Comprehensive Cancer Center Niedersachsen

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

UniversitätsKrebszentrum ▪ G-CCC
Göttingen ▪ Comprehensive Cancer Center

NIO Fortbildung 2021

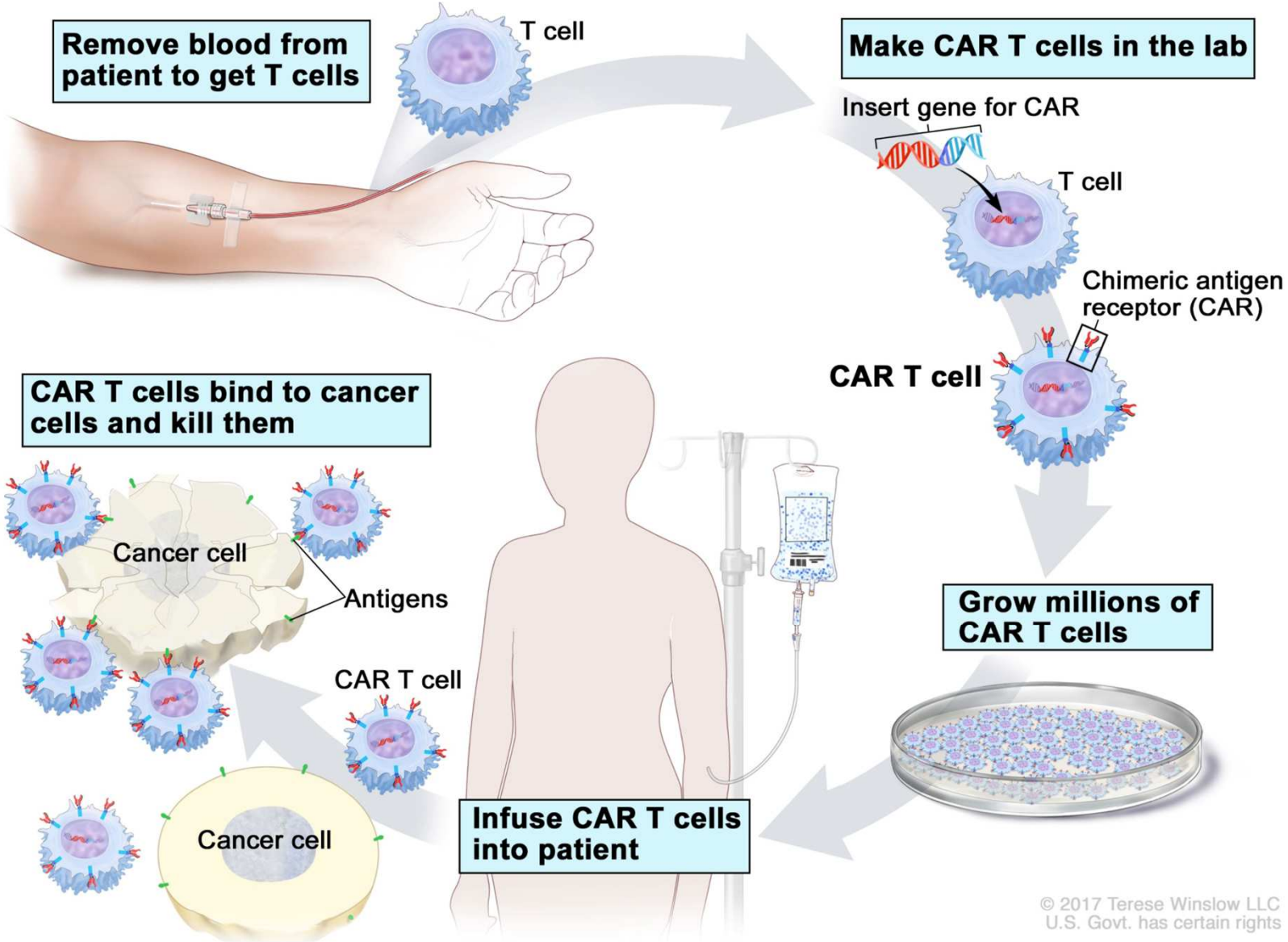
Nachsorge nach Therapie mit CAR-T-Zellen

Gerald Wulf

Hannover, 13.11.2021

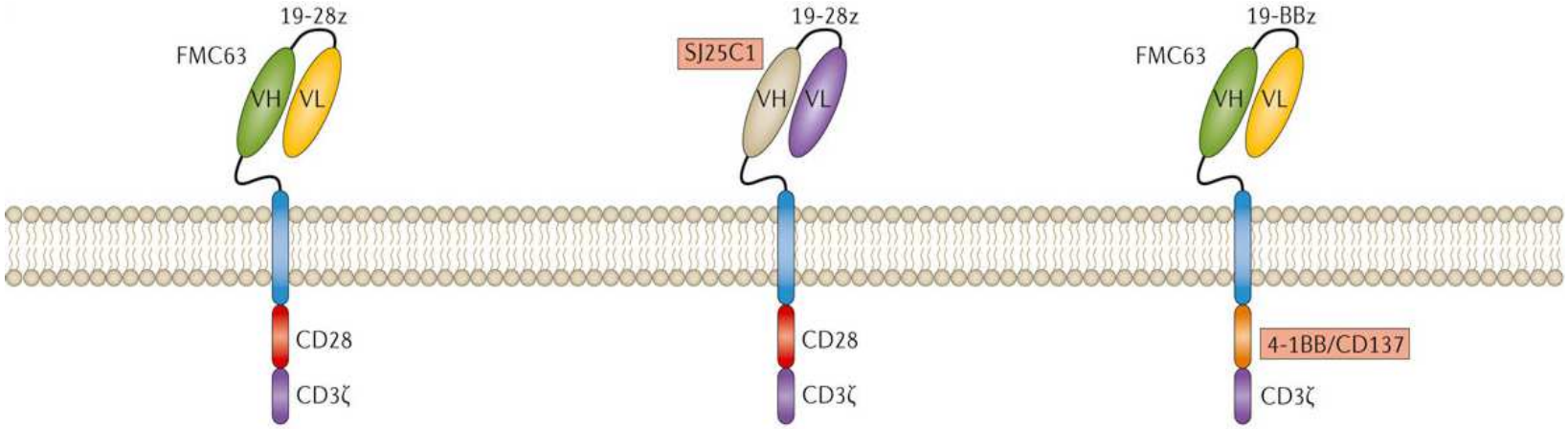
GLA German Lymphoma Alliance

Therapien mit CAR T-Zellen



https://nci-media.cancer.gov/pdq/media/images/774647.jpg

CD19 spezifische CARs der 2. Generation



Institute	Transfection	Hinge/ transmembrane
NCI	Retrovirus	CD28
Baylor	Retrovirus	IgG-CD28
City of hope	Lentivirus	IgG4-Fc
MDACC	Sleeping beauty	IgG4-Fc
Fred Hutchinson	Lentivirus	IgG1-CD4

Institute	Transfection	Hinge/ transmembrane
MSKCC	Retrovirus	CD28

Institute	Transfection	Hinge/ transmembrane
U Penn (CTL019)	Lentivirus	CD8
Fred Hutchinson	Lentivirus	IgG1-CD4

Kite Pharma → GILEAD

NOVARTIS

JUNO THERAPEUTICS → Celgene

Batlevi et al. *Nat Rev Clin Oncol* 2016

Zulassungsstatus von CAR-T-Produkten in Deutschland

- Axicabtagen ciloleucel (**Yescarta®**, Kite/Gilead)

  anti-CD19; r/r DLBCL, r/r PMBCL

- Tisagenlecleucel (**Kymriah®**, Novartis)

  anti CD19; r/r DLBCL, r/r B-ALL bis 25 Jahre

- *Lisocabtagene vicleucel (Maraleucel®, Bristol Myers Squibb)*

  anti CD19; r/r DLBCL

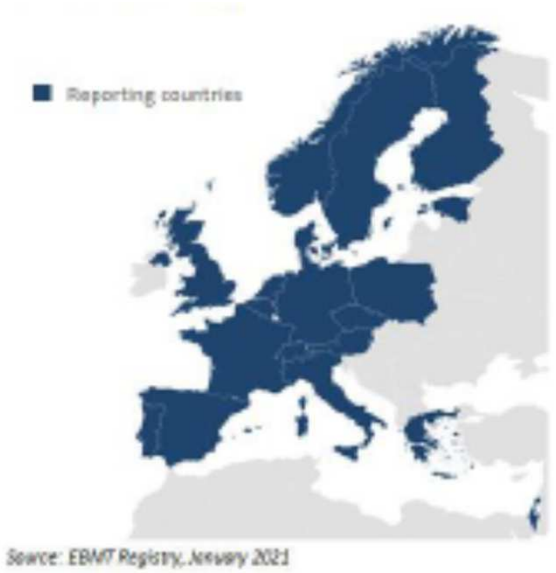
- Brexucabtagene autoleucel (**Tecartus®**, Kite/Gilead)

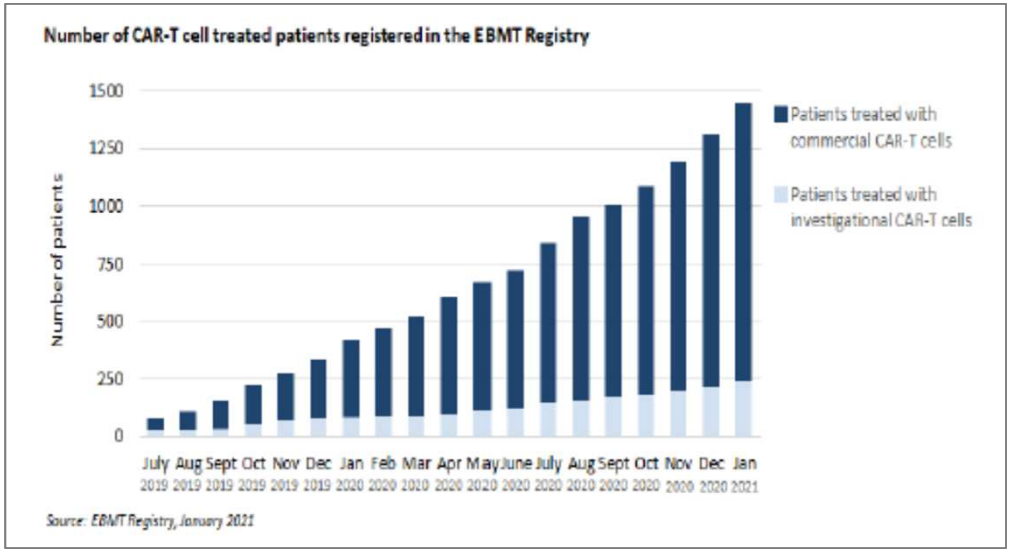
  anti CD19; Mantelzelllymphom-Rezidiv nach BTK-Inhibitor

- Idecabtagen vicleucel (**Abecma®**, Bristol Myers Squibb)

  anti BCMA; r/r Multiples Myelom mit mind. 3 Vortherapien (inkl. IMiD, PI, anti-CD38-AK)

EBMT
European Society
for Blood and Marrow Transplantation





Kymriah (24)

Yescarta (24)

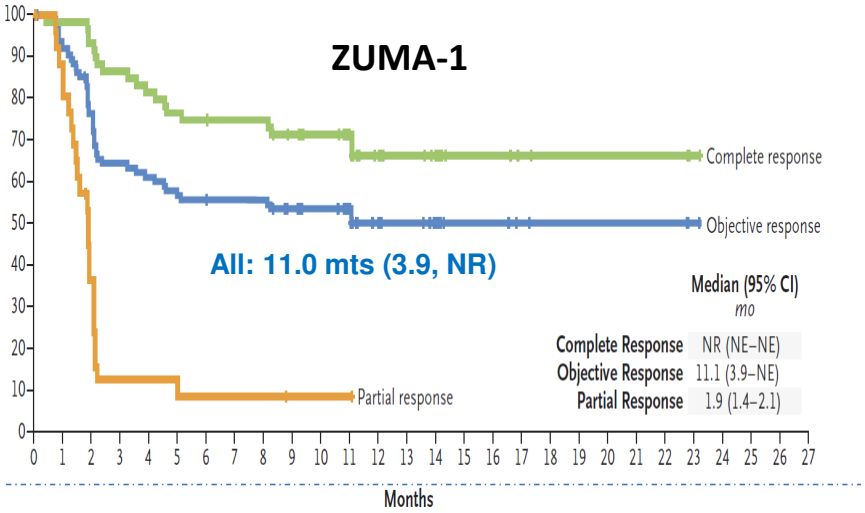
Tecartus (18)

Abecma

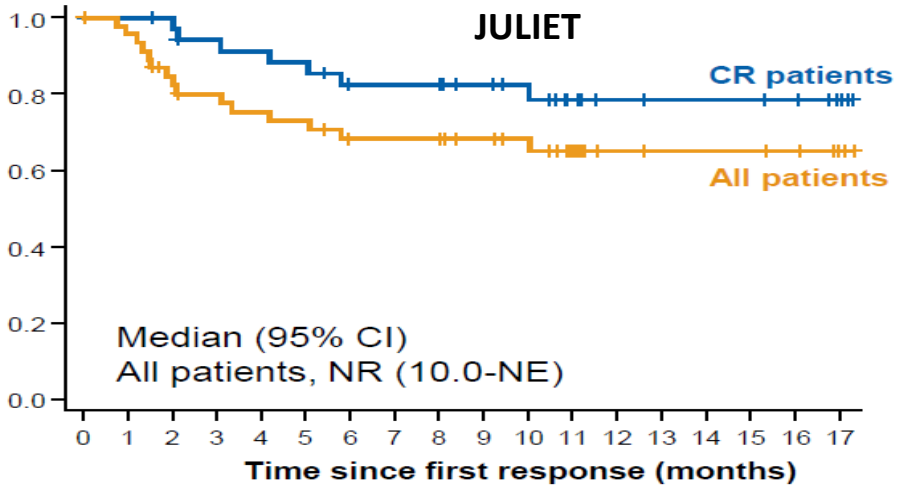
Wirksamkeit

	ORR	CR	OS
• **Yescarta®** (ZUMA-1):	82%	54%	44% (4 J.)
• **Kymriah®** (JULIET):	52%	40%	36% (3 J.)
• **Tecartus®** (ZUMA-2):	85%	59%	83% (1 J.)
• **Abecma®** (KarMMa):	73%	33%	median PFS 8,8 Monate

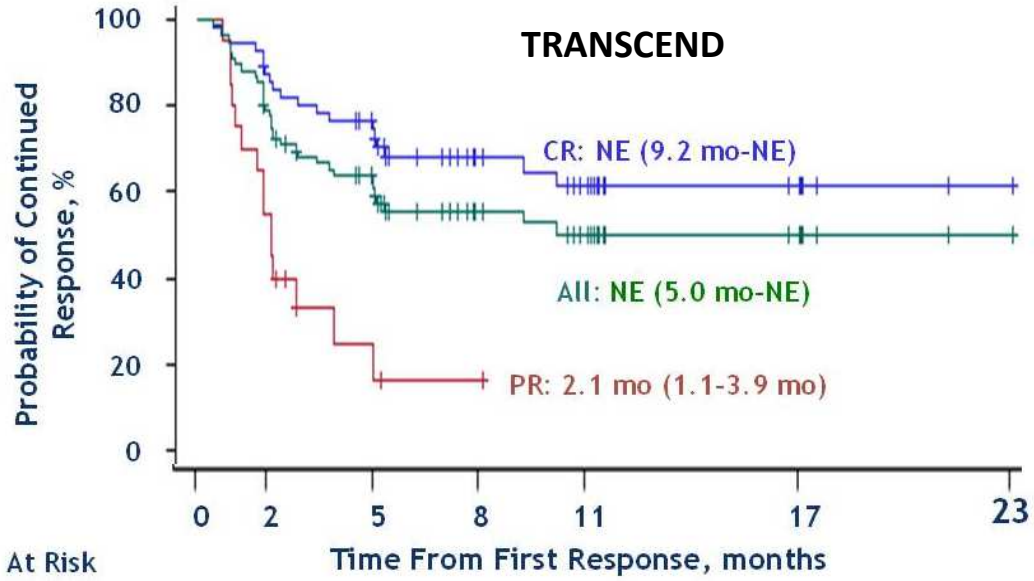
Duration of response



SS Neelapu, NEJM 2017

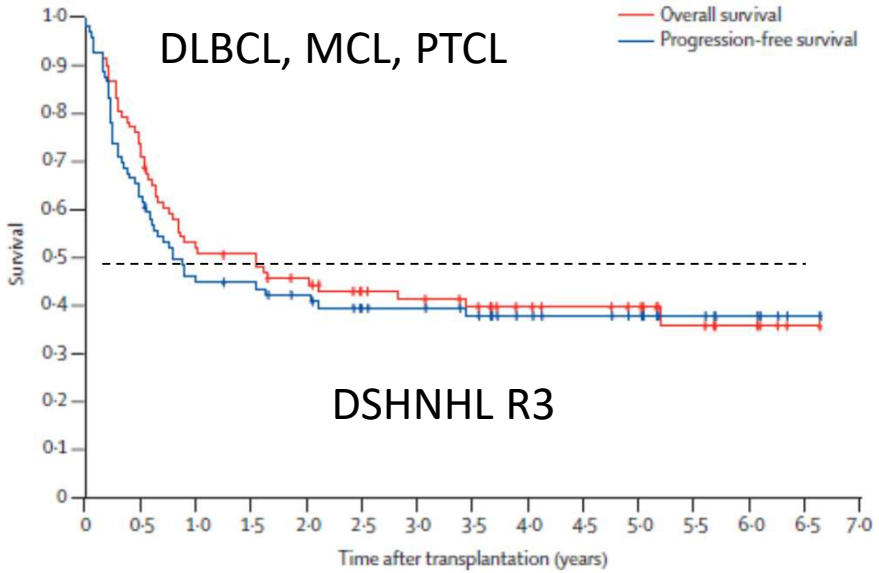


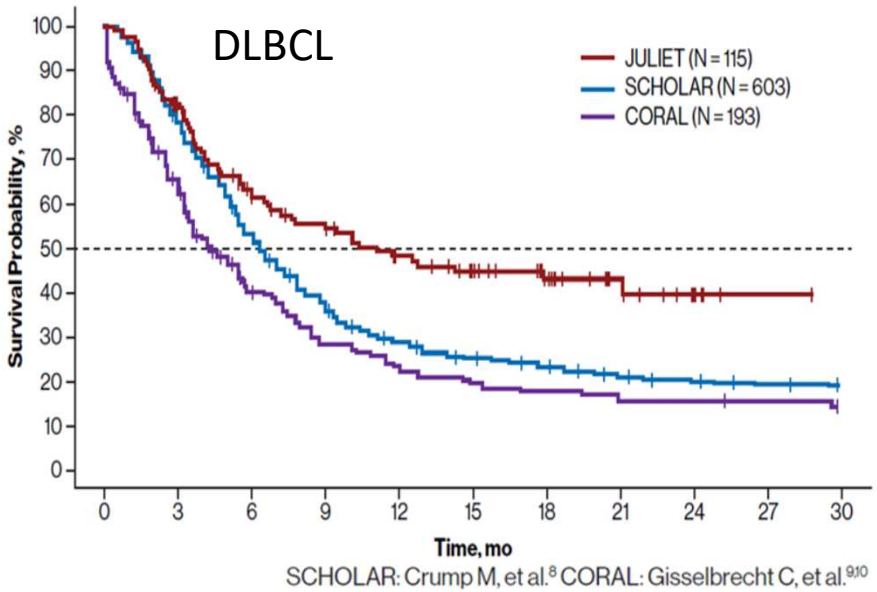
P Borchmann, ASH 2019



J Abramson, ASH 2019

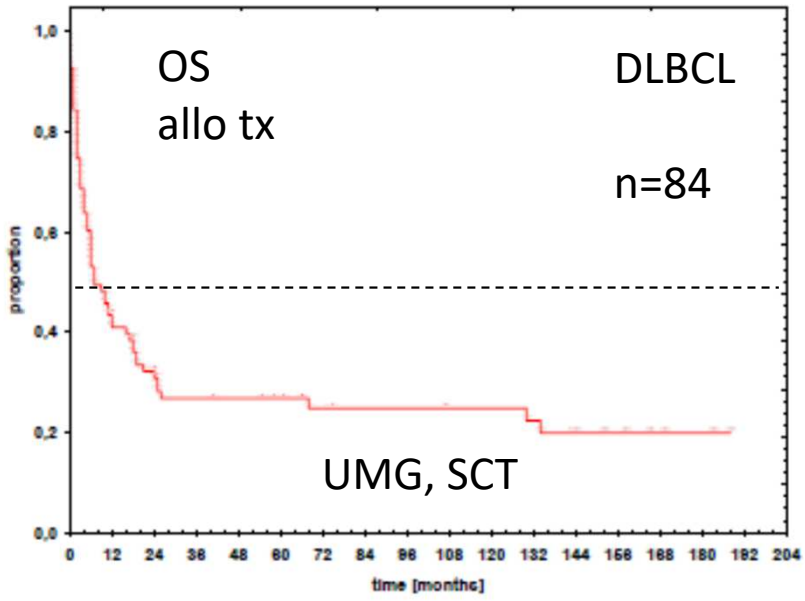
Zelluläre Therapie aggressiver Lymphome: allogene SCT vs. CAR-T





SCHOLAR: Crump M, et al.[8] CORAL: Gisselbrecht C, et al.[9,10]

Glass B, Hasenkamp J, Wulf G et al. .Lancet Oncol. 2014 Jun;15(7):757-66. doi: 10.1016/S1470-2045(14)70161-5.



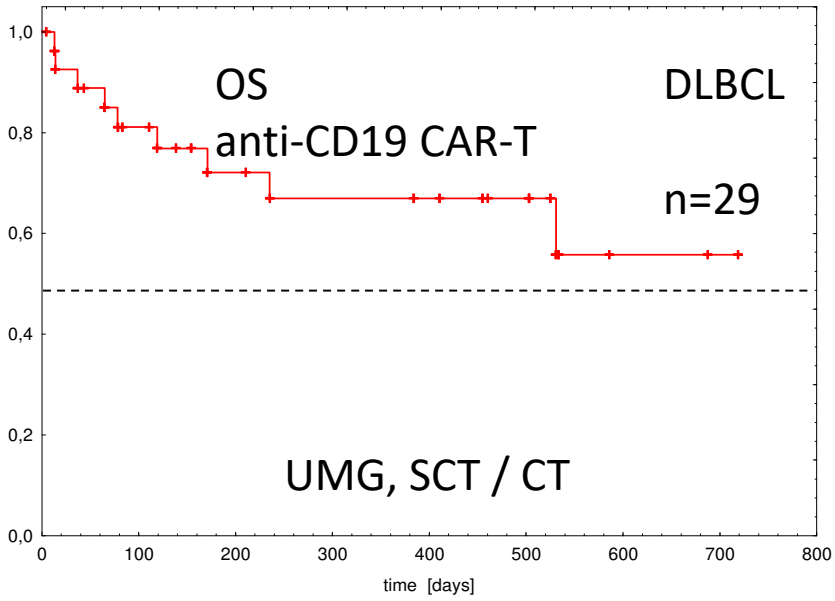
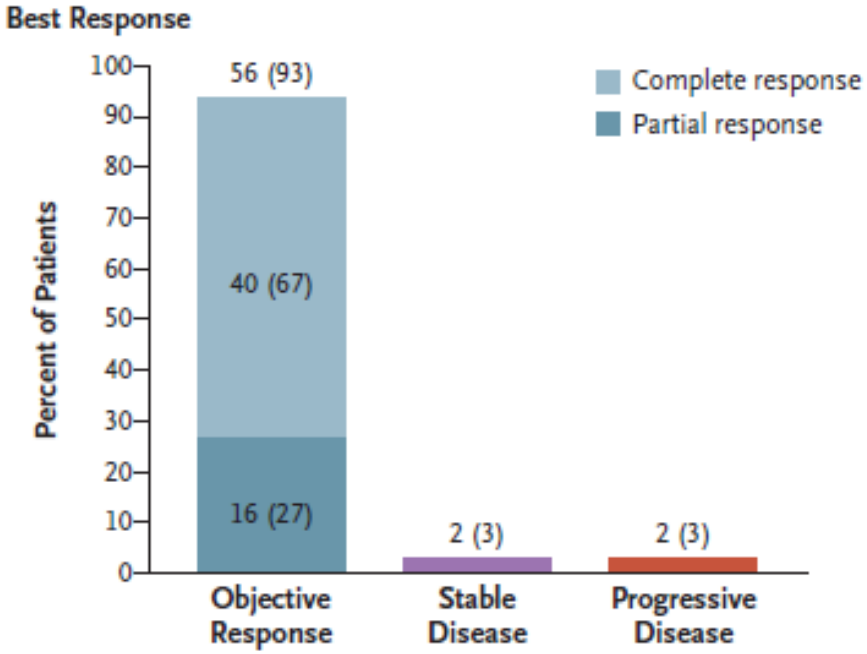
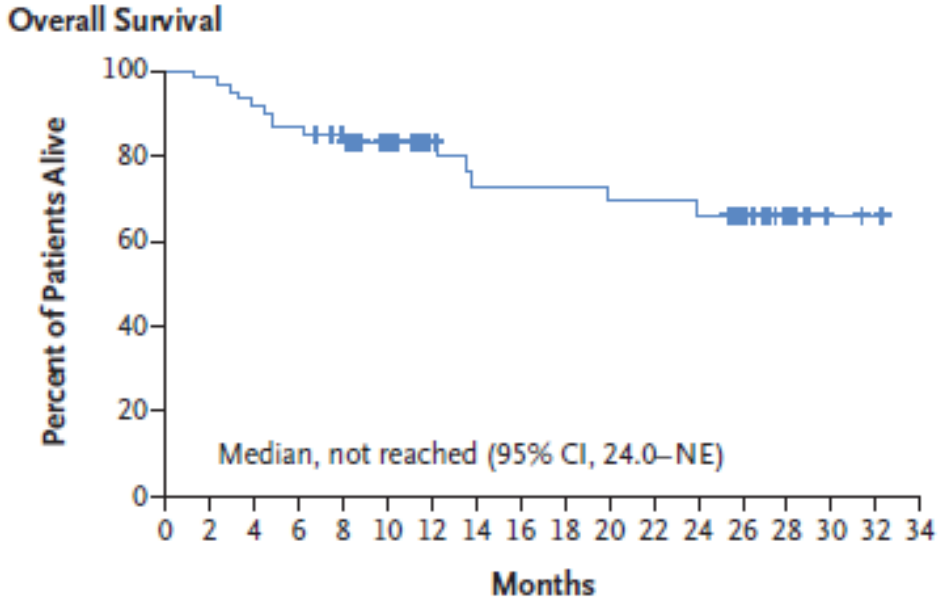


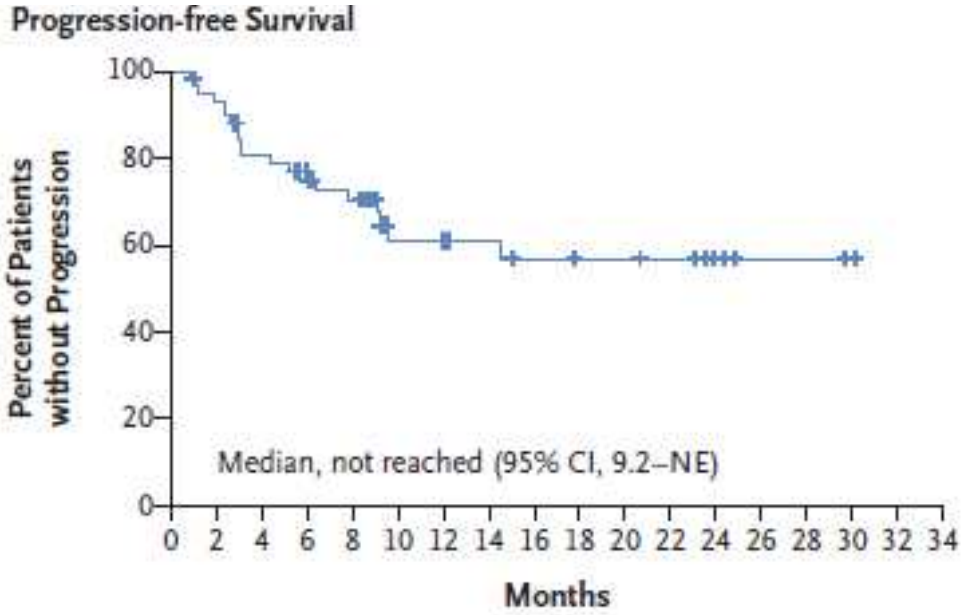
Plate C, Dissertation UMG2021

KTE-X19 (Tecartus) CAR T-cell Therapy für r/r Mantle Cell Lymphoma

Relapsed or refractory disease — no. (%)	
Relapse after autologous stem-cell transplantation	29 (43)
Refractory to most recent previous therapy	27 (40)
Relapse after most recent previous therapy	12 (18)
Disease that relapsed or was refractory to BTK inhibitor therapy — no. (%)	68 (100)
Refractory to BTK inhibitor therapy	42 (62)
Relapse during BTK inhibitor therapy	18 (26)
Relapse after BTK inhibitor therapy	5 (7)
Could not take BTK inhibitor therapy because of adverse events¶	3 (4)

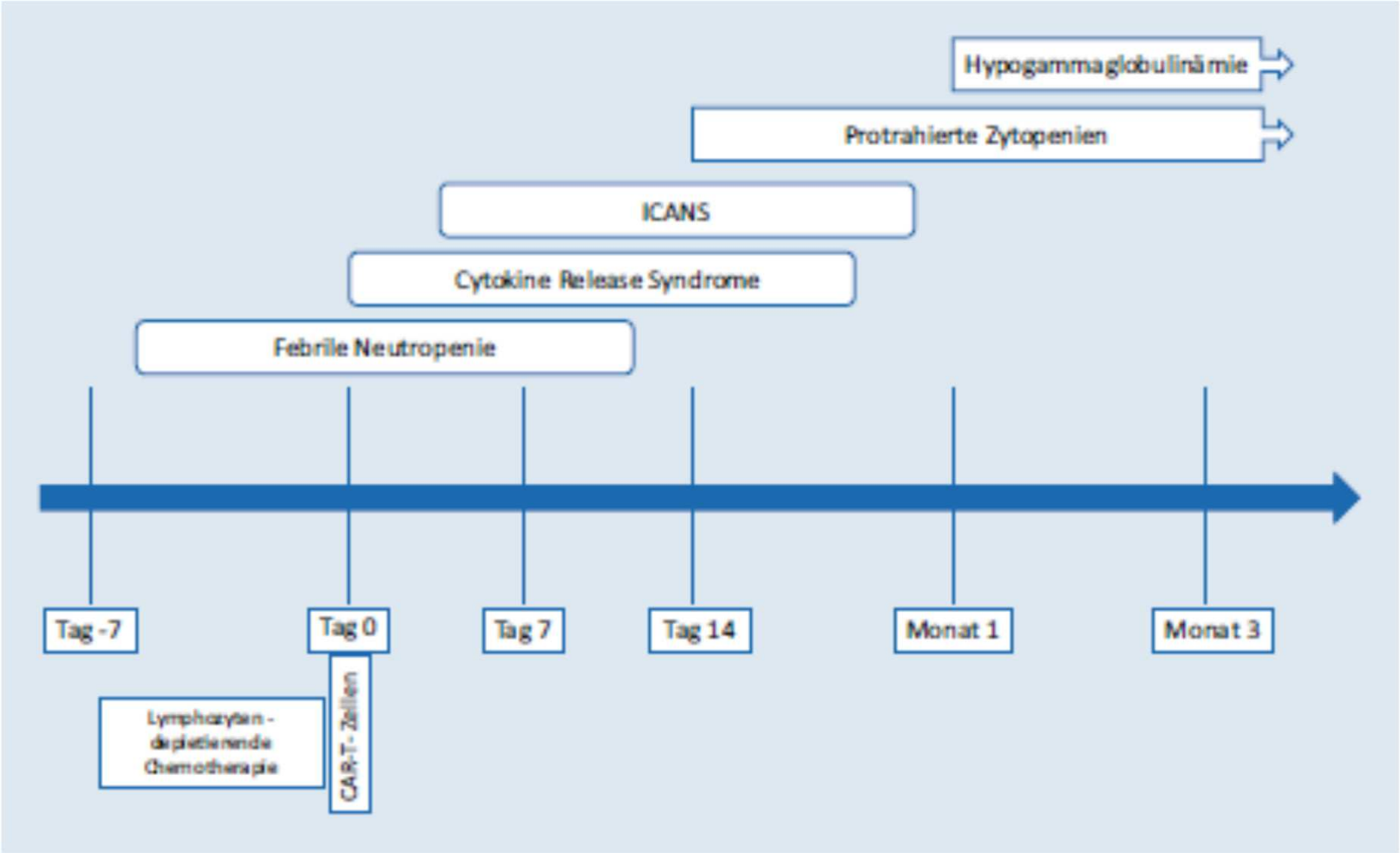






N Engl J Med 2020;382:1331-42.
DOI: 10.1056/NEJMoa1914347

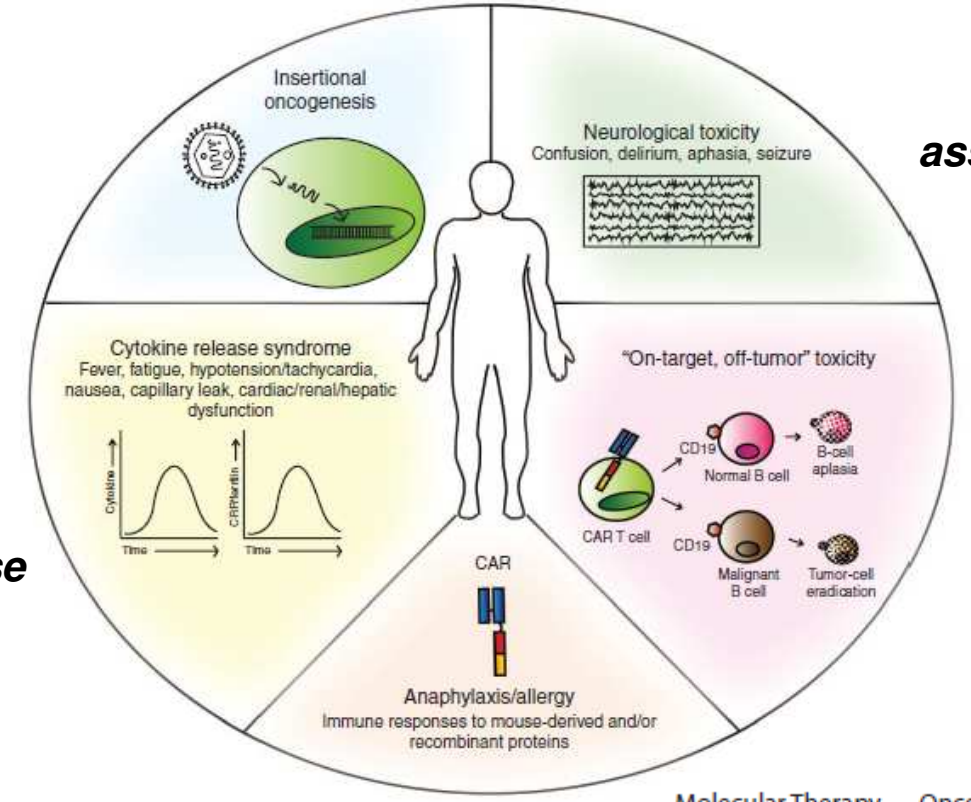
Toxizitäten nach Chimärer-Antigenrezeptor-T-Zell-Therapie



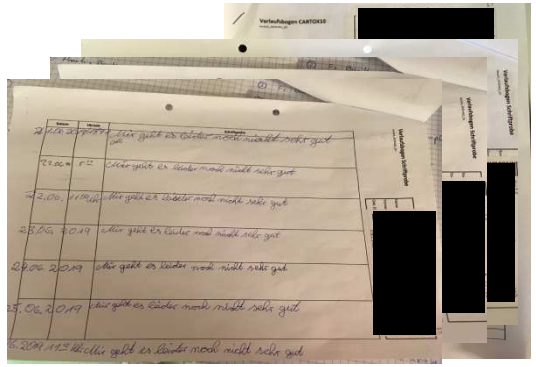
Internist 2021 · 62:611–619
https://doi.org/10.1007/s00108-021-01046-5

Toxizitäten und Management der CAR T- Cell Therapie

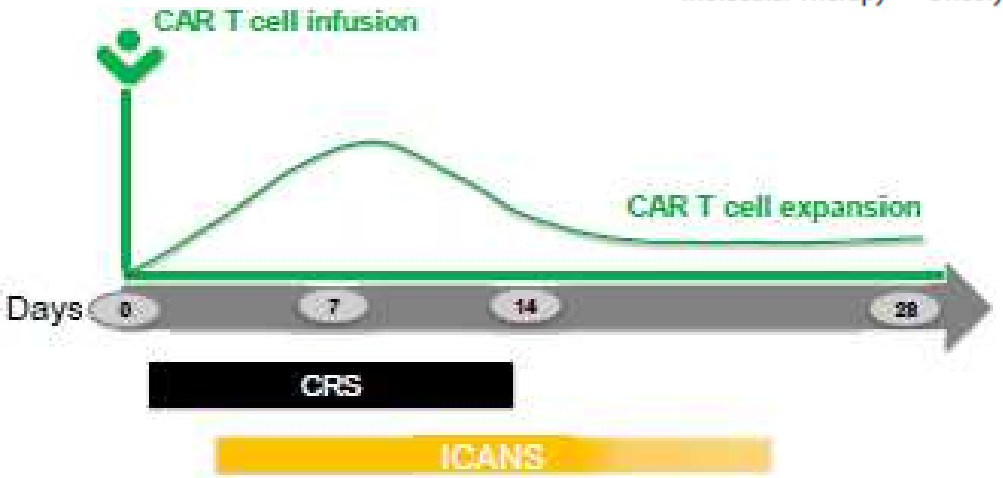
Zytokin-Release Syndrom



Immuneffektorzellen-assoziiertes Neurotoxizitäts-Syndrom

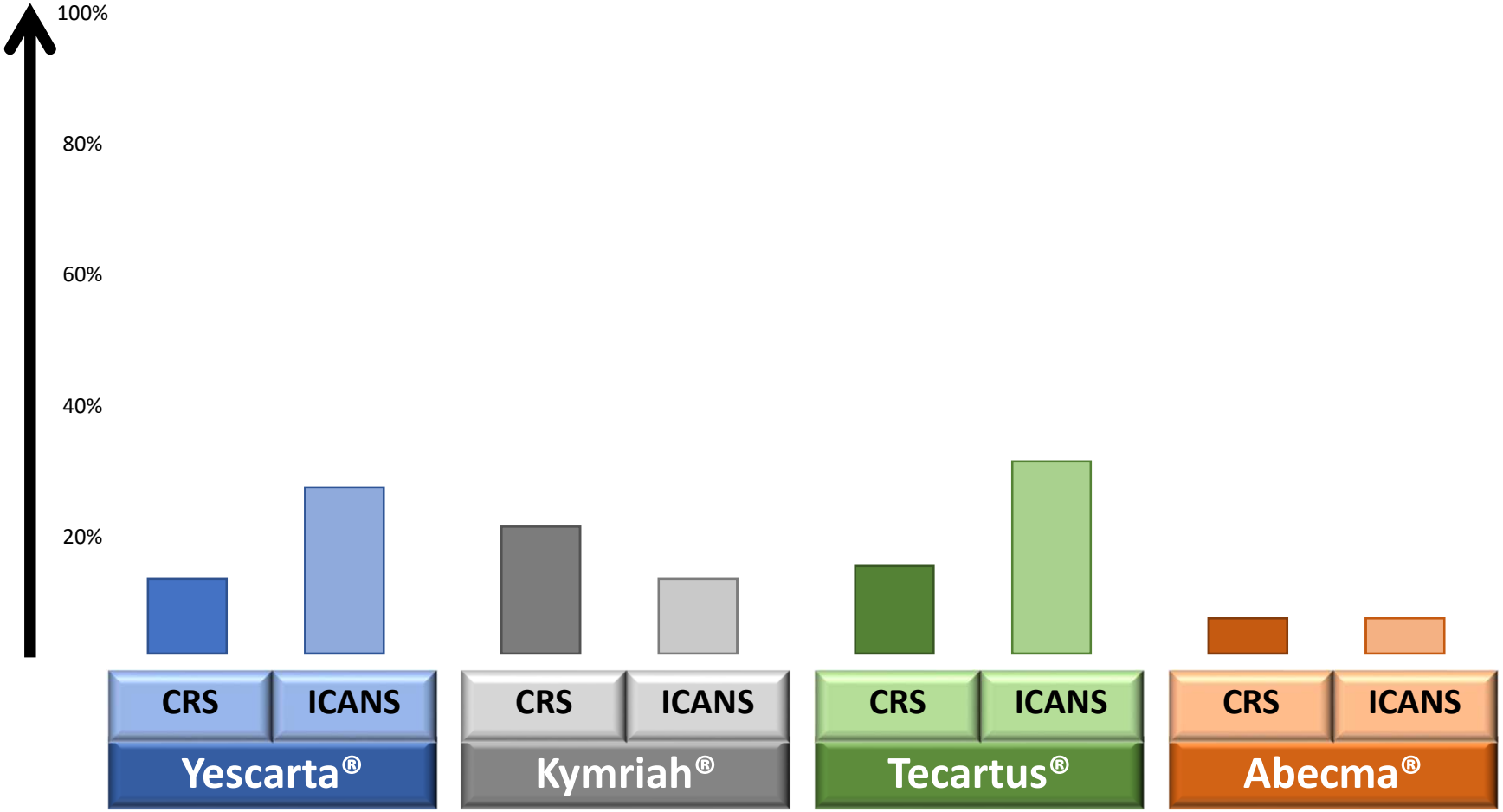


Molecular Therapy — Oncolytics (2016) **3**, 16011; doi:10.1038/mto.2016.11



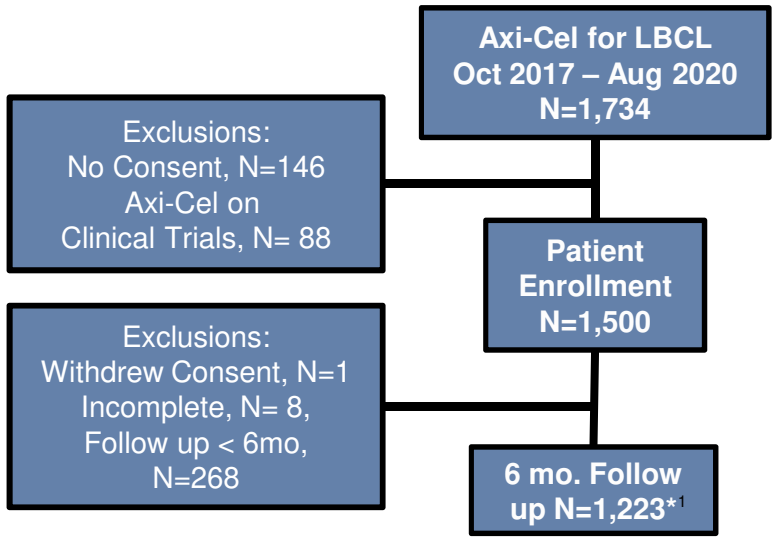
DOI https://doi.org/10.1200/EDBK_238691

Toxizität ≥ Grad3 in Zulassungsstudie



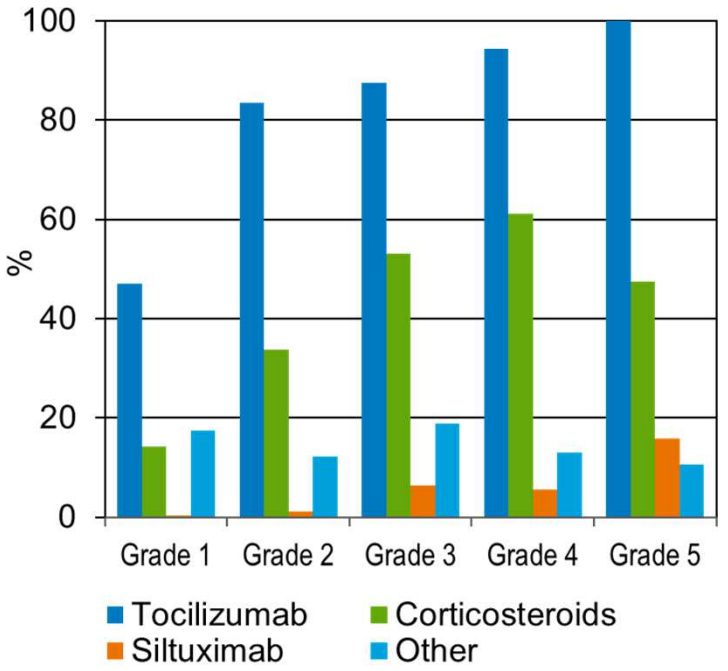
47th EBMT-Meeting (Caron Jacobson)
Schuster et al., Sep. 2021, Lancet Oncology
Munshi et al., Feb. 2021, NEJM
Wang et al., April 2020, NEJM

Real-World Evidence of Axicabtagene Ciloleucel (Axi-Cel) for the Treatment of Large B-Cell Lymphoma (LBCL) in the United States (US)



[2]

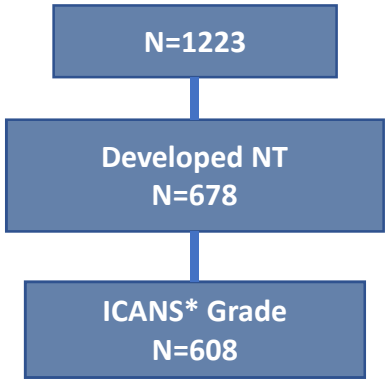
Characteristic	Total
Any CRS / Grade ≥3	82% / 9%
Time to CRS, median (range) in days	**4 (1-28)**
CRS resolved by day 14 post axi-cel	89%
Duration of CRS, median in days	7

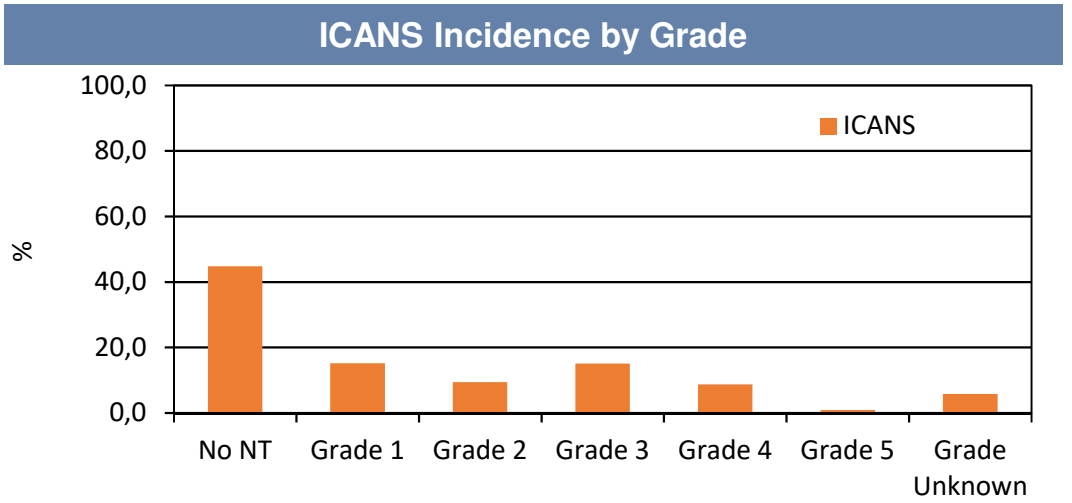


Jacobson CA, et al. ASCO 2021, Abstract #7552 (Poster)

Real-World Evidence of Axicabtagene Ciloleucel (Axi-Cel) for the Treatment of Large B-Cell Lymphoma (LBCL) in the United States (US)

‡





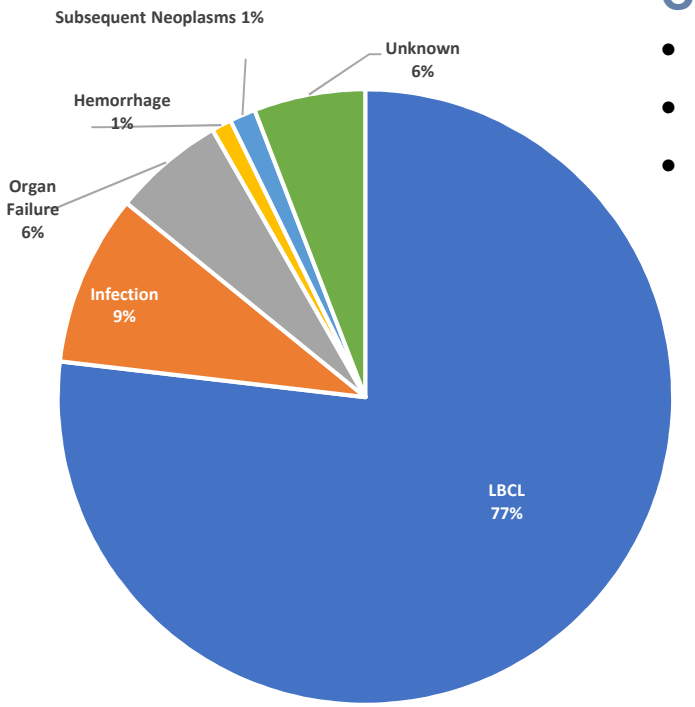
Characteristics	ICANS
Any ICANS / Grade ≥ 3 / Unknown Grade[1]	55% / 24% / 6%
Time from CT to onset, median (range) in days	**7 (1-82)**
Neurologic toxicity resolution at 21d post axi-cel	77%
Duration of Neurologic Toxicity, days – median	9
Corticosteroids / Tocilizumab / Siltuximab	73% / 17% / 3%

Jacobson CA, et al. ASCO 2021, Abstract #7552 (Poster)

Real-World Evidence of Axicabtagene Ciloleucel (Axi-Cel) for the Treatment of Large B-Cell Lymphoma (LBCL) in the United States (US)

‡

All Causes of Death (N=478)



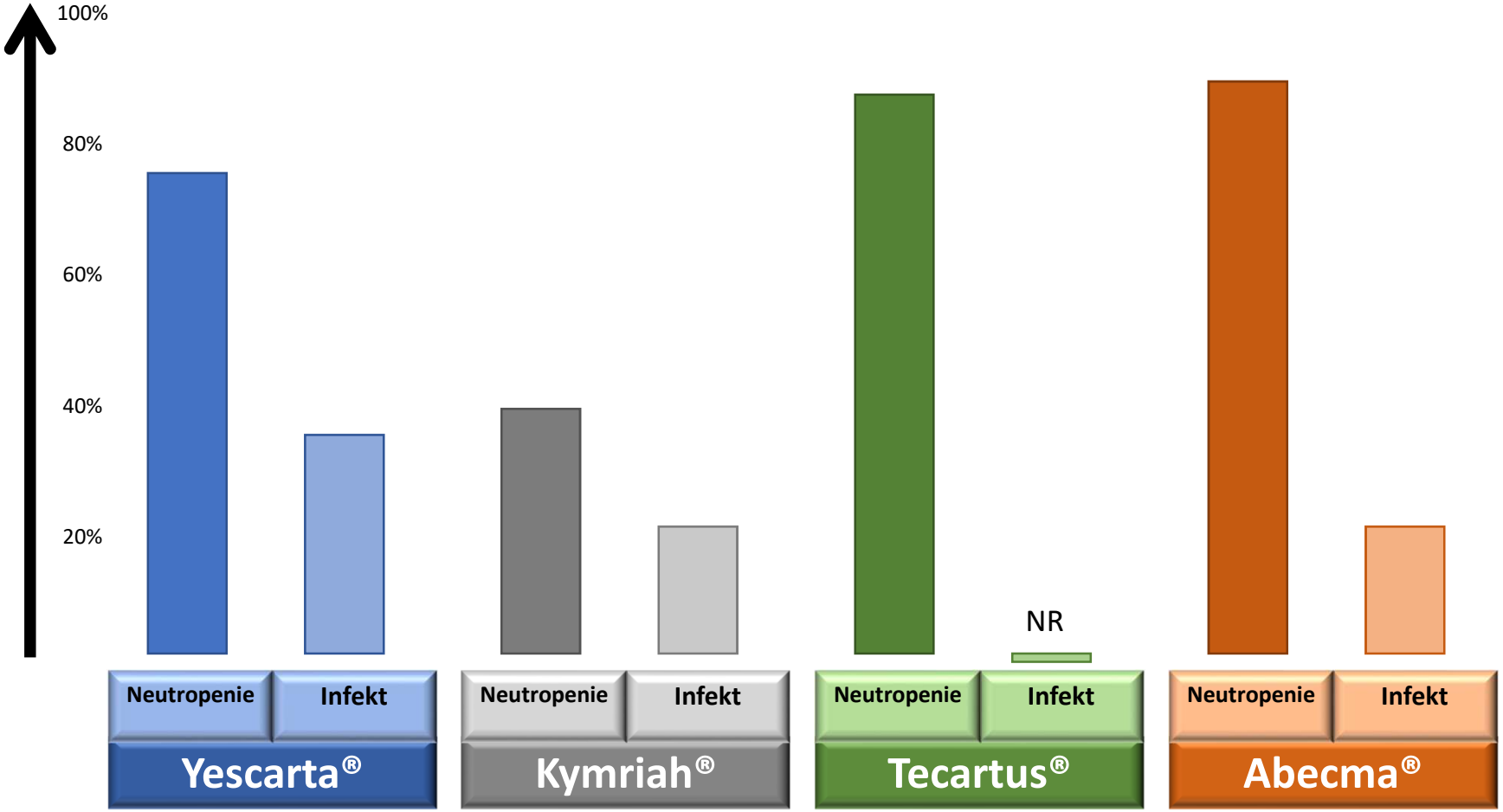
CAR T-Cell Specific Deaths:

- Neurologic Toxicity: N=4
- CRS: N=8
- Hemorrhage:
  - CNS: N=3
  - GI: N=2

Subsequent Neoplasms	Total
Myelodysplasia	18
Acute myeloid leukemia	2
GI malignancy	1
Lung cancer	1
Carcinoid tumor - lung	1
Melanoma	2
Non-melanoma skin carcinoma	8
Genitourinary malignancy	2
Other	3
Total (patients)	37

Jacobson CA, et al. ASCO 2021, Abstract #7552 (Poster)

Toxizität ≥ Grad3 in Zulassungsstudie



47th EBMT-Meeting (Caron Jacobson)
Schuster et al., Sep. 2021, Lancet Oncology
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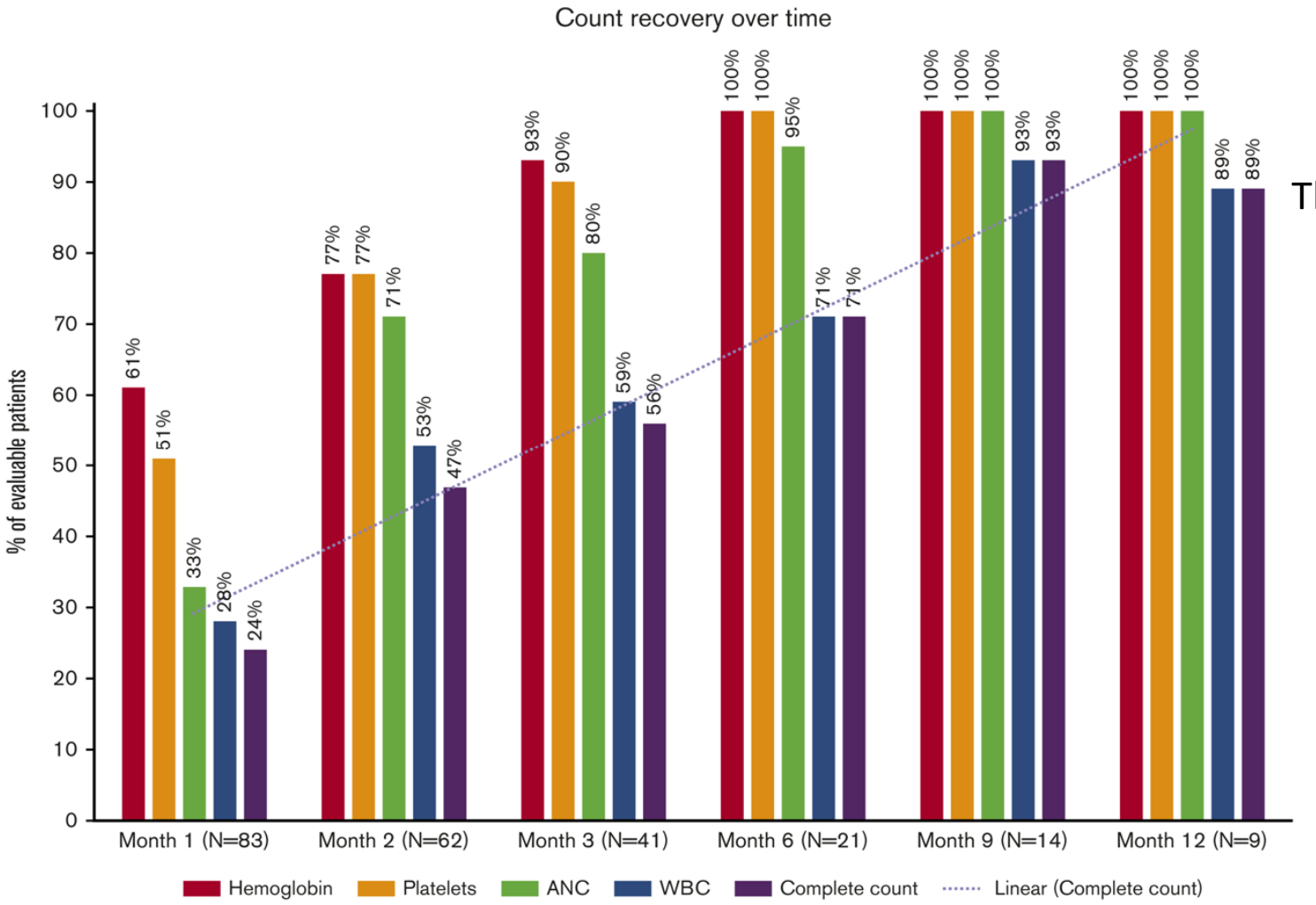
Wang et al., April 2020, NEJM

Hämatopoetische Regeneration nach CAR-T Therapie



Hb > 8 g/dl

Thrombozyten > 50000/µl

Neutrophile > 1000/µl

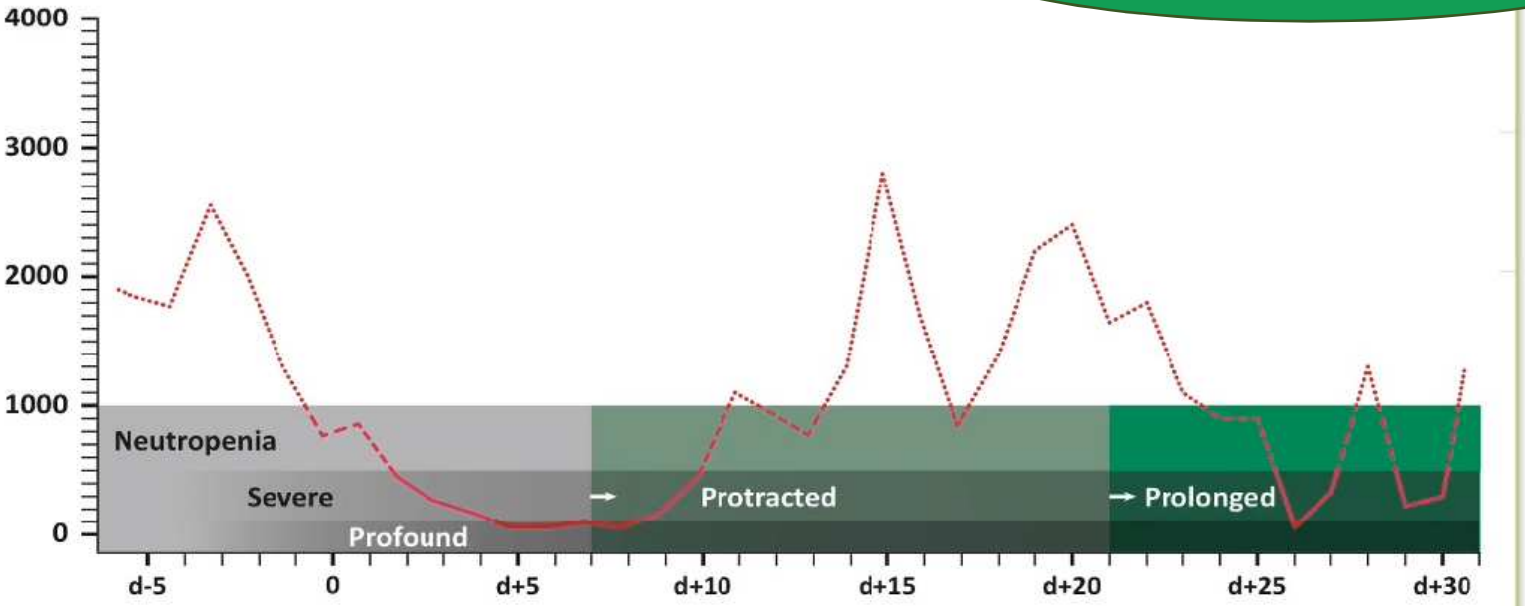
Leukozyten > 3000/µl

Jain et al. (Aug 2020), Blood

Hämatopoetische Regeneration nach CAR-T Therapie

frühe Zytopenien

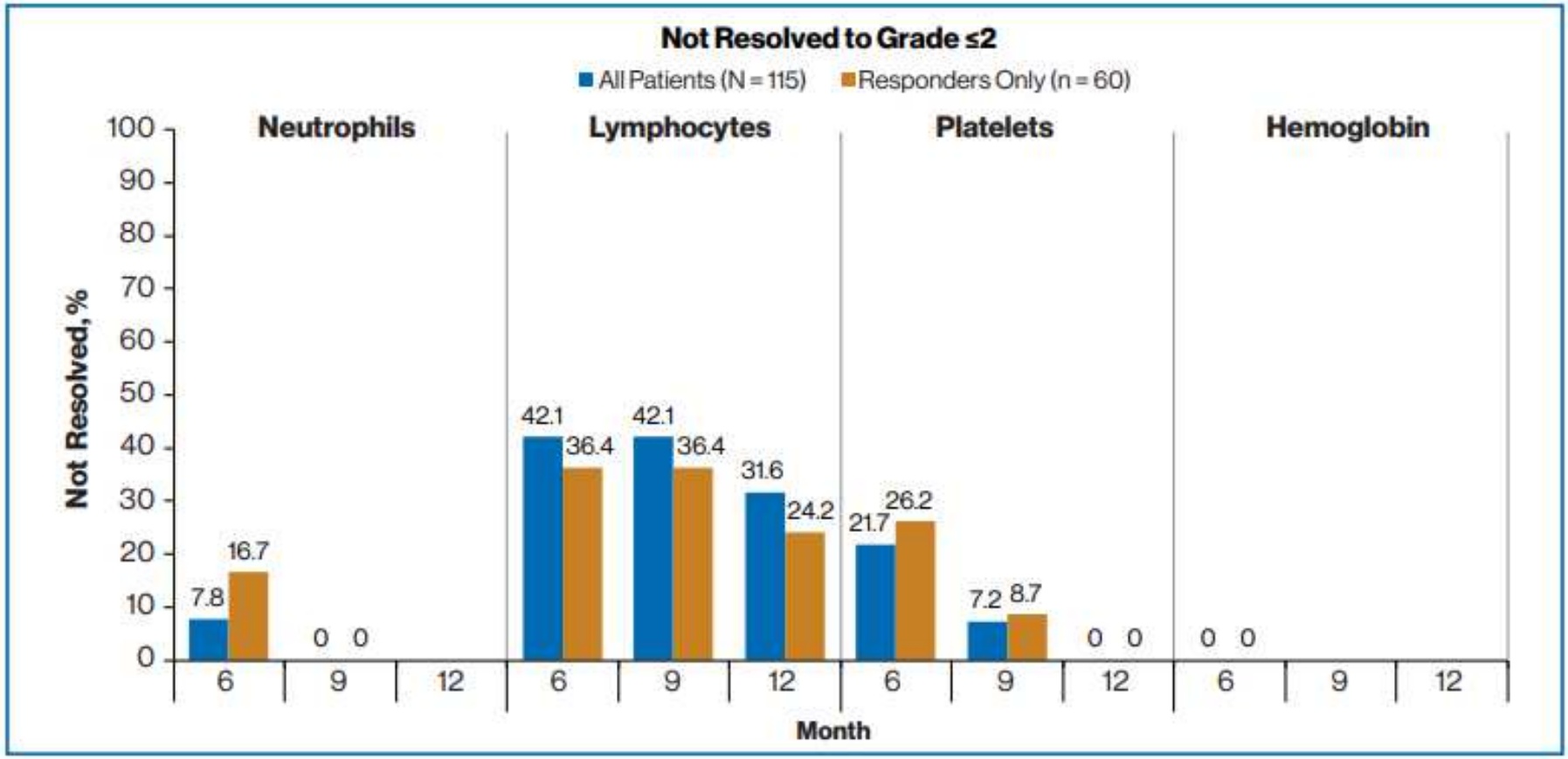
späte Zytopenien



Neutropenia	ANC < 1000/µl
Severe	ANC < 500/µl
Profound	ANC < 100/µl
Protracted	Neutropenia ≥ 7 days
Prolonged	ANC < 1000/µl measured ≥ 21 days after CAR infusion

Abb.: Rejenski K. et al;
Identification of Predictive Markers of Severe and Prolonged Neutropenia after CD19-specific CAR T-cell Treatment in Patients with r/r B-cell Malignancies; ASH 2020;

keine Assoziation von Ansprechen und hämatopoetischer Regeneration nach CAR-T Therapie



1. Westin J. R.. et al. Correlative Analyses of Patient and Clinical Characteristics Associated With Efficacy in Tisagenlecleucel-Treated Relapsed/Refractory Diffuse Large B-Cell Lymphoma Patients in the JULIET Trial; ASH 2020

Prolongierte Zytopenien nach CAR-T Therapie
prä-therapeutische Risikofaktoren

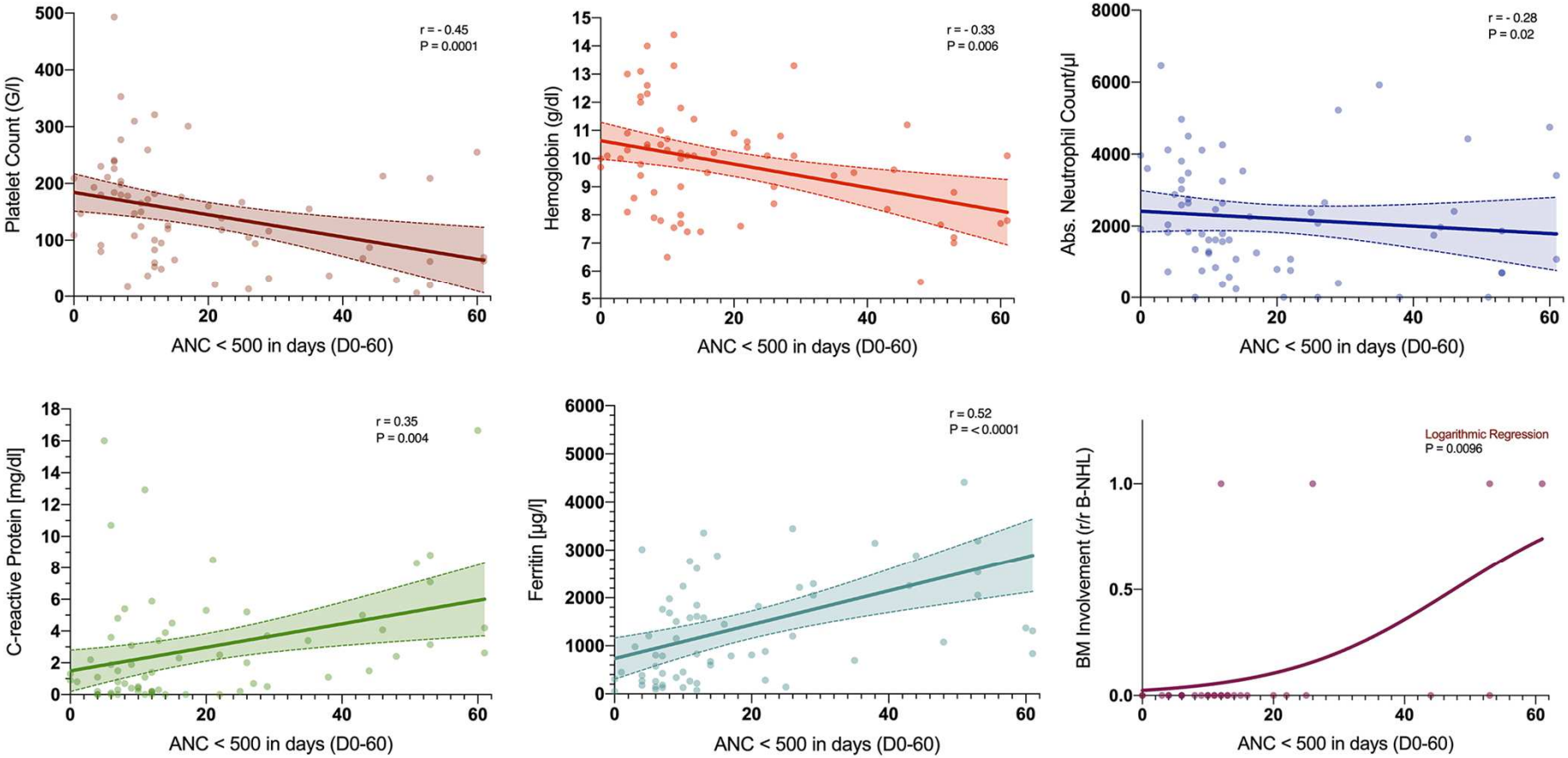


Figure 1 Pre-lymphodepletion predictive markers of clinically significant neutropenia (ANC < 500/µl during days 0 – 60). The Spearmann coefficient and P values of the univariate analysis are depicted in the graph inset.

Rejeski et al. (June 2021), Blood

Prolongierte Zytopenien nach CAR-T Therapie
- Risikofaktoren -

CAR-HAEMATOTOX

→ CAR-T Hämatotoxizität bei r/r B-NHL

→ Dauer einer schweren (Grad 3+) Neutropenie (<14d vs >14d)

Baseline features	0 point	1 point	2 points
Platelet count, per µL	>175,000	75,000–175,000	<75,000
ANC, per µL	>1,200	<1,200	—
Hemoglobin, g/dL	>9.0	<9.0	—
CRP, mg/dL	<3.0	>3.0	—
Ferritin, ng/mL	<650	650–2,000	>2,000

ANC, absolute neutrophil count; CRP, C-reactive protein.

**Adapted from Rejeski, et al.*[1]

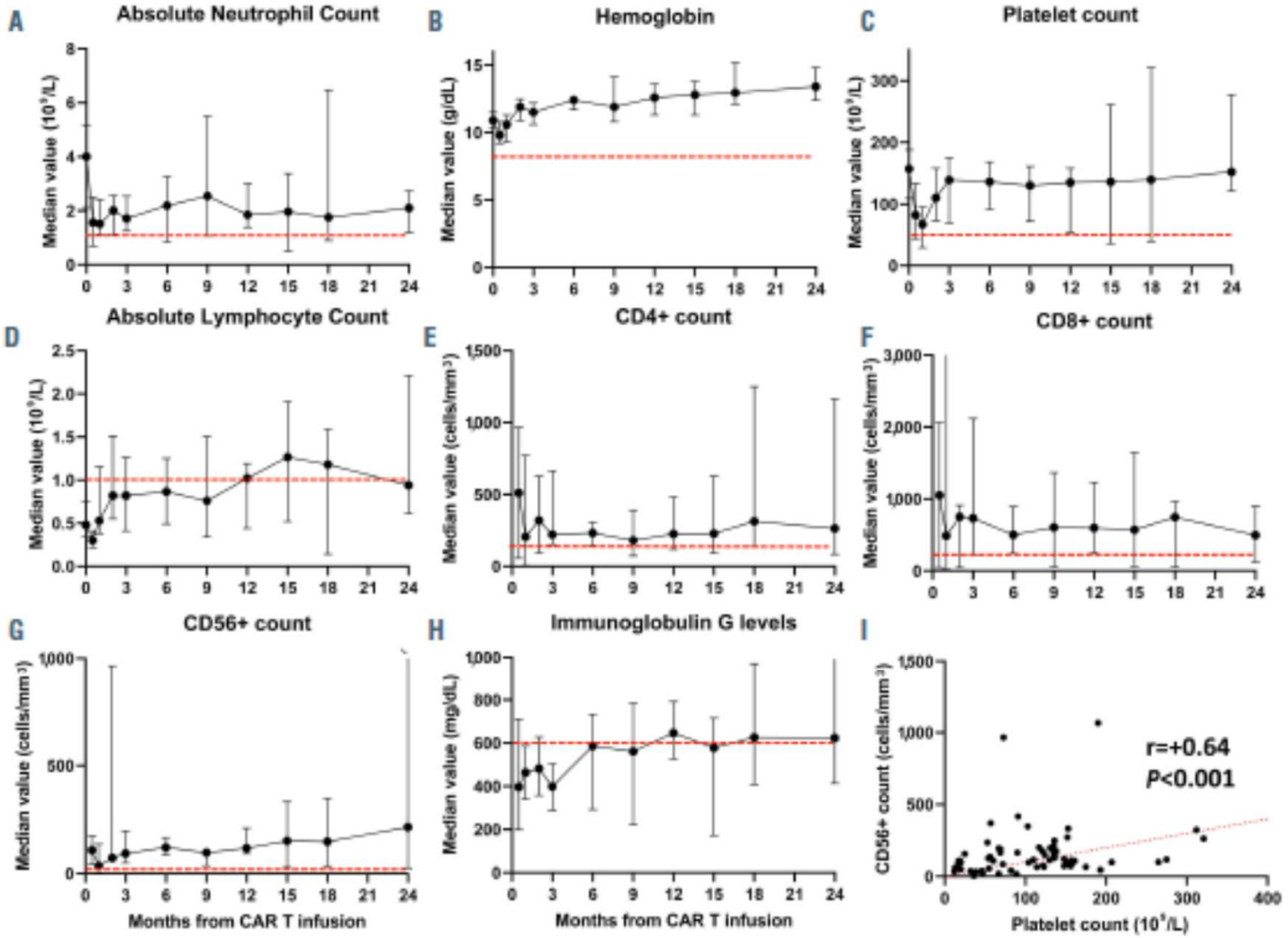
0-1 Punkt → „low risk“
≥ 2 Punkte → „high risk“ (>80% Grad 3 Neutropenie nach d21)

- https://www.lmu-klinikum.de/aktuelles/newsmeldungen/lmu-klinikum-entwickelt-mytcell-app/887ab5d4bd422e37

Rejeski et al. (June 2021), Blood

Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma

31 patients with relapsed or refractory large B-cell lymphoma treated with axicabtagene ciloleucel at our institution on two clinical trials, ZUMA-1 (clinicaltrials gov. Identifier: NCT02348216) and ZUMA-9 (clinicaltrials gov. Identifier: NCT03153462)



Haematologica 2021
Volume 106(10):2667-2672

Hematopoietic recovery and immune reconstitution after axicabtagene ciloleucel in patients with large B-cell lymphoma

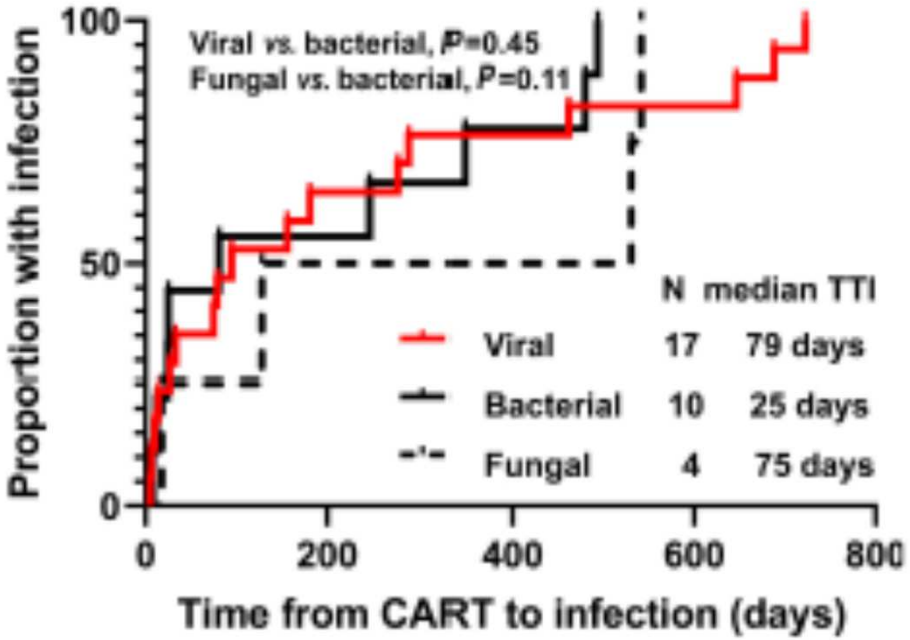


Table 2. Infection types (all grades included)

Total (N= 71)	Number (%)
No isolated organism (17 respiratory, 13 ENT, 3 skin, 4 GU, 2 GI, 1 sepsis)	40 (56)
Viral, total	17 (24)
Herpetic (5 VZV, 3 HSV, 2 CMV, 1 HHV6)	11 (15)
Respiratory	3 (4)
Enteric	1 (1)
Parvovirus	1 (1)
Hepatitis B	1 (1)
Bacterial, total	10 (14)
Gram negative (2 UTI, 2 GI, 1 bacteremia)	5 (7)
Gram positive (3 GI, 2 skin)	5 (7)
Fungal, total	4 (6)
Yeast (skin)	3 (4)
Pneumocystis (pneumonia)	1 (1)

ENT: ear nose throat; VZV: varicella zoster virus; CMV: cytomegalovirus; HSV: herpes simplex virus; HHV6: human herpes virus 6; UTI: urinary tract infection; GI: gastro-intestinal.

All 31 patients received granulocyte colony stimulating factor (**GCSF**) support for neutropenia; 13 (42%) received **prophylactic IVIG** and four (13%) therapeutic IVIG; two (6%) patients received antibacterial prophylaxis, 13 (42%) ***Pneumocystis jiroveci*** pneumonia (PJP) prophylaxis, and 22 (71%) **antiviral prophylaxis**, while no patient received antifungal prophylaxis. Overall, among patients with ongoing response, 24 (77%) developed infectious complications with grade 3 in 13 (42%).

Haematologica 2021
Volume 106(10):2667-2672

Infectious complications of CAR T-cell therapy: a clinical update

Reference	CAR T-cell therapy	*N*	Underlying malignancy	Severity grade	Timepoint	Bacterial infection incidence (*n*, %)	Viral infection incidence (*n*, %)	Fungal infection incidence (*n*, %)
Abramson *et al.*[34]	Lisocabtagene maraleucel	269	R/R B-cell lymphoma	⩾3	12 months	27/269 (10)	4/269 (1)	2/269 (1)
Locke *et al.*[38]	Axicabtagene ciloleucel	108	Refractory B-cell lymphoma	All	12 months	44/108 (40)	11/108 (10)	7/108 (6)
Logue *et al.*[35]	Axicabtagene ciloleucel	85	R/R B-cell lymphoma	All	⩽30 days	26/85 (31)	12/85 (14)	2/85 (2)
					>30 days	13/85 (15)	19/85 (22)	0/85 (0)
Wittmann Dayagi *et al.*[36]	CD28-based CAR T cells	88	R/R B-cell lymphoma	All	⩽30 days	22/85 (25)	14/85 (16)	0/85 (0)
					30–60 days	8/85 (9)	2/85 (2)	1/85 (1)
Baird *et al.*[37]	Axicabtagene ciloleucel	41	R/R B-cell lymphoma	All	⩽28 days	7/41 (17.1)	8/41 (19.5)	4/41 (9.8)
					>28 days	10/41 (24.4)	10/41 (24.4)	9/41 (22)
Wudhikarn *et al.*[22]	Axicabtagene ciloleucel OR tisagenlecleucel	60	R/R DLBCL	All	⩽30 days	20/60 (33)	10/60 (17)	1/60 (2)
					>30 days	14/60 (24)	17/60 (28)	3/60 (5)
Hill *et al.*[21]	Anti-CD19 CAR autologous T cells	133	ALL, CLL, NHL	All	⩽28 days	22/133 (16.5)	11/133 (8.3)	4/133 (3)
					>28 days	7/119 (5.9)	11/119 (9.2)	2/119 (1.7)
Munshi *et al.*[41]	Idecabtagene vicleucel	54	R/R multiple myeloma	All	12 months	13/54 (24)	15/54 (28)	4/54 (7)

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Behandlungsstrategien

Ziele:

- Vermeidung von schweren sekundären Ereignissen (Blutungen, Infekte)
- Verbesserung der Lebensqualität (Anämie-Symptome, Transfusionen)

Therapieoptionen:

- Transfusionen
- ggf. Einsatz von G-CSF (Hinweise für schwereren Verlauf eines CRS bei frühem Einsatz; EBMT-Empfehlung ab d+14)
- Bislang keine Daten zum Einsatz von EPO oder Thrombopoetin-Agonisten

Cave: langanhaltende zelluläre und humorale Immundefizienz durch Neutropenie, Hypogammaglobulinämie, reduzierte Anzahl CD3+/CD4+ Zellen

→**an anti-infektive Prophylaxen denken.** EBMT-Empfehlung:
Anti-viral und anti-Pneumocystis: 1 Jahr oder bis CD4+Zellen>200/µl
Anti-fungal: prolongierte Neutropenie, vorherige allo. SZT, vorheriger Pilzbefall
Anti-bakteriell: prolongierte schwere Neutropenie

Logue et al. (Apr 2021), Haematologica
Schubert et al. (Oct 2020), Annals of Oncology
Yakoub-Agha et al. (Feb 2020), Haematologica
Mahmoudjafari et al (Jan 2019), Biology of Blood and Marrow Transplantation

Impfungen nach allogener SZT und nach CAR-T

Vakzin (Art)	Generelle Empfehlung (Stärke, Evidenzlevel)	Impfbeginn	Impf-dosen
Pneumokokken (konjugiert)	ja (BI)	ab 3- 6 Monate	3 + 1
Tetanus	ja (BII)	ab 6 Monate	3 + 1
Diphterie	ja (BII)	ab 6 Monate	3 + 1
Pertussis	ja (CIII)	ab 6 Monate	3 + 1
Haemophilus (konjugiert)	ja (BII)	ab 6 Monate	3 + 1
Meningokokken (konjugiert)	ja (BII)	ab 6 Monate	1
Polio (inaktiviert)	ja (BII)	ab 6 Monate	3 + 1
Hepatitis B (rekombinant)	ja (BII)	ab 6 Monate	3 + 1
Influenza (inaktiviert)	ja (AII)	4-6 Monate 1x jährlich	1 - 2
Masern*	ja (BII)	frühestens ab 24 Mon.	1 - 2
Mumps*	ja (CIII)	frühestens ab 24 Mon.	1 - 2
Röteln*	ja (BIII)	frühestens ab 24 Mon.	1 - 2

anti-SARS-COV2

Shingrix

https://www.dag-kbt.de/

COVID-19 vaccines. Version 7, October 3, 2021

3) Response rates are lower than in healthy individuals especially if patients are vaccinated soon after HCT. Therefore, it makes sense to adapt the timing when vaccination should be initiated to the SARS-CoV-2 infection rate in the surrounding community.

   a. If the transmission rate in the surrounding community is high, vaccination could be initiated at the earliest three months after HCT. Whether an earlier start would give any protective effect is currently unknown.

   b. if transmission in the surrounding community is well controlled, it would be logical to wait until six months after transplantation to initiate vaccination

https://www.ebmt.org/ebmt

Zusammenfassung - allgemein

anti-CD19-CAR-T Zelltherapie ist sicher durchführbar und effektiv,

aktuell in der Drittlinie bei DLBCL und MCL

Indikationen zur CAR-T Therapie sind zunehmend,

durch Einsatz in früheren Therapielinien, weitere Entitäten (Myelom, …)

Zusammenfassung - Nachsorge

Überwachung akuter Nebenwirkungen (**CRS, ICANS**) stationär (bis mindestens Tag 10)

Bei Auftreten von Fieber oder unklarer neurolog. Symptomatik frühe Rücksprache mit CAR-T-TEAM, ggf. Einweisung

verzögerte **hämatopoetische Regeneration** (12 Monate), Zytopenien sehr häufig:

- ggf. Transfusionen, G-CSF, ggf. SZ-Boost
- frühe antibiotische / antimykotische Therapie

verzögerte **immunologische Regeneration**, Immunmonitoring:

- antivirale Prophylaxen (Aciclovir) bei CD4 < 200 /µl
- Pneumocystis-Prophylaxe (Cotrimoxazol) bei CD4 < 200 /µl
- Grundimmunisierung (Impfprogramm); bei AK-Mangel: Ig-Substitution

Lymphomkontrolle nach Standard

- UMG: **PET/CT** zum Therapieabschluß**,** dann CT nach Klinik

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https://haematologie-onkologie.umg.eu/
https://www.ebmt.org/
https://www.dag-kbt.de/