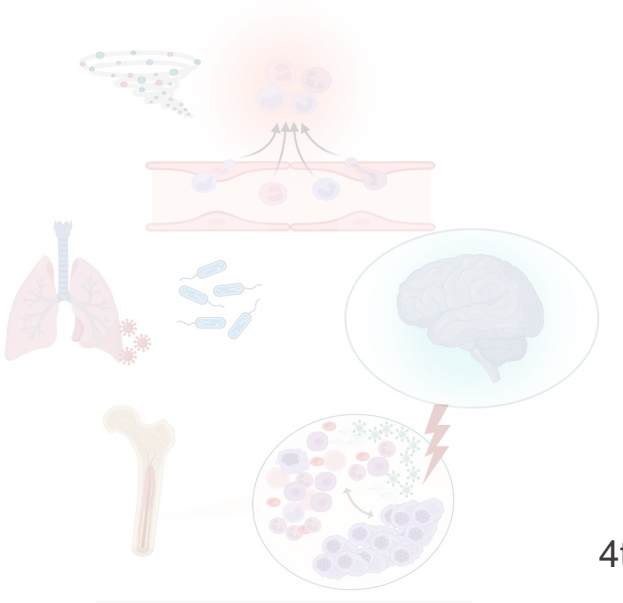
Memorial Sloan Kettering Cancer Center

LMU KLINIKUM

CAR-T toxicities in NHL and MM

Non-Relapse Mortality, Infections, Secondary Cancers and Delayed Neurotoxicities



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4th Meeting on Innovative Immunotherapies for Lymphoid Malignancies
Milano, Jan 23 2026

@KRejeski

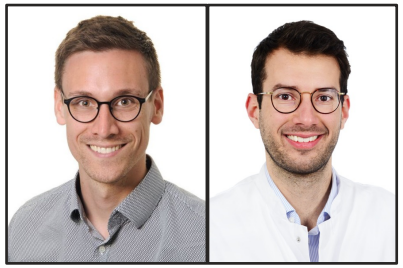
Disclosures

- **Research Support**
  Kite/Gilead

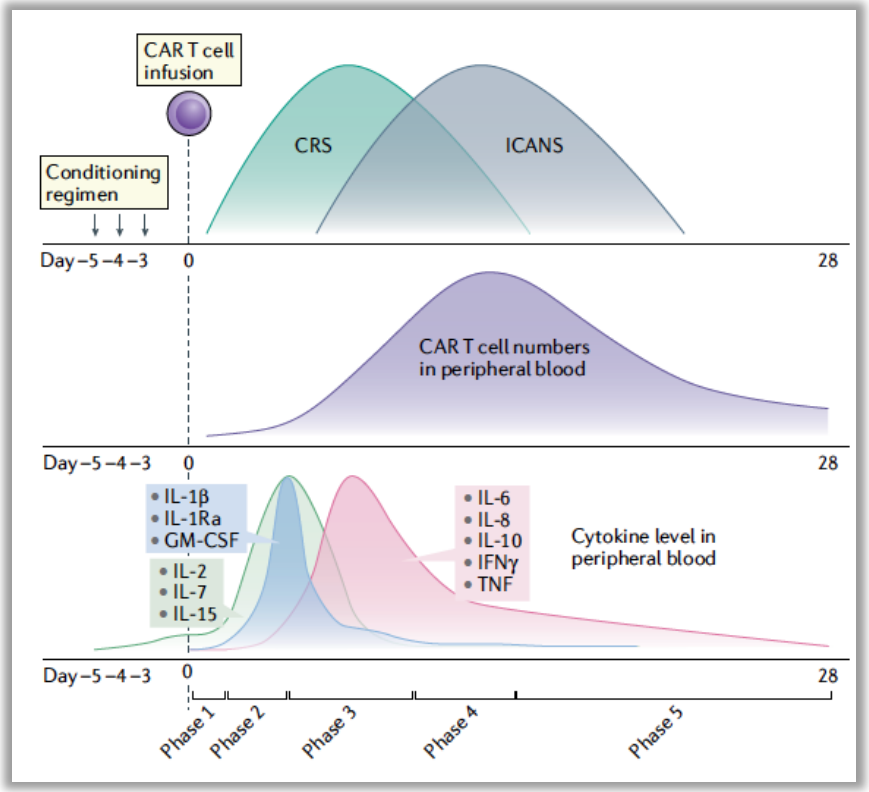
- **Honoraria/Consultancy**
  Kite/Gilead, Novartis, BMS/Celgene, CSL Behring, MSD

- **Travel Support**
  Kite/Gilead, Pierre-Fabre

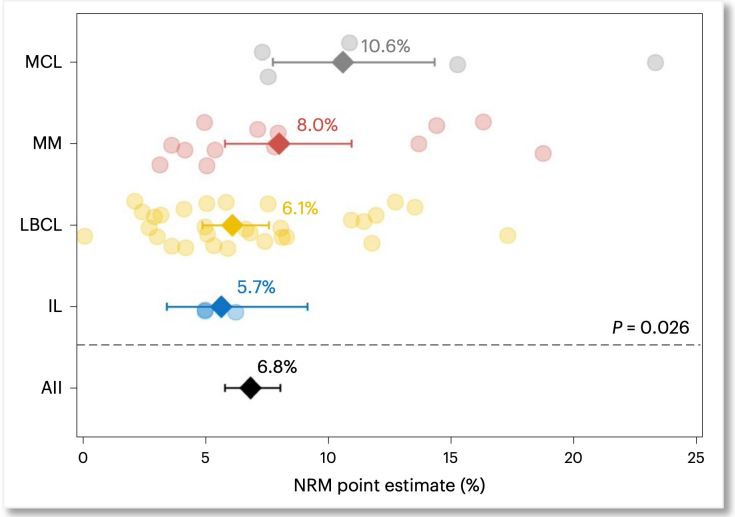
CAR-T therapy is associated with a unique toxicity profile that can result in NRM



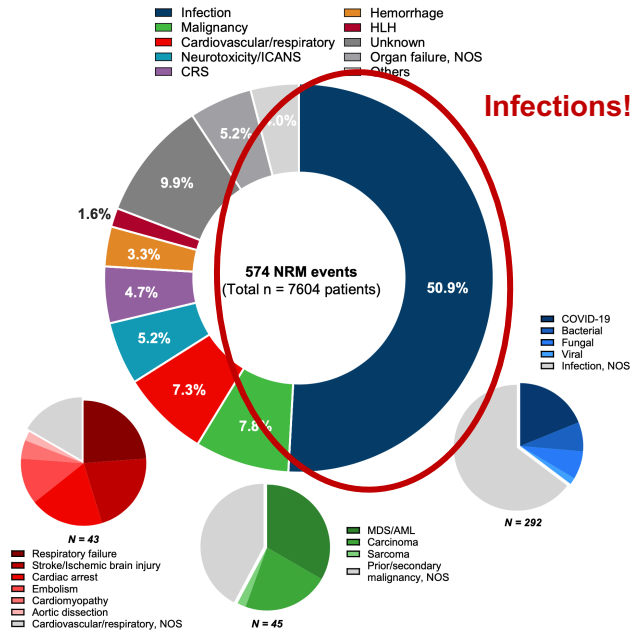
David Dos Santos Tobias Tix



Topline Results from Large Meta-Analysis:
7,604 Lymphoma and Multiple Myeloma patients



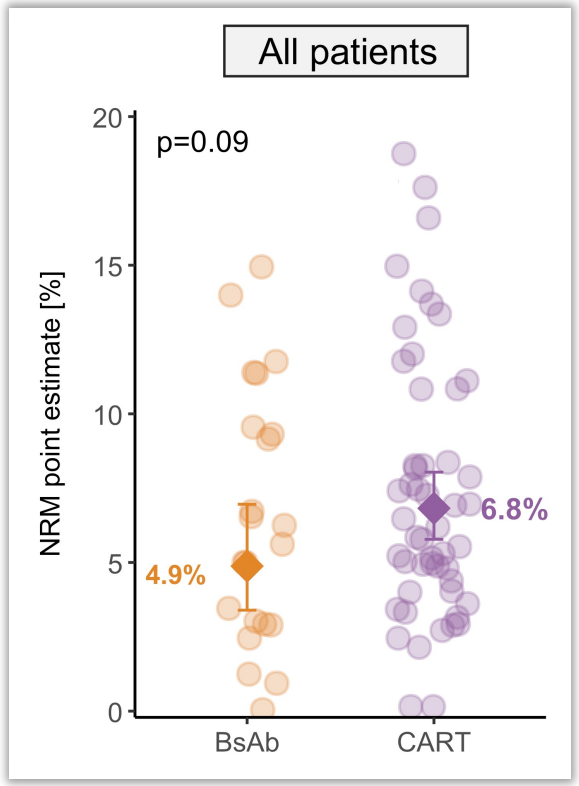
Causes of non-relapse mortality after CAR-T



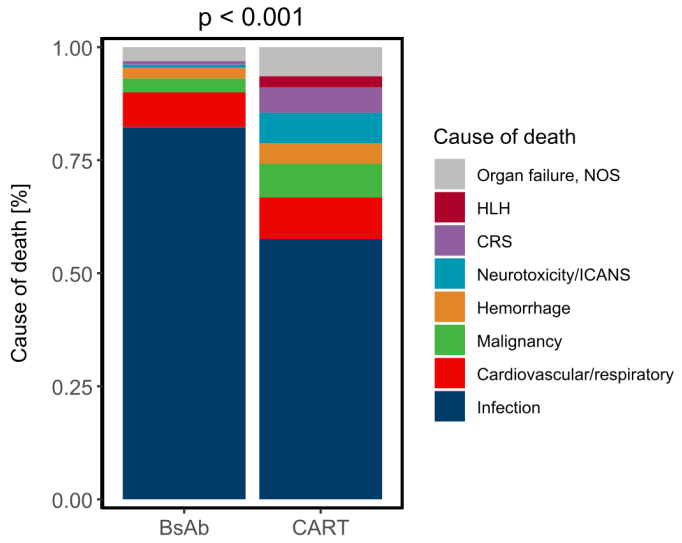
Considerable Toxicity Burden: CRS, ICANS, but also IEC-HS, ICAHT, Infections, Secondary Malignancy

- **Infections = main driver of NRM after CAR-T** (>50% of all NRM events)
- Prototypical side effects like CRS/ICANS/HLH only account for a minority of NRM events (11.5%)

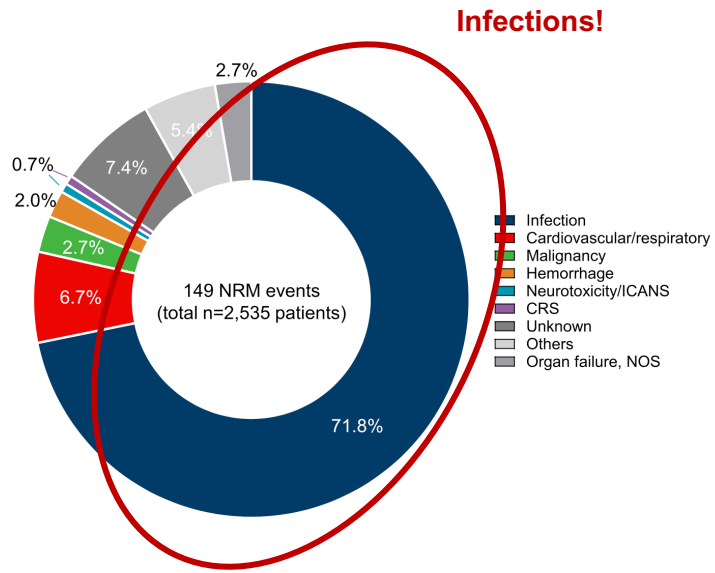
Similarly, infections predominate as the main mortality driver with bispecifics



First Meta-Analysis of NRM post BsAb:
2,535 Lymphoma and Multiple Myeloma patients



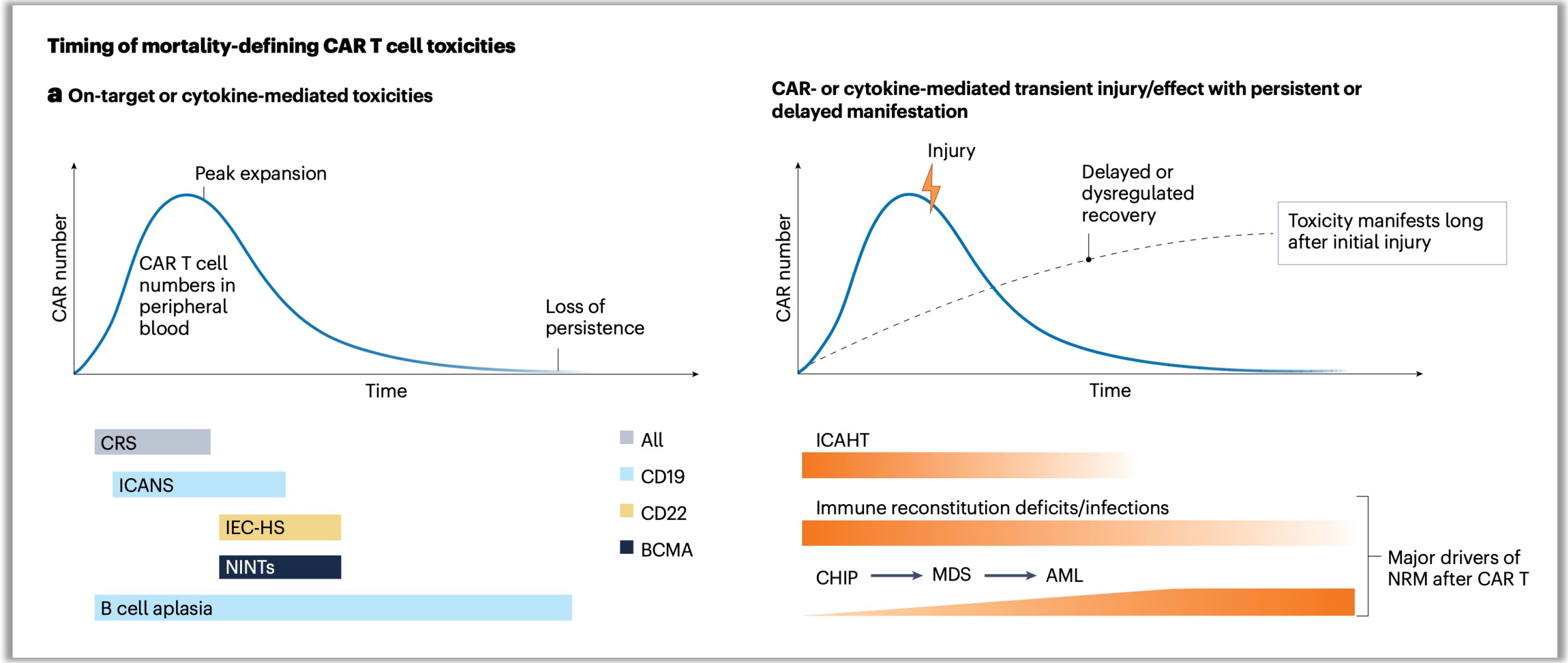
Causes of non-relapse mortality after BsAb



Numerically lower NRM with BsAb vs. CAR-T
(cave: does not extend to meta-regression accounting for study level risk factors)

- **Infections = main driver of NRM after BsAb** (>75% of all attributable NRM events)
- CRS and ICANS essentially a non-factor when it comes to mortality with BsAb; however, infections negate most of the safety / mortality advantages relative to CAR-T

Timing of mortality-defining CAR-T toxicities



Rejeski et al, Nature Medicine 2025

Agenda – Understanding Mortality Drivers of CAR-T

NRM
after CAR-T

1. Cytopenias (ICAHT)

2. Immune Deficits & Infectious Complications

3. Secondary Malignancies

ICAHT = Immune Effector Cell-Associated Hematotoxicity

Agenda – Understanding Mortality Drivers of CAR-T

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1. Cytopenias (ICAHT)

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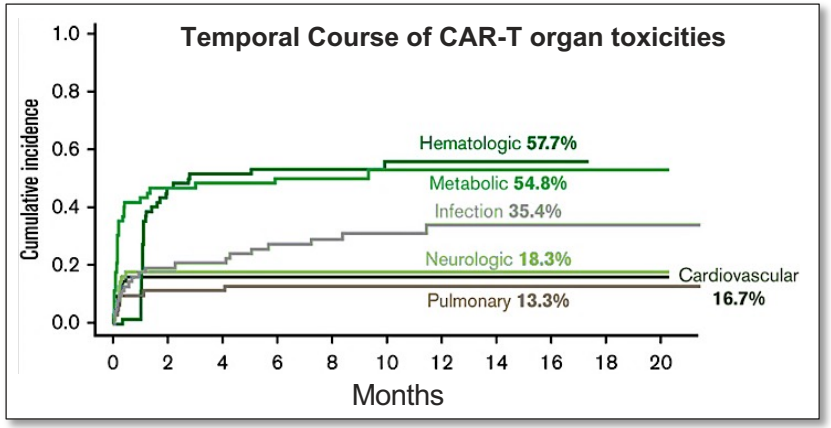
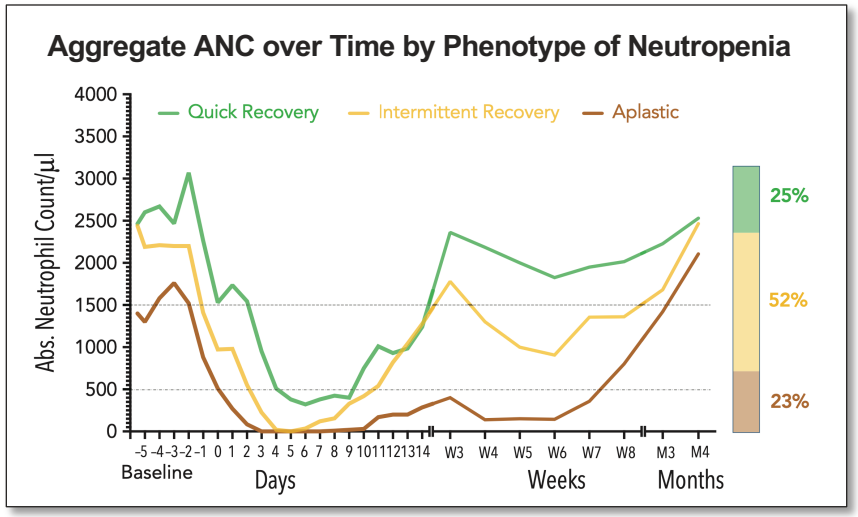
ICAHT = Immune Effector Cell-Associated Hematotoxicity

Why should we care about cytopenias following CAR-T?

Most common side effect of CAR-T, qualitatively unique and clinically relevant

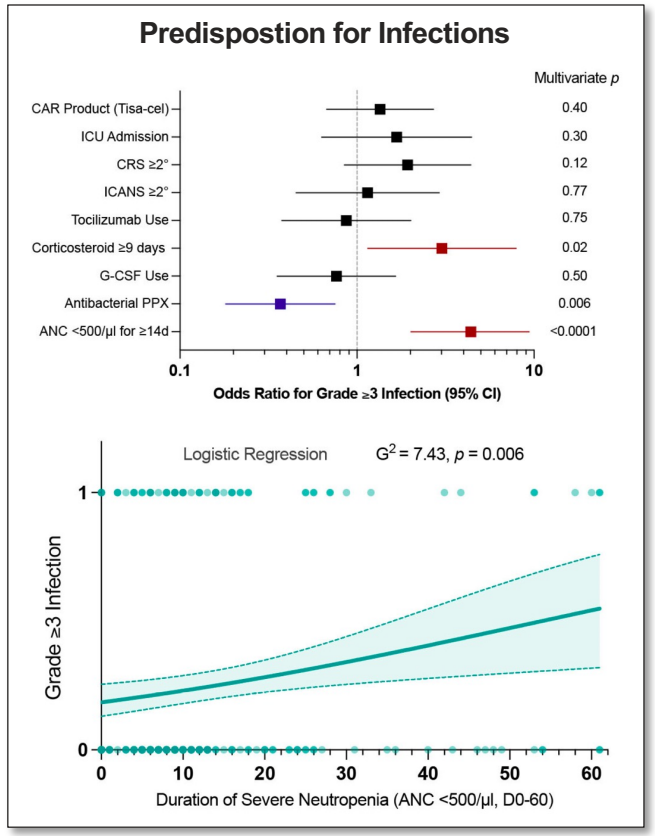


- **most common CTC grade ≥ 3 toxicity**



- Cytopenias = **qualitatively unique**

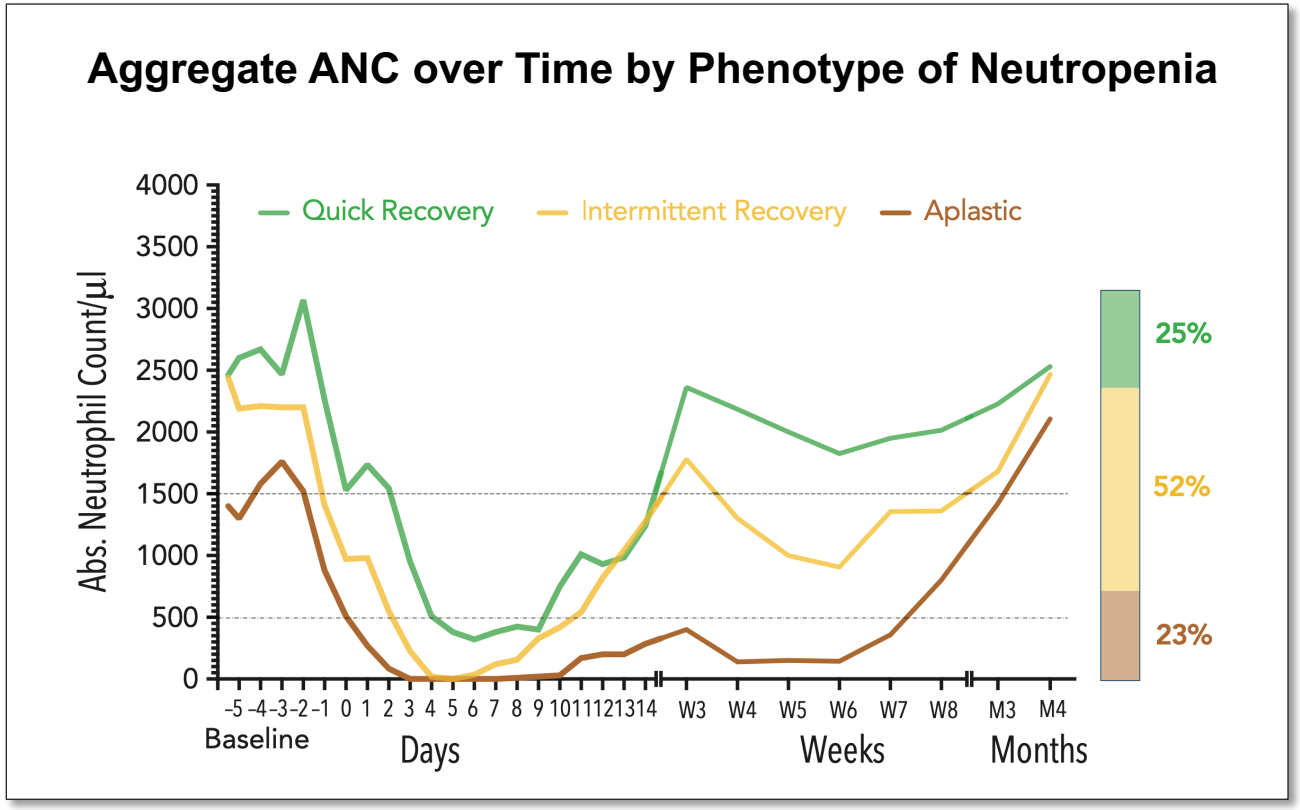
Biphasic = "Intermittent" vs. Monophasic = "Aplastic"



- Can predispose for **infections**, particularly extended neutropenia

Wudhikarn et al. Blood Adv 2020; Rejeski et al. Blood 2021; Rejeski et al. JITC 2022

Rationale:
CTCAE grading does not reflect the different phenotypes of neutrophil recovery



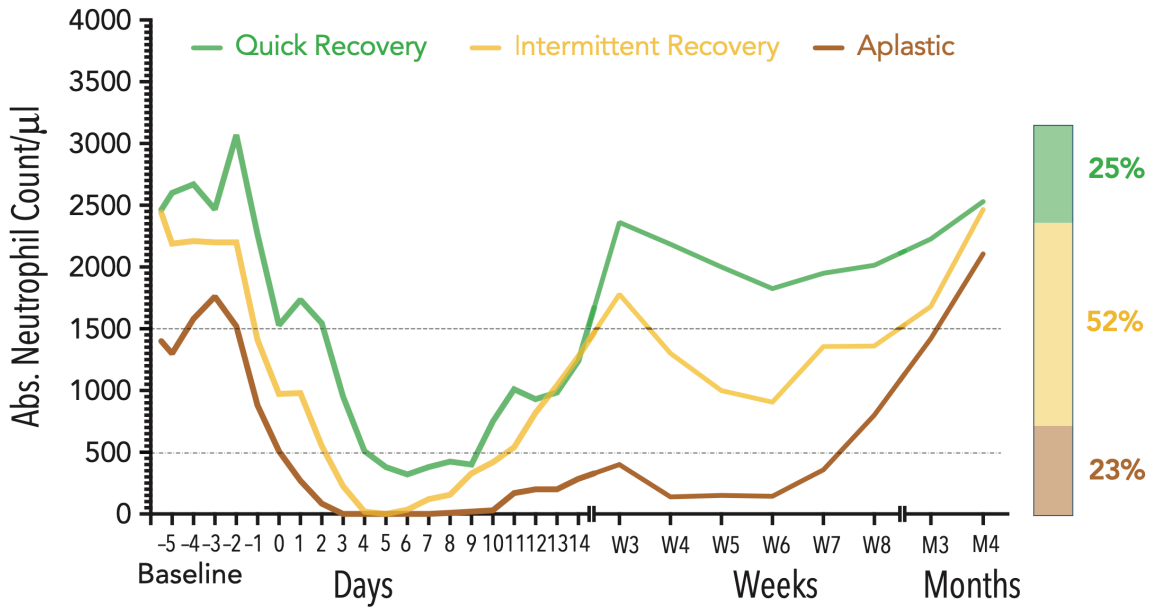
"Quick Recovery"	= sustained neutrophil recovery by day 14
"Intermittent Recovery"	= neutrophil recovery (ANC > 1500/µl) followed by a 2nd dip with an ANC < 1000/µl after d 21
"Aplastic"	= continuous severe neutropenia (ANC < 500/µl) ≥ 14 days

Rejeski et al, Blood 2021

Rationale:

CTCAE grading does not reflect the different phenotypes of neutrophil recovery nor do the CTCAE criteria reflect the risk of infections due to neutropenia

Aggregate ANC over Time by Phenotype of Neutropenia



ASCO / IDSA Guidelines

Grading:

- Severe (Grade ≥3°): ANC <0.5 G/l
- Profound neutropenia, ANC <0.1G/L
- Protracted neutropenia (> 7 days)

Recommendations:

- Prophylaxis Guidelines are based on **depth and duration** of neutropenia as risk of infection is associated with both

Taplitz et al, JCO 2018

”Quick Recovery” = sustained neutrophil recovery by day 14

”Intermittent Recovery” = neutrophil recovery (ANC > 1500/µl) followed by a 2nd dip with an ANC < 1000/µl after d 21

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Rejeski et al, Blood 2021

Novel EHA/EBMT Consensus Grading

Immune Effector Cell-Associated Hematological Toxicity (ICAHT) after CAR-T

Grading	I	II	III	IV
Early ICAHT (day 0-30)	**Mild**	**Moderate**	**Severe**	**Life-Threatening**
ANC ≤ 500/µL	<7 days	7-13 days	≥14 days	Never above 500/µL
ANC ≤ 100/µL	-	-	≥7 days	≥14 days
Late ICAHT (after day +30)*				
ANC	≤ 1500/µL	≤ 1000/µL	≤ 500/µL	≤ 100/µL

*measured ≥2 time points, or non-transient neutropenia

➢ **Early ICAHT: based on Depth and Duration; Late ICAHT: day 30 as cutoff**

Rejeski, Subklewe et al, Blood 2023

Consensus Guidelines: Diagnostic Work-Up

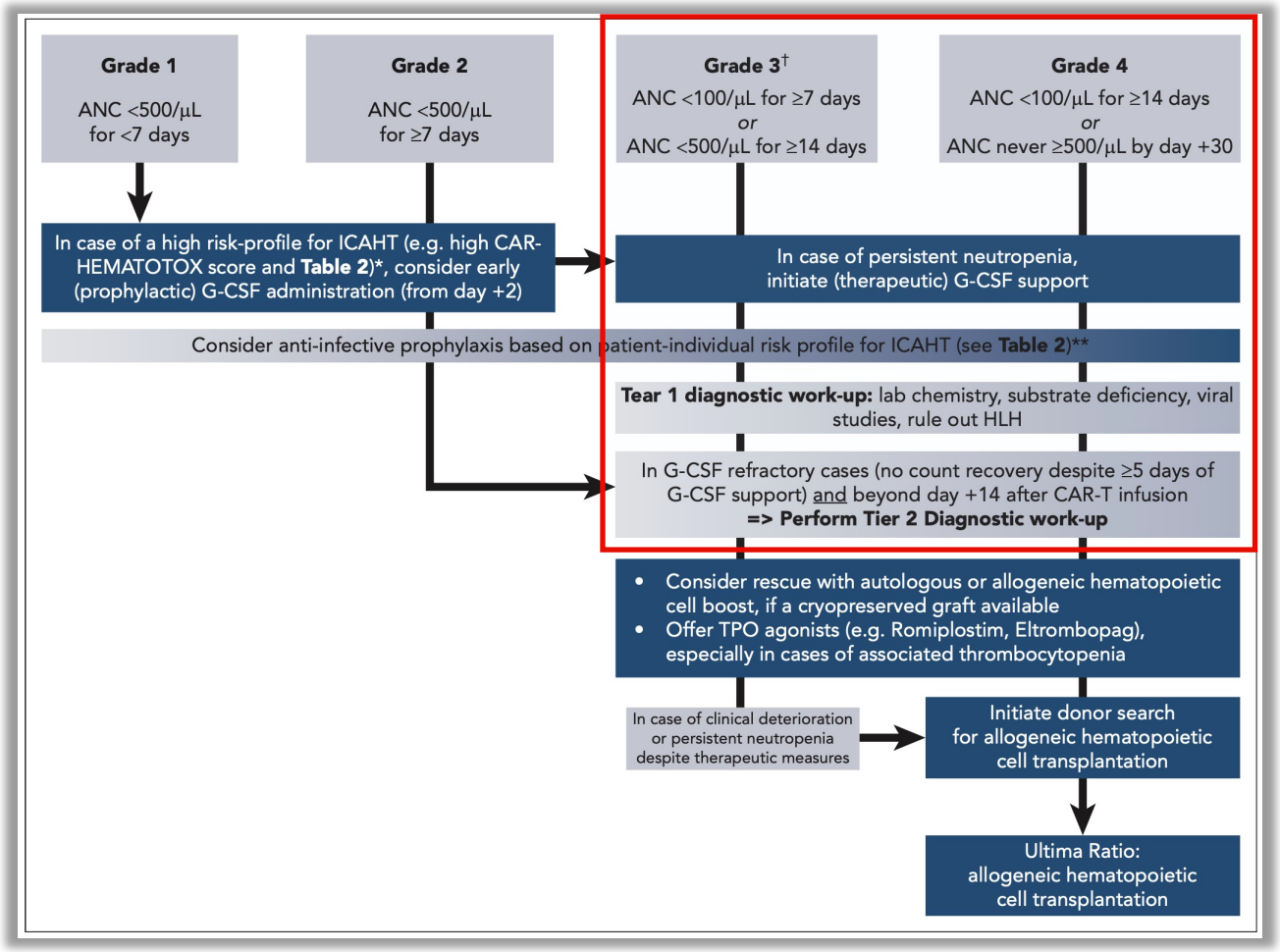
Two Diagnostic Tiers based on ICAHT severity

	Categories	Putative causes	Test	Time points	Comments from expert panel
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	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, JC	HHV6, JC PCR blood/CSF	In case of neurologic symptoms	Recommended
		EBV, adeno, 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, With B-cell panel	routinely	Recommended
	Other causes	Other rare hematologic diseases, myeloid diseases, PNH, autoimmune processes	Myeloid panel, PI-linked structures, Direct Antiglobulin Test (DAT)	In case of suspected MPN/PNH/ autoimmune processes	Recommended

Rejeski, Subklewe et al, Blood 2023

Consensus Guidelines: Management Strategies

Severity-based treatment measures: G-CSF, Prophylaxis, TPO-RA, Boosts



* High Risk: Baseline cytopenias, prior h/o prolonged cytopenias, high CAR-HEMATOTOX, underlying BM infiltration

G-CSF

Prophylactic	Based on individual risk profile*: Consider early G-CSF administration (from day +2) as prophylaxis in high risk for ICAHT. Low-risk: G-CSF probably not necessary - Dosing: 5 µg/kg once daily	- Reduced risk of febrile neutropenia (without increasing the risk of grade ≥3 CRS/ICANS). - No detrimental effect on CAR-T expansion kinetics or treatment outcomes
Therapeutic	In case of prolonged neutropenia with/without infectious complications. - Dosing: 5 µg/kg once daily, consider increasing dose in case of non-response	Patients with intermittent neutrophil recovery often rapidly respond to G-CSF stimulation, while aplastic patients are often G-CSF unresponsive

Anti-infective Prophylaxis

Anti-bacterial	In patients with a low risk for ICAHT, not recommended. In patients with a high-risk profile for ICAHT, prophylaxis may be considered once ANC <500/µL.	Look at local bacterial epidemiology. As per institutional guidelines. High local prevalence of MDR GNB might prevent the use of antibacterial prophylaxis.
Anti-fungal	May considered in severe neutropenia (ANC <500/µL) with a high-risk profile for ICAHT* and/or prolonged neutropenia	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids (long-term >72 h, or high-dose), prophylaxis is recommended

Hematopoietic Stem Cell Boost

Boost available	Consider in patients who are unresponsive and/or refractory to G-CSF beyond day +14 after CAR-T infusion (≥3° ICAHT). - Without prior conditioning chemotherapy.	Current evidence: multiple retrospective case series - High rates of neutrophil and platelet engraftment, clinically safe and feasible
Prophylactic Collection	Not recommended	Prospective evidence needed, evaluate number needed to treat, consider associated logistic and cost burden.

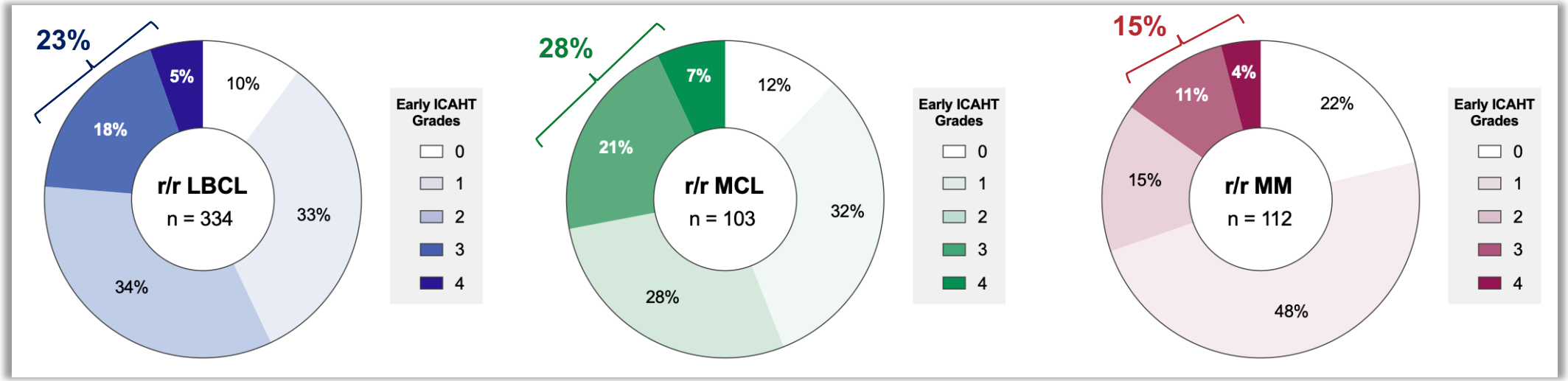
Advantages of the ICAHT grading – Harmonized Reporting

Disease-specific differences in the severity of hematologic toxicity

Multicenter Retrospective Observational Study

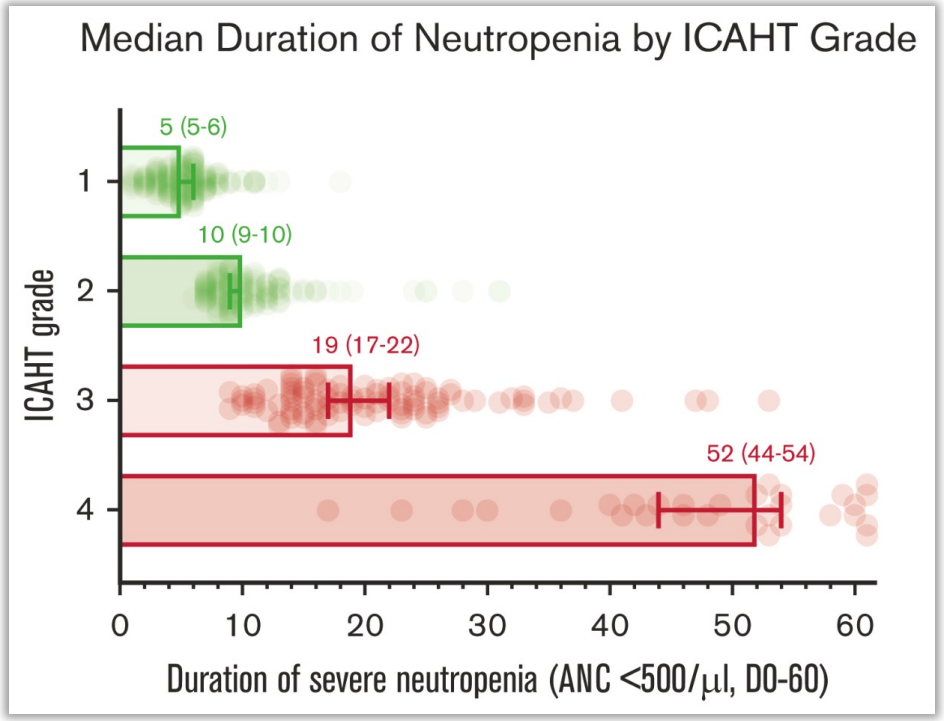
CD28z 4-1BB

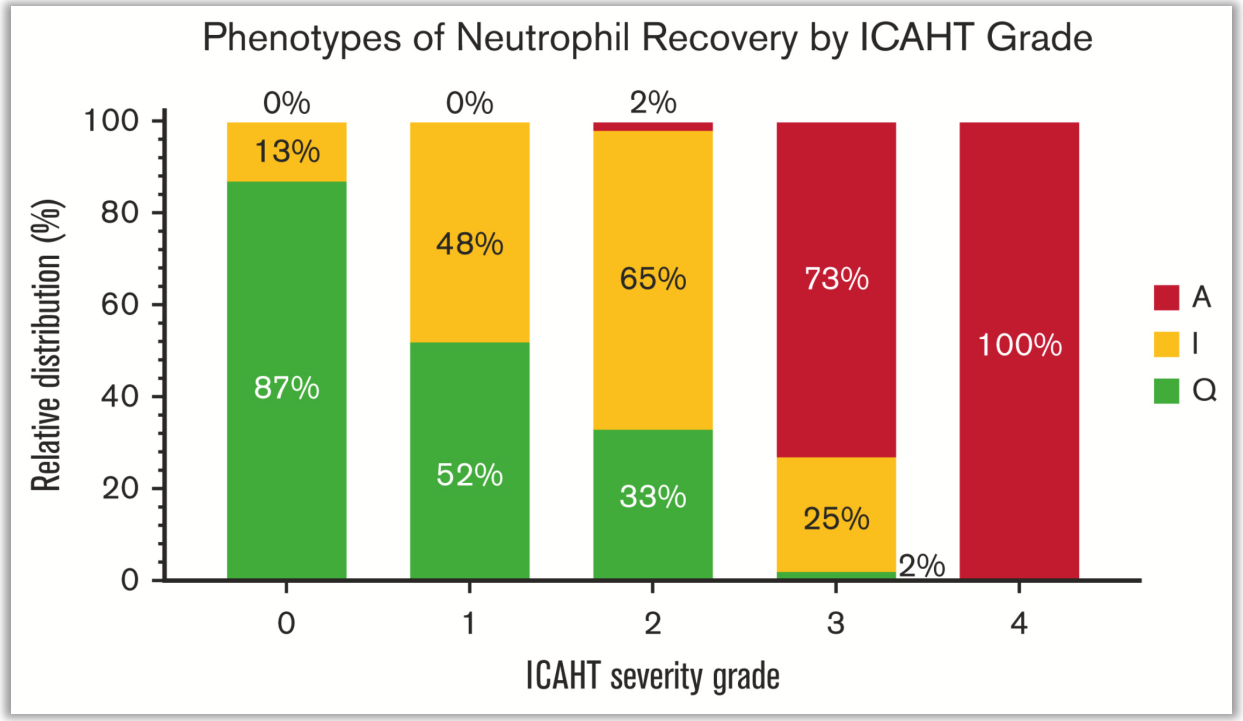
334 r/r **LBCL patients** (*Rejeski et al. Sci Adv 2023*)		103 r/r **MCL patients** (*Rejeski et al. Am J Hematol 2023*)	112 r/r **MM patients** (*Rejeski & Hansen et al. J Hematol Oncol 2023*)	
203 Axi-cel	131 Tisa-cel	103 Brexu-cel	105 Ide-cel	7 Cilta-cel



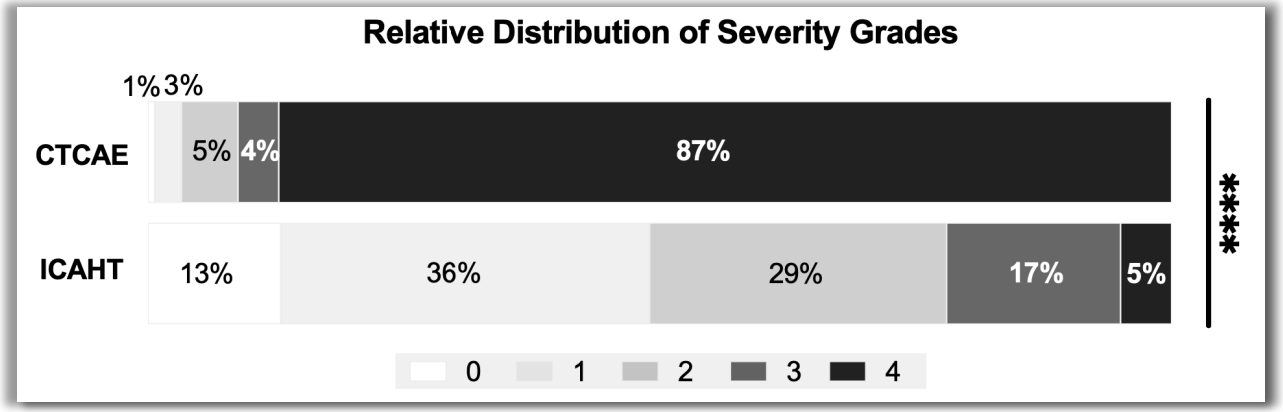
EHA/EBMT Consensus Grading of ICAHT

Severe ICAHT associated with **prolonged neutropenia** and **aplastic phenotype**

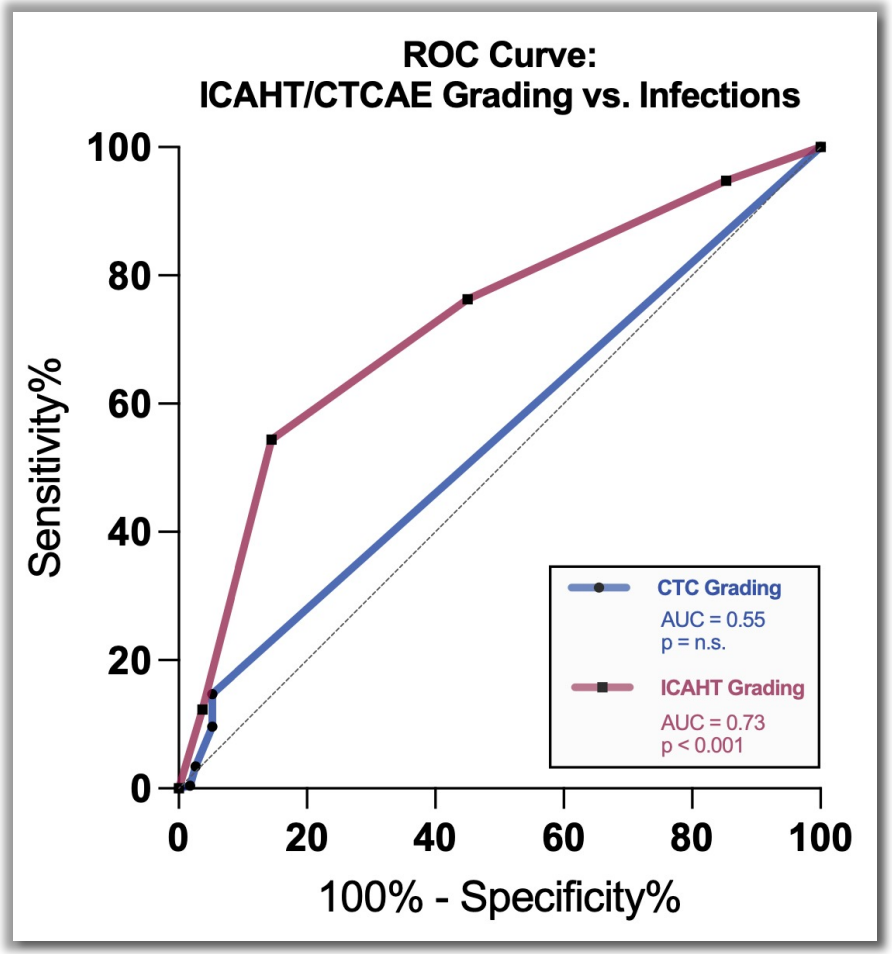




Superior discrimination for severe infections for ICAHT vs. CTCAE



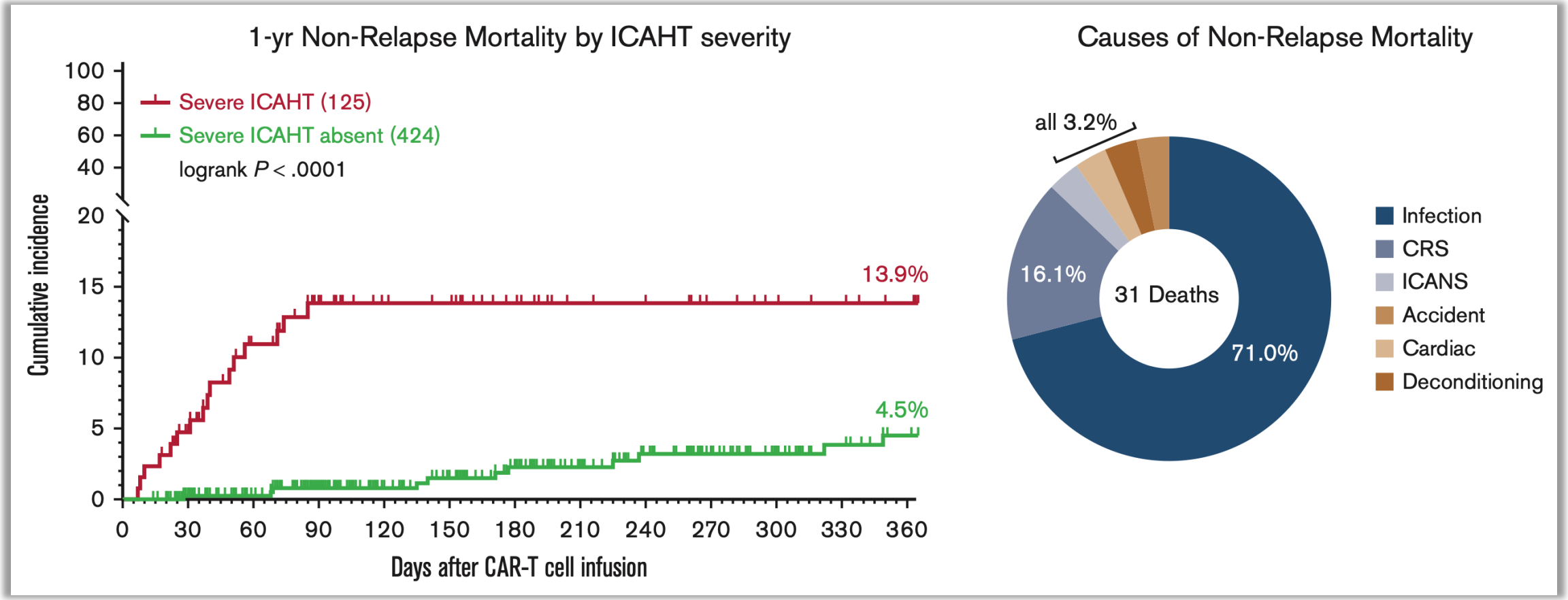
- One of the major deficits of the current CTCAE grading lies in the fact that the **overwhelming majority of CAR-T patients display grade 3-4 neutropenia (>90%).**
- A grading system wherein essentially all patients are classified as having severe hematotoxicity once a certain count threshold is met is **not particularly useful in clinical practice.**



Rejeski et al, Blood Adv 2024

ICAHT Grading and Non-Relapse Mortality (NRM)

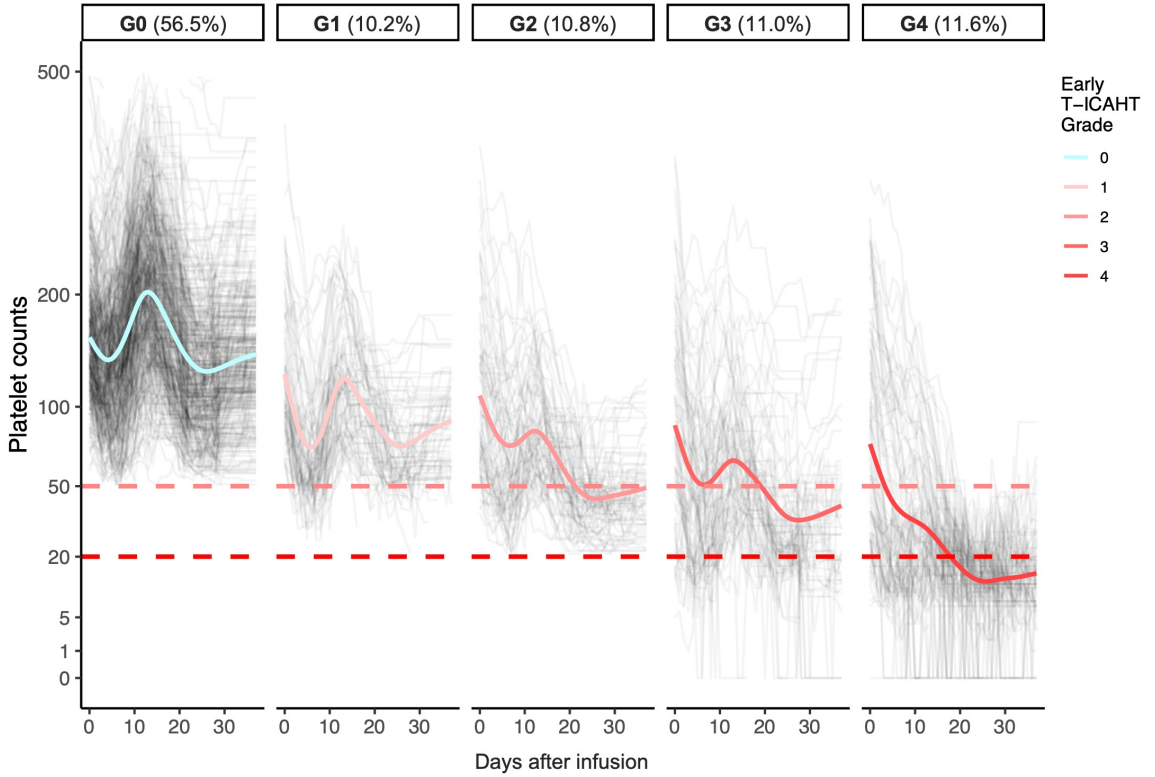
Severe ICAHT is associated with increased **infection-driven NRM**



What about Thrombocytopenia?

Development of T-ICAHT as a **Prognostically Relevant** Grading System

Grading	I	II	III	IV
Early T-ICAHT (day 0-30)				
PLT Count <50 G/L	1-6 days	≥7 days	-	-
PLT Count <20 G/L	-	-	1-13 days	≥14 days
Late T-ICAHT (after day +30)*				
PLT Count <100 G/L	≥1 day	-	-	-
PLT Count <50 G/L	-	≥1 day	-	-
PLT Count <20 G/L	-	-	1-13 days	≥14 days



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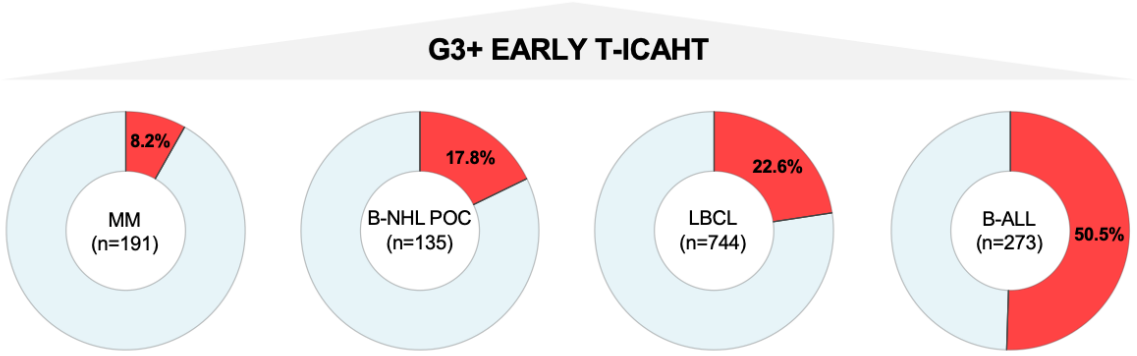
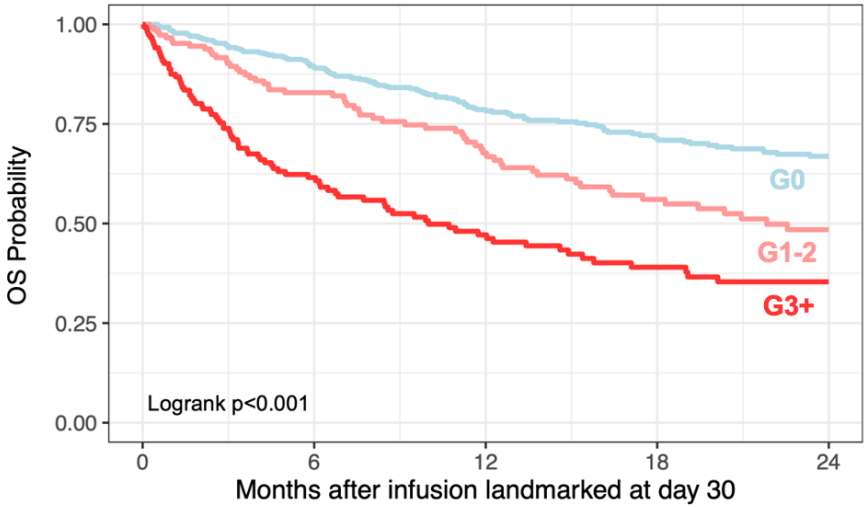
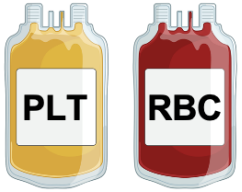


Independently associated with inferior survival outcomes





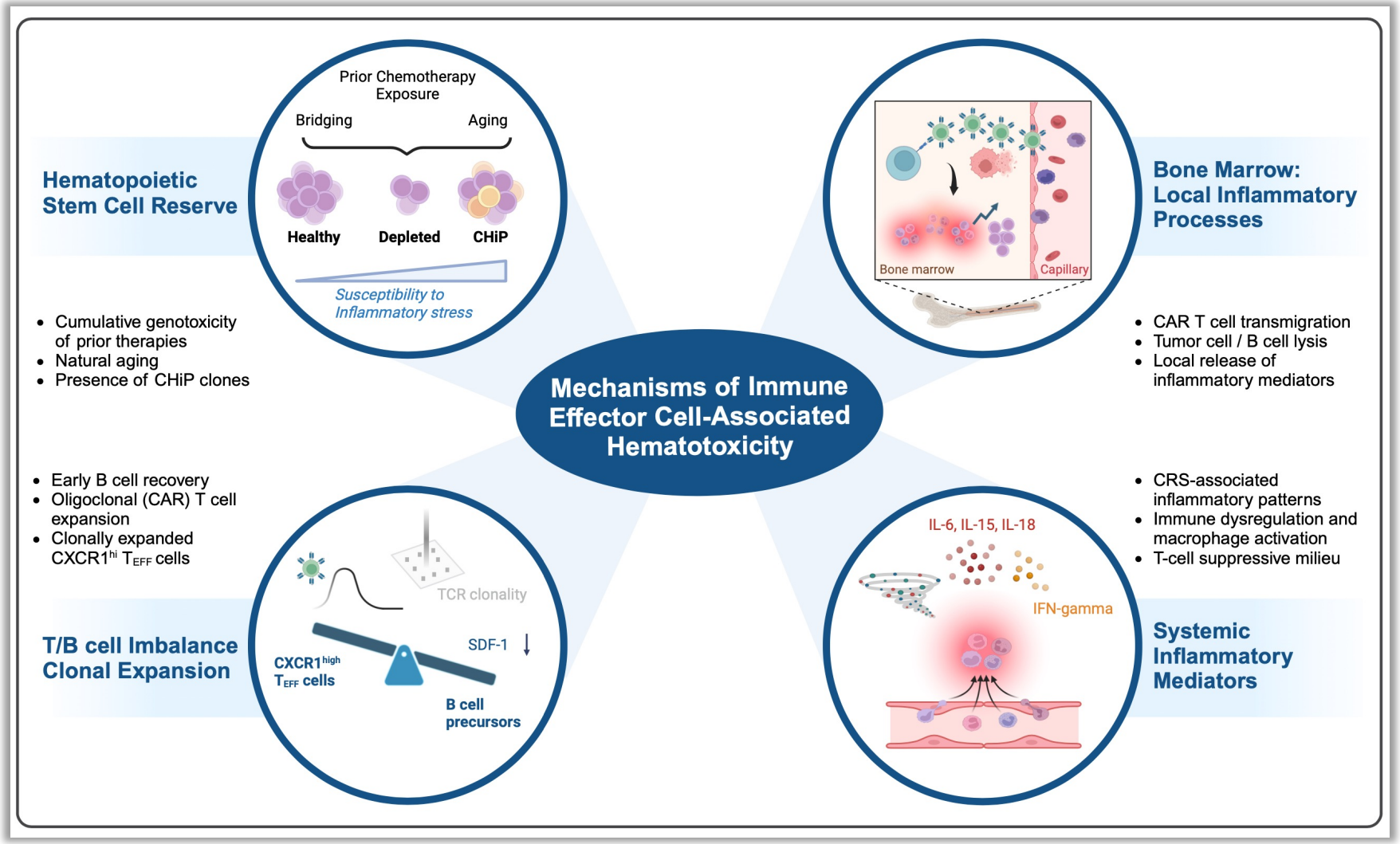
Increased Transfusion Burden

Increased Bleeding Events

Multifactorial pathogenesis of Immune Effector Cell-Associated Hematotoxicity

- King; *Nat Rev Clin Onc 2011*
- de Haan; *Blood 2018*
- Jaiswal; *Science 2019*
- Gibson; *JCO 2017*
- Weeks; *Blood 2023*
- Miller; *Blood Adv 2021*
- Rejeski; *Blood 2021*
- Saini; *Bl. Canc. Discov 2022*
- Panagiota; *Hemasphere 2023*
- Hamilton; *ASH 2023*

- Fried; *BMT 2019*
- Rejeski; *Blood 2022*
- Strati; *Cell Rep Med 2023*



- Hay; *Blood 2017*
- Pinho; *Nat Rev MCB 2019*
- Dhodapkar; *Bl. Canc. Discov 2022*
- Logue; *Haematologica 2021*
- Kitamura; *Br J Haematol 2023*
- Ben Khelil; *STM 2025*

- Leimkühler; *Hematology 2019*
- Jain; *Blood Adv 2021*
- Rejeski; *Blood 2021*
- Juluri; *Blood Adv 2022*
- Read; *TCT 2023*
- Rejeski; *Sci Adv 2023*
- Palacios-Berraquero; *Blood Adv 2024*
- Frigault; *Blood 2024*

Agenda – Understanding Mortality Drivers of CAR-T

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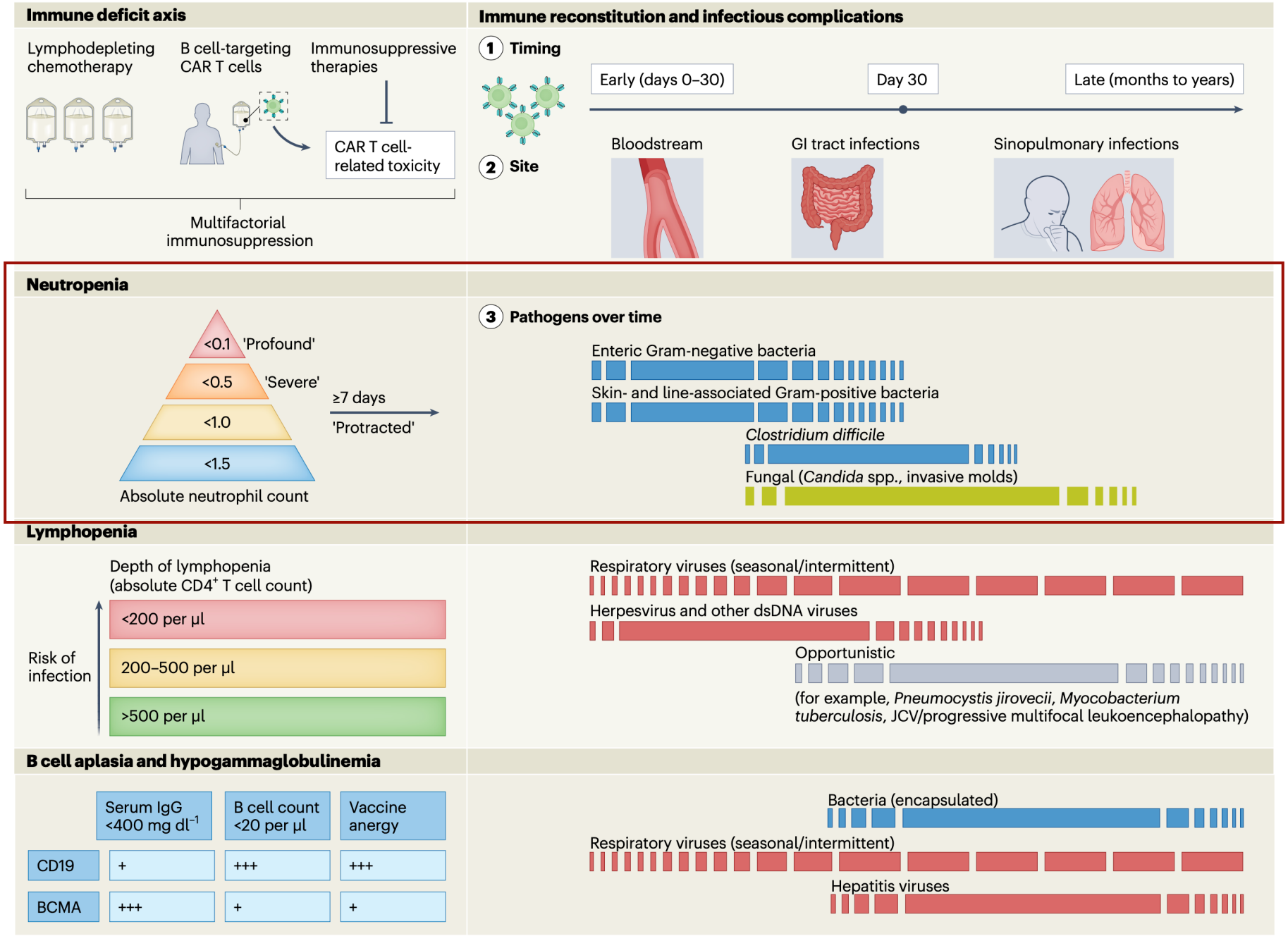
The Net State of Immunosuppresion with CAR T-cell therapy:

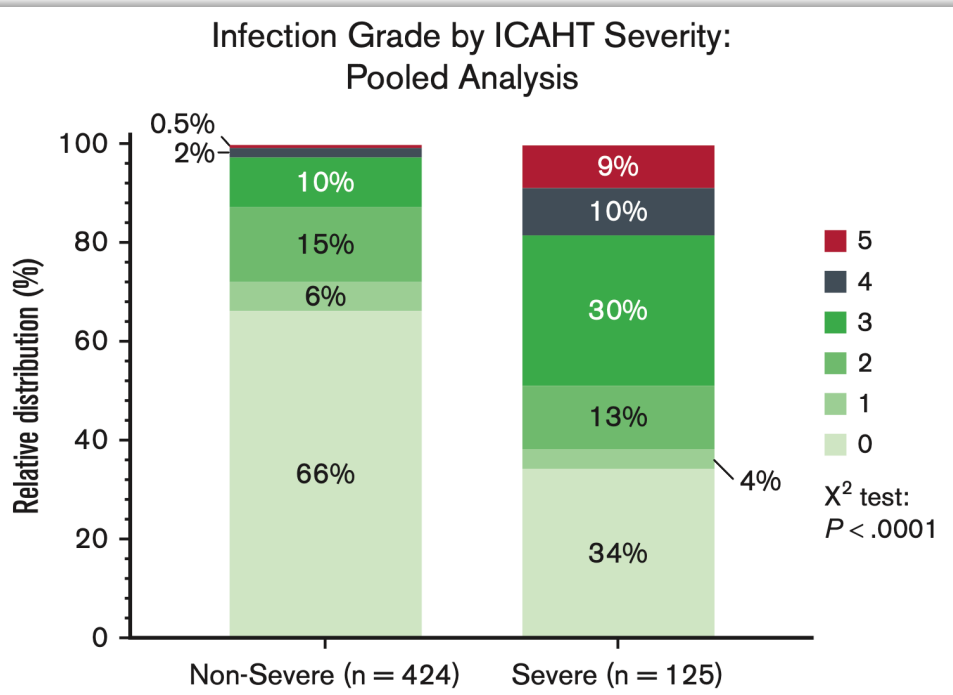
Major immune deficits and associated infectious sequalae following CAR-T therapy

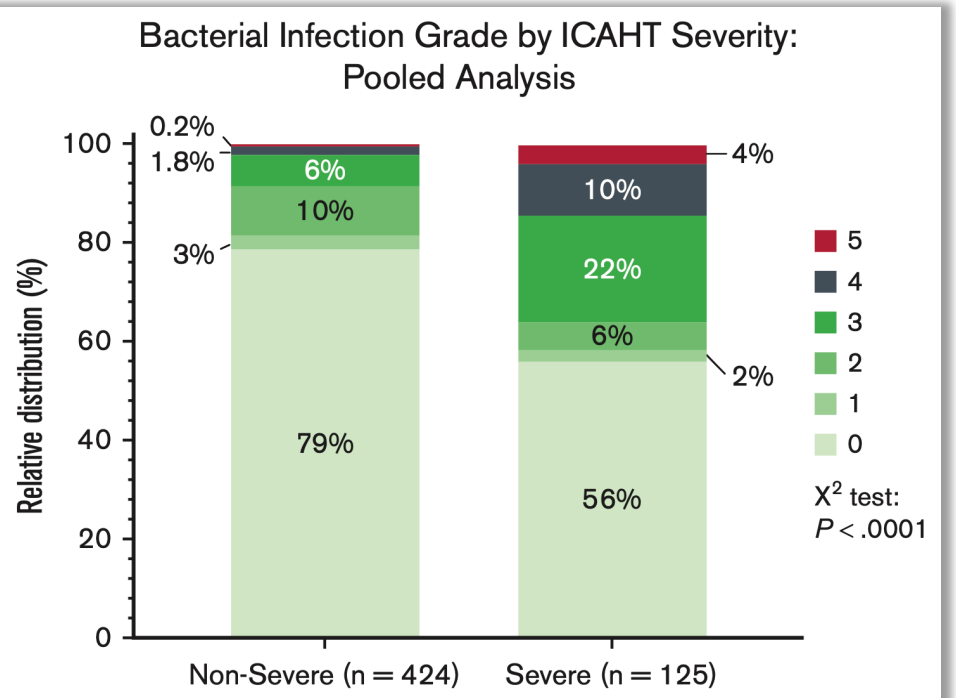


Rejeski et al, Nature Medicine 2025

EHA/EBMT ICAHT Grading and Infectious Complications

Severe ICAHT closely linked to severe infections, particularly bacterial infections





	Severe (≥3°) Infection Rate	Severe (≥3°) Bacterial Infection Rate	*P*
Severe ICAHT (≥3°)	61/125 (49%)	45/125 (36%)	Both < .0001
Absent or mild to moderate ICAHT (0-2°)	54/424 (13%)	36/424 (8%)	

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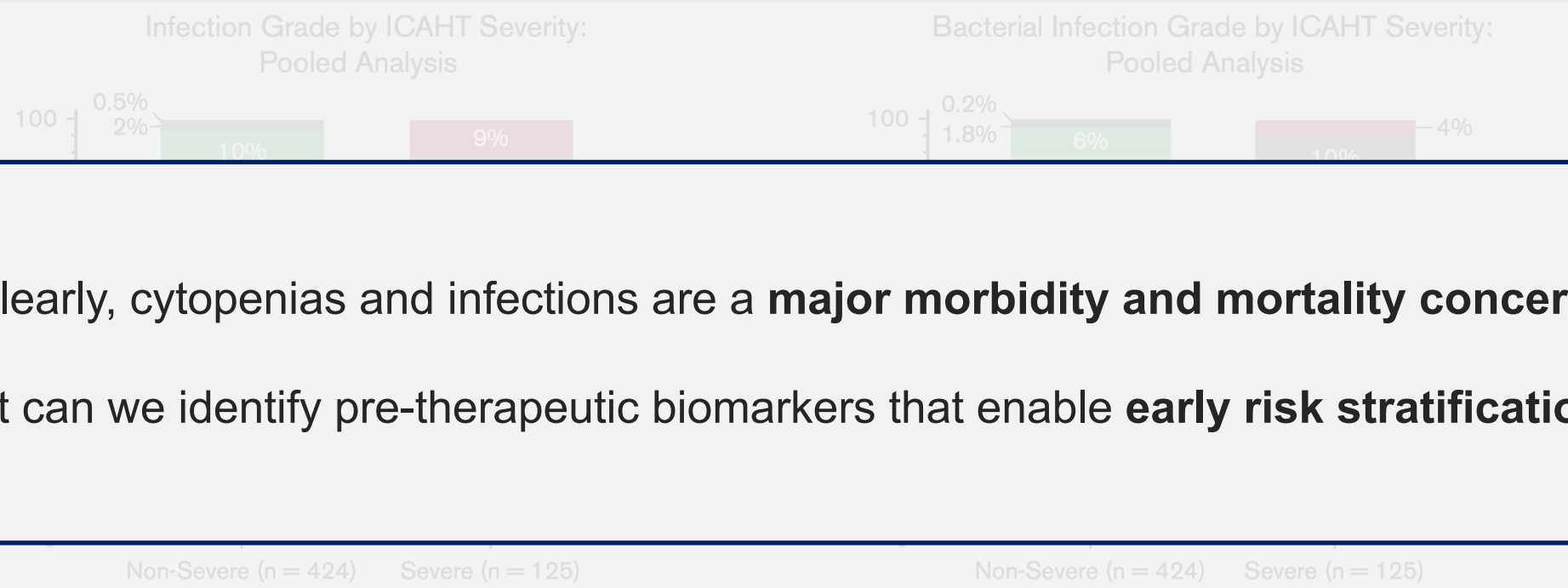

Clearly, cytopenias and infections are a **major morbidity and mortality concern.**

But can we identify pre-therapeutic biomarkers that enable **early risk stratification**?

	Severe (≥3°) Infection Rate	Severe (≥3°) Bacterial Infection Rate	*P*
Severe ICAHT (≥3°)	61/125 (49%)	45/125 (36%)	Both < .0001
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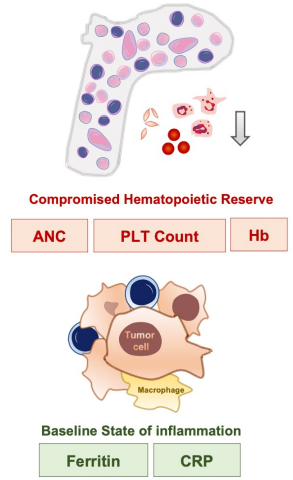
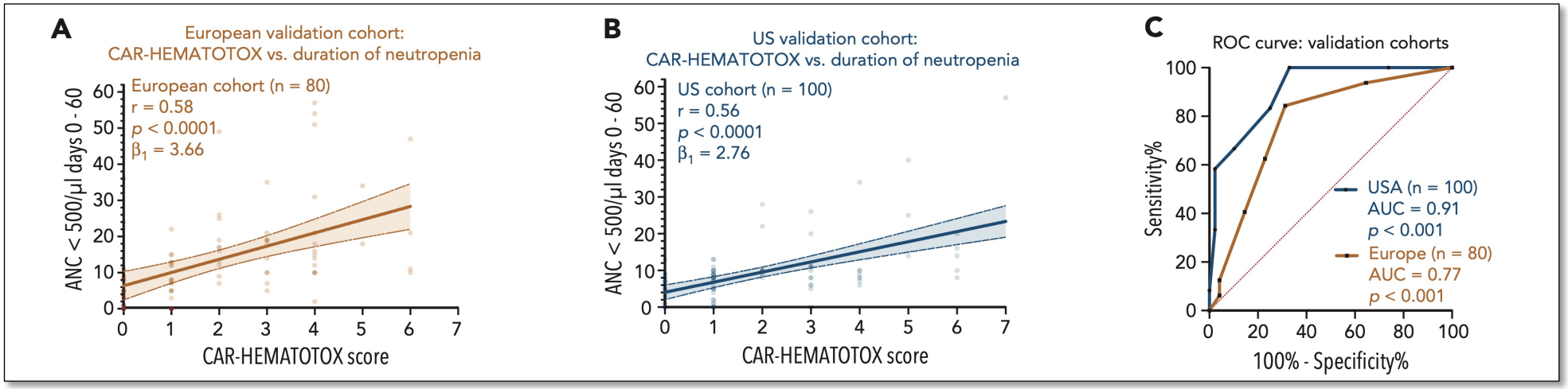
Pre-Lymphodepletion Risk Stratification

The CAR-HEMATOTOX score: low (0-1 points) vs high (2-7 points)

Features	0 Point	1 Point	2 Points
Platelet Count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml

Low: 0-1 **High: ≥ 2**

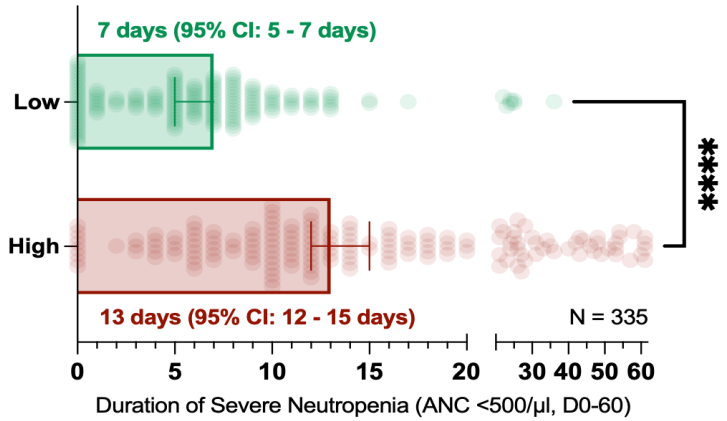


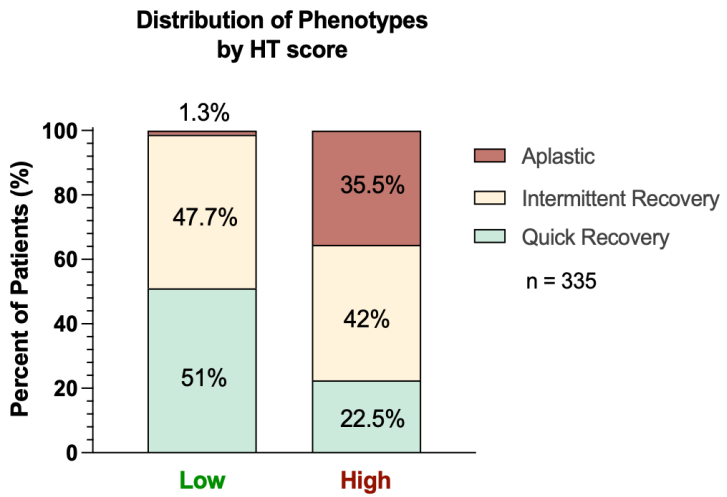


Rejeski et al, Blood 2021

CAR-HEMATOTOX in LBCL & MCL & MM: duration of neutropenia & phenotypes

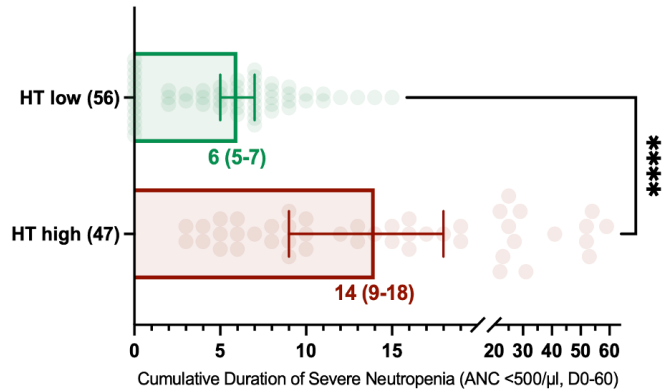
r/r LBCL

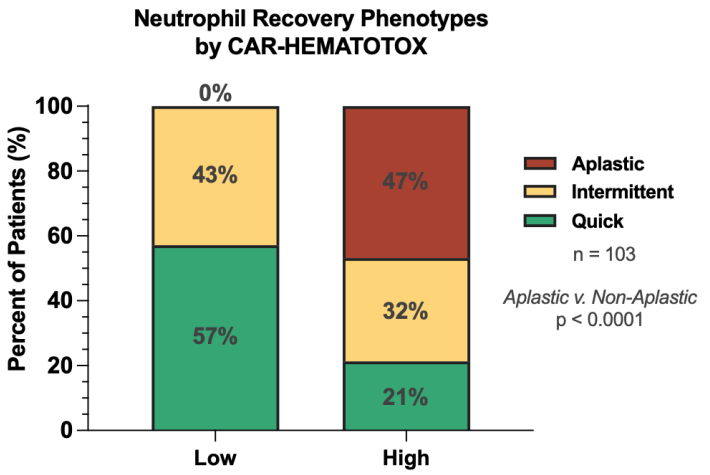




Rejeski et al, Blood 2021 & DGHO 2021

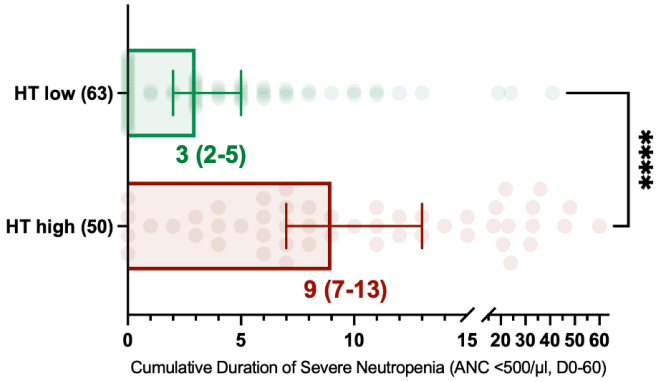
r/r MCL

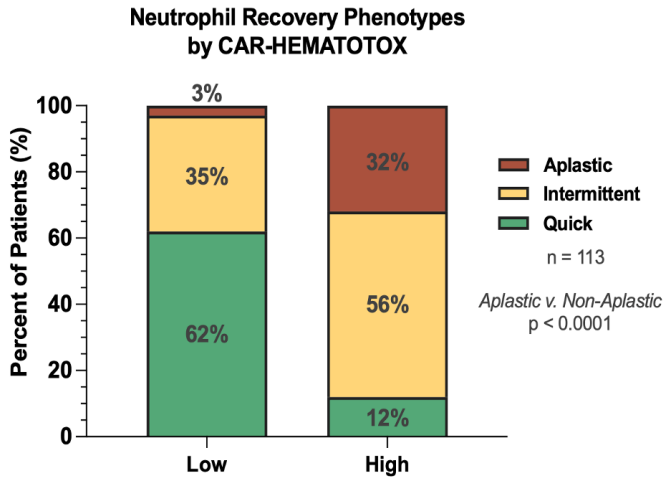




Rejeski et al, Am J Hematol 2023

r/r MM





Rejeski & Hansen et al, J Hematol Onc 2023

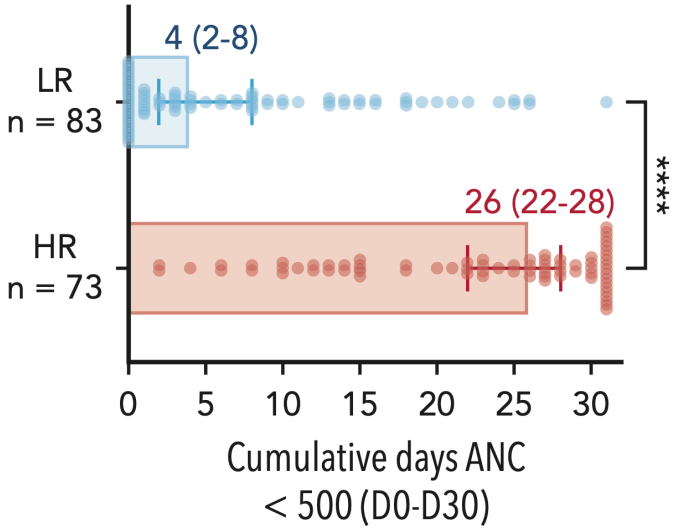
Adapting and Developing the ALL HEMATOTOX for adult and pediatric B-ALL

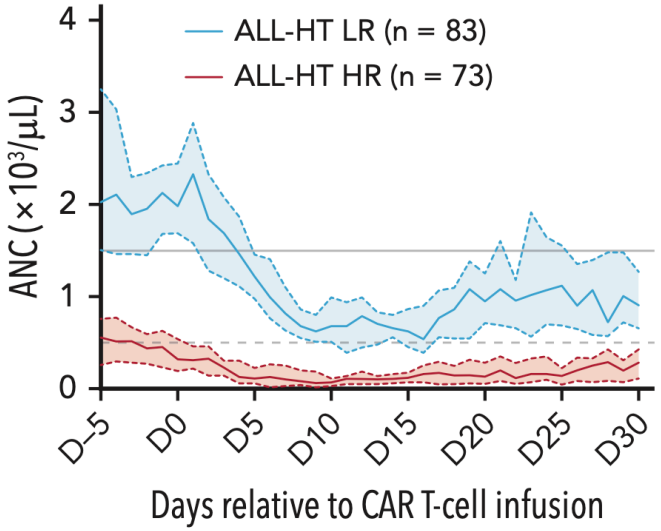
ALL-HT	0 point	1 point	2 points
Platelet Count	> 175,000/µL	75,000-175,000/µL	<75,000/µL
Absolute Neutrophil Count	> 1200/µL	≤ 1200/µL	
Hemoglobin	> 9 g/dL	≤ 9 g/dL	
C-reactive Protein	< 3 mg/dL	≥ 3 mg/dL	
Bone Marrow Disease	< 5%	5-25%	> 25%
Low Risk: <4 High Risk: ≥4			

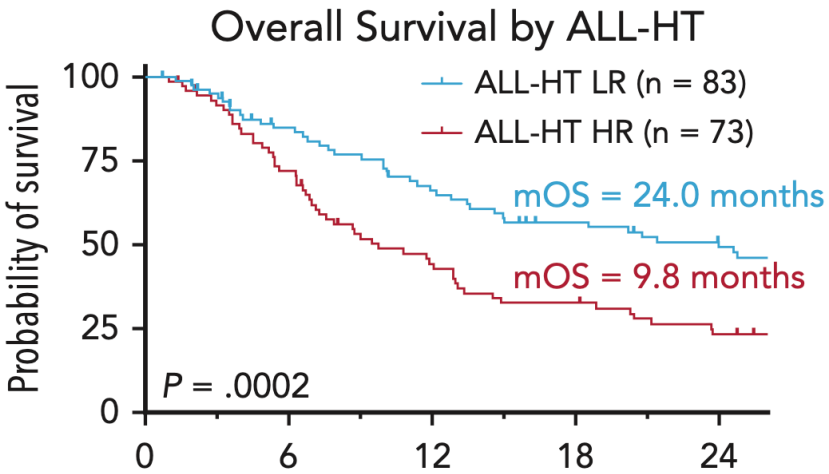
Rationale:
Using the traditional score essentially all patients were classified as being high risk. Almost all B-ALL patients had relevant elevations of ferritin.

→ BM Blast % instead of serum ferritin

→ Higher discriminatory threshold of 4 instead of the previous 2

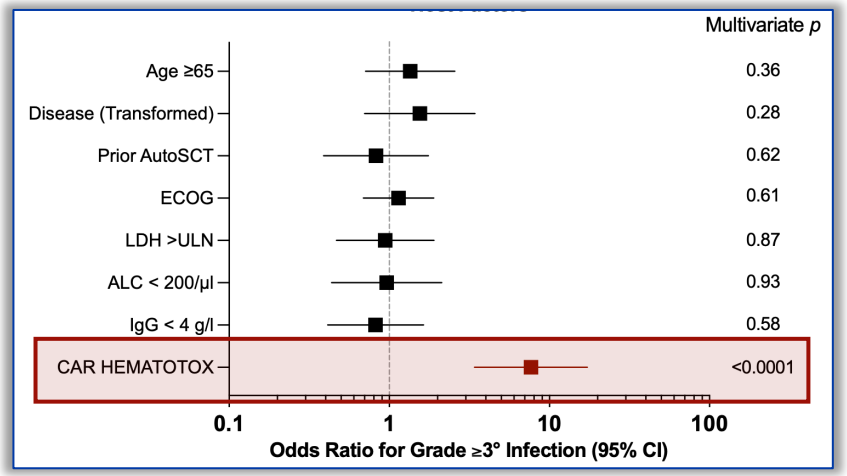




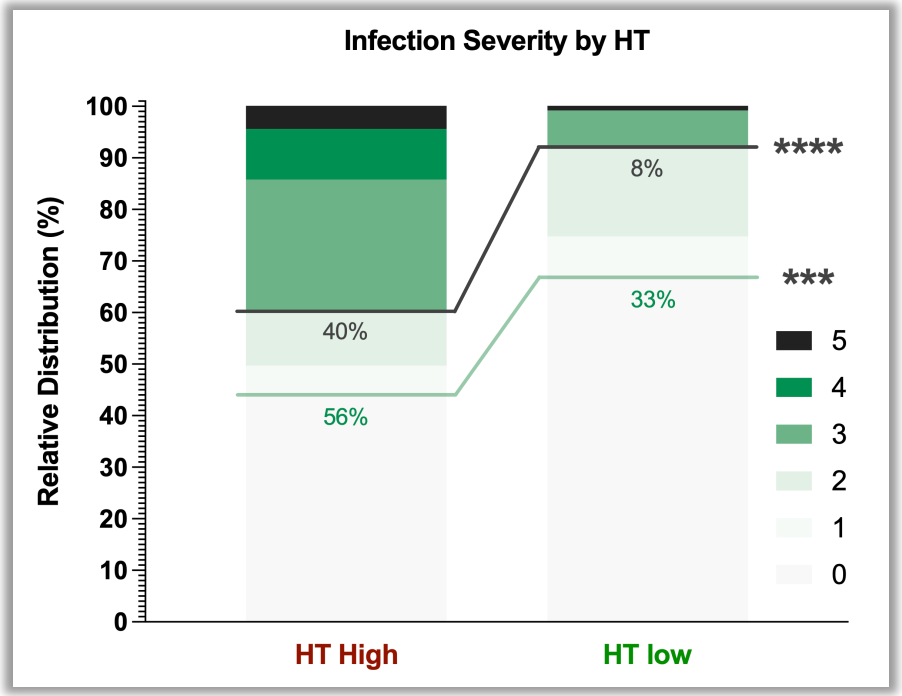


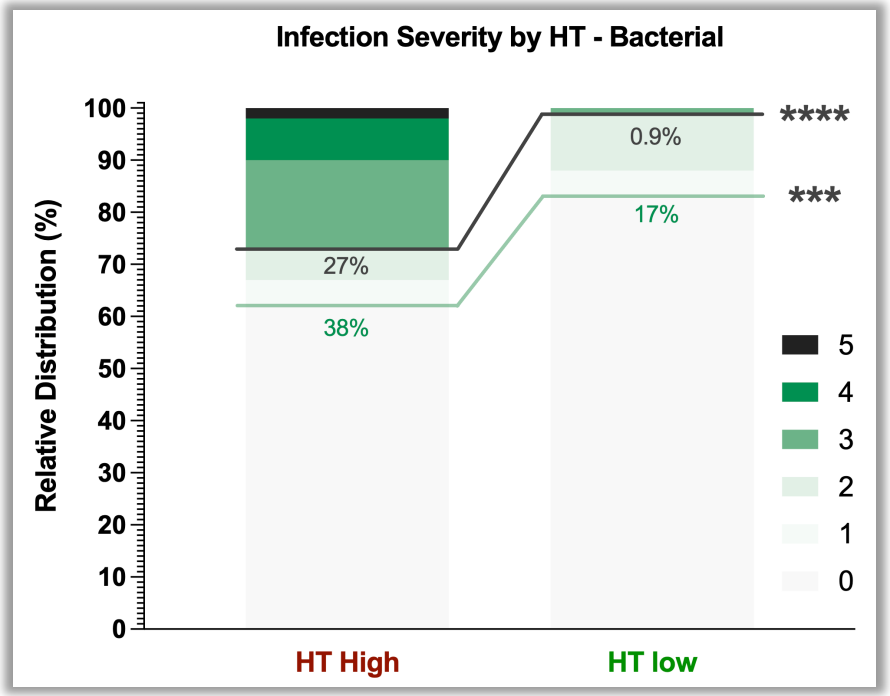
Nair*, Silbert*, Rejeski* et al, Blood 2025

The HT score represents an independent risk factor for severe infections



- **HT score: only pre lymphodepletion risk factor for severe infections**
  - adjusted OR = 7.7, 95% CI 3.4 – 17.3





Rejeski et al, JITC 2022

Exploring HT-adapted anti-infective strategies for antibiotic stewardship (HT^{low}) and mitigating infection risk (HT^{high})

STEP 1 Assess **individual risk profile** for heme-tox and infections using the CAR-HEMATOTOX score

When ? → ***Prior to lymphodepletion*** *(day -5 +/- 3 days)*

Features	0 Point	1 Point	2 Points
Platelet Count	> 175.000/µl	75.000 - 175.000/µl	< 75.000/µl
Absolute Neutrophil Count (ANC)	> 1200/µl	< 1200/µl	-
Hemoglobin	> 9.0 g/dl	< 9.0 g/dl	-
C-reactive protein (CRP)	< 3.0 mg/dl	> 3.0 mg/dl	-
Ferritin	< 650 ng/ml	650-2000 ng/ml	> 2000 ng/ml
Low: 0-1 **High: ≥ 2**			

Risk Profile*

Low Risk (HT 0-1)

	LBCL (n=235)	MCL (n=103)	MM (n=113)
Median duration of severe neutropenia (ANC<500/µL)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
Aplastic Phenotype	2.6%	0%	3%
Severe Infection Rate	8%	5%	5%
Severe Bacterial Infection Rate	0.9%	5%	3%

High Risk (HT 2-7)

	LBCL (n=235)	MCL (n=103)	MM (n=113)
Duration of severe neutropenia (ANC <500/µL)	12 days (95% CI 10-16 days)	14 days (95% CI 9-18 days)	9 days (95% CI 7-13 days)
Aplastic Phenotype	36%	47%	32%
Severe Infection Rate	40%	30%	40%
Severe Bacterial Infection Rate	27%	28%	34%

*Rejeski et al, Blood 2021; JITC 2022; J Hematol Oncol 2023; Am J Hematol 2023; **Lievin et al, BMT 2022; Miller et al, Blood Cancer Journal 2022

Practical Considerations: GLA Calculator of the CAR-HEMATOTOX Score

CAR-HEMATOTOX

When To Use | Pitfalls | Why Use

Background

Hematological toxicity represents a frequent adverse event after chimeric antigen receptor (CAR) T-cell therapy, and can predispose for severe infectious complications. Determined **prior to lymphodepleting chemotherapy (e.g. day -5)**, the CAR-HEMATOTOX score comprises five markers of hematotoxicity with additional weighting of the baseline platelet count and ferritin levels. The score discriminates between a high (CAR-HEMATOTOX score ≥2) and low (CAR-HEMATOTOX score 0-1) risk for hematotoxicity.

Please note that this score was established and validated only in patients with large B-cell lymphoma receiving Axicabtagene ciloleucel or Tisagenlecleucel in a real-world setting. The model was validated in two independent patient cohorts and discriminated patients with severe neutropenia ≥14 days vs. <14 days (pooled validation: AUC 0.89, sensitivity 89%, specificity 68%).

For details see CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. *Rejeski et al. Blood (2021) 138 (24): 2499-2513.*

In a multi-center follow-up study, the score further identified patients at risk for severe infections and disease progression: The CAR-HEMATOTOX risk-stratifies patients for severe infections and disease progression after CD19 CAR-T for R/R LBCL. *Rejeski et al. J Immunother Cancer (2022) May; 10 (5): e004475.*

Calculator

Here you can calculate the CAR-HEMATOTOX score and the resulting risk group (high versus low). By using this calculator, you accept that the GLA does not assume any liability.

Platelet Count	please select...
Absolute Neutrophil Count (ANC)	please select...
Hemoglobin	please select...
C-reactive protein (CRP)	please select...
Ferritin	please select...

CAR-HEMATOTOX score ---

Please select input...

Fenster schließen

Platelet Count	75,000 - 175,000 /µl
Absolute Neutrophil Count (ANC)	< 1,200 /µl
Hemoglobin	> 9.0 g/dl
C-reactive protein (CRP)	> 3.0 mg/dl
Ferritin	650 - 2,000 ng/ml

CAR-HEMATOTOX score 4

Patient belongs to CAR-HEMATOTOX *high* risk group.

Hematological Toxicity	
Median duration of neutropenia (days 0-60)	12 days (95% CI: 10-16 days)
Severe neutropenia (ANC <500/µl)	99%
Profound neutropenia (ANC <100/µl)	89%
Severe, protracted neutropenia (ANC <500/µl, ≥7 days)	88%
Profound, protracted neutropenia (ANC <100/µl, ≥7 days)	47%
Prolonged neutropenia (ANC <1000/µl after day 21)	81%
Severe thrombocytopenia (PLT count <50 G/l)	87%
Severe anemia (Hb <8 g/dl or requiring pRBC)	96%

Infectious Complications (Day 0-90)	
Infection Rate, Any-Grade	56%
Infection Rate, Severe (Grade ≥3)	40%
Infection Rate, Any-Grade Bacterial	38%
Infection Rate, Severe (Grade ≥3) Bacterial	27%

Clinical Outcomes	
Median Progression-Free Survival	3.4 months (95% CI: 3.0 - 5.2 mo)
Median Overall Survival	9.1 months (95% CI: 7.4 - 17.6 mo)

Possible Next Steps
Consider antibacterial (e.g. fluoroquinolone) and antifungal prophylaxis
Consider early G-CSF growth factor support

https://www.german-lymphoma-alliance.de/box.php?action=box.boilerplate.detail&site=scores&boilerplatePk=E4F11B34-59F8-E79A-E4E0-28BA86EAB60A

Exploring HT-adapted anti-infective strategies for antibiotic stewardship (HT^{low}) and mitigating infection risk (HT^{high})

STEP 2 **Risk-adapted** management strategies for anti-infective prophylaxis and G-CSF

Low Risk (HT 0-1)

	LBCL (n=235)	MCL (n=103)	MM (n=113)
Median duration of severe neutropenia (ANC<500/µL)	5.5 days (95% CI 5-8 days)	6 days (95% CI 5-7 days)	3 days (95% CI 2-5 days)
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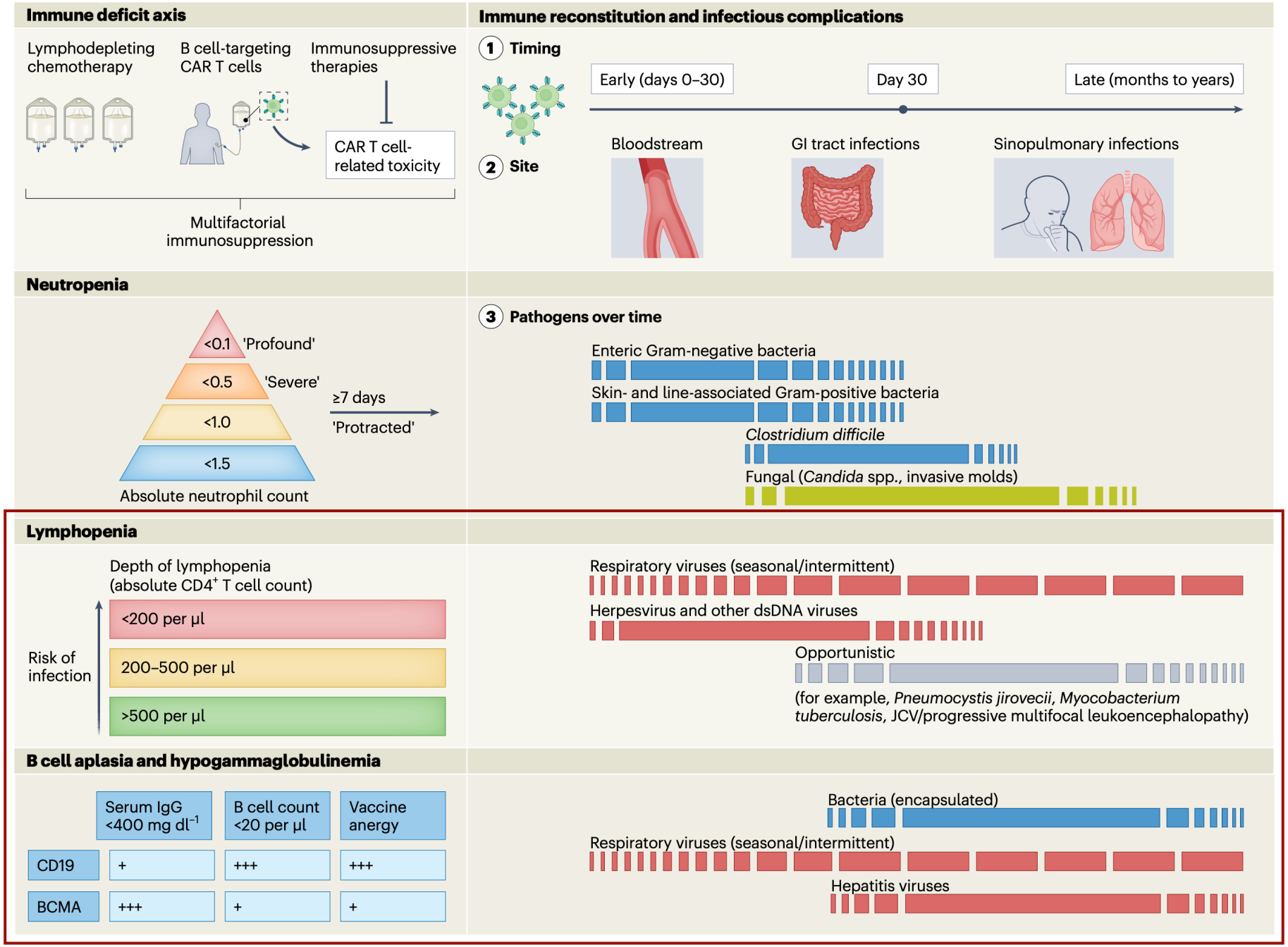
Aplastic Phenotype	36%	47%	32%
Severe Infection Rate	40%	30%	40%
Severe Bacterial Infection Rate	27%	28%	34%

✗	Only in case of prolonged neutropenia	**G-CSF***	Start of Day +2	✓
✗		**Antibacterial Ppx**	Ciprofloxacin *or* Levofloxacin p.o. when ANC < 0.5 G/l	✓
✗		**Antifungal Ppx**	Posaconazol p.o. *or* Micafungin i.v. when ANC < 0.5 G/l	✓

*Rejeski et al, Blood 2021; JITC 2022; J Hematol Oncol 2023; Am J Hematol 2023; **Lievin et al, BMT 2022; Miller et al, Blood Cancer Journal 2022

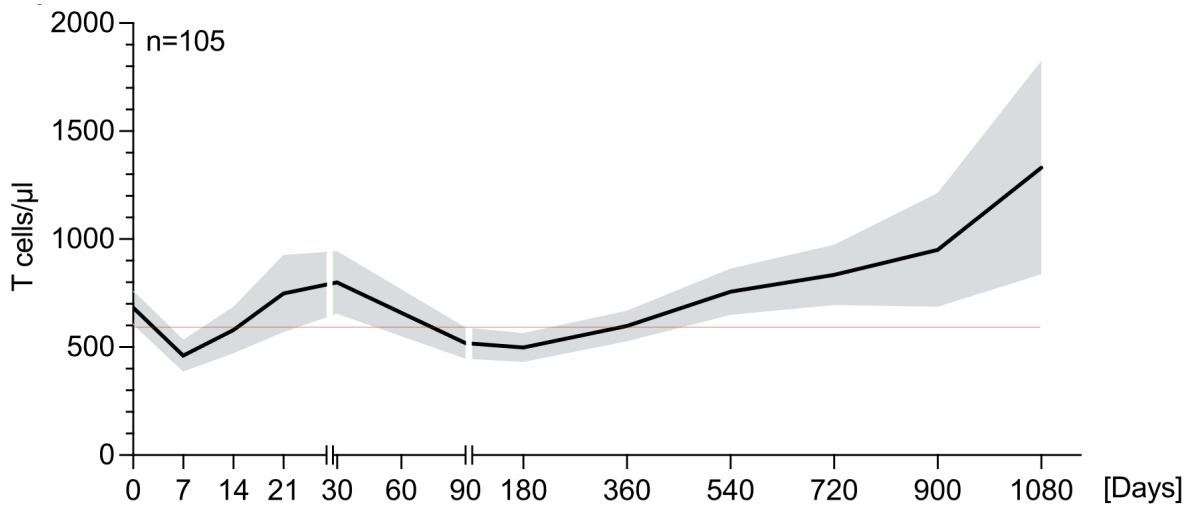
The Net State of Immunosuppresion with CAR T-cell therapy:

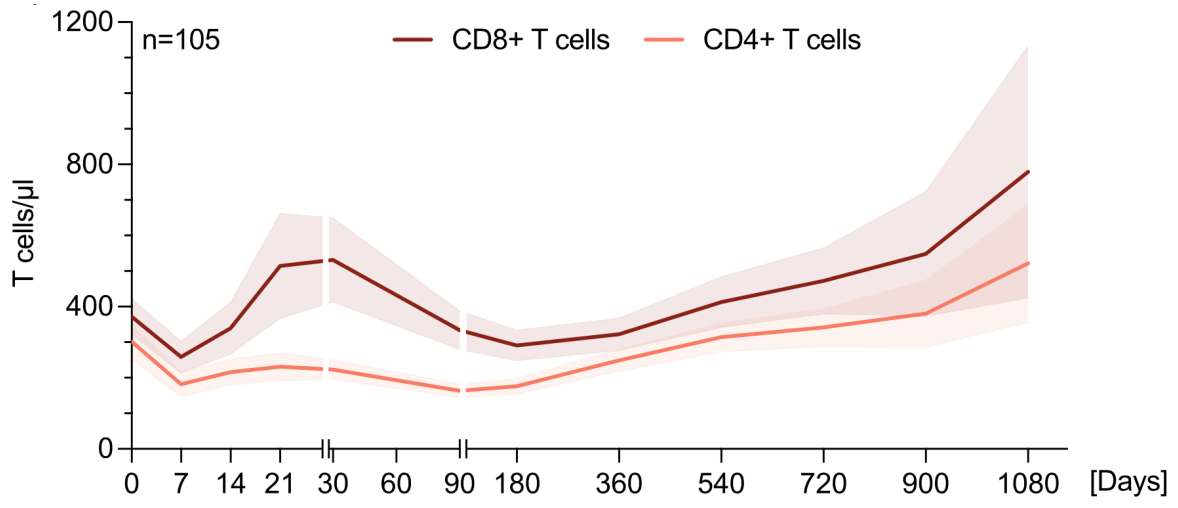
Major immune deficits and associated infectious sequelae following CAR-T therapy

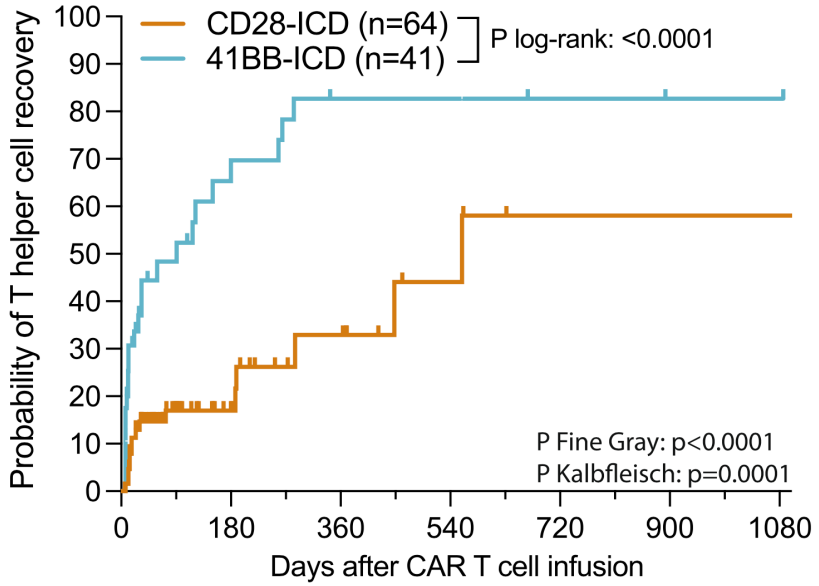


Rejeski et al, Nature Medicine 2025

T-cell lymphopenia can persist for months to years after CAR-T infusion

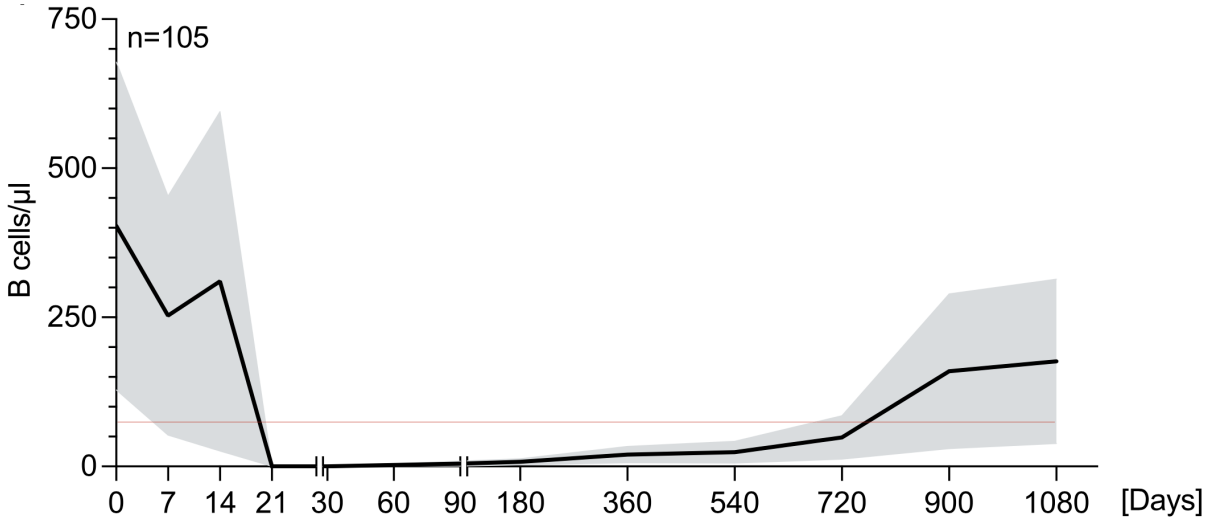


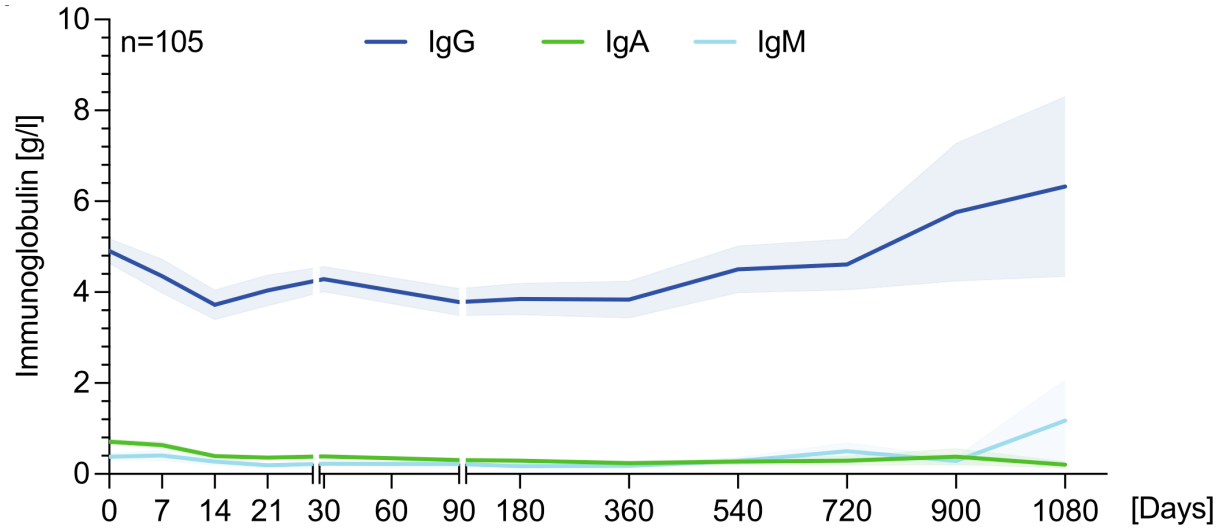


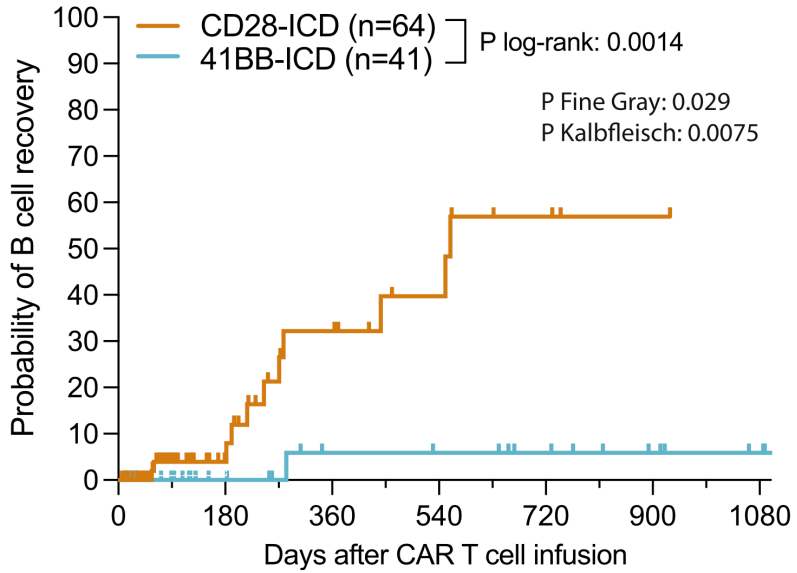


More extensive with CD28z CART
→ Deeper Lymphodepletion?

B-cell aplasia is an expected on-target / off-tumor side effect of B cell directed CAR-T







More extensive with 4-1BBz CART
→ Functional readout of CAR persistence?

Immune deficits can be long-lasting and are prognostically relevant

Three key IR criteria were defined as:

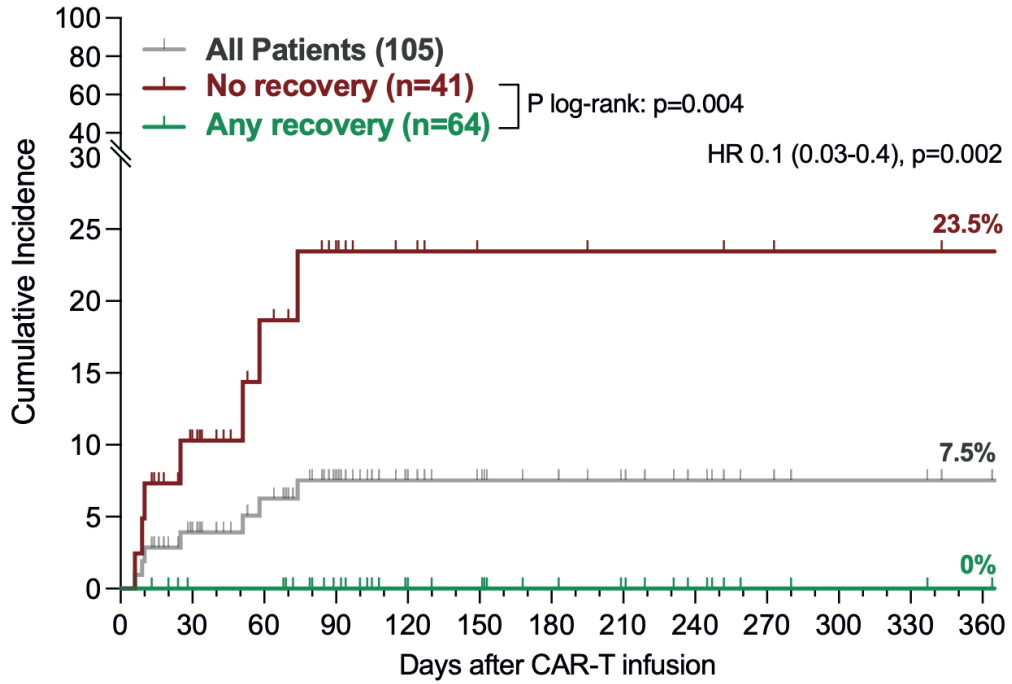
(1) CD4$^+$ T helper (T_H) cell count above >200/µL,

(2) B-cell recovery defined as any detectable B cells,

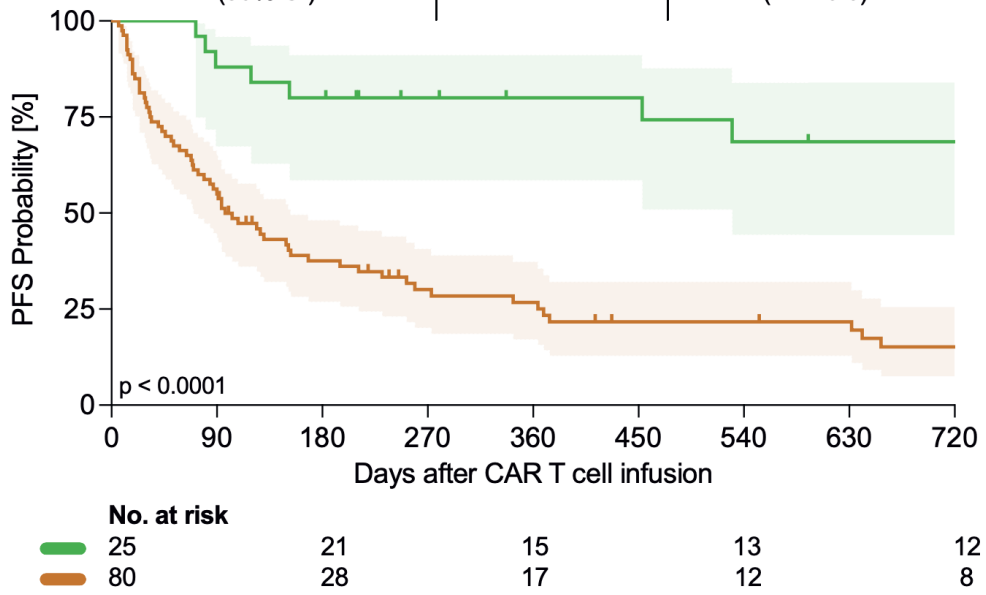
(3) IgG recovery defined as >4 g/L.

LMU Experience

1-yr NRM

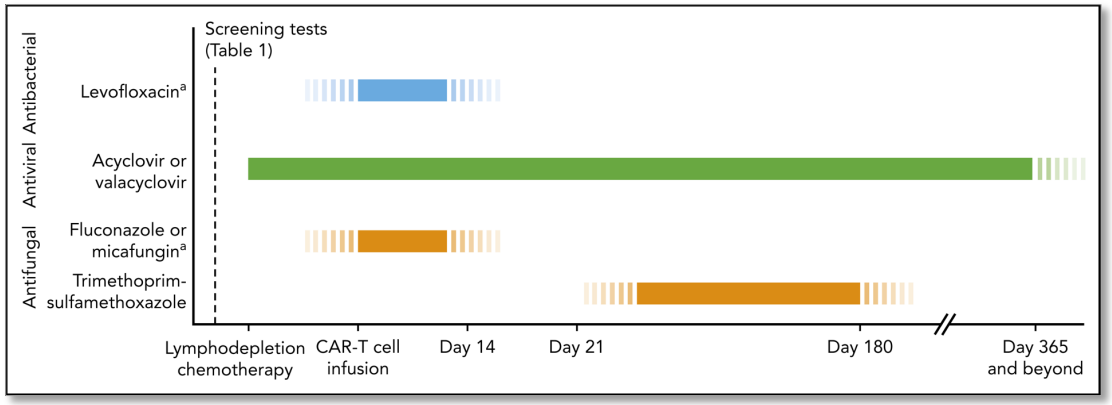


Median	2-3 criteria	0-1 criteria
Median PFS [months]	not reached	3.2
1-yr PFS rate (95% CI)	80% (54.4-91.2%)	26.7% (17-37.3%)
HR (95% CI)	-	4.7 (2.4-10.6)



Minimizing Long-term Infection Risks: Prophylaxis, IVIG, Vaccination

STEP 3 Continued **vigilance** for infectious complications and **survivorship care** (day +30 and beyond)



Prophylactic Agents:

- Antibacterial: risk-adapted during neutropenia phase
- Antiviral: until immune reconstitution (CD4 T_H >200/µL)
- Antifungal: risk-adapted during neutropenia phase
- PjP: until immune reconstitution (CD4 T_H >200/µL)

Prophylactic Immunglobulin Replacement Therapy (IGRT)

- Increased risk of recurrent infections esp. **sino-pulmonary infections** (encapsulated bacteria, viral infections)
- Treatment effect needs to be weighed with the associated financial **cost**, potential **side effects**, and **logistical challenges.**

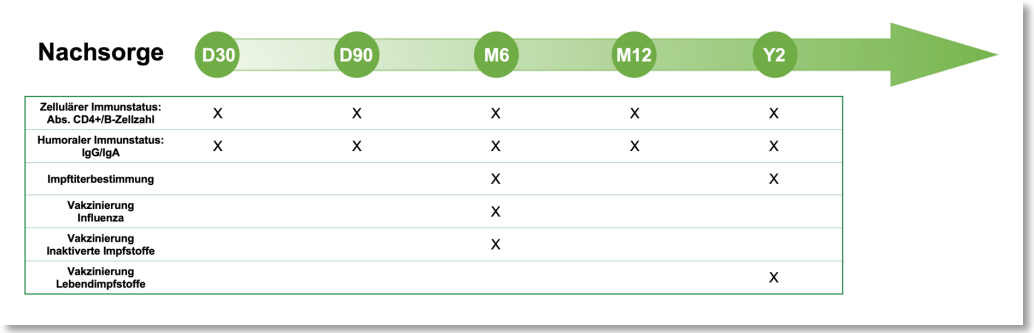
Serum IgG <4 g/L + Severe or Recurrent Infections (esp. bacterial)

IVIg or SCIg as per institutional standards and availability

Hill JA, Seo SK, Blood. 2020 Aug 20;136(8):925-935

Minimizing Long-term Infection Risks: Prophylaxis, IVIG, Vaccination

STEP 3 Continued **vigilance** for infectious complications and **survivorship care** (day +30 and beyond)



Develop an infection prevention plan

- Regular monitoring of cellular and humoral immune status
- Check vaccination titers
- From month 6 onward + immune reconstitution: plan re-vaccination

CAR Nachsorge: Impfschema

Inaktivierte/Todimpfstoffe [1]	PRÄ-CART	≥ 6. Monat	≥ 6. Monat	≥ 7. Monat	≥ 8. Monat	≥ 10. Monat	≥ 12. Monat	≥ 18. Monat	≥ 20. Monat	LMU / Extern: Minimales Zeitinterval zwischen Impfungen
Influenza [2] (quadrivalenter WHO-Impfstoff)	**FLU** *Empfehlung Umfeldimpfung*		**FLU**							
13-valenter **Pneumokokken** Konjugatimpfstoff		*Titer*	**PCV13**	*Titer* [3]	**PCV13** [3]	**PCV13** [3]				1-2 Monate
23-valenter **Pneumokokken** Polysaccharidimpfstoff								**Pneumo-vax** [3]	*Titer*	
Diphtheria, Tetanus und Pertussis		*Titer*	**DTaP**	*Titer*	**Td**	**Td**	*Titer*			1-2 Monate
Hepatitis A/B Virus [4]		*Titer*	**HAV/HBV**	**HAV/HBV**			**HAV/HBV**	*Titer*		0, 1 und 6 Monate
Lebend- oder adjuvantierter Todimpfstoff [5]										
Varizella Zoster Virus (VZV) (adjuvantierter Todimpfstoff) (attenuierter Lebendimpfstoff) *Bei VZV-seropositiven Patienten ≥50*	*Titer*						**VZV**	**VZV**		

[1] Für inaktivierte „Totimpfstoffe" sollte die Impfung mindestens 2 Monate nach der letzten prophylaktischen i.v. Immunglobulin-Substitution erfolgen
[2] Influenza-Saison nach RKI: Anfang Oktober bis Mitte Mai. Sofern keine zytostatische Bridging-Therapie angewandt wird, ist eine saisonale Grippeimpfung bis zu 2 Wochen vor Lymphodepletion anzustreben. Jährliche Folgeimpfung sind nach immunologischer Rekonstitution frühestens nach 6 Monaten durchzuführen. Ebenso sollte das Familienumfeld zur jährlichen Influenza-Impfung ermutigt werden.
[3] Bei Seroprotektion nach 1. Impfung (definiert als: ≥ 2x Anstieg des Serotyp-spezifischen IgG im Vergleich zu vor der Impfung, bzw. s. Referenzlabor), keine weitere Impfung. Bei positiven Anstieg aber ausbleibender Seroprotektion, weitere Pneumokokkenimpfung. Bei Non-Response Überpüfen der Immunrekonstitutionskriterien.
[4] Höhere HBV Impfdosen (40 µg) werden in stark immunkompromittierten und Hämodialyse-Patienten empfohlen. Bei fehlendem Ansprechen kann eine 2. Reihe HBV-Impfreihe mit 3 Dosen empfohlen werden.
[5] Frühestens 1 Jahr nach CAR-T-Zelltherapie, > 2 Jahre nach Transplantation, >1 Jahr nach Ende jeglicher systemischen Immunsuppression, min. 8 Monate seit der letzten prophylaktischen i.v. Immunglobulin-Substitution, absolute CD4 T-Zellzahl ≥ 200/µl. Bei Z.n. allogener oder autologen Stammzelltransplantation sollten die entsprechenden RKI-Empfehlungen für Lebendimpfungen befolgt werden (s. Laws et al, RKI 2020).

	Titer
Pneumokokken	*S. Pneumoniae* (IgG, 23 Serotypen)
DTaP	Anti-Tetanus Toxoid Titer
Hepatitis A/B	Anti-HAV IgG Anti-HBs IgG >100IE/L
VZV	Anti-VZV IgG

Kriterien der Immunrekonstitution

1. Serum IgA nachweisbar (> 0.06 g/L) [a] UND
2. Absolute CD19 oder CD20 B-Zellzahl > 20/µl UND
3. Absolute CD4 T Zellzahl > 200/µl

a) Surrogatparameter für die Fähigkeit zum Immunglobulin Class Switch

Hill JA, Seo SK, Blood. 2020 Aug 20;136(8):925-935

Recommended core reporting criteria for infectious diseases in CAR-T clinical trials

Core reporting criteria	
	Notes
Category	• Microbiologically defined • Clinically defined • Fever syndrome
Severity	Grading on scales of 1-5 (Teh et al, Lancet Infect Dis 2024) or 1-3 (Shahid et al, TCT 2024)
Organism	• Bacterial • Viral • Fungal ○ Categories of proven, probable, or possible as relevant • Parasitic
Site	• Bloodstream • Respiratory tract • Gastrointestinal tract • Genitourinary • Central nervous system • Skin and soft tissue • Ophthalmologic • Other • Unknown
Associated clinical outcomes	• Medically attended visit • Hospitalization (including length of stay) • High-flow or non-invasive ventilatory support • Intensive care unit • Death
Additional high priority reporting criteria	
Infection timing	Early (day 0-30) versus late (after day +30)
Infection incidence and rate	Preferably as a cumulative incidence curve accounting for NRM and relapse as competing events
Infection mitigation strategies	Provide institutional guidelines regarding the use of antimicrobial prophylaxis (antibacterial, antiviral, anti-Pneumocystis jirovecii, and antifungal) and immunoglobulin replacement therapy

Rejeski et al, Nature Medicine 2025

Agenda – Understanding Mortality Drivers of CAR-T

NRM
after CAR-T

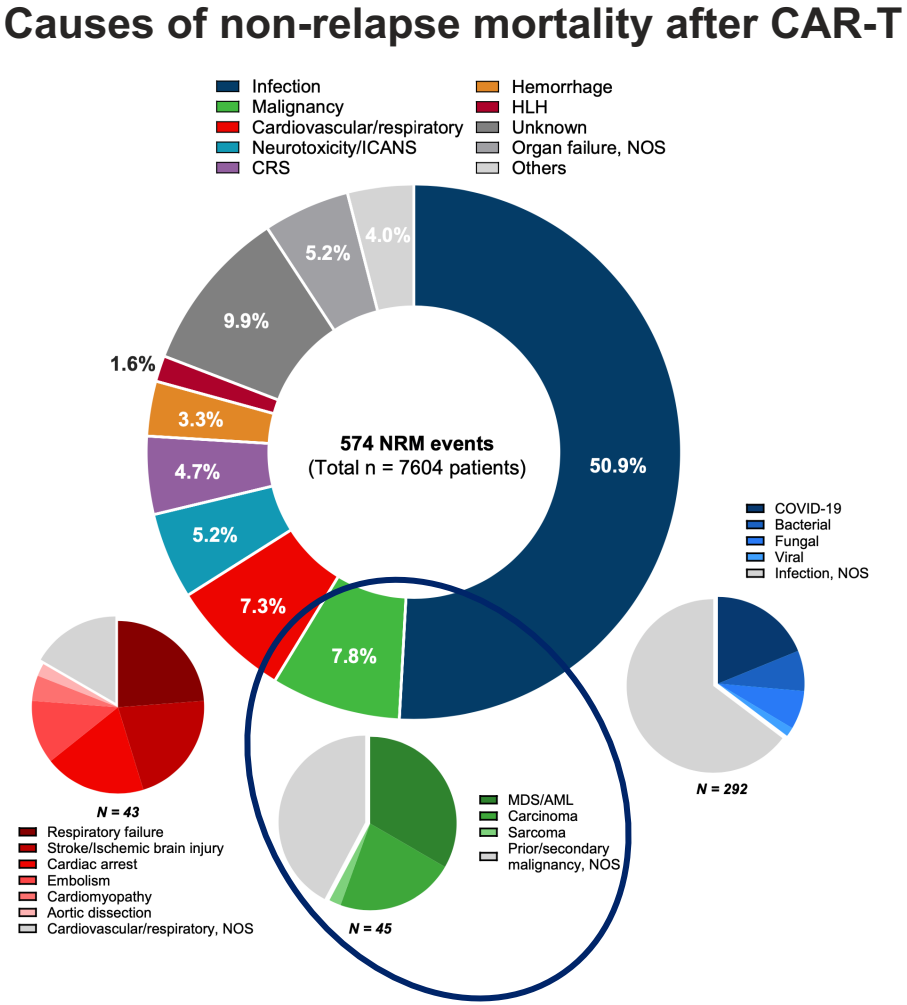
1. Cytopenias (ICAHT)

2. Immune Deficits & Infectious Complications

3. Secondary Malignancies

Non-relapse Mortality after CAR T-cell therapy

Cause of Death Analysis in CAR-T recipients

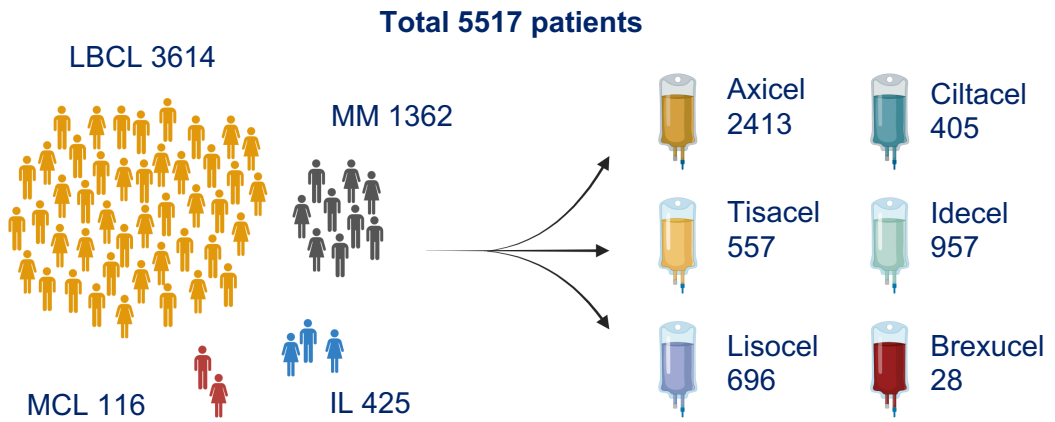


Second Primary Malignancy (SPM) = Second most common driver of NRM post CAR-T (predominantly driven by myeloid malignancy)

Dos Santos DMC, Tix T…..Rejeski K, Nature Medicine 2024

Secondary Malignancies after CAR T-cell therapy:

Results of large meta-analysis spanning >5,500 patients



Inclusion Criteria:

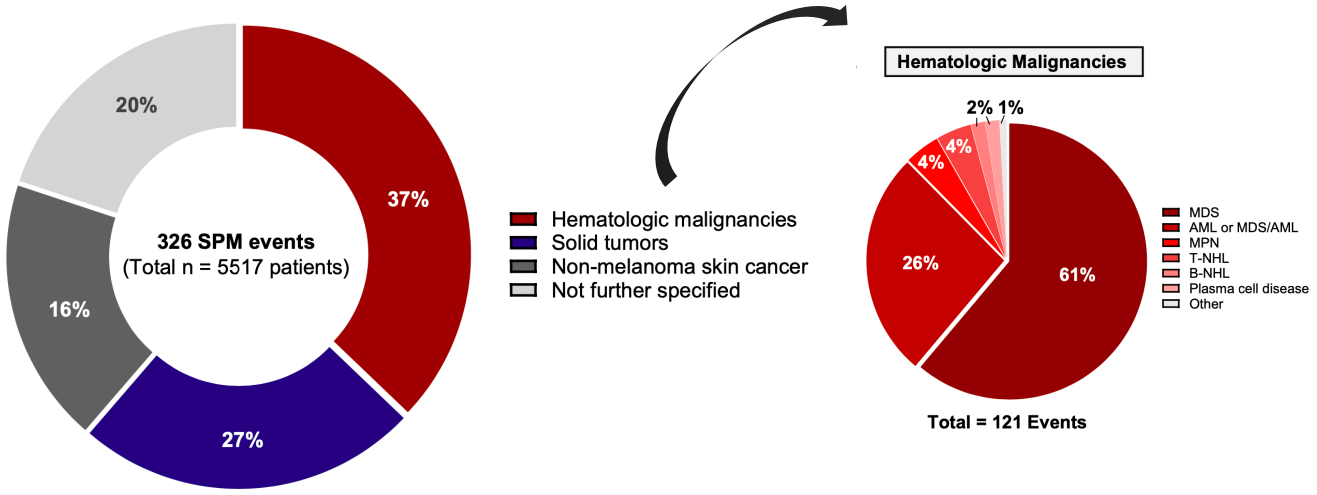
(1) Adult cancer patients with IL, LBCL, MM or MCL

(2) Use of CAR T cell products approved by the FDA

(3) Reporting of the absolute number of all second primary malignancies in the treated cohort during the entire follow-up

Topline Results:

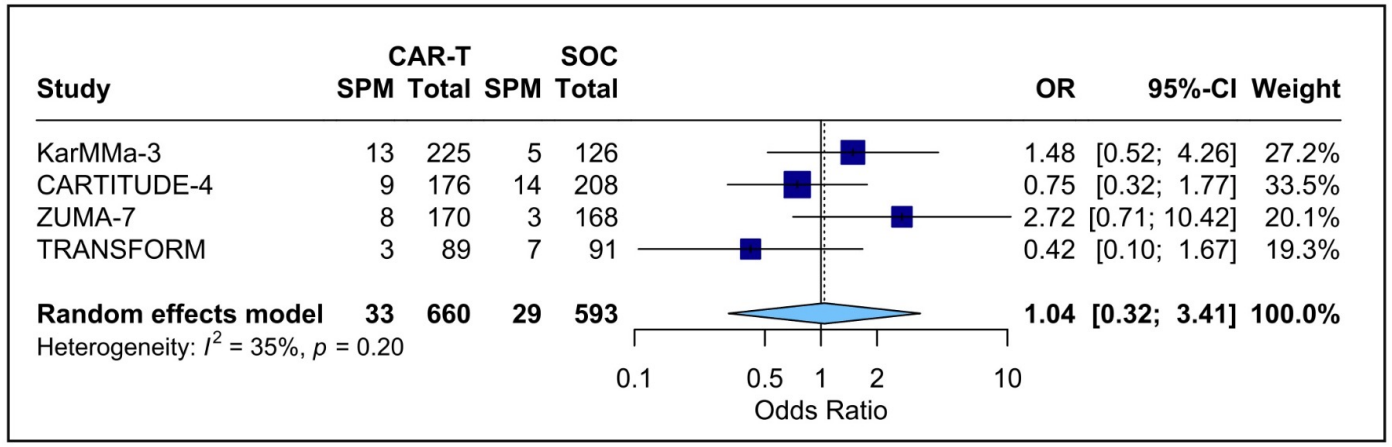
- We identified **326 SPMs** across 5,517 patients from 18 clinical trials (CT) and 7 real-world studies (RWS).
- With a median follow-up of 21.7 months, the **overall SPM point estimate was 5.8%** (95% CI 4.7-7.2%).
- The risk for **T-cell malignancies is below 0.1%** (less than 1:1.000), only a small proportion are CAR vector positive, and evidence regarding the pathogenetic significance of CAR vector insertion remains inconclusive.



Secondary Malignancies after CAR T-cell therapy:
Results of large meta-analysis spanning >5,500 patients

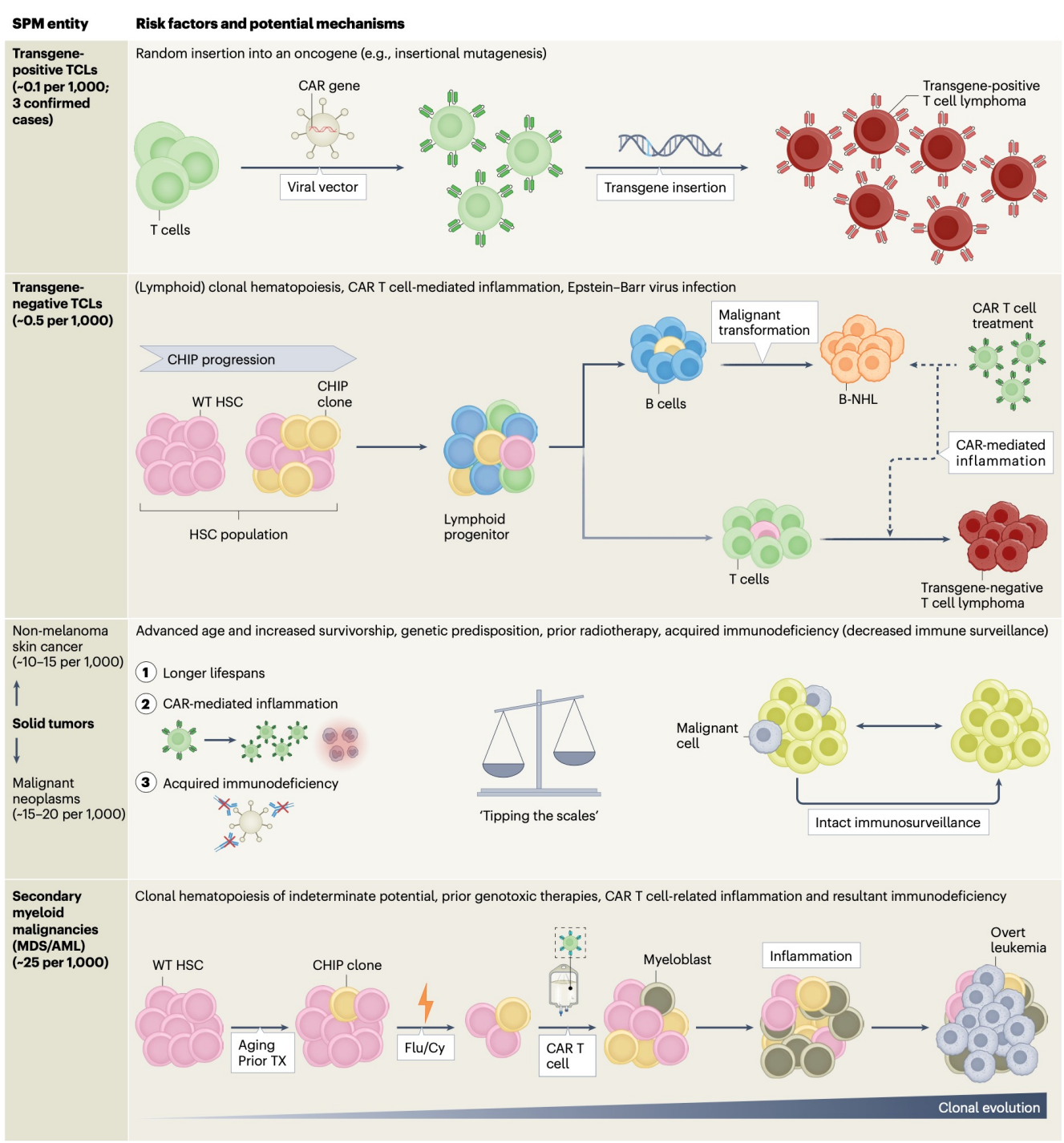
- SPM estimates do not vary significantly across disease entities and CAR-T products.
- Multivariate meta-regression analysis: SPM estimates were associated with **treatment setting** (CT>RWS), **duration of follow-up**, and **number of prior treatment lines.**

Covariate*	Estimate	Confidence Interval	p-value
Follow-up (months)	0.016	(0.001-0.031)	**0.035**
Prior HCT (% of pt.)	0.001	(-0.009-0.011)	0.878
Prior Lines (number)	0.268	(0.056-0.479)	**0.016**
Age (years)	0.016	(-0.063-0.095)	0.669
Treatment setting **- Real-world [ref.]** **- Clinical Trials**	0.415	(0.003-0.828)	**0.049**



- A subgroup meta-analysis of the four trials that randomized CAR-T versus standard-of-care revealed a **similar risk of SPM with either treatment strategy** (p=0.92)

Distribution and proposed pathophysiology of SPM arising after CAR-T

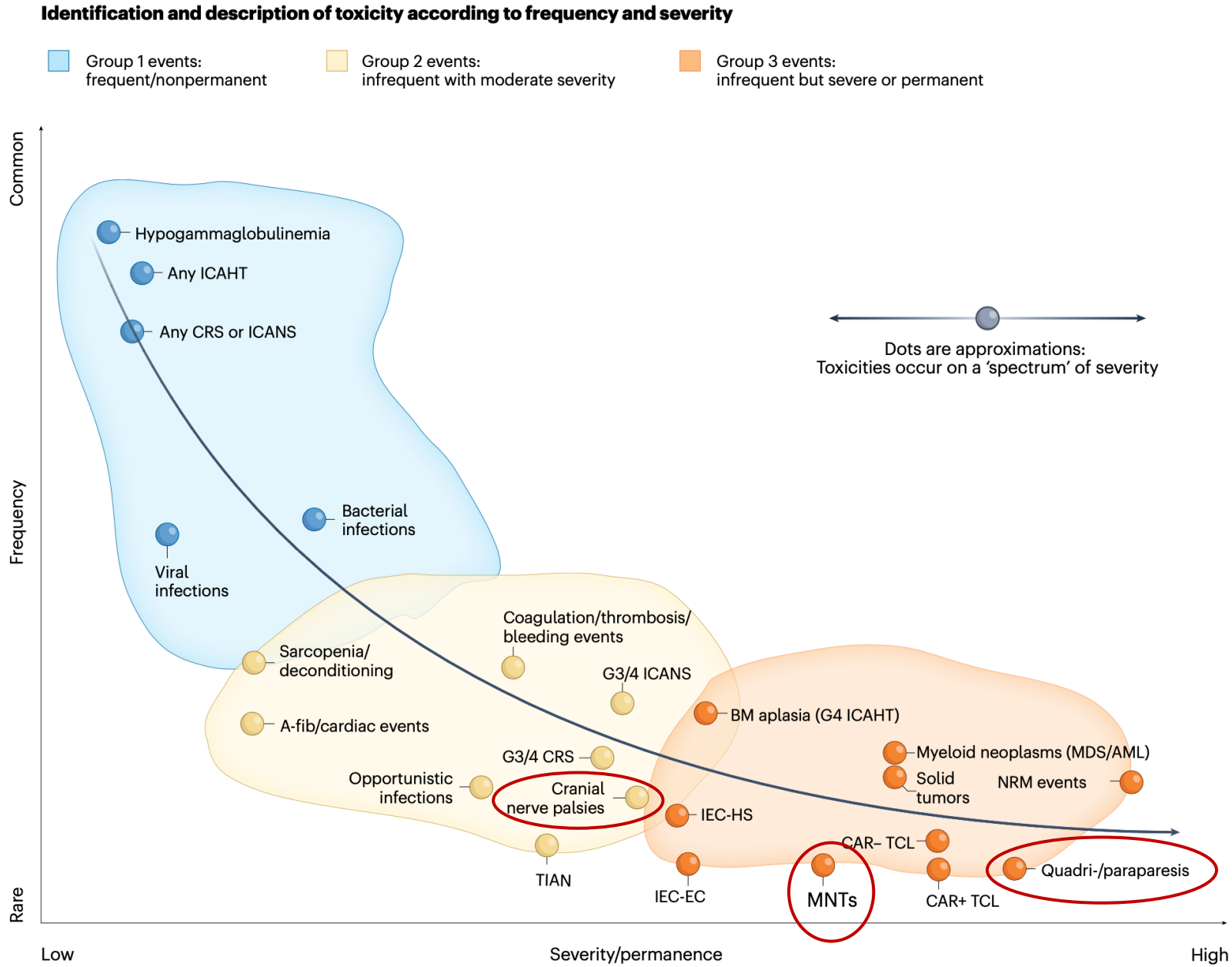


Surveillance & Reporting

1. Age-appropriate screening tests (e.g., rectal exam, mammogram, colonoscopy, low-dose CT in smokers).
2. Routine blood count monitoring.
3. In cases of T-cell malignancy, report to respective national authorities and rule out insertional mutagenesis with deep genomic integration site analysis.
4. CHiP mutation identification and post CAR-T infusion dynamics remains investigational and needs to be studied prospectively.

Rejeski et al, Nature Medicine 2025

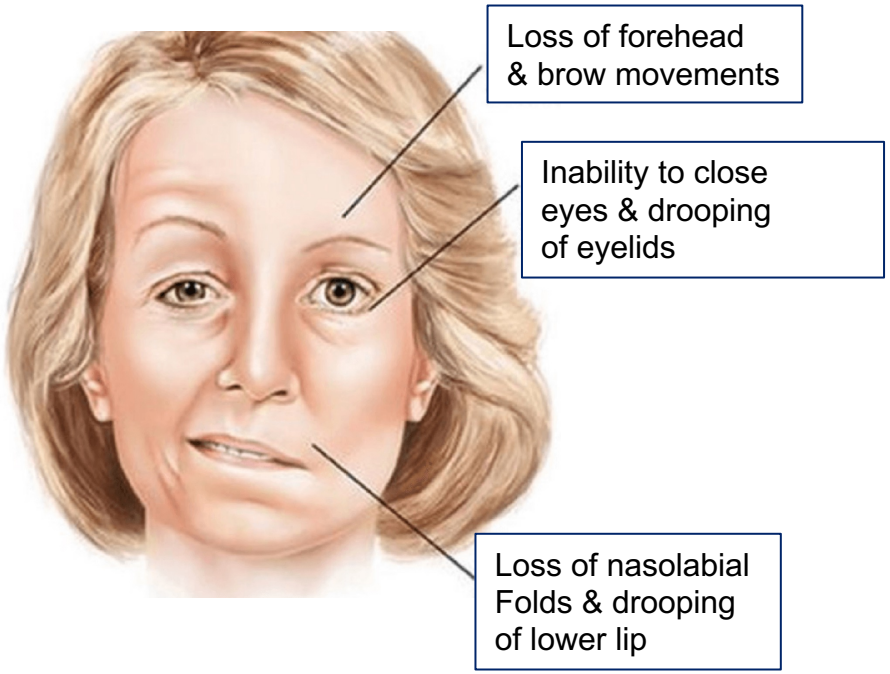
Non-ICANS Neurologic Toxicities (NINTs) as a major morbidity driver of CAR T-cell therapy



Rejeski et al, Nature Medicine 2025

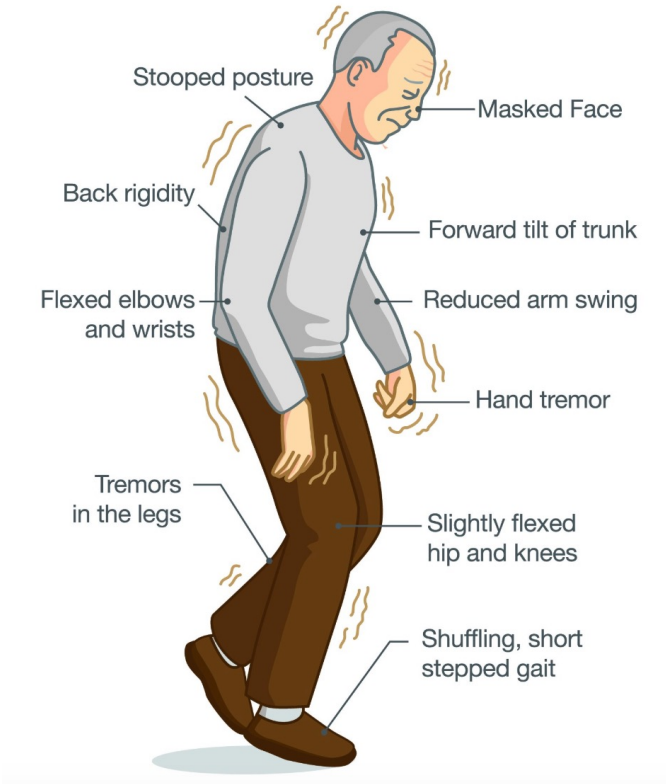
Non-ICANS Neurotoxicities (NINTS) with BCMA-directed CAR T in myeloma

Cranial Nerve Palsies



Median time to onset 22 d

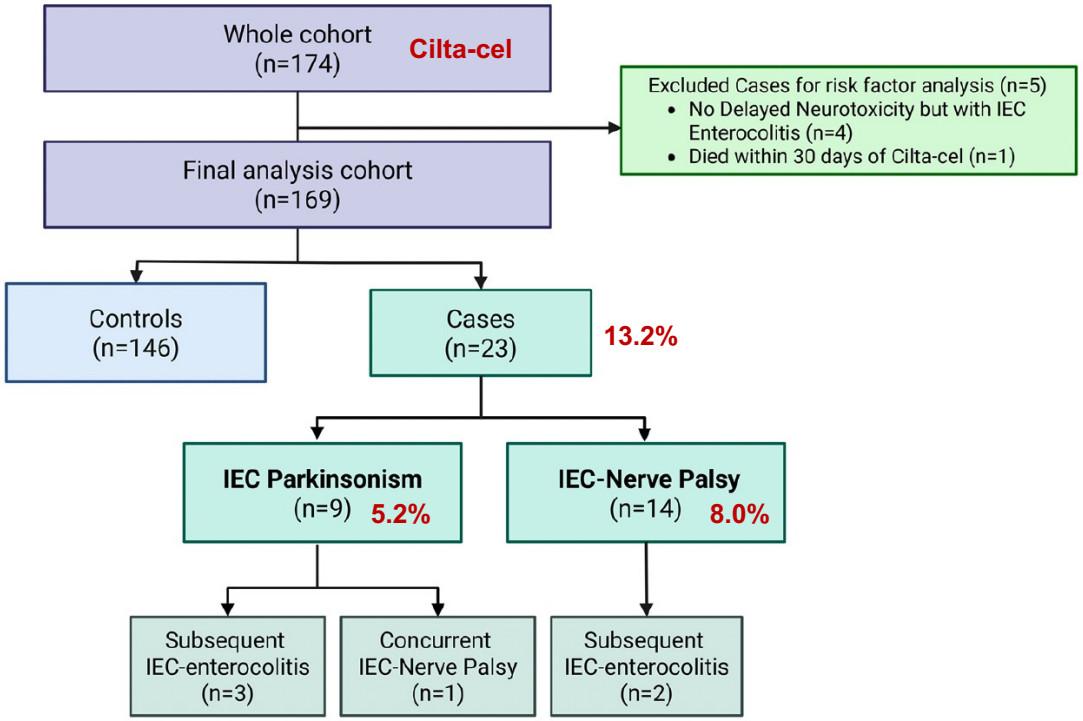
Parkinsonism

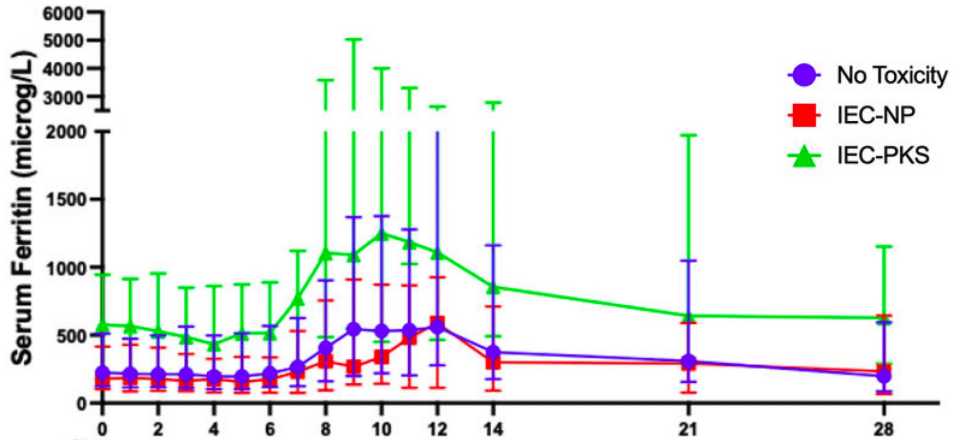


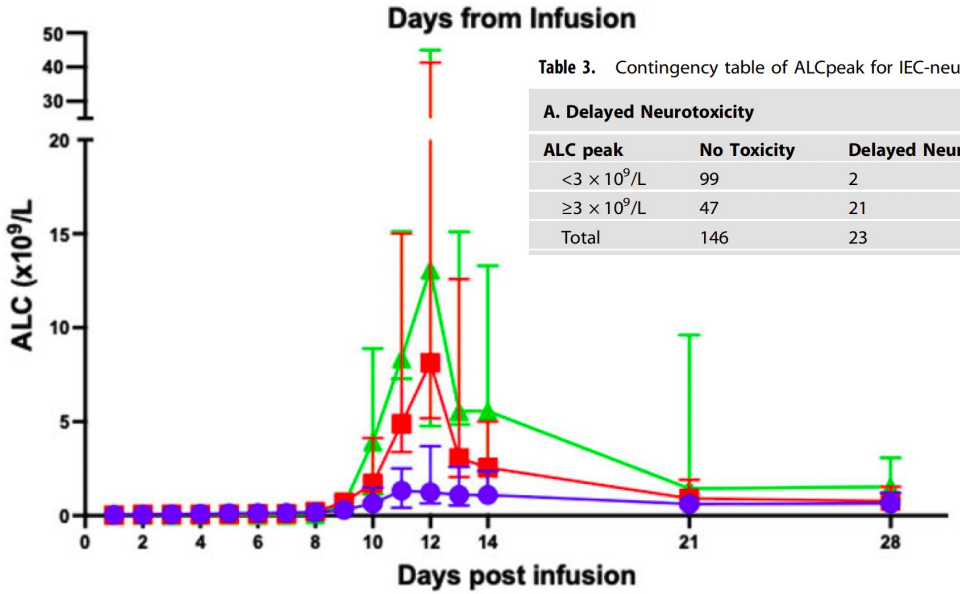
Median time to onset 27 d (range 14-108)

Courtesy Bianca Santomasso

Non-ICANS Neurotoxicities (NINTS) with BCMA-directed CAR T in myeloma







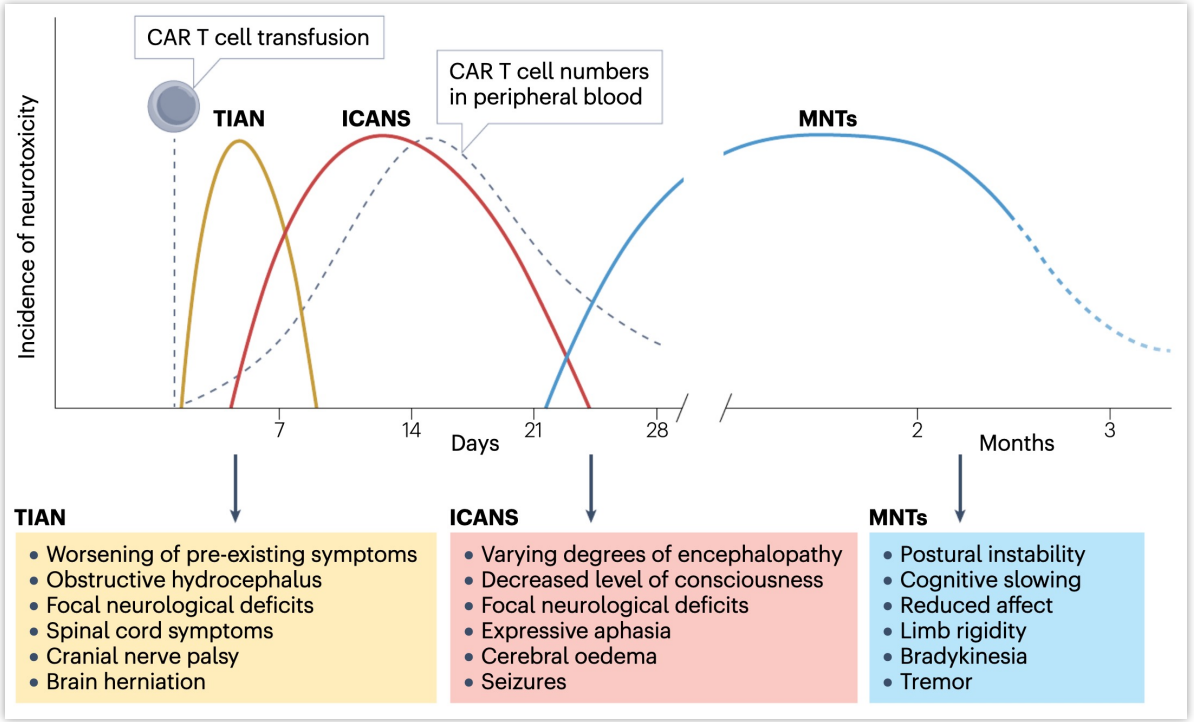
Days from Infusion

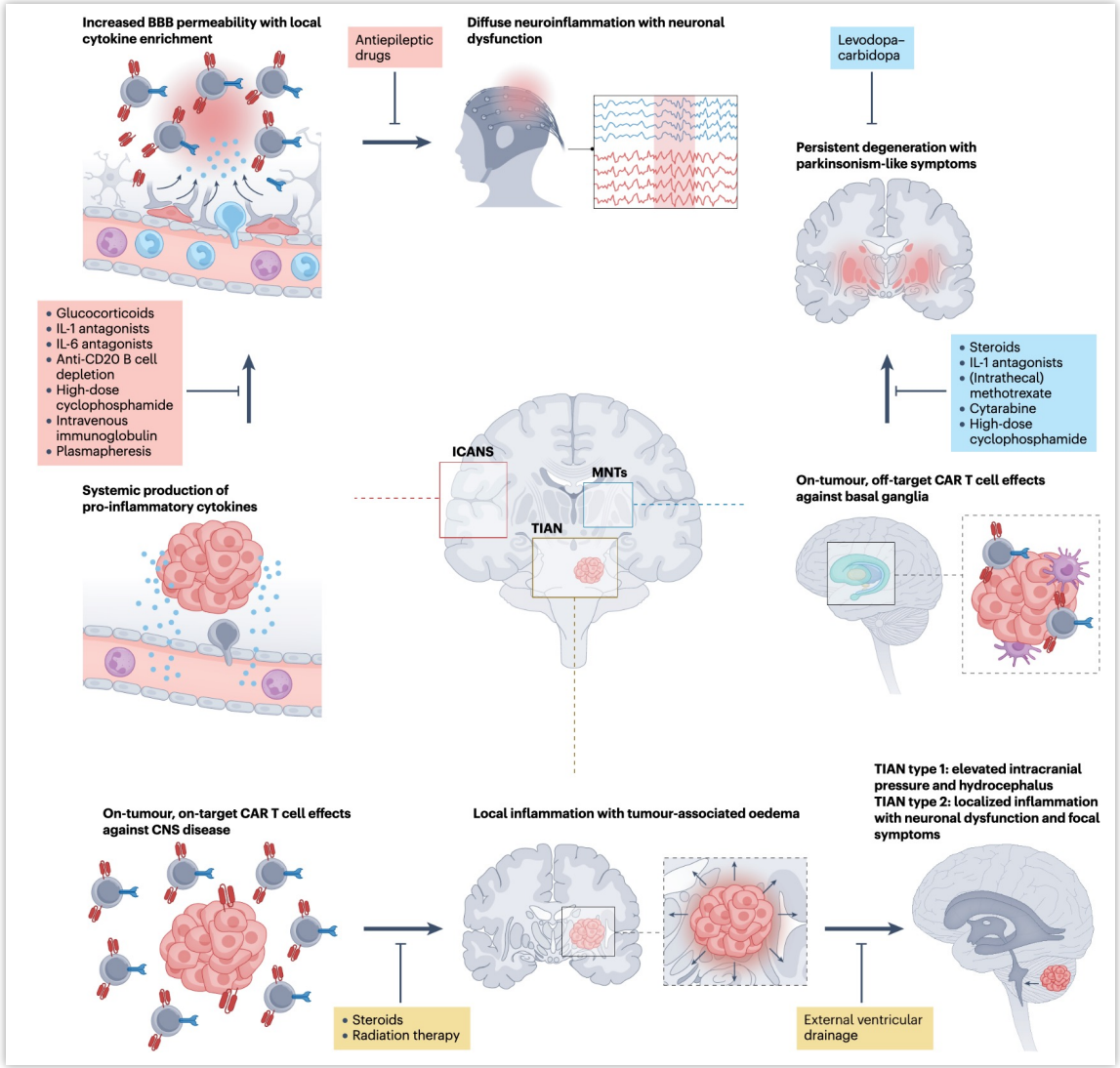
Table 3. Contingency table of ALCpeak for IEC-neurotoxicity.

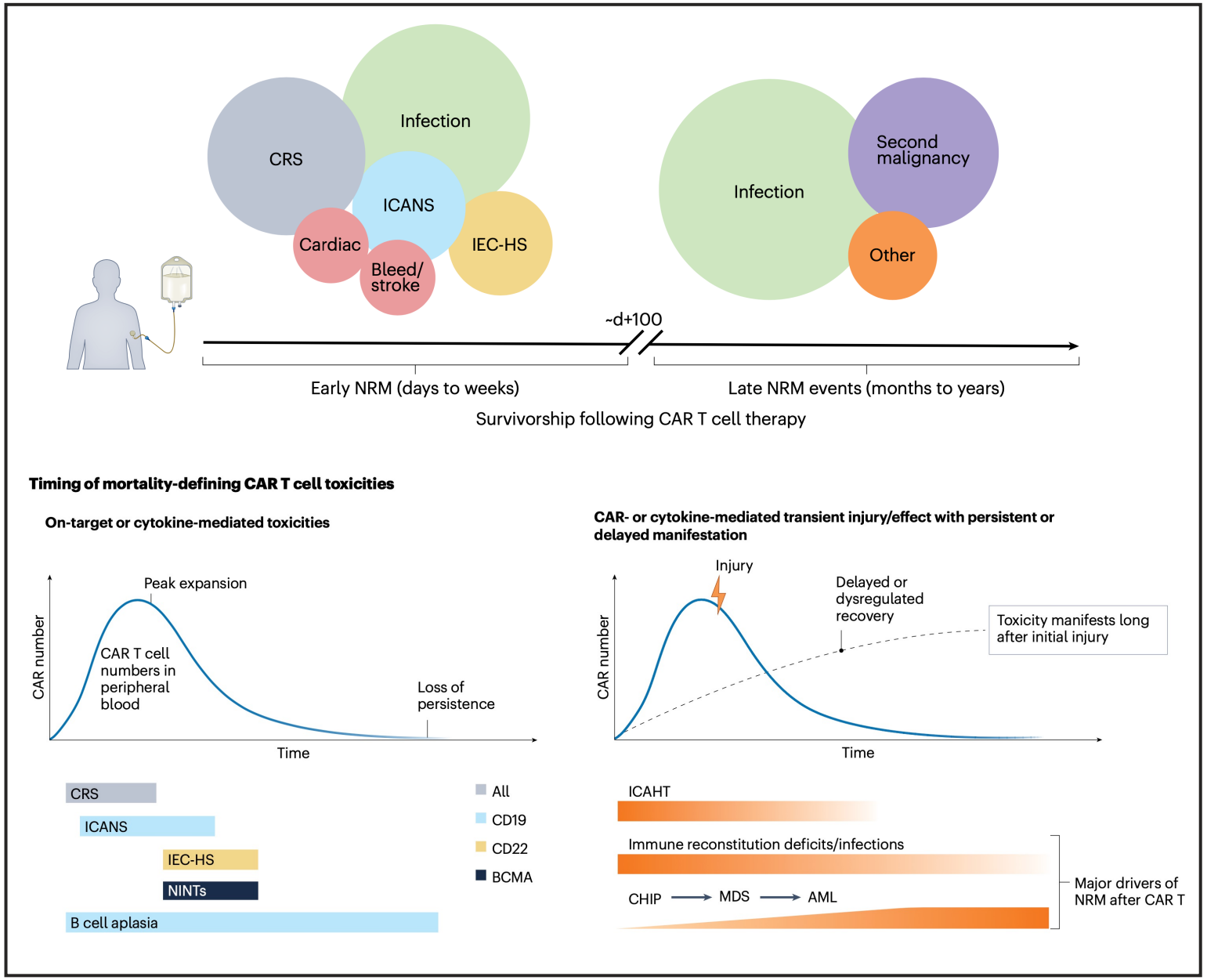
A. Delayed Neurotoxicity

ALC peak	No Toxicity	Delayed Neurotoxicity	Total
$<3 \times 10^9$/L	99	2	101
$\geq 3 \times 10^9$/L	47	21	68
Total	146	23	169

Non-ICANS Neurotoxicities (NINTS) with BCMA-directed CAR T in myeloma







Take-Home Messages

- NRM represents the **most devastating side effect of CAR-T therapy,** occurs in ~1:15 cases, dependent on the duration of follow-up, with product-specific variations.
- Not the prototypical CAR-T side effects (CRS, ICANS, HLH) drive NRM but rather side effects known to hematologists for >70 years: **cytopenias, infections and secondary malignancies.**

Unmet Needs

1. Establishing ICAHT grading in clinical trials and large registries to enable comparability
2. Developing harmonized reporting standards that comprehensively capture infectious complications.
3. Delineating the contributing role of CAR T cells during SPM development

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DKTK German Cancer Consortium

HELENE & BRUNO JÖSTER STIFTUNG

BZKF Bayerisches Zentrum für Krebsforschung

EHA EBMT

EHA TRANSLATIONAL RESEARCH TRAINING IN HEMATOLOGY

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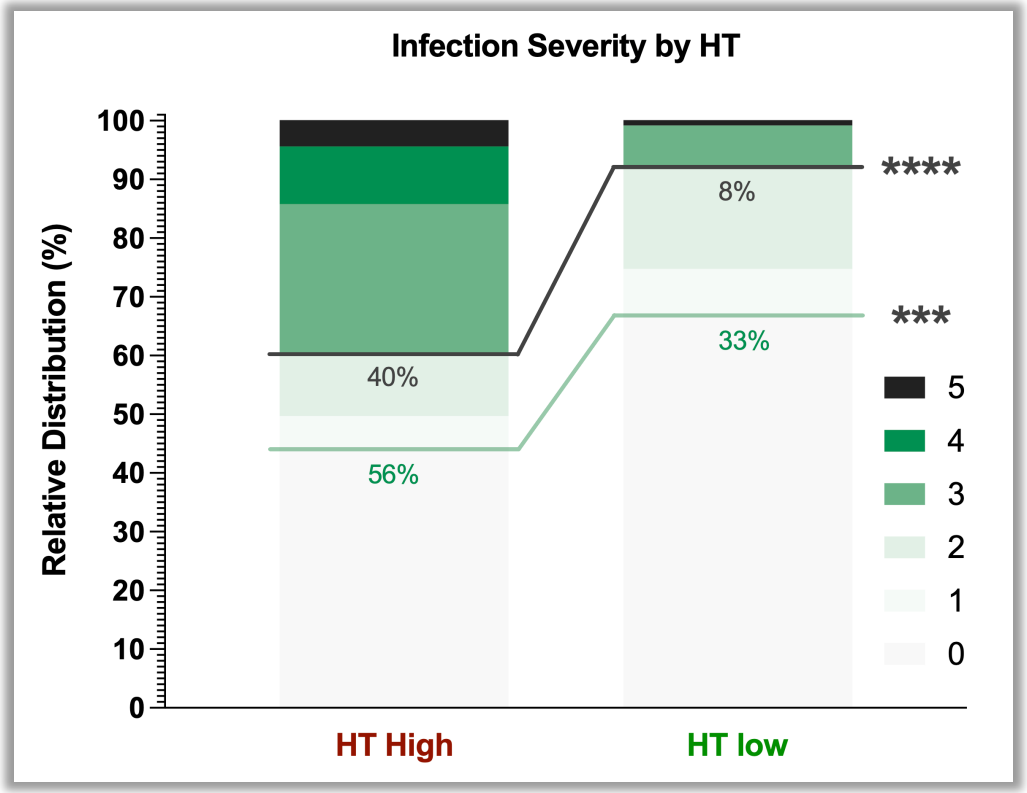
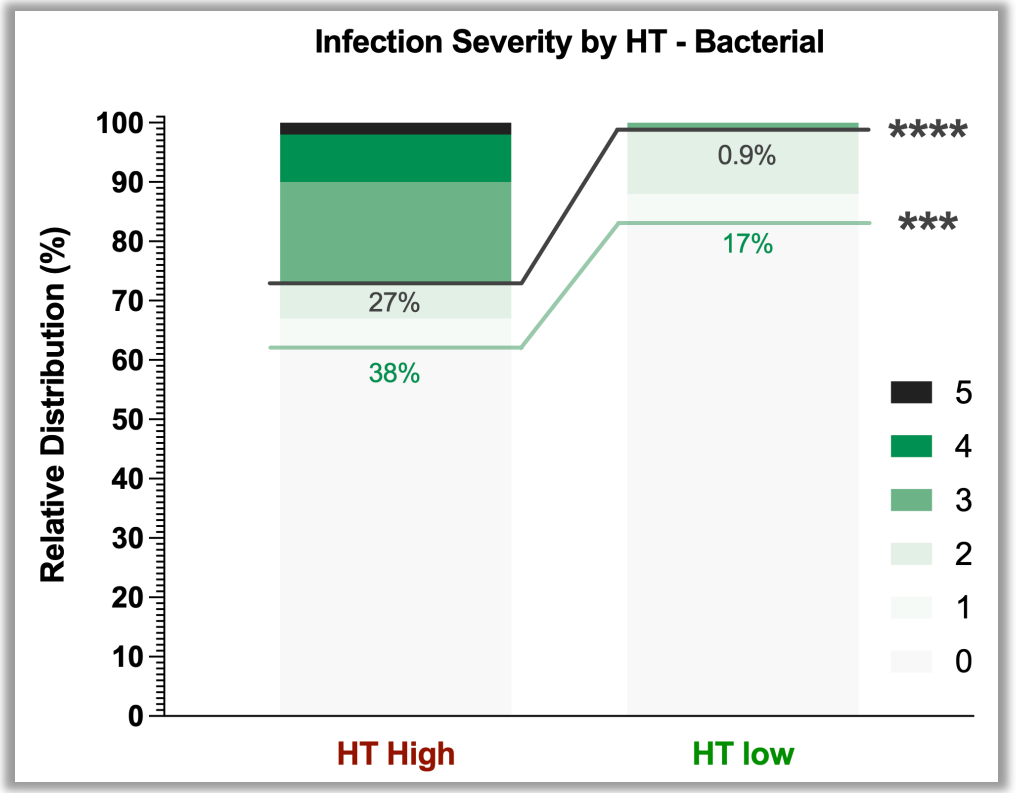
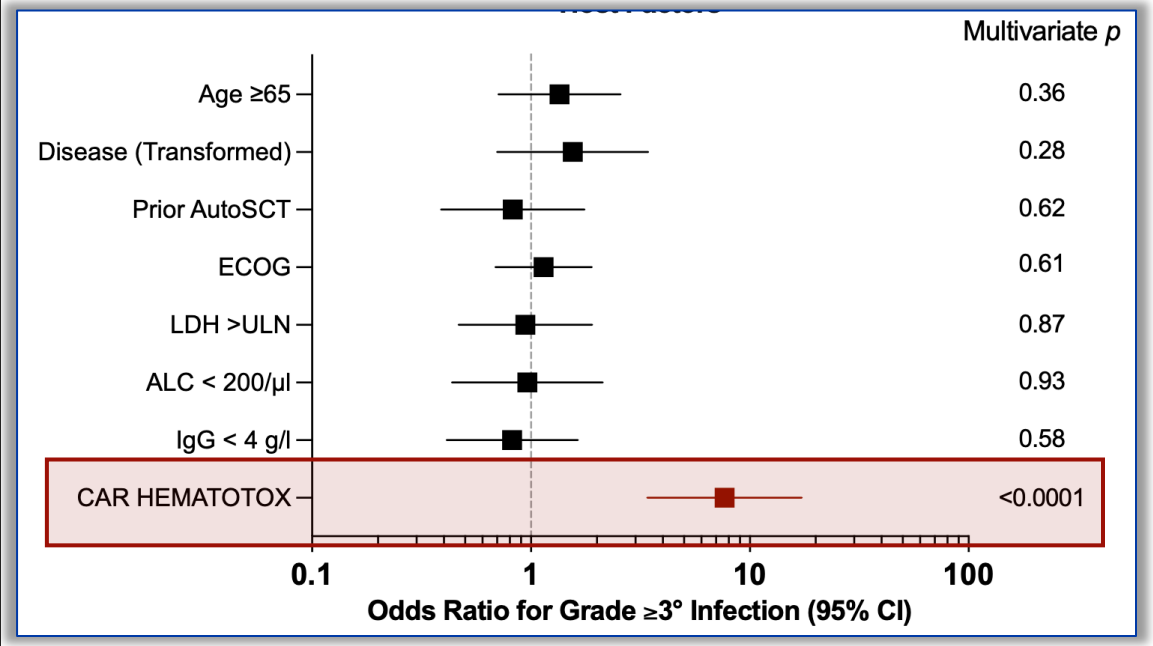
A high HT score results in a higher incidence rate of infectious complications – particularly for severe and bacterial infections





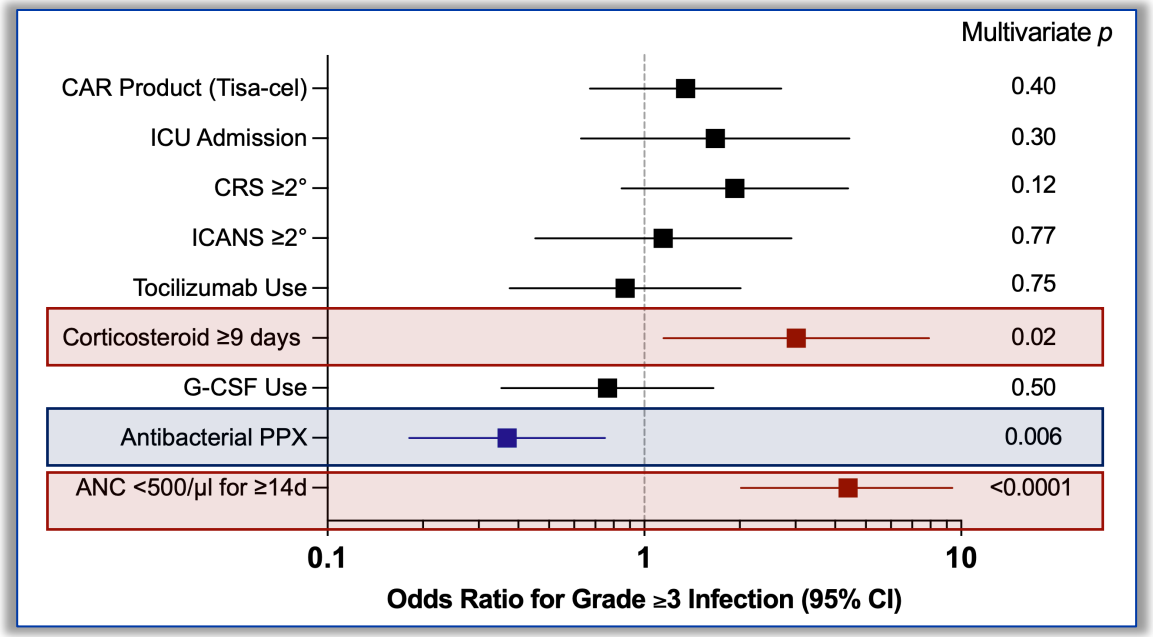
The HT score represents an independent risk factor for severe infections

Pre-CAR-T (host) factors



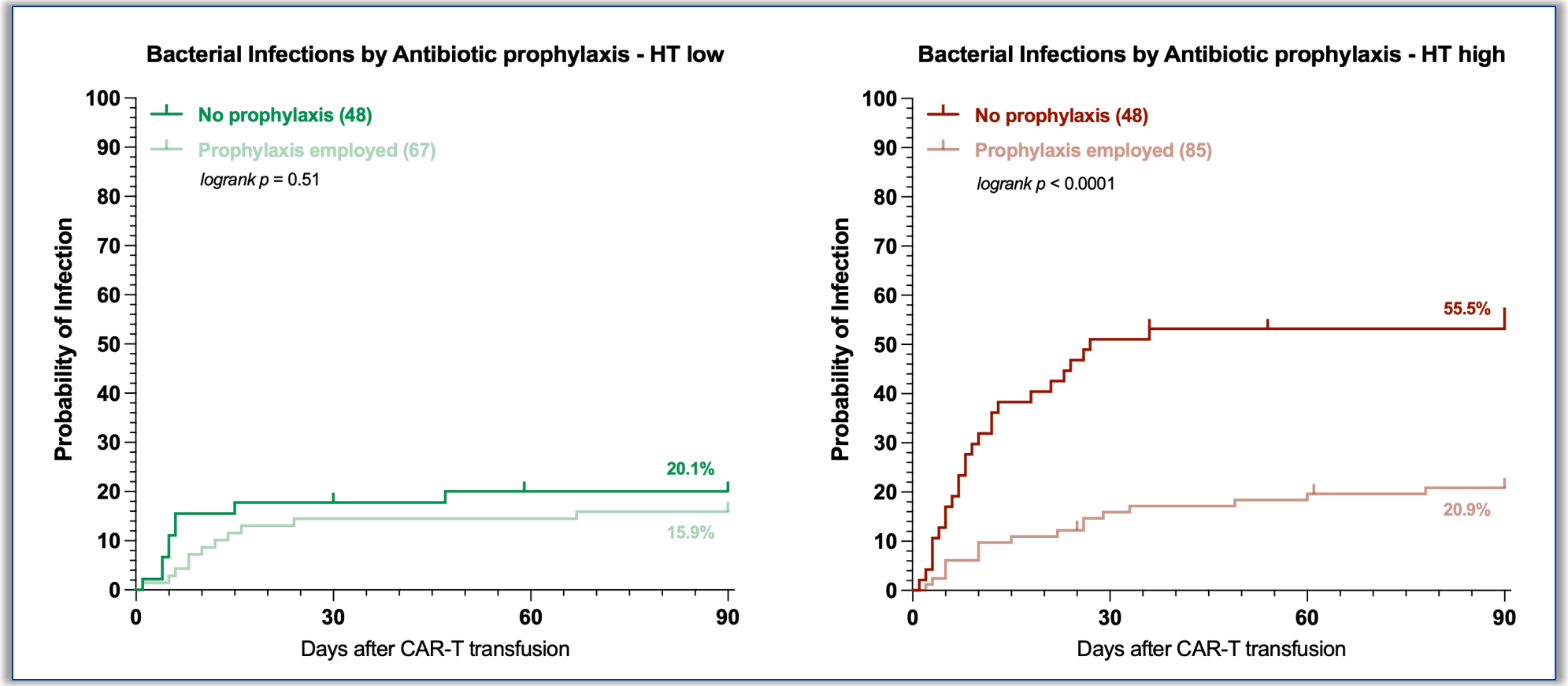
- **HT score: only pre lymphodepletion risk factor for severe infections**
  - adjusted OR = 7.7, 95% CI 3.4 – 17.3

Post-CAR-T factors



- **Cumulative corticosteroid use ≥9 days between days 0-21** (≥10 mg dexamethasone equivalent/ day)
  - adjusted OR: 3.2 (95% CI 1.2 – 8.2)
- **Prolonged severe neutropenia** (ANC < 500/µl between day 0-60)
  - adjusted OR: 3.7 (95% CI 1.9 – 7.0)
- **Fluorquinolone prophylaxis**
  - adjusted OR: 0.4 (95% CI 0.2 – 0.75)

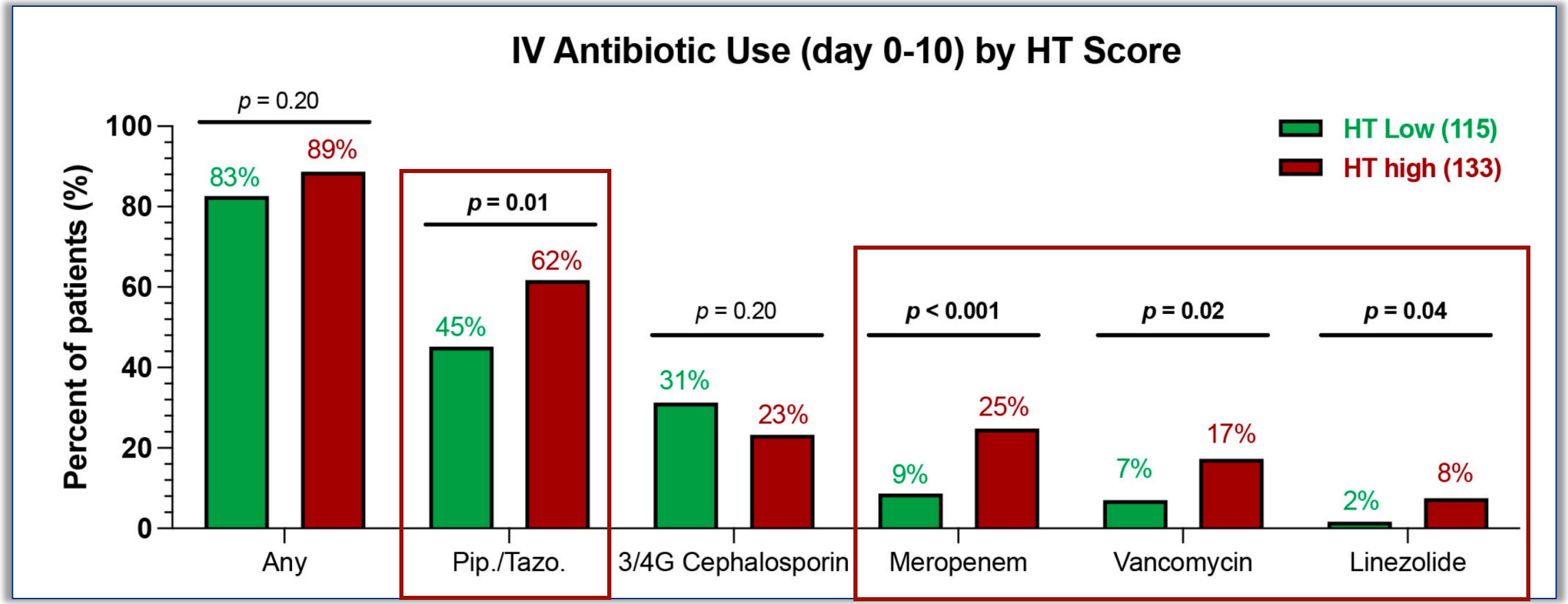
Antibacterial prophylaxis reduces the rate of severe infections in HT^{high} patients but not HT^{low} patients



- Can we prevent bacterial infections with fluorquinolone prophylaxis in HT high patients?
- Can we spare antibiotics in HT low patients?

Rejeski et al, JITC 2022

Patterns of Antibiotic use by HT score



- High HT score: Higher proportion of patients receiving IV broad-spectrum antibiotics (Piperacillin/Tazobactam, Meropenem, Vancomycin, Linezolide)

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Gut microbiome composition and CAR T-cell outcomes

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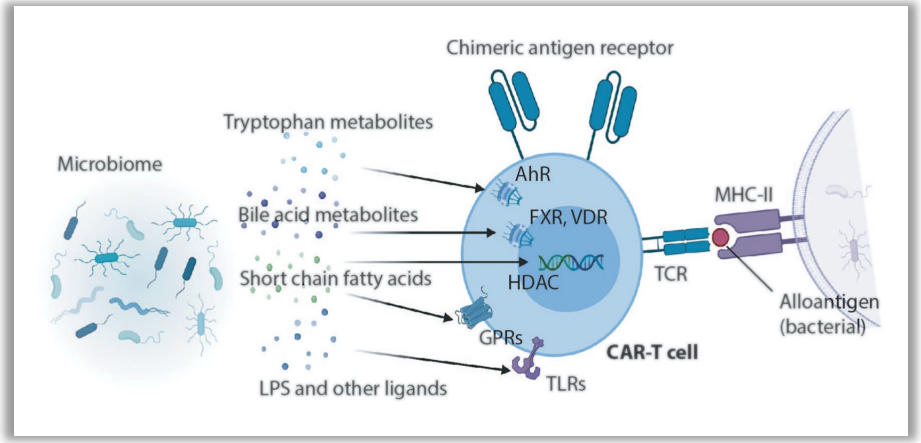

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A non-antibiotic-disrupted gut microbiome is associated with clinical responses to CD19-CAR-T cell cancer immunotherapy

Christoph K. Stein-Thoeringer, Neeraj Y. Saini, Eli Zamir, Viktoria Blumenberg, Maria-Luisa Schubert, Uria Mor, Matthias A. Fante, Sabine Schmidt, Eiko Hayase, Tomo Hayase, Roman Rohrbach, Chia-Chi Chang, Lauren McDaniel, Ivonne Flores, Rogier Gaiser, Matthias Edinger, Daniel Wolff, Martin Heidenreich, Paolo Strati, Ranjit Nair, Dai Chihara, Luis E. Fayad, Sairah Ahmed, Swaminathan P. Iyer, ... Eran Elinav

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