CAR-T-Zelltherapie – Best Practice und Patientenmanagement in Qualifikationszentren

Prof. Dr. Peter Borchmann (UK Köln)
Prof. Dr. Boris Böll (UK Köln)
Prof. Dr. Max Topp (UK Würzburg)

Hinweis: weitere CME der Reihe

CAR-T-Zelltherapie – Grundlagen & Patientenidentifikation

aufgenommener Fachvortrag mit Prof. Dr. Penack, 2 CME-Punkte, **hier klicken**

CAR-T-Zelltherapie – Überweisungsprozess & ambulante Nachsorge

aufgenommener Fachvortrag mit Prof. Dr. Penack, 2 CME-Punkte, **hier klicken**

Es wird empfohlen, alle Kurse zu durchlaufen, es ist jedoch nicht verpflichtend. Jede CME kann einzeln absolviert werden. Insgesamt können bis zu **6 CME-Punkte** erworben werden.

Agenda

- Therapievorbereitung (bridging therapy)
- Akut-Toxizität und infektiöse Komplikationen
- Langzeit-Toxizität, Sekundärmalignome und Rezidivtherapie
- Q&A-Lounge: offene Fragerunde

LeitMed Campus

Therapievorbereitung (bridging therapy)

Vorstellung

Prof. Dr. Peter Borchmann

Facharzt für Innere Medizin, Hämatologie und Onkologie mit Zusatzbezeichnung Palliativmedizin

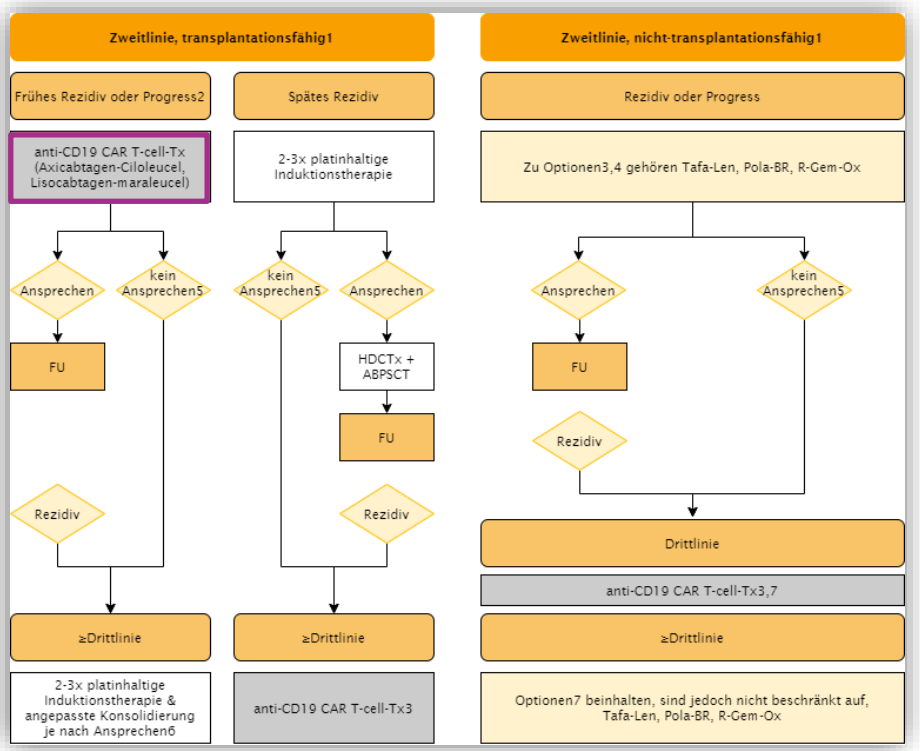
- Oberarzt an der Klinik I für Innere Medizin der Uniklinik Köln
- Leiter des DKG-zertifizierten Hämatologischen Zentrums der Uniklinik Köln
- Chairman der Deutschen Hodgkin Studiengruppe (GHSG)

Interessenkonflikte Prof. Borchmann

Prof. Borchmann hat in den letzten 12 Monaten Zuwendungen von folgenden Unternehmen erhalten:

- Beratende Funktion oder Sachverständigenaussage:
  Takeda Oncology, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Novartis, Amgen
- Honorare:
  Takeda Oncology, Novartis, Bristol-Myers Squibb, Roche, Merck Sharp & Dohme, Kite-Gilead, Incyte
- Zuwendungen für Forschungsprojekte:
  Takeda Oncology, MPI, Roche, Novartis, Merck Sharp & Dohme, Amgen

S3– Schlüsselempfehlungen zur Rezidivtherapie: Zweitlinie



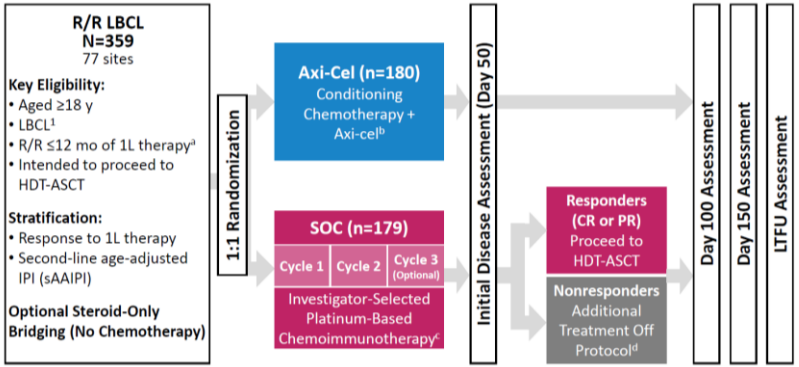
CAVE:

1. „Sollte"-Empfehlung
2. „Hochdosis-Fähigkeit" wird sehr gerne als Begriff verwendet, ist aber keineswegs definiert, ebenso wenig wie „CAR-T-Zellfähigkeit" (Onkopedia)
3. *Ich **persönlich** richte mich eher nach dem Therapieziel: Soll die Therapie in kurativer Intention erfolgen? Dann CARs, wenn keine KI vorliegt!*

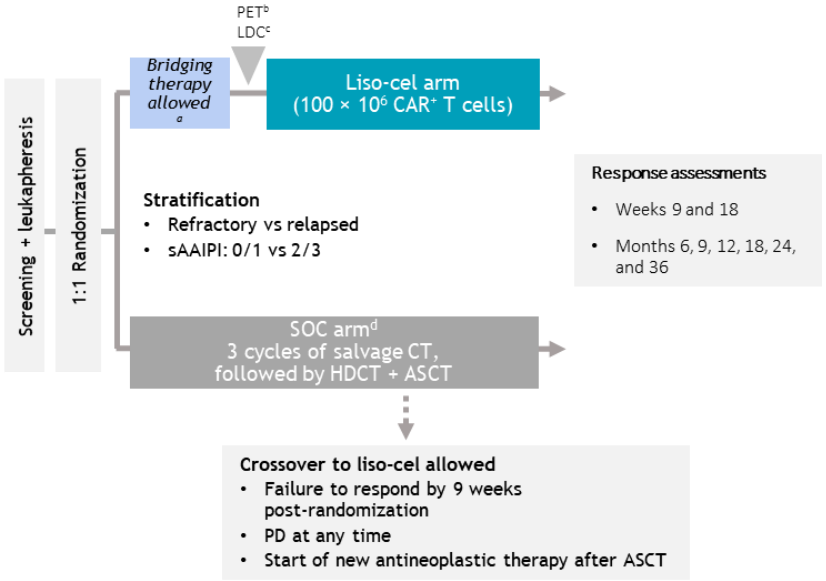
Zwei Phase-III-Studien

CAR-T-Zelltherapie ist Hochdosistherapie überlegen

ZUMA-7



TRANSFORM



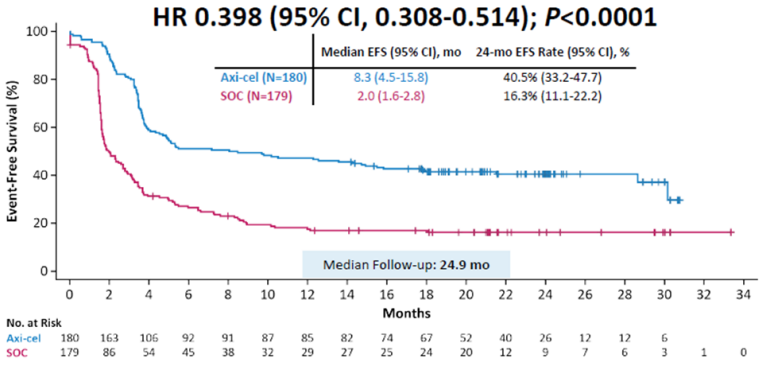
no bridging, no cross-over (out of protocol 56 % CARs in SOC), primary endpoint EFS, HDCT in SOC 36 %

Bridging allowed (63 %), cross-over allowed (51 %), primary endpoint EFS, HDCT in SOC 42 %

Zwei Phase-III-Studien

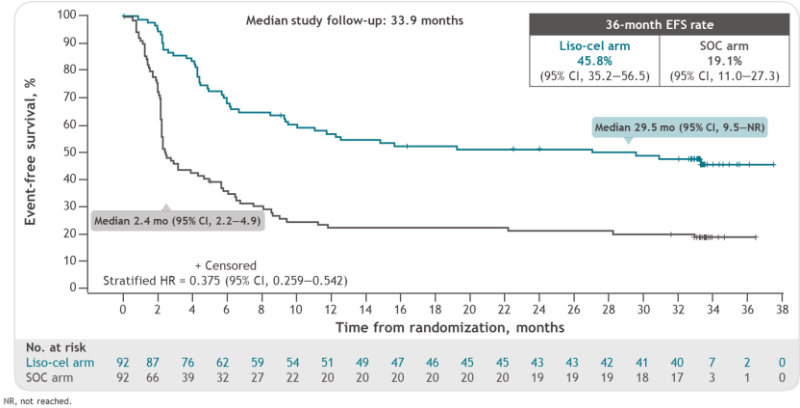
Axi-cel (ZUMA-7) und Liso-cel (TRANSFORM) in “transplant-eligible” patients: **primary endpoint EFS**

Axi-cel (ZUMA-7)



Locke et a., N Engl J Med. 2022 Feb 17;386(7):640-654

Liso-cel (TRANSFORM)

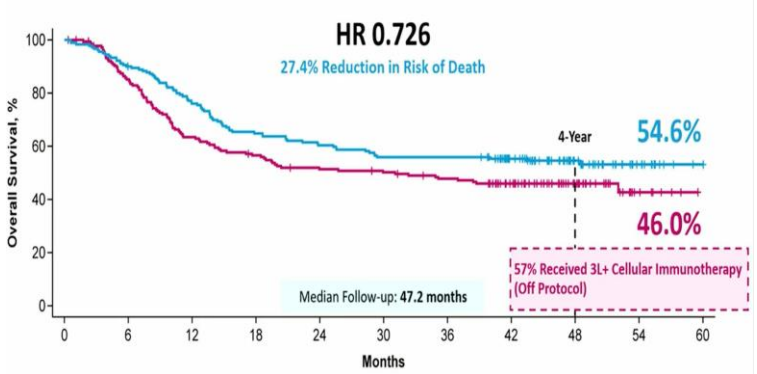


Kamdar et al., ASCO 2024 Abstract number 7013

Zwei Phase-III-Studien

Axi-cel (ZUMA-7) und Liso-cel (TRANSFORM) in "transplant-eligible" patients: **OS**

Axi-cel (ZUMA-7)

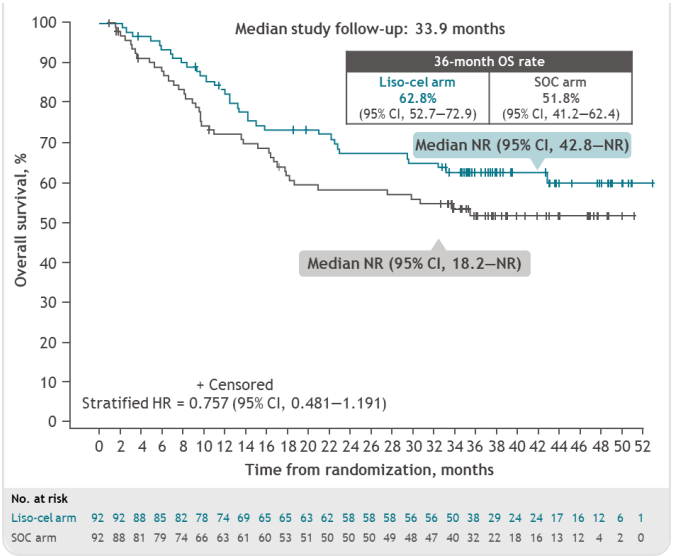


one-sided p=0.0168; HR 0,726 (95%CI 0,540—0977

27.4 % reduced risk of death compared to SOC, despite cross-over in 57 % of out-of-study patients

→ 1st study in 30 years to clearly show significant overall survival benefit in 2L DLBCL.

Liso-cel (TRANSFORM)



Locke et a., N Engl J Med. 2022 Feb 17;386(7):640-654

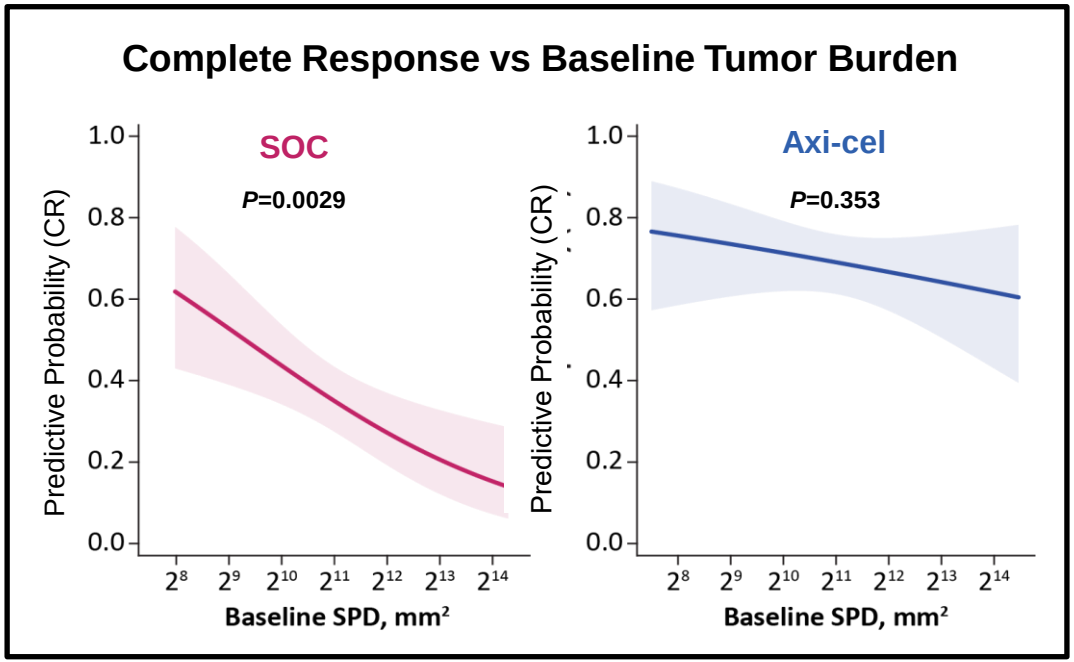
Kamdar et al., ASCO 2024 Abstract number 7013

Frage:

Ist es für das Therapieergebnis unerheblich, ob die PatientInnen vor der CAR-T-Zelltherapie eine aktive Lymphomerkrankung haben oder ob sie in Remission sind?

Phase-III-Studiendaten

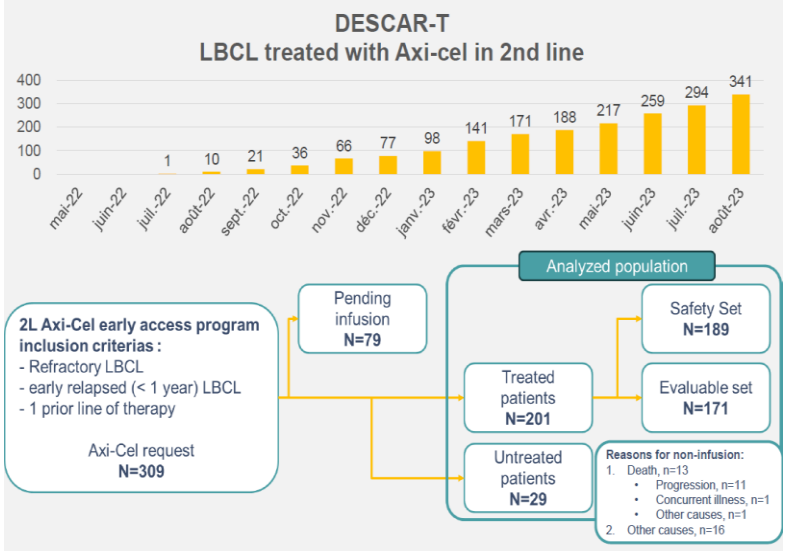
ZUMA-7 Tumor Burden Impacted CR Rate in the SOC Cohort, but to a much lesser degree in the CAR-T-cell treated cohort

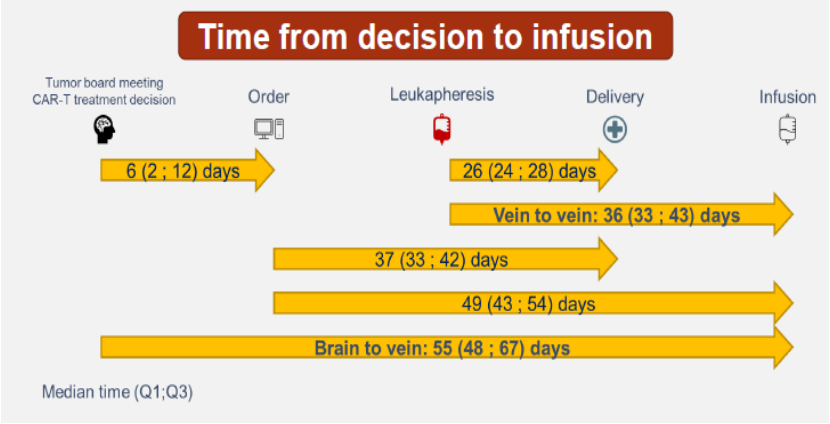


Locke FL et al. ASH 2021. Abstract #2.

„Real-World“-Data

Axicabtagene ciloleucel as second line therapy for patients with large b cell lymphoma: first results of a Lysa study from the French Descar-t registry (Lysa, Descar-t)





55 Tage sind eine lange Zeit.

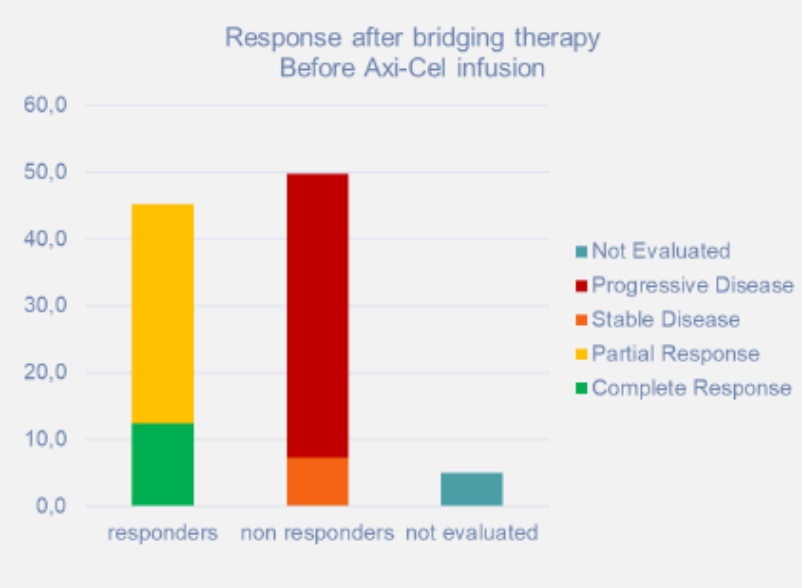
Brisou et al., ASH 2023 Abs 5138

Frage:

Geht es so wie in der ZUMA-7-Studie ohne Bridging?

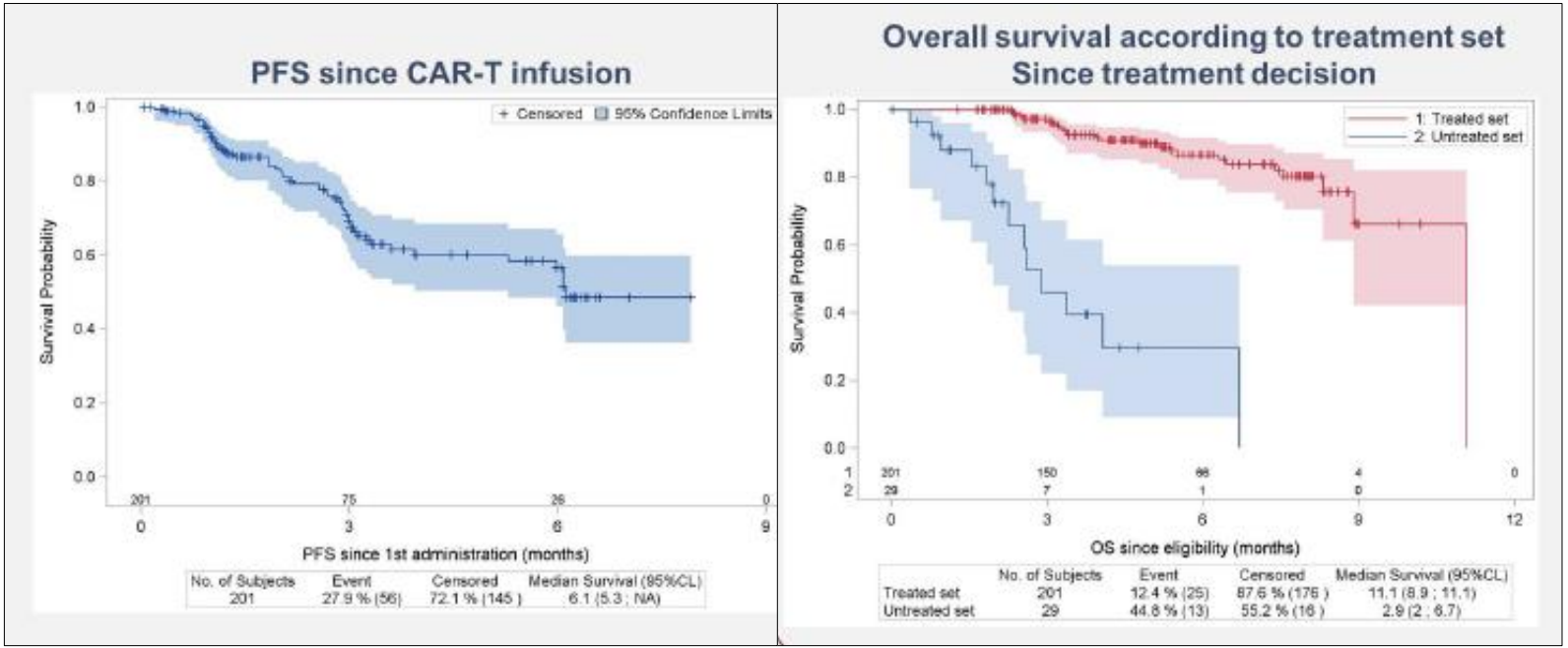
Bridging therapy	**177**	**(88.1%)**
Number of bridging lines		
1	**153**	**(86.4%)**
2	19	(10.7%)
3	4	(2.3%)
4	1	(0.6%)
Type of treatment*		
Monoclonal antibody	**155**	**(87.6%)**
Anti-CD20	**153**	**(86.4%)**
Chemotherapy	**162**	**(91.5%)**
Platine-based regimen	**124**	**(70.1%)**
Radiotherapy	14	(7.9%)
IMiD	11	(6.2%)
Kinase inhibitor	14	(7.9%)
Corticosteroids	13	(7.3%)

* Several treatment possible



Frage:

Wie ist die Wirksamkeit?



→ Tumorkontrolle vor CAR-T-Zelltherapie könnte doch vorteilhaft sein.

Phase-III-Studie

TRANSFORM: Outcomes by receipt of *bridging therapy* in the liso-cel group (safety set)

	Liso-cel group (n = 92)
Patients who received bridging therapy by regimen, n (%)	58 (63)
R-ICE	29 (32)
R-GDP	16 (17)
R-DHAP	13 (14)
Reasons for receiving bridging therapy[a], n (%)	58 (63)
High tumor burden	28 (30)
Rapid progression	23 (25)
Other	7 (8)

Phase-III-Studie

TRANSFORM: Outcomes by receipt of *bridging therapy* in the liso-cel group (safety set)

	Liso-cel group		
	PET-positive disease after bridging therapy (n = 47)[b]	**PET-negative disease after bridging therapy (n = 9)[c]**	**No bridging therapy (n = 34)**
Best overall response, n (%)			
CR	31 (66)	8 (89)	22 (65)
PR	9 (19)	0	8 (24)
SD	3 (6)	0	1 (3)
PD	2 (4)	1 (11)	2 (6)
Nonevaluable	2 (4)	0	1 (3)
Median EFS, months (IQR)	8.4 (4.3–NR)	NR (6.1–NR)	11.7 (4.9–NR)
Median PFS, months (IQR)	9.5 (4.4–NR)	NR (6.1–NR)	14.8 (6.2–NR)
Median OS, months (IQR)	NR (9.3–NR)	NR (NR–NR)	NR (NR–NR)

→ Tumorkontrolle vor CAR-T-Zelltherapie könnte doch vorteilhaft sein.

Therapievorbereitung (bridging therapy)

Fazit

- Bridging ist in der Regelversorgung oft erforderlich, da die Zeit zwischen Indikationsstellung und Therapie unverändert zu lang ist (55 Tage sind realistisch).
- Es gibt relativ starke Hinweise, dass die Lymphomkontrolle vor CAR-T-Zelltherapie für die Überlebensparameter (EFS, PFS, OS) einen positiven Einfluss hat.
- Offen bleibt daher die Frage nach dem „wie", nicht so sehr die Frage nach dem „ob überhaupt".

→ Die Frage nach dem „wie" ist aktuell unbeantwortet, da es dazu keine belastbaren Daten gibt und es unverändert individuelle Entscheidungen sind.

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Akut-Toxizität und infektiöse Komplikationen

Vorstellung

Prof. Dr. Boris Böll

Facharzt für Innere Medizin, Hämatologie und Onkologie, Intensivmedizin

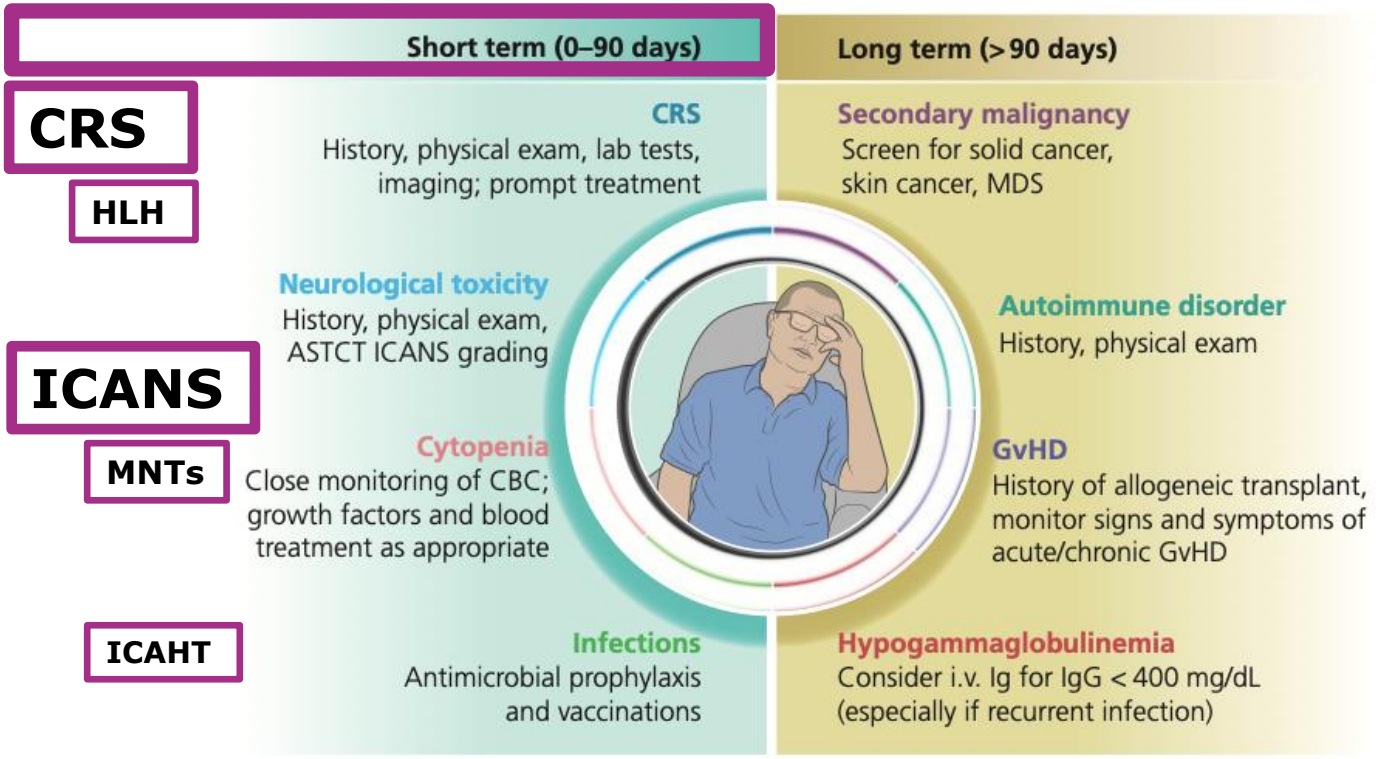
- Oberarzt an der Klinik I für Innere Medizin der Uniklinik Köln
- Studienarzt der Deutschen Hodgkin Studiengruppe (GHSG)

Interessenkonflikte Prof. Böll

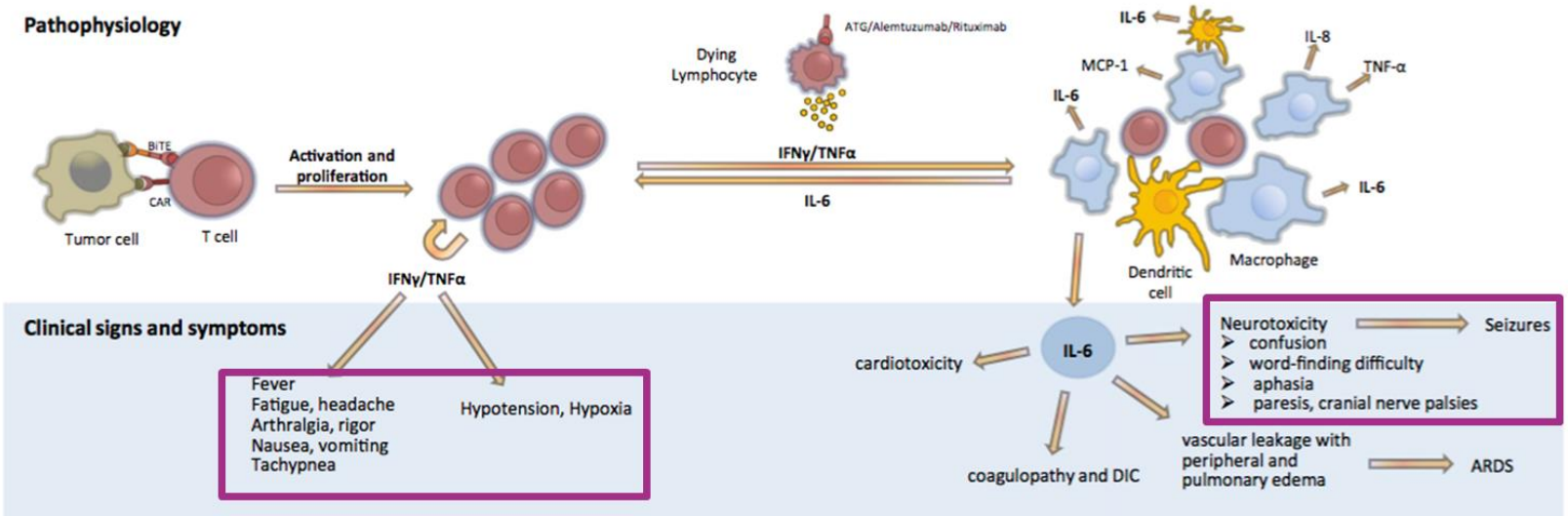
Prof. Böll hat in den letzten 12 Monaten Zuwendungen von folgenden Unternehmen erhalten:

- Beratungs- bzw. Gutachtertätigkeit:
  Amgen, Celgene, Janssen, Kite/Gilead, Miltenyi, MSD, Mundipharma, Noscendo, Novartis, Pfizer, Takeda
- Honorare:
  Amgen, Astellas, Celgene, J&J, Kite/Gilead, MSD, Novartis, Noscendo, Pfizer, Takeda
- Finanzierung wissenschaftlicher Untersuchungen:
  Astellas, Celgene, Kite/Gilead, MSD, Takeda

CAR-T-cells – common side effects…



CRS/ICANS – mechanism



Giavridis et al. Nat Med 2018, Parker et al. Cell 2022
Gödel et al. Int Care Med 2017, Garcia-Borrega et al, MKIN 2021

Frequency of CRS/ICANS (CD19 –CAR T-cells) in studies

TABLE 1. CRS and ICANS in Clinical Trials of US Food and Drug Administration–Approved CAR T-Cell Products

					CRS				ICANS			
Disease	Study	CAR T Product	Costim Domain	Target	All Grades, %	Grade ≥ 3, %	Start Day	Median Duration Days	All Grades, %	Grade ≥ 3, %	Start Day	Median Duration Days
LBCL	ZUMA-1	Axicabtagene ciloleucel	CD28	CD19	92	11	2	8	67	32	5	17
LBCL	JULIET	Tisagenlecleucel	41BB	CD19	58	22	3	7	21	12	6	14
LBCL	TRANSCEND NHL 001	Lisocabtagene maraleucel	41BB	CD19	42	2	5	5	30	10	9	11
iNHL	ZUMA-5	Axicabtagene ciloleucel	CD28	CD19	nr	11	4	nr	nr	17	7	nr
MCL	ZUMA-2	Brexucabtagene autoleucel	CD28	CD19	91	15	2	11	63	31	7	12
ALL	ELIANA	Tisagenlecleucel	41BB	CD19	77	47	3	8	40	13	nr	6
ALL	ZUMA-3	KTE-X19	CD28	CD19	89	24	5	7	60	25	9	7
MM	KarMMa	Idecabtagene vicleucel	41BB	BCMA	84	6	1	5	18	3	2	3
MM	CARTITUDE-1	Ciltacabtagene autoleucel	41BB	BCMA	95	4	7	4	21	3	8	4

Spanjaart et al. JCO-CP 2022

ASTCT consensus grading and management

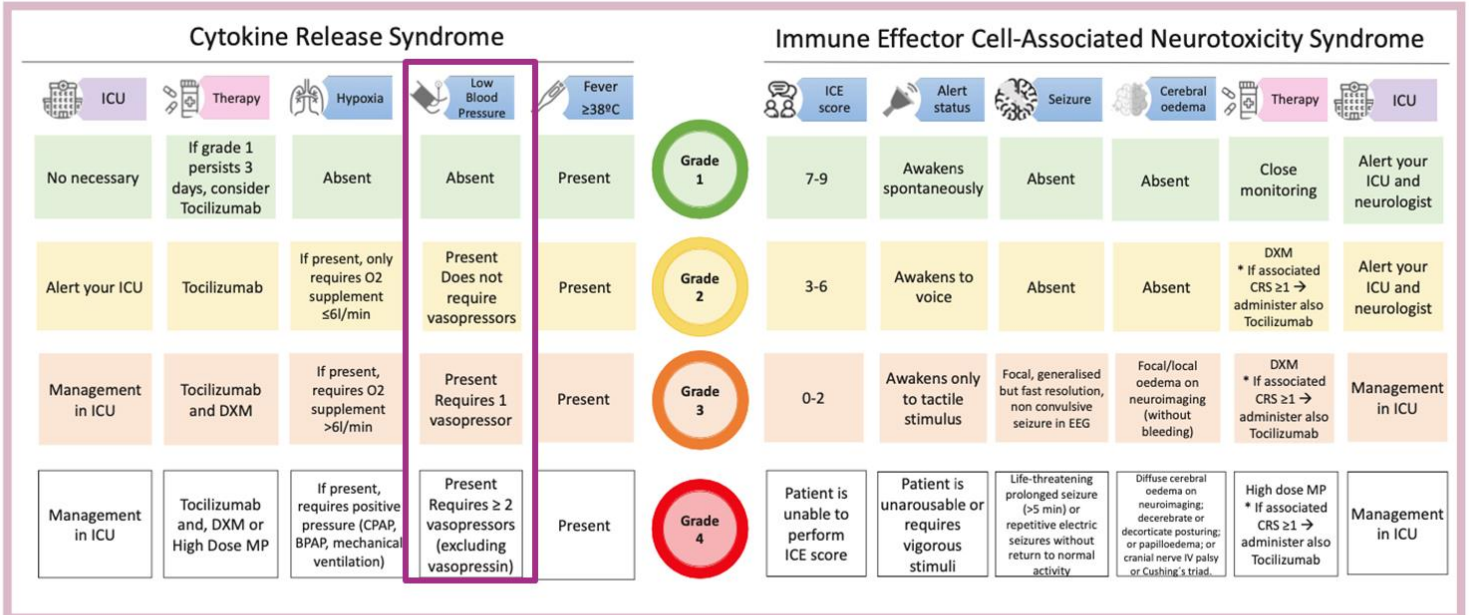


Figure 1 The American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading and recommended management for cytokine release syndrome (CRS) and neurological toxicity associated with immune effector cells (ICANS). DXM, Dexamethasone; ICE, immune effector cell-associated encephalopathy; ICU, intensive care unit; MP, Methylprednisolone.

Yáñez et al. ESMO Open 2020

Real life toxicity of CD19-CAR-T
(DESCAR-T, France)

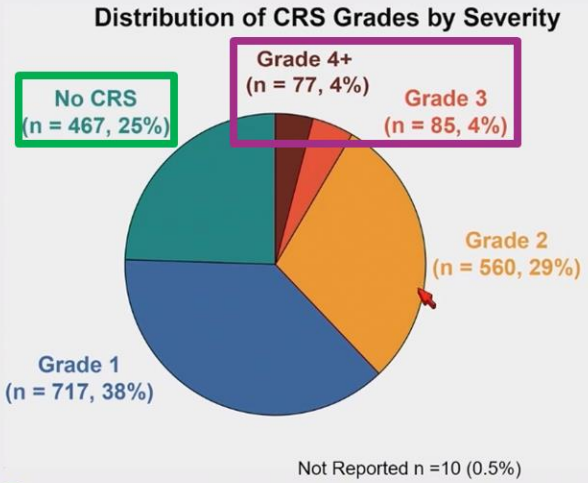
ASTCT GRADE		N=705
CRS	all grades (%)	587 (83,3)
	grade ≥3 (%)	61 (8,6)
	median time to CRS	2 days (Q1-Q3: 1-4)
	median time to resolution	6 days (Q1-Q3: 4-9)
ICANS	all grades (%)	289 (41)
	grade ≥3 (%)	78 (11)
	median time to ICANS	6 days (Q1-Q3: 4-8)
	median time to resolution	7 days (Q1-Q3: 5-12)
ICU	admission	180 (25,5%)
	mean duration	2 days (Q1-Q3: 0-3)

Sesques et al. Abstract S210 - EHA 2022

Real life toxicity of CD19-CAR-T

(CIMBMTR; N=1916)

Distribution of CRS Following CAR T



Characteristic	Value
Days from CAR T to CRS onset median (range)	4.0 (1.0-601.0)
Days from CAR T to CRS resolution, median (range)	9.0 (1.0-606.0)
Days from CRS onset to resolution, median (range)	6.0 (1.0-121.0)
Tocilizumab administration	N (%)
No	524 (27.3)
Yes	917 (47.9)
Not reported	475 (24.8)

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Shouval et al. ASH 2023

Severe CRS – Risk Factors

Konstrukt und Grunderkrankung

- hohe Tumorlast
- vorbestehende Inflammation/Infektion
- hohe CAR-T-Zelldosis/Expansion
- Timing: frühes Fieber
- mEASIX Score, Ferritin, CRP u. a.

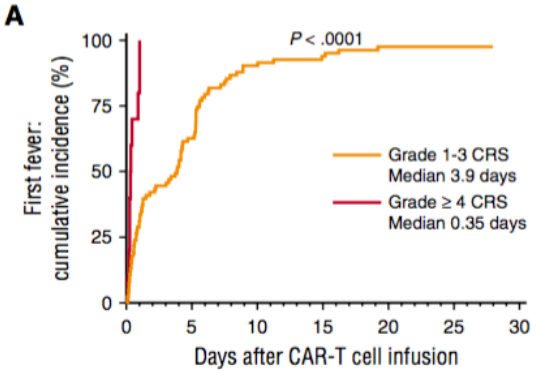


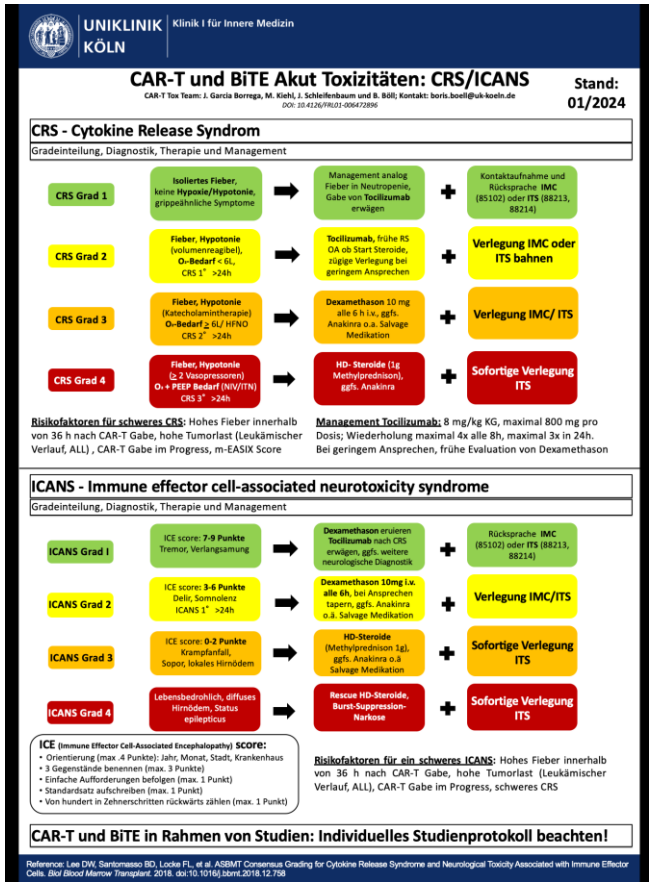
Table 2. Characterization of fever in patients who develop CRS

	CRS grade							
	1-3				4-5			
Fever	No.	Median	IQR	Range	No.	Median	IQR	Range
No. of patients	83				10			
Fever onset (days after CAR T-cell infusion)		3.9	0.8-5.6	0.1-19		0.4	0.3-0.9	0.2-1.0
Time to peak temperature (days after CAR T-cell infusion)		5.7	4.3-7.6	0.2-30		2.8	1.3-3.2	0.4-11
Maximum temperature (°C)		39.4	39.2-39.6	37.7-41.3		40.4	40.1-40.6	39.9-40.9
Fever duration (days after first fever)		2.5	1.2-4.7	0.02-15		4.4	3.6-5.4	3.1-6.8

*Two-sided *P* values were calculated by using the Wilcoxon test.

Hay et al. Blood 2017, Greenbaum et al. Blood Adv 2021

Center-specific management of CAR-T-toxicity



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CAR-T und BiTE Akut Toxizitäten: CRS/ICANS

Stand: 01/2024

CAR-T Tox Team: J. Garcia Borrega, M. Kiehl, J. Schleifenbaum und B. Böll; Kontakt: boris.boell@uk-koeln.de

DOI: 10.4126/FRL01-006472896

CRS - Cytokine Release Syndrom

Gradeinteilung, Diagnostik, Therapie und Management

CRS Grad 1	Isoliertes Fieber, keine Hypoxie/Hypotonie, grippeähnliche Symptome	Management analog Fieber in Neutropenie, Gabe von Tocilizumab erwägen	Kontaktaufnahme und Rücksprache IMC (85102) oder ITS (88213, 88214)
CRS Grad 2	Fieber, Hypotonie (volumenreagibel), O2-Bedarf < 6L, CRS 1° >24h	Tocilizumab, frühe RS OA ob Start Steroide, zügige Verlegung bei geringem Ansprechen	Verlegung IMC oder ITS bahnen
CRS Grad 3	Fieber, Hypotonie (Katecholamintherapie) O2-Bedarf ≥ 6L/ HFNO CRS 2° >24h	Dexamethason 10 mg alle 6 h i.v., ggfs. Anakinra o.a. Salvage Medikation	Verlegung IMC/ ITS
CRS Grad 4	Fieber, Hypotonie (≥ 2 Vasopressoren) O2 + PEEP Bedarf (NIV/ITN) CRS 3° >24h	HD- Steroide (1g Methylprednison), ggfs. Anakinra	Sofortige Verlegung ITS

Risikofaktoren für schweres CRS: Hohes Fieber innerhalb von 36 h nach CAR-T Gabe, hohe Tumorlast (Leukämischer Verlauf, ALL) , CAR-T Gabe im Progress, m-EASIX Score

Management Tocilizumab: 8 mg/kg KG, maximal 800 mg pro Dosis; Wiederholung maximal 4x alle 8h, maximal 3x in 24h. Bei geringem Ansprechen, frühe Evaluation von Dexamethason

ICANS - Immune effector cell-associated neurotoxicity syndrome

Gradeinteilung, Diagnostik, Therapie und Management

ICANS Grad I	ICE score: 7-9 Punkte Tremor, Verlangsamung	Dexamethason erwägen Tocilizumab nach CRS erwägen, ggfs. weitere neurologische Diagnostik	Rücksprache IMC (85102) oder ITS (88213, 88214)
ICANS Grad 2	ICE score: 3-6 Punkte Delir, Somnolenz ICANS 1° >24h	Dexamethason 10mg i.v. alle 6h, bei Ansprechen tapern, ggfs. Anakinra o.ä. Salvage Medikation	Verlegung IMC/ITS
ICANS Grad 3	ICE score: 0-2 Punkte Krampfanfall, Sopor, lokales Hirnödem	HD-Steroide (Methylprednison 1g), ggfs. Anakinra o.ä Salvage Medikation	Sofortige Verlegung ITS
ICANS Grad 4	Lebensbedrohlich, diffuses Hirnödem, Status epilepticus	Rescue HD-Steroide, Burst-Suppression-Narkose	Sofortige Verlegung ITS

ICE (Immune Effector Cell-Associated Encephalopathy) score:

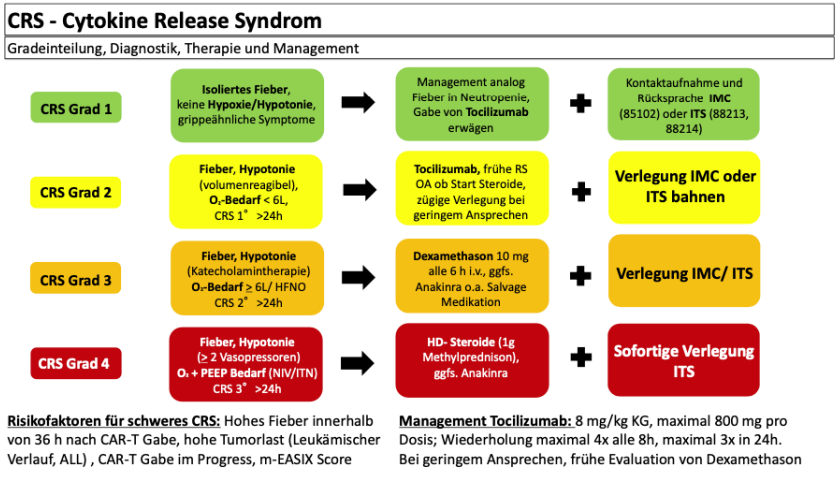
- Orientierung (max .4 Punkte): Jahr, Monat, Stadt, Krankenhaus
- 3 Gegenstände benennen (max. 3 Punkte)
- Einfache Aufforderungen befolgen (max. 1 Punkt)
- Standardsatz aufschreiben (max. 1 Punkt)
- Von hundert in Zehnerschritten rückwärts zählen (max. 1 Punkt)

Risikofaktoren für ein schweres ICANS: Hohes Fieber innerhalb von 36 h nach CAR-T Gabe, hohe Tumorlast (Leukämischer Verlauf, ALL), CAR-T Gabe im Progress, schweres CRS

CAR-T und BiTE in Rahmen von Studien: Individuelles Studienprotokoll beachten!

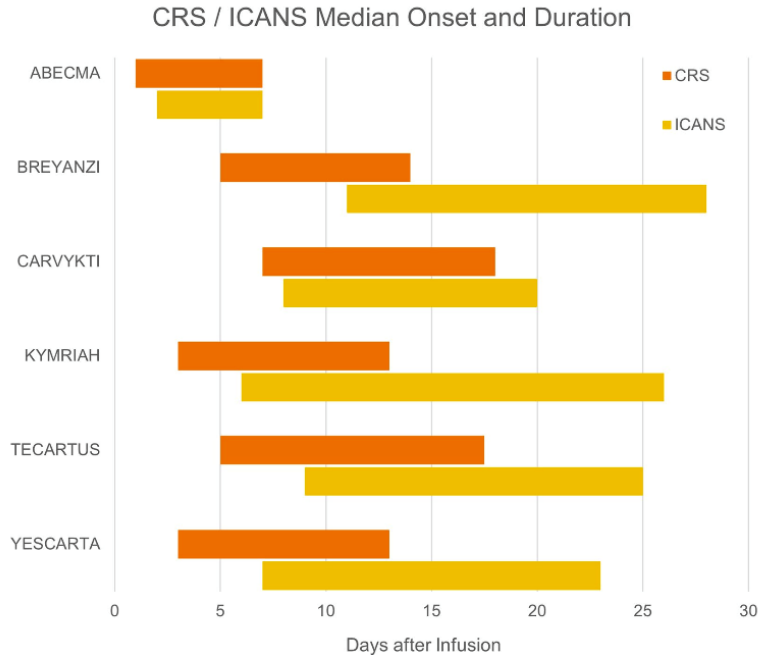
Reference: Lee DW, Santomasso BD, Locke FL, et al. ASBMT Consensus Grading for Cytokine Release Syndrome and Neurological Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant*. 2018. doi:10.1016/j.bbmt.2018.12.758

CRS management UKK



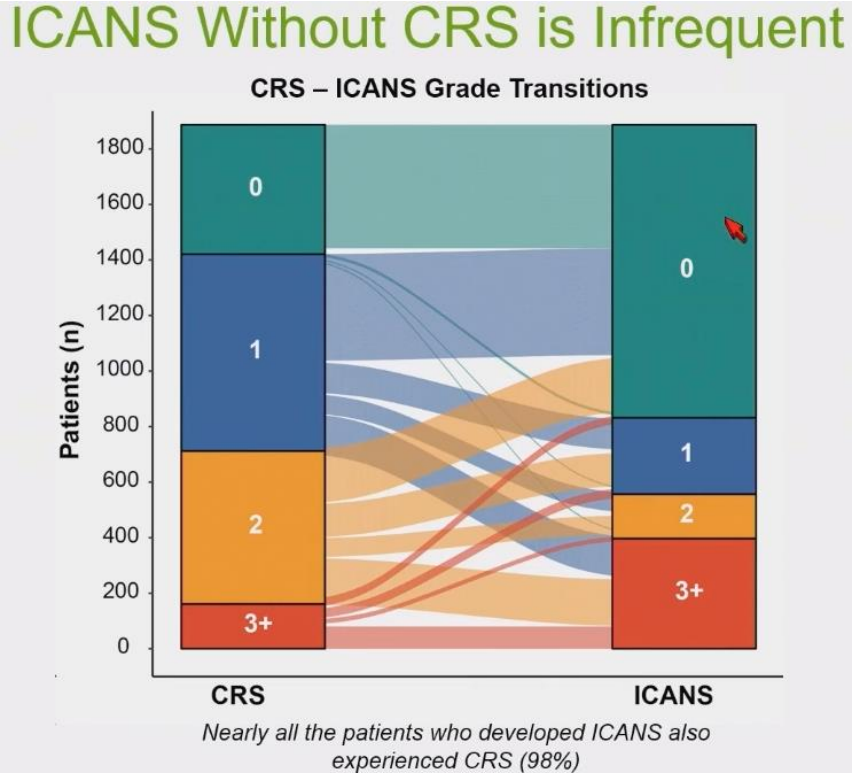
- Lymphodepletion/CAR-T-Gabe auf Normalstation
- CRS Tocilizumab ab Grad 1-2 CRS +/- Steroide
- Kontaktaufnahme IMC/ITS i. d. R. bei persistierendem CRS nach Toci
- repetitive Gabe von Tocilizumab > 2x
- i. d. R. nicht sinnvoll
- Differentialdiagnosen bedenken
- Ausbleibende Besserung führt zu Steigerung des Schweregrades und zur Reevaluation (DD Infektion, HLH, Progress der Grunderkrankung?).

Median onset and duration of CRS and ICANS after FDA-approved CAR-T-cell therapies

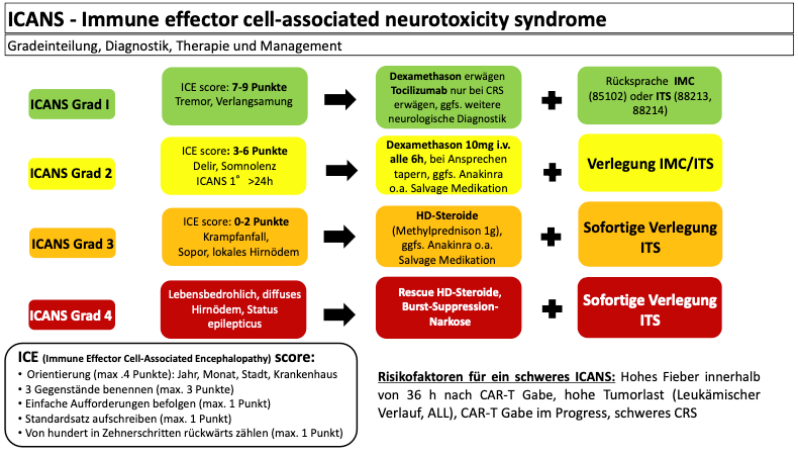


Yang et al. J Bio Science, 2023

CRS and ICANS as continuum?

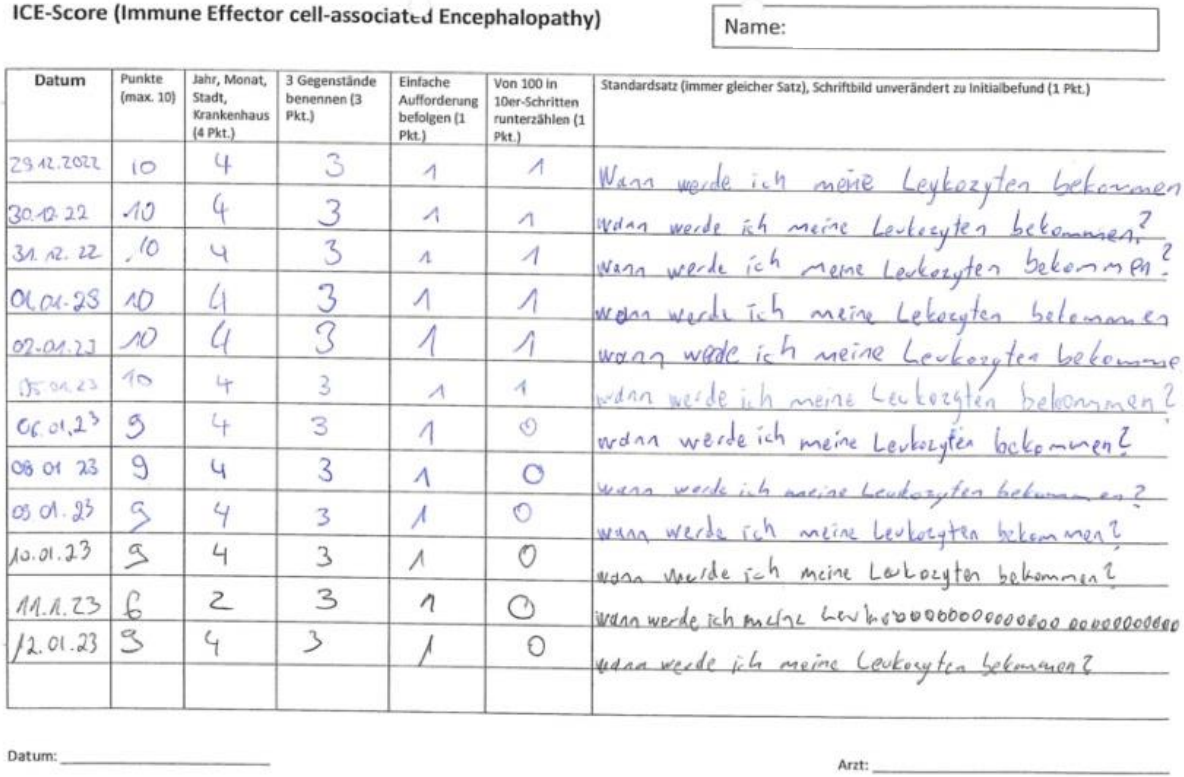


Management of ICANS (UKK)



- Screening nach ICANS (ICE-Score, Nachmittagsvisite mit Pflege, RS Angehörige)
- frühzeitige Verlegung bei ICANS + Diagnostik (CT/MRT, EEG, LP)
- Neuro-Konsil (EEG, MRT?) + Steroide ab Grad 1
- Salvage/Alternative: Anakinra (☐ HD Steroide i.th., Dasatinib…)
- Ausbleibende Besserung führt zu Steigerung des Schweregrades und zur Reevaluation (DD Infektion, ICB, Progress der Grunderkrankung?).

ICE-Score: Handwriting



ICE-Score (Immune Effector cell-associated Encephalopathy)

Name:

Datum	Punkte (max. 10)	Jahr, Monat, Stadt, Krankenhaus (4 Pkt.)	3 Gegenstände benennen (3 Pkt.)	Einfache Aufforderung befolgen (1 Pkt.)	Von 100 in 10er-Schritten runterzählen (1 Pkt.)	Standardsatz (immer gleicher Satz), Schriftbild unverändert zu Initialbefund (1 Pkt.)
29.12.2022	10	4	3	1	1	Wann werde ich meine Leykozyten bekommen
30.12.22	10	4	3	1	1	wann werde ich meine Leukocyten bekommen?
31.12.22	10	4	3	1	1	wann werde ich meine Leukozyten bekommen?
01.01.23	10	4	3	1	1	wann werde ich meine Lekocyten bekommen
02.01.23	10	4	3	1	1	wann werde ich meine Leukozyten bekomme
03.01.23	10	4	3	1	1	wann werde ich meine Leukozyten bekommen?
06.01.23	9	4	3	1	0	wann werde ich meine Leukozyten bekommen?
08.01.23	9	4	3	1	0	wann werde ich meine Leukozyten bekommen?
09.01.23	9	4	3	1	0	wann werde ich meine Leukozyten bekommen?
10.01.23	9	4	3	1	0	wann werde ich meine Leukozyten bekommen?
11.1.23	6	2	3	1	0	wann werde ich meine Leukozyten bekommen?
12.01.23	9	4	3	1	0	wann werde ich meine Leukozyten bekommen?

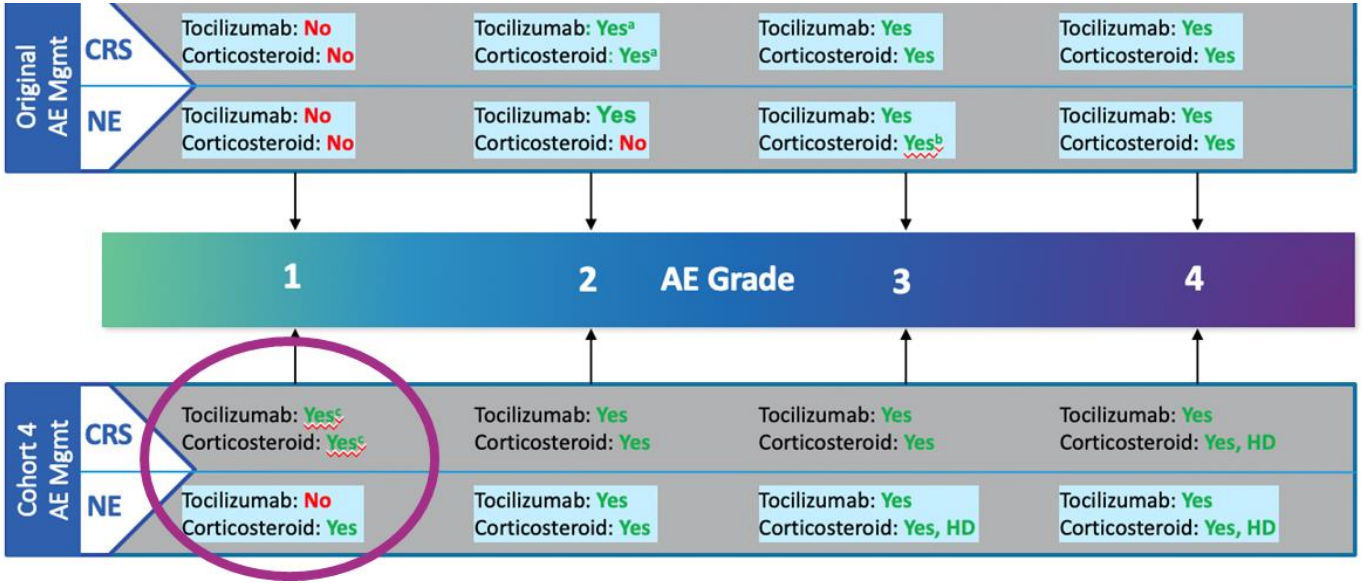
Datum: _____

Arzt: _____

Eigene Abbildung

Earlier use of tocilizumab/steroids

(ZUMA-1 cohort 4)



a Only in case of comordbidities or older age.

b Only if no improvement to tocilizumab, use standard dose.

c If no improvement after 3 days.

Topp et al. ASH 2019, Br J Haematol 2021

Earlier use of tocilizumab/steroids

(ZUMA-1 cohort 4)

AE Grade, n (%)		Phase 1 and Phase 2, Cohorts 1 + 2 (N = 108)	Phase 2 Cohort 4 (N = 21)
NEs	Grade 1 or 2	37 (34)	10 (48)
	Grade ≥ 3	35 (32)	2 (10)
CRS	Grade 1 or 2	88 (81)	21 (100)
	Grade ≥ 3	12 (11)	0 (0)

- Lower rate of severe CAR-T-cell treatment-related CRS and NEs
- Lower total cumulative steroid doses

Topp et al. ASH 2019, Br J Haematol 2021

Earlier use of tocilizumab/steroids

(ZUMA-1 cohort 4)

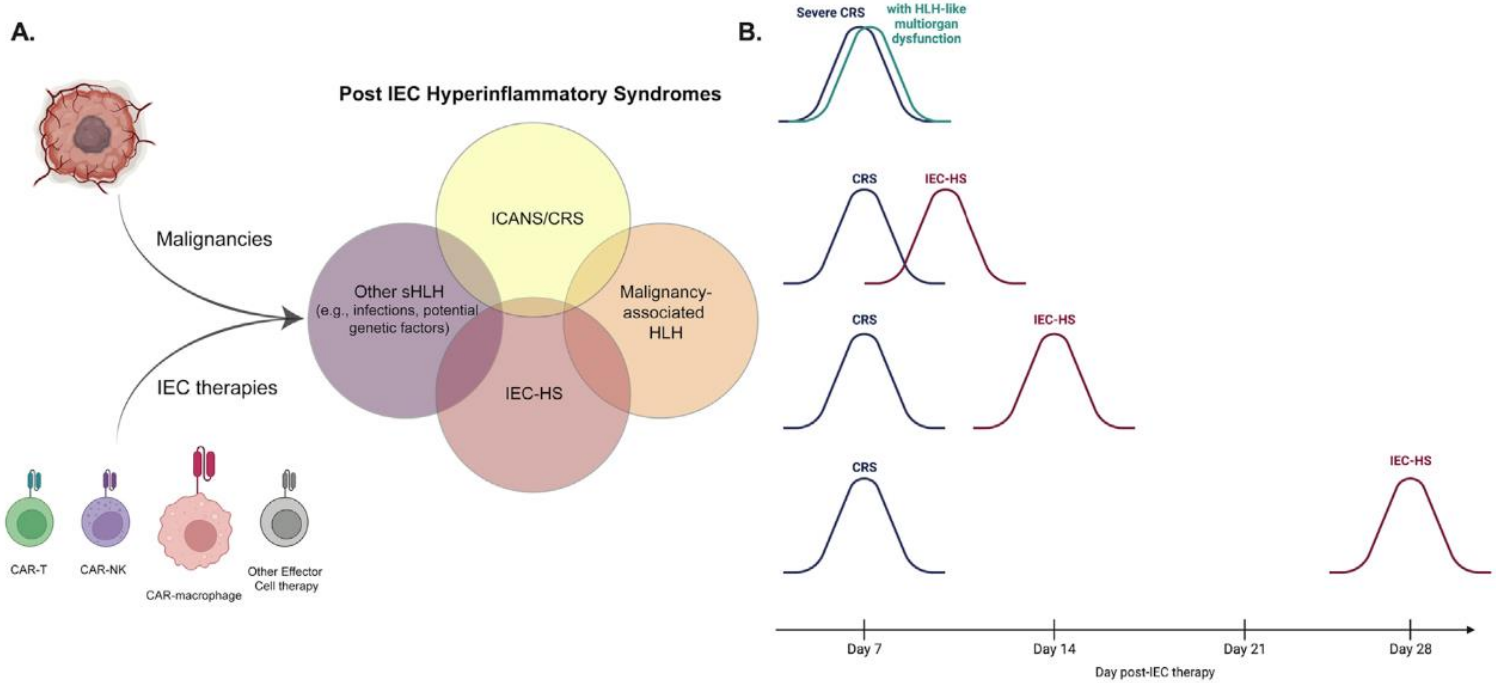
AE Grade, n (%)		Phase 1 and Phase 2, Cohorts 1 + 2 (N = 108)	Phase 2 Cohort 4 (N = 21)
NEs	Grade 1 or 2	37 (34)	10 (48)
	Grade ≥ 3	35 (32)	2 (10)
CRS	Grade 1 or 2	88 (81)	21 (100)
	Grade ≥ 3	12 (11)	0 (0)

- Lower rate of severe CAR-T-cell treatment-related CRS and NEs
- Lower total cumulative steroid doses

Investigator Assessment, n (%)	Phase 2 Cohorts 1 and 2 (N = 101)	Phase 2 Cohort 4 (N = 21)
ORR	84 (83)	17 (81)
CR	59 (58)	13 (62)
PR	25 (25)	4 (19)
SD	10 (10)	1 (5)
PD	5 (5)	3 (14)
Not evaluable	2 (2)	0

Topp et al. ASH 2019, Br J Haematol 2021

Immune Effector Cell-associated HLH-like syndrome (IEC-HS)



Teachey et al. Cancer Discovery 2016
Hines et al. Transpl cell Ther 2023

Immune Effector Cell-associated HLH-like syndrome (IEC-HS)

ASTCT expert consensus

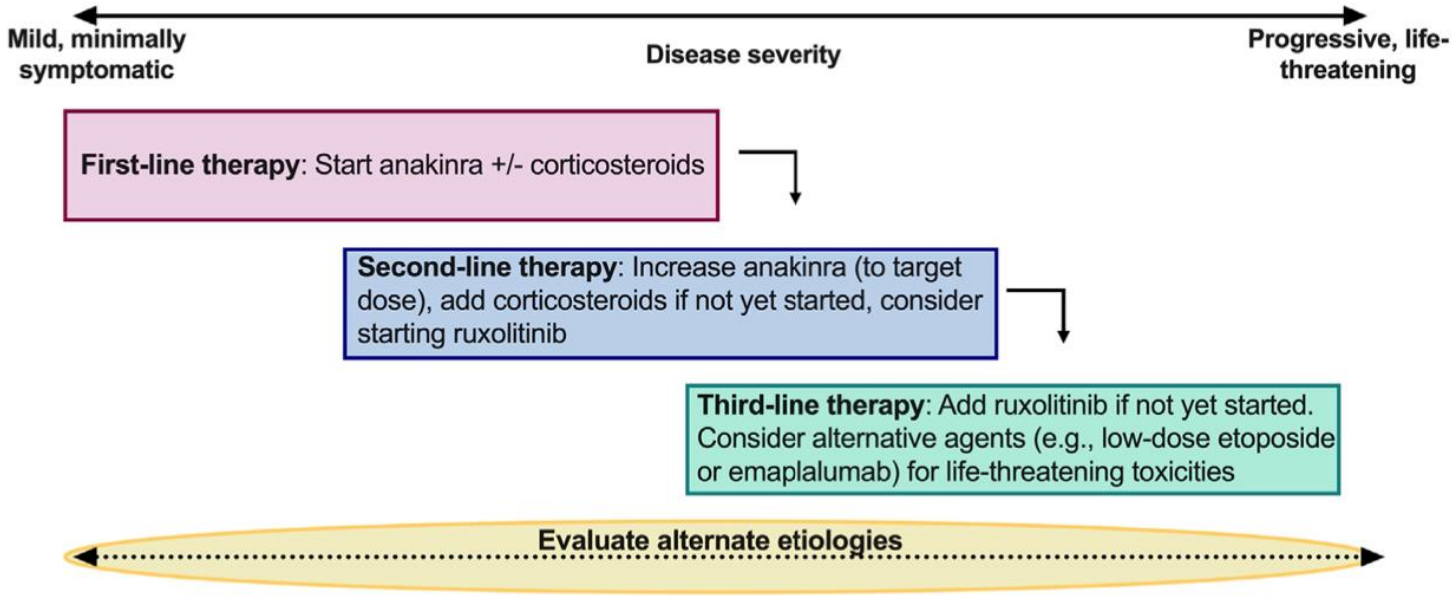
Table 1
IEC-HS: Definition and Identification

Definition of IEC-HS	The development of a pathological and biochemical hyperinflammatory syndrome independent from CRS and ICANS that (1) manifests with features of macrophage activation/HLH, (2) is attributable to IEC therapy, and (3) is associated with progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis
Criteria for Identifying IEC-HS*	**Clinical/Laboratory Manifestations**
Most common manifestations†	Required: elevated ferritin (>2 × ULN or baseline (at time of infusion)) and/or rapidly rising (per clinical assessment)
	Onset with resolving/resolved CRS or worsening inflammatory response after initial improvement with CRS-directed therapy‡
	Hepatic transaminase elevation§ (>5 × ULN (if baseline was normal) or >5 × baseline if baseline was abnormal)
	Hypofibrinogenemia (<150 mg/dL or <LLN)‖
	Hemophagocytosis in bone marrow or other tissue‖
	Cytopenias (new onset, worsening, or refractory¶)
Other manifestations that may be present	Lactate dehydrogenase elevations (>ULN)
	Other coagulation abnormalities (eg, elevated PT/PTT)
	Direct hyperbilirubinemia
	New-onset splenomegaly
	Fever (new# or persistent)‖
	Neurotoxicity
	Pulmonary manifestations (eg, hypoxia, pulmonary infiltrates, pulmonary edema)
	Renal insufficiency (new onset)
	Hypertriglyceridemia (fasting level, >265 mg/dL‖)

Hines et al. Transpl cell Ther 2023

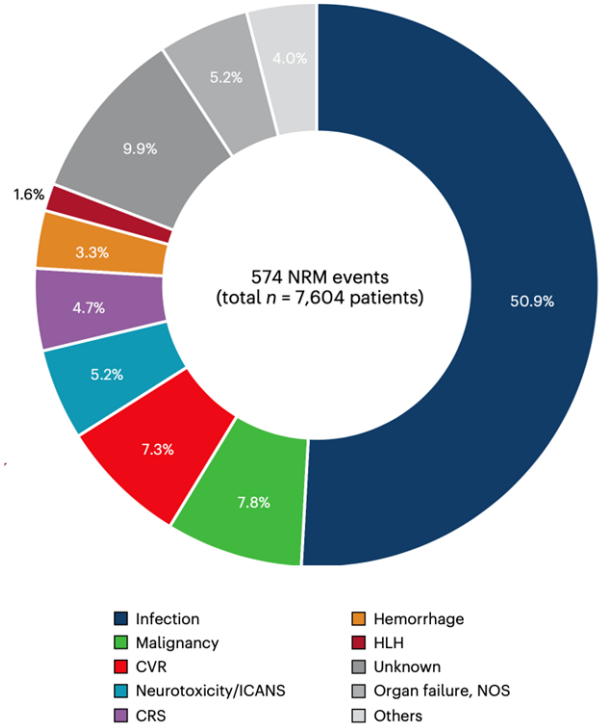
Immune Effector Cell-associated HLH-like syndrome (IEC-HS)

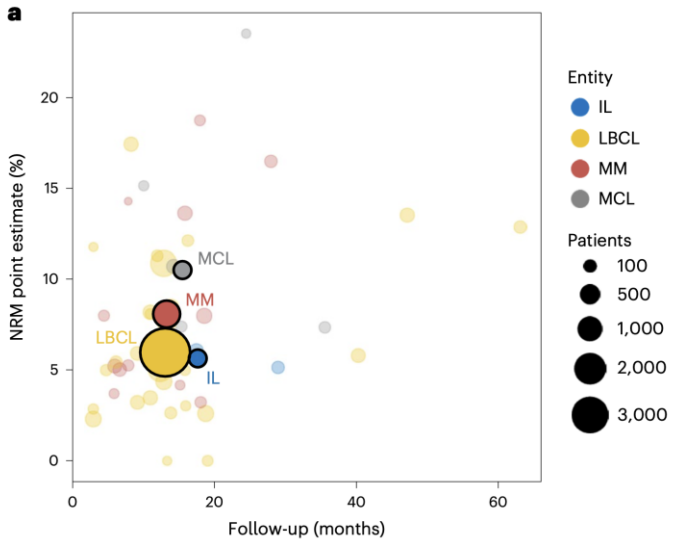
ASTCT expert consensus



Hines et al. Transpl cell Ther 2023

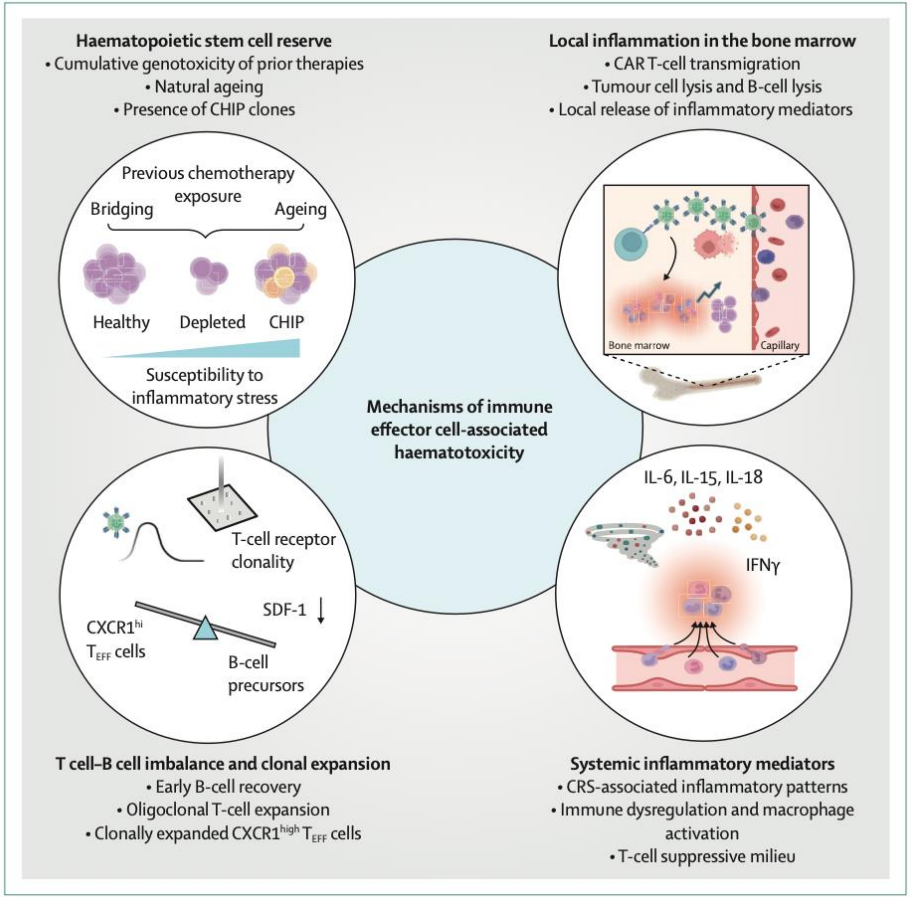
Meta Analysis of NRM after CAR-T-cell treatment





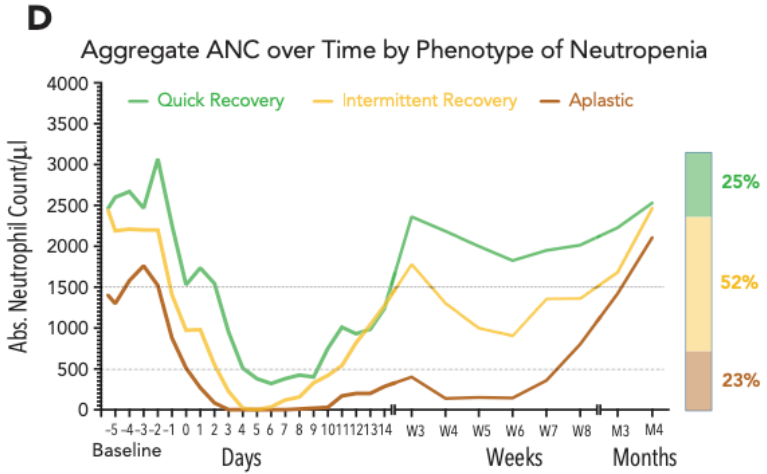
Dos Santos et al. Nature Medicine 2024, Shouval et al. ASH 2023,
Rejeski et al. Lancet Haematology 2024

Cytopenia (ICAHT) – Potential mechanism



Rejeski et al. Lancet Haematology 2024

Prolonged cytopenia in CAR-T-cell recipients



IMMUNOBIOLOGY AND IMMUNOTHERAPY

CAR-HEMATOTOX: a model for CAR T-cell–related hematologic toxicity in relapsed/refractory large B-cell lymphoma

Kai Rejeski,[1-3] Ariel Perez,[4] Pierre Sesques,[5] Eva Hoster,[1,6] Carolina Berger,[7] Liv Jentzsch,[8] Dimitrios Mougiakakos,[9] Lisa Frölich,[1,3] Josephine Ackermann,[1] Veit Bücklein,[1,2] Viktoria Blumenberg,[1,2] Christian Schmidt,[1] Laurent Jallades,[5] Boris Fehse,[7] Christoph Faul,[8] Philipp Karschnia,[3,10] Oliver Weigert,[1,3] Martin Dreyling,[1] Frederick L. Locke,[4] Michael von Bergwelt-Baildon,[1,3] Andreas Mackensen,[9] Wolfgang Bethge,[8] Francis Ayuk,[7] Emmanuel Bachy,[5] Gilles Salles,[5] Michael D. Jain,[4] and Marion Subklewe[1-3]

- Patterns of hematopoietic reconstitution (n=258, US+Europe)
- Neutropenia ANC < 100/ml in 72 %, median duration 9 days
- ≥ 21 days neutropenia in 64 %
- Predictors: base thrombocytopenia (r=-0.43; P = .001), hyperferritinemia (r=0.54; P < .0001)
- Age, Incidence and Severity of CRS, ICANS or peak cytokine levels not associated

Rejeski et al. Blood 2021

ICAHT – EBMT recommendations

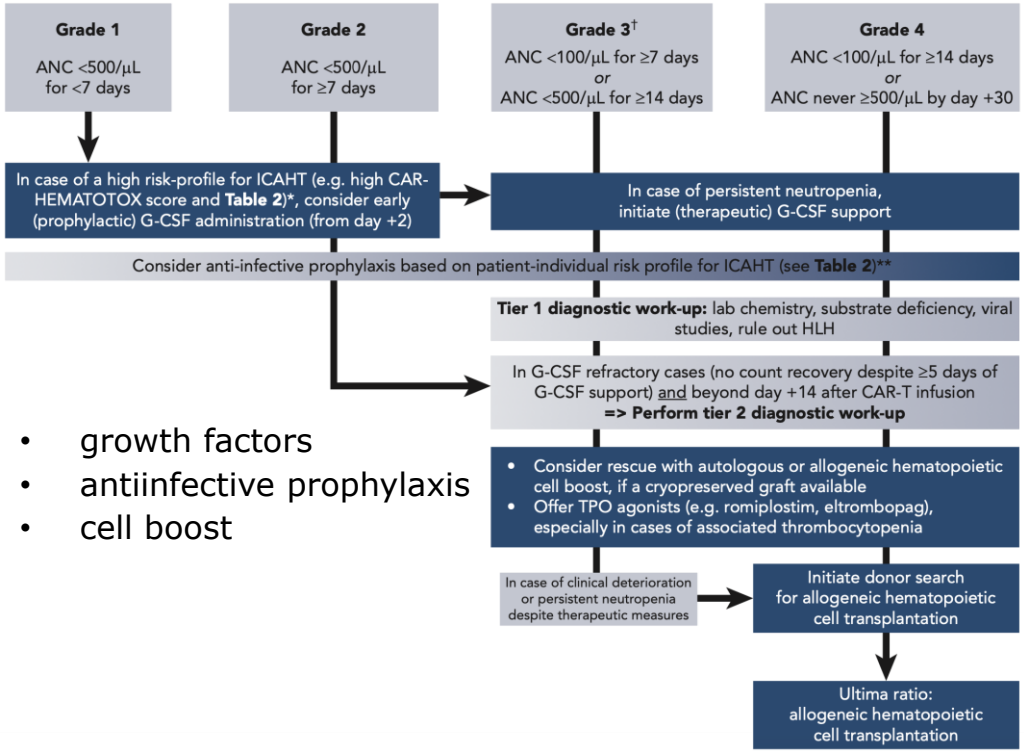
(work up)

	Categories	Putative causes	Test	Time points	Comments
TIER 1	Lower threshold to perform – minimal workup				
	Poor bone marrow reserve	Prior treatments including allo-HCT, fludarabine, marrow infiltration	Complete blood count (CBC), reticulocyte production index (RPI), peripheral blood smear	Routinely	Recommended
	Medication – drug side effects	Check for concomitant myelosuppressive medications		Routinely	
	Vitamin deficiencies	Vitamin B12, folic acid	Serum levels	Routinely	Recommended
	Rule out infections	Bacterial/viral/fungal infections	Blood cultures, CMV PCR, procalcitonin, $CD4^+$ T-cell, IgG, B-cell levels	Routinely	Recommended
	Rule out macrophage-activation syndrome*	CRS/MAS or IEC-HS	Serum ferritin, triglycerides	Routinely	Recommended
TIER 2	Subsequent work-up – In case of G-CSF refractory state, if tier 1 results are negative and/or risk factors are present				
	Viral PCR considering the clinical presentation	Parvovirus	Parvovirus B19 PCR	In case of prolonged anemia	Recommended
		HHV6, JCV	HHV6, JCV PCR blood/CSF	In case of neurologic symptoms	Recommended
		EBV, adenovirus, HSV	PCR	In case of HLH	Recommended
	Bone marrow disease	(MDS/AML/myelofibrosis) or relapse	BM aspirate, biopsy, flow cytometry, immunohistochemistry, cytogenetics, NGS	In case of prolonged cytopenia	Recommended
		Relapse of leukemia/lymphoma	Flow cytometry peripheral blood / bone marrow, including B-cell panel	Routinely	Recommended
	Other causes	Other rare hematologic diseases, myeloid diseases, PNH, autoimmune processes	Myeloid panel, GPI-linked structures, direct antiglobulin test (DAT)	In case of suspected MPN/ PNH/autoimmune processes	Recommended

Rejeski et al. Blood 2024

ICAHT – EBMT recommendations

(grading and treatment)



- growth factors
- antiinfective prophylaxis
- cell boost

Rejeski et al. Blood 2024

LeitMed Campus

Langzeit-Toxizität, Sekundärmalignome und Rezidivtherapie

Vorstellung

Prof. Dr. Max Topp

Facharzt für Innere Medizin, Hämatologie und Onkologie

- Schwerpunktleiter der Hämatologie und Leiter des CAR-T-Zellprogramms in der Medizinischen Klinik und Poliklinik II des Universitätsklinikums Würzburg

Interessenkonflikte Prof. Topp

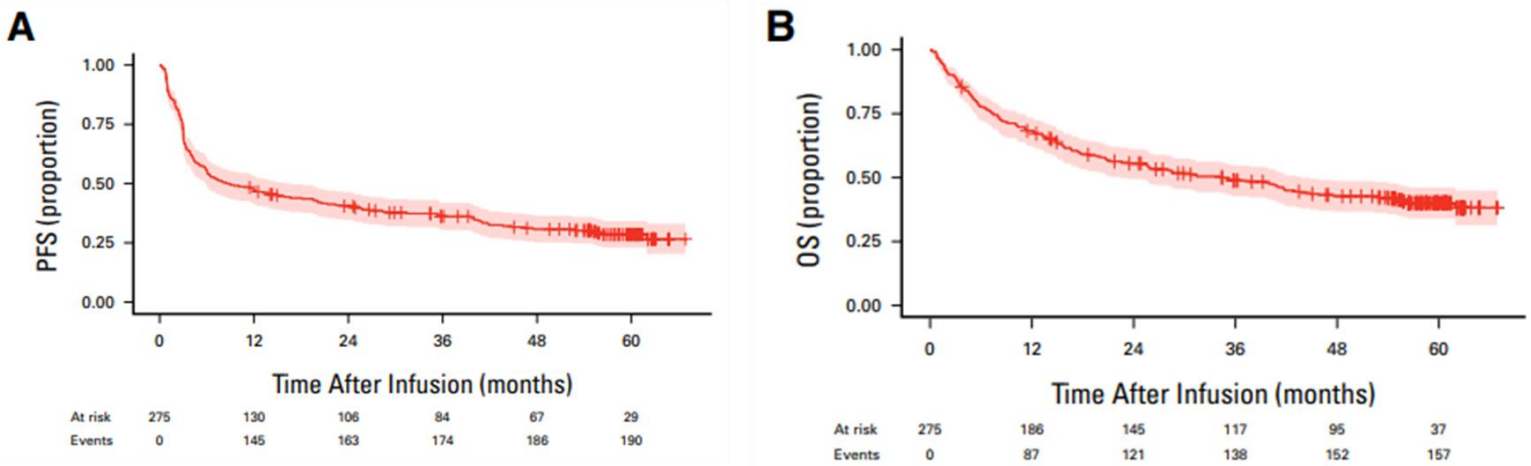
Prof. Topp hat in den letzten 12 Monaten Zuwendungen von folgenden Unternehmen erhalten:

- Beratungs- bzw. Gutachtertätigkeit:
  Astra Zeneca, Beigene, Gilead, Incyte, Janssen

- Finanzierung wissenschaftlicher Untersuchungen:
  Astra Zeneca, Abbvie, Janssen, KITE, Regeneron, Roche

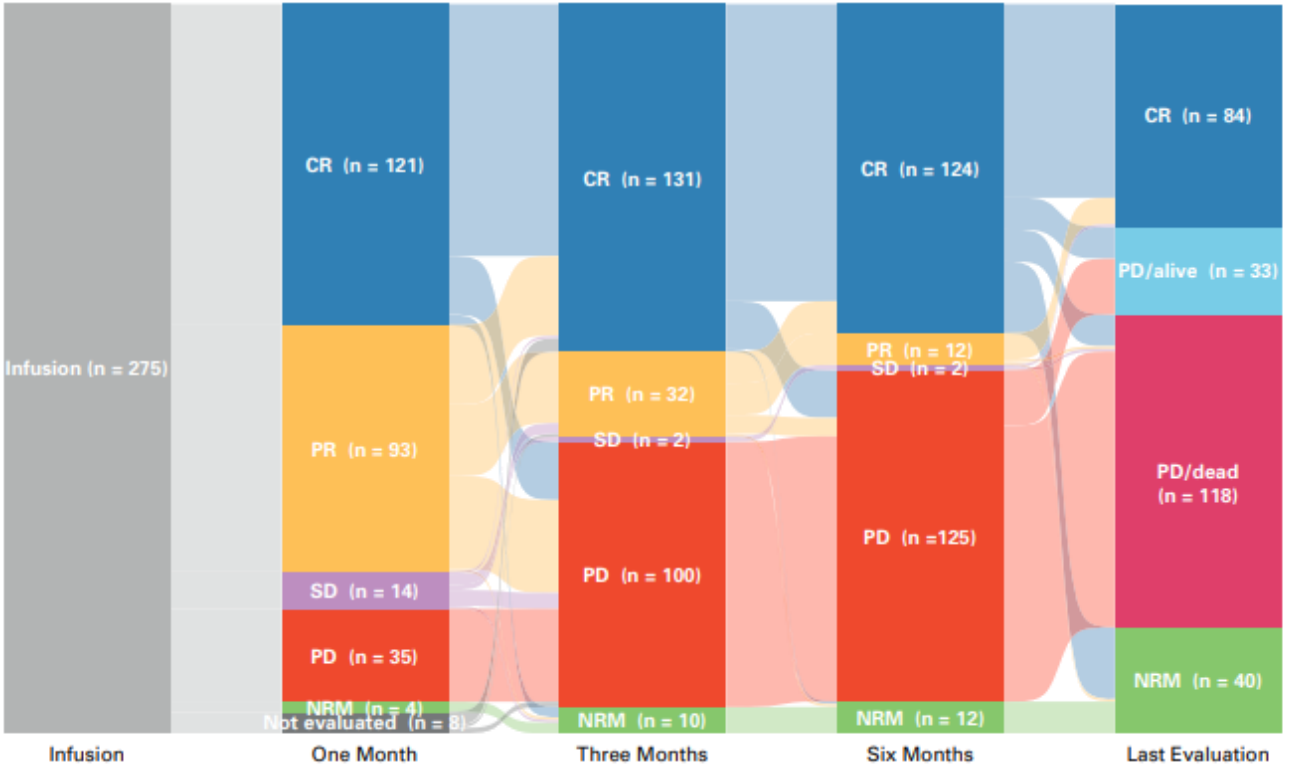
Five Year Follow-Up of Standard of Care Axicabtagene Ciloleucel for Large B-Cell Lymphoma:

Results from the US Lymphoma CAR Consortium



Jain M. et al, JCO 2024

Faith of patients being treated with Axicabtagene Ciloleucel



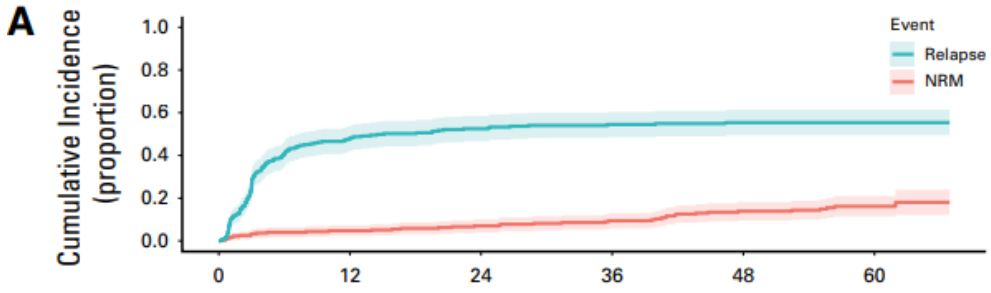
Jain M. et al, JCO 2024

Cause of NRM

TABLE 2. Causes of Death by Year After Axi-Cel Infusion

Cause of Death	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6 or Later	Total
Progressive disease	74	28	11	4	1	0	118
Infection	8	2	4	6	1	0	21
Secondary malignancy	0	3	1	3	1	1	9
CAR-T toxicity[a]	3	0	0	0	0	0	3
Unknown/Other[b]	2	1	1	1	2	0	7

NOTE. Infectious causes of death (n = 21) included unclassified infection (n = 6), pneumonia (n = 5), bacterial sepsis (n = 4), COVID-19 disease (n = 2), candidemia (n = 2), candidemia and concomitant pneumocystis jiroveci pneumonia (n = 1), and JC viral encephalitis (n = 1).
Abbreviations: axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; HLH, hemophagocytic lymphohistiocytosis.
[a]Includes HLH, cerebral edema, and intracranial hemorrhage.
[b]Unknown = 6, suicide = 1.



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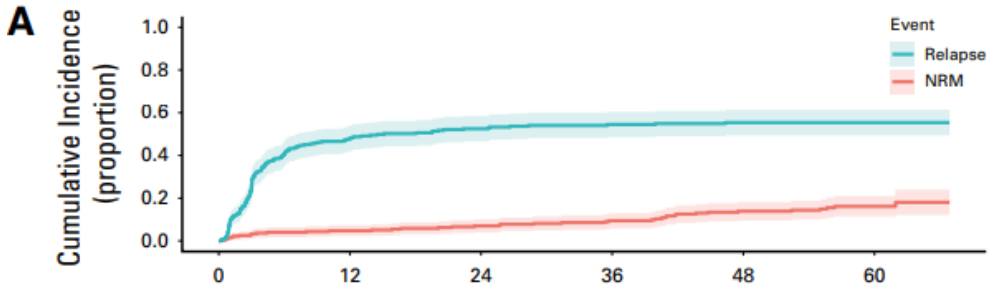

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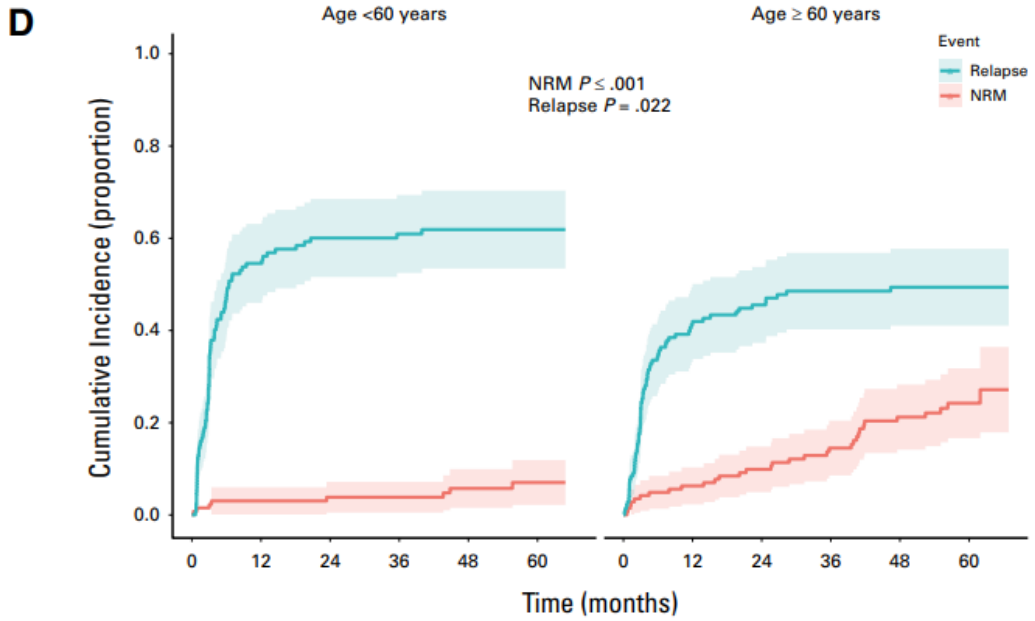
Relapse versus NRM as Cause of Death in Younger and Older DLCBL Patients



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tMn after Axicabtagene Ciloleucel

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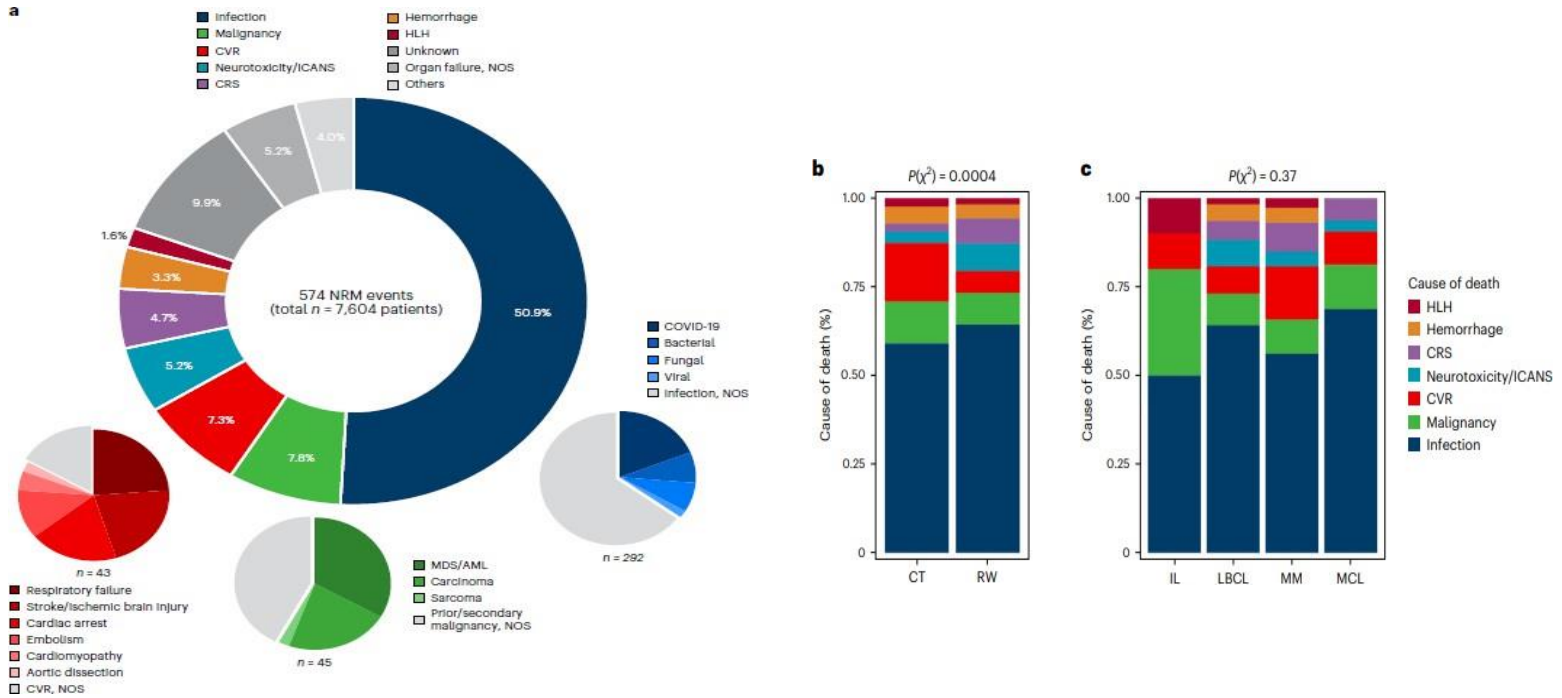
TABLE 3. tMN After Axi-Cel

Patient	Diagnosis	Lymphoma Progression	Time to tMN Diagnosis From Axi-Cel, months	Mutations	Karyotype	Marrow Blasts, %	Risk Stratification	Therapy for tMN	First tMN Regimen	Response to First tMN Regimen	HSCT	OS From tMN Diagnosis (months)	Vital Status
1	CMML	Yes	29.7	KRAS, RUNX1	Monosomy 7	3	High risk (CPSS mol 5)	Yes	Azacitidine	HI	No	13.3	Dead
2	MDS	No	16.2	TP53, IDH2	Complex	1	6.5	Yes	Decitabine	SD	Yes	7.2	Dead
3	MDS	No	12.6	PPM1D, PM1D, and BCOR	Del 4q	0.5	2.5	No	Epoetin alfa	HI	No	47.9	Dead
4	MDS	No	8.7	KRAS, SRSF2, and PPM1D	NA	1.5	3	No	Sargramostim	NR	No	8.8	Dead
5	MDS	No	8.5	TP53	Complex	1	Low risk (score = 2)	Yes	Decitabine	SD	Yes	19.2	Dead
6	AML	No	11.5	KMT2A, STAG2, and SF1	t(11:19); MLL2	88	Adverse risk per ELN	Yes	Decitabine + venetoclax	CR	Yes	14.1	Dead
7	MDS-EB2	Yes	2.7	PPM1D	Deletion 7	10	Very high	Yes	Decitabine	SD	No	5.5	Dead
8	MDS-MLD	No	1	NA	20q-	2	Low risk (score = 2)	No	Observation	NA	No	34.3	Dead[a]
9	MDS	Yes	18.3	TP53	Complex	2	NA	Yes	Azacitadine	NA	No	1.9	Dead
10	MDS	No	20	NA	Monosomy 7	2	NA	Yes	Azacitadine	SD	No	58.9	Alive
11	MDS	Yes	4.2	NA	Complex	2	NA	Yes	Azacitdine + venetoclax	SD	No	23.7	Dead
12	MDS	No	18.5	NA	Complex	2	NA	Yes	Azacitadine	CR	No	13	Dead
13	Mast cell leukemia	No	64	NA	Monosomy 7	NA	NA	No	NA	NA	No	2	Alive[b]
14	MDS	No	41	NA	Complex	NA	NA	No	NA	NA	No	0.7	Dead
15	AML	No	61.1	NA	Monsomy 7	NA	Adverse risk per ELN	No	NA	NA	No	0.5	Dead

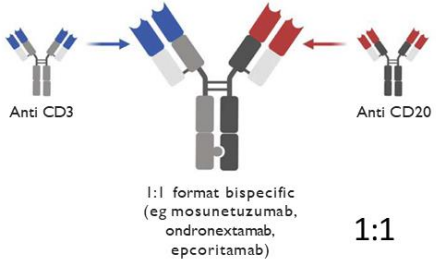
NOTE. Risk stratification for MDS is per R-IPSS, AML per ELN, and CMML per CMML-specific scoring system with molecular features (CPSS Mol).
Abbreviations: axi-cel, axicabtagene ciloleucel; CMML, chronic myelomonocytic leukemia; CR, complete response; ELN, European Leukemia Network; HI, hematologic improvement; HSCT, hematopoetic stem cell transplant; MDS, myelodysplastic syndrome; MLD, multilineage dysplasia; NA, not available; NR, no response; R-IPSS, revised international prognostic scoring system; SD, stable disease; tMN, therapy-related myeloid neoplasms.
[a]Died of trauma.
[b]In hospice at data cutoff.

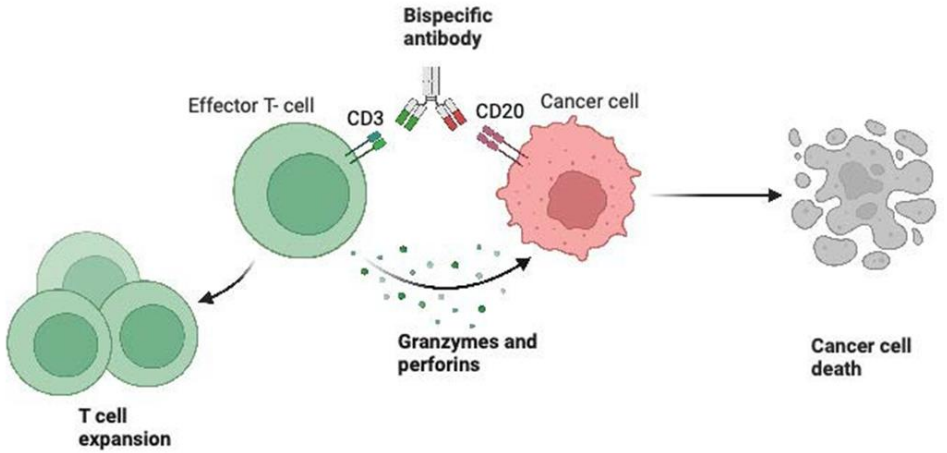
Jain M. et al, JCO 2024

Longterm NRM results are also seen with other CAR-T indications



How to treat Post-CAR-T relapses?





T-cell binding, activation, expansion, T-cell mediated target cell death at low receptor occupancy

Overview of Clinically Available CD20xCD3 Bispecific Antibodies*

Name	Format	Technology	CD20:CD3 ratio	CD3 clone	CD20 clone	Fc silencing mutations
Mosunetuzumab	IgG1	Knobs-into-holes (different Fabs)	1:1	UCHT1v9	2H7 (same as rituximab)	Yes
Glofitamab	IgG1	Head-to-tail fusion	2:1	SP34-der.	By-L1(same as obinutuzumab)	Yes
Epcoritamab	IgG1	Controlled Fab- arm exchange	1:1	huCACAO (SP34-der.)	7D8 (shared by ofatumomab)	Yes (prevents FcγR and C1q binding)
Odronexamab	IgG4	Heavy chains with different affinity	1:1	REG1250	3B9-10 (shared by ofatumomab)	Yes

Glofitamab in 3L+ DLBCL: Expansion Cohort (2.5/10/30 mg)

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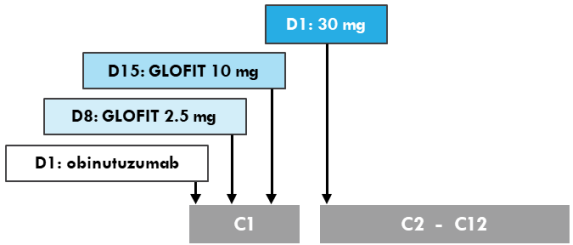
Key Inclusion Criteria

- DLBCL NOS, HGBCL, transformed FL or PMBCL
- ≥2 prior therapies (anti-CD20, anthracycline)

Study Schema

- N=154
- Premedication: acetaminophen, anti H2, and dex or equivalent steroid
- Hospitalization on C1D8 (1st GLOFI dose)

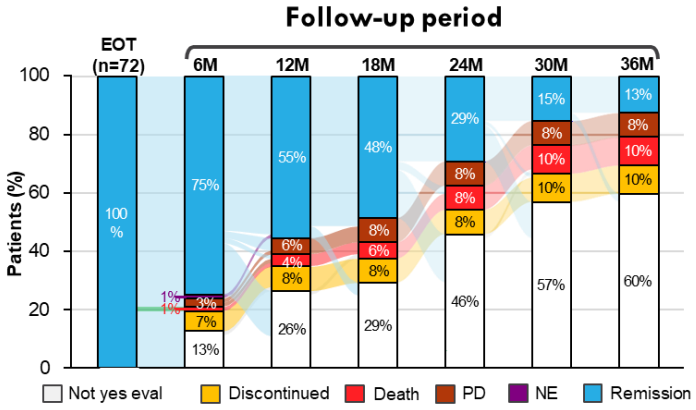


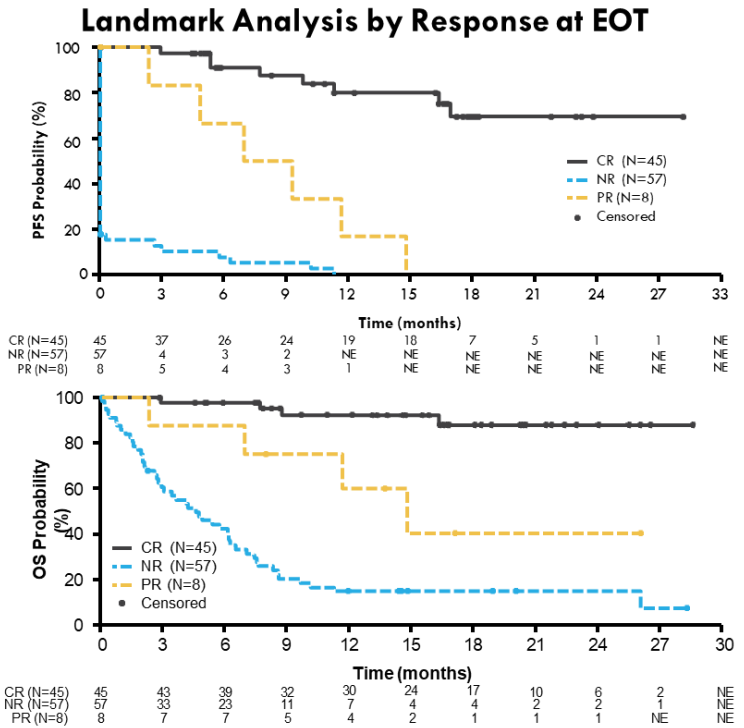
Characteristic		N (%)
Median age, years (range)		66.0 (21 to 90)
NHL subtype	DLBCL	110 (71.4)
	trFL	27 (17.5)
	HGBCL	11 (7.1)
	PMBCL	6 (3.9)
Bulky disease	>6cm	64 (41.6)
	>10cm	18 (11.7)
Median no. prior lines, (range)		3 (2 to 7)
2 prior lines		62 (40.3)
≥3 prior lines		92 (59.7)
Prior CAR T		51 (33.1)
Prior ASCT		28 (18.2)
Refractory to prior CAR T		46 (29.9)

Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-2231

Glofitamab: Responses and Outcomes

Endpoint	IRC (N=155)*
CR, n (%) [95% CI]	62 (40) [32.2 to 48.2]
ORR, n (%) [95% CI]	80 (52) [43.5 to 59.7]
Median follow-up, mos (rng)	18.2 (0 to 33)
Ongoing CRs, n/N (%)	42/62 (68)
Median DoCR, mos (95% CI)	26.9 (18.4 to NE)
*ITT population; CI, confidence interval; NE, not estimable.	





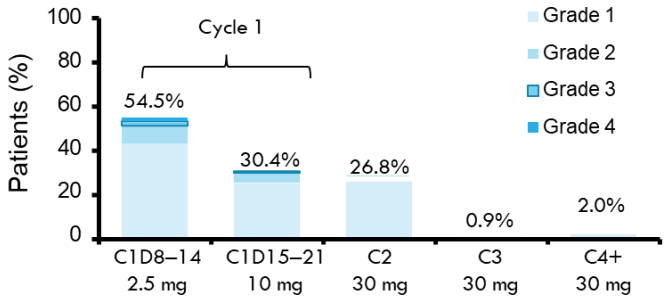
Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-2231

Glofitamab: Safety Profile (at the RP2D)

AESI	N (%)
Infections (all grades)	59 (38.3)
Grade ≥3	23 (14.9)
Neutropenia (all grades)	58 (37.7)
Grade ≥3	41 (26.6)
Febrile neutropenia (all grades)	4 (2.6)
Grade ≥3	4 (2.6)
Neurologic AEs (all grades)	59 (38.3)
Grade ≥3	5 (3.2)
ICANS (all grades)	12 (7.8)
Grade ≥3 (CTCAE)	4 (2.6)[§]

CRA Characteristic	n (%)
CRS (any grade)	97 (63.0)
Grade 1	73 (47.4)
Grade 2	18 (11.7)
Grade 3	4 (2.6)
Grade 4	2 (1.3)
Median time to CRS from C1D8, h (range)	13.6 (6.2 to 51.8)
Corticosteroid use	27/97 (27.8)
Tocilizumab use	31/97 (32.0)

CRS by Cycle and Grade



Dickinson MJ, et al. N Engl J Med. 2022;387(24):2220-2231

Epcoritamab in 3L+ DLBCL: Expansion Cohort (0.16/0.8/48 mg)

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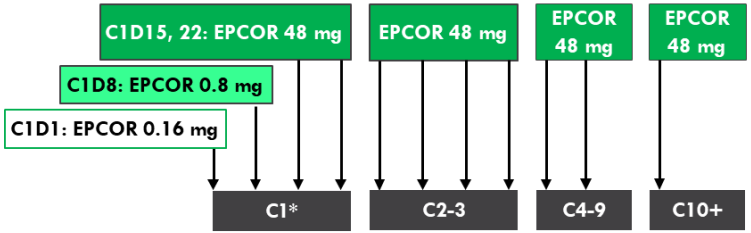
Key Inclusion Criteria

- CD20+ B-NHL, including DLBCL, HGBCL, PMBCL, and FL Grade 3B
- ≥2 prior therapies (anti-CD20, anthracycline)
- C1 step-up dosing, target dose 48 mg

Study Schema

- N=157
- Premed: acetaminophen, anti H2, and prednisone x4 days post-dose
- Hospitalization on C1D15 (1st full EPCOR dose)



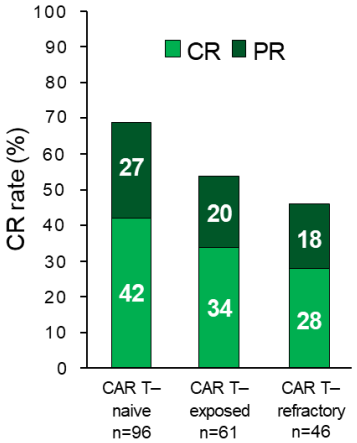
Characteristic	N=157 (LBCL cohort)
Median age (range), y	64 (20 to 83)
Disease type, n (%)	
DLBCL	139 (89)
De novo	97/139 (70)
Transformed	40/139 (29)
Unknown	2/139 (1)
HGBCL	9 (6)
PMBCL	4 (3)
FL Gr3B	5 (3)
Median n. prior lines (range)	3 (2 to 11)
≥3 Lines of therapy, n (%)	111 (71)
Primary refractory[b] disease, n (%)	96 (61)
Prior ASCT, n (%)	31 (20)
Prior CAR T therapy, n (%)	61 (39)
PD within 6 mos of CAR T	46/61 (75)

Thieblemont C, et al. J Clin Oncol. 2023;41(12):2238-2247.

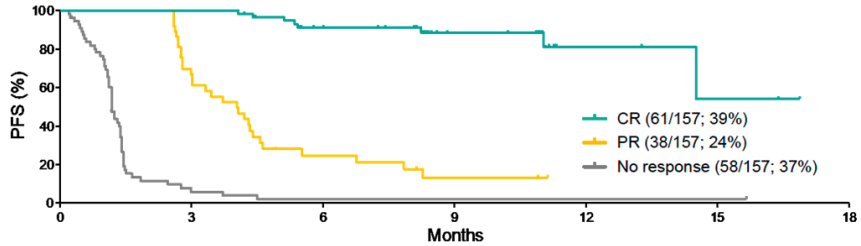
Epcoritamab: Responses and Outcomes

Median Follow-up: 10.7 mos

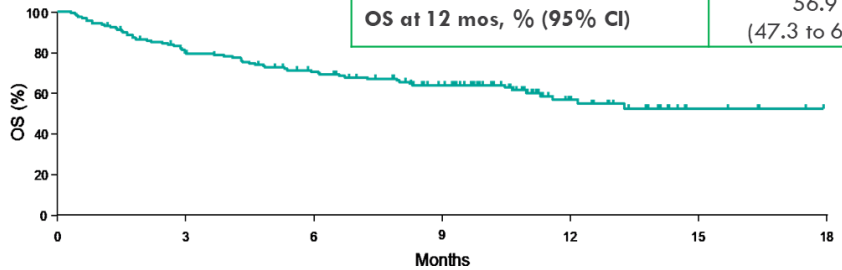
Response	All LBCL patients (n=157)
ORR	99 (63%) [95% CI: 55 to 71]
CR rate	61 (39%) [95% CI: 31 to 47]



Median PFS, mo (95% CI)	4.4 (3.0 to 7.9)
Complete responders in CR at 9 mos	89%



Median OS	Not reached
OS at 12 mos, % (95% CI)	56.9 (47.3 to 65.4)



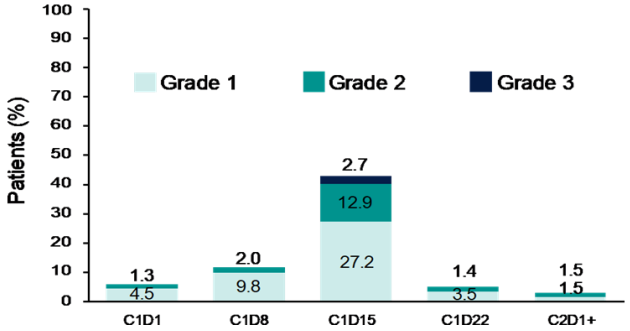
Thieblemont C, et al. J Clin Oncol. 2023;41(12):2238-2247.

Epcoritamab: Safety Profile

AE (≥15%)	%
Neutropenia	28
Grade ≥3	21
Anemia	18
Grade ≥3	10
Fatigue	23
Diarrhea	20
Injection site reactions	20
ICANS	6

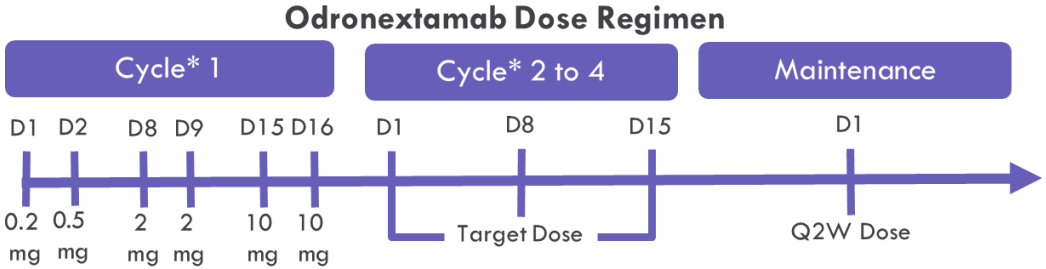
CRS Characteristic	n (%)
CRS events, n (%)	78 (49.7)
• Grade 1	50 (31.8)
• Grade 2	24 (15.3)
• Grade 3	4 (2.5)
Median time to onset from first full dose, d	0.8 (20 h)
Median time to resolution from first full dose, d	2 (48 h)
Treated with tocilizumab, n (%)	22 (14.0)

CRS by Cycle and Grade

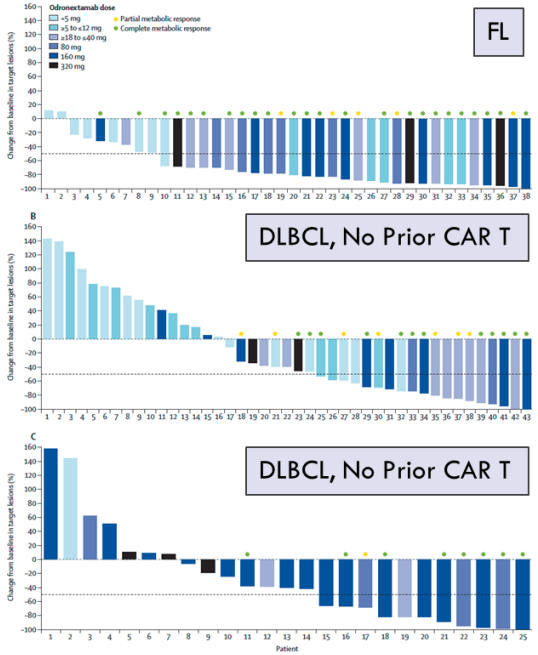


Thieblemont C, et al. J Clin Oncol. 2023;41(12):2238-2247.

Odronextamab in Patients with R/R B-NHL



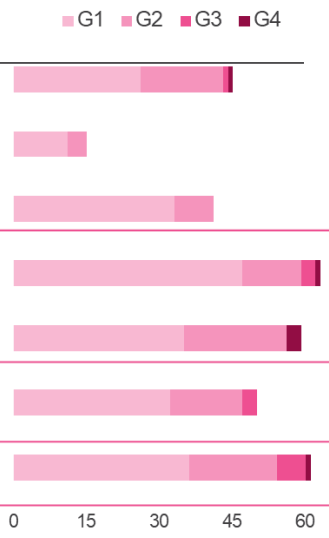
Characteristic (N=145)	% or median (range)
Median age, years	67 (57 to 73)
DLBCL	59
FL	28
MCL	8
MZL	4
N. prior therapies	3 (2 to 5)
Previous CAR T	29
Double refractory (anti-CD20 Ab and alkylators)	69



Bannerji R, Topp M.S.. Lancet Haematol. 2022;9(5):e327-e339.

CRS Mitigation and Incidence Across CD20xCD3 BsAb Trials*

Drug	N	Population	Route (target dose)	Mitigation strategies during Cycle 1			% CRS	% Toci use
				Step-up dosing	Hospitalization	Other	G1 G2 G3 G4	
Mosunetuzumab	90	FL, R/R	IV (30 mg)	Yes	Optional			8
	39	B-NHL, R/R	SC (45 mg)	Yes	Optional			10
	27	B-NHL, R/R	SC, rapid SUD (45 mg)	Yes	Optional			0
Glofitamab	154	DLBCL, R/R	IV (30 mg)	Yes	Mandatory	Obinutuzumab		32
	29	MCL, R/R	IV (0.6 to 30 mg)	Yes	Mandatory	Obinutuzumab		24
Epcoritamab	157	LBCL, R/R	SC (48 mg)	Yes	Mandatory	Post-dose steroids		28
Odronextamab	145	B-NHL, R/R	IV (0.5 to 320 mg)	Yes	Mandatory	Split-dose		5

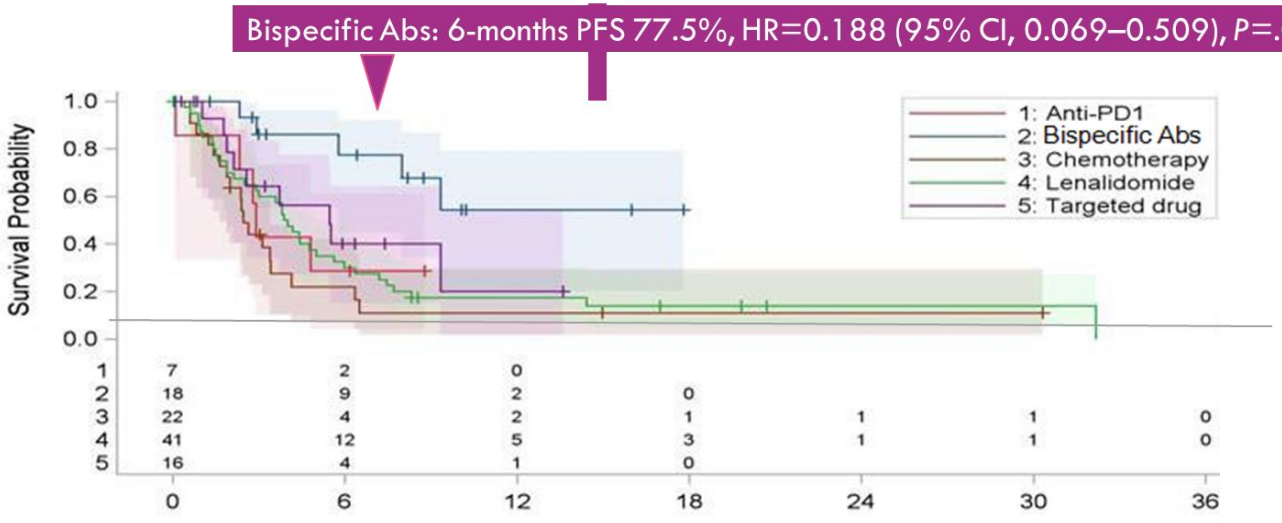


*This table is not intended to be comparative; direct cross-trial comparisons should be avoided
Modified from: Falchi L, et al. Blood. 2023;141(5):467-480.

PRIOR CAR-T – Complete remissions

Epcoritamab	Glofitamab	Ondroextamab
• CAR-T naive: 42 % • Exposed: 34 %	• CAR-T naive: 42 % • Exposed: 35 %	• CAR-T naive: 35 % • Exposed: 32.3 %

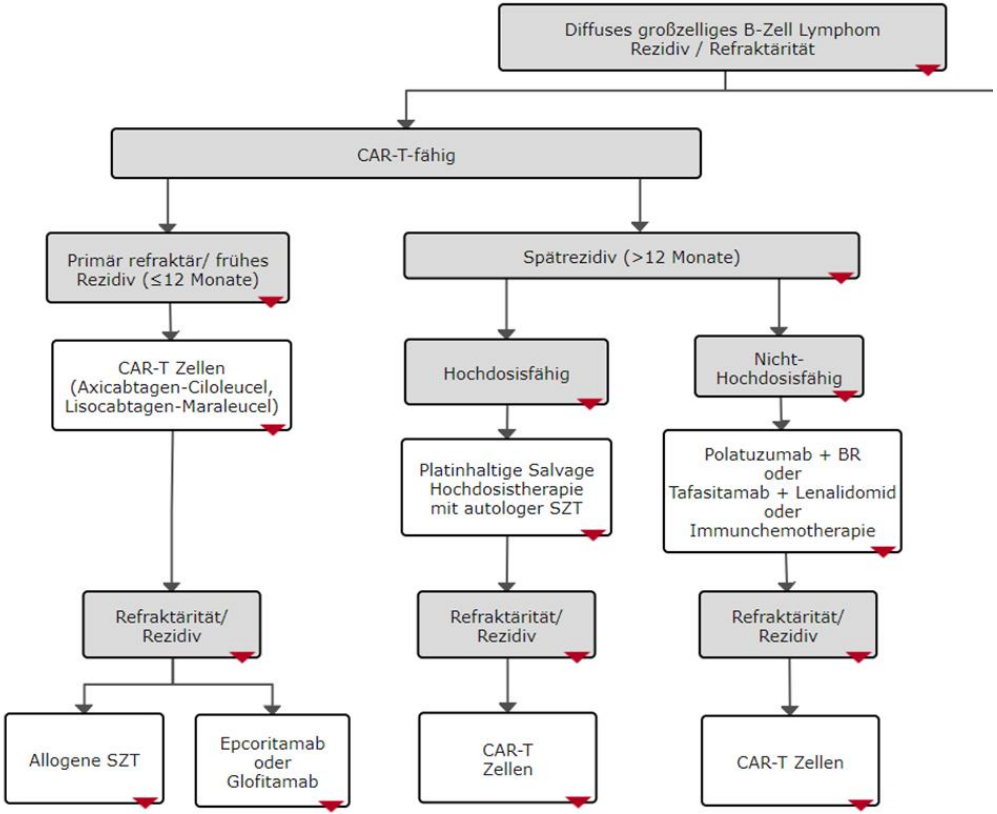
PFS After Late CAR-T-Cell Therapy Failure by Treatment Group
(DESCAR-T Registry)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
Anti-PD1	7	71.4 % (5)	28.6 % (2)	2.9 (0.1 ; NA)
Bispecific Abs	18	27.8 % (5)	72.2 % (13)	Not reached (5.8 ; NA)
Chemotherapy	22	81.8 % (18)	18.2 % (4)	2.5 (1.6 ; 3.4)
Lenalidomide	41	85.4 % (35)	14.6 % (6)	3.9 (2.5 ; 5)
Targeted drug	16	56.3 % (9)	43.8 % (7)	5.5 (1.9 ; NA)

* BTK Inhibitors, MALT-1 inhibitors, anti-CD19, anti-CD38, second CAR T-cells infusion, others
Erbella F, et al. Blood. 2022;140(Suppl 1):1325-1327.

Onkopedia Guidelines 2024



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Q&A-Lounge

Fragen Sie die Experten!

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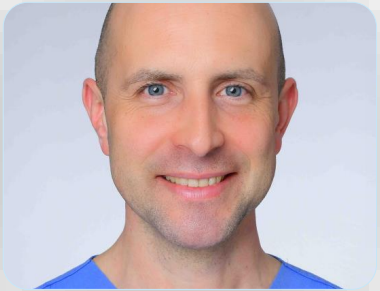
(UK Köln)

- Therapievorbereitung (bridging therapy)



Prof. Böll
(UK Köln)

- Akut-Toxizität
- infektiöse Komplikationen

Prof. Topp
(UK Würzburg)

- Langzeit-Toxizität
- Sekundärmalignome
- Rezidivtherapie

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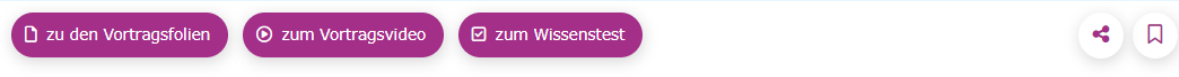

- Bearbeiten Sie das gesamte Fortbildungsmaterial.
- Absolvieren Sie den Wissenstest mit mindestens 70 % richtigen Antworten.
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