Neurologische Komplikationen nach CAR T-Zelltherapie

Update Neurologie 06.12.2025

Prof. Dr. Dr. Oliver Grauer

Klinik für Neurologie
Universitätsklinikum Münster

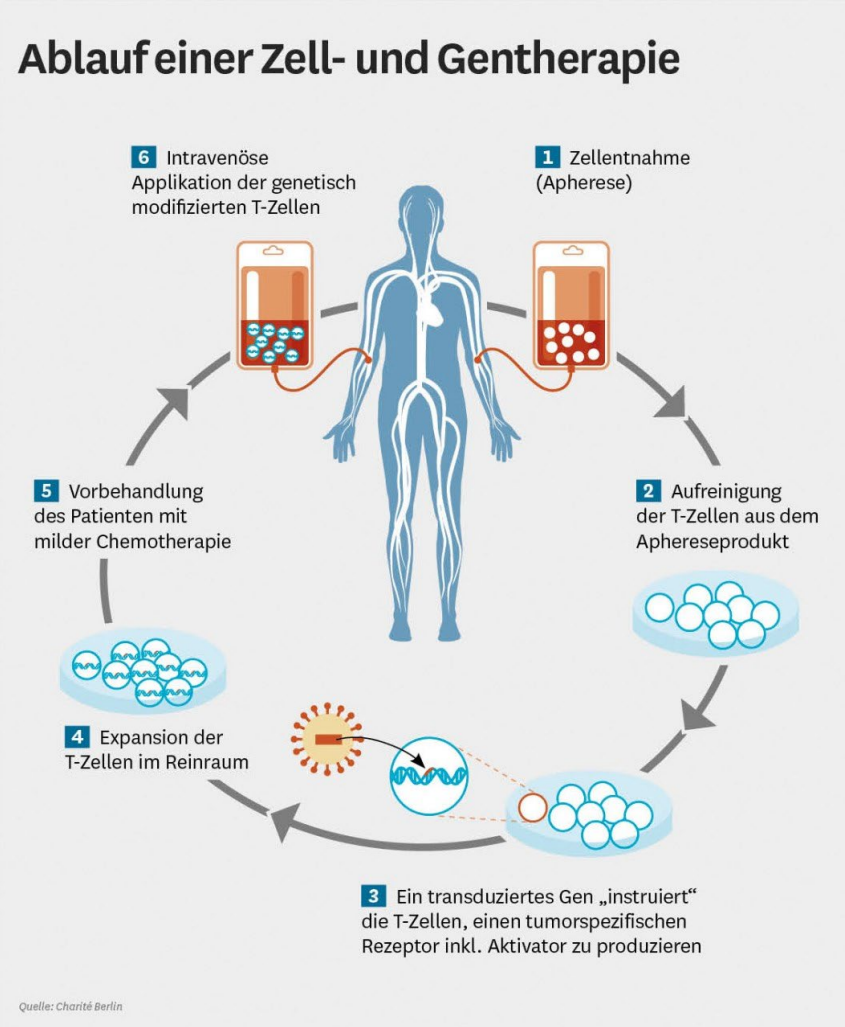
KFO 342

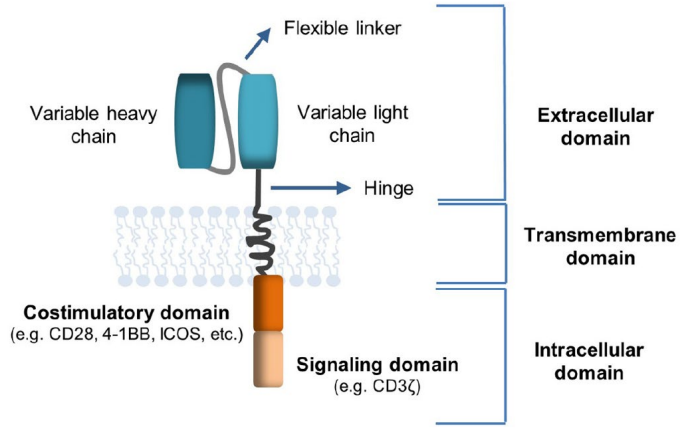
Darlegung potentieller Interessenkonflikte

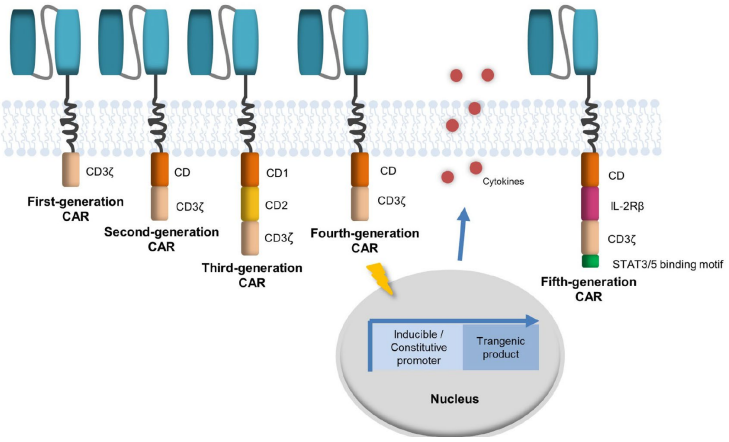
Der Inhalt des folgenden Vortrages ist Ergebnis des Bemühens um größtmögliche Objektivität und Unabhängigkeit.

Als Referent versichere ich, dass in Bezug auf den Inhalt des folgenden Vortrags keine Interessenskonflikte bestehen, die sich aus einem Beschäftigungsverhältnis, einer Beratertätigkeit oder Zuwendungen für Forschungsvorhaben, Vorträge oder andere Tätigkeiten ergeben.

CAR T-Zellen in der Onkologie



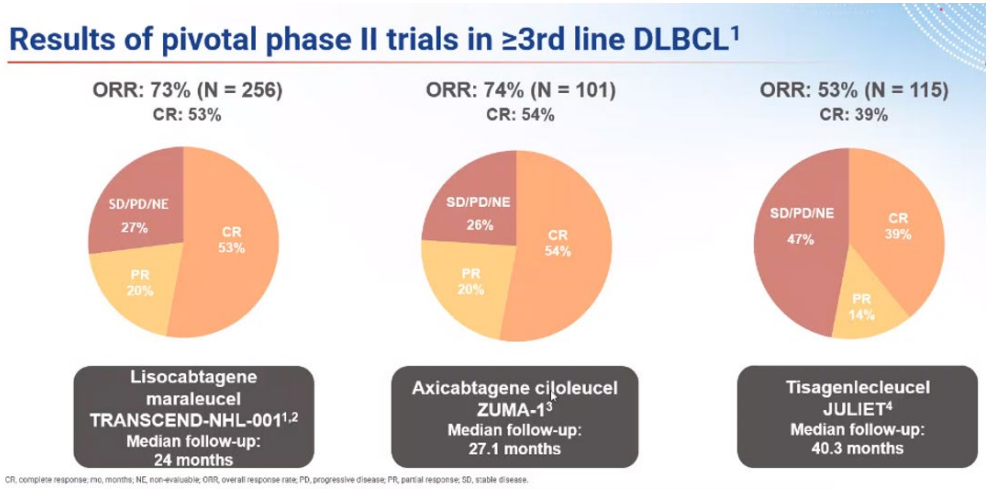




	Tisa-cel	Axi-cel	Liso-cel	Brexu-cel	Ide-cel	Cilta-cel
Indication	B-ALL, DLBCL, FL	LBCL, FL	LCBCL	B-ALL, MCL	MM	MM
Target	CD19	CD19	CD19	CD19	BCMA	BCMA
Co-stimulatory domain	4-1BB	CD28	4-1BB	CD28	4-1BB	4-1BB
Activation domain	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ

https:/www.onkopedia.com; Abreu et al. Journal of Controlled Release 2020

CAR T-Zelltherapie und assoziierte Neurotoxizität



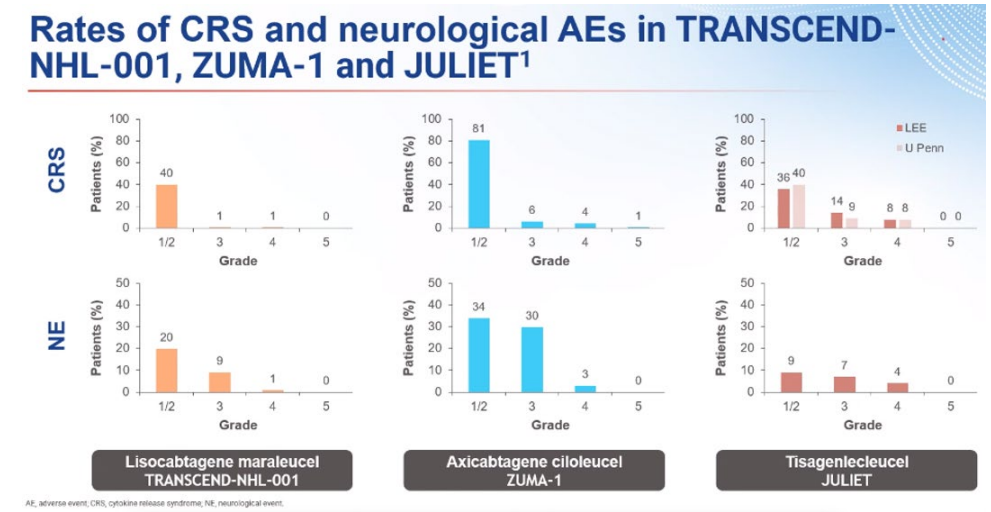
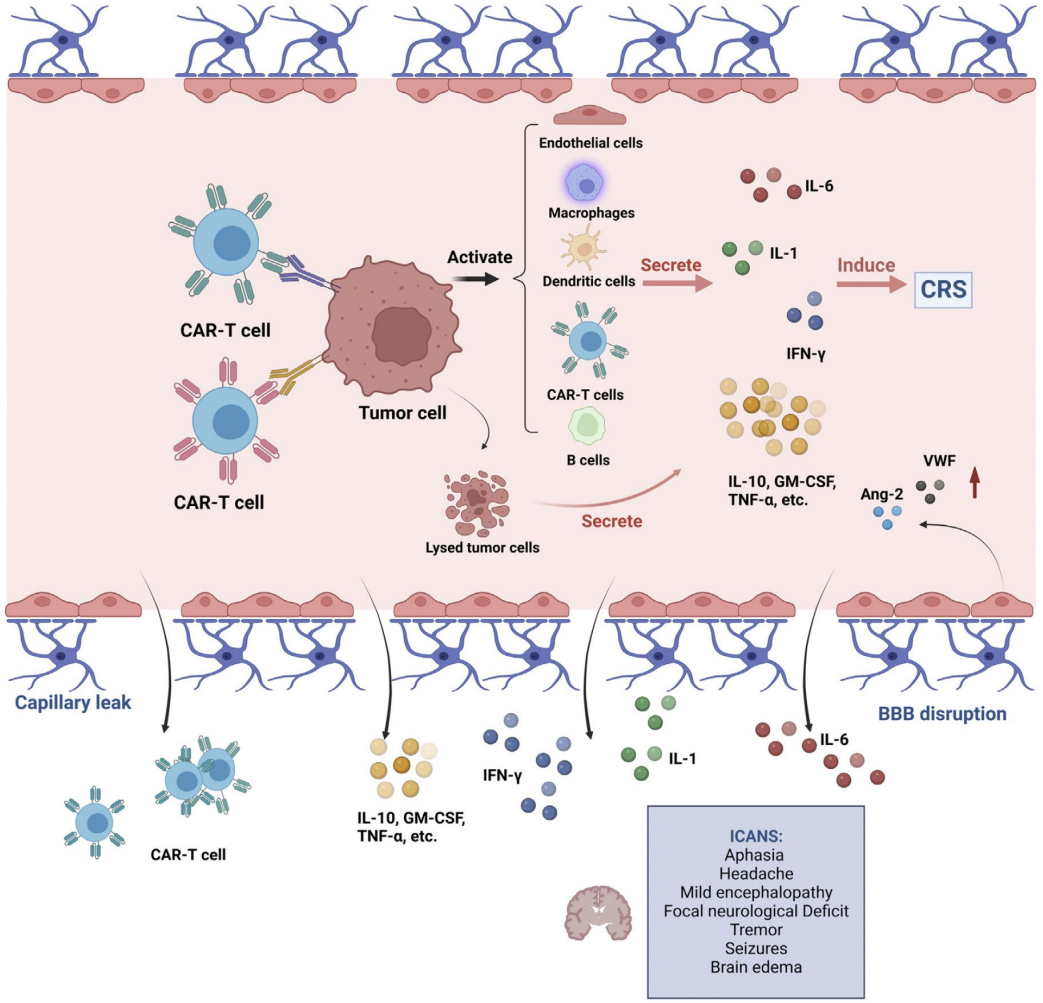


Table 1. Commercially available chimeric antigen receptor T-cell products and associated neurotoxicity

Product	Tisa-cel	Axi-cel	Liso-cel	Brexu-cel	Ide-cel	Cilta-cel
Indication	R/R B-ALL, R/R DLBCL, R/R FL	R/R LBCL, R/R FL	R/R LBCL	R/R B-ALL, R/R MCL	R/R MM	R/R MM
Target	CD19	CD19	CD19	CD19	BCMA	BCMA
Co-stimulatory domain	4-1BB	CD28	4-1BB	CD28	4-1BB	4-1BB
Activation domain	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ	CD3ζ
Pivotal trial	JULIET [5]	ZUMA-1 [6]	TRANSCEND [7]	ZUMA-2 [8]	KarMMA [9]	CARTITUDE-1 [10]
Neurotoxicity						
Any/grade ≥ 3 (%)	21/12	64/28	30/9	63/31	18/3	21/9
Median time to onset (range)	6 days (1–17)	5 days (1–17)	9 days (1–66)	7 days (1–32)	2 days (1–10)	8 days (6–8)
Median duration (range)	14 days (NR)	12 days (NR)	11 days (1–86)	12 days (NR)	3 days (1–26)	4 days (2–6.5)
Common neurotoxicities	Events aggregated	Encephalopathy Confusion Aphasia Somnolence	Encephalopathy Aphasia Tremor	Encephalopathy Confusion Aphasia	Events aggregated	Events captured as ICANS
Uncommon neurotoxicities		Tremor Memory impairment	Ataxia Dizziness Cerebellar	Cerebral edema Tremor Concentration impairment Dysesthesia		Parkinsonism Micrographia Tremor Cranial nerve palsy Peripheral nerve palsy Ataxia Diplopia Nystagmus Death

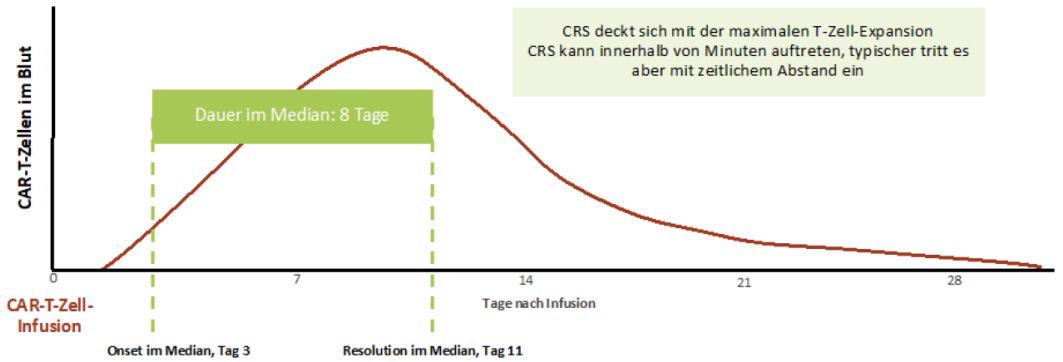
Bethge et al. Blood 2022; Shannon P. Forth Ensign. Curr Treat. Opinions in Oncol. 2022

Pathophysiologie des CRS (Cytokine-Release-Syndrom)



- **„Zytokinsturm“: ausgelöst v.a. durch IL-6, aber auch IL-1α, IL-2, IL-10, IL-12, IL-18, TNF-α, GM-CSF und IFN-γ**
- **Kann innerhalb von Minuten eintreten, meist jedoch ab Tag 2 bis Tag 11 nach Infusion**
- **In bis zu 90% nach CAR-T-Zell Infusion**
- **deckt sich mit maximaler T-Zell-Expansion**

Abbildung 2: Zeitlicher Verlauf des CRS. [14, 15]



Dorio et al. CCR 2022; Li et al. Frontiers in Pharmacology 2022

https:/www.onkopedia.com

CRS - Schweregrade

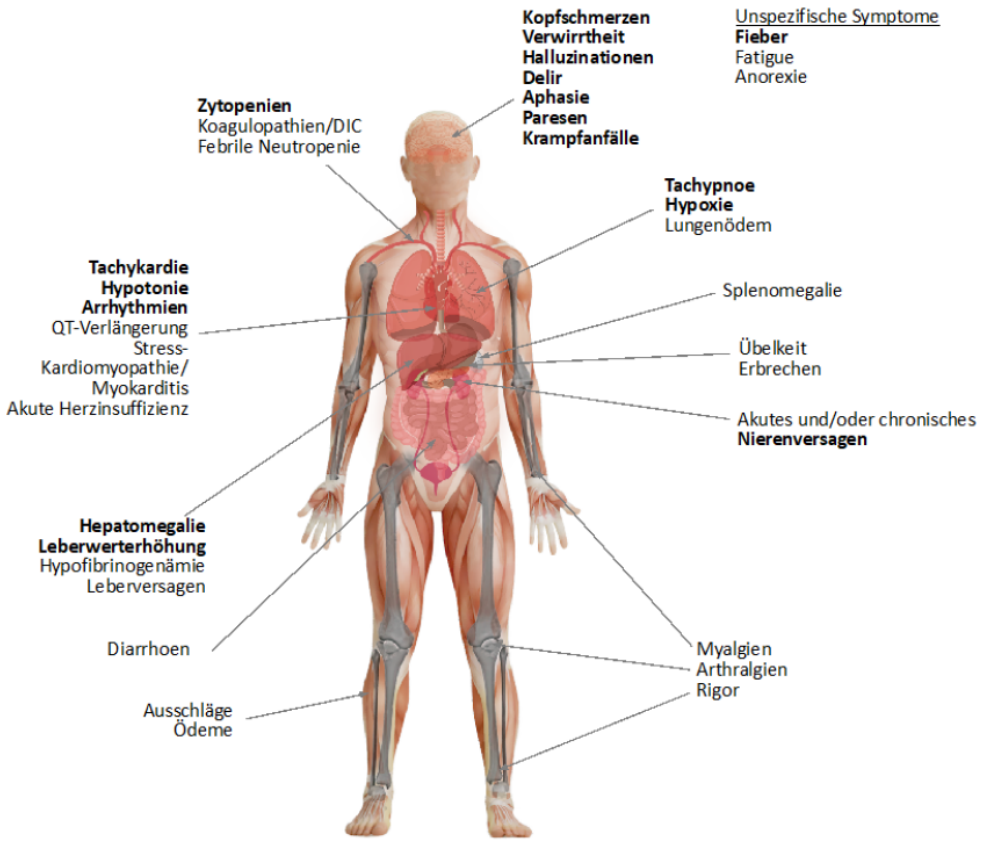
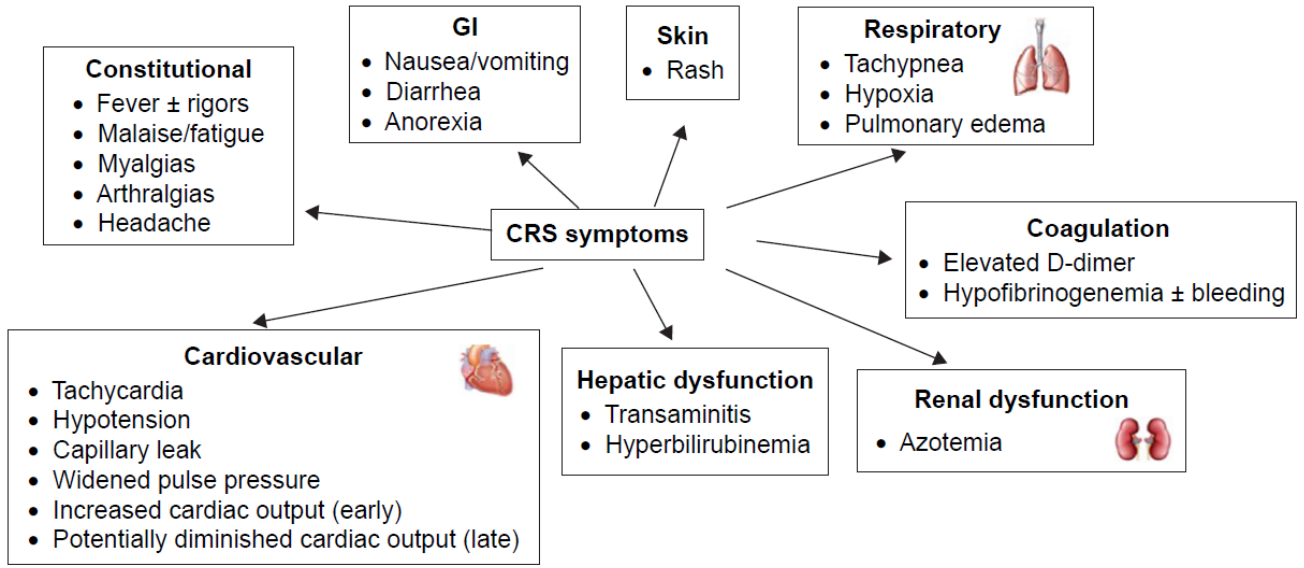


Tabelle 2: ASTCT CRS Consensus Grading*

Vitalzeichen	CRS Grad 1	CRS Grad 2	CRS Grad 3	CRS Grad 4
Körpertemperatur (°C)	>38°C**	>38°C**	>38°C**	>38°C**
Hypotonie	Keine	**Ohne** Vasopressor-Bedarf	Mit Bedarf an **einem** Vasopressor ± Vasopressin	Mit Bedarf an **mehreren** Vasopressoren (außer Vasopressin)
Hypoxie	Keine	Moderater O_2-Bedarf **(≤6 L/min** über NB)	Hoher O_2-Bedarf **(>6 L/min** über NB, RHM, **ohne PAP**)	Mit **PAP**-Bedarf/ Intubationsnotwendigkeit



https:/www.onkopedia.com; Riegler et al. Theurapeutics and Clinical Risk Management 2019

Therapie des CRS

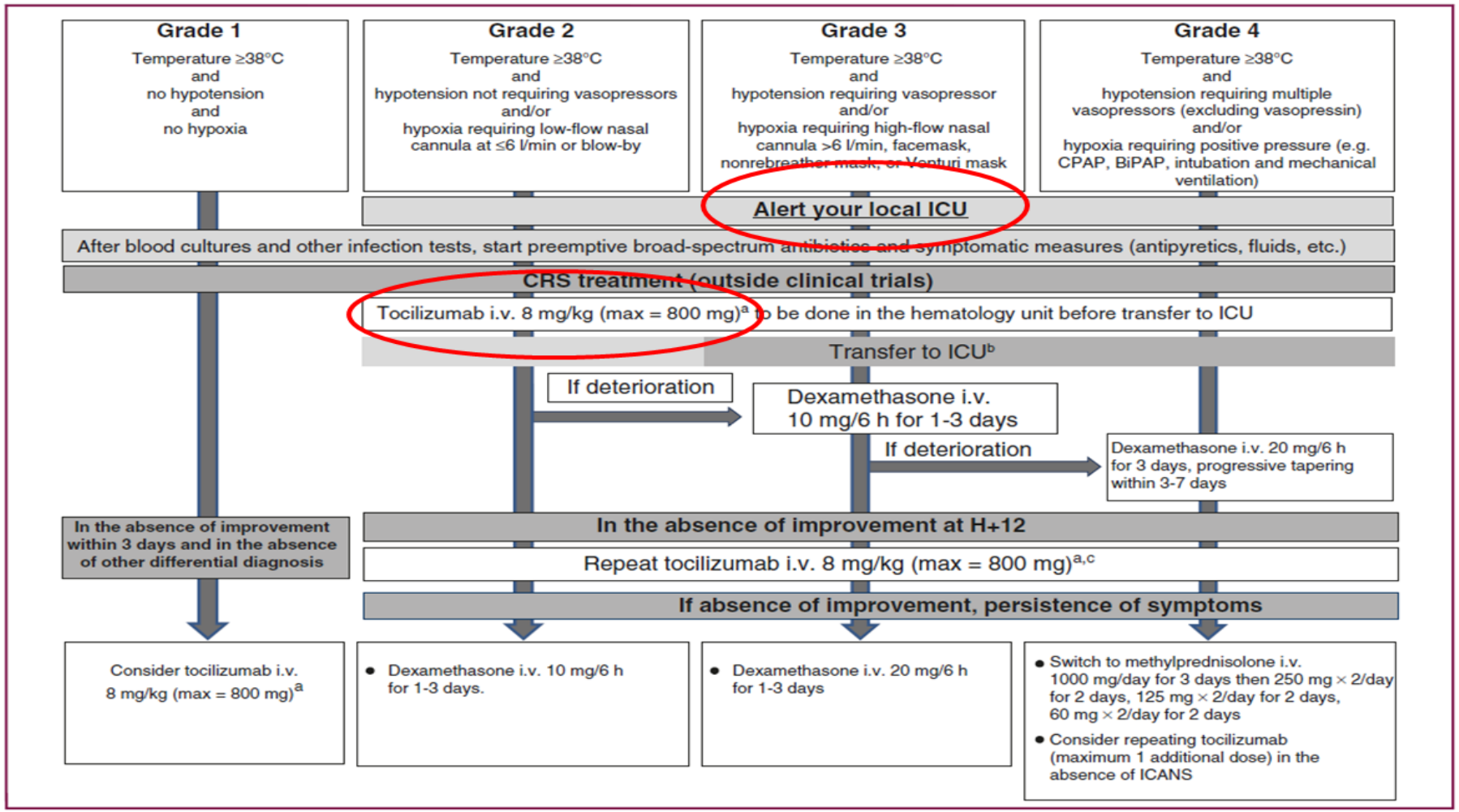


Figure 1. Algorithm outlining the grading and management of cytokine release syndrome (CRS).

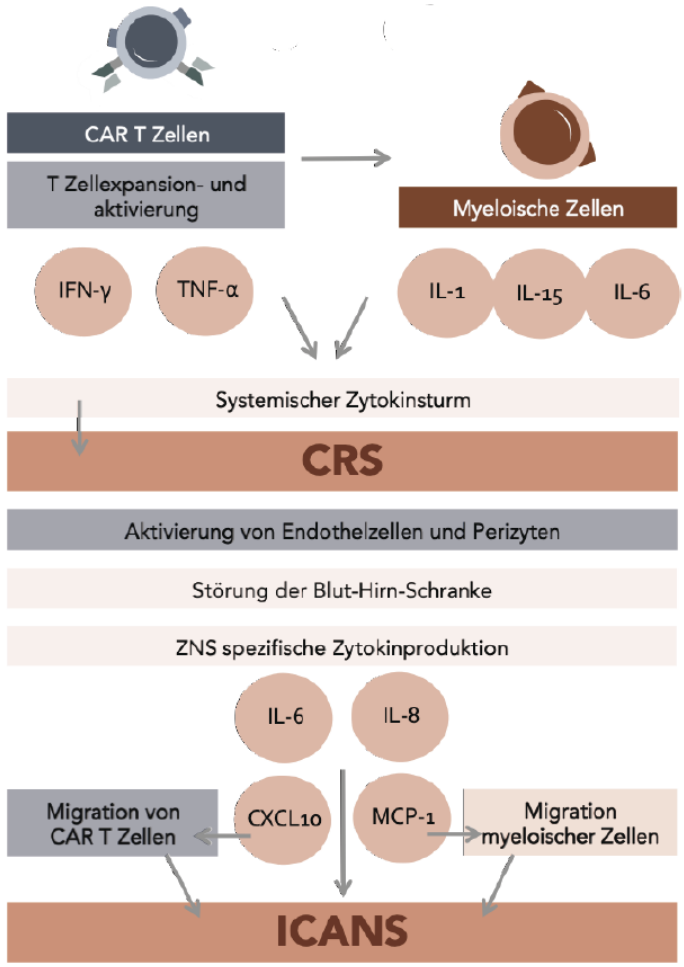
TABLE 3 Pharmacotherapy for the treatment of cytokine release syndrome.

CRS Grade	Pharmacotherapy Recommendations
Grade 1	• Broad-spectrum antibiotics if concomitant neutropenia • Anti-pyretics (acetaminophen) • Consider Tocilizumab for persistent or refractory cases
Grade 2	• Intravenous fluids for hypotension and/or supplemental oxygen • Tocilizumab 8 mg/kg IV may be given every eight hours for a maximum of four total doses • Consider adjunctive dexamethasone 10 mg IV every 12 hours for persistent or refractory cases
Grade 3 or Grade 4	• Vasopressors for hypotension and/or supplemental oxygen • Tocilizumab 8 mg/kg IV may be given every eight hours for a maximum of four total doses • Adjunctive dexamethasone 10 mg IV every 6 hours (or equivalent), which can be escalated up to a dose of methylprednisolone 1,000 mg IV every 12 hours for refractory cases • Consider alternative anti-cytokine or immunosuppressive therapies for refractory cases after tocilizumab
Alternative Therapies for Refractory CRS	
Anakinra – IL-1 receptor antagonist, case reports and retrospective studies demonstrating efficacy (63, 64)	
Siltuximab – IL-6 inhibitor, demonstrated efficacy (5, 65, 66)	
Etanercept – TNF-α receptor inhibitor, demonstrated efficacy in case reports (26, 67)	
Emapalumab – IFN-γ inhibitor, demonstrated efficacy in case report (69)	
Dasatinib – tyrosine kinase inhibitor, demonstrated efficacy in case report (72)	
JAK-STAT inhibitors • Itacitinib has been shown to reduce levels of CRS-related cytokines in pre-clinical studies (73), and has been shown to reduce grade ≥ 2 CRS when used as prophylaxis prior to axi-cel (79) • Ruxolitinib has demonstrated efficacy in several case reports (74–77)	

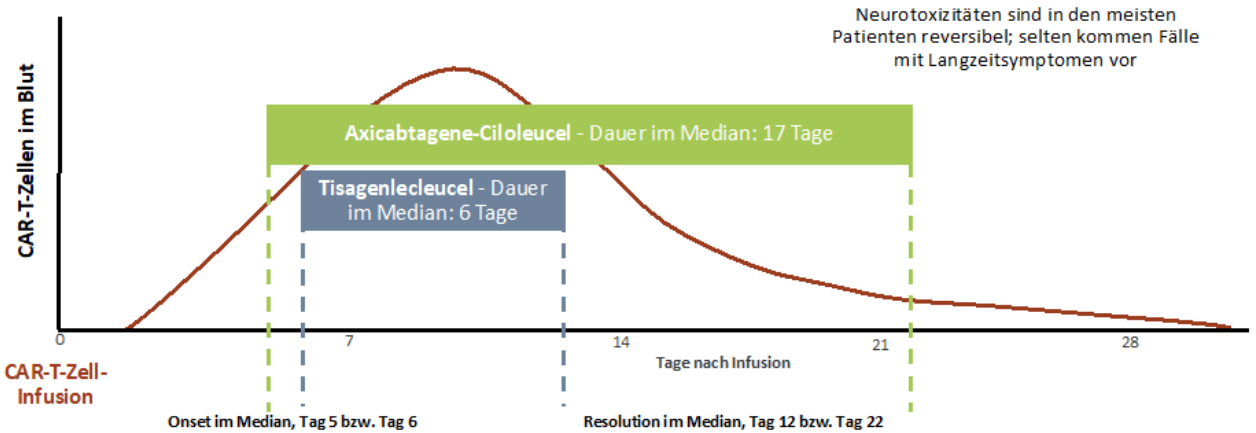
Hayden et al. ESMO Guidelines, Annals of Oncology 2021; Ferreri and Bhutani Frontiers in Oncology 2024

Pathophysiologie des ICANS (Immune-Effector-Cell-associated-Neurotoxicity-Syndrom)

Abbildung 6: Pathophysiologie.*

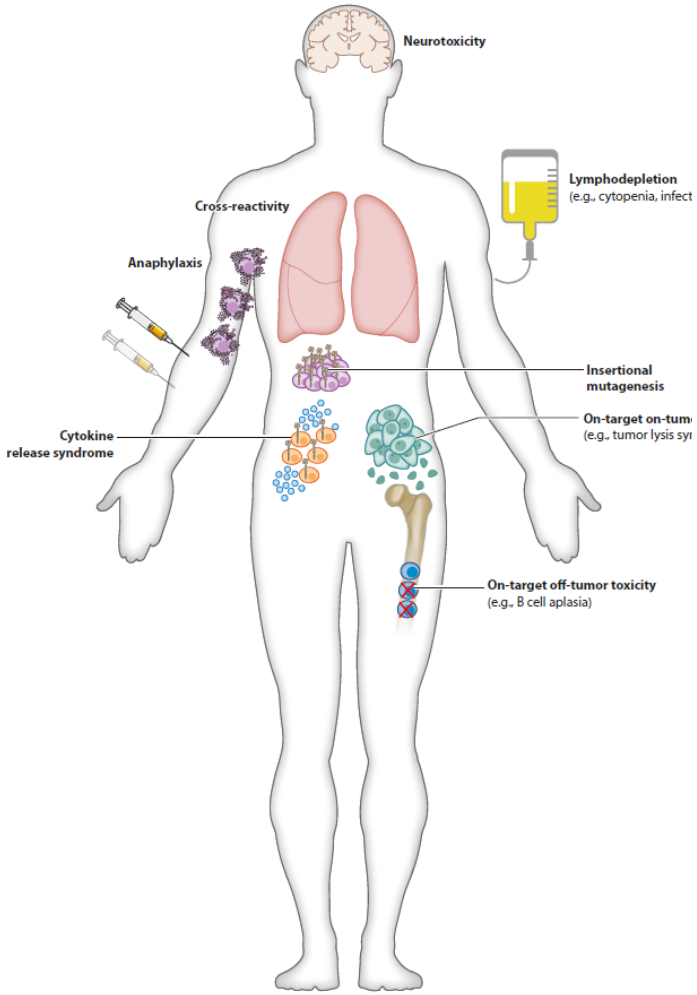


- Auch CRES (CAR-T-cell-reacted encephalopathy syndrome) genannt
- Auftreten in 30-80% je nach Studie
- Neurologische Symptome: reichen von Tremor über Vigilanzminderung und epileptische Anfälle bis zu schwerem Hirnödem
  - Häufiges Frühsymptom: Aphasie, Veränderung der Handschrift!
- Auftreten zu 90% in Kombination mit CRS
- Pathophysiologie: endotheliale Dysfunktion, Störung der Blut-Hirn-Schranke → Migration myeloider Zellen u. CAR-T-Zellen -> ZNS-spezifisch



https:/www.onkopedia.com

ICANS - Schweregrade



ICANS grading for adults adapted by ASTCT consensus guidelines

Neurotoxicity (NT)	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[a]	9–7	6–3	2–0	0 (unarousable, unable to perform ICE)
Depressed level of consciousness[b]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable, vigorous/repetitive tactile stimuli to arouse, stupor/coma
Seizure	N/A	N/A	Any clinical seizure, focal or generalized, that resolves rapidly; or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings[c]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal edema on neuroimaging[d]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing, cranial nerve VI palsy, papilledema, or Cushing's triad

Encephalopathy assessment tools for grading ICANS

CAR-TOX-10 / CRES

- **Orientation (5 points):** time (year, month), place (city, hospital), president/prime minister of country of residence
- **Naming (3 points):** ability to name three objects (e.g., pen, clock, jacket)
- **Writing (1 point):** ability to write standard sentence (e.g., my daughter's name is Sophie)
- **Attention (1 point):** ability to count backward from 100 by 10

Total (10 points)

ICE

- **Orientation (4 points):** time (year, month), place (city, hospital),
- **Naming (3 points):** ability to name three objects (e.g., pen, clock, jacket)
- **Writing (1 point):** ability to write standard sentence (e.g., my daughter's name is Sophie)
- **Attention (1 point):** ability to count backward from 100 by 10

+Following comands (1 point): ability to follow simple commands (e.g., show me 2 fingers or close your eyes and stick out your tongue)

Total (10 points) ICE score

Schmidts et al. Annual Review of Medicine 2020

Therapie des ICANS

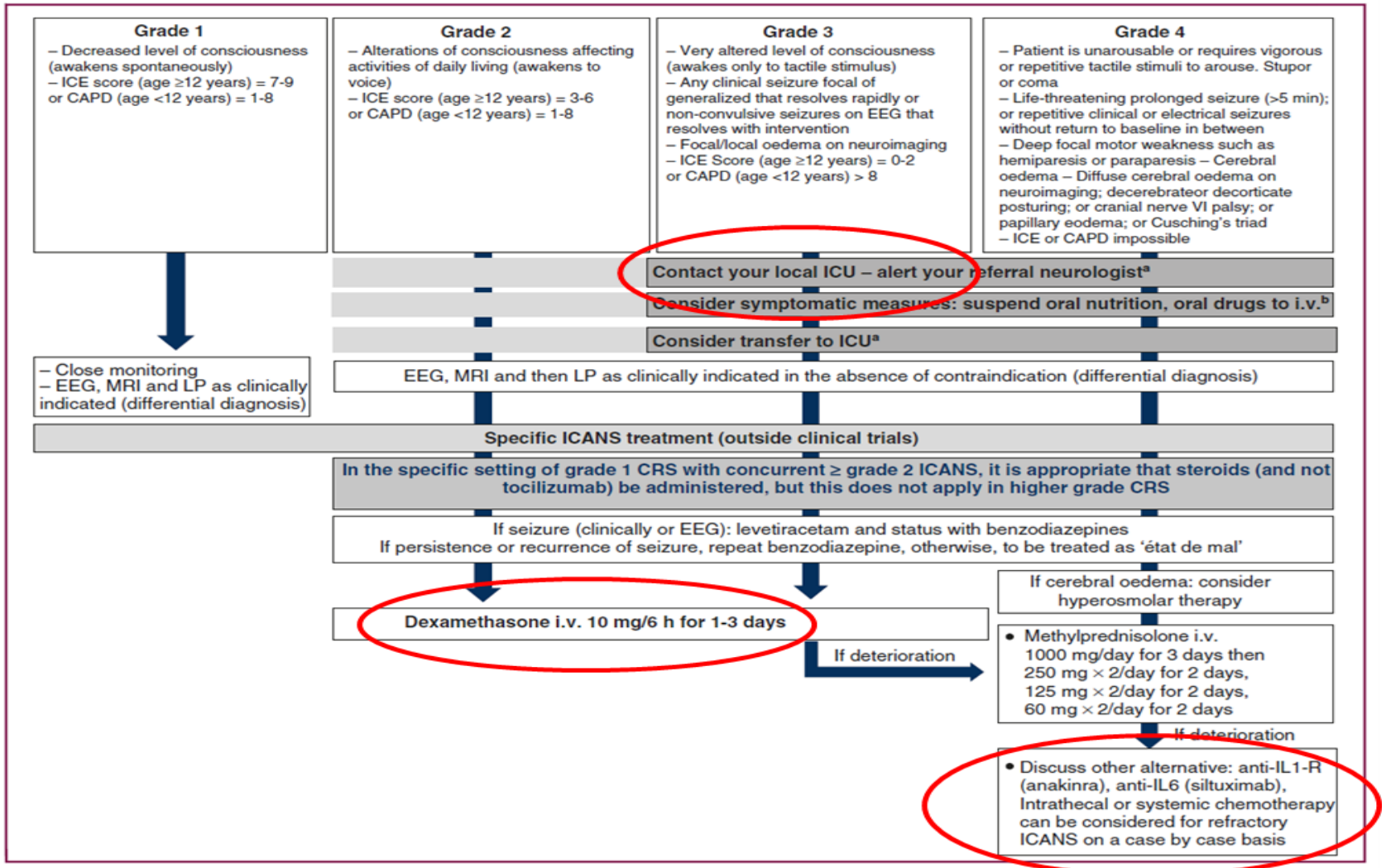


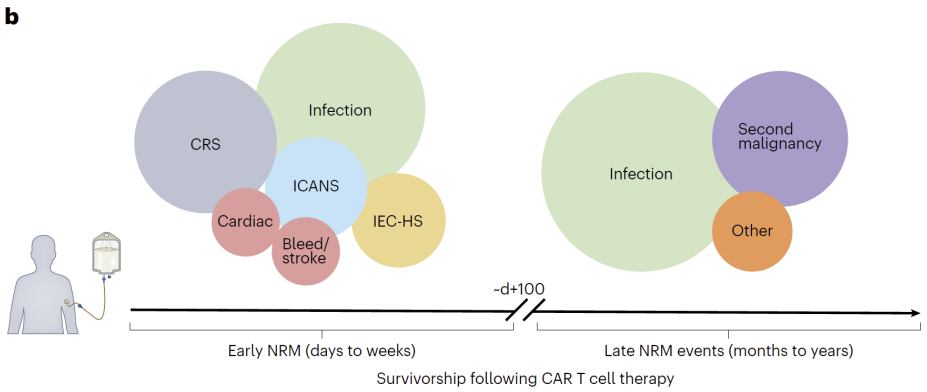
Figure 3. Grading and management of immune effector cell-associated neurotoxicity syndrome (ICANS).

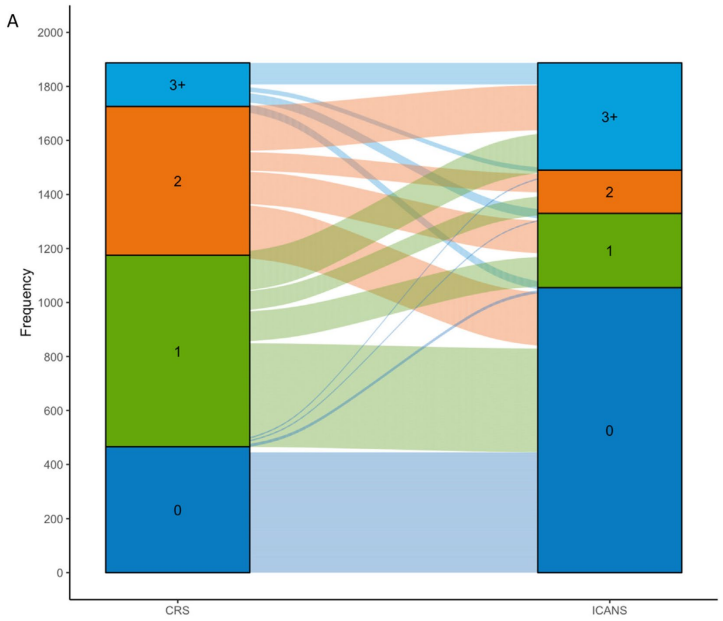
TABLE 7 Pharmacotherapy for the treatment of ICANS.

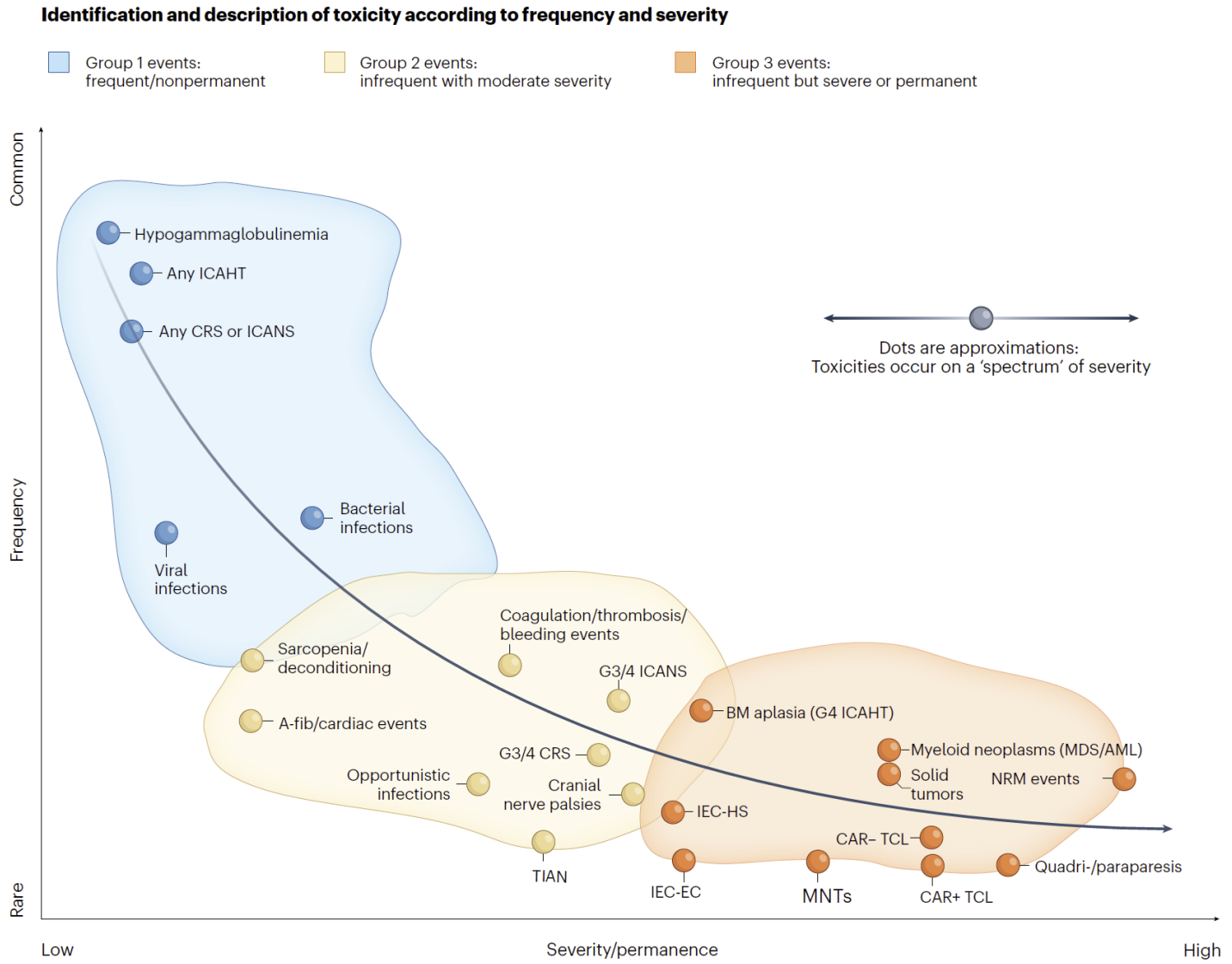
ICANS Grade	Pharmacotherapy Recommendations
Grade 1	• Supportive care, consider dexamethasone 10 mg and reassess
Grade 2	• Dexamethasone 10 mg IV every 12 hours, can escalate dosing to 10 mg every 6 hours for persistent grade 2 ICANS • Continue corticosteroids until improvement to grade 1 ICANS, then rapidly taper as clinically appropriate
Grade 3 or Grade 4	• Dexamethasone 10 mg IV every 6 hours • Can escalate up to methylprednisolone 1,000 mg IV given two to three times daily for refractory grade 3 or grade 4 ICANS • Seizures and/or status epilepticus should be managed with anti-epileptics with neurology assistance as per institutional guidelines • Alternative therapies should be considered for the treatment of ICANS refractory to corticosteroids
Alternative Therapies for Refractory ICANS	
Anakinra – IL-1 receptor antagonist, multiple retrospective studies demonstrating efficacy (64, 102, 103)	
Siltuximab – IL-6 inhibitor, pre-clinical rationale without significant clinical demonstration of efficacy. Note that tocilizumab (IL-6R inhibitor) should only be used for concomitant CRS as inhibition of the receptor causes transient increases in free IL-6 which may exacerbate ICANS (65, 97, 104)	
Dasatinib – tyrosine kinase inhibitor, demonstrated efficacy in case report (72)	
Intrathecal hydrocortisone and/or chemotherapy – direct targeting of CAR T cells in CSF, demonstrated efficacy in case reports and retrospective studies (105, 106)	
Antithymocyte globulin (ATG) – direct targeting of CAR T cells, demonstrated efficacy when used as part of multimodal therapy in case report (104)	
Cyclophosphamide – Chemotherapeutic targeting of CAR T cells, demonstrated efficacy in case report (107)	

Hayden et al. ESMO Guidelines, Annals of Oncology 2021; Ferreri and Bhutani Frontiers in Oncology 2024

Frequenz und Schweregrad der CAR-T-Zelltoxizität



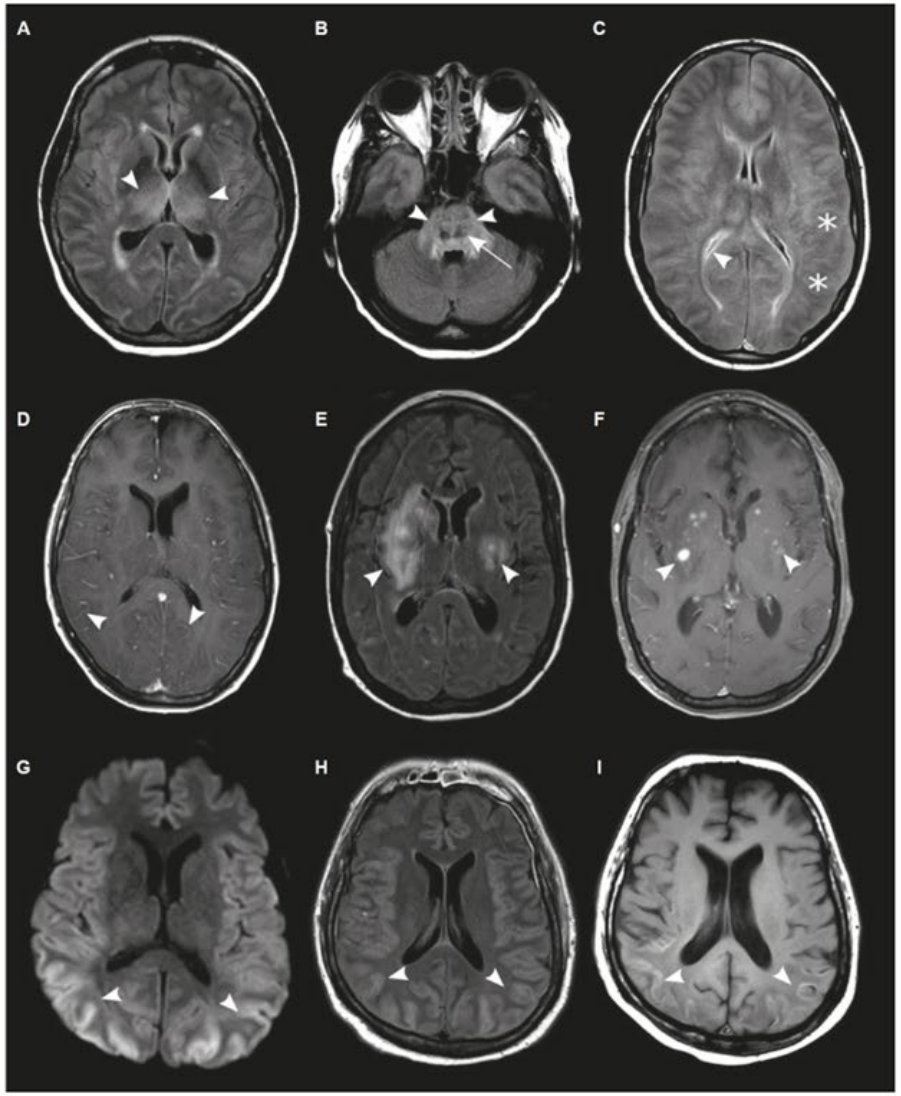


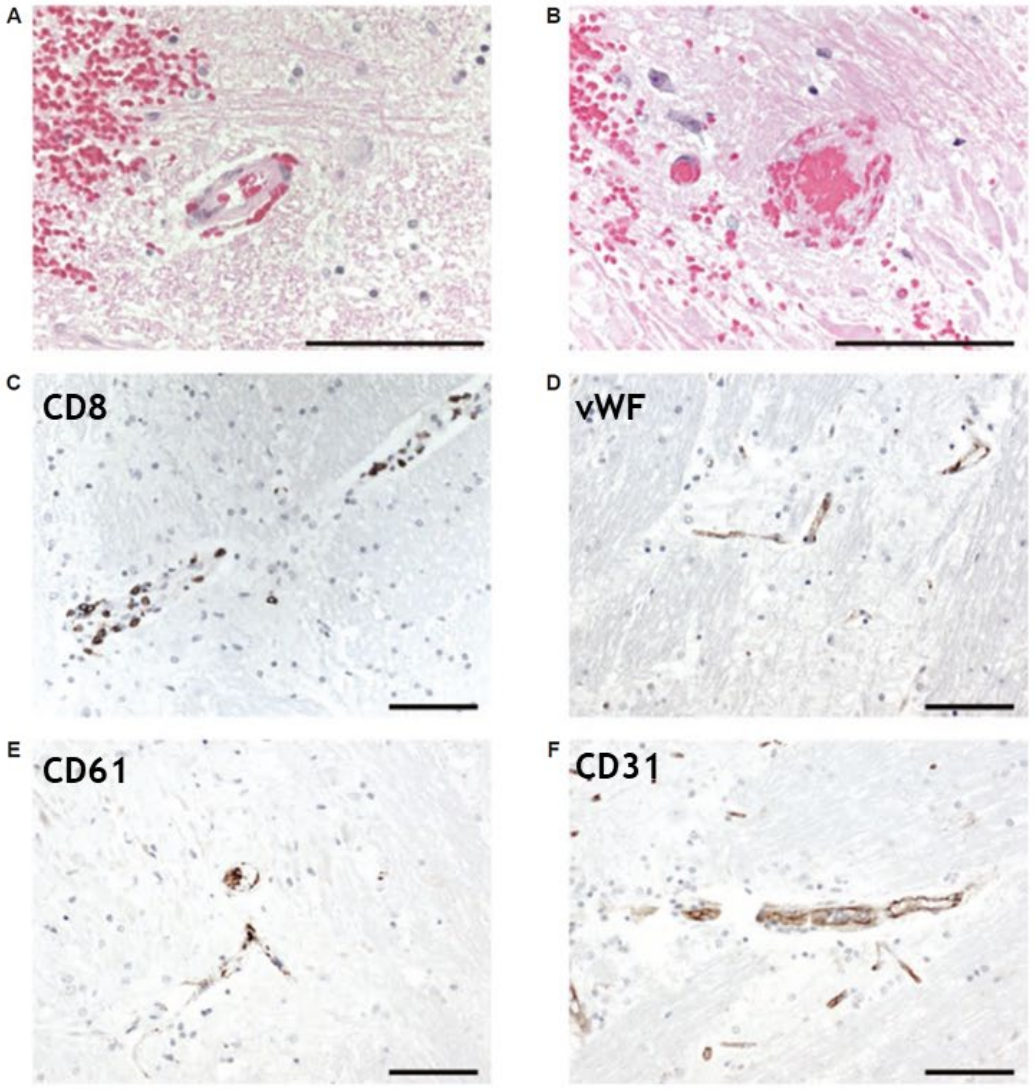


Shouval et al. Transplantation and Cellular Therapy 2025; Rejeski et al. Nature Medicine 2025

MRT-Diagnostik und Immunhistologie des ICANS

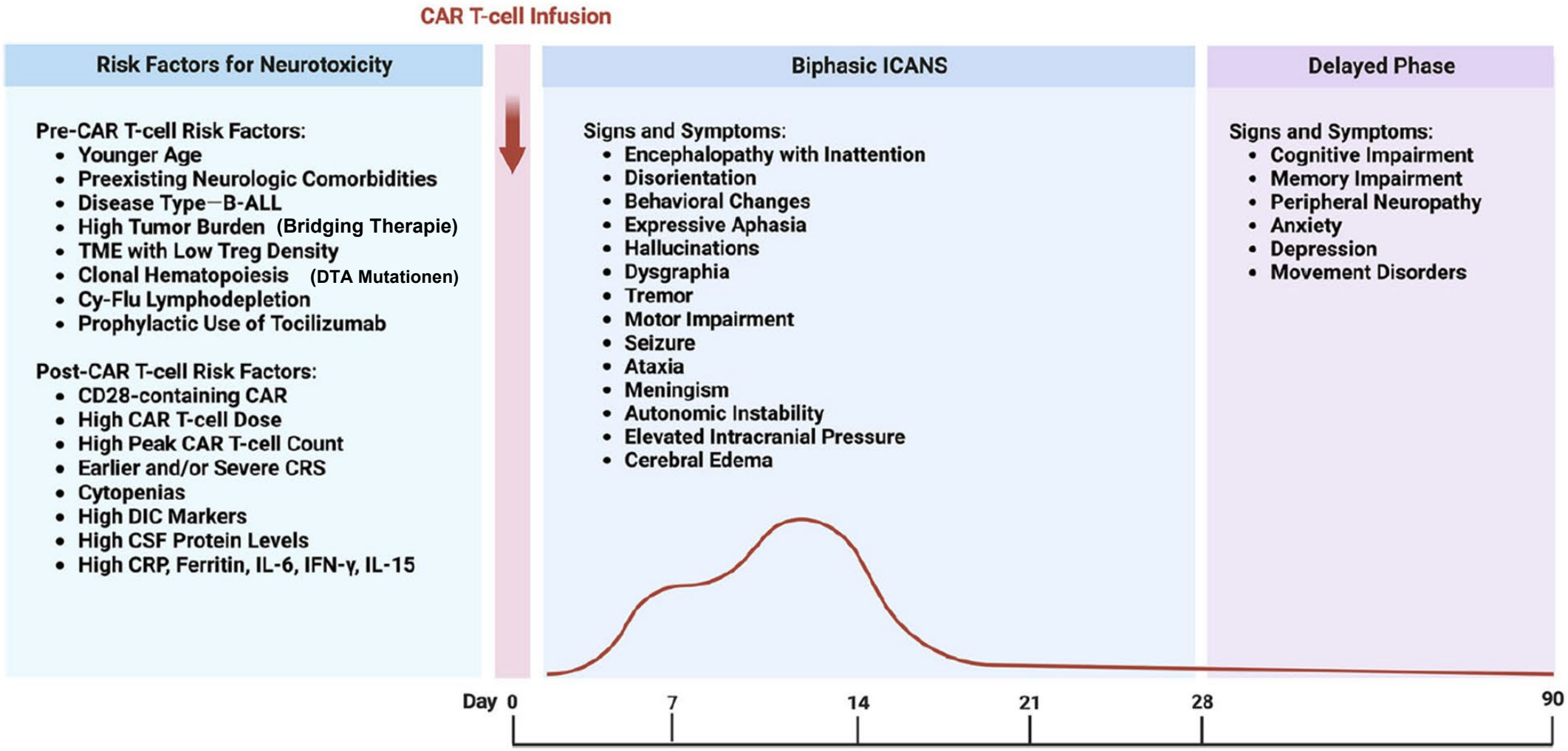
Endothelaktivierung und Störung der Bluthirnschranke





Gust et al. Cancer Discov 2017

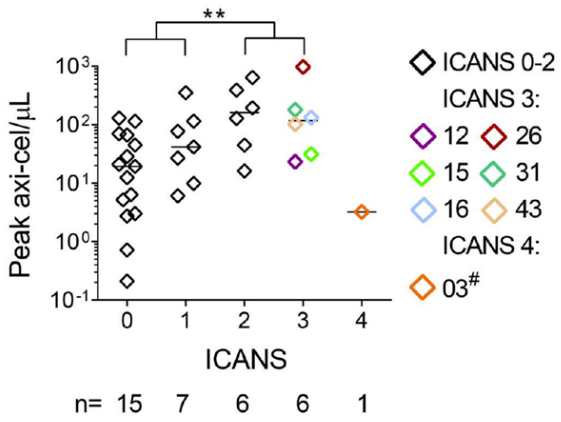
Biphasische Verläufe und späte Komplikationen

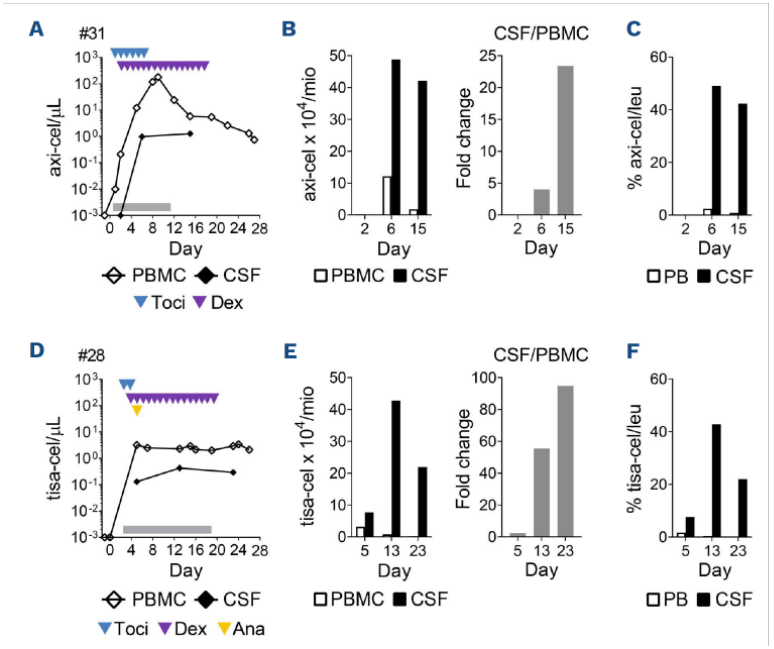


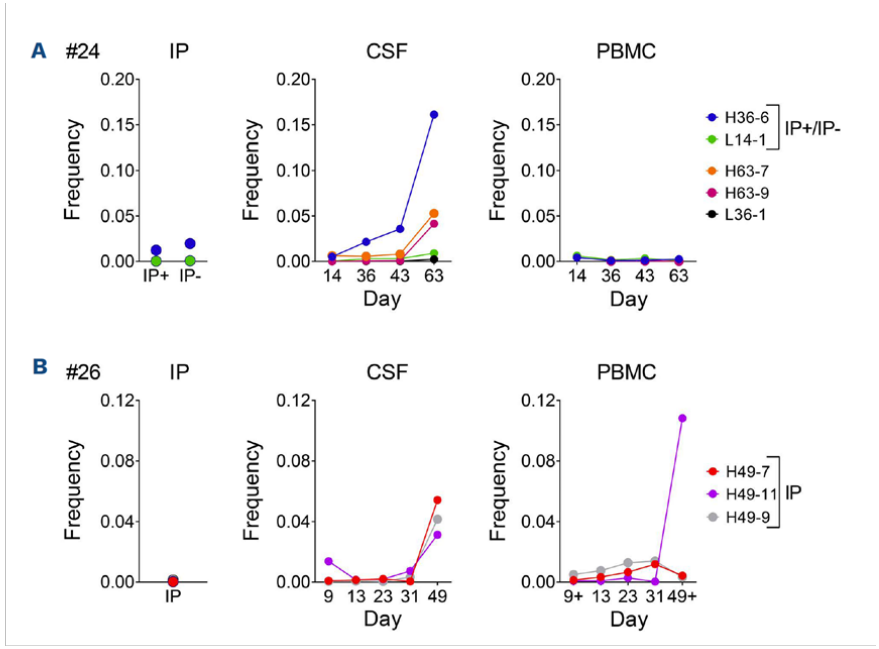
Shannon P. Forth Ensign. Curr Treat. Opinions in Oncol. 2022; Saini et al. Blood 2022

Post-CAR T-Zell-Risikofaktoren für die Entwicklung eines ICANS

- **Die Schwere der Neurotoxizität korreliert mit dem Spitzenspiegel der CAR T-Zellen im Blut**
- **CAR T-Zell-Persistenz und Anreicherung im Liquor trotz Therapie des ICANS**
- **Persistenz weniger hyperexpandierter CAR T-Zellklone im Liquor trotz Therapie des ICANS**



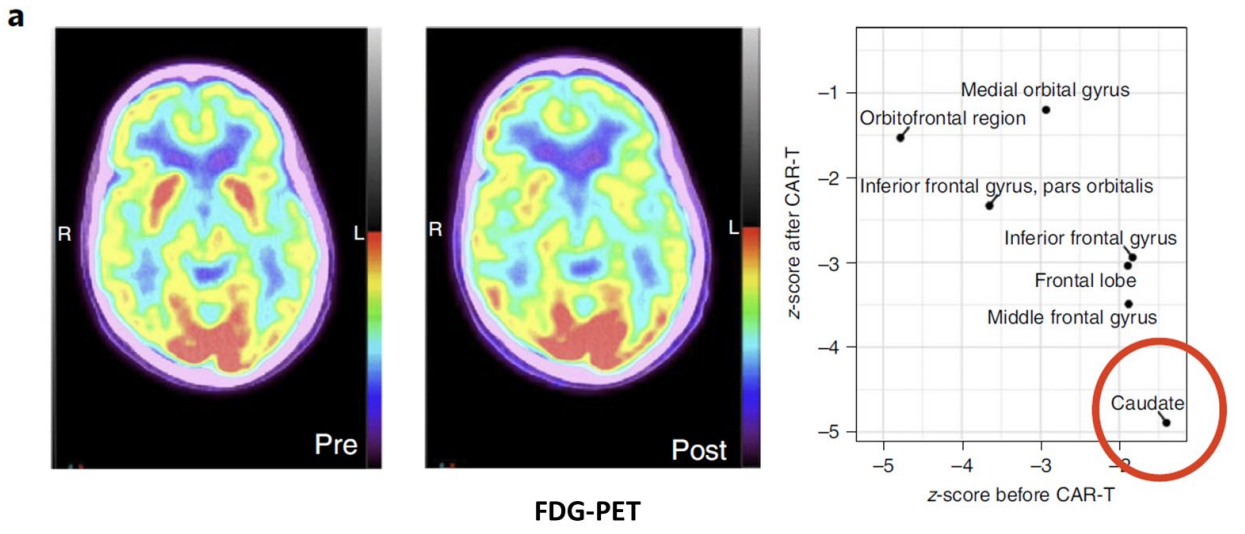




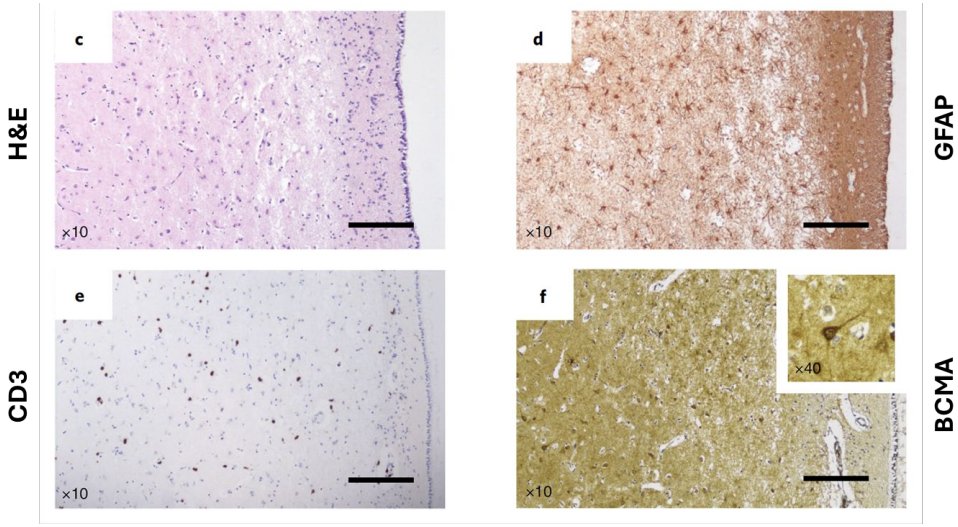
Berger et al. Cell Therapy & Immunotherapy 2023

Bewegungsstörungen und neurokognitive Störungen

- Assoziiert mit Persistenz von BCMA CAR T-Zellen, Nachweis im Blut und Liquor (Off Tumor-/On-Target Effekt)
- Verzögertes Auftreten nach CRS und ICANS, progressiver Verlauf
- Parkinsonismus (Bradykinese, Mikrographie, Rigor, Hypomimie, Ruhetremor, kleinschrittiges Gangbild)
- Kognitive Störungen: Aufmerksamkeits- und Gedächtnisstörungen, Persönlichkeitsveränderungen, Apathie
- Hypometabolismus im FDG-PET (Basalganglien, N. caudatus, Frontallappen)
- Kein Ansprechen auf L-Dopa



FDG-PET

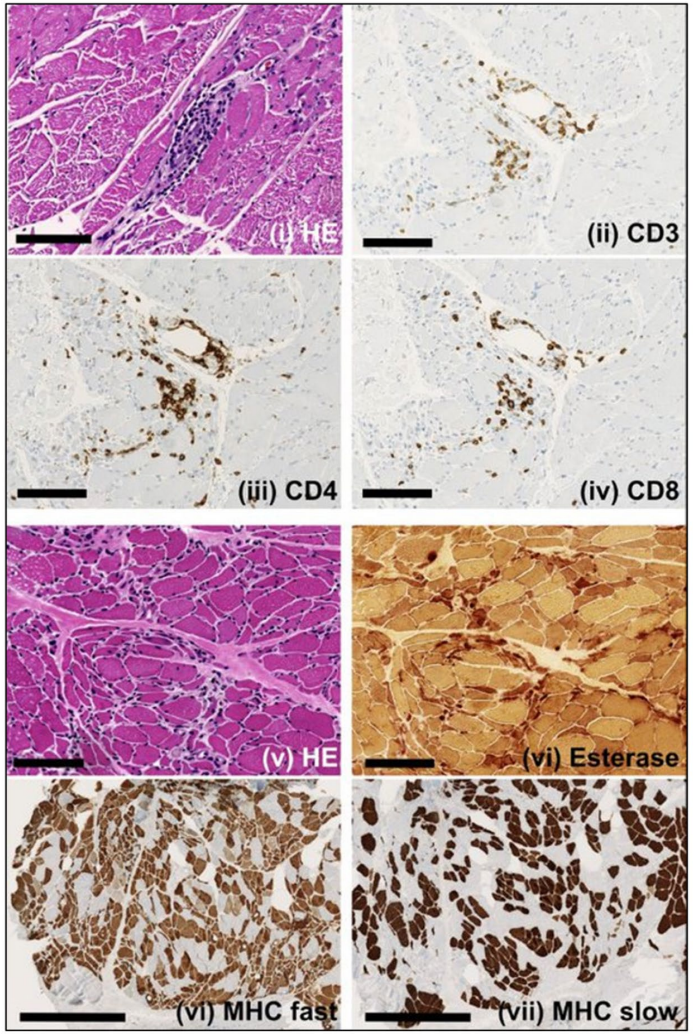


Nucleus caudatus

Graham et al. Lancet Oncology 2025; Van Oekelen et al. Nature Medicine 2021

Polyradikuloneuritis / GBS-Formenkreis

- **Häufig assoziiert mit BCMA CAR T-Zellen, aber auch CD19 CAR T-Zellen**
- **Häufig früher Onset nach Infusion, assoziiert mit stärkerer T-Zellexpansion**
- **Häufig ein- oder beidseitige Fazialisparese**
- **Spätere Manifestation mit peripherer Beteiligung Polyradikulitis/ GBS**
- **Nachweis einer zytalbuminärer Dissoziation im Liquor**
- **Kontrastmittelanreicherung der Nervenwurzeln im spinalen MRT**

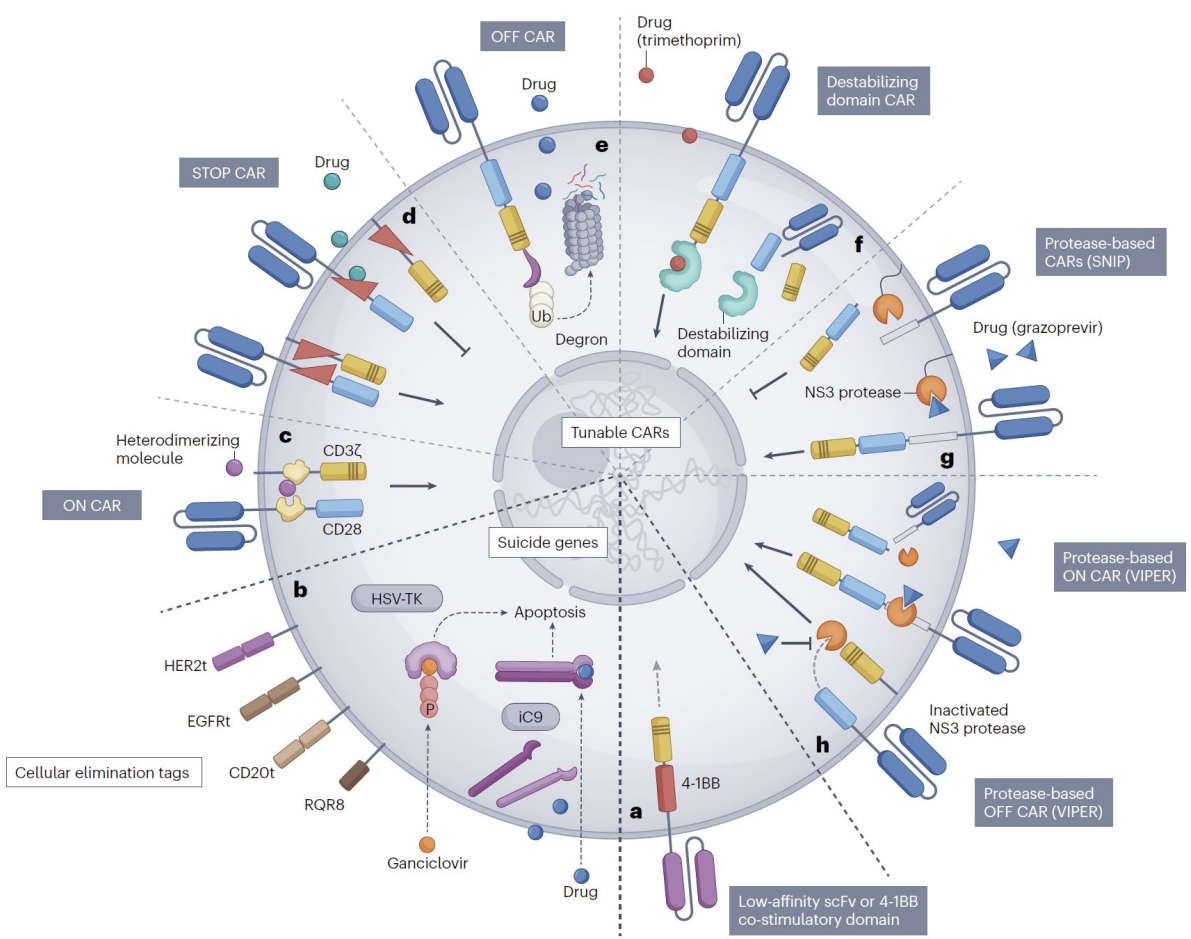


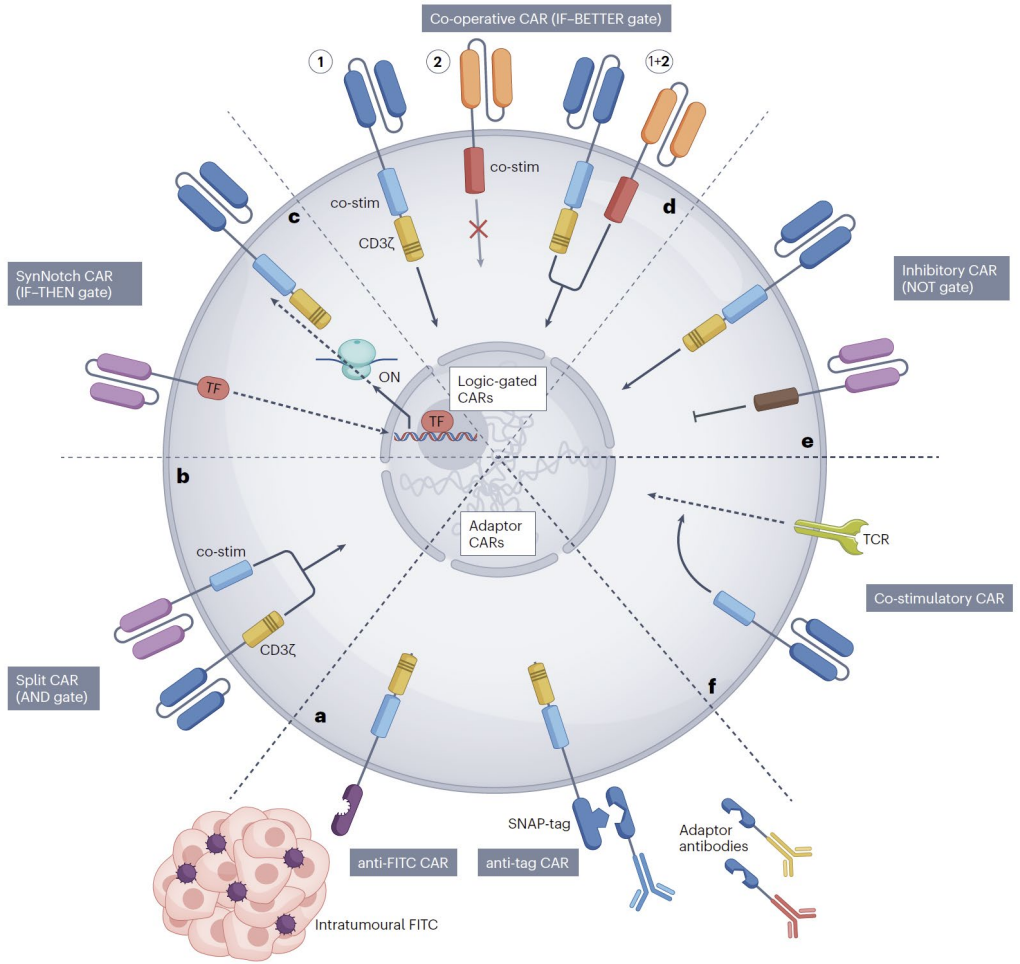
	Patients in trial, n	Patients with CNP,[a] n (%)	Maximum CN VII Impairment Grade, n		CN involvement in addition to CN VII, n
			Grade 2	Grade 3	
CARTITUDE-1	97	3 (3.1)	2	1	1 (CN V, gr 3)
CARTITUDE-2					
Cohort A	20	1 (5.0)	1	0	0
Cohort B	19	1 (5.3)	1	0	0
Cohort C	20	0	-	-	-
CARTITUDE-4	176	16 (9.1)	15	1	2 (CN III, gr 3; CN V; gr 3)
Total	**332**	**21 (6.3)**	**19**	**2**	**3**

[a]CNP defined as facial nerve (VII) palsy (n=21), oculomotor (III) nerve palsy (n=1), trigeminal (V) nerve palsy (n=2)
CN, cranial nerve; CNP, cranial neuropathy.

Van de Donk et al. Lancet Haematol 2025; Koch et al. Journal of Immuntherapy of Cancer 2025

CAR T-Zell-Engineering





Mulvey et al. Nature Reviews Drug Discovery 2025

CAR T-Zell-Therapie in der Neurologie

Phase-I, frühe Phase-II Studien

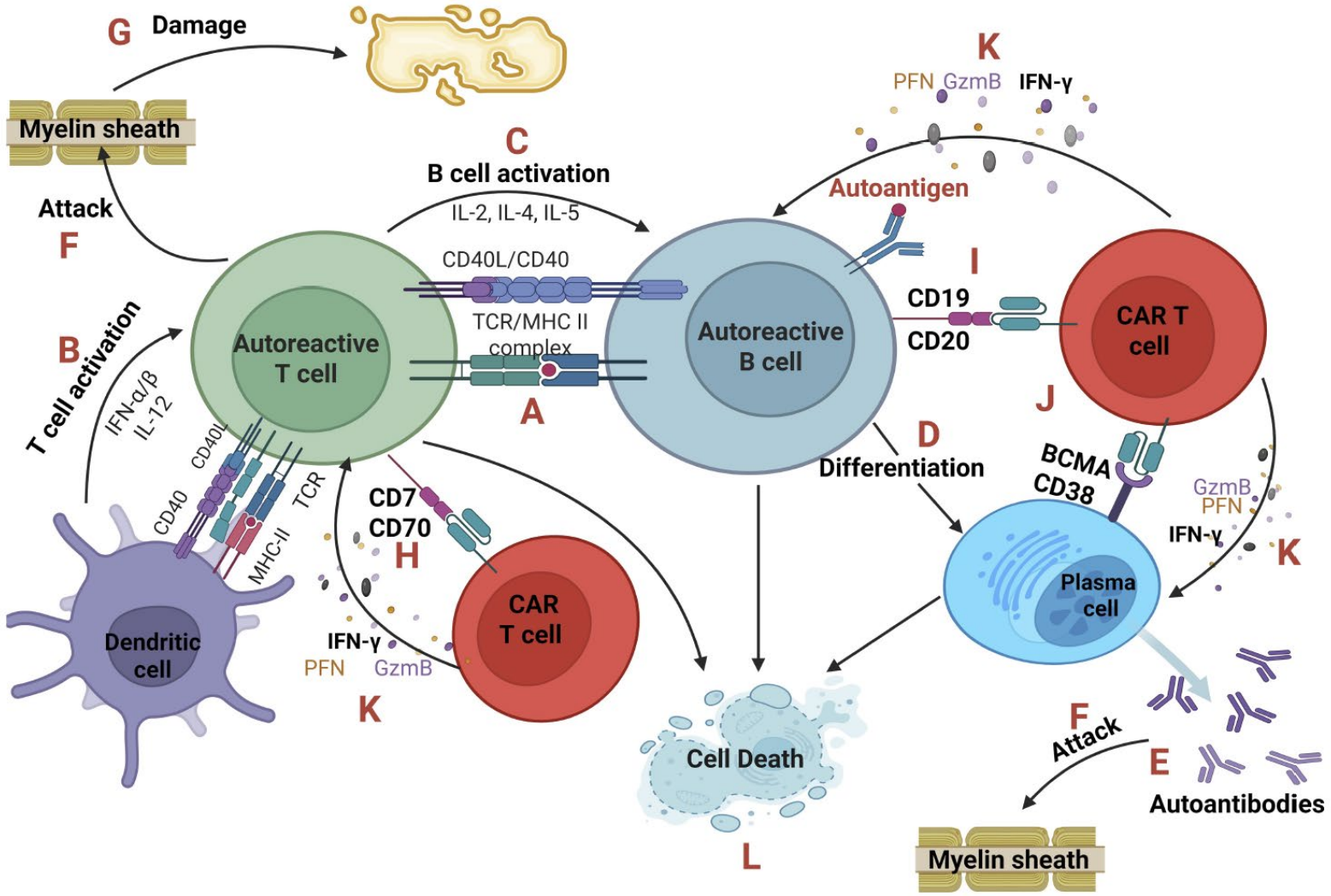
CD19 oder BCMA CAR T-Zellen

Multiple Sklerose
NMOSD
MOGAD
Stiff-Person-Syndrome
Myasthenia gravis
AE

CRS Grad 1-2

Infektiöse Komplikationen

Keine Langzeitdaten



Chinas and Alexopoulus Frontiers in Immunology 2025



Vielen Dank für Ihre Aufmerksamkeit!

oliver.grauer@ukmuenster.de