FONDAZIONE ITALIANA LINFOMI

IMMUNOTERAPIA E FARMACI BIOLOGICI NEL TRATTAMENTO DEI LINFOMI E LLC: ATTUALITÀ E FUTURO

I Linfomi a grandi cellule nell'era CAR-T: nuove sfide nella riduzione delle tossicità e aumento dell'efficacia

Beatrice Casadei

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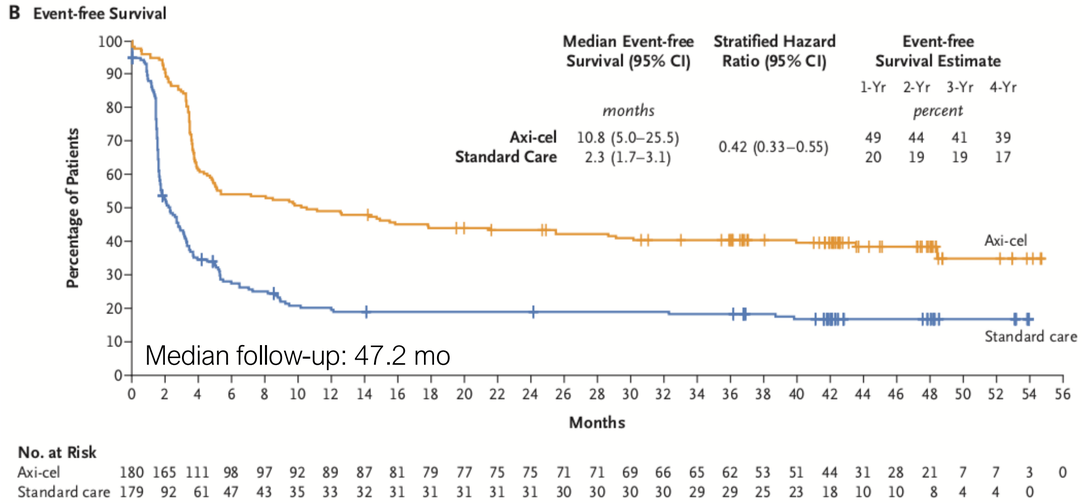
Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite-Gilead					x	x	
Novartis					x		
Celgene-BMS						x	
Abbvie					x	x	
Janssen					x	x	
Lilly					x		
Beigene						x	
Roche					x	x	
Incyte					x		
Takeda						x	

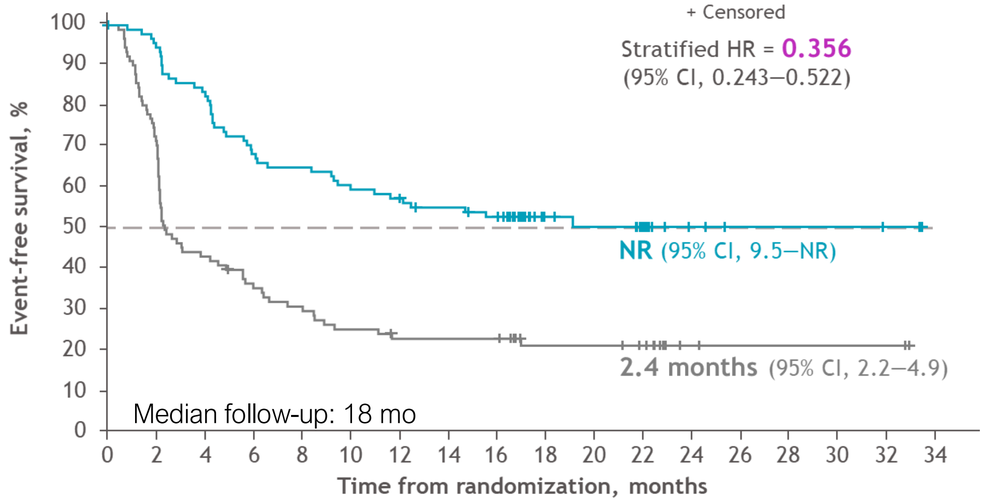
Efficacy: Where We Are Now (2L)?

EFS: Axicel vs SOC (ZUMA-7)



Response n (%)	Axicel (n=180)	SoC (n=179)	p
ORR	150 (83)	90 (50)	<0.0001
CR	117 (65)	58 (32)	
Survival, mo			HR
Median PFS	14.7	3.7	0.49
Median OS	NR	31.1	0.73

EFS: Lisocel vs SOC (TRANSFORM)

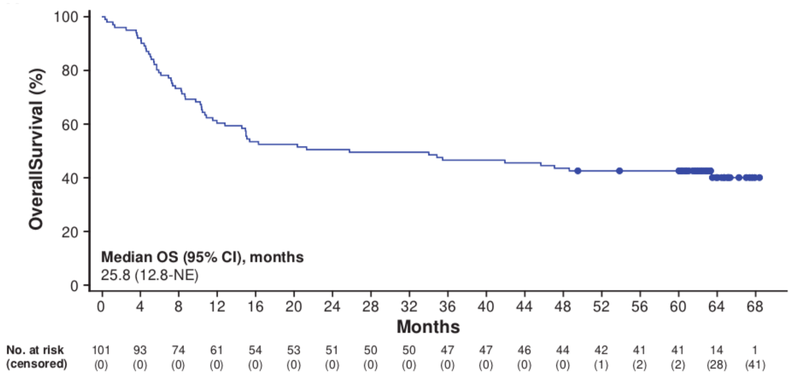


Response n (%)	Lisocel (n=92)	SoC (n=92)	p
ORR	80 (87)	45 (49)	<0.0001
CR	68 (74)	40 (43)	
Survival, mo			HR
Median PFS	NR	6.2 mo	0.4
Median OS	NR	29.9 mo	0.72

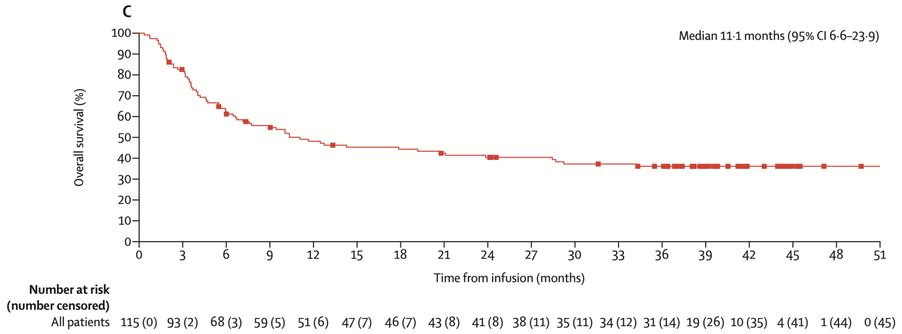
Westin JR et al, New Eng J Med 2023; Locke FL et al, New Engl J Med 2022; Abramson JS et al, Blood 2023.; Kamdar M et al, EHA 2024

Efficacy: Where We Are Now (3L)?

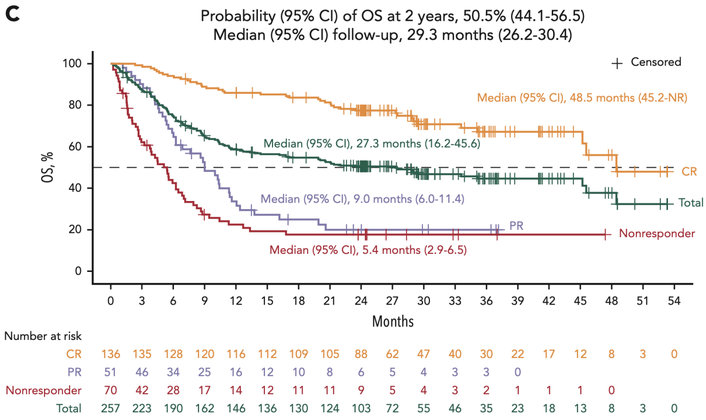
OS Axicel



OS Tisacel



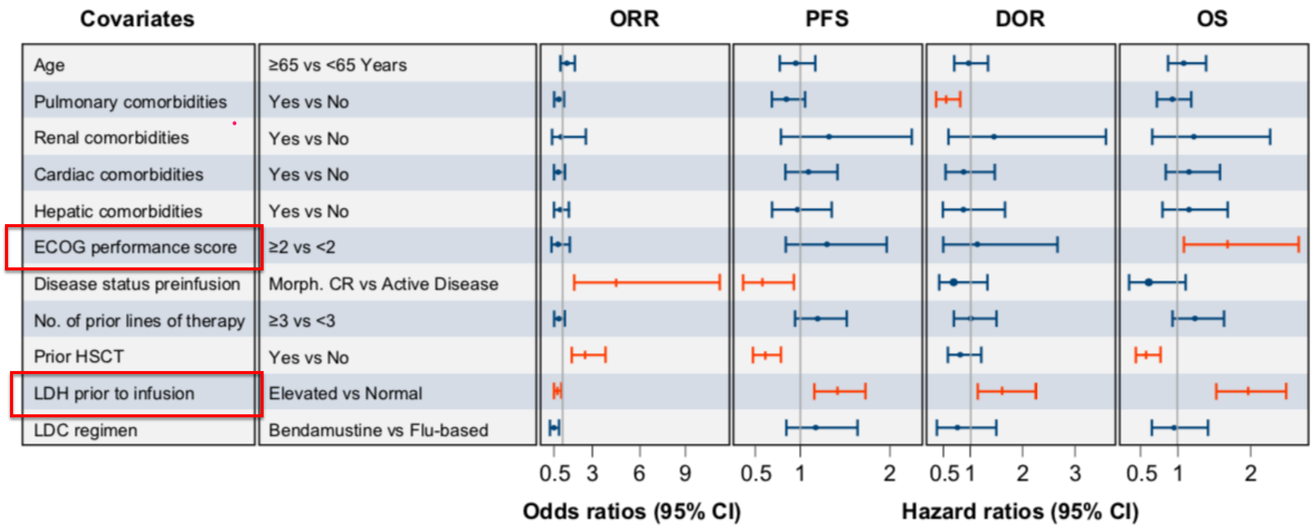
OS Lisocel

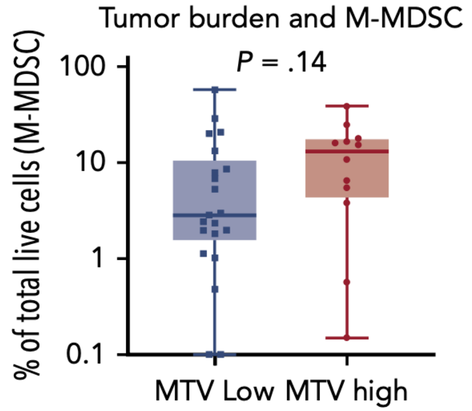


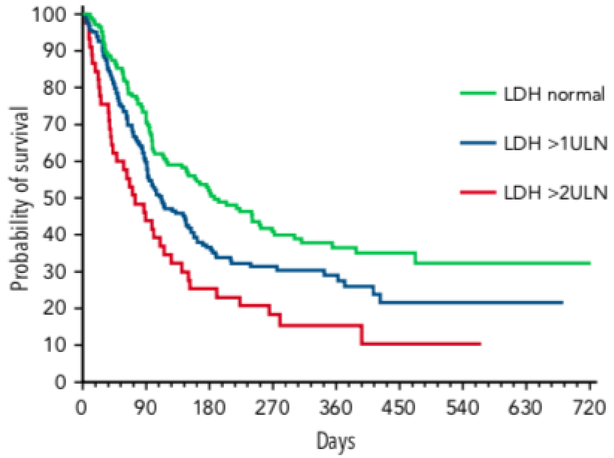
	Axicel (101)	Tisacel (115)	Lisocel (257)
Median follow-up, mo	63.1 (58.9-68.4)	40.3 (37.8-43.8)	19.9 (0.2-55.6)
ORR (CR), %	83 (58)	53 (39)	73 (53)
Median DoCR, mo (range)	62.2 (12.9, NE)	NR	26.1 (23.1, NR)
Median PFS, mo (range)	5.9 (3.3-15)	2.9 (2.3-5.2)	6.8 (3.3-12.7)
Median EFS, mo (range)	5.7 (3.1 13.9)	11.1 (6.6-23.9)	NA

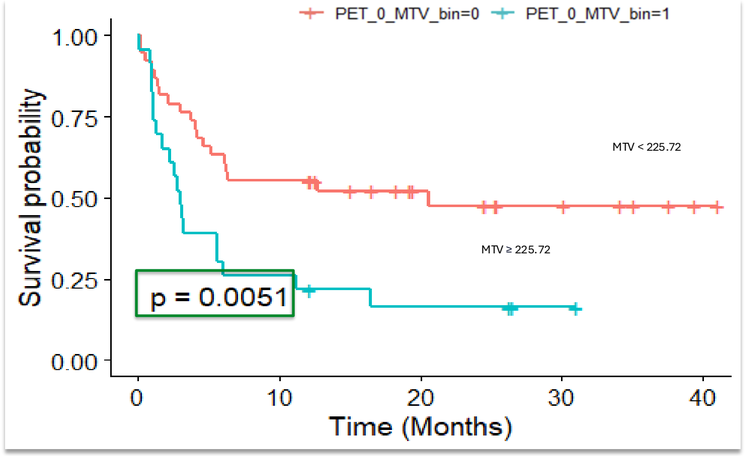
Abramson JS, et al. Blood. 2024; Abramson JS, et al. Blood. 2019; Neelapu SS, et al. Blood 2023; Locke FL, et al. Lancet Oncol. 2019; Neelapu SS, et al. N Engl J Med. 2017; Schuster SJ Lancet 2021; Schuster SJ, e al. N Engl J Med. 2019; Schuster SJ, et al. N Eng J Med 2017

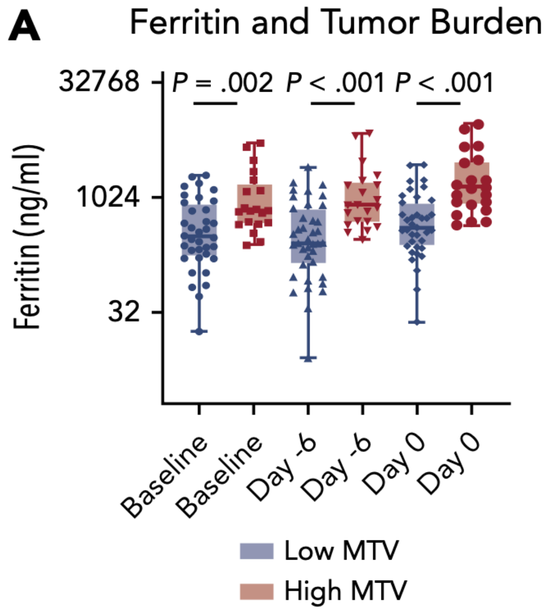
What Clinical Factors Influence Effectivness?







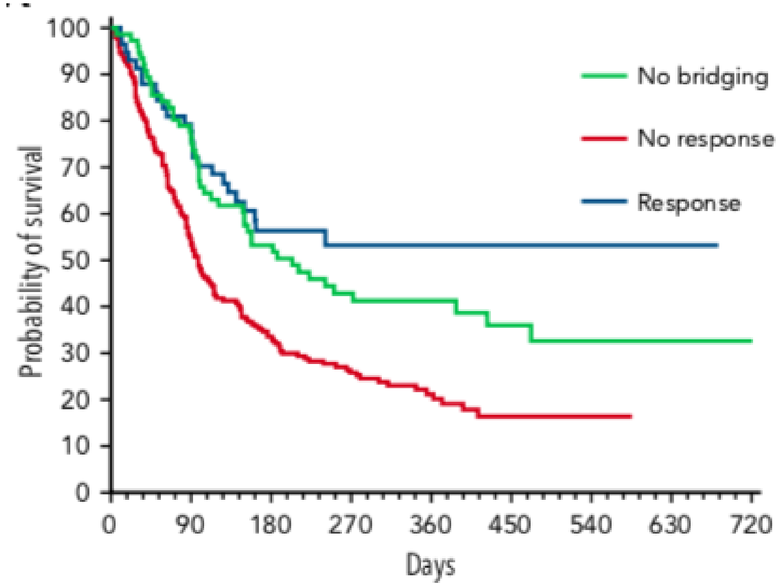


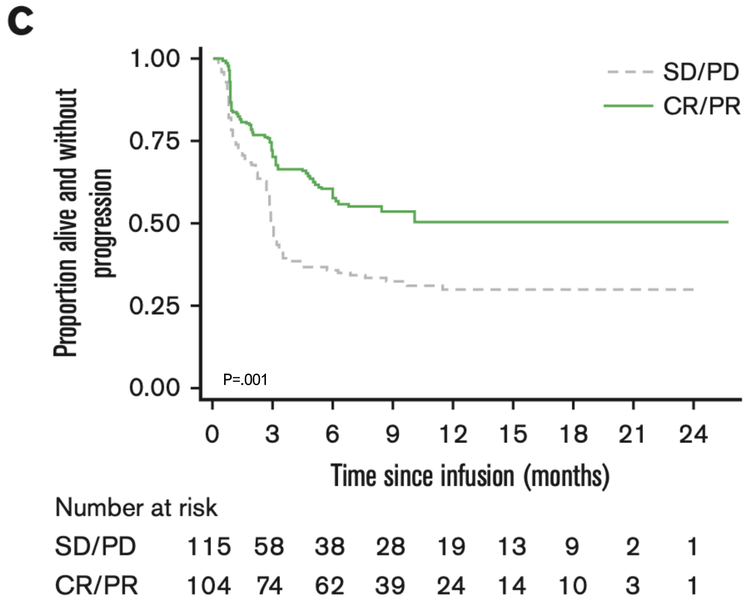


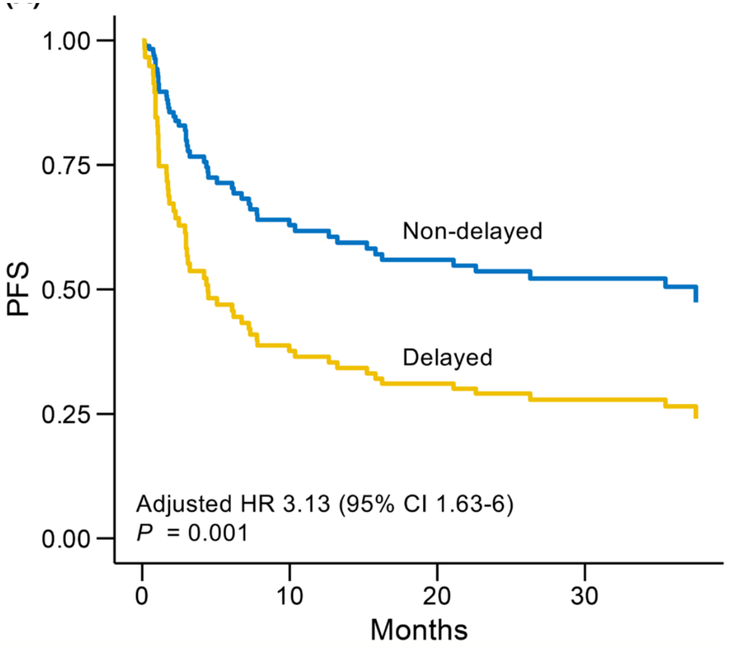
Jain MD et al, Blood 2021; Landsburg DJ. et al, ASH 2022; Bethge W, et al. Blood 2022; Gentilini M et al, SIE 2024 (not published)

How to Improve CAR T-cell Efficacy?

a) Choose the Right BT without delay CAR T-cell infusion



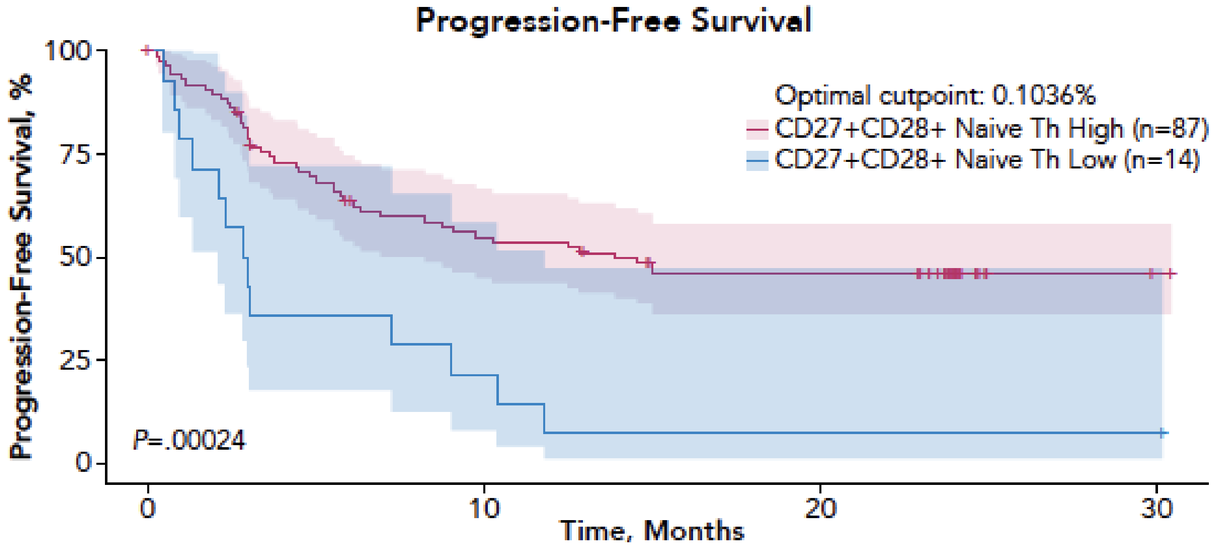




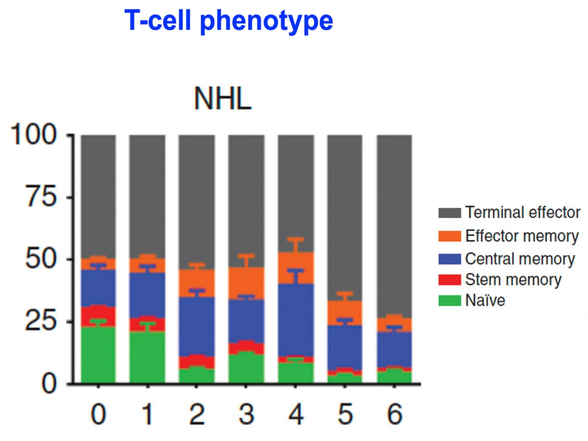
Morimoto S et al, Br J Hematol 2024; Bethge W, et al. Blood 2022; Roddie C et al, Blood Adv 2023

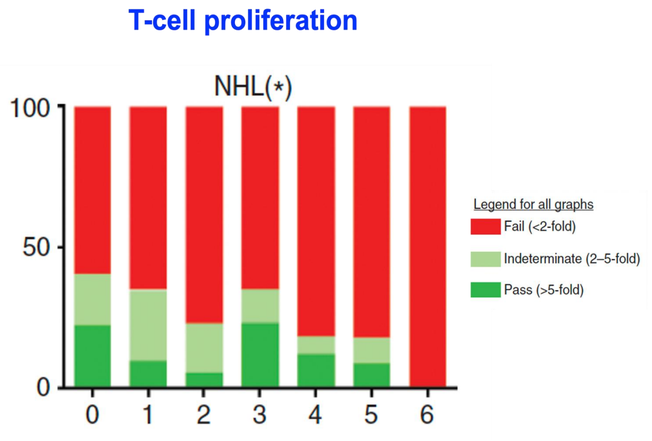
What Biological Factors Influence Effectivness?

CD27⁺CD28⁺ T stem like memory cells in the apheresis are associated with CART cell product fitness



Previous cycles of chemotherapy impairs immune cell phenotypes and fitness





Less differentiated T cell phenotypes (T_N, T_{SCM} and T_{CM}) in the apheresis is associated with CAR T-cell product fitness that correlates with CAR T-cells peak expansion in the PB which is associated with durable responses

Neelapu SS, et al. Blood 2023, Locke et al. Blood 2020; Das et al, Canc Disc 2019

How to Improve CAR T-cell Efficacy?

b) Improve T-cell fitness in the apheresis product: avoid some CHT + previous tx wash-out

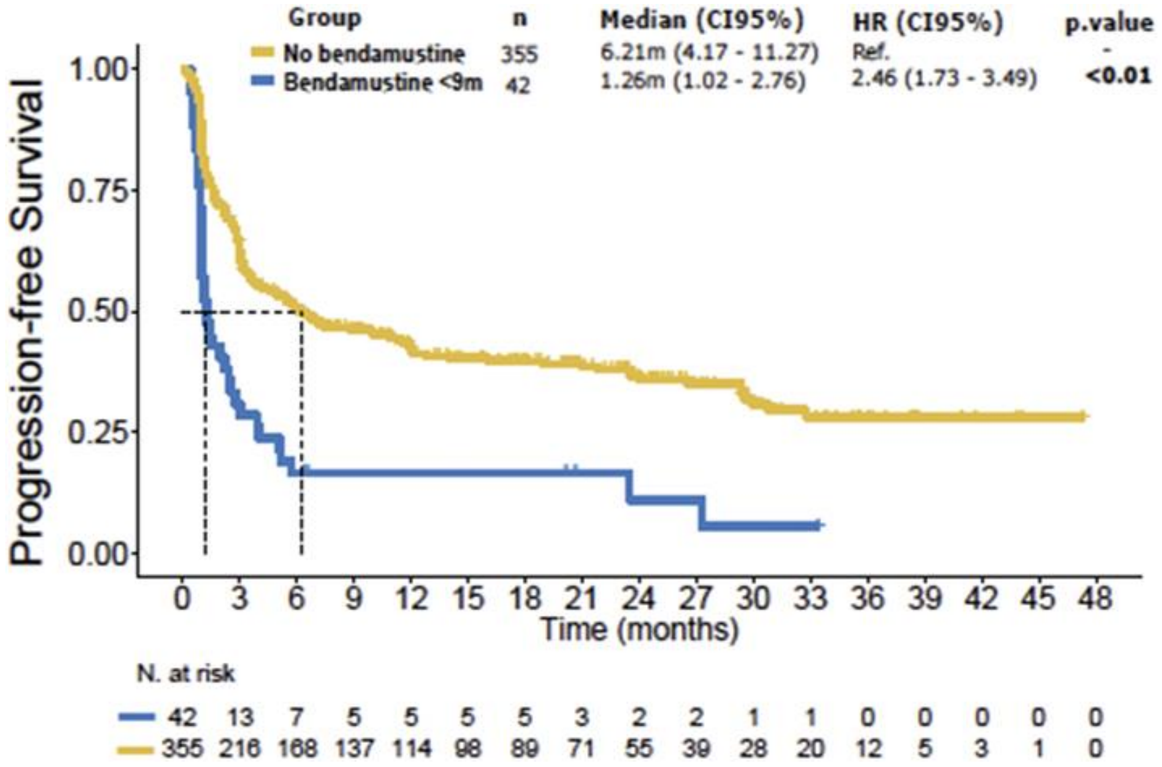


Table 4. Washout period before leukapheresis

Type of therapy	EBMT/EHA recommendations	Comments
Allo-HCT	Patients should be off immunosuppression and GvHD free	A minimum of 1 month is recommended with the requirement to be GvHD free and off immunosuppression
DLI	At least 4 weeks	6-8 weeks may be safer to rule out any GvHD
High-dose chemotherapy	3-4 weeks	Recovery from cytopenias is required
Intrathecal therapy	1 week	
Short-acting cytotoxic/anti-proliferative drugs	3 days	Recovery from cytopenias is required
Systemic corticosteroids	Minimum of 3 days but ideally 7 days	ALC $\geq 0.2 \times 10^9$/l is recommended

Adapted from Kansagra et al.[70]

ALC, absolute lymphocyte count; allo-SCT, allogeneic stem cell transplantation; DLI, donor lymphocyte infusion; EBMT, European Society for Blood and Marrow Transplantation; EHA, European Haematology Association; GvHD, graft-versus-host disease.

Iacoboni G et al, JCO 2024; Hayden PJ et al, Annals Oncol 2022

How to Improve CAR T-cell Efficacy?

b) Improve T-cell fitness in the apheresis product: CAR T-cell in 1st line

ZUMA- 1

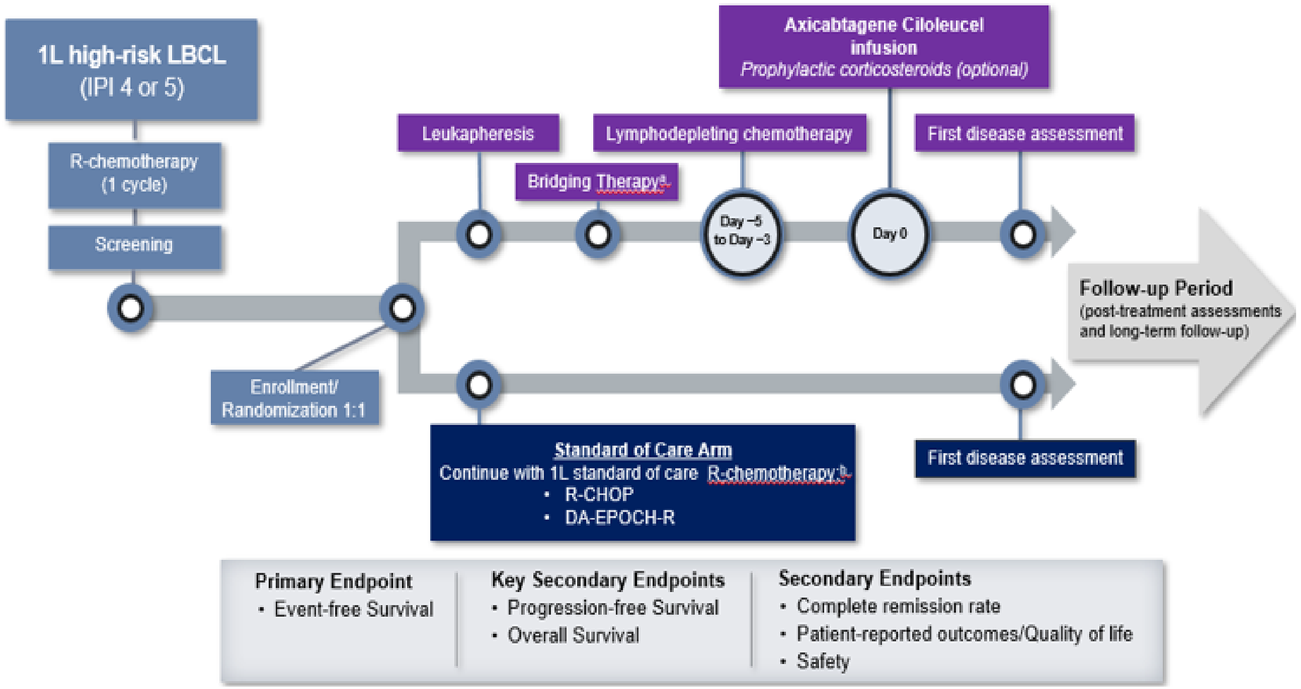
High-Risk LBCL
- High-grade B cell lymphoma, with and *BCL2* and/or *BCL6* translocatio
- LBCL with IPI score ≥ 3 any time be enrollment

Systemic Therapy
- 2 Cycles of an anti-CD20 mAb + anthracycline-containing regimen

Dynamic Risk Assessment
- Positive interim PET (DS 4 or 5)

Additional Key Inclusion Crite
- Age ≥ 18 years
- ECOG 0 – 1

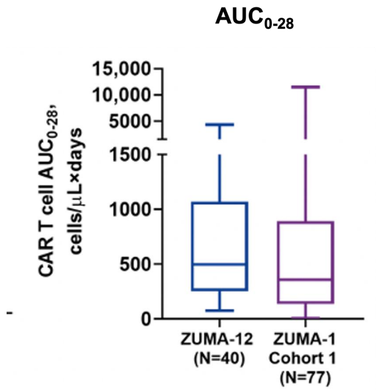
ZUMA-23: Axi-cel vs SOC for Newly Diagnosed High-Risk LBCL

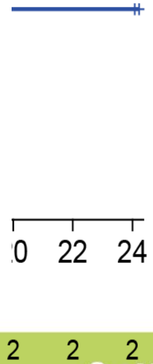


a) Bridging therapy with R-CHOP or DA-EPOCH-R will be administered during the cell manufacturing period.

https://clinicaltrials.gov/ct2/show/NCT05605899.

n in ZUMA-12 vs. ZUMA-1





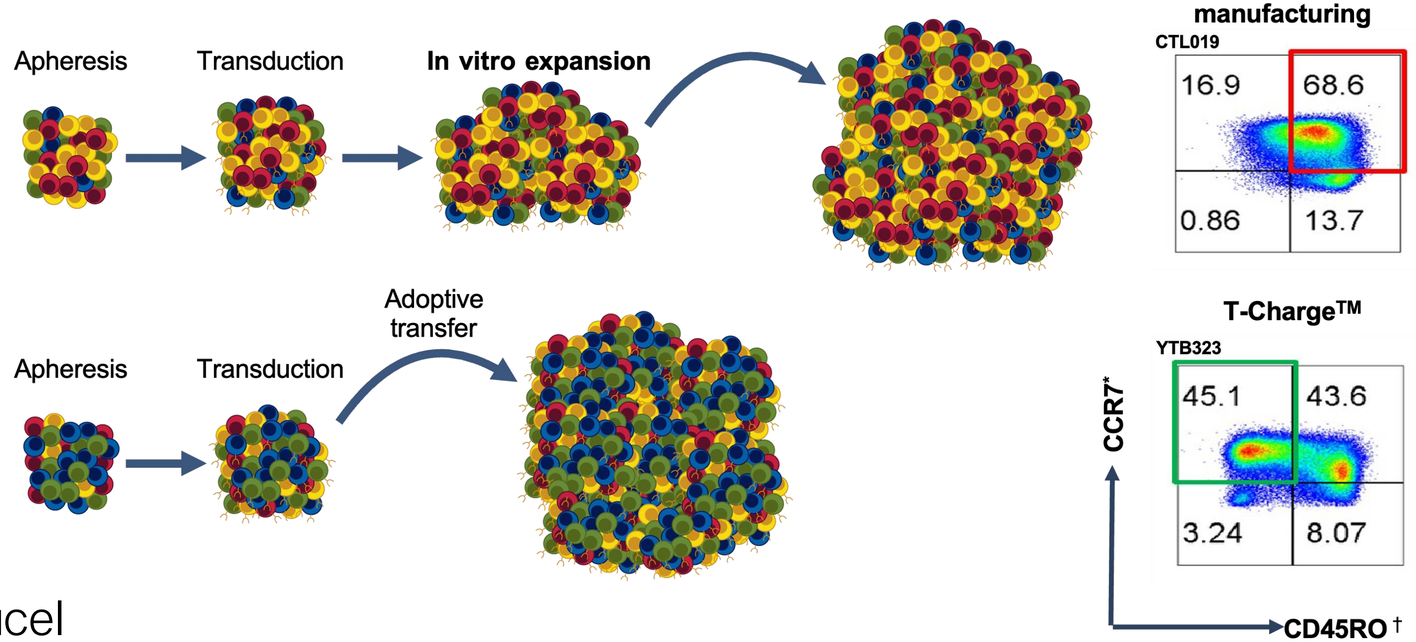
Neelapu SS et al, Nat Med 2022

How to Improve CAR T-cell Efficacy?

b) Improve T-cell fitness in the apheresis product: fast manufacturing and T cell selection

Traditional manufacturing
- Time and resource **intense**
- Results in **effector** differentiation

T-Charge™
- Requires **less reagent**
- Preserves **stem cell memory T** cells



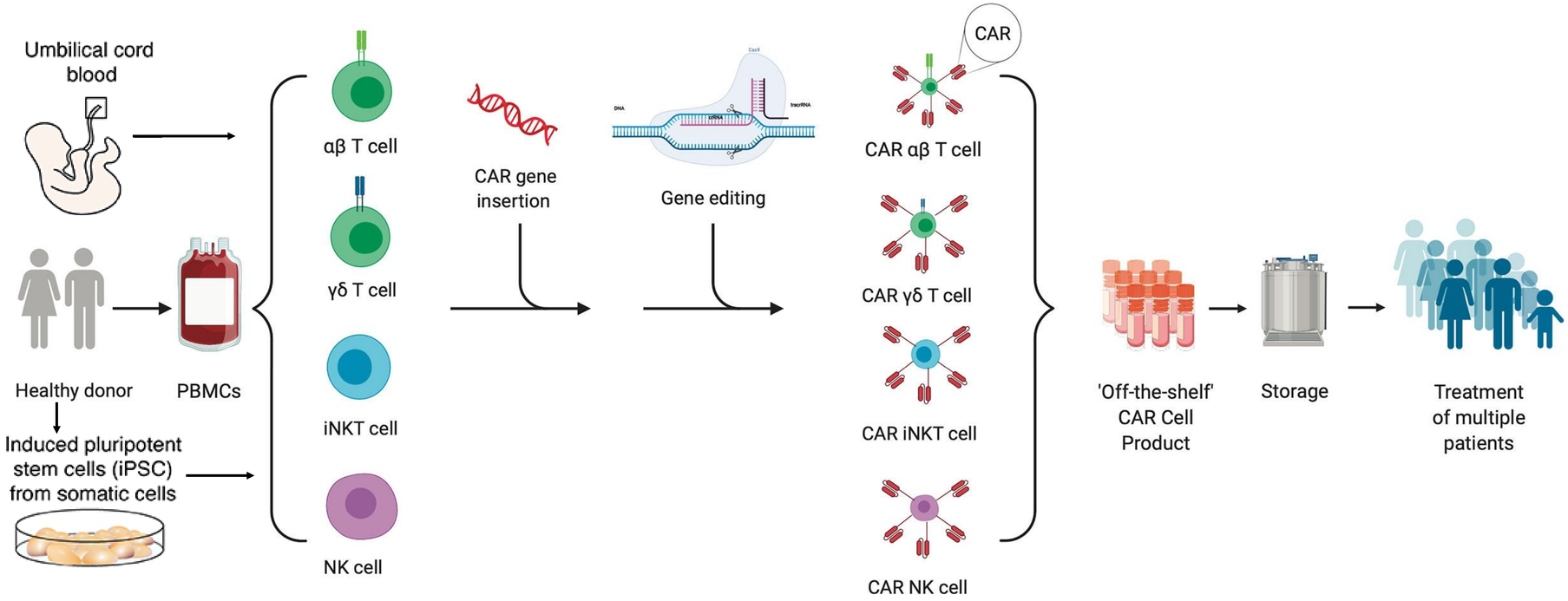
Rapcabtagene autoleucel

- Novel platforms such as T-Charge™ use an expansionless and therefore rapid manufacturing process and can preserve stemness in the CAR T-cell product
- Greater T-cell stemness results in a product with greater proliferative potential, fewer exhausted T cells, higher potency, and greater persistence[1]

Barba P et al, ASH 2022

How to Improve CAR T-cell Efficacy?

b) Improve T-cell fitness in the apheresis product: allo CART

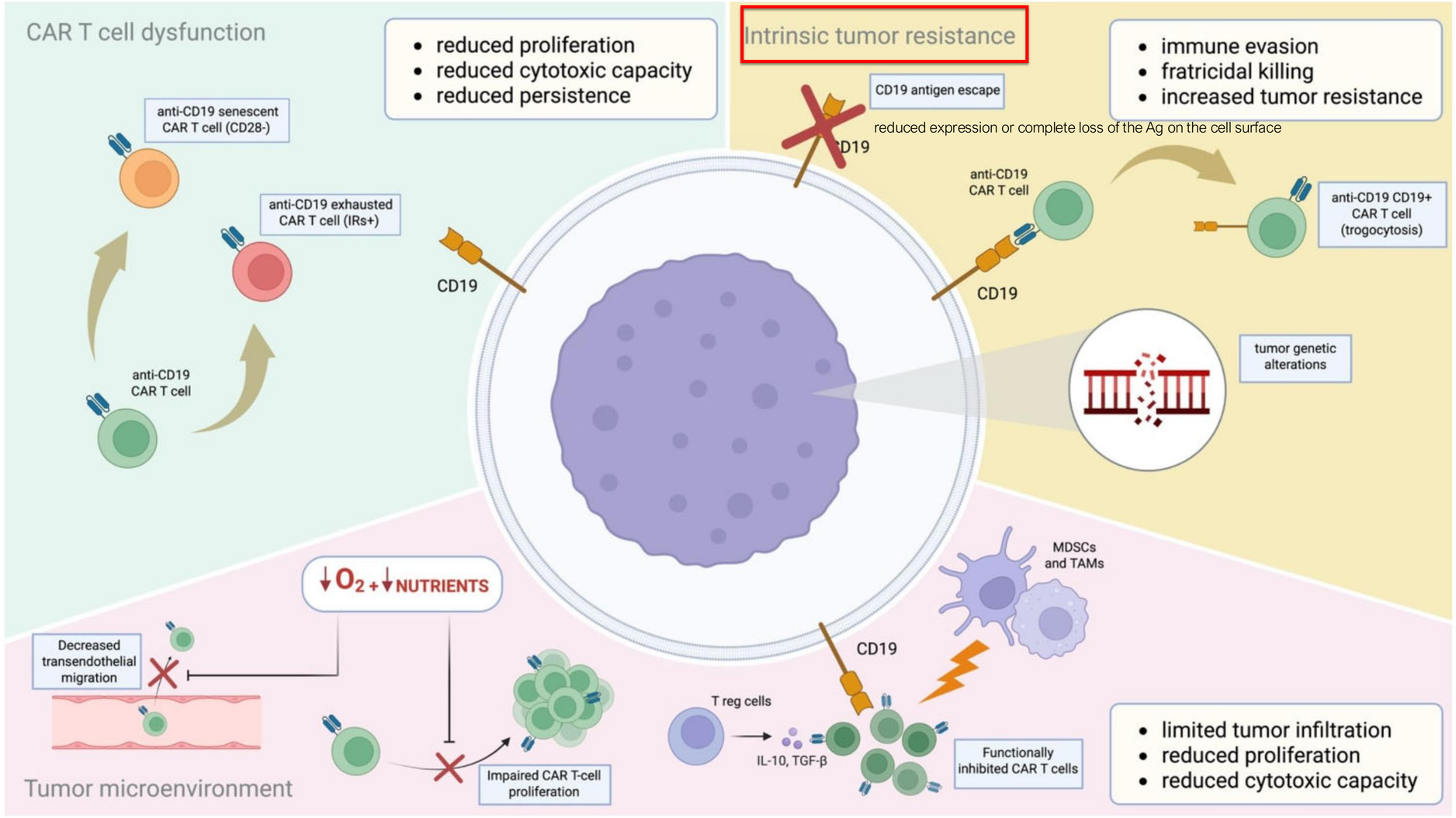


Pro:
- Off the shelf (reduced brain to vein)
- Multiple Infusion
- Accessibility
- Source: healthy donor → increase the T-cell fitness

Cons:
- Risk of CAR+ lymphocyte engraftment failure (host versus graft)
- Risk of GVHD (TCR knock-out/NK cells)
- Similar efficacy but higher infection rate in coparison to auto CART
- More effective approaches are needed to prevent immune reactions and thus allow for more consistent in vivo expansion and greater persistence of allo-CARTs

Barba P et al, ASH 2022

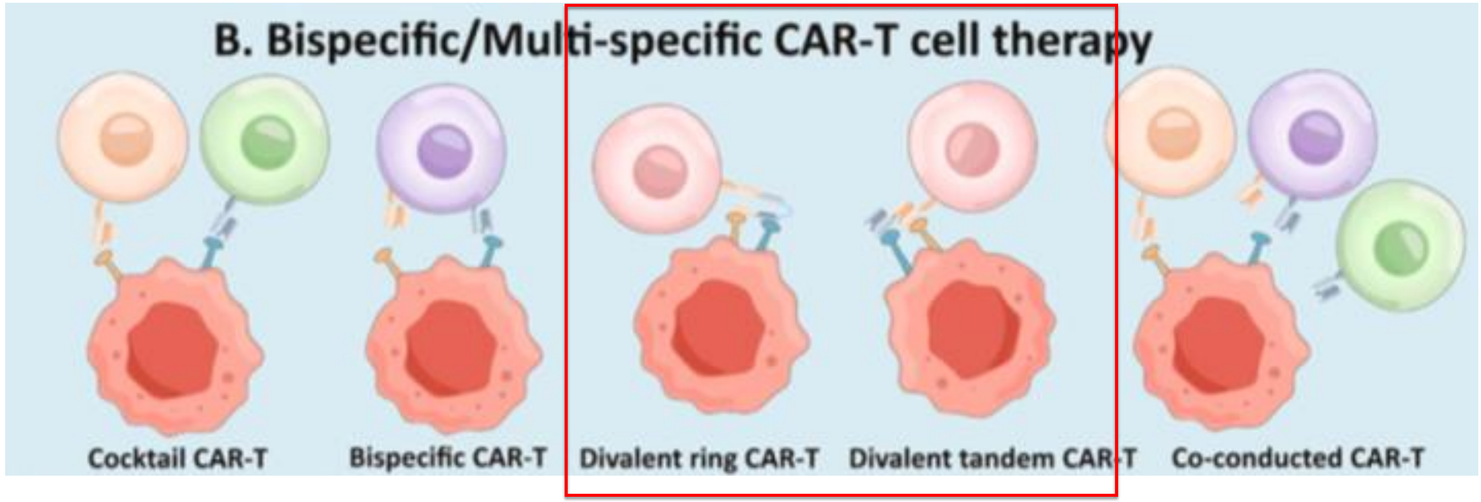
CAR T-cell Efficacy is Compromised by Mechanism of Resistance



Legato L et al, meth and Prot 2025; Lin H et al, Biomedicine and Pharmacotherapy 2024

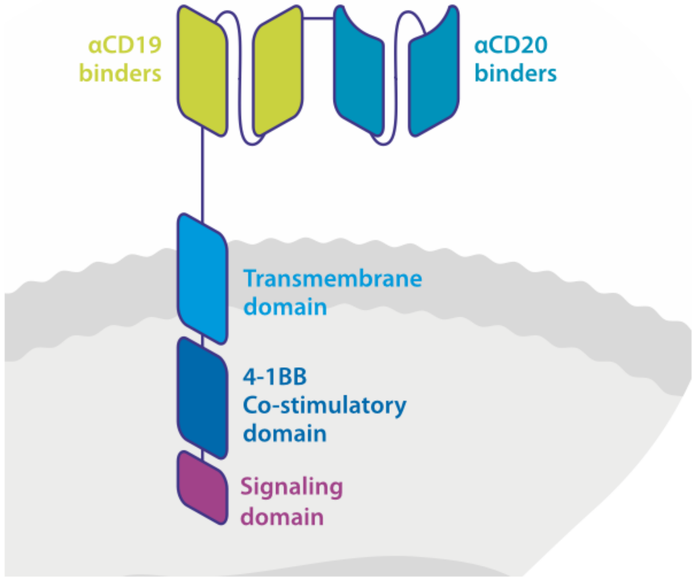
How to overcome Antigen Escape?

Dual Antigen Targeting



CD19/CD20 or CD19/CD79b

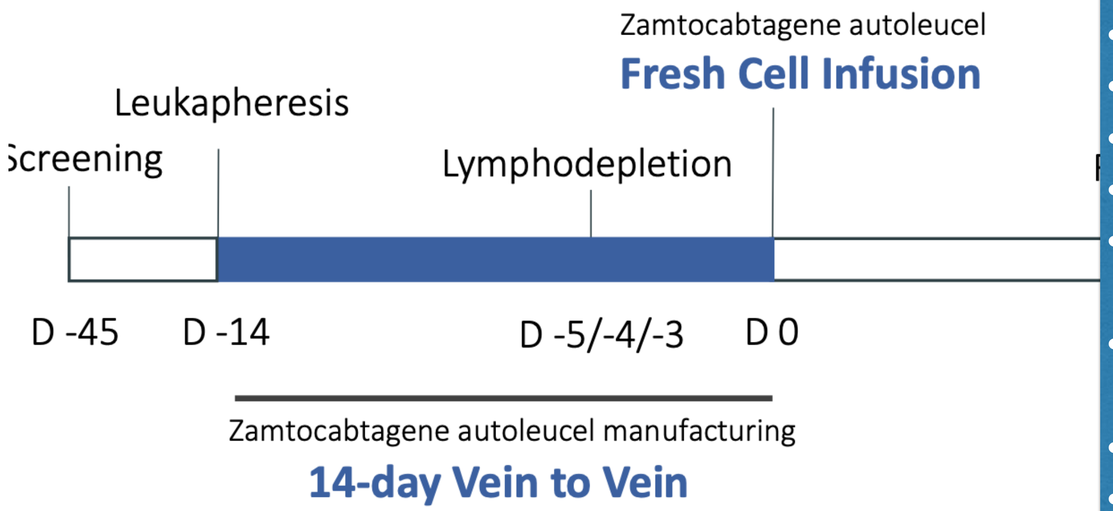
TandemCAR: Zamtocel (CD19/CD20)



Legato L et al, Meth and Prot 2025; Lin H et al, Biomedicine and Pharmacotherapy 2024

DALY II US TRIAL: Zamto-cell in RR DLBCL

Open label, single arm, Phase II study to determine the efficacy, safety, and PK (persistence) of zamtocabtagene autoleucel in adults with R/R DLBCL after receiving at least two lines of therapy



CliniMACS Prodigy® (Miltenyi Biotec), a closed, automated system with a
day vein-to-vein time and administered as a fresh formulation

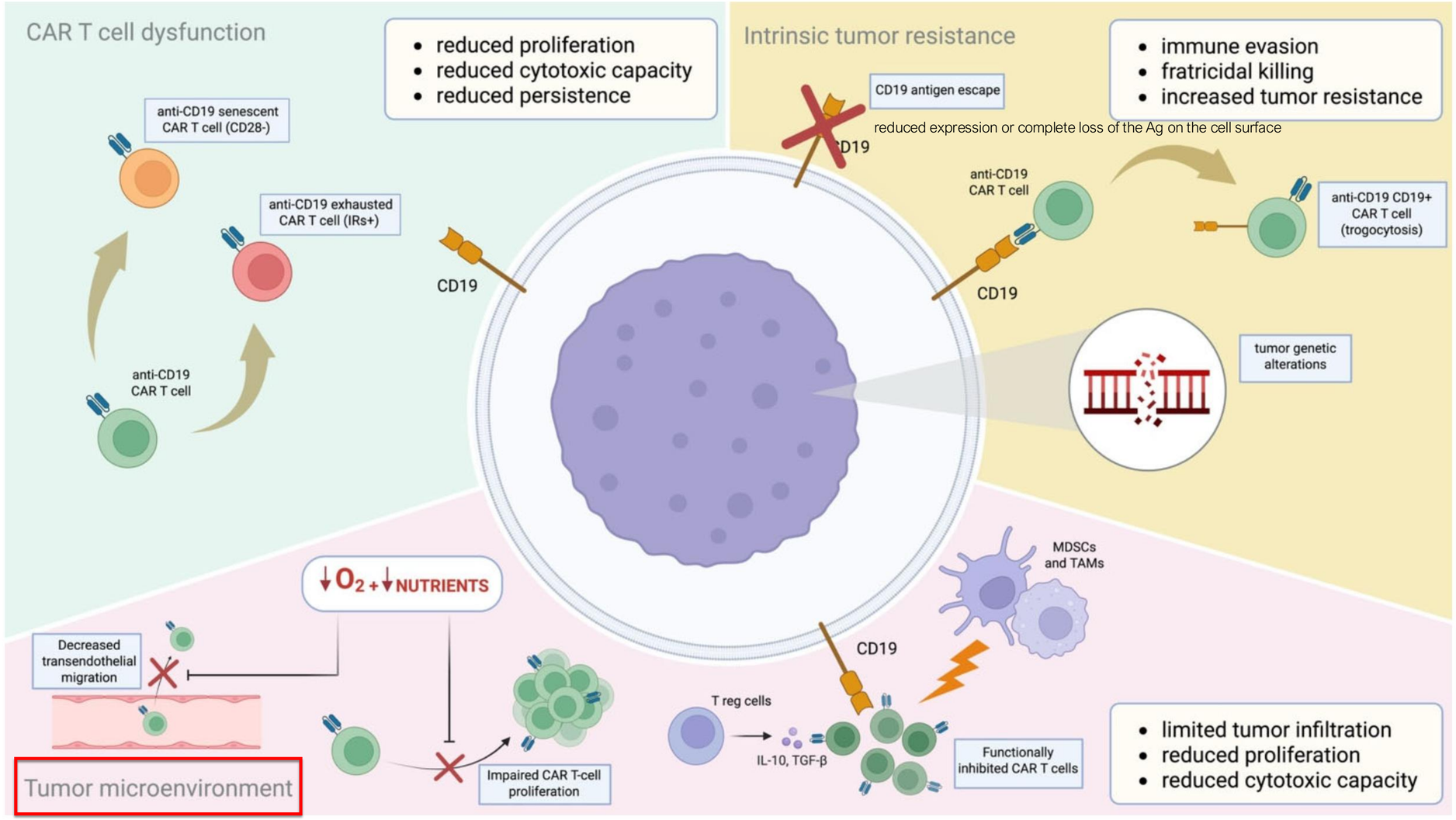
Key Eligibility Criteria

- 69 pts received zamtocel
- No pts received any bridging therapy
- **ORR (n=59) by IRC: 72.9%** (95% CI, 59.7-83.6),
- CRR of 49.2% (95% CI,35.9-62.5).
- 12 month-PFS: 42% (95%CI, 28-56),
- 12 month-OS: 72% (95%CI, 57-83).
- Median DOR: 11.4 months.

- TEAEs were mostly of grade 1-2, the majority of grade ≥ 3 were hematological.
- CRS any grade: 46.4% (all gr 1-2)
- ICANS any grade: 17.4% (grade 1-2 13.1%, gr 3: 4.3%).
- Biopsies at progression were available in 24 pts
- CD19-negative relapse 2 pts
- CD20-negative relapses 3 pts

Shah NN, Oral Abs ASH2024

CAR T-cell Efficacy is Compromised by Mechanism of Resistance



Legato L et al, meth and Prot 2025; Lin H et al, Biomedicine and Pharmacotherapy 2024

How to overcome adverse TME?

Combination: CAR T-cells + X

CAR T + CPI

NCT Number	Intervention	Disease
NCT05310591	CD19 CAR-T + Nivolumab	B-ALL
NCT05385263	CD19 CAR-T + Nivolumab	DLBCL
NCT04205409	(Post CAR-T) Nivolumab	R/R B-NHL, R/R MM
NCT05352828	CD30 CAR-T + Nivolumab	R/R cHL
NCT04134325	CD30 CAR-T + Nivolumab OR Pembrolizumab	R/R cHL
NCT06767956	(Post CD19 CAR-T) Nivolumab + Golcadomide,	R/R B-NHL
NCT06523621	(Post idecabtagene Vicleucel) Nivolumab	R/R MM
NCT05934448	CAR-T + Pembrolizumab	R/R PMBCL
NCT06242834	(Post CAR-T/ASCT) Pembrolizumab + Tazemetostat	R/R B-NHL
NCT05659628	CD19 CAR-T + Tislelizumab	R/R DLBCL
NCT06876688	Relmacabtagene autoleucel + Tislelizumab ± BTKi	R/R PCNSL
NCT04539444 (Uknown status)	CD19/22 CAR-T + Tislelizumab	R/R B-NHL
NCT00586391	CD19 CAR-T + Ipilimumab	R/R B-NHL R/R ALL, R/R CLL

CAR T + IMIDs

NCT06209619	CD19 CAR-T + Golcadomide + Rituximab	R/R B-NHL
NCT06271057	CD19 CAR-T + Golcadomide	R/R LBCL

CAR T + BTKi

NCT03331198	Lisocabtagene maraleucel + Ibrutinib or Venetoclax	R/R CLL/SLL
NCT03960840	Rapcabtagene autoleucel + Ibrutinib	R/R CLL/SLL
NCT06482684	Brexucabtagene autoleucel + Ibrutinib	MCL
NCT04234061	Tisagenlecleucel + Ibrutinib	R/R MCL
NCT05672173	Lisocabtagene maraleucel + Ibrutinib + Nivolumab	Richter's Syndrome
NCT05744037 (Uknown status)	CD19 CAR-T + Ibrutinib	R/R B-NHL
NCT05202782	CAR-T + Zanubrutinib	R/R B-NHL
NCT05873712	Lisocabtagene maraleucel + Zanubrutinib	Richter's Syndrome
NCT06646666	CAR-T + ATRA + Zanubrutinib ± radiotherapy ± PD-1 inhibitor	R/R B-NHL
NCT06695013	Zanubrutinib ± radiotherapy + CAR-T ± Zanubrutinib and Tislelizumab	R/R B-NHL
NCT05871684	CAR-T + Zanubrutinib + Tislelizumab	R/R B-NHL
NCT06167785	(Post CD19 CAR-T) Zanubrutinib + Tislelizumab	R/R B-NHL
NCT05020392	CD19 CAR-T + Zanubrutinib/Ibrutinib/Orelabrutinib	R/R B-NHL
NCT05495464	Acalabrutinib + Rituximab + Brexucabtagene autoleucel	MCL
NCT05256641	CD19 CAR-T + Acalabrutinib	R/R B-NHL
NCT04257578	Axicabtagene ciloleucel + Acalabrutinib	R/R B-NHL
NCT04484012	CD19 CAR-T + Acalabrutinib	R/R MCL
NCT05990465	CD19 CAR-T + Pirtobrutinib	R/R B-NHL
NCT06553872	Brexucabtagene autoleucel + Pirtobrutinib	R/R MCL
NCT06553872	CD19 CAR-T Brexucabtagene autoleucel + Pirtobrutinib	MZL

CAR T + BsAbs

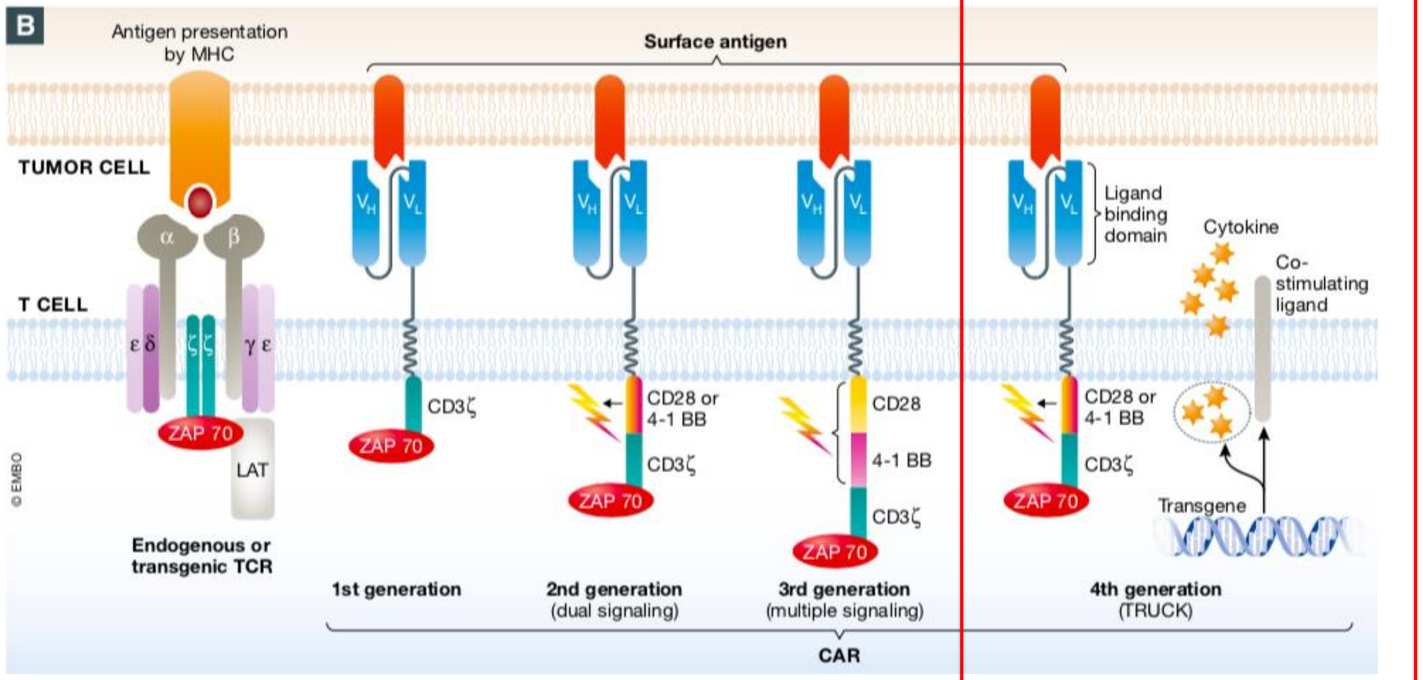
NCT06464185	CD19 CAR-T + Glofitamab	R/R B-NHL
NCT06567366	CAR-T + Glofitamab	R/R LBCL
NCT04703686	(Post CD19 CAR-T) Obinutuzumab + Glofitamab	R/R B-NHL
NCT07003295	(Post CD19 CAR-T) Obinutuzumab + Glofitamab	R/R MCL
NCT06552572	(PR post CD19 CAR-T): Obinutuzumab + Glofitamab	R/R DLBCL
NCT06071871	(Post CAR-T): Obinutuzumab + Glofitamab + Polatuzumab vedotin	R/R LBCL
NCT06015880	(Post CAR-T): Mosunetuzumab + Polatuzumab vedotin + Lenalidomide	R/R B-NHL
NCT04889716	(Post CD19 CAR-T): Mosunetuzumab or Obinutuzumab + Glofitamab	R/R LBCL
NCT05260957	CAR-T + Mosunetuzumab + Polatuzumab vedotin	R/R B-NHL
NCT05633615	CD19 CAR-T + Mosunetuzumab or Polatuzumab vedotin or Mosunetuzumab + Polatuzumab vedotin	R/R B-NHL

CAR T + Tazemetostat

NCT05934838	CAR-T + Tazemetostat	R/R B-NHL

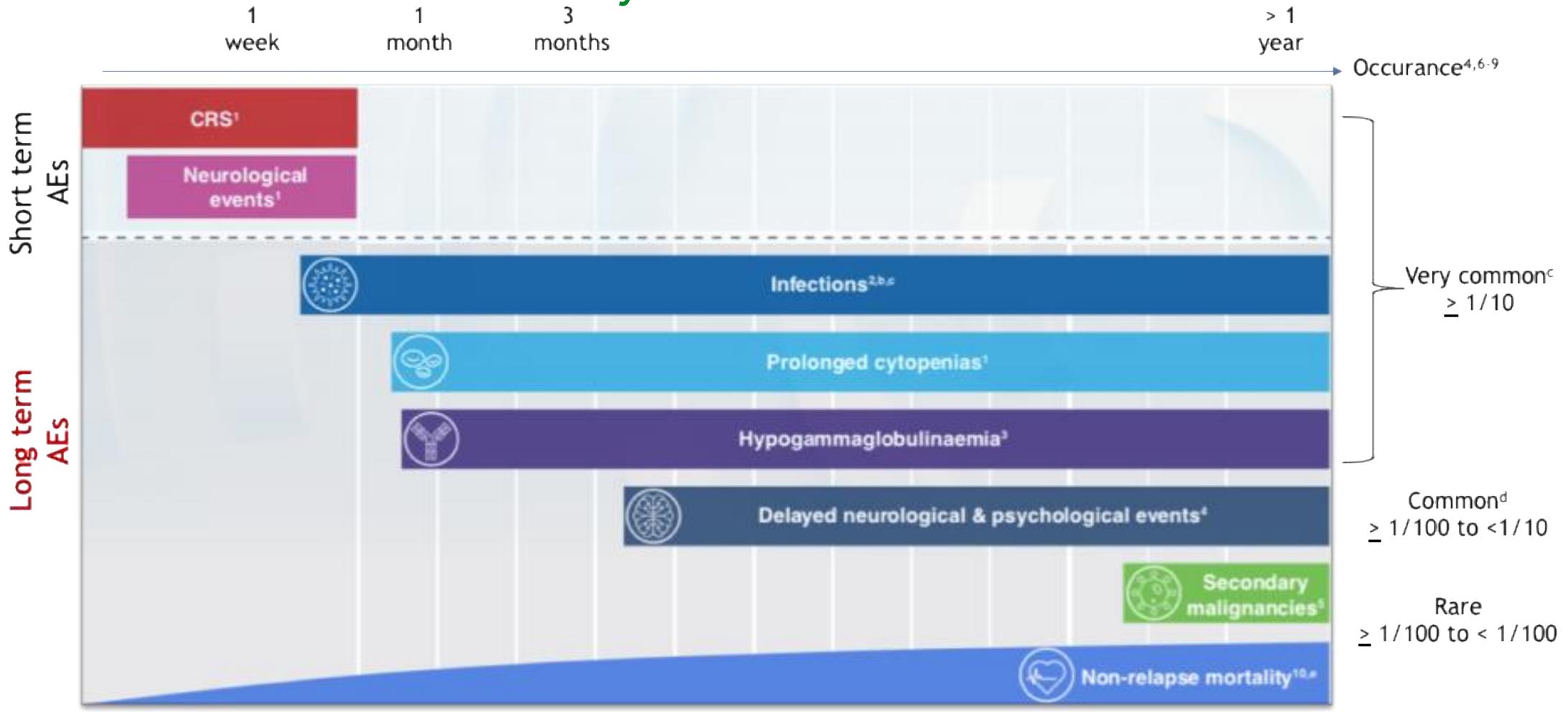
How to overcome adverse TME?

IV Generation CAR T-cells



- Release of active molecules like cytokines or checkpoint blocking minibodies
- Overcome immunosuppressive TME
- Improve invivo persistance

Toxicity: Where We Are Now?

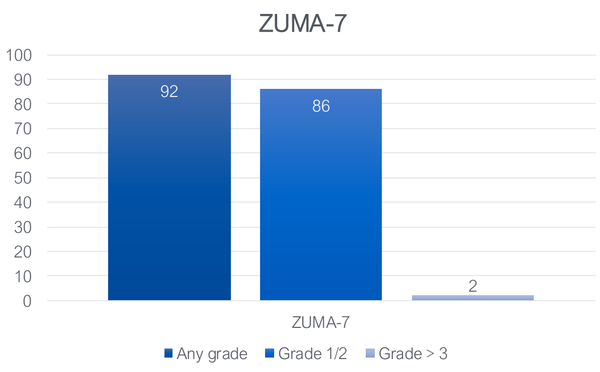


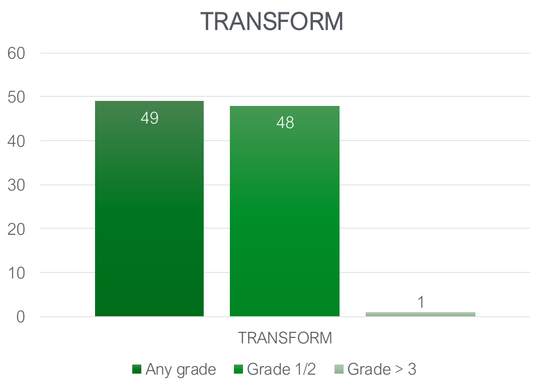
b Unspecified pathogen; viral, bacterial and fungal infection; c Unspecified pathogen infections, viral infections, and bacterial infections are very common; fungal infections are common; d Delirium and insomnia were very common, anxiety and affective disorder were common; e The overall NRM point estimate across all CAR T studies is 6.8%, with 6.1% for LBCL.

1.Locke FL, et al. New Eng J Med 2022; 2.Baird JH, et al. Blood Adv 2021; 3.Cappell KM, et al. J Clin Oncol 202; 4. Cordeiro A, et al. Biol Blood Marrow Transplant 2020; 5. Barone A, et al. Br J Haematol 2024; 6. The EBMT/EHA CART-cell Handbook 2022; 7. Jain T, t al. Blood 2023; 8.Axicabtagene ciloleucel Smp 2024; 9.Levine BL, et al. Nat Med 2024; 10. Cordas Dos Santos DM, et al. Nat Med 2024

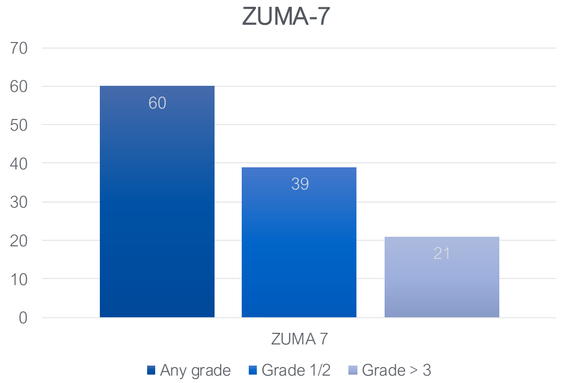
Toxicity: Where We Are Now?

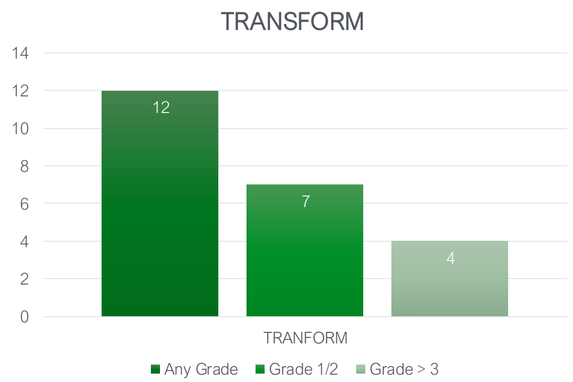
CRS

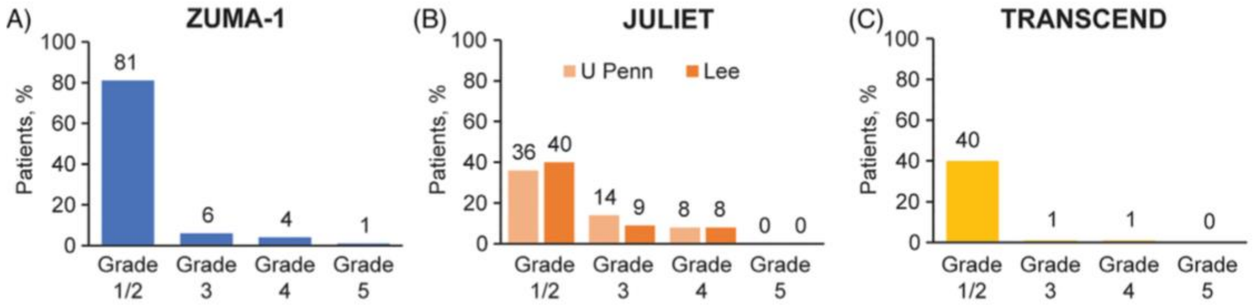


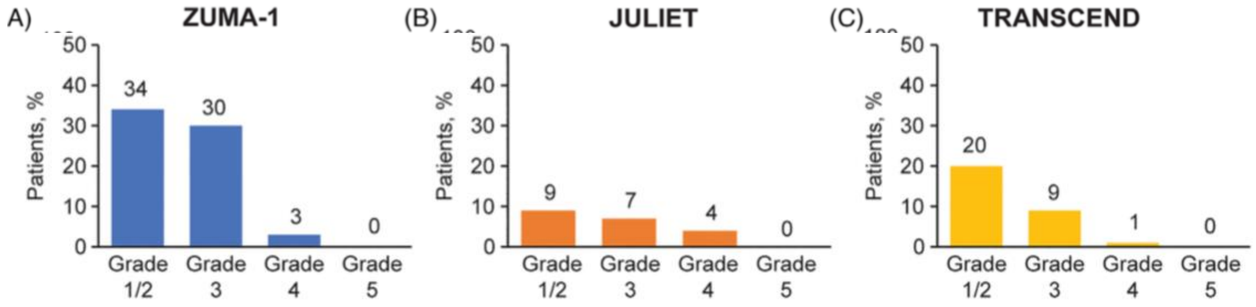


ICANS



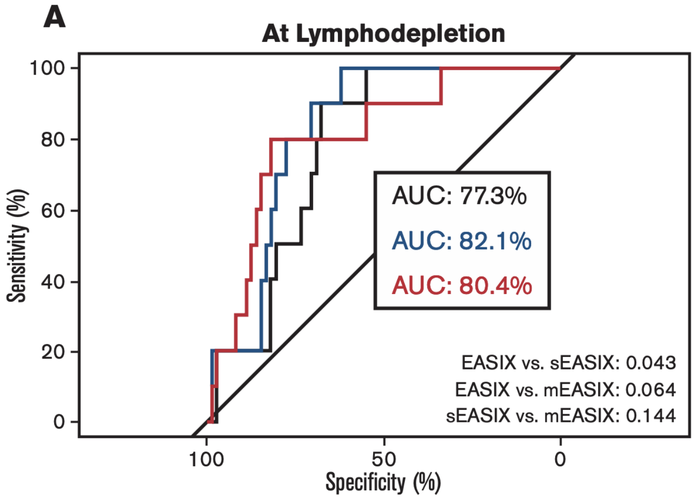


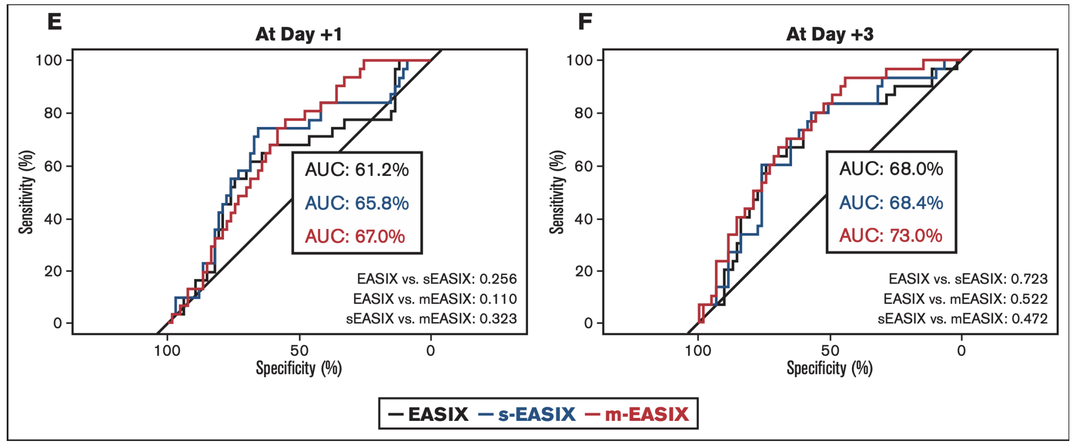




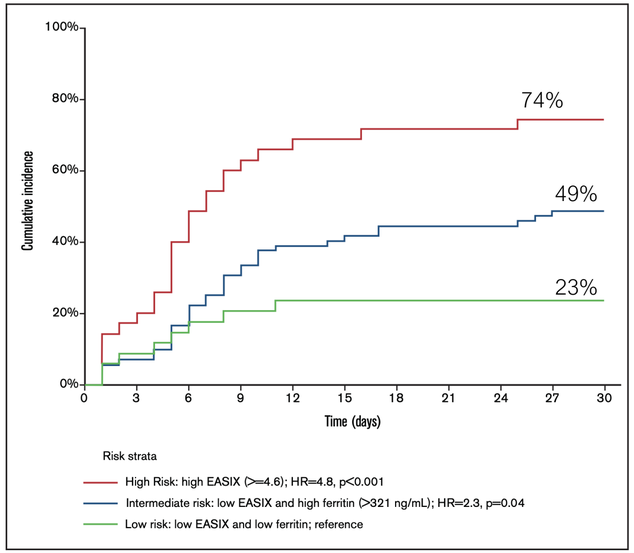
Locke FL et al, New Eng J Med 2022; Kamdar M et al, Lancet 2022; Westin J.R. et al, AJH 2021

mEASIX, F-EASIX, FC-EASIX to Predict Severe CRS and ICANS

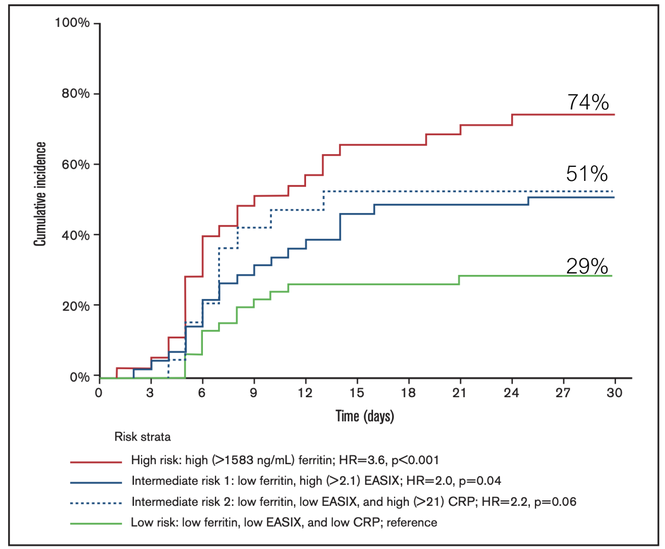




Gr 2-4 CRS

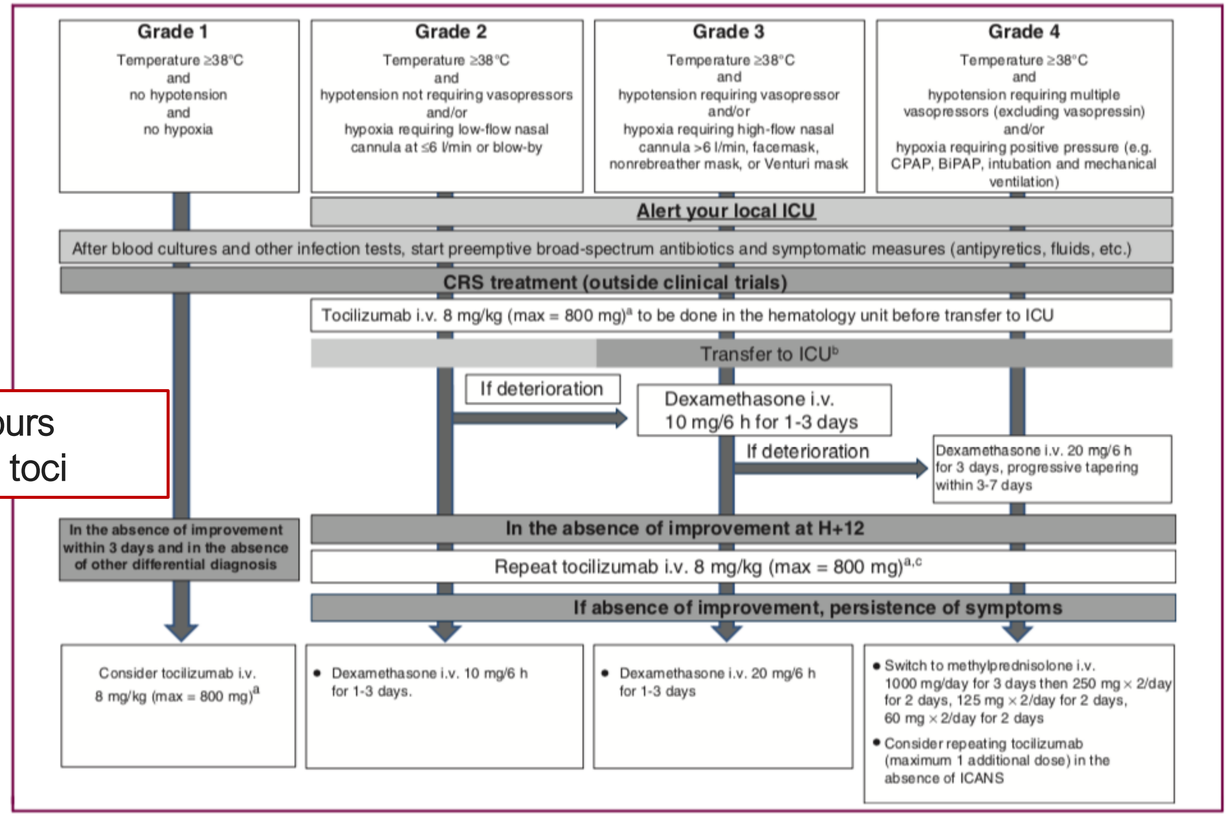


GR 2-4 ICANS



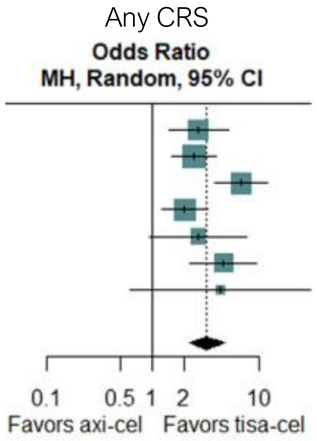
Pennisi M et al, Blood Adv 2020; Strati P et al, Blood Adv 2021

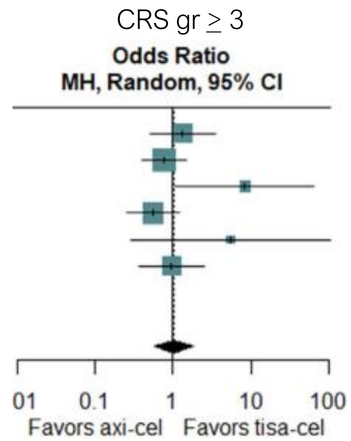
How to Reduce the Incidence of CRS and ICANS gr ≥ 3

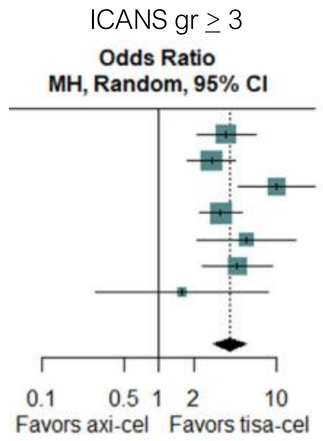


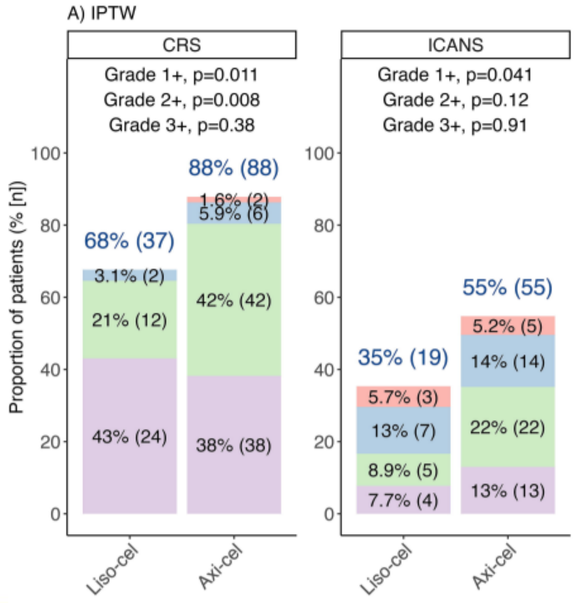
24 hours
Max 2 toci

Early use of dexamethasone reduced the onset of ICANS.



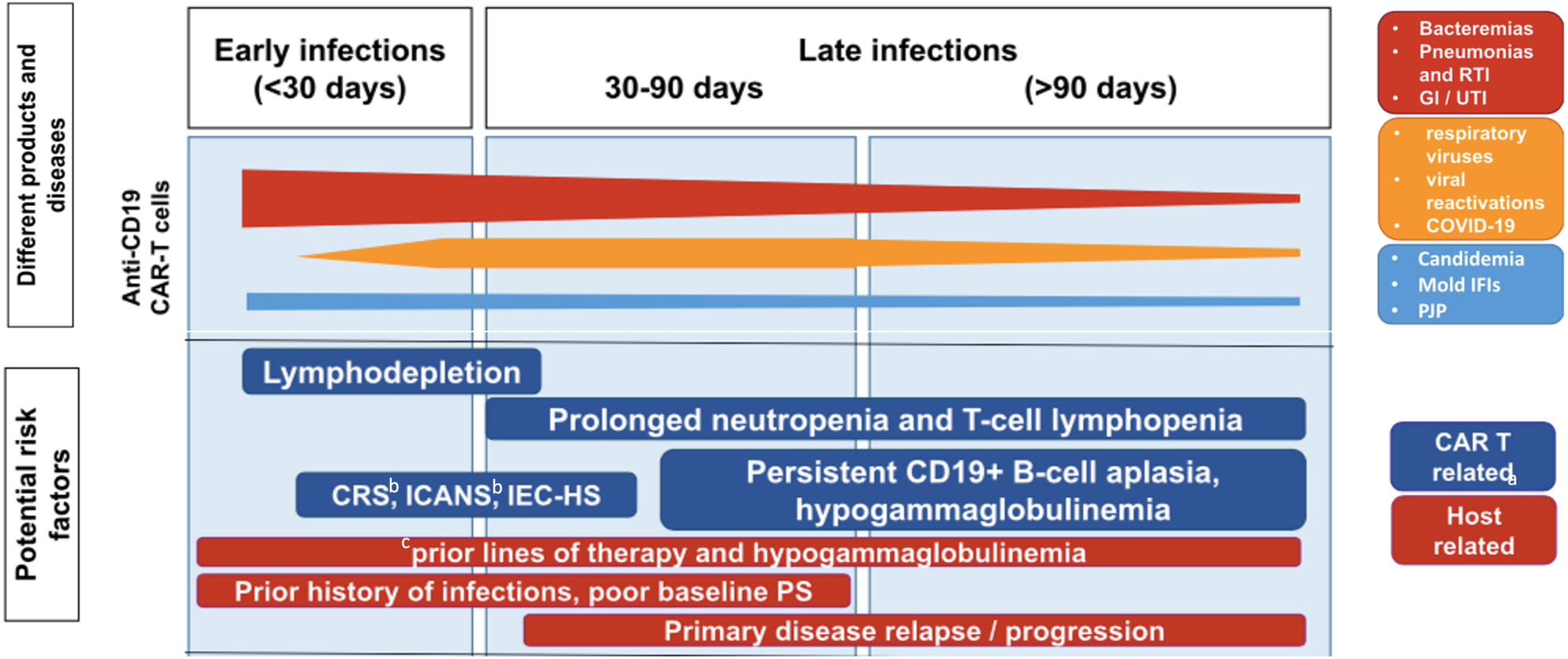






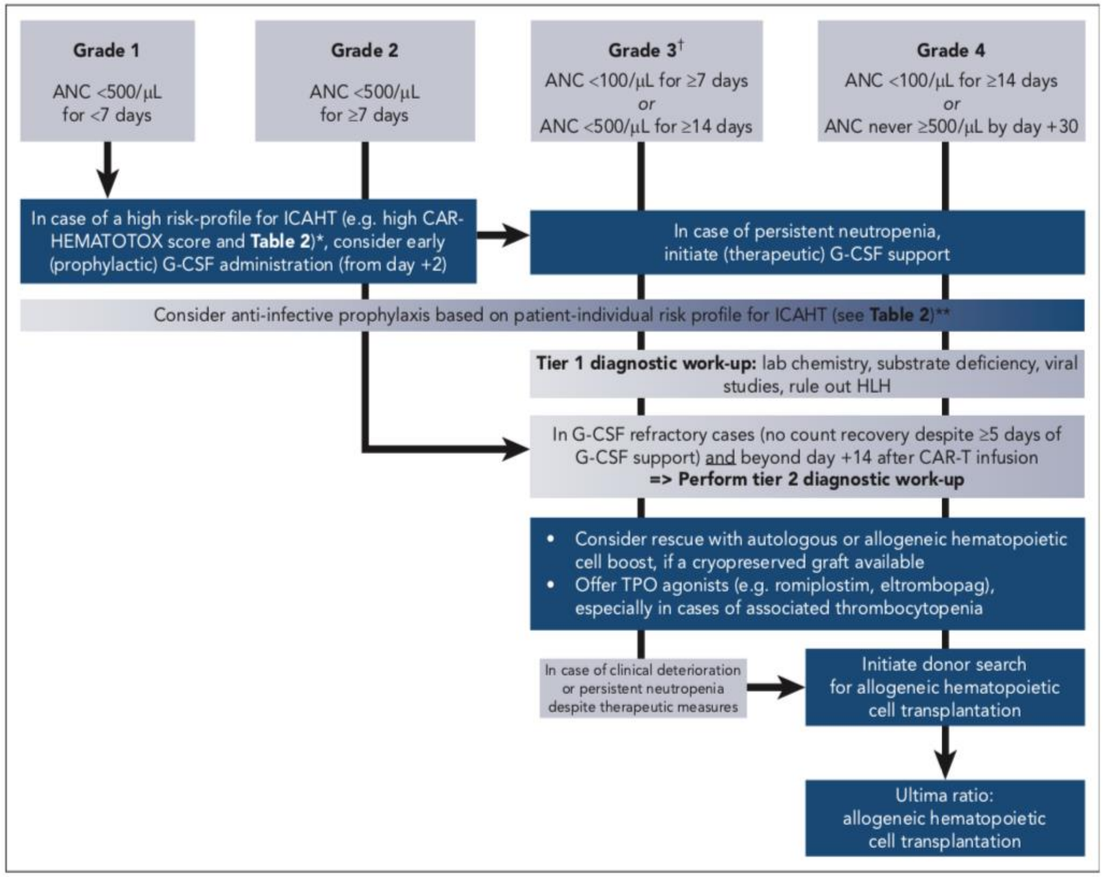
Gagelmann et al, Transplantation and Cellular Therapy, 2024; Portuguese et al, Haematologica 2024; Hayden PJ et al, Annals Oncol 2022

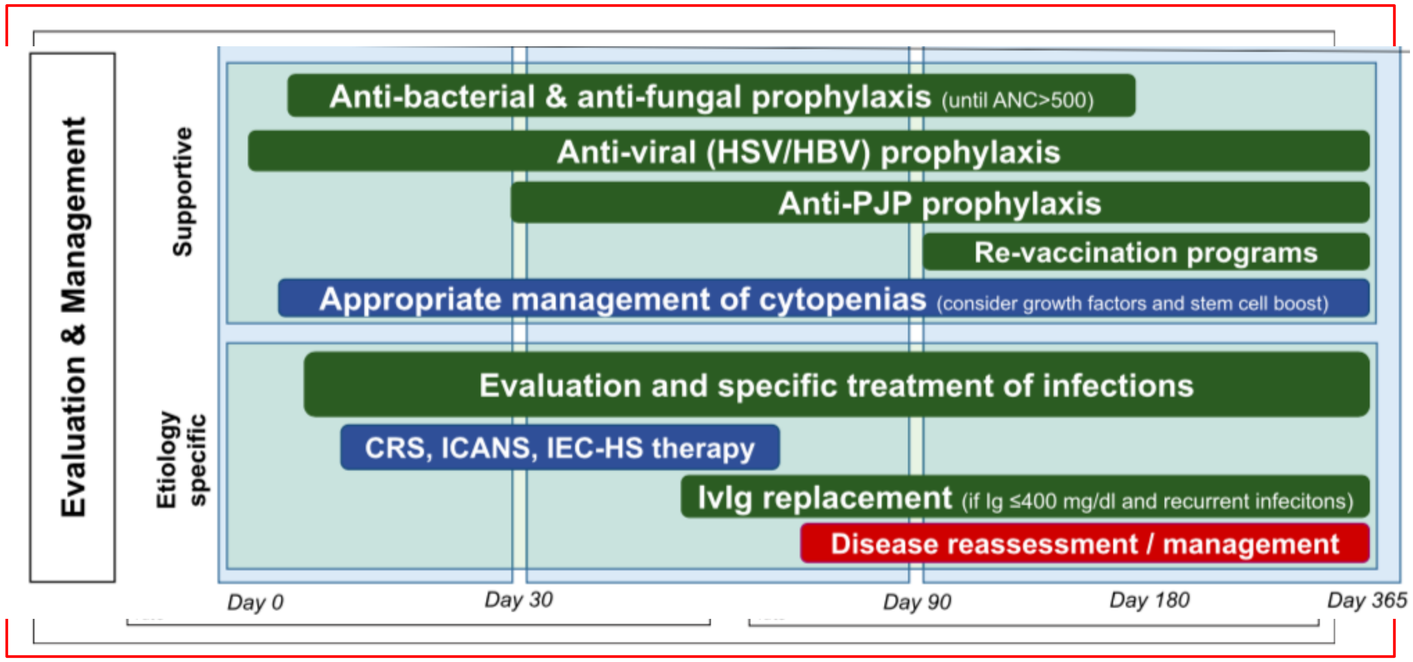
ICAHT, B-Cell Aplasia, Hypogammaglobulinemia, Infections and NRM



a.Including: underlying malignancies (B-ALL and MM > LNH); CAR-HEMATOTOX>2; older age. b.Including corticosteroid use. c. Including prior history of transplantation. IEC-HS: immune effector-cell associated hemophagocytic lymphohistocytosis-like syndrome

How to Reduce the Risk of ICAHT and Infections





Medium and long term follow-up!

Rejeski K, et al. Blood. 2021; Rejeski K, et al. Blood. 2023

Host Related Modulators Can Impact CAR T-cell Efficacy and Toxicity

nature medicine

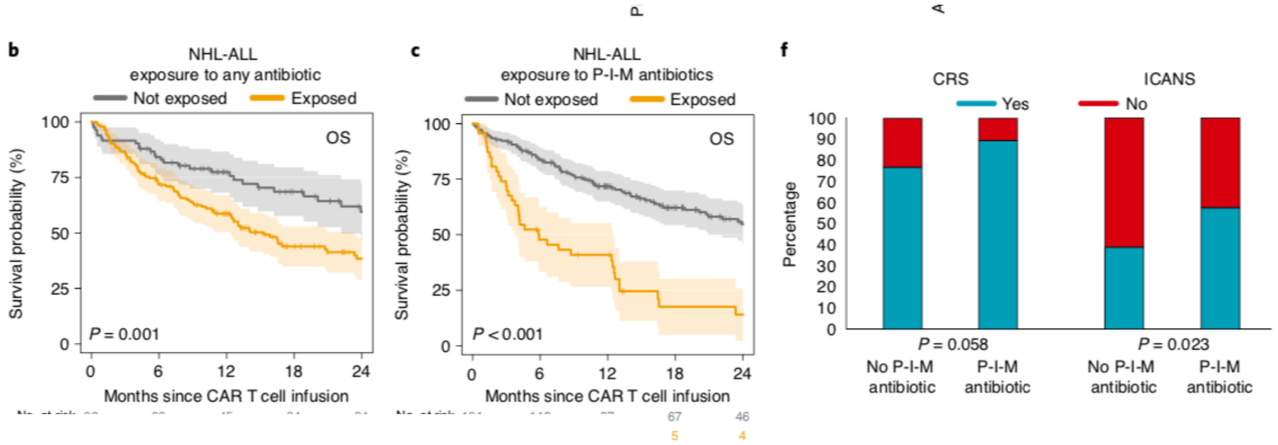
FOCUS | ARTICLES

https://doi.org/10.1038/s41591-022-01702-9

Check for updates

Gut microbiome correlates of response and toxicity following anti-CD19 CAR T cell therapy

Melody Smith[1,2,3,4], Anqi Dai[1,26], Guido Ghilardi[5,6,26], Kimberly V. Amelsberg[5,6], Sean M. Devlin[7], Raymone Pajarillo[5,6], John B. Slingerland[1], Silvia Beghi[8], Pamela S. Herrera[1,9], Paul Giardina[1], Annelie Clurman[1], Emmanuel Dwomoh[1], Gabriel Armijo[1], Antonio L. C. Gomes[1], Eric R. Littmann[10], Jonas Schluter[11], Emily Fontana[12], Ying Taur[13], Jae H. Park[2,3,14], Maria Lia Palomba[2,3,15], Elizabeth Halton[3,16], Josel Ruiz[1], Tania Jain[17], Martina Pennisi[18], Aishat Olaide Afuye[1], Miguel-Angel Perales[1,2], Craig W. Freyer[19], Alfred Garfall[5], Shannon Gier[5], Sunita Nasta[5,20], Daniel Landsburg[5,20], James Gerson[5,20], Jakub S
Sergio Giralt[1,2], Saar I. Gill[5,6], Isabelle Riviere[3,22]
Michel Sadelain[22], Noelle Frey[5,6], Renier J. Br
Jonathan U. Peled[1,2], Andrea Facciabene[5,8],
and Marco Ruella[5,6,20,26,27] ✉



Study code: **MICROCAR**

Role of the gut microbiome in the outcome of Diffuse Large B-Cell Lymphoma patients treated with CAR-T cell therapy

Author (s): Prof. Pier Luigi Zinzani, Patrizia Brigidi, Silvia Turroni, Serafina Guadagnuolo, Beatrice Casadei Francesca Bonifazi, Lisa Argnani

Conclusions

In the near future:

- Dual targeting
- Combinations: CPI/BTKi
- Early harvesting
- Platform for rapid manufacturing and in vivo expansion
- Low affinity CAR

In the long-term future:

- Advanced armored contruct
- Allo CART
- NK/Macrophages CART
- Genome edited platforms
- Gut Micorbiome

GRAZIE PER L'ATTENZIONE

UOC EMATOLOGIA
SSD LINFOMI E SDR LINFOPROLIFERATIVE CRONICHE
Prof. Pier Luigi Zinzani

UOC TERAPIE CELLULARI AVANZATE
Dott.ssa Francesca Bonifazi

CAR T- cell TEAM
UO Emolinfopatologia
UO Farmacia Clinica
Lab di Processazione Cellulare
UO Malattie Infettive
UO Med. Trasfusionale ed Aferesi
UO Medicina Nucleare
UO Neurologia
UO Neuroradiologia
UO Terapia Intensiva
UO Radioterapia
Tutto il personale infermieristico dei reparti DSV, BCM, II e I Sezione