Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-225-z Epcoritamab

Stand: Oktober 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Epcoritamab
[rezidivierendes oder refraktäres DLBCL; nach mindestens 2 Linien einer systemischen Therapie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie • Stammzelltransplantation
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Tisagenlecleucel (Beschluss vom 15. Februar 2024) • Glofitamab (Beschluss vom 1. Februar 2024) • Axicabtagen-Ciloleucel (Beschluss vom 21. Dezember 2023) • Loncastuximab tesirin (Beschluss vom 2. November 2023) • Lisocabtagen maraleucel (Beschluss vom 6. April 2023) • Tafasitamab (Beschluss vom 3. März 2022) • Polatuzumab Vedotin (Beschluss vom 20. August 2020) • Pixantron (Beschluss vom 16. Mai 2013) Richtlinie Methoden Krankenhausbehandlung, Stand 7. Dezember 2022: - § 4 - Ausgeschlossene Methoden: Allogene Stammzelltransplantation bei erwachsenen Patienten mit aggressiven B-Non-Hodgkin-Lymphomen, die noch nicht mit autologer Stammzelltransplantation behandelt wurden Anlage I - Methoden, die für die Versorgung im Krankenhaus erforderlich sind: Allogene Stammzelltransplantation bei erwachsenen Patienten mit aggressiven B-Non-Hodgkin-Lymphomen, die nach autologer Stammzelltransplantation rezidivieren und nach Salvage-Therapie ein Ansprechen mindestens im Sinne einer stabilen Erkrankung erreichen.
Die Vergleichstherapie soll nach dem allgemein anerkannten	

Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Epcoritamab L01FX27 Tepkinly	Indikation laut Zulassung: Tepkinly wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären diffusen großzelligen B-Zell-Lymphom (diffuse large B-cell lymphoma, DLBCL) nach mindestens 2 Linien einer systemischen Therapie.
Antineoplastische Mittel	
Bleomycin L01DC01 generisch	Non-Hodgkin-Lymphome von intermediärem oder hohem Malignitätsgrad im Erwachsenenalter. Bleomycinsulfat wird bei diesen Erkrankungen üblicherweise in Kombination mit anderen Zytostatika verwendet.
Cyclophosphamid L01AA01 generisch	Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Non-Hodgkin-Lymphome (in Abhängigkeit vom histologischen Typ und vom Krankheitsstadium auch als Monotherapie)
Cytarabin L01BC01 generisch	Cytarabin wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur: - Behandlung von Non-Hodgkin-Lymphomen von intermediärem und hohem Malignitätsgrad im Erwachsenenalter Cytarabin wird in Kombination mit anderen Zytostatika in der Hochdosistherapie eingesetzt bei: - - refraktären Non-Hodgkin-Lymphomen
Doxorubicin L01DB01 generisch	hochmaligne Non-Hodgkin-Lymphome
Etoposid L01CB01 generisch	Etoposid ist in Kombination mit anderen zugelassenen Chemotherapeutika angezeigt zur Behandlung von Non-Hodgkin-Lymphomen bei erwachsenen und pädiatrischen Patienten.
Ifosfamid	Non-Hodgkin-Lymphome:

L01AA06 generisch	Zur Kombinationschemotherapie bei Patienten mit hochmalignen Non-Hodgkin-Lymphomen, welche nicht oder nur unzureichend auf die Initialtherapie ansprechen. Zur Kombinationstherapie von Patienten mit rezidiven Tumoren.
Melphalan L01AA03 Phelinun	Hochdosiertes PHELINUN, das als Monotherapie oder in Kombination mit anderen zytotoxischen Arzneimitteln und/oder einer Ganzkörperbestrahlung angewendet wird, wird angewendet bei Behandlung von: - […] malignen Lymphomen (Hodgkin-Lymphom, Non-Hodgkin-Lymphom),
Methotrexat L01BA01 generisch	Non-Hodgkin-Lymphome: - im Erwachsenenalter: Zur Behandlung von Non-Hodgkin-Lymphomen von intermediärem oder hohem Malignitätsgrad in Kombination mit anderen zytostatischen Arzneimitteln
Mitoxantron L01DB07 generisch	Mitoxantron ist indiziert zur Behandlung des Non-Hodgkin-Lymphoms.
Pixantron L01DB11 Pixuvri[1]	Die Monotherapie mit Pixuvri ist indiziert zur Behandlung von erwachsenen Patienten mit mehrfach rezidivierten oder therapierefraktären aggressiven Non-Hodgkin-B-Zell-Lymphomen (NHL). Der Nutzen der Pixantron-Behandlung bei Anwendung als Fünft- und Mehrlinientherapie bei Patienten, die refraktär gegen die vorausgegangene Therapie waren, ist nicht erwiesen.
Trofosfamid L01AA07 generisch	Dieses Arzneimittel ist ein Zytostatikum. Trofosfamid wird zur Therapie von Non-Hodgkin-Lymphomen nach Versagen der Standardtherapie angewendet.
Vinblastin L01CA01 generisch	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: - maligne Non-Hodgkin-Lymphome
Vincristin L01CA02 generisch	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - malignen Lymphomen, einschließlich Morbus Hodgkin und Non-Hodgkin-Lymphomen
Vindesin L01CA03 generisch	Kombinationschemotherapie: aggressives Non-Hodgkin-Lymphom (Stadium I oder II)
Glucocorticoide	
Dexamethason	Onkologie:

[1] Derzeit nicht auf dem deutschen Markt verfügbar.

H02AB02 generisch	Palliativtherapie maligner Tumoren Prophylaxe und Therapie von postoperativem oder Zystostatika-induzierten Erbrechen im Rahmen antiemetischer Schmerz
Methylprednisolon H02AB04 Methylprednisolon JENAPHARM®	Blutkrankheiten/Tumorerkrankungen - Autoimmunhämolytische Anämie - Prophylaxe und Therapie von Zytostatika-induziertem Erbrechen, Anwendung im Rahmen antiemetischer Schemata […]“
Prednisolon H02AB06 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Prednison H02AB07 generisch	Hämatologie / Onkologie: Non-Hodgkin-Lymphome
Antikörper-Wirkstoff-Konjugate	
Polatuzumab Vedotin L01FX14 Polivy	Polivy in Kombination mit Bendamustin und Rituximab wird angewendet zur Behandlung erwachsener Patienten mit rezidivierendem oder refraktärem diffusem großzelligem B-Zell-Lymphom (DLBCL), die nicht für eine hämatopoetische Stammzelltransplantation in Frage kommen.
Loncastuximab tesirine L01FX22 Zynlonta	Zynlonta wird angewendet als Monotherapie bei Erwachsenen zur Behandlung des rezidivierten oder refraktären diffusen großzelligen B-Zell-Lymphoms (DLBCL) und des hochmalignen B-Zell- Lymphoms (HGBL) nach zwei oder mehr systemischen Behandlungslinien.
Monoklonale Antikörper	
Glofitamab L01FX28 Columvi	Columvi als Monotherapie ist angezeigt für die Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem diffusem großzelligem B-Zell-Lymphom (DLBCL) nach zwei oder mehr systemischen Behandlungslinien.
Rituximab L01XC02 MabThera	Non-Hodgkin-Lymphom (NHL): - MabThera ist für die Behandlung von Patienten mit CD20-positivem, diffusem großzelligen B-Zell-Non-Hodgkin-Lymphom in Kombination mit einer CHOP(Cyclophosphamid, Doxorubicin, Vincristin, Prednisolon)-Chemotherapie angezeigt.

Tafasitamab L01FX12 Minjuvi	MINJUVI wird angewendet in Kombination mit Lenalidomid gefolgt von einer MINJUVI-Monotherapie für die Behandlung bei erwachsenen Patienten mit rezidiviertem oder refraktärem diffusem großzelligem B-Zell-Lymphom (diffuse large B-cell lymphoma, DLBCL), für die eine autologe Stammzelltransplantation (ASZT) nicht infrage kommt.
CAR-T-Zell-Therapien	
Axicabtagen-Ciloleucel L01XL03 Yescarta	Yescarta wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem diffus großzelligem B-Zell Lymphom (DLBCL) und primär mediastinalem großzelligem B-Zell-Lymphom (PMBCL) nach zwei oder mehr systemischen Therapien.
Tisagenlecleucel L01XL04. Kymriah	Kymriah wird angewendet zur Behandlung von: erwachsenen Patienten mit rezidiviertem oder refraktärem diffus großzelligen B-Zell-Lymphom (DLBCL) nach zwei oder mehr Linien einer systemischen Therapie.
Lisocabtagen maraleucel L01XL08 Breyanzi	Breyanzi wird angewendet zur Behandlung des rezidivierten oder refraktären diffus großzelligen B-Zell-Lymphoms (DLBCL), primär mediastinalen großzelligen B-Zell-Lymphoms (PMBCL) und follikulären Lymphoms Grad 3B (FL3B) bei erwachsenen Patienten nach zwei oder mehr Linien einer systemischen Therapie

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-225z (Epcoritamab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	8. Oktober 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

(A)SCT	(autologous) stem cell transplantation
AE	Adverse Events
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CAR	Chimeric antigen receptor
CR	Complete response
CRS	Cytokine release syndrome
DLBCL	Diffuse large B-cell lymphoma
EFS	Event-free survival
G-BA	Gemeinsamer Bundesausschuss
GCB	Germinal centre B-cell
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HGBL	High-grade B-cell lymphoma
HR	Hazard Ratio
ICANS	immune effector cell-associated neurotoxicity syndrome
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LBCL	Large B-cell lymphoma
LoE	Level of Evidence
NE	Neurological events
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds Ratio
ORR	Overall response rate
OS	Overall Survival
PFS	Progression-free Survival
PMB(C)L	Primär mediastinales großzelliges B-Zell-Lymphom
QOL	Quality of Life
R/R	Relapsed/Refractory
RR	Relatives Risiko
SAE	Severe Adverse Events
SIGN	Scottish Intercollegiate Guidelines Network
SOC	standard of care

TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit einem rezidivierenden oder refraktären diffusen großzelligen B-Zell-Lymphom (diffuse large B-cell lymphoma, DLBCL) nach mindestens 2 Linien einer systemischen Therapie.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zu den Indikationen diffuses großzelliges B-Zell-Lymphom (DLBCL) und chronisch lymphatischer Leukämie durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum für die Recherche nach DLBCL wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 17.07.2024 abgeschlossen. Die Erstrecherche nach CLL wurde am 24.10.2023 durchgeführt, die folgende am 10.07.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die detaillierte Darstellung der Recherchestrategien inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben 1513 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherchen bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ernst M et al., 2021 [3].

Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma (Review)

Fragestellung

To assess the benefits and harms of chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory (r/r) DLBCL.

Methodik

Population:

- people with r/r DLBCL

Intervention/Komparator:

- Intervention: CAR T-cell therapy
- Comparison: not applicable; studies with either a single arm or multiple arms of CAR T-cell therapy without a control group only

Endpunkte:

- OS; QOL; AE; SAE; CRS; PFS; CR

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE and Embase
- until September 11th, 2020

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 13

Charakteristika der Population/Studien:

Table 2. Main study characteristics

Characteristic\study ID	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Arms	Single	Single	Single	Single	Parallel (varying doses)	Parallel (varying doses and combinations with other agents)	Single	Single	Single	Parallel (varying doses)	Single	Single	Single
Phase	1b/2	1/2	1/2	2	1/2	1/2 (data for 1 only)	2	2a	1/2a	1	1	1/2	1
Centre	Single	Multi	Single	Multi	Single	Multi	Single	Single	Single	Multi	Multi	Multi	Multi
Location	Israel	China	USA	Australia, Austria, Canada, France, Germany, Italy, Japan, Netherlands Norway, USA	USA	USA	China	USA	China	USA	China	Israel, USA	USA
Target	CD19	CD19	CD19	CD19	CD19	CD19	CD19 and CD20	CD19	CD19 and CD 20	CD19	CD19	CD19	CD19
Infusions	1	1-3	1	1	1	1	1	1	1	1-2	1	1	1

Table 2. Main study characteristics *(Continued)*

Dose CAR T-cells (median if not otherwise specified)	1 x 106/kg	Range 0.45-4.59 x 106/kg	2 x 106/kg	3 x 108 (range 0.1-6 x)	Reduced from 5 to 1 x 106/kg during study	50 or 100 x 106	CD19: 1 x 106/kg (range 0.2-4 x) CD20: 1 x 106/kg (range 0.1-4 x)	5.79 × 106/kg (range 3.08-8.87 x)	Range 1-6 x 106/kg	50 (in 1-2 doses), 100 or 150 x 106	2 x 106/kg	2 x 106/kg	2 x 106/kg
Co-interventions	None	None	None	None	None	Durvalumab	None	None	None	None	None	None	Atezolizumab
Type and dose of induction chemotherapy	Flu 25 mg/m² for 3 days Cyc 900 mg/m² for 1 day	Flu 30 mg/m² for 3 days Cyc 250 mg/m² for 3 days	Flu 25/30 mg/m² for 3/3 days Cyc 30-500 mg/m² for 1/3 days	Flu 25 mg/m² for 3 days and Cyc 250 mg/m² for 3 days or Bendamustine 90 mg/m² (in lieu of Cyc) for 2 days	Flu 30 mg/m² for 3 days Cyc 300 mg/m² for 3 days	Flu for 3 days (dose NR) Cyc for 3 days (dose NR)	n = 19: Flu 30 mg/m² for 3 days Cyc 750 mg/m² for 1 day n = 2: Ifosfamide 2 g for 3 days	n = 14 (DLBCL subgroup): Hyperfractionated Cyc 1.8 gm/m² (n = 6), Modified EPOCH incl. Cyc 750 mg/m² (n = 2), Cyc 1 gm/m² (n = 2), Bendamustine 90 mg/m² for 2 days (n = 2), Radiation therapy + Cyc 750 mg/m² (n = 1), Infusional etoposide + bolus Cyc incl. Cyc 750 mg/m² (n = 1)	Flu 20-30 mg/m² for 3 days Cyc 20-30 mg/m² divided over 3 days with or without doxorubicin liposome 10 mg/m² for 1 day	Flu 30 mg/m² for 3 days Cyc 300 mg /m² for 3 days	Flu 25 mg/m² for 3 days Cyc 250 mg/m² for 3 days	Flu 30 mg/m² for 3 days Cyc 500 mg/m² for 3 days	Flu 30 mg/m² for 3 days Cyc 500 mg/m² for 3 days
Participants enrolled	18[b]	NR	65 (203 according to CT.gov)	165 (by May 2018)	NR (43 according to CT.gov)	18 (recruitment ongoing)	25	38 (63 according to CT.gov)	33 (100 according to CT.gov)	344	32	119 across phase 1 and 2 (307	12 for phase 1 (37 accord-

Table 2. Main study characteristics *(Continued)*

												according to CT.gov)	ing to CT.gov across phase 1 and 2)
Participants receiving CAR T-cells [a]	18[b]	NR	48	111	22	15	21	28	28	269 (294 total, 25 receiving non-conforming product)	32	108 across phase 1 and 2	12
Participants evaluated	18	13	47	93	22	11	21	28	28	256	29	101 for phase 2	12
Proportion of enrolled participants receiving CAR T-cells [a]	Unclear[b]	Unclear	48/65 (74%)	111/165 (67%)	Unclear	15/18 (83%)	21/25 (84%)	28/38 (74%)	28/33 (85%)	269/344 (78%); 294/344 (85%) including those receiving a non-conforming product	32/32 (100%)	108/119 (91%) for phase 1 and 2	12/12 (100%) for phase 1
Proportion of enrolled participants evaluated	Unclear[b]	Unclear	47/65 (72%)	93/165 (56%)	Unclear	11/18 (61%)	21/25 (84%)	28/38 (74%)	28/33 (85%)	256/344 (74%)	29/32 (91%)	108/119 (91%) for phase 1 and 2	12/12 (100%) for phase 1

CT.gov = Clinicaltrials.gov
Cyc = cyclophosphamide
DLBCL = diffuse large B-cell lymphoma
EPOCH = etoposide, prednisolone, oncovin, cyclophosphamide, and hydroxydaunorubicin
Flu = fludarabine
NR = not reported
[a] The numbers of participants refer to efficacy data retrieved from the primary publication and may include participants with conditions other than r/r DLBCL.
[b] According to a secondary publication, this study enrolled 93 participants, of whom 90 received CAR T-cells including 37 participants with DLBCL whereas, in the primary publication we used to retrieve efficacy data from, only 18 participants with DLBCL were enrolled, of whom all received CAR T-cells and were evaluated.

Table 3. Main participant characteristics

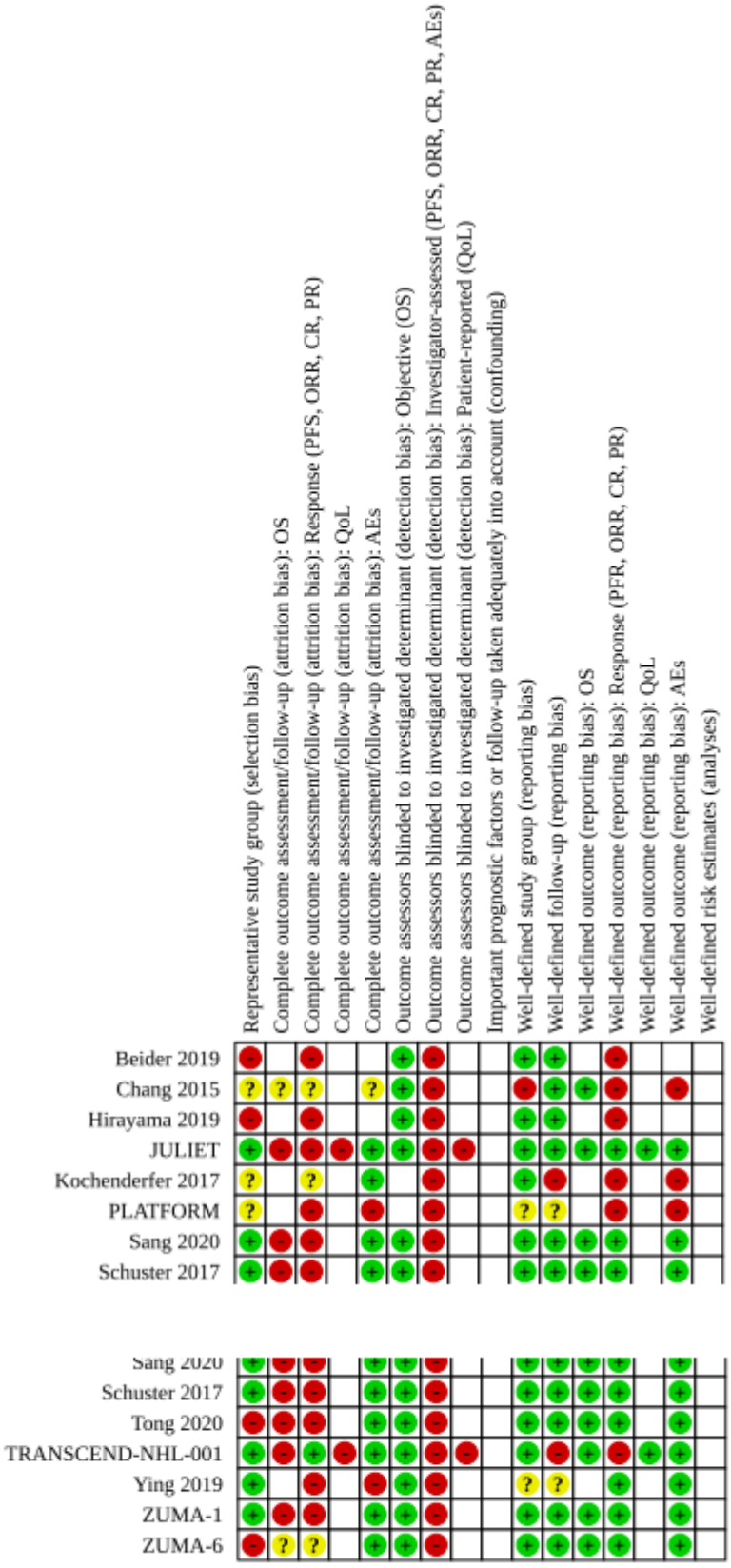
Characteristic\study ID	Beider 2019	Chang 2015	Hirayama 2019	JULIET	Kochenderfer 2017	PLATFORM	Sang 2020	Schuster 2017	Tong 2020	TRANSCEND-NHL-001	Ying 2019	ZUMA-1	ZUMA-6
Population[a] (proportion of participants with DLBCL, type of DLBCL and other conditions if reported)	n = 18 evaluated, n = 17 (94%) DLBCL Type of DLBCL NR	n = 13 evaluated, n = 12 (92%) DLBCL Type of DLBCL NR	n = 48 receiving CAR T-cells (n = 28 (58%) DLBCL (n = 18 DLBCL NOS, n = 10 DLBCL TF from indolent)) n = 47 evaluated, n = 27-28 (56-58%) DLBCL (exact number unclear)	n = 111 receiving CAR T-cells, (n = 109 (98%) DLBCL, n = 88 DLBCL NOS, n = 21 DLBCL TF from follicular lymphoma)	n = 22 receiving CAR T-cells, n = 19 (86%) DLBCL, n = 2 follicular lymphoma, n = 1 mantle cell lymphoma) n = 22 evaluated, NOS: n = 13, TF follicular lymphoma: n = 3, PMBCL: n = 2, TF from CLL: n = 1	n = 11 evaluated, n = 10 (91%) DLBCL Type of DLBCL NR	n = 21 evaluated, n = 21 (100%) (DLBCL (n = 15 refractory DLBCL)	n = 28 evaluated, n = 14 (50%) DLBCL DLBCL participants with performed immune-histochemical studies (n = 12): Relapsed and refractory germinal-centre DLBCL (n = 7); non–germinal-centre DLBCL (n = 5 Refractory DLBCL: 12/14 (86%)	n = 28 evaluated, n = 16 (57%) DLBCL Type of DLBCL NR	n = 256 evaluated, n = 206 (80%) DLBCL; n = 131 DLBCL NOS, n = 57 DLBCL TF from FLL, n = 18 DLBCL TF from other indolent NHL subtypes	n = 29 evaluated, n = 20 (69%) DLBCL Type of DLBCL: NR	n = 108 receiving CAR T-cells across phase 1 and 2; n = 77 DLBCL in phase 2 n = 101 evaluated in phase 2; n = 77 (76%) DLBCL Type of DLBCL: Non-germinal-centre DLBCL	n = 12 evaluated, n = 12 (100%) DLBCL Type of DLBCL NR
Age in years (median and/or range if reported)	40.5 (23-70) (n = 18)	38 (9-61) (n = 12)	58.5 (n = 48)	56 (22-76) (n = 111)	53 (26-67) (n = 19)	53-78 (n = 11)	55 (23-72) (n = 21)	58 (25-77) (n = 14)	≥ 60: 7/28 (25%)	63 (54-70) (n = 269)	52 (29-68) (n = 32)	58 (n = 101)	55 (30-66) (n = 12)

Table 3. Main participant characteristics *(Continued)*

Sex (male/total)	NR	NR	35/48 (73%)	60/93 (65%)	NR	7/11 (64%)	13/21 (62%)	11/14 (79%)	11/28 (39%)	174/269 (65%)	24/32 (75%)	73/108 (68%)	NR
Previous SCT (DLBCL subgroup if reported)	NR	NR	autoSCT: 16/48 (33%) alloSCT: 4/48 (8%) autoSCT and alloSCT: 3/48 (6%)	autoSCT: 54/111 (49%) alloSCT: 0/111 (0%)	autoSCT: 5/19 (26%) alloSCT: NR	NR	autoSCT: 1/21 (5%) alloSCT: NR	autoSCT: 7/14 (50%) alloSCT: 0/14 (0%)	autoSCT: NR alloSCT: 5/28 (18%)	autoSCT: 90/269 (33%) alloSCT: 9/269 (3%)	autoSCT: 1/10 (10%) alloSCT: NR	autoSCT: 16/81 (21%) alloSCT: NR	NR
Previous lines of treatment (median and/or range if reported)	NR	NR	Median: 4 (1-11) (n = 48)	1: 5/111 (5%); 2: 49/111 (44%); 3: 34/111 (31%); 4-6: 23/111 (20%)	Median: 4 (2-7) (n = 19)	NR	Median: 3 (1-6) (n = 21)	Median: 3 (1-8) (n = 14)	≤ 2: 6/28 (21%); 3-5: 15/23 (54%); ≥ 6: 7/23 (25%)	Median: 3 (n = 269)	Median: 4 (2-7) (n = 32)	Median: 3 (n = 108)	NR

alloSCT = allogeneic stem-cell transplantation
autoSCT = autologous stem-cell transplantation
CT.gov = Clinicaltrials.gov
DLBCL = diffuse large B-cell lymphoma
NOS = not otherwise specified
NR = not reported
SCT = stem-cell transplantation
TF = transformed
[a] Due to heterogeneous reporting of the composed sample including participants with conditions other than r/r DLBCL, the number of participants separated by condition is reported for participants receiving CAR T-cells, for participants evaluated, or both.

Qualität der Studien:



Studienergebnisse:

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Overall survival (follow-up: range 6 months to 24 months[a])	Overall survival was reported by eight uncontrolled studies. Four studies reported survival rates at 12 months which ranged between 48% and 59%, and one study reported an overall survival rate of 50.5% at 24 months.	567 (8 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2]
Quality of life (assessed with EQ-5D-5L VAS or FACT-Lym; follow-up: range 1 month to 18 months)	Two uncontrolled studies including 294 participants at baseline and 59 participants at the longest follow-up described improvements of quality of life over time; One study (186 participants at baseline, 38 participants evaluated at 12 months of follow-up) reported an increase in EQ-5D-5L VAS scores (indicating improvement); One study (108 participants at baseline, 21 participants evaluated at 18 months of follow-up) reported an increase in FACT-Lym total scores (indicating improvement).	294 (2 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2]
Any adverse events (follow-up: any time after CAR T-cell infusion)	Five uncontrolled studies reported the occurrence of adverse events among participants, ranging between 99-100% for any grade adverse events and 68-98% for adverse events grade ≥ 3.	550 (5 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2,3]
Any serious adverse events (follow-up: any time after CAR T-cell infusion)	In three uncontrolled studies, 56% to 68% of participants experienced serious adverse events while, in one uncontrolled study, no serious adverse events occurred.	281 (4 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2,3]
Cytokine release syndrome (follow-up: any time after CAR T-cell infusion)	Various grading criteria were used in 11 uncontrolled studies which reported the occurrence of cytokine release syndrome (CRS). Five studies reported between 42% and 100% of participants experiencing CRS according to criteria described in Lee 2014.	675 (11 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2,3]
Progression-free survival (follow-up: range 4 months to 18 months[a])	Nine uncontrolled studies reported results on progression-free survival, disease-free survival or relapse-free survival at any time of follow-up. 12-month progression-free survival rates were reported by four studies and ranged between 44% and 75%. In one study, relapse-free survival remained at a rate of 64% at both 12, and 18 months.	575 (9 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2]
Complete response (follow-up: range 1 month to 6 months[a])	All of the 13 uncontrolled studies provided data on complete response rates. At six months, three studies reported complete response rates between 40% and 45%.	620 (13 observational studies)	⊕⊝⊝⊝ VERY LOW [1,2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

EQ-5D-5L VAS = EuroQol 5-Dimension 5-Level visual analogue scale
FACT-Lym = Function Assessment of Cancer Therapy-Lymphoma
[1] The overall risk of bias was judged to be high for all studies (downgraded by 1 point for risk of bias).
[2] None of the included studies had a control group and effect estimates could not be calculated (downgraded by 1 point for imprecision).
[3] Duration of follow-up varied substantially (downgraded by 1 point for inconsistency).
For all outcomes, our assessment of the certainty of the evidence started with "low certainty" as we only included observational studies.
[a] Due to various follow-up times in the included studies, we included time point-specific outcome data in the summary of findings table only.

Anmerkung/Fazit der Autoren

The available evidence on the benefits and harms of CAR T-cell therapy for people with r/r DLBCL is limited, mainly because of the absence of comparative clinical trials. The results we present should be regarded in light of this limitation and conclusions should be drawn very carefully. Due to the uncertainty in the current evidence, a large number of ongoing investigations and a risk of substantial and potentially life-threatening complications requiring supplementary treatment, it is critical to continue evaluating the evidence on this new therapy.

Kommentare zum Review

Eigentlich geringe Relevanz, da es keinen Vergleich gibt. Aufgrund der geringen Anzahl relevanter Publikationen und der hohen Qualität von CRs wurde das Review trotzdem eingeschlossen.

3.2 Systematische Reviews

Oluwole OO et al., 2024 [6].

Network meta-analysis of CAR T-Cell therapy for the treatment of 3L+ R/R LBCL after using published comparative studies

Fragestellung

our aim was to identify all comparative studies of CAR T-cell therapies and salvage chemotherapy through a systematic literature review, and, where feasible, to provide a more robust evaluation of comparative efficacy and safety using an anchored network meta-analysis (NMA)

Methodik

Population:

- patients with relapsed/refractory DLBCL

Intervention:

- Axicabtagene ciloleucel (Yescarta)
- Tisagenlecleucel (Kymriah)
- Lisocabtagene maraleucel (Breyanzi)

Komparator:

- Salvage chemotherapy
- Standard of care
- Any of the above

Endpunkte:

- OS; PFS; ORR; CR; CRS; NE

Recherche/Suchzeitraum:

- Embase and Medline via Ovid
- inception - 16 January 2023

Qualitätsbewertung der Studien:

- Quality and risk of bias assessments were conducted using the Newcastle-Ottawa Scale (NOS) for cohort studies
- NMA: As there were closed loops in the extended network, inconsistency was assessed using node splitting.

Ergebnisse

Anzahl eingeschlossener Studien:

- 8
- a total of 3 studies were included in the primary evidence base
- with an additional 5 studies included in the extended network

Charakteristika der Population/Studien:

Table S4: Study mapping of the systematic literature review base

Study	Author	Title	Year
MAIC; Summary level tisa-cel (JULIET) vs IPD for liso-cel (TRANSCEND)	Cartron et al[5]	Matching-adjusted indirect treatment comparison of chimeric antigen receptor t-cell therapies for third-line or later treatment of relapsed or refractory large B-cell lymphoma: Lisocabtagene maraleucel versus tisagenlecleucel	2022
MAIC; Summary-level axi-cel (ZUMA-1) vs IPD for liso-cel (TRANSCEND-NHL-001)	Maloney et al[6]	Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B-cell lymphoma	2021
	Maloney et al[7]	Matching-adjusted indirect comparison (MAIC) of lisocabtagene maraleucel (liso-cel) vs axicabtagene ciloleucel (axi-cel) and tisagenlecleucel in relapsed/refractory (r/r) large b-cell lymphoma (LBCL)	2020
Propensity; IPD for tisa-cel (JULIET) vs IPD for SOC (CORAL)	Maziarz et al[8]	Indirect comparison of tisagenlecleucel and historical treatments for relapsed/refractory diffuse large B-cell lymphoma	2022
	Moradi-Lakeh et al[9]	Cost-effectiveness of tisagenlecleucel in paediatric acute lymphoblastic leukaemia (pALL) and adult diffuse large B-cell lymphoma (DLBCL) in Switzerland	2021
Propensity; IPD for sxi-cel (ZUMA-1) vs IPD for salvage (SCHOLAR-1)	Neelapu et al[10]	Comparison of 2-year outcomes with CAR-T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma	2021
	Neelapu et al[11]	A comparison of two-year outcomes in zuma-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory large b cell lymphoma	2019
	Neelapu et al[12]	A comparison of one-year outcomes in ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1 in patients with refractory, aggressive non-Hodgkin lymphoma (NHL)	2017
	Gisselbrecht et al[13]	A comparison of one-year outcomes in patients with refractory large b cell lymphoma from ZUMA-1 (axicabtagene ciloleucel) and SCHOLAR-1	2018
MAIC; IPD for axi-cel (ZUMA-1) vs population tisa-cel (JULIET)	Oluwole et al[14]	Pcn445 indirect treatment comparison of axicabtagene ciloleucel (axi-cel) versus tisagenlecleucel (tisa-cel) in relapsed/refractory large B cell lymphoma (rr-LBCL)	2019
	Oluwole et al[15]	Comparing efficacy, safety, and preinfusion period of axicabtagene ciloleucel versus tisagenlecleucel in relapsed/refractory large b cell lymphoma	2020
MAIC; IPD for axi-cel (ZUMA-1) vs aggregate level liso-cel (TRANSCEND-NHL-001)	Oluwole et al[16]	Matching-adjusted indirect comparison of axi-cel and liso-cel in relapsed or refractory large B-cell lymphoma	2022
	Oluwole et al[17]	Abcl-289: Matching-adjusted indirect comparison (MAIC) of axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) in relapsed or refractory (r/r) large b-cell lymphoma (LBCL) after two or more prior lines of therapy	2021
MAIC; IPD for liso-cel (TRANSCEND) vs summary-level salvage (SCHOLAR-1)	Salles et al[18]	Indirect treatment comparison of liso-cel vs. Salvage chemotherapy in diffuse large b-cell lymphoma: TRANSCEND vs. SCHOLAR-1	2021
MAIC; IPD for tisa-cel (JULIET) vs summary-level liso-cel (TRANSCEND)	Schuster et al[19]	Comparative efficacy of tisagenlecleucel and lisocabtagene maraleucel among adults with relapsed/refractory large b-cell lymphomas: An indirect treatment comparison	2022
	Schuster et al[20]	Abcl-166: Tisagenlecleucel and lisocabtagene maraleucel: Comparative efficacy in patients with relapsed/refractory diffuse large b-cell lymphoma	2021
	Maziarz et al[21]	Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in relapsed/refractory diffuse large b-cell lymphoma (r/r DLBCL)	2021
	Kersten et al[22]	Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in patients with relapsed/refractory diffuse large b-cell lymphoma (r/r DLBCL)	2021

DLBCL, diffuse large B-cell lymphoma; IPD, individual patient data; LBCL, large B-cell lymphoma; MAIC, matching-adjusted indirect comparison; r/r, relapsed/refractory

Qualität der Studien:

Table S5: Newcastle-Ottawa quality assessment of included MAICs

Study comparison	Treatment comparison	Selection (up to ****)	Comparability (up to **)	Outcomes (up to ***)
Historical evidence base				
ZUMA-1 IPD vs SCHOLAR-1 IPD (Propensity score)	Axi-cel vs SoC	****	**	***
TRANSCEND-NHL-001 IPD vs SCHOLAR-1 summary (MAIC)	Liso-cel vs SoC	***	*	***
JULIET IPD vs CORAL IPD (Propensity score)	Tisa-cel vs SoC	****	*	***
Extended evidence base				
ZUMA-1 IPD vs TRANSCEND-NHL-001 summary (MAIC)	Axi-cel vs Liso-cel	***	**	***
TRANSCEND-NHL-001 IPD vs ZUMA-1 summary (MAIC)	Liso-cel vs Axi-cel	***	*	**
JULIET IPD vs TRANSCEND-NHl-001 summary (MAIC)	Tisa-cel vs Liso-cel	***	**	***
TRANSCEND-NHl-001 IPD vs JULIET summary (MAIC)	Liso-cel vs Tisa-cel	***	*	***
ZUMA-1 IPD vs JULIET summary (MAIC)	Axi-cel vs Tisa-cel	***	**	***

Studienergebnisse:

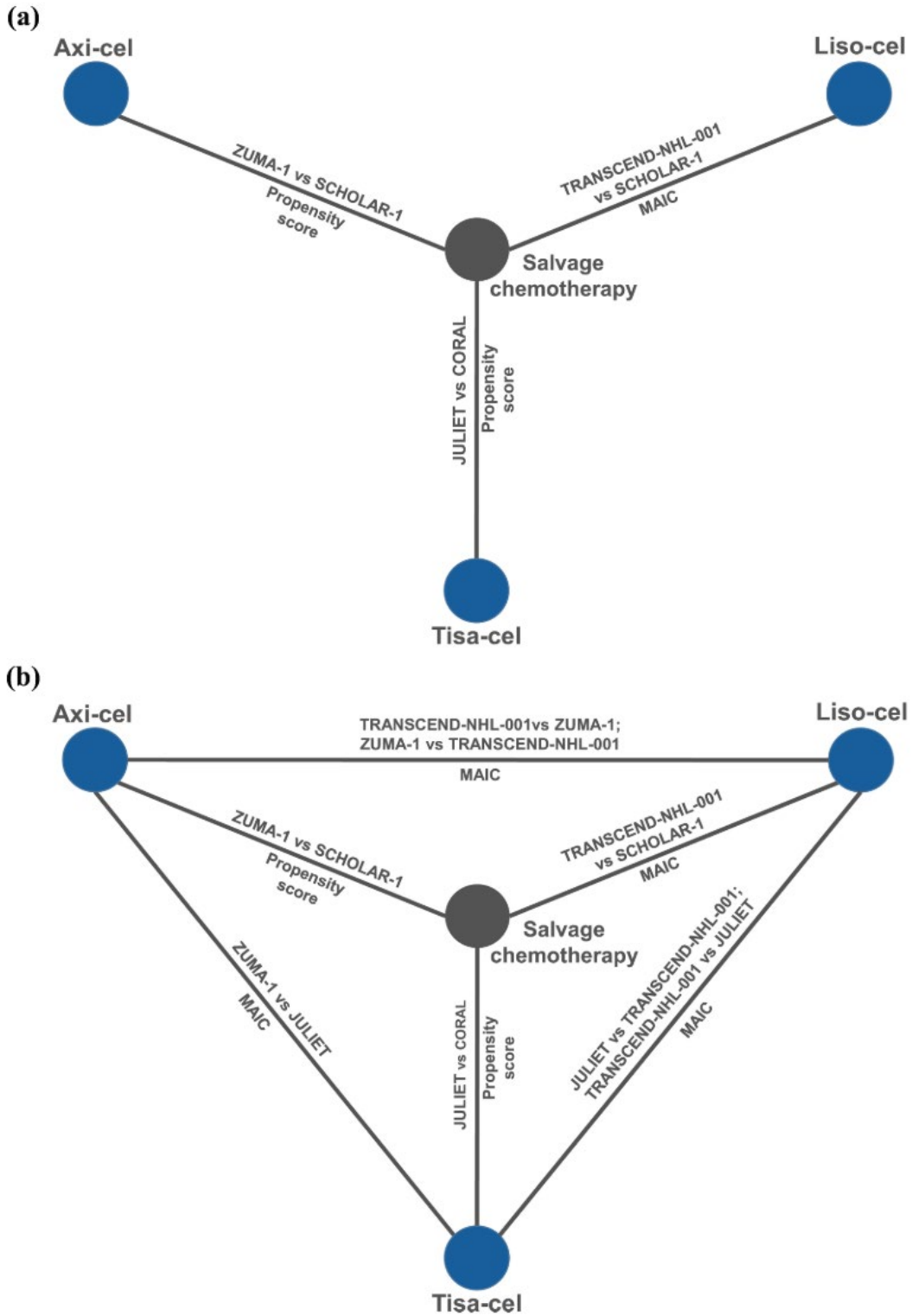


Figure 2. Network of evidence for (a) the primary evidence base; and (b) the extended evidence base. Axi-cel, axicabtagene ciloleucel; IPI, international prognostic index; liso-cel, lisocabtagene maraleucel; MAIC, matching-adjusted indirect comparison; SoC, standard of care, tisa-cel; tisagenlecleucel.

Table 2. Network meta-analysis results using the primary network.

	OS (HR, 95% CrI)	ORR (OR, 95% CrI)	CR (OR, 95% CrI)
Compared to salvage CT:			
Axi-cel vs salvage CT	**0.27 (0.19, 0.38)**	**9.29 (5.18, 18.16)**	**8.57 (4.95, 15.00)**
Liso-cel vs salvage CT	**0.50 (0.40, 0.60)**	**7.06 (4.71, 10.73)**	**12.89 (8.06, 20.87)**
Tisa-cel vs salvage CT	**0.57 (0.44, 0.73)**	**1.66 (1.05, 2.61)**	–
Between CAR T-cell therapy comparison:			
Axi-cel vs liso-cel	**0.54 (0.37, 0.79)**	1.32 (0.64, 2.89)	0.67 (0.32, 1.39)
Axi-cel vs tisa-cel	**0.47 (0.26, 0.88)**	**5.63 (2.66, 12.54)**	–
Liso-cel vs tisa-cel	0.87 (0.42, 1.78)	**4.26 (2.33, 7.93)**	–

Axi-cel, axicabtagene ciloleucel; CAR T-cell therapy, chimeric antigen receptor T-cell therapy; CrI, credible interval; CR, complete response; CT, chemotherapy; liso-cel, lisocabtagene maraleucel; ORR, overall response rate; OS, overall survival; SoC, standard of care; tisa-cel; tisagenlecleucel.

Table 3. Comparison of the three CAR T-cell treatments – NMAs vs published ITC results.

	Network	Axi-cel vs Liso-cel	Axi-cel vs Tisa-cel	Liso-cel vs Tisa-cel
Overall survival (HR)	ITC	**0.53 (0.34–0.82)** [32] 1.23 (0.67–2.27) [14]	**0.51 (0.31–0.83)** [31]	0.89 (0.49–1.61) [29] **0.67 (0.47–0.95)** [33]
	NMA	**0.54 (0.37, 0.79)**	**0.47 (0.26, 0.88)**	0.87 (0.42, 1.78)
Overall response rate (OR)	ITC	2.18 (0.96–4.98) [32] 0.71 (0.29–1.79) [14]	**4.77 (1.90–12.01)** [31]	**2.78 (1.63–4.74)** [33]
	NMA	1.32 (0.64, 2.87)	**5.62 (2.64, 12.42)**	**4.24 (2.28, 7.91)**
Complete response (OR)	ITC	1.84 (0.97–3.50) [32] 0.83 (0.38–1.79) [14]	**2.65 (1.26–5.58)** [31]	**2.01 (1.22–3.30)** [33]
	NMA	0.67 (0.32, 1.37)	–	–

ITC results are from published matching-adjusted indirect comparisons, anchored results are from the NMA we conducted. IPD was used for axi-cel in two studies [15]; 95% CI's were used in the published ITC studies, and 95% CrI's were used in the NMA comparisons and; IPD was used for liso-cel in two studies [14,43]; IPD was used for tisa-cel in one study [44]; otherwise summary level data was used. Note that for axi-cel vs liso-cel, the primary analysis did not include liso-cel patients who had received bridging therapy.
Axi-cel, axicabtagene ciloleucel; CI, confidence interval; CrI, credible interval; HR, hazard ratio; ITC, indirect treatment comparison; liso-cel, lisocabtagene ciloleucel; NMA, network meta-analysis; OR, odds ratio; tisa-cel, tisagenlecleucel.

Across all outcomes, CAR T-cell therapies performed significantly better than salvage chemotherapy. For OS, the HRs of 0.27 (95% credible interval [CrI]: 0.19–0.38), 0.50 (95% CrI: 0.40–0.60) and 0.57 (95% CrI: 0.44–0.73) favored axi-cel, liso-cel and tisa-cel, respectively, when compared to salvage chemotherapy. Similarly, response outcomes were in favor of CAR T-cell therapies in comparison to salvage chemotherapy, although CR was not reported in the tisa-cel study.

When comparing CAR T-cell therapies using the anchored network, axi-cel was associated with a significant improvement in OS compared to liso-cel (HR: 0.54; 95% CrI: 0.37–0.79) and tisa-cel (HR: 0.47; 95% CrI: 0.26–0.88). The comparison of OS between liso-cel and tisa-cel was not statistically differentiable (HR: 0.87; 95% CrI: 0.42–1.78). For ORR, axi-cel was associated with a higher response rate compared to tisa-cel (OR: 5.62; 95% CrI: 2.64–12.42), but not liso-cel (OR: 1.32; 95% CrI: 0.64–2.87), and liso-cel was associated with a higher response rate compared to tisa-cel (OR: 4.24; 95% CrI: 2.28–7.91). For CR, only a comparison between axi-cel and liso-cel was possible, and no significant difference was observed (OR: 0.67; 95% CrI: 0.32–1.37) between these treatments.

The extended network also provided an opportunity to analyze safety outcomes (Supplementary Table S9). There was an increased risk of CRS and NE with axi-cel relative to both liso-cel and tisa-cel. The odds ratio of grade ≥3 CRS with axi-cel relative to liso-cel was 4.63 (95% CrI: 2.01–11.48) and relative to tisa-cel was 0.47 (95% CrI: 0.17–1.13). The odds ratio of grade ≥3 NE with axi-cel relative to liso-cel was 4.53 (95% CrI: 2.68–7.69) and relative to tisa-cel was 2.85 (95% CrI: 1.47– 5.45). Liso-cel and tisa-cel were not statistically different with respect to NEs, but liso-cel led to reduced odds of CRS relative to tisa-cel.

Anmerkung/Fazit der Autoren

CAR T-cell therapies have addressed a substantial unmet need for R/R LBCL patients who previously experienced poor outcomes from salvage chemotherapy. Among these, axi-cel has been associated with improved survival relative to tisa-cel and liso-cel and these findings are consistent both with other published ITCs and a growing body of real-world evidence.

Gagelmann N et al., 2024 [4].

Axicabtagene Ciloleucel versus Tisagenlecleucel for Relapsed or Refractory Large B Cell Lymphoma: A Systematic Review and Meta-Analysis

Fragestellung

In the present study we aimed to synthesize the existing evidence on the actual outcomes of axi-cel and tisacel in patients with relapsed or refractory DLBCL.

Methodik

Population:

- adult patients

Intervention/Komparator:

- axi-cel or tisa-cel

Endpunkte:

- PFS; OS; relapse/progression, overall and complete response, adverse events, CRS, ICANS

Recherche/Suchzeitraum:

- MEDLINE; Cochrane Central Register of Controlled Trials etc.
- May 1, 2023

Qualitätsbewertung der Studien:

- ROBINS-I
- overall body of evidence was assessed using the GRADE approach
- the overall heterogeneity was assessed using the I^2 index

Ergebnisse

Anzahl eingeschlossener Studien:

- 8
- 2372 participants

Charakteristika der Population/Studien:

Table 1
Characteristics of the Included Studies

Study	Number of Patients		Age, yr, median		DLBCL, %		Prior Lines of Therapy, median (range)/(%)		Days from Apheresis to Infusion		Bridging, %		Prior SCT, %		LDH > Normal, %		ECOG PS 0-1, %	
	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel	Axi-cel	Tisa-cel
Bethge et al., 2022 [27]	173	183	60	61	88	93	≥3 (67)	≥3 (74)	35	55	72	84	33	35	65	55	84	84
Bachy et al., 2022 [29]	494	315	63	64	74	78	2 (2-8)	3 (2-10)	NR		82	86	21	26	55	50	86	82
Kwon et al., 2023 [25]	152	155	59	62	75	64	2 (2-6)	2 (2-7)	NR		78	83	31	29	50	60	95	93
Gauthier et al., 2022 [26]	68	31	62	64	74	58	3 (2-4)	3 (2-4)	27	40	59	71	NR		NR		NR	
Benoit et al., 2023 [28]	15	10	59	67	67	60	≥3 (0)	≥3 (5)	28	36	44		47	40	NR		100	
Kuhnl et al., 2022 [24]	292	112	57	63	64	75	≥3 (37)	≥3 (42)	40	50	88	82	18	12	71	73	90	91
Riedell et al., 2022 [30]	168	92	59	67			3 (2-10)	4 (2-9)	28	45								
Mian et al., 2023 [31]	55	29	<65: 65/41		100	100	≥4 (42)	≥4 (34)	NR		NR		45	24	NR		75	76

NR indicates not reported.

Qualität der Studien:

Table 1. Risk of bias of included studies.

Study	Confounding	Selection of participants	Classification of participants	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias
Bethge	Yes	No	PN	Yes	PN	Yes	Yes	Moderate
Bachy	Yes	Yes	Yes	Yes	PN	Yes	Yes	Low
Kwon	Yes	Yes	Yes	Yes	PN	Yes	Yes	Low
Gauthier	Yes	No	PN	Yes	PN	Yes	PN	Moderate
Benoit	No	No	PN	Yes	PN	Yes	PN	Serious
Kuhnl	Yes	Yes	Yes	Yes	PN	Yes	Yes	Low
Riedell	Yes	Yes	Yes	Yes	PN	Yes	Yes	Low
Mian	No	No	PN	Yes	PN	Yes	PN	Serious

Table 2. Quality assessment.

No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Axi-cel	Tisa-cel	Odds ratio (95% CI)	Quality	Importance
Overall response										
7	Low	Not Serious	Not serious	Not serious	NA	1009	755	1.93 (1.57-2.37)	⊕⊕⊕◯ Moderate	Critical
Complete response										
7	Low	Not Serious	Not serious	Not serious	NA	1009	755	1.65 (1.35-2.02)	⊕⊕⊕◯ Moderate	Critical
Progression-free survival										
6	Low	Not Serious	Not serious	Not serious	NA	941	725	0.60 (0.48-0.74)	⊕⊕⊕◯ Moderate	Critical
Overall survival										
5	Low	Not Serious	Not serious	Serious[a]	NA	926	715	0.84 (0.68-1.02)	⊕⊕◯◯ Low	Critical
Non-relapse mortality										
4	Low	Not Serious	Not serious	Not serious	NA	785	532	2.40 (1.38-4.16)	⊕⊕⊕⊕ High	Critical
CRS										
7	Low	Serious[b]	Not serious	Not serious	NA	991	728	3.23 (2.20-4.74)	⊕⊕⊕⊕ High	Critical
ICANS										
7	Low	Not Serious	Not serious	Not serious	NA	991	728	4.04 (2.90-5.65)	⊕⊕⊕⊕ High	Critical

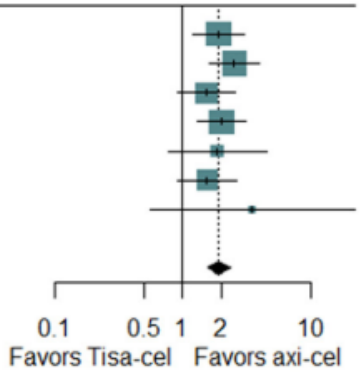
[a]Estimates crossing decision threshold
[b] I^2=53%, P=0.05

Studienergebnisse:

Overall response

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	91	152	68	155	20.5%	1.91 (1.21- 3.00)
Bethge 2021	128	173	97	183	21.1%	2.52 (1.61- 3.94)
Riedell 2022	87	168	38	92	16.0%	1.53 (0.91- 2.55)
Bachy 2022	168	209	140	209	21.1%	2.02 (1.29- 3.16)
Gauthier 2022	49	68	18	31	5.3%	1.86 (0.77- 4.53)
Kuhnl 2022	106	224	28	76	14.7%	1.54 (0.90- 2.63)
Benoit 2023	7	15	2	10	1.2%	3.50 (0.55-22.30)
Total (95% CI)	**1009**		**756**		**100.0%**	**1.93 (1.57- 2.37)**

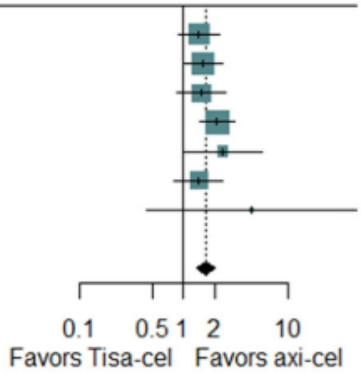
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.31$, df = 6 (P = .77); $I^2 = 0\%$
Test for overall effect: Z = 6.26 (P < .01)



Complete response

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	64	152	53	155	18.7%	1.40 (0.88- 2.22)
Bethge 2021	73	173	59	183	21.3%	1.53 (1.00- 2.36)
Riedell 2022	74	168	32	92	14.4%	1.48 (0.87- 2.50)
Bachy 2022	126	209	88	209	26.2%	2.09 (1.41- 3.08)
Gauthier 2022	36	68	10	31	5.0%	2.36 (0.97- 5.76)
Kuhnl 2022	94	224	26	76	13.5%	1.39 (0.81- 2.39)
Benoit 2023	5	15	1	10	0.7%	4.50 (0.44-46.17)
Total (95% CI)	**1009**		**756**		**100.0%**	**1.65 (1.35- 2.02)**

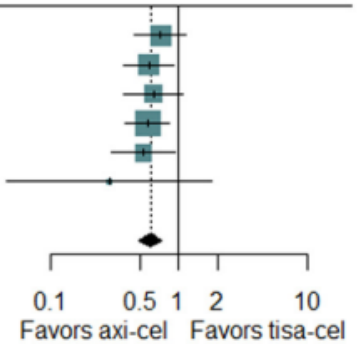
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.88$, df = 6 (P = .69); $I^2 = 0\%$
Test for overall effect: Z = 4.93 (P < .01)



Progression-free survival

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	90	152	104	155	20.4%	0.71 (0.45-1.13)
Bethge 2021	112	173	139	183	20.9%	0.58 (0.37-0.92)
Riedell 2022	97	168	63	92	15.4%	0.63 (0.37-1.07)
Bachy 2022	112	209	140	209	28.2%	0.57 (0.38-0.85)
Kuhnl 2022	130	224	55	76	13.7%	0.53 (0.30-0.93)
Benoit 2023	8	15	8	10	1.3%	0.29 (0.04-1.82)
Total (95% CI)	**941**		**725**		**100.0%**	**0.60 (0.48-0.74)**

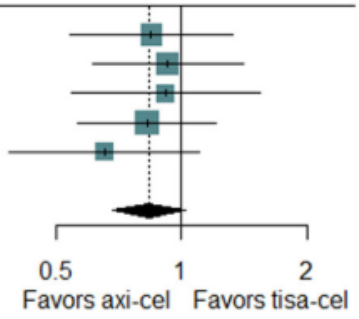
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.44$, df = 5 (P = .92); $I^2 = 0\%$
Test for overall effect: Z = -4.82 (P < .01)



Overall survival

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	74	152	82	155	20.1%	0.84 (0.54-1.32)
Bethge 2021	78	173	86	183	23.1%	0.93 (0.61-1.41)
Riedell 2022	64	168	37	92	14.9%	0.91 (0.54-1.54)
Bachy 2022	97	209	107	209	27.3%	0.83 (0.56-1.21)
Kuhnl 2022	103	224	43	76	14.6%	0.65 (0.39-1.10)
Total (95% CI)		**926**		**715**	**100.0%**	**0.84 (0.68-1.02)**

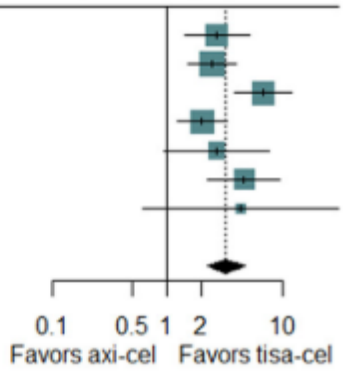
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.20$, df = 4 (P = .88); $I^2 = 0\%$
Test for overall effect: Z = -1.75 (P = .08)



Any CRS

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	118	134	93	127	15.8%	2.70 (1.40- 5.18)
Bethge 2021	141	173	118	183	19.8%	2.43 (1.49- 3.96)
Riedell 2022	133	168	33	92	17.9%	6.79 (3.86-11.96)
Bachy 2022	180	209	158	209	19.4%	2.00 (1.21- 3.31)
Gauthier 2022	59	68	22	31	9.2%	2.68 (0.94- 7.63)
Kuhnl 2022	208	224	56	76	14.4%	4.64 (2.26- 9.54)
Benoit 2023	13	15	6	10	3.4%	4.33 (0.61-30.57)
Total (95% CI)		**991**		**728**	**100.0%**	**3.23 (2.20- 4.74)**

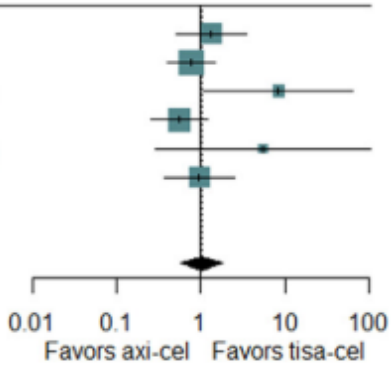
Heterogeneity: $Tau^2 = 0.131$; $Chi^2 = 12.81$, df = 6 (P = .05); $I^2 = 53\%$
Test for overall effect: Z = 5.99 (P < .01)



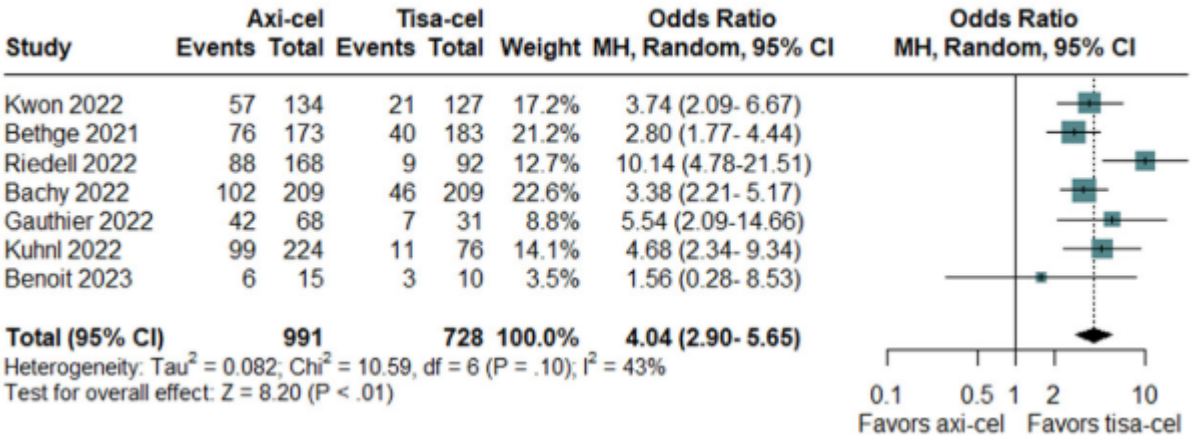
Severe CRS

Study	Axi-cel Events	Axi-cel Total	Tisa-cel Events	Tisa-cel Total	Weight	Odds Ratio MH, Random, 95% CI
Kwon 2022	11	134	8	127	19.6%	1.33 (0.52- 3.42)
Bethge 2021	18	173	24	183	27.5%	0.77 (0.40- 1.47)
Riedell 2022	14	168	1	92	6.5%	8.27 (1.07- 63.96)
Bachy 2022	11	209	19	209	24.0%	0.56 (0.26- 1.20)
Gauthier 2022	5	68	0	31	3.4%	5.46 (0.29-101.82)
Kuhnl 2022	17	224	6	76	19.0%	0.96 (0.36- 2.53)
Benoit 2023	0	15	0	10	0.0%	
Total (95% CI)		**991**		**728**	**100.0%**	**1.03 (0.59- 1.82)**

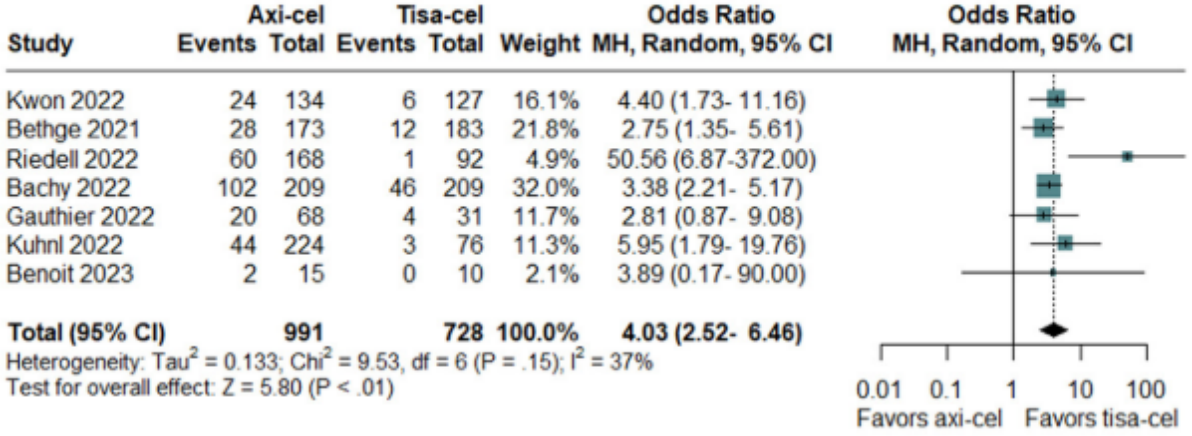
Heterogeneity: $Tau^2 = 0.194$; $Chi^2 = 8.69$, df = 5 (P = .12); $I^2 = 42\%$
Test for overall effect: Z = 0.11 (P = .92)



Any ICANS



Severe ICANS



Severe neutropenia

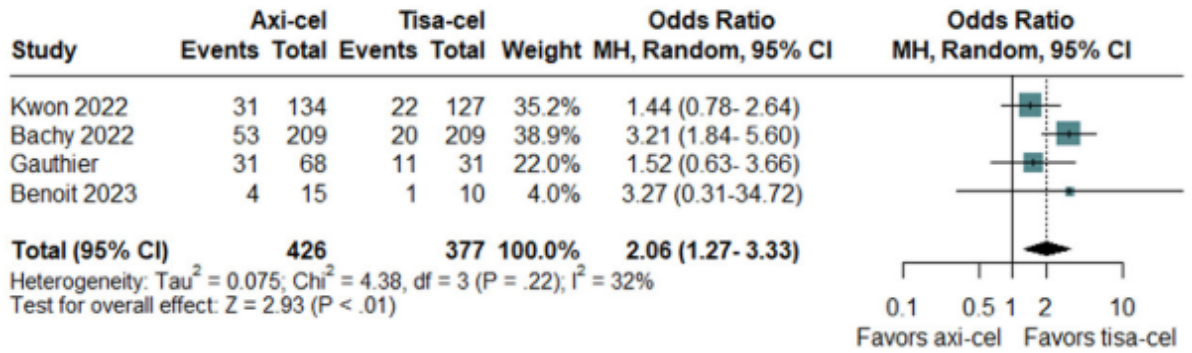


Figure 3. Safety outcomes of axi-cel versus tisa-cel in terms of CRS of any grade, CRS grade ≥ 3, ICANS of any grade, ICANS grade 3, and severe neutropenia at 1 month after CAR-T infusion.

Anmerkung/Fazit der Autoren

Our study provides strong evidence of the greater efficacy of axi-cel versus tisa-cel; however, the higher toxicity and NRM seen with axicel might not counterbalance the overall results and highlight the need for more careful screening and timely intervention for these patients. This study also highlights the need for adequate reporting of study results and may facilitate clinicians' choice of CAR-T product for a specific patient, balancing safety and efficacy.

3.3 Leitlinien

Leitlinienprogramm Onkologie, 2022 [1,2].

Deutsche Krebsgesellschaft (DKG), Deutsche Krebshilfe (DKH), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF).

Diagnostik, Therapie und Nachsorge für erwachsene Patient*innen mit einem diffusen großzelligen B-Zell-Lymphom und verwandten Entitäten; S3-Leitlinie

Zielsetzung/Fragestellung

Das primäre Ziel dieser S3-Leitlinie ist es, die Diagnostik, Therapie und Nachsorge von erwachsenen Patient*innen mit einem diffusen großzelligen B-Zell-Lymphom (DLBCL, diffuse large B-cell lymphoma) und verwandten Entitäten zu standardisieren und zu optimieren, um sowohl bei der Ersterkrankung als auch beim Rezidiv ein individuell adaptiertes, qualitätsgesichertes Therapiekonzept zu gewährleisten.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – **trifft zu**;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – **trifft zu**;
- Systematische Suche, Auswahl und Bewertung der Evidenz – **trifft zu**;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – **trifft zu**;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – **trifft zu**;
- Regelmäßige Überprüfung der Aktualität gesichert – **trifft zu** (Gültig bis: 30.10.2027)

Recherche/Suchzeitraum:

- Vom 10.06.2012 bis zum 10.06.2022.
- Am 09.06.2020 fand eine Suche nach relevanten Leitlinien statt. Es wurde jeweils mit den Suchbegriffen „aggressiv“, „diffus“, „DLBCL“, „Lymphom“ und „Hodgkin“ in der Datenbank des Guideline International Networks (www.g-i-n.net, GIN) sowie systematisch in Medline nach relevanten Leitlinien gesucht
- Zusätzlich zu eigenen systematischen Recherchen wurde auf der Website des IQWiG/G-BA mit den Suchbegriffen „DLBCL“ und „Lymphom“ nach Dossierbewertungen gesucht, die sich auf die Behandlung von Patient*innen mit einem DLBCL beziehen.

LoE/GoR

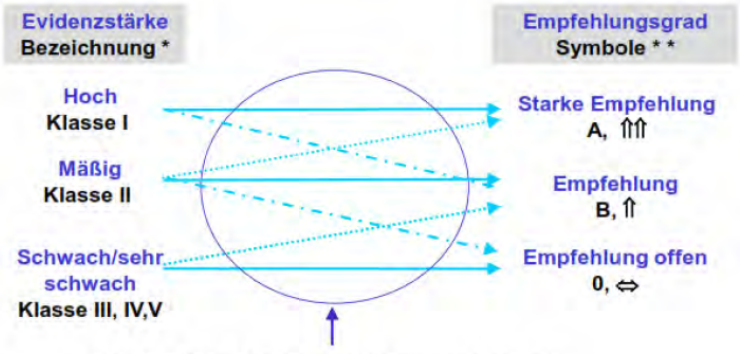
- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Tabelle 4: Vertrauen in den Evidenzkorper gemaß GRADE

Qualität der Evidenz	Beschreibung	Symbol
Hohe Qualität	Wir sind sehr sicher, dass der wahre Effekt nahe bei dem Effektschätzer liegt.	⊕⊕⊕⊕
Moderate Qualität	Wir haben mäßig viel Vertrauen in den Effektschätzer: der wahre Effekt ist wahrscheinlich nahe bei dem Effektschätzer, aber es besteht die Möglichkeit, dass er relevant verschieden ist.	⊕⊕⊕⊖
Geringe Qualität	Unser Vertrauen in den Effektschätzer ist begrenzt: Der wahre Effekt kann durchaus relevant verschieden vom Effektschätzer sein.	⊕⊕⊖⊖
Sehr geringe Qualität	Wir haben nur sehr wenig Vertrauen in den Effektschätzer: Der wahre Effekt ist wahrscheinlich relevant verschieden vom Effektschätzer.	⊕⊖⊖⊖

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Abbildung 1: Schema zur Darstellung der kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades



Kriterien für die Graduierung (Konsensusaspekte):

- Konsistenz der Studienergebnisse
- Klinische Relevanz der Endpunkte und Effektstärken
- Nutzen-Risiko-Verhältnis
- Ethische, rechtliche, ökonomische Erwägungen
- Patientenpräferenzen
- Anwendbarkeit, Umsetzbarkeit

*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;
**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien: Die Empfehlungen wurden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [777]

Empfehlungen

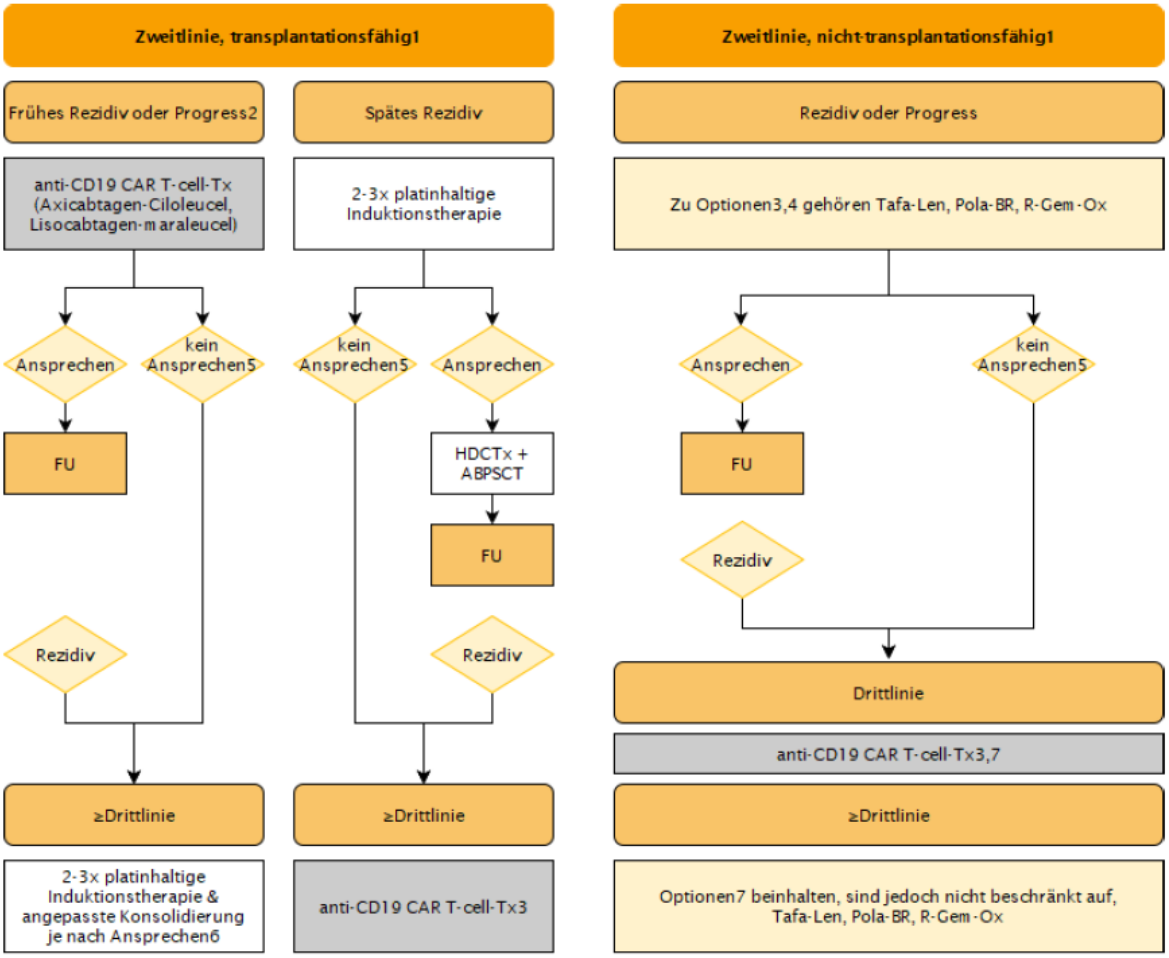


Abbildung 3: Therapie des rezidivierten DLBCL

1 Es gibt keine validierte Methode, um die Eignung für HDCT (Hochdosis-Chemotherapie) festzustellen. Die mit HDCT assoziierte Mortalität kann mit HCT-CI (Hematopoietic Cell Transplantation-specific Comorbidity Index) festgestellt werden.
2 Definiert als Rückfall oder Fortschreiten der Krankheit innerhalb von 12 Monaten nach Abschluss der Erstlinientherapie.
3 Es gibt keinen direkten Vergleich der verschiedenen Behandlungsmöglichkeiten. Eine individuelle Nutzen-Risiko-Abwägung ist bei Festlegung der Indikation notwendig. Der Einsatz von verschiedenen CAR TZell Behandlungen hängt vom Zulassungsstatus ab.
4 Bestrahlung.
5 Patient*innen mit einem PET-positiven Restbefall nach systemischer Zweitlinientherapie erhalten eine konsolidierende Ansprechen ist definiert als komplette oder partielle metabolische Remission, entsprechend den Lugano-Kriterien.
6 Bei Chemotherapie-sensitiver Erkrankung besteht die Option zur Konsolidierung mit autologer oder allogener Stammzelltransplantation.
7 In der Drittlinie und späteren Linien ist eine individuelle Nutzen-Risiko-Bewertung notwendig, diese beeinflusst die Reihenfolge der Behandlungsempfehlungen.
ABPSCT = autologe periphere Blutstammzelltransplantation; Anti-CD19 CAR T-cell-T = gegen CD19 gerichtete CAR (chimärer Antigenrezeptor) T-Zelltherapie; FU = Follow-up; HDCT = Hochdosis-Chemotherapie; Pola-BR = Polatuzumab vedotin, Bendamustin, Rituximab; R-Gem-Ox = Rituximab, Gemcitabin, Oxaliplatin; Tafa-Len = Tafasitamab, Lenalidomid

8.12	Konsensbasierte Empfehlung	2022
EK	Bei primär kurativer Therapieintention soll bei Patient*innen im ≥ 2. Rezidiv oder Progress eines DLBCL eine CAR T-Zelltherapie durchgeführt werden, falls diese nicht in der Zweitlinientherapie erfolgt ist.	
	Starker Konsens	

8.13	Konsensbasierte Empfehlung	2022
EK	Bei primär kurativer Therapieintention für Patient*innen im ≥ 2. Rezidiv oder Progress eines DLBCL und nach erfolgter CAR T- oder nicht durchführbarer CAR T-Zelltherapie soll die Möglichkeit einer allogenen Stammzelltransplantation angeboten werden.	
	Starker Konsens	

8.14	Konsensbasierte Empfehlung	2022
EK	Für Patient*innen im ≥ 2. Rezidiv oder Progress eines DLBCL und bei primär kurativer Therapieintention soll bei Hochdosistherapie-fähigen Patient*innen die Möglichkeit einer weiteren konventionellen Immunchemotherapie zur Remissionsinduktion angeboten werden.	
	Starker Konsens	

8.15	Konsensbasierte Empfehlung	2022
EK	Für Hochdosistherapie-fähige Patient*innen sollte bei Erreichen einer partiellen oder kompletten metabolischen Remission des DLBCL durch eine konventionelle Immunchemotherapie auch jenseits der Zweitlinientherapie eine konsolidierende Hochdosischemotherapie mit autologer Stammzelltransplantation angeboten werden.	
	Starker Konsens	

8.16	Konsensbasierte Empfehlung	2022
EK	Für Patient*innen im ≥ 2. Rezidiv oder Progress eines DLBCL und bei primär palliativer Therapieintention oder zur Remissionsinduktion vor einer geplanten Therapie in kurativer Intention („Bridging“) soll eine Therapie mit • Polatuzumab in Kombination mit Bendamustin und Rituximab oder • Tafasitamab und Lenalidomid oder • einer konventionellen Immunchemotherapie oder • zielgerichteten Substanzen oder • einer Bestrahlung angeboten werden. CAVE: Beim off-label use von zielgerichteten Substanzen ist die Kostenübernahme nicht gesichert.	
	Starker Konsens	

National Institute for Health and Care Excellence, 2016 [5]

Non-Hodgkin’s lymphoma: diagnosis and management.

Zielsetzung

This guideline covers diagnosing and managing non-Hodgkin’s lymphoma in people aged 16 years and over. It aims to improve care for people with non-Hodgkin’s lymphoma by promoting the best tests for diagnosis and staging and the most effective treatments for 6 of the subtypes. Tests and treatments covered include excision biopsy, radiotherapy, immunochemotherapy and stem cell transplantation.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium,
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt,
- Systematische Suche, Auswahl und Bewertung der Evidenz,
- Konsensfindung erwähnt, aber nicht detailliert beschrieben[1], externes Begutachtungsverfahren dargelegt,
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt,
- Regelmäßige Überprüfung der Aktualität gesichert: Last update: 10.2021.

Recherche/Suchzeitraum:

The following databases were included in the literature search:

- The Cochrane Library
- Medline and Premedline 1946 onwards
- Excerpta Medica (Embase) 1974 onwards

[1] In most cases the committee reaches decisions through a process of informal consensus, but sometimes formal voting procedures are used (siehe 'Developing NICE guidelines: the manual')

- Web of Science [specifically Science Citation Index Expanded (SCI-Expanded) 1900 onwards and Social Sciences Citation Index (SSCI) 1900 onwards]

Subject specific databased used for certain topics:

- Cumulative Index to Nursing and Allied Health Literature (CINAHL) 1937 onwards
- PsycINFO 1806 onwards
- Allied and Complementary Medicine (AMED) 1985 onwards

[…] searches were updated and re-run 8 weeks before the guideline was submitted to NICE for stakeholder consultation. […] Any evidence published after this date was not included. For the purposes of updating this guideline, 1st September 2015 should be considered the starting point for searching for new evidence.

LoE

Tabelle 4: Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GoR

The wording used in the recommendations in this guideline denotes the certainty with which the recommendations were made. […] Recommendations were based on the trade-off between the benefits and harms of an intervention, whilst taking into account the quality of the underpinning evidence. […] Terms used within this guideline are:

- 'Offer' – for the vast majority of patients, an intervention will do more good than harm (based on high quality evidence)
- 'Do not offer' – the intervention will not be of benefit for most patients (based on high quality evidence)
- 'Consider' – the benefit is less certain, and an intervention will do more good than harm for most patients (based on poor quality evidence or no evidence). The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for an 'offer' recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendations

Salvage therapy and consolidation with stem cell transplantation

Offer salvage therapy with multi-agent immunochemotherapy to people with relapsed or refractory diffuse large B-cell lymphoma who are fit enough to tolerate intensive therapy:

- Explain that this is primarily to obtain sufficient response to allow consolidation with autologous or allogeneic stem cell transplantation, but is also beneficial even if not followed by transplantation.

- Consider R-GDP immunochemotherapy, which is as effective as other commonly used salvage regimens and less toxic.

Offer consolidation with autologous stem cell transplantation to people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial response to chemotherapy) who are fit enough for transplantation.

Consider consolidation with allogeneic stem cell transplantation for people with chemosensitive diffuse large B-cell lymphoma (that is, there has been at least a partial reponse to chemotherapy):

- that relapses after autologous stem cell transplantation or
- in whom stem cell harvesting is not possible.

Quality of the evidence

The quality of the evidence was moderate to very low using GRADE.

Evidence comparing transplantation to non-transplantation strategies was lacking. The randomised trials involving autologous transplantation compared different salvage chemotherapy regimens. Only non comparative studies were available for allogeneic transplantation. This limited the strength of the recommendation that the Guideline Committee (GC) were able to make about allogeneic transplantation.

Trade-off between clinical benefits and harms

The GC considered that the recommendation to offer salvage therapy and consolidation with autologous transplantation would prolong overall survival. Evidence from trials comparing different salvage chemotherapies followed by autologous stem cell transplant indicated overall survival of around 40% and event free survival around 30%.

The use of high dose therapy with autologous transplantation however is associated with toxicity including late effects and in some cases treatment related mortality.

The GC considered that the increased overall survival outweighed the harms due to acute and late effects.

The recommendation to consider salvage therapy R-GDP instead of R-DHAP, has the potential to reduce treatment related toxicity without adversely affecting overall survival. This recommendation was informed by a randomised trial which indicated R-GDP was as effective as R-DHAP with similar overall and event free survival, but with fewer serious adverse events (47% versus 60%).

Evidence about allogeneic stem cell transplant indicated overall survival of around 40% at five years with similar rates of acute and chronic graft versus host disease.

4.4.3.1 Clinical evidence

Evidence came from three randomised controlled trials, three retrospective cohort studies and four retrospective case series.

4.4.3.1.1 R-BEAM followed by ASCT versus B-BEAM followed by ASCT

Low quality evidence from one study of 224 patients reported that overall rate of grade 3-5 non-haematologic toxicities and grade 3-5 mucositis, but not other individual grade 3-5 non-haematologic toxicities, overall survival, progression-free survival, and treatment-related mortality were significantly lower in R-BEAM than B-BEAM (HRs not reported [BMT CTN 0401]).

4.4.3.1.2 R-ICE followed by ASCT versus R-DHAP followed by ASCT

One study (CORAL) with 477 patients provided moderate quality evidence that overall survival, progression-free survival, and event-free survival did not differ significantly between R-ICE and R-DHAP (HRs not reported).

4.4.3.1.3 (R-)GDP followed by ASCT versus (R-)DHAP followed by ASCT

One study with 619 patients (NCIC-CTG LY-12) provided low quality evidence that quality of life was significantly better or similar in (R-)GDP compared to (R-)DHAP and grade 3-4 nausea, febrile neutropenia and overall occurred significantly less in (R-)GDP than in (R-)DHAP, but the treatment groups did not differ in other individual grade 3-4 adverse events, overall survival, overall survival after transplantation, event-free survival, event-free survival after transplantation, overall response rate and rate of ASCT transplantation (HRs not reported),

4.4.3.1.4 R-ICE versus R-GDP as salvage chemotherapy

Low quality evidence from an indirect comparison of two randomised trials (CORAL and NCIC-CTG LY.12) suggested uncertainty about whether outcomes are better with R-GDP than with RICE.

4.4.3.1.5 R(if CD+)-ICE followed by ASCT (if < 66 years and response) versus R(if CD+)-DHAP followed by ASCT (if < 66 years and response) versus R(if CD+)-GDP followed by ASCT (if < 66 years and response)

Very low quality evidence from one study with 113 patients (Kusano et al, 2014) reported median second progression-free survival was longer in (R-)ICE than in two other two treatment groups combined and in (R-)ICE compared to (R-)DHAP alone, but not to (R-)GDP alone. There was significantly more grade 3-4 renal dysfunction with (R-)DHAP than in other two treatment groups, but the three treatment groups did not differ in overall or complete response, overall survival ((R-)ICE versus the other two treatment groups combined), median time from first progression to second progression or last follow up, and grade 3-4 haematological side effects (HRs not reported).

4.4.3.1.6 R-MICE versus R-DICEP

Oh et al (2015) provided very low quality evidence that median time to progression was significantly longer in R-MICE than R-DICEP (HR not reported; n = 38).

4.4.3.1.7 R-GemOx versus RICE

Very low quality evidence from one study with 65 patients (Zhang et al, 2011) suggest that neutrocytopenia and gastrointestinal tract reactions occured significantly more in RICE than R-GemOx (HR not reported).

4.4.3.1.8 Allogeneic transplantation

Very low quality evidence about outcomes following allogeneic transplantation came from 4 retrospective case series (Avivi et al, 2014; Rigacci et al, 2012; Sirvent et al, 2010 and van Kampen et al, 2011) including 807 patients. Overall survival at five years after allogeneic stem cell transplant (allo-SCT) ranged from 34% to 43% and five year progression free survival ranged from 30% to 37%. The rates of non-relapse mortality ranged from 28% to 38%, rates of acute graft-versus-host disease ranged from 32% to 51% and rates of chronic graft-versus-host disease ranged from 35% to 42%.

Referenzen:

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2024) am 11.07.2024

#	Suchfrage
1	[mh "lymphoma, large b-cell, diffuse"]
2	(diffuse NEXT large NEXT b-cell NEXT lymphoma*):ti,ab,kw
3	large lymphoid lymphoma*:ti,ab,kw
4	((histiocytic OR b-cell) AND lymphoma*):ti,ab,kw
5	(dlbcl):ti,ab,kw
6	{OR #1-#5}
7	[mh "lymphoma, follicular"] OR [mh "lymphoma, non-hodgkin"]
8	((follicular OR nodular OR "small cleaved cell") AND lymphoma*):ti,ab,kw
9	{OR #7-#8}
10	(PMBCL OR rrPMBCL OR ((primary NEXT mediastinal) AND lymphoma*)):ti,ab,kw
11	((THRBCL OR histiocyte NEXT rich OR histiocyte-rich) AND lymphoma*):ti,ab,kw
12	[mh "Lymphoma, B-Cell"]
13	((b-cell OR bcell OR "double-hit" OR Burkitt) AND lymphoma*):ti,ab,kw
14	(BCL OR LBCL OR HGBCL OR HGBL):ti,ab,kw
15	{OR #6, #9-#14}
16	#15 with Cochrane Library publication date from Jul 2019 to present

Systematic Reviews in PubMed am 11.07.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	"Lymphoma, B-Cell"[mj] OR "Lymphoma, Large B-Cell, Diffuse"[mh]
2	diffuse[tiab] AND large[tiab] AND (b-cell[tiab] OR cell[tiab]) AND lymphoma*[tiab]
3	(b-cell[tiab] OR bcell[tiab] OR large b-cell[tiab] OR high-grade[tiab] OR highgrade[tiab] OR ((double[tiab] OR triple[tiab]) AND hit[tiab]) OR aggressive[tiab]) AND lymphoma*[tiab]
4	(histiocytic[tiab] OR (large[tiab] AND lymphoid[tiab])) AND lymphoma*[tiab]
5	DLBCL[tiab] OR BCL[tiab] OR HGBCL[tiab] OR LBCL[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	lymphoma, follicular[mh] OR lymphoma, non-hodgkin[mh:noexp]
8	(follicular[tiab] OR nodular[tiab] OR small cleaved cell[tiab]) AND lymphoma*[tiab]

#	Suchfrage
9	#7 OR #8
10	PMBCL[tiab] OR rrPMBCL[tiab] OR (primary mediastinal[tiab] AND lymphoma*[tiab])
11	THRBCL[tiab] OR ((histiocyte rich[tiab] OR histiocyte-rich[tiab]) AND lymphoma*[tiab])
12	#6 OR #9 OR #10 OR #11
13	(#12) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	((#13) AND ("2019/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 11.07.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	Lymphoma, B-Cell"[mh] OR "Lymphoma, Large B-Cell, Diffuse"[mh]
2	diffuse[tiab] AND large[tiab] AND (b-cell[tiab] OR cell[tiab]) AND lymphoma*[tiab]

#	Suchfrage
3	(b-cell[tiab] OR bcell[tiab] OR large b-cell[tiab] OR high-grade[tiab] OR highgrade[tiab] OR ((double[tiab] OR triple[tiab]) AND hit[tiab]) OR aggressive[tiab]) AND lymphoma*[tiab]
4	(histiocytic[tiab] OR (large[tiab] AND lymphoid[tiab])) AND lymphoma*[tiab]
5	DLBCL[tiab] OR BCL[tiab] OR HGBCL[tiab] OR LBCL[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	lymphoma, follicular[mh] OR lymphoma, non-hodgkin[mh:noexp]
8	(follicular[tiab] OR nodular[tiab] OR small cleaved cell[tiab]) AND lymphoma*[tiab]
9	#7 OR #8
10	PMBCL[tiab] OR rrPMBCL[tiab] OR (primary mediastinal[tiab] AND lymphoma*[tiab])
11	THRBCL[tiab] OR ((histiocyte rich[tiab] OR histiocyte-rich[tiab]) AND lymphoma*[tiab])
12	#6 OR #9 OR #10 OR #11
13	(#12) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
14	(((#13) AND ("2019/07/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur für DLBCL, abgeschlossen am 17.07.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

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1. **(DKG) LODK, (DKH) DK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge für erwachsene Patient*innen mit einem diffusen großzelligen B-Zell-Lymphom und verwandten Entitäten; S3-Leitlinie, Langfassung [online]. AWMF-Registernummer 018-038OL. Berlin (GER): Leitlinienprogramm Onkologie; 2022. [Zugriff: 11.07.2024]. URL: https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/DLBCL/Version_1/LL_DLBCL_Langversion_1.0.pdf.

2. **(DKG) LODK, (DKH) DK, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)).** Diagnostik, Therapie und Nachsorge für erwachsene Patient*innen mit einem diffusen großzelligen B-Zell-Lymphom und verwandten Entitäten; S3-Leitlinie, Leitlinienreport [online]. AWMF-Registernummer 018-038OL. Berlin (GER): Leitlinienprogramm Onkologie; 2022. [Zugriff: 11.07.2024]. URL: https://register.awmf.org/assets/guidelines/018-038OLm_Diagnostik-Therapie-Nachsorge-erwachsene-PatientInnen-diffusen-grosszelligen-B-Zell-Lymphom-verwandten-Entitaeten-DLBC-2022-10.pdf.

3. **Ernst M, Oeser A, Besiroglu B, Caro-Valenzuela J, Abd El Aziz M, Monsef I, et al.** Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database of Systematic Reviews [online]. 2021(9):Cd013365. URL: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013365.pub2/epdf/full.

4. **Gagelmann N, Bishop M, Ayuk F, Bethge W, Glass B, Sureda A, et al.** Axicabtagene Ciloleucel versus Tisagenlecleucel for Relapsed or Refractory Large B Cell Lymphoma: A Systematic Review and Meta-Analysis. Transplant Cell Ther 2024;30(6):584 e581-584 e513.

5. **National Institute for Health and Care Excellence (NICE).** Non-Hodgkin's lymphoma: diagnosis and management [online]. 10.2021. London (GBR): NICE; 2016. [Zugriff: 11.07.2024]. (NICE Guideline; Band NG52). URL: https://www.nice.org.uk/guidance/ng52/resources/nonhodgkins-lymphoma-diagnosis-and-management-pdf-1837509936325.

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO