LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

SUBKLEWE LAB Translational Cancer Immunology

Gene Center Munich

CART Cells and bispecific Antibodies in elderly Patients

Univ.-Prof. Dr. med. Marion Subklewe

Head of the Cellular Immunotherapy Program at the LMU – University Hospital Munich
Head of the Lab for Translational Cancer Immunology at the LMU – Gene Center Munich

Disclosures

Research Support:
Amgen, BMS/Celgene, Miltenyi, Molecular Partners, Roche, Seagen

Educational Grant:
BMS/Celgene, Gilead/Kite, Johnson & Johnson, Novartis, Roche, Takeda

Consulting/ Scientific Advisory Board:
AbbVie, Crossbow, Debiopharm, Gilead/Kite, Interius, Johnson & Johnson, Molecular Partners, Novartis, Otsuka

Speakers‘ Bureau:
Amgen, BMS, Gilead/Kite, Miltenyi, Novartis, Roche, Takeda

Travel Support:
AbbVie, Amgen, Molecular Partners, Pierre Fabre, Roche

Agenda – Focus on patients with Large B-Cell Lymphoma treated with CD19-CART

- **Age & Geriatric Assessment in Lymphoma patients**

- **Response rates in older vs younger patients**
  - Randomized Clinical Trials: Outcome after CART in older, but transplant eligible patients
  - Non-randomized Clinical Trials: Outcome after CART in non-transplant eligible patients and bispecifics
  - RWE: Outcome from registry + consortia data

- **NRM higher in elderly patients treated with CART**
  - NRM in CART treated patients
  - Early vs Late NRM, Infections drive NRM

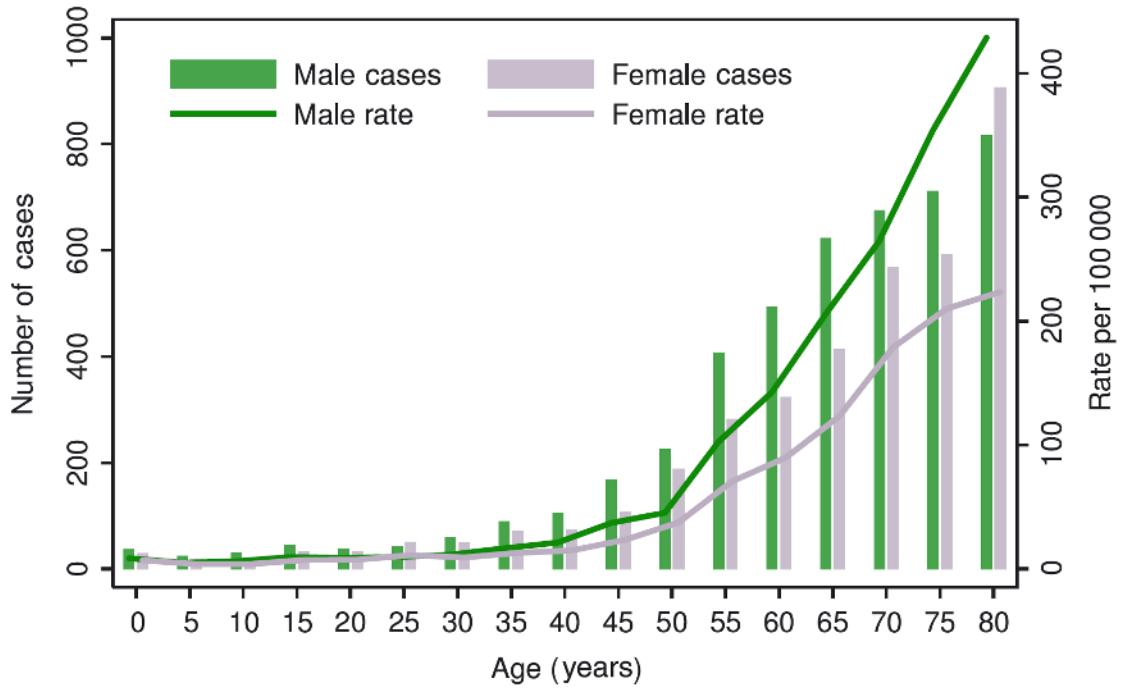
- **Infections drive NRM**
  - Hematotoxicity
  - Protracted Immune Reconstitution

- **Treatment Algorithm in R/R LBCL in older adults**

The Majority of Patients with hematological Malignancies are 65 or older

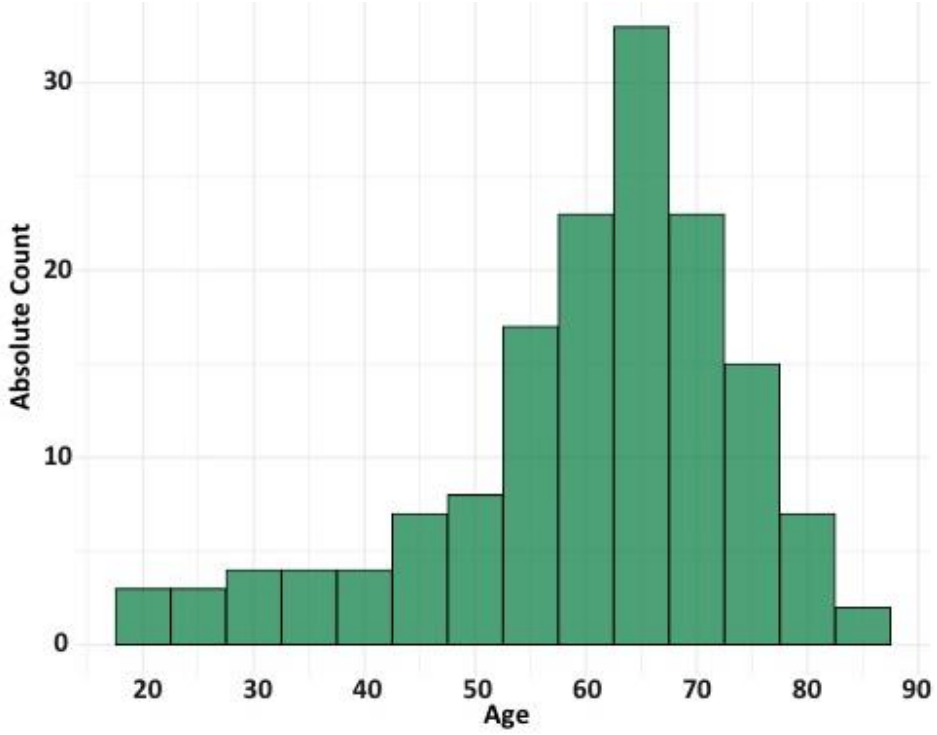
Median Age of DLBCL at Diagnosis is 70 Years, with 35% of the Cases over 75

HMRN Age and Sex Distribution



Haematological Malignancy Research Network (HMRN), 2004–2008

LMU: Age Distribution of CART treated Patients



Subklewe, LMU data

It is more challenging to treat older Patients with Cancer due to Comorbidities & Health Issues

- Cardiovascular morbidity
- Deterioration in GFR
- Decrease in liver function
- Pre-existent peripheral neuropathy
- Polypharmacy
- Loss of muscle and increase in fat
  - lean body mass loss of 1-2%/year, 3% if over 70
  - Impact on drug metabolism
- Haematopoietic reserve is often reduced
- Memory issues and depression

Lymphoma-specific Fitness Assessment developed by the Fondazione Italiana Linfomi: Age + Activities of the daily living (ADL), instrumental ADLs (IADL) and CIRS-G

	Fit	Unfit	Unfit	Frail
ADL[a]	≥5	<5	6	<6
IADL[b]	≥6	<6	8	<8
CIRS-G[c]	No comorbidities with score 3-4, ≤8 comorbidities with score 2	≥1 comorbidities with score 3-4, >8 comorbidities with score 2	No comorbidities with score 3-4, <5 comorbidities with score 2	≥1 comorbidities with score 3-4, ≥5 comorbidities with score 2
Age	<80	<80	≥80	≥80

ADL, Activities of daily Living (6 is the perfect score); **CIRS-G Cumulative Illness Rating Scale-Geriatric**; **IADL, Instrumental Activities of Daily Living** (8 is the perfect score) **aADL is assessed using the Katz ADL and assesses independenc**e (1) or dependence (0) in six activities - bathing, dressing, toileting, transferring, continence, and feeding. Independence in all ADLs=a score of 6, dependence in one ADL=a score of 5 bIADL is assessed using the Lawton IADL and assesses ability (unable - 0, needs assistance – 1, independence – 2) to perform eight activities: meal preparation, housework, laundry, travel, taking medications, and finance management. Independence in all IADLs=a score of 8, needs assistance in two IADL=6. cCIRS-G assesses medical problems by 14 organ system/comorbidities based on 0 (no problem) to 4 (extremely severe) rating for each system.

Wallace et al, Blood 2024

Simplified Geriatric Assessment (GA) considers Age > 80 as unfit or frail

	Fit	Unfit	Unfit	Frail
ADL[a]	≥5	<5	6	<6
IADL[b]	≥6	<6	8	<8
CIRS-G[c]	No comorbidities with score 3-4, ≤8 comorbidities with score 2	≥1 comorbidities with score 3-4, >8 comorbidities with score 2	No comorbidities with score 3-4, <5 comorbidities with score 2	≥1 comorbidities with score 3-4, ≥5 comorbidities with score 2
Age	<80	<80	≥80	≥80

International accepted SoC with DLBCL patients > 80 years: mini-R-CHOP

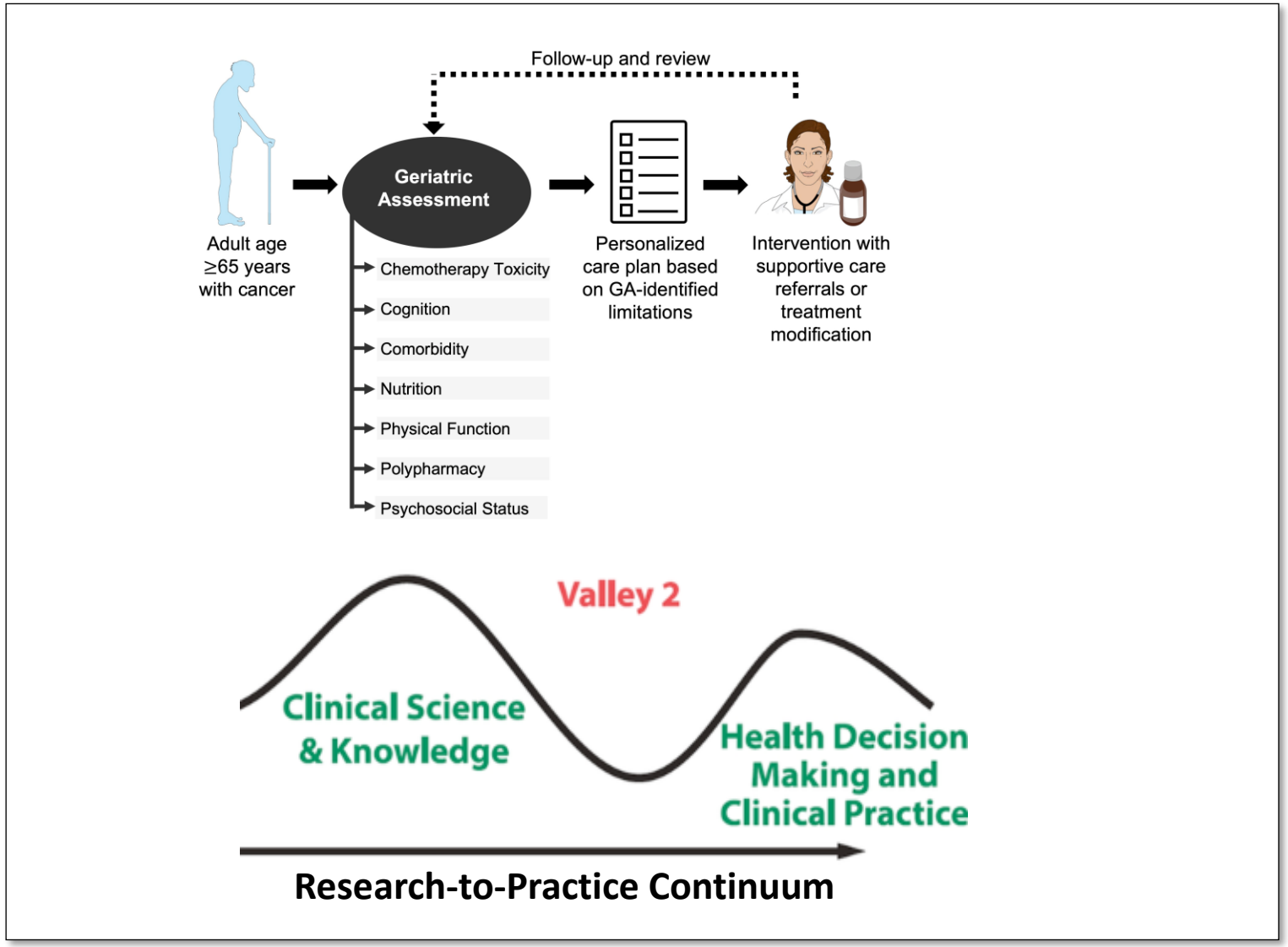
Wallace et al, Blood 2024

Elderly Prognostic Index (EPI) in Lymphoma integrates the simplified GA with the IPI + Hemoglobin and categorizes into 3 Risk groups for prognostication (only ID)

Factors	Categories	Score	
Simplified geriatric assessment	Fit	0	
	Unfit	3	
	Frail	4	
International prognostic index	1	0	
	2	1	
	3-5	3	
Hemoglobin <12 g/dL		1	
			3-year overall survival (95% confidence interval)
Risk groups	Low	0-1	87% (81-91)
	Intermediate	2-5	69% (63-73)
	High	6-8	42% (36-49)

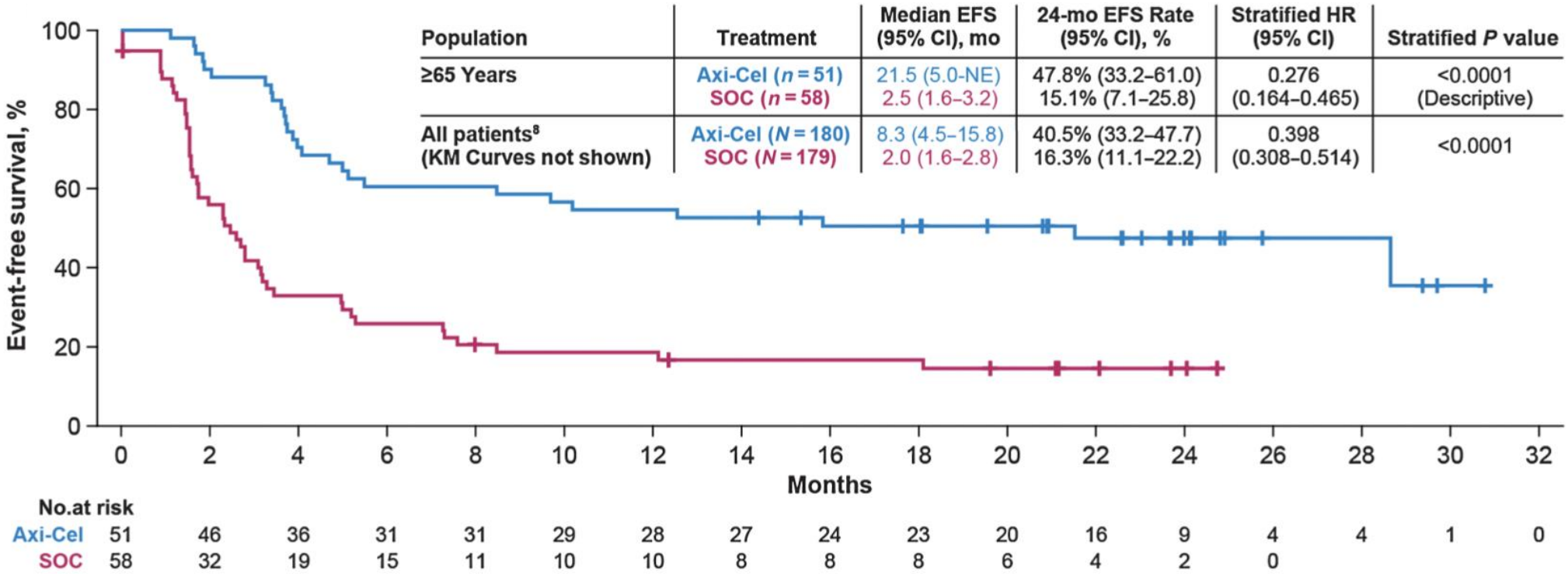
Wallace et al, Blood 2024

So far, the simplified GA is rarely reported in Clinical Trials or RWE of CART or bispecific treated pts with R/R LBCL, making a personalized approach more challenging



Singhal et al, Front Oncol 2023, Tavares et al, Critical Reviews in Oncology/Heamtology 2021

ZUMA-7: Outcome with Axi-Cel better in 65+ pts eligible for auto SCT vs younger pts

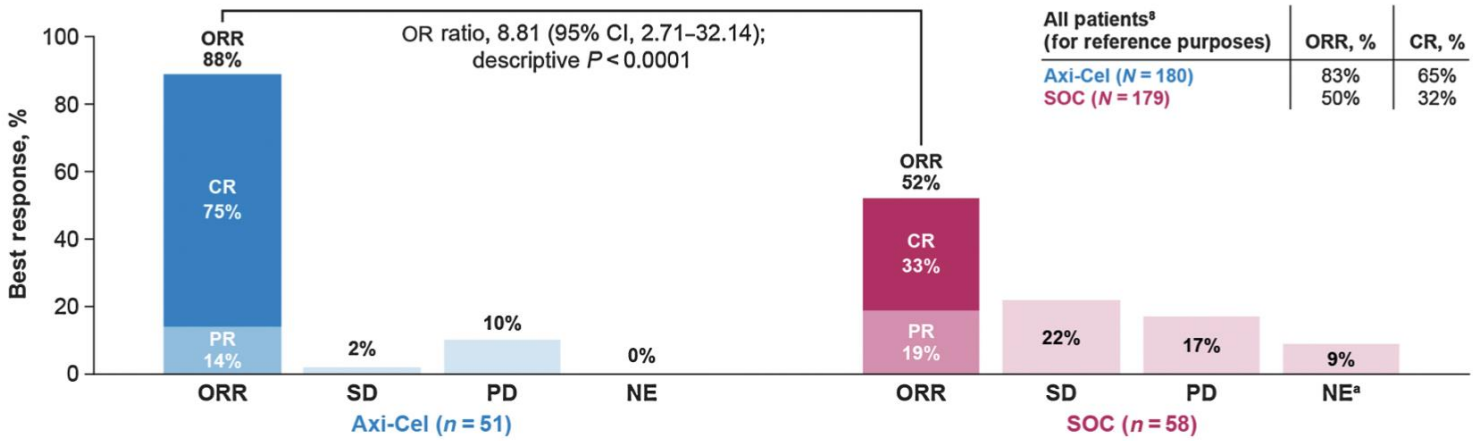


Population	Treatment	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %	Stratified HR (95% CI)	Stratified *P* value
≥65 Years	Axi-Cel (*n* = 51)	21.5 (5.0-NE)	47.8% (33.2–61.0)	0.276 (0.164–0.465)	<0.0001 (Descriptive)
	SOC (*n* = 58)	2.5 (1.6–3.2)	15.1% (7.1–25.8)		
All patients[8] (KM Curves not shown)	Axi-Cel (*N* = 180)	8.3 (4.5–15.8)	40.5% (33.2–47.7)	0.398 (0.308–0.514)	<0.0001
	SOC (*N* = 179)	2.0 (1.6–2.8)	16.3% (11.1–22.2)		

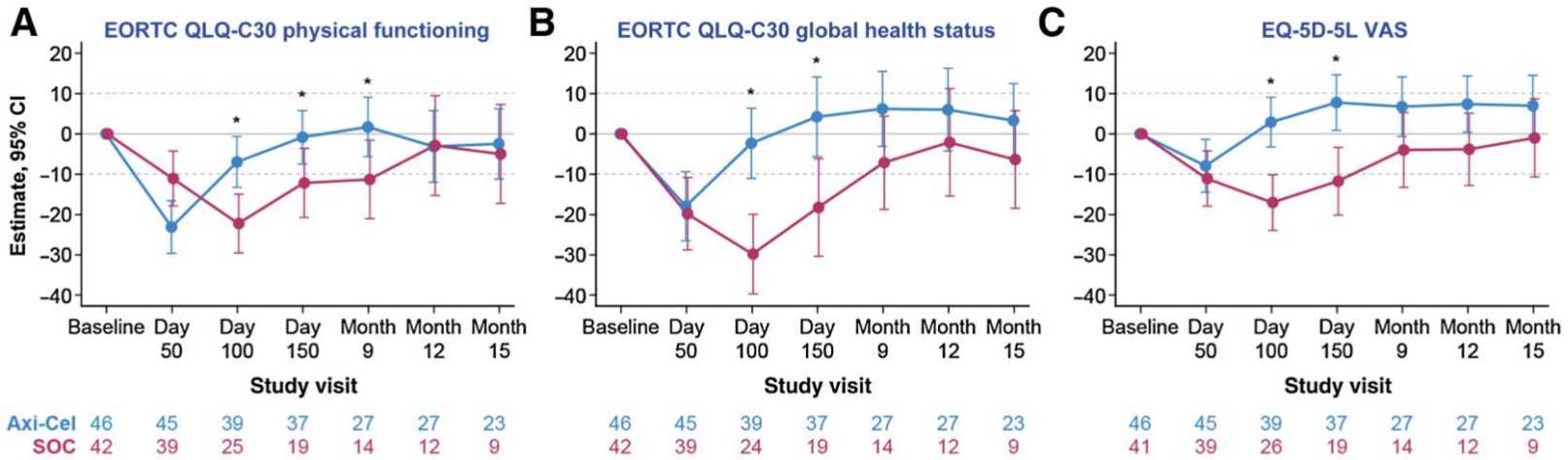
Westin et al, CCR 2023

ZUMA-7: overall improved Quality of Life in CART treated pts vs SoC

Zuma 7: Over 65y



All patients[8] (for reference purposes)	ORR, %	CR, %
Axi-Cel (*N* = 180)	83%	65%
SOC (*N* = 179)	50%	32%



Westin et al, CCR 2023

What about ”Transplant Ineligible“ LBCL pts?

Alycante

Article

https://doi.org/10.1038/s41591-023-02572-5

Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial

Received: 25 May 2023

Accepted: 29 August 2023

Published online: 14 September 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Axicabtagene ciloleucel (axi-cel) demonstrated superior efficacy compared to standard of care as second-line therapy in patients with high-risk relapsed/refractory (R/R) large B cell lymphoma (LBCL) considered eligible for autologous stem cell transplantation (ASCT); however, in clinical practice, roughly half of patients with R/R LBCL are deemed unsuitable candidates for ASCT. The efficacy of axi-cel remains to be ascertained in transplant-ineligible patients. ALYCANTE, an open-label, phase 2 study, evaluated axi-cel as a second-line therapy in 62 patients with R/R LBCL

Pilot

Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study

Alison Sehgal, Daanish Hoda, Peter A Riedell, Nilanjan Ghosh, Mehdi Hamadani, Gerhard C Hildebrandt, John E Godwin, Patrick M Reagan, Nina Wagner-Johnston, James Essell, Rajneesh Nath, Scott R Solomon, Rebecca Champion, Edward Licitra, Suzanne Fanning, Neel Gupta, Ronald Dubowy, Aleco D'Andrea, Lei Wang, Ken Ogasawara, Jerill Thorpe, Leo I Gordon

Lancet Oncol 2022; 23: 1066–77

Published Online July 12, 2022 https://doi.org/10.1016/S1470-2045(22)00339-4

University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA, USA (A Sehgal MD); Intermountain Healthcare, LDS Hospital, Salt Lake City, UT, USA (D Hoda MD); Department of Medicine, Section of Hematology/

Summary

Background Patients with relapsed or refractory large B-cell lymphoma after first-line treatment who are not intended for haematopoietic stem-cell transplantation (HSCT) have poor outcomes and limited treatment options. We assessed the antitumour activity and safety of lisocabtagene maraleucel, an autologous, CD19-directed chimeric antigen receptor (CAR) T-cell product, as second-line treatment in adults with relapsed or refractory large B-cell lymphoma not intended for HSCT.

Methods PILOT, an open-label, phase 2 trial done at 18 clinical sites in the USA, included adults aged 18 years or older who had relapsed or refractory large B-cell lymphoma and PET-positive disease, had received first-line therapy containing an anthracycline and a CD20-targeted agent, were not intended for HSCT by their physician, and met at least one prespecified transplantation not intended criterion. Patients received lymphodepleting chemotherapy (intravenous fludarabine 30 mg/m² and intravenous cyclophosphamide 300 mg/m² daily for 3 days) followed 2–7 days

Age and Comorbidities

Houot R et al, Nat Med 2023; Sehgal A et al, Lancet Oncol. 2022

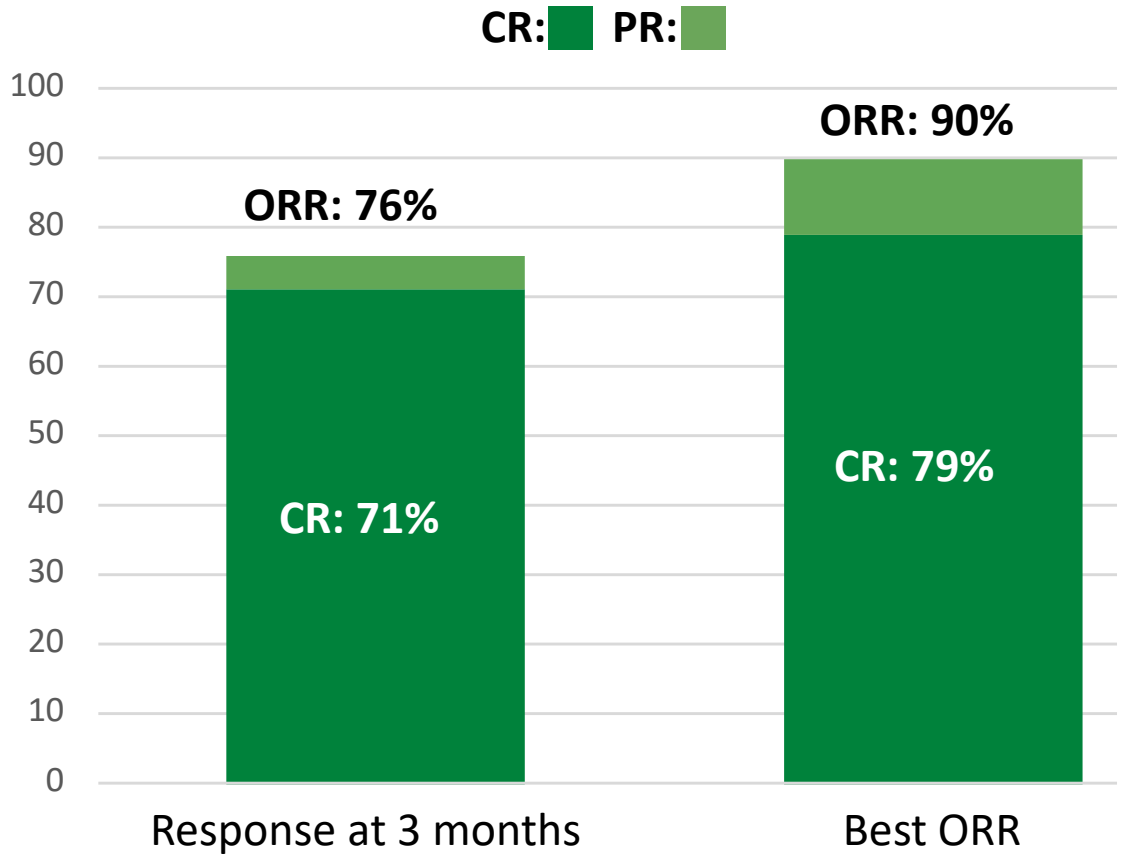
Alycante: Phase II Trial – Axi-Cel in R/R DLBCL pts not eligible for auto SCT

Age ≥ 65y

HCT-CI ≥3

Prior ASCT

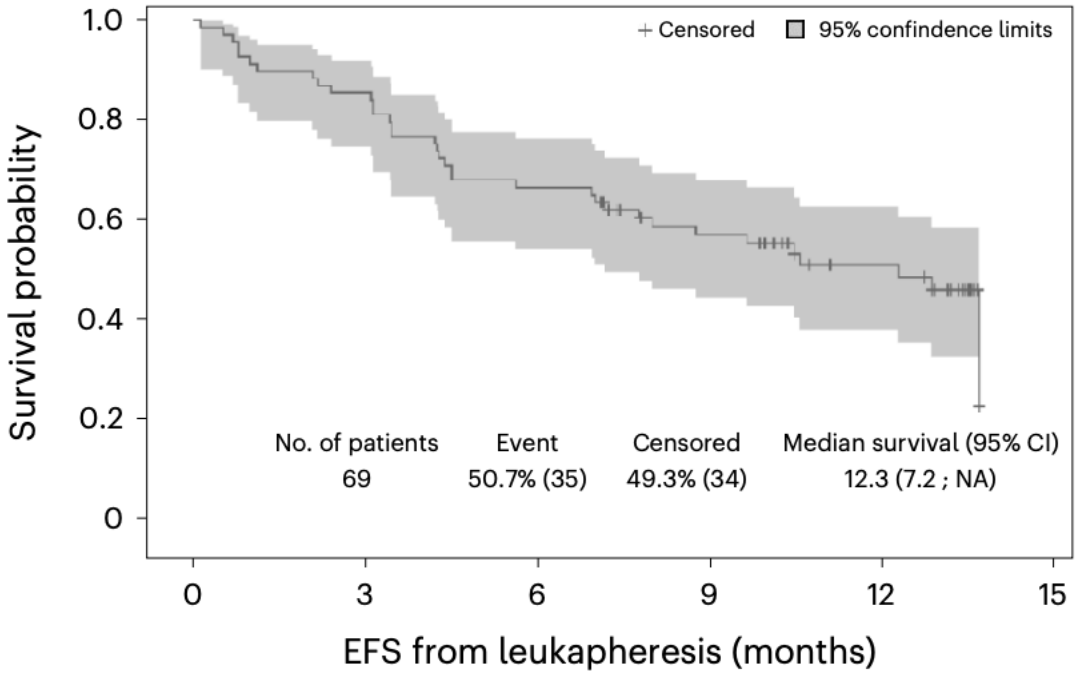
1. ECOG performance status of 0, 1 or 2
2. Absolute neutrophil count ≥1.0 × 10^9
3. Absolute lymphocyte count ≥0.1 × 10^9
4. Platelet count ≥ 75 x 10^9
5. Creatinine clearance ≥ 40 ml min
6. Left ventricular ejection fraction ≥ 45%



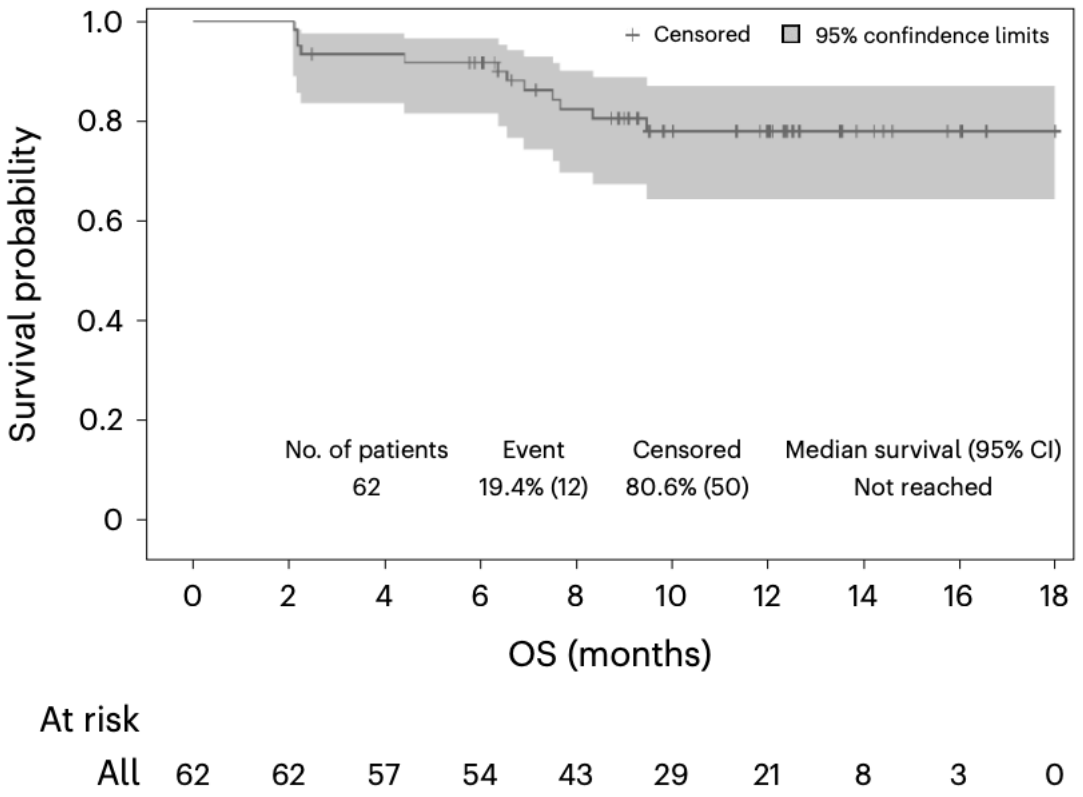
Houot R et al, Nat Med 2023

Alycante: Efficacy of Axi-Cel in Transplant-Ineligible LBCL pts equivalent to ZUMA-7

EFS from leukapheresis (months)



OS from axi-cel infusion (months)

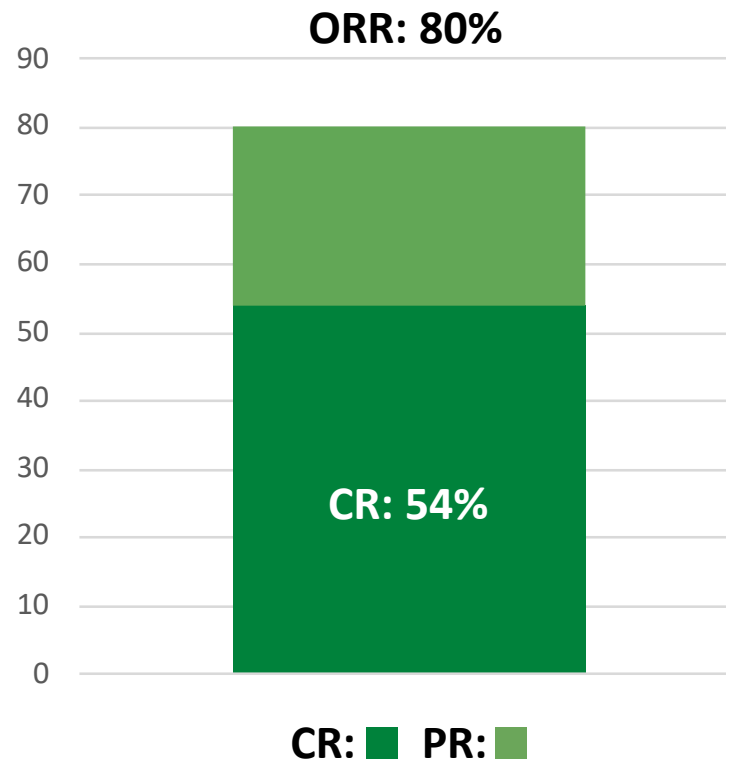


Houot R et al, Nat Med 2023

PILOT: Phase II Trial – Liso-Cel in R/R DLBCL pts not eligible for auto SCT

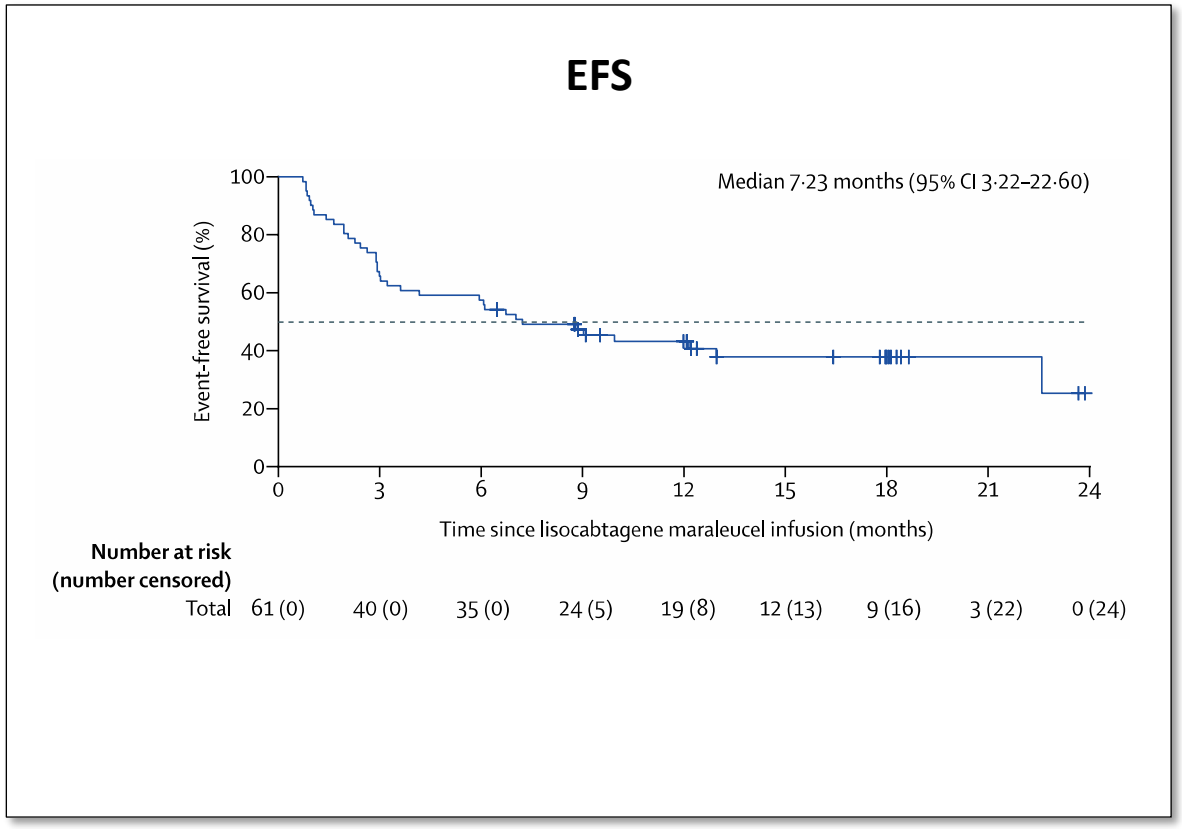
At least 1:

- **Age ≥ 70y**
- **ECOG 2**
- **DLCO ≤ 60%**
- **EF ≤ 50%**
- **CrCl ≤ 60mL/min**
- **AST/ALT 2x ULN**

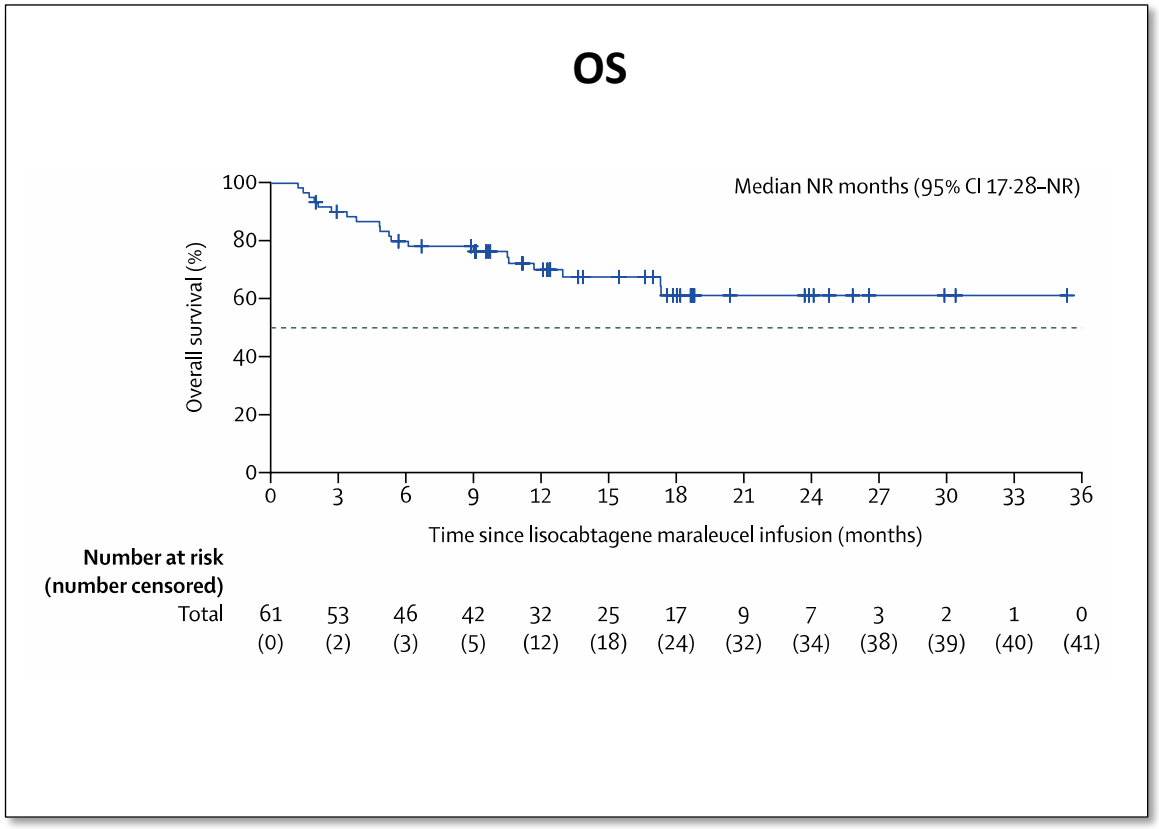


PILOT: Efficacy of Liso-cel in transplant-ineligible LBCL Equivalent to TRANSFORM Trial

EFS



OS



Sehgal A et al, Lancet Oncol. 2022

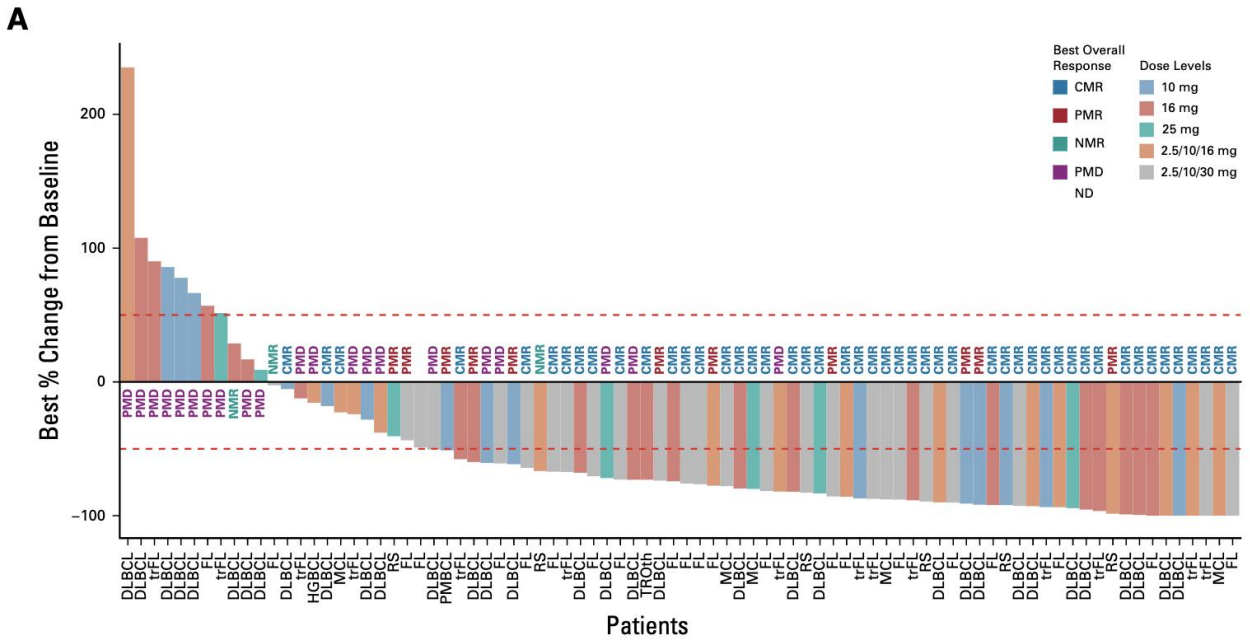
Summary of Efficacy & Toxicity in pts treated with CD19 CART

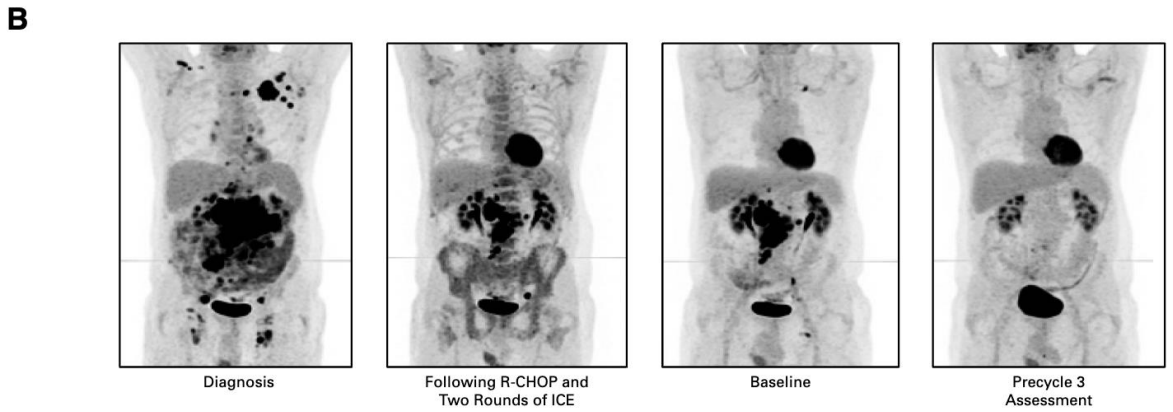
Alycante vs ZUMA-7, Pilot vs TRANSFORM

CAR Product	Axi-Cel		Liso-Cel	
Trial	**Alycante**	**ZUMA-7**	**Pilot**	**TRANSFORM**
ORR	90%	83%	80%	86%
CR-Rate	79%	65%	54%	66%
Median PFS	12.3m	14.7 mo	9 m	14.8 mo
Grade ≥ 3 CRS	8%	6%	1.6 %	1%
Grade ≥ 3 ICANS	14,5%	21%	5%	4%

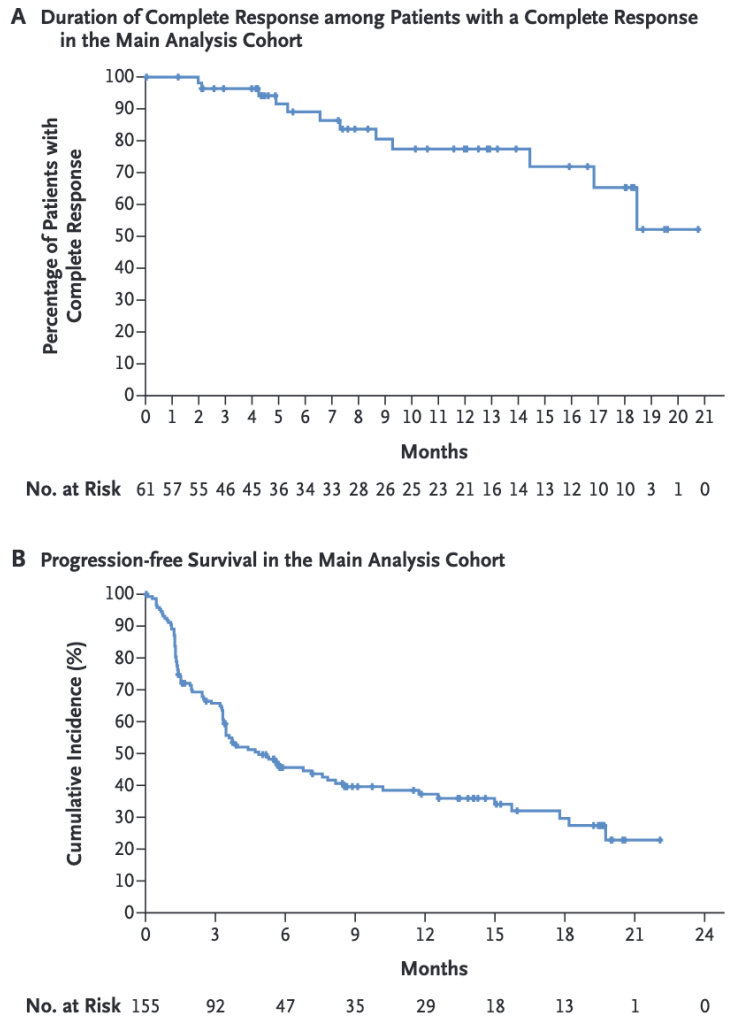
Houot R et al, Nat Med 2023; Sehgal A et al, Lancet Oncol. 2022

Bispecifics in R/R LBCL: Glofitamab (CD3xCD20)



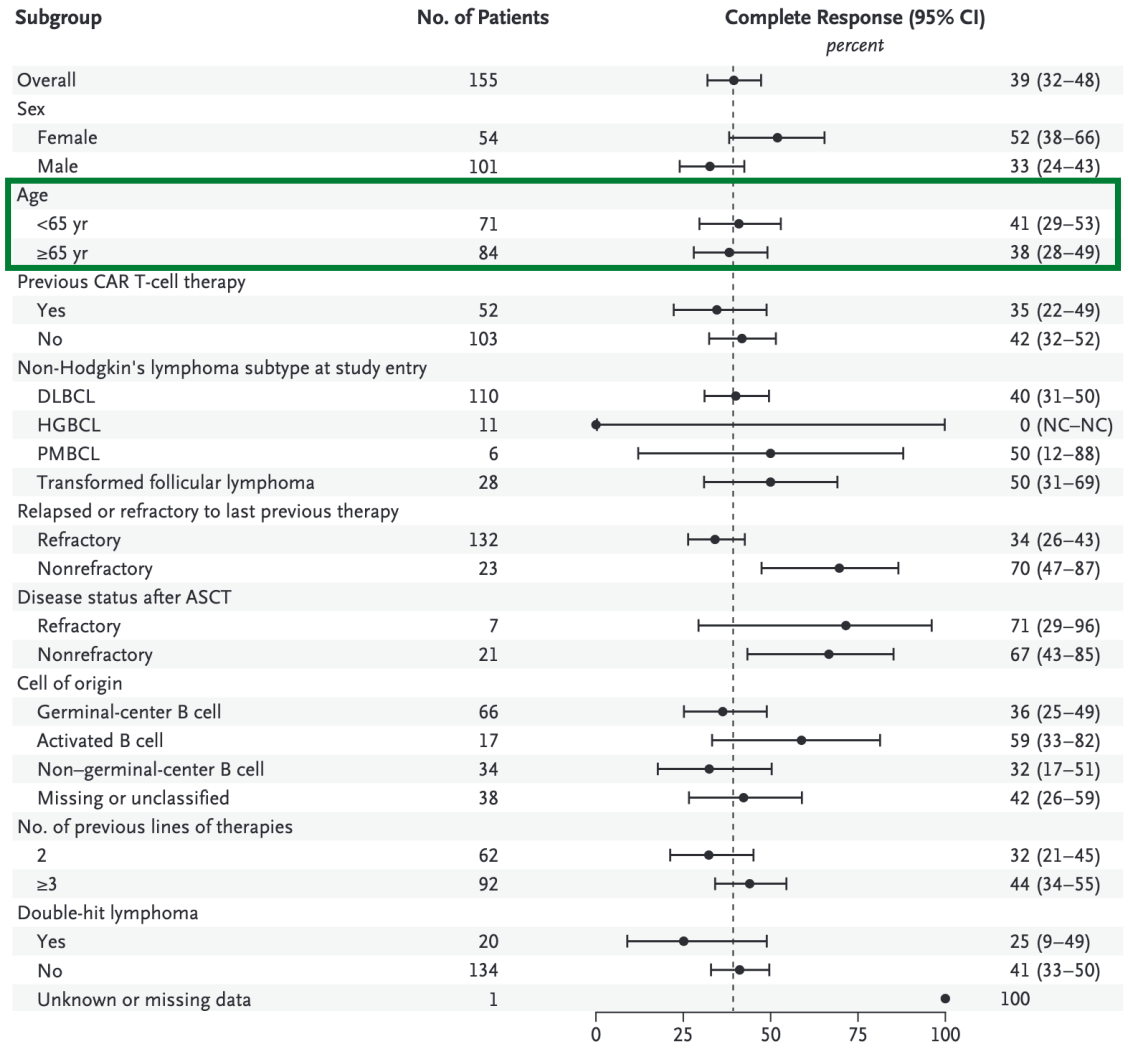


r/r DLBCL cohort



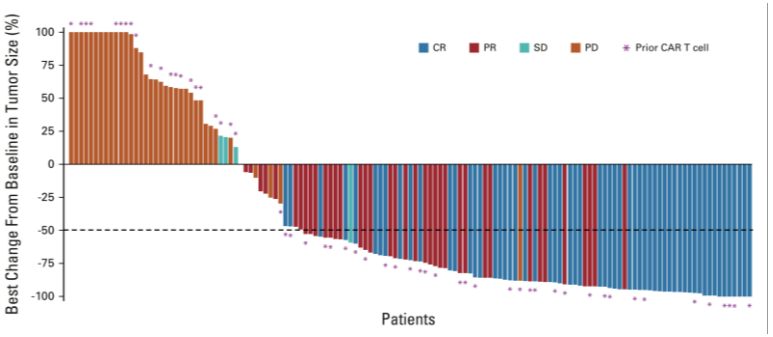
Hutchins et al. J Clin Oncol 2021; Dickinson et al. N Engl J Med 2022

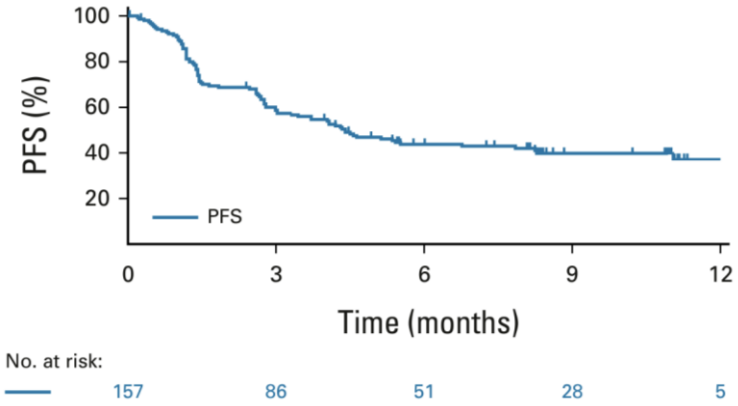
Glofitamab: Age does not impact Response Rate

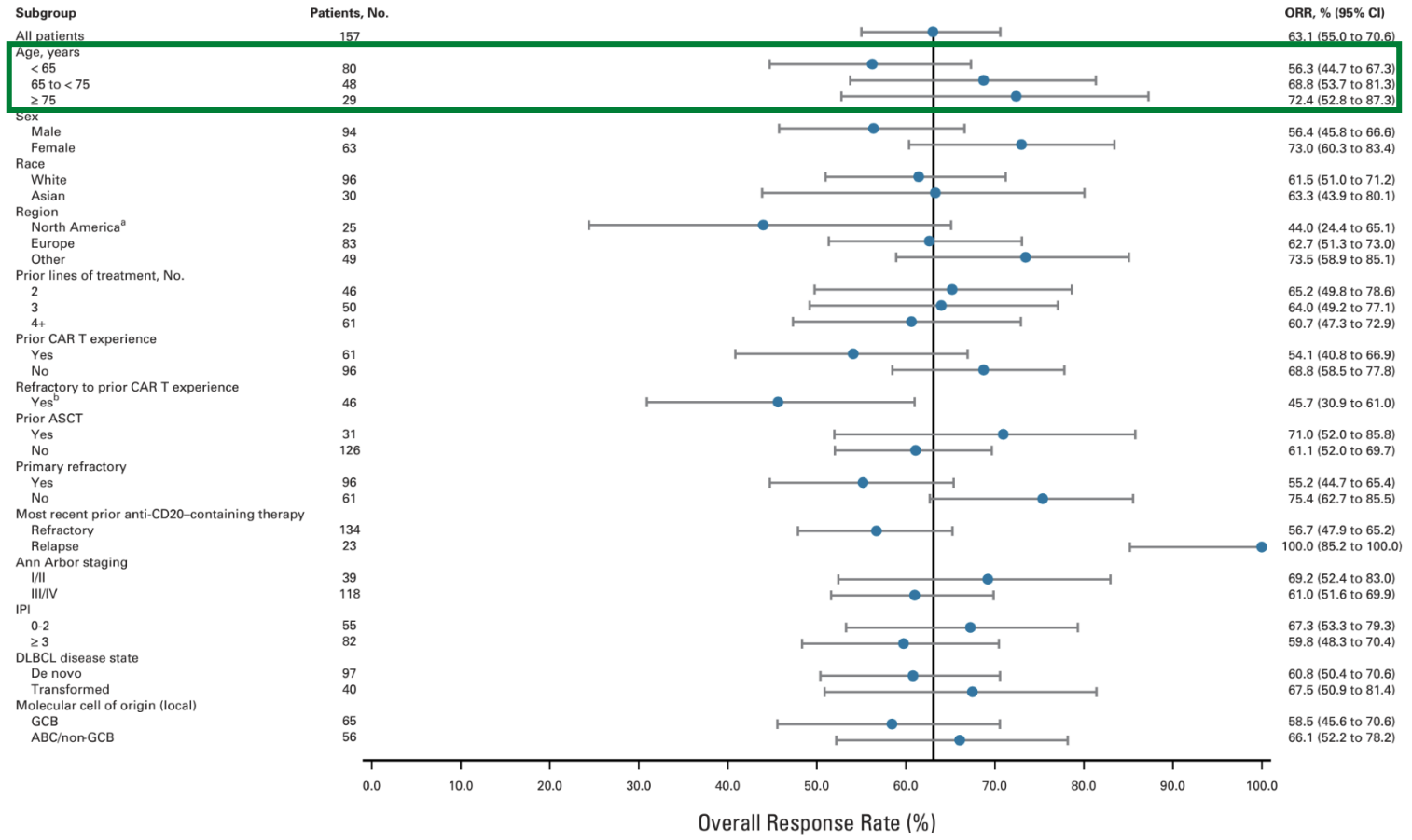


Hutchins et al. J Clin Oncol 2021; Dickinson et al. N Engl J Med 2022

Epcoritmab, CD20xCD3, Responses were consistent across all age groups, higher in the elderly







Thieblemont et al, JCO 2022

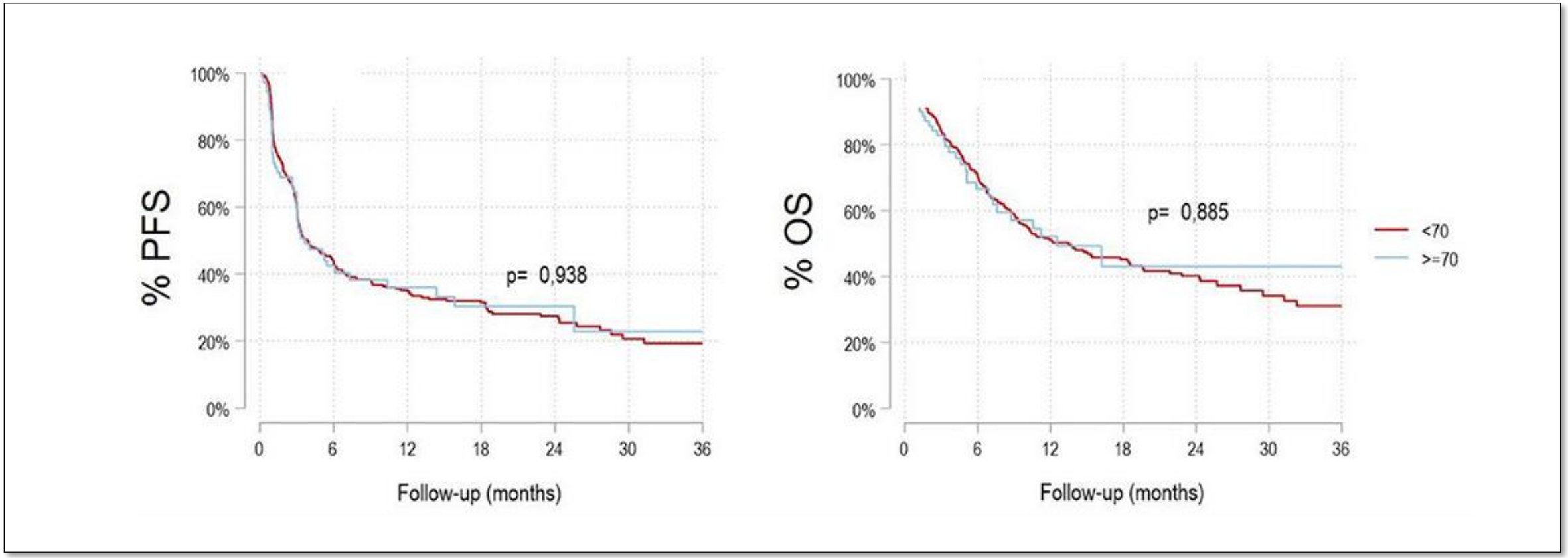
Very low Frequency of CRS & ICANS in Bispecifics, no statistics in relation to age

	Glofitamab (CD3xCD20)	Epcoritamab (CD3xCD20)	Odranexatamab (CD3xCD20)
Patients	R/R LBCL	R/R LBCL	R/Rj LBCL
Pat.	154	157	127
Median FU	20.1 mo	20 mo	30 mo
Response Rate (ORR)	59%	63%	52%
CR/CMR	38% (CR)	39.5% (CR)	31%
Median Do CR	24.1 mo	20.8 mo	18 mo
Grade ≥ 3 CRS	4%	3%	1%
Grade ≥ 3 ICANS	NR	1%	NR

Liu et al., J Hematol Oncol 2023

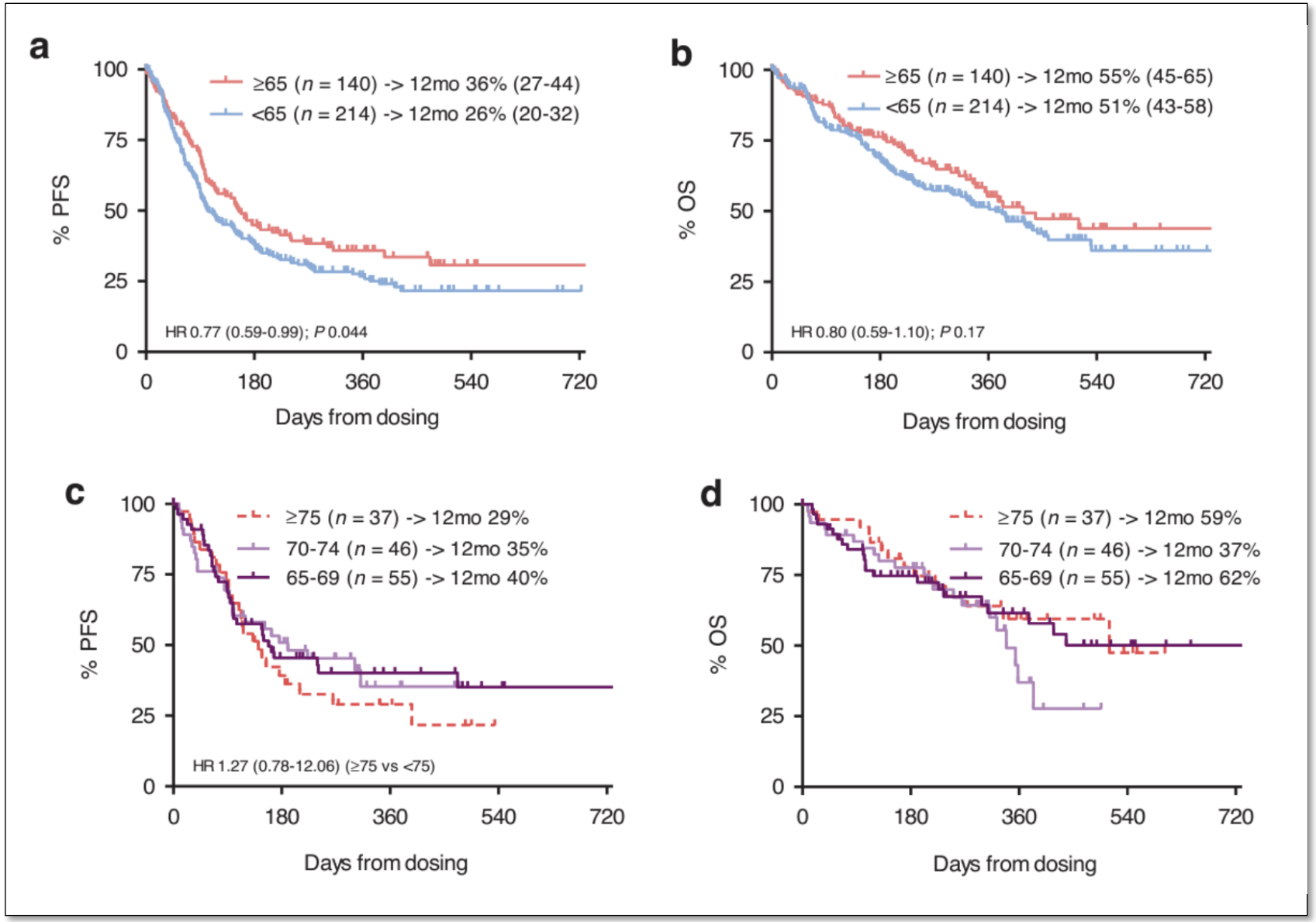
RWE of the GETH-TC/GELTAMO Study Group

- CART cell therapy was safe and effective in elderly patients **(< 70 years, n=341), > 70 years, n=71**)
- Response, OS and EFS in patients older and younger than 70 years were comparable
- No difference in NRM



Bailén et al, Transplant Cell Therapy 2024

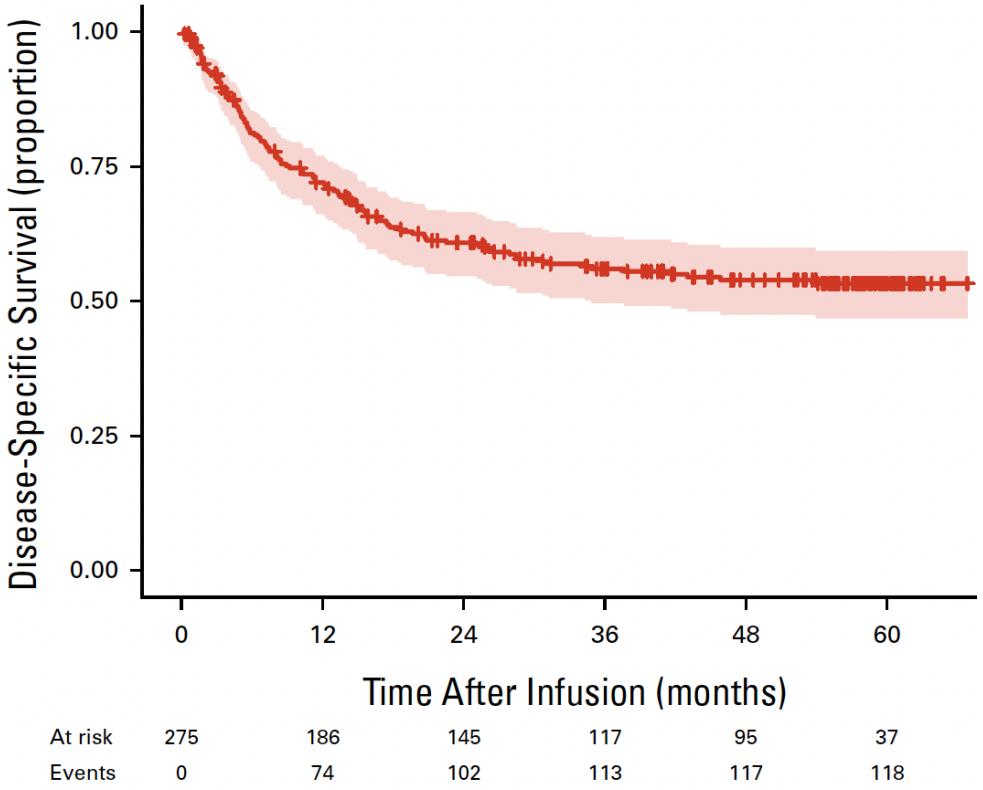
RWE form the GLA/DRST: no meaningful upper age limit could be defined

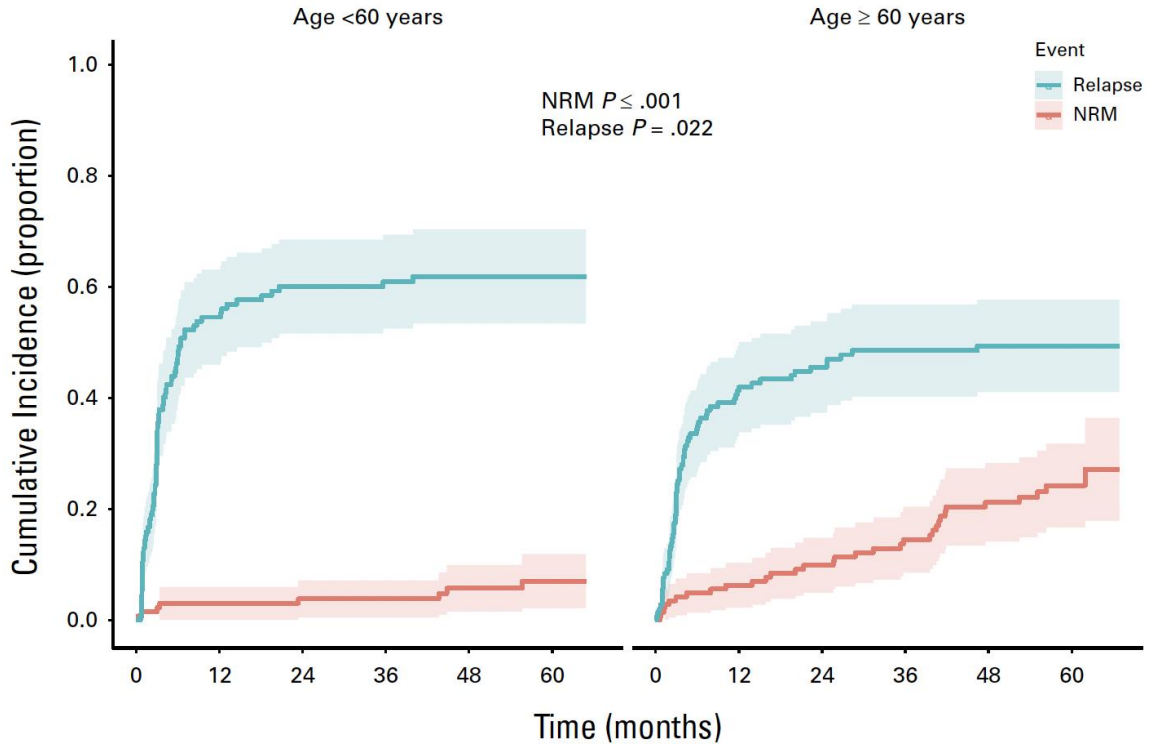


Dreger et al, BMT 2022

RWE: 5-year FU after Axi-Cel in LBCL from the US Lymphoma CAR T consortium

Patients > 60 years and older had a lower risk of relapse,
but a higher risk of NRM compared with patients younger than 60 years (n=275)





Jain et al, JCO 2024

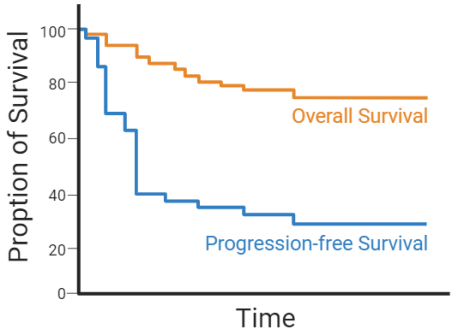
A Meta-Analysis of Non-Relapse Mortality (NRM) after CART cell therapy

- Non-relapse mortality (NRM) is typically used in allogeneic stem cell transplantation.
- NRM is defined as **death for whatever cause, without experiencing a prior disease relapse or progression**
  - Events: deaths from any cause without prior progression
  - Competing events: disease relapse or progression
  - Censoring: loss to follow-up
- NRM is assessed by **cumulative incidence function**.

Survival

Time from randomization/ intervention to

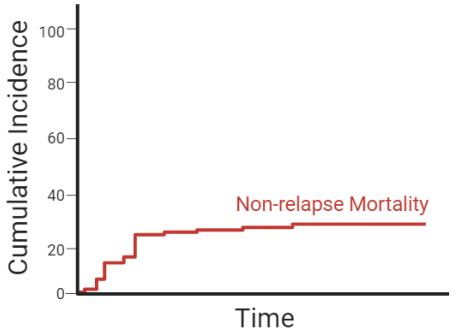
- OS: death
- PFS: progression or death



NRM

Time from randomization/ intervention to

- NRM: death prior to relapse or progression

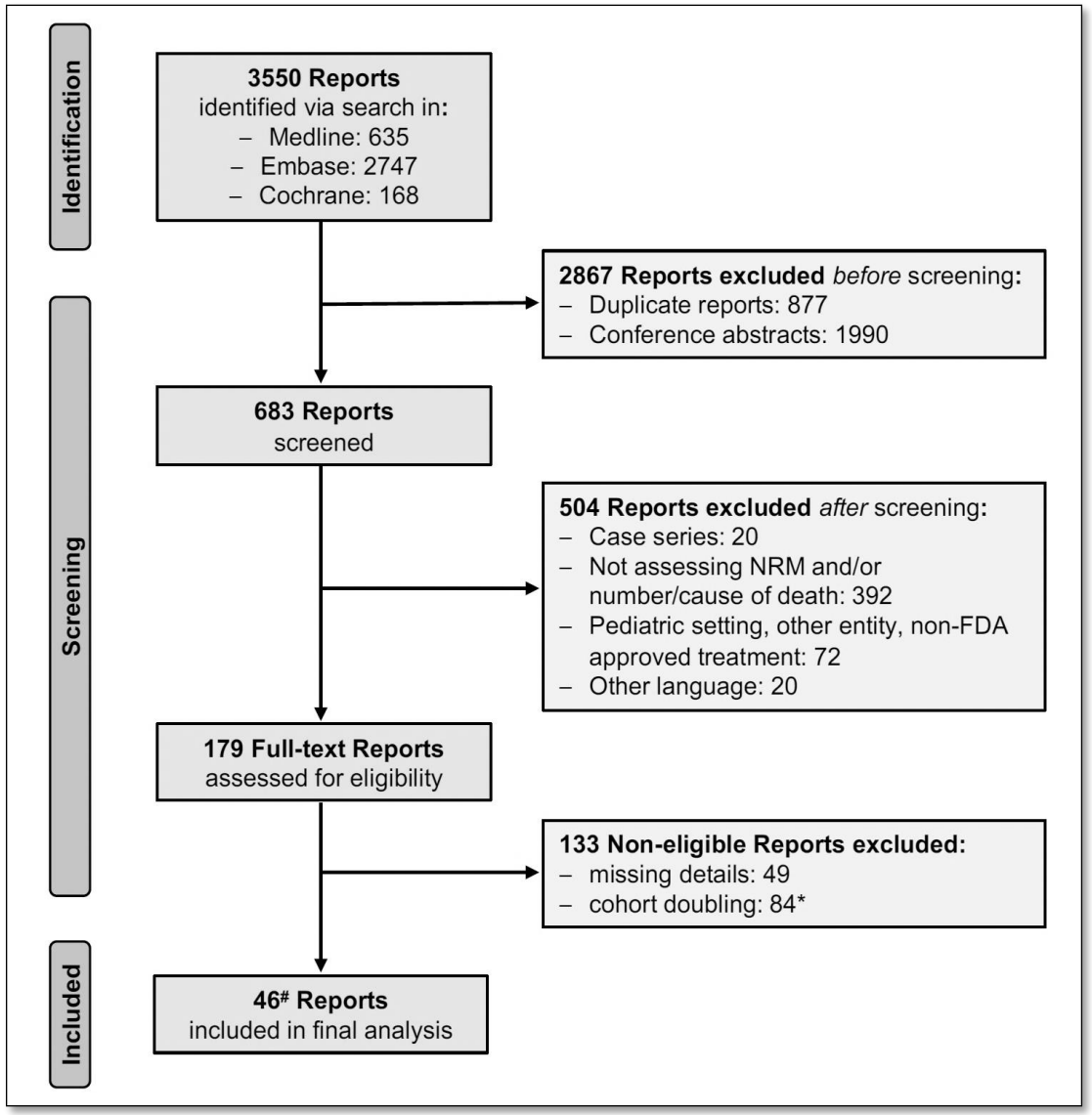


Study aims:

1. Characterize **NRM** of lymphoma and myeloma patients treated with CD19 or BCMA-directed CAR T-cells
2. Identify the **underlying causes** leading to NRM-related death

Cordas dos Santos, Tix et al, Subklewe, Perales, Rejeski. Nature Medicine, July 8, 2024

Study Retrieval and Identification for Meta-Analysis



Inclusion of articles published until September 2023 with following criteria:

(1) adult cancer patients with either indolent lymphoma (**IL**), large B-cell lymphoma (**LBCL**), multiple myeloma (**MM**) or mantle cell lymphoma (**MCL**)

(2) use of **CAR products approved by FDA**: axi-cel, tisa-cel, ide-cel, cilta-cel, liso-cel, brexu-cel

(3) data available on **NRM and/or number and causes of death**

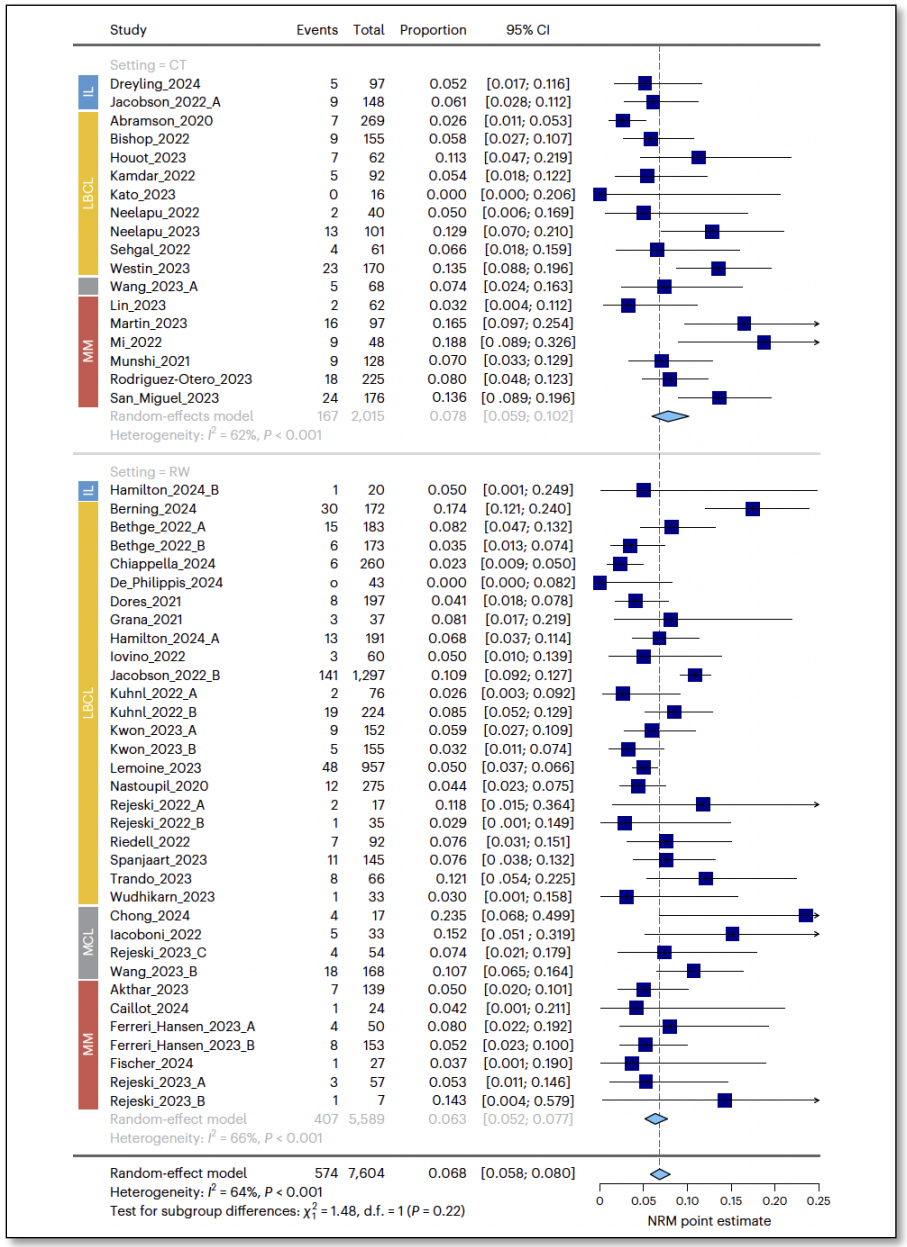
(4) RWS: report on **at least 80 patients**

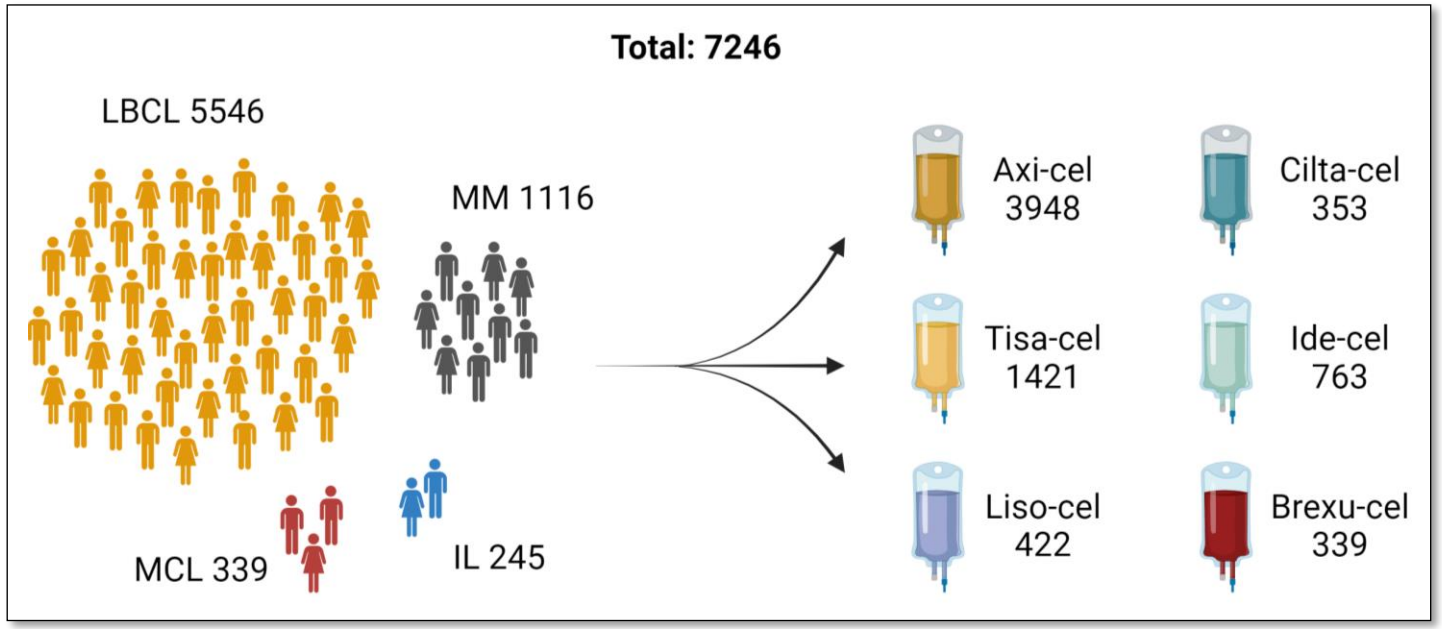
(5) CT: phase I-III **trials led to CAR product approval**

Exclusion of case studies, reviews, conference abstracts and meta-analyses.

Cordas dos Santos, Tix et al, Subklewe, Perales, Rejeski. Nature Medicine, July 8, 2024

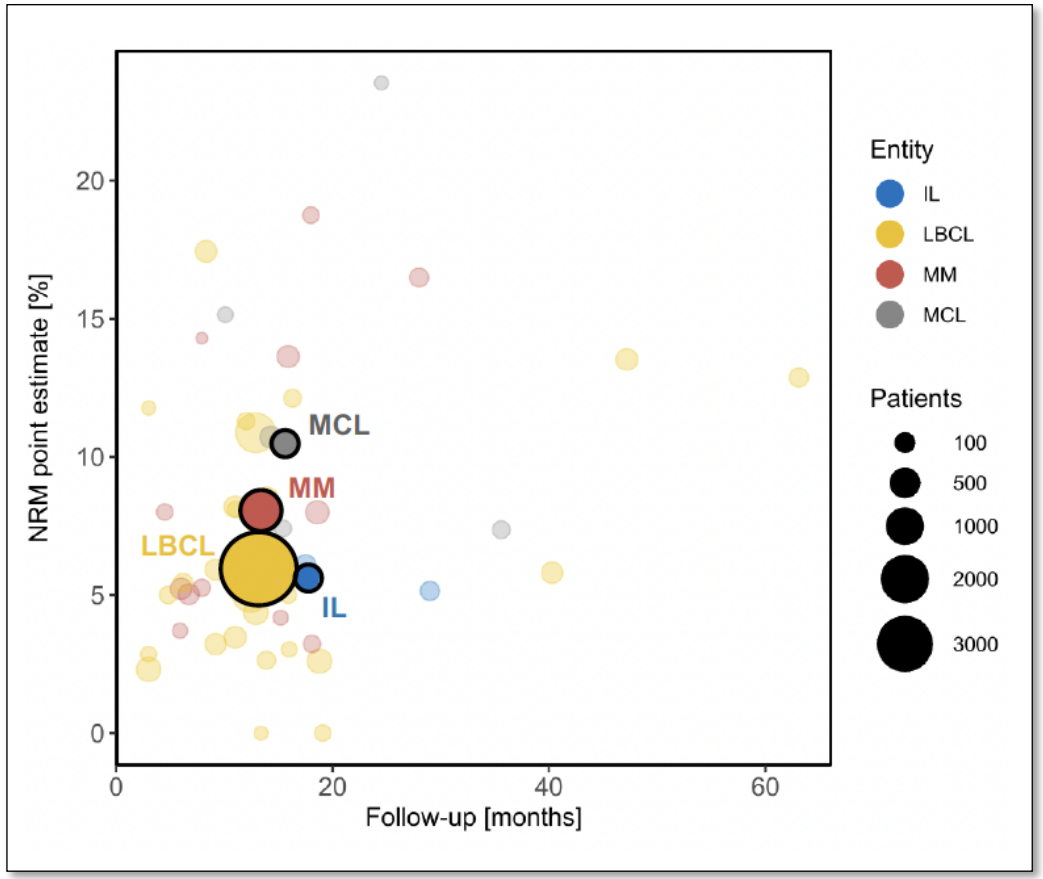
Characteristics of included Studies (34): 16 Clinical Trials + 18 RWE Reports

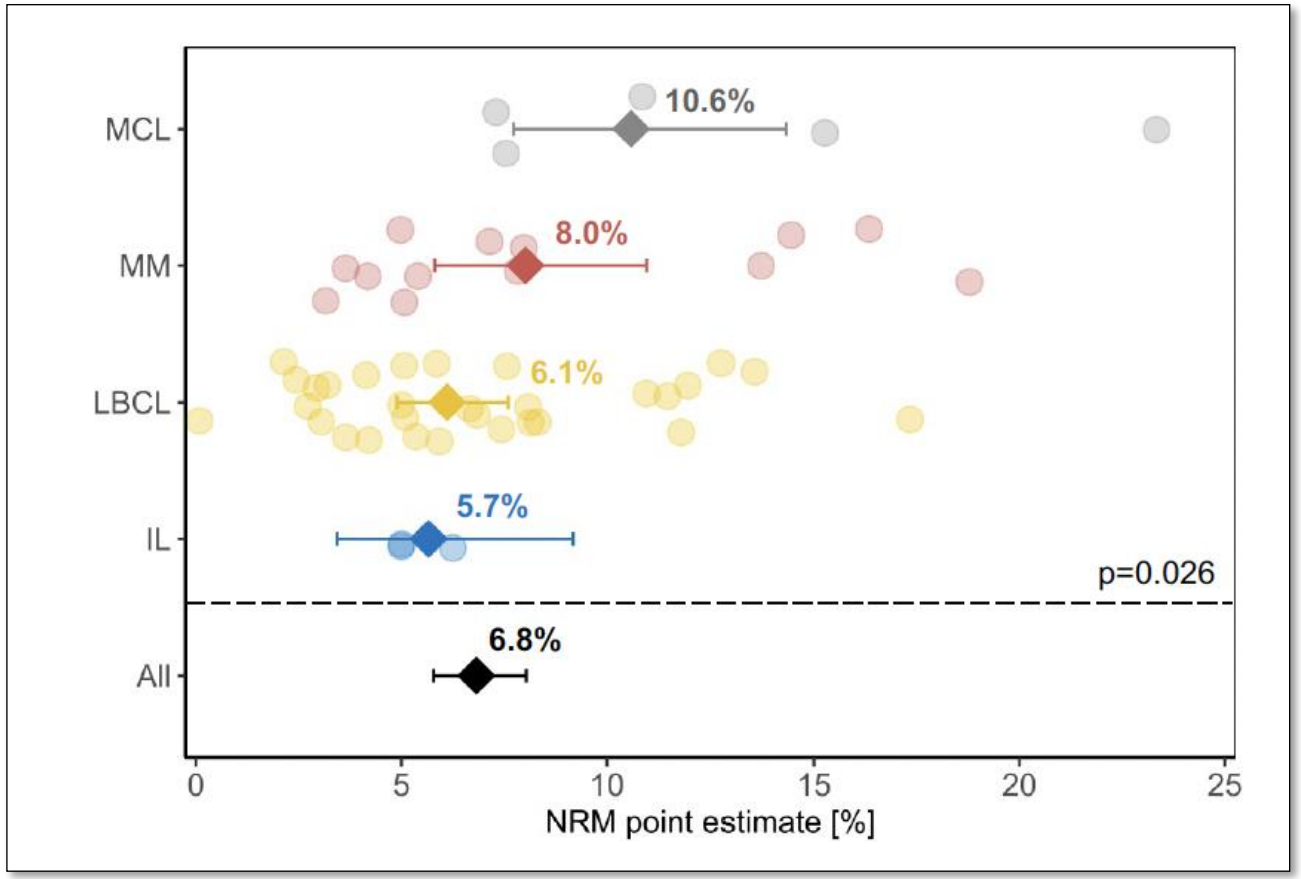




Cordas dos Santos, Tix et al, Subklewe, Perales, Rejeski. Nature Medicine, July 8, 2024

NRM across Disease Entities: 6.8 %; point Estimates are higher in pts with MCL & MM

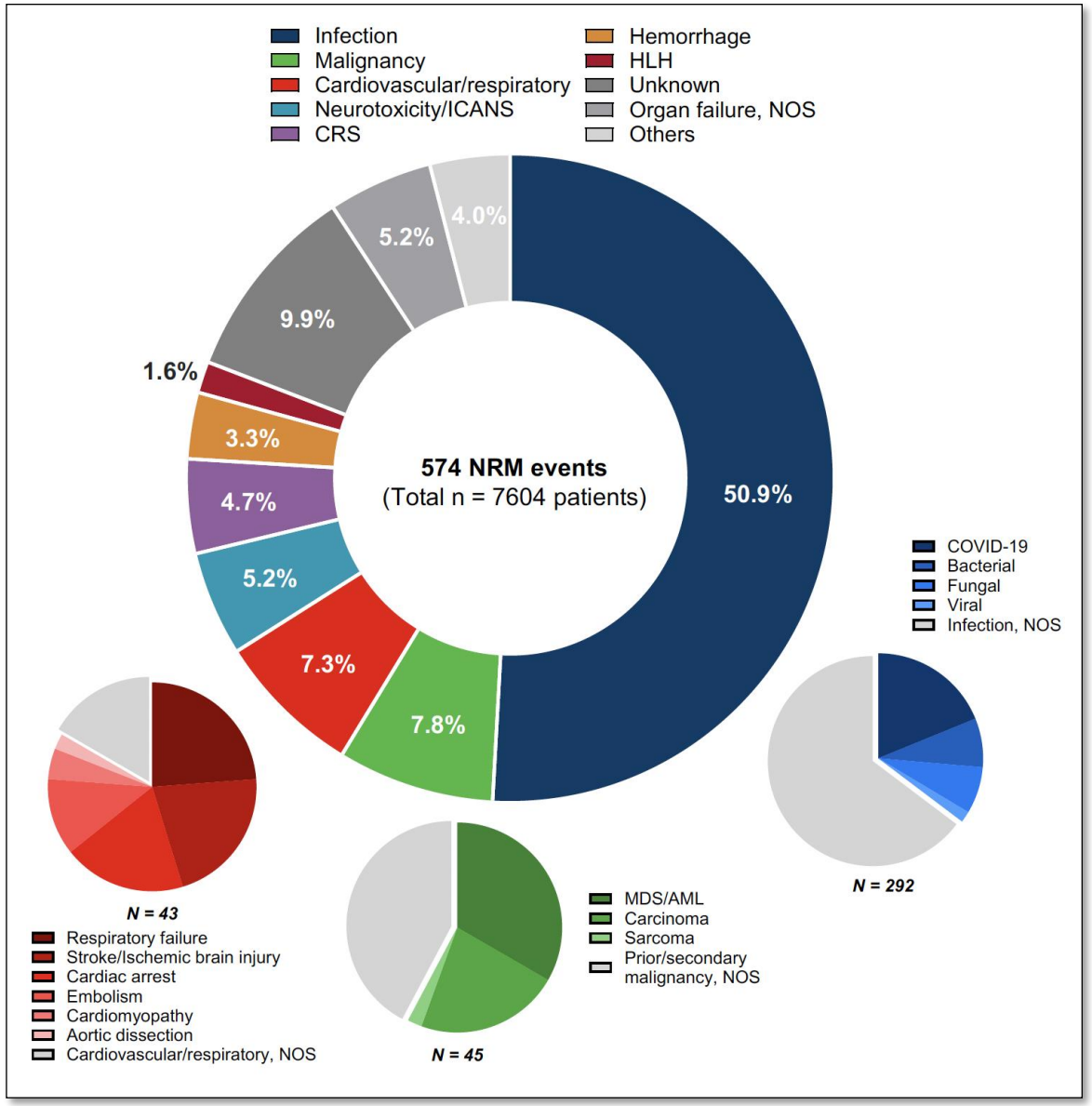




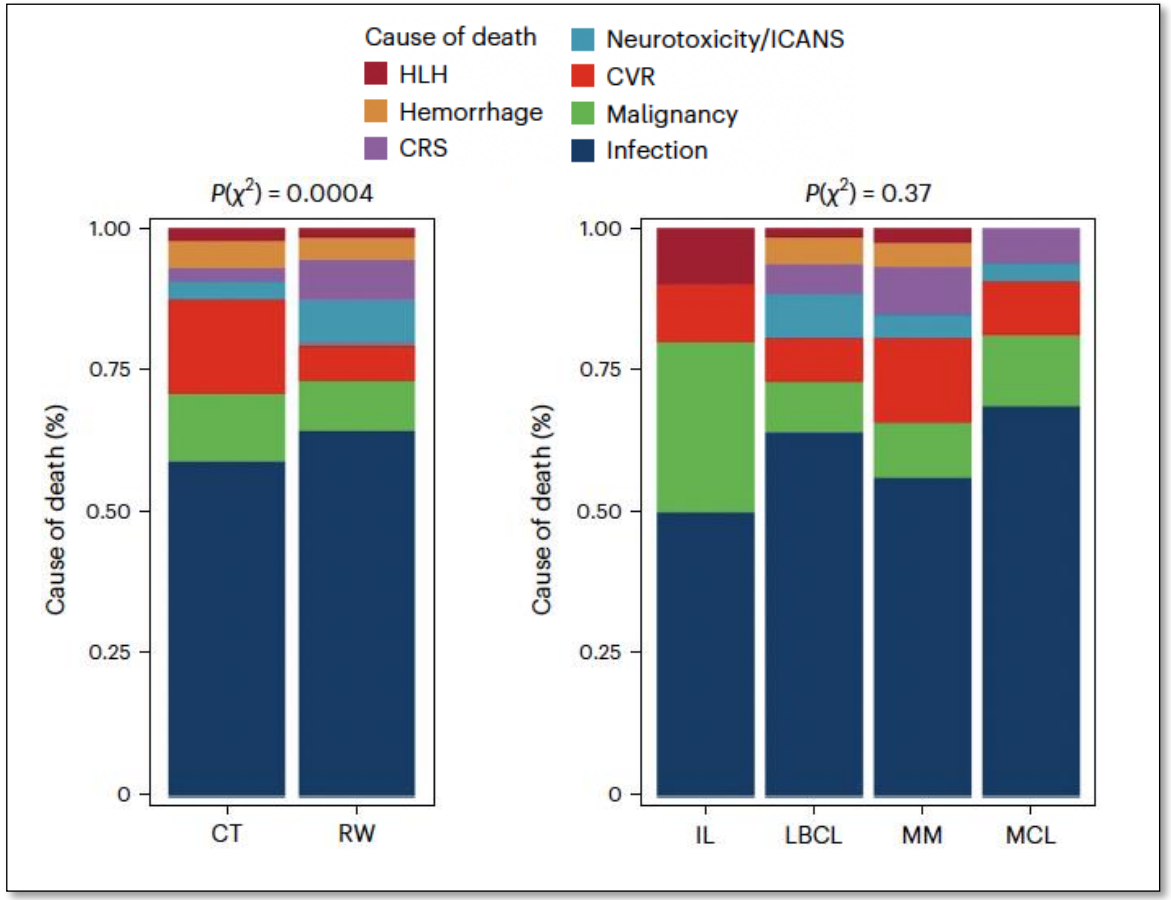
- **NRM** across all disease entities was **6.8 % (CAVE: in LBCL mainly 3rd Line, MM mainly 4th line, CART starter years)**
- **NRM** point estimates increase from **IL (4.4%) to LBCL (7.2%) to MCL (9.4%) and MM (9.6%) (CAVE: COVID Pandemic)**
- FU times of cohorts based on tumor entities were similar (p = 0.15).

Cordas dos Santos, Tix et al, Subklewe, Perales, Rejeski. Nature Medicine, July 8, 2024

Causes of NRM: Infections > Second Primary Malignancy > Cardio / Pulmonary Events

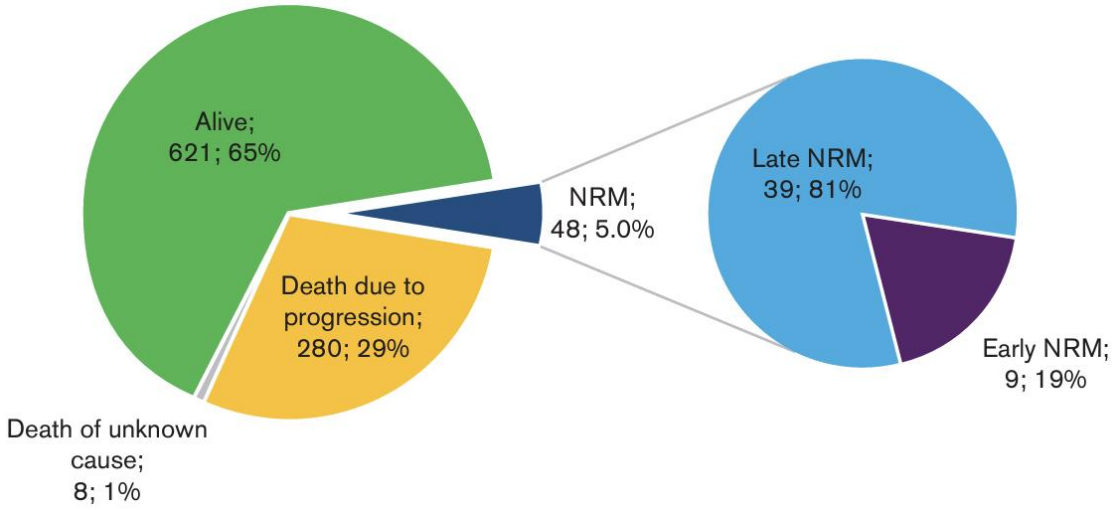


- **Infections** caused nearly **half of NRM-related deaths** in CAR-T patients (50.9 %), ca. 50% COVID asssociated
- **Second Primary Malignancy (SPM)** are the **second most common cause of NRM** post CAR-T (7.8 %)

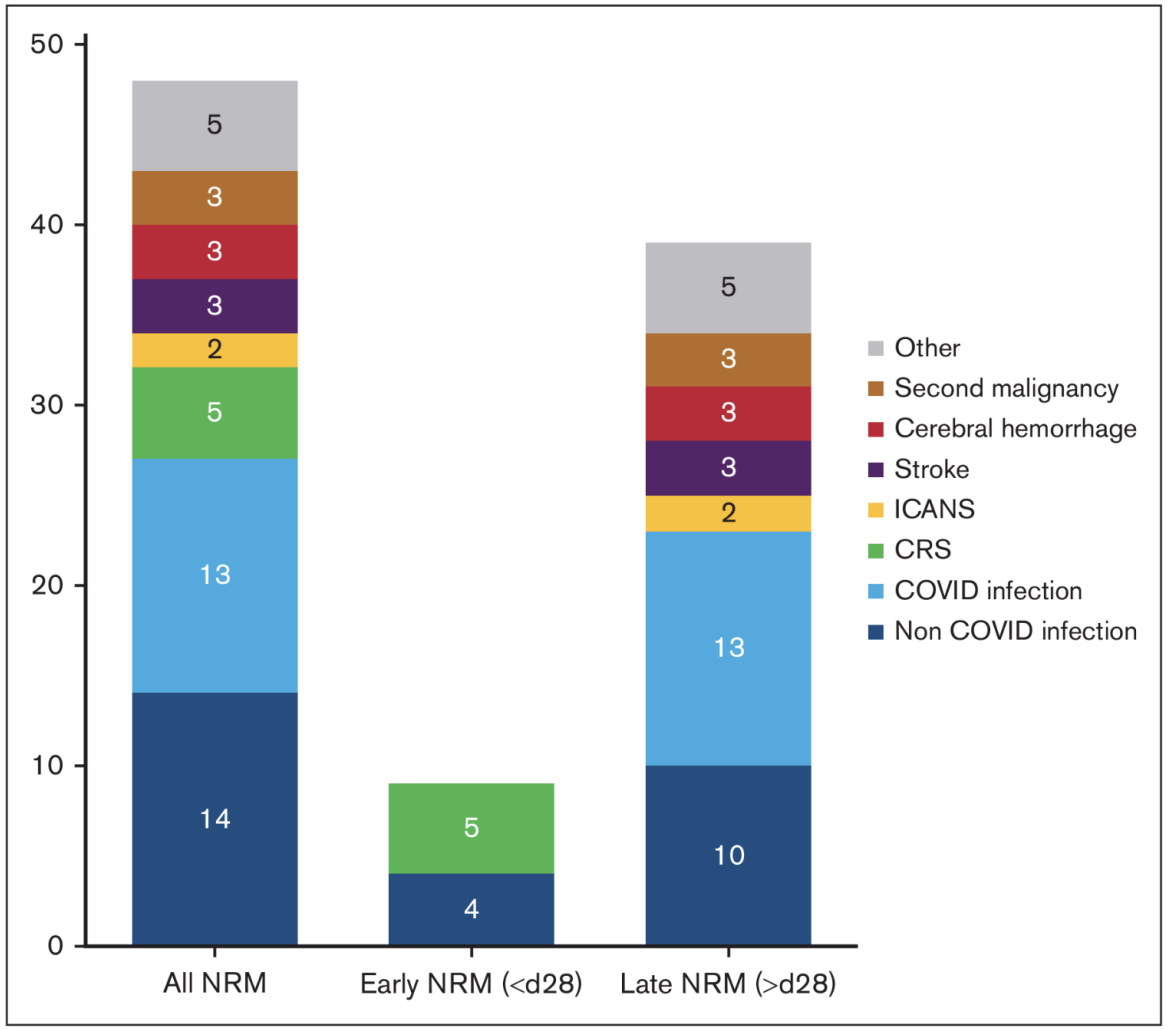


Cordas dos Santos, Tix et al, Subklewe, Perales, Rejeski. Nature Medicine, July 8, 2024

DESCAR-T Registry (Lysa Study): NRM after CD19 CART in R/R LBCL



- NRM in DLBCL: **5%**
- The majority are **late NRM** (after day 28 – 81 %)
- Fatal acute toxicities are uncommon
- **Infections are responsible for the majority of NRM**
- Comparison between early vs late (n=9 vs n= 39)



Lemoine J et al, Blood Adv 2023

Bispecifics: High Rate of Infections, in particular in MM

Multiple Myeloma

Author Year	Trial	Product	Target	All-grade infection	Grade ≥3 infection	Grade 5 infections
BCMA target (monotherapy)						
Wong et al, 2022[7]	CC-93269-MM-001	Alnuctamab (CC-93269)	BCMA	34%	9%	0%
D'Souza et al, 2022[8]	TNB383B.0001	ABBV-383	BCMA	41%	25%	6%
Topp et al, 2020[9]		Pacanalotamab (AMG-420)	BCMA	33%	24%	5%
Harrison et al, 2020[10]		Pavurutamab (AMG-701)	BCMA	NR	15%	2%
Bumma et al,[11] 2022	LINKER-MM1	Linvoseltamab (REGN5458)	BCMA	54%	29%	4%
Raje et al,[12] 2022	MagnetisMM-1	Elranatamab	BCMA	NR	29%	2%
Bahlis et al,[13] 2022	MagnetisMM-3	Elranatamab	BCMA	67%	32%	5%
Moreau et al,[14] 2022	MajesTEC-1	Teclistamab	BCMA	76%	45%	12%
Abdallah et al,[15] 2022	HPN217-3001	HPN217 Trispecific	BCMA, albumin	45%	16%	NR
BCMA target (combination therapy)						
Grosicki et al,[16] 2022	MagnetisMM-5	Elranatamab + daratumumab	BCMA + CD38	NR	NR	24%
Rodriguez-Otero et al,[17] 2022	TRIMM-2	Teclistamab + daratumumab	BCMA + CD38	68%	28%	5%
Searle et al,[31] 2022	MajesTEC-2	Teclistamab + dara + len	BCMA + CD38 + IMID	91%	38%	6%
Non-BCMA target (monotherapy)						
Trudel et al,[18] 2021		Cevostamab (BFCR4350A)	FcRH5	46%	20%	0%
Carlos-Stella et al,[19] 2022		Forimtamig (RG6234)	GPR5CD	53%	24%	2%
Chari et al,[20] 2022	MonumenTAL-1	Talquetamab	GPRC5D	66%	18%	0%
Non-BCMA target (combination therapy)						
van de Donk et al,[21] 2022	TRIMM-2	Talquetamab + Daratumumab	GPRC5D + CD38	53%	17%	2%

Lymphome

Malignant Target	Bispecific antibody	Number of Trials	Lymphoma subtype (No. of trials)	Number of patients	All Grade Infection (%, *95%CI*)	Median length of follow-up (IQR)
CD20	Epcoritamab	7	Aggressive (5), Indolent (1), B-cell NHL NOS (1)	470	39 *(29 - 47)*	11.4 (6.1-17.1
	Glofitamab	7	Aggressive (6), B-cell NHL NOS (1)	618	42 *(30 – 53)*	10.6 (6 – 15)
	Mosunetuzumab	6	Aggressive (3), Indolent (2), B-cell NHL NOS (1)	599	43 *(47 - 50)*	12.5 (8 – 28.5)
	Odronextamab	3	Aggressive (1), Indolent (1), B-cell NHL NOS (1)	414	59 *(48 – 69)*	21 (N/A)

Reynolds et al., Blood Adv 2023, Reynolds et al., Blood Adv 2024

Bispecifics: High Rate of Infections, in particular in MM

Multiple Myeloma

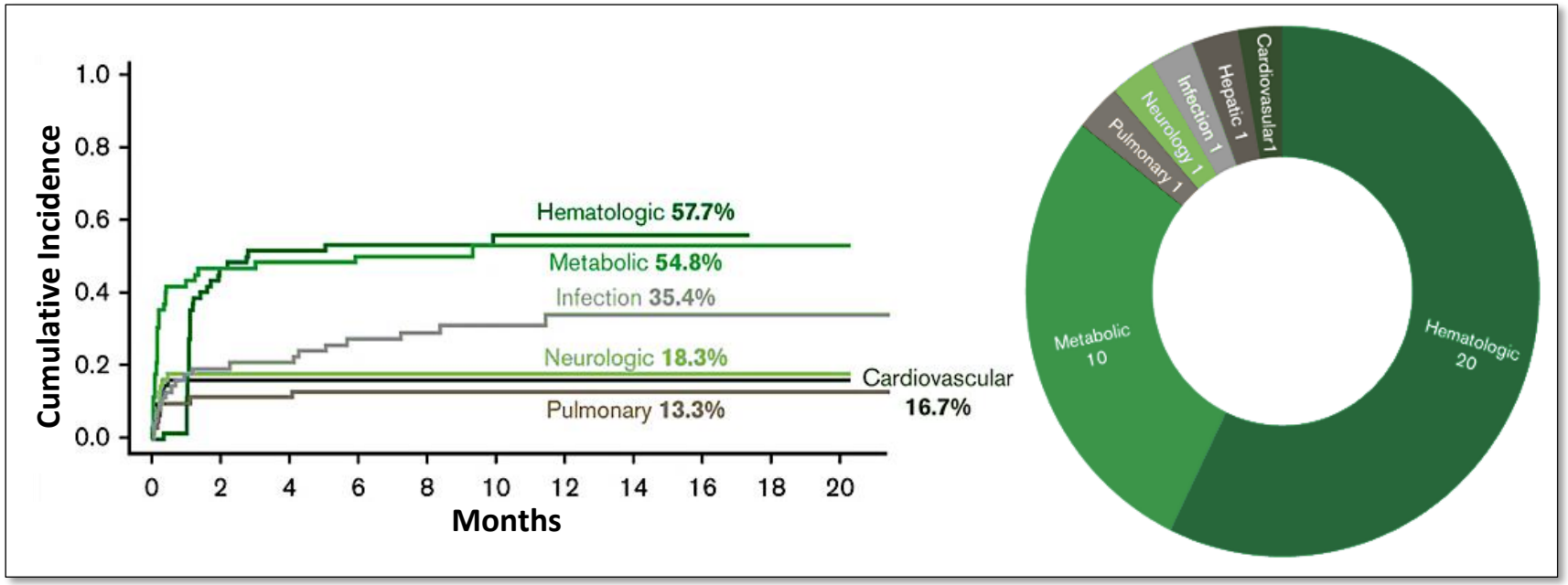
Author Year	Trial	Product	Target	All-grade infection	Grade ≥3 infection	Grade 5 infections
BCMA target (monotherapy)						
Wong et al, 2022[7]	CC-93269-MM-001	Alnuctamab (CC-93269)	BCMA	34%	9%	0%
D'Souza et al, 2022[8]	TNB383B.0001	ABBV-383	BCMA	41%	25%	6%
Topp et al, 2020[9]		Pacanalotamab (AMG-420)	BCMA	33%	24%	5%
Harrison et al, 2020[10]		Pavurutamab (AMG-701)	BCMA	NR	15%	2%
Bumma et al,[11] 2022	LINKER-MM1	Linvoseltamab (REGN5458)	BCMA	54%	29%	4%
Raje et al,[12] 2022	MagnetisMM-1	Elranatamab	BCMA	NR	29%	2%
Bahlis et al,[13] 2022	MagnetisMM-3	Elranatamab	BCMA	67%	32%	5%
Moreau et al,[14] 2022	MajesTEC-1	Teclistamab	BCMA	76%	45%	12%
Abdallah et al,[15] 2022	HPN217-3001	HPN217 Trispecific	BCMA, albumin	45%	16%	NR
BCMA target (combination therapy)						
Grosicki et al,[16] 2022	MagnetisMM-5	Elranatamab + daratumumab	BCMA + CD38	NR	NR	24%
Rodriguez-Otero et al,[17] 2022	TRIMM-2	Teclistamab + daratumumab	BCMA + CD38	68%	28%	5%
Searle et al,[31] 2022	MajesTEC-2	Teclistamab + dara + len	BCMA + CD38 + IMID	91%	38%	6%
Non-BCMA target (monotherapy)						
Trudel et al,[18] 2021		Cevostamab (BFCR4350A)	FcRH5	46%	20%	0%
Carlos-Stella et al,[19] 2022		Forimtamig (RG6234)	GPR5CD	53%	24%	2%
Chari et al,[20] 2022	MonumenTAL-1	Talquetamab	GPRC5D	66%	18%	0%
Non-BCMA target (combination therapy)						
van de Donk et al,[21] 2022	TRIMM-2	Talquetamab + Daratumumab	GPRC5D + CD38	53%	17%	2%

		N, %
	Fatal Infections	79
Malignant Target	**Microbiologically Confirmed**	**42 (53% of fatal infections)**
	Viral	32 (41% of fatal infections)
	SARS-COV-2	> 29*
	Epstein-Barr Virus	1
	CMV	1**
	PML	1
CD20	*Bacterial*	4 (5% of fatal infections)
	Gram negative bacteraemia	4
	Fungal	5 (6% of fatal infections)
	Candidemia	1
	Pneumocystis jirovecii pneumonia	3
	Systemic mycoses	1
	Protozoan	
	Toxoplasmosis	1
	Clinically Diagnosed	**12 (15% of fatal infections)**
	Sepsis	4
	Pneumonia	8
	Aetiology not reported	**25 (32% of total infections)**

* Some studies reported > the reported number of SARS-COV-2 infections
** Following first-line therapy

Reynolds et al., Blood Adv 2023, Reynolds et al., Blood Adv 2024

Hematotoxicity: severe and prolonged Cytopenias



Hematotoxicity

57.7%

CRS or Metabolic

54.8%

ICANS or Neurologic

18.3%

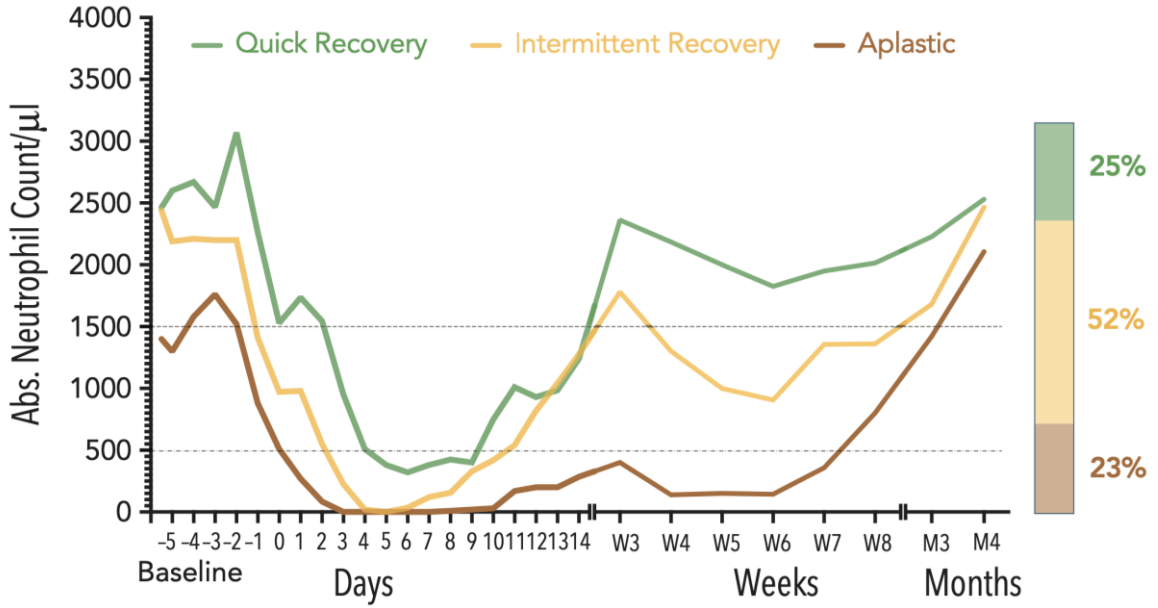
Profile:

- **Hematotoxicity = most common CTC grade** ≥ 3 toxicity in first year post CART
- CAR T-cell mediated **Hematotoxicity** can present long after lymphodepletion and resolution of acute CRS
- **Prolonged cytopenias predispose for serious infectious complications**

Wudhikarn et al, Blood Advances 2020

CTCAE grading does not reflect the different Phenotypes of Neutrophil Recovery missing the Integration of Depth and Duration of 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 (n = 37)
"Intermittent Recovery"	= neutrophil recovery (ANC > 1500/µl) followed by a 2nd dip with an ANC < 1000/µl after d 21 (n = 78)
"Aplastic"	= continuous severe neutropenia (ANC < 500/µl) ≥ 14 days (n = 34)

Rejeski et al, Subklewe; Blood 2021, Jain T. et al, Blood 2023

Grading: Immune Effector Cell associated Hematotoxicity (ICAHT)

Early (day 0 – 30): based on Depth and Duration
Late (> day 30): based on Depth

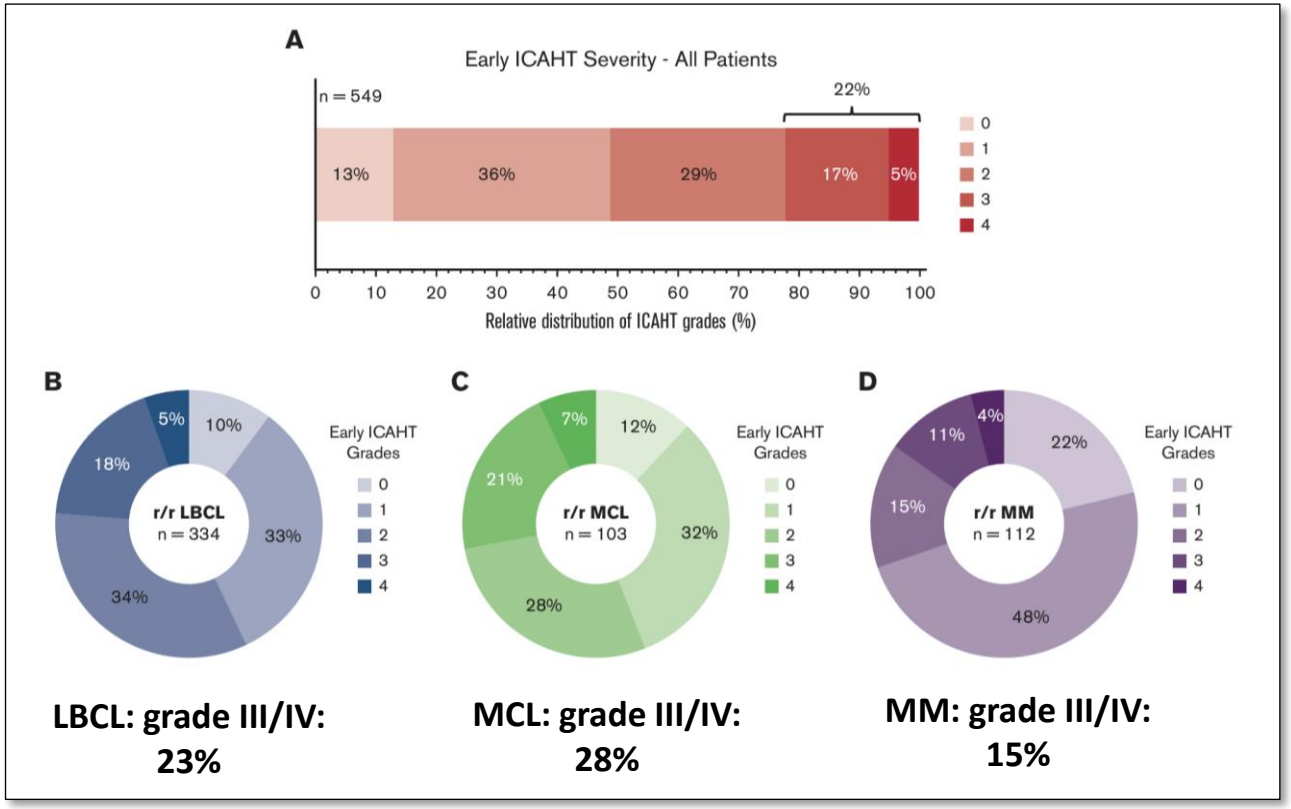
Grading	I	II	III	IV
Early ICAHT (day 0-30)				
ANC ≤ 500/µL	<7 days	7-14 days	≥14 days	Never above 500/µL
ANC ≤ 100/µL	–	–	≥7 days	≥14 days
Late ICAHT (after day +30)*				
ANC	≤ 1500/µL	≤ 1000/µL	≤ 500/µL	≤ 100/µL

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

Rejeski & Subklewe et al, Blood 2023

Early ICAHT Severity across Disease Entities: Grade III/IV in 15 – 28% of patients

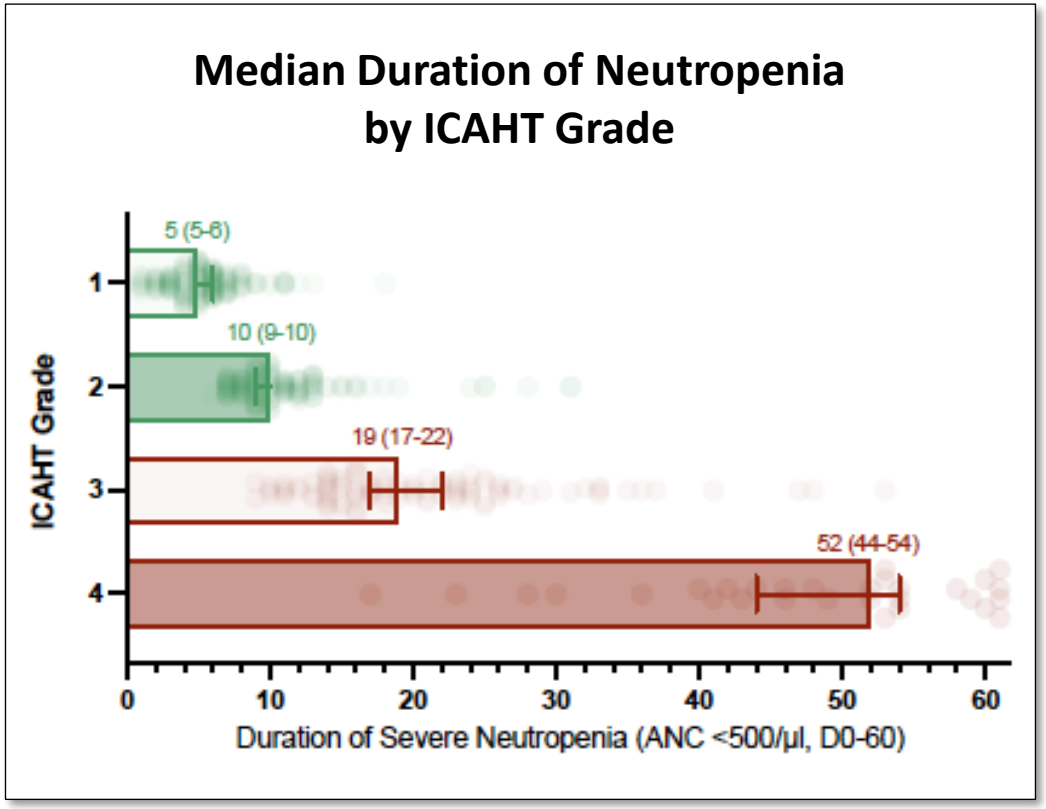
(n=549, r/r LBCL, r/r MCL, r/r MM)



LBCL: grade III/IV: 23%

MCL: grade III/IV: 28%

MM: grade III/IV: 15%



Rejeski et al, Subklewe. Blood Advances 2024

Current Grading System: CTCAE

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anemia	> 10.0 g/dL	> 8.0 g/dL	< 8.0 g/dL; trans-fusion indicated	Life-threatening	Death
Neutropenia	**> 1500/mm^3**	**> 1000/mm^3**	**> 500/mm^3**	**< 500/mm^3**	**N/A**
Thrombocytopenia	> 75,000/mm^3	> 50,000/mm^3	> 25,000/mm^3	< 25,000/mm^3	N/A

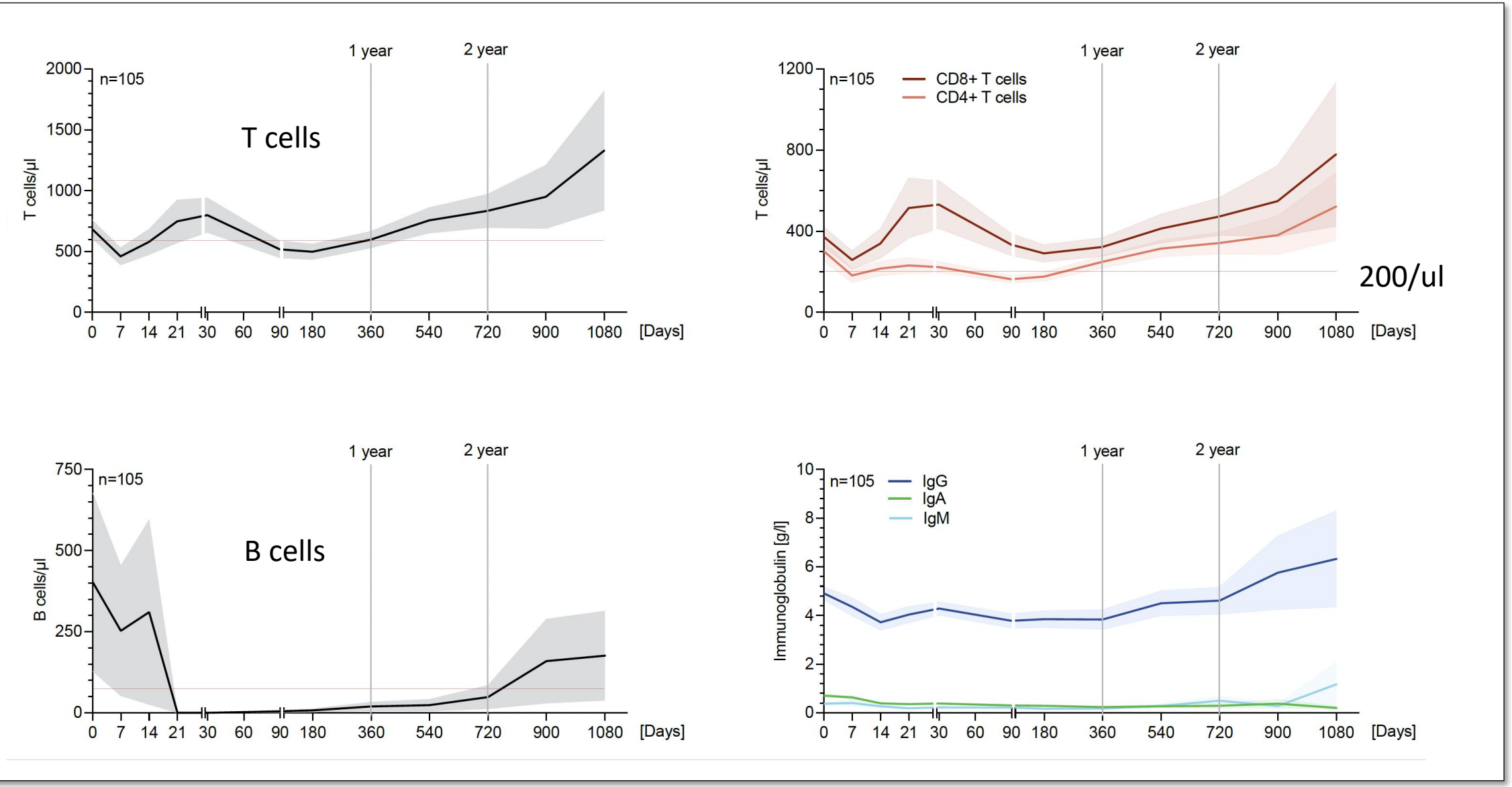
Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. -5.0

Bispecifics associated Hematotoxicy (CAVE CTCAE grading)

	Epcoritamab (CD3xCD20)	Glofitamab (CD3xCD20)	Mosunetuzumab (CD3xCD20)	Teclistamab (CD3xBCMA)	Talquetamab (CD3xGPRC5D)
Patients	R/R LBCL	R/R LBCL	R/R FL	R/R MM	R/R MM
Pat.	157	154	90	165	143*/145**
Neutropenia	22%	38%	28%	71%	34%*/28%**
Neutropenia ≥Gr 3 ***	15%	27%	26%	64%	31%*/22%**

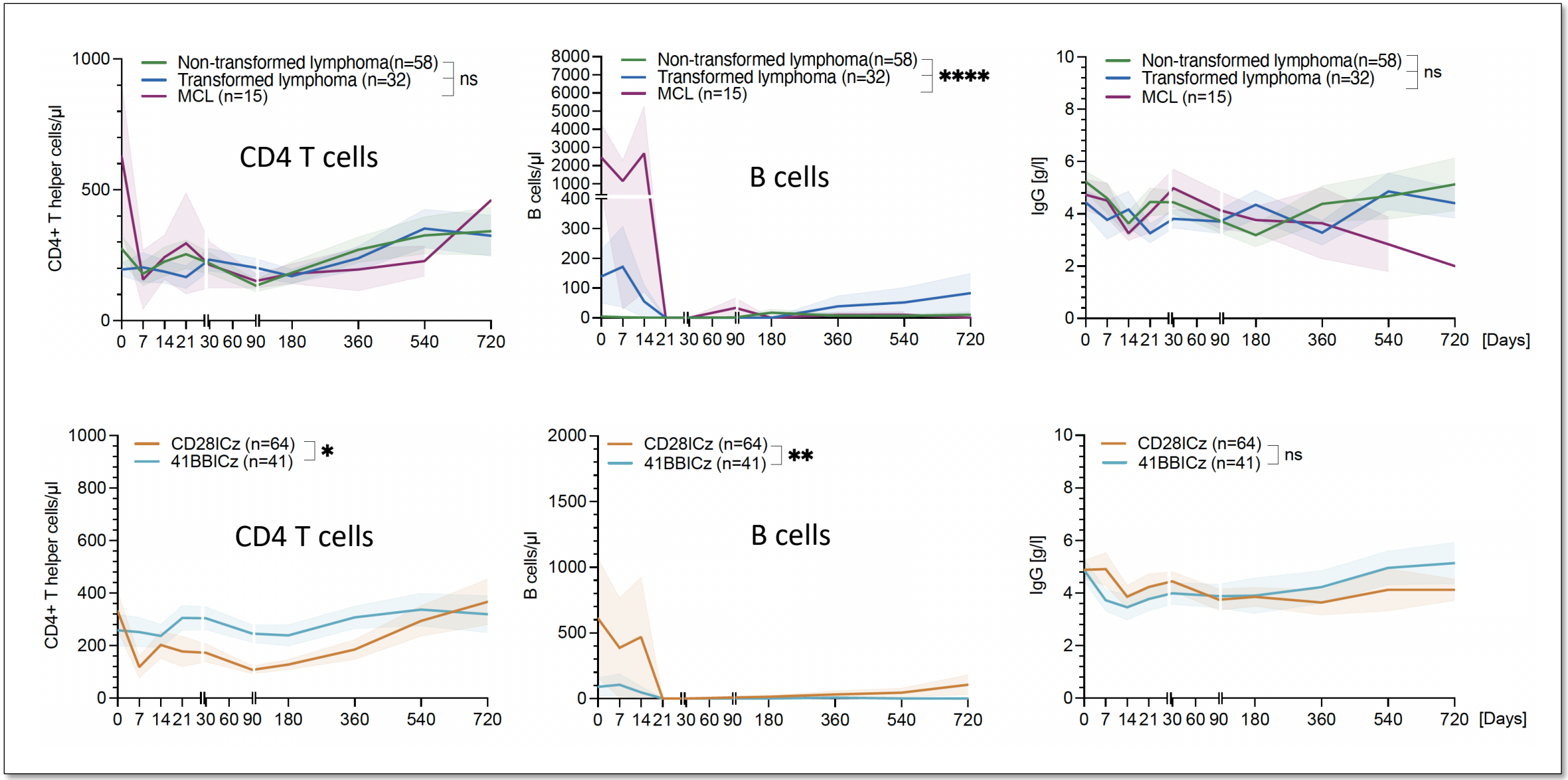
*0,4mg/kg q1wk, **0,8mg/kg q2 wks, *** based on the CTCAE criterae which does not integrate the lenght of neutropenia, which is commonly much schorter compared to CART

Protracted Lymphocyte and Immunglobuline Recovery following anti-CD19 CAR T Cell



Stock et al, 2024, DGHO 2024, in revision

Lymphocytes and Immunglobuline Recovery according to Disease Entity & CART Product



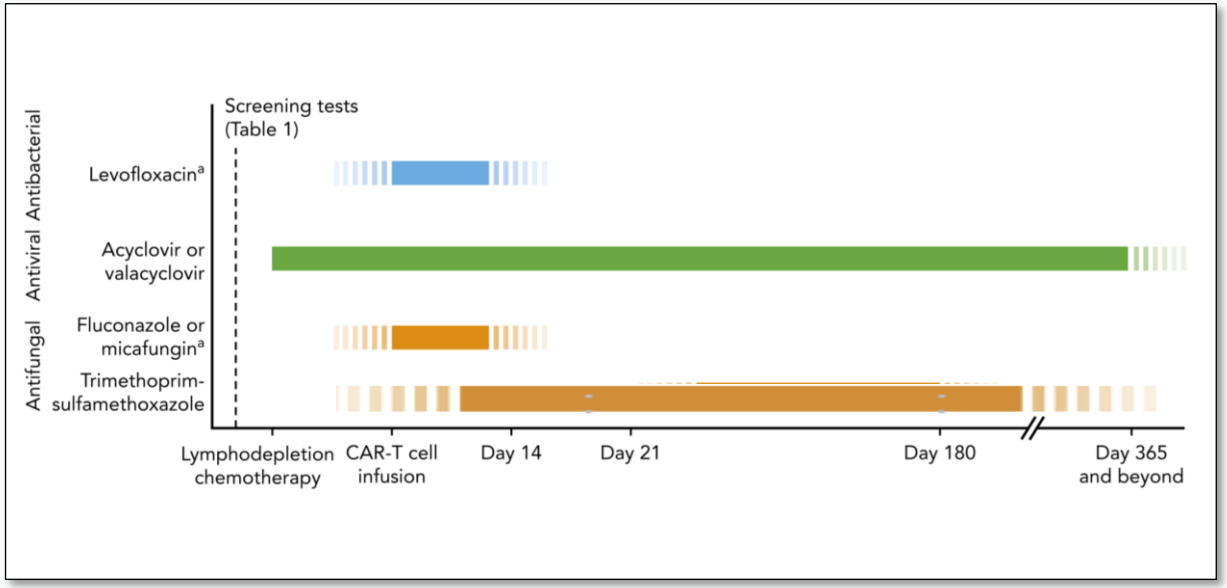
Stock et al, 2024, i DGHO 2024, n revision

Prophylaxis Recommendations for Patients treated with CART at the LMU

Prophylaxis	LMU Standard	Alternatives	vulnerable Phase	diagnostic Parameter	Escalation in susp. infection
Bacterial	HT score adjusted, e.g. Ciprofloxacin		Day 0 until ANC reconstitution	Neutrophil counts > 500/ul w/o G-CSF support	Pseudomonas-active, e.g. Piperacillin/Tazobactam
Fungal	After Risikoprofil: Posoconazol	Micafungin	Day 0 – Day 30 (Candida spp.) Day 14 – Day 60 (Aspergillus spp.)	ANC < 500/µl, RF for a prolonged Cytopenia ≥10 Days	Ambisome Voriconazol
Viral	Aciclovir	Valaciclovir	Day 0 **until immunological Reconstitution**	LySub: Absolute CD4+ Count <200/µl, B-cell Count < 20/ul	Aciclovir 10mg/kg i.v. 1-1-1
HBV	Entecavir		Day 0 – Day 180, viral Load Control	Anti-HBc positive, HBs-Ag positive	
Pneumocystis	Cotrimoxazol	Dapson Atovaquone	Day 0 – 28 **until immunological Reconstitution**	LySub: Absolute CD4+ Count <200/µl, B-cell Count < 20/ul	Cotrimoxazol

Minimize Risk for Infection

Late Phase (post day +30): Prophylactic anti-virals, anti-PJP, IVIG-Substitution, Vaccines



Prophylaxis:

- Antibakteriell: risk adapted during cytopenia
- Antifungal: risk adapted during cytopenia, cave steroids
- Antiviral: until immunreconstitution (CD4 T_H >200/µL)
- PjP: until immune reconstitution (CD4 T_H >200/µL)
- Starting month 3 : Covid & Influenza Vaccine, RSV Vaccines depending on pts risk profile

Prophylactic IgG Substitution

- Cave: increased risk of recurrent infection in particular of the upper respiratory tract (e.g. bekapselte Bakterien, virale Erreger)
- Therapeutic Benefit has to consider IgG values, pts risk profile, prior infectious complications, consider s.c. application

Serum IgG <4 g/L or Severe or recurrent bacterial infections

Immunglobulin-Substitution 20 g i.v. absolut (e.g. 400 – 500 mg/kg) every 4 weeks

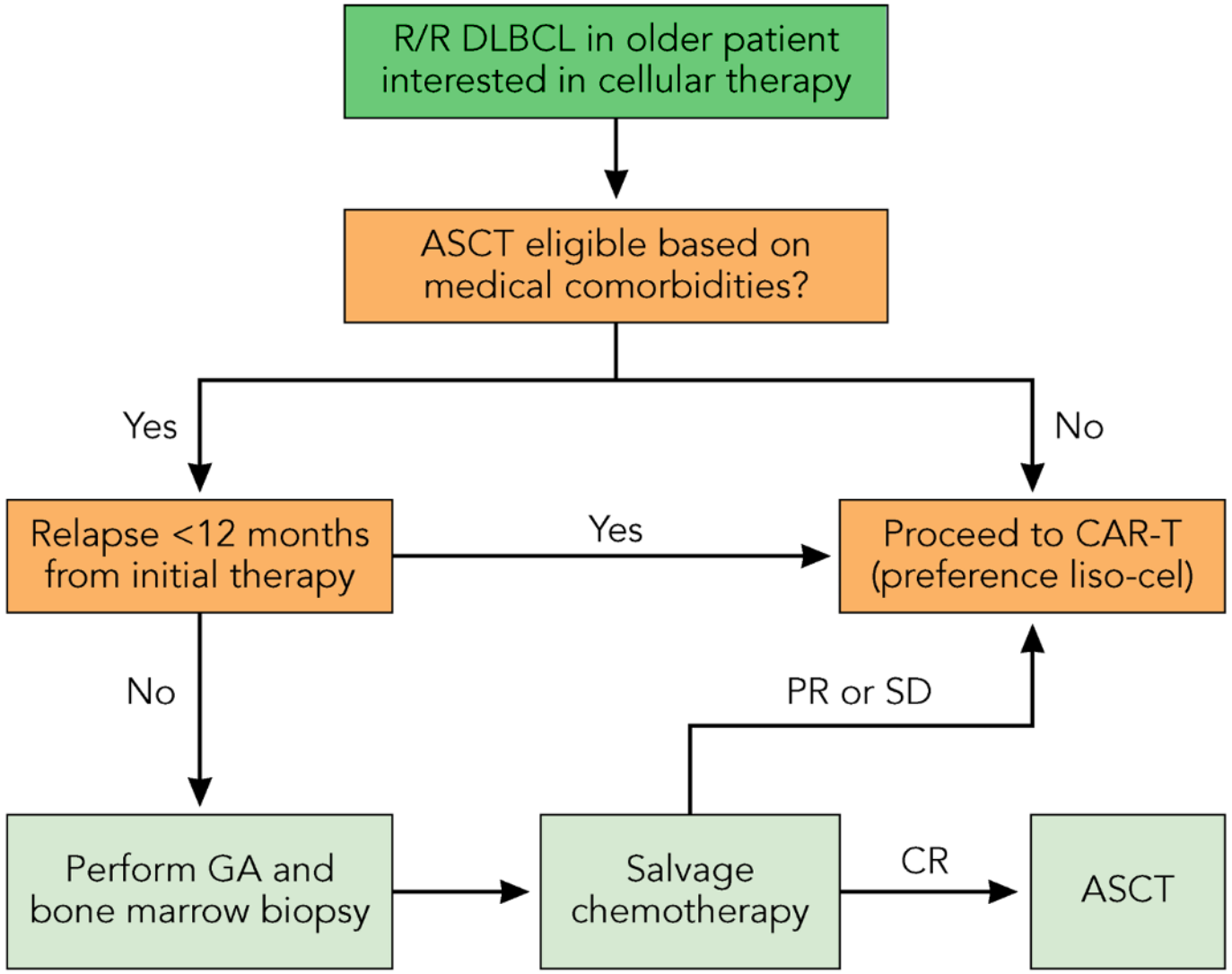
Adapted from Hill JA, Seo SK, Blood. 2020 Aug 20;136(8):925-935

Prophylaxis Recommendations for Bispecifics at the LMU

Prophylaxe	LMU Standard	Alternativen	Vulnerable Phase	
Viral	Aciclovir	Valaciclovir	Tag 0 **bis zur immunologischen Rekonstitution**	?? (6 Monate post-Therapy or rather until immune reconstitution)
HBV	Entecavir		Tag 0 – Tag 180	
Pneumocystis	Cotrimoxazol	Dapson Atovaquone	Tag 28 – **Tag 180**	

+ ggf. Immunglobulin-Substitution (IgG <4g/dl und rez. Infekte)

Treatment Algorithm for older Pts with 1st relapse LBCL

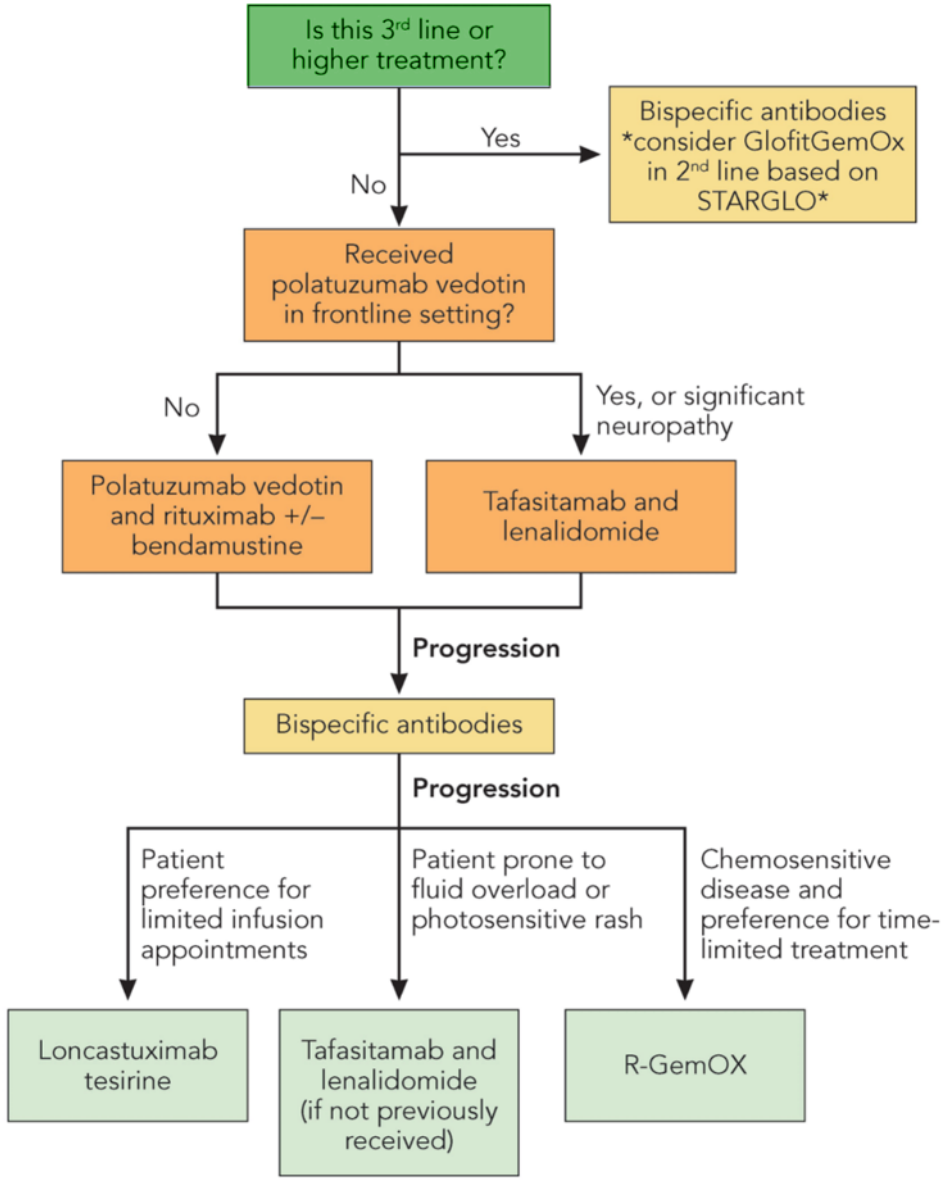


Wallace et al, Blood 2024

Downloaded from http://ashpublications.org/blood/article-pdf/doi/10.1182/blood.2024024788/2245219/blood.2024024788.pdf by guest on 02 October 2024

Treatment Algorithm for older Pts in 2nd relapse LBCL

CAVE: Bendamustin might negatively impact response to bispecifics, depending on length of time prior to Tx initiation



Wallace et al, Blood 2024

Accessibility

Hotlines

24h-Arzt-zu-Arzt

Campus Großhadern
08:00-20:00 Uhr

☎ +49 1525 4 84 87 69

Campus Innenstadt
08:00-17:00 Uhr

☎ +49 1525 4 71 33 90

Nach 20:00 Uhr, Wochenende, Feiertag

☎ +49 1525 4 84 87 69

CART / Bispecifics

Ansprechpartner:in:
Prof. Dr. M. Subklewe;
Dr. V. Bücklein
+ 49 89 – 4400-73133
+ 49 89 – 4400-75551

Koordinatorinnen:
Frau S. Grießhammer,
Frau A. Lahi
+ 49 89 – 4400-73096

Email:
cart@med.lmu.de
marion.subklewe@med.lmu.de
veit.buecklein@med.lmu.de

Virtuelle CART Sprechstunde jeden Mittwoch von 13.30 – 14.00

LMU KLINIKUM
Medizinische Klinik und Poliklinik III

Celebration of Life
45+5 Jahre Zelltherapie am LMU Klinikum

Acknowledgements

Contact: marion.subklewe@med.uni-muenchen.de

@MSubklewe
@LMU_Immutherapy

Laboratory for Translational Cancer Immunology

Viktoria Blumenberg
Veit Bücklein
Gerulf Hänel
Alexandra Leutbecher
Amelie Muth
Anne-Sofie Neumann
Daniel Nixdorf
Nora Phillip
Giulia Rappa
Kai Rejeski
Lisa Rohrbacher
Sabine Sandner
Monika Sponheimer
Kieron White
Lis Winter

Nadja Fenn
Karl-Peter Hopfner
Veit Hornung
Tobias Straube

Department of Medicine III – Oncology and Hematology

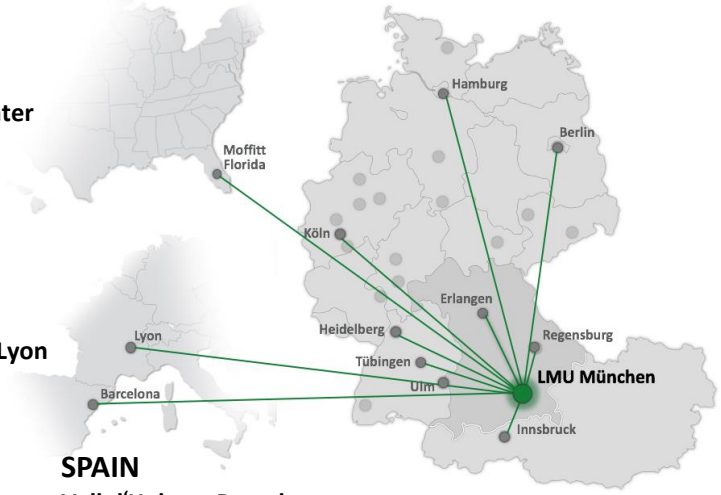
Michael v. Bergwelt
Veit Bücklein
Martin Dreyling
Adrian Gottschlich
Stefanie Griesshammer
Alice Haberkorn
Frederike Hildebrand
Alessandra Holzem
A Lahi
Giulia Magno
Christian Rausch
Michael Ruzika
Christian Schmidt
Sophia Stock
Sebastian Theurich
Oliver Weigert

Laboratory of Leukemia Diagnostics

Veit Bücklein
Elke Habben
Tobias Herold
Bianca Kirschbaum
Bianca Kostrau
Stephanie Schneider
Karsten Spiekermann
Ewelina Zientara

LMU – Department of ATMZH, Neurology,Dermatology Neurosurgery, Radiology, Nuclear Medicine, IZB

Natalie Albert
Louisa von Baumgarten
Eva Hoster
Lucie Heinzerling
Andreas Humpe
Florian Schöberl
Michael Winkelmann
Wolfgang Kunz



USA
Moffitt Cancer Center
Omar Albanyan
Michael Jain
Frederick Locke
Ariel Perez

FRANCE
Hospices Civils de Lyon
Emmanuel Bachy
Laurent Jallades
Pierre Sesques

SPAIN
Vall d'Hebron Barcelona
Pere Barba
Cecilia Carpio
Gloria Iacoboni

GERMANY
University Hospital Tübingen
Wolfgang Bethge
Christoph Stein-Thöringen

University Hospital Erlanger
Andreas Mackensen
Fabian Müller
Sam Völkl

Berlin Charité
Lars Bullinger
Olaf Penack

Heidelberg
Michael Schmidt

myT·Cell
www.mytcell.de
iOS Android