL) und das primär mediastinale B-Zell-Lymphom (PMBCL) sind bösartige Erkrankungen, die meist in den Lymphknoten entstehen (= Lymphome). Beide Lymphomarten gehören zu den Non-Hodgkin Lymphomen und werden in diesem Bericht als large B-cell lymphoma (LBCL) zusammengefasst. Sowohl bei der B-ALL und die LBCL wird der Begriff „Blutkrebs“ verwendet.

seltene Erkrankungen, Standardbehandlung: Chemotherapie und Stammzelltransplantation

Über das Blut oder lymphatische System können sich die malignen, also die veränderten, B-Zellen schließlich im gesamten Körper verteilen und auch andere Organe befallen. Die genannten Blutkrebsarten gelten als besonders aggressiv und führen unbehandelt innerhalb von Monaten zum Tod. Während die akute lymphatische B-Zell Leukämie häufig bei Kindern und jungen Erwachsenen unter 20 Jahren auftritt, betreffen die beiden Lymphomarten (LBCL) meist Erwachsene über 65 Jahre. Beide Blutkrebsarten werden aufgrund ihrer geringen Anzahl an Betroffenen als sogenannte „seltene Krankheiten“ eingestuft. Die derzeitige Standardbehandlung dieser Krankheiten ist in erster Linie die Chemotherapie. In weiterer Folge kann auch – abhängig vom Krankheitsverlauf – eine Stammzelltransplantation empfohlen werden, bei der kranke Blutzellen durch gesunde ersetzt werden. Es sind jedoch nicht alle Patient*innen für eine solche Stammzelltransplantation geeignet oder sprechen darauf an. Aus diesem Grund wird intensiv an neuen Therapieansätzen für diese Patient*innengruppe geforscht. In jüngster Zeit sind neue Behandlungen entwickelt worden, die auf den Funktionen des Immunsystems basieren. Beispielsweise benutzt man Antikörper um gezielt Krebsmedikamente an die richtige Stelle im Körper zu bringen oder nützt die Funktion von Immunzellen, Krebszellen zerstören zu können. Diese neuen Therapien sind bei Patient*innen und allen, die in der Krebsbehandlung tätig sind, mit großen Hoffnungen und Erwartungen verbunden sind.

neue immunologische Therapien

CAR-T Zelltherapie als neue Behandlungsoption

CAR-T Zelltherapie: körpereigene modifizierte T-Zellen zur Eliminierung von Krebszellen

Eine dieser Behandlungen ist die sogenannte CAR-T Zelltherapie (Chimäre Antigen Rezeptor T-Zellen, Chimeric Antigen Receptor T-cell). Hier werden der*dem Patient*in zunächst körpereigene T-Zellen (Immunzellen) entnommen und gentechnisch so verändert, dass sie an ihrer Oberfläche einen neuen Rezeptor tragen. Mit diesem Rezeptor können sie spezifische Turmorzellen erkennen und gezielt eliminieren. Die entnommenen und veränderten T-Zellen werden dann im Labor vervielfältigt und wieder in den Körper der*des

Patient*in zurückgeführt, wo sie anschließend die Krebszellen bekämpfen. Aktuell findet dieser Prozess in Laboren der Pharmahersteller statt, allerdings ist in Zukunft geplant, die CAR-T Zellen auch im Krankenhauslabor herzustellen („hospital-based production").

Zulassung durch FDA und EMA: Kymriah® (B-ALL, DLBCL) und Yescarta® (DLBCL, PMBCL)

Zwei CAR-T Zelltherapien wurden von der Food and Drug Administration (FDA) und der European Medicines Agency (EMA) in den Jahren 2017 und 2018 für jene Krebspatient*innen zugelassen, bei denen bereits zwei oder mehrere Therapien nicht erfolgreich waren:

- Kymriah® (für B-ALL und DLBCL)
- Yescarta® (für DLBCL und PMBCL).

Die entsprechenden Zulassungsstudien waren ELIANA (Kymriah®) für B-ALL, sowie ZUMA-1 (Yescarta®) und JULIET (Kymriah®) für die beiden Lymphomerkrankungen (LBCL).

Kriterien für die Durchführung von CAR-T Zelltherapien in Österreich

In Österreich werden beide CAR-T Zelltherapien im klinischen Alltag eingesetzt. Für eine qualitätsgesicherte Durchführung der CAR-T Zelltherapien wurde eine Empfehlung der CAR-T Zellplattform der Österreichischen Gesellschaft für Hämatologie und Medizinische Onkologie veröffentlicht. Die Empfehlungen richten sich an österreichische CAR-T Zentren und beschreiben die notwendigen technischen Voraussetzungen und personale Kompetenzen für die Behandlung von Patient*innen mit CAR-T Therapien. Die in der Empfehlung beschriebenen Struktur-, Personal- und Prozesskriterien müssen von den Zentren erfüllt werden. Aktuell wird in sechs österreichischen Zentren eine Behandlung mit CAR-T Zelltherapien durchgeführt (Medizinische Universitäten Wien, Graz, Innsbruck, Salzburg, St. Anna Kinderspital, Elisabethinen Ordensklinikum Linz). Für die Anwendung von CAR-T Zelltherapien bei Lymphompatient*innen im klinischen Alltag außerhalb von Studien gibt es eine strenge Patient*innenselektion welche einem genau festgelegten Ablauf (Algorithmus) unterliegt. Zusätzlich ist die Dokumentation aller CAR-T Patient*innen im Register der Europäischen Gesellschaft für Blut- und Knochenmarktransplantation (European Society for Blood & Marrow Transplantation, EBMT) verpflichtend.

Algorithmus zur Patient*innenselektion

Aufgrund der geringen Patient*innenzahlen und dem neuartigen Charakter der CAR-T Zelltherapie, gibt es erst wenige klinisch aussagekräftige Studien in Österreich als auch international, welche die Wirksamkeit und Sicherheit, aber auch die Patient*innencharakteristika beschreiben.

Methoden

Ziel: Ergebnisse anderer HTAs zusammenfassen

Ziel dieses Berichts war es, einerseits die Ergebnisse anderer Health Technology Assessments (HTAs) hinsichtlich der verfügbaren Evidenz zur Wirksamkeit und Sicherheit und ihrer kritischen Beurteilung der zugelassenen CAR-T Zelltherapien zu sammeln und zusammenzufassen.

Evidenzsynthese von Versorgungsstudien, Vergleich mit Zulassungsstudien

Andererseits wurde in diesem Bericht eine systematische Übersichtsarbeit zu den beiden CAR-T Zelltherapien Kymriah® und Yescarta® auf Basis von Versorgungsstudien[1] durchgeführt. Die Versorgungsstudien inkludieren Beobachtungs- und Registerstudien, die auch als Real-World Evidenz bezeichnet werden. Die Ergebnisse der Versorgungsstudien wurden anschließend den Ergebnissen der Zulassungsstudien hinsichtlich Patient*innencharakteristika

[1] Versorgungsstudien beinhalten die Ergebnisse von CAR-T Zelltherapie Patient*innen, die im klinischen Alltag nach der Therapiezulassung erhoben werden.

und ausgewählten Wirksamkeits- und Sicherheitsendpunkten gegenübergestellt. Somit konnten mögliche Unterschiede in den Ergebnissen der Zulassungsstudien mit denen aus einem Real-World Setting kontrastiert werden und Differenzen in den Selektionskriterien festgestellt werden.

HTA Kapitel: Publikation von 2022 erweitert

Aufbauend auf einer aktuellen Studie von Gye et al. aus dem Jahr 2022 wurden die Ergebnisse anderer HTA Institutionen kontrolliert, überarbeitet und erweitert.

systematische Suche

Zur Bewertung der Wirksamkeit und Sicherheit von Real-World-Evidenz (RWE) zur akuten lymphoblastischen B-Zell Leukämie und den beiden Lymphomarten (LBCL), wurde eine systematische Suche nach Studien in den folgenden Datenbanken durchgeführt: Medline, Embase, The Cochrane Library. Die Auswahl der Studien, die Extraktion der Studiendaten und die Bewertung der methodischen Qualität wurde von zwei unabhängigen Wissenschaftler*innen des AIHTA durchgeführt. Die Ergebnisse aus den Versorgungsstudien wurden anschließend mit denen der Zulassungsstudien verglichen. Für LBCL wurde eine systematische Übersichtsarbeit von Cochrane herangezogen, welche die Evidenz zu den Zulassungsstudien abdeckt.

systematische Übersichtsarbeit von Cochrane für LBCL herangezogen

Auswahl der Ereignisse (Endpunkte) zu Wirksamkeit und Sicherheit

relevante Wirksamkeits- und Sicherheitsendpunkte

Zur Bewertung der klinischen Wirksamkeit wurden folgende Endpunkte als entscheidende Endpunkte definiert:

- *Gesamtüberleben:* wieviele Patient*innen sind nach einem bestimmten Zeitraum noch am Leben
- *Ereignisfreies/progressionsfreies Überleben:* wieviele Patient*innen hatten nach einem bestimmten Zeitraum weder einen Rückfall, ein Fortschreiten der Erkrankung, noch sind sie gestorben
- *Ansprechrate:* wieviele Patient*innen haben vollständig oder teilweise auf die Therapie angesprochen
- *Rückfallrate:* wieviele Patient*innen hatten eine Rückkehr der Erkrankung
- *Lebensqualität:* unterschiedliche Definitionen, abhängig von Bewertungssystemen

Für die Sicherheit wurden folgende Endpunkte als entscheidende Endpunkte definiert:

- *(schwerwiegende) unerwünschte Ereignisse:* z. B. Zytokin-Freisetzungssyndrom, Neurotoxizität, Infektionen
- *(behandlungsbedingte) Sterblichkeit*

Ergebnisse

Identifizierte Studien

HTA von 10 Institutionen aus 9 Ländern

Um die Ergebnisse anderer HTA Institutionen zusammenzufassen, wurden die Bewertungen von zehn HTA Institutionen aus neun Ländern verwendet. Zusammenfassend wurde den Zulassungsstudien umfangreiche Limitationen attestiert. Ein möglicher klinischer Nutzen von Kymriah® oder Yescarta® gegenüber anderen Therapien wurde jedoch von manchen Institutionen eingeräumt. Aufgrund der geringen Evidenz wurde dieses Ergebnis aber als sehr unsicher eingestuft.

12 Beobachtungsstudien für B-ALL

Für die Evidenzsynthese von B-ALL wurden 12 Beobachtungsstudien identifiziert, die vorwiegend ein retrospektives Studiendesign hatten. Beim retrospektiven Studiendesign wird auf Daten zurückgegriffen, die bereits vor dem Studienbeginn erhoben wurden. Insgesamt wurden 641 Patient*innen analysiert, wobei die Möglichkeit besteht, dass Fälle doppelt publiziert wurden. Die Dauer der Nachbeobachtung reichte von 7,6 bis 24 Monaten in den Versorgungsstudien und betrug in der Zulassungsstudie 13,1 Monate.

15 Beobachtungsstudien + 2 nRCTs für LBCL

Bei der Evidenzsynthese zu den beiden Lymphomarten wurden 15 vorwiegend retrospektive Beobachtungsstudien und 2 nicht-randomisierte kontrollierte Studien (engl. nRCTs) identifiziert. Bei den nRCTs werden verschiedene Behandlungen miteinander verglichen: Die Studienteilnehmer*innen werden dabei nicht nach dem Zufallsprinzip einer Behandlung zugeteilt (nicht-randomisiert), sondern nach bestem Ermessen des*der behandelnden Ärzt*in, wodurch es zu einer Verzerrung kommen kann. Insgesamt wurden 2.105 Patient*innenen analysiert. Die Dauer der Nachbeobachtung reichte von 4 bis 19,8 Monaten (RWE Studien) und von 19,3 bis 27,1 Monaten (Zulassungsstudien).

Patient*innencharakteristika

Unterschiede hinsichtlich Patient*innen-Charakteristika zwischen Zulassungs- und Versorgungsstudien

Die Patient*innenmerkmale unterschieden sich zwischen den Versorgungs- und Zulassungsstudien, da die Zulassungskriterien in letzteren deutlich restriktiver waren.

deutlich striktere Einschlusskriterien in Zulassungsstudien

- In ELIANA wurden nur Patient*innen mit ≥5 % Lymphoblasten eingeschlossen und Patient*innen mit einem Rückfall (Rezidiv) oder Beteiligung anderer Organe (Rezidive außerhalb des Knochenmarks wie z. B. im Zentralnervensystem, extramedulläre Rezidive) ausgeschlossen. Patient*innen bei denen bereits immunologische anti-CD19/CD3[2] Therapien durchgeführt worden sind, wurden in ELIANA ebenfalls ausgeschlossen
- Eine vorherige allogene Stammzelltransplantation war in den beiden Zulassungsstudien ZUMA-1 und JULIET nicht erlaubt. In ZUMA-1 war eine Überbrückungstherapie, welche Patient*innen im Zeitraum zwischen T-Zell Entnahme und CAR-T Zell Behandlung bekommen, nicht erlaubt. Weitere Unterschiede in ZUMA-1 und JULIET betrafen die Anzahl der vorangegangenen Therapien oder den ECOG-Performance Status, der das allgemeine Wohlbefinden der Patient*innen beschreibt.

Die Patient*innen waren in allen drei Zulassungsstudien etwas jünger als in den Versorgungsstudien.

Verzerrungspotential: moderat bis hoch

Das Verzerrungspotential der Versorgungsstudien, also die Gefahr eines Bias, wurde bei beiden Erkrankungen (B-ALL und LBCL) als moderat bis hoch eingeschätzt. Bei diesen Studien gibt es daher ein hohes Risiko für eine Verzerrung, was die Studienqualität und -aussagekraft schmälert.

[2] CD19 und CD3 sind Rezeptoren an der Oberfläche von T-Zellen

Klinische Wirksamkeit und Sicherheit

Gesamtüberlebensrate (OS), ereignisfreien Überlebens (EFS), Rückfallraten

Wirksamkeitsergebnisse B-ALL und LBCL

- Bei B-ALL lag die Gesamtüberlebensrate (OS) nach 12 Monaten in der ELIANA-Studie bei 76 % und schwankte in den Versorgungsstudien zwischen 38,5 % und 100 %. Die Rate des ereignisfreien Überlebens (EFS) nach 12 Monaten lag bei ELIANA bei 50 % und reichte in den Versorgungsstudien von 31 % bis 72 %. Die Rückfallrate lag in den Versorgungsstudien zwischen 28 % und 100 % und trat bei 36 % der ELIANA-Patient*innen auf.

B-ALL:
OS: 76 % vs. 38,5-100 %

- Bei LBCL lag das mediane Gesamtüberleben in den Versorgungsstudien zwischen 10,7 und 19,3 Monaten, bei JULIET betrug es 12 Monate und wurde bei ZUMA-1 nicht erreicht. Die progressionsfreie Überlebensrate nach 12 Monaten reichte von 29,3 bis 55,7 % in RWE Studien und betrug 44 % in ZUMA-1. Die Ansprechraten (komplettes Ansprechen) betrugen 40 % und 58 % in ZUMA-1 and JULIET und betrugen 41.5 %-48 % nach einem Monat, 25 %-40 % nach 3 Monaten und 37.8 % nach sechs Monaten.

LBCL:
OS: 12, nicht erreicht Monate vs. 10,7-19,3 Monate

Unerwünschte Ereignisse (AE, SAE)

Die häufigsten unerwünschten Ereignisse bei B-ALL und LBCL Patient*innen waren Zytokin-Freisetzungssyndrom (CRS), Neurotoxizität, Infektionen und Zytopenien.

Sicherheitsergebnisse: häufige Nebenwirkungen, hohe Sterblichkeit trotz CAR-T

- Das Zytokin-Freisetzungssyndrom (CRS) trat bei 77 % (ELIANA) und 42 %-86 % (RWE), Neurotoxizität bei 40 % (ELIANA) und 0 %-36 % (RWE) der Patient*innen auf. CRS trat in ZUMA-1 (93 %) häufiger auf als in JULIET (58 %) und bei 68 %-93 % der Patient*innen aus den Versorgungsstudien.

CRS:
B-ALL: 77 % vs. 42-86 %
LBCL: 93 %, 58 % vs. 68-93 %

- Neurotoxizität betraf 67 % (ZUMA-1), 21 % (JULIET) und zwischen 15 %-68,7 % (RWE) der Patient*innen.
- Die Sterblichkeit lag bei ELIANA bei B-ALL Patient*innen bei 25 %, in den Versorgungsstudien dagegen bei 0-42 %. Bei ZUMA-1 und JULIET lag die Sterblichkeit bei LBCL Patient*innen bei 50 % beziehungsweise 61 %, in den Versorgungsstudien zwischen 25 % und 48 %.

Sterblichkeit:
B-ALL: 25 % vs. 0-42 %
LBCL: 50 %, 61 % vs. 25-48 %

Laufende Studien

zwei laufende RCTs zu Kymriah® und Yescarta® bei LBCL

Derzeit werden zwei randomisierte kontrollierte Studien (RCTs) durchgeführt. In diesen werden bei LBCL Patient*innen, bei denen bereits eine Therapie erfolglos durchgeführt wurde, eine Behandlung mit Kymriah® und Yescarta® im Vergleich zu Standardtherapien untersucht (Zweitlinientherapie). Für die Anwendung von Kymriah® bei B-ALL Patient*innen werden derzeit keine RCTs durchgeführt.

Diskussion

unsichere Evidenz aufgrund von unkontrollierten, unverblindeten, oft retrospektiven Studien mit kurzem follow-up

Die Evidenz für die Wirksamkeit und Sicherheit von Kymriah® und Yescarta® bei Patient*innen mit B-ALL und LBCL ist unsicher: laut den anderen HTA Institutionen und der systematischen Übersichtsarbeit von Cochrane gehören zu den Limitationen der Zulassungsstudien das unkontrolliertes Studiendesign, die kurze Nachbeobachtungszeit, kleine Patient*innenkohorten und das Fehlen von Langzeits-Wirksamkeits- und Sicherheitsdaten.

intransparentes Zensieren in RWE

Zu den Limitationen der Versorgungsstudien gehörten ebenfalls das Fehlen eines Kontrollarms, ein unverblindetes, retrospektives Studiendesign der meisten Studien, heterogene Kohorten und die Heterogenität der Bewertungssysteme für unerwünschte Ereignisse. Eine allgemeine Limitation onkologischer Studien ist das intransparente Aussortieren (Zensieren) von Patient*innen durch die Studienautor*innen: Dabei ist unklar welche Patient*innen zu welchem Zeitpunkt von der Analyse ausgenommen werden, wodurch es zu einer Verzerrung der Studienergebnisse kommen kann. Aufgrund der großen Schwankungsbreite in den RWE Studienergebnissen waren aussagekräftige Schlussfolgerungen zur Wirksamkeit und Sicherheit erschwert. Eine sorgfältige Auswahl der Patient*innen scheint unabdingbar.

hohe Kosten, Reduktion durch alternative Produktionsformen

Zuletzt sind nicht nur die unsichere Evidenz, sondern auch die Kosten zu berücksichtigen. Aktuell gehören die CAR-T Zelltherapien mit mehr als 300.000 € je Infusion zu besonders teuren Therapien. Ein Potential zur Verringerung der Kosten wird in der dezentralisierten Herstellung („hospital-based production“) gesehen

Fazit

Evidenzlücken

Überlegenheit von CAR-T bleibt unsicher

Die vorliegenden Versorgungsstudien können die Evidenzlücken aus den Zulassungsstudien nicht schließen. Die Unterschiede zwischen den Zulassungs- und Versorgungsstudien hinsichtlich der Patient*innen-charakteristika sowie Wirksamkeits- und Sicherheitsergebnissen sind in diesem Bericht zwar zusammengefasst, aufgrund der Limitationen in der Studienqualität, dem Studiendesign und Heterogenität der Daten, sowie des Fehlens von vergleichenden Studien, ist der Nachweis einer Überlegenheit von CAR-T Zelltherapien im Vergleich zu Standardtherapien weiterhin unsicher.

1. Introduction and background

1.1 Overview of the disease, health condition and target population

Various malignant diseases of the haematopoietic system arise from malignant B-cells. Depending on the B-cells of origin, a differentiation is made between the various types of blood cancer. Acute lymphoblastic leukaemia (ALL) is a disease of the lymphoid cells from the bone marrow [9]. Diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) belong to the non-Hodgkin's lymphomas (NHL) and are malignancies that usually arise in the lymph nodes [10, 11]. The malignant B cells can eventually spread throughout the body through the blood or lymphatic system and affect other organs. These blood cancers are considered particularly aggressive and lead to death within months if left untreated.

maligne, hämatologische B-Zell Erkrankungen

B-Zellen verbreiten sich im Blut und können andere Organe befallen

aggressive, tödliche Krebsarten

Acute lymphoblastic leukaemia

Acute lymphoblastic leukaemia (ALL) is a rare disease characterised by the uncontrolled proliferation of lymphocytes in the bone marrow, accounting for around 2% of all lymphoid neoplasms in the US [12]. According to the World Health Organisation (WHO), ALL is classified into three different major subtypes depending on the cell type, surface markers and genetic abnormalities [13]:

ALL: seltene Erkrankung des Knochenmarks

- B lymphoblastic leukaemia/lymphoma, not otherwise specified
- B lymphoblastic leukaemia/lymphoma with recurrent cytogenic abnormalities
- T lymphoblastic leukaemia/lymphoma.

verschiedene Subtypen

Approximately 75% of ALL cases are caused by B-cells (B-ALL) [9, 14]. Depending on the antibody expression, different immunophenotypic subtypes such as pro-, common-, pre- and mature B-ALL (Burkitt Lymphoma) can be distinguished. Different therapeutic approaches in adult patients are applied, depending on the immunophenotypic and genetic subtype [15]. Prognostic factors for a favourable course of the disease include age, no abnormal cytogenetics, white blood count of <30,000 and complete remission within four weeks after induction therapy, including the absence of minimal residual disease [12].

verschiedene immunophänotypische Subtypen

prognostische Faktoren

Incidence of leukaemia in Austria is 12 per 100,000 persons (2017) [16]. Incidence rates of B-ALL are limited, however, the incidence of ALL in Germany is 1.1 per 100,000 individuals, and around 1,000 new cases are registered per year [17]. It affects slightly more males than females. ALL most commonly occurs in children under five years. With an incidence of 5.3 per 100,000 children, ALL accounts for 30% of childhood cancer types [18]. A second incidence peak occurs in patients over 80 years. The survival rate in children is around 85%, depending on the different risk factors; long-time survival rates in adults up to 55 years are between 60-70% [15, 18].

Kinder unter 5 Jahren am häufigsten von ALL betroffen

Heilungsraten: Kinder 85 % Erwachsene bis 50 Jahre 60-70 %

Symptoms relate to anaemia, thrombocytopenia and neutropenia and can include fatigue, breathlessness, increased risk of bleeding, infections and fever [12]. In cases of central nervous system (CNS) involvement, neurological symptoms include headaches and seizures.

Symptome: Blutung, Abgeschlagenheit, Infektionen

Large B-cell lymphoma

NHL: häufigste hämatologische Krebserkrankung

Non-Hodgkin's lymphoma (NHL) is one of the most common haematological malignancies worldwide and accounts for 3% of cancer diagnoses [19]. While B-cell-derived lymphomas are most common, a minority of NHL derive from T-cells or natural killer (NK) cells [20]. NHLs are further classified. The WHO listed more than 50 subtypes, which differ in their prevalence, geographic location and clinical manifestations [21].

entsteht hauptsächlich durch B-Zellen

DLBCL: aggressives Lymphom, betrifft Lymphknoten

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, accounting for 30% to 40% of adult NHL cases [10]. It is a heterogenous group of tumours characterised by rapidly growing tumour mass which involves the lymph nodes and, in the case of approximately 40% of the patients, also extranodal sites [10]. Depending on the morphological and molecular presentation or organs involved, several subtypes of DLBCL can be distinguished (WHO classification of 2016) [21]. Two major subtypes are classified according to the cell-of-origin [22]:

2 molekulare Subtypen abhängig von der Ursprungszelle

- Germinal centre B-cell-like (GCB)
- Activated B-cell-like (ABC).

prognostische Faktoren unsicher durch heterogene Subtypen

Additionally, a subset of DLBCL with specific genetic mutations (MYC and BCL2/BCL6 translocation) are categorized as double-hit or triple-hit high-grade B-cell lymphoma [23]. Due to the heterogeneity in the disease subgroups, the clinical progression is very heterogeneous between different patients. Clinicians usually allocate disease progression and prognosis of NHL after factors such as age, sex, stage, number of extranodal sites and performance status. However, with DLBCL, different molecular markers of the cell of origin can predict the response to therapy [24]. For example, GCB DLBCL is associated with a better prognosis than ABC DLBCL [25].

Personen über 65 Jahre am häufigsten von DLBCL betroffen

In Austria, incidence rate of NHL is 16 in 100,000 persons (2017), with B-cell lymphoma accounting for 70% of all newly diagnosed NHL. Relative survival rates of NHL in Austria are 79% (one year survival) and 67% (five year survival), respectively [16]. Global data on incidence rates of DLBCL are limited, however, it varies between 5-7 per 100,000 [26, 27]. It is more prevalent in men than women, with incidence rates between 6.7 and 4.6 per 100.000 persons, respectively. DLBCL frequently affects people over 65 years, with a median of 66 years at diagnosis [26]. However, it can also occur in young adults.

Symptome: Abgeschlagenheit, Fieber, Gewichtsverlust

Patients often experience symptoms of enlarged lymph nodes, night sweats, weight loss, fatigue or fever [28]. DLBCL is diagnosed by biopsy of the lymph node upon radiographic imaging. The sites of the disease can be determined by positron emission tomography-computed tomography (PET-CT) scan [24].

PMBCL: seltene Form des B-Zell Lymphoms, wird von DLBCL durch Genexpression unterschieden

Other large B-cell lymphomas include the primary mediastinal large B-cell lymphoma (PMBCL), a rare form of lymphoid tumours that accounts for 2 to 3% of all NHLs [29]. Formerly classified as a subtype of DLBCL, PMBCL has been recognized by the WHO as a separate entity of mature B-cell lymphomas. Though similar in clinical presentation and therapy, it can be distinguished from DLBCL subtypes by molecular gene expression signatures [29].

Frauen zwischen 30 und 40 Jahre am häufigsten betroffen

The actual incidence of PMBCL is controversial, one study using a US-based database estimated the annual incidence rate at 0.4 per one million persons [30]. It occurs more frequently in young women between 30 and 40 years of age [31].

1.1.1 Current clinical practice: Clinical management of the disease

Acute lymphoblastic leukaemia

Induktions-, Konsolidierungs und Erhaltungstherapie

The therapeutic approach for ALL is complex and depends on the immunophenotypic and genetic subtype, as well as the age of the patient. The therapy comprises induction therapy, consolidation therapy and maintenance therapy. The induction phase lasts four to five weeks, intending to achieve complete remission (CR) by using chemotherapeutic agents. With consolidation and maintenance treatment CR is maintained. Maintenance treatment lasts up to two years after initial diagnosis. CR is defined as less than 5% blasts in bone marrow (by cytological report) and no extramedullary disease.

Induktionstherapie durch Chemotherapie

komplette Remission bei <5 % Blasten

Rezidivbehandlung abhängig vom Risikoprofil

Relapse occurs in 10 to 15% of paediatric patients with ALL. Patients with an early relapse have unfavourable outcomes than those with late relapses. Treatment of relapsed ALL is similar to first-line treatment. Chemotherapy as induction therapy – often in a higher dose – is applied to all patients [32]. Patients with an unfavourable risk profile in first- or second-line receive additional allogenic stem cell transplantation (alloHSCT). An unfavourable risk is defined, among other things, as having >5% blasts after 4 to 5 weeks of induction therapy and specific genetic alterations [15, 18, 33].

neue immunotherapeutische Ansätze (CAR-T)

In the past years, immunotherapeutic treatments have emerged. The CD3/19 targeting antibody Blinatumomab has led to better survival and less toxicity in B-ALL (CD19 expressing) patients with bone marrow recurrence. Antibody-drug conjugates (ADCs) are immunological oncological therapies where drugs are linked to an antibody for the specific delivery of the drug to leukemia cells: Inotuzumab ozogamicin, the anti-CD22 antibody linked to calicheamicin led to complete remission rates of 60–80% in patients with relapsed/refractory B-ALL [34]. Additionally, the CAR-T cell therapy Kymriah© was approved by the European Medicines Agency (EMA) in paediatric and young adult r/r B-ALL patients [35].

Table 1-1: Therapy (line) recommendations according to guidelines for ALL

Treatment strategy for ALL	Reference: AWMF [18]
First line therapy	
All patients	Induction therapy (chemotherapy) – consolidation – maintenance therapy
in the case of a significantly increased risk of recurrence	alloHSCT
with CNS involvement	Radiation therapy
Relapse/refractory cancer	
Unfavorable risk profile	Induction therapy + alloHSCT
Favorable risk profile	Induction therapy (chemotherapy) – consolidation – maintenance therapy
Bone marrow recurrence of B-cell ALL (CD19 expressing ALL)	CD3/19 antibody Blinatumomab or CD22 ADC Inotuzumab Ozogamicin
CNS/testicular involvement	Radiation therapy
No response to previous treatment, recurring cancer ≥2 times	CAR-T (Kymriah©)

Abbreviations: ADC: antibody-drug conjugate, alloHSCT: allogenic stem cell transplantation, CAR-T: chimeric antigen receptor T-cells, CNS: central nervous system

Large B-cell lymphoma

Stadieneinteilung durch Lugano Kriterien

Standard of Care: Immunochemotherapie (Rituximab-CHOP); Heilungsrate bei Erslinientherapie: 50-60 %; Rezidivbehandlung abhängig vom Risikoprofil (Alter); schlechte Erfolgsaussichten nach fehlgeschlagener Zweitlinientherapie; CAR-T als neue Option nach >2 Behandlungen

Lymphoma staging is determined by PET/CT scans and classified according to Lugano criteria [36]. Due to heterogeneity in clinical manifestation and progression, individualised therapies must be tailored to different patients. However, the standard of care in treating DLBCL as well as PMCBL is in first-line immunochemotherapy (CHOP), generally in combination with the antibody Rituximab (R-CHOP) [27]. This regimen can cure approximately 50-60% of patients. Some, however, relapse or are refractory to R-CHOP [24]. High-dose therapy in combination with autologous stem cell transplantation (autoHSCT) is generally recommended for younger patients who are compliant to high-dose therapy, while older ones are often treated with another cycle of chemotherapy. The prognosis of these patients or patients not responding to second-line therapy or being unable to undergo autoHSCT is poor. For these patients are often only palliative options available. Other immunological therapies for patients who are not capable for high-dose therapy include combinations of Polatuzumab-Rituximab-Bendamustin (Pola-BR) or Tafasitamab-Lenalidomide [27]. Since 2018 two CAR-T cell therapies (Kymriah© and Yescarta©) have been approved for the treatment of r/r DLBCL and PMBCL after two or more lines of failed therapy.

Table 1-2: Therapy (line) recommendations according to guidelines for DLBCL/PMBCL

Treatment strategy for DLBCL and PMBCL	Reference: Onkopedia [27], planned completion of the AWMF guideline in Nov 23
First line therapy	
All patients	Immunochemotherapy (R-CHOP)
1. Relapse/refractory cancer	
Patients suitable for high doses	High-dose therapy (chemotherapy) with autoHSCT
Patients suitable for high doses	Immunochemotherapy, Polatuzumab-Rituximab-Bendamustin combination, Tafasitamab-Lanalidomide combination
2. Relapse/refractory cancer	
All patients	alloHSCT, CAR-T (Kymriah© and Yescarta©), palliation

Abbreviations: alloHSCT: allogenic stem cell transplantation, R-CHOP: Rituximab-immunochemotherapy

1.2 Features of the intervention: CAR-T cell therapy

CAR-T:
genetisch modifizierte, körpereigene T-Zellen

CAR-T cells are genetically modified T-cells, where a patient's (autologous) T cells are manipulated ex vivo to express the antigen-binding domain from a B-cell receptor, which is fused to the intracellular signalling domain CD3ζ (CD3-zeta) of the T-cell receptor. As a result, recognition of a specific cell surface antigen activates T cell response and, subsequently, the elimination of the target cell, independently of MHC recognition [5]. This effect can be used for CAR-T cells to target and eliminate cancer cells specifically.

Ziel:
gezielte Eliminierung von Krebszellen

2 zugelassene CAR-T in der EU in 2018: Kymriah® und Yescarta®

Two CAR-T cell therapies were approved by the U.S. Food and Drug Administration (FDA) and the EMA in 2017 and 2018, respectively. **Tisagenlecleucel (Kymriah®, Novartis)** and **axicabtagen-ciloleucel (Yescarta®, Kite, Gilead)** are approved to treat patients with acute lymphoblastic leukaemia (ALL, tisagenlecleucel) and diffuse-large B cell lymphoma (DLBCL, tisagenlecleucel and axicabtagen-ciloleucel) [35, 37]. Since then, three further CAR-T cell therapies have been approved by the EMA: Tecartus© (mantel cell lymphoma), Abecma© (multiple myeloma) and Breyanzi© (large B-cell lymphoma) [38].

CAR-T hauptsächlich für Blutkrebs

Forschung für solide Tumore und andere Oberflächenantigene

CAR-T cells have been studied most extensively in haematologic malignancies in clinical trials targeting the cluster of differentiation (CD)19, including Kymriah® and Yescarta® (see Figure 1-1) [5]. Novel CAR targets are required to effectively treat patients with haematological malignancies that do not express CD19. New CAR-T cell targets include, among others, CD20, CD22 and B-cell maturation antigen (BCMA) [39]. So far, only CAR-T cell therapies for blood cancers have been approved, although extensive research has been done in the field of solid tumours. However, different antigens are targeted [39].

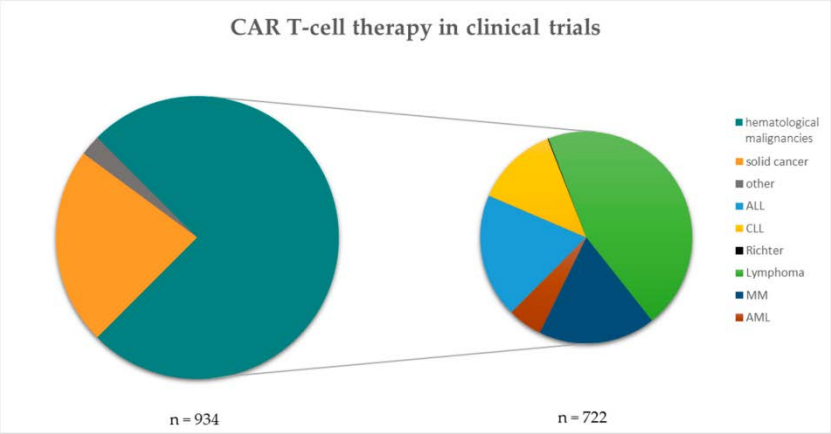


Figure 1-1: CAR-T cell therapies in clinical trials (2021) [8]

verschiedene Modifikationen von CAR-T zur Verbesserung und Erhöhung der Sicherheit

In addition to different targeted antigens, several strategies are under development to improve CAR-T-cell-mediated antitumour responses (e.g. 'armoured' CAR-T cells, dual receptor/cytokine-based CARs, CARs based on natural-killer-cell receptors and other cell receptors, Figure 1-2) and several strategies to improve the safety of CAR-T-cell therapy (e.g. management of cytokine-release syndrome, as well as engineered CAR-T cells that are easier to eradicate in case of adverse events) [39-41].

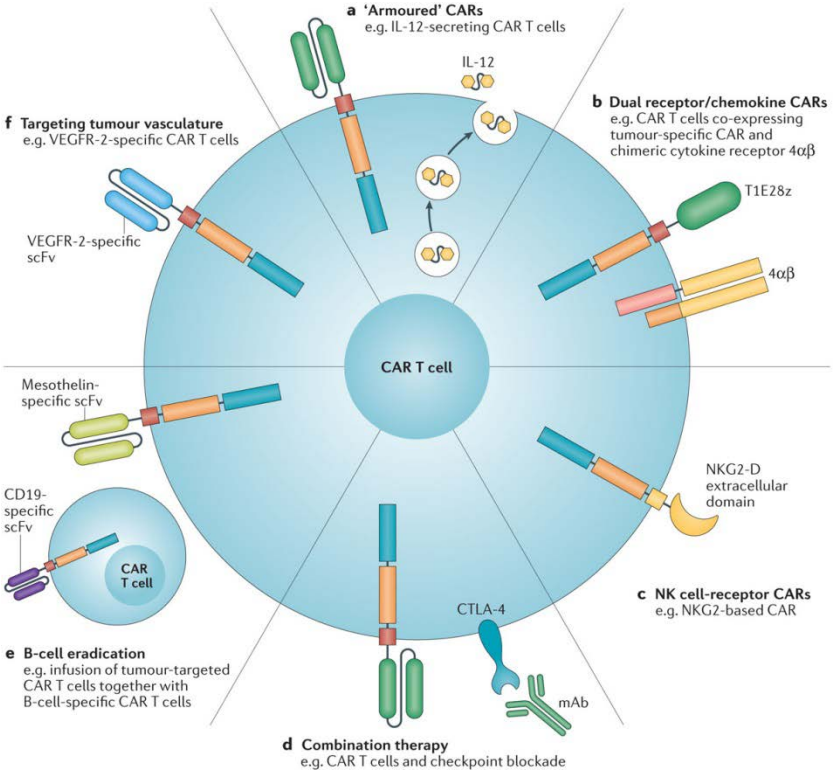


Figure 1-2: Approaches to improve CAR-T cell therapy [5]

Overview of the improvements to CAR-T cell therapy and clinical trials testing those strategies: a | Engineered CAR T-cells that secrete pro-inflammatory cytokines (armoured CAR T-cells). b | Dual receptor expression to target tumour cells and convert tumour derived cytokines into T-cell activators. c | Using natural killer (NK)-cell-based recognition domains, such as NKG2-D, in CARs. d | Combination therapy with monoclonal antibodies (mAb) targeting immune-checkpoint inhibitory receptors to relieve immunosuppression. e | Infusion of two populations of CAR T-cells to eradicate B cells and enable increased persistence of tumour specific CAR T-cells by preventing antibody responses against their foreign antigen components. f | Targeting the tumour vasculature with CAR T-cells, such as VEGFR-2-specific CAR T-cells.

4αβ, 4αβ chimeric cytokine receptor; CTLA-4, cytotoxic T-lymphocyte-associate antigen-4; T1E28z, T1E28z chimeric antigen receptor; VEGFR-2, vascular endothelial growth factor receptor 2.

1.2.1 CAR-T cell production for clinical application (administration and dosing)

Produktionsprozess dauert 12-14 Tage

In general, T-cells from the patient are isolated and genetically modified ex vivo, amplified to clinically relevant numbers and re-infused into the patient after nonmyeloablative pre-conditioning ("lymphodepletion") (Figure 1-3) [42]. The entire manufacturing process includes [43]:

Leukapherese

- **Cell Collection (at the hospital):** Leukapheresis, when a patient's T cells are collected from the blood, occurs over 3 to 6 hours. Within 24 hours, the leukapheresis material is cryopreserved or freshly shipped.

Gentransfer, Vermehrung von CAR-T Zellen

- **Manufacturing (by a pharmaceutical company):** The patient's cryopreserved cells are shipped via specialized courier to the approved manufacturing facility, where the patient's cells are genetically reprogrammed into Kymriah© or Yescarta©.

- **Infusion:** While waiting for CAR-T infusion most patients require bridging therapies to control the disease. Before infusion, the patient will receive lymphodepleting chemotherapy to prepare the body for CAR-T cells. The patient receives their reprogrammed Kymriah© or Yescarta© CAR-T cells during a single infusion. CAR-T cell therapies are administered in an inpatient setting (at the treating hospital).

Überbrückungstherapie, vorbereitende Chemotherapie und Zellinfusion

- **Monitoring:** The patient is monitored two to three times during the first week following infusion. The patient should stay within proximity of the treatment centre for at least four weeks after CAR-T cell infusion to be both monitored and eventually treated for potential side effects.

Beobachtung und Nachsorge

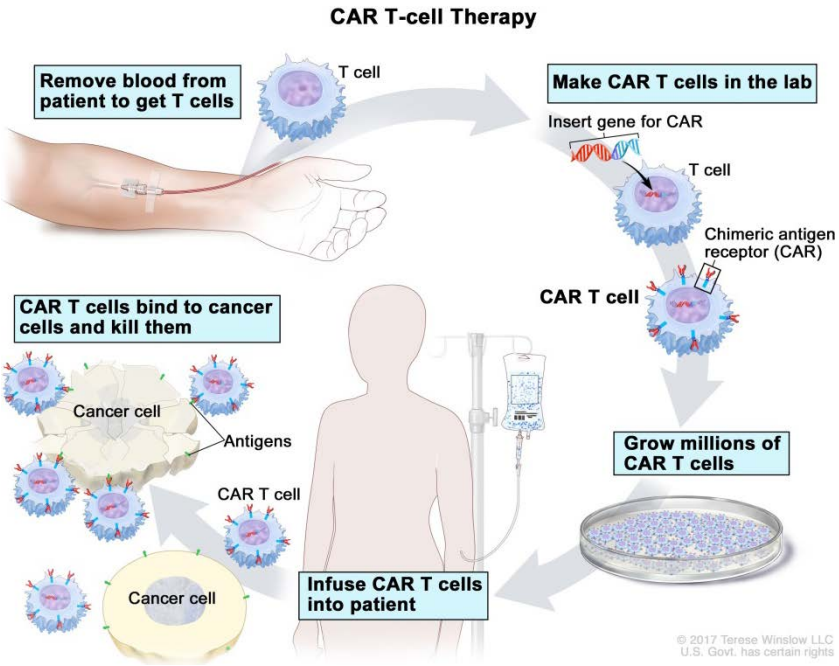


Figure 1-3: Schematic representation of CAR-T cell therapy [6]

Manufacturing of commercially available CAR-T cell therapy occurs at a central facility and must be coordinated closely with the treatment centre to ensure timely management of each patient leading up to infusion. The duration of the centralized manufacturing process is around three to four weeks, the time from cell collection to infusion ("vein-to-vein time") accounts for approximately six to eight weeks [44, 45]. This is a long time period for patients with high-risk profiles and aggressive disease. During the manufacturing process and while waiting for CAR-T infusion, the disease can be controlled by bridging therapy which includes combinations of various cytostatic agents, steroids but also immunological therapies like Pola-BR [46]. Currently, patients' T-cells are manufactured on an individual basis by pharmaceutical facilities. The supply of Kymriah© in Europe is manufactured in three centres (France, Switzerland, Germany), while Yescarta© is manufactured in Amsterdam [1, 47]. The entire process is cost-intensive and time-consuming (e.g. cryopreservation and shipping) [48]. Manufacturing in the US leads to longer turnaround times in Europe due to longer shipment duration [47]. Therefore, research also focuses on in-hospital manufacturing processes by automated

lange Produktionszeiten

Überbrückungstherapie zur Kontrolle der Tumorlast

Produktion an verschiedenen Standorten in Europa

Optimierung der CAR-T Produktion durch Automatisierung und krankenhausbasierte CAR-Ts

and entirely controlled procedures with a high degree of standardization (e.g., CliniMACS Prodigy from Miltenyi Biotech [49]) and on the production in advance of ideally "universal" allogeneic T cells for the "off-the-shelf" administration [50].

Dosis von CAR-T

A single dose of Yescarta© contains $2x10^6$ CAR-positive viable T-cells per kilogram of body weight. For subjects weighing >100kg, a dose of maximum $2x10^8$ cells/kg was fixed [37]. Dosing for Kymriah© depends on the indication. For DLBCL patients, $0.6\text{-}6x10^8$ cells are used, independent of the patient's weight. Paediatric B-ALL patients under 50kg receive $0.2\text{-}5x10^6$ cells/kg, patients over 50kg receive $0.1\text{-}2.5x10^8$ kg/cells [35].

1.2.2 Regulatory requirements

klassifiziert als gentherapeutische medizinische Produkte

CAR-T cell therapies are classified as gene therapy medicinal products (GTMP), a subgroup of advanced therapy medicinal products (ATMPs) in the European Union (EU) defined in the EU Regulation 1394/2007. Therefore, the production and marketing authorisation comes along with comprehensive regulatory requirements provided by the EMA [48, 51]. Yescarta© and Kymriah© are both orphan drugs classified as medicines under additional monitoring by the EMA and, therefore, intensively monitored as they are biological medicines [52].

besondere Beobachtung durch EMA

verpflichtende Dokumentation in (nationalen) Registern

The EMA also required documentation of the long-term safety and efficacy of Kymriah and Yescarta in a patient registry as a condition for marketing authorisation [53]. There are national registries and one European-wide registry from the European Society for Blood and Marrow Transplantation (EBMT) (Table 1-3). Over 2,750 patients have been treated and registered in the EBMT Registry until the end of 2021, with a rising tendency [7].

Table 1-3: Examples of (national) CAR-T registries in Europe

Country	Registry
Europe	European Society for Blood and Marrow Transplantation Registry (EBMTR)
Austria	Austrian Stem Cell Transplantation Registry (ASCTR)
Germany	Deutsches Register für Stammzelltransplantation (DRST) Pädiatrischen Register für Stammzelltransplantation (PRST)
France	DESCAR-T Registry

Horizon Scanning neuer CAR-T Therapien

The intensive research in the field of ATMPs/CAR-T cell therapy brings up new technologies facing regulatory, ethical and financial challenges. National Horizon Scanning reports identified emerging CAR-T cell therapies [38, 54].

unterschiedliche Finanzierung von CAR-T Studien

Most studies regarding CAR-T cells are conducted in China and the US, with Europe clearly behind. Funding of these studies varies, in Europe, 60% of studies are sponsored by industry, and in Germany it is as high as 90%. In contrast, in the USA and China, more than 50% of the studies are initiated and funded by the academic sector (see Figure 1-4) [1].

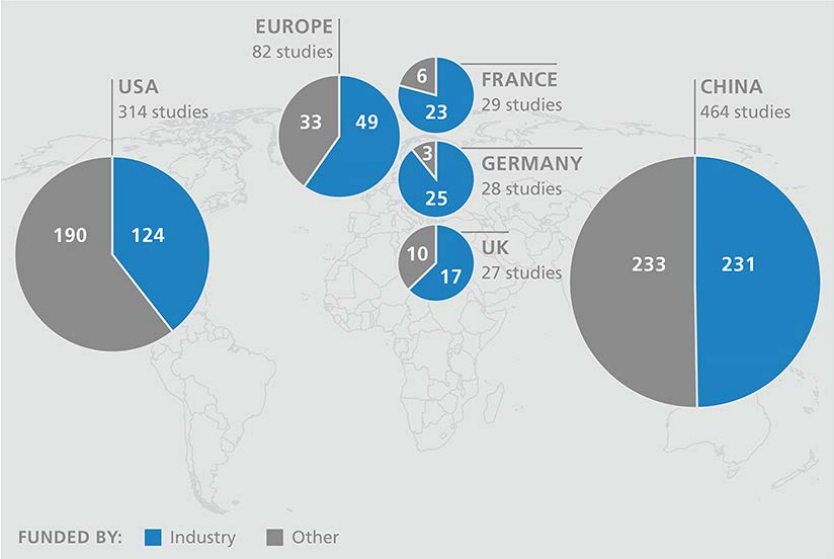


Figure 1-4: Top 5 countries conducting CAR-T cell studies according to source of funding [1]

1.3 Pivotal trials for CAR-T cell therapies

1.3.1 Acute lymphoblastic leukaemia: Tisagenlecleucel/Kymriah®

Zulassungsstudie ELIANA

2 Publikationen (Maude et al., Laetsch et al.)

ELIANA is the pivotal trial for the use of tisagenlecleucel as a treatment for relapsed or refractory (r/r) B-ALL in children, adolescents, and young adults (CAYA). The study was funded by Novartis Pharmaceutics (ClinicalTrials.gov number, NCT02435849). The results on effectiveness and safety were published in February 2018 by Maude et al. in the New England Journal of Medicine [55]. Additionally, Health-related Quality of Life assessment for this cohort was published in a second publication by Laetsch et al. in October 2019 in Lancet Oncology [56].

Study characteristics

ELIANA: globale, Phase 2 Studie

ELIANA is a phase 2, single-cohort, 25 centre, global study of tisagenlecleucel in CAYA with r/r CD19-positive B-cell ALL with the primary endpoint of the overall remission rate (ORR) within three months.

Patient characteristics, follow-up and outcomes

92 Pts. rekrutiert, 75 Pts. infundiert

medianes Alter: 11 Jahre

ELIANA enrolled 92 patients, of which 75 were infused with tisagenlecleucel. The reason for patients not being infused were death (seven patients; four from disease progression and one each from sepsis, respiratory failure, and fungaemia), product-related issues (seven patients) and adverse events (three patients; one each from graft-versus-host disease, systemic mycosis, and fungal pneumonia). The median age of infused patients was eleven years at enrolment (range three to 23 years), with 43% of patients being female.

8 % primär refraktäre B-ALL

61 % vorherige alloHSCT

At study entry, six patients (8%) had a primary refractory B-ALL, while 69 patients (92%) suffered from a chemotherapy refractory or relapsed disease. Patients had a median of three previous therapies (range one to eight) and 46 patients (61%) had undergone a prior alloHSCT.

hohe Tumorlast (>50 % Knochenmarkblasten): 68 %

37 % der Pts. mit genetischen Mutationen

At enrolment, patients had a median bone marrow blast percentage of 74% (range 5% to 99%), with 51 patients (68%) having a high tumour burden defined as >50% marrow blasts and 24 patients (32%) a low tumour burden with 5% to 50% of marrow blasts. 28 patients (37%) had any high-risk mutation (BCR-ABL1, MLL rearrangement, hypoploidy, lesions associated with BCR-ABL1–like gene signature, or complex karyotype) and six patients (8%) had Down syndrome.

87 % der Pts. mit Überbrückungstherapie

65 patients (87%) received bridging chemotherapy between enrolment and infusion and 72 patients (96%) received lymphodepleting chemotherapy before tisagenlecleucel infusion.

Nachbeobachtung: 13,1 Monate

The median time from tisagenlecleucel infusion to data cut-off was 13.1 months with a minimum follow-up of three months.

primärer Endpunkt: ORR über 20 %

The primary endpoint was an overall remission rate (ORR) higher than 20%. The **ORR** was defined as the rate of a best overall response of either complete remission (CR) or complete remission with incomplete haematologic recovery (CRi) within three months based on analysis of blood, bone marrow, cerebrospinal fluid, and physical examination. Responses had to be maintained for at least 28 days.

sekundäre Endpunkte: CR, CRi, DOR, EFS, OS

Secondary endpoints included CR or CRi with undetectable minimal residual disease (<0.01% bone marrow blasts) assessed by flow cytometry, duration of remission (DOR), event-free survival (EFS), overall survival (OS), cellular kinetics and safety. For **CR**, all of the following criteria had to be met: <5% lymphoblasts in bone marrow by morphology, <1% circulating blasts in peripheral blood, no evidence of extramedullary disease, neutrophils $>1.0\times10^9$/L, platelets $>100\times10^9$/L, and no platelet and/or neutrophil transfusions within seven days of peripheral blood sample for disease assessment. **CRi** was defined by all criteria for CR including ≥1 of the following: neutrophils $\leq1.0\times10^9$/L, platelets $\leq100\times10^9$/L, or platelet/neutrophil transfusions within seven days of peripheral blood sample for disease assessment. **DOR** was defined as the time to relapse after the onset of remission. Relapse-free survival rate (RFS) was reported in patients with a response to treatment after six and 12 months. **EFS** was defined as the time from infusion to no response, relapse before response was maintained for at least 28 days or relapse after having complete remission with censoring for HSCT, other new cancer therapy or lack of adequate assessment. **OS** was defined as the time from infusion to death from any cause.

Time to B-cell recovery was defined as the time from onset of remission to reaching ≥1% CD19+ cells in viable white blood cells or ≥3% CD19+ cells in lymphocytes in the blood.

quantitative PCR Messung für Zellkinetiken

Cellular kinetics of tisagenlecleucel after infusion were determined from peripheral blood by quantitative polymerase chain reaction methods. “Genoptix” was used to detect the CD19 CAR transgene sequence [57].

CTCAE Version 4.03 für unerwünschte Ereignisse

Adverse events were assessed per the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. CRS was graded according to the Pennsylvania Children’s Hospital of Philadelphia (Penn/CHOP) scale [58, 59], and graft-versus-host disease (GVHD) was graded after protocol-defined criteria [60].

Patient-reported health-related quality of life (HRQoL) was assessed in 58 of the 75 infused patients with the Pediatric Quality of Life Inventory (PedsQL) and European Quality of Life-5 Dimensions questionnaire (EQ-5D).

Lebensqualität mit PedsQL und EQ-5D gemessen

The questionnaires were completed at baseline, day 28 and months three, six, nine and 12 after treatment. The median follow-up of this group was 9.9 months (IQR 5.3-13.5) [56].

mediane Nachverfolgung zur Lebensqualität: 9,9 Monate

Trial characteristics and results are displayed inTable 1-4.

Table 1-4: Patient characteristics, efficacy and safety in pivotal study ELIANA

Author, year	Maude, 2018 (ELIANA) [55]	Laetsch, 2019 (ELIANA) [56]
Country	USA	
Sponsor	Novartis	
Intervention/Product	Tisagenlecleucel	Quality of life after therapy with tisagenlecleucel
Study design	Phase 2, single cohort, multicentre prospective study	
Number of patients	92 enrolled, 75 infused	75 infused, 58 included in HRQoL analysis
Inclusion criteria (selection of relevant criteria)	■ 3-21 years ■ 04/2015-04/2017 ■ r/r B-ALL: ■ > 2nd BM relapse ■ Any BM relapse after allogeneic stem cell transplant (alloHSCT) ■ Primary refractory (not achieving CR after 2 cycles of a standard chemotherapy regimen) ■ Chemorefractory (not achieving CR after one cycle of standard chemotherapy for relapsed leukaemia) ■ Philadelphia chromosome-positive ALL intolerant of or with two failed lines of tyrosine kinase inhibitor (TKI) therapy or if TKI therapy is contraindicated ■ Ineligible for alloHSCT ■ BM with ≥5% lymphoblasts by morphologic assessment at screening ■ For relapsed patients, documentation of CD19 tumour expression in BM or peripheral blood by flow cytometry ■ Selected age defined laboratory values ■ Defined pulmonary, cardiac, and psychological criteria	■ Inclusion in ELIANA Trial ■ Infusion with tisagenlecleucel ■ > 8 years of age
Exclusion Criteria (selection of relevant criteria)	■ Isolated extramedullary disease relapse ■ Concomitant genetic syndromes associated with BM failure; patients with Down syndrome were not excluded ■ Burkitt lymphoma/leukaemia ■ Prior malignancy ■ Treatment with any prior gene therapy product ■ Treatment with any prior anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy ■ Active or latent hepatitis B, active hepatitis C, positive HIV test or any uncontrolled infection at screening ■ Grade 2 to 4 or extensive chronic GVHD ■ Active CNS involvement by malignancy ■ Exactly defined wash-out times for diverse medications before leukapheresis and/or infusion such as steroids, GVHD therapy, TKIs, salvage chemotherapy, radiation therapy and others.	Patients younger than 8 years
Age (years)	median 11 (range 3-23)	8-23
Sex (F)	43%	43%
Pre-Treatment	■ Prior alloHSCT: 46/75 (61%) ■ Previous line of therapies: median 3 (range 1-8) ■ Prior bridging therapy: 65/75 (87%) ■ Pre-treatment with lymphodepleting chemotherapy: 72/75 (96%)	prior alloHSCT: 35/58 (60%)

Author, year	Maude, 2018 (ELIANA) [55]				Laetsch, 2019 (ELIANA) [56]
Other patient characteristics and definitions	■ CNS1: 63/75 (84%) ■ CNS2: 10/75 (13%) ■ CNS3: 1/75 (15%) ■ High-risk genomic lesions: 28/75 (37%) ■ Down Syndrome: 6/75 (8%) ■ Low disease burden (< 50% blasts in BM): 24/75 (32%) ■ High disease burden (≥ 50% blasts in BM): 51/75 (68%)				■ Responder to treatment: 48/58 (83%) ■ Non-responder: 10/58 (17%)
Line of Treatment	■ Primary refractory: 6/75 (8%) ■ Chemo-refractory or relapsed: 69/75 (92%)				■ Primary refractory: 5/58 (9%) ■ Chemo-refractory or relapsed: 53/58 (91%)
Median follow-up (months)	13.1, minimum 3				9.9 (IQR 5.3-15.3)
Loss to follow-up, n (%)	n=27 ■ Death: n=11 ■ Lack of efficacy: n= 9 nonresponse or relapse ■ New therapy while in complete remission: n=5 ■ Patient or guardian decision: n=2				NR
Efficacy					
Overall survival	■ 6mo: 90% (95% CI, 81-95) ■ 12mo: 76% (95% CI, 63-86)				n.a.
Disease-specific survival	■ RFS: 6mo 80% (95% CI, 65-89), 12mo 59% (95% CI, 41-73) ■ EFS: 6mo 73% (95% CI, 60-82), 12mo 50% (95% CI, 35-64)				n.a.
Response Rates n (%)	■ ORR within 3mo: 81% (95% CI, 71-89) (60% CR, 21% CRi) ■ CR(d28): 31% ■ CRi(d28):49% ■ ITT (n= 92): ORR: 66% (95% CI, 56-76) ■ Probability of B-cell aplasia at 6mo: 83% (95% CI, 69-91)				n.a.
Recurrence, n (%)	Recurrence after remission: 22/61 (36%)				n.a.
Quality of life	s. Laetsch 2019				mean change from baseline to month 3: PedsQL: 13.3 (95% CI, 8.9-17.6) EQ-5D VAS: 16.8 (95% CI, 9.4-24.3) MCID at 3 months: PedsQL: 30/37 (81%) EQ-5D-VAS: 24/36 (67%)
Safety					
Overall complications, n (%)	75/75 (100%)				n.a.
SAE, n (%)		**Any**	**Grade3**	**Grade4**	n.a.
	AE of special interest	67/75 (89%)	26/75 (35%)	30/75 (40%)	
	CRS	58/75 (77%)	16/75 (21%)	19/75 (25%)	
	Neurologic event	30/75 (40%)	10/75 (13%)	0	
	Infection	32/75 (43%)	16/75 (21%)	2/75 (3%)	
	Febrile neutropenia	26/75 (35%)	24/75 (32%)	2/75 (3%)	
	Cytopenia > d28	28/75 (37%),	12/75 (16%)	12/75 (16%)	
	TLS	3/75 (4%)	3/75 (4%)	0	
AE, n (%)	71-75 (95-100%) ■ Pyrexia: 30/75 (40%) ■ Decreases appetite: 29/75 (39%) ■ Hypotension: 22/75 (29%) ■ Aspartate aminotransferase increased: 20/75 (27%) ■ Hypokalaemia: 20/75 (27%) ■ Hypoxia: 18/75 (24%) ■ Hypophosphatemia: 18/75 (24%) ■ Blood bilirubin increased: 13/75 (17%)				n.a.
Mortality/Procedure-related mortality, n (%)	25%/ 3/75 (4%)				n.a.

Abbreviations: (S)AE: (severe) adverse event, alloHSCT: allogenic haematopoetic stem cell transplantation, BM: bone marrow, BOR: best overall respone, CNS: central nervous system, CR: complete remission, CRi: complete remission with incomplete haematologic recovery, CRS: cytokine release syndrome, d28: day 28, EFS: event-free survival, EQ-5D: European Quality of Life-5 Dimensions questionnaire, GVHD: graft-versus-host-disease, ITT: intention to treat, n.a.: not applicable, ORR: overall response rate, RFS: relapse-free survival, PedsQL: Pediatric Quality of Life Inventory, r/r B-ALL: refractory/relapsed B-cell acute lymphoblastic leukaemia, TKI: tyrosine kinase inhibitor, TLS: tumour lysis syndrome

Results: Efficacy

Gesamtansprechrate nach min. 3 Monaten FU: 81 %

The **overall remission rate (ORR)** of the 75 infused patients with at least three months of follow-up was 81% (95% CI, 71-89). 45 patients (60%) had complete remission and 16 (21%) had complete remission with incomplete haematologic recovery.

Dauer des Ansprechens: nicht erreicht, rückfallfreies Überleben nach 12 Monaten: 59 %

The median **duration of response (DOR)** among the 61 patients with complete remission with or without complete haematologic recovery was not reached. At six months, the relapse-free survival rate (RFS) among those patients was 80% (95% CI, 65-89) and 59% (95% CI, 41-73) at 12 months.

ereignisfreies Überleben nach 12 Monaten: 50 %

The rate of **event-free survival (EFS)** among the 75 patients who received the infusion was 73% (95% CI, 60 to 82) at six months and 50% (95% CI, 35-64) at 12 months. Median event-free survival was not reached.

Gesamtüberleben nach 12 Monaten: 76 %

The **overall survival rate (OS)** was 90% (95% CI, 81-95) at six months and 76% (95% CI, 63-86) at 12 months after infusion.

B-Zell Aplasie nach 6 Monaten: 83 %

The probability of **maintenance of B-cell aplasia** at six months after infusion was 83% (95% CI, 69-91).

Lebensqualität mit PedsQL und EQ-5D gemessen

Health-Related Quality of Life (HRQoL) was assessed with the Pediatric Quality of Life Inventory (PedsQL) and European Quality of Life-5 Dimensions questionnaire (EQ-5D) in patients that were eight years or older (58 eligible patients). Of those, 83% had a quality-of-life assessment at baseline and at least one post-baseline visit. The questionnaires were completed at baseline, day 28 and months three, six, nine and 12 after treatment. The median follow-up of this group was 9.9 months (IQR 5.3-13.5). The number of patients participating in the assessment decreased with every visit. Mean baseline values for all patients were less than the normative means for all scores.

mediane Nachverfolgung zur Lebensqualität: 9,9 Monate

verbesserte Lebensqualität nach 3-12 Monaten bei PedsQL und EQ-5D

For the PedsQL the mean change from baseline to month three was 13.3 (95% CI, 8.9-17.6) and an improvement in HRQoL until month 12 was measured by all scores. For the EQ-5D VAS, mean change from baseline was 16.8 (95% CI, 9.4-24.3) at month three and improved continuously to 24.7 (95% CI, 13.5-35.9) at month 12. 30 of 37 patients (81%) achieved the minimal clinically important difference (from literature point estimates) at month three for the PedsQL total score and 24 of 36 (67%) patients for the EQ-5D visual analogue scale.

Results: Safety

unerwünschte Ereignisse bei 100 % der Patient*innen, ≥3 Grad bei 88 %

Adverse events (AE) of any grade were reported in all 75 patients (100%). In 71 patients (95%), the side effects were suspected to be related to tisagenlecleucel. 66 patients (88%) had a grade 3 or 4 adverse event, in 55 patients those were suspected to be related to tisagenlecleucel. In 52 of the latter, grade 3 and 4 serious AEs (SAE) occurred within eight weeks post infusion.

CRS: 77 % neurologische Ereignisse: 40 %

Cytokine release syndrome (CRS) occurred in 58 of 75 patients (77%), grade ≥3 in 35 patients (47%). Also, 35 patients were admitted to ICU for management of CRS. **Neurologic events** occurred in 30 of 75 patients (40%) within eight weeks post infusion. Ten patients (13%) had grade 3 neurologic events and no grade 4 events or cerebral oedema occurred.

andere unerwünschte Ereignisse: Infektionen, Neutropenie, Zytopenie

Other reported grade 3 or 4 AEs of special interest within eight weeks after infusion were **infections** in 18 patients (24%), **febrile neutropenia** in 26 patients (35%), **cytopenia** not resolved by day 28 in 24 patients (32%) and **tumour lysis syndrome** in three patients (4%).

Other Grade 3 or 4 AEs suspected to be related to tisagenlecleucel and occurred in at least 5% of patients were **hypotension** (17%), decrease in **lymphocyte** count (13%), **hypoxia** (11%), **hyperbilirubinemia** (11%), increased **aspartate aminotransferase** (10%), **pyrexia** (10%), decreased **neutrophil count** (11%), decreased **white-cell count** (9%), decreased **platelet count** (9%), decreased **appetite** (9%), **acute kidney injury** (8%), **hypophosphatemia** (8%), **hypokalaemia** (8%), **pulmonary oedema** (6%), **thrombocytopenia** (7%), **encephalopathy** (5%), increase in **alanine aminotransferase** (5%) and **fluid overload** (5%).

Mortalität: 25 % behandlungsassoziierte Mortalität: 4 %

Nineteen of the 75 infused patient died (25%). 3% died within 30 days after infusion and 22% later. Deaths occurring from severe adverse events that could be related to tisagenlecleucel infusion were identified in three patients (4%).

1.3.2 Large B-cell lymphoma: Tisagenlecleucel/Kymriah® and Axicabtagen Ciloleucel/Yescarta®

Zulassungsstudien ZUMA-1 (axi-cel) und JULIET (tisa-cel)

ZUMA-1 and JULIET are the pivotal trials for axi-cel and tisa-cel, respectively. Study characteristics and results of pivotal trials are based on a recent Cochrane report 2021 [61] (see Table 1-5 and Table A-3).

Study characteristics

Ergebnisse basierend auf Cochrane Bericht 2021

Both pivotal trials are ongoing observational, single-arm, multicenter studies. ZUMA-1 is a phase 1/2 clinical trial, and JULIET is a phase 2 trial.

Patient characteristics, follow-up and outcomes

108 Pts. zu ZUMA-1 111 Pts. zu JULIET

gemischte Population mit DLBCL als Hauptdiagnose

hauptsächlich Krankheitsstadium 3-4

The number of patients infused with axi-cel (ZUMA-1) and tisa-cel (JULIET) was 108 and 111, respectively. While JULIET only enrolled patients with DLBCL or with DLBCL transformed from follicular lymphoma, patients in ZUMA-1 were diagnosed with DLBCL (76%) or PMBCL (24%). The median age in ZUMA-1 was 58 years and 56 years in JULIET. In ZUMA-1, 32% of the patients were female, in JULIET, the female population accounted for 35%. Between 15% (ZUMA-1) and 24% (JULIET) of the patients were in disease stage 1-2, whereas patients with disease stage 3-4 was 85% (ZUMA-1) to 76% (JULIET).

In both trials, patients had a median of three prior therapies. 69% and 52% underwent three or more prior therapies in ZUMA-1 and JULIET. 21% and 59% of patients underwent prior autoHSCT in ZUMA-1 and JULIET, respectively. AlloHSCT was an exclusion criterion in ZUMA-1 and JULIET.

keine alloHSCT erlaubt

While in ZUMA-1, no bridging therapy was allowed; 92% of the patients in JULIET received such. 58% of the patients in ZUMA-1 and 45% in JULIET had an ECOG score of 1.

keine Überbrückungstherapie erlaubt in ZUMA-1

The median follow-up period was up to 27.1 months for ZUMA-1 and 19.3 months for JULIET.

Nachbeobachtung: 19,3 bis 27,1 Monate

Primary endpoints in ZUMA-1 were the ORR for up to 12 months and the incidence and severity of CRS and ICANS for up to 12 months. Secondary endpoints included, among others, ORR, PFS, OS and the percentage of patients experiencing AE for up to 12 months. Changes in HRQoL by the European Quality of Life Five Dimension Five Level Scale (EQ-5D) for up to 5 years.

primäre Endpunkte ZUMA-1: ORR und CRS/ICANS

Primary endpoints in JULIET were (best)ORR, CR rate and PR rate. Secondary outcomes included OS, PFS, duration of response, time to response and incidence and severity of AE. OS was defined as the time from infusion to date of death in ZUMA-1 and not defined in JULIET. PFS was defined as the time from infusion date to disease progression via the International Working Group (IWG) Response Criteria for Malignant Lymphoma or death from any cause (ZUMA-1). JULIET did not report a definition. ORR was defined as the incidence of a CR or PR via IWG Response Criteria for Malignant Lymphoma as determined by study investigators (ZUMA-1). In JULIET, ORR was planned in a time frame of five years and determined by an independent review committee using the Lugano classification.

primäre Endpunkte JULIET: ORR, CR, PR Raten

In ZUMA-1, CTCAE version 4.03 was used for grading all adverse events; additionally, Lee criteria were used for CRS. JULIET used CTCAE version 4.03 and the Medical Dictionary for Regulatory Activities version 20.1 to grade adverse events. Additionally, the University of Pennsylvania grading scale was used for grading CRS.

CTCAE Version 4.03 für unerwünschte Ereignisse

Trial characteristics and results are displayed in Table 1-5 and the Appendix (Table A-3).

A recent Cochrane report 2021 assessed a high risk in complete outcome assessment for OS and response rates as analyses were based on infused patients only [61]. The outcome assessment for HRQoL in JULIET is attributed to a high risk of bias due to the limited availability of patients (only CR and PR) during the follow-up. Lack of blinding of outcome assessors was also a reason for the rating as high risk.

Verzerrungsrisiko nach Cochrane: teilweise hoch, wegen Patient*innenselektion in den Ergebnisanalysen, unverblindet

The detailed RoB assessment is displayed in the Appendix (Table A-5 and Table A-6).

Table 1-5: Patient characteristics, efficacy and safety in pivotal studies ZUMA-1 and JULIET

Study ID		ZUMA-1 [62, 63]	JULIET [64, 65]
Source		Cochrane 2021 [61]	
Sponsor		Kite, Gilead	Novartis
Study characteristics			
CAR-T product		Axi-cel (Yescarta®)	Tisa-cel (Kymriah®)
n		119 enrolled, 108 infused[3] ■ DLBCL, n=77 (76%) ■ PMBCL, n=24 (24%)[5]	165 enrolled, 111 infused, 93 evaluated ■ n=88 DLBCL NOS ■ n=21 DLBCL TF from follicular lymphoma
Age (years)†		58 (51;64)[4]	56 (22-76)
Sex (F)		32%	35%
Prior autoHSCT Prior alloHSCT		21% not allowed	59% not allowed
Prior therapy† ≥3/4 prior therapies		3 ≥3: 69%[5]	3 ≥3: 52%
ECOG ≥2		Not allowed ECOG 1: 58%[5]	Not allowed ECOG 1: 45%
Disease stage		1-2: 15%[5] 3-4: 85%[5]	1-2: 24% 3-4: 76%
Bridging therapy		Not allowed	92%
Median FU, months		Up to 27.1[6]	19.3
Efficacy			
CR		58% (NR) (median FU 15.4)[3]	40% (NR) (median FU 19.3) at 3 mo: 32% at 6 mo: 29%
OS	6 mo (95%CI)	78% (69%-85%)[3]	NR
	12 mo (95%CI)	59% (49%-68%)[3]	48% (38%-57%)
	18 mo (95%CI)	52% (41%-62%)[3]	43% (33%-35%)
	24 mo (95%CI)	Estimated: 50.5% (40.2%-59.7%)[4]	NR
	Median OS, mo (95%CI)	NR* (12.8-NR*)[4]	12 (7-NR*) ITT[7]: 8.3 (5.8-11.7)
PFS	6 mo (95%CI)	49% (39%-58%)[4]	NR
	12 mo (95%CI)	44% (34%-53%)[4]	Estimated: 83% (patients with CR or PR at 3 mo)
	24 mo (95%CI)	NR	NR
	Median PFS, mo (95%CI)	5.9 (3.3-15.0)[4]	NR* for patients with CR
HRQoL		NR	**FACT-G TS** (MCID upper-lower limit: 3-7), 18 mo: +10.0 (11.1) **FACT-Lym S** (MCID upper-lower limit: 2.9-5.4), 18 mo: +3.1 (6.6) **FACT-Lym TOI** (MCID upper-lower limit: 5.5-11), 18 mo: +9.2 (13.6) **FACT-Lym TS** (MCID upper-lower limit: 6.5-11.2), 18 mo: +13.1 (16.1) [8] **SF-36 Physical health TS** (MCID 3), 18 mo: +3.9 (10.6) **SF-36 Mental health TS** (MCID 3), 18 mo: +2.1 (9.9)

[3] Phase 1&2 (n=108 infused)

[4] Data from phase 2 (n=101)

[5] Data from all enrolled patients from phase 2 (n=111)

[6] Longer-term safety and activity assessment (Aug 2018)

[7] ITT: intention-to-treat analysis included all 165 enrolled patients

[8] According to the authors, the improvement was above the MCID upper limit

Study ID		ZUMA-1 [62, 63]	JULIET [64, 65]
Safety			
CRS		93%	58%
CRS ≥ grade 3		11%	22%
Neurotoxicity		67%	21%
Neurotoxicity ≥ grade 3		32%	12%
Mortality/NRM		At data cutoff (median FU 27.1): 50% NRM: 3.7% (2 axi-cel related)	61%
(S)AE	any AE (grade ≥3)	100% (98%)	100% (89%)
	any SAE (grade ≥3)	56% (48%)	65% (NR)
	Anaemia (grade ≥3)	68% (45%)	48% (39%)
	Leukopenia (grade ≥3)	19% (17%)	NR (NR)
	Neutropenia (grade ≥3)	44% (39%)	20% (20%)
	Thrombocytopenia (grade ≥3)	35% (24%)	13% (12%)
	Prolonged cytopenias lasting ≥ 30 days (grade ≥3)	45% (30%)	44% (34%)
	Febrile neutropenia (grade ≥3)	36% (32%)	15% (14%)
	Infections (grade ≥3)	NR (28%)	34% (20%)

Abbreviations: CAR-T: chimeric antigen receptor T cell therapy, CR: complete remission, CRS: cytokine release syndrome, EFS: event-free survival, mo: months, FACT-Lym S: Functional Assessment of Cancer Therapy-Lymphoma subscale, FACT-G: FACT- General, NR: not reported, NR: not reached, NRM: non-relapse mortality, OS: overall survival, PD: progressive disease, PFS: progression-free survival, pts: patients, (S)AE: (serious) adverse event,SF-36: Short Form-36 Health Survey, TOI: Trial Outcome Index, TS: total score*

Ranges are indicated with – and the IQR with ; between the numbers.
The standard deviation is indicated with ± † Values for age and prior therapy are reported in median

Results: Efficacy

This section describes the evidence for efficacy and safety of the pivotal trials ZUMA-1 and JULIET based on a recent Cochrane report 2021 [61].

medianes Überleben ZUMA-1: nicht erreicht, JULIET: 12 Monate

Median **overall survival (OS)** in ZUMA-1 at 24 months FU was not reached (95%CI 12.8-NR), while the six, 12 and 18-month OS rates were 78% (95% CI 69-85), 59% (95%CI 49-68) and 52% (95% CI 41-62), respectively. The estimated OS rate at 24 months was 50.5% in ZUMA-1 and not reported in JULIET. Median OS in JULIET was 12 months (7-not reached), while the estimated OS at 12 months was 49% (95%CI 39-59).

medianes progressionsfreies Überleben ZUMA-1: 5,9 Monate JULIET: nicht erreicht

Median **progression-free survival (PFS)** in ZUMA-1 was 5.9 months (95%CI 3.3-15), with a 12-month PFS rate of 44% (95%CI 34-53). Median PFS in JULIET was not reached, while the estimated PFS at 12 months was only reported among patients with CR or PR at three months with 83%.

Gesamtansprechrate nach 12 Monaten ZUMA-1: 82 %, JULIET: nicht erreicht

The **overall response rate (ORR)** was reported in ZUMA-1 and JULIET. Best ORR after 12 months in ZUMA-1 was 82%, with a CR rate of 58%. ORR after 12 months in JULIET was not reported. However, at a median FU of 19.3 months, the best ORR was 54% (95%CI 43-64) and CR 40% (95%CI NR). PR after 19.3 months FU was 13% (95%CI NR).

Lebensqualität in JULIET mit FACT-Lym und SF-36 Scores gemessen

For the **Health-Related Quality of Life (HRQoL)**, FACT-Lym (0-168) and SF-36 (range 0-100) scores[9] were surveyed at baseline, at three, six, 12 and 18 months in JULIET. Changes were compared to baseline and reported for participants with CR or PR. Fifty-seven patients with CR or PR completed

[9] Higher scores indicate improvement

the questionnaires at baseline, 39 at three months, 34 at six months, 30 at 12 months and 21 at 18 months.

Lebensqualität nach 18 Monaten bei Patient*innen in Remission (CR+PR) verbessert bei FACT-Lym

keine signifikante Verbesserung von mentaler Gesundheit nach 18 Monaten bei SF-36

Baseline FACT-G TS and FACT-Lym TS scores for patients with CR/PR were 79.2 (SD 15.2) and 124.1 (SD 22.8), respectively. At 18 months, the mean FACT-G TS and FACT-Lym TS score increased by +10.0 (SD 11.1) and +13.1 (SD 16.1), respectively. Both scores exceeded the upper MCID limit, which was defined by the authors. All evaluable FACT-Lym scores improved at 18 months after baseline and surpassed the defined lower MCID limit. Compared to baseline, the greatest mean change for functional, physical and social/family FACT-G domains occurred at 18 months, and the largest mean change in the emotional domain at 12 months. Baseline SF-36 scores in patients with CR and PR for physical and mental health were 45.6 (SD 9.9) and 51.9 (SD 10.0) (total scores). SF-36 total scores for physical health surpassed the predefined MCID after 18 months; the total score for mental health did not surpass the MCID limit.

Results: Safety

unerwünschte Ereignisse bei 100 % der Patient*innen, ≥3 Grad bei 98 % und 89 %

Adverse and serious adverse events were reported in ZUMA-1 and JULIET. In both trials, 100% of the patients experienced any adverse events (AE); 98% (ZUMA-1) and 89% (JULIET) experienced any adverse event grade ≥3. 56% and 65% experienced any serious adverse events (SAE).

CRS ZUMA-1: 93 %, JULIET: 58 % ICANS ZUMA-1: 67 %, JULIET: 21 %

For ZUMA-1 and JULIET, **cytokine release syndrome (CRS)** was reported in 93% and 58%, grade ≥3 in 11% and 22% of all patients, respectively. **Neurotoxicity** was reported in 67% and 21%, grade ≥3 in 32% and 12% of all patients, respectively.

Grade ≥3 **anaemia** occurred in 45% and 39% of patients from ZUMA-1 and JULIET, while grade ≥3 **neutropenia** occurred in 39% and 20% of the patients. 24% and 12% experienced grade ≥3 **thrombocytopenia**. **Leukopenia** grade ≥3 appeared in 17% of ZUMA-1 patients and was not reported in JULIET. **Prolonged** cytopenias grade ≥3 lasting longer than one month were reported in 30% (ZUMA-1) and 34% (JULIET) of the patients. **Febrile neutropenia** grade three and higher were reported in 32% and 14% of all patients in ZUMA-1 and JULIET, respectively. Grade ≥3 **infections** were reported in 28% (ZUMA-1) and 20% (JULIET) of the patients.

Mortalität: 50 % (ZUMA-1) und 61 % (JULIET)

Mortality was 50% at the data cutoff (27.1 months) in ZUMA-1 and 61% in JULIET.

1.4 CAR-T cell therapy in Austria

1.4.1 Requirements for quality assurance

Indikations- und Strukturkriterien für CAR-T Zelltherapieanwendung in Ö durch OeGHO; rasche Initiative notwendig wegen schwerer Nebenwirkungen

Since the approval of two commercial CAR-T cell products by the EMA, the Austrian Society for Haematology and Medical Oncology (OeGHO, CAR-T cell platform) has developed detailed criteria for the quality-assured implementation of CAR-T cell therapy in Austria. The rationale for this early and fast initiative is that these two cell products include serious side effects, which make a careful selection of patients to be treated a necessity. Side effects include cytokine release syndrome (CRS), CAR-T-Cell-Related Encephalopathy

Syndrome (CRES), cytopenias, infections, and long-lasting B-cell aplasias, but also multi-organ failure and severe cerebral oedema. The requirements for a quality-assured implementation of CAR-T cell therapy are defined by criteria (indication- and structural criteria) [3, 66].

6 CAR-T Zentren in Ö

Based on these criteria, six qualified CAR-T cell centres have been assigned: Medical University Hospitals of Vienna (MUW), Graz (MUG) and Innsbruck (MUI), Salzburg (PMU) as well as St. Anna children's hospital and Elisabethinen (Linz).

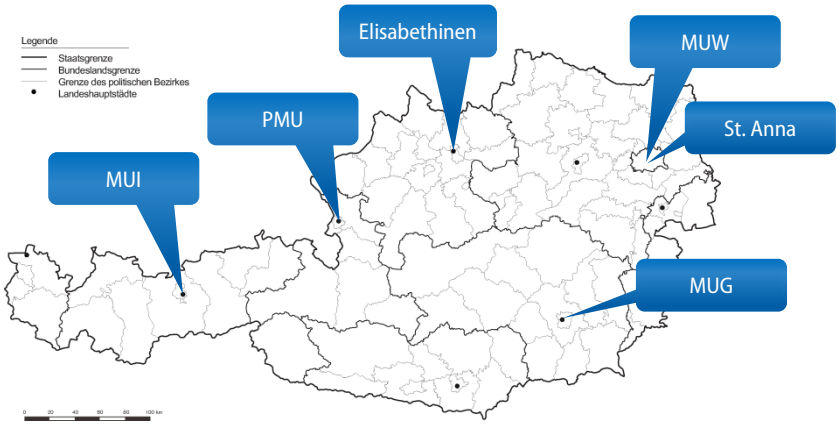


Figure 1-5: Austrian CAR-T Network [2]
(Map: © Österreichischer Bundesverlag Schulbuch GmbH & Co. KG und Freytag-Berndt u. Artaria KG, Wien)

Structural, personnel and procedural criteria for CAR-T cell centres:

- Extensive experience in the treatment of the respective underlying malignant disease (participation in clinical trials and experience in the administration of experimental therapies).

  umfangreiche Erfahrungen in der Behandlung von malignen Grunderkrankungen (Stammzelltransplantation), Teilnahme an klinischen Studien

- Extensive experience in allogeneic and/or autologous first transplantations (documented in Austrian Stem Cell Transplantation Registry (ASCTR)/European Society for Blood and Marrow Transplantation (EBMT) registry within the last three years).

- Extensive experience with the necessary equipment, the possibility of endoscopy at any time, bronchoscopy, invasive ventilation and renal replacement therapy. Furthermore: specific Standard Operating Procedures (SOPs) for the management of complications of CAR-T cell therapy, including the use and availability of tocilizumab on-site at all times. Rapid admission of patients requiring intensive care is mandatory.

  Struktur-, Personal- und Prozesskriterien für CAR-T Zentren

- Hygiene-concept: due to immune suppression, accommodation in an isolated room must be guaranteed at all times, infusion should be performed in defined rooms (according to the regulations for working with genetically modified microorganisms).

  Hygienekonzept und Abfallentsorgung

- Integration of hospital pharmacy and tissue bank: binding arrangements for timely fulfilment of regulatory requirements.

  Apotheke und Gewebebank

- Detailed waste-management in accordance with local biosafety regulations.

ambulante Betreuung und Nachsorge

- Availability of outpatient care. A suitable infrastructure must be available for infusion therapy and the transfusion of blood products and for counselling patients during follow-up on prophylaxis and therapy of long-term side effects.

geschultes und berufserfahrenes Personal

- The medical staff involved (medical director: specialists in internal medicine and haematology and oncology, physicians and nursing staff) must have sufficient training and documented experience in therapy with cytotoxic and immunosuppressive substances as well as cryopreserved cells and with treating patients with severe immunodeficiency or alloHSCT. etc. [3, 66]

spezifische Geräte, Prozesse und Materialien

Dokumentation in Register

- Procedural criteria: equipment and materials for the collection, labelling and storage of starting cells and genetically modified cells must be available; SOPs for recording and reporting adverse events, as well as for transferring the patient to the ICU, and the management of CRS and neurotoxicity of any degree must be in place; a qualification plan, quality assurance measures must be available; involvement of tumour board; documentation of patient-relevant data and side effects in the EBMT-registry according to EMA's requirements [35, 37, 52]

Indication criteria

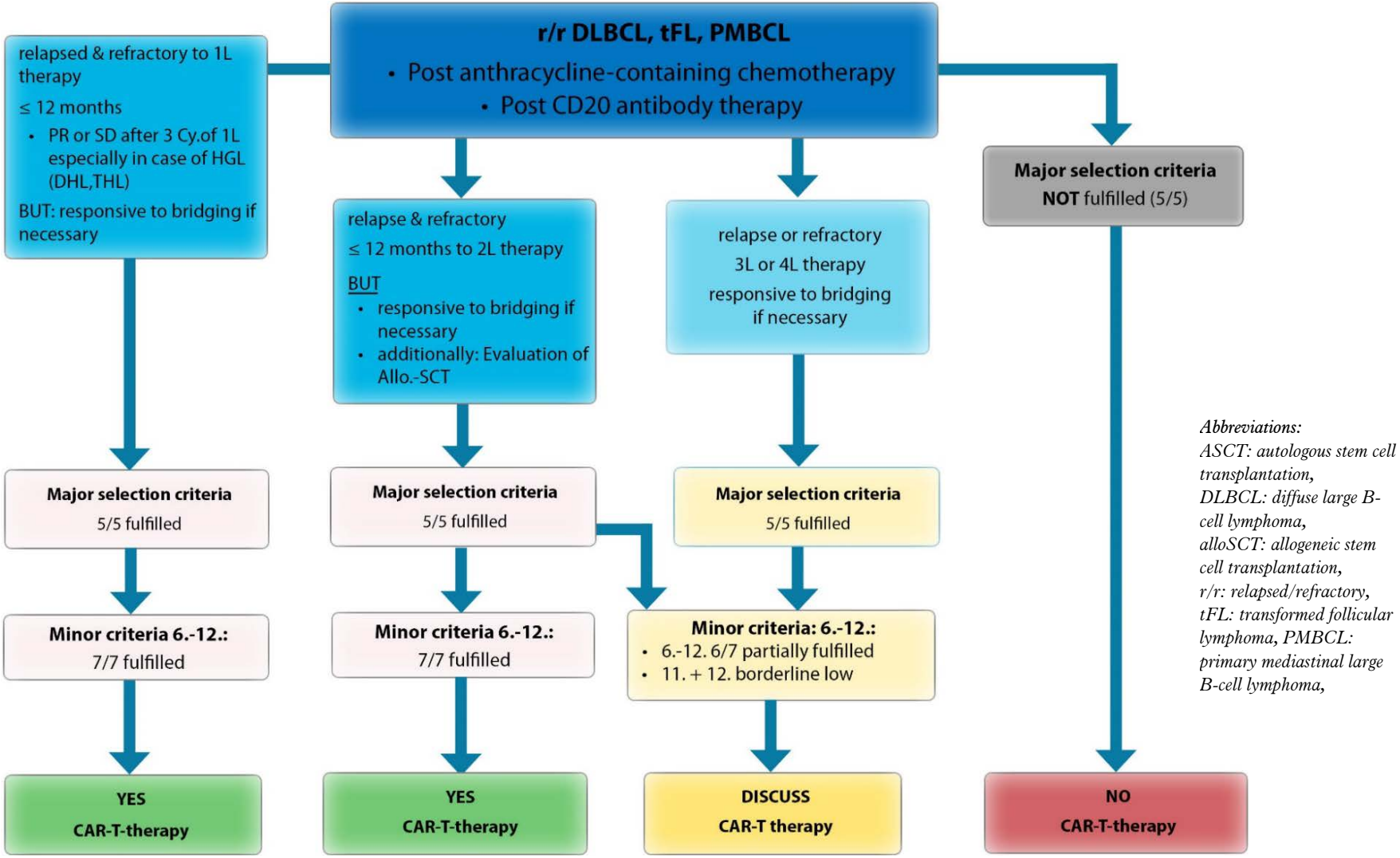
Indikationskriterien

The following algorithm (Figure 1-6) and table (Table 1-6) show the current decision-rules for indications for clinical use of approved CAR-T cell products (for DLBCL, PMBCL and tFL) outside of trials in Austria. Furthermore, the core and selection criteria for patient selection are defined. The selection criteria are currently being revised and adapted to second line. However, they have not yet been published.

Table 1-6: Major and minor Criteria for CAR-T cell therapy
*(*1st amendment proposed during CAR-T 2020 Sitges at the 31st of Jan 2020; Jäger U. et al. [2])*

Major criteria		
1. Cardiac function	EF	> 50%
2. Lung function	SpO_2	> 91-92% at room air
3. ECOG PS		0-1
4. CNS		■ No involvement ■ No major neurologic disease as contraindication
5. Infection		**No active/symptomatic CNS involvement at time of infusion***
Minor criteria		
6. ANC	G/L	≥ 1.0
7. ALC	G/L	> 0.1-0.3
8. NFP	eGFR	≥ 60 mL/min/1.73 m^2
9. LFP	S-ALT/AST	< 2.5 × ULN
10. LFP	Total Bilirubin	< 2.0 mg/dL
11. Plt	G/L	≥ 50-75
12. Hb	g/dL	> 8.0

Abbreviations: ANC: absolute neutrophil count, ALC: absolute lymphocyte count, CI: contraindication, CNS: central nervous system, ECOG: Eastern Cooperative Oncology Group Performance Status, EF: ejection fraction, eGFR: estimated glomerular filtration rate, NFP: net filtration pressure/renal function parameter, LFP: liver function parameter, PT: platelets, Hb: haemoglobin, SpO2: blood oxygen saturation, ALT/AST: alanine transaminase, aspartate transaminase, ULN: upper limit normal



Abbreviations:
ASCT: autologous stem cell transplantation,
DLBCL: diffuse large B-cell lymphoma,
alloSCT: allogeneic stem cell transplantation,
r/r: relapsed/refractory,
tFL: transformed follicular lymphoma, PMBCL: primary mediastinal large B-cell lymphoma,

Figure 1-6: Refined Selection algorithm for DLBCL patients in clinical routine Austrian CAR-T Cell Network Algorithm (ACA) criteria [2, 3]

1.4.2 Application of CAR-T cell therapies in Austria

CAR-T in Ö seit Aufnahme in MEL Katalog 60-mal refundiert

regionales pay-for-performance Modell

Since the approval and the introduction of a reimbursement code via the Austrian Hospital Benefit Catalogue (Medizinischer Einzelleistungs- (MEL-) Katalog), CAR-T cell therapies have been reimbursed (2020, 2021) 60 times (see Table 1-7). This information is somewhat misleading since – apart from reimbursed therapies in "routine care" (= billed via MEL) – CAR-T cell therapies are applied within clinical studies (since 2016) in the approved indications as well as in further indications. Additional to the general MEL-code, regional pay-for-performance (P4P) payment models have been negotiated.

Indikationserweiterung in Aussicht, vermehrte Inanspruchnahme von CAR-T; krankenhausbasierte Produktion könnte Kosten senken, 3 Maschinen in Ö

So far, only "small indications" have been treated in their last line, but soon Multiple Myeloma and Follicular Lymphoma will be approved, additional to earlier lines of therapy [38]. It can be foreseen that the demand for the production of CAR-T cell therapies will grow in the near future. Not only but also due to the costs of CAR-T products, hospital-based production has started in several countries. Three CAR-T production devices have already been purchased in Austrian hospitals for adopting on-site manufacturing of CAR-T cells. However, they will not be in use within the next few years.

Table 1-7: "Routine" application of CAR-T cell therapies with approved products

FZ120 Administration of CAR-T cells – Number of services provided	2020	2021*
C82 Follicular lymphoma (FL)	1	2
C83 Non-follicular lymphoma (nFL)	14	18
C85 Other and unspecified types of non-Hodgkin's lymphoma (NHL)	6	10
C91 Lymphatic leukaemia (LL)	3	6
Summe	**24**	**36**

*Data source: Diagnosis and performance reports, * Data 2021: preliminary & unaudited [67]*

österreichische Patient*innendaten in EBMT CAR-T Register

über 700.000 Patient*innendaten insgesamt in EBMT CAR-T Register (Dez. 2021)

As requested, all Austrian patient data must be registered in the EBMT CAR-T Data Collection Initiative (CAR-T registry). The European Society for Blood and Marrow Transplantation (EBMT) has held a patient registry since 1974 and has now signed a contract with EMA to establish a CAR-T registry for the purpose of a post-authorisation safety study (PASS). As of December 2021, the EBMT Registry has acquired data on over 700,000 patients that received a haematopoietic stem cell transplantation (HSCT) procedure, as well as data on 2,750 patients that received CAR-T cell therapy (see Figure 1-7)

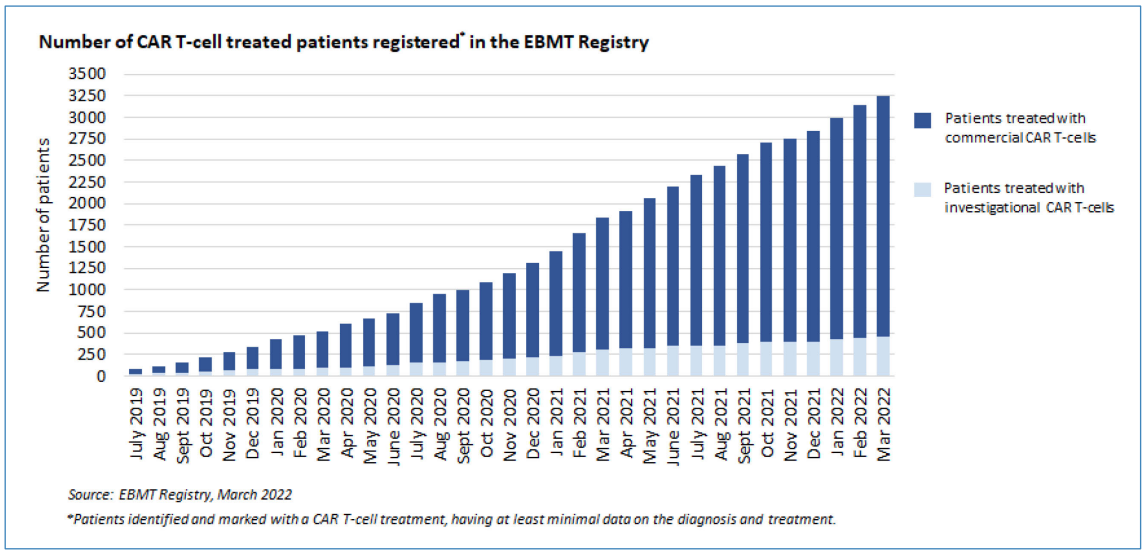


Figure 1-7: Number of CAR-T cell treated patients registered in the EBMT-registry [7]

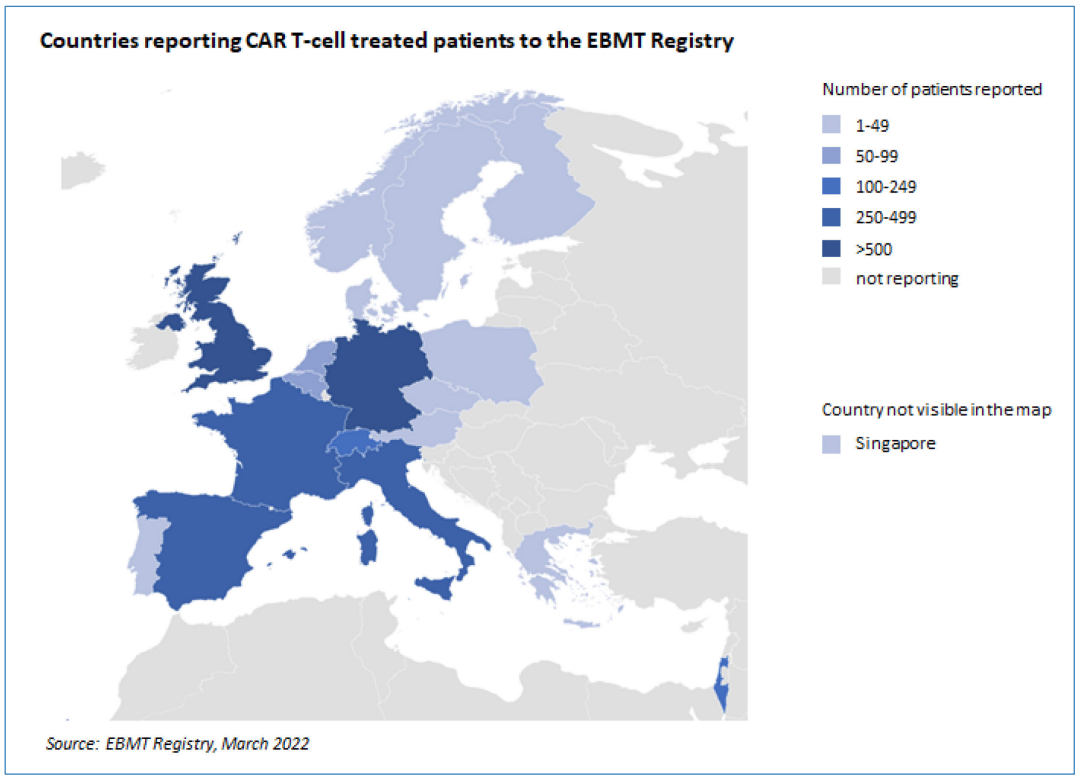


Figure 1-8: Countries reporting CAR-T cell treated patients to the EBMT registry [7]

For Austria, only data on "routine" patients treated with approved products are documented: between 25 Sept 2019 and 12 Jan 2022, approximately 52 patients were documented, the majority of which are large cell lymphoma. An extended Austrian registry, that would record more parameters and could also include study patients, is planned.

52 Routinepatien*innen dokumentiert in Ö (09/19-01/22)

Table 1-8: Characteristics auf Austrian CAR-T cell treated patients (n=52) [2]

Patients´ characteristics	N=52
Age	60 (IQR: 48, 64)
Product	
Tisagenlecleucel	31 (60%)
Axicabtagen Ciloleucel	21 (40%)
Indication	
DLBCL	44 (85%)
ALL	6 (12%)
PMBCL	2 (3.8%)
Number of previous lines	
2	16 (35%)
3	11 (24%)
4	14 (30%)
≥5	5 (11%)
Not available	6
Previous autoHSCT	16 (31%)
Bridging	46 (88%)

medianes Alter: 60, v.A. DLBCL Patient*innen (Pt.) (85 %); 65 % Pt. drei oder mehr vorherige Therapien; 88 % Pt. mit Überbrückungstherapie, 31 % autoHSCT

Regarding patient characteristics (see Table 1-8) treated patients (n=52) were on average 60 (IQR: 48 to 64) years, with indications DLBCL (n= 44, 85%), PMBCL (n=2, 3.8%) and ALL (n=6, 12%). The majority (n= 31, 60%) were treated with Tisagenlecleucel compared to treatment with Axicabtagen Ciloleucel (n=21, 40%). The majority (n=30, 65%) had ≥3 previous lines of therapies, while 35% (n=16) had only two lines. For six patients, this information was not available. One-third (n=16, 31%) of the patients had undergone a previous autoHSCT, nearly all (n=46, 88%) have received bridging therapy.

Table 1-9: Results (safety and effectiveness) in Austrian CAR-T cell treated patients (n=52) [2]

Results (safety and effectiveness)	N=52
CRS	
Grade 0	17 (37%)
Grade 1	11 (24%)
Grade 2	16 (35%)
Grade 3	2 (4.3%)
Not available	6
ICANS	
Grade 0	40 (77%)
Grade 1	5 (9.6%)
Grade 2	4 (7.7%)
Grade 3	2 (3.8%)
Grade 4	1 (1.9%)
Response @3 months	
Complete response (CR)	26 (62%)

Results (safety and effectiveness)	N=52
Partial response (PR)	5 (12%)
Stable disease (SD)	1 (2.4%)
Progressive disease (PD)	10 (24%)
Not available	10
Status at last follow-up	
Alive, complete remission	31 (62%)
Alive, active disease	9 (18%)
Dead	10 (20%)
Not available	2
Time to last follow-up (months)	5 (2, 15)

Abbreviations: CRS: cytokine release syndrome,
ICANS: immune effector cell-associated neurotoxicity syndrome

beinahe alle Pt mit unerwünschten Ereignissen

Regarding effectiveness and safety results (see Table 1-9), nearly all patients (n=44, 96%) suffered from the side effects of CRS up to grade two. Two patients (4.3%) experienced CRS grade three, none were reported for grade 4. For six patients, no information on CRS was available. Equally, nearly all patients (n=49, 94.3%) suffered from ICANS up to grade two. Three patients (5.7%) experienced ICANS grade three and higher.

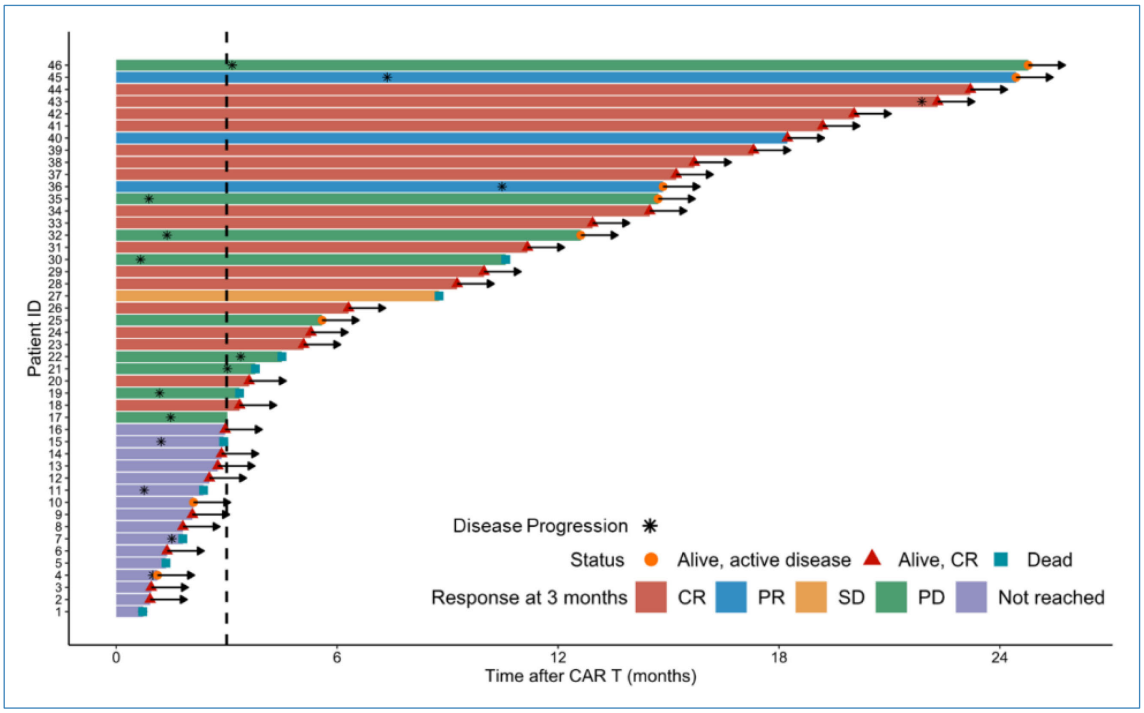


Figure 1-9: Response rates at 3 months of Austrian CAR-T cell treated patients (n=46) [4]

62 % Pt in CR zum Zeitpunkt des letzten follow-ups (5 Monate)

Progressionsfreies Überleben nach 20 Monaten: 55 %

Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) was reported in 26 (62%), five (12%), one (2.4%) and ten (24%) patients, respectively (see Figure 1-9). For ten patients, this information was not available. At the last follow-up (5, 2-15 months), 31 patients (62%) were alive in complete remission, nine (18%) were alive but with active disease, ten died and for two patients, no information was available. A Caplan-Meier curve on progression-free survival (PFS) for 46 (of the 52) patients show that 55% of patients were in remission at 20 months (see Figure 1-10) [2].

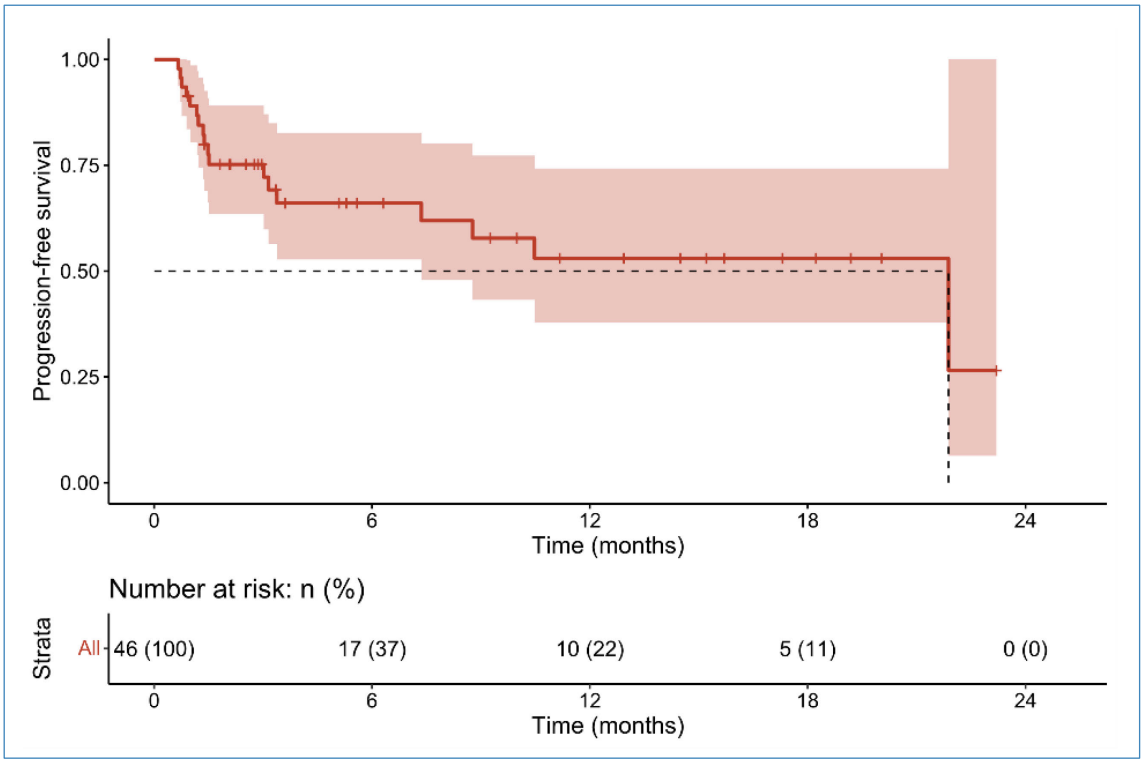


Figure 1-10: Progression-free survival (DLBCL) of Austrian CAR-T cell treated patients (n=46) [2]

österreichweiter Algorithmus für die Anwendung von CAR-T Zelltherapien; mögliche Verschlechterung der Ergebnisdaten bei Indikationserweiterung

To conclude: The Austrian-wide consensus-based stringent algorithm (narrow patient selection) based on numerous reasons for exclusion at an early point in the introduction of CAR-T cell therapies has led to consistent local decisions on the application of CAR-T cell therapies in the six centres. With the foreseen broadening of the indications (approval of CAR-T cell therapies for second-line treatment of DCBLC or for not transplant-eligible patients), the outcome data might worsen.

1.5 Objective and Policy Question

Due to the small number of patients and the resulting small cohorts in the pivotal studies, an analysis of the patient-relevant benefit and safety by comparing the results of post-approval studies to registry studies is needed. Initial systematic reviews of the beneficial effects of CAR-T cell therapies in DLBCL have already been conducted in 2021 and are updated in this report [61].

Vergleich Zulassungsstudien und real-world Studien nach der Zulassung aufgrund fehlender Daten notwendig

Project aims and research questions: The primary aim of this project is to systematically synthesize the evidence from health care studies (RWE: observational and registry studies) on the use of CAR-T cell therapies since their approval in 2018, and to compare the results from pivotal studies and health care studies regarding patient characteristics, efficacy/safety endpoints. Instead of a separate HTA, a summary of the results of HTAs – based on the pivotal studies – is provided in section 3.1.

Ziel: systematische Evidenzsynthese von Zulassungsstudien und real-world Studien hinsichtlich Wirksamkeits- und Sicherheitsendpunkten

2 Methods

2.1 Research questions

Based on the study objectives, we defined the following research questions (RQ):

2 Forschungsfragen

RQ1: What are the results of HTAs regarding the available evidence (clinical trials) and their critical evaluation of approved CAR-T cell therapies:

Bewertungsergebnisse anderer HTA Berichte

1. Kymriah® in r/r B-cell acute lymphoblastic leukaemia (B-ALL), children, adolescents and young adults up to and including 25 years of age.
2. Yescarta® or Kymriah® in adult patients with r/r diffuse large B cell lymphoma (DLBCL) with at least two prior systemic therapies.
3. Yescarta® in adult patients with r/r primary mediastinal large B-cell lymphoma (PMBCL) with at least two prior systemic therapies.

RQ2: What are the differences in patient characteristics, efficacy, and safety in the results of pivotal studies and in real-world studies (observational and registry studies) regarding therapy with

Ergebnisse zu Patient*innencharakteristika und Wirksamkeits-/Sicherheitsendpunkten

1. Kymriah® in r/r B-cell acute lymphoblastic leukaemia (B-ALL), children, adolescents and young adults up to and including 25 years of age.
2. Yescarta® or Kymriah® in adult patients with r/r diffuse large B cell lymphoma (DLBCL) with at least two prior systemic therapies.
3. Yescarta® in adult patients with r/r primary mediastinal large B-cell lymphoma (PMBCL) with at least two prior systemic therapies.

2.2 HTA results

A hand search and systematic summary of assessments from (selected) national HTA institutions for health policy decision-making were conducted for the first research question. Reports from the following ten institutions in nine countries were deemed relevant.

Handsuche und systematische Zusammenfassung von HTA Berichten

- CADTH (Canada)
- ICER (USA)
- MSAC (Australia)
- NICE (UK)
- NoMA (Norway)
- **GBA/IQWiG (Germany)**
- **HAS (France)**
- **TLV (Sweden)**
- **ZIN (Netherlands)**

One systematic review, published in 2021 that covered five out of ten HTA institutions was identified [68]. This report was consulted, and the table of results was taken, controlled, revised, and expanded with the additional five HTA institutions (marked in bold).

systematischer Review herangezogen und erweitert

2.3 PICO Question: Inclusion criteria

For the second research question, a systematic review was conducted in order to compare the real-world evidence with the pivotal trials. Eligibility criteria for relevant studies are summarised in Table 2-1 (B-ALL) and Table 2-2 (DLBCL/PMBCL).

Table 2-1: PICO (in-/exclusion criteria) for B-ALL

Population	Patients with refractory or relapsed B-cell acute lymphoblastic leukaemia (children and adolescents aged 3 to 25 years)
Intervention	■ Commercial CAR-T cell therapy with Kymriah®/Tisagenlecleucel (independent of previously administered therapy). NOT: ■ Alternative, not yet approved (CD-19) CAR-T cell therapies and dual-target CAR-T cell therapies (e.g., anti-CD19/CD22/CD20). ■ Allogeneic (donor-derived CAR-T) and non-autologous CAR-T cell therapies
Control	Standard treatment without CAR-T cell therapy
Outcomes	
Effectiveness	■ Overall survival ≥ 6 months of FU ■ Event-free survival ≥ 6 months of FU ■ Overall response, complete/partial response ■ Relapse ■ Quality of life
Safety	■ Serious adverse events (cytokine release syndrome (CRS), neurologic toxicities, cytopenia, SAE) ■ Other adverse events (AE) ■ Treatment associated death NOT: ■ Studies using only surrogate endpoints
Study design	■ (Non) Randomized Control Trials (nRCTs/RCTs) ■ Retrospective studies ■ Prospective case series with ≥ 5 patients ■ Registry studies ■ Other observational studies with real-world evidence
Publication period	2017 until 03/2022
Language	German, English

Table 2-2: PICO (in-/exclusion criteria) for DLBCL/PMBCL

Population	Adult patient (≥ 18 years) with 1. relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) after two or more systemic therapies 2. relapsed or refractory primary mediastinal B-cell lymphoma (r/r PMBCL) after two or more systemic therapies
Intervention	Commercial CAR-T cell therapies with ■ Axicabtagen-ciloleucel (Yescarta®) or Tisagenlecleucel (Kymriah®), regardless of previously administered therapy – (r/r DLBCL) ■ Axicabtagen-ciloleucel (Yescarta®), regardless of previously administered therapy – (r/r PMBCL) NOT: ■ Alternative, not yet approved (CD-19) CAR-T cell therapies and dual-target CAR-T cell therapies (e.g., anti-CD19/CD22/CD20). ■ Studies in which allogeneic (donor-derived CAR-T) and non-autologous CAR-T were used
Control	Standard treatment without CAR-T cell therapy 1. Systemic relapse therapy: allogenic HSCT, palliation 2. Systemic relapse therapy: allogenic HSCT, palliation Or no control
Outcomes	
Effectiveness	■ Overall survival after ≥ 3 months (r/r DLBCL), resp. ≥ 6 months (r/r PMBCL) follow-up (FU) ■ Life quality ■ Progression-free survival after ≥ 3 months (r/r DLBCL), resp. ≥ 6 months (r/r PMBCL) FU ■ Overall response, complete/partial response
Safety	■ Serious adverse events (cytokine release syndrome (CRS), neurologic toxicities, cytopenia, SAE) ■ Other adverse events (AE) NOT: ■ Studies using only surrogate endpoints
Study design	■ (Non) Randomized Control Trials (nRCTs/RCTs) ■ Retrospective studies with ≥ 40 patients ■ Prospective studies ■ Registry studies ■ Other observational studies with real-world evidence NOT: ■ Studies with mixed LBCL cohorts where DLBCL or PMBCL do not makeup ≥50% of the population ■ Letter to the editors ■ Studies from vigilance databases ■ Studies investigating CAR-T not as a primary intervention but only outcome (e.g. effect of hypoalbuminemia on CAR-T outcome) ■ No aggregated data for the whole cohort reported ■ Publications from pivotal trials
Publication period	until 04/2022
Language	German, English

2.4 Systematic literature search

Acute lymphoblastic leukaemia

systematische Literatursuche in 3 Datenbanken

The systematic literature search was conducted on the 30th March 2022 in the following databases:

- Medline via Ovid
- Embase.com
- The Cochrane Library

625 Zitate identifiziert

The systematic search was limited to articles published in English or German from 2017 until March 2022. After removal of duplicates, 617 citations were screened by title and abstract. By hand-search, eight additional publications could be identified, resulting in overall 625 hits.

The specific search strategy employed can be found in the Appendix.

Suche in Studienregistern

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EudraCT) was conducted on the 16th May 2022, identifying 74 potential relevant hits.

Large B-cell lymphoma

Systematischer review (SR) von Cochrane 2021

For the summary and assessment of the pivotal studies, a recent systematic review from Cochrane 2021, covering the evidence from pivotal studies, was identified [61]. The evidence was summarised in Section 1.3.

Systematische Literatursuche in 3 Datenbanken

The systematic literature search to identify real-world studies was conducted between 4th-5th May 2022 in the following databases:

- Medline via Ovid
- Embase.com
- The Cochrane Library

493 Zitate identifiziert

The systematic search was limited to articles published until April 2022 in English or German. After removal of duplicates, 493 were screened by title and abstract. By hand-search, no additional publications were identified.

The specific search strategy employed can be found in the Appendix.

Suche in Studienregistern

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EudraCT) was conducted on the 16th May 2022, identifying 38 potential relevant hits.

2.4.1 Flow chart of study selection

Acute lymphoblastic leukaemia

Literaturauswahl B-ALL

Overall, 625 hits were identified. The references were screened by two independent researchers (AT and AP), and in case of disagreement, a third researcher (CW) was involved in solving the differences. The selection process is displayed in Figure 2-1.

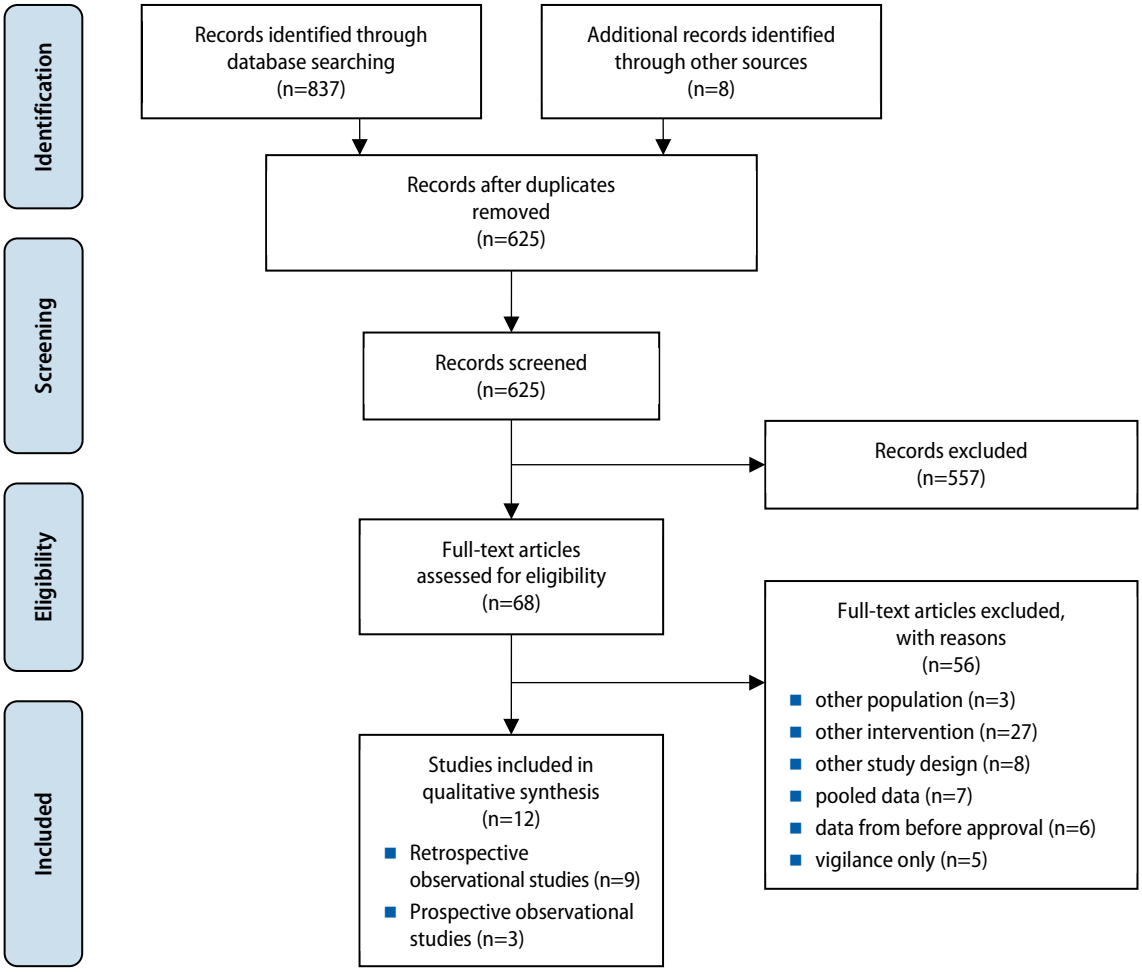


Figure 2-1: Flow chart of study selection B-ALL (PRISMA Flow Diagram)

Large B-cell lymphoma

Literaturauswahl DLBCL/PBMCL

Overall, 493 hits were identified. Titles and abstracts were screened by two independent researchers (AP, GG), and in case of disagreement, a third researcher was involved in solving the differences (CW). The selection process is displayed in Figure 2-2. The final selection of full-text articles was based on the a priori established inclusion criteria presented in Table 2-2.

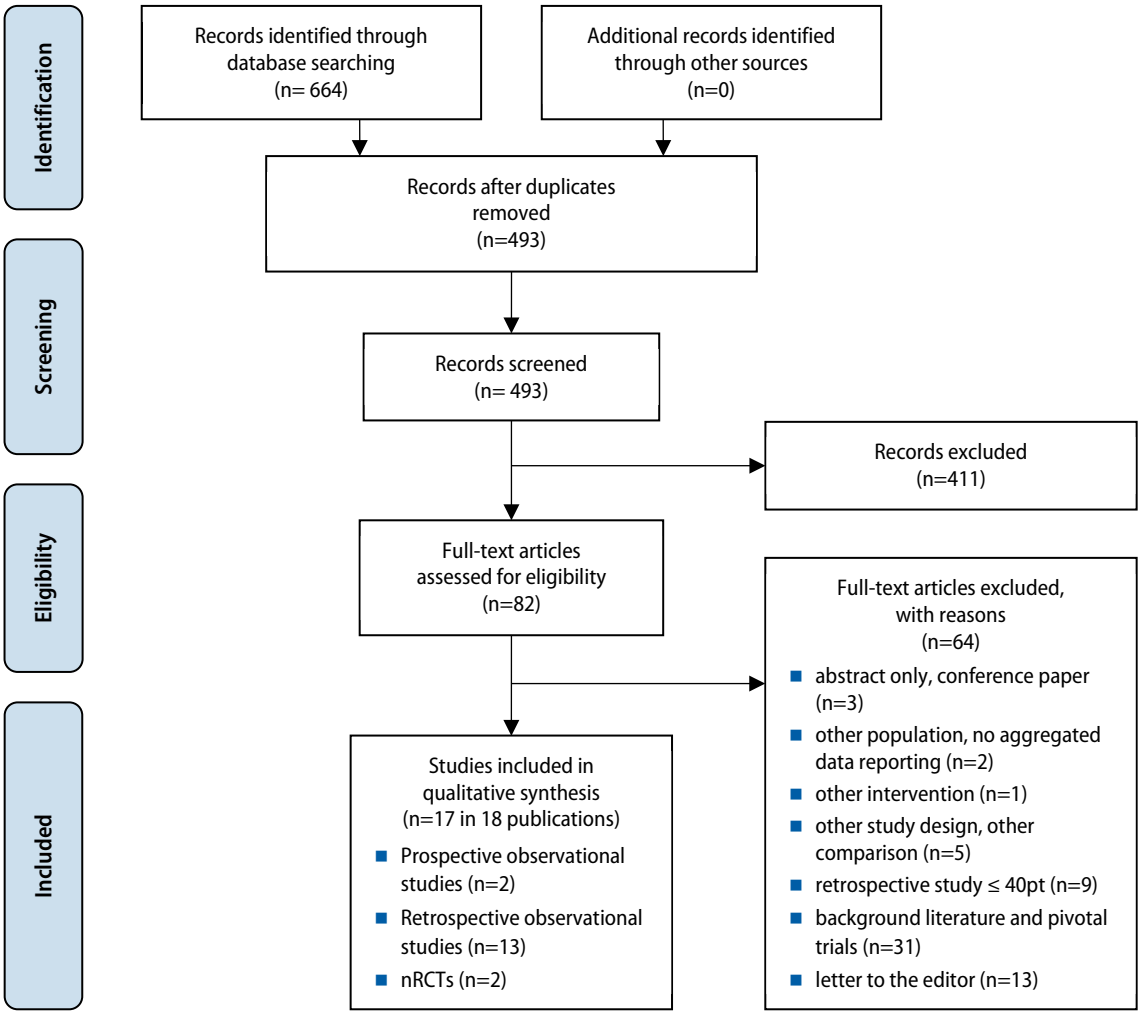


Figure 2-2: Flow chart of study selection DLBCL/PMBCL (PRISMA Flow Diagram)

2.4.2 Analysis

Extraktion der Daten

Relevant data were systematically extracted into data extraction tables from eligible studies. For each indication, one researcher (AT: B-ALL, AP: LBCL) systematically extracted relevant data from the included studies into data extraction tables. A second researcher (AP: B-ALL, GG: LBCL) cross-checked the data extraction tables with the data source and validated them for accuracy.

Bewertung der Studienqualität durch IHE checklist und ROBINS-I

The studies were systematically assessed for internal validity and risk of bias (RoB) by two researchers for each indication (AT, AP: B-ALL, AP, GG: LBCL) independently, using the Institute of Health Economics (IHE) Risk of Bias checklist for all identified records [69] and the ROBINS-I tool for non-randomised controlled studies (n=2) [70]. Results are presented in the Appendix Table A-9, Table A-10 and Table A-11. RoB Results for the pivotal studies for LBCL were adopted from the Cochrane report 2021 [61] and presented in the Appendix Table A-5 and Table A-6.

Overall, RoB was assessed using a predefined point score (IHE range: 0-20; Table 2-3): a high score indicates a low RoB, and a low score indicates a higher RoB. Detailed thresholds are presented in Table 2-4.

Table 2-3: Overall risk of bias (RoB) point scores for RoB assessment of observational studies

Answers to specific questions of the IHE-20 checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 2-4: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of observational studies

Criteria	Points
Low risk	**> 18**
Moderate risk	**14.5 to 18**
High risk	**≤ 14**

2.4.3 Synthesis

qualitative Synthese

A qualitative synthesis of the evidence was performed. The research questions were answered in plain text format. Due to the heterogeneity of the studies, no quantitative synthesis was performed. Minimal clinically important differences (MCID) were considered when this information was available for a certain outcome and indicated in the report.

All discrepancies were resolved by consensus. In case of disagreement, a third researcher (CW) was consulted.

3 Results

3.1 Results Health Technology Assessments on Tisagenlecleucel/Kymriah® and Axicabtagen Ciloleucel/Yescarta®

In order to assess the available evidence and the critical evaluation of other health technology assessment (HTA) institutions on Kymriah® and Yescarta®, HTA reports were described.

ausgewählte HTA Institutionen

To extract information from different HTA reports on Tisagenlecleucel (Kymriah®) and Axicabtagene Ciloleucel (Yescarta®), the following HTA ten institutions (from nine countries) were considered for our overview:

- CADTH (Canada)
- ICER (USA)
- MSAC (Australia)
- NICE (UK)
- NoMA (Norway)
- GBA/IQWiG (Germany)
- HAS (France)
- TLV (Sweden)
- ZIN (Netherlands)

Bericht von Gye 2022 herangezogen, adaptiert und erweitert

Only the conclusions on efficacy and safety regarding Kymriah® and Yescarta® were extracted from the HTA reports, and specific attention was given to mentioning of shortcomings of the pivotal trials that need to be overcome and tackled in further clinical studies. For the extraction, a publication by Gye et al. [68] was consulted, and their table of results was taken but controlled, revised when deemed necessary and expanded (see Table A-1).

Tisagenlecleucel/Kymriah® for B-ALL

9 Berichte

Nine reports from nine HTA institutions (in eight countries) were considered [71-80].

indirekte Vergleiche mit anderen Therapien

To assess the clinical efficacy of Kymriah® (ELIANA and ENSIGN pivotal trials, single-arm) in comparison to other treatments, indirect comparisons were considered as controls [81-89]. Other therapies included treatment with Blinatumomab, Clofarabine monotherapy or Clofarabine/Etoposide/Cyclophosphamide (CEC) chemotherapy.

6/9 HTA: klinischer Effekt möglich

While six out of nine reports suggest that Kymriah® has at least a plausible potential for clinical efficacy (ICER, MSAC, NICE, NoMA, HAS, ZIN), only ZIN comes to the conclusion that Kymriah® has a clinically relevant effect of at least 3 months life prolongation compared to blinatumomab treatment.

Unsicherheiten in Ermangelung an Daten

Due to lacking data, all nine reports concluded that uncertainties regarding clinical evidence with respect to efficacy and safety still remain [71-80].

Tisagenlecleucel/Kymriah® for DLBCL

10 Berichte

Ten reports from ten HTA institutions (in nine countries) were considered [71, 72, 90-98].

Vergleiche mit historischen Kontrollen

heterogene Herstellerdaten konnten nicht berücksichtigt werden

To assess the efficacy of Kymriah® (JULIET pivotal trial and UPENN supporting study, single arm) in comparison to salvage chemotherapy, data from the CORAL or SCHOLAR-1 trials were used as historical controls (matched-indirect comparison). This data provided by the manufacturer were often deemed too heterogeneous and could not be considered in the evaluation due to differences in the study design. Possible selection bias (ICER) and differences in the study population (from the control-studies) compared with the target patient population infused with Kymriah® (GBA/IQWiG) were identified.

3/10: geringer klinischer Zusatznutzen, dennoch signifikante Unsicherheiten 7/10: zu unsichere Evidenz für Fazit

MSAC, HAS and ZIN conclude that there is at least a minor clinical added benefit, while significant uncertainties still remain. Reports from the other HTA institutions consider the evidence presented as too uncertain to draw any conclusions about the clinical benefit (CADTH, ICER, NICE, NoMA, GBA/IQWiG, TLV).

fehlender Vergleich

A lack of comparison regarding the application of Kymriah® or Yescarta® for patients with DLBCL was noted by ICER, MSAC, NICE, GBA/IQWiG, HAS, TLV and ZIN.

Axicabtagene ciloleucel/Yescarta® for DLBCL/PMBCL

11 Berichte

Eleven reports from ten HTA institutions (in nine countries) were found and considered [72, 99-109].

Vergleiche mit historischen Kontrollen wurden teilweise nicht anerkannt, fehlende Vergleichsstudien

To assess the efficacy of Yescarta® (ZUMA-1 pivotal trial, single-arm) in comparison to salvage chemotherapy, data from the SCHOLAR-1 trial were used as historical controls (matched-indirect comparison). However, G-BA/IQWiG did not consider SCHOLAR-1 to be an appropriate control for the report due to missing data. Additionally, also other HTA institutions reported the lack of a head-to-head comparison of Yescarta® with salvage chemotherapy or other standard therapies, addressing differences in the study populations of ZUMA-1 and SCHOLAR-1.

5/10: geringer klinischer Zusatznutzen

ICER, MSAC, NICE, HAS and ZIN report at least a small net health benefit of Yescarta® compared with other standard treatments (salvage chemotherapy with or without stem cell transplant).

3.1.1 Conclusion of Health Technology Assessments (HTAs)

hohes Verzerrungpotential für alle untersuchten CAR-T Anwendungen, weil kleine Studien, einarmig, kurze Nachbeobachtung, fehlende Sicherheitsdaten

For all three CAR-T cell therapy indications (B-ALL, DLBCL, PMBCL), low certainty of evidence and high risk of bias due to the following limitations were frequently listed in the HTA reports:

- Single arm study/lack of control arm
- Historical control provided by the manufacturer could not be considered due to heterogeneity in patient populations or differences in study design
- No long-term follow-up and short trial duration
- Small patient cohort
- Lack of safety data/severe adverse events

3.2 Outcomes effectiveness and safety

definierte Effektivitätsendpunkte: OS, PFS/EFS, ORR, CR, PR, BCA, HRQoL

To compare the effectiveness data of CAR-T between real-world evidence and pivotal trials, the following endpoints were defined:

- Overall survival (OS)
- Progression-free survival (PFS)/Event-free survival (EFS)
- Response Rates (ORR, CR, PR)
- B-cell aplasia (BCA)
- Health-Related Quality of Life (HRQoL)

Definitionen der Endpunkte

Overall survival (OS) is defined as the time from leukapheresis[10] or CAR-T infusion to death from any cause [110-128].

Progression-free survival (PFS) is defined as the time from CAR-T infusion until relapse, disease progression or death from any cause, whichever occurred first [110-120].

Event-free survival (EFS) is defined as the time from CAR-T infusion to progression, relapse or death from any cause or second malignancy [121, 122, 125-129].

The **overall response rate (ORR)** is defined as the percentage of patients achieving CR, CRi or PR [110, 116, 122, 129].

Cumulative incidence of loss of B-cell aplasia (BCA) is defined as the time from CR/CRi to loss of BCA [122].

Duration of BCA (in patients achieving BCA) is defined as time from infusion to loss of BCA with censoring for relapse, death or HSCT [124, 128].

Loss of BCA is defined as >5 B-cells/μl [33], > 10 B-cells/μl in peripheral blood at two time points [122], ≥ 1 CD19+ B cell/μl in peripheral blood [123, 124], ≥1% CD19+ B cells in BM aspirate or ≥3% B cells by peripheral blood flow cytometry [129], ≥1%CD19+ cells at two time points or ≥ 50 CD19+ B cells/μl in peripheral blood [126] or 2 x >1% CD19+ cells [130].

Health-Related Quality of Life (HRQoL) refers to a patient's well-being and the ability to pursue activities of daily living [131]. HRQoL was assessed by different health survey questionnaires.

Messung von Lebensqualität durch EQ-5D und PedsQL (B-ALL)

minimal klinisch relevante Unterschiede der Lebensqualität aus der Literatur

For B-ALL (ELIANA), the Pediatric Quality of Life Inventory (PedsQL) and European Quality of Life-5 Dimensions questionnaire (EQ-5D) were used. The PedsQL consists of emotional, social, school functioning and psychosocial health summary scores and a total score of all items. All scores range from 0 to 100, with higher scores indicating better HRQoL. The EQ-5D questionnaire is a descriptive system and a visual analogue scale (VAS). The score also ranges from 0 to 100, with higher scores indicating better HRQoL [132, 133]. For outcome measurement, minimal clinically important differences (MCIDs) [132, 133] and normative means for healthy children [134, 135] were used from literature.

[10] Leukapheresis as start point was used for the intention-to-treat cohort, where patients undergoing leukapheresis but not receiving a CAR-T cell product were included [110].

Messung von Lebensqualität durch EORTC QLQ-C30, FACT-Lym und SF-36 Fragebögen (LBCL)

For LBCL (real-world studies and JULIET), the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) and the Short Form-36 (SF-36) Health Survey questionnaires were used.

The EORTC QLQ-C30 version three questionnaire for cancer patients covers domains including disability assessment, cancer/toxicity-associated symptoms, emotional symptoms, overall health self-assessment, and overall quality of life self-assessment [136]. The disease-specific FACT-Lym questionnaire for lymphoma patients and SF-36 cover domains including physical, social/family, emotional and functional well-being and response to lymphoma-associated treatment and symptoms [65, 137, 138]. The FACT-Lym questionnaire includes FACT-General (FACT-G), which includes general questions in physical, social, emotional and functional well-being domains and FACT-lymphoma subscale (FACT-Lym S), which focuses on lymphoma-associated treatment and symptoms. The FACT-Lym Trial Outcome Index (TOI) includes FACT-Lym S and physical and functional well-being. FACT-Lym total score (TS) is the sum of FACT-G and FACT-Lym S.

minimal klinisch relevante Unterschiede der Lebensqualität in JULIET von Autor*innen definiert

Both scores, FACT-Lym and SF-36, were applied in JULIET, where the authors considered the following values for the minimum clinically important difference (MCID): 6.5-11.2 for FACT-Lym TS, 3-7 for FACT-G TS, 2.9-5.4 for FACT-Lym S and 5.5-11 for FACT-Lym TOI. The MCID for SF-36 was three for vitality, physical and mental scores, four for role-emotional, role-physical and social-functioning and two for general health. Surpassing the MCID for any subscale was considered a clinically significant improvement.

definierte Sicherheitsendpunkte: (schwere) unerwünschte Ereignisse, Mortalität

To compare the safety data of CAR-T between real-world evidence and pivotal trials, the following endpoints were defined:

- (Serious) adverse events (AE/SAE)
- Non-relapse mortality/mortality

The National Institute on Aging (NIA) Adverse Event guideline defines AE and SAE as following [139]:

Definition der Endpunkte

An **adverse event** (**AE**) is defined as any untoward or unfavourable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

A **serious adverse event (SAE)** is defined as any adverse event that (a) results in death, (b) is life-threatening, or places the participant at immediate risk of death from the event as it occurred, (c) requires or prolongs hospitalization, (d) causes persistent or significant disability or incapacity, (e) results in congenital anomalies or birth defects, (f) is another condition which investigators judge to represent significant hazards [139].

Different grades of AE refer to the severity of the adverse event. AE grade ≥3 are severe or medically significant and life-threatening, respectively. Grade 5 AE is defined as death when appropriate [140].

Definition von CRS und ICANS

According to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5.0, **cytokine release syndrome (CRS)** is defined as a disease caused by the release of cytokines leading to fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia [140].

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a combination of neurotoxicity symptoms, including tremor, dysgraphia and headache. These symptoms can be diverse, however, many patients develop a stereotypic set of symptoms. The American Society for Blood and Marrow Transplantation (ASTCT) defined ICANS as "a disorder characterised by a pathologic process involving the central nervous system following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells" [141]. The most severe occurring event determines the final ICANS grade.

unterschiedliche Bewertungssysteme für CRS und ICANS

Toxicities like CRS and neurotoxicity (ICANS) are associated with CAR-T therapies and have not been observed to such an extent in other cellular therapies. Toxicity assessment varies among clinical studies and institutions, as different systems for grading CRS and ICANS have been established over time: American Society for Transplantation and Cellular Therapy (ASTCT), National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), CAR-T associated toxicity 10-point (CARTOX), University of Pennsylvania or Lee criteria. All systems apply an ascending grading scale from one to five, referring to the severity of the symptoms [141]. Differences between the systems can be found in the Appendix (Table A-12 and Table A-13).

Definition von behandlungsassoziierter Mortalität

Non-relapse mortality (NRM) or **treatment-related mortality** is defined as the proportion of deaths not related to the disease or disease progression [118, 121].

3.3 B-ALL: Results from Real-world evidence (RWE)

3.3.1 Characteristics of included studies

12 Beobachtungsstudien inkludiert

For the assessment of the real-world evidence (RWE), 12 observational, non-randomised, non-controlled studies were included in the analysis [33, 122-130, 142].

Study characteristics

3 prospektive und 9 retrospektive Studien

All twelve studies are of observational character; one study primarily evaluates an active intervention of pre-emptive Tocilizumab therapy after CAR-T-cell infusion in a cohort with a high tumour burden [129], but for this report this represents a co-intervention and data on efficacy and safety of tisagenlecleucel remains observational. Three studies were conducted prospectively [122, 125, 129] and nine studies analysed data retrospectively. Six studies analysed data from patients registries [123-125, 127, 128].

Studienorte: USA/Kanada (11), Frankreich (1), Niederlande (1)

Ten studies were conducted in the USA [123-130, 142]. Nine of those reported on patients from the USA and one on patients from USA and Canada [125]. One study was conducted in France [122] and one in the Netherlands [33].

6 Registerdatenstudien, 5 Single-Center Studien, 1 Studie von 2 Zentren

Five studies reported on data from the Paediatric Real World CAR Consortium (PRWCC) that includes patients from 15 centres across the USA [123, 124, 127, 128]. One study extracted data from the Center for International Blood and Marrow Transplant Research Registry (CIBMTR) and reported on data from 75 centres across the USA and Canada [125]. Five studies presented data from one single centre each [33, 129, 130, 142]. One study included patients from two study centres [126].

Studienfinanzierung

Studies from the USA were mainly funded by NIH/NCI grants and other grants, depending on research centre [123-126, 128, 129]. The Dutch study was supported by Princess Maxima Center for Pediatric Oncology and the ODAS Foundation [33]. One study declared not to have any financial support or sponsorship [123] and four studies did not report on funding [122, 127, 130, 142].

Einschlusskriterien: Indikation, Alter, Co-morbidität

Inclusion criteria in ten of the twelve studies were CAYA with r/r B-ALL and indication for tisagenlecleucel therapy as defined by FDA [143] or EMA, [144] but also beyond the approved indication (out of specification). One further study analysed only infants [123] and another only patients with extramedullary disease [130]. More specific inclusion criteria were reported only in one study [129].

Ausschlusskriterien unter anderem Infektionen, Schwangerschaft, Länge des FU

Pre-defined exclusion criteria were reported in two studies. One excluded patients with active hepatitis B or C, HIV Infection, active acute or chronic graft-versus-host disease requiring systemic therapy, CNS3 disease that is progressive on therapy, pregnant or nursing (lactating) women or patients with an uncontrolled active infection [129]. The second study excluded patients that participated in other studies, had an incomplete data set, had no consent or had a follow-up of less than three months [125]. Five studies stated reasons for excluding patients, without explicitly naming pre-defined exclusion criteria, or excluded patients retrospectively. In those, patients were excluded, because of disease progression [122, 128], poor clinical status [122, 126, 128], tisagenlecleucel manufacturing failure [123, 126, 128], death [123, 128], incomplete reporting [123, 128], or remission from bridging therapy [128]. Five studies did not specify any pre-defined exclusion criteria or reasons for excluding patients [33, 124, 127, 130, 142].

Effektivität und Sicherheitsdaten zu B-ALL Patient*innen (allgemein) und verschiedene Subgruppen (Säuglinge)

Eight studies provide data on effectiveness and safety of an overall real-world cohort, meaning that all available patients treated with tisagenlecleucel were included in data analysis, regardless of their specific characteristics. This also included patients that received tisagenlecleucel beyond the market approved authorization [33, 122, 123, 125, 126, 128, 129, 142].

Further studies report on effectiveness and safety of specific subgroups. One study analyses RWE in infants only [123] while another reports exclusively on patients with isolated extramedullary disease [130].

verschiedene Subgruppen

One study compares outcomes in patients that received tisagenlecleucel within the market approved authorisation (standard of care, SOC) versus those that received it beyond the approved indication (out of specification, OOS) [127]. Another compares outcomes in patients with CNS disease versus patients with non-CNS extramedullary disease and patients with exclusive bone marrow disease [124]. Two studies analysed the effect of fludarabine concentrations for lymphodepletion on patients' outcome after tisagenlecleucel infusion [33, 123].

2 Studien Fokus auf Sicherheitsdaten

Two studies focus on safety – one on the diagnosis of immune effector cell associated neurotoxicity (ICANS) [142] and one on pre-emptive therapy with tocilizumab in patients with high tumour burden before CAR-T cell infusion [129].

5 Studien zu Auswirkungen der Tumorlast auf Ergebnisse

Five studies analysed the effect of tumour burden before tisagenlecleucel infusion on outcome [122, 124, 126, 128, 129] and four studies searched for determinants influencing patients' outcome [122, 124, 126, 128].

Patient characteristics, follow-up, and outcomes

Insgesamt 641 Patient*innen (Pt), medianes Alter unter 12 Monaten bis 17 Jahren

The number of patients with r/r B-ALL treated with tisagenlecleucel ranged from seven in a case series to 255 in a multicentre cohort study. Five publications reported on the same cohort from the PRWCC registry [123, 124, 127, 128]. Overall 641 patients were included in the analysis (counting patients from the PRWCC cohort only once). The median age at infusion ranged from zero (infants <12 months) [123] to 17 years [122] with the youngest patient being less than a year and the oldest 29.2 years across studies.

primär refraktär: 12 %-36 %, Rückfallpatient*innen: 62,3 %-88 %

In nine studies percentage of female participants ranged from 39%-42% [33, 122-129]. One study had included only male participants [130] and two studies did not specify patients' sex ratio [123, 142]. The percentage of patients with a primary refractory disease ranged from 12% [122] to 36% [123]. Patients with relapsed disease accounted for 62.3% [125] to 88% of patients [122].

medianer Nachbeobachtungszeitraum: 7,6-24 Monate

Median follow-up was reported in ten studies and ranged from 7.6 months [123] to 24 months [129]. One study reported on range of follow-up of 16-29 months [130] while one study did not specify time of follow-up [127].

Anzahl an früheren Therapien heterogen

vorherige alloHSCT: 5 %-59 %
vorherige CD19/22 Therapie: 10,6 %-33 %
vorherige CAR-T Therapie: 2 %-4 %

The median number of previous therapies was reported in four studies and was three [122, 125, 127, 128], ranging from 0-15 therapies [125]. One study stated that all patients had >2 lines of previous therapies [130], and in another study, 81% of patients had between 1-2 lines while 19% had 3-5 lines of prior therapy [33]. Four studies did not specify the prior lines of therapy [123, 126, 129, 142]. Ten studies [33, 122, 123, 125-130] reported on the percentage of patients that had undergone alloHSCT before therapy with tisagenlecleucel. Those ranged from 5% [123] to 59% [122]. Prior anti CD19 or CD22 directed therapy was reported in eight studies [33, 122, 123, 125-128]. The percentage of patients receiving blinatumomab prior to tisagenlecleucel ranged from 14.9% [125] to 33% [122]. Inotuzumab application was reported in 10.6 % [125] to 22% of patients [122]. Two studies reported on prior CAR-T cell therapy. In the first study, 3% of patients had received anti CD19 CAR-T and 2% anti CD22 CAR-T cells [128]. In the second study, 4% of patients had received anti CD19 CAR-T cells prior to tisagenlecleucel therapy [33]. Three studies reported on aggregated prior blinatumomab, inotuzumab or CAR-T cell therapy [123, 126, 127] in which overall percentages ranged from 21%-25.8%.

genetische Mutationen in fast allen Studien: 14 %-61 %

Other important patient characteristics were high-risk genetics, tumour burden and line of therapy. All but one study [142] reported on the occurrence of high-risk genetics. The percentage ranged from 14% [122, 130] to 61% [126] of patients. Two studies reported on specific mutations and reported TP53 mutations in 8% of patients [33] and KMT2Ar in 86% of patients [123]. Two studies reported on the occurrence of trisomy 21 in 4.7% [125] and 8.6% of patients [129].

niedrige Tumorlast (≤5 % Knochenmarkblasten): 22 %-65 %

Eight studies reported on the tumour burden of patients before tisagenlecleucel infusion [33, 122, 123, 125, 126, 128, 129]. Low disease burden was generally defined as ≤5% blasts in bone marrow and ranged from 22% of patients [123, 128] to 65% [33]. The percentage of patients with ≥5% bone marrow blasts ranged from 33% [125] to 51% [128]. One study reported 21% of patients with ≥40% of blasts [129] and one on 24% of patients having ≥50% bone marrow blasts [122].

nicht nachweisbare Krankheit vor Infusion: 10 %-43 %

Ten studies reported on **MRD negativity** or undetectable disease before infusion [33, 122, 123, 125-130]. The rate of MRD negative patients before therapy with tisagenlecleucel ranged from 10% [126] to 43% [130].

primäre und sekundäre Endpunkte: ORR, CR, EFS, LFS, OS, BCA, AE

Primary and secondary endpoints were pre-defined in eight studies [33, 123-125, 127-129]. The most common endpoints were ORR, CR(d28), EFS, LFS, OS, CD19 positive/negative relapse, BCA, CRS and ICANS.

Definitionen der Endpunkte

CR was defined by all 12 studies as ≤5% bone marrow blasts and no extramedullary disease [122, 125] and no circulating blasts [123, 124, 127, 128] or <1 % circulating blasts [129]. In three studies MRD negativity was required for definition of CR [33, 123, 142]. Two studies defined **CRi** as CR with <1 G/L neutrophils and ≤100 G/L thrombocytes [122, 129]. Two studies defined **ORR** as the percentage of patients achieving CR or CRi at day 28 [122, 129]. A third study defined CR and thus ORR by MRD negativity at two different time points [33]. Six studies defined **MRD negativity** as <0.01% blasts in bone marrow by flow cytometry [33, 123, 124] or <10-4 by polymerase chain reaction [122] or <10-5 by next generation sequencing [126]. Four studies defined **duration of response (DOR)** as time from first response to morphologic relapse or death [125, 129] or time from infusion to relapse or death [127, 128] as was **relapse-free survival (RFS)** [124]. **Leukaemia-free survival (LFS)** was defined as time from infusion to relapse [33]. Six studies defined **EFS** as the time from CAR-T infusion to non-response, relapse or death from any cause [122, 125-127, 129] or second malignancy [128]. **OS** was defined by seven studies as time from CAR-T infusion to death from any cause [122-128]. One study defined OS in responding patients from day of response (day 28) to death from any cause [123]. Eight studies provided definitions on a variety of BCA outcomes [33, 122, 124, 126, 128-130] [123].

verschiedene Bewertungssysteme von unerwünschten Ereignissen

For grading CRS, nine studies used ASTCT [122-126, 128, 130, 142] and one study used the Penn scale [129]. The grading of ICANS was performed with ASTCT in seven studies [122-125, 130, 142], with CTCAE v. 4.03 in two studies [126, 129]. Three studies stated that grading of ICANS was performed with ASCTC or other methods depending on institutional standards [123, 124, 128]. Two studies did not report on the grading method of either CRS or ICANS [33, 127].

keine Definition zu behandlungsassoziierter Mortalität

Treatment-related mortality was not clearly defined in any study. Therefore, cases were counted as 'treatment-related', if death occurred from severe adverse events most likely caused by tisagenlecleucel (severe CRS or neurotoxicity, sepsis or infection or organ failure in proximity to the therapy).

Study characteristics and results of included studies are displayed in Table 3-1 and in the Appendix (Table A-2).

Verzerrungsrisiko: moderat bis hoch, weil retrospektiv, unverblindet, keine Kontrollgruppe

Of the 12 analysed studies, six had a moderate risk of bias [33, 122, 125, 126, 128, 129] and six a high risk of bias [123, 124, 127, 130, 142]. No study fulfilled the criteria to be categorized as low risk of bias (RoB). Aspects increasing the risk of bias covered, among others, the retrospective nature of the studies, retrospective exclusion of patients, the lack of a control group and blinding as well as heterogeneous disease stages in the patient cohort.

Detailed RoB assessments (on study level) are displayed in the Appendix (Table A-7 and Table A-8).

Table 3-1: Main characteristics of included RWE studies (B-ALL)

Study ID	Study design	n	Primary (1) and secondary (2) end point	Age (years)†	Sex (F)	Prior HSCT	Prior therapies	Lines of prior therapy†	Disease stage	Other patient characteristics	FU‡
Pasquini, 2020 [125]	Prospective observational cohort study	255	CRS, ICANS, SPM, haematologic recovery, ORR, DOR, EFS, PFS, OS	13.2 (0.4-26.2)	41%	28%	Blina: 14.9% Ino: 10.6%	3 (0-15)	Prim. r/r: 62.3%	■ HR genetics: 18% ■ Down syndrome: 4.7% ■ MRD neg: 17.3% ■ No BMB: 28% ■ 0-<5% BMB: 20% ■ ≥ 5% BMB: 33% ■ CNS involvement: 9.4% ■ Age <3y: 5.9%	13.4 (3.5-27.9)
Rubinstein, 2020 [130]	Retrospective case series	7	NR	8 (5-16)	0%	14%	NR	> 2 in 100%	■ Prim. refractory 14% ■ 1st relapse: 14% ■ 2nd relapse: 71%	■ EM disease: 100% ■ HR genetics: 14% ■ No detectable disease: 43%	NR (16-29)
Brown, 2021 [142]	Retrospective case series	14	NR	≤ 25	NR	NR	NR	NR	NR	NR	9 (3-28)
Dourthe, 2021 [122]	Prospective cohort study	51	NR	17 (1-29.2)	39%	59%	Blina: 33% Ino: 22%	3 (1-6)	■ Prim. refractory: 12% ■ Relapse: 88%	■ HR genetics: 14% ■ MRD neg: 18% ■ MRD pos: 31% ■ <5% BMB: 58% ■ 5-50% BMB: 18% ■ ≥50% BMB: 24%	15.5 (12.2-17.9)
Kadauke, 2021 [129]	Prospective two cohort open label pilot study	70	(1) Grade 4 CRS (2) ORR, DOR, EFS, safety	11.2 (1.4-29.1)	41%	36%	NR	NR	■ Prim. refractory: 20% ■ Relapsed: 80%	■ HR genetics: 37% ■ Trisomy 21: 8.6% ■ MRD neg: 39% ■ <5% BMB: 24% ■ 5-40% BMB: 16% ■ ≥40% BMB: 21%	24 (5-36)
Rossoff, 2021 [127]	Retrospective cohort study	185	(1) CR(d28) OOS vs SOC (2) OS & EFS at 6 & 12 months	10.5 vs 13 (0 – 26)	39%	25.5%	Prior CD19 directed therapy: 21%	3 (1-10)	■ Prim. refractory: 20% ■ >2nd relapse: 47% ■ Other: 33%	■ HR genetics: 32% ■ MRD neg: 36% ■ MRD pos: 49% ■ SOC: 87% ■ OOS: 13%	NR
Schultz, 2021 [128]	Retrospective cohort study	185	(1) ORR(d28) (2) OS & EFS at 6 & 12 months	12 (0-26)	40%	25%	Blina: 8% Ino: 17% CD19-CAR: 3% CD22-CAR: 2%	3 (1-10)	■ Prim. refractory: 16% ■ 1st relapse: 37% ■ 2nd relapse: 37% ■ 3rd relapse: 4% ■ > 3rd relapse: 5%	■ HR genetics: 36% ■ UD: 25% ■ <5% BMB: 22% ■ ≥5% BMB: 51% ■ CNS disease: 17% ■ SOC: 87% ■ OOS: 13%	11.4 (0.2-28.4)

Study ID	Study design	n	Primary (1) and secondary (2) end point	Age (years)†	Sex (F)	Prior HSCT	Prior therapies	Lines of prior therapy†	Disease stage	Other patient characteristics	FU‡
Dekker, 2022 [33]	Retrospective cohort study	28	(1) Effect of flu on LFS (2) BCA, CD19+/- relapse, infections	14.4 (4-24.5)	42%	42%	Blina: 27% CD19-CAR: 4%	1-2: 81% 3-5: 19%	■ Prim. refractory: 15% ■ Relapse: 85%	■ TP53 mut: 8% ■ MRD neg: 15% ■ <5% BMB: 65% ■ ≥5% BMB: 35% ■ Low flu: 42% ■ High flu: 58%	12.8 (1.7-26.3)
Fabrizio, 2022a [124]	Retrospective cohort study	184	(1) OS, RFS, BCA (2) CR(d28), toxicity, relapse rates, CD19+/- relapse	Range <1-26	40%	NR	NR	> 3 in 64-93%	■ Prim. refractory: 17% ■ ≥1 relapse: 83%	■ HR genetics ■ CNS-Cohort: 10/40 (25%) ■ Non-CNS EM: 3/15 (33%) ■ BM-only: 53/129 (41%)	11 (0-28)
Fabrizio, 2022b [123]	Retrospective cohort study	152	(1) OS, CIR, CICE (2) Response rate, CRS, ICANS	12.5 (<1-26y)	39%	5%	Prior CD19 directed therapy 22%	mean 3.5 (1-10)	■ Prim. refractory: 16% ■ ≥1 relapse: 84%	■ HR genetics: 45% ■ UD: 28% ■ LDB_<5% BMB: 22% ■ HDB_≥5% BMB: 50% ■ Low flu: 33% ■ optimal flu: 67%	13.2 (IQR 9.6-20.4)
Moskop, 2022 [123]	Retrospective case series	14	(1) CR(d28) (2) OS & EFS at 6 months, toxicity incl. CRS & ICANS	0 (0-9y)	NR	29%	Blina: 21% Ino: 21%	NR	■ Prim. refractory: 36% ■ 1st relapse: 36% ■ ≥2nd relapse: 29%	■ Only infants < 1year ■ HR genetics (KMT2Ar): 86% ■ MRDneg CR: 21% ■ MRDpos CR: 43% ■ > 5% BMB: 36%	7.6 (1.4-28.4)
Ravich, 2022 [126]	Retrospective cohort study	31	NR	7.9 (0.8-23.6)	42%	12.9%	Prior Blina, CD19-CAR or Ino: 25.8%	NR	■ Prim. refractory: 35.5% ■ 1st relapse: 45.2% ■ 2nd relapse: 16% ■ >3rd relapse: 3.2%	■ HR genetics: 61% ■ MRDneg: 10% ■ 0-5% BMB: 48% ■ >5% BMB: 42% ■ CNS3: 3.2%	12.7 (0.4-39)

Abbreviations: BCA: B-cell aplasia, Blina: Blinatumomab, BM: bone marrow, BMB: bone marrow blasts, CIBMTR: Center for International Blood and Marrow Transplant Research, CICE: cumulative incidence of composite end point (relapse or loss of B-cell aplasia), CIR: cumulative incidence or relapse, CNS: central nervous system, CRS: cytokine release syndrome, DOR: duration of response, EFS: Event-free survival, EM: extramedullary, Flu: fludarabine, Haem: haematologic, HDB: High disease burden (defined as ≥5% lymphoblasts, CNS3 and/or isolated EM disease), HR: High-risk, ICANS: immune effector cell-associated neurotoxicity syndrome, Ino: Inotuzumab, LDB: low disease burden (defined as <5% BMB, CNS disease ≤ 2, and/or no detectable EM disease), LFS: leukaemia-free survival, NR: not reported, MR: moderate risk, MRD: minimal residual disease, Neg: negative, OOS: out of specification (= beyond approved indication), ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, Prim: primary, pos: positive, PRWCC: Pediatric real-world CAR Consortium, RoB: risk of bias, r/r: refractory or relapsed, SOC: standard of care, SPM: subsequent primary malignancy, UD: undetectable disease (no disease by flow cytometry + no EM disease)

Highlighted in grey: same cohort of PRWCC

† Values for age and prior therapy are reported in median (range)

‡ Median follow up in months (range)

3.3.2 Effectiveness

(Best) ORR was reported in five studies [122, 125, 129, 130, 142] and ranged from 71% [142] to 100% [130].

Gesamtansprechrate: 71 %-100 %

CR was reported in all twelve analysed studies. CR after one month (28-30 days) was reported by nine studies [33, 122, 123, 127-130, 142] and ranged from 74% [142] to 100% [130]. Three studies did not specify the time point of CR measurement, with CR of 85.5% [125], 83.3% [126] and 66%-88% depending on subgroups [124]. Three studies differentiated between CR and CRi and reported a CRi(d28) of 50% [129], 25% [122] and 7% [142].

vollständige Ansprechrate nach 1 Monat: 74 %-100 %

Eight studies reported on an overall cohort that included all infused patients, regardless of their characteristics [33, 122, 123, 125, 126, 128, 129, 142], in which CR ranged from 74% [142] to 96% [122].

Diverse studies analysed outcomes in special subgroups. One study exclusively included patients with extramedullary disease and had a CR(d28) of 100% [130]. Another included only infants of less than one year at diagnosis and reported a CR(d28) of 64% [123]. One study compared patients receiving tisagenlecleucel beyond approved indication with standard of care tisagenlecleucel therapy and demonstrated a CR(d28) of 83% and 85%, respectively [127]. Another reported on three subgroups: patients with non-CNS extramedullary disease had a CR of 66%, patients with CNS disease 88% and those with exclusive bone marrow disease 86% [124].

One study reported a CR(d28) of 73% (95% CI, 63-81) in patients with ≥5% blasts in the BM, compared to 98% (95% CI, 87-100) in patients with <5% blasts, and 100% in the group of patients with undetectable disease before infusion (p<0.0001) [128]. Another study reported a CR(d28) of 80% in patients with ≥40% blasts versus CR(d28) of 98% in patients with <5% blasts (p= 0.029) [129].

vollständige Ansprechrate in Patient*innen < und > 5 % Knochenmarkblasten vergleichbar

In a study where the impact of fludarabine exposure for lymphodepletion on disease outcome was assessed, 55% of the patients with a low fludarabine dose (<13.5mg*h/L) achieved complete remission, compared to 93% patients with more than 13.5mg*h/L (p=0.05) [33].

Probability of continuous remission (or **duration of response DOR**) was reported by four studies [125, 127-129]. For an overall mixed real-world cohort Schultz et al. [128] and Pasquini et al. [125] reported a DOR at six months of 75% and 78.1% (95% CI, 70.5-84.0) and a DOR at 12 months of 62% and 60.9% (95% CI, 49.4-70.5) respectively. Patients who received tisagenlecleucel beyond approved indication versus patients with standard of care therapy had a DOR at six months of 79% versus 75% and at 12 months 66% versus 63%, respectively [127].

Dauer des Ansprechens nach 6 Monaten: 75 %-78,1 % nach 12 Monaten: 60,9-62 %

Patients with ≥5% blasts in bone marrow before infusion had a DOR at six months of 65% versus 91% in patients with <5% blasts and 75% in patients with undetectable disease. DOR at 12 months was 45% versus 74% and 75%, respectively [128].

Dauer des Ansprechens in Patient*innen ≥5 % Knochenmarkblasten nach 6 Monaten: 65 % nach 12 Monaten: 45 %

Patients with ≥40% blasts in bone marrow before infusion had a probability of continued remission at 12 months of 49% (95% CI, 27-88) compared to 86% (95% CI, 77-96) in patients with <5% blasts in bone marrow. At 24 months, rates were 34% (95% CI, 16-73) and 78% (95% CI, 67-91) respectively [129].

rückfallfreies Überleben nach 12 Monaten: 59,4 %

One study reported **relapse-free survival (RFS)** rates at 12 months in patients with CNS disease, non-CNS extramedullary disease and exclusive bone marrow disease of 59.4% (95% CI, 43.7-80.7), 50% (95% CI, 26.9-92.9) and 59.4% (95% CI, 50.2-70.2), respectively [124].

medianes leukämiefreies Überleben 1,8 und 12,9 Monate abhängig von Fludarabine Dosis

The median duration of **leukaemia-free survival (LFS)** was reported by one study that showed a median LFS of 1.8 months in patients that received a fludarabine dose below 14mg*h/L before infusion, compared to a median LFS of 12.9 months in patients with a dose of above 14mg*h/L [33].

ereignisfreies Überleben nach 6 Monaten: 46,9 %-68,6 %

Event-free survival (EFS) at six months was reported by five studies [123, 125-128]. Of those three reported on an overall mixed real-world cohort with EFS at six months of 46.9% (95% CI, 28.4-63.4) [126], 62% [128] and 68.6% (95% CI, 62.0-74.4) [125]. In the infant cohort an EFS at six months of 48% was reported [123]. The comparison of beyond approved indication versus standard of care treatment showed an EFS at six months of 65% versus 63% respectively [127]. Patients with ≥5% bone marrow blasts had an EFS at six months of 46% compared to 86% of patients with <5% blasts and 75% of patients with undetectable disease [128].

ereignisfreies Überleben nach 12 Monaten: 35,2 %-52,4 %

EFS at 12 months for the mixed real-world cohort was 35.2% (95% CI, 18.4-52.5) [126], 50% [128] and 52.4% (95% CI, 43.4-60.7) [125]. Patients with beyond approved indication tisagenlecleucel had an EFS at 12 months of 55% compared to 51% of patients with standard of care therapy [127]. Schultz et al. [128] and Ravich et al. [126] report for patients with ≥5% bone marrow blasts an EFS at 12 months of 31% and 15.4% (95% CI, 2.5-38.8) compared to 70% and 46.2% (95% CI, 18.2-70.4) in patients with <5% bone marrow blasts and 72% and 66.7% (95% CI, 5.4-94.5) in patients with undetectable disease respectively. Another study reported an EFS at 12 months of 42% (95% CI, 23-79) in patients with ≥ 40% bone marrow blasts compared to 86% (95% CI, 77-96) in patients with <5% blasts [129].

niedrigeres ereignisfreies Überleben in Patient*innen mit höherer Tumorlast

One study reports on EFS at 18 months for a mixed real-world cohort of 44% (95% CI, 28-59) [122]. EFS at 24 months was reported by one study with and EFS of 34% (95% CI, 16-73) in patients with ≥ 40% bone marrow blasts compared to 78% (95% CI, 67-91) in patients with <5% blasts [129]. One study reports an EFS of 57% (4 out of 7 patients) with isolated extramedullary disease after 16 to 24 months [130]. Another study reported a median EFS time of 4.3 months for a mixed overall cohort [126].

Tumorlast ≥5 % Blasten und Blinatumomab möglicherweise assoziiert mit ereignisfreiem Überleben

Determinants that have been associated with EFS in multivariate analysis were a tumour burden of ≥5% bone marrow blasts with a hazard ratio (HR) of 5.98 (95% CI, 1.10-32.4; p=0.038) [126] and a therapy with blinatumomab prior to tisagenlecleucel with a HR of 2.63 (95% CI, 1.34-6.05; P= 0.02) [122], while another study did not find a statistical significance for blinatumomab on EFS [126].

Gesamtüberlebensrate nach 6 Monaten: 80,6 %-88,5 %

Out of the twelve included studies ten provide data on overall survival (OS) [122-130]. OS at six months for mixed cohorts was reported by three studies with 80.6% (95% CI, 61.9-90.8) [126], 85% [128] and 88.5% (95% CI, 83.6-92.0) [125]. OS at six months of patients with isolated bone marrow disease was 100% [130], of the infant only cohort 71% [123], patients that received standard of care tisagenlecleucel 83% versus beyond approval treatment 96% [127]. Patients with 5% bone marrow blasts or more had an OS at six months of 75% compared to 94% in patients with <5% bone marrow blasts and 98% in patients with undetectable disease [128].

niedrigere Gesamtüberlebensrate in Patient*innen mit höherer Tumorlast

Gesamtüberlebensrate nach 12 Monaten: 67,4 %-77,2 %

OS at 12 months of mixed cohorts was reported by four studies with 67.4% (95% CI, 47.9-81.0) [126], 72% [128], 75.1% (95% CI, 67.6-82.6) [123] and 77.2% (95% CI 69.8-83.1) [125]. Seven patients with isolated extramedullary disease had an OS at 12 months of 100% [130]. In contrast patients with non-CNS extramedullary disease were reported to have an OS at 12 months of 55.8% (95% CI, 34.6-90.1) compared to 75.7% (95% CI, 62.1-92.2) in patients with CNS disease and 72.8% (64.8-81.9) in patients with exclusive bone marrow disease [124]. Patients that received tisagenlecleucel beyond the approved indication had an OS at 12 months of 85% compared to an OS of 70% in the standard of care group [127]. Three studies reported on OS at 12 months depending on tumour burden. Ravich et al. [126] and Schultz et al. [128] describe in patients with ≥5% bone marrow blasts an OS at 12 months of 38.5% (95% CI, 14.1-62.8) and 58% respectively, compared to 86.2% (95% CI, 54.9-96.4) and 85% in patients with <5% blasts and 100% and 95% in patients with undetectable disease with p-values of 0.0027 and 0.0001 respectively. In the third study patients with ≥ 40% bone marrow blasts had an OS at 12 months of 67% (95% CI, 47-95) compared to 96% (95% CI, 92-100) in the low tumour burden patients (p=0.004) [129].

Gesamtüberlebensrate nach 24 Monaten: 56,5 %

OS at 18 months was 74% (95% CI, 57-85) in one study with a mixed cohort [122] and 100% in a cohort with isolated extramedullary disease [130]. The OS at 24 months of 56.5% (95% CI, 41.8-71.2) was reported for a mixed real-world cohort [124]. Subgroup analysis showed OS at 24 months of 69.3% (95% CI, 53.4-90.1) in patients with CNS disease, 55.8% (95% CI, 34.6-90.1) in patients with non – CNS extramedullary disease and 53.3% (95% CI, 39.4-72.1) in patients with exclusive bone marrow disease [124]. Further the comparison of patients with ≥ 40% bone marrow blasts with patients with <5% blasts showed an OS at 24 months of 60% (95% CI, 40-91) versus 92% (95% CI, 85-100) (p=0.004) [129].

Tumorlast ≥5 % Blasten, Alter und Intensität von Lymphodelpetionstherapie möglicherweise assoziiert mit Gesamtüberleben

Several studies analysed determinants influencing overall survival. Three studies found that a tumour burden of ≥5% blasts impacted OS with a HR of 2.9 (95% CI, 1.2-7.0; p=0.013) [123], 4.2 (95% CI, 1.33-13.39; p=0.148) [126] and 5.10 (95% CI, 1.790-14.56; p=0.002) [128], while a fourth demonstrated a HR of 16.59 (95% CI, 2.54–108.52; p=0.003) in patients with ≥50% blasts before tisagenlecleucel infusion [122]. Further significant determinants in multivariate analysis were age at diagnosis of one to ten years with a HR of 0.34 (95% CI, 0.14-0.80; p=0.01) in one study [123], while another did not find a statistical significance on age [122]. Also a more intense lymphodepletion therapy impacted overall survival with a HR of 0.2 (95% CI, 0.1-0.8) and a p-value of 0.0144 [126] while another study did not find a statistical significant influence on overall survival [123].

BCA nach 12 Monaten: 55 %
hohe Variationsbreite in Dauer von BCA

The probability of maintaining B-cell aplasia (BCA) at six and 12 months after infusion (in patients that had achieved CR) was reported to be 66% and 55% respectively, for a mixed cohort [128]. Another reported on a cumulative incidence of BCA as time from CR/CRi to loss of BCA with relapse and death as competing events with 33% at three months, 48% at six months and 55% at 12 months [122]. A third study reported on a median time of BCA of 2.8 months with a range of 0.7 to 31.1 months [126].

kürzere BCA Dauer in Patient*innen mit höherer Tumorlast

In subgroup analysis patients with ≥5% bone marrow blasts before infusion had a probability of maintaining BCA at six months post infusion of 60% compared to 68% of patients with <5% blasts and 72% in patients with undetectable disease and at 12 months 45%, 60% and 68% respectively [128]. Patients with ≥40% blasts had a probability of BCA at six months of 69%

(95% CI, 40-100) compared to 65% (95% CI, 54-80) in patients with <5% blasts [129]. Patients with CNS disease had a 12-month duration of B-cell-aplasia (from infusion) of 66.4% (95% CI, 49.3-89.5), patients with extramedullary non-CNS disease of 38.9% (95% CI, 14.8-100) and patients with exclusive bone marrow disease of 59.4% (95% CI, 49.7-71) [124]. The infant cohort had a median duration of B-cell aplasia of 171 days [123]. Dekker et al. reported a six months B-cell recovery of 77.3% (BCA maintained in 22.7%) in patients with a low fludarabine area under the curve (<14mg*h/L) compared to 37.3% (BCA maintained in 63,7%) in patients with ≥ 14mg*h/L (p=0.009) [33]

Rückfallrate: 28 %-48 %

The rate of **relapsed** patients at end of follow-up was reported by eight studies. While rates ranged from 28% [129] to 48% [126] in the five studies that reported on a mixed cohort [122, 123, 126, 128, 129], patients with isolated extramedullary had a relapse rate of 29% [130] and infants of 33% [123]. Patients with CNS disease had a relapse rate of 42% compared to non-CNS extramedullary disease of 60% and exclusive bone marrow disease of 41% [124]. Patients with ≥ 40% bone marrow blasts had a relapse in 85% of cases compared to 31% of patients with <5% blasts [129].

höhere Rückfallrate in Patient*innen mit höherer Tumorlast

One study associated the suboptimal fludarabine exposure for lymphodepletion prior to tisagenlecleucel with an increased risk of relapse (HR=2.45, p=0.05) [123] and another reported a cumulative incidence of CD19 positive relapse within a year of 100% in patients with suboptimal fludarabine compared to 27.4% in patients with adequate fludarabine dosage (p=0.0001) [33].

keine Untersuchung der Lebensqualität

HRQoL was not reported in any of the analysed studies. One study reports that the inclusion criteria for the study was a minimum Lansky/Karnofsky score [129] and one study states that the score was measured [142], but none of those studies provides results on the score.

Effectiveness outcomes of included studies are displayed in Table 3-2.

Table 3-2: Results on effectiveness of RWE studies (B-ALL)

Study ID	n	CR (95% CI)	ORR	OS				EFS				Relapse % of CR
				6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	
Pasquini, 2020 [125]	255	85.5% (80.6-89.75)	85.5%	88.5% (83.6-92)	77.2% (69.8-83.1)	NR	NR	68.6% (62-74.4)	52.4% (43.4-60.7)	NR	NR	NR
Rubinstein, 2020 [130]	EM disease only 7	100%	100%	100%	100%	100%	NR	NR	NR	57%	NR	29%
Brown, 2021 [142]	14	CR(d30): 64% CRi(d30): 7%	71%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dourthe, 2021 [122]	51	CR(d28): 71% CRi(d28): 25%	96%	NR	NR	74% (57-85)	NR	NR	NR	44% (28-59%)	NR	45%
Kadauke, 2021 [129]	Overall: 70 HTB (≥ 40%): 15 LTB (<5%): 55	Overall: 94% HTB: 80% LTB: 98%	(Best) overall: 97% HTB: 87% LTB: 100%	NR	Overall: NR HTB: 67% (47-95) LTB: 96% (92-100)	NR	Overall: NR HTB: 60% (40-91) LTB: 92% (85-100)	NR	NR	HTB: 42% (23-79) LTB: 86% (77-96)	HTB: 34% (16-73) LTB: 78% (67-91)	Overall: 28% HTB: 85% LTB: 31%
Rossoff, 2021 [127]	Overall: 185 OOS: 24 SOC: 161	OOS: 83% SOC: 85%	NR	OOS: 96% SOC: 83%	OOS: 85% SOC: 70%	NR	NR	OOS: 65% SOC: 63%	OOS: 55% SOC: 51%	NR	NR	NR
Schultz, 2021 [128]	Overall: 185 HTB (≥5%): 94 LTB (<5%): 41 UD (MRD neg): 46	Overall: 85% (79-89) HTB: 73% (63-81) LTB: 98% (87-100) UD: 100%	NR	Overall: 85% HTB: 75% LTB: 94% UD: 98%	Overall: 72% HTB: 58% LTB: 85% UD: 95%	NR	NR	Overall: 62% HTB: 46% LTB: 86% UD: 75%	Overall: 50% HTB: 31% LTB: 70% UD: 72%	NR	NR	37%
Dekker, 2022 [33]	Overall: 26 Low Flu: 11 High Flu: 15	Overall: 77% Low Flu: 55% High Flu: 93%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Fabrizio, 2022a [124]	Overall: 184 CNS: 40 Non-CNS EM: 15 BM only: 129	CNS: 88% Non-CNS EM: 66% BM only: 86%	NR	NR	CNS: 75.7% (62.1-92.2) Non-CNS EM: 55.8% (34.6-90.1) BM only: 72.8% (64.8-81.9)	NR	CNS: 69.3% (53.4-90.1) Non-CNS EM: 55.8% (34.6-90.1) BM only: 53.3% (39.4-72.1)	NR	NR	NR	NR	CNS: 42% Non-CNS EM:60% BM only: 41%

Study ID	n	CR (95% CI)	ORR	OS				EFS				Relapse % of CR
				6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	
Fabrizio, 2022b [123]	152	86%	NR	NR	75.1% (67.6-82.6)	NR	56.5% (41.8-71.2)	NR	NR	NR	NR	40%
Moskop, 2022 [123]	Infants only 14	64%	NR	71%	NR	NR	NR	48%	NR	NR	NR	33%
Ravich, 2022 [126]	Overall: 31 HTB (≥5%): 13 LTB (0-5%): 15 UD (MRD neg): 3	83.3%	NR	80.6% (61.9-90.8)	Overall: 67.4% (47.9-81) HTB: 38.5% (14.1-62.8) LTB: 86.2% (54.9-96.4) UD: 100%	NR	NR	46.9% (28.4-63.4)	Overall: 35.2% (18.4-52.5) HTB: 15.4% (2.5-38.8) LTB: 46.2% (18.2-70.4) UD: 66.7% (5.4-94.5)	NR	NR	48%

Abbreviations: BM: bone marrow, CNS: central nervous system, CR: complete remission, EFS: Event-free survival, EM: extramedullary, HTB: high tumour burden, LTB: low tumour burden, Neg: negative, NR: not reported, MRD: minimal residual disease, OOS: out of specification (= beyond approved indication), ORR: Overall survival, SOC: standard of care, UD: undetectable disease

Highlighted in grey: same cohort of PRWCC

3.3.3 Safety

All twelve studies provide information on at least a part of severe adverse events (SAE). Eleven studies [122-130, 142] reported on the occurrence of cytokine release syndrome (CRS) and neurotoxicity (ICANS).

12 Studien berichten Sicherheitsendpunkte
11 Studien berichten CRS, ICANS

The prevalence of any CRS in seven studies that reported on a mixed real-world cohort [122, 123, 125, 126, 128, 129, 142] ranged from 54.9% [125] to 86% [142] and for CRS ≥ grade 3 from 16.1% [125] to 22% [123]. The occurrence of neurotoxicity in this cohort ranged from 21% [128] to 36% [142] and ≥ grade 3 neurotoxicity from 7% [128] to 29% [142].

CRS: 54,9 %-86 %,
≥ Grad 3: 16,1 %-22 %
ICANS: 21 %-36 %,
≥ Grad 3: 7 %-29 %

Patients with isolated extramedullary disease experienced CRS in 42% of cases and grade 3 or 4 CRS in 14% while neurotoxicity did not occur [130]. Infants experienced CRS in 79% of cases with 21% ≥ grade 3 CRS and no neurotoxicity [123]. The comparison of patients with CNS-disease, non-CNS extramedullary disease and exclusive bone marrow disease showed CRS in 63%, 80% and 61% of cases and neurotoxicity in 35%, 13% and 17% of cases, respectively [124]. Patients that received tisagenlecleucel beyond approved indication suffered from CRS in 46% of cases with ≥ grade 3 CRS in 17% of cases and 8% suffered from neurotoxicity while patients with standard of care tisagenlecleucel experienced CRS in 61% of cases, ≥ grade 3 CRS in 19% and neurotoxicity in 22% of cases [127].

CRS in Säuglingen:
79 %, ≥ Grad 3: 21 %

CRS und ICANS verschieden in unterschiedlichen Subgruppen

One study reports on CRS and neurotoxicity depending on tumour burden. While patients with ≥40% bone marrow blasts experienced any CRS in 100% and ≥ grade 3 CRS in 60% of cases, patients with <5% blasts suffered in 67% of cases from any CRS and in 5% from ≥ grade 3 CRS. Neurotoxicity occurred in patients with high tumour burden in 60% and ≥ grade 3 neurotoxicity in 20% compared to 18% and 4% respectively in the low tumour burden cohort [129].

CRS und ICANS abhängig von Tumorlast

Other severe adverse events than CRS and neurotoxicity were reported in eight studies [33, 122, 123, 125-129]. Infections were reported by six studies [33, 123, 125-128] and ranged from 37% [127] to 54% [33]. Cytopenias were reported by five studies as “prolonged cytopenia” (27.8%) [125], “decreased neutrophil count” (54%) [129], “neutropenia grade ≥3 (d28)” (37%) [122] and “Neutropenia grade 4” (66% and 67% in [123] and [128] respectively). “Decreased platelet count” was reported in 27% [129] and “thrombocytopenia Grade ≥ 3 (d28”) in 37% [122] of patients while anaemia occurred in 14% of patients [129].

andere unerwünschte Ereignisse: Infektionen, Zytopenien

Paediatric intensive care unit (PICU) – admission was reported by two studies with rates of 35% [122] and 31% [128]. One study reported on the occurrence of tumour lysis syndrome with 7% [128] and another on CAR-T associated haemophagocytic lymphohistiocytosis (HLH) with 6.5% [126].

Patient*innen auf der Intensivstation: 31 %-35 %

Nine publications reported on mortality of patients [123-130] that ranged from 0% [130] to 42% [126]. Two studies reported on mortality within 30 days after infusion, which was 3% each [125, 127].

Mortalität: 0-42 %

Treatment-related death was not clearly defined in any study. Therefore, in this report, cases were counted as ‘treatment-related’, if death occurred from severe adverse events most likely caused by tisagenlecleucel (severe CRS or neurotoxicity, sepsis or infection, organ failure or HLH in proximity to the therapy). Those rates could be extracted from eight publications [122-126, 128, 130] and ranged from 0% [130] to 6.5% [126].

behandlungsassoziierte Mortalität: 0-6,5 %

Safety outcomes are displayed in Table 3-3.

Table 3-3: Results on safety of RWE studies (B-ALL)

First Author, Year	n	CRS overall	CRS ≥ Grade 3	Neurotoxicity	Neurotoxicity ≥ Grade 3	Mortality	Treatment-related death	Other SAE	
Pasquini, 2020 [125]	255	54.9%	16.1%	27.1%	9%	Death within 30 days post infusion: 3.1%	0.4-2%	Hypogammaglobulinemia: 52.5% Prolonged cytopenia: 27.8% Clinically significant infections: 46.3% Grade 3/4 organ toxicities: 8.2% Secondary malignancies: 2.4% Deaths overall: 18.4%	
Rubinstein, 2020 [130]	7	42%	14%	0%	0%	0%	0%	NR	
Brown, 2021 [142]	14	86%	NR	36%	29%	NR	NR	NR	
Dourthe, 2021 [122]	51	59%	20%	24%	8%	NR	2%	ICU admission: 35% Neutropenia Grade ≥ 3 (d28): 37% Thrombocytopenia Grade ≥ 3 (d28): 37%	
Kadauke, 2021 [129]	Overall: 70 HTB (≥ 40%): 15 LTB (<5%): 55	Overall: 74% HTB: 100% LTB: 67%	Overall: 17% HTB: 60% LTB: 5%	Overall: 27% HTB: 60% LTB: 18%	Overall: 7% HTB: 20% LTB: 4%	17%	NR	Hypoxia: 13% Hypophosphatemia: 14% AST ↑: 14% Anorexia: 7.1% Fibrinogen ↓: 4.3% Hypotension: 11% Acidosis: 5.7% Bilirubin ↑: 5.7% Anaemia: 14% aPTT↑: 4.3% Hyperglycaemia: 4.3% Hyperkalaemia: 4.3%	Lymphocytes ↓: 60% Hypokalaemia: 11% ALT ↑: 13% Fever: 5.7% URT infection: 4.3% Encephalopathy: 5.7% Neutrophiles ↓: 54% Leukocytes ↓: 54% Platelet count ↓: 27%
Rossoff, 2021 [127]	Overall: 185 OOS: 24 SOC: 161	OOS: 46% SOC: 61%	OOS: 17% SOC: 19%	OOS: 8% SOC: 22%	NR	Death before day 28 post infusion: 3%	NR	Infections: ■ OOS: 54% ■ SOC: 37%	
Schultz, 2021 [128]	185	63%	21%	21%	7%	27.5%	4.3%	Neutropenia grade 4: 67% Tumour lysis syndrome: 7% Infectious complication: 40% PICU-Stay: 31%	

First Author, Year	n	CRS overall	CRS ≥ Grade 3	Neurotoxicity	Neurotoxicity ≥ Grade 3	Mortality	Treatment-related death	Other SAE
Dekker, 2022 [33]	26	NR	NR	NR	NR	NR	NR	Infection: 54%
Fabrizio, 2022a [124]	Overall: 184 CNS: 40 Non-CNS EM: 15 BM only: 129	CNS: 63% non-CNS EM: 80% BM only: 61%	NR	CNS: 35% Non-CNS EM: 13% BM only: 17%	NR	27.7%	4.3%	NR
Fabrizio, 2022b [123]	152	64%	22%	24%	8%	26.3%	5%	Infection: 38% Grade 4 neutropenia: 66%
Moskop, 2022 [123]	14	79%	21%	0%	0%	29%	0%	NR
Ravich, 2022 [126]	31	61.3%	19%	29%	10%	42%	6.5%	Therapy associated HLH: 6.5% Late onset bacteraemia: 6.5%

Abbreviations: BM: bone marrow, CNS: central nervous system, CRS: cytokine release syndrome, EM: extramedullary, HTB: high tumour burden, LTB: low tumour burden, Neg: negative, NR: not reported, MRD: minimal residual disease, OOS: out of specification (= beyond approved indication), SAE: serious adverse events, SOC: standard of care, UD: undetectable disease
Highlighted in grey: same cohort of PRWCC

3.4 B-ALL: Comparison of Results from observational studies (RWE) with pivotal trials

3.4.1 Study and patient characteristics

Unterschiede in Kohortengröße

In the analysed real-world studies, the number of patients with r/r B-ALL infused with tisagenlecleucel ranged from seven in a case series to 255 in a multicentred cohort study, while in ELIANA 75 patients were infused with tisagenlecleucel.

medianes Alter in Zulassungsstudien tendentiell etwas niedriger

The median age at infusion ranged from zero (<1 year) to 17 years with a rage of less than one year to 29.2 years across real-world studies. Patients included in ELIANA had a median age of eleven years with a range of three to 23 years. The sex ratio was comparable between ELIANA with 43% female participants and 39%-42% female participants in the real-world cohort.

restriktivere Zulassungskriterien in ELIANA

Patient*innen <3 Jahren, <5 % Lymphoblasten, CNS Involvierung, extramedullärem Befall und vorheriger CD19/22 Therapie in ELIANA exkludiert

ELIANA had generally more restrictive inclusion and exclusion criteria than the real-world studies. In ELIANA, patients under the age of three years were excluded, while nine real-world studies included those patients in their report [122-129]. Further, ELIANA included only patients with ≥ 5% lymphoblasts at infusion, while eight real-world studies also included patients that had <5% lymphoblasts [33, 122, 123, 125, 126, 128, 129] and ten reported MRD negativity at time of infusion [33, 122, 123, 125-130]. Patients with isolated extramedullary disease, relapse or active CNS involvement were excluded from ELIANA, while in the clinical setting those patients are treated with tisagenlecleucel. Two studies explicitly report on patients with extramedullary disease [124, 130] and four on CNS involvement [124-126, 128] while also other studies included those patients in their cohort. Further, patients that received prior anti CD19 or anti CD22 therapy were excluded from ELIANA, while eight of the analysed real-world studies report on prior CD19 or CD22 directed therapy [33, 122, 123, 125-128] ranging from 2% to 33% of patients.

mediane Therapieanzahl vor CAR-T: 3 (ELIANA und RWE)

Patients in ELIANA had a median of three prior therapies (range one to eight) which was similar in real-world studies in which the median of prior therapies was reported (median three, range zero to 15) [122, 125, 127, 128].

Vorherige HSCT 61 % (ELIANA) vs. 5 %-59 % (RWE)

61% of patients in ELIANA had undergone prior alloHSCT, while in real-world studies percentages of patients who had undergone prior HSCT ranged from 5% to 59% [33, 122, 123, 125-130].

medianer Nachbeobachtungszeitraum in ELIANA und RWE meist ähnlich

The median follow-up in ten real-world studies ranged from 7.6 months to 24 months [33, 122-126, 128, 129, 142] while in ELIANA the median follow-up was 13.1 months.

verschiedene aber vergleichbare Definitionen der Ergebnisse und Endpunkte

Primary endpoint in ELIANA was overall remission rate (ORR) and secondary endpoints included CR, CRi, DOR, EFS, OS, cellular kinetics (BCA) and safety. In real-world studies similar or comparable endpoints were defined.

Several differences in definitions of outcomes were observed between ELIANA and throughout the real-world studies, however definitions of outcomes were somewhat comparable.

verschiedene Bewertungssysteme der unerwünschten Ereignisse

Grading for CRS was performed in RWE studies with ASTCT and Penn scale and grading for ICANS with ASTCT, CTCAE, and other institutional standards. ELIANA used Penn/CHOP scale for CRS and CTCAE V 4.03 for ICANS.

For detailed information, see Table 3-4.

Table 3-4: Comparison of study characteristics between pivotal studies and RWE studies (B-ALL)

First author, Year	Study design	n	Primary (1) and secondary (2) end point	Age (years)†	Sex (F)	Prior HSCT	Prior therapies	Lines of prior therapy†	Disease stage	Other patient characteristics	FU‡
Maude, 2018 [55]	Phase 2, single cohort, multicentre prospective study	75	(1) ORR (2) CR, CRi, DOR, EFS, OS, cellular kinetics (BCA), safety	11 (3-23)	43%	61%	■ Prior bridging therapy 87% ■ Prior lymphodepletion 96%	3 (1-8)	■ Prim. refractory: 8% ■ Chemo-refractory or relapsed: 92%	■ CNS1: 84%; CNS2: 13%; CNS3: 1% ■ HR genetics: 37% ■ Down syndrome: 8% ■ < 50% BMB: 32% ■ ≥ 50% BMB: 68%	13.1, Min 3
Laetsch, 2019 [56]	Phase 2, single cohort, multicentre prospective study	58	HRQoL	8-23y	43%	60%	NR	NR	■ Prim. refractory: 9% ■ Chemo-refractory or relapsed: 91%	■ Responder to treatment n= 48 ■ Non-responder n=10	9.9 IQR 5.3-15.3
Pasquini, 2020 [125]	Prospective observational cohort study	255	CRS, ICANS, SPM, haematologic recovery, ORR, DOR, EFS, PFS, OS	13.2 (0.4-26.2)	41%	28%	■ Blina: 14.9% ■ Ino: 10.6%	3 (0-15)	Prim. r/r: 62.3%	■ HR genetics: 18% ■ Down syndrome: 4.7% ■ MRD neg: 17.3% ■ No BMB: 28% ■ 0-<5% BMB: 20% ■ ≥ 5% BMB: 33% ■ CNS involvement: 9.4% ■ Age <3y: 5.9%	13.4 (3.5-27.9)
Rubinstein, 2020 [130]	Retrospective case series	7	NR	8 (5-16)	0%	14%	NR	> 2 in 100%	■ Prim. refractory 14% ■ 1st relapse: 14% ■ 2nd relapse: 71%	■ EM disease 100% ■ HR genetics 14% ■ No detectable disease 43%	Range 16-29
Brown, 2021 [142]	Retrospective case series	14	NR	≤ 25	NR	NR	NR	NR	NR	NR	9 (3-28)
Dourthe, 2021 [122]	Prospective cohort study	51	NR	17 (1-29.2)	39%	59%	■ Blina: 33% ■ Ino: 22%	3 (1-6)	■ Prim. refractory: 12% ■ Relapse: 88%	■ HR genetics: 14% ■ MRD neg: 18% ■ MRD pos: 31% ■ <5% BMB: 58% ■ 5-50% BMB: 18% ■ ≥50% BMB: 24%	15.5 (12.2-17.9)
Kadauke, 2021 [129]	Prospective two cohort open label pilot study	70	(1) Grade 4 CRS (2) ORR, DOR, EFS, safety	11.2 (1.4-29.1)	41%	36%	NR	NR	■ Prim. refractory: 20% ■ Relapsed: 80%	■ HR genetics: 37% ■ Trisomy 21: 8.6% ■ MRD neg: 39% ■ <5% BMB: 24% ■ 5-40% BMB: 16% ■ ≥40% BMB: 21%	24 (5-36mo)

First author, Year	Study design	n	Primary (1) and secondary (2) end point	Age (years)†	Sex (F)	Prior HSCT	Prior therapies	Lines of prior therapy†	Disease stage	Other patient characteristics	FU‡
Rossoff, 2021 [127]	Retrospective cohort study	185	(1) CR(d28) OOS vs SOC (2) OS & EFS at 6 & 12 months	10.5 vs 13 (0 – 26)	39%	25.5%	Prior CD19 directed therapy: 21%	3 (1-10)	■ Prim. refractory: 20% ■ >2nd relapse: 47% ■ Other: 33%	■ HR genetics: 32% ■ MRD neg: 36% ■ MRD pos: 49% ■ SOC: 87% ■ OOS: 13%	NR
Schultz, 2021 [128]	Retrospective cohort study	185	(1) ORR(d28) (2) OS & EFS at 6 & 12 months	12 (0-26)	40%	25%	■ Blina: 8% ■ Ino: 17% ■ CD19-CAR: 3% ■ CD22-CAR: 2%	3 (1-10)	■ Prim. refractory: 16% ■ 1st relapse: 37% ■ 2nd relapse: 37% ■ 3rd relapse: 4% ■ > 3rd relapse: 5%	■ HR genetics: 36% ■ UD: 25% ■ <5% BMB: 22% ■ ≥5% BMB: 51% ■ CNS disease: 17% ■ SOC: 87% ■ OOS: 13%	11.4 (0.2-28.4)
Dekker, 2022 [33]	Retrospective cohort study	28	(1) Effect of flu on LFS (2) BCA, CD19+/- relapse, infections	14.4 (4-24.5)	42%	42%	■ Blina: 27% ■ CD19-CAR: 4%	■ 1-2: 81% ■ 3-5: 19%	■ Prim. refractory: 15% ■ Relapse: 85%	■ TP53 mut: 8% ■ MRD neg: 15% ■ <5% BMB: 65% ■ ≥5% BMB: 35% ■ Low flu: 42% ■ High flu: 58%	12.8 (1.7-26.3)
Fabrizio, 2022a [124]	Retrospective cohort study	184	(1) OS, RFS, BCA (2) CR(d28), toxicity, relapse rates, CD19+/- relapse	Range <1-26	40%	NR	NR	> 3 in 64-93%	■ Prim. refractory: 17% ■ ≥1 relapse: 83%	■ HR genetics ■ CNS-Cohort: 10/40 (25%) ■ non-CNS EM: 3/15 (33%) ■ BM-only: 53/129 (41%)	11 (0-28)
Fabrizio, 2022b [123]	Retrospective cohort study	152	(1) OS, CIR, CICE (2) Response rate, CRS, ICANS	12.5 (<1-26y)	39%	5%	Prior CD19 directed therapy 22%	Mean 3.5 (1-10)	■ Prim. refractory: 16% ■ ≥1 relapse: 84%	■ HR genetics: 45% ■ UD: 28% ■ LDB_<5% BMB: 22% ■ HDB_≥5% BMB: 50% ■ Low flu: 33% ■ Optimal flu: 67%	13.2 (IQR 9.6-20.4)
Moskop, 2022 [123]	Retrospective case series	14	(1) CR(d28) (2) OS & EFS at 6 months, toxicity incl. CRS & ICANS	0 (0-9y)	NR	29%	■ Blina: 21% ■ Ino: 21%	NR	■ Prim. refractory: 36% ■ 1st relapse: 36% ■ ≥2nd relapse: 29%	■ Only infants < 1year ■ HR genetics (KMT2Ar): 86% ■ MRDneg CR: 21% ■ MRDpos CR: 43% ■ > 5% BMB: 36%	7.6 (1.4-28.4)

First author, Year	Study design	n	Primary (1) and secondary (2) end point	Age (years)†	Sex (F)	Prior HSCT	Prior therapies	Lines of prior therapy†	Disease stage	Other patient characteristics	FU‡
Ravich, 2022 [126]	Retrospective cohort study	31	NR	7.9 (0.8-23.6)	42%	12.9%	Prior Blina, CD19-CAR or Ino: 25.8%	NR	■ Prim. refractory: 35.5% ■ 1st relapse: 45.2% ■ 2nd relapse: 16% ■ >3rd relapse: 3.2%	■ HR genetics: 61% ■ MRDneg: 10% ■ 0-5% BMB: 48% ■ >5% BMB: 42% ■ CNS3: 3.2%	12.7 (0.4-39)

Abbreviations: BCA: B-cell aplasia, Blina: Blinatumomab, BM: bone marrow, BMB: bone marrow blasts, CIBMTR: Center for International Blood and Marrow Transplant Research, CICE: cumulative incidence of composite end point (relapse or loss of B-cell aplasia), CIR: cumulative incidence or relapse, CNS: central nervous system, CRS: cytokine release syndrome, DOR: duration of response, EFS: Event-free survival, EM: extramedullary, Flu: fludarabine, Haem: haematologic, HDB: High disease burden (defined as ≥5% lymphoblasts, CNS3 and/or isolated EM disease), HR: High-risk, ICANS: immune effector cell-associated neurotoxicity syndrome, Ino: Inotuzumab, LDB: low disease burden (defined as <5% BMB, CNS disease ≤ 2, and/or no detectable EM disease), LFS: leukaemia-free survival, NR: not reported, MR: moderate risk, MRD: minimal residual disease, Neg: negative, OOS: out of specification (= beyond approved indication), ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, Prim: primary, pos: positive, PRWCC: Pediatric real-world CAR Consortium, RoB: risk of bias, r/r: refractory or relapsed, SOC: standard of care, SPM: subsequent primary malignancy, UD: undetectable disease (no disease by flow cytometry + no EM disease)

Highlighted in green: Pivotal studies; Highlighted in grey: same cohort of PRWCC

† Values for age and prior therapy are reported in median (range)

‡ Median follow up in months (range)

3.4.2 Effectiveness/Efficacy

Gesamtansprechrate 81 % (ELIANA) vs. 71 %-100 % (RWE)

Best overall response rate (ORR) within three months was 81% (95% CI, 71-89) in ELIANA while in the five RWE studies that reported on ORR, it ranged from 71% to 100% [122, 125, 129, 130, 142].

vollständige Ansprechrate

Complete remission (CR) at day 28, was reached by 80% of patients (31% with haematologic recovery, 49% with incomplete haematological recovery) in ELIANA. In real-world studies CR(d28) ranged from 74% to 100% [33, 122, 123, 127-130, 142]. Three studies reported a CRi(d28) of 7% to 50% [122, 129, 142].

ähnliches rückfallfreies Überleben bei Patient*innen in CR

In ELIANA, among the 61 patients who achieved CR, the relapse free survival (RFS) at six months was 80% (95% CI, 65-89) and at 12 months 59% (95% CI, 41-73). Two real-world studies defined RFS similarly as ELIANA. One reported a RFS at six months of 78.1% (95% CI, 70.5-84) and at 12 months 60.9% (95% CI, 49.4-70.5) [125]. The other differentiated between patients with high (≥ 40% blasts in bone marrow) and low (< 5% blasts in bone marrow) tumour burden before infusion and reported a RFS at 12 months of 49% (95% CI, 27-88) and at 24 months of 39% (95% CI, 19-82) in the high tumour burden group, compared to 86% (95% CI, 77-96) at 12 months and 78% (95% CI, 67-91) at 24 months in patients with low tumour burden [129].

Unterschiede im ereignisfreien Überleben zwischen Subgruppen

Event-free survival (EFS) among the 75 patients who received tisagenlecleucel infusion in ELIANA was 73% (95% CI, 60-82) at six months and 50% (95% CI, 35-64) at 12 months while median event-free survival was not reached. In RWE studies six months EFS ranged from 46%-86% depending on the subgroup [123, 125-128]. 12 months EFS ranged from 31%-72% depending on analysed cohort [125-128]. EFS at 18 months of 44% (95% CI, 28-59%) was reported for a mixed real-world cohort [122] and EFS at 24 months was reported by one study with an EFS of 34% (95% CI, 16-73) in patients with ≥ 40% bone marrow blasts compared to 78% (95% CI, 67-91) in patients with <5% blasts before infusion [129].

heterogene Gesamtüberlebensraten in RWE

The overall survival (OS) rate at six months was 90% (95% CI, 81-95) and at 12 months after infusion 76% (95% CI, 63 to 86) in ELIANA. In RWE studies OS at six months ranged from 71%-100% [123, 125-128, 130]. OS at 12 months ranged from 38.5% (95% CI, 14.1-62.8) to 100% depending on subgroup [123-130]. Two studies reported on OS at 18 months with 74% (95% CI, 57-85) in a mixed cohort [122] and 100% in a cohort with isolated extramedullary disease [130]. 24 months OS ranged from 53.3% (95% CI, 39.4-72.1) to 92% (95% CI, 85-100) in different cohorts [123, 124, 129].

heterogene BCA Dauer in RWE

The probability of maintenance of B-cell aplasia (BCA) at six months after infusion was 83% (95% CI, 69 to 91) in ELIANA. In RWE definition of maintenance of B-cell aplasia varied in terms of time point measured but also in quantity of B-cells for defining loss of B-cell aplasia. However, in analysed studies maintenance of BCA at six months ranged from 22.7% to 72% depending on subgroup. At 12 months BCA was maintained in 38.9% to 68% in varying cohorts.

breite Range der Rückfallrate in RWE

The rate of relapsed patients at the end of follow up ranged from 28%-100% in RWE depending on analysed cohort, while 36% of patients that had achieved CR relapsed at the end of follow-up in the ELIANA trial.

kein Vergleich der Lebensqualität zwischen ELIANA und RWE möglich

In ELIANA quality of life (HRQoL) improved in 81% of patients measured with the PedsQL and in 67% of patients measured with EQ-5D visual analogue scale. No study on RWE reported on HRQoL.

For detailed information, see Table 3-5.

Table 3-5: Comparison of effectiveness/efficacy outcomes between pivotal trials and RWE studies (B-ALL)

First author, Year	n	CR (95% CI)	ORR (95% CI)	OS				EFS				Relapse % of CR
				6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	
Maude, 2018 [55]	75	80%	81% (71-89)	90% (81-95)	76% (63-86)	NR	NR	73% (60-82)	50% (35-64)	NR	NR	36%
Laetsch, 2019 [56]	58	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pasquini, 2020 [125]	255	85.5% (80.6-89.75)	85.5%	88.5% (83.6-92)	77.2% (69.8-83.1)	NR	NR	68.6% (62-74.4)	52.4% (43.4-60.7)	NR	NR	NR
Rubinstein, 2020 [130]	EM disease only 7	100%	100%	100%	100%	100%	NR	NR	NR	57%	NR	29%
Brown, 2021 [142]	14	CR(d30): 64% CRi(d30): 7%	71%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dourthe, 2021 [122]	51	CR(d28): 71% CRi(d28): 25%	96%	NR	NR	74% (57-85)	NR	NR	NR	44% (28-59%)	NR	45%
Kadauke, 2021 [129]	Overall: 70 HTB (≥ 40%): 15 LTB (<5%): 55	Overall: 94% HTB: 80% LTB: 98%	(Best) overall: 97% HTB: 87% LTB: 100%	NR	Overall: NR HTB: 67% (47-95) LTB: 96% (92-100)	NR	Overall: NR HTB: 60% (40-91) LTB: 92% (85-100)	NR	NR	HTB: 42% (23-79) LTB: 86% (77-96)	HTB: 34% (16-73) LTB: 78% (67-91)	Overall: 28% HTB: 85% LTB: 31%
Rossoff, 2021 [127]	Overall: 185 OOS: 24 SOC: 161	OOS: 83% SOC: 85%	NR	OOS: 96% SOC: 83%	OOS: 85% SOC: 70%	NR	NR	OOS: 65% SOC: 63%	OOS: 55% SOC: 51%	NR	NR	NR
Schultz, 2021 [128]	Overall: 185 HTB (≥5%): 94 LTB (<5%): 41 UD (MRD neg): 46	Overall: 85% (79-89) HTB: 73% (63-81) LTB: 98% (87-100) UD: 100%	NR	Overall: 85% HTB: 75% LTB: 94% UD: 98%	Overall: 72% HTB: 58% LTB: 85% UD: 95%	NR	NR	Overall: 62% HTB: 46% LTB: 86% UD: 75%	Overall: 50% HTB: 31% LTB: 70% UD: 72%	NR	NR	37%
Dekker, 2022 [33]	Overall: 26 Low Flu: 11 High Flu: 15	Overall: 77% low Flu: 55% high Flu: 93%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

First author, Year	n	CR (95% CI)	ORR (95% CI)	OS				EFS				Relapse % of CR
				6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	6mo (95% CI)	12mo (95% CI)	18mo (95% CI)	24mo (95% CI)	
Fabrizio, 2022a [124]	Overall: 184 CNS: 40 non-CNS EM: 15 BM only: 129	CNS: 88% Non-CNS EM: 66% BM only: 86%	NR	NR	CNS: 75.7% (62.1-92.2) Non-CNS EM: 55.8% (34.6-90.1) BM only: 72.8% (64.8-81.9)	NR	CNS: 69.3% (53.4-90.1) Non-CNS EM: 55.8% (34.6-90.1) BM only: 53.3% (39.4-72.1)	NR	NR	NR	NR	CNS: 38% Non-CNS EM: 40% BM only: 35%
Fabrizio, 2022b [123]	152	86%	NR	NR	75.1% (67.6-82.6)	NR	56.5% (41.8-71.2)	NR	NR	NR	NR	40%
Moskop, 2022 [123]	Infants only 14	64%	NR	71%	NR	NR	NR	48%	NR	NR	NR	21%
Ravich, 2022 [126]	Overall: 31 HTB (≥5%): 13 LTB (0-5%): 15 UD (MRD neg): 3	83.3%	NR	80.6% (61.9-90.8)	Overall: 67.4% (47.9-81) HTB: 38.5% (14.1-62.8) LTB: 86.2% (54.9-96.4) UD: 100%	NR	NR	46.9% (28.4-63.4)	Overall: 35.2% (18.4-52.5) HTB: 15.4% (2.5-38.8) LTB: 46.2% (18.2-70.4) UD: 66.7% (5.4-94.5)	NR	NR	48%

Abbreviations: BM: bone marrow, CNS: central nervous system, CR: complete remission, EFS: Event-free survival, EM: extramedullary, HTB: high tumour burden, LTB: low tumour burden, Neg: negative, NR: not reported, MRD: minimal residual disease, OOS: out of specification (= beyond approved indication), ORR: Overall survival, SOC: standard of care, UD: undetectable disease

Highlighted in green: Pivotal studies; highlighted in grey: same cohort of PRWCC

3.4.3 Safety

detailliertere Sicherheitsdaten in Zulassungsstudien

In ELIANA adverse events of any grade were reported in all 75 patients (100%) of which in 71 patients (95%) those were suspected to be related to tisagenlecleucel. The adverse events in real-world studies mainly focus on cytokine release syndrome (CRS) and neurotoxicity (ICANS).

CRS und ICANS in RWE und Zulassungsstudien

CRS occurred in 77%, grade ≥3 in 47% of patients included in ELIANA. In RWE, overall CRS ranged from 42%-86% [122-130, 142] and grade ≥3 in 14% to 22% of patients [122, 123, 125-130]. Neurologic events occurred in 40% of patients and 13% of patients had a grade 3 neurologic events, while no grade 4 events or cerebral oedema occurred in ELIANA. In RWE, neurotoxicity ranged from 0% to 36% [122-130, 142] and grade ≥3 neurotoxicity from 0% to 29% [122, 125, 126, 128-130, 142].

Infektionen und Zytopenien unerwünschte Ereignisse in ELIANA und RWE

Infections occurred in ELIANA in 24% of cases while in RWE studies rate of infection ranged from 37% to 54% [33, 123, 125, 127, 128]. Cytopenias not resolved by day 28 occurred in 32% of ELIANA patients while cytopenias in RWE studies ranged from 27% to 66% [122, 123, 125, 128, 129]. Tumour lysis syndrome was reported in 4% of patients in ELIANA. One study reported on tumour lysis syndrome with an occurrence of 7% [128].

Mortalität in RWE heterogen

In ELIANA 19 of the 75 infused patient died (25%); 3% within 30 days after infusion and 22% later. Mortality in RWE studies ranged from 0% to 42% [123-130]. Two studies reported on mortality within 30 days after infusion and was 3% each [125, 127].

behandlungsassoziierte Mortalität vergleichbar in ELIANA und RWE

Deaths that occurred from severe adverse events likely to be related to tisagenlecleucel infusion (treatment-related mortality) were identified in 4% of patients in ELIANA (n=3). Those cases could be extracted from eight publications in which percentages ranged from 0% to 6.5% [122-126, 128, 130].

The comparative safety outcomes of the pivotal trial and RWE studies are displayed in Table 3-6.

Table 3-6: Comparison of safety outcomes between pivotal trials and RWE studies (B-ALL)

Study ID	n	CRS overall	CRS ≥ Grade 3	Neurotoxicity	Neurotoxicity ≥ Grade 3	Mortality	Treatment-related death	Other SAE	
Maude, 2018 [55]	75	77%	46%	40%	13%	25.3%	4%	Infection: 43% Febrile neutropenia: 35% Cytopenia not resolved by day 28: 37% Tumour lysis syndrome: 4%	
Laetsch, 2019 [56]	58	NR	NR	NR	NR	NR	NR	NR	
Pasquini, 2020 [125]	255	54.9%	16.1%	27.1%	9%	Death within 30 days post infusion: 3.1%	0.4-2%	Hypogammaglobulinemia: 52.5% Prolonged cytopenia: 27.8% Clinically significant infections: 46.3% Grade 3/4 organ toxicities: 8.2% Secondary malignancies: 2.4% Deaths overall: 18.4%	
Rubinstein, 2020 [130]	7	42%	14%	0%	0%	0%	0%	NR	
Brown, 2021 [142]	14	86%	NR	36%	29%	NR	NR	NR	
Dourthe, 2021 [122]	51	59%	20%	24%	8%	NR	2%	ICU admission: 35% Neutropenia Grade ≥3 (d28): 37% Thrombocytopenia Grade ≥ 3 (d28): 37%	
Kadauke, 2021 [129]	Overall: 70 HTB (≥ 40%): 15 LTB (<5%): 55	Overall: 74% HTB: 100% LTB: 67%	Overall: 17% HTB: 60% LTB: 5%	Overall: 27% HTB: 60% LTB: 18%	Overall: 7% HTB: 20% LTB: 4%	17%	NR	Hypoxia: 13% Hypophosphatemia: 14% AST ↑: 14% Anorexia: 7.1% Fibrinogen ↓: 4.3% Hypotension: 11% Acidosis: 5.7% Bilirubin ↑: 5.7% Anaemia: 14% aPTT↑: 4.3% Hyperglycaemia: 4.3% Hyperkalaemia: 4.3%	Lymphocytes ↓: 60% Hypokalaemia: 11% ALT ↑: 13% Fever: 5.7% URT infection: 4.3% Encephalopathy: 5.7% Neutrophiles ↓: 54% Leukocytes ↓: 54% Platelet count ↓: 27%

Study ID	n	CRS overall	CRS ≥ Grade 3	Neurotoxicity	Neurotoxicity ≥ Grade 3	Mortality	Treatment-related death	Other SAE
Rossoff, 2021 [127]	Overall: 185 OOS: 24 SOC: 161	OOS: 46% SOC: 61%	OOS: 17% SOC: 19%	OOS: 8% SOC: 22%	NR	Death before day 28 post infusion: 3%	NR	Infections: ■ OOS: 54% ■ SOC: 37%
Schultz, 2021 [128]	185	63%	21%	21%	7%	27.5%	4.3%	Neutropenia grade 4: 67% Tumour lysis syndrome: 7% Infectious complication: 40% PICU-Stay: 31%
Dekker, 2022 [33]	26	NR	NR	NR	NR	NR	NR	Infection: 54%
Fabrizio, 2022a [124]	Overall: 184 CNS: 40 Non-CNS EM: 15 BM only: 129	CNS: 63% Non-CNS EM: 80% BM only: 61%	NR	CNS: 35% Non-CNS EM: 13% BM only: 17%	NR	27.7%	4.3%	NR
Fabrizio, 2022b [123]	152	64%	22%	24%	8%	26.3%	5%	Infection: 38% Grade 4 neutropenia: 66%
Moskop, 2022 [123]	14	79%	21%	0%	0%	29%	0%	NR
Ravich, 2022 [126]	31	61.3%	19%	29%	10%	42%	6.5%	Therapy associated HLH: 6.5% Late onset bacteraemia: 6.5%

Abbreviations: BM: bone marrow, CNS: central nervous system, CRS: cytokine release syndrome, EM: extramedullary, HTB: high tumour burden, LTB: low tumour burden, Neg: negative, NR: not reported, MRD: minimal residual disease, OOS: out of specification (= beyond approved indication), SAE: serious adverse events, SOC: standard of care, UD: undetectable disease

Highlighted in green: pivotal studies, highlighted in grey: same cohort of PRWCC

3.5 LBCL: Results from Real-world evidence (RWE)

3.5.1 Characteristics of included studies

17 Studien (inklusive 2 nRCTs)

To synthesize the real-world evidence, two nRCTs and 15 observational, uncontrolled studies (16 publications) were included in the analysis [49, 110-121, 145-149].

Study characteristics

2 prospektive und 15 retrospektive Studien

While two studies were prospective case series [49, 115], 15 studies were conducted retrospectively, including both nRCTs. Of these, ten studies were retrospective case series, one study had a retrospective cohort study design [148], and two were retrospective registry analyses [111, 113].

Studienorte: USA/Kanada (9), Frankreich (3), Deutschland (2), Spanien (1), UK (1), Israel (1)

Eight and three studies were conducted in the USA [112, 114, 116, 118, 119, 121, 145, 147, 149] and in France [115, 117, 120], respectively. One further study enrolled patients at sites in the USA and Canada [113]. Two further studies were conducted in Germany [49, 111]. One study each was conducted in Spain [110], the UK [146] and Israel [148]. The US studies were funded by NIH/NCI grants and other grants, depending on the research center [113, 116, 118, 119, 121, 145, 147, 149]. Two French studies were supported by the FEHH-Fundacion CRIS grant, individual fellowships, and French research grants [115, 117]. Two studies claimed that they did not have any sponsor [114, 148], and the remaining did not report on funding [49, 110-112, 120, 146].

Studienfinanzierung

Fokus der Einschlusskriterien auf Indikation

Inclusion criteria mainly focused on the indication. Eight studies included patients with r/r LBCL [110, 111, 114, 116, 119, 145-147], four studies only included patients with DLBCL [120, 121, 148, 149]. In four studies, a broader indication spectrum than DLBCL, including PMBCL and tFL was allowed [49, 112, 115, 117, 118]. More detailed in/exclusion criteria were reported only in seven studies [111-113, 115, 118, 146, 148]. One study only included patients with prior autoHSCT failure [113]. One study enrolled only patients with an ECOG status below four [148]. No further inclusion criteria were specified.

Ausschlusskriterien unter anderem autoHSCT, Schwangerschaft, CNS Erkrankung

Exclusion criteria were patients in the CAR-T cohort with prior autoHSCT [118, 146], unapproved indications, active CNS disease [146], pregnancy [115] or patients being treated with other CAR-T products (including other indications) [111, 112].

5 Studien zu axi-cel, 1 Studie zu tisa-cel, 11 Studien beide Interventionen

Five studies enrolled patients receiving axi-cel [49, 114, 118, 145, 147] and one study receiving tisa-cel [110]. The remaining studies did not exclude patients based on the CAR-T cell product [111-113, 115-117, 119-121, 146, 148, 149].

Patient characteristics, follow-up and outcomes

insgesamt 2.105 Patient*innen (Pt.), medianes Alter zwischen 56 und 76 Jahren

The number of patients infused with CAR-T products in all included studies ranged from 21 to 356 (n=2,105), with most patients diagnosed with DLBCL. Other indications included tDLBCL, PMBCL and transformed follicular lymphoma (tFL). The median age ranged from 56 (21-76) to 76.2 (SD 4.4) years.

Pt. vermehrt in Erkrankungsstadium 3-4

While female participants accounted for 28-42% of the study population, reflecting the gender-specific distribution of DLBCL incidence [26], two studies included more women than men [114, 148]. Between 8% and 30% of the patients were in disease stage 1-2, whereas 55%-92% were in stage 3-4 [110, 115-118, 120, 121, 145-147, 149].

All included studies reported the median follow-up period, ranging from four to 19.8 months.

medianer Nachbeobachtungszeitraum: 4-19,8 Monate

The distribution concerning the number of previous therapies was heterogeneous among included studies. Overall, 15 (of 17 included) studies reported on prior therapies. In nine studies, the median number of prior therapies ranged from two to five previous therapies [49, 110, 112, 116, 118-121, 145, 149]. In further seven studies, the number of patients receiving three or more lines of treatment ranged from 27% to 100% [49, 111, 115, 145-148]. Five studies reported ≥4 treatment lines in 28%-70% of the patients [110, 112, 117-119]. Between 7.3% and 57% of patients received prior autoHSCT [49, 110, 112, 115-117, 119-121, 146-149], 1.7-20% received prior alloHSCT [49, 112, 116, 117, 120, 121, 146, 147, 149]. One study did not differentiate between autoHSCT and alloHSCT but reported aggregated priorHSCT of 34% [111].

Anzahl an früheren Therapien heterogen

zwischen 7,3 %-57 % Pt unterzogen sich autoHSCT vor CAR-T

Primary and secondary endpoints were only defined by one study as PFS and OS, NRM, respectively [118].

Twelve studies defined **OS** as time from leukapheresis[11] or CAR-T infusion to death from any cause [110-121]. Eleven studies defined **PFS** as time from CAR-T infusion until relapse, disease progression or death from any cause, whichever occurred first [110-120]. Two studies reported **EFS**, one study defined EFS as the time from CAR-T infusion to progression, relapse or death from any cause [121] and another study did not sufficiently report on how this endpoint was defined. **ORR** was defined by two studies as percentage of patients achieving CR or PR [110, 116]. In another study, response assessment was performed by institutional practice and based on the Lugano criteria [49].

Definitionen der Endpunkte

One study included **HRQoL** as an outcome, using the EORTC QLQ-C30 version three questionnaire for cancer patients [148].

eine Studie zu Lebensqualität, EORTC QLQ-C30 Fragebogen

Ten studies used the ASTCT score for grading CRS and ICANS [49, 110, 111, 113, 117, 118, 121, 145, 146, 148], CTCAE version 4.03 and version 5.0 were used to grade adverse events by two and six studies, respectively [110, 112, 114, 117, 121, 145, 147-149]. CARTOX grading was applied in three studies [114, 119, 147], while another three studies referred to Lee criteria [112, 114, 147].

verschiedene Bewertungssysteme von unerwünschten Ereignissen

Study characteristics and results of included studies are displayed in Table 3-7 and in the Appendix (Table A-4)

Three out of 15 observational studies had a moderate risk of bias (RoB), while the remaining studies had a high RoB. Aspects increasing the risk of bias covered, among others, the retrospective nature of the studies, a lack of a control group and blinding as well as heterogeneous disease stages in the patient cohort. In addition, all studies were written by authors with potential conflicts of interest. Both non-randomized controlled trials were assessed with the ROBINS-I tool, and their overall bias was rated as “Critical”. This was mainly due to the retrospective study design, which caused critical selection bias, possible missing data and lack of blinding.

Verzerrungsrisiko: moderat bis hoch, weil retrospektiv, unverblindet, keine Kontrollgruppe

Detailed RoB assessments (on study level) are displayed in the Appendix (Table A-9 and Table A-10)

[11] Leukapheresis as start point was used for the intention-to-treat cohort, where patients undergoing leukapheresis but not receiving a CAR-T cell product were included [110].

Table 3-7: Main characteristics of included RWE studies (LBCL)

Study ID	n	CAR-T product⋄	Age (years)†	Sex (F)	Prior autoHSCT Prior alloHSCT	Prior therapy† ≥3/4 prior therapies	ECOG ≥2	Disease stage	Bridging therapy	FU‡
Ayuk, 2021 [49]	21	A	58 (24-67)	29%	57% 4.8%	5 (3-8) ≥3: 100%	14.3%	NR	90.5%	4 (0.7-12.5)
Baird, 2021 [145]	41	A	56 (21-76)	41%	NR	3 (2-4) ≥3: 61%	7.3%	1-2: 22% 3-4: 78%	43.9%	19.8 (3.3-27.6)
Bethge, 2022 [111]	356	A&T	60 (19-83)	34%	Prior HSCT: 34%	NR ≥3: 71%	16%	NR	78%	11 (1-29)
Ghafouri, 2021 [112]	53	A&T	63 (18-82)	42%	9% 4%	3 (1-6) ≥4: 32%	11%	NR	58%	15.2 (NR)
Hamadani, 2022 [113]	181 (only CAR-T)	A&T	61 (21.9-80)	35%	NR	NR	NR	NR	19.3%	13 (1-27.7)
Holtzman, 2021 [114]	45	A	60 (26-75)	51%	NR	NR	NR	NR	67%	7.1 (3;9.9)
Iacoboni, 2021 [110]	75	T	60 (52;67)	41%	39% NR	3 (2-4) ≥4: 28%	7%	1-2: 8% 3-4: 92%	87%	14.1 (95%CI: 13.1-17.4)
Kuhnl, 2022 [146]	300	A&T	59.0 (18-78)	38.3%	15% 1.7%	NR ≥3: 37.3%	9.7%	1-2: 21.6% 3-4: 78.4%	87%	13.9 (9.1;19.4)
Lamure, 2021 [115]	60	A&T	64 (18-79)	37%	20% NR	NR ≥3: 27%	NR	1-2: 30% 3-4: 60%	90%	6.9 (0.5-26.1)
Nastoupil, 2020 [147]	275	A	60 (21-83)	36%	32.9% 2.4%	NR ≥3: 74.5%	19.5%	1-2: 17.6% 3-4: 82.4%	53%	13.8 (3.9-21.6)
Ram, 2022[12] **[148]**	82 (41 vs 41)	A&T	76.2 (±4.4) vs 55.4 (±15)	61% vs 54%	7.3% vs 34.1% NR	NR ≥3: 46% vs 51%	61% vs 61%	NR	17.1% vs 29%	7 (1.3-17.2) vs 7 (1.3-16.7)
Sermer, 2020[13] **[116]**	215 (69 vs 146)	A&T	63 (19-85) vs 66 (27-91)	30% vs 42%	20% vs 14%; p=0.2 6% vs 2%; p=0.2	3 (2-7) vs 2 NR	13% vs 8.5%	limited: 16% vs 16% advanced: 84% vs 84%	NR	14.6 (1.2-18.9) vs 30.6 (2.1-162)
Shadman, 2022[14] **[118]**	411 (145 vs 266)	A	60 (24-91) vs 58 (18-80)	39% vs 37%	NR	3 (2-11) vs 2 (1-6); p<0.001 ≥4: 31% vs 13%	NR	3-4: 55% vs 61%	16%	12 (3-26)

[12] Experiental vs experiental (elderly vs young cohort)

[13] **nRCT**: CAR-T vs alternate therapies

[14] **nRCT**: CAR-T vs autoHSCT

Study ID	n	CAR-T product⬨	Age (years)†	Sex (F)	Prior autoHSCT Prior alloHSCT	Prior therapy† ≥3/4 prior therapies	ECOG ≥2	Disease stage	Bridging therapy	FU‡
Sesques, 2020 [117]	61	A&T	59 (27-75)	34%	28% 2%	NR ≥4: 70%	30%	3-4: 78%	97%	5.7 (NR)
Steiner, 2021 [119]	165	A&T	60 (18-88)	28%	26% NR	3 (2-11) ≥4: 29.3%	78%	NR	NR	16.2 (14.3-19.1)
Vercellino, 2020 [120]	116	A&T	60.7 (49.2;67.6)	35%	29% 2.6%	3 (IQR 2-4) NR	12.1%	3-4: 76.7%	87.1%	8.2 (NR)
Wudhikarn, 2020a+b [121, 149]	60	A&T	63 (19.5-85.9)	30%	8.3% 20%	3 (2-9) NR	20%	1-2: 23.3% 3-4: 63.3%	63.3%	9 (NR)

Abbreviations: autoHSCT: autologous stem cell transplantation, alloHSCT: allogenic stem cell transplantation, CAR-T: chimeric antigen receptor T cell therapy, ECOG: Eastern Cooperative Oncology Group, F: female, FU: follow-up, NR: not reported

Both nRCTs are highlighted in light orange

The number of patients refer to patients infused with CAR-T cells. Ranges are indicated with – and the IQR with ; between the numbers. The standard deviation is indicated with ±

† Values for age and prior therapy are reported in median (range)

‡ Follow up in months (range).

⬨ A: Axi-cel, T: Tisa-cel, A&T: Axi-cel and Tisa-cel

3.5.2 Effectiveness

The body of evidence for the effectiveness and safety of the included studies will be described in this section.

vollständige Ansprechrate nach 1 Monat: 41,5 %-48 %

nRCT: signifikanter Unterschied zw. CAR-T (52 %) und alternativen Therapieformen (22 %)

CR was reported in eleven studies [110-112, 114-117, 145-148]. CR after one month (28-30 days) was reported by four studies, ranging from 41.5%-48% [117, 145, 147, 148]. One of these studies reported CR for axi-cel and tisa-cel separately, observing 46% and 48%, respectively [117]. Another study reported a CR of 40% and 37.8% at three and six months, respectively [146]. Four studies reported CR of 32%, 37%, 49% and 64%, however, without stating when these measurements were made [110-112, 114]. One nRCT found a statistically significant difference in the CR rate of 52% in the CAR-T cohort compared with 22% in the alternate therapy cohort ($p<0.001$) [116].

medianes Gesamtüberleben zwischen 10,7-19,3 Monaten, nicht erreicht in 3 Studien

Gesamtüberlebensrate nach 12 Monaten: 49 %-73,4 %

OS was reported in all studies. Seven studies reported a median OS ranging from 10.7 to 19.3 months [110, 112, 114-117, 146]. Two of these studies reported a median OS for axi-cel and tisa-cel separately. While one study reported a median OS of 15.6 months (axi-cel) and 10.2 months (tisa-cel) [146], in the other study the median OS of axi-cel was not reached and 7.4 months for tisa-cel [117]. In further three studies, median OS was not reached (FU 19.8, 13.9 and 7 months) [145, 147, 148]. The estimated OS probability at six months was reported in five studies and ranged from 68% to 78.5% in CAR-T patients [112, 116, 117, 120, 148]. The estimated OS probability at 12 months was reported in twelve studies and ranged from 49% to 73.4% [49, 111-113, 116, 118-121, 146-149]. Differences in 12-month OS probability dependent on CAR-T product were estimated between axi-cel (55%-57.1%) and tisa-cel (43.8%-53%) [111, 146]. One study reported outcomes for patients with and without major adverse cardiovascular events (MACE) separately, accounting for 58% and 62% estimated OS at 12 months, respectively [119].

2 nRCTs: Gesamtüberleben einmal in CAR-T Kohorte besser als in Vergleichskohorte, einmal schlechter

Two of the aforementioned studies were nRCTs, comparing CAR-T to standard care [116, 118]: In one nRCT ($n=215$), the median OS of CAR-T (19.3 months) was compared to alternate therapies (6.5 months), and this finding was statistically significant ($p=0.006$) [116]. The other nRCT did not report a median OS [118]. The six month OS rate was 71% (95%CI: 61-82) and 55% (95%CI: 47-64), respectively (p-value not reported) [116] and not reported in the other nRCT [118]. The 12-month OS rates of both studies were 64%-67% in the CAR-T cohorts and 39%-76% in the control groups, both findings were not statistically significant ($p=0.1$ and not reported) [116, 118]. One nRCT ($n=411$) reported a significant difference in the 24 month OS probability between the CAR-T (47%, 95%CI: 33-60) and the autoHSCT cohort (69%, 95%CI: 63-74; $p=0.004$) [118].

medianes progressionsfreies Überleben: 3-8,3 Monate, nicht erreicht in 1 Studie

PFS was reported in 16 out of 17 studies [49, 110-120, 145-148], including both nRCTs. Ten studies reported a median PFS ranging from 3 to 8.3 months [110, 112, 115-117, 120, 145-148]. In one further study, the median PFS was not reached (median FU 7.1 mo) [114]. An estimated median PFS of 7.4 was reported in one study [120]. Two studies reported a median PFS for axi-cel and tisa-cel separately. The median PFS for axi-cel was 5.5 [146] and 3.1 [117] months, respectively, and the median PFS for tisa-cel was 2.9 [146] and 3 [117] months.

progressionsfreie Überlebensrate nach 12 Monaten: 33,3 %-49 %

The estimated PFS probability at six months was reported in four studies, ranging from 33.3% to 49% in CAR-T patients [110, 116, 117, 148]. The estimated PFS probability at 12 months was reported in eleven studies and ranged from 29.3% to 55.7% [49, 110, 111, 113, 115, 116, 118, 119, 146-148].

Differences in 12-month PFS probability dependent on CAR-T product were estimated between axi-cel (35%-41.8%) and tisa-cel (24%-27.4%) [111, 146]. One study reported outcomes for patients with and without major adverse cardiovascular events (MACE) separately, accounting for 38% and 42% estimated PFS at 12 months, respectively [119].

2 nRCTs: progressionsfreies Überleben einmal in CAR-T Kohorte besser als in Vergleichskohorte, einmal schlechter

Two of the aforementioned studies were nRCTs [116, 118]. In one nRCT (n=215), PFS statistically significantly differed between CAR-T and alternate therapies, with a median PFS of 5.2 and 2.3 months, respectively (p=0.01) [116]. The six month PFS rate was 49% (95%CI: 39-63) and 29% (95%CI: 23-38), respectively (p-value not reported) [116]. The 12-month PFS rates of both studies were 44%-52% in the CAR-T cohorts and 25%-59% in the control group, both findings were not statistically significant (p=0.2 and not reported) [116, 118]. One nRCT (n=411) reported 24 month PFS probabilities of 42% (95%CI: 30-53) in the CAR-T and 52% (95%CI: 46-58) in the auto-HSCT cohort (p=0.1) [118]. **EFS** was reported in two studies [112, 121]. One study reported a median EFS of 11.9 months and an estimated EFS at six months of 54% [112]. Two studies reported an estimated EFS after 12 months of 40% [121] and 50% [112], respectively.

(nicht signifikante) Verbesserung der Lebensqualität nach 3 Monaten

HRQoL was reported in one study by the EORTC QLQ-C30 questionnaire [148]. 56% of the patients completed the questionnaire. Thirty days after CAR-T infusion, no change in overall health perception or quality of life was observed. Three months after infusion, a statistically significant improvement in overall health perception compared to baseline from 3.83 to 5.6 (p=0.005) and a non-statistically significant difference in overall quality of life (3.87 to 5.4, p=0.081) was documented.

Gesamtansprechrate nach 1 Monat: 58 %-67 %

nRCT: statistisch signifikanter Unterschied zwischen CAR-T und alternativen Therapien

The **ORR** was reported in eleven studies [49, 110-112, 115-117, 145-148]. An ORR after one month (28-30 days) was reported by four studies, ranging from 58% to 67% [49, 115, 117, 148]. One of these studies reported similar ORR for axi-cel and tisa-cel, observing 64% and 61%, respectively [117]. Another study reported an ORR of 48% and 41% at three and six months, respectively [146]. Four studies reported ORR of 60%, 65%, 72% and 87.8%, however, without stating when these measurements were made [110-112, 145]. One nRCT reported a statistically significant difference in ORR of 72% in the CAR-T cohort compared with 32% in the alternate therapy cohort (p<0.001) [116]. Detailed ORR results are displayed in the Appendix (Table A-4).

Teilansprechen nach 1 Monat: 13 %-43,9 %

PR was reported in ten studies [110-112, 114, 115, 117, 145-148]. PR after one month (28-30 days) was reported by four studies, ranging from 13% to 43.9% [117, 145, 147, 148]. One of these studies reported PR for axi-cel and tisa-cel separately, observing 18% and 13%, respectively [117]. Another study reported a PR of 8% and 3.4% at three and six months, respectively [146]. However, three studies reported PR of 8% and 28% without stating when these measurements were made [110-112]. Detailed PR results are displayed in the Appendix (Table A-4).

Effectiveness outcomes of included studies are displayed in Table 3-8 and in the Appendix (Table A-4).

Table 3-8: Results on effectiveness in RWE-studies

Study ID	n	FU‡	CR (95%CI)	OS				PFS†				HRQoL‡
				6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median OS, mo (95%CI)	6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median PFS, mo	
Ayuk, 2021 [49]	21	4 (0.7-12.5)	NR	NR	49% (25%-73%)	NR	NR	NR	37% (15%-59%)	NR	NR	NR
Baird, 2021 [145]	41	19.8 (3.3-27.6)	65.9% d28: 41.5%	NR	NR	NR	NR* (16.6-NE)	NR	NR	NR	6.1 (3.1-NE)	NR
Bethge, 2022 [111]	356	11 (1-29)	37% A: 42% T: 32%	NR	52% A: 55% T: 53%	NR	NR	NR	30% A: 35% T: 24%	NR	NR	NR
Ghafouri, 2021 [112]	53	15.2 (NR)	64%	69% (56-80)	55% (41-68)	NR	17,7	54% (30-97)†	50% (26-97)†	NR	7.9 11,9†	NR
Hamadani, 2022 [113]	181	13 (1-27.7)	NR	NR	73.4% (66.4-79.9)	NR	NR	NR	55.7% (48-63.2)	NR	NR	NR
Holtzman, 2021 [114]	45	7.1 (3;9.9)	49% d30: 36.5%	NR	NR	NR	15.1 (NR)	NR	NR	NR	NR*	NR
Iacoboni, 2021 [110]	75	14.1 (95%CI: 13.1-17.4)	32%	NR	NR	NR	10.7 (7.4-NR*)	33.3%	31.7%	NR	3 (2.6-4.7)	NR
Kuhnl, 2022 [146]	300	13.9 (9.1;19.4)	3 mo: 40% 6 mo: 37.8% Best CR: 50%	NR	53.9% A: 57.1% (49.8-63.8) T: 43.8% (31.1-55.9)	NR	14.8 A: 15.6 (11.1-NR*) T: 10.2 (7.7-NR*)	NR	Responders: 52% (44.7-58.8) A: 41.8% (35-48.4) T: 27.4% (17.5-38.3)	NR	3.5 A: 5.5 (3.3-10.1) T: 2.9 (1.7-3.6)	NR
Lamure, 2021 [115]	60	6.9 (0.5-26.1)	1 mo: 35% 3 mo: 25%	NR	NR	NR	12.3 (32.9-63.1)	NR	29.3% (17-42.8)	NR	3.1	NR
Nastoupil, 2020 [147]	275	13.8 (3.9-21.6)	Best CR: 64% (58%-69%) d30: 44%	NR	68% (63%-74%)	NR	NR*	NR	47% (41%-53%)	NR	8.3 (6-15.1)	NR
Ram, 2022[15] [148]	82 (41 vs 41)	7 (1.3-17.2) vs 7 (1.3-16.7)	1 mo: 46% vs 59%	74% vs 76%	69% vs 53%	NR	NR* vs NR*; p=0.792	39% vs 54%	32% vs 54%	NR	3.6 (1.6-5.6) vs NR*; p=0.209	23/41 (56%) pts with EORTC QLQ-C30 questionnaire (version 3) in study cohort

[15] Experimental vs experimental (elderly vs young cohort)

Study ID	n	FU‡	CR (95%CI)	OS				PFS†				HRQoL‡
				6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median OS, mo (95%CI)	6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median PFS, mo	
Ram, 2022 [148] *(continuation)*												baseline vs 1 mo: ND baseline vs 3 mo: ■ Overall health perception: 3.83 vs 5.6; p=0.005 ■ Overall quality of life: 3.87 vs 5.4; p=0.081
Sermer, 2020[16] [116]	215 (69 vs 146)	14.6 (1.2-18.9) vs 30.6 (2.1-162)	52% vs 22%; p<0.001	71% (61-82) vs 55% (47-64)	64% (54-77) vs 39% (31-48)	NR	19.3 vs 6.5; p=0.006	49% (39-63) vs 29% (23-38)	44% (33-58) vs 25% (19-33)	NR	5.2 vs 2.3; p=0.01	NR
Shadman, 2022[17] [118]	411 (145 vs 266)	12 (3-26)	NR	NR	67% (59-75) vs 76% (70-81); p=0.1	47% (33-60) vs 69% (63-74); p=0.004	NR	NR	52% (43-61) vs 59% (53-65); p=0.2	42% (30-53) vs 52% (46-58); p=0.1	NR	NR
Sesques, 2020 [117]	61	5.7 (NR)	1 mo: A: 46% T: 48%	68% (53-80)	NR	NR	11.8 (6-12.6) A: NR* (4.6-NR*) T: 7.4 (4.8-12.6)	44% (30-57)	NR	NR	3 (2.8-8.8) A: 3.1 (2.9-NR*) T: 3 (2.1-8.8)	NR
Steiner, 2021 [119]	165	16.2 (14.3-19.1)	NR	NR	MACE: 58% No-MACE: 62%	NR	NR	NR	MACE: 38% No-MACE: 42%	NR	NR	NR
Vercellino, 2020 [120]	116	8.2 (NR)	NR	78.5% (71-87)	67% (57-79)	NR	NR	NR	NR	NR	Estimated: 7.4 (3-NR*)	NR
Wudhikarn, 2020a+b [121, 149]	60	9 (NR)	NR	NR	69% (57-82)	NR	NR	NR	40% (28-56)†	NR	NR	NR

Abbreviations: A: Axi-cel, AE: adverse event, CR: complete remission, CRS: cytokine release syndrome, EFS: event-free survival, EORTC: European Organisation for Research and Treatment of Cancer, ICANS: Immune effector cell-associated neurotoxicity syndrome, mo: months, NA: not available, ND: no statistical significant difference, NE: not evaluable, NR: not reported, NR: not reached, OS: overall survival, PD: progressive disease, PFS: progression-free survival, pts: patients, T: Tisa-cel*

Both nRCTs are highlighted in light orange

† EFS and not PFS was reported

‡ Values for follow-up are reported in median (months), values for HRQoL are reported in mean

[16] nRCT: CAR-T vs alternate therapies

[17] nRCT: CAR-T vs autoHSCT

3.5.3 Safety

15 Studien berichteten Sicherheitsendpunkte (hauptsächlich CRS und ICANS)

Regarding **safety**, 15 studies (of the 17 included) reported (serious) adverse events (AE, SAE), all of them CRS or ICANS. Most frequent reported AE and SAE were cytokine release syndrome (CRS) and neurotoxicity (ICANS), which were reported by the 15 studies [49, 110-115, 117-119, 121, 145-149], followed by haematological complications and cytopenias (including neutropenia and thrombocytopenia) (7/17) and infections (5/17). Anaemia, acute kidney injury and cardiovascular complications were only reported by two studies [121, 148].

CRS: 68 %-93 %, ≥ Grad 3: 2,4 %-14,3 %

ICANS: 15 %-68,7 %, ≥ Grad 3: 1 %-40 %

Between 68% and 93% of patients experienced **CRS** of any grade. 2.4%-14.3% experienced grade ≥3 CRS. Differences were observed in axi-cel and tisa-cel patients (81%-93% and 65%-79%) [111, 117]. One patient each died due to CRS [111] and toxicity [117]. Between 15% and 68.7% of patients experienced **ICANS** of any grade. 1%-40% experienced grade 3 ICANS and higher. However, only three studies reported grade ≥3 ICANS in under 10% of the patients [110, 117, 148]. Differences were observed in axi-cel and tisa-cel patients (32%-44% and 22%-24%) [111, 117].

andere unerwünschte ereignisse: Zytopenien, Infektionen, Anämie

Other frequent serious adverse events included among others grade ≥3 neutropenia (three studies; 19.8%-97.6%) [117, 145, 146] and grade ≥3 thrombocytopenia (three studies; 14.5%-68%) [117, 145, 146]. Grade ≥3 cytopenia after lymphodepletion was reported in 98% of all patients [115]. Infections within one month occurred in 46.3% [145] of the patients, with 37% [117] experiencing grade 3 and higher. Cumulative incidence of ≥3 infections within one year was 35.4% [121]. Two other studies reported an infection incidence in 26.8% and 33% of the patients [115, 148]. A detailed list of all (S)AEs can be found in Table 3-9.

Mortalität: 25 %-48 %

Mortality was reported in nine studies (ten publications) and ranged from 25%-48% of all patients [49, 111-113, 115, 118, 120, 121, 147, 149].

rückfallfreie Mortalität nach 1 Jahr: 1,7 %-7,3 %

Ten studies (11 publications) reported **non-relapse mortality (NRM)** [110, 111, 113, 118, 120, 121, 145-149]. Five studies reported on one year NRM ranging from 1.7% to 7.3% [111, 113, 118, 121, 146]. Among those studies is one nRCT, which reported NRM in CAR-T patients of 3%, in contrast to 7% in the autoHSCT cohort, with a p=0.05 [118]. Differences in NRM between axi-cel and tisa-cel patients were observed in one study (8.7% and 3.1%), however, without stating when these measurements were made [146]. Five studies reported an NRM between 1.7% and 6%, however, without specifying the time of measurement [110, 111, 120, 145, 147].

Safety outcomes are displayed in Table 3-9 and in the Appendix (Table A-4).

Table 3-9: Results on safety in RWE-studies

Study ID	n	FU‡	CRS	CRS ≥ grade 3	Neurotoxicity	Neurotoxicity ≥ grade 3	Mortality/ NRM†	(S)AE
Ayuk, 2021 [49]	21	4 (0.7-12.5)	71.4%	14.3%	47.6%	19%	48%	
Baird, 2021 [145]	41	19.8 (3.3-27.6)	NR	2.4%	NR	24.4%	NRM: 2.4%	SAE until d28: Severe cytopenias: 97.6% grade ≥3 neutropenia: 97.6% grade ≥3 thrombocytopenia: 56.1% Infection until d28: 46.3% → mild to moderate: 68.4% Infection beyond d365: 47.1%
Bethge, 2022 [111]	356	11 (1-29)	73% (A vs T: 81% vs 65%; p=0.0003)	12%	33% (A vs T: 44% vs 22%; p<0.0001)	11%	46% NRM: 6% 1y NRM: 5.5%	Grade 4 neutropenia: 81% median duration: 13 days (1-419) Severe thrombocytopenia: 37% median duration: 34 days (2-375)
Ghafouri, 2021 [112]	53	15.2 (NR)	68%	6%	30%	19%	43%	NR
Hamadani, 2022 [113]	181 (only CAR-T)	13 (1-27.7)	82.3%	9.9%	61.9%	20.9%	30.3% 1y NRM: 4.8%	NR
Holtzman, 2021 [114]	45	7.1 (3;9.9)	80%	NR	56%	40%	NR	NR
Iacoboni, 2021 [110]	75	14.1 (95%CI: 13.1-17.4)	71%	5%	15%	1%	NRM: 4%	NR
Kuhnl, 2022 [146]	300	13.9 (9.1;19.4)	88%	7.7%	36.8%	15.7%	1y NRM: 7.3% A: 8.7% T: 3.1%	Cytopenia: Grade ≥ 3 neutropenia: 19.8% Grade ≥ 3 thrombocytopenia: 14.5%
Lamure, 2021 [115]	60	6.9 (0.5-26.1)	NR	5%	NR	12%	48%	Grade 3-4 cytopenia after lymphodepletion and CAR-T infusion: 98% Infections: 33%
Nastoupil, 2020 [147]	275	13.8 (3.9-21.6)	91%	7%	68.7%	31%	35% NRM: 4.4%	NR
Ram, 2022[18] [148]	82 (41 vs 41)	7 (1.3-17.2) vs 7 (1.3-16.7)	NR	9.8% vs 7.3%	NR	2.5% vs 4.9%	3 mo NRM: 0	Acute kidney injury: 7.3% vs 7.3 Atrial fibrillation: 7.3% vs 7.3 Late pancytopenia: 22% vs 26.8% Clinical or microbiology documented infections: 26.8% vs 19.5%

[18] Experimental vs experimental (elderly vs young cohort)

Study ID	n	FU‡	CRS	CRS ≥ grade 3	Neurotoxicity	Neurotoxicity ≥ grade 3	Mortality/ NRM†	(S)AE
Sermer, 2020[19] [116]	215 (69 vs 146)	14.6 (1.2-18.9) vs 30.6 (2.1-162)	NR	NR	NR	NR	NR	NR
Shadman, 2022[20] [118]	411 (145 vs 266)	12 (3-26)	74% (95%CI: 67-81)	7% (95%CI: 4-12)	24% (95%CI: 17-33)	15% (95%CI: 9-22)	36% vs 34% 100d NRM: 2% (0-5) vs 4% (2-7); p=0.3 1y NRM: 3% (1-6) vs 7% (4-11); p=0.05 2y NRM: 6% (1-16) vs 9% (5-13); p=0.6	NR
Sesques, 2020 [117]	61	5.7 (NR)	A: 93% T: 79%	A: 7% T: 9%	A: 32% T: 24%	A: 11% T: 9%	NR	Axi-cel vs Tisa-cel Anemia: 93% vs 80%: Grade ≥ 3: 21% vs 6% Thrombocytopenia: 96% vs 80% Grade ≥ 3: 68% vs 29% Neutropenia: 78% vs 53% Grade ≥ 3: 36% vs 35% Infection within 28d: Grade 3: NR vs 34%
Steiner, 2021 [119]	165	16.2 (14.3-19.1)	92%	14%	61%	31%	NR	MACE until d30: 16%
Vercellino, 2020 [120]	116	8.2 (NR)	NR	NR	NR	NR	25% NRM: 1.7%	NR
Wudhikarn, 2020a+b [121, 149]	60	9 (NR)	80%	11.7%	24%	21.7%	35% 1y NRM: 1.7% (0.1-8)	Neutropenic fever within 30d: 86.7% Overall 539 grade ≥ 2 events in 59 pt Cumulative incidence of grade ≥ 3 toxicities 1y after infusion: ■ Cardiovascular: 16.7 (8.5-27.2) ■ Metabolic: 54.8 (40.5-67.1) ■ Haematologic: 57.5 (43.4-69.9) ■ Pulmonary: 13.3 (6.2-23.3) ■ Neurologic: 18.3 (9.7-29.1) ■ Infections: 35.4 (22.6-48.4)

Abbreviations: A: Axi-cel, CRS: cytokine release syndrome, d: day, mo: month, MACE: major adverse cardiovascular events, NRM: non-relapse mortality, NR: not reported, T: Tisa-cel, y: year
Both nRCTs are hightlighted in light orange

† Mortality represents overall deaths, numbers are crude values. 95%CI are shown in brackets, if they have been reported.

‡ Values for follow-up are reported in median (months)

[19] nRCT: CAR-T vs alternate therapies

[20] nRCT: CAR-T vs autoHSCT

3.6 LBCL: Comparison of Results from observational studies (RWE) with pivotal trials

3.6.1 Study and patient characteristics

Unterschiede in Kohortengröße

The number of patients infused with CAR-T products ranged from 21 to 356 in real-world studies, while ZUMA-1 and JULIET infused 108 and 111 patients, respectively. Eleven out of 17 real-world studies had a mixed cohort with patients treated with axi-cel and tisa-cel. In contrast, ZUMA-1 patients were only infused with axi-cel, and in JULIET only with tisa-cel.

medianes Alter in Zulassungsstudien etwas niedriger

The median age ranged from 56 to 76.2 years in the real-world studies, 13 out of 17 studies had a patient cohort with a median of at least 60 years. With a median age of 56 (JULIET) and 58 (ZUMA-1), the patients in the pivotal trials were slightly younger. The sex ratio was comparable between pivotal studies and RWE.

restriktivere Zulassungskriterien in Zulassungsstudien

Eligibility criteria were generally more restrictive in the pivotal trials compared to the real-world studies. While eight real-world studies included patients with a broader spectrum of indications (LBCL) [110, 111, 114, 116, 119, 145-147], ZUMA-1 included only patients with DLBCL and PMBCL and JULIET only patients with (transformed) DLBCL.

Patient*innen mit alloHSCT oder ECOG >1 exkludiert

Differences between the pivotal trials and observational studies in the eligibility criteria included the application of allogenic stem cell transplantation (alloHSCT) and the ECOG performance status, which describes the impact of the disease on a patient's daily living abilities [150].

vorherige autoHSCT in RWE und Zulassungsstudie erlaubt

Patients with prior alloHSCT were not allowed in either one of the pivotal trials. In contrast, 1.7% [146] and 20% [121] of patients of the real-world studies underwent prior alloHSCT [49, 112, 116, 117, 120, 121, 146, 147, 149]. Prior autologous stem cell transplantation (autoHSCT) was allowed in pivotal trials and RWE studies. 21% (ZUMA-1) and 59% (JULIET) of the patients in the pivotal studies and between 7.3% and 57% of the patients in the real-world studies received prior autoHSCT [49, 110, 112, 115-117, 119-121, 146-149].

Both pivotal trials only included patients with an ECOG score of 0-1. In contrast, no such restrictions were made in real-world studies. The percentage of patients with an ECOG performance status of ≥2 ranged from 7% to 76% [49, 110-112, 116, 117, 119-121, 145-149].

mediane Therapieanzahl vor CAR-T: 3 (Zulassungsstudien) vs. 2-5 (RWE)

The median of prior therapies in both trials was three, while the median of prior therapies ranged from two to five in real-world studies [49, 110, 112, 116, 118-121, 145, 149]. In the real-world studies, between 55% and 92% of the patients were in disease stage 3-4 [110, 115-118, 120, 121, 145-147, 149] and between 76% and 85% of the patients were in this stage in the pivotal trials.

keine Überbrückungstherapie erlaubt in ZUMA-1

Fifteen out of 17 RWE studies reported bridging therapy, which was administered to 16%-97% of the included patients [49, 110-115, 117, 118, 120, 121, 145-149]. Similarly, 92% of the patients in JULIET received bridging therapy. In stark contrast, no bridging therapy was allowed in ZUMA-1. Four of the RWE studies explicitly described that between 9.5%-89% of their enrolled patients would have been eligible for ZUMA-1 or JULIET enrolment [49, 111, 112, 145].

medianer Nachbeobachtungszeitraum in Zulassungsstudien höher

The median follow-up ranged from four to 19.8 months in all real-world studies, compared to 27.1 (ZUMA-1) and 19.3 (JULIET) months in the pivotal studies.

Primary and secondary endpoints were only defined in one RWE study as PFS and OS, NRM, respectively, while ZUMA-1 and JULIET defined endpoints, focusing on response rates and adverse events as primary endpoints.

verschiedene Bewertungssysteme der unerwünschten Ereignisse

The definition of outcomes was equal in RWE and pivotal studies. However, regarding safety, different grading systems for CRS and ICANS were used. While RWE studies used ASTCT, CTCAE, CARTOX and Lee criteria, ZUMA-1 and JULIET used CTCAE, Lee criteria and the University of Pennsylvania grading scale for grading AE. One RWE study reported on adverse events, however, it did not report on any grading system for adverse events [115].

For detailed information, see Table 3-10.

Table 3-10: Comparison of study characteristics between pivotal trials and RWE studies

Study ID	n	CAR-T product⋄	Age (years)†	Sex (F)	Prior autoHSCT Prior alloHSCT	Prior therapy† ≥3/4 prior therapies	ECOG ≥2	Disease stage	Bridging therapy	FU‡
ZUMA-1	108	A	58 (51;64)[21]	32%	21% not allowed	3 ≥3: 69%[22]	Not allowed ECOG 1: 58%[22]	1-2: 15%[22] 3-4: 85%[22]	Not allowed	Up to 27.1[23]
JULIET	111	T	56 (22-76)	35%	59% not allowed	3 ≥3: 52%	Not allowed ECOG 1: 45%	1-2: 24% 3-4: 76%	92%	19.3
Ayuk, 2021 [49]	21	A	58 (24-67)	29%	57% 4.8%	5 (3-8) ≥3: 100%	14.3%	NR	90.5%	4 (0.7-12.5)
Baird, 2021 [145]	41	A	56 (21-76)	41%	NR	3 (2-4) ≥3: 61%	7.3%	1-2: 22% 3-4: 78%	43.9%	19.8 (3.3-27.6)
Bethge, 2022 [111]	356	A&T	60 (19-83)	34%	Prior HSCT: 34%	NR ≥3: 71%	16%	NR	78%	11 (1-29)
Ghafouri, 2021 [112]	53	A&T	63 (18-82)	42%	9% 4%	3 (1-6) ≥4: 32%	11%	NR	58%	15.2 (NR)
Hamadani, 2022 [113]	181	A&T	61 (21.9-80)	35%	NR	NR	NR	NR	19.3%	13 (1-27.7)
Holtzman, 2021 [114]	45	A	60 (26-75)	51%	NR	NR	NR	NR	67%	7.1 (3;9.9)
Iacoboni, 2021 [110]	75	T	60 (52;67)	41%	39% NR	3 (2-4) ≥4: 28%	7%	1-2: 8% 3-4: 92%	87%	14.1 (95%CI: 13.1-17.4)
Kuhnl, 2022 [146]	300	A&T	59.0 (18-78)	38.3%	15% 1.7%	NR ≥3: 37.3%	9.7%	1-2: 21.6% 3-4: 78.4%	87%	13.9 (9.1;19.4)
Lamure, 2021 [115]	60	A&T	64 (18-79)	37%	20% NR	NR ≥3: 27%	NR	1-2: 30% 3-4: 60%	90%	6.9 (0.5-26.1)
Nastoupil, 2020 [147]	275	A	60 (21-83)	36%	32.9% 2.4%	NR ≥3: 74.5%	19.5%	1-2: 17.6% 3-4: 82.4%	53%	13.8 (3.9-21.6)
Ram, 2022[24] [148]	82 (41 vs 41)	A&T	76.2 (±4.4) vs 55.4 (±15)	61% vs 54%	7.3% vs 34.1% NR	NR ≥3: 46% vs 51%	61% vs 61%	NR	17.1% vs 29%	7 (1.3-17.2) vs 7 (1.3-16.7)

[21] Data from patients in phase 2 (n=101)

[22] Data from all enrolled patients from phase 2 (n=111)

[23] Longer-term safety and activity assessment (Aug 2018)

[24] Experiental vs experiental (elderly vs young cohort)

Study ID	n	CAR-T product⋄	Age (years)†	Sex (F)	Prior autoHSCT Prior alloHSCT	Prior therapy† ≥3/4 prior therapies	ECOG ≥2	Disease stage	Bridging therapy	FU‡
Sermer, 2020[25] [116]	215 (69 vs 146)	A&T	63 (19-85) vs 66 (27-91)	30% vs 42%	20% vs 14%; p=0.2 6% vs 2%; p=0.2	3 (2-7) vs 2 NR	13% vs 8.5%	limited: 16% vs 16% advanced: 84% vs 84%	NR	14.6 (1.2-18.9) vs 30.6 (2.1-162)
Shadman, 2022[26] [118]	411 (145 vs 266)	A	60 (24-91) vs 58 (18-80)	39% vs 37%	NR	3 (2-11) vs 2 (1-6); p<0.001 ≥4: 31% vs 13%	NR	3-4: 55% vs 61%	16%	12 (3-26)
Sesques, 2020 [117]	61	A&T	59 (27-75)	34%	28% 2%	NR ≥4: 70%	30%	3-4: 78%	97%	5.7 (NR)
Steiner, 2021 [119]	165	A&T	60 (18-88)	28%	26% NR	3 (2-11) ≥4: 29.3%	78%	NR	NR	16.2 (14.3-19.1)
Vercellino, 2020 [120]	116	A&T	60.7 (49.2;67.6)	35%	29% 2.6%	3 (IQR 2-4) NR	12.1%	3-4: 76.7%	87.1%	8.2 (NR)
Wudhikarn, 2020a+b [121, 149]	60	A&T	63 (19.5-85.9)	30%	8.3% 20%	3 (2-9) NR	20%	1-2: 23.3% 3-4: 63.3%	63.3%	9 (NR)

Abbreviations: autoHSCT: autologous stem cell transplantatino, alloHSCT: allogenic stem cell transplantation, CAR-T: chimeric antigen receptor T cell therapy, ECOG: Eastern Cooperative Oncology Group, F: female, FU: follow-up, NR: not reported

Both nRCTs are highlighted in light orange

The number of patients refer to patients infused with CAR-T cells. Ranges are indicated with **–** *and the IQR with* **;** *between the numbers. The standard deviation is indicated with* **±**

† *Values for age and prior therapy are reported in median*

‡ *Follow up in months (range).*

⋄ *A: Axi-cel, T: Tisa-cel, A&T: Axi-cel and Tisa-cel*

[25] **nRCT**: CAR-T vs alternate therapies

[26] **nRCT**: CAR-T vs autoHSCT

3.6.2 Effectiveness/Efficacy

medianes Gesamtüberleben

Median OS was 12 months in JULIET and not reached in ZUMA-1. In seven real-world studies reporting a median OS, it ranged from 10.7 to 19.3 months [110, 112, 114-117, 146]. The estimated OS at 12 months ranged from 49% to 73.4% in the RWE [49, 111-113, 116, 118, 120, 121, 146-149], while it was 59% in ZUMA-1 (axi-cel) and 48% in JULIET (tisa-cel). Real-world studies reporting axi-cel and tisa-cel separately underlined the tendency of a higher 12-month OS of axi-cel (55%-57.1%) compared to tisa-cel (43.8%-53%) [111, 146].

medianes progressionsfreies Überleben

Median PFS was only reached in ZUMA-1 (5.9 months). In real-world studies, it ranged from three to 8.3 months [110, 112, 115-117, 120, 145-148]. The estimated PFS at 12 months ranged from 29.3% to 55.7% in the RWE and was 44% in ZUMA-1. Specific PFS outcomes at 12 months for axi-cel only were similar compared with ZUMA-1 results (35%-41.8%) [111, 146]. JULIET only reported 12-month PFS for patients with CR (83%).

breite Konfidenzintervalle für OS und PFS

With regard to OS and PFS, there was a high uncertainty with regard to the reported values in both pivotal and RWE studies, reflected in broad reported 95% confidence intervals.

vollständige Ansprechrate

CR rates in ZUMA-1 and JULIET ranged from 40%-58%. In real-world studies, CR ranged from 41.5%-48% after one month, 25%-40% after three months and 37.8% after six months.

hohes Verzerrungsrisiko bei Lebensqualität in JULIET

HRQoL was measured by using different questionnaires. One real-world study (with a mixed CAR-T cohort) used the EORTC QLQ-C30 questionnaire [148], JULIET (only tisa-cel) used FACT-Lym and SF-36 surveys. Both studies observed differences in health perception and HRQoL compared to baseline over time. Due to a high selection bias (only participants with CR or PR, no control group), the evidence about the effect of CAR-T cell therapy on HRQoL is very uncertain [61, 65].

For detailed information, see Table 3-11.

Table 3-11: Comparison of effectiveness/efficacy outcomes between pivotal trials and RWE studies (LBCL)

Study ID	n	FU‡	CR (95%CI)	OS				PFS†				HRQoL‡
				6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median OS, mo (95%CI)	6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median PFS, mo	
ZUMA-1	108	Up to 27.1[27]	58% (NR) (median FU 15.4)[28]	78% (69%-85%)[28]	59% (49%-68%)[28]	Estimated: 50.5% (40.2%-59.7%)[29]	NR* (12.8-NR*)[29]	49% (39%-58%)[29]	44% (34%-53%)[29]	NR	5.9 (3.3-15.0)[29]	NR
JULIET	111	19.3	40% (NR) (median FU 19.3)	NR	48% (38%-57%)	NR	12 (7-NR*) ITT[30]: 8.3 (5.8-11.7)	NR	Estimated: 83% (patients with CR or PR at 3 mo)	NR	NR* for patients with CR	**FACT-G TS** (MCID upper-lower limit: 3-7), 18 mo: +10.0 (11.1) **FACT-Lym S** (MCID upper-lower limit: 2.9-5.4), 18 mo: +3.1 (6.6) **FACT-Lym TOI** (MCID upper-lower limit: 5.5-11), 18 mo: +9.2 (13.6) **FACT-Lym TS** (MCID upper-lower limit: 6.5-11.2), 18 mo: +13.1 (16.1) [31] **SF-36 Physical health TS** (MCID 3), 18 mo: +3.9 (10.6) **SF-36 Mental health TS** (MCID 3), 18 mo: +2.1 (9.9)
Ayuk, 2021 [49]	21	4 (0.7-12.5)	**OR** (PR or CR) around day 30: 67%	NR	49% (25%-73%)	NR	NR	NR	37% (15%-59%)	NR	NR	NR
Baird, 2021 [145]	41	19.8 (3.3-27.6)	65.9% d28: 41.5%	NR	NR	NR	NR* (16.6-NE)	NR	NR	NR	6.1 (3.1-NE)	NR

[27] Longer-term safety and activity assessment (Aug 2018)

[28] Phase 1&2 (n=108 infused)

[29] Data from phase 2 (n=101)

[30] ITT: intention-to-treat analysis included all 165 enrolled patients

[31] According to the authors, the improvement was above the MCID upper limit

Study ID	n	FU‡	CR (95%CI)	OS				PFS†				HRQoL‡
				6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median OS, mo (95%CI)	6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median PFS, mo	
Bethge, 2022 [111]	356	11 (1-29)	37% A: 42% T: 32%	NR	52% A: 55% T: 53%	NR	NR	NR	30% A: 35% T: 24%	NR	NR	NR
Ghafouri, 2021 [112]	53	15.2 (NR)	64%	69% (56-80)	55% (41-68)	NR	17,7	54% (30-97)†	50% (26-97)†	NR	7.9 11,9†	NR
Hamadani, 2022 [113]	181 (only CAR-T)	13 (1-27.7)	NR	NR	73.4% (66.4-79.9)	NR	NR	NR	55.7% (48-63.2)	NR	NR	NR
Holtzman, 2021 [114]	45	7.1 (3;9.9)	49% d30: 36.5%	NR	NR	NR	15.1 (NR)	NR	NR	NR	NR*	NR
Iacoboni, 2021 [110]	75	14.1 (95%CI: 13.1-17.4)	32%	NR	NR	NR	10.7 (7.4-NR*)	33.3%	31.7%	NR	3 (2.6-4.7)	NR
Kuhnl, 2022 [146]	300	13.9 (9.1;19.4)	3 mo: 40% 6 mo: 37.8% Best CR: 50%	NR	53.9% A: 57.1% (49.8-63.8) T: 43.8% (31.1-55.9)	NR	14.8 A: 15.6 (11.1-NR*) T: 10.2 (7.7-NR*)	NR	Responders: 52% (44.7-58.8) A: 41.8% (35-48.4) T: 27.4% (17.5-38.3)	NR	3.5 A: 5.5 (3.3-10.1) T: 2.9 (1.7-3.6)	NR
Lamure, 2021 [115]	60	6.9 (0.5-26.1)	1 mo: 35% 3 mo: 25%	NR	NR	NR	12.3 (32.9-63.1)	NR	29.3% (17-42.8)	NR	3.1	NR
Nastoupil, 2020 [147]	275	13.8 (3.9-21.6)	Best CR: 64% (58%-69%) d30: 44%	NR	68% (63%-74%)	NR	NR*	NR	47% (41%-53%)	NR	8.3 (6-15.1)	NR
Ram, 2022[32] [148]	82 (41 vs 41)	7 (1.3-17.2) vs 7 (1.3-16.7)	1 mo: 46% vs 59%	74% vs 76%	69% vs 53%	NR	NR* vs NR*; p=0.792	39% vs 54%	32% vs 54%	NR	3.6 (1.6-5.6) vs NR*; p=0.209	23/41 (56%) pts with EORTC QLQ-C30 questionnaire (version 3) in study cohort baseline vs 1 mo: ND baseline vs 3 mo: ■ Overall health perception: 3.83 vs 5.6; p=0.005 ■ Overall quality of life: 3.87 vs 5.4; p=0.081

[32] Experimental vs experimental (elderly vs young cohort)

Study ID	n	FU‡	CR (95%CI)	OS				PFS†				HRQoL‡
				6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median OS, mo (95%CI)	6 mo (95%CI)	12 mo (95%CI)	24 mo (95%CI)	Median PFS, mo	
Sermer, 2020[33] [116]	215 (69 vs 146)	14.6 (1.2-18.9) vs 30.6 (2.1-162)	52% vs 22%; p<0.001	71% (61-82) vs 55% (47-64)	64% (54-77) vs 39% (31-48)	NR	19.3 vs 6.5; p=0.006	49% (39-63) vs 29% (23-38)	44% (33-58) vs 25% (19-33)	NR	5.2 vs 2.3; p=0.01	NR
Shadman, 2022[34] [118]	411 (145 vs 266)	12 (3-26)	NR	NR	67% (59-75) vs 76% (70-81); p=0.1	47% (33-60) vs 69% (63-74); p=0.004	NR	NR	52% (43-61) vs 59% (53-65); p=0.2	42% (30-53) vs 52% (46-58); p=0.1	NR	NR
Sesques, 2020 [117]	61	5.7 (NR)	1 mo: A: 46% T: 48%	68% (53-80)	NR	NR	11.8 (6-12.6) A: NR* (4.6-NR*) T: 7.4 (4.8-12.6)	44% (30-57)	NR	NR	3 (2.8-8.8) A: 3.1 (2.9-NR*) T: 3 (2.1-8.8)	NR
Steiner, 2021 [119]	165	16.2 (14.3-19.1)	NR	NR	MACE: 58% No-MACE: 62%	NR	NR	NR	MACE: 38% No-MACE: 42%	NR	NR	NR
Vercellino, 2020 [120]	116	8.2 (NR)	NR	78.5% (71-87)	67% (57-79)	NR	NR	NR	NR	NR	Estimated: 7.4 (3-NR*)	NR
Wudhikarn, 2020a+b [121, 149]	60	9 (NR)	NR	NR	69% (57-82)	NR	NR	NR	40% (28-56)†	NR	NR	NR

Abbreviations: A: Axi-cel, AE: adverse event, CR: complete remission, CRS: cytokine release syndrome, EFS: event-free survival, EORTC: European Organisation for Research and Treatment of Cancer, FACT-Lym S: Functional Assessment of Cancer Therapy-Lymphoma subscale, FACT-G: FACT- General, ICANS: Immune effector cell-associated neurotoxicity syndrome, mo: months, NA: not available, ND: no statistical significant difference, NE: not evaluable, NR: not reported, NR: not reached, OS: overall survival, PD: progressive disease, PFS: progression-free survival, pts: patients, SF-36: short-form 36 Health Survey, T: Tisa-cel, TOI: Trial Outcome Index, TS: total score*

Both nRCTs are highlighted in light orange

† EFS and not PFS was reported

‡ Values in real-world studies for follow-up are reported in median (months), values for HRQoL are reported in mean

[33] nRCT: CAR-T vs alternate therapies

[34] nRCT: CAR-T vs autoHSCT

3.6.3 Safety

detailliertere Sicherheitsdaten in Zulassungsstudien

Both pivotal trials reported an overall adverse event incidence of 100%. Adverse events were reported in more detail in pivotal trials than in real-world studies. The real-world studies reporting adverse events (15 out of 17) mainly focused on CRS and neurotoxicity (ICANS) [49, 110-115, 117-119, 121, 145-149].

CRS und ICANS in RWE und Zulassungsstudien

While CRS incidence tended to be higher in ZUMA-1 (93%) compared with JULIET (58%), CRS grade ≥3 occurred more often in JULIET (22%) than ZUMA-1 (11%). In contrast, CRS was reported in 68%-93% of the patients in the real-world studies, and CRS grade ≥3 in 2.4-14% of the patients. CRS results for axi-cel (81-93%) and tisa-cel (65-79%) in real-world studies showed a similar tendency in CRS incidence depending on the CAR-T product compared with pivotal trials [111, 117].

Neurotoxicity and neurotoxicity grade ≥3 occurred more often in ZUMA-1 (67% and 32%) than in JULIET (21% and 12%). Neurotoxicity incidences in real-world studies were between 15% and 68.7%. Grade ≥3 neurotoxicity occurred in 1%-40% of the patients.

heterogene Daten zu Neutropenie in RWE und Zulassungsstudien

Neutropenia grade ≥3 occurred in 39% (ZUMA-1) and 20% (JULIET) of the patients in the pivotal trials and between 19.8% and 97.6% of the patients in the pivotal trials [117, 145, 146]. 24% of the patients in ZUMA-1 and JULIET experienced thrombocytopenia grade ≥3, in contrast, it occurred in 14.5%-68% of real-world study patients [117, 145, 146]. No remarkable differences could be observed between the pivotal studies and the real-world studies regarding infections.

vergleichbare rückfallfreie Mortalitätsrate in ZUMA-1 und RWE; höhere Mortalität in Zulassungsstudien

NRM rates were comparable between ZUMA-1 (3.7%) and real-world studies (12 month NRM: 1.7%-7.3%) [111, 113, 121, 146]. Overall mortality tended to be slightly higher in pivotal studies (50% and 61%) compared with real-world studies (25%-48%), however, as follow-up periods are heterogeneous, no substantiated comparison is possible.

For detailed information, see Table 3-12.

Table 3-12: Comparison of safety outcomes between pivotal trials and RWE studies (LBCL)

Study ID	n	FU‡	CRS	CRS ≥ grade 3	Neurotoxicity	Neurotoxicity ≥ grade 3	Mortality/ NRM†	(S)AE
ZUMA-1	108	Up to 27.1[35]	93%	11%	67%	32%	At data cutoff (median FU 27.1): 50% NRM: 3.7% (2 axi-cel related)	Any AE (≥3): 100% (98%) Any SAE (≥3): 56% (48%) Anaemia (≥3): 68% (45%) Leukopenia (≥3): 19% (17%) Neutropenia (≥3): 44% (39%) Thrombocytopenia (≥3): 35% (24%) Any prolonged cytopenias lasting ≥ 30 days (≥3): 45% (30%) Febrile neutropenia (≥3): 36% (32%) Any infections (≥3): NR (28%)
JULIET	111	19.3	58%	22%	21%	12%	61%	Any AE: 100% (89%) Any SAE (≥3): 65% (NR) Anaemia (≥3): 48% (39%) Leukopenia (≥3): 20% (20%) Neutropenia (≥3): 13% (12%) Thrombocytopenia (≥3): 35% (24%) Any prolonged cytopenias lasting ≥ 30 days (≥3): 44% (34%) Febrile neutropenia (≥3): 15% (14%) Any infections (≥3): 34% (20%)
Ayuk, 2021 [49]	21	4 (0.7-12.5)	71.4%	14.3%	47.6%	19%	48%	NR
Baird, 2021 [145]	41	19.8 (3.3-27.6)	NR	2.4%	NR	24.4%	NRM: 2.4%	SAE until d28: Severe cytopenias: 97.6% grade ≥3 neutropenia: 97.6% grade ≥3 thrombocytopenia: 56.1% Infection until d28: 46.3% → mild to moderate: 68.4% Infection beyond d365: 47.1%

[35] Longer-term safety and activity assessment (Aug 2018)

Study ID	n	FU‡	CRS	CRS ≥ grade 3	Neurotoxicity	Neurotoxicity ≥ grade 3	Mortality/ NRM†	(S)AE
Bethge, 2022 [111]	356	11 (1-29)	73% (A vs T: 81% vs 65%; p=0.0003)	12%	33% (axi-cel vs tisa-cel: 44% vs 22%; p<0.0001)	11%	46% NRM: 6% 1y NRM: 5.5%	Grade 4 neutropenia: 81% median duration: 13 days (1-419) Severe thrombocytopenia: 37% median duration: 34 days (2-375)
Ghafouri, 2021 [112]	53	15.2 (NR)	68%	6%	30%	19%	43%	NR
Hamadani, 2022 [113]	181 (only CAR-T)	13 (1-27.7)	82.3%	9.9%	61.9%	20.9%	30.3% 1y NRM: 4.8%	NR
Holtzman, 2021 [114]	45	7.1 (3;9.9)	80%	NR	56%	40%	NR	NR
Iacoboni, 2021 [110]	75	14.1 (95%CI: 13.1-17.4)	71%	5%	15%	1%	NRM: 4%	NR
Kuhnl, 2022 [146]	300	13.9 (9.1;19.4)	88%	7.7%	36.8%	15.7%	1y NRM: 7.3% A: 8.7% T: 3.1%	Cytopenia: Grade ≥ 3 neutropenia: 19.8% Grade ≥ 3 thrombocytopenia: 14.5%
Lamure, 2021 [115]	60	6.9 (0.5-26.1)	NR	5%	NR	12%	48%	Grade 3-4 cytopenia after lympho-depletion and CAR-T infusion: 98% Infections: 33%
Nastoupil, 2020 [147]	275	13.8 (3.9-21.6)	91%	7%	68.7%	31%	35% NRM: 4.4%	NR
Ram, 2022[36] [148]	82 (41 vs 41)	7 (1.3-17.2) vs 7 (1.3-16.7)	NR	9.8% vs 7.3%	NR	2.5% vs 4.9%	3 mo NRM: 0	Acute kidney injury: 7.3% vs 7.3 Atrial fibrillation: 7.3% vs 7.3 Late pancytopenia: 22% vs 26.8% Clinical or microbiology documented infections: 26.8% vs 19.5%
Sermer, 2020[37] [116]	215 (69 vs 146)	14.6 (1.2-18.9) vs 30.6 (2.1-162)	NR	NR	NR	NR	NR	NR
Shadman, 2022[38] [118]	411 (145 vs 266)	12 (3-26)	74% (95%CI: 67-81)	7% (95%CI: 4-12)	24% (95%CI: 17-33)	15% (95%CI: 9-22)	36% vs 34% 100d NRM: 2% (0-5) vs 4% (2-7); p=0.3 1y NRM: 3% (1-6) vs 7% (4-11); p=0.05 2y NRM: 6% (1-16) vs 9% (5-13); p=0.6	NR

[36] Experimental vs experimental (elderly vs young cohort)

[37] nRCT: CAR-T vs alternate therapies

[38] nRCT: CAR-T vs autoHSCT

Study ID	n	FU‡	CRS	CRS ≥ grade 3	Neurotoxicity	Neurotoxicity ≥ grade 3	Mortality/ NRM†	(S)AE
Sesques, 2020 [117]	61	5.7 (NR)	A: 93% T: 79%	A: 7% T: 9%	A: 32% T: 24%	A: 11% T: 9%	NR	Axi-cel vs Tisa-cel Anemia: 93% vs 80% Grade ≥ 3: 21% vs 6% Thrombocytopenia: 96% vs 80% Grade ≥ 3: 68% vs 29% Neutropenia: 78% vs 53% Grade ≥ 3: 36% vs 35% Infection within 28d: Grade 3: NR vs 34%
Steiner, 2021 [119]	165	16.2 (14.3-19.1)	92%	14%	61%	31%	NR	MACE until d30: 16%
Vercellino, 2020 [120]	116	8.2 (NR)	NR	NR	NR	NR	25% NRM: 1.7%	NR
Wudhikarn, 2020a+b [121, 149]	60	9 (NR)	80%	11.7%	24%	21.7%	35% 1y NRM: 1.7% (0.1-8)	Neutropenic fever within 30d: 86.7% Overall 539 grade ≥ 2 events in 59 pt: Cumulative incidence of grade ≥ 3 toxicities 1y after infusion: Cardiovascular: 16.7 (8.5-27.2) Metabolic: 54.8 (40.5-67.1) Haematologic: 57.5 (43.4-69.9) Pulmonary: 13.3 (6.2-23.3) Neurologic: 18.3 (9.7-29.1) Infections: 35.4 (22.6-48.4)

Abbreviations: A: Axi-cel, CRS: cytokine release syndrome, d: day, mo: month, MACE: major adverse cardiovascular events, NRM: non-relapse mortality, NR: not reported, T: Tisa-cel, y: year
Both nRCTs are highlighted in light orange

† Mortality represents overall deaths, numbers are crude values. 95%CI are shown in brackets, if they have been reported.

4 Discussion

CAR-T Zelltherapie als neue Therapiemethode für Blutkrebs

B-cell acute lymphatic leukaemia (B-ALL) and large B-cell lymphoma (LBCL) are haematologic cancers involving malignant B-cells. Apart from established treatment options such as chemotherapy, new immunological treatments have emerged. CAR-T cells are genetically modified T-cells targeting cancer antigens, thereby specifically eliminating tumour cells. This new but very cost-intensive therapy is associated with high expectations and considered a new achievement and milestone in cancer therapy.

Ziel: Vergleich Patient*innen-charakteristika, klinischer Wirksamkeit und Sicherheit von Kymriah® und Yescarta® zwischen RWE und Zulassungsstudien

This report aimed to assess the real-world evidence (RWE) on patient characteristics, clinical effectiveness and safety of the two CAR-T cell therapies Kymriah® (Tisagenlecleucel) and Yescarta® (Axicabtagene Ciloleucel) for refractory and relapsed B-ALL in children, adolescents and young adults and LBCL (DLBCL and PMBCL) in adults and to compare the results with those of the pivotal studies ELIANA, ZUMA-1 and JULIET. Additionally, the results of other health technology assessments (HTAs) regarding the available evidence and their critical evaluation of the CAR-T cell therapies were described and summarised in section 3.1.

Summary of findings

HTA reports

Zusammenfassung der HTA Berichte: Erweiterung eines systematischen Reviews (SR)

historische Kontrollen aufgrund Heterogenität oft nicht anerkannt

The summary of HTA results complements another recent systematic review of HTAs of CAR-T therapies [68]. Results from the systematic review were controlled, revised when deemed necessary and expanded by reports from five further institutions (in four countries). In slight contrast to this review, a detailed overview of the economic analysis of the HTA reports was provided. This report primarily focused on a summary of the clinical evidence and the critical evaluation of the HTA reports. Both reviews conclude that the HTA reports mainly criticise the uncontrolled study design, small patient numbers and short follow-up of the pivotal trials. Some HTA reports considered the historical controls as a comparative arm provided by the manufacturer (SCHOLAR-1 for ZUMA-1; SCHOLAR-1, CORAL for JULIET). However, these were often not considered reliable to high heterogeneity in the study design.

Acute lymphoblastic leukaemia

Evidenz aus 12 nicht-randomisierten, unkontrollierten Studien

Insgesamt 641 Patient*innen, Verzerrungs-potential: moderat bis hoch

strengere Einschlusskriterien in Zulassungsstudie (ELIANA)

The available evidence for the systematic review on ALL includes twelve non-randomized, uncontrolled observational studies. Five studies reported on the same cohort of patients from the Paediatric Real World CAR Consortium (PRWCC). Overall, outcome data were reported for 641 patients (PRWCC patients only counted once). All studies are unblinded and non-randomized, leading to a moderate to high risk of bias evaluation by the IHE checklist for observational studies.

The patient characteristics of the real-world population often differed from pivotal trials due to the restrictive inclusion and exclusion criteria of the latter. Hence, the age span in RWE ranged from 0 to 29.2 years, compared to three to 23 years in the pivotal study. Patients had a lower tumour burden in the real-world studies compared with ELIANA (<5% blasts in bone marrow or MRD negative before infusion). Further, patients with extramedullary

disease, patients with active CNS infiltration, patients with prior anti-CD19 or CD22 therapy and infants were included in real-world data, while those patients were excluded in the pivotal trial. The median number of prior therapies was three in both real-world studies and ELIANA.

ähnliche Wirksamkeitsergebnisse in RWE und ELIANA

keine RWE Studie zu Lebensqualität

Due to high heterogeneity of patients in the RWE studies, direct comparison of effectiveness and safety is challenging. Nevertheless, rates of complete remission (CR), relapse-free survival (RFS), event-free survival (EFS) and overall survival (OS) in RWE studies are in line with results from ELIANA. CR at day 28 ranged from 74% to 100% in real-world studies and was 80% in ELIANA. EFS at 12 months ranged from 31%-72% and OS at 12 months was 38.5%-100%. In contrast, 12-month EFS and OS in ELIANA were 50% and 76%, respectively. Outcomes on health related quality of life (HRQoL) were not reported by any study.

vergleichbare Sicherheitsergebnisse in RWE und ELIANA

The safety profile of tisagenlecleucel seems to be comparable to the pivotal trial (overall cytokine release syndrome (CRS) 42%-86% vs 77%; grade ≥3 CRS 14%-22% vs 46%; overall neurologic events 0%-36% vs 40%; grade ≥3 neurologic events 0%-29% vs 13%, infections 37%-54% vs. 24%). Deaths that could be associated with severe adverse events ranged from 0% to 6.5% in RWE and were in this range in ELIANA with 4%.

hohe Gesamtmortalität

Overall mortality was high, with 25% of all patients in ELIANA and 0%-42% dying despite CAR-T therapy.

Large B-cell lymphoma

Evidenz aus 17 Beobachtungsstudien (inkl. 2 nRCTs); unkontrollierte, nicht-randomisierte Studien: Verzerrungspotential: moderat bis hoch; Interessenskonflikte der Autor*innen

The available evidence for the systematic review on LBCL includes 17 observational studies, two of them being nRCTs. The majority of them are small, retrospective single-arm studies, including patients with LBCL, most of them with DLBCL. However, also patients with diseases beyond the approved indications were included. All studies are unblinded and non-randomized, leading to a moderate to high risk of bias evaluation by the IHE checklist for observational studies and ROBINS-I for nRCTs. Most study authors declared conflicts of interest with the manufacturer (Novartis and Kite Gilead). Both pivotal studies are single-arm, unblinded observational studies that are still ongoing.

insgesamt 2,105 Patient*innen

Overall, outcome data were reported for 2,105 patients. The pivotal trials included 108 (ZUMA-1) and 111 (JULIET) patients.

strengere Einschlusskriterien in Zulassungsstudien (ZUMA-1, JULIET)

keine Überbrückungstherapie, alloHSCT, ECOG >1 erlaubt in Zulassungsstudien

Differences between real-world studies and pivotal studies include eligibility criteria. While the inclusion criteria in real-world studies were broadly defined based on the received intervention and clinical indications, the pivotal studies were far more selective. For example, patients undergoing bridging therapy were excluded in ZUMA-1, but not in JULIET. Furthermore, the authorization of bridging therapies better reflects the real-world situation. In the pivotal trials, only patients with an ECOG performance status of one were admitted to the trial, while in the real-world studies patients frequently had a status of two and higher. Patients with prior alloHSCT were excluded in both pivotal trials. Patients in the pivotal studies tended to be younger compared with real-world studies. Regarding the number of patients with advanced disease stages (3-4), the pivotal studies (76%-85%) were comparable to real-world studies (55%-92%). The number of prior therapies was heterogeneous within real-world studies (27%-100% receiving ≥3 therapies). In contrast, 52% and 69% of the patients in the pivotal trials received three or more prior therapies.

heterogene Studien, medianes Gesamtüberleben zwischen 10,7 und 19,3 Monaten

In both pivotal trials and real-world studies, there was a lack of high-quality comparative data on effectiveness and safety. The median OS in the real-world studies ranged from 10.7 to 19.3 months (seven studies), and the median PFS ranged from three to 8.3 months (ten studies). The median OS in JULIET was 12 months and was not reached after 24 months in ZUMA-1. Median PFS in ZUMA-1 was 5.9 months and was not reached in JULIET. 12-month OS rates in real-world studies ranged from 49%-73.4% and PFS rates from 29.3%-55.7%. Two studies investigated OS and PFS depending on the two CAR-T products, with Yescarta® tending to better results. ORR after one month ranged from 58%-67% (real-world studies) and was only reported after 12 months in ZUMA-1 with 82%.

widersprüchliche Ergebnisse in nRCTs hinsichtlich Überlegenheit der CAR-T Zelltherapie

The two nRCTs compared CAR-T patients with alternate therapies (e.g. alloHSCT) and reported contrary results. One nRCT reported a significantly higher median OS and PFS in CAR-T patients compared to alternate therapies. However, these effects were no longer significant after adjusting for unfavourable pre-treatment disease characteristics. Additionally, patients in the alternate cohort had a significantly increased incidence of refractory disease as well as elevated lactate dehydrogenase (LDH) levels, suggesting less favourable lymphoma biology compared with CAR-T patients [116]. In the second nRCT, patients undergoing salvage therapy and achieving PR were then either referred to autoHSCT or CAR-T. Possible patient crossover is not reported. No difference in 12-month OS and PFS rates and significantly lower 24-month OS rates in the CAR-T cohort compared with autoHSCT were reported. With only two trials, with a comparative study design, selection criteria and contradicting results, there is no reliable evidence favouring CAR-T cell therapy over standard therapy.

Lebensqualität nur von einer Studie berichtet, keine statistisch signifikante Verbesserung

Health-Related Quality of Life (HRQoL) was reported in one study. Improvements in overall health perception were documented after three months, and no statistical difference in overall quality of life was observed [148]. HRQoL was reported in JULIET, though only for patients with CR and PR. Due to a lack of data from nonresponding patients, it is impossible to quantify the impact of tisa-cel on HRQoL.

häufig unerwünschte Ereignisse (CRS, Neurotoxizität)

In both pivotal trials and real-world studies, adverse events often occurred in CAR-T patients. Most commonly, cytokine release syndrome (CRS) (68%-93%) and neurotoxicity (15%-68.7%) occurred. Other adverse events (AE) included haematological complications (cytopenias, anaemia), infections, acute kidney injury and cardiovascular complications. Some studies observe higher AE incidences in Yescarta® compared with Kymriah® [117, 148]. In the pivotal studies, all patients experienced adverse events. CRS was reported in 93% (ZUMA-1) and 58% (JULIET) and neurotoxicity in 67% (ZUMA-1) and 21% (JULIET). Other complications included the adverse events mentioned above.

hohe Gesamtmortalität

Overall mortality despite CAR-T was high in both pivotal (50%-61%) and RWE studies (25%-48%). However, as pivotal studies have a longer follow-up, mortality in observational studies might be even higher.

Embedding our evidence into existing knowledge

erster systematischer Review (SR) über Vergleich zwischen RWE und Zulassungsstudien

To the best of our knowledge, this report represents the first systematic review of real-world studies of CAR-T therapies Kymriah® and Yescarta®, comparing real-world and pivotal evidence.

keine SRs für Kymriah® bei B-ALL CAYAs

For B-ALL, one systematic review and meta-analysis conducted in 2020 summarised the evidence on various anti CD19 CAR-T cell therapies: The review only included the pivotal trial ELIANA and a publication of its Japanese subcohort [151]. Another systematic review and meta-analysis from 2021 evaluated effectiveness and safety of all market-approved CAR-T cell products in haematologic malignancies. In this study, data on tisagenlecleucel for CAYA with r/r ALL included the ELIANA trial and a publication of the same group of authors from 2014, three years before tisagenlecleucel market authorization [152]. No systematic review focusing only on Kymriah® in CAYA with r/r ALL could be identified.

Cochrane SR für CAR-T bei r/r DLBCL: unsichere Evidenz zu Wirksamkeit und Sicherheit

For LBCL, one Cochrane report conducted in 2021 summarised the evidence on CAR-T cell therapy for patients with r/r DLBCL: The report regarded the clinical evidence on CAR-T therapy as uncertain due to a lack of direct comparison with other treatments. The report included both pivotal trials ZUMA-1 and JULIET, however, without comparing them with real-world evidence.

SR mit Metaanalyse zu CAR-T in LBCL Patient*innen: Limitationen in der Durchführung

One other systematic review, including a meta-analysis, reports the effectiveness and safety of anti-CD19 CAR-T cell therapies in patients with r/r LBCL. The report includes 1,687 patients and demonstrates a pooled 12-month OS of 63% (95%CI: 56-70%). It concludes that CAR-T cells show good results in effectiveness with a durable safety profile. However, limitations of the report include pooling data of heterogeneous studies as this might lead to wrong correlations and conclusions. Differences include patient population, lymphoma subtypes, follow-up time, CAR-T product and duration of treatment. Parameters for statistical heterogeneity (I^2) were high. Additionally, all studies were uncontrolled studies without comparison with alternative treatments, underlining once more the need for randomized controlled studies [153].

Limitations of the evidence

Limitationen der Evidenz: unkontrollierte, retrospektive Studien, heterogene Kohorte

Almost all identified studies were observational studies with no control group, including the pivotal trials. The retrospective study design limits data quality and granularity. Patient selection varies between centres and leads to a highly heterogeneous cohort.

fehlende Daten (Zeitpunkte der Messung)

The reporting of studies was poor. Studies did not clearly describe the timing of data collection of outcome parameters. Therefore, data presented without a time point could not be compared (e.g. survival rates). Data on the number of initially enrolled patients were often missing. Due to the retrospective nature of most studies, only infused patients were included in the analysis. However, these results might over-estimate the actual benefit. For comparing CAR-T therapy with alternate therapies, results from the entire intention-to-treat cohort should be taken. In addition, numbers on how many patients fail to be infused or manufacturing failure could be relevant information for decision-makers.

nur infundierte Patient*innen analysiert

Heterogenität hinsichtlich Bewertungssysteme für unerwünschte Ereignisse

Although all grading systems utilised by our identified studies are valid to report on adverse events in a standardised way, there is still heterogeneity between grading systems. A report from 2020 compared the different grading systems and concluded that although all systems agreed on the diagnosis, substantial heterogeneity was observed in the final grades [154]. Hence,

the possibility of biased grading results cannot be fully excluded. Unified grading should be used across clinical trials and real-world studies to avoid discrepancies.

generelles Problem onkologischer Studien: intransparentes Zensieren von Patient*innen

A general limitation in oncological trials is the issue of intransparent censoring of patients. Missing information if, when and how many patients were censored could lead to altered Kaplan-Meier curves and biased outcome parameters. Additionally, it is possible that due to censoring, therapy-related deaths were not recognised as such. The issue has been addressed by others [155], who propose clearly defined censoring rules for oncological studies or consideration of this limitation in the risk of bias grading [156]. In addition, the different statistical approaches, specifically in CAR-T studies, have been addressed by another study, in which the authors concluded that the use of inappropriate methods leads to different results [157].

Limitations of the report

Limitationen des Berichts: nur Beobachtungsstudien inkludiert (keine RCTs vorhanden)

The results of our report should be seen in light of its limitations: First, we have included observational studies in the absence of randomised controlled trials. Although such studies are generally more prone to internal validity concerns, it still represents the best available evidence on this topic. We carefully selected and evaluated these studies aligned with Cochrane Methodology to mitigate concerns.

mögliche Doppelmeldung von Patient*innen

Second, the risk of overlapping data within identified studies exists, especially if study authors did not adequately disclose the name or identifier of the study they reported on. However, although overlapping samples cannot be excluded, this should not alter the results as most of the identified publications were referable to respective studies.

keine etablierte Methode für Ergebnisvergleich zwischen RWE und Zulassungsstudien

Third, there is no established methodology to compare patient characteristics and results between pivotal trials and real-world studies. In order to reduce bias in this analysis, we solely descriptively presented these differences noting that causal inference is not possible (e.g., in how far different patient characteristics influenced different results between pivotal and real-world studies).

Approval and remuneration

CAR-T kein Fertigarzneimittel, daher keine vorgeschriebene Arzneimittelpreisverordnung

The evidence for the superiority of CAR-T cells compared with standard therapies is uncertain. Still, Kymriah® and Yescarta® got approved by the FDA in 2017 and by the EMA in 2018 as orphan drugs. In the European Union, CAR-T cell therapies are classified as advanced therapy medicinal products (ATMPs) by Regulation 1394/2007. ATMPs are classified as medicinal products according to § 2 of the legislation on medicinal products, including pricing specifications. However, as CAR-T products are not regarded as proprietary medicinal products, pricing regulations do not apply and there are no legal restrictions on the manufacturers' pricing [158].

kostenintensive CAR-T Therapie (300.000 € pro Infusion)

nationale erfolgsabhängige Erstattungsmodelle

Commercial CAR-T cell therapies are extremely cost-intensive. Prices vary between countries but amount to more than 300,000€ per infusion (list price) [159]. To prevent overwhelming the solidarity community, costs could be reduced by hospital-based or off-the-shelf CAR-T products and by alternative financing models. A pay-for-performance (P4P) model could be such an alternative where payments are only made after successful treatments [1]. In countries like Germany, Italy and Spain, reimbursement is already linked to

zusätzliche kostenintensive Medikamente

individual patient outcomes [159]. Regional P4P payment models have been negotiated in Austria. In addition, the treatment of adverse events is costly. CRS is often managed with the antibody tocilizumab. Tocilizumab has an ex-factory price of 637.20€ for 400mg/20ml in Austria. At a dose of 8mg/kg and repeated administration up to 4 doses, considerable costs per patient are generated.

Ungleichheiten in Gesundheitssystemen führen zu Ungleichheiten in CAR-T Behandlungen

6 CAR-T Zentren in Ö

In case that CAR-T proves to be superior to alternative therapies, inequalities due to economical differences in healthcare systems might arise. Healthcare systems with smaller budgets remain behind in their access to CAR-T cell therapy, leading to increased inequalities in health care. Additionally, not all European countries have their own CAR-T treatment program or centres. Therefore, patients must travel to neighbouring countries to get access to the therapy. Besides language or travelling issues, different governments and reimbursement agencies increase the complexity of the topic. In Europe, the Eastern countries are particularly affected, mainly due to the high costs of the therapy and thereby "a consequent lack of interest from companies" [160]. However, specialized cancer centres optimize patients' clinical care with specialized staff and play an important part in cancer research. In Austria, six such specialized centres comply with strict criteria.

dezentralisierte (krankenhausbasierte) Produktion senkt Kosten und Produktionszeiten

Apart from alternative financing models, costs and duration between leukapheresis and infusion could be reduced by a decentralized "on-site" production. This "in-house" production is an alternative made possible by production automation technologies like the CliniMACS Prodigy [49]. Experts of the German institute for cancer research (DKFZ) calculated a non-profit model for decentralized CAR-T cell production. They concluded that the manufacturing duration could be almost halved (12-14 days) and the costs reduced to a fifth (60,000€) with further room for improvement [44]. In Austria, three production devices have been purchased for hospital-based CAR-T production.

Ongoing studies (new evidence awaited: pivotal ongoing)

keine RCTs für Kymriah® bei B-ALL

No RCTs are currently running for Tisagenlecleucel in B-ALL patients. A single-arm phase II study (CASSIOPEIA) evaluating Kymriah® in special children, adolescents and young adults (CAYA) with refractory high-risk B-ALL that have a dismal prognosis and high treatment-related toxicity with conventional therapy and HSCT is currently ongoing. Results will be compared to a matched historical group [161].

zwei RCTs als Zweitlinientherapie für LBCL: BELINDA und ZUMA-7

Two RCTs are currently investigating both CAR-T cell therapies described in this report for second-line treatment in r/r LBCL: BELINDA (Tisagenlecleucel vs salvage chemotherapy and autoHSCT) and ZUMA-7 (Axicabtagene Ciloleucel vs standard care).

hohes cross-over von Patient*innen von einer Kohorte zur anderen

primäre Ergebnisse mit Vorsicht zu beachten: bessere Ergebnisse in CAR-T Kohorte

Preliminary results do not favour one intervention over the other (event-free-survival in the BELINDA trial. However, there is a high cross-over of patients in the standard care group to the tisa-cel cohort (50.6%) [162]. Therefore, outcome analyses including these patients may bias the evidence. In the ZUMA-7 trial, better outcome effects were observed in the CAR-T cohort. However, these results must be treated with caution, as only 36% of the patients in the standard care cohort responded to chemoimmunotherapy and proceeded to high-dose chemotherapy with autoHSCT. 56% of the patients switched from standard therapy to CAR-T, although a switching sensitivity analysis was conducted [163]. One systematic review analyzed three availa-

ble RCTs (ZUMA-7, BELINDA, TRANSFORM) and concluded that CAR-T therapies are superior to standard therapies in second-line for patients with LBCL [164]. However, this was not considered sufficient evidence due to the limitations of the individual studies mentioned above. In addition, the majority of the authors have a conflict of interest and received honoraria from the manufacturers (Kite, Gilead and Novartis).

Indikationserweiterungen in Aussicht, andere ZUMA Studien

There are several other ZUMA trials for other indications, interventions and therapy lines. ZUMA-12 even investigates the use of Axicabtagene Ciloleucel as first-line therapy [165]. The FDA approved Axicabtagene Ciloleucel for second-line treatment of LBCL in April 2022 [166]. The EMA extended the recommendation of Axicabtagene Ciloleucel, including adult patients with r/r follicular lymphoma after three or more lines of systemic therapy [167].

Evidence gaps & Lessons Learnt

fehlende Evidenz: RCTs, Einfluss von Überbrückungstherapie und Lymphodepletion, Vergleich zwischen Kymriah® und Yescarta® für LBCL Patient*innen, Indikationserweiterung für Erst- und Zweitlinientherapie, Lebensqualität

Whether these new studies and trials close the present evidence gaps is uncertain. Currently, one of the most pressing limitations is the lack of RCTs. Long-term effectiveness and safety data are necessary to detect not only severe but also more subtle toxicities. As CAR-T cell therapies are currently used as third line rescue therapy, no randomised data are or will be available. However, with the widening of the indication to first or second line, comparable data will be essential to make evidence-based decisions for the benefit of the patient. Apart from the unclear superior effect of CAR-T to standard therapy, there is no clear evidence of the impact of bridging therapy before CAR-T infusion or the impact of different lymphodepletion regimens. In addition, there is missing evidence on the order and combination of different treatment options for the best clinical outcome for the patients. A head-to-head comparison between Yescarta® and Kymriah® would be necessary to estimate the risks and benefits for individual LBCL patients. Another outcome which is relevant for patients and practitioners and should be reported more transparently in future studies is treatment-related mortality. Further, only one study reporting on health-related quality of life could be identified, however, this outcome is especially of interest for patients.

fehlende Erkenntnisse aus CAR-T Registern

Although the documentation in CAR-T registers is mandatory, data from these registers have been published only scarcely.

hohe Heterogenität zwischen den Studien

In conclusion, all data presented in this report must be treated with caution due to a high heterogeneity between the studies. Heterogeneity occurred, among others, in reported outcomes (and time points), length of follow-up, eligibility and grading criteria and CAR-T product. More controlled trials with standardized measurements and a longer follow-up are needed to draw any meaningful conclusions. Furthermore, evidence or recommendations on how to proceed after CAR-T cell therapy to maintain remission are still lacking.

5 Conclusion

hohe Heterogenität: unsichere Evidenz

Potential von CAR-T in B-ALL Patient*innen

Overall, evidence from both pivotal trials and real-world data is too heterogeneous and uncertain to clearly show superiority of CAR-T cell therapies to standard therapy in adult patients with r/r LBCL. Missing head-to-head data between Kymriah® and Yescarta® also does not suggest a favourable CAR-T product. More research (comparative trials) is necessary, and the evidence should be continually evaluated. However, as far as a conclusion can be drawn, real-world evidence confirms feasibility and safety of CAR-T cell therapy as a treatment for relapsed young B-ALL patients, as presented in the pivotal trial. It thereby provides the potential for the treatment of patients in which other therapies have failed.

mehr prospektive Studien notwendig

Real-world studies often retrospectively included all patients infused with CAR-T in a certain time period which distinguishes them from pivotal trials which carefully (prospectively) selected a narrow patient collective. Further, real-world evidence shows that CAR-T therapy was often used beyond the approved indications.

keine ausreichende Evidenz zu Überlegenheit von CAR-T Zelltherapien

The real-world studies identified in this report do not close the knowledge gap as to whether and in which patient groups CAR-T therapies are superior to alternative established therapies.

Fokus auf Evidenz, ethische und ökonomische Erwägungen notwendig; Patientenselektion essentiell

Both decision-makers and clinicians should reflect on the available evidence instead of expanding CAR-T therapies in the context of everyday clinical practice (e.g., off-label use). In so doing, the benefit-harm needs to be carefully considered, as there are substantial, potentially life-threatening side effects. For these ethical reasons but also reasons of cost-effectiveness, the selection of patients is of utmost importance.

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Appendix

Summary of HTA reports

Table A-1: Comparison of HTA reports (table adopted and extended from [68])

Agency	Year	Comparator	Evidence	Comparative analysis	Interpretation of the clinical evidence
Tisagenlecleucel, paediatric ALL					
CADTH [71]	2019	Blinatumomab	ELIANA, ENSIGN, and B2101J vs von Stackelberg et al [83]	Naive comparison using ELIANA only. CADTH considered it inappropriate to pool data because of differences in dosing and study designs	There is **uncertainty** in the clinical evidence because of the **lack of long-term follow-up, single-arm trial design, and small patient numbers** in the studies Tisa-cel has potential to exert severe adverse events, is resource intensive
ICER [72]	2018	Clofarabine	ELIANA, ENSIGN, and B2101J vs Jeha et al. [81]	Naive indirect comparison, descriptive with potentially significant selection bias and other confounding factors No formal statistical comparisons undertaken	There is at least a small net health benefit compared with salvage chemotherapy, but it may be substantial, although the magnitude is **uncertain** because of **noncomparative trials** of **short duration**
MSAC [73]	2019	Blinatumomab	ELIANA, ENSIGN, and B2101J vs von Stackelberg et al [83]	Naive comparison using pooled ELIANA and ENSIGN data	Tisa-cel shows promising rates of remission, although there are clinical **uncertainties** (because of **single-arm studies, small patient numbers, heterogeneous patient characteristics, and short follow-up**)
NICE [74]	2021	Blinatumomab	ELIANA, ENSIGN, and B2101J vs von Stackelberg et al [83]	Naive comparison using pooled ELIANA, ENSIGN, and B2101J data	Tisa-cel is clinically effective, but a **lack of comparative data** is a challenge; clinical evidence beyond 30 months is **uncertain** because of **small patient numbers** and differences in trial populations. No robust evidence that tisa-cel is curative
NoMA [75]	2018	Clofarabine + Etoposide + Cyclophosphamide (CEC) chemotherapy	ELIANA, ENSIGN, and B2101J vs Hijiya et al [82]	Naive comparison using pooled ELIANA and ENSIGN data	Plausible potential for Tisa-cel to be a cost-effective treatment, however, the gain in OS and quality-adjusted survival compared to CEC+alloSCT is highly **uncertain**. Limitations in clinical trials are **lack of control arm, no long-term FU, small cohort**.
GBA/IQWiG [76, 77]	2020	-	ELIANA, ENSIGN vs MT103-205 (von Stackelberg et al [83], Gore et al [84])	Matched adjusted indirect comparison (by Pharmaunternehmer pU)/ According to GBA it is a naïve comparison, no comparison was included in the report	ELIANA: **high bias potential** due to **uncontrolled study design**, incomplete information on the course of the study, re-enrolment, probably retrospective ENSIGN: high bias potential due to **uncontrolled study design**, incomplete information on the course of the study **Unsuitable control populations** for benefit assessment, heterogeneity in comparison populations **Small patient numbers, no control group, short follow-up** make it impossible to assess mortality, morbidity, safety and life quality

Agency	Year	Comparator	Evidence	Comparative analysis	Interpretation of the clinical evidence
HAS [78, 79]	2021	Blinatumomab Clofarabine monotherapy CEC chemotherapy	ELIANA, ENSIGN vs MT103-205 [83], RIALTO [85], Miano et al [86], Locatelli et al [87], Hijiya et al [82], Jeha et al [81], von Stackelberg et al [88], Kuhlen et al [89]	Indirect comparison meta-analysis by company to compare tisa-cel to currently available salvage therapies (blinatumomab, clofarabine monotherapy and other therapies. Indirect comparison for information purposes only, no reliable conclusions. Indirect comparison using pooled data from MT103-205, RIALTO (blinatumomab), Miano et al, Locatelli et al, Hijiya et al (clofarabine, etoposide, cyclophosphamide chemotherapy), Jeha et al (clofarabine monotherapy), Stackelberg et al, Kuhlen et al (salvage chemotherapy)	Despite limitations, indirect comparison results suggest benefit of Kymriah® compared to standard treatments. Safety profile marked by significant short-term toxicity → Tisa-cel provides moderate clinical added value (CAV III), uncertainties like the **absence of medium and long-term clinical efficacy and safety data**, real-world efficacy and robust comparison with therapeutic alternatives persist.
TLV	No report found				
ZIN [80]	2018	Blinatumomab (±SCT)	ELIANA vs von Stackelberg et al [83]	Indirect comparison	Clinically relevant effect of at least three months life prolongation by tisa-cel compared to usual treatment (blinatumomab), **though limited experience, (acceptable) adverse effects, uncertainty of indirect comparison** The conclusion is that tisagenlecleucel has added therapeutic value compared to blinatumomab (±SCT).
Tisagenlecleucel, adult DLBCL					
CADTH [71]	2019	Salvage chemotherapy	JULIET and UPENN vs SCHOLAR-1	Naive comparison using JULIET only	There is **uncertainty** in the clinical evidence because of **lack of long-term follow-up, single-arm pivotal trial and small patient numbers** in the studies Tisa-cel has potential to exert severe adverse events, is resource intensive
ICER [72]	2018	Salvage chemotherapy	JULIET and UPENN vs SCHOLAR-1	Naïve indirect comparison using JULIET, descriptive with potentially significant selection bias and other confounding factors	**Short-term follow-up, no long-term comparison** with axi-cel or salvage regimens possible, **high uncertainty regarding safety** due to **small sample size** and lack of head-to-head studies **Possible selection bias, uncontrolled studies, small cohort, short follow-up**, wide 95%CI → no conclusions for long-term efficacy and safety
MSAC [90]	2019	Salvage chemotherapy	JULIET and UPENN vs SCHOLAR-1	Naive indirect comparison using JULIET only	ESC considered claims of superior effectiveness and **uncertainty** are unsubstantiated because of **immature survival data** (short median duration of follow-up) MSAC acknowledged that tisa-cel was clinically effective in some patients, however there are still concerns regarding the effectiveness and cost-effectiveness of tisa-cel
NICE [91]	2019	Salvage chemotherapy	JULIET and UPENN vs CORAL	Naive indirect comparison using pooled JULIET and UPENN data compared with CORAL data	Tisa-cel benefit is **uncertain** because of the **single-arm study design and immature survival data, short follow-up**, tisa-cel associated with frequent adverse events
NoMA [92]	2019	Salvage chemotherapy	JULIET vs CORAL	Naive comparison using JULIET only, with censoring of early deaths in CORAL study	The analysis was considered **uncertain** because of the **single-arm study design, small patient numbers, and short follow up**
GBA/IQWiG [93, 94]	2018	-	JULIET vs SCHOLAR-1, CORAL	According to GBA, JULIET is a naïve comparison, no comparison was included in the report	Significantly younger (and fitter) study population compared to registration population, **single-arm study design**, Study cohort with better risk profile than the registration cohort, **no control group, and short follow-up** makes it impossible to assess mortality, morbidity, safety and life quality, low significance of results for benefit assessment.

Agency	Year	Comparator	Evidence	Comparative analysis	Interpretation of the clinical evidence
HAS [95, 96]	2021	Salvage chemotherapy	JULIET vs SCHOLAR-1, CORAL, PIX301, Eyre 2016 [168]	As a result, these indirect comparisons were only presented for illustrative purposes in the 2018 opinion. The method and main results analysed are recalled below as well as an update of the results with the JULIET study data at the analysis date of 20/02/2020. No reliable estimate of the difference in the effect of this drug compared to current management could be made from these indirect comparisons.	Despite limitations, indirect comparison results suggest benefit of Kymriah® compared to standard treatments. Safety profile marked by significant short-term toxicity → Tisa-cel provides minor clinical added value (CAV IV), **uncertainties** like **absence of medium and long-term clinical efficacy and safety data**, real-world efficacy and robust comparison with therapeutic alternatives still persist.
TLV [97]	2019	Salvage chemotherapy	JULIET vs SCHOLAR-1 and CORAL	Indirect comparison between JULIET and SCHOLAR-1 and pooled extension studies of CORAL	TLV considers that the relative efficacy between tisagenleucel and comparator therapy is numerically very difficult to assess. This is because many patients did not receive treatment with tisagenlecleucel, there is no control arm in the study and the follow-up time is limited. **High uncertainty** regarding treatment effect due to **short follow-up, lack of control arm**
ZIN [98]	2022	Salvage chemotherapy	JULIET vs ZUMA-1, CORAL, SCHOLAR-1	No indirect comparison between tisa and axi-cel possible	**Experience** with tisa-cel and axi-cel is **limited** There is no relevant difference in applicability between tisa-cel and axi-cel. The effects of both tisa-cel and axi-cel on **quality of life** are **uncertain** and it is highly uncertain how these effects relate to each other (very low quality of evidence). Initially: **immature data regarding OS, median follow-up** Treatment with tisa-cel and axi-cel results in clinically relevant increase of OS
Axicabtagene ciloleucel, adult DLBCL & PMBCL					
CADTH [99]	2019	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Adjusted indirect comparison using propensity score matching	Long-term benefit of axi-cel **uncertain** because of **small population size and lack of head-to-head comparisons** or any **randomization** design
ICER [72]	2018	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Naive indirect comparison, descriptive with potentially significant selection bias and other confounding factors No formal statistical comparisons undertaken	There is at least a small net health benefit compared with salvage chemotherapy but it may be substantial although the magnitude is uncertain because of small, **noncomparative trials** of **short duration**
MSAC [100]	2019	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Naive comparison	ESC considered claims of superior effectiveness and non-inferior safety are unsubstantiated because of **immature survival data** (short median duration of follow-up) **Immature survival data, considerable uncertainty** remains around size and durability of the benefit of Axi-cel treatment compared with salvage chemotherapy due to missing RCT and **limited follow-up** MSAC considered that treatment with axi-cel is superior to salvage chemotherapy in terms of effectiveness and likely inferior in terms of safety, however **high bias in comparison of ZUMA-1 and SCHOLAR-1** remain and benefit cannot be accurately quantified
NICE [101]	2019	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Adjusted indirect comparison	Axi-cel is clinically effective but the **lack of comparative data** made the assessment of comparative effectiveness challenging

Agency	Year	Comparator	Evidence	Comparative analysis	Interpretation of the clinical evidence
NoMA [102]	2018	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Adjusted indirect comparison using propensity score matching	Estimated gain in overall and quality-adjusted survival **uncertain** because of **lack of comparative data, small sample sizes, and short follow up**
GBA/IQWiG [103-105]	2019	-	ZUMA-1 vs SCHOLAR-1	According to GBA it is a naïve comparison, no comparison was included in report	**High bias potential** due to **uncontrolled study design, missing data** on study population, certain endpoints (mortality and safety) and long time follow-up **No control** possible due to missing data on patients characteristic, different endpoints, differences in prognostic factors **Small patient cohort** (especially for PMBCL), **no control group, short follow-up** make it impossible to assess mortality, morbidity, safety and life quality
HAS [106, 107]	2021	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Indirect comparison with pooled historical data, questionable evidence of results	Despite limitations, indirect comparison results suggest benefit of Yescarta® compared to standard treatments. Safety profile marked by significant short-term toxicity → Axi-cel provides moderate clinical added value (CAV III), **uncertainties** like **absence of medium and long-term clinical efficacy and safety data**, real-world efficacy and robust comparison with therapeutic alternatives still persist. **Lack of comparative data** partially due to heterogeneity of studies
TLV [108]	2018	Salvage chemotherapy	ZUMA-1 vs SCHOLAR-1	Naive indirect comparison	TLV notes that there is a great deal of uncertainty in Yescarta's® clinical effectiveness, related to number of potentially cured patients and their long-term survival. These factors greatly impact the cost-benefit relationship associated with the treatment. These new, advanced gene therapies show great potential and will have a significant impact on cancer treatment. Nevertheless, these substantial uncertainties must be addressed through follow-up of Yescarta® in order to establish how the treatment is used in clinical practice. This observation should be continuous and will help reduce uncertainties associated with the treatment effect → **High uncertainty** regarding treatment effect due to **short follow-up, lack of control arm**. High uncertainty in results regarding PMBCL due to **small sample size** Serious side effects, potential for milder course and slightly reduced risk with use of tocilizumab. Heterogeneity in studies, **uncertainty in comparison of different treatments**.
ZIN [109]	2018	Chemotherapy (+SCT)	ZUMA-1 vs SCHOLAR-1	Indirect comparison	Comparison of ZUMA-1 and SCHOLAR does not provide reliable evidence regarding OS between axi-cel and standard treatment, **low quality of evidence**. Clinically relevant beneficial effect of axi-cel compared to chemotherapy. Frequent adverse effects, lack of studies comparing AE between chemotherapy (+SCT) and axi-cel. Axi-cel has therapeutic added value compared to chemotherapy (+SCT)

Abbreviations: ALL: acute lymphoblastic leukaemia, CAV: clinical added value, CEC: carboplatin, etoposide and cyclophosphamide chemotherapy, DESCAR-T: French national registry for patients treated with CAR-T, DLBCL: diffuse large B-cell lymphoma, OS: overall survival, SCT: stem cell therapy, vs: versus

Evidence tables of included studies for clinical effectiveness and safety for B-ALL

RWE

Table A-2: CAR-T cell therapy for B-ALL: results from observational studies (part 1/2)

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Country	USA (MD Anderson, Houston)	Netherlands (Utrecht Princess Maxima)	France (Paris, Robert Debre AP-HP)	USA (Colorado + PRWCC=15 US institutions))	USA (Colorado + PRWCC=15 US institutions))	USA (Philadelphia)
Sponsor	NR	supported by: ■ Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands ■ ODAS Foundation, Den Hoorn, The Netherlands.	NR	supported by: ■ St Baldrick's/StandUp2 Cancer Pediatric Dream Team Translational Cancer Research Grant (C.L.M.). ■ Virginia and D.K. Ludwig Fund for Cancer Research.	supported by: ■ St Baldrick's/StandUp2 Cancer Pediatric Dream Team Translational Cancer Research Grant (C.L.M.). ■ Virginia and D.K. Ludwig Fund for Cancer Research. ■ National Cancer Institute, ■ National Institutes of Health, ■ Cancer Center Support Grant P30 CA008748.	supported by: ■ NCI grant 5P01CA214278 ■ the Frontier Program at Children's Hospital of Philadelphia ■ the St. Baldrick's-Stand Up To Cancer Pediatric Dream Team Translational Research Grant (SU2C-AACR-DT-27-17) ■ The V Foundation, the Gerdin Fund ■ investigator-initiated funding from Novartis Pharmaceuticals Corporation.
Intervention/ Product	Tisagenlecleucel	Tisagenlecleucel/ Fludarabine	Tisagenlecleucel	Tisagenlecleucel	Tisagenlecleucel/ Fludarabine	Tisagenlecleucel & Tocilizumab
Comparator	Analysis of Cornell Assessment of Pediatric Dellirium (CAPD) as score for prediction of ICANS	Analysis of Fludarabine dosis on Tisagenlecleucel outcome	Analysis of determinants for CD19 neg or CD19 pos relapse	Comparison of isolated BM cohort with extramedullary disease cohort (= out of specification cohort)	Comparison of outcome in optimal vs suboptimal Fludarabine exposure	Evaluation of preemptive Tocilizumab in high and low tumour burden patients with Tisagenlecleucel therapy (to prevent severe CRS)
Study design	Retrospective case series	Retrospective cohort study	Prospective cohort study	Retrospective cohort study	Retrospective cohort study	Prospective two cohort, open-label pilot study
Number of pts	14 CAYAs with r/r B-ALL 1 pt primary mediastinal large B cell lymphoma (PMBCL)	28 CAYAs screened, 26 included	56 consecutive CAYAs, 51 infused with Tisagenlecleucel	Total: 184 from PRWCC ■ CNS: 40 ■ non-CNS EM: 15 ■ BM only: 129	200 pts planned for tisagenlecleucel therapy Included in analysis: 152 CAYA from PRWCC	70 pts, (80 pts enrolled, 10 excluded) from 08/2016 to 01/2019 data cutoff 01/2020 HTB (≥40% BMB) n=15 LTB (<40% BMB) n=55

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Inclusion criteria	Patients treated with standard of care CAR T-cell therapies (tisagenlecleucel for B-ALL, axicabtagene ciloleucel for PMBCL) treated at the Children's Cancer Hospital at MD Anderson Cancer Center from 03/2018 to 04/2020 Aged ≤ 25 years	CAYA with r/r CD19+ B-ALL Received standard of care tisagenlecleucel Between 04/2019 to 06/2021	CAYA with r/r B-ALL from 04/2016 to 12/2019; Inclusion criteria as in ELIANA (n=10), French early access programm (n=21) or marketing authorization cirteria (n=25)	CAYA with r/r B-ALL with tisagenlecleucel infusion from 08/2017 to 03/2020 CNS – disease non-CNS EM disease BM only (comparator) Part of the Pediatric Real World CAR Consortium (PRWCC)	CAYA with r/r B-ALL with tisagenlecleucel infusion from 08/2017 to 03/2020 Part of the Pediatric Real World CAR Consortium (PRWCC)	CAYAs aged 1-29 with r/r CD19+ B-ALL assigned for Tisagenlecleucel infusion Signed informed consent Documentation of CD19 tumour expression by flow cytometry at relapse Adequate organ function Evidence of disease by standard morphologic or MRD criteria. Age 1-29 years. Patients ages 24-29 years are eligible if their original leukaemia diagnosis was prior to age 21. Adequate performance status (Lansky or Karnofsky score ≥50). acceptable birth control methods
Exclusion Criteria	Not specified	Not specified 2 pt excluded	Not specified 5 pt excluded, AE n=2; disease progression n=3	Not specified	Excluded patients: ■ Did not receive Tisagenlecleucel (n=15) ■ No data (n=1) ■ Alternative lymphodepletion (n=7) ■ Wrong weight (n=2) ■ Days from lymphodepletion to infusion > 3 (n=23)	Active hepatitis B or active hepatitis C. HIV Infection. Active acute or chronic graft-versus-host disease (GVHD) requiring systemic therapy CNS3 disease progressive on therapy, or CNS parenchymal lesions Pregnant or nursing women. Uncontrolled active infection.
Median age of patients (range) (years)	≤ 25y	14.4 (4-24.5)	17 (1-29.2)	CNS: 10 (<1 – 25) non-CNS EM: 13 (2-26) BM only: 13 (<1-26)	12.5 (<1-26)	11.2 (1.4-29.1)
Sex	NR	Male 15/26 (58%)	Female 20/51 (39%)	Female 73/184 (40%)	Female 59/152 (39%)	Male 41/70 (59%)
Pre-Treatment	NR	Prior alloHSCT: 11/26 (42%) Prior Blina: 7/26 (27%) Prior CD19 CAR-T: 1/26 (4%) 1-2 Prior lines of therapy: 21/26 (81%) 3-5 prior lines of therapy: 5/26 (19%)	Prior HSCT: 30/51 (59%) Prior Blina: 17/51 (33%) Prior Ino: 11/51 (22%) Previous lines of therapy: median 3 (range 1-6)	> 3 lines of treatment: ■ CNS-Cohort: 80% ■ non-CNS EM: 93% ■ BM only: 64% (8% HSCT)	Prior lines of therapy: mean 3.5 (1-10): Prior alloHSCT: 8/152 (5%) Prior CD19 directed therapy: 33/152 (22%)	Prior alloHSCT: 25/70 (36%)

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Line of Treatment	NR	Prim. refractory: 4/26 (15%) Relapse: 22/26 (85%)	Prim. refractory: 6/51 (12%) Relapse: 45/51 (88%)	Prim. refractory: ■ CNS: 1/40 (2.5%) ■ non-CNS EM: 1/15 (7%) ■ BM-only: 29/129 (22%) ≥ 1 relapse: ■ CNS-Cohort: 39/40 (98%) ■ non-CNS EM: 14/15 (93%) ■ BM-only: 100/129 (78%)	Prim. refractory: 24/152 (16%) ≥ 1 relapse: 128/152 (84%)	Prim. refractory:14/70 (20%) Relapsed: 56/70 (80%)
Other patients characteristics before CAR T infusion	NR	<5% BMB: 17/26 (65%) MRDneg: 4/26 (15%) ≥5% BMB: 9/26 (35%) TP53 mut: 2/26 (8%) Low flu: 11/26 (42%) High flu: 15/26 (58%)	HR genetics 7/51 (14%) HTB > 50% BMB: 12/51 (24%) 5-50% BMB: 9/51 (18%) LTB < 5% BMB: 30/51 (58%) MRD neg: 9/51 (18%) MRD pos: 26/51 (31%)	HR genetics: ■ CNS-Cohort: 10/40 (25%) ■ non-CNS EM: 3/15 (33%) ■ BM-only: 53/129 (41%)	HR genetics: 53/152 (45%) HDB=≥5% BMB, CNS3 disease, and/or isolated EM disease): 74/152 (50%) LDB=<5% BMB, CNS ≤ 2, and/or no EM disease: 33/152 (22%) UD: 41/152 (28%) Low flu: 33% optimal flu: 67%	HR genetics: 26/70 (37%) Trisomy 21: 6/70 (8.6%) HTB (≥40% BMB): 15/70 (21%) 5-40% BMB: 11/70 (16%) LTB <5% BMB: 17/70 (24%) MRD neg: 27/70 (39%)
Median Follow-up (range) (months)	9 (3-28)	12.8 (1.7-26.3)	15.5 (12.2-17.9)	11 (0-28)	13.2 (IQR 9.6 – 20.4)	24 (5-36)
Loss to follow-up, n (%)	None	None	None, 49 pt evaluable at d28 due to death of 2/51 pt before d28	None	None	None Censored: ■ For DOR: HSCT: 3LTB, alternative treatment: 2HTB + 7LTB ■ For OS: 12pt died: 6HTB, 6LTB ■ Loss of BCA: 3HTB, 20LTB.
Primary (1) and secondary (2) endpoints	NR	(1) effect of fludarabine exposure on LFS (2) B-cell recovery, Occurrence of CD19pos/neg relapse, Infections	NR	(1) OS, RFS, BCA (2) CR(d28), toxicity, relapse rates, CD19pos/neg relapse	(1) OS, CIR, CICE (relapse or loss of BCA) (2) Response rate, CRS, ICANS	(1) Incidence of grade 4 CRS (Penn Scale) (2) ORR, DOR, EFS, CAR T expansion and persistence, safety events
Statistics used	Descriptive statistics to summarize demographics	Association Flu-LFS: martingale residuals and univariable Cox prop. hazards model Kaplan-Meier and cumulative incidence, compared with log-rank tests	Univariate and multivariate analyses with Cox model	Analysis of differences for categorical data → Fishers exact test; for continuous data → Kruskal Wallis test Kaplan-Meier analysis for OS, RFS, duration of BCA	Continuous variables: Mann-Whitney Wilcoxon test For categorical variable: $\chi 2$ or Fisher's exact test Logistic regression for multivariable analysis	Continuous variables: Wilcoxon rank sum test Categorical variables: Fishers's exact test Analyses with R (v 4.0) and Stata (v. 14.0)

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Statistics used *(continuation)*		Comparison AUC between exposure groups; comparison patient characteristics: Mann-Whitney U test			Kaplan-Meier for OS Aalen-Johansen for CIR and composite endpoint	Kaplan-Meier for DOR, EFS, OS, duration of BCA Cohort differences by log-rank test
Effectiveness						
Definition Overall Survival	NR	NR	Time from infusion to death from any cause	time from infusion to death from any cause	OS for all treated patients: time from infusion to death from any cause OS in responding patients: time from day of response (d28) to death from any cause	NR
Overall survival, (%)	NR	NR	18mo: 74% (95% CI, 57-85)	CNS: 12mo: 75.7% (95% CI, 62.1-92.2); 24mo: 69.3% (95% CI, 53.4-90.1) Non-CNS EM: 12 & 24 OS: 55.8% (95% CI, 34.6-90.1) BM only: 12mo: 72.8% (95% CI, 64.8-81.9); 24mo: 53.3% (95% CI, 39.4-72.1)	12mo: 75.1% (95% CI, 67.6-82.6) 24mo: 56.5% (95% CI, 41.8-71.2) Survival status 112/152 (74%) (dead 40/152=36%)	Overall: at end of follow-up 58/70 alive (83%) – data only in fig. but not in text HTB: 12mo: 67% (95% CI, 47-95), 24mo: 60% (95% CI, 40-91) LTB: 12mo: 96% (95% CI, 92-100), 24mo: 92% (95% CI, 85-100)
Definition of disease specific survival (EFS, RFS, LFS, DOR, BCA)	NR	LFS: time between Tisagenlecleucel infusion and relapse Loss of BCA: >5 B cells/µl	EFS: time from Tisagenlecleucel infusion to absence of OR, relapse after OR, death from any cause Loss of BCA: > 10 B cells/µl in peripheral blood at 2 time points Cumulative incidence of loss of BCA: time from CR/CRi to loss of BCA (relapse and death = competing events)	RFS: time from infusion to relapse or death (pt who died before d28 or who did not achieve CR were not included in RFS analysis) B-cell recovery: > 1 CD19+ B cell/µl in peripheral blood Duration of BCA: time from infusion to loss of BCA (SCT as censored event)	B-cell recovery = > 1 CD19+ B cell/µl in peripheral blood by flow cytometry	EFS: time from infusion to no response, relapse or death (HSCT or alternative therapy censored) DOR (probability of continued remission): time from first response to morphologic relapse or death Duration of BCA (censored for relapse) BCA: time to emergence of ≥1% CD19+ B cells in BM aspirate or ≥3% B cells by PB flow cytometry
Disease-specific survival – EFS, RFS, LFS, DOR, BCA	NR	Leukaemia-free survival: ■ Low flu: median 1.8mo ■ High flu: 12.9mo No overall data available Cumulative incidence of B-cell recovery within 6mo: ■ Low Flu: 77.3% ■ High Flu: 37.3% No overall data available	EFS 18mo: 44% (95% CI, 28-59) Cumulative incidence of loss of BCA: ■ 3mo: 33% ■ 6mo: 48% ■ 12mo: 55%	Relapse-free survival at 12mo: ■ CNS: 59.4% (95% CI, 43.7-80.7) ■ Non-CNS EM: 50% (95% CI, 26.9-92.9) ■ BM only: 59.4% (95% CI, 50.2-70.2) B-cell aplasia at 12mo: ■ CNS: 66.4% (95% CI, 49.3-89.5) ■ Non-CNS EM: 38.9% (95% CI, 14.8-100)	Cumulative incidence of composite end point (relapse or loss of BCA) at 12mo: 55.2% (95% CI, 46.0-64.4)	Overall: -data only in fig. but not in text. High tumour burden: ■ DOR at 12mo 49% (95% CI, 27-88%); at 24mo 39% (95% CI, 19-82%) ■ EFS at 12mo: 42% (95% CI, 23-79%); at 24mo: 34% (95% CI, 16-73%) ■ probability of BCA at 6mo: 69% (95% CI, 40-100%)

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Disease-specific survival – EFS, RFS, LFS, DOR, BCA *(continuation)*				■ BM only: 59.4% (95% CI, 49.7-71)		Low tumour burden: ■ DOR 12mo: 86% (95% CI, 77-96%); 24mo: 78% (95% CI, 67-91) ■ EFS: 12mo: 86% (91% CI, 77-96%); 24mo: 78% (95% CI, 67-91) ■ probability of BCA at 6mo: 65% (95% CI, 54-80)
Definition of ORR, CR, CRi	NR	CR: MRD neg (d28) ORR: MRD neg (<0.01%) leukemic BMB at 2 different time points by flow cytometry and PCR including CRi, on day 28	ORR: CR + CRi at day 28 CR: ≤5% BMB (>1 G/L neutrophils & > 100 G/L thrombocytes) + no extramedullary disease CRi: ≤5% BMB (<1 G/L neutrophils & ≤ 100 G/L thrombocytes) MRDneg: negative RQ-PCR with detection sensitivity of ≤ 10-4	CR: ≤5% BMB, no blasts in peripheral blood, no extramedullary disease MRDneg: < 0.01% abnormal B cells by flow cytometry	CR: ≤5% BMB, no blasts in peripheral blood, no extramedullary disease MRDneg: < 0.01% abnormal B cells by flow cytometry	On d28: ■ CR: <5% BMB (>1 G/L neutrophils & > 100 G/L thrombocytes) + <1% circulating blasts + no extramedullary disease + no transfusion 1 week prior to assessment ■ CRi same with (< 1 G/L neutrophils OR < 100 G/L thrombocytes) ■ ORR: rate of a best overall response of either CR or CRi
Response Rates – OOR, CR, CRi	CR with MRDneg after 30 days post CAR-T infusion: 9/14 (64%): ■ CRi: 1/14 (7%) ■ ORR: 71%	CR(d28): overall 20/26 (77%) ■ Low Flu: 6/11 (55%) ■ High Flu: 14/15 (93%)	ORR: 49/51 (96%) CR(d28): 36/51 (71%) CRi(d28): 13/51 (25%) MRDpos(d28): 8/49 (16%) MRDneg(d28) 40/49 (82%)	Complet remission: ■ CNS: 35/40 (88%); of which MRDneg 97% ■ Non-CNS EM: 10/15 (66%); of which MRD neg 90% ■ BM only: 111/126 (86%); of which MRD neg 95%	Response at day 28: ■ CR: 131/152 (86%) ■ No CR: 16/152 (11%) ■ Died prior d28: 5/152 (3%)	ORR d28: ■ Overall: 66/70 (94%) ■ HTB: 12/15 (80%) ■ LTB: 54/55 (98%) Best ORR: ■ Overall: 68/70 (97%) ■ HTB: 13/15 (87%) ■ LTB: 55/55 (100%)
Definition Recurrence/ Relapse	NR	Relapse: 1) >5% BMB 2) >0.01% to <5% BMB at 2 different time points using flow cytometry or quantitative PCR 3) >0.01% leukemic blasts in the cerebral spinal fluid by 2 subsequent measurements using flow cytometry	Relapse: ≥ 1% blasts in peripheral blood or ≥ 5% BMB Cumulative incidence of relapse: time from CR/CRi to relapse (death = competing event)	Any evidence of medullary or extramedullary primary disease	Any evidence of medullary or extramedullary primary disease Time to relapse: time from infusion to date of disease relapse Time to composite endpoint: time from infusion to relapse or loss of BCA Cumulative incidence of relapse: exclusion of deaths before d28 or nonresponders	DOR: time from first response to morphologic relapse or death (HSCT or alternative therapy censored)
Recurrence n (%)	NR	Cumulative incidence of CD19+ relapse within 1 year ■ Low Flu: 100% ■ High Flu: 27.4%	Cumulative incidence of relapse 18mo 51% (95% CI, 37-68%) 22/49 in CR relapsed (45%)	CNS: 15/35 (42%) Non-CNS EM: 6/10 (60%) BM only: 45/111 (41%)	52/131 (40%) relapsed 12mo cumulative incidence of relapse 36.4% (95% CI 27.5-45.2)	Overall: 19/68 (28%) HTB: 9/13 (69%) +2/13 (85%) LTB: 10/55 (18%) + 7/55 (31%)

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
Quality of life	NR – Lansky/Karnofsky performed but not reported	NR	NR	NR	NR	NR – minimum of 50 score (lansky/Karnofsky) for inclusion, no post infusion data reported
Safety						
Overall complications, n (%)	NR	NR	NR	NR	NR	NR
Definition, Scoring system	American Society for transplantation and cellular therapy (ASTCT) score for CRS and ICANS Cornell Assessment of pediatric delirium (CAPD) = rapid screening for delirium in Pediatric intensive care units	Definition infection: positive blood culture, PCR proven infection or clinical (zoster, pulmonary fungal)	CRS and neurological events graded after ASTCT	Depending on institution CRS graded by ASTCT Neurotoxicity (= ICANS) graded by ASTCT and other	CRS and neurological events (= ICANS) graded after ASTCT Severe CRS: ≥ grade 3 Severe Neurotoxicity: ≥ grade 3	CRS graded after Penn Scale All other AE graded according to CTCAE (V4.03)
SAE, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	Any CRS: 12/14 (86%) Any ICANS: 5/14 (36%) ICANS Grade ≥3: 4/14 (29%)	Infection: 14/26 (54%) Low Flu: 4/11 High flu: 10/15	CRS any grade: 30/51 (59%) CRS Grade ≥3: 10/51 (20%) Any neurotoxicity: 12/51 (24%) Neurotoxicity Grade ≥3: 4/51 (8%) ICU admission: 18/51 (35%) Neutropenia Grade ≥3 (d28): 18/49 (37%) Thrombocytopenia Grade ≥ 3(d28): 18/49=37%	CNS: CRS: 25/40 (63%), Neurotoxicity 12/40 (35%); Non-CNS EM: CRS: 12/15 (80%), Neurotoxicity 2/15 (13%); BM only: CRS: 79/129 (61%), Neurotoxicity 22/129 (17%),	CRS: 97/152 (64%) Severe CRS: 33/152 (22%) optimal Flu: 18/102 (18%) suboptimal Flu: 15/50 (30%) Neurotoxicity: 36/152 (24%) Severe neurotoxicity: 12/152 (8%) Infection: 57/152 (38%) Optimal Flu: 36/102 (35%) Suboptimal Flu: 21/50 (42%) Grade 4 neutropenia: 97/148 (66%)	CRS (Penn Scale): ■ Overall: any CRS 52/70 (74%), Grade 3+4CRS 12/70(17%) ■ HTB: any CRS 15/15 (100%), Grade 3+4CRS 9/15 (60%) ■ LTB: any CRS 37/55 (67%), Grade 3+4CRS 3/55 (5%) ■ Neurotoxicity (CTCAE 4.03) ■ Overall: any grade 19/70 (27%), Grade3+4: 5/70 (7%) ■ HTB: any grade 9/15 (60%), Grade 3+4: 3/15 (20%) ■ LTB: 10/55 (18%), Grade 3+4: 2/55 (4%) febrile neutropenia: ■ overall: 40/70 (57%) ■ HTB: 15/15 (100%) ■ LTB: 25/55(45%)
AE, n (%)	Other than ICANS and CRS not reported	Other than infection not reported	Other than SAE not reported	Other than SAE not reported	Other than SAE not reported	Grade 3-4 AE: ■ CRS: 12 (17%), Hypoxia: 9 (13%), Hypophosphatemia: 10(14%), AST ↑: 10(14%), Anorexia: 5(7.1%), Fibrinogen ↓: 3(4.3%), Hypotension: 8(11%), Acidosis: 4 (5.7%), billirubin ↑: 4(5.7%), Anaemia: 10(14%), aPTT prolonged: 3(4.3%),

Author, year	Brown, 2021 [142]	Dekker, 2022 [33]	Dourthe, 2021 [122]	Fabrizio, 2022a [124]	Fabrizio, 2022b [123]	Kadauke, 2021 [129]
AE, n (%) *(continuation)*						Hyperglycemia: 3(4.3%), Hyperkalemia: 3(4.3%), Lymphocyte count ↓: 42(60%), Hypokalemia: 8(11%), ALT ↑: 9(13%), Fever: 4(5.7%), URT infection: 3(4.3%), Encephalopathy: 4(5.7%), neutrophil count ↓: 38(54%), white blood cell ↓: 38(54%), Platelet count ↓: 19(27%), – data for subgroubs available.
Definition of Procedure related mortality	NR	NR	NR	NR	NR	NR
Procedure-related mortality, n (%)	NR	NR	1 pt died from CRS 1 pt died from early progression 7 patients with prior inotuzumab therapy died Data not complete	CNS / Non-CNS EM / BM only Relapse: 7 / 5 / 26 Infection: 2 / 0 / 4 CRS: 0 / 0 / 1 Neurotox: 0 / 0 / 1 HSCT related: 0 / 1 / 3 Cardiac relatd: 0 / 0 / 1	Cause of death (total n=40): ■ Leukaemia: 30/40 (74%) ■ Infection: 4/40 (10%) ■ CRS: 1/40 (2%) ■ Neurotoxicity: 1/40 (2%) ■ Transplant related: 3/40 (7%) ■ ARDS/cardiac arrest: 1/40 (2%)	Mortality: 12/70 (17%) Procedure related mortality: NR
Comments	Safety only, analysis of CAPD Score as prediction tool for ICANS risk	Low Fludarabine significantly associated with lower LFS, higher relapse rate, shorter BCA	10 patients published in ELIANA Leukemic tumour burden and prior exposition to blinatumomab as major prognostic factors of response and outcome after tisagenlecleucel	PRWCC – Cohort	PRWCC – Cohort Suboptimal fludarabine exposure associated with increased risk of relapse; preinfusion disease burden and age associated with overall survival	NR

Abbreviations: BCA: B-cell aplasia, Blina: Blinatumomab, BM: bone marrow, BMB: bone marrow blasts, CAPD: Cornell Assessment of Paediatric Delirium, CAYAs: children, adolescents, and young adult, CIBMTR: Center for International Blood and Marrow Transplant Research, CICE: cumulative incidence of composite end point (relapse or loss of B-cell aplasia), CIR: cumulative incidence or relapse, CNS: central nervous system, CR: complete remission, CRS: cytokine release syndrome, DOR: duration of response, EFS: Event-free survival, EM: extramedullary, Flu: fludarabine, Haem: haematologic, HDB: High disease burden, HR: High-risk, HSCT: haematopoietic stem cell transplantation, HTB: high tumour burden, ICANS: immune effector cell-associated neurotoxicity syndrome, Ino: Inotuzumab, IQR: interquartile range, LDB: low disease burden, LFS: leukaemia-free survival, LTB: low tumour burden, Neg.: negative, NR: not reported, mo: months, MR: moderate risk, MRD: minimal residual disease, mut.: mutation, OOS: out of specification (= beyond approved indication), ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, (P)ICU: (paediatric) intensive care unit, Prim: primary, pos: positive, PRWCC: Pediatric real-world CAR Consortium, pts: patients, HRQoL: Health-related Quality of life, RoB: risk of bias, r/r: refractory or relapsed, (S)AE: (severe) adverse event, SOC: standard of care, SPM: subsequent primary malignancy, UD: undetectable disease, URT: upper respiratory tract, ↓ decreased, ↑ increased

Table A-2: CAR-T cell therapy for B-ALL: results from observational studies (part 2/2)

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Country	USA (Wisconsin) + PRWCC	USA (73 centers in USA & Canada) + CIBMTR	USA	USA + PRWCC	USA	USA + PRWCC
Sponsor	None	The CIBMTR is supported by: ■ NIH/NCI grants ■ Be the Match Foundation, Boston Children's Hospital, Dana-Farber, Japan ■ Hematopoietic Cell Transplantation Data Center, St Baldrick's Foundation, ■ the National Marrow Donor Program, the Medical College of Wisconsin ■ commercial entities:	Supported by: ■ National Institutes of Health (NIH)/National Cancer Institute (NCI) grant P30CA021765, ■ American Society of Transplantation and Cellular Therapy (A.T.), ■ St. Baldrick's Foundation Scholar Award (C.L.B.), ■ Johns Hopkins Summer Provost's Undergraduate Research Award (J.W.R.), ■ Johns Hopkins Woodrow Wilson Fellowship (J.W.R.), ■ American Lebanese Syrian Associated Charities (ALSAC). Parts of the laboratory studies were performed by the Center for Translational Immunology and Immunotherapy (CeTI2), which is supported by St. Jude.	NR	NR	Supported by: ■ St Baldrick's/Stand Up 2 Cancer Pediatric Dream Team Translational Cancer Research Grant (C.L.M.). ■ Parker Institute for Cancer Immunotherapy ■ the Virginia and D.K. Ludwig Fund for Cancer Research.
Intervention/ Product	Tisagenlecleucel	Tisagenlecleucel	Tisagenlecleucel	Tisagenlecleucel	Tisagenleceucel	Tisagenlecleucel
Comparator	Observation/ no comparison Outcome of Tisagenlecleucel in patients < 3 years of age	Outcomes pivotal study	Observation/no comparison Analysis of disease burden on survival outcome	Out of specification (OOS) vs. standard of care (SOC) tisagenlecleucel therapy	Observation/ no comparison Analysis of tisagenlecleucel in isolated extramedullary disease (out of specification)	LDB vs. HDB vs. UD before tisagenlecleucel on outcomes
Study design	Retrospective case series	Noninterventional prospective registry study	Retrospective cohort study	Retrospective cohort study from PRWCC registry	Retrospective case series	Retrospective cohort study from PRWCC registry
Number of pts	16 recruited, 14 infused – infants up to 12 months at prim. diagnosis with r/r B-ALL	511 pt enrolled, 410 pt included: ■ ALL n=255 ■ NHL n=155	N=33 included, 31 infused	200 in database, 185 infused; 24/185 OOS	7 patients	200 pt in database, 185 infused

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Inclusion criteria	14 infants up to 12 months at original diagnosis with r/r B-ALL included in the PRWCC 08/2017 to 03/2020	CAYAs with r/r B- ALL or adult NHL Receiving Tisagenlecleucel from 08/2017 to 01/2020 From USA or Canada (from 73 centers) Center for International Blood and Marrow Transplant Research Registry (CIBMTR)	CAYAs with r/r B-ALL with indication for Tisagenlecleucel infusion from 03/2018 to 11/2020 Also included: Pt <3y, pt with HR genetics, CNS pos leukaemia, prior treatment with CD19-directed therapies, low preinfusion disease burden.	CAYAs with r/r B-ALL who received Tisagenlecleucel and were included in PRWCC	CAYAs with r/r B-ALL with extramedullary disease infused with tisagenlecleucel from 2018 to 2019	CAYAs with r/r B-ALL from 08/2017 to 03/2020
Exclusion Criteria	NR 2 pt did not receive tisagenlecleucel due to manufacturing failure/death	Participation in other clinical trials Incomplete data No consent Follow-up of less than 3mo	NR 2pt excluded due to poor clinical status or manufacturing failure	NR	NR	15 of 200 excluded: ■ Manufacturin failure n=6 ■ Leukaemia progression n=5 ■ Toxicity prior therapy n=6 ■ Remission from bridging therapy n=2 ■ Death n=7 ■ Incomplete reporting
Median age of patients (range) (years)	0 (0-9y) 0-12 months at initial diagnosis	13.2 (0.41-26.17)	7.9 (0.8-23.6y)	OOS (n=24): 10.5 (0-25) SOC (n=161): 13 (0-26)	8 (5-16)	12 (0-26)
Sex	NR	Female: 105/255 (41%)	Female: 13/31 (42%)	OOS: female 8/24 (33%) SOC: female 66/161 (41%) Total female: 72/185 (39%)	Male: 7/7 (100%)	Female: 74/185 (40%)
Pre-Treatment	Prior HSCT: 4/14 (29%) Prior Blina: 3/14 (21%) Prior Ino: 3/14 (21%)	Prior lines of treatment: median 3 (range 0-15) Prior HSCT: 73/255 (28%) Prior blina: 38/255 (14.9%) Prior ino: 27/255 (10.6%)	Prior HSCT: 4/31 (12.9%) Prior Blina, CD19 CAR or Ino: 8/31 (25.8%)	Prior lines of treatment: OOS: median 3 (range 1-8) SOC:me.dian 3 (range1-10) Prior HSCT: OOS: 10/24 (41.7%) SOC: 37/161 (19.9%) Prior CD19 directed therapy: OOS: 6/24 (25%) SOC: 32/161 (19.9%)	Prior HSCT: 1/7 (14%) >2 lines of treatment: 7/7 (100%)	Prior lines of treatment Median 3 (range 1-10): ■ Prior HSCT: 47/185 (25%) ■ Prior Blina: 34/185 (18%) ■ Prior CD19 CAR T: 6/185 (3%) ■ Prior Ino: 31/185 (17%) ■ Prior CD22 CAR T: 3/185 (2%)
Line of Treatment	Prim. refractory: 5/14 (36%): ■ 1st relapse: 5/14 (36%) ■ ≥2nd relapse: 4/14 (29%)	Prim. refractory or relapsed: 159/255 (62.3%) CR prior to Tisagenlecleucel: 95/255 (37.2%) of which MRD pos 50/95 (53%) and MRD neg 44/95 (46%), no MRD assessment 1/95	Prim. refractory: 11 (35.5%) ■ 1st relapse: 14 (45.2%) ■ 2nd relapse: 5 (16%) ■ ≥3rd relapse: 1 (3.2%)	Prim. refractory: OOS: 6/24 (25%) SOC: 31/161 (23%) ≥2nd relapse: OOS: 11/24 (45.8%) SOC: 76/161 (47.2%) Other: OOS: 7/24 (29.2%) SOC: 54/161 (33.5%)	CNS relapse or EM relapse: ■ 5/7 2nd relapse ■ 1/7 1st relapse and unfit for HSCT ■ 1/7 refractory first CNS relapse	Prim. refractory: 30/185 (16%): ■ 1st relapse: 68/185 (37%) ■ 2nd relapse: 68/185 (37%) ■ 3rd relapse: 8/185 (4%) ■ ≥3rd relapses: 10/185 (5%)

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Other patients characteristics before CAR T infusion	HR genetics (KMT2Ar): 12/14 (86%) MRDneg: 3/14 (21%) MRDpos CR: 6/14 (43%) > 5% BMB: 5/14 (36%)	Age <3y: 15/255 (5.9%) Down syndrome: 12/255 (4.7%) Prior CNS involvment: 24/255 (9.4%) MRDneg: 44/255 (17.3%) HR genetics: 46/255 (18%) No BMB: 28% 0-<5% BMB: 20% ≥5% BMB: 33%	HR genetics: n=19/31 (61%) MRDneg: 3/31 (10%) 0-5% BMB: 15/31 (48%) > 5% BMB: 13/31 (42%) CNS3: 1/31 (3.2)	HR genetics: OOS: 7/24 (29.2%) SOC: 53/161 (32.9%) MRDneg: OOS: 8/24 (33.3%) SOC: 58/161 (36%) MRDpos: OOS: 13/24 (54.2%) SOC: 77/161 (47.8%)	HR genetics: 1/7 (14%) No detectable disease: 3/7 (43%)	HR genetics: 66/185 (36%) SOC: 161/185 (87%) OOS: 24/185 (13%) (17/24 of products had viability of 70-80% of CARTs) HDB (≥5% BMB, any peripheral lymphoblasts): 94/185 (51%) LDB (<5% BMB): 41/185 (22%) UD (no disease by flow cytometry + no EM disease): 46/185 (25%) CNS disease 13/185 (17%)
Median follow-up (range) (months)	7.6 (1.4-28.4)	13.4 (3.5-27.9)	12.7 (0.4-39)	NR	Range 16-29	11.4 (0.2-28.4)
Loss to follow-up, n (%)	None	Not clearly reported, 255 pt infused, only 249 pt included in outcome analysis	None	None	None	None
Primary (1) and secondary (2) end points	CR(d28) OS and EFS at 6 months, toxicity incl. CRS, neurotoxicity	CRS, ICANS, SPM, haematologic recovery, ORR, DOR, EFS, PFS, OS	NR	Compare efficacy of OOS vs SOC tisagenlecleucel – CR(d28) OS and EFS at 6 and 12 months	NR	ORR(d28) OS and EFS at 6 and 12 months
Statistics used	NR	Descriptive statistics, Kaplan-meier estimates for OS, EFS, DOR Event-free probabilities at 6 and 12mo with 95% CI Logistic regression for CRS, ICANS	Fisher's exact test, the Wilcoxon rank-sum test, or the Kruskal-Wallis test Kaplan-Meier for OS, EFS,	χ2 test to analyse differences OOS vs SOC Kaplan-Meier for OS, EFS, probability of continued CR	NR/descriptive	Differences between subgroups: Fisher's exact test for d28 CR, CRS, neurotoxicity Kaplan-Meier for OS, EFS, DOR, DBA
Effectiveness						
Definition Overall Survival	NR	Time from infusion to death from any cause	Time from infusion to death	Time from infusion to death from any cause with data censored at the time of last follow-up	NR	Time from infusion to death from any cause – censoring at last follow-up (not HSCT)
Overall survival, n (%)	6mo OS: 71%	N=249 at risk 6mo: 88.5% (95% CI, 83.6-92.0%) 12mo: 77.2% (95% CI, 69.8-83.1%)	Overall ■ 6mo: 80.6% (95% CI, 61.9-90.8%) ■ 12mo: 67.4% (95% CI, 47.9-81.0%) ■ Overall survival rate: 51.5% OS 12mo: ■ High tumour burden > 5% BMB: 38.5% [95% CI, 14.1%-62.8%]	6mo: OOS (n=24): 96% SOC (n=161): 83% 12mo: OOS (n=24): 85% SOC (n=161): 70%	7/7 (100%)	Of 184 pt evaluated ■ 6months: Overall: 85% HDB: 75% LDB: 94% UD: 98%

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Overall survival, n (%) *(continuation)*			■ 0-5% BMB: 86.2% [95% CI, 54.9%-96.4%] ■ MRD neg: 100% [NA]; P=,0027			■ 12months: Overall: 72% HDB: 58% LDB: 85% UD: 95%
Definition of disease specific survival (EFS, RFS, LFS, DOR, BCA)	NR	EFS: time from infusion to death of any cause, relaspse or treatment failure; censoring for HSCT or other anticancer therapy DOR: time from first CR or partial remission to date of progression, relapse or death from underlying desease	EFS: time from infusion to nonresponse (d28), relapse or death – censoring for HSCT B-cell rocvery: ≥1%CD19+ cells at 2 time points or ≥ 50 CD19+ B cells/µl in peripheral blood	EFS: time from infusion to non response, relapse or death; censoring at date of last follow-up and HSCT DOR: includes patients with CR at d28 at time from infusion to relapse, death, censoring at date of last follow-up and HSCT.	BCA: 2 x >1% CD19+ cells	EFS (all infused patients): time from infusion to progression/ Relapse/2nd Malignancy – censoring at last follow-up (not HSCT) DOR (all who achieved CR): time from infusion to relapse/ 2nd malignancy – censoring at death in CR and last follow-up (not HSCT) Duration of BCA (patients achieving BCA): time from infusion to loss of BCA – censoring for relapse/death/HSCT
Disease specific survival (EFS, RFS, LFS, DOR, BCA)	6mo EFS: 48% BCA: median duration 171 days (28-414d)	N=249 at risk Event-free survival: 6mo 68.6% (95% CI, 62.0-74.4) 12mo 52.4% (95% CI, 43.4-60.7) Duration of response: 6mo 78.1% (95% CI, 70.5-84.0) 12mo 60.9% (95% CI, 49.4-70.5)	Event-free survival (n=31) Overall: ■ 6mo 46.9% (95% CI, 28.4-63.4%) ■ 12mo 35.2% (95% CI, 18.4-52.5%) ■ Median EFS time 4.3mo EFS 12mo: ■ HTB >5% BMB: 15.4% (95% CI, 2.5%-38.8%) ■ 0-5% BMB: 46.2% (95% CI.18.2%-70.4%) ■ MRDneg: 66.7% (95% CI, 5.4%-94.5%); P=,0392) ■ BCA: 10/25 (40%) B-cell recovery until end of follow-up (median 4,1mo), 15 patients ongoing BCA at end of follow-up (median2,8mo)	Event-free survival: ■ 6mo: OOS (n=24): 65% SOC (n=161): 63% ■ 12mo: OOS (n=24): 55% SOC (n=161): 51% Probability of continued remission: ■ 6mo: OOS (n=24): 79% SOC (n=161): 75% ■ 12mo: OOS (n=24): 66% SOC (n=161): 63%	Event-free survival: 4/7 after 16-24months Median time to loss of BCA: 6,5mo disease free survival: 100%	Event-free survival of 184 infused: ■ 6 months: Overall: 62% HDB: 46% LDB: 86% UD: 75% ■ 12 months Overall: 50% HDB: 31% LDB: 70% UD: 72% Duration of response: ■ 6 months: overall75% HDB: 65% LDB: 91% UD: 75% ■ 12 months: Overall: 62% HDB: 45% LDB: 74% UD: 75%

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Disease specific survival (EFS, RFS, LFS, DOR, BCA) *(continuation)*						Duration of BCA: ■ 6 months: Overall: 68% HDB: 60% LDB: 68% UD: 72% ■ 12 months: Overall: 57% HDB: 45% LDB: 60% UD: 68%
Definition OOR, CR, CRi	CR = MRD neg (< 0.01%) by flow cytometry at d28	CR = <5% BM blasts	MRDneg CR: <5% BMB by morphology + < 0.01% BMB by flow cytometry, <10-4 by PCR or < 10-5 by NGS MRDpos CR: <5% blasts by morphology and ≥0.01% blasts by flow cytometry, ≥10-4 by PCR or < 10-5 by NGS	CR: <5% BMB, no circulating blast, no EM disease	CR: was measured at d28	Intent-to-treat response analysis excluded pt non-infused because of CR from prior therapy CR: <5% BMB and absence of circulating blasts and EM disease
Response Rates (OOR, CR, CRi)	MRDneg CR(d28): 9/14 (64%)	N=249 at risk CR: 85.5% (95% CI, 80.6-89.75%) N=116 pt in CR evaluated for MRD MRDneg 115/116 (99.1%)	CR: 25/30 (83.3%); → MRDneg 21/25 (84%)	CR (d28): ■ OOS: 83% ■ SOC: 85%	CR(d28): 7/7 100% MRDneg(d28): 7/7 (100%)	CRd28 in all patients intended to treat: 156/197 =79% (95% CI, 72-84%) CRd28 in all infused patients: 156/184 =85% (95% CI, 79-89%) HTB: 73% (95% CI, 63-81) LTB: 98% (95% CI, 87-100) UD: 100% (95% CI, 92-100) MRDmeasured in 153Pt: MRDneg 148/153 (97%)
Definition Recurrence	NR	NR	Relapse: any detectable disease incl. MRDpos BM or extramedullary disease Cumulative incidence of relapse – censoring for death or HSCT	NR	NR	Only measured in responders
Recurrence, n (%)	3/9 (33%)	NR	12/25 (48%)	NR	2/7 (29%)	57/156 (37%)
Quality of life	NR	Prior to infusion: Karnofsky/Lansky: ■ 90-100: 174/255 (68.2%) ■ 80: 37/255 (14.5%) ■ <80 31/255 (12.2%)	NR	NR	NR	NR

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Safety						
Overall complications, n (%)	NR	NR	NR	NR	NR	NR
SAE, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	any CRS: 11/14 (79%) CRS ≥ Grade 3: 3/14 (21%) Neurotoxicity: 0/14	Any CRS: 140/255 (54.9%) CRS Grade ≥ 3: 41/255 (16.1%) Any Neurotoxicity: 69/255 (27.1%) Neurotoxicity Grade ≥ 3: 23/255 (9%)	Any CRS: 19/31 (61.3%) CRS Grade ≥ 3: 6/31 (19%) Any Neurotoxicity (ICANS): 9/31 (29%) Neurotoxicity Grade ≥ 3: 3/31 (10%) Therapy associated hemophagocytic lymphohistiocytosis: 2/31 (6.5%) Late onset bacteriaemia: 2/31 (6.5%)	Any CRS: OOS (n=24): 46% SOC (n=161): 61% CRS Grade ≥ 3: OOS (n=24): 17% SOC (n=161): 19% ICANS: OOS (n=24): 8% SOC (n=161): 22% Infections: OOS (n=24): 54% SOC (n=161): 37%	Any CRS: 3/7 (42%) CRS Grade 3: 1/7 (14%) ICANS: 0/7	Any CRS: 116/183 (63%) CRS Grade ≥3: 39/183 (21%) HLH 1/183 (0.5%) Neurotoxicity overall 38/179 (21%) Neurotox Grade ≥ 3: 12/179 (7%) Neutropenia grade 4: 118/175 (67%) Tumour lysis syndrome: 13/173 (7%) Infectious complication: 73/181 (40%) PICU-Stay: 57/184 (31%)
AE, n (%)	NR	Hypogammaglobulinemia: 134/255 (52.5%) Prolonged cytopenia: 71/255 (27.8%) significant infections: 118/255 (46.3%) Gr.3/4 organ toxicities: 21/255 (8.2%) Secondary malignancies: 6/255 (2.4%) Deaths: 47/255 (18.4%)	NR	NR	NR	NR
Definition/ Scoring system	CRS and Neurotoxicity according to ASTCT, or institutional standard	CRS and ICANS scored after ASTCT	CRS scored after ASTCT ICANS scored after CTCAE	Not available	CRS and ICANS scored after ASTCT	CRS and Neurotoxicity according to ASTCT, or institutional standard
Procedure-related mortality, n (%)	None 4 deaths: refractory disease n=3, transplant related mortality n=1	1 death from CRS Deaths within 30 days of infusion 8/255 (3.1%): ■ Progressive disease 3/255 (1.2%) ■ Other 5/255 (2.0%)	2/31 (6.5%) carHLH d11 post infusion, multi-organism infection d35 postinfusion Other deaths (refractory leukaemia n=4, relapsed leukaemia n=5, other toxicities n=2)	5 patients died prior day 28 evaluation (reasons not stated, all in the SOC group)	0/7	Total of 51 deaths after tisagenlecleucel infusion 5 < d28: Leukaemia n=1, Infection n=2, CRS n=1, Neurotoxicity n=1 Remaining 46 deaths: infection n=3, HSCT complication n=5, cardiac n=1; leukaemia n=37 Nonrelapse mortality rate 13/184 =7%

Author, year	Moskop, 2022	Pasquini, 2020 [125]	Ravich, 2021 [126]	Rossoff, 2021 [127]	Rubinstein, 2020 [130]	Schultz, 2021 [128]
Subsequent treatment	HSCT while in CAR T-mdiated remission 1/14 (7%) Refractory to CAR T 4/14 (29%) CR post CAR T 7/14 (50%) Relapse post CAR T 3/14 (21%) Death 4/14 (29%)	HSCT: 55/255 (22%) (of which 34 in remission for consolidation, 21 as treatment for relapse)	second CART infusion 4/31 3 of 4 no remission or relapse again, 1 of 4 HSCT due to relapse Of all 25 pt with CR 4 proceeded with alloHSCT 9 additional patients HSCT for therapy relapse: 5/9 remained in remission, 2 died of HSCT-complications, 2/9 relapsed	NR	1/7 CNS relapse treated with chemotherapy → disease free 29mo post infusion 1/7 2nd CAR-T because of B cell recovery + Pembrolizumab → disease free 18 mo post infusion 1/7 2 more relapses, 2 more CAR T + HSCT → disease free 24 mo post infusion	Of pt who achieved CR 41/156 (28%) underwent post-CAR HSCT 20/41 while in remission 19/41 after relapse 2 for myelodysplastic syndrome
Comment	PRWCC – Cohort		High pretreatment leukaemic burden (≥5% blasts) is an independent risk factor for EFS (HR 5.98 [95% CI 1.10-32.4]) p=,0380 and OS (HR4.2 [95% CI 1.33-13.39]) p=,0148	Letter to the editor! PRWCC – Cohort		PRWCC – Cohort

Abbreviations: BCA: B-cell aplasia, Blina: Blinatumomab, BM: bone marrow, BMB: bone marrow blasts, CAPD: Cornell Assessment of Paediatric Delirium, CAYAs: children, adolescents, and young adult, CIBMTR: Center for International Blood and Marrow Transplant Research, CICE: cumulative incidence of composite end point (relapse or loss of B-cell aplasia), CIR: cumulative incidence or relapse, CNS: central nervous system, CR: complete remission, CRS: cytokine release syndrome, DOR: duration of response, EFS: Event-free survival, EM: extramedullary, Flu: fludarabine, Haem: haematologic, HDB: High disease burden, HR: High-risk, HSCT: haematopoietic stem cell transplantation, HTB: high tumour burden, ICANS: immune effector cell-associated neurotoxicity syndrome, Ino: Inotuzumab, IQR: interquartile range, LDB: low disease burden, LFS: leukaemia-free survival, LTB: low tumour burden, Neg.: negative, NR: not reported, mo: months, MR: moderate risk, MRD: minimal residual disease, mut.: mutation, OOS: out of specification (= beyond approved indication), ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, (P)ICU: (paediatric) intensive care unit, Prim: primary, pos: positive, PRWCC: Pediatric real-world CAR Consortium, pts: patients, HRQoL: Health-related Quality of life, RoB: risk of bias, r/r: refractory or relapsed, (S)AE: (severe) adverse event, SOC: standard of care, SPM: subsequent primary malignancy, UD: undetectable disease, URT: upper respiratory tract, ↓ decreased, ↑ increased

Evidence tables of included studies for clinical effectiveness and safety for LBCL

Pivotal trials

Table A-3: Eligibility criteria from pivotal studies of LBCL

	ZUMA-1 [62, 63]	JULIET [64, 65]
Country	USA, Israel	Multicentre (Australia, Austria, Canada, France, Germany, Italy, Japan, Netherlands, Norway, USA)
Sponsor	Kite, a Gilead Company	Novartis
Intervention/Product	Axicabtagene Ciloleucel (Yescarta)	Tisagenlecleucel (Kymriah)
Comparator	-	-
Study design	Phase 1/2 non-randomied, single-arm, multicentre	Phase 2, observational, single-arm, multicentre study
Population (proportion of participants with DLBCL, type of DLBCL and other conditions if reported)39	Phase 1&2: 119 pt enrolled (307 accoriding to CT.gov) 108/119 pt (91%) receiving CAR-T 108/119 pt (91%) evaluated Phase 1&2: n=108 receiving CAR-T-cells Phase 2: n=111 enrolled, n=101 infused and evaluated: ■ DLBCL, n=77 (76%) ■ PMBCL, n=24 (24%)	165 pt enrolled 111/165 pt (67%) receiving CAR-T 93/165 pt (56%) evaluated n=109 (98%) DLBCL: ■ n=88 DLBCL NOS ■ n=21 DLBCL TF from follicular lymphoma
Inclusion criteria	Key eligibility criteria: ■ Histologically confirmed large B-cell lymphoma (according to the 2008 WHO guidelines, retrospectively centrally confirmed) ■ DLBCL (cohort 1) ■ Primary mediastinal B-cell lymphoma or transformed follicular lymphoma (cohort 2) ■ Refractory disease, defined as ■ PD or SD as the best response to the most recent chemotherapy regimen or ■ Disease progression or relapse within 12 months after autoHSCT ■ Aged 18 years or older ■ ECOG performance status of 0 or 1 ■ Absolute neutrophil count ≥ 1000/µL ■ Adequate organ function	■ Age ≥18 years ■ Histologically confirmed DLBCL at last relapse ■ Relapsed/refractory DLBCL after at least 2 lines of chemotherapy including rituximab and an anthracycline ■ Either relapsed or ineligible for autoHSCT ■ DLBCL that transformed from follicular lymphoma ■ High-grade B-cell lymphoma with MYC rearrangements plus rearrangement of BCL2, BCL6, or both genes ■ *Life expectancy ≥ 12 weeks* ■ *ECOG performance status either 0 or 1 at screening*
Exclusion criteria	■ Prior regimen containing an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen ■ autoHSCT within 6 weeks of planned axi-cel infusion	■ History of prior treatment with anti-CD19/anti-CD3 therapy, or any other anti-CD19 therapy ■ Primary mediastinal DLBCL

[39] Due to heterogeneous reporting of the composed sample including participants with conditions other than r/r DLBCL, the number of participants separated by condition is reported for participants receiving CAR-T cells, for participants evaluated, or both

	ZUMA-1 [62, 63]	JULIET [64, 65]
Exclusion criteria *(continuation)*	■ Prior alloHSCT ■ Prior CD19 targeted therapy or CAR-T therapy with the exception of subjects who received axi-cel in this study and are eligible for re-treatment	■ Prior gene therapy ■ Prior alloHSCT ■ Active central nervous system involvement of DLBCL
Age of patients, median (range) (yrs)	58 (IQR: 51-64)[40]	56 (22-76) (n=111)
Sex (male/total)	73/108 (68%)	60/93 (65%)
Pre-Treatment	Prior autoHSCT: 16/81 (21%) Prior alloHSCT: not allowed	Prior autoHSCT: 54/111 (49%) Prior alloHSCT: 0/111 (0%) (not allowed) *Bridging therapy: 92%*
Bridging therapy	Not allowed	*Rituximab, gemcitabine, etoposide, dexamethasone, cisplatin, cytarabine, ibrutinib, lenalidomide*
Line of Treatment	Previous lines of treatment, median:3 (n=108) *≥ 3 previous therapies: 70/111 (69%)*[41] *Disease stage 1-2: 15/111 (15%)*[41] *Disease stage 3-4: 86/111 (85%)*[41]	*Prior therapies, median: 3* 1 previous therapy: 5/111 (5%) 2 previous therapy: 49/111 (44%) 3 previous therapy: 34/111 (31%) 4-6 previous therapy: 23/111 (21%) *Disease stage 1-2: 27/111 (24%)* *Disease stage 3-4: 84/111 (76%)*
ECOG, IPI scores	*ECOG 1: 59/111 (58%)*[41] *IPI 0-2: 53/111 (52%)*[41] *IPI 3-4: 48/111 (48%)*[41]	*ECOG 0: 61/111 (55%)* *ECOG 1: 50/111 (45%)*
Follow-up	Median follow-up, reported for ***phase 1***: 9 months Median follow-up, reported for ***phase 2***: ■ Primary analysis (Jan 2017): 8.7 months ■ Updated analysis (Aug 2017): 15.4 months ■ Longer-term safety and activity assessment (Aug 2018): 27.1 months	Median follow-up: 19.3 months post-infusion (n=115)
Loss to follow-up, n (%)	0	NR
Statistics used	*Descriptive statistics for incidence of AE, changes in laboratory values, proportion of pt with OR* *Kaplan-Meier for time-to-event analyses of DOR, PFS and OS* *Clopper-Pearson for 95% CIs for responses* *Statistical analysis in SAS (version 9.4)*	*Kaplan-Meier for survival distributions* *BOR rate: two-sided exact Clopper-Pearson CIs, assessed using Lugano classification* *Kaplan-Meier for DOR, PFS, EFS, OS* *Statistical analysis by SAS version 9.4 and Rstudio version 2019* *Summary scores of FACT-Lym total score* (range 0-168, higher scores indicate improvement, MCID: 6.5-11.2), *SF-36 physical health total score and SF-36 mental health total score*

[40] Data from patients in phase 2 (n=101)

[41] All enrolled patients from phase 2 (n=111)

	ZUMA-1 [62, 63]	JULIET [64, 65]
Statistics used *(continuation)*		*FACT-G TS: 4 domains: physical, social/family, emotional and functional well-being* *FACT-Lym S: response to lymphoma-associated treatment and symptoms and other concerns* *FACT-Lym TOI: physical and functional well-being + Lym S* *FACT-Lym TS: FACT-G + Lym S*
Outcomes		
Efficacy		
	Sample size (if not otherwise specified)[42]: n=108 [101 for phase 2 (n=77 (76%) DLBCL)] evaluated/n=108 receiving CAR Tcells/n=119 enrolled	Sample size (if not otherwise specified)[42]: n=93 [99] evaluated/n=111 [115 at data cut-off May 2018] receiving CAR-T cells/n=165 enrolled
Overall survival, n (%)	Reported for phase 1 and phase 2 population (n=108, proportion of DLBCL unclear): ■ At 6 months: 78% (95% CI 69% to 85%) ■ At 12 months: 59% (95% CI 49% to 68%) ■ At 18 months: 52% (95% CI 41% to 62%) Reported for phase 2 population (n=101, n=77 (76%) DLBCL): ■ Median at 24 months follow-up: NR* (95% CI 12.8 to NR*) ■ Estimated at 24 months: 50.5% (95% CI 40.2% to 59.7%)	At 12 months:48% (95% CI 38% to 57%) At 18 months: 43% (95% CI 33% to 35%) *Median OS, mo: 12 (95%CI: 7-NR*)* *ITT[43] median OS, mo: 8.3 (95%CI: 5.8-11.7)*
Disease-specific survival, n (%)	NR	NR
Progression-free survival, event-free survival, n (%)	Estimated proportion of patients with PFS reported for entire group for phase 2 (n=101, n=77 (76%) DLBCL): ■ Median: 5.9 months (95% CI 3.3 to 15.0) ■ At 6 months: 49% (95% CI 39% to 58%) ■ At 12 months: 44% (95% CI 34% to 53%) ■ At 15 months: 41% (95% CI 31% to 50%)	Probability of being relapse-free at 6 months: 66% (95% CI 51% to 78%) Probability of being relapse-free at 12 or 18 months: 64% (95% CI 48% to 76%) *Median PFS, mo: NR* for patients with CR* *Estimated PFS at 12 mo: 83% (patients with CR or PR at 3 mo)*
Response Rates (OR, CR, PR) n (%)	***Updated analysis (median FU 15.4 mo)[44]*** *1y ORR: 89/108 (82%)* *CR rate: 63/108 (58%)* *Median duration of response: 11.1 mo (95%CI 3.9-NE[45])*	bOR at median follow-up of 19.3 months post-infusion: 54% (95% CI 43% to 64%) bCR at 19.3 months median follow-up post-infusion: 40% (95%CI NR) bPR at 19.3 months median follow-up post-infusion: 13% (95%CI NR) *Median duration of response: NE[45] (95%CI 10-NE)*
Recurrence, n (%)	NR	NR
Mortality, n (%)	*Dead at data cutoff (median FU 27.1): 54/108 (50%)* ■ Disease progression: 50/108 ■ NRM: 4/108 (2 axi-cel related)	*Overall 70/115 (61%) died*

[42] Please note the numbers of participants refer to efficacy data retrieved from the primary publication unless otherwise specified. The numbers of participants enrolled, receiving CAR-T cells and evaluated are reported only when provided.

[43] ITT: intention-to-treat analysis included all 165 enrolled patients

[44] Patients from Phase 1&2 (n=108)

[45] Not estimable

	ZUMA-1 [62, 63]	JULIET [64, 65]
Health-Related Quality of Life	NR	*All pts: n=108/pts with CR/PR: n= 57/non-responders: n=51*[46] *Statistically signficant differences from baseline to 3, 6, 12 and 18 months:* ■ **FACT-G TS** (MCID upper-lower limit: 3-7): Baseline: all: 77.0 (16.1)/ pts with CR/PR: 79.2 (15.2)/nonresponders: 74.6 (17.0) 3mo: +5.8 (11.9) 6mo: +15.8 (13.9) 12mo: +16.3 (12.2) 18 mo: +10.0 (11.1) ■ **FACT-Lym S** (MCID upper-lower limit: 2.9-5.4): Baseline: all: 44.4 (9.1)/pt with CR/PR: 45.2 (9.3)/nonresponders: 43.6 (9.0) 3mo: +3.2 (7.4) 6mo: +3.0 (7.7) 12mo: +3.7 (6.5) 18 mo: +3.1 (6.6) ■ **FACT-Lym TOI** (MCID upper-lower limit: 5.5-11) Baseline: all: 82.0 (19.0)/pt with CR/PR: 84.7 (18.3)/nonresponders: 79.1 (19.5) 3mo: +5.9 (14.5) 6mo: +6.2 (15.5) 12mo: +6.8 (15.6) 18 mo: +9.2 (13.6) ■ **FACT-Lym TS** (MCID upper-lower limit: 6.5-11.2): Baseline: all: 121.2 (24.0)/pt with CR/PR: 124.1 (22.8)/nonresponders: 118.1 (25.1) 3mo: +9.4 (17.1) [47] 6mo: +8.6 (20.3) [47] 12mo: +9.6 (17.9) [47] 18 mo: +13.1 (16.1) [48] ■ **SF-36 Physical health TS** (MCID 3): Baseline: all: 43.4 (9.2)/pt with CR/PR: 45.6 (9.9)/nonresponders: 43.1 (8.4) 3mo: +1.3 (9.1) 6mo: +1.8 (11.1) 12mo: +1.3 (10.5) 18 mo: +3.9 (10.6 ■ **SF-36 Mental health TS** (MCID 3): Baseline: all: 50.6/pt with CR/PR: 51.9 (10.0)/nonresponders: 49.7 (11.1) 3mo: +0.7 (9.3) 6mo: +1.9 (8.5) 12mo: +1.1 (9.6) 18 mo: +2.1 (9.9

[46] Questionnaire completion: BL: 108/115 (94%), 3 mo: 47/62, 6 mo: 35/43, 12 mo: 31/36, 18 mo: 22/34. Reasons for not completing questionnaires were disease progression and death

[47] According to the authors, the improvement was above the MCID lower limit

[48] According to the authors, the improvement was above the MCID upper limit

	ZUMA-1 [62, 63]	JULIET [64, 65]
Safety		
	Sample size (if not otherwise specified)[49]: n=108 (phase 1 and 2, proportion of DLBCL unclear) evaluated/n=108 receiving CAR Tcells	Sample size (if not otherwise specified)[49]: n=111 (data cut-off Dec 2017) (n=109 (98%) DLBCL) evaluated/n=111 receiving CAR-T cells
Definition/Scoring System	*Lee criteria for CRS* *CTCAE version 4.03 for grading CRS symptoms, neurologic events and adverse events*	*CTCAE version 4.03 and Medical Dictionary for Regulatory Activities for grading adverse events version 20.1* *University of Pennsylvania grading scale for CRS*
Overall complications, n (%)	Any AE in Phase 1&2: 108/108 (100%), Grade ≥ 3: 106/108 (98%)	Any AE: 111/111 (100%), Grade ≥ 3: 99/111 (89%)
(Serious) adverse events, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	Any SAE: 60/108 (56%), Grade ≥3 52/108 (48%) CRS (Lee 2014): 100/108 (93%) Grade ≥3: 12/108 (11%) Neurotoxicity: 72/108 (67%) Grade ≥3: 35/108 (32%) Cytopenias: ■ Anaemia: 73/108 (68%) Grade ≥3: 49/108 (45%) ■ Leukopenia: 20/108 (19%) Grade ≥3: 18/108 (17%) ■ Neutropenia: 48/108 (44%) Grade ≥3: 42/108 (39%) ■ Thrombocytopenia: 38/108 (35%) Grade ≥3: 26/108 (24%) Any prolonged cytopenias lasting ≥ 30 days: 49/108 (45%) Grade ≥3: 32/108 (30%) Febrile neutropenia: 39/108 (36%) Grade ≥3: 35/108 (32%) Any infections: NR Grade ≥3: 30/108 (28%)	Any SAE: 72/111 (65%) CRS: 64/111 (58%) Grade ≥3: 24/111 (22%) Neurotoxicity (during the first 8 weeks post-infusion): 23/111 (21%) Grade ≥3: 13/111 (12%) Cytopenias: ■ Anaemia: 53/111 (48%) Grade ≥3: 43/111 (39%) ■ Leukopenia: NR ■ Neutropenia: 22/111 (20%) Grade ≥3: 22/111 (20%) ■ Thrombocytopenia: 14/111 (13%) Grade ≥3: 13/111 (12%) Any prolonged cytopenias lasting >28 days: 49/111 (44%) Grade ≥3: 36/111 (34%) Febrile neutropenia (during the first 8 weeks post-infusion): 17/111 (15%) Grade ≥3: 16/111 (14%) Any infections (during the first 8 weeks post-infusion): 38/111 (34% Grade ≥3: 22/111 (20%)

Abbreviations: alloHSCT: allogenic stem-cell transplantation, autoHSCT: autologous stem-cell transplantation, BL: baseline, CT.gov: Clinicaltrials.gov, FACT-Lym: Function Assessment of Cancer Therapy-Lymphoma, DLBCL: diffuse large B-cell lymphoma, MCID: minimum clinically important difference, M: mean, NR: not reported, NR: not reached, SD: standard deviation, TF: transformed, +: positive changes from baseline*

This table was retrieved and expanded when necessary (italic) from Cochrane 2021 [61].

[49] Please note that the numbers of participants refer to safety data retrieved from the primary publication unless otherwise specified.

RWE

Table A-4: CAR-T cell therapy for LBCL: results from observational studies (part 1/3)

Author, year	Ayuk, 2021 [49]	Baird, 2021 [145]	Bethge, 2022 [111]	Ghafouri, 2021 [112]	Hamadani, 2022 [113]	Holtzman, 2021 [114]
Country	Germany	USA	Germany	USA	USA and Canada	USA
Sponsor	Not specified	NIH/NCI grants	Not specified	Not specified	NIH/NCI grants Health Resources and Service Administration/Naval Research grants Be the Match Foundation, National Marrow Donor program, commercial entities	None
Intervention/ Product	antiCD19 CAR-T ■ Axicabtagene ciloleucel	antiCD19 CAR-T ■ Axicabtagene ciloleucel	antiCD19 CAR-T ■ Axicabtagene ciloleucel 173/356 (49%) ■ Tisagenlecleucel 183/356 (51%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel 45/53 (85%) ■ Tisagenlecleucel 8/53 (15%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 181/584 (31%) alloHSCT: 403/584 (69%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel
Indication	r/r DLBCL or PMBCL	r/r CD19+ LBCL	LBCL	r/r aBCL	DLBCL	r/r LBCL
Comparator	-	-	-	-	noncomparative description of CAR-T and alloHSCT[50]	-
Study design	Prospective case series	Retrospective case series	Retrospective registry analysis	Retrospective case series	Retrospective noncomparative registry analysis (CIBMTR registry)	Retrospective case series
Number of pts	22, 21 infused with axi-cel (1 not infused due to disease progression) ■ DLBCL: 18/21 (85.7%) ■ PMCBL: 3/21 (14.3%)	41 ■ DLBCL: 26/41 (63.4%) ■ PMCBL: 3/41 (7.3%) ■ tFL: 12/41 (29.3%)	356 ■ DLBCL 323/356 (91%) ■ PMBCL 16/356 (5%) ■ tFL/Other 17/356 (5%)	53 ■ DLBCL (GCB): 23/53 (43%) ■ DLBCL (ABC): 18/53 (34%) ■ DLBCL (NOS): 12/53 (23%) ■ Transformed DLBCL: 18/53 (34%) Non-DHL/THL: 39/53 DHL/THL: 14/53	584	45 ■ DLBCL: 35/45 (78%) ■ tFL: 7/45 (16%) ■ PMBCL: 3/45 (7%)
Inclusion criteria	■ Pts with r/r DLBCL or PMCBL planning to receive axi-cel in a nontrial setting at University Medical Center Hamburg-Eppendorf ■ Between 03/2019-07/2020	■ Pts with r/r CD19+ LBCL trated with axi-cel at Stanford University's Cancer Institute ■ Between 09/2017-03/2019	■ Adult LBCL pts (≥18y) treated with commercially tisa-cel or axi-cel ■ Pts treated in 21 German CAR-T cell centers ■ Documented in the German Registry for Stem Cell Transplantation (DRST)/EBMT database ■ From 08/2019-04/2021	■ All pts diagnosed with r/r aggressive BCL (including DLBCL, DHL/THL, follicular lymphoma with histologic transformation to large cell lymphoma and Richter's transformation of chronic lymphocytic leukaemia (CLL) receiving axi-cel or tisa-cel at University of California, Los Angeles	CAR-T ■ Adult pts with DLBCL undergoing a first alloHSCT (reduced-intensity or nonmyeloablative conditioning platforms) or CAR-T (axi-cel) therapy ■ Between 2012 and 2019 alloHSCT ■ History of failed prior autoHSCT ■ Eligible donors for the alloHSCT cohort included matched sibling,	■ Pts with r/r LBCL treated with axi-cel at Baltimore center ■ Between 04/2018-05/2019

[50] Data from alloHSCT were not extracted due to noncomparative study design

Author, year	Ayuk, 2021 [49]	Baird, 2021 [145]	Bethge, 2022 [111]	Ghafouri, 2021 [112]	Hamadani, 2022 [113]	Holtzman, 2021 [114]
Inclusion criteria *(continuation)*				■ Between 10/2017-06/2020 ■ Pathologic diagnosis locally confirmed	8/8 matched unrelated (allele-level match at HLA-A, -B, -C, and -DRB1), or related haploidentical donors	
Exclusion Criteria	Not specified	Not specified	Pts treated with other CAR-T cell constructs or within clinical trials	Pts receiving anti-CD19 CAR-T for ALL and pts enrolled on investigational protocols	Pts receiving ex vivo graft manipulation or history of DLBCL transforming from indolent histologies	Not specified
Age of patients, median (range) (yrs)	58 (24-67)	56 (21-76)	60 (19-83)	63 (18-82)	61 (21.9-80)	60 (26-75)
Sex	F (29%)/M (71%)	F (41%)/M (49%)	F (34%)/M (66%)	F (42%)/M (58%)	F (35%)/M (65%)	F (51%)/M (49%)
Pre-Treatment, n (%)	1 prior autoHSCT: 10/21 (47.6%) 2 prior autoHSCT: 2/21 (9.5%) 1 prior alloHSCT: 1/21 (4,8%) Prior bridging therapy: 19/21 (90.5%)	Bridging therapy: 18/41 (43.9%)	Prior HSCT: 121/356 (34%) Bridging therapy for disease control prior to lympho-depletion: 278/356 (78%)	Prior autoHSCT: 5/53 (9%) Prior alloHSCT: 2/53 (4%) Bridging therapy: 31/53 (58%)	Bridging therapy use: 35/181 (19.3%)	Bridging therapy: 30/45 (67%)
Bridging therapy	R-ICE, R-Pixantrone, R-GemOx, Irradiation, MTX + cytarabine, R-LEAM, Pembrolizumab, R-Polantuzumab	Chemotherapy, Radiation Therapy, Steroids, Combination Therapy	Platinum-based standard salvage CIT or similar, other Rituximab-based CIT, Polatuzumab-based HDT – autoHSCT, other chemotherapy, other antibodies mono, Lenalidomide-based, pathway inhibitors, checkpoint inhibitors, steroids only, radiotherapy only	NR	NR	Cytotoxic chemotherapy (47%), radiation (13%), steroids, biologics, combination (remaining)
Eligibility for ZUMA-1/JULIET	Eligibility ZUMA-1: 2/21 (9.5%)	ZUMA-1 ineligible at apharesis: 16/41 (39%)	Eligibility ZUMA-1: 45/356 (13%) Eligibility JULIET: 318/356 (89%)	Eligibility for ZUMA-1 or JULIET: 16/53 (30%)	NR	NR
Line of Treatment	Prior therapies, median: 5 (range: 3-8) 3-4 prior therapies: 8/21 (38%) >4 prior therapies: 13/21 (62%)	Prior therapies, median: 3 (range: 2-4) ≥3 treatment lines 25/41 (61%) Relapse after autoHSCT: 8/41 (19.5%) Disease stage 1-2: 9/41 (22%) Disease stage 3-4: 32/41 (78%)	≥3 treatment lines: 252/356 (71%) ≥5 treatment lines: 51/252 (20%)	Prior therapies, median: 3 (range: 1-6) ≥4 prior lines of therapy: 17/53 (32%)	Disease status: ■ CR: 9/181 (5%) ■ PR: 39/181 (21.5%) ■ Resistant/untreated relapse: 122/181 (67.4%) ■ Unknown: 11/181 (6.1%)	NR
ECOG, IPI scores	ECOG ≥2: 3/21 (14.3%) IPI 0-2: 13/21 (61.9%) IPI 3-5: 8/21 (38.1%)	ECOG ≥2: 3/41 (7.3%) IPI 0-2: 24/41 (58.5%) IPI 3-4: 17/41 (41.5%)	ECOG ≥2: 56/356 (16%) sIPI high/high-intermediate: 171/356 (52%)	ECOG ≥2: 6/53 (11%) Secondary IPI 0-2: 39/53 (74%) Secondary IPI 3-5: 14/53 (26%)	NR	NR
Follow-up, median (range) (months)	4 (0.7-12.5)	19.8 (3.3-27.6)	Pts alive: 11 (1-29)	15.2 (IQR: NR)	13 (1-27.7)	7.1 (IQR: 3-9.9)
Loss to follow-up, n (%)	22 pt enrolled, 21 pt infused and analysed	NR	NR[51]	NR	NR	NR

[51] No detailed reporting: 344/356 pt evaluable for response, 319/356 pt evaluable for neutropenia, 311/356 pt evaluable for thrombocytopenia

Author, year	Ayuk, 2021 [49]	Baird, 2021 [145]	Bethge, 2022 [111]	Ghafouri, 2021 [112]	Hamadani, 2022 [113]	Holtzman, 2021 [114]
Statistics used	Peak CAR-T blood concentration (CAR-T-C_{max}) and cumulative CAR-T-cell levels (CAR-T-AUC) by GraphPad Prism Software Statistical analyses performed by SPSS Software	Categorical variables: Fisher's exact test and Pearson's χ^2 Kaplan-Meier for median PFS and OS 2-sample comparison by log-rank test Univariate and stepwise multivariate Cox proportional-hazards regression Analyses by GraphPad Prism 8.0.2 and R 3.6.1	Descriptive statistics Differences between groups: χ^2 or Mann-Whitney's rank sum test, log-rank test Kaplan-Meier for probabilities of OS and PFS Cumulative incidence to estimate NRM Simple and multiple Cox regression analysis for predictive factors for OS and PFS Analysis performed by SPSS 26.0 and GraphPad Prism Software 9.1.2, incidence curves with R software	Descriptive statistics Fisher's exact test for comparison between groups Kaplan-Meier for OS, PFS, DOR and calculation fo 6- and 12mo event rates Univariate and multivariate cox regression analysis to evaluate prognostic variables and confounding effects	Pearson χ^2 test for categorical variables Kruskal-Wallis test for continuous variables Kaplan-Meier for OS and PFS Cumulative incidence rates of haematopoietic recovery, NRM and relapse/progression rates were calculated while accountig for competing events All statistical analyses performed by SAS version 9.4	Categorical variables: frequency counts and percentages, compared with Fisher's exact test Continuous variables: medians and interquartivle ranges compared with Wilcoxon rank sum test
Outcomes						
Effectiveness						
Definition OS	NR	NR	OS: Time from cellular therapy to death from any cause	OS: duration of time from CAR-T cell infusion until death from any cause or last documented FU	OS: time from treatment to death from any cause No censoring of 5 relapsed pts who received alloHSCT after CAR-T	OS: from time of treatment to death
Overall survival	Estimated OS at 12 mo: 49% (25%-73%)	Median OS, mo: NR* (95%CI 16,6-NE)	Estimated OS rate at 12 mo: 52% ■ Axi-cel: 55% ■ Tisa-cel: 53%	Median OS, mo: 17,7 ■ 6mo OS: 69% (95%CI 56-80) ■ 12mo OS: 55% (95%CI 41-68)	1y OS probability: 73.4% (95%CI 66.4-79.9) Subset analysis for pt receiving CAR-T with refractory or untreated relapse (n=122): 1y OS: 51.5% (95%CI NR)	Median OS: 15.1mo (95%CI NR)
Disease-specific survival	NR	NR	NR	NR	NR	NR
Definition of PFS/EFS	NR	NR	PFS: time from cellular therapy to relapse or disease progression or death from any cause (whatever came first)	PFS: defined as duration of time from CAR-T cell infusion until time of relapse, death, or last follow- up	PFS: time from either alloHSCT or CART treatment to relapse/ progression or death from any cause	PFS: from time of treatment to either disease progression or death
Progression-free survival, event-free survival	Estimated PFS at 12 mo: 37% (15%-59%)	Median PFS, mo: 6,1 (95%CI: 3.1-NE)	Estimated PFS rate at 12 mo: 30% ■ Axi-cel: 35% ■ Tisa-cel: 24% ■ Without bridging: 41% ■ Successful bridging: 53% ■ Bridging failure: 20%	Median PFS, mo: 7,9 Median EFS, mo: 11,9 ■ 6mo EFS: 54% (95%CI 30-97) ■ 12mo EFS: 50% (95%CI 26-97)	1y PFS probability: 55.7% (95%CI 48-63.2) Subset analysis for pt receiving CAR-T with refractory or untreated relapse (n=122): 1y PFS: 71% (95%CI NR)	Median PFS: NR*

Author, year	Ayuk, 2021 [49]	Baird, 2021 [145]	Bethge, 2022 [111]	Ghafouri, 2021 [112]	Hamadani, 2022 [113]	Holtzman, 2021 [114]
Definition of OR, CR, PR	Response assessment performed per institutional practice and based on Lugano criteria	NR	NR	DOR: defined as duration of time from initial radiographic CAR-T response to relapse, death, or last follow-up	Neutrophil recovery: the first of 3 successive days with an absolute neutrophil count ≥ 500/µLafter CAR-T nadir Platelet recovery: the first of 3 consecutive days with a platelet count of 20 000/µL or higher in the absence of platelet transfusion for 7 consecutive days.	NR
Response Rates (OR, CR, PR)	OR (PR or CR) around day 30: 14/21 (67%)	ORR: 36/41 (87.8%) CRR: 27/41 (65.9%) Response at d28: ■ CR: 17/41 (41.5%) ■ PR: 18/41 (43.9%) ■ SD: 3/41 (7.3%) ■ PD: 3/41 (7.3%) Median duration of response, mo: 8.3 (95%CI: 5.8-10.9)	CR: 126/344 (37%) PR: 96/344 (28%) SD: 38/344 (11%) PD: 85/344 (24%) ORR: 222/344 (65%) ORR axi-cel (CR): 74% (42%) ORR tisa-cel (CR): 53% (32%)	ORR: 38/53 (72%) CR: 34/53 (64%) PR: 4/53 (8%) Median DOR, mo: NR* 6mo DOR: 71% (95%CI 57-82) 12mo DOR: 60% (95%CI 44-74)	Cumulative incidence of ■ neutrophil recovery at d28: 89.7% (95%CI 84.7-93.8) ■ platelet recovery at d100: 86.7 (95%CI 81.2-91.4)	CR: 22/45 (49%) PR or SD: 16/45 (35.6%) PD: 5/45 (11.1%) Early CR by d30: 16/45 (36.5%)
Definition Recurrence/Relapse	NR	NR	NR	NR	Cumulative incidence of relapse/ progression: time from treatment to relapse or disease progression	NR
Recurrence	NR	NR	NR	Post CAR-T relapse: 48% Refractory at d28: 15/53 (28%) Among 38 repsponders: relapse: 12/38 (7=CR, 5=PR)	Cumulative incidence rate of relapse/progression at 1y: 39.5% (95%CI 32.1-47.2)	NR
Definition NRM	NR	NR	NR	NR	NR	NR
Mortality, n (%)	Overall 10/21 pt died due to disease progression	NRM: 1/41 (2.4%) due to infection related pneumonia	Overall 164 pt (46%) died ■ 143/164 (40%) due to disease progression ■ 21/164 (6%) non-relapse-related (NRM): ■ Infections: 13/21 (62%) ■ CRS, bleeding, hyper-inflammatory syndorme, unknown, secondary neo-plasia: 1 pt each = 5/21 ■ Neurotoxicity 2/21 (10%) ■ Unspecified: 1/21 Cumulative incidence of NRM[52] at 12 mo: 5.5%	Overall 23/53 (43%) died ■ Disease progression: 19/53 (36%) ■ Infection: 2/53 (4%) ■ Unknown: 2/53 (4%)	Overall 55/181 (30.3%) died ■ Disease progression: 40/55 (73%) ■ Infection: 5/55 (9.1%) ■ Second cancers: 3/55 (5.5%) Cumulative incidence of NRM[53] at 1y: 4.8% (95% CI 2.1-8.6)	2 pts with persistent neurotoxicity died due to relapse

[52] defined as death after cellular therapy without prior lymphoma relapse or progression

[53] defined as death without preceding disease progression

Author, year	Ayuk, 2021 [49]	Baird, 2021 [145]	Bethge, 2022 [111]	Ghafouri, 2021 [112]	Hamadani, 2022 [113]	Holtzman, 2021 [114]
Quality of life	NR	NR	NR	NR	NR	NR
Safety						
Overall complications, n (%)	NR	NR	NR	NR	NR	NR
Definition, Scoring system SAE	ASTCT score for CRS and ICANS	ASTCT score for CRS and ICANS CTCAE version 5.0 for grading adverse events	ASTCT score for CRS and ICANS	Lee criteria from 10/2017-03/2019 and CTCAE version 5.0 from 03/2019-06/2020 for CRS and neurotoxicity	ASTCT score for CRS and ICANS	ICANS: CTCAE version 4.03 for grading, CARTOX-10 for screening Lee criteria for CRS
(Serious) adverse events, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	CRS: 15/21 (71.4%) ■ Grade 1: 2/21 (9.5%) ■ Grade 2: 10/21 (47.6%) ■ Grade 3: 3/21 (14.3%) ■ Grade 4: 0/21 (0%) ICANS: 10/21 ■ Grade 1: 5/21 (23.8%) ■ Grade 2: 1/21 (4.8%) ■ Grade 3: 3/21 (14.3%) ■ Grade 4: 1/21 (4.8%)	CRS: 37/41 (90.2%) ■ Grade 1: 7/41 (17.1%) ■ Grade 2: 29/41 (70.7%) ■ Grade 3: 1/41 (2.4%) ■ Grade 4: 0/41 (0%) ICANS: 23/41 (56.1%) ■ Grade 1-2: 13/41 (31.7%) ■ Grade 3-4: 10/41 (24.4%) SAE until d28: Severe cytopenias: 40/41 (97.6%) ■ grade ≥3 neutropenia: 40/41 (97.6%) ■ grade ≥3 thrombo-cytopenia: 23/41 (56.1%) Infection until d28: 19/41 (46.3%) → mild to moderate 13/19 (68.4%) Infection beyond d365: 8/17 (47.1%)	Grade 4 neutropenia: ■ 261/319 (81%) ■ median duration: 13 days (1-419) Severe thrombocytopenia: ■ 115/311 (37%) ■ median duration: 34 days (2-375) any CRS: 73% (axi vs tisa: 81% vs 65%; p=0.0003) grade ≥3 CRS: 12% ICANS: 33% (axi vs tisa: 44% vs 22%; p<0.0001) grade ≥3 ICANS: 11%	CRS: 36/53 (68%) ■ Grade 1: 12/53 (23%) ■ Grade 2: 21/53 (40%) ■ Grade 3: 3/53 (6%) ■ Grade 4: 0/53 (0%) ICANS: 16/53 (30%) ■ Grade 1: 4/53 (8%) ■ Grade 2: 2/53 (4%) ■ Grade 3: 7/53 (13%) ■ Grade 4: 3/53 (6%)	CRS grade 1-5: 149/181 (82.3%) CRS grade ≥3: 18/181 (9.9%) ICANS grade 1-4: 112/181 (61.9%) ICANS grade ≥3: 38/181 (20.9%)	CRS: 36/45 (80%) Grade 3-4: NR ICANS: 25/45 (56%) Grade 3-4: 18/45 (40%)

Abbreviations: AE: adverse event, CAR-T associated toxicity 10-point (CARTOX-10), CR: complete remission, CRS: cytokine release syndrome, CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, EFS: event-free survival, GVHD: graft-versus-host disease, ICANS: Immune effector cell-associated neurotoxicity syndrome, mo: months, NA: not available, NE: not evaluable, NIH/NCI: National Institutes of Health/National Cancer Institute, NR: not reported, NR: not reached, ORR: overall response rate, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PR: partial remission, pts: patients, SD: stable disease, SD*: standard deviation, tFL: transformed follicular lymphoma*

Table A-4: CAR-T cell therapy for LBCL: results from observational studies (part 2/3)

Author, year	Iacoboni, 2021 [110]	Kuhnl, 2022 [146]	Lamure, 2021 [115]	Nastoupil, 2020 [147]	Ram, 2022 [148]	Sermer, 2020 [116]
Country	Spain	UK	France	USA	Israel	USA
Sponsor	NR	NR	CHU Montpellier ITMO AVIESAN fellowship French national research grants, FRM, ARC, Sidaction, ANRS, Labex EpiGenMed, CALYM	NIH/NCI, Moffitt Cancer Center grants	None	NIH/NCI grants
Intervention/ Product	antiCD19 CAR-T ■ Tisagenlecleucel	antiCD19 CAR-T ■ Axicabtagene ciloleucel 224/300 (75%) ■ Tisagenlecleucel 76/300 (25%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel 49/60 (82%) ■ Tisagenlecleucel 11/60 (18%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel	antiCD19 CAR-T ■ Axicabtagene ciloleucel 15/82 (18%) ■ Tisagenlecleucel 67/82 (82%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 47/69 (68%) ■ Tisagenlecleucel 22/69 (32%)
Indication	r/r LBCL	r/r LBCL	r/r DLBCL or tFL	r/r LBCL	r/r DLBCL	r/r DLBCL
Comparator	-	-	-	-	-	CAR-T vs alternate therapies
Study design	Retrospective case series	Retrospective multicenter case series	Prospective case series	Retrospective case series	Retrospective cohort study	nRCT
Number of pts	91 recruited, 75 (82%) infused	404 approved, 300 (74%) infused ■ DLBCL: 200/300 (66.7%) ■ tFL: 64/300 (21.3%) ■ Transformed other: 17/300 (5.7%) ■ PMBCL: 19/300 (6.3%)	60 ■ DLBCL: 43/60 (71%) ■ tFL: 10/60 (17%) high-grade BCL: 7/60 (12%)	298 undergoing leukapheresis, 275 (92%) infused	82 (41 vs 41) Study cohort (older pts ≥70y) vs control (younger pts, matched control based on ECOG score, <70y)	215 (69 vs 146)
Inclusion criteria	■ r/r LBCL pts undergoing leukapheresis intended to receive tisa-cel ■ from 12/2018 to 06/2020 ■ for safety analysis: minimum FU 1 mo ■ survival analysis: all pt who underwent leukaphereis (intention-to-treat) and who received tisa-cel	■ r/r LBCL pts (at least two prior lines of systemic treatment) submitted to NCCP for approval of treatment with CD19 CAR-T ■ between 12/2018-11/2020 ■ confirmed CD19 positivity	■ adult r/r DLBCL or tFL pts receiving axi-cel or tisa-cel at the University Hospital of Montpellier ■ between 02/2019-03/2021	■ all r/r LBCL pts in 17 US centers undergoing leukapheresis ■ up until 30/09/2018	■ all pts referred for CD19-directed CAR-T in DLBCL CAR-T surveillance database (from 3 accredited centers in Israel) ■ between 04/2019-10/2020 ■ ECOG <4	***CAR-T*** ■ r/r LBCL pts with at least 2 prior lines of systemic therapy receiving tisa-cel or axi-cel ■ between 02/2018-09/2019 ■ long enough FU to reach first response assessment time point (generally after 30d) ***alternate therapies*** ■ r/r LBCL pts wit 2 prior lines of aggressive lymphoma-directed systemic therapy ■ Long enough FU to reach first response assessment to 3rd line therapy
Exclusion Criteria	NR	■ active CNS disease ■ comorbidity deemed significant for tolerability of CAR-T ■ previous treatment with geneticall modified auto or allo-T-cell immunotherapy	■ refusal to sign consent form ■ pregnancy ■ major protected	NR	■ current chemotherapy or impending organ dysfunction	■ no exclusion if pt got CAR-T after alternate therapies → data censored at time of infusion and analysed in CAR-T cohort

Author, year	Iacoboni, 2021 [110]	Kuhnl, 2022 [146]	Lamure, 2021 [115]	Nastoupil, 2020 [147]	Ram, 2022 [148]	Sermer, 2020 [116]
Age of patients, median (range) (yrs)	60 (IQR 52-67)	59.0 (18-78)	64 (18-79)	60 (21-83)	76.2 (SD* 4.4) vs 55.4 (SD* 15)	63 (19-85) vs 66 (27-91)
Sex	F (41%)/M (59%)	F (38.3%)/M (61.7%)	F (37%)/M (63%)	F (36%)/M (64%)	F (61%)/M (39%) vs F (54%)/(46%)	F (30%)/M (70%) vs F (42%)/M (58%)
Pre-Treatment, n (%)	Previous autoHSCT: '29/75 (39%) Bridging therapy: 65/75 (87%)	Prior autoHSCT: 45/300 (15%) Prior alloHSCT: 5/300 (1.7%) Bridging therapy: 260/300 (87%)	autoHSCT: 12/60 (20%) Bridging therapy: 54/60 (90%)	Prior autoHSCT: 98/298 (32.9%) Prior alloHSCT: 7/298 (2.4%) Bridging therapy: 158/298 (53%)	***Study cohort vs control*** ■ Prior autoHSCT: 3/41 (7.3%) vs 14/41 (34.1%) ■ Bridging therapy: 7/41 (17.1%) vs 12/41 (29%)	***CAR-T vs alternate*** ■ Prior autoHSCT: 14/69 (20%) vs 20/146 (14%); p=0.2 ■ Prior alloHSCT: 4/69 (6%) vs 3/146 (2%) ■ Bridging therapy CAR-T: NR
Bridging therapy	Cyclophosphamide-Prednisone, Platinum-based, Benda-mustine-based, Rituximab-CHOP, Steroids, Radiotherapy, Rituximab-Lenalidomide, other chemotherapy	Corticosteroids only, systemic treatment (+steroids), radiation therapy (+corticosteroids), combined modality treatment	NR	Chemotherapy (+other therapy), corticosteroids, radiation (+corticosteroids), targeted therapies	Steroids, chemotherapy (+radiation), radiation, novel agents	NR
Eligibility for ZUMA-1/JULIET	NR	NR	NR	NR	NR	NR
Line of Treatment	Prior therapies, median: 3 (range 2-4) 2-3 prior therapies: 54/75 (72%) >3 prior therapies: 21/75 (28%) Disease stage 1-2: 6/75 (8%) Disease stage 3-4: 69/75 (92%)	≥3 prior therapies: 112/300 (37.3%) Disease stage 1-2: 64/300 (21.6%) Disease stage 3-4: 232/300 (78.4%)	≥ 3 prior therapies: 16/60 (27%) Disease stage 1-2: 18/60 (30%) Disease stage 3-4: 36/60 (60%)	≥3 prior therapies: 222/298 (74.5%) Disease stage 1-2: 52/298 (17.6%) Disease stage 3-4: 244/298 (82.4%)	***Study cohort vs control*** ■ ≥ 3 prior therapies: 19/41 (46%) vs 21/41 (51%) ■ CR: 7/41 (8.5%) ■ PR: 30/41 (34.1%) ■ SD: 3/41 (7.3%) ■ PD: 20/41 (48.8%)	***CAR-T vs alternate*** ■ Prior therapies, median: 3 (range 2-7) vs 2 ■ Disease stage limited: 11/69 (16%) vs 24/146 (16%) ■ Disease stage advanced: 58/69 (84%) vs 122/146 (84%)
ECOG, IPI scores	ECOG ≥2: 5/75 (7%) IPI 0-2: 25/75 (33% IPI 3-5: 46/75 (62%)	ECOG at time of lymphodepletion ≥ 2: 29/300 (9.7%) IPI at time of approval 0-2: 149/300 (52.3%) IPI at time of approval 3-4: 136/300 (47.7%)	Age adjusted IPI ■ Low: 16/60 (27%) ■ Intermediate-1: 24/60 (40%) ■ Intermediate-2: 17/60 (28%) ■ High: 3/60 (5%)	ECOG ≥2: 58/298 (19.5%) IPI 0-2: 136/298 (45.6%) IPI 3-5: 162/298 (54.4%)	ECOG ≥ 2: 25/41 (61%) vs 25/41 (61%)	ECOG ≥ 2: 9/69 (13%) vs 12/146 (8.5%)
Follow-up, median (range) (months)	14.1 (95%CI 13.1-17.4)	13.9 (IQR 9.1-19.4)	6.9 (0.5-26.1)	13.8 (3.9-21.6)	7 (1.3-17.2) vs 7 (1.3-16.7)	14.6 (1.2-18.9) vs 30.6 (2.1-162)
Loss to follow-up, n (%)	NR	NR	NR	NR	NR	NR
Statistics used	Continuous variables: median and interquartile range Categorical variables: absolute values and percentages Kaplan-Meier for OS and PFS Log-rank for statistical comparison	Continuous variables: Wilcoxon Mann-Whitney/ Kruskal Wallis Discrete variables: χ^2 test/Fisher's exact test Kaplan-Meier and Cox regression for OS, PFS	Categorical variables: compared via χ^2 test/Fisher's exact test Quantitative variables: compared via Student's t-test or Wilcoxon Mann-Whitney test Response to treatment: logistic regression	Continuous variables: compared via Wilcoxon rank sum test or Kuskal-Wallis test Categorical variables: compared via χ^2 test/Fisher's exact test Kaplan-Meier for OS, PFS	Comparison between study cohort and control by Pearson χ^2 test or non-parametric Student t-test One-way ANOVA with F calculation for comparison of quality-of-life domains	Comparison via χ^2 test Categorical variables: Fisher's exact test Continuous variables: Wilcoxon rank-sum test Kaplan-Meier for OS and PFS Statistical analyses: R v3.6.1

Author, year	Iacoboni, 2021 [110]	Kuhnl, 2022 [146]	Lamure, 2021 [115]	Nastoupil, 2020 [147]	Ram, 2022 [148]	Sermer, 2020 [116]
Statistics used *(continuation)*	Cox proportional hazard model for hazard ratios with 95% CI Data analyses performed by R version 3.6.2		Time to death/progression: univarate Cox proportional hazard model Statistical analyses: enterprise Guide 8.2 and GraphPad software version 9	Statistical analyses: SAS 9.4 and Spotfire S+ 8.2		
Outcomes						
Effectiveness						
Definition OS	OS: time from apheresis (ITT) or CAR-T-cell infusion until death of any cause	NR	OS: time between CAR-T cell treatment and death, if any, during follow-up	NR	NR	OS: duration of time from start of treatment until time to death of any cause
Overall survival	***Infused pts:*** Median OS, mo: 10.7 (95%CI 7.4-NA) **ITT:** Median OS, mo: 11.1 (95% 7.9-NA)	Median OS, mo: 14.8 ■ Axi-cel: 15.6 (95% 11.1-NR*) ■ Tisa-cel: 10.2 (95%CI 7.7-NR*) 12 mo OS: 53.9% ■ Axi-cel: 57.1% (95% CI 49.8-63.8) ■ Tisa-cel: 43.8% (95%CI 31.1-55.9)	Median OS, mo: 12.3 (95%CI 32.9-63.1)	***Infused pts:*** Median OS, mo: NR* 12 mo OS estimate: 68% (95%CI 63%-74%)	***Study cohort vs control:*** Median OS: NR* vs NR*; p=0.792 3M projected OS: 84% vs 87% 6M projected OS: 74% vs 76% 12M projected OS: 69% vs 53%	***CAR-T vs alternate*** Median OS, mo: 19.3 vs 6.5; p=0.006 6mo OS: 71% (95%CI 61-82) vs 55% (95%CI 47-64) 12mo OS: 64% (95%CI 54-77) vs 39% (95%CI 31-48)
Disease-specific survival	NR	NR	NR	NR	NR	NR
Definition of PFS/EFS	PFS: time from apheresis (ITT population) or CAR-T cell infusion until relapse, progression, or death from any cause.	NR	PFS: the time between CAR-T cell infusion and progression, if any, during follow-up	NR	NR	PFS: time from start of treatment until time of aggressive lymphoma progression or relapse or death from any cause
Progression-free survival, event-free survival	***Infused:*** Median PFS, mo: 3 (95%CI 2.6-4.7) Overall 6mo PFS: 33.3% Overall 12mo PFS: 31.7% ***ITT:*** Median PFS, mo: 4.6 (95%CI 4.1-6.9)	Median PFS, mo: 3.5 ■ Axi-cel: 5.5 (95%CI 3.3-10.1) ■ Tisa-cel: 2.9 (95%CI 1.7-3.6) 12 mo PFS rate in responders: 52% (95%CI 44.7-58.8) ■ Axi-cel: 41.8% (95%CI 35-48.4) ■ Tisa-cel: 27.4% (95%CI 17.5-38.3)	Median PFS, mo: 3.1 12mo PFS (probability): 29.3% (95%CI 17-42.8)	***Infused pts:*** Median PFS, mo: 8.3 (95%CI 6-15.1) 12mo PFS estimate: 47% (95%CI 41%-53%)	***Study cohort vs control:*** Median PFS, mo: 3.6 (95%CI 1.6-5.6) vs NR*; p=0.209 3mo projected PFS: 51% vs 67% 6mo projected PFS: 39% vs 54% 12mo projected PFS: 32% vs 54%	***CAR-T vs alternate:*** Median PFS, mo: 5.2 vs 2.3; p=0.01 6mo PFS: 49% (95%CI 39-63) vs 29% (95%CI 23-38) 12mo PFS: 44% (95%CI 33-58) vs 25% (95%CI 19-33)
Definition of OR, CR, PR	ORR: percentage of pts who achieved a partial remission (PR) or complete remission (CR) after CAR-T cell infusion.	NR	BOR: defined as the best response (complete metabolic response: CMR) or partial metabolic response (PMR)) to CAR-T cell within the 6-mo following infusion and before any re-treatment for progression	NR	NR	ORR: the sum of CR and PR rates

Author, year	Iacoboni, 2021 [110]	Kuhnl, 2022 [146]	Lamure, 2021 [115]	Nastoupil, 2020 [147]	Ram, 2022 [148]	Sermer, 2020 [116]
Response Rates (OR, CR, PR)	***Infused pts:*** CR: 24/75 (32%) PR: 21/75 (28%) ORR: 60% Median DOR: 8.9 mo (95%CI 2.2-NA) ***ITT:*** CR: 24/92 (26%) ORR: 45/91 (49%)	***Response at 3 mo:*** CR: 120/300 (40%) PR: 24/300 (8%) PD: 143/300 (47.7%) 3 mo ORR (CR) rate: 48% (40%) ***Response at 6 mo:*** CR: 111/300 (37.8%) PR: 10/300 (3.4%) PD: 158/300 (53.7%) 6 mo ORR (CR) rate: 41% (38%) Best ORR (CR) rate: 72% (50%)	***1 mo:*** ORR: 35/60 (58%) CMR: 21/60 (35%) PMR: 14/60 (23%) SD: 8/60 (13%) PD: 15/60 (25%) ***3 mo:*** ORR: 24/60 (40%) CMR: 15/60 (25%) PMR: 9/60 (15%) BOR at any point: 38/60 (63%)	***Infused pts:*** Best ORR: 82% (95%CI 77%-86%) Best CR: 64% (95%CI 58%-69%) CR d30: 121/275 (44%) PR d30: 93/275 (34%)	***Study cohort vs control – 1 mo*** CR: 19/41 (46%) vs 24/41 (59%) PR: 7/41 (17%) vs 8/41 (19%) PD: 13/41 (32%) vs 9/41 (22%) ORR: 63% vs 78%; p=0.337	***CAR-T vs Alternate:*** ORR: 72% vs 32%; p<0.001 CR rate: 52% vs 22%; p<0.001
Definition Recurrence/Relapse	NR	NR	NR	NR	NR	NR
Recurrence	NR	NR	NR	NR	NR	NR
Definition NRM	Treatment-related mortality	NR	NR	NR	NR	NR
Mortality	NRM: 3/75 (4%) due to bacterial infection and macrophage activation syndrome by day90	Overall: NR 1y NRM: 21 (7.3%) ■ Axi-cel: 8.7% ■ Tisa-cel: 3.1% Death post-PD: 117 pt ■ Disease progression: 101/117 ■ Infection: 6/117 ■ Other: 4/117 ■ Unknown: 6/117	Overall 29/60 (48%) died ■ Disease progression 26/29 (89%) ■ Acute myeloid leukaemia 2/29 (7%) ■ Fungal infection 1/29 (3%)	Among pts who received axi-cel infusion 97/275 (35%) died ■ Disease progression 84/275 (30.5%) ■ Graft-vs-host disease: 1/275 (<1%) ■ NRM: 12/275 (4.4%)	NRM after 3 mo: 0 vs 0	NR
Quality of life	NR	NR	NR	NR	23/41 (56%) pts with EORTC QLQ-C30 questionnaire (version 3) in study cohort ***30 days:*** increased disability in 4/5 domains, increase in cancer/treatment related symptoms in 6/11 domains, worsening of emotional symptoms in 4/12 domains. No change in overall health perception or overall quality of life ***3 mo:*** improvement in disability 5/5 domains, improvement in cancer/treatment related symptoms, improvement of emotional symptoms in 10/12 domains.	NR

Author, year	Iacoboni, 2021 [110]	Kuhnl, 2022 [146]	Lamure, 2021 [115]	Nastoupil, 2020 [147]	Ram, 2022 [148]	Sermer, 2020 [116]
Quality of life *(continuation)*					Mean baseline vs mean 3 mo: ■ Overall health perception: 3.83 vs 5.6; p=0.005 ■ Overall quality of life: 3.87 vs 5.4; p=0.081	
Safety						
Overall complications, n (%)	NR	NR	NR	NR	NR	NR
Definition, Scoring system SAE	ASTCT score for CRS and ICANS, severe defined as grade ≥3 CTCAE version 5.0 for other AE	ASTCT score for CRS and ICANS	NR	Lee for CRS CTCAE version 4.03 for neurotoxicity CARTOX for CRS and neurotoxicity	ASTCT and EBMT score for CRS and ICANS CTCAE version 5.0 for adverse events	NR
(Serious) adverse events, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	Infused pts: CRS: 53/75 (71%) ■ Grade ≥2: 21/75 (28%) ■ Grade ≥3: 4/75 (5%) ICANS: 11/75 (15%) ■ Grade ≥ 2: 5/75 (7%) ■ Grade ≥ 3: 1/75 (1%)	CRS: 264/300 (88%) Grade ≥ 3: 23/300 (7.7%) ICANS: 110/300 (36.8%) Grade ≥ 3: 47/300 (15.7%) Cytopenia ■ Grade ≥ 3 neutropenia: 26/300 (19.8%) ■ Grade ≥ 3 thrombocytopenia: 19/300 (14.5%)	CRS: 55/60 (92%) ■ Grade 1-2: 52/60 (87%) ■ Grade 3-4: 3/60 (5%) ICANS: 23/60 (38%) ■ Grade 1-2: 16/60 (27%) ■ Grade 3-4: 7/60 (12%) Grade 3-4 cytopenia after lymphodepletion and CAR-T infusion: 59/60 (98%) Infections: 20/60 (33%)	CRS: 251/275 (91%) ■ Grade 1: 94/275 (34.2%) ■ Grade 2: 138/275 (50.2%) ■ Grade 3: 12/275 (4.4%) ■ Grade 4: 6/275 (2.2%) ■ Grade 5: 1/275 (0.4%) Neurotoxicity: 189/275 (68.7%) ■ Grade 1: 49/275 (17.8%) ■ Grade 2: 55/275 (20%) ■ Grade 3: 66/275 (24%) ■ Grade 4: 18/275 (6.6%) ■ Grade 5: 1/275 (0.4%)	Study cohort vs control Acute kidney injury: 3/41 (7.3%) vs 3/41 (7.3) Atrial fibrillation: 3/41 (7.3%) vs 3/41 (7.3) Late pancytopenia: 9/41 (22%) vs 11/41 (26.8%) Clinical or microbiology documented infections: 11/41 (26.8%) vs 8/41 (19.5%) CRS ■ Grade 1: 9/41 (22%) vs 7/41 (17.1%) ■ Grade 2: 15/41 (36.6%) vs 18/41 (43.9%) ■ Grade 3: 4/41 (9.8%) vs 3/41 (7.3%) ■ Grade 4: 0 vs 0 ICANS ■ Grade 1: 5/41 (12.5%) vs 3/41 (7.3%) ■ Grade 2: 5/41 (12.5%) vs 2/41 (4.9%) ■ Grade 3: 1/41 (2.5%) vs 2/41 (4.9%) ■ Grade 4: 0 vs 0	NR

Abbreviations: AE: adverse event, CAR-T associated toxicity 10-point (CARTOX-10), CR: complete remission, CRS: cytokine release syndrome, CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, EFS: event-free survival, GVHD: graft-versus-host disease, ICANS: Immune effector cell-associated neurotoxicity syndrome, mo: months, NA: not available, NE: not evaluable, NIH/NCI: National Institutes of Health/National Cancer Institute, NR: not reported, NR: not reached, ORR: overall response rate, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PR: partial remission, pts: patients, SD: stable disease, SD*: standard deviation, tFL: transformed follicular lymphoma*

Table A-4: CAR-T cell therapy for LBCL: results from observational studies (part 3/3)

Author, year	Sesques, 2020 [117]	Shadman, 2022 [118]	Steiner, 2021 [119]	Vercellino, 2020 [120]	Wudhikarn, 2020a+b [121, 149]
Country	France	USA	USA	France	USA
Sponsor	FEHH-Fundación CRIS grant	NIH/NCI grants Health Resources and Service Administration/Naval Research grants Be the Match Foundation, Medical College of Wisconsin, National Marrow Donor program, commercial entities	NIH/NCI, Cancer Center Support grants	NR	NIH/NCI grants
Intervention/ Product	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 28/61 (46%) ■ Tisagenlecleucel 33/61 (54%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 145/411 (35%) ■ autoHSCT: 266/411 (65%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 155/165 (94%) ■ Tisagenlecleucel 10/165 (6%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 49/116 (42%) ■ Tisagenlecleucel 67/116 (58%)	antiCD19 CAR-T ■ Axicabtagene ciloleucel: 43/60 (71.7%) ■ Tisagenlecleucel 17/60 (28.3%)
Indication	r/r aggressive BCL	DLBCL (including 15 PMBCL pt)	r/r LBCL	r/r DLBCL	r/r DLBCL
Comparator	-	CAR-T vs autoHSCT	-	-	-
Study design	Retrospective case series	nRCT registry analysis (CIBMTR registry)	Retrospective case series	Retrospective case series	Retrospective case series
Number of pts	70 undergoing leukapheresis, 61 infused with CAR-T ■ DLBCL: 38/61 (62%) ■ PMBCL: 4/61 (7%) ■ tFL: 18/61 (29%) ■ trMLZ: 1/61 (2%)	411 (145 vs 266)	165	116 ■ DLBCL: 93/116 (80.2%) ■ PMBL: 6/116 (5.2%) ■ tFL: 17/116 (14.7%)	60 ■ de novo DLBCL: 35/60 (58.3%) ■ transformed indolent lymphoma: 25/60 (41.7%)
Inclusion criteria	■ Adult (>18y) r/r DLBCL, PMBCL, tFL, trMZL pts approved for CAR-T by EMA regulations ■ Treatment outside of clinical trial setting ■ Between 01/2017-11/2019	■ Adult (≥ 18y) DLBCL, high-grade BCL with MYC and BCL2/BCL6 rearrangements or PMCBL pts ■ Achieved PR per international working group criteria ■ Undergoing autoHSCT between 2013-2019 or axi-cel CAR-T between 2018-2019	■ Adult (≥ 18y) r/r LBCL pts after ≥2 lines of systemic therapy treated with axi-cel or tisa-cel at University of Texas MD Anderson Cancer Center ■ Between 01/2018-04/2020	■ r/r DLBCL pts treated with tisa-cel or axi-cel in 5 French Lymphoma Study Association centers ■ Between 06/2018-01/2020	■ r/r DLBCL pts who received FDA-approved CAR-T cell therapy treated at Memorial Sloan Ketterin Cancer Center ■ Between 01/2018-06/2019
Exclusion Criteria	NR	■ Pts with available negative PET scan excluded as they did not meet 2014 Lugano definition ■ Pts in CAR-T cohort with prior autoHSCT	■ Pts with unapproved indications (e.g. Richter syndrome, post-transplant lymphoproliferative disorders)	NR	NR
Age of patients, median (range) (yrs)	59 (27-75)	60 (24-91) vs 58 (18-80)	60 (18-88)	60.7 (IQR 49.2-67.6)	63 (19.5-85.9)
Sex	F (34%)/M (66%)	F (39%)/M (61%) vs F (37%)/M (63%)	F (28%)/M (72%)	F (35%)/M (65%)	F (30%)/M (70%)
Pre-Treatment, n (%)	Prior autoHSCT: 17/61 (28%) Prior alloHSCT: 1/61 (2%) Bridging therapy: 59/61 (97%)	Bridging therapy 23/145 (16%)	Prior autoHSCT: 42/165 (26%) Bridging therapy: NR	Prior alloHSCT: 3/116 (2.6%) Prior high-dose therapy plus autoHSCT: 33/116 (29%) Bridging therapy: 101/116 (87.1%)	Prior autoHSCT: 5/60 (8.3%) Prior alloHSCT: 12/60 (20%) Bridging therapy: 38/60 (63.3%)

Author, year	Sesques, 2020 [117]	Shadman, 2022 [118]	Steiner, 2021 [119]	Vercellino, 2020 [120]	Wudhikarn, 2020a+b [121, 149]
Bridging therapy	Rituximab, radiotherapy, chemotherapy backbone	NR	NR	Immunochemotherapy, immuno-therapy, radiotherapy, corticosteroids	Radiation, immunochemotherapy, combined modality
Eligibility for ZUMA-1/JULIET	NR	NR	NR	NR	NR
Line of Treatment	≥4 prior therapies: 43/61 (70%) Disease stage 3-4: 46/61 (78%)	***CAR-T vs autoHSCT:*** ■ Prior therapies, median: 3 (2-11) vs 2 (1-6); p<0.001 ■ ≥4 prior therapies: 45/145 (31%) vs 34/266 (13%) ■ Disease stage 3-4: 80/145 (55%) vs 163/266 (61%)	Prior therapies, median: 3 (2-11)	Prior therapies, median: 3 (IQR 2-4) ≥4 prior therapies: 34 (29.3%) Disease stage 3-4: 89/116 (76.7%) Disease status at infusion: ■ PR: 22/116 (19%) ■ SD: 18/116 (16%) ■ PD: 76/116 (66%)	Prior therapies, median: 3 (2-9) Disease stage 1-2: 14/60 (23.3%) Disease stage 3-4: 38/60 (63.3%)
ECOG, IPI scores	ECOG ≥2: 18/61 (30%)	NR	ECOG ≥2: 129/165 (78%)	ECOG ≥2: 14/116 (12.1%) High-intermediate IPI: 28 (24.1%) High IPI: 17 (14.7%)	ECOG ≥2: 12/60 (20%)
Follow-up, median (range) (months)	5.7 (IQR: NR)	12 (3-26)	16.2 (14.3-19.1)	8.2 (IQR: NR)	9[54] (IQR: NR)
Loss to follow-up, n (%)	NR	NR[55]	NR	NR	NR
Statistics used	Kaplan-Meier for time-to-event curves Log-rank analysis for group comparisons Statistical analyses performed by SPSS version 21 and SAS version 9.3	Pearson χ^2 test for categorical variables Kruskal-Wallis test for continuous variables Kaplan-Meier and log-rank test for OS and PFS Cumulative incidence rates with Gray's test for comparison of haematopoietic recovery, NRM and relapse/ progression rates All statistical analyses performed by SAS version 9.4 and R version 4.0.4	Categorical variables: Fisher's exact test or χ^2 test Continuous variables: Wilcoxon rank sum test Kaplan-Meier for OS and PFS	Kaplan-Meier for OS and PFS Statistical analyses by R	Kaplan-Meier for EFS and OS with infections as as time-dependent covariates Statistical analyses performed by R version 3.6.0 and 3.6.1 Data from clinical databases and patients' electronic medical records
Outcomes					
Effectiveness					
Definition OS	OS: time from CAR-T cell therapy infusion (except for ITT survival analysis, where date of leukapheresis was used instead) until death of any cause	OS: time from treatment to death of any cause	OS: calculated from the start of CAR-T cell infusion to death or last follow-up	OS: calculated from the date of CAR-T cell infusion until the date of death from any cause or the date of last contact	OS: time from the CAR-T cell infusion date to death from any causes

[54] Wudhikarn, 2020a: 6 (0.8-12)

[55] No detailed reporting: 138/145pt evaluable for NRM, progression/relapse, PFS; 145/145 evaluable for OS

Author, year	Sesques, 2020 [117]	Shadman, 2022 [118]	Steiner, 2021 [119]	Vercellino, 2020 [120]	Wudhikarn, 2020a+b [121, 149]
Overall survival	Median OS, mo: 11.8 (95%CI 6-12.6) ■ Axi-cel: NR* (95%CI 4.6-NR*) ■ Tisa-cel: 7.4 (95%CI 4.8-12.6) 6 mo OS: 68% (95%CI 53-80)	***CAR-T vs autoHSCT*** 1y OS: 67% (95%CI 59-75) vs 76% (95%CI 70-81); p=0.1 2y OS: 47% (95%CI 33-60) vs 2y OS: 69% (95%CI 63-74); p=0.004	12mo OS ■ MACE: 58% ■ No-MACE: 62%	6mo OS: 78.5% (95%CI 71-87) 12mo OS: 67% (95%CI 57-79)	Estimated 1y OS: 69% (95%CI 57-82)
Disease-specific survival	NR	NR	NR	NR	NR
Definition of PFS/EFS	PFS: time from CAR-T cell infusion until relapse, progression or death from any cause	PFS: time from either autoHSCT or CAR-T to relapse or death from any cause	PFS: calculated from the start of CAR-T cell infusion to the progression of disease or death, whichever occurred first	PFS: measured from the date of CAR-T cell infusion to the date of death from any cause, disease relapse, or progression or the date of last contact	EFS: time from the day of CAR-T cell infusion to progression, relapse, or death from any causes
Progression-free survival, event-free survival	Median PFS, mo: 3 (95%CI 2.8-8.8) Axi-cel: 3.1 (95%CI 2.9-NR*) Tisa-cel: 3 (95%CI 2.1-8.8) 6 mo PFS: 44% (95%CI 30-57)	***CAR-T vs autoHSCT*** 1y PFS: 52% (95%CI 43-61) vs 59% (95%CI 53-65); p=0.2 2y PFS: 42% (95%CI 30-53) vs 52% (95%CI 46-58); p=0.1	12mo PFS ■ MACE: 38% ■ No-MACE: 42%	Estimated PFS, median: 7.4 (95%CI 3- NA)	Estimated 1y EFS: 40% (95%CI 28-56)
Definition of OR, CR, PR	NR	NR	NR	NR	NR
Response Rates (OR, CR, PR)	***1 mo:*** Axi-cel: ORR: 18/28 (64%) CR: 13/31 (46%) PR: 5/31 (18%) SD/PD: 10/28 (36%) Tisa-cel: ORR: 19/31 (61%) CR: 15/31 (48%) PR: 4/31 (13%) SD/PD: 12/31 (39%) ***3 mo:*** Axi-cel ORR: 12/25 (48%) CR: 10/25 (40%) PR: 2/25 (8%) SD/PD: 13/25 (52%) Tisa-cel: ORR: 13/31 (42%) CR: 12/31 (39%) PR: 1/31 (3%) SD/PD: 18/31 (39%)	NR	NR	NR	NR
Definition Recurrence/ Relapse	NR	Cumulative incidence of relapse/ progression: defined as the time from treatment to relapse or disease progression and haematopoietic recovery	NR	Relapse or progression: defined using Cheson criteria published in 2014 based on CT scan and 18 FDG-PET/CT	NR

Author, year	Sesques, 2020 [117]	Shadman, 2022 [118]	Steiner, 2021 [119]	Vercellino, 2020 [120]	Wudhikarn, 2020a+b [121, 149]
Recurrence	NR	***CAR-T vs autoHSCT (cumulative incidence):*** 1y progression/relapse: 45% (95%CI 37-54) vs 34% (95%CI 28-40); p=0.03 2y progression/relapse: 52% (41-63) vs 40% (95%CI 33-46); p=0.05	NR	Relapse: 55/116 (47.4%)	Relapse: 33/60 (55%)
Definition NRM	NR	Death without preceding disease progression	NR	NR	The proportion of pts who died of other causes unrelated to disease relapse/recurrence
Mortality	ICU pts: ■ 2pt died due disease progression ■ 1pt died due to toxicity	***CAR-T vs autoHSCT:*** Overall 52/145 pt (36%) vs 91/266 (34%) died Cumulative incidence: ■ Primary disease: 75% vs 74% ■ Infections: 4% vs 6% ■ CRS: 4% vs NR ■ Organ failure: 4% vs 4% ■ Malignancies: 4% vs NR 100d NRM: 2% (95%CI 0-5) vs 4% (95%CI 2-7); p=0.3 1y NRM: 3% (95%CI 1-6) vs 7% (95%CI 4-11); p=0.05 2y NRM: 6% (95%CI 1-16) vs 9% (95%CI 5-13); p=0.6	15/27 pts with MACE died ■ Disease progression: 8/15 (53%) ■ Sepsis: 2/15 (13%) ■ Multifactorial etiologies: 2/15 (13%) ■ Cardiovascular cause: 1/15 (7%) ■ Unknown: 2/15 (13%)	Overall 29/116 pt (25%) died ■ Disease progression: 27/116 (23.3%) ■ NRM: 2/116 (1.7%)	Overall 21/60 (35%) died ■ Disease progression: 19/60 (32%) ■ Infection: 1/60 (2%) ■ Thrombosis: 1/60 (2%) 1y NRM: 1.7% (95%CI 0.1-8)
Quality of life	NR	NR	NR	NR	NR
Safety					
Overall complications, n (%)	NR	NR	NR	NR	NR
Definition, Scoring system SAE	ASTCT score for CRS and ICANS CTCAE version 5.0 for adverse events	ASTCT score for CRS and ICANS	CARTOX grading for CRS and ICANS from 01/2018-04/2019 ASTCT score for CRS and ICANS from 05/2019-	NR	ASTCT score for CRS and ICANS Toxicities sorted according to CTCAE version 5.0
(Serious) adverse events, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome)	***Axi-cel:*** CRS: 26/28 (93%) Grade ≥ 3: 2/28 (7%) ICANS: 9/28 (32%) Grade ≥ 3: 3/28 (11%) Anemia: 26/28 (93%) Grade ≥ 3: 6/28 (21%)	Probabilities: CRS grade 1-4: 74% (95%CI 67-81) CRS grade 3-4: 7% (95%CI 4-12) ICANS grade 1-4: 24% (95%CI 17-33) ICANS grade 3-4: 15% (95%CI 9-22)	CRS: 151/165 (92%) Grade ≥ 3: 23/165 (14%) ICANS: 100/165 (61%) Grade ≥ 3: 51/165 (31%) MACE until d30: 27/165 (16%)	NR	CRS: 48/60 (80%) Grade ≥ 3: 7/60 (11.7%) ICANS: 24/60 (24%) Grade ≥ 3: 13/60 (21.7%)[56] Neutropenic fever within 30d: 52/60 (86.7%)[56]

[56] Data from Wudhikarn 2020a

Author, year	Sesques, 2020 [117]	Shadman, 2022 [118]	Steiner, 2021 [119]	Vercellino, 2020 [120]	Wudhikarn, 2020a+b [121, 149]
(Serious) adverse events, n (%) (CRS, severe toxicities, cytopenia, Infection, febrile neutropenia, tumour lysis syndrome) *(continuation)*	Thrombocytopenia: 27/28 (96%) Grade ≥ 3: 19/28 (68%) Neutropenia: 22/28 (78%) Grade ≥ 3: 10/28 (36%) ***Tisa-cel:*** CRS: 26/33 (79%) Grade ≥ 3: 3/33 (9%) ICANS: 8/33 (24%) Grade ≥ 3: 3/33 (9%) Anemia: 25/33 (80%) Grade ≥ 3: 2/33 (6%) Thrombocytopenia:25/33 (80%) Grade ≥ 3: 9/33 (29%) Neutropenia: 16/33 (53%) Grade ≥ 3: 11/33 (35%) Infection within 28d: ■ Grade 3: 21/61 (34%) ■ Grade 4: 2/61 (3%)				Overall 539 grade ≥ 2 events in 59 pt: ■ Grade 2: 250 ■ Grade 3: 254 ■ Grade 4: 33 ■ Grade 5: 2 ■ Metabolic complications: 141 ■ Infections: 125 ■ Haematologic complications: 101 Cumulative incidence of grade ≥ 3 toxicities 1y after infusion ■ Cardiovascular: 16.7 (95%CI 8.5-27.2) ■ Metabolic: 54.8 (95%CI 40.5-67.1) ■ Haematologic: 57.5 (95%CI43.4-69.9) ■ Pulmonary: 13.3 (95%CI6.2-23.3) ■ Neurologic: 18.3 (95%CI 9.7-29.1) ■ Infections: 35.4 (95%CI22.6-48.4)

Abbreviations: AE: adverse event, CAR-T associated toxicity 10-point (CARTOX-10), CR: complete remission, CRS: cytokine release syndrome, CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, EFS: event-free survival, GVHD: graft-versus-host disease, ICANS: Immune effector cell-associated neurotoxicity syndrome, mo: months, NA: not available, NE: not evaluable, NIH/NCI: National Institutes of Health/National Cancer Institute, NR: not reported, NR: not reached, ORR: overall response rate, OS: overall survival, PD: progressive disease, PFS: progression-free survival, PR: partial remission, pts: patients, SD: stable disease, SD*: standard deviation, tFL: transformed follicular lymphoma*

Risk of bias tables

Table A-5: Risk of bias – ZUMA-1 (pivotal trial) – Axicabtagene ciloleucel, from Cochrane 2021 (see [61])

Trial	Endpoints	Selection bias	Attrition bias	Detection bias	Reporting bias	Overall risk of bias
ZUMA-1, [62, 63]	OS	Low	High[57]	Low	Low	High
	Response (PFS, ORR, CR, PR)	Low	High[57]	High[58]	Low	
	AE	Low	Low	NR	Low	

Abbreviations: AE: adverse events, CR: complete response, NR: not reported, ORR: overall response rate, PFS: progression-free survival, PR: partial response

Table A-6: Risk of bias – JULIET (pivotal trial) – Tisagenlecleucel, from Cochrane 2021 (see [61])

Trial	Endpoints	Selection bias	Attrition bias	Detection bias	Reporting bias	Overall risk of bias
JULIET, [64, 65]	OS	Low	High[59]	Low	Low	High
	Response (PFS, ORR, CR, PR)	Low	High[59]	High[58]	Low	
	HRQoL	Low	High[60]	High[58]	Low	
	AE	Low	Low	Low	Low	

Abbreviations: AE: adverse events, CR: complete response, NR: not reported, ORR: overall response rate, PFS: progression-free survival, PR: partial response, HRQoL: Quality of life

RoB judgements are retrieved (and shortened) from Cochrane 2021 [61]

[57] OS and response rates included infused patients only

[58] No blinding

[59] OS and PFS data from abstract reporting on long-term follow-up until May 2018 included infused patients only

[60] Outcomes available only for subset of participants in CR/PR (e.g. n=39 at month 3 and n=21 at month 12 compared to n=108 participants with HRQoL assessments at baseline)

Acute lymphoblastic leukaemia

Table A-7: Risk of bias – RWE study level (observational studies), B-ALL (part 1/2), see [4]

Study reference/ID	Brown, 2021	Dekker, 2022	Dourthe, 2021	Fabrizio, 01/2022	Fabrizio, 03/2022	Kadauke, 2021	Pasquini, 2020	Ravich, 2021	Rossoff, 2021
Study objective									
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design									
2. Was the study conducted prospectively?	No	No	Yes	No	No	Yes	Yes	No	No
3. Were the cases collected in more than one centre?	No	No	No	Yes	Yes	Unclear	Yes	Yes	Yes
4. Were patients recruited consecutively?	Yes	Yes	Yes	Unclear	Unclear	Unclear	Unclear	No	Unclear
Study population									
5. Were the characteristics of the patients included in the study described?	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Partial	Partial	Partial	Yes	Yes	Yes	Partial	Partial
7. Did patients enter the study at a similar point in the disease? *Yes: all patients had a similar line of therapies before CAR T infusion* *No: patients had different lines of treatment before CAR T infusion*	No	No	No	No	No	No	No	No	No
Intervention and co-intervention									
8. Was the intervention of interest clearly described?	Yes	Partial	Yes	Partial	Partial	Yes	Yes	Yes	Partial
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Outcome measures									
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Statistical Analysis									
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions									
15. Was follow-up long enough for important events and outcomes to occur? *Note: "long enough" defined as a minimum of a median follow-up of 12 months*	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear
16. Were losses to follow-up reported?	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study reference/ID	Brown, 2021	Dekker, 2022	Dourthe, 2021	Fabrizio, 01/2022	Fabrizio, 03/2022	Kadauke, 2021	Pasquini, 2020	Ravich, 2021	Rossoff, 2021
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	No
18. Were the adverse events reported?	Partial	Partial	Partial	Partial	Partial	Yes	Yes	Partial	Partial
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
Competing interests and sources of support									
20. Were both competing interests and sources of support for the study reported?	Partial	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Partial
Overall Risk of bias	**12.5**	**14.5**	**15.5**	**14**	**14**	**16.5**	**17.5**	**15**	**12.5**
	High risk	**Moderate risk**	**Moderate risk**	**High risk**	**High risk**	**Moderate risk**	**Moderate risk**	**Moderate risk**	**High risk**

Abbreviations: AUC: area under the curve; CAPD: Cornell Assessment of Pediatric Delirium; CNS: central nervous system; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; mo: months; PRWCC: Pediatric Real World CAR Consortium; SAE: (severe) adverse events; vs: versus

Table A-8: Risk of bias – RWE study level (observational studies), B-ALL (part 2/2), see [4]

Study reference/ID	Rubinstein, 2020	Schultz, 2021	Moskop, 2022
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study objective			
2. Was the study conducted prospectively?	No	No	No
3. Were the cases collected in more than one centre?	No	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear
Study population			
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Partial	Partial
7. Did patients enter the study at a similar point in the disease?	No	No	No
Intervention and co-interventions			
8. Was the intervention of interest clearly described?	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes

Study reference/ID	Rubinstein, 2020	Schultz, 2021	Moskop, 2022
Outcome measures			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes
Statistical Analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Yes	No
Results and Conclusion			
15. Was follow-up long enough for important events and outcomes to occur? *Note: "long enough" defined as a minimum of a median follow-up of 12 months*	Yes	Yes	No
16. Were losses to follow-up reported?	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	No
18. Were the adverse events reported?	Partial	Partial	Partial
19. Were the conclusions of the study supported by results?	Yes	Yes	Partial
Competing interests and sources of support			
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes
Overall Risk of bias	**14**	**15.5**	**12**
	High risk	**Moderate risk**	**High risk**

Abbreviations: AUC: area under the curve; CAPD: Cornell Assessment of Pediatric Delirium; CNS: central nervous system; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; mo: months; PRWCC: Pediatric Real World CAR Consortium; SAE: (severe) adverse events; vs: versus

Large B-cell lymphoma

Table A-9: Risk of bias – RWE study level (observational studies), LBCL (part 1/2), see [4]

Study reference/ID	Ayuk, 2021	Baird, 2021	Bethge, 2022	Ghafouri, 2021	Hamadani, 2022	Holtzman, 2021	Iacoboni, 2021	Kuhnl, 2022	Lamure, 2021
Study objective									
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study design									
2. Was the study conducted prospectively?	Yes	No	No	No	No	No	No	No	Yes
3. Were the cases collected in more than one centre?	No	No	Yes	No	Yes	No	Yes	Yes	No
4. Were patients recruited consecutively?	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Study population									
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Partial	Yes	Yes	Yes	Partial	Partial	Yes	Yes
7. Did patients enter the study at a similar point in the disease? *Yes: all patients had a similar line of therapies before CAR-T infusion* *No: patients had different lines of treatment before CAR-T infusion*	No	No	No	No	No	No	No	No	No
Intervention and co-intervention									
8. Was the intervention of interest clearly described?	Yes	Yes	Partial	Yes	Partial	Partial	Yes	Partial	Partial
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Partially	Yes	Yes	Yes	Yes
Outcome measures									
10. Were relevant outcome measures established a priori?	Unclear	No	No	No	No	No	No	No	Unclear
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial	Partial	Yes	Yes	Yes	Yes	Yes	Partial	Partial
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis									
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions									
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	No	No	No	No	No	No	No	No

Study reference/ID	Ayuk, 2021	Baird, 2021	Bethge, 2022	Ghafouri, 2021	Hamadani, 2022	Holtzman, 2021	Iacoboni, 2021	Kuhnl, 2022	Lamure, 2021
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
18. Were the adverse events reported?	Partial	Yes	Yes	Yes	Partial	Partial	Partial	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes	Partial[61]	Yes	Yes
Competing interests and sources of support									
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Partial	Partial	Yes	Yes	Partial	Partial	Yes
Overall Risk of bias	**15**	**13**	**14**	**13.5**	**12.5**	**11**	**13**	**13.5**	**14.5**
	Moderate risk	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**High risk**	**Moderate risk**

Abbreviations: CRS: cytokine release syndrome, ICANS: immune effector-cell associated neurotoxicity syndrome, OS: overall survival, PFS: progression-free survival

Table A-10: Risk of bias – RWE study level (observational studies), LBCL (part 2/2), see [4]

Study reference/ID	Nastoupil, 2020	Ram, 2022	Sesques, 2020	Steiner, 2021	Vercellino, 2020	Wudhikarn, 2020a+b
Study objective						
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	No	No	No	No	No	No
3. Were the cases collected in more than one centre?	Yes	Yes	No	No	Yes	No
4. Were patients recruited consecutively?	No	Yes	No	Yes	Yes	Yes
Study population						
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Yes	Partial	Yes	Partial	Partial
7. Did patients enter the study at a similar point in the disease?	No	No	No	No	No	No
Intervention and co-intervention						
8. Was the intervention of interest clearly described?	Partial	Yes	Partial	Partial	Partial	Partial
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	Yes

[61] Conclusion was not adequately defined

Study reference/ID	Nastoupil, 2020	Ram, 2022	Sesques, 2020	Steiner, 2021	Vercellino, 2020	Wudhikarn, 2020a+b
Outcome measures						
10. Were relevant outcome measures established a priori?	No	No	No	No	No	No
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial	Partial	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Results and Conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	No	No	No	No	No	No
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	No	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support						
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	Yes	Partial	Yes
Overall Risk of bias	**12.5**	**14.5**	**12**	**13.5**	**12.5**	**13**
	High risk	**Moderate risk**	**High risk**	**High risk**	**High risk**	**High risk**

Abbreviations: CRS: cytokine release syndrome, ICANS: immune effector-cell associated neurotoxicity syndrome, OS: overall survival, PFS: progression-free survival

Table A-11: Risk of bias – RWE study level (non-randomized controlled studies), see [70]

Study reference/ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of intervention	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall Bias	Comments
Sermer, 2020 [116]	Critical	Critical	Critical	Critical	Critical	Critical	Moderate	Critical	Retrospective study design, missing information about possible confounders
Shadman, 2022 [118]	Critical	Critical	Critical	Critical	Critical	Critical	Moderate	Critical	Retrospective study design

Grading systems

Table A-12: CRS Grading Systems, from Lee et al., 2019 (expanded) [141]

Grading System	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE version 5.0 [140]	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Death
CTCAE version 4.03	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate	Life-threatening consequences; pressor or ventilatory support indicated	Death
Lee criteria	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: ■ Oxygen requirement <40% FiO_2 OR ■ Hypotension responsive to i.v. fluids or low dose of one vasopressor OR ■ Grade 2 organ toxicity[62]	Symptoms require and respond to aggressive intervention: ■ Oxygen requirement ≥40% FiO_2 OR ■ Hypotension requiring high-dose or multiple vasopressors OR ■ Grade 3 organ toxicity[62] or grade 4 transaminitis	Life-threatening symptoms: ■ Requirement for ventilator support OR ■ Grade 4 organ toxicity[62] (excluding transaminitis)	Death
CARTOX	Temperature ≥38°C Grade 1 organ toxicity[63]	Hypotension responds to i.v. fluids or low-dose vasopressor Hypoxia requiring FiO_2 <40% Grade 2 organ toxicity[63]	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO_2 ≥40% Grade 3 organ toxicity[63] or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity[63] except grade 4 transaminitis	Death
ASCTC	Temperature ≥38°C	Temperature ≥38°C Hypotension without vasopressor requirement And/or hypoxia requiring low-flow nasal cannula[64] or blow-by	Temperature ≥38°C Hypotension requiring a vasopressor with or without vasopressin And/or hypoxia requiring high-flow nasal cannula[64], facemask, nonrebreather mask or Venturi mask	Temperature ≥38°C Hypotension requiring multiple vasopressors (excluding vasopressin) And/or requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	Death

[62] as per CTCAE v4.03

[63] Cardiac (tachycardia, arrhythmias, heart block, low ejection fraction), respiratory (tachypnea, pleural effusion, pulmonary edema), gastrointestinal (nausea, vomiting, diarrhea), hepatic (increased serum alanine aminotransferase, aspartate aminotransferase, bilirubin level), renal (acute kidney injury, increased serum creatinine, decreased urine output), dermatologic (rash), or coagulopathy (disseminated intravascular coagulation).

[64] Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in paediatrics.
High-flow nasal cannula is defined as oxygen delivered at >6L/minute.

Grading System	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
University of Pennsylvania [64]	Mild reaction: ■ Treated with supportive care such as antipyretics and antiemetics	Moderate reaction: ■ Requiring intravenous therapies or parenteral nutrition ■ Some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs]) related to CRS and not attributable to any other condition ■ Hospitalization for management of CRS related symptoms including fevers with associated neutropenia	More severe reaction: ■ Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions[65] ■ Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS	Life-threatening ■ Complications such as hypotension requiring high dose vasopressors[66] or hypoxia requiring mechanical ventilation	Death

Abbreviations: CRS: cytokine release syndrome, CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events, LFT: liver function test, NSAIDs: non-steroidal anti-inflammatory drug, O_2: oxygen

Table A-13: ICANS Grading Systems, from Lee et al., 2019 (expanded) [141]

Grading System	Adverse Event Term/ Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE version 5[67]	Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
	Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New-onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences	
	Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly		
	Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL		
	Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL		

65 Excludes management of fever or myalgias. Includes hypotension treated with intravenous fluids or low dose vasopressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]).

66 Vasopressors dose for ≥3 hours: norepinephrine monotherapy, ≥0.2 µg/kg/min; dopamine monotherapy, ≥10 µg/kg/min; phenylephrine monotherapy, ≥200 µg/min; epinephrine monotherapy, ≥0.1 µg/kg/min. If on vasopressin: high dose if vasopressin + norepinephrine equivalent of ≥0.1 µg/kg/min (using Vasopressin and Septic Shock Trial [VASST] formula‡) for ≥3 hours. If on combination vasopressors (not vasopressin): norepinephrine equivalent of ≥20 µg/min (using VASST formula‡) for ≥3 hours.

67 CTCAE: under CRS listing: "Also consider neurologic toxicities such as psychiatric disorders; hallucinations or confusion; nervous system disorders; seizure, dysphasia, tremor, headache"

Grading System	Adverse Event Term/ Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
	Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	
	Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	
	Cerebral edema			New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated	
CARTOX criteria	Neurologic Assessment Score (CARTOX-10)	7-9 (mild impairment)	3-6 (moderate impairment)	0-2 (severe impairment)	Patient in critical condition, and/or obtunded and cannot perform assessment of tasks	Death
	Elevated ICP[68]	N/A	N/A	Stage 1-2 papilledema[69] or CSF opening pressure <20 mmHg	Stage 3-5 papilledema[69], or CSF opening pressure ≥20 mmHg, or cerebral edema	
	Seizures or motor weakness	N/A	N/A	Partial seizure or nonconvulsive seizures on EEG with response to benzodiazepine	Generalized seizures or convulsive or nonconvulsive status epilepticus, or new motor weakness	
ASTCT	ICE score[70]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)	Death
	Depressed level of consciousness (excluding sedating medication)	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma	
	Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between	
	Motor findings[71]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis	
	Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[72]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad	

Abbreviations: ADL: activities of daily living, CSF: cerebrospinal fluid, EEG: electroencephalography, ICE: immune effector cell-associated encephalopathy score, N/A: not applicable

[68] ICP: intracranial pressure

[69] Papilledema grading is performed according to the Modified Frisén scale

[70] ICE score: Immune Effector Cell-Associated Encephalopathy score

[71] Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading

[72] Intracranial haemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Literature search strategies

ALL: Tisagenlecleucel/Kymriah®

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to March 29, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to March 29, 2022>	
Search date: 30.03.2022	
ID	Search
1	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/(37313)
2	(acute adj3 (lymphoblastic or lymphocytic or lymphoid) adj leuk?emia*).mp. (50798)
3	ALL.ti,ab. (6062787)
4	1 or 2 or 3 (6088765)
5	(chimeric antigen* adj2 T cell*).mp. (4835)
6	CAR-T cell*.mp. (10034)
7	exp Receptors, Antigen, T-Cell/tu [Therapeutic Use] (1063)
8	(CAR-T adj3 (therap* or treat* or program* or regimen* or interven*)).mp. (6622)
9	5 or 6 or 7 or 8 (12888)
10	4 and 9 (3246)
11	limit 10 to clinical trial, all (250)
12	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ab.) not (exp animals/not humans.sh.) (1880344)
13	10 and 12 (566)
14	limit 10 to observational study (16)
15	exp epidemiologic studies/or exp clinical trial/or comparative study/(5840477)
16	((control and study) or program).mp. (3112976)
17	15 or 16 (7759960)
18	(animals/not humans/) or comment/or editorial/or exp review/or meta analysis/or consensus/or exp guideline/(10724569)
19	hi.fs. or case report.mp. (819281)
20	18 or 19 (11439129)
21	17 not 20 (6489352)
22	10 and 21 (497)
23	Epidemiologic studies/or exp case control studies/or exp cohort studies/or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/(4492469)
24	10 and 23 (337)
25	(real-world adj3 (data or evidence or research)).mp. (21611)
26	RWE.ti,ab. (746)
27	25 or 26 (21774)
28	10 and 27 (18)
29	exp Registries/(142102)
30	(regist$4 adj3 (data or evidence)).mp. (32245)
31	29 or 30 (161377)
32	10 and 31 (12)
33	11 or 13 or 14 or 22 or 24 or 28 or 32 (979)
34	limit 33 to yr="2017 - 2022" (922)
35	limit 34 to (english or german) (888)
36	remove duplicates from 35 (471)

Search strategy for Embase.com

Search date: 30.03.2022		
No.	Query Results	Results
#69.	#67 NOT #68	342
#68.	#67 AND 'Conference Abstract'/it	1,586
#67.	#66 AND ([english]/lim OR [german]/lim)	1,928
#66.	#65 AND [2017-2022]/py	1,943
#65.	#18 OR #54 OR #55 OR #60 OR #64	2,146
#64.	#17 AND #63	22
#63.	#61 OR #62	194,321
#62.	(registry OR registries OR register*) NEAR/2 (data OR evidence)	30,463
#61.	'register'/exp	178,449
#60.	#17 AND #59	73
#59.	#56 OR #57 OR #58	24,005
#58.	'real-world' NEAR/2 (data OR evidence OR research)	24,005
#57.	'real world data'/exp	40
#56.	'real world evidence'/exp	48
#55.	#17 AND ('observational study'/de OR 'prospective study'/de OR 'retrospective study'/de)	683
#54.	#17 AND #53	1,249
#53.	#38 NOT #52	5,106,461
#52.	#39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51	3,942,435
#51.	'animal experiment'/de NOT ('human experiment'/de OR 'human'/de)	2,411,014
#50.	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR trout:ti,tt OR marmoset*:ti,tt) AND 'animal experiment'/de	1,148,978
#49.	(databases NEAR/5 searched):ab	53,177
#48.	'update review':ab	122
#47.	'we searched':ab AND (review:ti,tt OR review:it)	40,953
#46.	review:ab AND review:it NOT trial:ti,tt	965,567
#45.	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,537
#44.	'random field*':ti,ab,tt	2,631
#43.	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt	17,680
#42.	'systematic review':ti,tt NOT (trial:ti,tt OR study:ti,tt)	204,393
#41.	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT ('randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt)	19,540
#40.	'cross-sectional study' NOT ('randomized controlled trial'/de OR 'controlled clinical study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'control group':ti,ab,tt OR 'control groups':ti,ab,tt)	324,932
#39.	((random* NEXT/1 sampl* NEAR/8 ('cross section*' OR questionnaire* OR survey OR surveys OR database OR databases)):ti,ab,tt) NOT ('comparative study'/de OR 'controlled study'/de OR 'randomised controlled':ti,ab,tt OR 'randomized controlled':ti,ab,tt OR 'randomly assigned':ti,ab,tt)	2,821
#38.	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	5,759,798
#37.	trial:ti,tt	360,921
#36.	'human experiment'/de	572,505
#35.	volunteer:ti,ab,tt OR volunteers:ti,ab,tt	267,920
#34.	(controlled NEAR/8 (study OR design OR trial)):ti,ab,tt	411,848
#33.	assigned:ti,ab,tt OR allocated:ti,ab,tt	442,709
#32.	((assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants)):ti,ab,tt	414,848
#31.	crossover:ti,ab,tt OR 'cross over':ti,ab,tt	115,797

#30.	(parallel NEXT/1 group*):ti,ab,tt	29,133
#29.	'double blind procedure'/de	194,168
#28.	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab,tt	256,833
#27.	(open NEXT/1 label):ti,ab,tt	95,431
#26.	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,469,249
#25.	compare:ti,tt OR compared:ti,tt OR comparison:ti,tt	584,038
#24.	placebo:ti,ab,tt	339,603
#23.	'intermethod comparison'/de	283,409
#22.	'randomization'/de	93,475
#21.	random*:ti,ab,tt	1,770,924
#20.	'controlled clinical trial'/de	436,558
#19.	'randomized controlled trial'/de	704,298
#18.	#17 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)	919
#17.	#4 AND #16	5,762
#16.	#14 OR #15	14,163
#15.	('car t*' OR 'chimeric antigen*') NEAR/2 (cell* OR therap* OR treat* OR program* OR regimen* OR interven*)	13,227
#14.	#13 AND 'therapy'/lnk	3,209
#13.	#10 OR #11 OR #12	15,180
#12.	'chimeric antigen*' NEAR/2 't-cell*'	11,759
#11.	'chimeric antigen receptor t-cell'/exp	5,903
#10.	'car-t cell*'	11,272
#9.	('car t*' OR 'chimeric antigen*') NEAR/2 (cell* OR therap* OR treat* OR program* OR regimen* OR interven*)	13,227
#8.	#7 AND 'therapy'/lnk	2,631
#7.	#5 OR #6	11,759
#6.	'chimeric antigen*' NEAR/2 't-cell*'	11,759
#5.	'chimeric antigen receptor t-cell'/exp	5,903
#4.	#1 OR #2 OR #3	7,708,962
#3.	all:ti,ab	7,665,892
#2.	acute NEAR/2 (lymphoblastic OR lymphocytic OR lymphoid) NEAR/1 leuk*mia*	95,075
#1.	'acute lymphoblastic leukemia'/exp	73,367

Search strategy for Cochrane

Search Name: CAR-T Cell Therapy in ALL	
Last saved: 30/03/2022 18:22:16	
Comment: CW/Extern 300322	
ID	Search
#1	MeSH descriptor: [Precursor Cell Lymphoblastic Leukemia-Lymphoma] explode all trees
#2	(acute NEAR ((lymphoblastic OR lymphocytic OR lymphoid) NEXT (leukemia* OR leukaemia*))) (Word variations have been searched)
#3	(ALL):ti,ab,kw
#4	#1 OR #2 OR #3
#5	(chimeric antigen* NEAR T-Cell*) (Word variations have been searched)
#6	(CAR-T Cell*) (Word variations have been searched)
#7	MeSH descriptor: [Receptors, Antigen, T-Cell] explode all trees
#8	("CAR-T*" NEAR (therap* OR treat* OR program* OR regimen* OR interven* OR procedur*)) (Word variations have been searched)
#9	#5 OR #6 OR #7 OR #8
#10	#4 AND #9
#11	#4 AND #9 with Publication Year from 2017 to 2022, in Trials

#12	#4 AND #9 with Cochrane Library publication date Between Jan 2017 and Mar 2022, in Trials
#13	#11 OR #12
#14	(conference abstract):pt
#15	(abstract):so
#16	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#17	#14 OR #15 OR #16
#18	#13 NOT #17
Total hits: 24	

LBCL: DLBCL + PMBCL: Tisagenlecleucel/Kymriah® and Axicabtagen Ciloleucel/Yescarta®

Search strategy for Medline via Ovid

Database: Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to May 03, 2022>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to May 03, 2022>	
Search date: 04.05.2022	
ID	Search
1	exp Lymphoma, Large B-Cell, Diffuse/(26440)
2	(diffuse adj4 lymphoma*).mp. (38990)
3	histiocytic lymphoma*.mp. (1229)
4	DLBCL.ti,ab. (12730)
5	exp Mediastinal Neoplasms/(14980)
6	exp Lymphoma, B-Cell/(60171)
7	5 and 6 (845)
8	(mediastinal adj3 lymphoma*).mp. (1432)
9	PMBCL.ti,ab. (234)
10	1 or 2 or 3 or 4 or 7 or 8 or 9 (41264)
11	axicabtagene*.mp. (598)
12	ciloleucel*.mp. (598)
13	yescarta*.mp. (170)
14	axi-cel.mp. (153)
15	fkc 876.mp. (0)
16	fkc876.mp. (0)
17	kte c19.mp. (16)
18	ktec19.mp. (0)
19	tisagenlecleucel*.mp. (746)
20	kymriah*.mp. (198)
21	cart 19.mp. (28)
22	cart19.mp. (90)
23	ctl 019.mp. (3)
24	ctl019.mp. (115)
25	lg 740.mp. (0)
26	lg740.mp. (0)
27	11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (1251)
28	10 and 27 (418)
29	limit 28 to (english or german) (406)
30	remove duplicates from 29 (208)

Search strategy for Embase.com

Search date: 04.05.2022		
No.	Query Results	Results
#31.	#29 NOT #30	451
#30.	#29 AND 'Conference Abstract'/it	713
#29.	#28 AND ([english]/lim OR [german]/lim)	1,164
#28.	#8 AND #27	1,165
#27.	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	2,721
#26.	lg740	
#25.	'lg 740'	1
#24.	ctl019	218
#23.	'ctl 019'	82
#22.	cart19	265
#21.	'cart 19'	84
#20.	kymriah*	454
#19.	tisagenlecleucel*	1,913
#18.	'tisagenlecleucel t'/exp	1,754
#17.	ktec19	64
#16.	'kte c19'	69
#15.	fkc876	
#14.	'fkc 876'	
#13.	'axi-cel'	518
#12.	yescarta*	370
#11.	ciloleucel*	1,511
#10.	axicabtagene*	1,520
#9.	'axicabtagene ciloleucel'/exp	1,394
#8.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	53,309
#7.	pmbcl:ti,ab	637
#6.	mediastinal NEAR/3 lymphoma*	2,326
#5.	'mediastinal large b cell lymphoma'/exp	19
#4.	dlbcl:ti,ab	21,638
#3.	(diffuse OR histiocytic) NEAR/4 lymphoma*	47,033
#2.	'histiocytic lymphoma'/exp	7,314
#1.	'diffuse large b cell lymphoma'/exp	21,218

Search strategy for Cochrane

Search Name: Yescarta or Kymriah in DLBCL/PMBCL	
Last saved: 05/05/2022 15:42:51	
Comment: AP/GG 040522	
ID	Search
#1	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees
#2	(diffuse NEAR lymphoma*) (Word variations have been searched)
#3	(histiocytic lymphoma*) (Word variations have been searched)
#4	(DLBCL):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Mediastinal Neoplasms] explode all trees
#6	MeSH descriptor: [Lymphoma, B-Cell] explode all trees

#7	#5 AND #6
#8	(mediastinal NEAR lymphoma*) (Word variations have been searched)
#9	(PMBCL):ti,ab,kw (Word variations have been searched)
#10	#1 OR #2 OR #3 OR #4 OR #7 OR #8 OR #9
#11	(axicabtagene*) (Word variations have been searched)
#12	(yescarta*) (Word variations have been searched)
#13	(axi-cel) (Word variations have been searched)
#14	(fkc 876) (Word variations have been searched)
#15	(fkc876) (Word variations have been searched)
#16	("kte c19") (Word variations have been searched)
#17	(ktec19) (Word variations have been searched)
#18	(tisagenlecleucel*) (Word variations have been searched)
#19	(kymriah*) (Word variations have been searched)
#20	("cart 19") (Word variations have been searched)
#21	(cart19) (Word variations have been searched)
#22	("ctl 019") (Word variations have been searched)
#23	(ctl019) (Word variations have been searched)
#24	("lg 740") (Word variations have been searched)
#25	(lg740) (Word variations have been searched)
#26	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	#10 AND #26
#28	(conference abstract):pt
#29	(abstract):so
#30	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#31	#28 OR #29 OR #30
#32	#27 NOT #31
Total hits: 5	

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