HTA Austria
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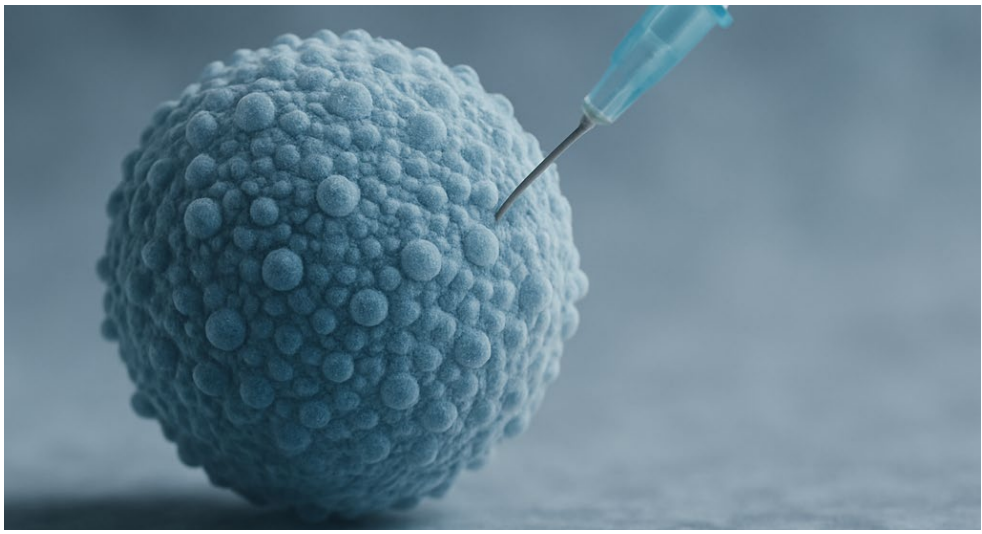
CAR-T cell therapy: Updated effectiveness and safety results from real-world evidence

A systematic review



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Vienna, June 2025

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Content

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List of abbreviations

AE……..……..... adverse events
aHSCT…….… .... autologous hematopoietic stem cell transplantation
AIHTA…….... .. Austrian Institute for Health Technology Assessment
ALL…… .. acute lymphoblastic leukemia
Axicel……..... axicabtagene
B-cell ALL…… ... B-cell acute lymphoblastic leukemia
BSC…….…..... best supportive care
Brexucel……... .... brexucabtagene
BTKi……..... Bruton's tyrosine kinase inhibitor
CAR ……..... chimeric antigen receptor
CAR-T cell……..….... chimeric antigen receptor-T cell
CC……..... conventional care
CIBMTR……..…. ... Center for International Blood and Marrow Transplant Research
Ciltacel……..... Ciltacabtagene
CIT…… ... chemoimmunotherapy
CMV……. .... cytomegalovirus
CR…… .... complete response
CRS…….. .... cytokine release syndrome
DLBCL……. ... diffuse large B-cell lymphoma
DLBCL NOS…… ... diffuse large B-cell lymphoma - not otherwise specified
EBMT…….…..... European Society for Blood and Marrow Transplantation
ECOG PS…… ..... Eastern Cooperative Oncology Group Performance Status
EFS……..…..... event free survival
EMA ……. ... European Medicines Agency
FL……..... follicular lymphoma
FL3B……. ... follicular lymphoma grade 3B
HCT…….…..... historical control trial
HGBCL……..... high-grade B-cell lymphoma
HGBCL NOS…….. high-grade B-cell lymphoma - not otherwise specified
HR……. ... hazard ratio
HRQoL……..... health related quality of life

HSCT…… ... hematopoietic stem cell transplantation
HTA……..... health technology assessment
ICANS…..……..... immune effector cell-associated neurotoxicity syndrome
ICER……..... incremental cost-effectiveness ratio
ICI…….. ... immune checkpoint inhibitors
ICU…… ... intensive care unit
Idecel…… .... idecabtagene
IPTW……..... inverse probability treatment weighting
ITT…… intention to treat
LBCL……..... large B-cell lymphoma
Lisocel…….. .... lisocabtagene
MAIC……..... matching-adjusted indirect comparison
MCL……. .... mantle cell lymphoma
n…… .... number of participants, sample size
NHL…….. ... non-Hodgkin lymphoma
NR……. ... not reported
nRCT's……. .... non-randomized controlled trials
OR……..... odds ratio
ORR…… ..... overall response rate
OS……..…….. ..... overall survival
PASS……..... post-authorisation safety study
PFS……..……. ..... progression free survival
PMBCL…… .... primary mediastinal large B-cell lymphoma
PRISMA……..... Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO……. ..... patient reported outcome
PSM……. ..... propensity score matching
QALY…… ... quality-adjusted life year
QoL……..... quality of life
RCT's…….. .... randomized controlled trials
RFS……..... relapse free survival
RoB…….. ..... risk of bias
R/R…… ... relapsed/refractory
RWCP…….. .... real-world clinical practice
RWE……. .... real-world evidence
SMR……..... standardized mortality ratio weighting
SoC…….. ..... standard of care
tFL…….. transformed follicular lymphoma
TEAE……..... treatment emergent adverse events
Tisacel…….. .... tisagenlecleucel
TRM……. .... treatment-related mortality

Executive Summary

Background: Malignant hematologic diseases are of great importance worldwide with increasing incidence rates. CAR-T cell therapies have been approved as a treatment option for some of these types of cancer. CAR-T cells are the patient's own T immune cells, which are genetically modified outside the body, returned to the patient and used for autologous immunotherapy. The aim of this work was to analyze the effectiveness and safety of CAR-T cell therapies based on real-world evidence and to provide an update of the current evidence.

increasing incidence of malignant haematological tumours

efficacy and safety of CAR-T (RWE)

Methods: A systematic literature search was performed based on an a priori defined PICO research question and the six CAR-T products, that were approved by the EMA. The following databases were searched: Pubmed, Cochrane Library and Epistemonikos. The results were presented for the relevant cancer types using data extraction tables. A quality and risk of bias assessment was performed.

systematic literature research on 6 approved products;
quality and RoB assessment

Results: A total of 26 full texts with a total of 2716 real-world patient data were identified for the search period from April 2022 to July 2024 and included in this analysis. All included studies were non-randomized, of which 14 were observational single-arm studies and 12 were indirect comparative studies with external control arms. The quality of the observational studies was rated as poor for six of them and as fair for eight. The risk of bias in the comparative studies is high and was rated as critical in all of them. Due to the heterogeneity of the studies and the characteristics of the cohorts, a narrative presentation of the results was made. The outcomes indicated that the treatment results in real-world settings are largely comparable to the results of pivotal trials. The comparative studies showed that treatment with CAR-T cells is associated with better results than treatment without CAR-T cells. Compared to previous publications, studies with longer follow-up times, further cancer types and products could be included. When comparing the outcomes with previous publications, largely similar effectiveness and safety real-world results were found. This review identified better survival rates in some cases, but also OS and PFS rates that decreased with increasing follow-up time. The response rates for the newer indications treated with CAR-T cells appeared to be higher. MCL patients treated with brexucabtagene had the highest incidence rates of relevant safety outcomes.

26 studies, 2716 pts.
single-arm and indirect comparative studies

low to medium quality, high RoB in comparative studies

RWE comparable with approval data

CAR-T associated with better outcomes

partially better survival rates: OS, PFS

highest safety risks: MCL/Brexucabtagene

Conclusion: Although there is an increasing body of evidence of CAR-T cell treatment in practice, the effectiveness and safety results cannot be assessed with certainty due to the identified limitations.

increasing RWE, limited conclusiveness

Keywords: CAR-T cell therapy; hematologic cancers; real-world evidence; effectiveness; safety, systematic review

Zusammenfassung

Einleitung: Maligne hämatologische Erkrankungen sind mit steigenden Inzidenzraten weltweit von großer Bedeutung. Für einige dieser Krebsarten sind CAR-T Zelltherapien als Behandlungsoption für die autologe Immuntherapie zugelassen. CAR-T-Zellen sind patient:inneneigene T-Immunzellen, welche außerhalb des Körpers genetisch verändert und den Patient:innen wieder zugeführt werden. Das Ziel dieser Arbeit war es, die Wirksamkeit und Sicherheit dieser Therapien auf der Basis von Real-World Evidenz Ergebnissen zu analysieren und ein Update der aktuellen Evidenz zu liefern.

steigende Inzidenz hämatologischer Malignome

Wirksamkeit und Sicherheit von CAR-T-Zelltherapien (RWE)

Methode: Eine systematische Literaturrecherche erfolgte auf Basis einer vorher festgelegten PICO-Forschungsfrage zu sechs, von der EMA zugelassenen, CAR-T-Produkten in den Datenbanken: Pubmed, Cochrane Library und Epistemonikos. Die Ergebnispräsentation erfolgte jeweils für die einzelnen hämatologischen Krebsarten mithilfe von Datenextraktionstabellen. Eine Qualitäts- und Risk of Bias Bewertung wurden durchgeführt.

systematische Literaturrecherche zu 6 zugelassenen Produkten, Qualitäts- und RoB-Bewertung

Ergebnisse: 26 Volltexte mit Daten von 2716 real-world Patient:innen konnten für den Suchzeitraum von April 2022 bis Juli 2024 identifiziert und in die Analyse inkludiert werden. Alle Studien waren nicht randomisiert, 14 waren beobachtende einarmige Studien und 12 indirekte Vergleichsstudien mit externen Kontrollarmen. Die Qualität der Beobachtungsstudien wurde bei sechs Studien als schlecht und bei acht als mittelmäßig eingestuft. Das Risiko einer Verzerrung in den Vergleichsstudien ist hoch und wurde in allen Studien als kritisch eingestuft. Es erfolgte eine narrative Ergebnispräsentation. Die Resultate deuten darauf hin, dass die Behandlungsergebnisse unter realen Bedingungen zum großen Teil mit den Ergebnissen der Zulassungsstudien vergleichbar sind. Die Vergleichsstudien zeigen, dass eine Behandlung mit CAR-T Zellen im Vergleich zu einer Behandlung ohne CAR-T Zellen mit besseren Ergebnissen assoziiert ist. Im Vergleich zu früheren Veröffentlichungen konnten Studien mit längeren Nachbeobachtungszeiten, weiteren Krebsarten und CAR-T Produkten inkludiert werden. Beim Vergleich der Outcomes mit früheren Veröffentlichungen, wurden zum großen Teil ähnliche RWE-Ergebnisse festgestellt. In dieser Arbeit wurden teilweise bessere Überlebensraten, aber auch OS und PFS-Raten, die mit zunehmender Nachbeobachtungszeit abnahmen, festgestellt. Die Ansprechraten für die neueren Indikationen schienen höher zu sein. Patient:innen mit MCL, die mit brexucabtagene behandelt wurden, wiesen die höchsten Inzidenzraten relevanter Sicherheitsoutcomes auf.

26 Studien, 2716 pts. einarmige und indirekte Vergleichsstudien

niedrige bis mittlere Qualität; hohes Verzerrungsrisiko bei Vergleichsstudien

RWE vergleichbar mit Zulassungsdaten

CAR-T mit besseren Outcomes assoziiert

tlw. besseres OS, PFS

höchste Sicherheitsrisiken bei MCL/brexucabtagene

Diskussion: Die Evidenzlage der Behandlung mit CAR-T Zelltherapien unter realen Bedingungen steigt zwar an, allerdings lassen sich die Effektivitäts- und Sicherheitsergebnisse aufgrund der identifizierten Limitationen nicht sicher bewerten.

steigende RWE, limitierte Aussagekraft

Schlüsselwörter: CAR-T Zelltherapie, Hämatologische Krebsarten, real-world Evidenz; Sicherheit; Wirksamkeit; Systematisches Review

1 Introduction and background

1.1 Overview of the diseases

globale Relevanz

Hematologic malignancies are a worldwide concern and of interest to the public health field. The incidence rates of hematologic malignancies have increased worldwide in recent years from 1990 to 2019. In 2019, the worldwide age-standardized incidence rate of all types of hematologic malignancies reached 1,343,850 cases. At the same time, the mortality rate for all types has declined due to improvements in prevention, early detection and treatment [2]. Chimeric antigen receptor T-cells (CAR-T cells) are an innovative autologous immunotherapy option for some of these patients [3].

zunehmende Inzidenz

Rückgang der Mortalität

CAR-T-Zelltherapie

NHL, Leukämie, Multiples Myelom

The cancer types relevant to this review in relation to CAR-T cell therapies are hematologic malignancies including non-Hodgkin lymphomas (NHL), a type of leukemia, and multiple myeloma [4]. The average annual age-standardized incidence rates in Austria for the period 2020-2022 were 15.5 cases/100,000 people for all types of NHL, 14.0 cases/100,000 people for all types of leukemia and 5.8 cases/100,000 people for multiple myeloma. The average annual age-standardized mortality rates in Austria for the period 2020-2022 were 6.7 cases/100,000 people for all types of NHL, 9.1 cases/100,000 people for all types of leukemia and 3.8 cases/100,000 people for multiple myeloma. The prevalence of NHL in Austria in December 2022 was 14,773, of leukemia 10,340 and of multiple myeloma 3,008 [5].

Ø Inzidenzraten in Ö (2020-2022)

Leukämie mit höchster Sterblichkeit

2022: NHL am häufigsten, Myelom am seltensten

Table 1: Subtypes of relevant hematologic malignancies

Cancer Type	Relevant subtypes
Non-Hodgkin lymphoma (NHL)	Follicular lymphoma (FL), including grade 3B (FL3B) (≈22% of all NHL cases)
	Diffuse large B-cell lymphoma (DLBCL) (≈31% of all NHL cases)
	High grade B-cell lymphoma (HGBCL) (HGBCL not otherwise specified: ≈ 2% of all NHL cases)
	Primary mediastinal large B-cell lymphoma (PMBCL) (≈2.4% of all NHL cases)
	Mantle cell lymphoma (MCL) (≈ 6% of all NHL cases)
Leukemia	B-cell acute lymphoblastic leukemia (ALL) (> 66% of all leukemia cases)
Multiple myeloma	No specific subtype

1.1.1 Lymphoma – Non-Hodgkin Lymphoma (NHL)

alle NHL-Typen für CAR-T geeignet

mehr Männer betroffen

jährlich in Ö:
Ø 1.436 Neuerkrankungen
Ø 621 Todesfälle

The types of lymphoma that are suitable for CAR-T cell therapies are all non-Hodgkin lymphoma (NHL) types. NHL accounts for approximately 3 % of all cancer diagnoses worldwide and is the most common hematological cancer. The malignancy refers to B-cells and T-cells, which are part of the white blood cells and immune response. In 2018, an estimated 509,600 new diagnoses were identified worldwide and the number of deaths related to NHL was estimated at 248,700. Most NHL types are associated with higher incidence rates in men [6]. In the period 2020-2022, an average of 1,436 people per year were newly diagnosed with NHL in Austria and 621.3 people per year died as a result of NHL [5].

Follicular lymphoma (FL)

Follikuläres Lymphom: unkontrolliertes Wachstum von B-Zellen

Einteilung nach Graden

FL3B relevant

Patients with follicular lymphoma have uncontrolled B-lymphocytes grow, that build up in the lymph nodes or body organs, have a nodular growth pattern and don't work right. The cell morphology consists of centrocytes and centroblasts. This cancer form is typically slow-growing. Most of the patients affected, present asymptomatic lymph node enlargements (adenopathy) in peripheral regions. FL can be divided into grades, depending on the proportion of centroblasts found in the sample. Grade 3B being relevant for this study. 3B follicular lymphoma (FL3B) is characterized with more than 15 centroblasts, which form solid layers.

22 % aller NHL-Fälle

Ø Diagnosealter:
65 Jahre

Follicular lymphoma occurs worldwide and is the second most common subtype of NHL [7]. FL accounts for 22 % of NHL cases [6]. The worldwide incidence is unknown but data is available for the US and Europe. In the US the estimated annual incidence is 3.18 cases/100,000 of the population and in Europe the estimated incidence is 2.18 cases/100,000 of the population. The average age at FL diagnosis is 65 years and the incidence increases with age [7].

Diffuse large B-cell lymphoma (DLBCL)

DLBCL entsteht aus reifen B-Zellen

Diffuse large B-cell lymphoma emerges from mature B-cells and is characterized by a mostly rapidly increasing lymph nodal enlargement. Patients present an enlarging symptomatic mass often in the neck or abdomen [8].

häufigster NHL-Subtyp bei Erwachsenen, 31 % der NHL-Fälle

FL kann in DLBCL transformieren

DLBCL is the most common type of NHL and accounts for approximately 31 % NHL cases among adults in western countries [6]. The annual incidence rate of DLBCL in the US and England is approximately 7 cases/100,000 of the population and in Europe the annual incidence rate is approximately 4.92 cases/100,000 of the population [8]. A previous FL can histologically transform to an aggressive DLBCL and is specified as transformed follicular lymphoma (tFL) [9].

High-grade B-cell lymphoma (HGBCL)

HGBCL:
DLBCL und
HGBCL-NOS

HGBCL-NOS; nur 1–2 % aller NHL-Fälle

High-grade B-cell lymphoma is an aggressive and fast-growing form of NHL with two subtypes. The previously described DLBCL and high-grade B-cell lymphoma, not otherwise specified (HGBCL-NOS). HGBCL cancer cells and symptoms can look similar to DLBCL, like the typical painless rapid swelling of lymph nodes [10]. The not otherwise classified HGBCL form is rare and accounts only for around 1 % to 2 % of all NHL diagnoses [11].

Primary mediastinal large B-cell lymphoma (PMBCL)

Primary mediastinal large B-cell lymphoma arises from B-cells that are produced in the thymus organ, which is located in the mediastinum. The patients often present with oncologic emergencies with a locally invasive malignant mass in the mediastinum, which can lead to airway compromise, blood flow obstruction in the central vein, heart complications or thrombosis. PMBCL accounts for 2.4 % of all NHL cases and in contrast to the other forms, women have higher incidence rates [12].

PMBCL entsteht aus thymischen B-Zellen
häufige Notfälle

2,4 % aller NHL-Fälle, mehr Frauen betroffen

Mantle cell lymphoma (MCL)

Mantle cell lymphoma is an aggressive and rare form of NHL and can involve lymph nodes and areas outside the lymph nodes. The gastrointestinal tract, blood or bone marrow can be affected. MCL consists of small to medium-sized lymph cells. Lymphadenopathy with enlarged or increased numbers of lymph nodes and unexplained gastrointestinal discomfort can be symptoms. The annual incidence rate in the US and Europe is estimated at 4 to 8 cases per million people of the population [13]. Mantle cell lymphoma accounts for approximately 6 % of NHL cases among adults in Western countries [6].

MCL als seltene, aggressive Form von NHL

Inzidenz US/Europa: 4–8 Fälle pro Million

ca. 6 % aller NHL-Fälle

1.1.2 Leukemia: B-cell acute lymphoblastic leukemia (ALL)

When B-lymphocytes are affected in acute lymphoblastic leukemia, it is named B-cell acute lymphoblastic leukemia. The B-cells are produced in the bone marrow and in case of cancer, large numbers of abnormal immature cells start overmultiplying. Normally, B-cells produce antibodies that immobilize and mark pathogens that invade the body. In more than two-thirds of cases of ALL, the B-lymphocytes are affected. The most affected group of patients with ALL are children under the age of 15 (85%). The remaining patients are adults mainly over the age of 50. The estimated annual incidence of B-cell ALL is 1 to 4.75 cases/100,000 of the population. Lifestyle factors, genetic disorders and chromosome abnormalities may play a factor in developing the disease. In relation to children and the first years of life, pesticides, magnetic exposure and an overstimulation of the immune response are associated with an increase in B-cell ALL [14]. Clinical features are anemia, neutropenia and thrombocytopenia which can cause symptoms like fatigue, infections, bone pain, bleeding, arthralgias, constitutional and central nervous system symptoms [15].

ALL: unreife B-Zellen entarten im Knochenmark

85 % der Betroffenen sind Kinder unter 15 J.

auch Erwachsene über 50 Jahren betroffen

Inzidenz: 1–4,75 Fälle pro 100.000

zahlreiche Risikofaktoren

1.1.3 Multiple myeloma

Multiple Myeloma is characterized by the formation of new plasma cells in the bone marrow, which produce a monoclonal immunoglobulin that does not work properly. Normally, white plasma cells are part of the immune response. Symptoms and complications of multiple myeloma are skeletal wrecking, osteopenia fractures, hypercalcemia, kidney impairment, anemia and infections [16].

maligne Plasmazellen im Knochenmark

Knochen- und Nierenschäden

The incidence of multiple myeloma varies worldwide and is between 0.54 and 5.3 cases/100,000 of the population. They account for 10% of all blood cancers. Highest rates were found in New Zealand, Australia, UK, Israel and Norway [17]. Current rates from Austria show that the age-standardized rate there is comparatively high at 5.8 cases per 100,000 people. In the period 2020-2022, an average of 538.3 people per year were newly diagnosed with multiple myeloma in Austria and 353.7 people per year died as a result of multiple myeloma [5].

10 % aller Blutkrebserkrankungen

jährlich in Ö:
Ø 538 Neuerkrankungen
Ø 354 Todesfälle

1.2 Overview of the treatments

Treatment of non-Hodgkin lymphoma

The treatment plan of patients with NHL can include radiation therapy, systemic combination chemotherapy, intrathecal chemotherapy, immunotherapy, targeted therapy, plasmapheresis, antibiotic therapy, surgery to remove certain lymphoma, stem cell transplantation (hematopoietic cell transplantation, HSCT) and watchful waiting. During a systemic combination chemotherapy two or more anticancer drugs enter the blood circulation system through mouth, vein or muscle and can fight cancer cells throughout the body. During intrathecal chemotherapy the anticancer drugs are injected into the cerebrospinal fluid. A targeted therapy includes drugs which can identify and attack cancer cells. In case of NHL this therapy can include monoclonal antibodies, which are made in the laboratory and are immune system proteins. Another form of targeted therapies are proteasome inhibitors, which block proteasome in cells with the possible effect of dying cancer cells. The kinase inhibitor therapy is another form of targeted therapies and includes Bruton's tyrosine kinase inhibitors (BTKi). These inhibitors block proteins which may lead to cancer cell growth and may kill the cells. During stem cell transplantation high doses of chemotherapy and/or radiation therapy are administered and then blood-forming cells are replaced. The stem cells can be transplanted autologously (aHSCT), when immature blood cells are taken from the patient, or allogeneically, when they are taken from a donor. The reinfused stem cells restore the patient's blood cells. Vaccine therapy is a new type and is currently being tested in clinical trials [18].

vielfältige Therapieoptionen bei NHL

systemische Chemo: mehrere Wirkstoffe kombiniert

intrathekale Chemo zur ZNS-Behandlung

Zieltherapien: monoklonale AK, BTKi, PI

Hochdosistherapie vor Stammzelltransplant

neue Ansätze: Impftherapien in Studien

Chemoimmunotherapy (CIT) is a used NHL cancer treatment which combinates a systemic therapy and an immunotherapy with the aim to kill or slow the growth of cancer cells and to stimulate or restore the patient's immune system to fight the disease [19]. One medication group of immunotherapies are immune checkpoint inhibitors (ICI), which have the effect to block specific binding proteins and as a result T cells can kill cancer cells. Another form of immunotherapy uses the ex vivo manipulated patient-specific immune cells, called CAR-T cell therapy [3].

CIT: Kombination aus Chemo- und Immuntherapie

Immuntherapien: Therapie mit ICI
CAR-T-Zelltherapie

Treatment of B-cell acute lymphoblastic leukemia

The main type of treatment for patients with ALL is a systemic combination chemotherapy with different drugs. Maintenance chemotherapy is also used. Another option for selected patients is the allogeneic stem cell transplantation from a donor. In addition, immunotherapy is used to treat patients with ALL, including CAR-T cells. The often intensive, complex, and lengthy treatment process should be supported by complementary therapies such as protective measures for the central nervous system [20].

ALL: Kombinationstherapie als Standard

CAR-T-Zellen als zusätzliche Option

Treatment of multiple myeloma

The treatment plan for patients with multiple myeloma may include an autologous stem cell transplantation using the patient's cells, chemotherapy drugs that target the cancer cells and immunotherapies including CAR-T cells. Conventional therapy will not cure patients. The aim with the therapies is to suppress the cancer and extend overall survival with an improved quality of life. If patients are eligible for autologous stem cell transplantation, they will first receive chemotherapy for three to six months prior to transplantation.

autologe Stammzelltransplantation, Chemo- und Immuntherapie

keine Heilung durch konventionelle Behandlung

If patients are ineligible for an autologous transplant, for example due to their general condition, they only receive chemotherapy [16].

Table 2: Appropriate treatments (combination of multiple treatments possible)

Treatment type	NHL	ALL	Multiple myeloma
Radiation therapy	x		
Systemic chemotherapy	x	x	x
Intrathecal chemotherapy	x		
Immunotherapy (e.g., CAR-T cells)	x	x	x
Targeted therapy (e.g., monoclonal antibodies, proteasome inhibitors)	x		
Surgery	x		
Allogeneic hematopoietic stem cell transplantation (HSCT)	x	x	
Autologous hematopoietic stem cell transplantation (aHSCT)	x		x
Supplementary therapies (e.g., antibiotics, plasmapheresis)	x	x	x

***Abbreviations**: ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma*

ECOG Performance Status

The Eastern Cooperative Oncology Group developed a performance status scale in 1982, which is still used today to assess the baseline characteristics of cancer patients in trials. The performance score indicates how cancer impacts daily living activities. The scale is from 0 to 5 and the lower the value, the less the daily activities are affected by the disease. The lowest score is associated with a fully active daily life and the highest score with death [21].

ECOG-Skala zur funktionellen Einschätzung

niedrige Werte = bessere Funktion

The detailed original ECOG PS (Eastern Cooperative Oncology Group Performance Status) scale is presented in the Appendix in Table 16.

Originalskala in Anhang, Tabelle 16

1.3 CAR-T cell therapy

CAR-T: neue Form der Immuntherapie

A therapy option to treat the described cancers includes CAR-T cells. CAR-T cells are genetically modified white blood T cells and used for autologous immunotherapy to treat patients with certain hematologic cancers [3].

erstmalige Zulassung: 2017 (USA), 2018 (EU)

The first CAR-T cell therapy was approved by the FDA in the US in 2017 for children with relapsed ALL [4]. In Europe, the first CAR-T cell therapy received EMA approval in 2018 [22]. Since then, more approved therapies and indications have been added.

Prozess der CAR-T-Zelltherapie

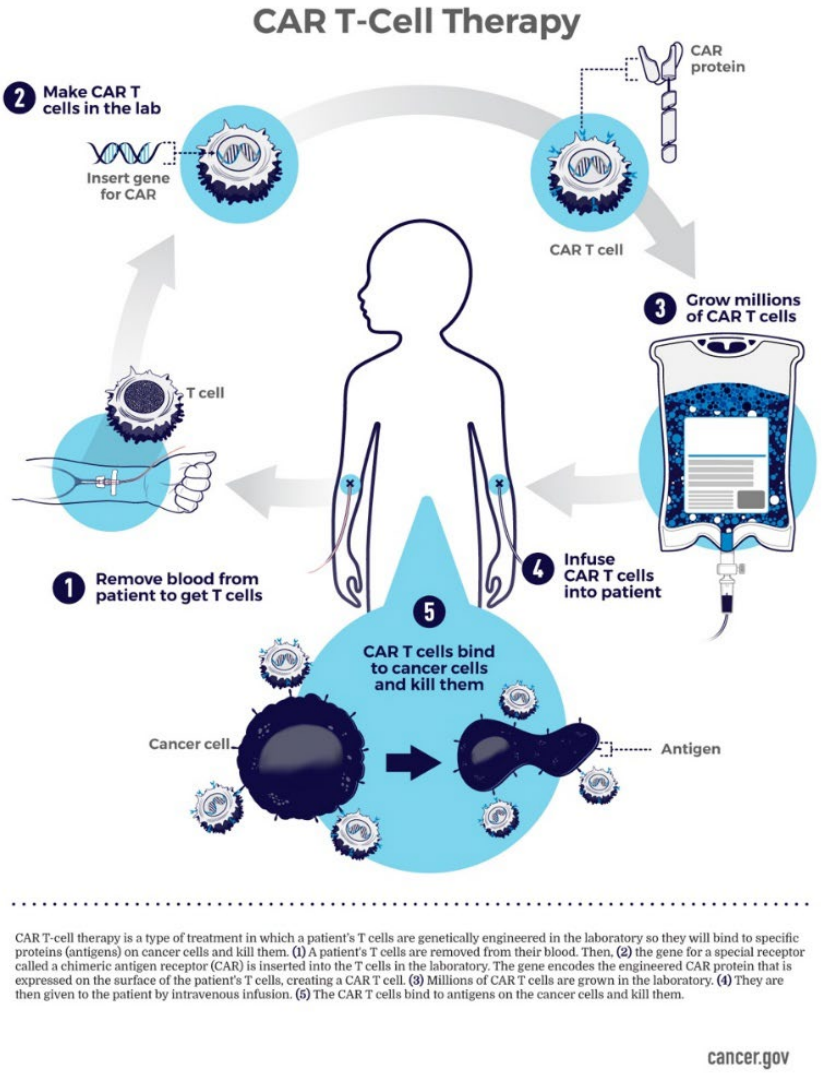

Figure 1: Scheme of CAR-T cell Therapy [1]

This therapy option represents a new category and innovation in immune therapy for cancer treatment and, alongside surgery, chemotherapy, radiation therapy and other drug therapies, offers a new field of research and treatment and hope for cancer patients and their practitioners. Immune system-boosting drugs as cancer treatment are designed to activate and strengthen the ability of the patient's immune system to fight the cancer with the aim of shrinking and eradicating tumors. CAR-T cell therapy can be defined as a form of immunotherapy, which also includes the immune checkpoint inhibitors. The basis of the innovative therapy is the use of T-cells, which are collected from the blood from the patients and customized for each patient. Each patient receives individual therapy with their own adapted T-cells. The collected T-cells are adapted in the laboratory by introducing a gene. The result of the re-engineering is the characteristic of T-cells to produce proteins on their surface. These proteins are called chimeric antigen receptors (CARs) and can bind to specific proteins or antigens on the surface of tumor cells. In the laboratory millions of CAR-T cells are produced and grown. After infusing the CAR-T cells into the patient the cells can kill cancer cells with their new characteristics. Ideally, the CAR-T cells continue to multiply in the patient's body and fight the cancer. The CAR-T cell therapies currently used target the two antigens CD19 or BCMA on the surface of cancer cells [4].

CAR-T als personalisierte Zelltherapie

gentechnisch veränderte T-Zellen bilden CAR-Proteine

Bindung an Antigene auf Krebszellen

CAR-T-Zellen vermehren sich im Körper und greifen Krebs an

derzeit eingesetzte CAR-T Zelltherapien zielen auf Antigene CD19 oder BCMA ab

Side effects

The therapy with CAR-T cells can lead to serious side effects, one of the most common and serious one being cytokine release syndrome (CRS). When this syndrome occurs, the infused T cells release many cytokines quickly, which are chemical messengers, into the bloodstream of the patients. Normally, the cytokines help to stimulate and direct the immune response, but in case of a CRS the cytokines are released fast at an increased level. This response can lead to high fevers and a rapid drop in blood pressure and can be life threatening in some cases. On the other hand, the reaction shows that the T cells are working in the blood and against the cancer. Most of the treated cancer patients show mild forms of CRS, which can be handled with standard supportive therapies. Serious reactions with multiple organ dysfunction can be treated with tocilizumab, which blocks the activity of relevant cytokines [1].

starke Nebenwirkungen möglich

CRS: schnelle Freisetzung von Immunbotenstoffen

Tocilizumab bei schweren Formen

To avoid a potentially life-threatening condition through a CRS, which is indicated by fever, vomiting, pain, dyspnea and low blood pressure, the drug tocilizumab must be available after CAR-T cell infusion. Additionally, close monitoring after treatment for side effects is necessary. To ensure a safe and effective treatment, the healthcare professionals must be educated regarding relevant information and a qualified and competent facility must be ensured [19, 22-26]. CRS can progress very rapidly and begins within 1 to 14 days after the CAR-T cell infusion and monitoring on an intensive care unit (ICU) can be necessary in severe cases [27].

Verfügbarkeit von tocilizumab zentral

Frühsymptome wie Fieber, Erbrechen, Atemnot, Hypotonie

Monitoring, geschultes Personal notwendig

Another side effect associated with CAR-T cell therapy is a neurologic effect with symptoms such as confusion, seizure-like activity and impaired speech. These symptoms are best treated with steroids [4]. This syndrome is defined as immune effector cell-associated neurotoxicity syndrome (ICANS) and can lead to severe outcomes [28].

Neurotoxizität (ICAN) (z.B. Sprachstörungen)

Behandlung mit Steroiden

Incidence rates from a systematic review that, among other things, analyzed the safety results of CAR-T cell therapies in patients with hematologic malignancies showed a 13 % proportion rate for severe CRS of all 1,860 included patients. For the ICANS incidence evaluation, 2,079 patients were included and the

1 SR mit 3939 pts.

13 % mit schwerem CRS

22 % mit schwerem ICANS nach CAR-T

overall proportion for severe ICANS was 22 % among all included patients with hematologic malignancies and treated with CAR-T cells [29].

Other side effects of CAR-T cell therapies are hypersensitivity reactions, severe infections, persistent cytopenias and hypogammaglobulinemia, malignancies and neoplasms [28].

weitere Nebenwirkungen möglich

Costs and cost-effectiveness

A CAR-T cell infusion currently costs around 200,000 to 250,000 euros ($214,810 to $268,512) in Germany, not including additional costs such as hospital costs [30].

bis zu € 250.000 pro Infusion ohne Krankenhauskosten

In a research study that estimated US commercial healthcare costs per multiple myeloma patients treated with CAR-T cell therapy, the total costs were reported at $160,933. The costs of a 12-month follow-up period after infusion were taken into account. The direct costs for the used CAR-T cell product and infusion were not included. The study provided an overview of each non-CAR-T cost component (pre-infusion, peri-infusion and post-infusion) and pointed out that the management of adverse events was responsible for the main overall costs. The total costs for adverse event management over the 12-month follow-up period were reported as $114,928. These costs could offer potential for savings in the future, if appropriate measures are taken, such as a better understanding by health care workers on how to prevent adverse events or how to proactively manage them. The direct costs for the analyzed CAR-T cell product for multiple myeloma in the study were reported with $465,000 and in combination with the estimated commercial health care costs a total amount of $625,933 has been investigated for the therapy, infusion and the 12-month follow-up period [31].

Studie zu Kosten nach CAR-T-Zelltherapie bei Myelom in USA: $ 161.000

Follow-up: 12 M.

teures Nebenwirkungsmanagement

direkte Produktkosten: $ 465.000

Gesamtkosten: $ 625.933

Another analysis focused on total real-world setting costs for DLBCL patients treated with CAR-T cell therapy in the US. The results and costs were similar, but a bit lower compared to the previously described study. The mean total costs for product, treatment and health care costs in a 3-month follow-up period ranged from $380,000 to $526,000. The costs were generally higher among patients who experienced CAR-T cell associated adverse events like a CRS [32].

3-Monats-Kosten für CAR-T bei DLBCL: $ 380.000–526.000

noch höher bei CRS und Nebenwirkungen

In relation to the European region a comparative study assessed the cost-benefit relation of DLBCL treatments including CAR-T cells and other third-line interventions in Germany. The real-world treatment costs were retrieved from the data warehouses of two hospitals and combined with the results of clinical benefits, which were measured in median overall survival (OS). The per-patient median costs for two used CAR-T cell therapies were specified as €310,496 and €340,458. The manufacturing and administration process costs of CAR-T cells made up a large part of the total median treatment costs. In contrast, the per patient median costs for best supportive care (BSC) and allogeneic stem cell transplantation were specified with €26,918 and €73,829. The cost-benefit relation analysis showed that stem cell transplantation and an examined CAR-T product are the most efficient interventions for third-line DLBCL treatment [33].

Vergleichsstudie zu DLBCL-Therapien in D

CAR-T: hohe Herstellungs- & Verwaltungskosten € 310.000–340.000/ Pt.

BSC allo-HSCT günstiger; CAR-T und HSCT am effizientesten (3L)

A systematic review analyzed the economic evaluation of CAR-T cell therapies for cancers. They used the incremental cost-effectiveness ratio (ICER) outcome per quality-adjusted life year (QALY) for comparison. They included data from cost-effectiveness analyses of current used and approved CAR-T cell therapies compared to standard therapy. They presented data for pediatric patients separately from data for adult patients.

ICER-Werte zwischen $ 9.000 und 4 Mio. (Erwachsene) und $ 20.000 und 243.000 (Kinder) pro QALY

The ICERs ranged from $9,424 to $4,124,105 per QALY for adults and from $20,784 to $243,177 per QALY for children depending on the type of CAR-T cell therapy, study outcomes, country and compared standard therapy.

ICER abhängig von Population, Krebsart, Komparator etc.

According to the review, the cost-effectiveness was highly uncertain due to different patient populations, cancer types, compared therapies and model assumptions in the included studies. However, CAR-T cell therapies turned out to be more expensive, more effective and can lead to more QALYs than their relevant standard therapies [34].

CAR-T wirksamer, aber teurer im Vergleich zu Standardtherapie

1.4 EMA approved and authorized CAR-T cell therapies

Currently the European Medicines Agency (EMA) has approved and authorized six CAR-T cell products for the treatment of cancer in European patients with the described diseases. These products are Kymriah®, Yescarta®, Tecartus®, Breyanzi®, Abecma® and Carvykti®.

aktuell 6 CAR-T-Produkte mit EMA-Zulassung

Kymriah® with the active substance *tisagenlecleucel* is one of the first authorized CAR-T cell products, which happened in 2018. This product is used for treating children and adults up to 25 years with acute lymphoblastic leukemia and a refractory disease, two or more relapses or a relapse after stem cell transplantation. Other indications for treatment with Kymriah® are adult patients with diffuse large B-cell lymphoma or follicular lymphoma with a relapse or resistance after two or more systemic treatments [22].

Kymriah: Zulassung 2018

bei ALL bei Kindern & jungen Erwachsenen bzw. bei DLBCL & FL nach 2+ Therapien

Yescarta® with the active substance *axicabtagene ciloleucel* was also authorized throughout the EU in 2018. It is used for treatment of adult patients with four types of blood cancer. Two of them are diffuse large B-cell lymphoma and high-grade B-cell lymphoma. Treatment is authorized when cancer has relapsed or is refractory within 12 months of receiving one previous chemoimmunotherapy. If adult patients with DLBCL or primary mediastinal large B-cell lymphoma experience relapse or refractory disease after two or more systemic therapies, Yescarta® is also indicated. Adult patients with relapsed or refractory follicular lymphoma after receiving three or more systemic therapies are eligible for Yescarta® [24].

Yescarta: Zulassung 2018

bei DLBCL, HGBCL, PMBCL, FL bei Rückfall/Refraktärität nach Vortherapien

Tecartus® with the active substance *brexucabtagene autoleucel* is a therapy used to treat adult cancer patients with mantle cell lymphoma with relapsed or refractory tumor after two or more systemic treatments including Bruton's tyrosine kinase inhibitor cancer intervention. The second indication for treatment with Tecartus® is a relapsed or refractory acute lymphoblastic leukemia among adults 26 years and older. Tecartus® received authorization throughout the EU in 2020 [23].

Tecartus: Zulassung 2020

bei MCL und ALL ab 26 J. bei Rückfall/Refraktärität nach Vortherapien

Breyanzi® with the active substance lisocabtagene maraleucel was authorized throughout the EU in 2022 and can be used for adults with four cancer types. The product is indicated for patients with diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma or follicular lymphoma with grade 3B, when they experience a relapse or a refractory cancer within one year from completion of receiving one previous chemoimmunotherapy. Breyanzi® is also used to treat adult patients with relapsed or refractory DLBCL, PMBCL or FL3B after two or more systemic therapies [19].

Breyanzi: Zulassung 2022

bei DLBCL, PMBCL, HGBCL, FL3B bei Rückfall/Refraktärität nach Vortherapien

Abecma® with the active substance *idecabtagene vicleucel* received due to less comprehensive clinical data a conditional marketing authorization in 2021 throughout the EU and a standard marketing authorization in 2024. The product is indicated for adult patients with multiple myeloma and a relapsed or refractory progress after two prior treatments and disease progression after the last one [25].

Abecma: Zulassung 2024

bei MM nach Vortherapien

Carvykti® with the active substance *ciltacabtagene autoleucel* is one of the newer products and was granted conditional marketing authorization in 2022 throughout the EU and a standard marketing authorization in 2024. This product is used for adult patients with relapsed or refractory multiple myeloma. Carvykti® is indicated when patients received at least one prior treatment with an immunomodulating agent to stimulate the immune system and a proteasome inhibitor to slow cancer cell growth and who have experienced disease progression after the last treatment. When the drug lenalidomide did not work and the cancer is refractory, Carvykti® is also approved for treatment [26].

Carvykti: Zulassung 2024

bei MM nach Vortherapien

auch bei Versagen von lenalidomid und Refraktäriät

In summary, none of the CAR-T cell products approved by the EMA are authorized for first-line therapy for the types of cancer described. They are used in the event of relapse or refractory disease after defined cancer therapies or periods.

kein Produkt in Erstlinie zugelassen

Table 3: CAR-T cell products with indications

CAR-T cell product	FL (NHL)	DLBCL (NHL)	HGBCL (NHL)	PMBCL (NHL)	MCL (NHL)	ALL	Multiple myeloma
Kymriah® *(tisagenlecleucel)*	x	x				x	
Yescarta® *(axicabtagene ciloleucel)*	x	x	x	x			
Tecartus® *(brexucabtagene autoleucel)*					x	x	
Breyanzi® *(lisocabtagene maraleucel)*	x	x		x			
Abecma® *(idecabtagene vicleucel)*							x
Carvykti® *(ciltacabtagene autoleucel)*							x

Abbreviations: *ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high grade B-cell lymphoma MCL: mantle cell lymphoma; NHL: non-Hodgkin Lymphoma; PMBCL: primary mediastinal large B-cell lymphoma*

A summary of all CAR-T cell products approved by the EMA with indications and approval dates is presented in the Appendix in Table 17. An overview of relevant pivotal trials for the various indications is also presented in the Appendix in Table 18.

Anhang: Übersicht zu Indikationen und Zulassungen

Special characteristics

orphan medicine- und ATMP-Status

zusätzliche Überwachung vorgeschrieben

Wirkprinzip: Gentransfer

All approved therapies except Breyanzi® are classified by the EMA as *orphan medicines*, which means that they were developed for treatment against a rare, life-threatening or chronically debilitating disease. CAR-T cells are used in rare diseases and all therapies are subject to *additional monitoring*, which implies more intensive monitoring than other drugs. Additionally, all approved therapies are classified as *advanced therapy medicinal products* and referred to as *gene therapy products*, meaning the products work by delivering genes into the patients' cells. This classification describes a new offered opportunity for treatment for certain diseases [19, 22-26].

1.5 Current state of research

AIHTA-Review zu Kymriah & Yescarta (2022)

viele Limitationen, Wirksamkeit & Sicherheit unklar

starke Unterschiede bei Pts.-Charakteristika

methodische Schwächen in beiden Settings

fehlende RCTs

keine Überlegenheit gegenüber Standard belegt

The Austrian Institute for Health Technology Assessment (AIHTA) published a critical systematic review report about CAR-T cell therapies and the results from international health technology assessments (HTAs), pivotal trials and real-world evidence (RWE) in 2022. They analyzed patient characteristics, effectiveness and safety outcomes for the products Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene). The results described that the pivotal studies for both of these therapies have wide limitations and only some institutions acknowledged a possible positive effect of Kymriah® and Yescarta® in their HTAs. In relation to the results of RWE and the identified observational studies the report described large differences in patient characteristics between the pivotal trials and the observational real-world studies. The follow-up times of the studies ranged from 4 to 27.1 months. The risk of bias of the identified and included studies was classified as moderate to high. As a result of the limitations, they conclude that the evidence for the effectiveness and safety of the two therapies in patients with acute lymphoblastic leukemia and large B-cell lymphoma is uncertain. The limitations within the pivotal studies were uncontrolled study designs, short follow-up times, small numbers of participants and a lack of safety data. The limitation characteristics within the RWE studies were unblinding, lack of control, retrospective study design and heterogeneity. In addition to the limitations, there is an evidence gap due to lack of RCTs. As a conclusion from the report the superiority of Kymriah® and Yescarta® for the diseases examined compared with standard therapies is uncertain and cannot be confirmed [35].

Another review analyzed late relapses and the duration of response after CAR-T cell therapies among adult patients. It was determined that the relapse rate in the first year after CAR-T cell infusion was higher than during longer follow-up periods. They searched data on the six currently approved and used CAR-T products until May 2022. In total eight studies were included with 814 enrolled patients. However, they only identified and included studies that used Yescarta® (axicabtagene), Kymriah® (tisagenlecleucel) and Breyanzi® (lisocabtagene) as CAR-T cell therapies. Patients with acute lymphoblastic leukemia and relevant non-Hodgkin lymphomas were treated in the included studies. However, no data and studies on multiple myeloma were included. The most common indication in the included studies was a diffuse large B-cell lymphoma. For the therapies and cancer types analyzed, the pooled prevalence of relapse within the first 12 months after therapy was 61 % (95% CI, 43 - 78). The calculated pooled prevalence of relapses that occurred after 12 months from therapy was 24 % (95% CI, 11 - 42). Combining the two periods shows that the pooled prevalence of relapse is high and more than three quarters of patients from the included studies were affected. The authors call for further studies with long-term follow-up periods from real-world data to assess the efficacy and safety associated with CAR-T cell therapies [36].

Review zu späten Rückfällen und Ansprechraten (CAR-T)

Datenanalyse zu 3 Produkten (814 Pts.)

DLBCL am häufigsten

gepoolte Rückfallrate im 1. Jahr: 61 %

gepoolte Rückfallrate nach 12 Monaten: 24 %

Rückfälle bei mehr als 75 % der Pts.

A current research study and systematic review examined approved CAR-T cell therapies among patients with large B-cell lymphoma who were treated with Yescarta® (axicabtagene) or Kymriah® (tisagenlecleucel) with data up to July 2022. They compared real-world outcomes with clinical trials. In conclusion, the analyzed effectiveness outcomes align with data from the comparable respective pivotal clinical trials ZUMA-1 and JULIET. Treatment with axicabtagene was associated with longer OS and PFS and higher ORR and CR rates compared to treatment with tisagenlecleucel in this study. The review characterized the CAR-T therapies examined in the study as effective in a wide range for patients with LBCL [37]. The comparison of the results is shown in Table 4.

Review zu LBCL mit Yescarta/Kymriah

RWE vs. ZUMA-1 & JULIET

axicabtagene: OS, PFS, ORR besser

CAR-T-Therapien als wirksam bewertet

Table 4: LBCL CAR-T treatment results with comparison of RWE and pivotal trials [37]

	Axicabtagene RWE	Axicabtagene Pivotal trial (ZUMA-1)	Tisagenlecleucel RWE	Tisagenlecleucel Pivotal trial (JULIET)
ORR	73.4% (95% CI, 67.9 - 78.3)	83%	57.7% (95% CI, 53.1 - 62.1)	53%
Estimated CR	51.0% (95% CI, 44.5 - 57.4)	58%	39.0% (95% CI, 34.6 - 43.7)	39%
Estimated median OS	19.5 months (95% CI, 16.9 - 25.8)	25.8 months	11.7 months (95% CI, 10.2 - 13.0)	11.1 months
Estimated median PFS	7.3 months (95% CI, 6.1 -9.3)	5.9 months	3.3 months (95% CI, 3.3 - 3.8)	2.9 months

Abbreviations: *CR: complete response; PFS: progression free survival; RWE: real-world evidence; ORR: overall response rate; OS: overall survival*

Safety analysis

Nebenwirkungen bei NHL-Therapien

Regarding the safety and toxicity of CAR-T cell therapies, a recent systematic review and meta-analysis from June 2024 analyzed differences between used CAR-T therapies in terms of common adverse events among patients with non-Hodgkin lymphoma. They focused on the approved NHL treatments with axicabtagene, lisocabtagene and tisagenlecleucel. The examined adverse events were cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, cytopenias and infections. Fifteen clinical trials with in total 1364 patients were included in the systematic review. The pooled incidence rates for the treatments and adverse events analyzed in this review are shown in the following table.

Vergleich von drei CAR-T-Produkten (2024)

15 Studien mit 1364 Pts.

Table 5: NHL CAR-T cell treatment: Pooled incidence rates for adverse events [38]

	Axicabtagene	Lisocabtagene	Tisagenlecleucel
CRS	90 % (95% CI, 81 - 97)	43 % (95% CI, 38 - 49)	57 % (95% CI, 51 - 63)
Severe CRS	7 % (95% CI, 5 - 9)	1 % (95% CI, 0,1 - 18)	6 % (95% CI, 0 - 3)
ICANS	51 % (95% CI, 26 - 77)	22 % (95% CI, 12 - 34)	28 % (95% CI, 14 - 43)
Severe ICANS	19 % (95% CI, 11 - 18)	6 % (95% CI, 3 - 10)	6 % (95% CI, 2 - 11)
Anemia	31 % (95% CI, 21 - 42)	49 % (95% CI, 17 - 63)	41 % (95% CI, 25 - 58)
Thrombocytopenia	27 % (95% CI, 16 - 40)	47 % (95% CI, 12 - 84)	22 % (95% CI, 9 - 38)
Neutropenia	35 % (95% CI, 26 - 46)	64 % (95% CI, 64 -81)	32 % (95% CI, 19 - 46)
Infections	59 % (95% CI, 13 - 60)	10 % (95% CI, 3 - 45)	31 % (95% CI, 10 - 55)
Lymphoma subtypes	DLBCL, FL, HGBCL, PMBCL,	DLBCL, FL, HGBCL, PMBCL, tFL	DLBCL, FL, HGBCL, PMBCL, tFL

Abbreviations: *DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high grade B-cell lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; tFL: transformed follicular lymphoma*

axicabtagene: höchste CRS- und ICANS-Raten (alle Grade)

Patients treated with axicabtagene showed the highest incidence rates for CRS of any grade and the results were statistically significant compared to lisocabtagene and tisagenlecleucel. Significant differences for severe CRS between the three examined products were not found. Patients treated with axicabtagene showed also highest and significant greater rates for ICANS compared to the other products.

keine Unterschiede bei Anämie und Thrombozytopenie

The incidence rates of anemia and thrombocytopenia showed no significant differences between the three products. However, significantly higher incidence rates of neutropenia were found for the treatment with lisocabtagene compared with treatment with axicabtagene and tisagenlecleucel.

mehr schwere Infektionen; nicht-standardisierte Einschlusskriterien

The incidence rates for all grades of infections among the three therapies examined showed no significant differences. When it came to serious infections,

patients treated with axicabtagene showed increased rates. Limitations of the studies are due to non-standardized inclusion criteria across the studies [38].

axicabtagene: 80 % schwerwiegende Nebenwirkungen; davon 20 % tödlich oder andauernd

Another safety study of axicabtagene, which analyzed adverse event reports from the EudraVigilance Database with data uploaded up to December 2022, indicated that 80 % of the reported events related to axicabtagene were serious and 20 % of them led to death or did not disappear completely. Most reported events were nervous system disorders (25.6%), including ICANS and neurotoxicity and immune system disorders (23.1%), including CRS. In total 2905 individual case safety reports were analyzed with DLBCL as the most frequently reported indication, accounting for 1369 cases. In most cases, patients were affected by several adverse events [39].

häufig: ICANS, CRS, meist bei DLBCL

niedrigere CRS-/ICANS-Raten in RWE

ggf. Unterschiede bei Bewertung & Vortherapie

The systematic review and meta-analysis from Jacobson et al. (2024) reported that the approved and examined CAR-T cell products (axicabtagene and tisagenlecleucel) have manageable safety profiles. In a comparison between real-world data and the pivotal clinical trials, the incidence rates of CRS and ICANS were more favorable in real-world studies. This could be due to differences in grading criteria or previous drug interventions to treat these adverse events.

1.6 Objective and research question

CAR-T: aktuelle Evidenz notwendig

CAR-T cell therapies are part of a very dynamic field in cancer research and an expensive treatment option. Therefore decision makers depend on updated evidence on the results of therapy and research.

bisherige Reviews oft veraltet (bis 2022)

Current systematic reviews regarding effectiveness have only analyzed the literature up to 2022 and the data were often limited. Furthermore, not all approved CAR-T cell therapies, diseases and relevant outcomes, particularly the therapies newly approved by the EMA in 2022, were analyzed and included in the reviews. In terms of safety and toxicity, not all therapies and diseases have been examined in the current reviews.

berücksichtigen nicht alle Produkte & Indikationen

hier: mehr Therapien & längeres Follow-Up

This review focuses on a wider range of CAR-T cell therapies and indications. Longer follow-up times are of interest in this systematic review and the latest publications from 2022 will be analyzed with the following research question:

Wirksamkeit & Sicherheit von CAR-T vs. Standard-therapie basierend auf RWE

- How effective and safe is CAR-T cell therapy compared to standard therapy without CAR-T cells for patients with ALL, DLBCL, FL, HGBCL, PMBCL, MCL and multiple myeloma based on real-world evidence studies?

2 Methods

The study methodology followed the PRISMA 2020 guideline, checklist and flow diagram for reporting systematic reviews [40].

Methodik nach PRISMA 2020

2.1 Literature search strategy and inclusion/exclusion criteria

The following electronic databases were searched: PubMed, Cochrane Library and Epistemonikos from April 2022 to July 11, 2024 to identify relevant publications, answering the research question. The time period is derived from relevant reviews, such as the AIHTA report, which contains the results up to this point in time.

Datenbanken: PubMed, Cochrane, Epistemonikos

The search terms were aimed at identifying relevant publications containing the approved CAR-T cell therapies used with the active substances *tisagenlecleucel, axicabtagene, brexucabtagene, lisocabtagene, idecabtagene and ciltacabtagene.*

Suchbegriffe: relevante Substanzen

Seven effectiveness and two safety outcomes were of interest and can be seen in Table 6. In terms of the adverse events, CRS, neurotoxicity and ICANS were of interest as they are the most common and are associated with serious outcomes.

Schlüsseloutcomes; AEs

A hand-search aimed at identifying publications related to the CAR-T registries EBMT (European Society for Blood and Marrow Transplantation) and DESCAR-T was performed.

Handsuche: EBMT & DESCAR-T

Publications in English and German were eligible. The selected study types can be seen in Table 6. Only fully published studies were used for analysis. Publications with data solely from pivotal trials and letters to the editor were excluded.

Publikationen: Deutsch & Englisch

The literature search was based on a PICO research question summarized in Table 6.

Tabelle 6: PICO-Übersicht

Table 6: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Patients of all ages with**:** ALL, DLBCL, FL, HGBCL, PMBCL, MCL,multiple Myeloma	▪ Other cancer types ▪ Autoimmune diseases ▪ Patients with secondary lymphoma or secondary central nervous system lymphoma ▪ Cohorts with only certain secondary diseases (e.g., HIV)
Intervention	Treatment with EMA approved CAR-T cell products: ▪ Kymriah®/tisagenlecleucel ▪ Yescarta®/axicabtagene ▪ Tecartus®/brexucabtagene ▪ Breyanzi®/lisocabtagene ▪ Abecma®/idecabtagene ▪ Carvykti®/ciltacabtagene	▪ Other medication ▪ Follow-up therapies after CAR-T cell treatment ▪ Donor CAR-T cells ▪ Combination of CAR-T cells with other medication ▪ CAR-T cell therapy for not approved therapy options, e.g., as first line therapy ▪ Reinfusion with CAR-T cells
Control	Standard treatment with: radiation therapy, chemotherapy, targeted therapy, surgery, stem cell transplantation (allogeneic and autologous), immuno-therapy without CAR-T cells	
Outcome	Effectiveness outcomes: OS, EFS, PFS, ORR, CR, relapse, HRQoL Safety outcomes: TRM, AE (CRS, neurotoxicity and ICANS)	▪ Cost analyses ▪ Prognostic factors on the results (e.g., bridging therapy, number of CAR-T cells in blood)
Study design	▪ RCT's and nRCT's ▪ Prospective and retrospective studies ▪ Registry studies ▪ Observational studies with real-world evidence	▪ Studies with ≤ 10 patients ▪ Comparative studies of: different CAR-T pro-ducts for one indication, different age groups, different treatment settings, different patient characteristics
Publication date	April 2022 – July 2024	Before April 2022
Language	English and German	Other languages

Abbreviations: *AE: adverse events; ALL: acute lymphoblastic leukemia; CR: complete response; CRS: cytokine release syndrome; DLBCL: diffuse large B-cell lymphoma; EFS: overall survival; EMA: European Medicines Agency; FL: follicular lymphoma; HGBCL: high grade B-cell lymphoma; HRQoL: health related quality of life; ICANS: immune effector cell-associated neurotoxicity syndrome; MCL: mantle cell lymphoma; nRCT's: non-Randomized Control Trials; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PMBCL: primary mediastinal large B-cell lymphoma; RCT's: Randomized Control Trials; TRM: treatment-related mortality*

The following search terms and operators were used for advanced searches in the three databases: CAR-T OR CAR T AND tisagenlecleucel OR axi-cabtagene OR brexucabtagene OR lisocabtagene OR idecabtagene OR cil-tacabtagene. For the hand-search CAR-T was combined with DESCAR-T or EBMT. The year filter from 2022-2024 was used for all searches.

Suchsyntax

Filter für alle Suchen: 2022 - 2024

2.2 Study selection and presentation of results

1041 records were identified through systematic searches and hand-search of databases (PubMed: 680, included 79 from hand-search, Cochrane Library: 60, Epistemonikos: 301). After removal of duplicates, 762 records were screened by title and abstract. Reasons for exclusions were recorded and summarized. For the analysis and presentation of results, the studies were assigned to the individual types of cancer. Publications were not found for all individual types of cancer in the search period described. The lymphoma types HGBCL and PMBCL were not examined in more detail and classified and summarized as large B-cell lymphomas (LBCL). For this reason, the results for the cancer types and subtypes DLBCL, DLBCL NOS, HGBCL, PMBCL and tFL will be presented in the following as LBCL.

762 Hits nach Deduplikation

Studien nach Tumorart

keine Publikationen zu allen Entitäten gefunden

HGBCL & PMBCL als LBCL dargestellt

Reasons for exclusion of records during title and abstract screening were publication dates, languages, handbook contributions or generally informative articles about CAR-T cell therapies, letters/comments, publications about management options of adverse events or therapies, publications of current studies like the clinical trial registry records or protocols and studies for which only an abstract has been published so far.

Ausschlusskriterien: Sprache, Publikationsart, Verfügbarkeit des Volltextes

Ineligible populations, interventions, outcomes and study designs were excluded (see exclusion criteria in Table 6). In cases where more than one publication from the same study on the same outcome was available, the publication with the longer follow-up period was selected. Studies were eligible if inclusion criteria were fulfilled. Patients of all ages with relevant cancer types must have received one of the EMA approved CAR-T therapies and predefined safety and effectiveness outcomes of the therapies must be evaluated.

weitere Ein- und Ausschlusskriterien: Alter, Krebsarten, zugelassene Therapien

81 reports that met the inclusion criteria were selected and their full texts were reviewed. 55 reports were excluded and 26 full-text reports were included in this work. Of these 26 reports, 12 were indirect comparative studies and 14 were single-arm observational studies. Four reports could be included for ALL, eight for LBCL, three for FL, three for MCL and eight for multiple myeloma.

81 Volltexte geprüft, 26 eingeschlossen

14 einarmige Studien, 12 indirekte Vergleiche

The selection process is displayed in the PRISMA 2020 flow diagram in Figure 2. The recorded exclusion reasons for the reports after full-text screening are presented in the flow diagram.

Studienauswahl in PRISMA-Flowchart

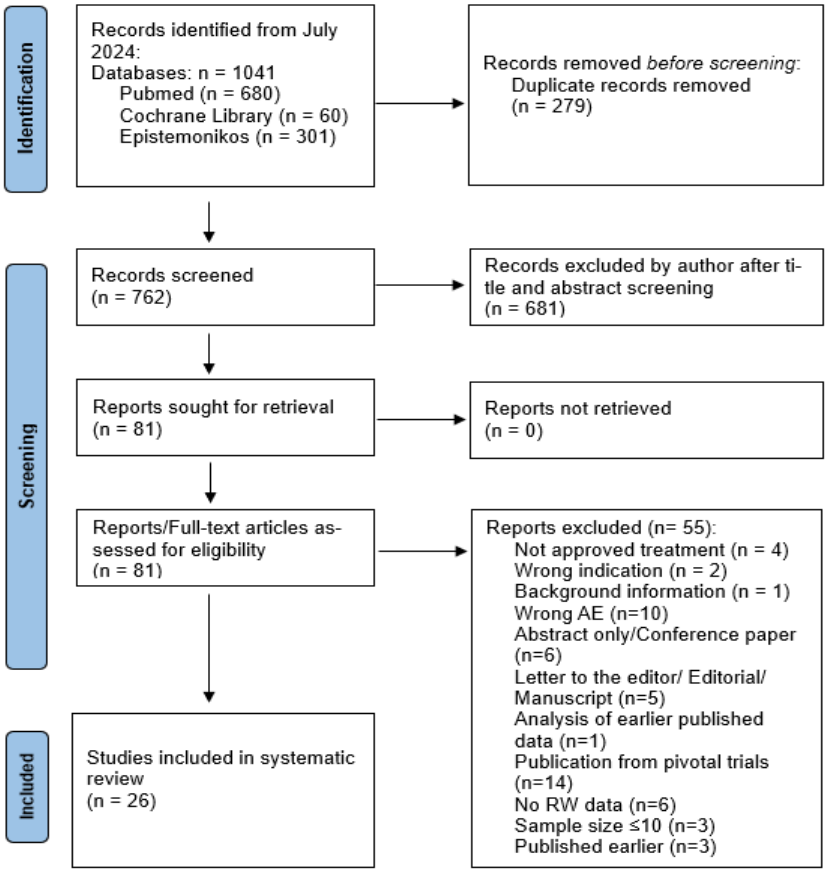

Figure 2: PRISMA 2020 flow diagram of study selection [40]

Data extraction tables for each relevant indication were used to extract relevant data systematically from eligible studies. The tables for study characteristics contain: Study ID, study design, number of participants, primary and secondary endpoints, median age, median number of prior therapy lines, median follow-up, disease stage, other patient characteristics, patient population and underlying studies and trials and the CAR-T product used.

Datenextraktion: tabellarisch nach Indikation, Population & Produkt

The tables relating to the effectiveness and safety results contain the described outcomes of interest.

Wirksamkeits- & Sicherheitsdaten

2.3 Quality and risk of bias assessment

Quality and risk of bias assessments were conducted using *the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies* from the National Heart, Lung, and Blood Institute (NHLBI) for the observational single-arm real-world studies [41]. The CAR-T interventions were considered as exposure and assessed in this sense in the evaluation questions. The overall assessment of quality was rated as good, fair or poor for the 14 studies. This tool is presented in the Appendix in Table 25.

NHLBI-Tool für einarmige Beobachtungsstudien

Bewertung: gut, mittel, schlecht (14 Studien)

The *ROBINS-I* tool for comparative non-randomized studies of interventions was used for the indirect comparative studies [42]. The overall assessment of risk of bias for 12 comparative reports was classified as low, moderate, serious or critical.

ROBINS-I für Vergleichsstudien; RoB: niedrig bis kritisch

3 Results

The results of eligible studies are presented and compared for each relevant indication. If available, weighted cohort data meeting the inclusion criteria of clinical trials from comparative studies are presented.

gewichtete Ergebnisse nach Indikation & Verfügbarkeit

3.1 Outcomes

The definitions of examined oncology clinical outcomes are:

Klinische Outcomes: OS, EFS, PFS, RFS

- Overall survival (OS):
  The overall survival rate is the time from randomization, study start or treatment to the final point: death.
- Event-free survival (EFS):
  The event free survival rate is the time from randomization, study start or treatment to an event, which could be a disease progression, an ending of the treatment or death.
- Progression-free survival (PFS) / Relapse-free survival (RFS):
  The progression free survival rate or relapse-free survival rate describes the time from randomization, study start or treatment to a first evidence of disease progression or death.

Response-Raten: ORR & CR

- Overall response rate (ORR):
  The overall response rate describes the proportion of patients who respond partially or fully to the treatment within a certain period of time.
- Complete response (CR):
  The complete response rate is defined as a lack of verifiable evidence of a tumor.

Lebensqualität (HRQoL) & Rückfall

- Health related quality of life (HRQoL/QoL):
  Health related quality of life or Quality of life is a patient reported outcome (PRO) and demonstrates clinical benefit. It is usually assessed with survey questionnaires and covers the four core concepts: overall health, physical health, mental health and activities of daily living [43].
- Relapse:
  Relapse means the return of a disease or the signs and symptoms of a cancer disease after a period of improvement.

Nebenwirkungen (AE) & therapiebedingte Mortalität (TRM)

- Adverse event (AE):
  An adverse event is described as an undesired effect or reaction of a treatment. These events can range from mild to severe [44].
- Treatment-related mortality (TRM):
  The treatment-related mortality is defined as the proportion of deaths not related to the cancer and with an absence of progressive disease at the time of death [45].

3.3 Real-world evidence of CAR-T treatment among patients with acute lymphoblastic leukemia

3.3.1 Characteristics of included studies

4 ALL-RWE-Publikationen

Daten aus UK und DE (n = 206)

tisagenlecleucel: Hochrisiko- und vorbehandelte Pts.

Follow-up: DE 20,8 M., UK 26,3 M.

Four publications could be identified during the selection process that are ALL relevant and of interest for an update of current RWE. Two of them are retrospective observational studies with data from CAR-T cell centers from Germany and the UK [46, 47]. The CAR-T product used for treatment in these observations was tisagenlecleucel. The cohort from the UK study is a subgroup of an ITT analysis. This subgroup included 125 tisagenlecleucel-infused patients and the cohort from the centers in Germany included 81 treated patients. 80 % of the 81 patients received prior HSCT. In total 206 patients with a median age of 11.5 and 11.7 years were evaluated for tisagenlecleucel outcomes. The median follow-up duration for the German cohort was 20.8 months and for the UK cohort 26.3 months. Both cohorts were classified as mostly high-risk and heavily pretreated patients.

ZUMA-3 vs. SCHOLAR-3 (Vergleichsstudien)

brexucabtagene vs. SoC bei B-ALL

Follow-up: 26,8 Monate

Vergleich per MAIC/PSM,

Alter: ≥18 bzw. ≥26 Jahre

matched Pts.: 49 vs. 40 (SoC)

The two other publications are retrospective comparative analyses of the pivotal single-arm ZUMA-3 trial, which evaluated the efficacy and safety of brexucabtagene in adult patients and the historical control study SCHOLAR-3, which acts as a synthetic control arm [48, 49]. Both publications used data from the same databases with the same patient cohorts. Patients in the pivotal trial were treated with the CAR-T product brexucabtagene and in the synthetic control arm with standard of care (SoC) treatment without CAR-T cells. The median follow-up duration in both analyses was 26.8 months and matching-adjusted indirect comparison (MAIC) or propensity scoring (PSM) was used to match patient characteristics and groups. The difference of these two comparative analyses was the age group examined. In the cohort of Minnema et al. (2024), the examined and treated group was patients with B-ALL aged ≥26 years and in the cohort of Shah, B. D. et al. (2022) the treated group was patients with B-ALL aged ≥ 18 years. Due to the greater age range in the second comparative analysis more brexucabtagene-treated patients could be included in the comparison (n=55; matched: n=49). The SoC control arm included 40 matched patients, in the larger analysis.

4 Studien: 295 ALL-Pts.

tisagenlecleucel, brexucabtagene, SoC

Follow-up: 2 J.

In total, 295 patients were evaluated across the 4 studies, including the pivotal ZUMA-3 cohort. All publications have a two-year follow-up character and included ALL patients with refractory or relapsed disease. 206 patients were treated with tisagenlecleucel and 49 with brexucabtagene in the pivotal trial. 40 patients received historical standard treatment. All studies had pre-defined primary and secondary endpoints. The examined outcomes were CR, OS, RFS, EFS and safety outcomes, including CRS, neurotoxicity and ICANS.

Details in Tabelle 7

Study characteristics of the four included publications are presented in Table 7.

Beobachtungsstudien: mittlere Qualität
RoB: keine Verblindung

The quality of the two real-world observational single-arm studies was rated as fair. The follow-up periods seemed to be sufficient and potential confounding variables were measured, but risk of bias arises from unblinded outcome assessors and different baseline characteristics.

Vergleichsstudien: RoB insgesamt kritisch

The overall risk of bias (RoB) was classified as critical in both comparative studies. The main reasons for this were bias due to confounding and due to the selection of participants into the studies.

Generally, all domains were classified as serious or critical. Quality and risk of bias assessment are presented in the Appendix in Table 26 and Table 30.

Bewertung von Qualität und RoB im Anhang

Table 7: Main characteristics of included studies for patients with ALL

Study ID (first author, year)	Bader, 2023	Minnema, 2024	Oporto Espuelas, 2024	Shah, B. D., 2022
Study design	Retrospective RWE, 2-year follow-up	Comparative retrospective, 2-year follow-up, MAIC, HCT	Retrospective ITT analysis, subgroup analysis of CAR-T patients	Comparative retrospective, 2-year follow-up, PSM
n	81	*CAR-T matched: 39* HCT: 39	CAR-T infused: 125	*CAR-T: 55 matched: CAR-T: 49* HCT: 40
Primary and secondary endpoints	CR, EFS, OS, RFS, Safety	CR, OS, RFS, Safety	CR, OS, EFS, Safety	OS, CR, RFS
Median Age (years)	11.5	*CAR-T: 45* HCT: 46	11.7	*CAR-T: 41* HCT: NR
Median prior therapy lines	NR	NR	3	*CAR-T: 2* HCT: NR
Median follow up (months)	20.8	26.8	26.3	26.8
Disease stage	R/R	R/R	R/R	R/R
Other patient characteristics	-High risk pediatric, adolescent and young adult patients with precursor B-cell ALL -80% with prior HSCT	B-ALL patients aged ≥26, from ZUMA-3 treated with CAR-T compared with SoC data from SCHOLAR-3 (historical control study)	-Heavily pretreated cohort -High risk cohort -Data from subgroup	-Most heavily treated -adults aged ≥18 with B-ALL compared with historical clinical trial (HCT) with SoC
Patient population/ underlying studies and trials	From 18 CAR-T cell centers in Germany	*ZUMA-3 (Phase 2)* and SCHOLAR-3 (synthetic control arm)	From UK, multicenter	*ZUMA-3* and SCHOLAR-3
CAR-T product	Tisagenlecleucel	Brexucabtagene	Tisagenlecleucel	Brexucabtagene

Abbreviations: *B-cell ALL: B-cell acute lymphoblastic leukemia; CR: complete response; EFS: event free survival; HCT: historical control trial; HSCT: hematopoietic stem cell transplantation; ITT: intention to treat; MAIC: matching-adjusted indirect comparison; n: number of participants; NR: not reported; OS: overall survival; PSM: propensity score matching; RFS: relapse free survival; R/R: relapsed/refractory; SoC: standard of care; UK: United Kingdom;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.3.2 Effectiveness outcomes

The **ORR** was not reported and analyzed in the included studies.

ORR nicht berichtet

The **CR** was reported in both tisagenlecleucel studies and was around 90 % after one month. After two years the percentage of patients with complete response fell to 40 % and 59 % with median follow-up periods of 23.3 and 20.8 months, respectively [46, 47]. In the comparative studies with brexucabtagene only the CR rate of the pivotal trials was reported, which was around 70 % after the two-year follow-up period for the cohorts [48, 49].

CR für tisagenlecleucel

CR für brexucabtagene

The **OS** was reported in all publications and ranged from around 50 % [46] to 70 % [47] in the observational studies after follow-up periods of around two years. The comparative studies analyzed the median OS of patients treated with brexucabtagene and historical standard of care. The median OS of the ZUMA-3 cohorts was about 25 months and the matched HCT cohorts showed about one fifth of that duration for median OS [48, 49].

OS zwischen ~50–70 % nach 2 Jahren

ZUMA-3: OS ~25 M. Kontrollen: OS ~5 M.

The **EFS** was reported for the German and UK observational cohorts and was approximately 50 % or slightly lower [46, 47]. In the Oporto Espuelas study a higher disease burden was associated with worse EFS.

EFS: ~50 % (UK & DE) höhere Tumorlast und schlechtere EFS

After 20.8 months about one third of the 81 patients treated with tisagenlecleucel in German centers suffered a **relapse** [46]. Other relapse rates were not specifically reported.

Rezidiv: ~1/3 nach 20,8 M. (DE)

About half of the patients in the German Bader et al. (2023) cohort showed **RFS**. The comparative studies only reported the median RFS rates for the ZUMA-3 cohorts, which were around 10 and 11 months [48, 49].

RFS: ~50 % (DE); ZUMA-3: 10–11 M.

HRQoL was not analyzed in the included studies. Effectiveness outcomes of the four included publications are presented in Table 8.

HRQoL nicht berichtet, Outcomes in Tabelle 8

*Table 8: Results on effectiveness outcomes of included studies for patients with **ALL***

Study ID (first author, year)	Bader, 2023	Minnema, 2024	Oporto Espuelas, 2024	Shah, B. D., 2022
CR	-Day 28: 87.8% -20.8 months: 59% of them remained in remission	*CAR-T: 72.1%* (95% CI, 56-85)	-Day 30: 92% -23.3 months: 40%	*CAR-T: 70.9%* (95% CI, 57–82)
OS	53.2%	Median OS: *CAR-T: 25.4 months* HCT: 6.2 months	70% (95% CI, 61.7-79.4)	Median OS: *CAR-T: 25.4 months* HCT: 5.5 months
EFS	Probability EFS: 45.3%	NR	51,7% (95% CI, 42.1-63.5)	NR
Relapse	37%	NR	NR	NR
PFS/RFS	RFS: 51.7%	Median RFS: *CAR-T:* *10.3 months*	NR	Median RFS: *CAR-T: 11.6 months* (95% CI, 2.7-20.5)

Abbreviations: *CR: complete response; EFS: event free survival; HCT: historical control trial; NR: not reported; OS: overall survival; PFS: progression free survival; RFS: relapse free survival; SoC: standard of care;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.3.3 Safety outcomes

Three publications reported new safety outcomes, although the comparative analysis only refers to the pivotal trial data.

3 Publikationen zu Sicherheit

The overall rates for **CRS** in the observational studies were around 77 % and 86 %, with around 6 % and 13 % having severe grade 3 or higher [46, 47]. In the Bader et al. (2023) publication, no difference was seen in safety outcomes between patients who were pretreated with aHSCT or without. The subgroup analysis of patients aged 26 years or older from the ZUMA-3 trial showed rates

CRS: 77–86 %, schwer: 6–13 %

keine Unterschiede bei Vorbehandlung

of grade 3 or higher CRS and neurotoxicity in slightly more than 20 % of cases [48].

The prevalence of **ICANS** in the observational cohorts ranged from about 7 % to 21 % of treated patients, with less than 10 % having a grade 3 or higher [46, 47].

ICANS: 7–21 %, schwer <10 %

The **TRM** was reported only in the German cohort. Less than 5 % of the infused and responding patients died while in remission due to neurotoxicity and infection.

TRM <5 % (nur DE)

Other **AE** were reported in the UK cohort, where around two-thirds of infused patients had cytopenias and around one-third had infections [47]. Nearly 90 percent of the ZUMA-3 subgroup had a brexucabtagene related treatment-emergent adverse event [48].

UK: ⅔ mit Zytopenie, ⅓ mit Infektionen
ZUMA-3: 90 % AE behandlungsbedingt

Safety outcomes of the publications reporting results are presented in Table 9.

Sicherheitsergebnisse in Tabelle 9

*Table 9: Results on safety outcomes of included studies for patients with **ALL***

Study ID (first author, year)	Bader, 2023	Minnema, 2024	Oporto Espuelas, 2024
CRS	67.9% Grade ≥3: 6.2%	CAR-T: Grade ≥3: 23%	86.2% Grade ≥3: 13%
Neurotoxicity/ neurologic events	NR	*CAR-T:* *Grade ≥3: 21%*	NR
ICANS	7.4% Grade ≥3: 4.9%	NR	21.1% Grade ≥3: 8.1%
TRM	2.5% (2 patients)	NR	NR
Other severe AE	NR	TEAE: Brexucel related: 88%	-Cytopenias: 58.9% -Infections: 28.5%

Abbreviations**: AE: adverse events; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; NR: not reported; TEAE: treatment emergent adverse events; TRM: treatment-related mortality; **results of CAR-T cohorts from pivotal trials are written in italics

3.4 Real-world evidence of CAR-T treatment among patients with large B-cell lymphoma

The identified relevant LBCL studies included patients with DLBCL, DLBCL NOS, HGBCL, PMBCL and tFL.

eingeschlossene Studien: DLBCL, NOS, HGBCL, PMBCL, tFL

3.4.2 Characteristics of included studies

Eight publications could be identified during the selection process that are relevant to LBCL and of interest for an update of current RWE. These include five RWE observational studies of CAR-T treatment with tisagenlecleucel or axicabtagene. One of them has a prospective design [50] and one of them has a mixed retrospective and prospective design [51]. The others were carried out retrospectively [52-54].

8 LBCL-relevante Studien

5 Beobachtungsstudien

The three other publications are comparative studies of CAR-T treatment with axicabtagene, tisagenlecleucel or lisocabtagene and conventional care [55], previous SoC [56] or chemoimmunotherapy [57].

3 Vergleichsstudien zu mehreren Produkten/SoC

The non-comparative cohorts included patients from centers in Canada [52], Japan [53], the Netherlands [51] and one center in the US [54] and data from the Center for International Blood and Marrow Transplant Research registry (CIBMTR). The PASS study from the CIBMTR included data from 79 centers in the US, with 57 % of the patients ineligible for inclusion in the pivotal ZUMA-1 trial [50]. The 66 patients from the single center analysis from San Diego, US might also be included in the CIBMTR study cohort. The Canadian study focused on refractory diseases and the single US study included patients aged 70 and older and with poor ECOG status.

RWE-Kohorten: Kanada, Japan, NL, USA

CIBMTR: 79 US-Zentren

US-Studie: Alter ≥70, schlechter ECOG

The comparative study from Bastos-Oreiro et al. (2022) used real-world data from CAR-T centers in Spain and a synthetic control arm (GELTAMO-IPI) with a historical cancer population, including patients with DLBCL and treated with previous SoC. The comparative study from Lunning et al. (2024) used the same real-world database as Jacobson et al. (2022) from the PASS CIBMTR registry study, but with a longer follow-up period. They compared axicabtagene treatment in the PASS study with chemoimmunotherapy treatment results in the SCHOLAR-1 cohort, which is an international retrospective cohort. The third comparative study from Van Le et al. (2023) compared lisocabtagene treatment with non-CAR-T conventional care treatment results from a retrospective and observational real-world study with patients from the US and Europe in a synthetic control arm. Data for lisocabtagene treatment were from the clinical TRANSCEND NHL 001 trial.

3 Vergleichsstudien: Spanien: axicabtagene vs. SoC (GELTAMO-IPI)

PASS CIBMTR: axicabtagene vs. SCHOLAR-1

TRANSCEND: lisocabtagene vs. konventionelle Therapie (USA/EU)

In total, 2031 patients treated with CAR-T cells and 803 patients treated with non-CAR-T cell therapies from 10 cohorts (n=2834) were evaluated across the eight studies.

8 Studien: 2031 CAR-T vs. 803 Nicht-CAR-T Pts.

Within all cohorts most patients suffered from DLBCL or DLBCL NOS. The median number of prior therapy lines ranged from 2 to 3 lines. The median age ranged from 55 years to 63 years. Median follow up time differed from 5.3 months to 93 months in all publications. The specified endpoints of the studies were ORR, OS, PFS, EFS, CR, HRQoL and safety outcomes. All included patients had a relapsed or refractory disease [50-57].

meist DLBCL/NOS mit mind. 2 Vorbehandlungen

Alter: 55-63 J.; alle mit r/r Erkrankung

Study characteristics of the eight included publications are presented in Table 10.

Details in Tabelle 10

The quality of the five real-world observational single-arm studies was rated for two of them as fair and for three of them as poor. Reasons were short follow-up times, data from single institutions with small sample sizes or potentially different outcome measures, when data came from different centers.

Qualität: mittel-niedrig
Gründe: kurzer Follow-up, kleine Fallzahlen, heterogene Outcomes

The overall risk of bias was classified as critical across all comparative studies. The main reasons for this were bias due to confounding, due to the selection

RoB in Vergleichsstudien durchgängig kritisch

of participants into the studies and due to the measurement of outcomes. The other domains were rated ranging from critical to moderate in the assessment, with a majority of critical and serious ratings.

Quality and risk of bias assessment is presented in the Appendix in Table 27 and Table 31.

Qualitäts- und RoB-Bewertung im Anhang

*Table 10: Main characteristics of included studies for patients with **LBCL***

Study ID (first author, year)	Bastos-Oreiro, 2022	Benoit, 2022	Goto, 2023	Jacobson, 2022
Study design	-Comparative, retrospective, RWE -Two CAR-T therapies with previous SoC	Retrospective, Observational, RWE	Retrospective, RWE	Prospective, observational, RWE
n	CAR-T: 192 Axicel: 101 Tisacel: 91 SoC: 81	25 Axicel: 15 Tisacel: 10	89	1297
Primary and secondary endpoints	PFS, OS, Safety	ORR, PFS, Safety	OS, EFS, ORR, Safety	ORR, CR, PFS, OS, Safety
Median Age (years)	CAR-T: 55 SoC: 62	63	59	62.1
Median prior therapy lines	CAR-T: 2 SoC: 2	2	Most had: 3L	3
Median follow up (months)	CAR-T: 11 SoC: 93	Axicel: 5.3 Tisacel: 11.2	6.6	12.9
Disease stage	R/R	R/R	R/R	R/R
Other patient characteristics	-Most patients with DLBCL -according to Scholar-1 criteria -SoC: historical population of R/R DLBCL patients	-Most patients with DLBCL, -Focus on refractory diseases	Patients with DLBCL (79.8%) and tFL (20.2%)	-57% ineligible for ZUMA-1 inclusion, -Patients in clinical trials or expanded access programs not eligible -Patients with DLBCL (79%), PMBCL (3%) or HGBCL (16%)
Patient population/ underlying studies and trials	-8 centers in Spain -GELTAMO-IPI (1998-2014)	-Single center in Canada	-Centers in Japan	-CIBMTR registry -78 centers -PASS
CAR-T product	-Axicabtagene, -Tisagenlecleucel	-Tisagenlecleucel, -Axicabtagene	Tisagenlecleucel	Axicabtagene
Study ID (first author, year)	Lunning, 2024	Spanjaart, 2023	Trando, 2023	Van Le, 2023
Study design	-Comparative observational, RWE -Subgroup analysis: Axicel and chemoimmunotherapy (CIT) -PSM	-Retro and prospective, RWE	-Retrospective, RWE	-Comparative, retrospective - CAR-T and conventional care treatment (CC) with synthetic non-CAR-T control arm -MAIC
n	CAR-T: 1146	CAR-T:	66	*CAR-T: 257*

	CIT: 469 After PSM: Response: CAR-T: 493 CIT: 289 Survival: CAR-T: 659 CIT: 406	145		CC: 257
Primary and secondary endpoints	ORR, CR, OS	ORR, CR, OS, HRQoL, Safety	ORR, CR, Safety	ORR, CR, OS, PFS
Median Age (years)	CAR-T: 62.3 CIT: 55.4	60	59.5	*CAR-T: 63* CC: 62
Median prior therapy lines	CAR-T: 3 CIT: 2	2	3	*CAR-T: 3* CC: 3
Median follow up (months)	CAR-T: 24.5 CIT: 59.8	13.0	16.3	*CAR-T: 17.4* CC: 6.3
Disease stage	R/R	R/R	R/R	R/R
Other patient characteristics	-Patients with DLBCL (92% and 95%), PMBCL (4% and 2 %), tFL (5% and 3 %) -Older patients (aged ≥65) or patients with poor ECOG PS = 2, -≥2 lines of prior therapy	-Adults with DLBCL (50%), tFL (33%), HGBCL (14%), PMBCL (3%) - After ≥2 lines of systemic therapy,	-21% ≥70 years -20% ECOG status ≥ 2 or -DLBCL (56%)	-TRANSCEND: DLBCL NOS: 51% -Real-world cohort: DLBCL NOS: 60% (CC)
Study ID	**Lunning, 2024**	**Spanjaart, 2023**	**Trando, 2023**	**Van Le, 2023**
Patient population/ underlying studies and trials	-79 centers in the US -PASS (prospective CIBMTR research study) - SCHOLAR-1 (international retrospective cohort for CIT treatment)	-CAR-T Tumorboard Netherlands -Multicenter	-Single Institution in California, San Diego, US	*-TRANSCEND NHL 001* -DS-NHL-001 (real-world cohort from US and Europe, retrospective observational study)
CAR-T product	Axicabtagene	Axicabtagene	-Tisagenlecleucel (11%) -Axicabtagene (89%)	Lisocabtagene

Abbreviations: 3L: three lines of therapy; CC: conventional care; CIBMTR: Center for International Blood and Marrow Transplant Research; CIT: chemoimmunotherapy; CR: complete response; DLBCL: diffuse large B-cell lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: event free survival; HGBCL: high-grade B-cell lymphoma; HRQoL: health related quality of life; MAIC: matching-adjusted indirect comparison; n: number of participants; ORR: overall response rate; OS: overall survival; PASS: post-authorisation safety study; PFS: progression free survival; PMBCL: primary mediastinal large B-cell lymphoma; PSM: propensity score matching; R/R: relapsed/refractory; RWE: real-world evidence; SoC: standard of care; tFL: transformed follicular lymphoma; US: United States; ***results of CAR-T cohorts from pivotal trials are written in italics***

3.4.4 Effectiveness outcomes

All non-comparative studies reported response outcomes. The **ORR** in the cohorts with follow-up periods of less than one year was around one third and the CR rates were between 24 % and 55 %. For both outcomes of the Canadian cohort, treatment with axicabtagene was associated with higher response rates compared to tisagenlecleucel treatment [52, 53]. The non-comparative studies with follow-up periods of more than one year showed higher response rates. The ORR ranged between 67 % and 84 % and the CR rate ranged between 53 % and 66 % [50, 51, 54].

Kanada: axicabtagene mit höheren Ansprechraten als tisagenlecleucel

unter 1 Jahr Follow-up:
ORR 67–84 %,
CR 53–66 %

Two comparative studies reported response rate outcomes. The reported ORR in the CAR-T cell cohorts was approximately 75 %, compared to less than 40 % in the chemoimmunotherapy and conventional care real-world cohorts. The CR rates in the CAR-T cohorts were between 50 % and 60 %, compared to less than 25 % in the CIT and CC [55, 57].

Vergleich: ORR ~75 % (CAR-T) vs. <40 % (CIT/CC)
CR: 50–60 % (CAR-T) vs. <25 % (CIT/CC)

Patients from the Lunning et al. (2024) cohort and treatment with axicabtagene had a significantly higher ORR and CR compared to patients treated with CIT.

axicabtagene mit signifikant höherem ORR

The 12-month **OS** in four real-world CAR-T cohorts ranged from 55 % to 67 % [51, 53, 56, 57] and in one study around half of the patients had an OS after 24 months [50]. The reported median OS in four real-world CAR-T cohorts was between 15 and 28.4 months [50, 51, 54, 56]. Data from the single center US cohort indicated that patients who relapse after CAR-T treatment have poor outcomes with a median OS reduction from 28.4 months to 4.8 months. About half of the cohort died at the time of data cut-off, largely due to lymphoma progression.

RWE: CAR-T
12-Monats-OS:
55–67 %
24-Monats-OS: ~50 %

medianes OS:
15–28,4 M

The comparative studies reported median OS rates of 15 and 23.5 months in the CAR-T groups, compared with rates of less than 10 months in the SoC and CC groups. The 12-month OS rate was 55 % or higher in the CAR-T groups, compared to around one third in the SoC and CIT groups [55-57]. In the comparative analysis from Lunning et al. (2024), axicabtagene was associated with a longer OS.

Vergleichsstudien:
OS (median):
CAR-T 15–23,5 M. vs. SoC/CC <10 M.
12-M.-OS: ≥55 % (CAR-T) vs. ~33 % (SoC/CIT)

Individual **relapse** rates were not reported in the selected studies. The **EFS** rate was only reported in one publication. Almost half of the Japanese cohort had a 12-month EFS. In general, the study found that patients with a high tumor volume had a poorer prognosis [53].

EFS: ~50 %, 12 M. (JP)
hohe Tumorlast = schlechtere Prognose

The median **PFS** rate in five real-world CAR-T cohorts ranged from 2.8 months to 10.3 months with reported 6-month rates from 21 % to 42 %, 12-month rates from 37 % to 48 % and one 24-months rate of 39.2 % [50-52, 54-56]. In the cohort from the Trando et al. (2023) study, the PFS rate for patients with an ECOG PS of 0–1 was significantly longer, compared to patients with a worse ECOG PS of 2-4 (HR 2.49, 95% CI, 1.23–5.05; p = 0.009).

PFS median:
2,8–10,3 M.
6-M.: 21–42 %, 12-M.: 37–48 %, 24-M.: 39 %
besseres ECOG = längeres PFS

One study reported **HRQoL** outcomes. The study from Spanjaart et al. (2023) assessed the HRQoL score from 45 CAR-T cell treated patients. Initially, a worsening of the score was noted one month after treatment. However, clinical improvements in the overall health domain were observed from month 9 onwards. Clinically meaningful improvements were observed in the emotional functioning and physical functioning domain at month 12. Howver, not all patients participated in all follow-up points due to disease progression, death or logistical challenges.

HRQoL (n=45):
Verschlechterung nach 1. M.,
Besserung nach 9.M.

Verbesserung bei physischer & emotionaler Funktion

Effectiveness outcomes of the eight included publications are presented in Table 11.

Details zu Outcomes in Tabelle 11

*Table 11: Results on effectiveness outcomes of included studies for patients with **LBCL***

Study ID (first author, year)	Bastos-Oreiro, 2022	Benoit, 2022	Goto, 2023	Jacobson, 2022
CR	NR	-3-months: 24% Tisacel: 10% Axicel: 33%	55%	55.5% (95% CI, 53 -58)
ORR	NR	-3-months: 36% Tisacel: 20% Axicel: 47%	NR	73% (95% CI, 71% -75%)
OS	-Median OS: CAR-T: 15 months SoC: 8.2 months (95%CI, 6.6-9.9) -12-months: CAR-T: 55% SoC: 36%	NR	12-months: 67% (95% CI, 54.3-76.9)	-Median OS: 21.8 months (95% CI, 17.4 - 28.8) -24-months: 49.5%
EFS	NR	NR	12 -months: 46.3% (95% CI, 34.5-57.2)	NR
PFS/RFS	-Median PFS: CAR-T: 5.6 months (95% CI, 3.7-7.5) SoC: 4.6 (95%CI, 1.5-7.7) -12-months PFS: CAR-T: 37% SoC: 22%	-Median PFS: Tisacel: 2.8 months Axicel: 3.2 months -6-months PFS: Tisacel: 21% Axicel: 42%	NR	-Median PFS: 8.6 months (95% CI, 6.5- 12.1) -24-months: 39.2%
HRQoL/ QoL	NR	NR	NR	NR
Study ID (first author, year)	Lunning, 2024	Spanjaart, 2023	Trando, 2023	Van Le, 2023
CR	-CAR-T: 58% -CIT: 16% - CAR-T significant higher CR (OR: 6.07; 95% CI, 4.15–8.86)	66%	53%	*CAR-T: 50.1%* CC: 24.1%
ORR	-CAR-T: 76% -CIT: 28% -CAR-T significant higher ORR (OR: 7.73; 95% CI, 5.21–11.45)	84%	67%	*CAR-T: 73.8%* CC: 38.8%
OS	12-months: CAR-T: 62% (95% CI, 58–66) CIT: 28% (95% CI, 24–33)	-Median OS: 31.9 months -12-months: 62.2% (95% CI: 54.7–70.7)	-Median OS: 28.4 months -Median OS after CAR-T cell therapy relapse: 4.8 months	Median OS: *CAR-T: 23.5 months* CC: 6.8 months

	-CAR-T associated with longer OS (HR: 0.30 95% CI, 0.24-0.37)			
EFS	NR	NR	NR	NR
PFS/RFS	NR	-Median PFS: 9.4 months -12-months PFS: 48% (95% CI: 40.5–56.9)	Median PFS: 10.3 months	Median PFS: *CAR-T: 3.5 months* CC: 2.2 months
HRQoL/ QoL	NR	-n= 45 -Worsening HRQoL score at months 1 -clinically improve-ments in some domains from month 9 onwards (overall health) -clinically meaningful improvements at months 12 (emotional functioning, physical functioning)	NR	NR
Study ID (first author, year)	Lunning, 2024	Spanjaart, 2023	Trando, 2023	Van Le, 2023
CR	-CAR-T: 58% -CIT: 16% - CAR-T significant higher CR (OR: 6.07; 95% CI, 4.15–8.86)	66%	53%	*CAR-T: 50.1%* CC: 24.1%
ORR	-CAR-T: 76% -CIT: 28% -CAR-T significant higher ORR (OR: 7.73; 95% CI, 5.21–11.45)	84%	67%	*CAR-T: 73.8%* CC: 38.8%
OS	12-months: CAR-T: 62% (95% CI, 58–66) CIT: 28% (95% CI, 24–33) -CAR-T associated with longer OS (HR: 0.30 95% CI, 0.24-0.37)	-Median OS: 31.9 months -12-months: 62.2% (95% CI: 54.7–70.7)	-Median OS: 28.4 months -Median OS after CAR-T cell therapy relapse: 4.8 months	Median OS: *CAR-T: 23.5 months* CC: 6.8 months
EFS	NR	NR	NR	NR
PFS/RFS	NR	-Median PFS: 9.4 months	Median PFS: 10.3 months	Median PFS: *CAR-T: 3.5 months* CC: 2.2 months

		-12-months PFS: 48% (95% CI: 40.5–56.9)		
HRQoL/ QoL	NR	-n= 45 -Worsening HRQoL score at months 1 -clinically improvements in some domains from month 9 onwards (overall health) -clinically meaningful improvements at months 12 (emotional functioning, physical functioning	NR	NR

Abbreviations: *CC: conventional care; CIT: chemoimmunotherapy; CR: complete response; EFS: event free survival; HR: hazard ratio; HRQoL: health related quality of life; NR: not reported; OR: odds ratio; ORR: overall response rate; OS: overall survival; PFS: progression free survival; QoL: quality of life; RFS: relapse free survival; SoC: standard of care;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.4.5 Safety outcomes

Six studies reported safety outcomes for real-world CAR-T cohorts. The occurrence of **CRS** (all grades) was reported to range from 60 % to 92 %. The frequency of severe (grade 3 or higher) CRS was between 2% and 8% [50-54, 56]. In the Spanish cohort **neurotoxicity** occurred in around one third of the cases and in 11 % of the cases as severe grade 3 or higher. In the other cohorts the incidence of **ICANS** was assessed. The occurrence of ICANS (all grades) after CAR-T treatment was reported with a wide range. Incidence rates were between 5.6 % and 56 %. Rates for the severe grade 3 or higher were between 1.1 % and 26 % within the different cohorts and treatment products.

CRS (alle Grade): 60–92 %, schwer: 2–8 %

Neurotoxizität (ES): ~33 %, schwer: 11 %

ICANS: 5,6–56 %, schwer: 1,1–26 %

TRM was only reported in one study. In the San Diego, US cohort 4 of 66 patients died due to treatment-related causes. Other reported severe **AE** refer to hematological toxicities and disorders and infections. Most treated patients suffered from cytopenia, neutropenia, thrombocytopenia and anemia in relation to hematological disorders. In the largest cohort of the CIBMTR study, cytopenia occurred in 24 % of cases, neutropenia in 7 % of cases and thrombocytopenia in 22 % of cases. Clinically significant infections occurred in 45 % of cases. Similar infection rates were reported in other studies. In the San Diego, US cohort the infection rate in patients over 70 years was nearly twice as high.

TRM in 1 Studie: 4/66 Pts.

CIBMTR-AEs: Zytopenie (24 %), Neutropenie (7 %), Thrombozytopenie (22 %) Infektionen (45 %)

Safety outcomes of the publications reporting results are presented in Table 12.

Sicherheitsoutcomes in Tabelle 12

*Table 12: Results on safety outcomes of included studies for patients with **LBCL***

Study ID (first author, year)	Bastos-Oreiro, 2022	Benoit, 2022	Goto, 2023	Jacobson, 2022	Spanjaart, 2023	Trando, 2023
CRS	CAR-T: Any grade: 78% Grade ≥3: 6%	-Axicel: 87% -Tisacel: 60%	Any grade: 89.9% Grade ≥3: 6.7%	Any grade: 83% Grade ≥3: 8%	Any grade: 92% Grade ≥3: 5%	Any grade: 88% Grade ≥3: 2%
Neurotoxicity/ neurologic events	CAR-T: Any grade: 29% Grade ≥3: 11%	NR	NR	NR	NR	NR
ICANS	NR	-Axicel: 40% -Tisacel: 30%	Any grade: 5.6% Grade ≥3: 1.1%	Any grade: 55% Grade ≥3: 24%	Any grade: 62% Grade ≥3: 22%	Any grade: 56% Grade ≥3: 26%
TRM	NR	NR	NR	NR	NR	6% (4 of 66 died)
Other severe AE	NR	Hematological toxicities grade ≥3: -Axicel: 60% -Tisacel: 20%	Most common AE between day 1 and 30 after infusion: CMV, sepsis and bacteremia	-Clinically significant infections: 45% -Cytopenia: 24% -Neutropenia: 7% -Thrombocyto-penia: 22%	-ICU: 14% -Infections: 43% Month 3: -Thrombocyto-penia: 45% -Anemia: 73% -Neutropenia: 47%	-Infections: 48% >70 years: 79% -Anemia: 100% Grade ≥3: 68% -Neutropenia: 100% Grade ≥3: 100% -Thrombocyto-penia: 100% Grade ≥3: 61%

Abbreviations: *AE: adverse events; CMV: cytomegalovirus; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neu rotoxicity syndrome; ICU: intensive care unit; NR: not reported; TRM: treatment-related mortality*

3.6 Real-world evidence of CAR-T treatment among patients with follicular lymphoma

3.6.1 Characteristics of included studies

Three publications could be identified during the selection process that are FL relevant and of interest for an update of current RWE. All of them are comparative and retrospective studies, comparing CAR-T cell treatment outcomes of pivotal and clinical single-arm trials with real-world outcomes of non-CAR-T cell treatment. The analyzed CAR-T cohorts were from the pivotal ELARA trial, which evaluated tisagenlecleucel treatment and the pivotal ZUMA-5 trial, which evaluated axicabtagene treatment. The ELARA cohort included 97 CAR-T cell treated patients and the ZUMA-5 cohort 86 CAR-T cell treated patients. The ELARA database was used in two comparative analyses with different cohorts for standard and usual real-world care. The Hao et al. (2023) study used data for SoC from the US Flatiron Health Research Database (FHRD), including 280 clinics in the US. The Salles et al. (2022) study used data from the ReCord-FL study, which is a global study with data from ten centers in North America and Europe. An overlap of the cohorts of the comparison groups for non-CAR-T therapy is therefore possible. The comparative study of CAR-T outcomes from ZUMA-5 used data for SoC from the external multi-country SCHOLAR-5 cohort [58]. The number of patients in the non-CAR-T cell treatment cohorts was weighted and ranged from 85 to 99. The analyzed endpoints in the studies were CR, ORR, OS, PFS and EFS. Safety outcomes were not analyzed. Median age ranged from 56.1 to 62 years and the median lines of prior therapy ranged from 3 to 4. Median follow up time ranged from 15 to 29.4 months for the CAR-T cohorts and from 13.6 to 57 months for non-CAR-T treatment cohorts. The disease stage from all included patients was relapsed or refractory [58-60].

3 FL-Vergleichsstudien: Update von RWE

CAR-T-Kohorte: ELARA; ZUMA-5

Kontrollen aus FHRD, ReCORD-FL, SCHOLAR-5
n: 85–99 (gewichtet), medianes Alter: 56–62 J.

Vorbehandlung: 3-4 Linien

Follow-up:
CAR-T: 15–29 M.
Nicht-CAR-T: 14–57 M.

Sicherheit nicht berichtet

In total, 183 pivotal trial patients treated with CAR-T cells and 273 patients treated with non-CAR-T cell therapies from 5 cohorts (n=456) were evaluated across the three comparative studies.

3 Studien: 183 CAR-T (pivotal) vs. 273 Nicht-CAR-T (5 Kohorten)

Study characteristics of the three included publications are presented in Table 13.

Studiendetails: Tabelle 13

The overall risk of bias of the three comparative studies was classified and rated as critical. Due to the retrospective design and the comparison of clinical studies with real-world data, the confounding was inherently uncontrollable. The RoB domains in the assessment for the studies were rated from moderate to critical , with a majority rated as critical and serious.

RoB in allen FL-Studien kritisch
RoB-Domänen: mehrheitlich kritisch oder schwerwiegend

The risk of bias assessment is presented in the Appendix in Table 32.

RoB-Assessment im Anhang

*Table 13: Main characteristics of included studies for patients with **FL***

Study ID (first author, year)	Hao, 2023	Palomba, 2023	Salles, 2022
Study design	-Comparative, retrospective - CAR-T and non-CAR-T real-world SoC -MAIC	-Comparative, retrospective -CAR-T and non-CAR-T real-world SoC -SMR weighting	-Comparative, retrospective -CAR-T and non-CAR-T real-world SoC
n	*CAR-T: 97* SoC: 89 (weighted)	*CAR-T: 86* SoC: 85 (weighted)	*CAR-T: 97* SoC: 99 (weighted)
Primary and secondary endpoints	CR, ORR, OS, PFS	PFS, OS, ORR, CR,	CR, ORR, PFS/EFS, OS,
Median Age (years)	*CAR-T: 58* SoC: 55	*CAR-T: 62* SoC: 61	*CAR-T: 56.5* SoC: 56.1
Median prior therapy lines	NR	Both: 3	*CAR-T: 4* SoC: 4
Median follow up (months)	*CAR-T: 15.1* SoC: 13.6	*CAR-T: 29.4* SoC: 25.4	*CAR-T: 15* SoC: 57
Disease stage	R/R	R/R	R/R
Other patient characteristics		-≥3L of therapy -Scholar patients meeting Zuma eligibility criteria	
Patient population/ underlying studies and trials	*-ELARA Phase 2* (pivotal trial) -US Flatiron Health Research Database (FHRD) (280 clinics in US)	*-ZUMA-5* -SCHOLAR-5 (external multi-country control cohort)	*-ELARA Phase 2* -ReCord-FL (global retrospective study with usual care, 10 centers in North America and Europe)
CAR-T product	Tisagenlecleucel	Axicabtagene	Tisagenlecleucel

Abbreviations: *CR: complete response; EFS: event free survival; MAIC: matching-adjusted indirect comparison; n: number of participants; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; R/R: relapsed/refractory; SMR: standardized mortality ratio; SoC: standard of care; US: United States;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.6.2 Effectiveness outcomes

CR/ORR/OS in allen FL-Vergleichsstudien

Follow-up: ~1–5 J.

All comparative studies analyzed CR, ORR and OS outcomes. The **ORR** in the studies was for the pivotal trial CAR-T cohorts (ELARA and ZUMA-5) between 85.6% and 94.2 %, compared to 50% to 60% in the SoC cohorts. The **CR** rate in the studies was between 70% and 80% in the pivotal trial cohorts, while it was 20% to 40% in the SoC cohorts. The median follow-up periods ranged from around one to five years [58-60].

24-Monats-OS:
ELARA: CAR-T ~90 %, SoC 65–80 %
ZUMA-5: CAR-T ~80 %, SoC ~20 %

The **OS** rate was reported in all studies for the 24-month time point. In studies that analyzed the ELARA results, the OS was nearly 90% for CAR-T cell treatment and around 65% and 80% in the comparative cohorts for SoC treatments [59, 60]. In the study that analyzed the ZUMA-5 results, the OS for CAR-T cell treatment was around 80% and in the comparative study for SoC treatment about 20%[58].

The study from Salles et al. (2022) reported **EFS** or **PFS** outcomes. The rates at 24 months were 54.1% in the CAR-T cohort, compared to around ten percent less in the SoC cohort. The study from Hao et al. (2023) reported an estimated 24-month PFS rate. The rate in the CAR-T cohort was reported at 56.1 % and in the SoC cohort as about half. The study from Palomba et al. (2023) reported a median PFS and a 24-month PFS. The median PFS was 39.6 months in the CAR-T cohort and about a quarter of that in the SoC cohort. The 24-month PFS in the CAR-T cohort was reported at 59 %, compared to 5.7 % in the SoC cohort.

24-Monats-PFS:
CAR-T 54 %, SoC~44 %
CAR-T 56 %, SoC~28 %

median PFS 40 M. (CAR-T), SoC ~10 M.
24-Monats-PFS:
59 % vs. 5,7 %

Individual **relapse** rates and **HRQoL** outcomes were not reported in the selected studies.

keine Angaben zu Rückfallraten; HRQoL

Effectiveness outcomes of the three included publications are presented in Table 14.

Details in Tabelle 14

*Table 14: Results on effectiveness outcomes of included studies for patients with **FL***

Study ID (first author, year)	Hao, 2023	Palomba, 2023	Salles, 2022
CR	*CAR-T: 69.1 %* (95% CI, 59.8-78.4) SoC: 17.7% (95% CI, 3.8-46.9)	*CAR-T: 79.1%* SoC: 29.9%	*CAR-T: 69.1%* (95% CI, 59.8-78.3) SoC: 37.3% (95% CI, 26.4-48.3)
ORR	*CAR-T: 85.6 %* (95% CI, 78.4 – 91.8) SoC: 58.1% (95% CI, 21.3-88.2)	*CAR-T: 94.2%* SoC: 49.9%	*CAR-T: 85.6%* (95% CI, 78.7-92.5) SoC: 63.6 % (95% CI, 52.5-74.7)
OS	24-months OS: *CAR-T 87.8%* (95% CI, 77.3-96.2) SoC: 79.1% (95% CI, 58.5-92.5)	24-months: *CAR-T: 81.2%* SoC: 63.4%	24-months: *CAR-T: 87.8%* (95% CI, 78.0-97.6) SoC: 64.8% (95% CI, 53.3-76.2)
EFS	NR	NR	EFS or PFS 24 months: *CAR-T: 54.1%* (95% CI, 41.2, 66.9) SoC: 42.2 % (95% CI, 31.0, 53.5)
PFS/RFS	Estimated 24 months PFS: *CAR-T: 56.1%* (95% CI, 41.8-68.9) SoC: 26.2% (95% CI, 8.1-52.0)	Median PFS: *CAR-T: 39.6 months* SoC: 12.7 24 months PFS: *CAR-T: 59 %* (95% CI, 44.5–71.0) SoC: 5.7% (95% CI, 0.0–12)	NR

Abbreviations: *CR: complete response; EFS: event free survival; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RFS: relapse free survival; SoC: standard of care;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.6.3 Safety outcomes

None of the three comparative studies analyzed safety outcomes for patients with FL.

keine Sicherheitsdaten für FL in Vergleichsstudien

3.7 Real- world evidence of CAR-T treatment among patients with mantle cell lymphoma

3.7.1 Characteristics of included studies

Three publications could be identified during the selection process that are MCL relevant and of interest for an update of current RWE. One indirect comparative retrospective study, evaluating CAR-T cell treatment outcomes of the ZUMA-2 pivotal trial and the real-world outcomes of treatment with non-CAR-T SoC from an external European cohort was included. The majority of the ZUMA-2 cohort were from the US and three weighting methods were used to match the cohorts [61]. The two other included publications are real-world observational studies with an ITT analysis by O´Reilly et al. (2024), including a subgroup analysis of CAR-T cell-infused patients and a retrospective data collection. The patient data were from 12 institutions from the UK. The other study by Wang, Y. et al. (2023) is a retrospective analysis of standard practice with CAR-T cell treatment. The data came from the US Lymphoma CAR-T Consortium, which included 12 US institutions. 65 % of the included cohort were not eligible for the ZUMA-2 pivotal trial. All publications examined the CAR-T product brexucabtagene, the only CAR-T product approved by the EMA for the treatment of MCL.

3 MCL-Studien eingeschlossen

1 Vergleichsstudie: ZUMA-2 vs. externes europäisches SoC

2 RWE-Studien: UK (O'Reilly), USA (Wang)

65 % nicht ZUMA-2-geeignet

behandeltes Produkt: brexucabtagene

Primary and secondary endpoints examined in the studies were OS, ORR, CR, PFS, and safety outcomes. The median age of the cohorts treated with CAR-T cells ranged from 63.2 to 68 years and was 69.5 years in the SoC cohort. The median of the previous treatment lines was 2 or 3 in the CAR-T cohorts and 3 in the SoC cohort. The median follow-up periods of the non-comparative studies were 13.3 and 14.3 months. The median follow-up time of the ZUMA-2 cohort in the comparative study was 35.8 months compared to 27.6 months in the SoC cohort. The disease stage of all included patients was relapsed or refractory [61-63].

OS, ORR, CR, PFS, Sicherheit

Alter: CAR-T 63–68 J., SoC ~69,5 J. Vorbehandlungen: 2–3 L.

alle Pts. = r/r

In total, 319 patients treated with CAR-T cells, including 68 patients from the ZUMA-2 pivotal trial and 60 patients treated with non-CAR-T cells, were analyzed across the three studies with a total of 4 cohorts (n=379).

3 Studien (n=379) CAR-T: 319 SoC: 60

Study characteristics of the three included publications are presented in Table 15.

Studiendetails in Tabelle 15

The quality of the two real-world observational single-arm studies was rated as fair for one of them and poor for the other. Bias can result from different definitions of outcomes and different measurement methods.

RWE- Studien: Qualität moderat - schlecht

The overall risk of bias was classified as critical in the comparative study. In addition to the risk of bias due to the retrospective design, the cohorts have very different median follow-up times and substantial follow-up time was likely missing. This resulted in a critical rating in the domain for bias due to

RoB kritisch

retrospektiv, unterschiedliche Follow-ups, fehlende Daten

missing data. The other domains were rated from critical to moderate in the assessment, with a majority of critical and serious ratings.

Quality and risk of bias assessment is presented in the Appendix in Table 28 and Table 33.

Qualitäts- und RoB-Bewertung im Anhang

*Table 15: Main characteristics of included studies for patients with **MCL***

Study ID (first author, year)	Hess, 2024	O'Reilly, 2024	Wang, Y., 2023
Study design	-Comparative, retrospective -Indirect comparison of CAR-T and SoC treatment -Three weighting methods	-Retrospective data collection, ITT analysis with analysis of CAR-T infused patients, RWE	Retrospective SoC practice
n	*CAR-T: 68* SoC: 60	CAR-T: 83	168
Primary and secondary endpoints	OS	ORR, OS, PFS, Safety	ORR, CR, PFS, Safety
Median Age (years)	*CAR-T: 63.2* SoC: 69.5	68	67
Median prior therapy lines	*CAR-T: 3.3* SoC: 3.0	2	3
Median follow up (months)	*CAR-T: 35.8* SoC: 27.6	13.3	14.3
Disease stage	R/R	R/R	R/R
Other patient characteristics	-Patients with prior BTKi exposure and failure -Majority in ZUMA-2 from US	Analysis of CAR-T cell infused patients	65% ineligible for ZUMA-2
Patient population/underlying studies and trials	*-ZUMA-2* -SCHOLAR-2 (extern retrospective, observational study from European centers, real-world)	12 Institutions from UK	US Lymphoma CAR-T Consortium (16 US institutions)
CAR-T product	Brexucabtagene	Brexucabtagene	Brexucabtagene

Abbreviations: *BTKi: Bruton's tyrosine kinase inhibitor; ITT: intention to treat; n: number of participants; ORR: overall response rate; OS: overall survival, PFS: progression free survival, SoC: standard of care; US: United States;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.7.2 Effectiveness outcomes

In the comparative study by Hess et al. (2024), only the **OS** outcomes of the CAR-T pivotal study were reported and analyzed in relation to the OS outcomes of the synthetic control arm with SoC treatment. The median OS rate was around four years in the CAR-T cohort with a median follow-up time of 35.8 months, compared to just over one year in the SoC cohort with a median follow-up time of 27.6 months. The 36-month OS was slightly more than half in the CAR-T cohort, compared to around one-quarter in the SoC cohort. Both observational real-world studies reported ORR, CR, OS and PFS outcomes. In both studies, the **ORR** was almost 90%, and the **CR** rate was around 80%. The median follow-up periods were more than one year. About three quarters of the cohorts had a 12-month **OS** and the median **PFS** was between 16 and 21 months in the cohorts. The 12-month PFS rates were reported with around 60% [62, 63].

Hess (2024):
median OS: CAR-T ~4 J. vs. SoC ~1 J.
36-Monats-OS: CAR-T >50 %, SoC ~25 %

RWE:
ORR ~90 %, CR ~80 %
12-Monats-OS ~75 %

median PFS: 16–21 M.,
12-M.-PFS ~60 %

Individual **relapse** rates, **EFS**, and **HRQoL** outcomes were not reported in the selected studies.

keine Daten zu Rückfällen, EFS, HRQoL

Effectiveness outcomes of the three included publications are presented in Table 16.

Studiendetails in Tabelle 16

*Table 16: Results on effectiveness outcomes of included studies for patients with **MCL***

Study ID (first author, year)	Hess, 2024	O'Reilly, 2024	Wang, Y., 2023
CR	NR	81%	82%
ORR	NR	87%	90%
OS	-Median OS: *CAR-T: 46.6 months* SoC: 15.4 months -36-months OS rate: *CAR-T: 57.9%* SoC: 25.9% -CAR-T improved OS in relation to SoC, HR: 0.42% (95% CI, 0.26 - 0.68, p < 0.001)	12-months OS: 74% (95% CI, 62 - 83)	12-months OS: 75% (95% CI, 67 - 81)
Study ID	**Hess, 2024**	**O'Reilly, 2024**	**Wang, Y., 2023**
PFS/RFS	NR	-Median PFS: 21 months -12-months PFS: 62% (95% CI, 49 - 73)	-Median PFS: 16.4 months -12-months PFS: 59% (95% CI, 51 - 66)

Abbreviations**: CR: complete response; HR: hazard ratio; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RFS: relapse free survival; SoC: standard of care; **results of CAR-T cohorts from pivotal trials are written in italics

3.7.3 Safety outcomes

The two non-comparative studies reported on safety outcomes and adverse events following treatment with CAR-T cells. **CRS** occurred in around 90% of patients in both cohorts, with approximately 10% experiencing grade 3 or higher. More than half of the patients in the cohorts had **ICANS**, with 22% and 32% experiencing grade 3 or higher. In one cohort, the infection rate within one month after infusion was reported as 35% and neutropenia and thrombocytopenia rates were reported for month 1 and month 3. The incidence of an ICU stay ranged from 20% to 27% in the cohorts [62, 63].

Sicherheit (RWE):
CRS ~90 %
(schwer:~10 %)

ICANS >50 %
(schwer: 22–32 %)
ICU-Aufenthalt:
20–27 %

Neurotoxicity and **TRM** rates were not reported in the selected studies.

Neurotoxicity/TRM

Safety outcomes of the publications reporting results are presented in Table 17.

Sicherheitsoutcomes in Tabelle 17

*Table 17: Results on safety outcomes of included studies for patients with **MCL***

Study ID (first author, year)	O'Reilly, 2024	Wang, Y., 2023
CRS	Any grade: 93% Grade ≥3: 12%	Any grade: 90% Grade ≥3: 8%
ICANS	Any grade: 55% Grade ≥3: 22%	Any grade: 61% Grade ≥3: 32%
Other severe AE	-Infections within one month: 35% -ICU: 27% -Neutropenia: 1 months: 59%, 3 months: 25% -Thrombocytopenia: 1 months: 60%, 3 months: 31%	ICU: 20%

Abbreviations: *AE: adverse events; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit*

3.8 Real-world evidence of CAR-T treatment among patients with multiple myeloma

3.8.1 Characteristics of included studies

During the selection process, eight publications were identified that are relevant to multiple myeloma and of interest for updating the current RWE. Of these eight studies, three are indirect comparative studies of clinical pivotal trials analyzing CAR-T cell therapies and external control arms analyzing real-world outcomes of standard therapies without CAR-T cell use [64-66]. The other five studies are observational studies of real-world use and results of CAR-T cell products with one prospective study, analyzing patient-reported outcomes (PROs), and four studies with retrospective design [67-71].

8 Studien zu MM
3 indirekte Vergleiche
(pivotal vs. SoC)

5 RWE-Studien:
1 prospektiv (PROs),
4 retrospektiv

The two CAR-T products analyzed in the studies are ciltacabtagene and idecabtagene. However, ciltacabtagene was only analyzed in two comparative studies. Costa et al. (2022) and Mateos et al. (2023) both used the CARTITUDE-1 pivotal trial for the comparison of ciltacabtagene and non-CAR-T cell treatment. The synthetic comparison groups were determined from MAMMOTH and LocoMMotion cohorts, which included patients from the US and Europe. Patients from the CARTITUDE-1 pivotal trial were triple-class exposed, which means that they had previously been treated with an immunomodulatory drug, a proteasome inhibitor and an anti-CD38 monoclonal. The external comparison cohort included patients who were refractory to an anti-CD38 monoclonal antibody [64]. In the comparative study by Mateos et al. (2023) both cohorts were triple-class exposed. The third comparative study by Shah, N. et al. (2022) used the KarMMa pivotal trial for comparing idecabtagene with real-world non-CAR-T cell treatment and as an external comparison group also the MAMMOTH cohort. The included patients were triple-class exposed.

idecabtagene & ciltacabtagene

CARTITUDE-1
Kontrollen: MAMMOTH & LocoMMotion

alle Kohorten:
triple-class refraktär

CARTITUDE-1
vs. MAMMOTH

KarMMa
vs. MAMMOTH

The five observational CAR-T cell treatment real-world studies used patient data from centers in the US, Europe and Switzerland. The study by Ferment et al. (2024) is based on the DESCAR-T registry, the data came from eleven French centers, 25 % of patients were ineligible for KarMMa-1 pivotal trial inclusion and 79 % were triple refractory. The study by Sanoyan et al. (2023) is a single-center study, the data came from Switzerland and triple-class exposed patients were included in the cohort. The patient data and outcomes from the studies by Dima et al. (2024), Hansen et al (2023) and Oswald et al. (2023) all come from US institutions, and an some cohort overlap cannot be ruled out. While the study by Oswald et al. (2023) analyzed PROs and the HRQoL, this is not the case in the other US studies. In this study 71 % of patients did not meet KarMMa eligibility and 40.5 % had an extramedullary disease at baseline. The two other US cohorts included patients who were also not eligible for the KarMMa trial. In the cohort in the study by Hansen et al. (2023) 75 % were ineligible for KarMMa.

5 RWE-Studien aus USA, FR & CH

registry und single-center-Studien

häufig triple-refraktär / EMD vorhanden

nur eine Studie mit HRQoL/PRO-Daten

viele Pts. nicht KarMMa-geeignet

The median age in the publications ranged from 61 to 68.6 years in the CAR-T treatment cohorts and from 62.7 to 65 years in the comparative cohorts without CAR-T cell treatment. Mateos et al. (2023) only reported the percentage distribution of age groups under and over 65 years. The median number of prior therapy lines was between 4 and 7 in the CAR-T cohorts and between 5 and 6 in the non-CAR-T cohorts. Mateos et al. (2023) only reported the percentage distribution of prior therapy lines of four and fewer and more than five. The median follow-up times in the studies were 5.7, 6.1, 10, 12.2, 12.4, 15.4 and 21.7 months for the CAR-T cohorts. A median follow-up time of 11 months was reported for one non-CAR-T cohort. The analyzed primary and secondary endpoints in the publications were ORR, CR, OS, PFS, HRQoL and safety outcomes. The disease stage of multiple myeloma was relapsed or refractory in all studies.

Alter:
CAR-T: 61–68,6 J.,
Komparator: 62,7–65 J.

Vorbehandlung:
4–7 Linien
Follow-up: 6–22 M.

Endpunkte: ORR, CR, OS, PFS, HRQoL, Sicherheit
alle Pts.: r/r MM

In total, 660 patients treated with CAR-T cells, including 225 patients from the CARTITUDE-1 and KarMMa pivotal trials, and 419 patients treated with non-CAR-T cells, were analyzed across the eight studies with a total of nine cohorts (n=1079).

MM: 8 Studien (n = 1079)
660 CAR-T Pts.

Study characteristics of the eight included publications are presented in Table 18.

Studiendetails in Tabelle 18

The quality of the five real-world observational single-arm studies was rated for three of them as fair and for the others as poor. Reasons included a high

RWE-Qualität:
schlecht-moderat

number of losses to follow-up, short and insufficient follow-up times and non-blinded outcome assessors.

The overall risk of bias was classified as critical in the three comparative studies. The main reasons for this were bias due to confounding, the selection of participants and measurement of outcomes. The other domains were rated from critical to moderate in the assessment, with a majority of critical and serious ratings.

RoB in allen Vergleichsstudien kritisch

Quality and risk of bias assessment are presented in the Appendix in Table 29 and Table 34.

Qualitäts- und RoB-Bewertung im Anhang

*Table 18: Main characteristics of included studies for patients with **multiple myeloma***

Study ID (first author, year)	Costa, 2022	Dima, 2024	Ferment, 2024	Hansen, 2023
Study design	-Comparative, retrospective analysis of modified ITT populations -CAR-T and non-CAR-T -PSM 1:1	-Retrospective, observational, RWE	-Retrospective, observational, RWE -Registry based	Retrospective, observational, RWE
n	*CAR-T: 69 (matched)* SoC: 69 (matched)	69	159	159
Primary and secondary endpoints	ORR, PFS, OS	ORR, CR, PFS, OS, Safety	ORR, CR, PFS, OS, Safety	CR, ORR, OS, PFS, Safety
Median Age (years)	*CAR-T: 62.6* SoC: 62.7	64	61	64
Median prior therapy lines	*CAR-T: 5.9* SoC: 6	6	4	7
Median follow up (months)	*CAR-T: 12.4*	10	12.2	6.1
Disease stage	R/R	R/R	R/R	R/R
Other patient characteristics	-Pivotal trial: triple-class exposed (immunomodulatory drug, proteasome inhibitor, anti-CD38 monoclonal antibody) -extern real-world: refractory to anti-CD38 monoclonal antibody	Included patients not eligible for KarMMa-1 pivotal trial criteria	-25% ineligible for KarMMA-1 inclusion -79% triple-refractory	75% ineligible for KarMMa
Patient population/ underlying studies and trials	*-CARTITUDE-1* (pivotal trial) - MAMMOTH (14 US centers, real-world, retrospective, SoC)	3 US centers	DESCAR-T Registry (11 French centers)	11 US institutions
CAR-Tproduct	Ciltacabtagene	Idecabtagene	Idecabtagene	Idecabtagene
Study ID (first author, year)	Mateos, 2023	Oswald, 2023	Sanoyan, 2023	Shah, N., 2022

Study design	-Comparative analysis -CAR-T and non-CAR-T real-world clinical practice (RWCP) -probability weighting	-Prospective -real-world PROs -CAR-T in SoC	Retrospective, observational, RWE	-Comparative, observational -indirect comparison of CAR-T and conventional care (CC) -MAIC
n	*CAR-T: 97* RWCP: 170	42	16	*CAR-T: 128* CC: 249
Primary and secondary endpoints	ORR, CR, PFS, OS, HRQoL, Safety	HRQoL	ORR, Safety	ORR, PFS, OS
Median Age (years)	Median: NR *CAR-T: <65: 63.9%, 65+: 36.1%* RWCP: <65: 35.9%, 65+: 64.1% Weighted RWCP: <65: 66.5%, 65+: 33.5%	66	68.6	*CAR-T: 60.5* CC: 65
Median prior therapy lines	Median: NR *CAR-T: ≤4: 34%, 5+:66%* RWCP: ≤4: 51.2%, 5+: 48.8% Weighted RWCP: ≤4: 29.9%, 5+: 70.1%	6	6	*CAR-T: 6* CC: 5
Median follow up (months)	*CAR-T: 21.7* RWCP: 11	Assessment at 14 time-points	5.7	*CAR-T: 15.4*
Disease stage	R/R	R/R	R/R	R/R
Other patient characteristics	Both cohorts triple-class exposed	-71% not meeting KarMMa eligibility -40.5% extramedullary disease	Triple class exposed	Triple class exposed
Study ID	**Mateos, 2023**	**Oswald, 2023**	**Sanoyan, 2023**	**Shah, N., 2022**
Patient population/ underlying studies and trials	*-CARTITUDE-1* -LocoMMotion (external cohort, prospective, multinational study, US and Europe)	Data from US single institution, Florida	Single center in Switzerland, Bern	*-KarMMa (pivotal trial)* -MAMMOTH (observational study, 14 US centers, retrospective)
CAR-T product	Ciltacabtagene	Idecabtagene	Idecabtagene	Idecabtagene
Study ID (first author, year)	Mateos, 2023	Oswald, 2023	Sanoyan, 2023	Shah, N., 2022

Abbreviations**: CC: conventional care; CR: complete response; HRQoL: health related quality of life; ITT: intention to treat; MAIC: matching-adjusted indirect comparison, n: number of participants; NR: not reported; ORR: overall response rate; OS: overall survival; PFS: progression free survival; PRO: patient reported outcome; PSM: propensity score matching; R/R: relapsed/refractory; RWCP: real-world clinical practice; SoC: standard of care; US: United States;* ***results of CAR-T cohorts from pivotal trials are written in italics

3.8.2 Effectiveness outcomes

The **ORR** reported in the observational studies after CAR-T cell treatment varied between 69 % and 93 %. The reported **CR** rates were similar in the studies and were around 45 %. The median follow-up period was less than one year in all these real-world setting studies [67-69, 71]. The study by Sanoyan et al. (2023) reported a more frequent tumor response to CAR-T cells in patients with higher CAR-T cell expansion after infusion.

RWE: ORR 69–93 %, CR: 45 %
Follow-up: <1 Jahr
höhere CAR-T-Expansion: stärkere Tumorantwort

All comparative studies analyzed ORR and one of them analyzed ORR and CR rates. The ORR for the partially matched CAR-T pivotal trial cohorts (CARTITUDE-1 and KarMMa) ranged from around 71 % to almost 100 %, compared to rates around 30 % to 40 % for the SoC cohorts. The reported CR rate was 82.5 % for the CAR-T pivotal trial cohort, compared to 0.6 % for the real-world clinical practice cohort. The median follow-up periods were between about one and two years [64-66].

Vergleichsstudien: ORR CAR-T 71–100 %, SoC 30–40 %
CR: CAR-T 82,5 %, SoC 0,6 %
Follow-up: 1–2 Jahre

Median **OS** rates in three real-world studies reporting CAR-T cell use ranged from 12.5 months to 20.8 months. The median **PFS** in these studies ranged from 8.5 to 12.5 months [67-69]. In the French registry study, an estimated 12-month OS of around three-quarters of the cohort was additionally reported. Patients with extramedullary disease in the French cohort had a significantly shorter PFS of around half of the time compared to the cohort as a whole.

RWE: medianes OS 12,5–20,8 M.
PFS: 8,5–12,5 M.

12-Monats-OS (FR): ~75 %

The 12-month OS in the comparative studies was stated with around 80 % to 90 % for the matched pivotal CAR-T cohorts, compared to half that percentage or less for the non-CAR-T cohorts. The reported 12-month PFS rates ranged between around 40 % to 80 % for the matched pivotal CAR-T cohorts, compared to rates of 15 % or less for the non-CAR-T cohorts. In one study the median OS for non-CAR-T treatment was about 10 months. Median PFS rates were reported in two studies for non-CAR-T treatment at around 3 to 4 months. In comparison, a median PFS twice as long was reported for one CAR-T treatment cohort. One comparative study reported adjusted HR results for OS and PFS outcome analysis [64-66].

12-Monats-OS: CAR-T 80–90 %, SoC ≤50 %
12-Monats-PFS: CAR-T 40–80 %, SoC ≤15 %

median OS (SoC): ~10 M.
median PFS (SoC): 3–4 M. CAR-T doppelt so lang

Two studies reported **HRQoL** outcomes. In the comparative study by Mateos et al. (2023) both cohorts, CAR-T and non-CAR-T treatment, showed HRQoL improvements over time. However, measured on day seven, HRQoL initially decreased after treatment. The improvements in score differences from baseline to week 52 were significantly better for CAR-T treatment in the pivotal trial, compared to RWCP. The other reporting study by Oswald et al. (2023) focused on HRQoL assessment and outcomes of real-world patients, treated with idecabtagene. The reported mean standard deviation score was 83.3 for the overall HRQoL at day 90 and presented a significant and meaningful improvement in HRQoL from baseline up to 90 days after treatment. Most patients reported improvement or maintenance at day 60 in the cohort. In the analyzed and reporting cohort, fatigue and functional well-being worsened significantly at day 7 before returning to baseline scores. The overall HRQoL and physical well-being improved significantly at day 60 in the cohort. Patients with an extramedullary disease at baseline time point experienced worse physical well-being, global pain, performance status and overall symptom burden.

HRQoL in 2 Studien: anfänglicher Rückgang, dann Verbesserung

CAR-T mit stärkeren Effekten als SoC

EMD mit negativerem HRQoL-Verlauf

EFS and **relapse** rates were not reported in the selected studies.

EFS/Rückfälle nicht erfasst

Effectiveness outcomes of the eight included publications are presented in Table 19.

Details zur Wirksamkeit in Tabelle 19

*Table 19: Results on effectiveness outcomes of included studies for patients with **multiple myeloma***

Study ID (first author, year)	Costa, 2022	Dima, 2024	Ferment, 2024	Hansen, 2023
CR	NR	48%	6-months CR: 47%	42%
ORR	*CAR-T: 96%* SoC: 30%	93%	6-months ORR: 88%	84%
Study ID	**Costa, 2022**	**Dima, 2024**	**Ferment, 2024**	**Hansen, 2023**
OS	-12-months OS: *CAR-T: 88%* (95% CI, 81-96) SoC: 35% (95% CI, 24-51) -CAR-T superior OS (HR, 0.05; 95% CI, 0.01-0.22)	Median OS: 19.4 months	Median OS: 20.8 months -Estimated 12-months OS: 73.3%	Median OS: 12.5 months
PFS/RFS	-12-months PFS: *CAR-T: 79%* (95% CI, 69-90) SoC: 15% (95% CI, 7-28) -CAR-T superior PFS (HR, 0.02; 95% CI, 0.01-0.14)	Median PFS: 8.5 months (95% CI, 6.2–10.9)	Median PFS: 12.5 months	Median PFS: 8.5 months
HRQoL/ QoL	NR	NR	NR	NR
Study ID (first author, year)	Mateos, 2023	Oswald, 2023	Sanoyan, 2023	Shah, N., 2022
CR	*CAR-T: 82.5%* RWCP: 0.6 %	NR	NR	NR
ORR	*CAR-T: 97.9%* RWCP: 42.9%	NR	3-months ORR: 69%	*-CAR-T: 73.4%* *Matched* *CAR-T: 70.8%* CC: 31.3% -CAR-T improved ORR: OR: 5.3 (95% CI, 2.96–9.51)
OS	Adjusted HR for OS: Favoring CAR-T: 0.2 (95% CI, 0.09-0.41)	NR	NR	Median OS: CC: 9.9 months -12-months OS: *CAR-T: 77.9 %* *Matched* *CAR-T: 78.8 %* CC: 40.8% -CAR-T improved OS: HR: 0.37 (95% CI, 0.25–0.56)
Study ID	**Mateos, 2023**	**Oswald, 2023**	**Sanoyan, 2023**	**Shah, N., 2022**
PFS/RFS	Median PFS:	NR	NR	Median PFS:

	RWCP: 4.34 months -Adjusted HR for PFS: Favoring CAR-T: 0.15 (95% CI, 0.08-0.29)			*CAR-T: 8.8 months* *Matched CAR-T: 8.9 months* CC: 3.4 months -12-months PFS: *CAR-T: 38.3%* *Matched CAR-T: 40.1 %* CC: 11.8% - CAR-T improved PFS: OR: 0.5 (95% CI, 0.36–0.70)
HRQoL/ QoL	-Improvement of score differences for CAR-T compared to RWCP from baseline to week 52, significant better -Both cohorts showed improvements over time, after initial worsening at day 7	-Overall HRQoL: Mean standard deviation score: D90: 83.3 -D7: Fatigue ($p < 0.001$) and functional well-being ($p = 0.003$) worsened significantly before returning to baseline levels -Day 60: Overall HRQoL ($p = 0.008$) and physical well-being ($p < 0.001$) improved significantly -Day 90: most reported improvement (10–57%) or maintenance (23–69%)	NR	NR

Abbreviations: *CC: conventional care; CR: complete response; HR: hazard ratio; HRQoL: health related quality of life; NR: not reported; OR: odds ratio; ORR: overall response rate; OS: overall survival; PFS: progression free survival; RFS: relapse free survival; RWCP: real-world clinical practice; SoC: standard of care;* ***results of CAR-T cohorts from pivotal trials are written in italics***

3.8.3 Safety outcomes

Four single-arm real-world observational studies reported safety outcomes and one comparative study analyzed CAR-T cell and non-CAR-T cell treatment safety outcomes.

Sicherheit: 4 RWE-Studien + 1 Vergleichsstudie

The occurrence of **CRS** after CAR-T cell treatment varied from 81% to 94% for each grade and from 0% to 4% for a grade 3 or higher in the non-comparative real-world study cohorts [67-69, 71]. The CRS rate in the CARTITUDE-1 pivotal trial was reported with 94.8% for each grade and with 4.1% for grade 3 or higher [65].

CRS meist mild, schwere Verläufe selten (0–4 %)

RWE & CARTITUDE-1

Neurotoxicity or neurologic event rates were reported in the studies by Ferment et al. (2024) and Hansen et al. (2023). Neurotoxicity after CAR-T cell use in practice occurred in 13% and 18% for each grade and in about a third of these rates for grade 3 or higher in the cohorts. The neurotoxicity rate in the CARTITUDE-1 pivotal trial was reported with 12.4% for each grade and with 8.2% for grade 3 or higher.

Neurotoxizität: 13–18 % ~1/3 ≥ Grad 3 (RWE)

CARTITUDE-1: ähnlich (12,4 % / 8,2 %)

ICANS rates were reported in the studies by Dima et al. (2024) and Sanoyan et al. (2023). ICANS after CAR-T cell use in practice occurred in 28% and 6% for each grade and in 3% and 0% for grade 3 or higher in the cohorts. The ICANS rate in the CARTITUDE-1 pivotal trial was reported with 16.5% for all grades and with 2.2 % for grade 3 or higher.

ICANS: RWE 6–28 % (alle), 0–3 % (≥ Grad 3)

CARTITUDE-1: 16,5 % / 2,2 %

Other severe and comparable **AE** reported in the publications were the occurrence of an ICU stay, infections, and hematological disorders. The probability of an ICU stay was around one-tenth in two CAR-T real-world cohorts. Infection rates were reported at 58% and 34% after CAR-T cell real-world use with 30% and 25% of infections being grade 3 or higher. The rates for any grade of neutropenia ranged from 91% to 100% and from 35% to 75% for grade 3 or higher in the CAR-T real-world cohorts. The rates for any grade of anemia ranged from 94% to 100% and from 13% to 88% for grade 3 or higher in the CAR-T real-world cohorts. The rates for any grade of thrombocytopenia ranged from 91% to 94% and from 35% to 75% for grade 3 or higher in the CAR-T real-world cohorts [67-69, 71]. The comparative study by Mateos et al. (2023) reported CAR-T pivotal trial results for hematological disorders compared to RWCP. All disorders examined had higher rates in the CAR-T cohort compared to the RWCP cohort. Neutropenia occurred in almost all patients of the CAR-T cohort, compared to a rate of around 15 % in the RWCP cohort. Anemia and thrombocytopenia occurred in around four-fifths of the CAR-T cohort, compared to around a quarter of the RWCP cohort. **TRM** was not reported in the selected studies.

ICU-Aufenthalt ~10 %

Infektionen: 34–58 %, schwer bis 30 %

hämatologische Toxizität: sehr häufig, v. a. Neutropenie

CAR-T vs. RWCP: deutlich höhere Raten bei CAR-T Neutropenie: ~100 % vs. 15 %

TRM nicht erfasst

Safety outcomes of the publications, reporting results are presented in Table 20.

Sicherheitsergebnisse in Tabelle 20

*Table 20: Results on safety outcomes of included studies for patients with **multiple myeloma***

Study ID (first author, year)	Dima, 2024	Ferment, 2024	Hansen, 2023	Mateos, 2023	Sanoyan, 2023
CRS	Any grade: 81% Grade ≥3: 4%	Any grade: 90% Grade ≥3: 2%	Any grade: 82% Grade ≥3: 3%	*CAR-T:* *Any grade: 94.8%* *Grade ≥3: 4.1%* RWCP: NR	Any grade: 94% Grade ≥3: 0%
Neurotoxicity/ neurologic events	NR	Any grade: 13% Grade ≥3: 4%	Any grade: 18% Grade ≥3: 6%	*CAR-T:* *Any grade: 12.4%* *Grade ≥3: 8.2%* RWCP:NR	NR
ICANS	Any grade: 28% Grade ≥3: 3%	NR	NR	*CAR-T:* *Any grade: 16.5%* *Grade ≥3: 2.1%* RWCP: NR	Any grade: 6% Grade ≥3: 0%
Other severe AE	-ICU: 10% -Infections: 58%, severe infections: 30%, -Neutropenia: 94% -Anemia: 94% -Thrombocytopenia: 91%	-Thrombocytopenia grade ≥3: 35% -Neutropenia grade ≥3: 59% -Anemia grade ≥3: 13% -Infections: 34%,	-ICU: 8 % -Neutropenia: 97%, grade ≥3: 88% -Anemia: 95%, grade ≥3 51% -Thrombocytopenia: 95%, grade ≥3 68%	-Any AE: *CAR-T: 100%* RWCP: 83.5% -Neutropenia: *CAR-T: 95.9%, grade≥ 3: 94.8%* RWCP: 15.7%, grade≥ 3: 13.3%	-Anemia: 100%, grade≥ 3: 88% -Neutropenia: 100%, grade≥ 3: 100% -Thrombocytopenia: 94%, grade≥ 3: 75%

		grade ≥3: 26% (in first 6 months)		-Anemia: *CAR-T: 81.4%* *grade≥ 3: 68%* RWCP: 25.8%, grade≥ 3: 10.9% -Thrombocytope-nia: *CAR-T: 79.4%,* *grade≥ 3: 59.8%* RWCP: 23%, grade≥ 3: 17.7%	

Abbreviations**: AE: adverse events; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: intensive care unit; NR: not reported; RWCP: real-world clinical practice;* ***results of CAR-T cohorts from pivotal trials are written in italics

4 Discussion

4.1 Summary of findings

CAR-T-Nutzung nimmt zu

Vergleichsstudien selten, Qualität & Bias kritisch

Vergleich CAR-T vs. SoC auf RWE-Basis nur eingeschränkt möglich

This work demonstrates that CAR-T cell therapies are a dynamic field and have been approved and used for an increasing number of hematologic cancers in recent years. Worldwide use, as demonstrated by the real-world cohorts, is increasing and the results are of great interest to patients, medical staff and decision-makers. Despite this and apart from pivotal and clinical trials, there are only a few comparative studies comparing real-world CAR-T cell outcomes with other established treatment options. Most of the real-world data came from observational retrospective single-arm cohorts. In addition, the included studies have a high risk of bias and a fair or poor quality assessment. Due to the predominance of certain study designs among the included research, it is difficult to answer the research question regarding the effectiveness and safety comparison of CAR-T cell therapies with non-CAR-T cell therapies based on real-world evidence.

Limitation: Evidenzlücken & Studiendesigns

nicht alle Subtypen & Outcomes berücksichtigt

The results of this work are limited by the lack of evidence and the limitations of the included studies. Not all a predefined characteristics and outcomes could be included in this work. Not all cancer subtypes and outcomes were assessed in the studies relevant to this review. However, all CAR-T products approved by the EMA were used in the identified studies. When analyzing the results for the respective cancer types, the various CAR-T products were not differentiated if several products delivered study results for one indication. For example, tisagenlecleucel and brexucabtagene were combined in the presentation of the results for the disease ALL.

RWE vs. Zulassungsstudien & SoC-Kohorten

However, it was possible to compare current CAR-T real-world results with pivotal trials and earlier publications and additionally to compare pivotal trial cohorts with real-world non-CAR-T treatment cohorts.

gegenüber AIHTA (2022): neue Therapien & längeres Follow-up

ALL & LBCL: RWE-Daten nun bis 24,5 Monate (vorher max. 19,8)

neue Indikationen: meist 1–2,5 Jahre Follow-up

In contrast to the 2022 AIHTA report, this review includes newer CAR-T cell therapies and additional indications. With regard to the indications ALL and LBCL included in the previous report, studies with longer follow-up times could be included. In this review, all ALL real-world studies had median follow-up times of nearly two years. In the AIHTA report, the follow-up time for the ALL studies in question ranged from 7.6 to 24 months. In the real-world results of the LBCL studies in this review, the maximum median follow-up time was extended by around six months. RWE studies reached a maximum of 19.8 months in the AIHTA report, whereas this review includes a study with 24.5 months [35]. For the newer indications and therapies, the median follow-up times in this analysis were around one to 2.5 years. Most of them were around one year. Some of the pivotal trials had longer follow-up periods of up to 35.8 months.

ALL

RWE vs. ELIANA:
CRS (68 % vs. 77 %)
ICANS (7 % vs. 40 %)

Ansprechen gleich hoch (87,8 %)

Bader et al. (2023) compared several outcomes to thoe from the ELIANA trial. This pivotal trial evaluated the efficacy and safety of tisagenlecleucel in pediatric and young adult patients. The CRS and ICANS rates in the observed German cohort were lower than in the ELIANA trial. The overall CRS rate was 67.9% compared to 77.3%. The ICANS rate was 7.4% compared to 40%. The response rate at day 28 was 87.8%, just as high as in the ELIANA trial.

In the Bader et al. cohort, most patients had a poor prognosis, 45.3% were rescued with a single dose of tisagenlecleucel after the two-year follow-up period. The other real-world CAR-T cohort from the UK had higher rates of adverse events, but also a higher OS rate (70%) compared to the German cohort (53.3%) and the pivotal trial cohort (63.5%).

UK-Kohorte: mehr AEs, aber höchstes OS (70 %)

The comparative studies evaluated CAR-T cell therapies in comparison with non-CAR-T standard treatments. The pivotal trial cohort of patients aged 26 years and older, treated with brexucabtagene, showed better response rates than patients treated with standard care. The reduction in risk of death in the CAR-T cohort ranged from 52% to 66%, depending on different standard treatments. However, the comparison could only be carried out with the SCHOLAR-3 population group who was 18 years and older [48]. The results of the other comparative study confirmed the improved outcomes of brexucabtagene treatment among patients with ALL, compared to non-CAR-T cell treatment with standard care in the historical clinical trial [49]. The strength of all ALL publications is the similar follow-up period of two years.

ALL: CAR-T (brexucabtagene): besseres Ansprechen & OS als SoC

Sterberisiko um 52–66 % reduziert

alle Studien mit 2 J. Follow-up

Compared to the AIHTA report of 2022, the OS in the RWE studies now ranged from 50% to 70% after two years, compared to around 56.5% in the 2022 report [35], in addition to the longer average follow-up time. It is also that CR rates were reported for the period after two years. Slightly higher CRS rates were observed in this review compared to the AIHTA report. The results for relapse, EFS, PFS and CR after one month are consistent with the previous results. All of the compared observational studies used tisagenlecleucel as therapy.

OS nach 2 J. : 50–70 % (AIHTA 2022: 56,5 %)

CRS leicht erhöht

alle Studien mit tisagenlecleucel

LBCL

The outcome rates and median follow-up periods varied across the included real-world studies and different CAR-T products were analyzed.

heterogene Follow-up-Zeiten & Wirksamkeit

In the Canadian cohort with a small sample size and short follow-up period the rate of relapse after three months was higher than in pivotal trials and low response rates were observed at three months follow-up [52]. In contrast, the Dutch cohort in the study from Spanjaart et al. (2023) had comparable outcomes to the pivotal ZUMA-1 study. Results of the Trando et al. (2023) study were comparable with large clinical studies. The results of the Japanese cohort indicate that the analyzed CAR-T product is feasible and effective, even for heavily pretreated patients. The effectiveness outcomes were slightly higher in the analyzed cohort than in previous observational studies [53]. Outcomes from the largest analyzed real-world cohort with a majority of patients with DLBCL showed a durable response to CAR-T treatment despite ZUMA-1 ineligibility. Efficacy outcomes were comparable to clinical trials [50].

Kanada: hohe Relapse-Raten, schwaches Ansprechen

Niederlande, Japan, USA: gute bis vergleichbare Ergebnisse zu ZUMA-1

größte RWE-Kohorte: Ansprechen anhaltend

Outcomes from older and frail patients in the CAR-T San Diego cohort suggest that treatment with CAR-T cells is feasible, but the risk of infections and complications is higher [54].

ältere Pts. bei CAR-T: erhöhtes Infektionsrisiko

The comparative studies of CAR-T cell treatment and non-CAR-T cell treatment have demonstrated superior efficacy of CAR-T therapy compared to treatment with SoC, CIT and CC. CAR-T treatment in the Bastos-Oreiro et al. (2022) study was associated with longer OS and PFS rates. The superior benefit of CAR-T treatment with higher response and longer OS rates compared to CIT was demonstrated in the Lunning et al. (2024) study. Additionally, the subgroup analysis showed that axicabtagene was an effective treatment option for the subgroups in this cohort. The beneficial effect of axicabtagene was shown regardless of age and ECOG PS of the patients.

CAR-T vs. SoC/CIT: besseres Ansprechen & OS

axicabtagene wirksam über Alters- & ECOG-Gruppen hinweg

The favorable effect of lisocabtagene compared to CC in the study from Van Le et al. (2023) was shown through significant and clinically meaningful benefits in relation to ORR, CR, OS and PFS outcomes in the examined cohorts.

lisocabtagene: sign. Vorteile bei ORR, CR, OS & PFS vs. CC

Additional evidence for the superiority of CAR-T cell treatment compared to SoC as second line therapy was shown in the open label phase 3 TRANSFORM pivotal trial. This trial was not included in this analysis. This randomized trial compared lisocabtagene with SoC treatment and randomized patients 1:1. The OS rate for the CAR-T cohort was 73.1 %, compared to 60.6 % in the SoC cohort. The CR rate was 74 % for the CAR-T cohort, compared to 43 % for the SoC cohort. EFS and PFS outcomes strengthened the superiority of lisocabtagene. The reported adverse events and low rates of severe CRS and neurotoxicity confirm good tolerability of the treatment [72].

TRANSFORM (2L, RCT): lisocabtagene mit besserem OS (73 %) & CR (74 %) vs. SoC

gute Verträglichkeit (niedrige CRS/ Neurotoxizität.)

Due to many relapses or refractory cases, a unmet medical need still exists for patients with LBCL after CAR-T cell treatment. Alternatives are also needed for patients who are unfit for CAR-T cell treatment.

LBCL: Bedarf bei Rezidiv & CAR-T-Ineligiblen

In the Dutch cohort from Spanjaart et al. (2023) 84% of all CAR-T treated patients responded to CAR-T cells, but after 12 months only 33% were alive and progression free. Among patients initially assessed for CAR-T eligibility, 32% were considered unfit for treatment..

NL-Kohorte: 84 % Ansprechen, aber nur 33 % PFS nach 12 M.

Compared to previous publications, one study analyzing the newer approved CAR-T product lisocabtagene was included in this review. The other studies also analyzed axicabtagene and tisagenlecleucel. The ORR and CR rates for lisocabtagene were comparable with previous outcomes of treatment with axicabtagene and tisagenlecleucel. But the median OS was longer for lisocabtagene in comparison to most of the other studies. At the same time, the median PFS for lisocabtagene was comparable to the lower end of results reported in other studies.

lisocabtagene: ähnliche ORR/CR

längeres OS

kürzeres PFS

Similar effectiveness and safety outcomes were found in the studies that examined LBCL patients in comparison to the previous publications for the OS and PFS after one year and the HRQoL, CRS and ICANS rates. New findings are that OS and PFS data are available for a two-year period. OS and PFS declined over time. The median OS of 15 to 28.4 months in the real-world studies was higher in this review than in the previous AIHTA report, where it was between 10.7 and 19.3 months. The CR and ORR results of the studies showed similar or improved rates in this review. The best ORR in this review was around 84%, higher than in the previous AIHTA report, where the best rate was 67%. The best CR in this review was around 66%, higher than in the previous AIHTA report, where the best rate was 48% [35, 37].

LBCL: OS und PFS nach zwei Jahren verfügbar

OS und PFS nehmen mit der Zeit ab

höhere CR (66 %) und ORR (84 %) als im AIHTA-Bericht (2022) (48 %, 67 %)

FL

Real-world studies without pivotal trial data could not be found in the literature search for FL.

FL: keine reine RWE-Studie gefunden

The analysis by Hao et al. (2023) favored CAR-T treatment compared to SoC. A reduction in the risk of death was reported. Treatment with tisagenlecleucel showed a trend towards improved efficacy outcomes compared to SoC.

CAR-T (tisagenleucel) mit besserer CR, PFS und OS

The analysis by Salles et al. (2022) reported a 1.9-fold higher CR rate and a 1.4-fold higher PFS rate for patients treated with CAR-T cell therapy compared to usual care, which indicates a benefit of tisagenlecleucel treatment for patients with more than two lines of prior treatment. Tisagenlecleucel was also associated with a reduction in the risk of a death by 80%.

1.9-fach höherer CR & 1.4-fach höhere PFS & Sterberisiko 80 % geringer

The analysis by Palomba et al. (2023) examined the CAR-T product axicabtagene compared to SoC and reported a longer follow-up period. The positive benefit of CAR-T cell treatment was maintained after 24 months compared to 18 months of follow-up.

CAR-T-Vorteil mit axicabtagene auch nach 24 M. bestätigt

The CAR-T products analyzed in the studies are not new products, but the indication is new. Overall, good response rates and survival rates were observed in the relevant pivotal trials.

neue Indikationen – bekannte Produkte

MCL

The outcomes of the real-world study by O'Reilly et al. (2024) were comparable to the ZUMA-2 trial and other real-world publications. The real-world study by Wang, Y. et al. (2023) also showed that SoC CAR-T cell treatment outcomes were consistent with ZUMA-2 trial results, although the real-world study included patients who were ineligible for pivotal ZUMA-2 participation. Higher risks for infections and death were seen in this real-world cohort than in pivotal trial results. The ORR and CR rates of the ZUMA-2 pivotal trial cohort were 91% and 68% after a median follow-up period of 35.6 months [73].

MCL: RWE bestätigt ZUMA-2 – aber mehr Infektionen und Todesfälle

ORR 91 %, CR 68 % Follow-up: 35,6 M. (ZUMA-2)

The comparison of CAR-T cell treatment within the pivotal trial and an external SoC control arm showed a substantial survival benefit for patients treated with brexucabtagene, compared to non-CAR-T cell treatment (HR: 0.42, 95% CI: 0.26-0.68, $p < 0.001$). However, the cohorts came from different regions (US and Europe), which can affect outcomes and the median follow-up time differed between the compared treatments [61].

brexucabtagene: klarer Überlebensvorteil (HR 0.42) vs. SoC

regionale Limitationen

Overall, good response rates and survival rates after one year were observed in patients treated with brexucabtagene, which is one of the newer CAR-T products.

gute 1-J.- Ergebnisse bei Ansprechen & Überleben

Multiple myeloma

The survival outcomes (OS and PFS) in the study by Dima et al. (2024) were comparable to KarMMa pivotal trial results. In the study the response rates for real-world CAR-T use were higher. The safety outcomes were manageable and also comparable but higher rates for ICANS and hematological disorders were seen in the real-world outcomes. The cohort included patients who were ineligible for KarMMa, but the comparable results of the studies indicate that the patients' characteristics that led to exclusion, should not prevent CAR-T treatment. The follow-up period in this study was short at only 10 months.

MM: vergleichbare OS/PFS zu KarMMa

höhere Raten: ICANS und Hämatotoxizität

gute Wirksamkeit, kurzes Follow-up

The study by Hansen et al. (2023) described the safety and effectiveness outcomes in their study of CAR-T cell treatment in a standard setting as comparable to the KarMMa trial. The results were comparable, although baseline characteristics were different and 75 % of the real-world cohort did not meet KarMMa trial eligibility. However, the short follow-up time of 6.1 months in the real-world cohort should be noted.

KarMMa: ähnliche Ergebnisse trotz 75 % nicht-geeigneter Pts.

kurzes Follow-up

The French registry study reported safety of CAR-T cell treatment, which is comparable to KarMMa pivotal trial results and the effectiveness outcomes were consistent with previous studies. The study supports the feasibility of CAR-T cell treatment for indicated patients in a real-world setting. However, the limited follow-up time is a limitation [68].

FR-Register bestätigt KarMMa-Ergebnisse

kurzes Follow-up

The prospective HRQoL study had similar results to the KarMMa trial. However, the follow-up time was shorter in the real-world study and only a small sample size was available [70].

HRQoL vergleichbar kleine Stichprobe, kurzes Follow-up

Patients in the pivotal KarMMa study evaluating CAR-T treatment with idecabtagene had ORR and CR rates of 73% and 33%, after a median follow-up of 13.3 months. CRS and ICANS occurred in 84% and 18 % of the cohort and severe infections occurred in 69% of patients [67].

KarMMa – ORR 73 %, CR 33 %, CRS 84 %, ICANS 18 %, SI 69%

Not all cohorts in the multiple myeloma studies had comparable characteristics. Some studies only included triple-class exposed patients and others only had them proportionally in their cohort. The different preconditions and characteristics could produce different outcomes, which must be taken into account when comparing the different outcome rates of the included studies.

Kohorten: TCE-Anteil variiert

Ergebnisse nur bedingt vergleichbar

In the comparative analysis of ciltacabtagene treatment and non-CAR-T SoC treatment by Costa et al. (2022), the ORR was significantly higher and the OS and PFS rates significantly longer among patients treated with CAR-T cells. The reported HR for OS and PFS rates were 0.05 and 0.02, in favor of treatment with CAR-T cells.

ciltacabtagene mit deutlich besserer ORR, OS & PFS vs. SoC (HR: 0.05 / 0.02)

In the comparative analysis of ciltacabtagene treatment and non-CAR-T real-world clinical practice by Mateos et al. (2023) patients with CAR-T treatment were 3.12-fold more likely to respond to therapy. The adjusted HR for OS and PFS rates were 0.2 and 0.15 favoring CAR-T treatment. This corresponded to an 85% risk reduction of progression or death and a lowered risk of death by 80% for CAR-T treatment, compared to RWCP in the analyzed cohorts. An improvement in PFS of 85% was reported with CAR-T cell treatment. Patients treated with CAR-T cells showed more adverse events and higher rates of hematologic disorder in that analysis.

ciltacabtagene: 3,1-fach höheres Ansprechen & 80–85 % Risikoreduktion

CAR-T mit mehr AEs & Hämatotoxizität

In the comparative analysis of idecabtagene treatment and non-CAR-T conventional care (CC) treatment by Shah, N. et al. (2022) the CAR-T cell therapy provided better clinical outcomes. The improved CAR-T clinical outcomes compared to CC were reported with an OR of 5.3 for the ORR favoring CAR-T treatment, a HR of 0.37 for the OS, favoring CAR-T treatment and an OR of 0.5 for PFS, favoring CAR-T treatment.

idecabtagene mit besserem Outcome vs. CC (ORR OR 5.3, OS HR 0.37, PFS HR 0.5)

Two of the recently approved CAR-T products were examined in the multiple myeloma cohorts. The HRQoL analysis should be emphasized, as this outcome was only rarely examined in the included studies. A significant improvement from baseline to day 90 was observed in real-world patients treated with CAR-T [70].

HRQoL selten untersucht

sign. Verbesserung

Summary

In summary the RWE differs across studies and cohorts and a comparison of results is uncertain due to the evidence gap, different cohort characteristics and follow-up periods. However, there is a tendency indicating that CAR-T cell therapies are associated with better outcomes compared to standard therapies without CAR-T cells and can also be used successfully in real-world settings with results largely comparable to those in pivotal trials. The reports of the studies point out that in addition to CRS and ICANS, other adverse events, such as infections and hematologic disorders, are relevant in clinical practice.

RWE uneinheitlich

CAR-T tendenziell effektiver als SoC trotz heterogener Daten

CRS, ICANS, AEs klinisch relevant

In regard to ITT cohorts and patients eligible for treatment with CAR-T cells, it is noticeable that a considerable proportion of eligible and harvested patients did not receive treatment with CAR-T cells.

viele geeignete Pat. erhielten keine CAR-T-Infusion

In the study by O'Reilly et al. (2024), 30% of eligible and 20% of harvested patients did not receive treatment and cell infusion. In the French registry study, 10% of leukapheresed patients were not infused with CAR-T cells [68].

bis zu 30 % geeigneter Pts. ohne CAR-T-Infusion

Most real-world observational studies were identified for multiple myeloma and LBCL. Data from a total of 2716 patients treated with CAR-T cells in real-world settings were included in this work. For the indications ALL and LBCL, as examined in the 2022 AIHTA report, longer follow-up periods were available in the included real-world studies.

2716 RWE-Pts., v. a. MM & LBCL

längeres Follow-up bei ALL & LBCL

Regarding the more recently approved CAR-T products (brexucabtagene, lisocabtagene, idecabtagene, and ciltacabtagene), the following observations were made: For the indication ALL, the newly approved CAR-T product brexucabtagene was included in comparative pivotal trials, which were not part of the 2022 AIHTA report. However, no real-world data for this CAR-T product in ALL patients were available, and the existing data did not allow a comparison with earlier pivotal trials. For patients with MCL, two real-world studies analyzing brexucabtagene were included. The safety outcomes from these studies indicated a higher incidence of CRS and ICANS compared to other included studies, indications, and CAR-T products in this review [62, 63].

ALL: keine RWE für brexucabtagene

höhere CRS- und ICANS-Raten im Vergleich zu anderen CAR-T-Therapien

Data for lisocabtagene were only available from one pivotal trial analyzing patients with LBCL, and the results were comparable with current real-world data [55]. In all LBCL studies that reported a median OS, the median OS was the shortest in patients treated with lisocabtagene. More studies were found for the more recently approved products idecabtagene and ciltacabtagene, which are used for multiple myeloma patients. These studies also reported real-world results, but only with follow-up periods of up to one year.

1 Studie zu lisocabtagene mit kürzerem OS

RWE zu idecatagene & ciltacabtagene: kurzes Follow-up

Overall, the response rates for the newer indications FL, MCL and multiple myeloma were higher, but the follow-up times were not as long as for ALL and LBCL. The outcomes of the studies for the FL indication provide the best results in terms of effectiveness, but only pivotal trial data were reported.

allgemein hohes Ansprechen bei neuen Indikationen und kürzeres Follow-up

The increasing evidence for the use of CAR-T therapies in practice and real-world could expand the range of patients who benefit from treatment with CAR-T cells. In real-world settings patients often have a higher ECOG PS, more comorbidities, a more extensive pretreatment and a different disease status.

mehr RWE könnte Zugang erweitern; reale Pts. oft stärker vorbelastet

The observational, non-randomized nature of the studies makes them susceptible to unintentional bias and confounding. A control group is missing in these studies. A crucial limitation is the retrospective design and data collection of most RWE studies. As a result, interventions are not prespecified, patient selection and outcome measurement are not controlled, and outcome assessment is often not centralized.

nicht-randomisierte retrospektive Designs

RoB und fehlende Standardisierung

Various score-matching methods were used in the indirect comparative studies to match patient characteristics, obtain weighted results and contextualize outcomes, but overall, the risk of bias is high due to the retrospective design, different co-interventions, different outcome assessments or different clinical care in the cohorts. The external historical trials used in some comparative studies were often conducted in the more distant past and may not reflect current standard treatments without CAR-T cells. RCTs for CAR-T cell treatment among cancer patients are often not feasible because of ethical and practical obstacles.

hoher RoB trotz Matching

RCTs selten realisierbar

historische Daten oft veraltet

Therefore, external cohorts with real-world data were used in comparative studies as an option to contextualize effectiveness and safety results of single arm trials to reach the highest possible quality of comparative analysis and evidence.

externe RWE-Kohorten zur Ergänzung einarmiger Studien

None of the single-arm real-world studies were rated as good in the quality assessment. Six were rated as poor and eight as fair. The main reasons were limitations such as insufficient follow-up periods, non-blinded outcome assessment, inconsistent measurement methods, and heterogeneous baseline characteristics. Poor or critical quality ratings indicate a higher risk of bias.

keine RWE-Einzelstudie mit guter Qualität; häufig kurzes Follow-up und hohes RoB

All comparative studies were rated as having a critical risk of bias. None of the assessed domains received a low-risk rating. The main reason was that each study had at least one critically rated domain. This was mainly due to the retrospective study design, which involved retrospective assessment of patient characteristics, inconsistent outcome definitions, and varying start times for follow-up and interventions across cohorts.

alle Vergleichsstudien mit hohem RoB

retrospektives Design & uneinheitliche Struktur

In summary, the real-world evidence for ALL, LBCL, and multiple myeloma appears comparatively more reliable, as these cohorts either had consistently fair-quality studies or a higher number of included publications.

mehr Studien & bessere Qualität bei RWE für ALL, LBCL und Myelom

Public health relevance and research question

This work relates to the public health core competence of applying quantitative and qualitative methods.

The updated evidence of effectiveness and safety results of CAR-T cell therapies is of interest to health systems and decision makers. The number of patients suffering from the diseases and the new therapy options require an evaluation of the current study results. A growing body of evidence over the last two years of real-world data was presented in this work, although data were not available for all indications and limitations should be considered when using the data. The heterogeneity of the studies is high, which is why the summary and comparison of the results should be interpreted with caution. The baseline characteristics among the cohorts are different, patient selection is different, follow-up times are different and the assessment and grading of the outcomes may vary between institutions of the cohorts. Most of the studies only analyzed outcomes for patients who actually received CAR-T cell infusions.

heterogene RWE mit Relevanz für Public Health

begrenzte Vergleichbarkeit der Daten:

Baseline-Daten, Pts.-Charakteristika, Follow-up

The research question cannot be answered with certainty, as relevant studies are lacking in this context or have a critical risk of bias. A summary of observational RWE results for several cohorts, indications and CAR-T products and a comparison of pivotal trials and synthetic control arms was presented. Since most real-world studies have comparable results to pivotal trials, CAR-T cell therapies may provide a benefit over standard treatment without CAR-T cell treatment in real-world settings. However, the limitations of the studies prevent a reliable conclusion from being drawn.

unsichere Evidenzlage

mögliche Vorteile von CAR-T in RWE

keine belastbare Schlussfolgerung möglich

4.2 Limitations

In contrast to what is usual in a systematic review, the study selection, data extraction and RoB assessment were performed by a single author, who conducted the work independently. The methodological standard for systematic reviews is to have at least two independent authors performing title and abstract screening. Therefore, there were no disagreements in the study selection, data extraction and RoB assessment in this work, which constitutes a significant methodological limitation.

methodische Limitation:

keine unabhängige Validierung von Auswahl & Bewertung

weitere Limitationen: Sprachfilter, Suchzeitraum, Datenbanken

In addition, some studies may have been excluded due to language restrictions. Studies published before the search period and not included in previous reviews may also be missing. Furthermore, relevant publications might not have been identified, as the database search was not comprehensive.

Überschneidungen möglich

Another limitation of this review is the risk of overlapping patient data across some studies and patients being included in more than one cohort. Sample overlap could not be definitively excluded.

4.3 Implications for further research

RCTs, standardisierte Erhebung & weitere Forschung zu neuen Therapien und früherem Einsatz notwendig

If ethically justifiable, RCTs should be conducted to achieve a higher level of evidence. Standardized outcome measurements and longer follow-up periods are needed to answer questions on effectiveness and safety. In particular, newly approved therapies such as CAR-T treatment with lisocabtagene should be further investigated to generate robust and comprehensive real-world data. Another relevant research question is whether CAR-T cells can be used earlier in the treatment line, provided they are proven safe, in order to reduce the burden of prolonged treatment and improve patient outcomes.

weiterführende Forschung zu:

Biomarkern, Auswahl geeigneter Pts. und Gründe für Nicht-Infusion

Additional areas of research include the influence of biomarkers and baseline characteristics on the success of CAR-T cell therapies to enable a more targeted application. Identifying which patients are most likely to benefit and introducing tailored screening of relevant characteristics prior to therapy could help reduce costs for health care systems. Furthermore, analyzing why some eligible patients do not ultimately receive CAR-T cell infusion and identifying causes for failure could provide valuable insights for decision makers.

5 Conclusion

Reproduzierbarkeit der Zulassungsstudien

The RWE data indicates that the results of pivotal studies are reproducible in routine clinical practice, even when patients have different baseline characteristics, do not meet the eligibility criteria of the pivotal trials and are heavily pretreated. A comparison of the data from the pivotal trials with the data from the synthetic control arms demonstrated the superiority of CAR-T cell treatment.

CAR-T: Überlegenheit gegenüber Kontrollarmen

häufige Rückfälle

The results show that although a large proportion of patients respond and to CAR-T cell therapy, many still suffer a relapse after some time. The response rates of the indications that have not been treated with CAR-T cells for so long indicate a better response compared to the older indications.

neue Indikationen: besseres Ansprechen

Sicherheitsprofil vertretbar; mehr CRS-/ICANS bei MCL mit brexucabtagene

The safety profiles of CAR-T cell therapies in real-world patients are generally manageable, but infections and hematologic disorders remain major challenges, particularly with the newly approved products. In particular, patients with MCL treated with brexucabtagene had a higher rate of CRS and ICANS compared to other indications and CAR-T cell products.

ALL: OS verbessert, mehr Nebenwirkungen

LBCL: OS/ PFS sanken bei längerem Follow-Up; medianes OS verbessert

The latest publications and longer follow-up periods of the studies that analyzed CAR-T treatment for patients with ALL and LBCL showed partly similar effectiveness and safety outcomes in comparison with previous reports and reviews. However, some differences could be identified. An improved OS of real-world patients with ALL was mentioned and higher rates of certain adverse events. In real-world patients with LBCL, it was found that the OS and PFS rates worsened over a longer follow-up period. At the same time, the median OS has improved compared to previous publications.

keine belastbare Bewertung der aktuellen RWE möglich

Due to the limitations, variability and high RoB of the included studies, no robust evaluation of the current RWE can be made. Studies and RCTs of CAR-T cell treatment with longer follow-up periods are needed to improve understanding and generate higher level of evidence of these therapies.

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Appendix

ECOG PS Scale

Table 21: ECOG PS Scale [74]

Grade	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Summary of EMA approved CAR-T cell products and indications

Table 22: EMA approved CAR-T cell products and indications

Name of product, active substance and sobriquet	Indications (with relapse or refractory process after standard therapy)	Date of approval
Kymriah® (***tisagenlecleucel) – "tisa-ce/tisacell"***	- *Patients up to and including 25 years with B-cell acute lymphoblastic leukemia (ALL)* - *adults with diffuse large B-cell lymphoma (DLBCL)* - *adults with follicular lymphoma (FL)*	Marketing authorization: On 23 August **2018**
Yescarta® (***axicabtageneciloleucel) – "axi-cel/axicel"***	- *adults with DLBCL or high-grade B-cell lymphoma (HGBCL)* - *adults with primary mediastinal large B-cell lymphoma (PMBCL)* - *adults with FL*	Marketing authorization: On 23 August **2018**
Tecartus® (***brexucabtagene autoleucel) – "brexu-cel/ brexucel"***	- *adults with mantle cell lymphoma (MCL)* - *adults of 26 years or older with B-cell acute lymphoblastic leukemia (ALL)*	Marketing authorization: On 14 December **2020**
Breyanzi® ***(lisocabtagene maraleucel) – "liso-cel/lisocel"***	*adults with:* - *DLBCL* - *PMBCL* - *follicular lymphoma grade 3B (FL3B)*	Marketing authorization: On 4 April **2022**
Abecma® ***(idecabtagene vicleucel) – "ide-cel/idecel"***	- *adults with multiple myeloma*	Conditional marketing authorization: On 18 August 2021 Standard marketing authorization: On 19 March **2024**
Carvykti® ***(ciltacabtagene autoleucel) – "cilta-cel/ ciltacel"***	- *adults with multiple myeloma*	Conditional marketing authorization: On 25 May 2022 Standard marketing authorization: On 19 April **2024**

Overview relevant pivotal trials per indications

Table 23: Relevant pivotal trials per indications

Indication	CAR-T product and pivotal trial
ALL	Kymriah®/tisagenlecleucel: **ELIANA**
	Tecartus®/brexucabtagene: **ZUMA-3**
LBCL (including: DLBCL, HGBCL, PMBCL, tFL)	Yescarta®/axicabtagene: **ZUMA-1; ZUMA-7**
	Breyanzi®/lisocabtagene: **TRANSFORM; TRANSCEND, TRANSCEND WORLD**
	Kymriah®/tisagenlecleucel: **JULIET**
FL	Kymriah®/tisagenlecleucel: **ELARA**
	Yescarta®/axicabtagene: **ZUMA-5**
MCL	Tecartus®/brexucabtagene: **ZUMA-2**
Multiple myeloma	Abecma®/idecabtagene: **KarMMa-1, KarMMa-3**
	Carvykti®/ciltacabtagene: **CARTITUDE-1; CARTITUDE-4**

Abbreviations: *ALL: acute lymphoblastic leukemia; DLBCL; diffuse large B-cell lymphoma; FL: follicular lymphoma; HGBCL: high-grade B-cell lymphoma; LBCL: large B-cell lymphoma; MCL: mantle cell lymphoma; PMBCL: primary mediastinal large B-cell lymphoma; tFL: transformed follicular lymphoma*

Literature search strings

Table 24: Search strings and results

Database	Search string	Results
Pubmed	(((((((CAR-T) OR (CAR T)) AND (tisagenlecleucel)) OR (axicabtagene)) OR (brexucabtagene)) OR (lisocabtagene)) OR (idecabtagene)) OR (ciltacabtagene) Filters: from 2022 - 2024	601
	Handsearch: DESCAR-T Filters: from 2022-2024	6
	Handsearch: CAR-T AND EMBT Filters: from 2022 - 2024	73
Cochrane Library	(CAR-T and (tisagenlecleucel or axicabtagene or brexucabtagene or lisocabtagene or idecabtagene or ciltacabtagene)).mp. [mp=ti, ot, ab, tx, kw, ct, sh, fx, hw] 2022-2024	60
Epistemonikos	(CAR-T and (tisagenlecleucel or axicabtagene or brexucabtagene or lisocabtagene or idecabtagene or ciltacabtagene)) 2022-2024	301

Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Table 25: Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [41]

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? **Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?**			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			
Quality Rating (Good, Fair, Poor)			
Additional Comments			

Abbreviations: *CD; cannot determine; NA: not applicable; NR: not reported*

Quality rating tables for observational studies

Table 26: Quality rating observational studies (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies), ***ALL*** *[41]*

Study ID	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Rating
Bader, 2023	Yes	Yes	CD	No	No	Yes	Yes	NA	CD	Yes	CD	No	NR	No	Fair
Oporto Espuelas, 2024	Yes	Yes	Yes	No	No	Yes	Yes	NA	CD	Yes	CD	No	No	No	Fair

Abbreviations: *CD; cannot determine; NA: not applicable; NR: not reported; Q: Question*

Table 27: Quality rating observational studies (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies), ***LBCL*** *[41]*

Study ID	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Rating
Benoit, 2023	Yes	Yes	CD	Yes	No	Yes	No	Yes	CD	Yes	CD	NR	No	No	Poor
Goto, 2023	Yes	Yes	NR	No	No	Yes	No	No	CD	CD	CD	NR	No	Yes	Poor
Jacobson, 2022	Yes	Yes	Yes	Yes	No	Yes	Yes	No	CD	Yes	CD	NR	No	Yes	Fair
Spanjaart, 2023	Yes	Yes	Yes	No	No	Yes	Yes	No	CD	Yes	CD	NR	No	NR	Fair
Trando, 2023	Yes	Yes	NR	Yes	No	Yes	Yes	Yes	CD	CD	CD	NR	No	Yes	Poor

Abbreviations: *CD; cannot determine; NA: not applicable; NR: not reported; Q: Question*

Table 28: Quality rating observational studies (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies), ***MCL*** *[41]*

Study ID	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Rating
O'Reilly, 2024	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	CD	Yes	CD	NR	No	No	Fair
Wang, 2023	Yes	Yes	Yes	CD	No	Yes	Yes	No	CD	CD	CD	NR	No	No	Poor

Abbreviations: *CD; cannot determine; NA: not applicable; NR: not reported; Q: Question*

Table 29: Quality rating observational studies (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies), ***multiple myeloma*** *[41]*

Study ID	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Q 10	Q 11	Q 12	Q 13	Q 14	Rating
Dima, 2024	Yes	Yes	CD	CD	No	Yes	No	NA	CD	NR	No	NR	No	No	Poor
Ferment, 2024	Yes	Yes	Yes	CD	No	Yes	Yes	NA	CD	Yes	CD	NR	No	No	Fair
Hansen, 2023	Yes	Yes	Yes	CD	No	Yes	No	NA	CD	Yes	CD	NR	NR	No	Poor
Oswald, 2023	Yes	Yes	Yes	Yes	No	Yes	No	NA	CD	Yes	Yes	No	No	NA	Fair
Sanoyan, 2023	Yes	Yes	CD	Yes	No	Yes	No	NA	CD	Yes	Yes	No	Yes	No	Fair

Abbreviations: *CD; cannot determine; NA: not applicable; NR: not reported; Q: Question*

RoB tables for comparative studies

Table 30: Risk of bias, comparative studies (ROBINS-I tool), ***ALL*** *[42]*

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias	Comments
Minnema, 2024	Critical	Critical	Serious	Critical	Critical	Serious	Serious	Critical	Retrospective design, PSM, MAIC, cohort from larger group
Shah, B. D. 2022	Critical	Critical	Serious	Critical	Serious	Serious	Serious	Critical	Retrospective design, PSM

Abbreviations*: MAIC: matching-adjusted indirect comparison; PSM: propensity score matching*

Table 31: Risk of bias, comparative studies (ROBINS-I tool), ***LBCL*** *[42]*

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias	Comments
Bastos-Oreiro, 2022	Critical	Serious	Serious	Critical	Serious	Critical	Serious	Critical	Retrospective design,
Lunning, 2024	Critical	Critical	Moderate	Moderate	Serious	Critical	Serious	Critical	Retrospective design, PSM,
Van Le, 2023	Critical	Critical	Serious	Serious	Serious	Critical	Serious	Critical	Retrospective design MAIC, IPTW, PSM

Abbreviations: *IPTW: inverse probability treatment weighting; MAIC: matching-adjusted indirect comparison; PSM: propensity score matching*

Table 32: Risk of bias, comparative studies (ROBINS-I tool), ***FL*** *[42]*

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias	Comments
Hao, 2023	Critical	Critical	Serious	Serious	Serious	Critical	Serious	Critical	Retrospective design, MAIC
Palomba, 2023	Critical	Critical	Serious	Serious	Serious	Critical	Moderate	Critical	Retrospective design, SMR
Salles, 2022	Critical	Critical	Moderate	Serious	Critical	Critical	Moderate	Critical	Retrospective design

Abbreviations: *MAIC: matching-adjusted indirect comparison; SMR: standardized mortality ratio weighting*

Table 33: Risk of bias, comparative studies (ROBINS-I tool), ***MCL*** *[42]*

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias	Comments
Hess, 2024	Critical	Critical	Moderate	Serious	Critical	Critical	Moderate	Critical	Retrospective design, three weighting methods

Table 34: Risk of bias, comparative studies (ROBINS-I tool), ***multiple myeloma*** *[42]*

Study ID	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias	Comments
Costa, 2022	Critical	Critical	Serious	Serious	Serious	Critical	Moderate	Critical	Retrospective design, PSM
Mateos, 2023	Critical	Critical	Serious	Moderate	Moderate	Critical	Moderate	Critical	Included studies: prospective, probability weighting
Shah, N. 2022	Critical	Critical	Serious	Serious	Serious	Critical	Serious	Critical	Retrospective Design, MAIC

Abbreviations: *MAIC: matching-adjusted indirect comparison; PSM: propensity score matching*

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