4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic

Scientific board:
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CAR T-cell therapy – update and future perspectives

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Disclosures Marie José Kersten	Received honoraria from and has a consulting/advisory role for BMS/Celgene, Kite, a Gilead Company, Miltenyi Biotec, Galapagos, Novartis, Adicet Bio, Mustang Bio, Janssen and Roche, and travel support from Abbvie, Roche, Janssen and BMS ***(all to institution)***.

CD19 CAR-T cell therapy in Amsterdam UMC:

1st ever patient treated in NL in 2016; currently 200 patients infused

DLBCL phase I/II

- JULIET: CTL019
- ZUMA-1 KTE-C19

DLBCL phase III

- ZUMA-7 axicel CAR T vs autoSCT
- BELINDA: tisacel CAR T vs autoSCT
- DALY-2 CD20-19 CAR

FL phase II

- ELARA: CTL019

MCL phase I/II

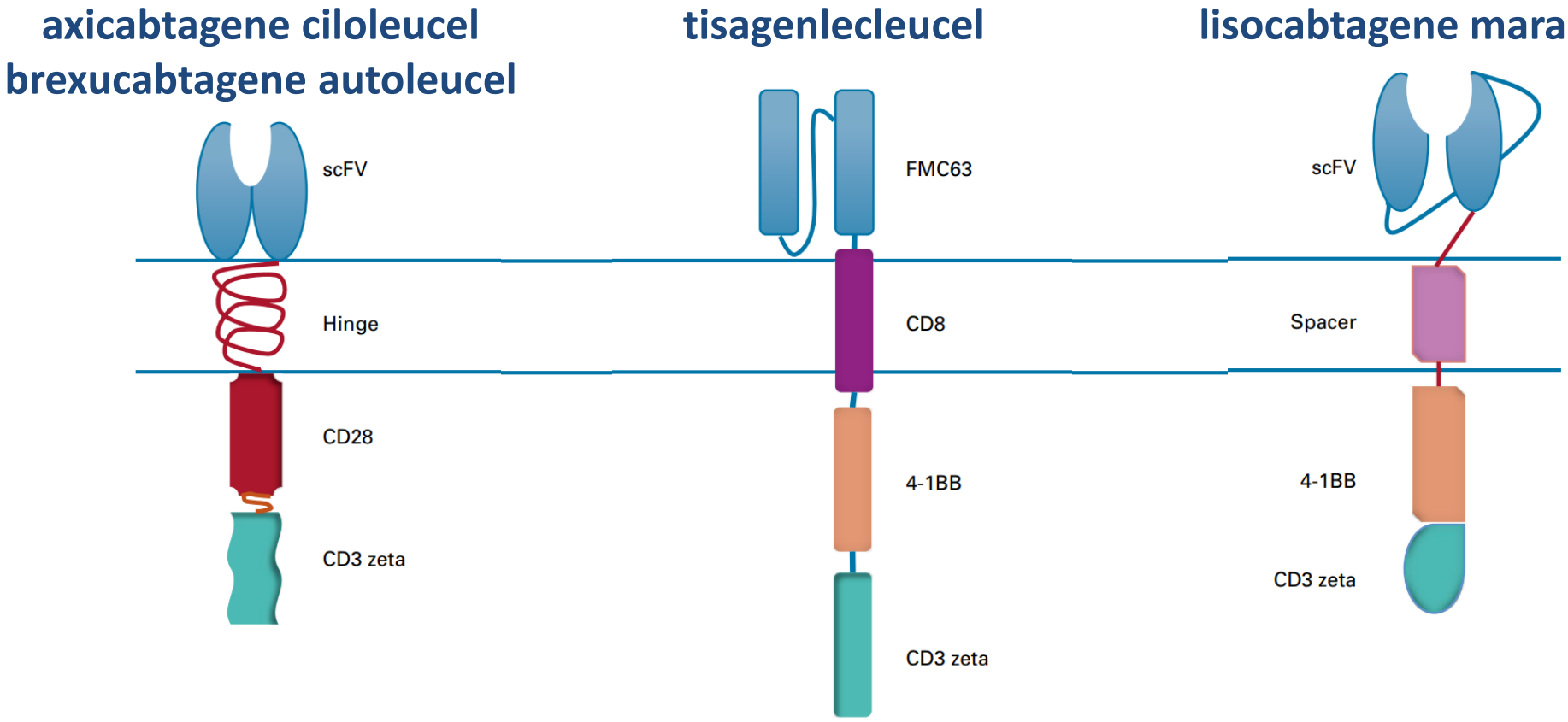
- ZUMA-2 brexucel R/R MCL (cohort 1-3)

Studies 2026

- ZUMA-23 axicel vs RCHOP 1st line
- HOVON161 'PoC' vs commercial
- Atalanta-1 'fast CAR'
- KTE-363/753 CD19/CD20phase I/II

2016 — 2019 — 2020 — 2026

Anti-CD19 CAR T-cell Constructs Licensed and Launched in Pivotal Trials for Lymphoma (EU/FDA)



NCI
ZUMA-1&5 : KTE-C19
ZUMA-2 : KTE-X19

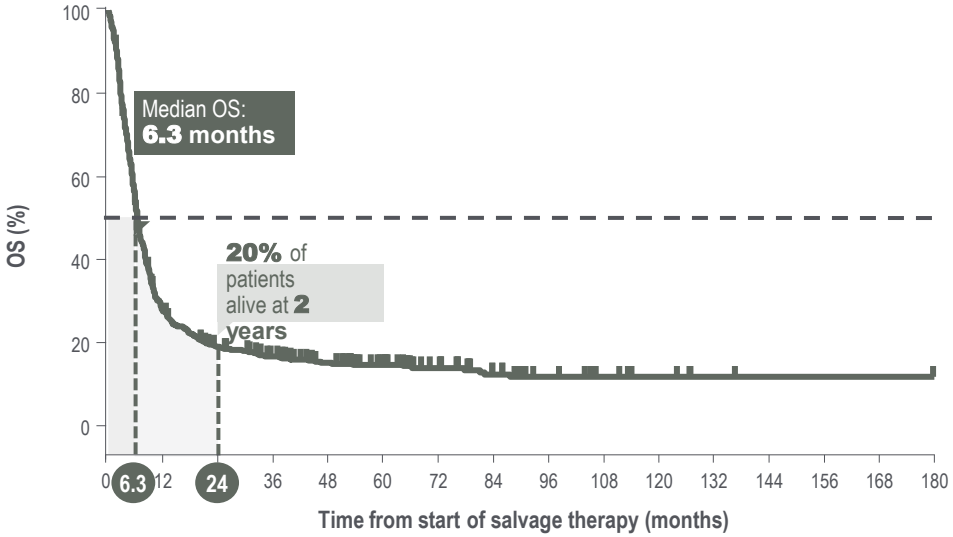
U Penn
ELIANA/JULIET
CTL-019

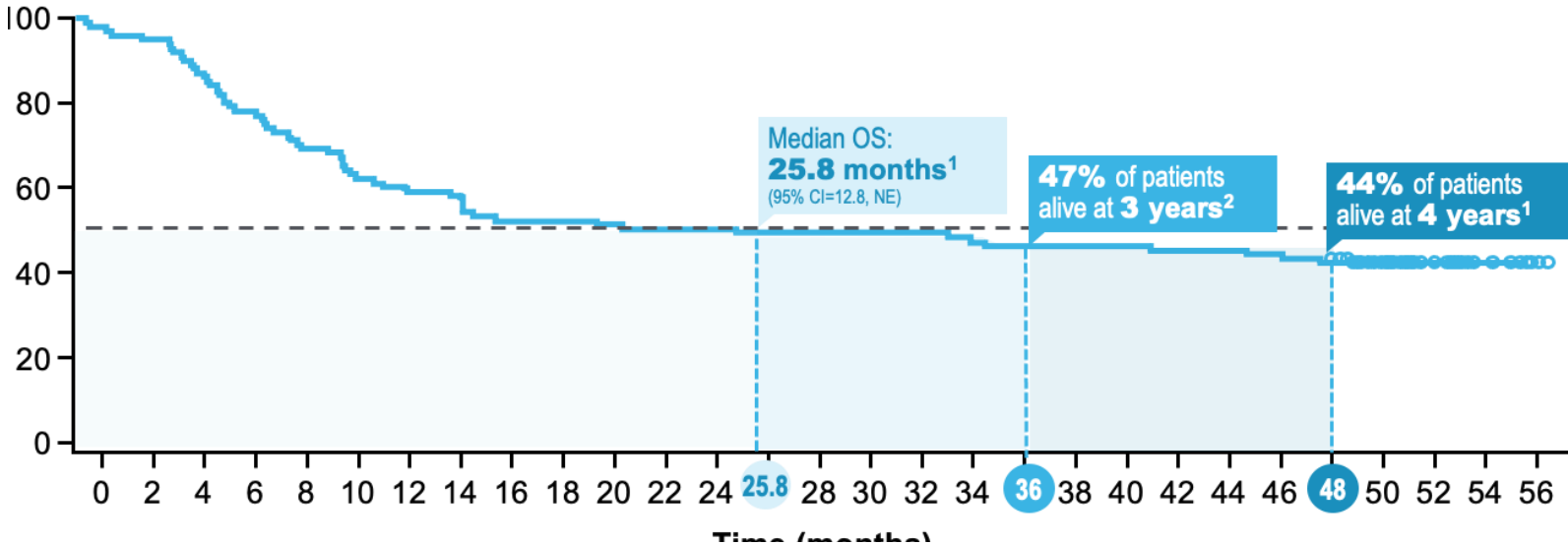
FHCRC/SCH
TRANSCEND
JCAR017 / CD4:CD8 = 1.1

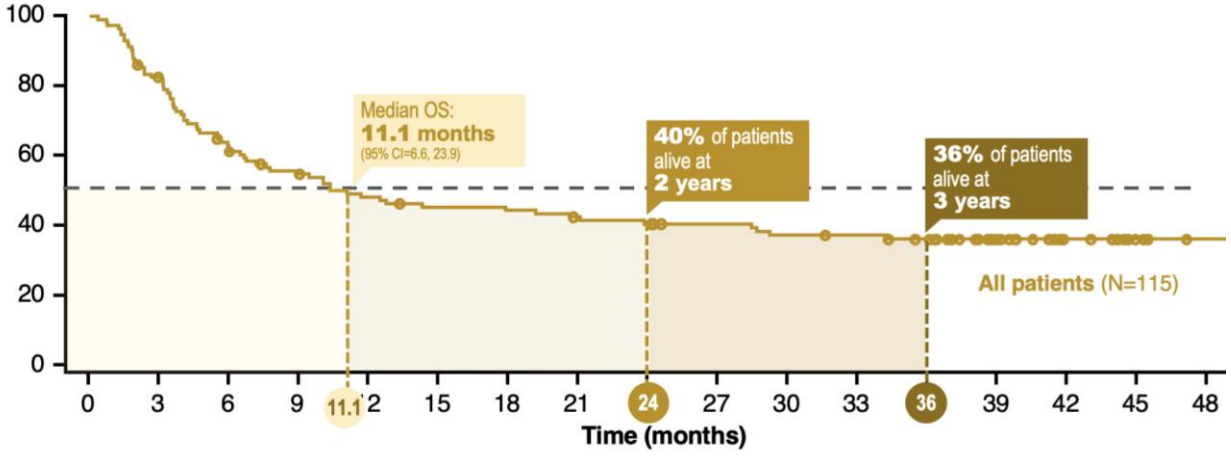
Jacobson C, JCO. 2018; DOI: 10.1200/JCO.18. 01457.

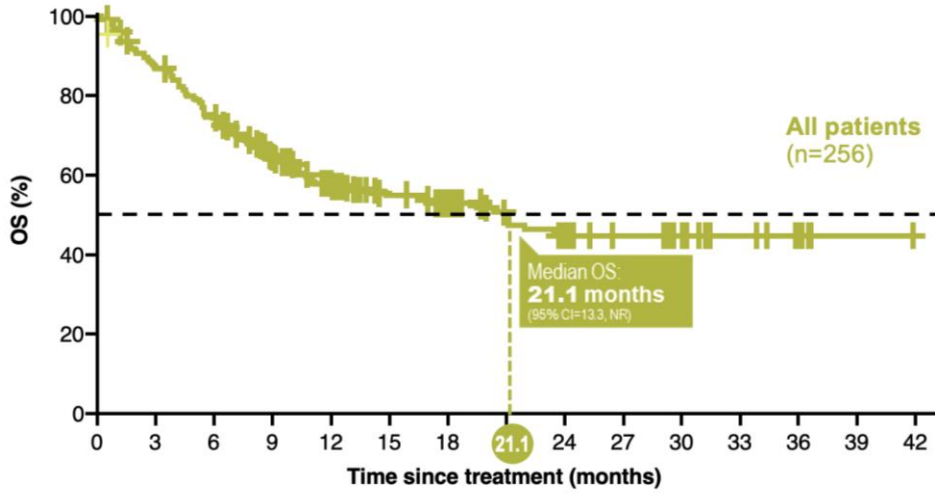
Overall survival in SCHOLAR-1, ZUMA-1, JULIET and TRANSCEND

≥3rd line DLBCL/tFL/PMBCL









SCHOLAR-1: Crump ZUMA-1, Blood 2017: Locke, Lancet Oncol 2019; JULIET: Jaeger, ASH 2020; TRANSCEND: Abramson JS, *et al. Lancet* 2020

Dutch CAR T-cell national tumorboard

Twice weekly online meeting

- Eligibility of referred patients
- Joint protocols
- Population-based real world data (Follow that CAR! Register)
- Biobank
- Imaging database (radiomics)

Results

Flowchart of all referred patients in ≥3rd line (May 2020 - May 2022)

Referred patients to Tumorboard
N= 250[a]

Ineligible: N=90[b] (36%)
- N=41 Rapid progression
- N=3 Performance status ≥ 3
- N=2 Performance status ≥ 2 + comorbidity[c]
- N=6 CNS localization
- N=17 No LBCL
- N=10 <2 systemic lines of therapy
- N=8 No relapse or refractory disease
- N=3 Other[d]

Apheresis completed
N= 160 (64%)

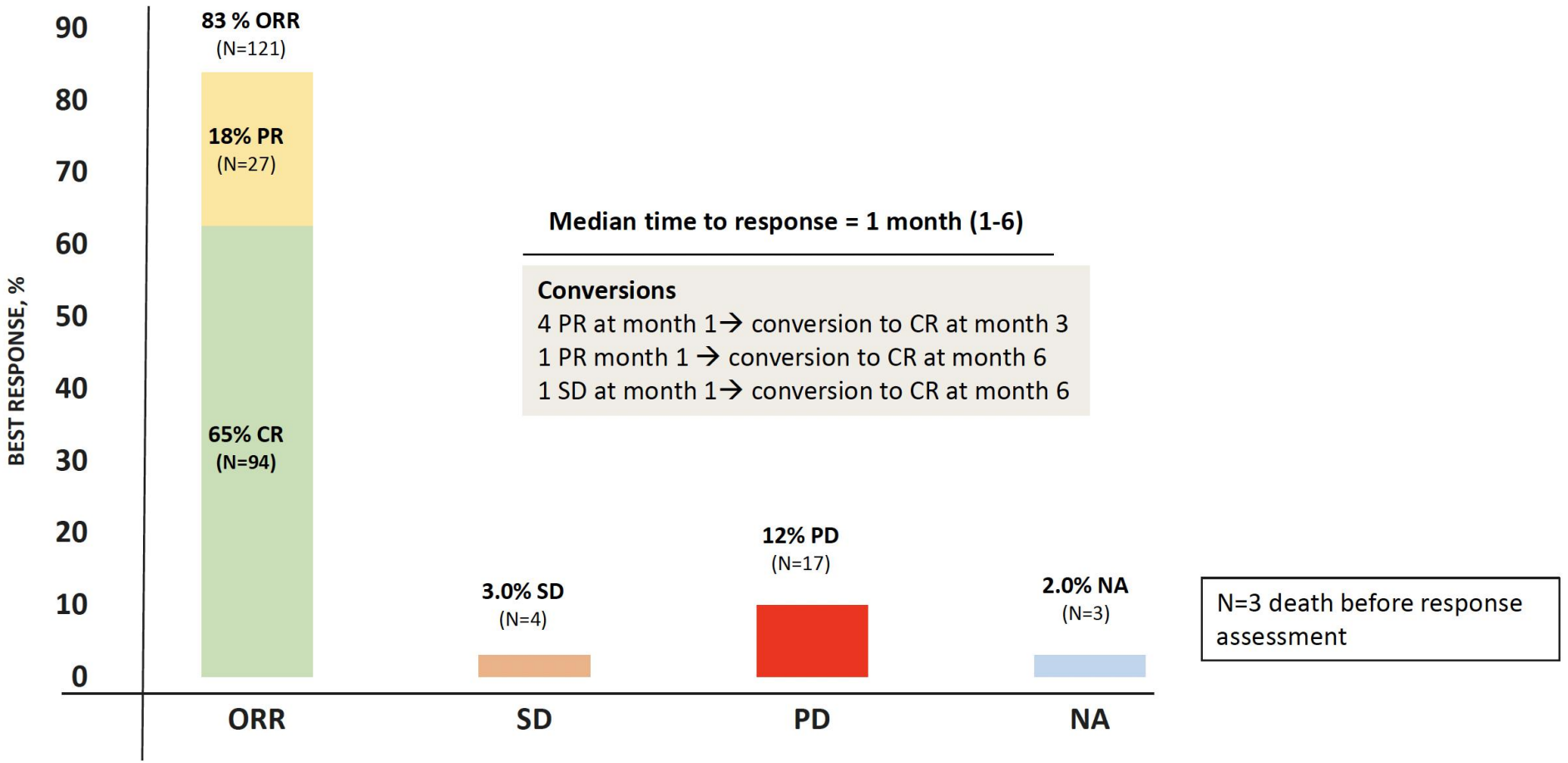
Leukapheresis only: N=15 (15/160 =9%)
- N=8 Rapid progression
- N=1 CNS localization
- N=2 No relapse or refractory disease
- N=1 Fludarabin neurotoxicity
- N=1 Uncontrolled infection
- N=1 Development of Acute Myeloid Leukemia
- N=1 CAR T production failure

CAR T Infused
N=145 (58%)

Many patients drop off because of rapid PD and long vein-to-vein time!

Spanjaart, Pennings et al., Cancers 2023

Response rates



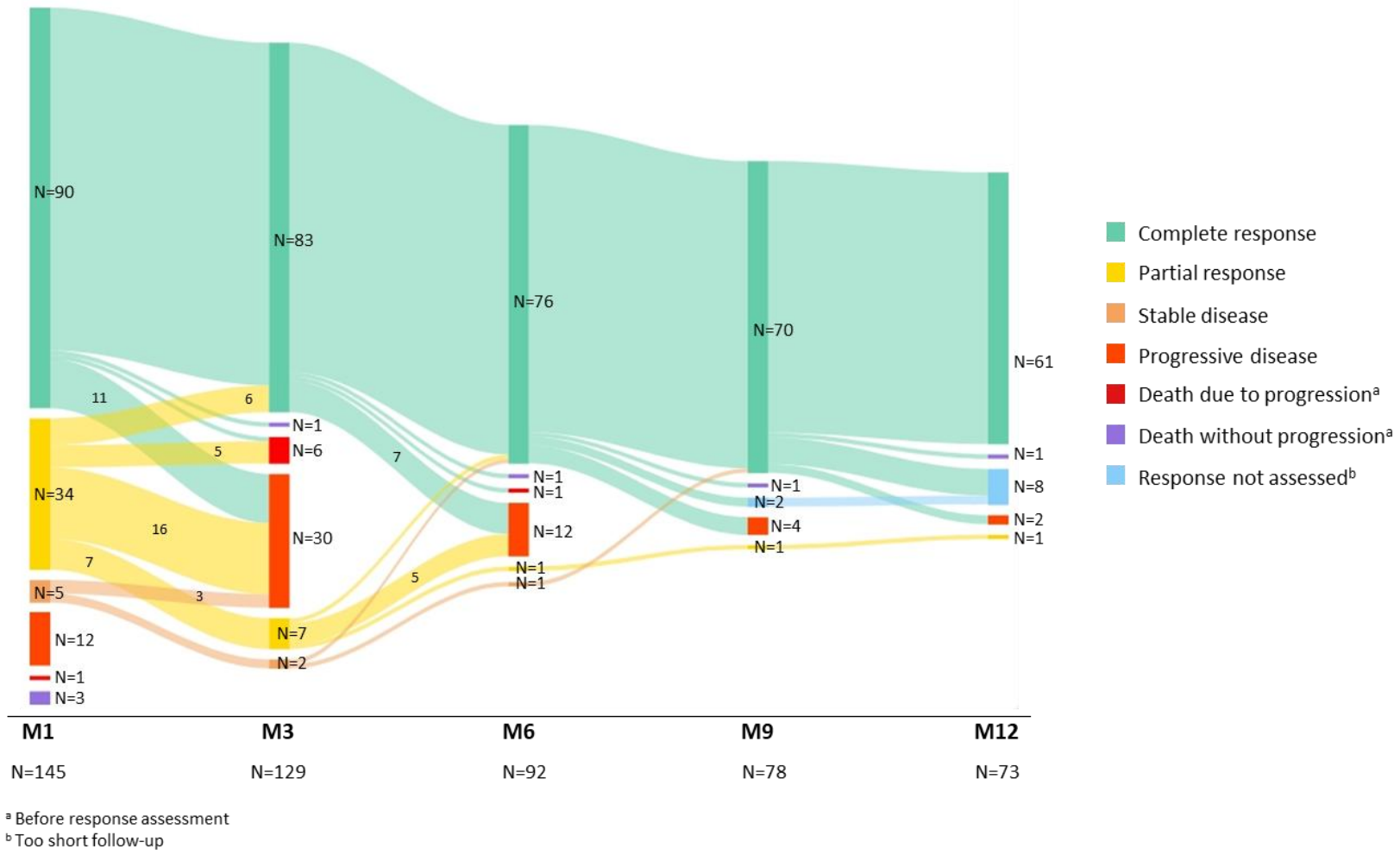
Median time to response = 1 month (1-6)

Conversions
4 PR at month 1→ conversion to CR at month 3
1 PR month 1 → conversion to CR at month 6
1 SD at month 1→ conversion to CR at month 6

N=3 death before response assessment

Spanjaart and Pennings et al Cancers 2023

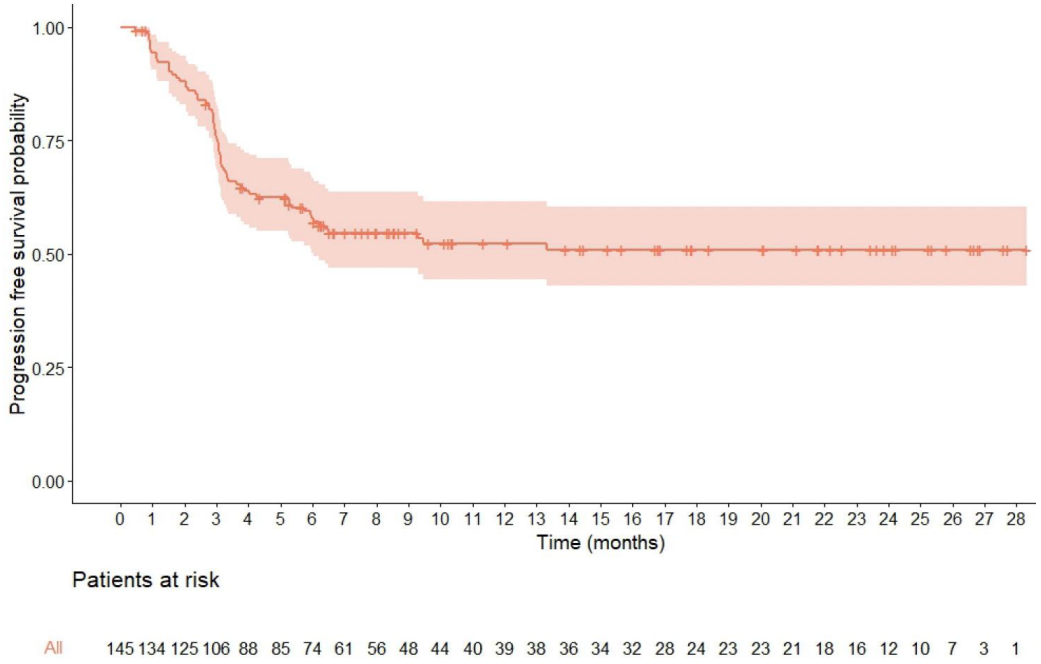
CD19 CAR T real world data in the Netherlands

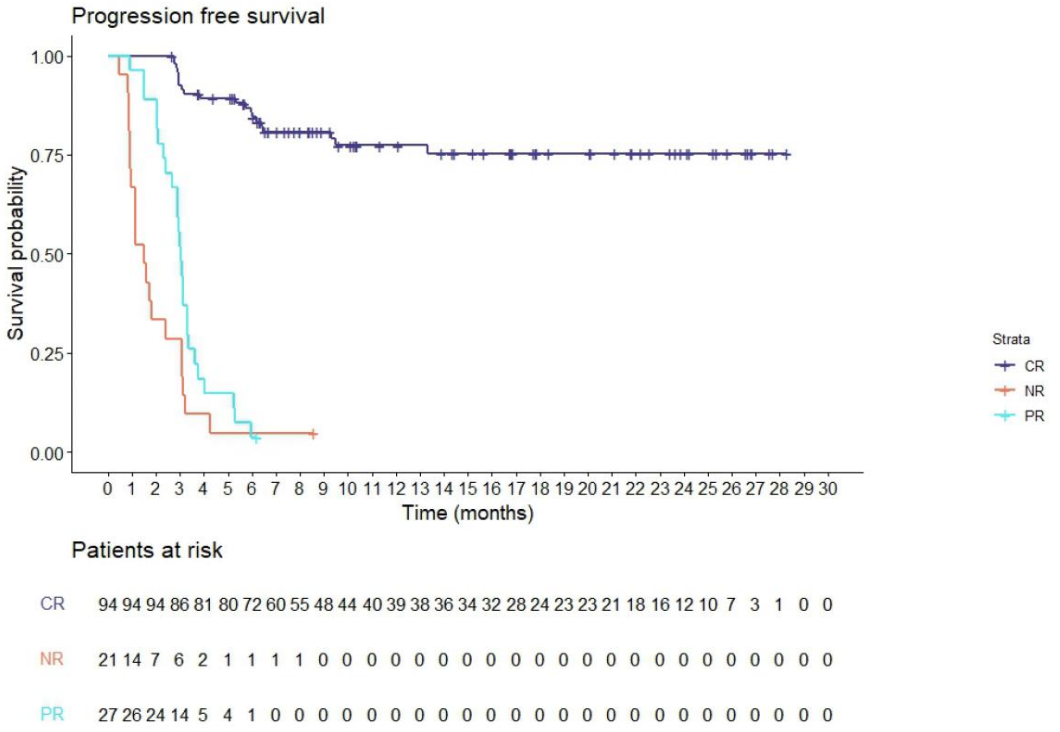


[a] Before response assessment
[b] Too short follow-up

Spanjaart and Pennings et al Cancers 2023

Progression-free survival



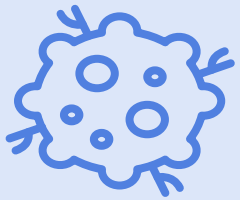


Median follow-up 9.1 months (IQR: 5.1-15.8)
Median PFS 6.2 months (95% CI, 5.10-NR)

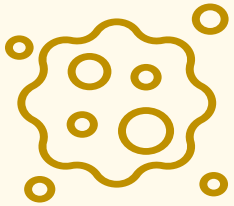
Spanjaart, Pennings et al. Cancers 2023

Why do some patients experience relapse post-CAR T-cell therapy?

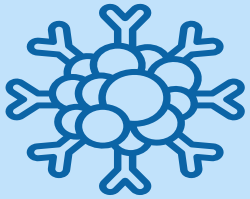
T-cell fitness[1]



Systemic inflammation[1]



Tumour burden[1]



Immunosuppressive tumour microenvironment[2]

Genetic mutations[3]

Antigen loss[4,5]

Improving durability of response to CAR T-cell therapy requires strategies to overcome several mechanisms of resistance

References can be requested from Gilead Switzerland.
CAR, chimeric antigen receptor.
1. Locke FL, *et al. Blood Adv*. 2020;4:4898–4911; 2. Liu Z, *et al. Exp Hematol Oncol.* 2024;13:22; 3. Shouval R, et al. *J Clin Oncol.* 2022;40:369–381; 4. Zhang C, et al. *J Immunol Res.* 2025; 2025:5845167; 5. Byrne M, et al. *Bone Marrow Transplant*. 2019;25:e344–51.

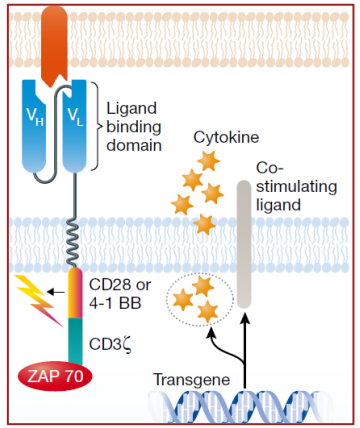
Better, safer and faster CARs/combinations are needed

Combination with other agents

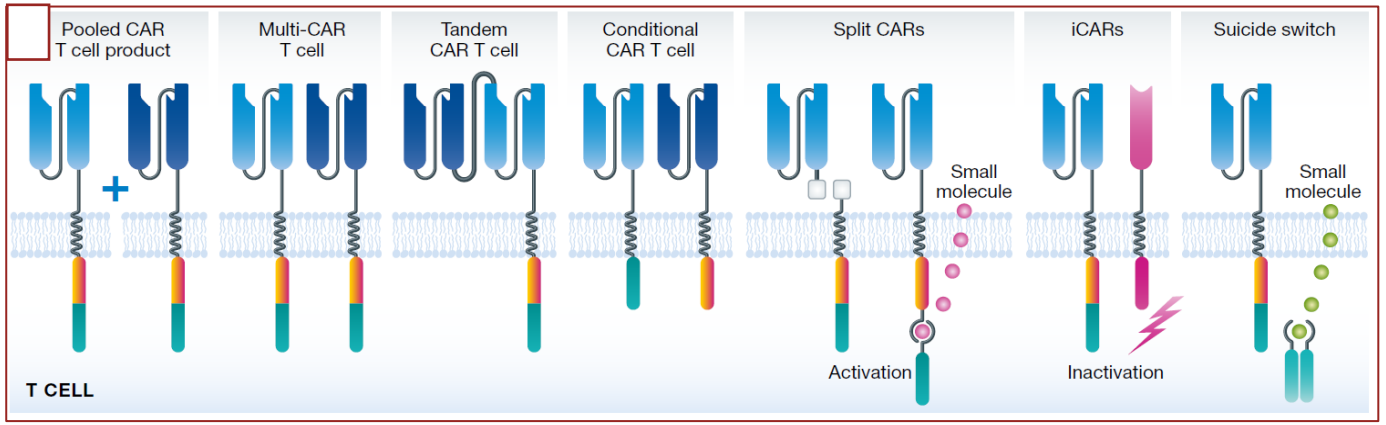
- Ibrutinib
- Lenalidomide
- Immune checkpoint inhibitors

- PoC, faster CARs
- Modulate cellular composition
- Metabolic reprogramming
- Gene editing
- Fully humanized CAR constructs
- Dual or tandem CARs
- Allogeneic CARs
- NK-CARs
- In vivo CAR

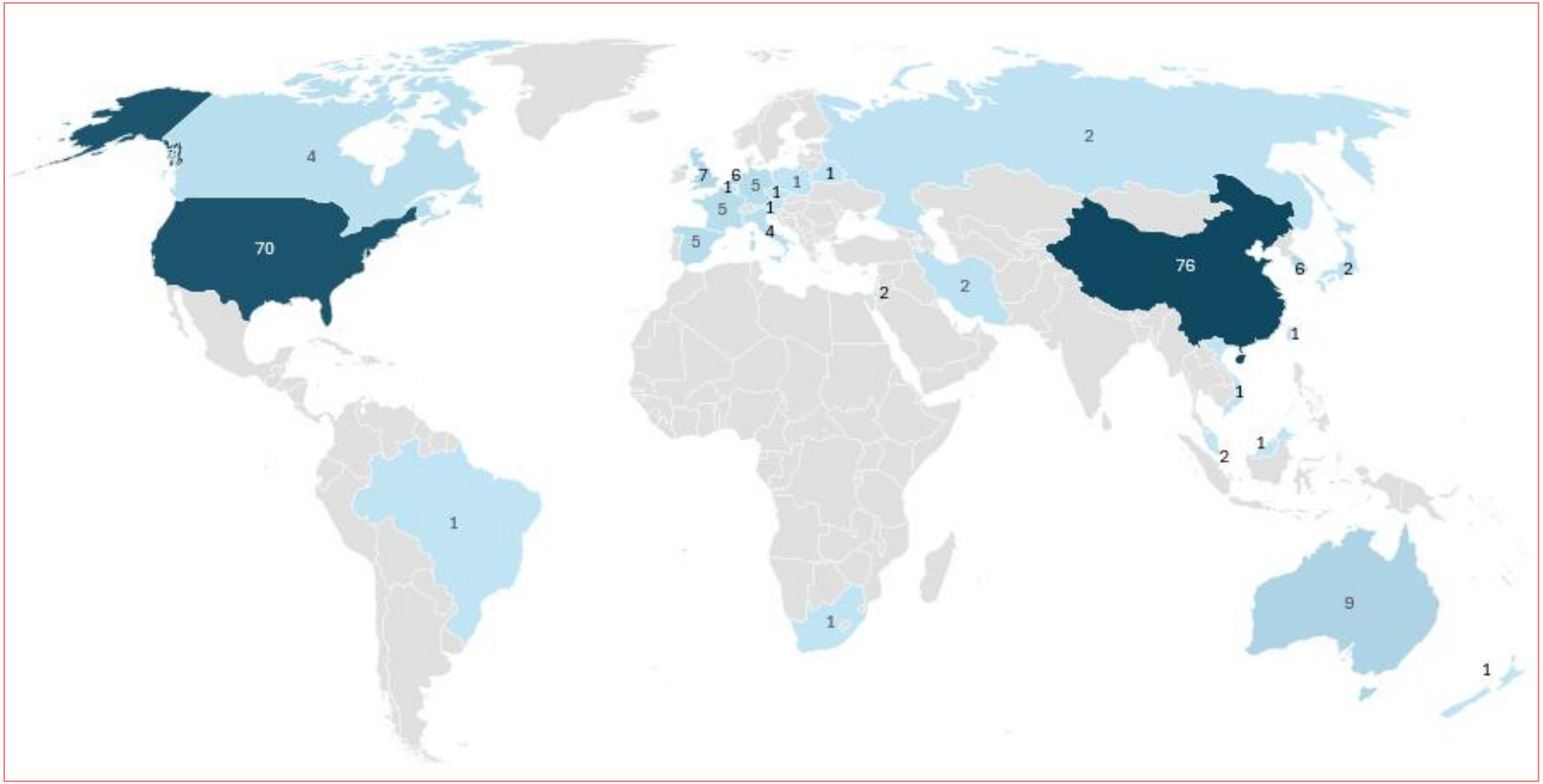
4th generation (TRUCKs)



Novel CAR T-cell constructs



CAR T clinical trials currently recruiting



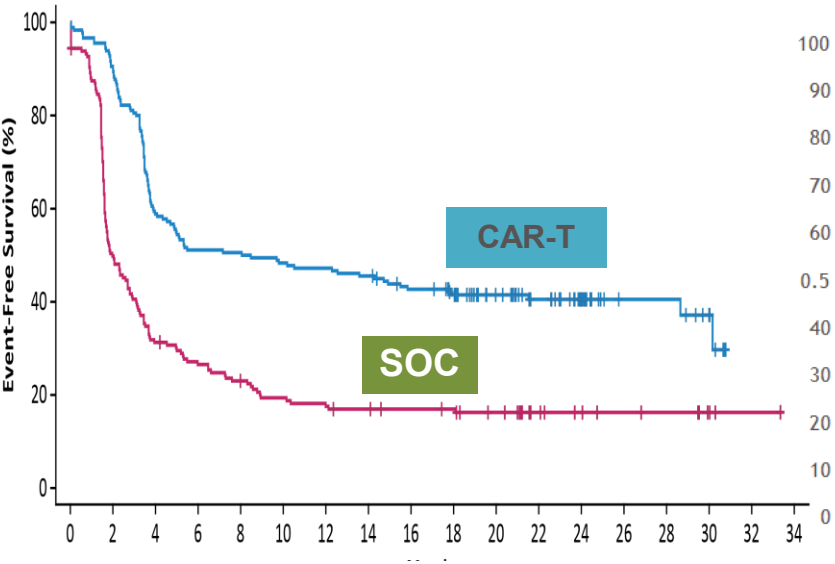
eha

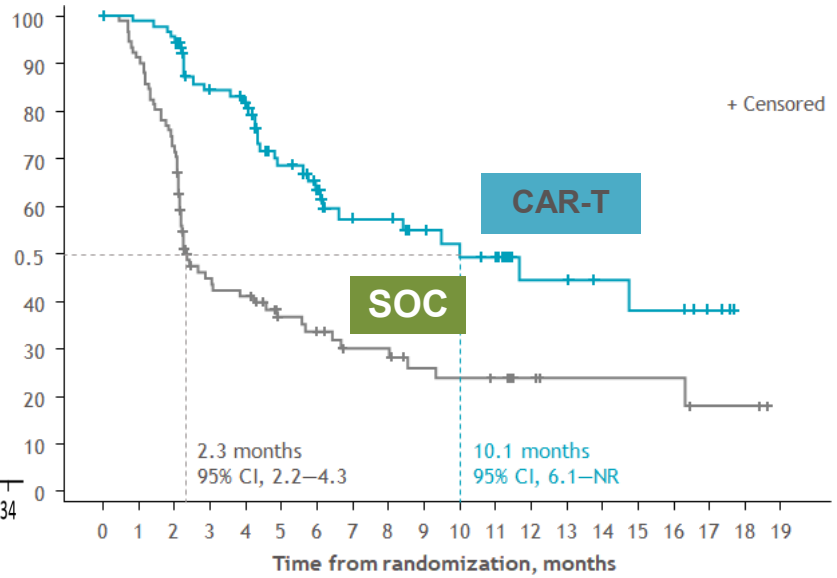
Move up! Is 2nd line CAR T better than autoSCT?

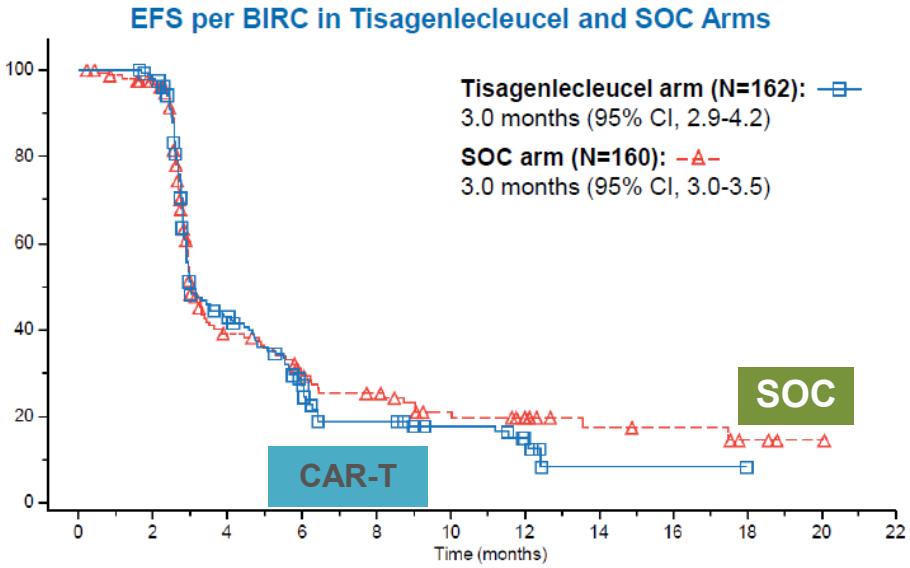
Axi-cel	**ZUMA-7**
Liso-cel	**TRANSFORM**
Tisa-cel	**BELINDA**

NCT03391466; NCT03575351; NCT03570892; slide courtesy of Gilles Salles

Event-Free Survival ZUMA-7, TRANSFORM and BELINDA

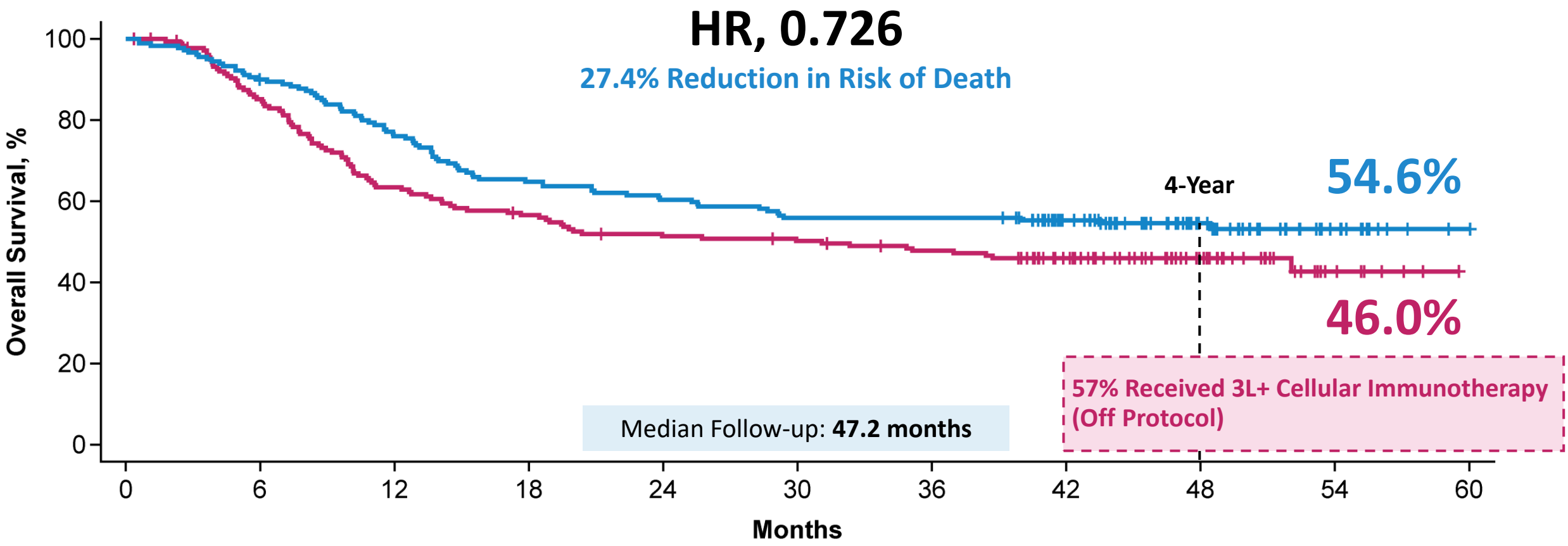






ZUMA-7	Transform	BELINDA
Median EFS = 8.3 vs. 2 mons	Median EFS = 10.1 vs. 2.3 mons	Median EFS = 3 vs. 3 mons
1. Progression or death 2. New treatment 3. No CR/PR by 150 days	1. Progression or death 2. New treatment 3. No CR/PR by 9wks	1. Progression or death 2. SD/PD @/after 12wks

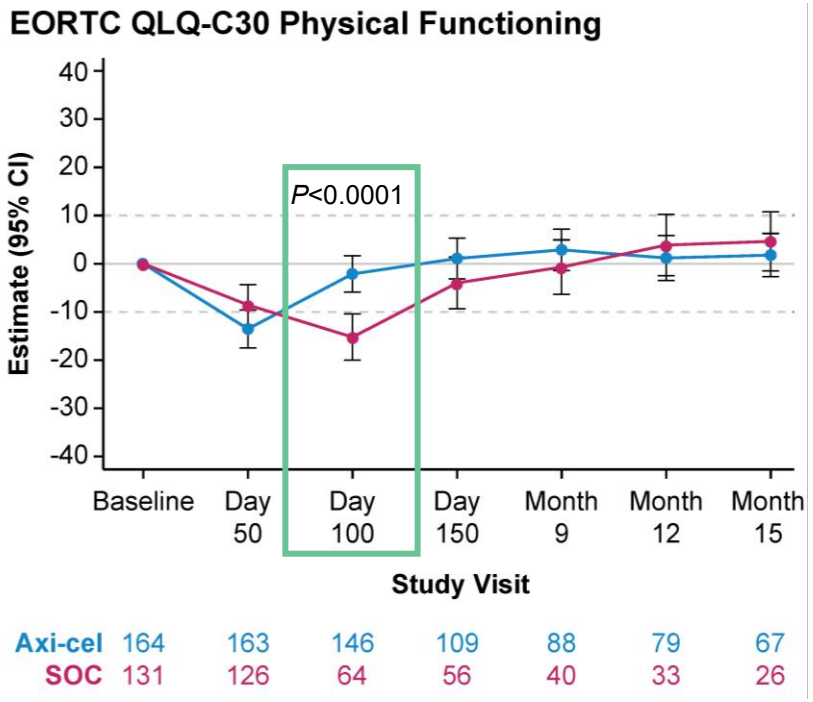
Axi-Cel leads to better Overall Survival Versus SoC

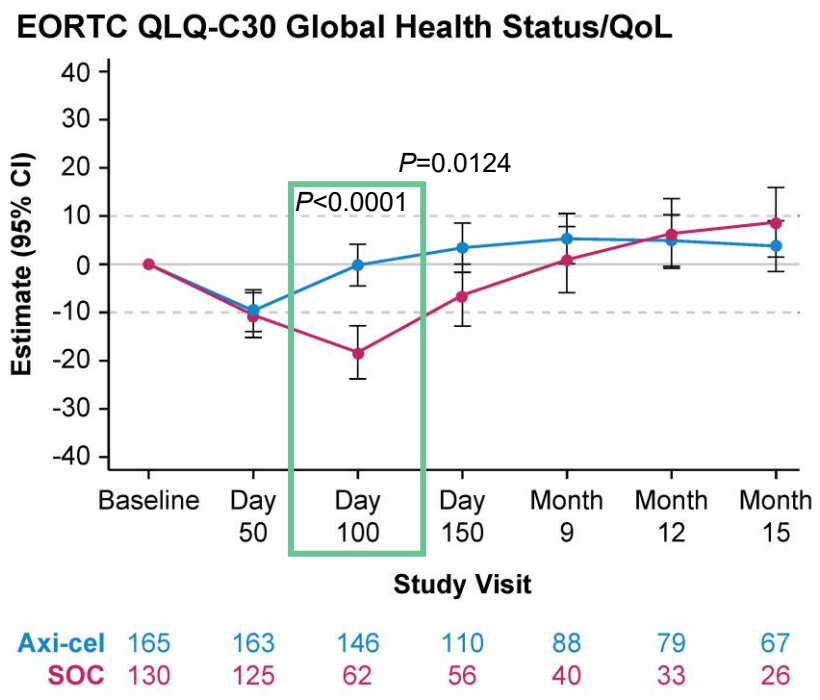


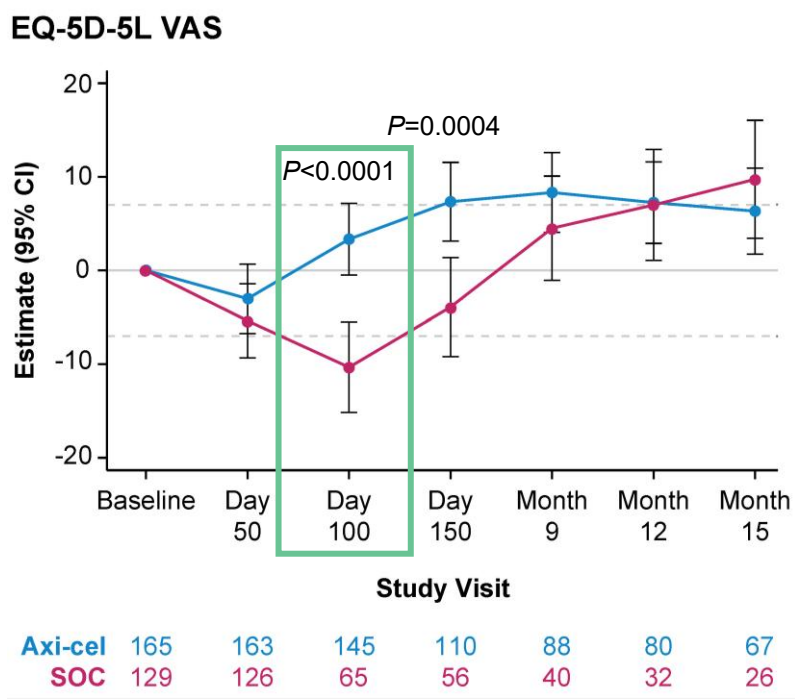
- 57% (n=102/179) of SOC patients received subsequent cellular immunotherapy (off protocol)
- Despite the increased survival in the SOC arm versus historical studies, axi-cel increased survival over SOC[1,2]

1. Approximately 30% for early R/R LBCL in ORCHARRD (van Imhoff GW, et al. *JCO*. 2017;35:544-551). 2. <40% for those with prior rituximab and early R/R LBCL in CORAL (Gisselbrecht C, et al. *JCO*. 2010;28:4184-4190).
3L+, third line or later; axi-cel, axicabtagene ciloleucel; HR, hazard ratio; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; SOC, standard of care.

Change From Baseline for Prespecified PRO Endpoints





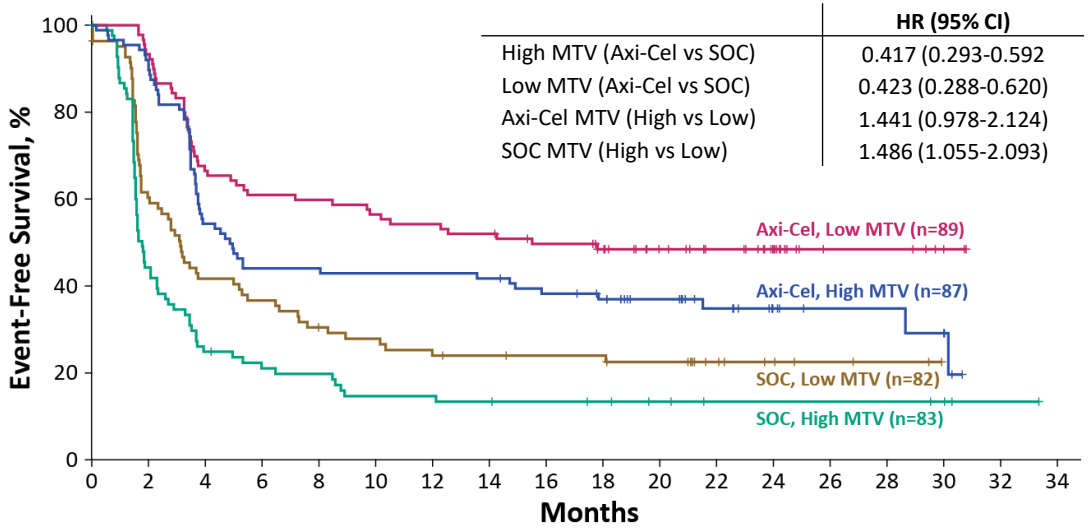


For patients in the QoL analysis set treated with axi-cel versus SOC, there was a statistically significant and clinically meaningful difference in mean change of scores from baseline at Day 100 in favor of axi-cel on all prespecified PRO domains

Evaluated via mixed-effect model with repeated measures. Statistical significance and clinical meaningfulness coincide for all except for EORTC QLQ-C30 Global Health Status/QoL at Day 150, which was less than a 10-point change (9.8).

What about high tumorload (TMTV)?

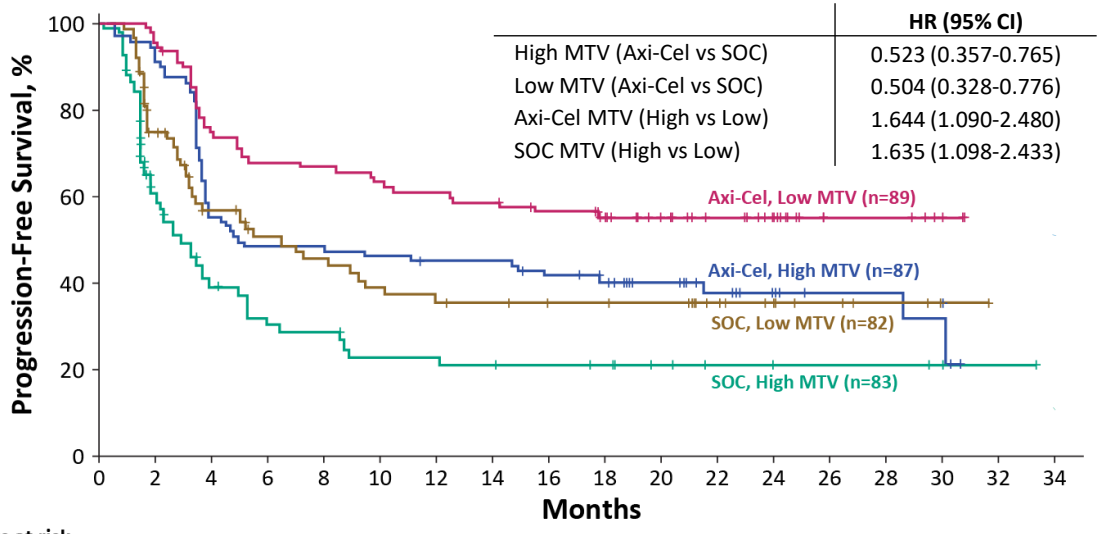
EFS



	HR (95% CI)
High MTV (Axi-Cel vs SOC)	0.417 (0.293-0.592
Low MTV (Axi-Cel vs SOC)	0.423 (0.288-0.620)
Axi-Cel MTV (High vs Low)	1.441 (0.978-2.124)
SOC MTV (High vs Low)	1.486 (1.055-2.093)

Patients at risk																		
Axi-Cel, High MTV	87	80	47	38	38	37	37	36	32	29	22	16	9	6	6	4		
Axi-Cel, Low MTV	89	83	59	54	53	50	48	46	42	38	30	24	17	6	6	2		
SOC, High MTV	83	36	20	16	15	11	11	10	9	8	6	4	4	4	4	3	1	0
SOC, Low MTV	82	48	33	29	23	21	18	17	16	16	14	8	5	3	2	0		

PFS



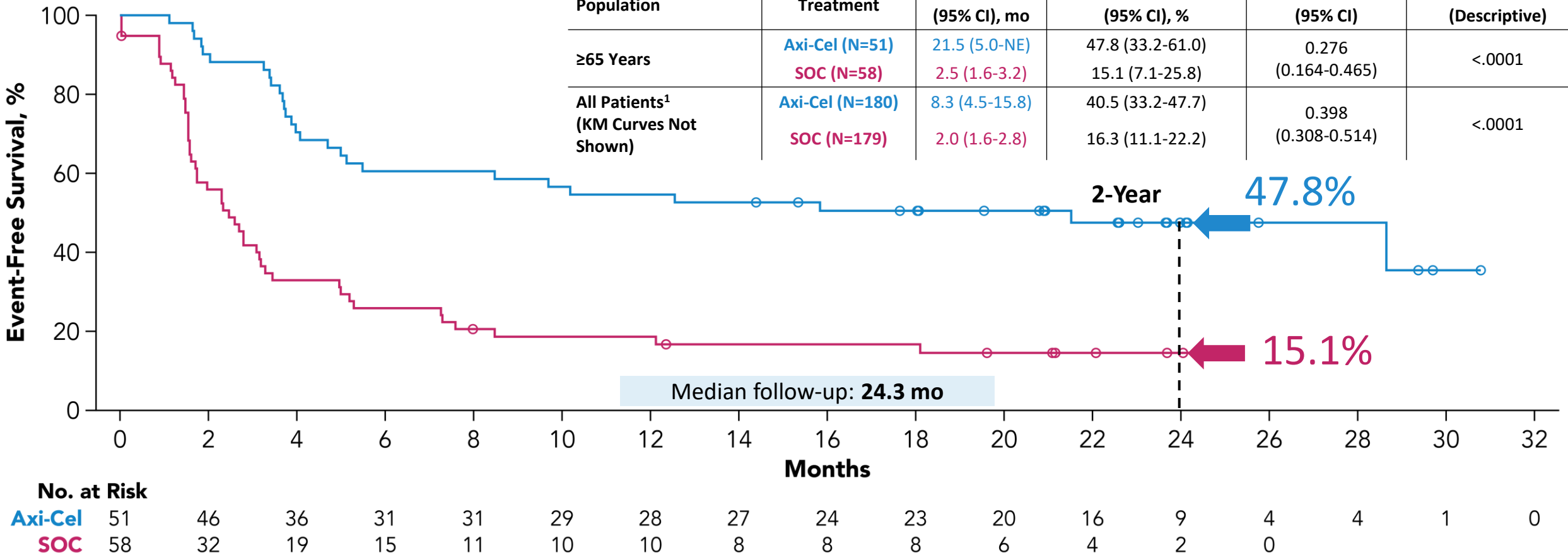
	HR (95% CI)
High MTV (Axi-Cel vs SOC)	0.523 (0.357-0.765)
Low MTV (Axi-Cel vs SOC)	0.504 (0.328-0.776)
Axi-Cel MTV (High vs Low)	1.644 (1.090-2.480)
SOC MTV (High vs Low)	1.635 (1.098-2.433)

Patients at risk																		
Axi-Cel, High MTV	87	82	48	42	42	40	38	38	34	31	23	17	10	6	6	4		
Axi-Cel, Low MTV	89	84	64	58	57	54	52	50	46	42	33	26	18	6	6	2		
SOC, High MTV	83	38	23	17	16	12	12	11	10	9	7	5	4	4	4	3	1	0
SOC, Low MTV	82	54	37	30	27	23	21	20	18	18	17	10	7	5	3	1	0	

- Axi-cel EFS and PFS were superior to SOC for both low (≤median) and high (>median) MTV
- Axi-cel EFS trended shorter in patients with high MTV and EFS was shorter in SOC patients with high MTV
- PFS was shorter in both axi-cel and SOC patients with high MTV compared with low MTV

What about elderly patients?
ZUMA-7: EFS in Patients Aged ≥65 Years

Population	Treatment	Median EFS (95% CI), mo	24-mo EFS Rate (95% CI), %	Stratified HR (95% CI)	Stratified *P* Value (Descriptive)
≥65 Years	Axi-Cel (N=51)	21.5 (5.0-NE)	47.8 (33.2-61.0)	0.276 (0.164-0.465)	<.0001
	SOC (N=58)	2.5 (1.6-3.2)	15.1 (7.1-25.8)		
All Patients[1] (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)	<.0001
	SOC (N=179)	2.0 (1.6-2.8)	16.3 (11.1-22.2)		



- Kaplan-Meier estimates of the 24-month EFS rates were higher for axi-cel than for SOC (47.8% vs 15.1%, respectively)

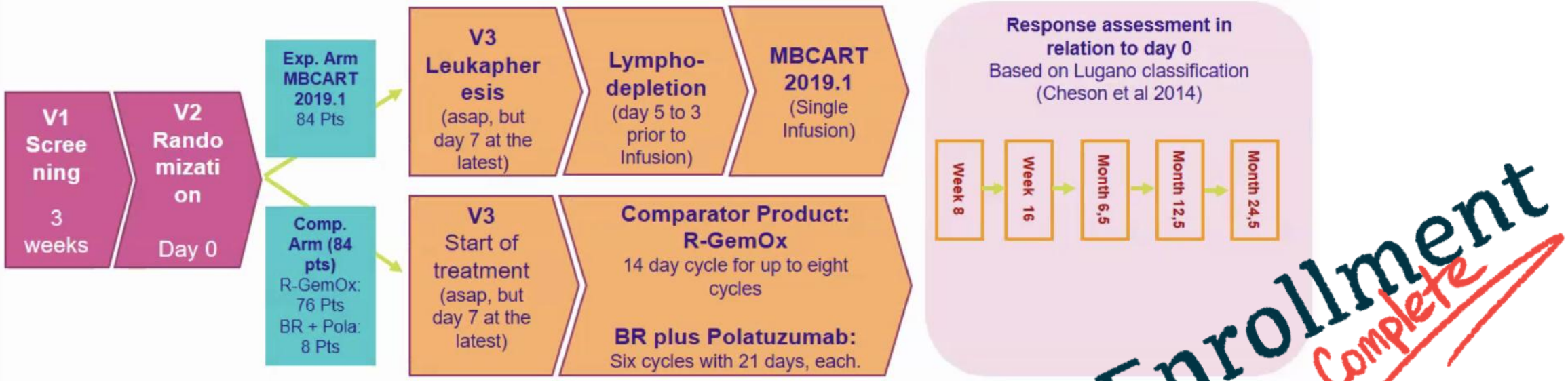
1. Locke FL, et al. *N Engl J Med*. 2022;386:640-654.

Axi-cel, axicabtagene ciloleucel; EFS, event-free survival; HR, hazard ratio; KM, Kaplan-Meier; mo, month; NE, not evaluable; SOC, standard of care.

What about non-SCT eligible patients?
DALY-2 study: CD20-19 CAR T vs SoC

MB-CART2019.1 in r/r DLBCL: DALY-2 Trial Europe
Schematic overview

Miltenyi Biomedicine



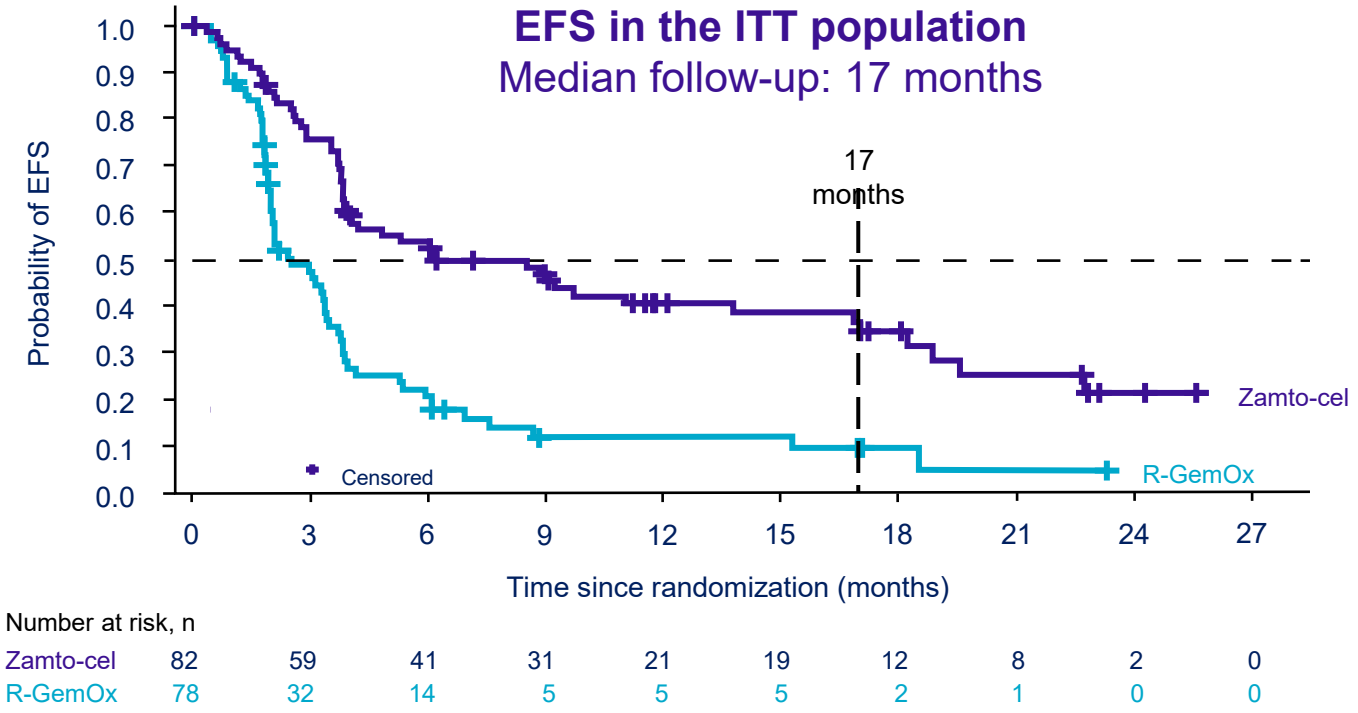
Enrollment Complete

Important to consider:

Success in the treatment arm depends on timely Infusion of MBCART2019.1, therefore:

- Leukapheresis has to be scheduled and fixed during screening prior to randomization for all patients
- Manufacturing slot has to be scheduled prior to randomization for all patients

Primary endpoint: significant EFS benefit with zamto-cel

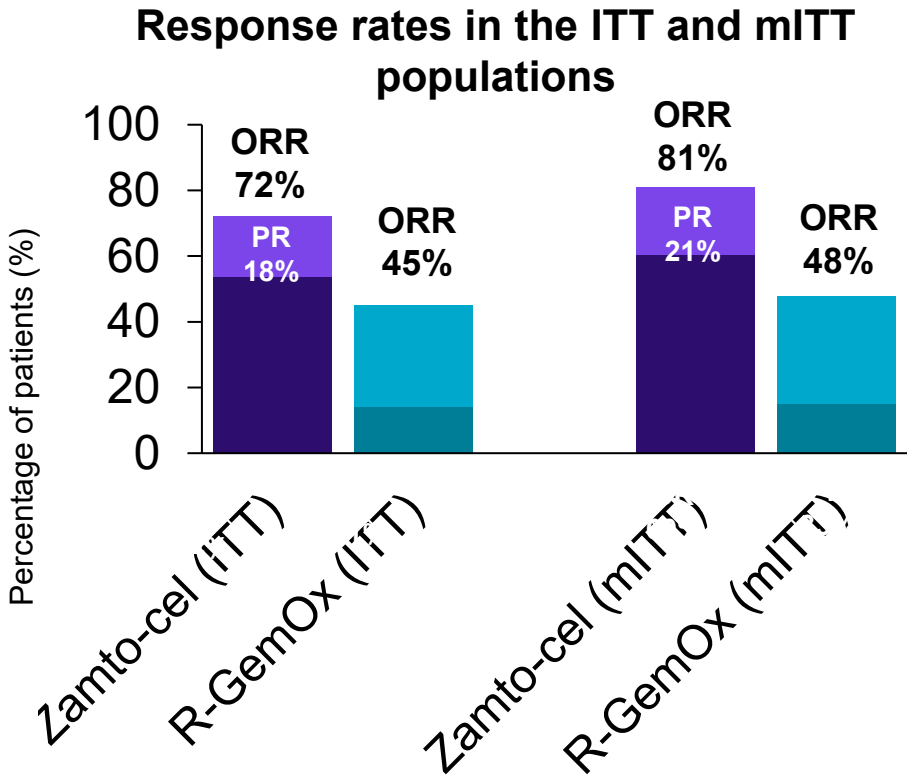


Primary endpoint	Zamto-cel (n=82)	R-GemOx (n=78)
EFS based on IRC assessment[a]		
Median EFS, months (95% CI)	6.21 (3.84, 13.77)	2.53 (1.97, 3.35)
Patients with events, n (%)	52 (63.4)	63 (80.8)
HR (95% CI) p-value	0.39 (0.27, 0.58) p<0.0001	

Zamto-cel arm demonstrated highly statistically significant and clinically meaningful superiority over R-GemOx for EFS, with a HR of 0.39

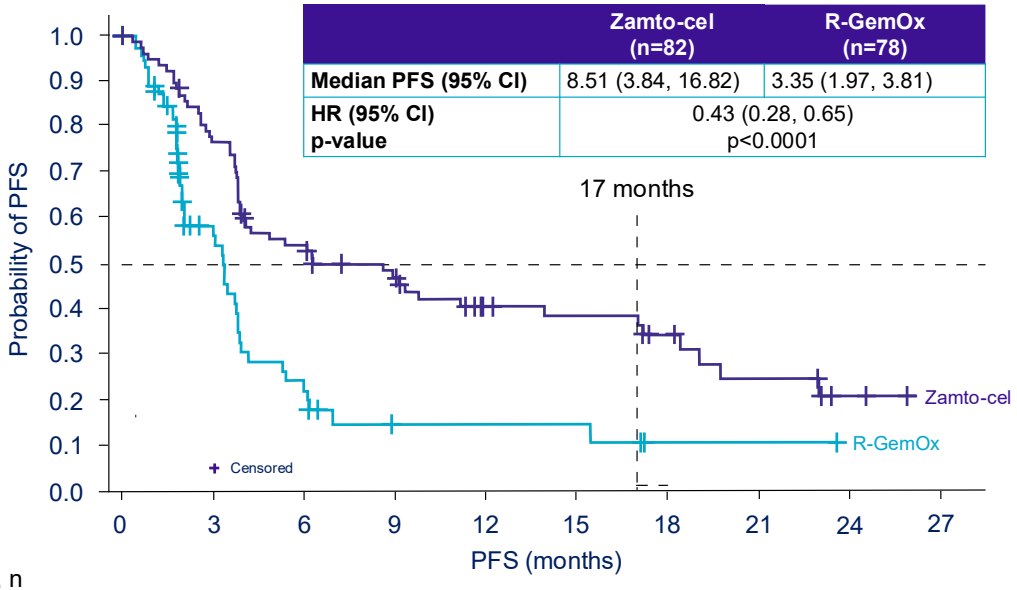
All p-values are one-sided. [a]EFS was defined as the time between the date of randomization and the date of objective disease progression, failure to achieve PR or CR at or beyond Week 8 after randomization leading to a new anti-lymphoma therapy or death of any cause, whichever occurs first. Treatment effects were estimated as HRs with 95% CIs using a Cox proportional hazards models. P-value was from the log-rank test stratified by IPI. Superiority was concluded if the 1-sided p-value was ≤0.025.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; IRC, independent review committee; ITT, intent-to-treat; R-GemOx, rituximab gemcitabine oxaliplatin.

Secondary endpoints:
CR rate in zamto-cel 3.8x higher than R-GemOx



Median PFS by IRC

Median follow-up: 17 months



	Zamto-cel (n=82)	R-GemOx (n=78)
Median PFS (95% CI)	8.51 (3.84, 16.82)	3.35 (1.97, 3.81)
HR (95% CI)	0.43 (0.28, 0.65)	
p-value	p<0.0001	

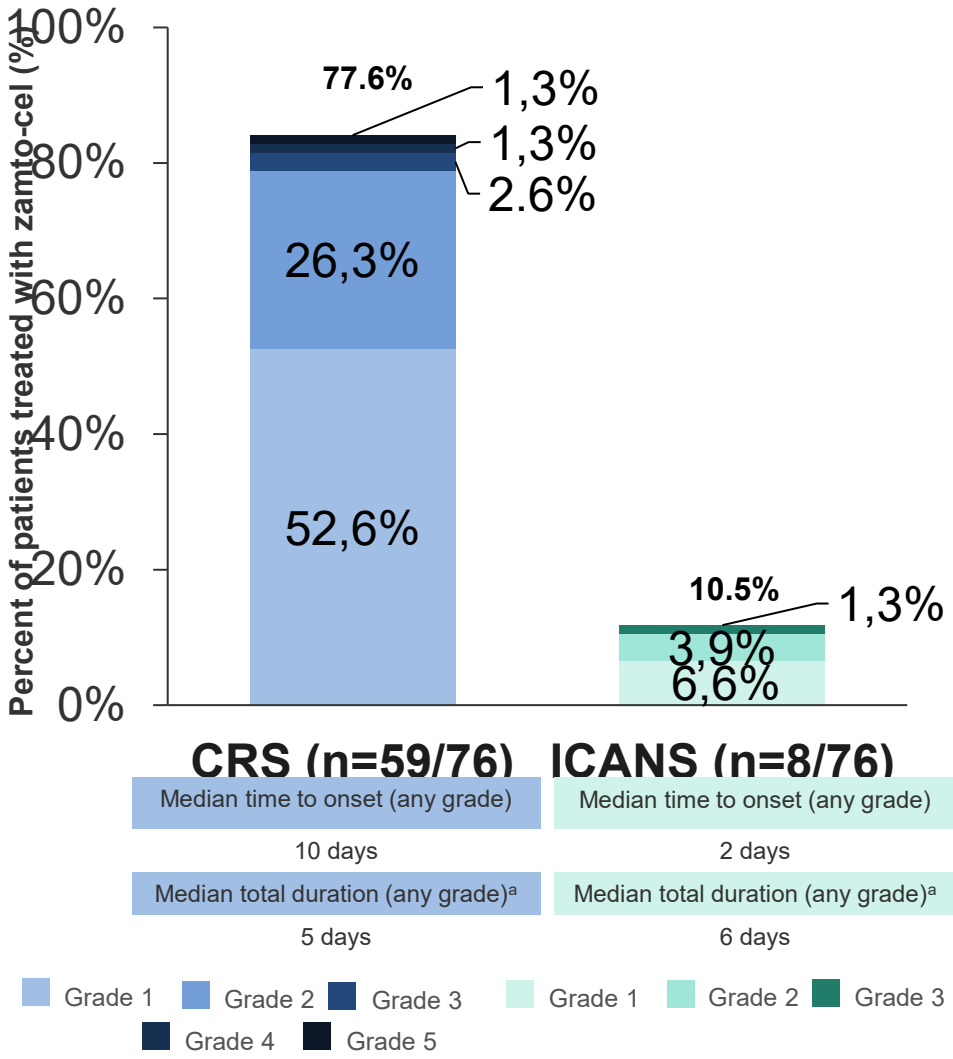
Number at risk, n

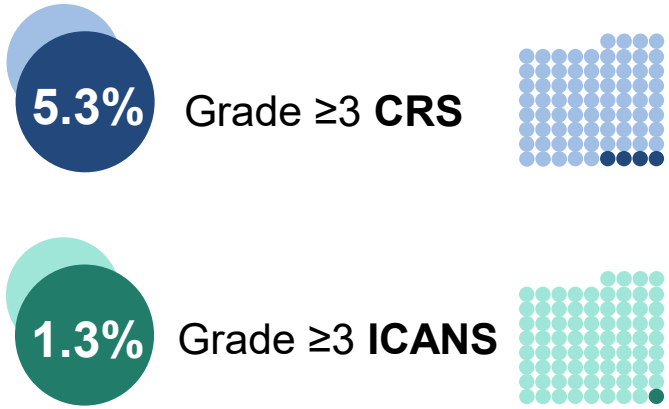
Zamto-cel	82	59	41	31	21	19	12	8	2	0
R-GemOx	78	27	11	4	4	4	1	1	0	0

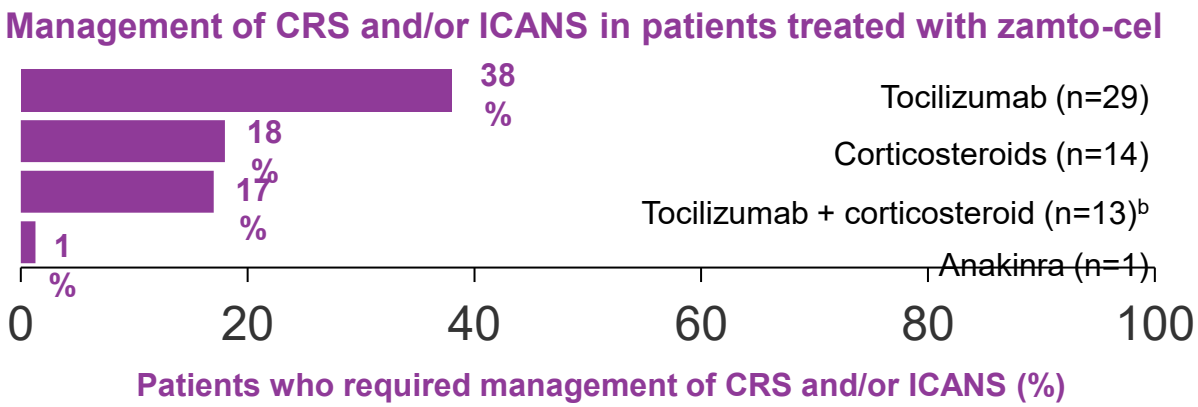
- ✓ **PFS (HR [95% CI]: 0.43 [0.28, 0.65]; p<0.0001) for zamto-cel was statistically superior**
- ✓ **Zamto-cel demonstrated higher CR rate vs. R-GemOx**

CR, complete response; CRR, complete response rate; DoCR, duration of complete response; HR, hazard ratio; IRC, independent review committee; (m)ITT, (modified) intent-to-treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response; R-GemOX, rituximab gemcitabine oxaliplatin.

Zamto-cel was well tolerated, with low rates of severe CRS and ICANS

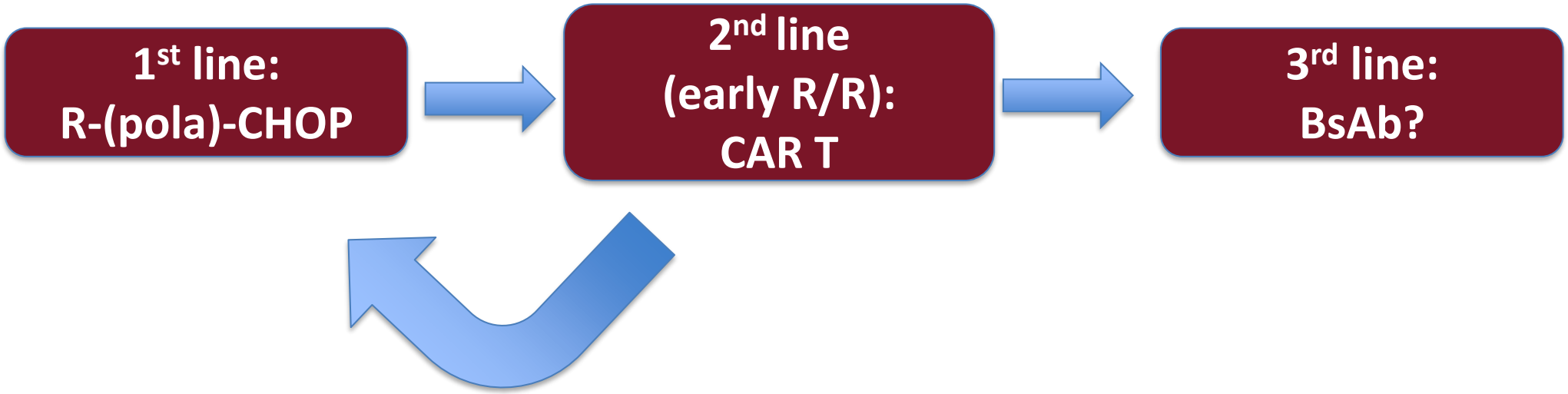






[a] Total duration includes gaps between episodes. [b] Combination therapy used for the management of CRS in the absence of clinical improvement after tocilizumab treatment (i.e., intravenous dexamethasone 10 mg every 6 hours in addition to intravenous tocilizumab 8 mg/kg administered over 1 hour). AE, adverse event; AESI, adverse events of special interest; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; c R-GemOx, rituximab gemcitabine oxaliplatin.

Should we move from 2nd line to 1st line?

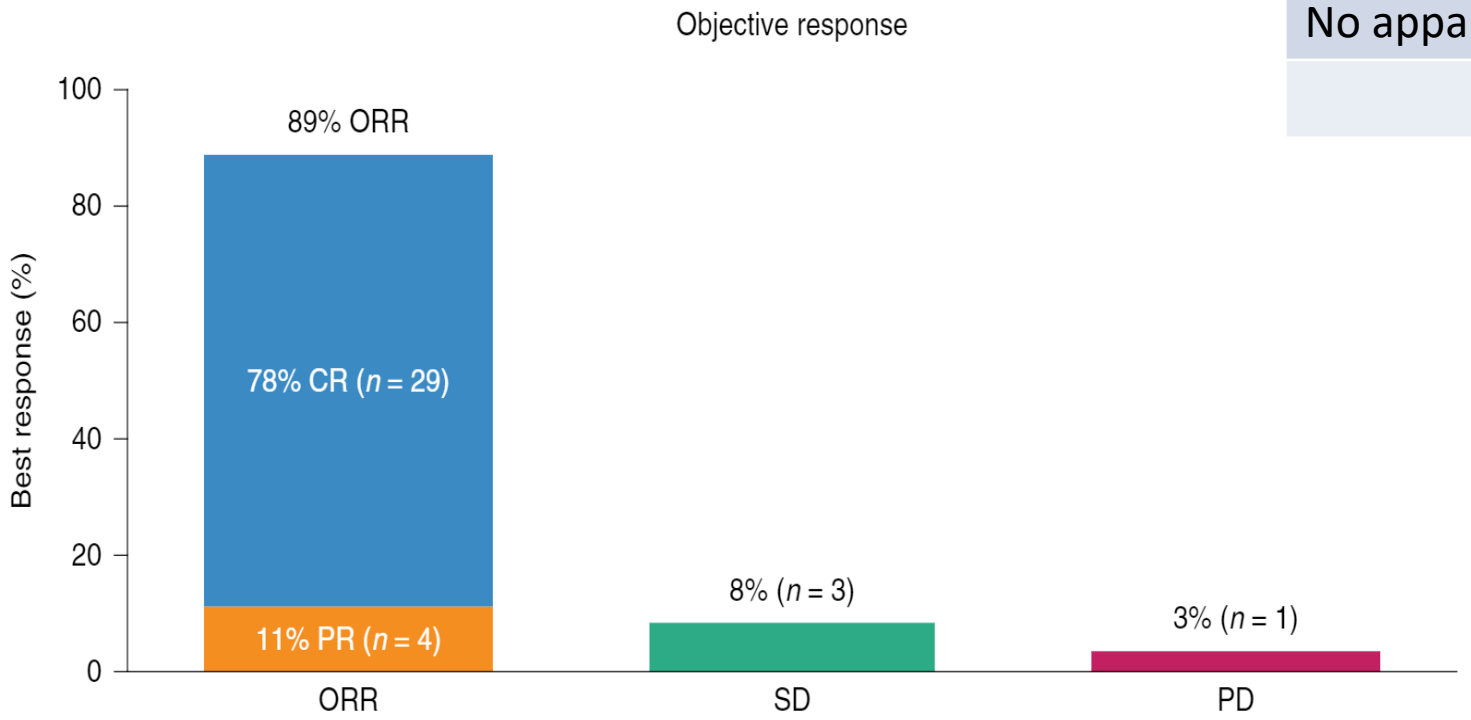


CD19 CAR T in high risk DLBCL with suboptimal response to 1st line therapy: ZUMA-12 results

Patient characteristics:

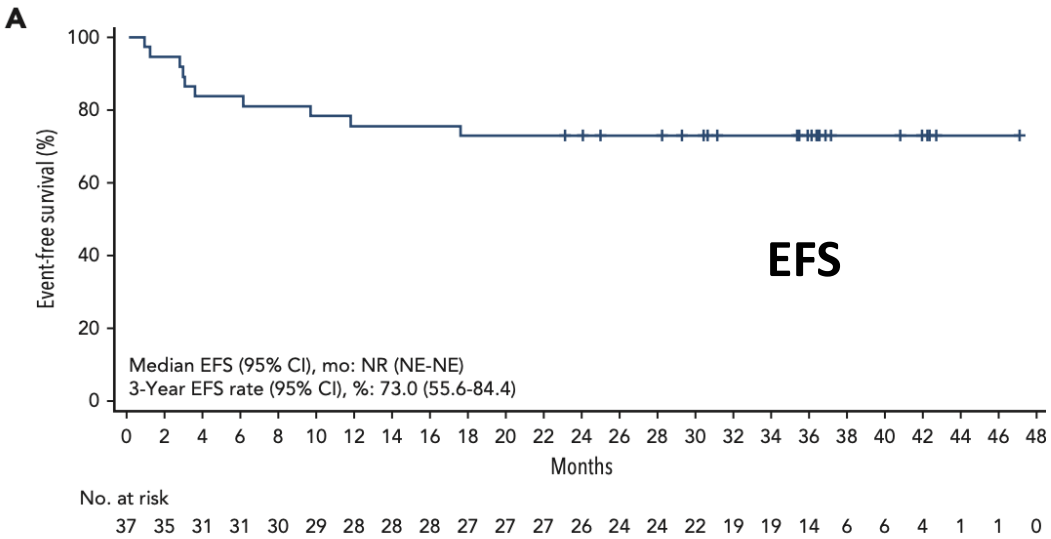
- **N=40 patients enrolled**
- **N=16 DH/THL**
- **Best response to 1st line: 21 PR, 5 SD, 16 PD**

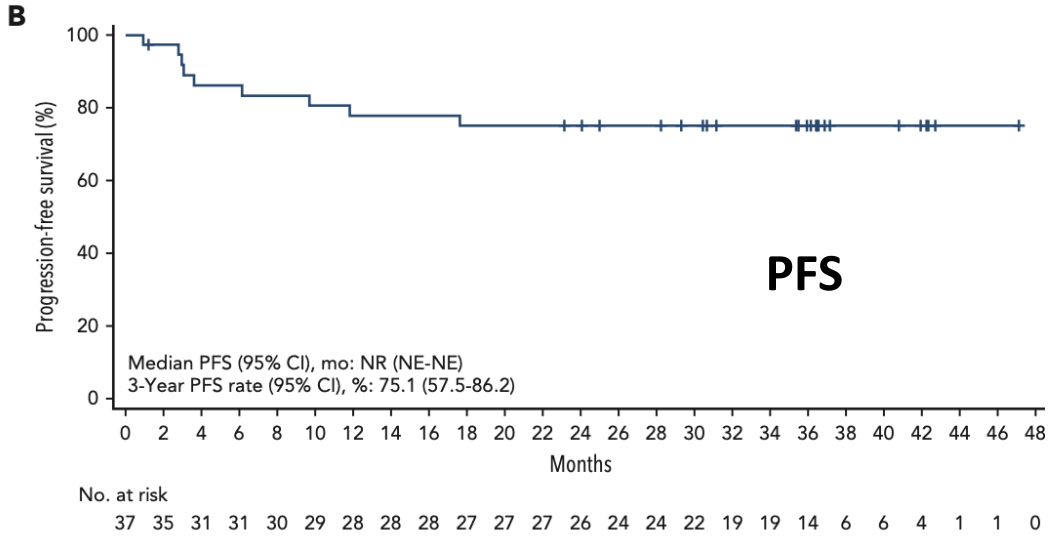
Compared to ZUMA-1 study
Higher median nr of CCR7+ CD45RA+ T-cells in the final product (105 vs 40x106)
Higher peak expansion and AUC of CAR T
No apparent difference in toxicity

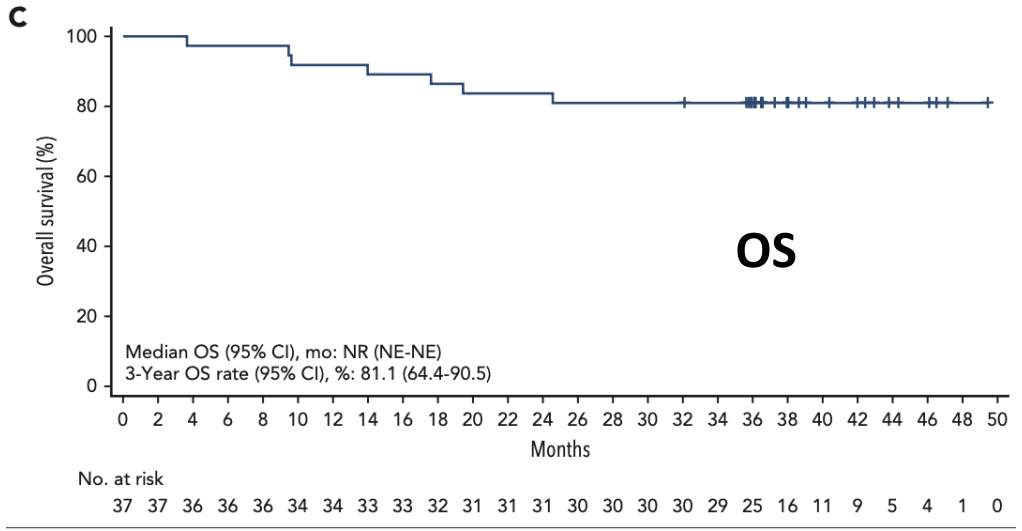


Neelapu S, et al. Nat Med 2022.

ZUMA-12: 3 yr follow-up





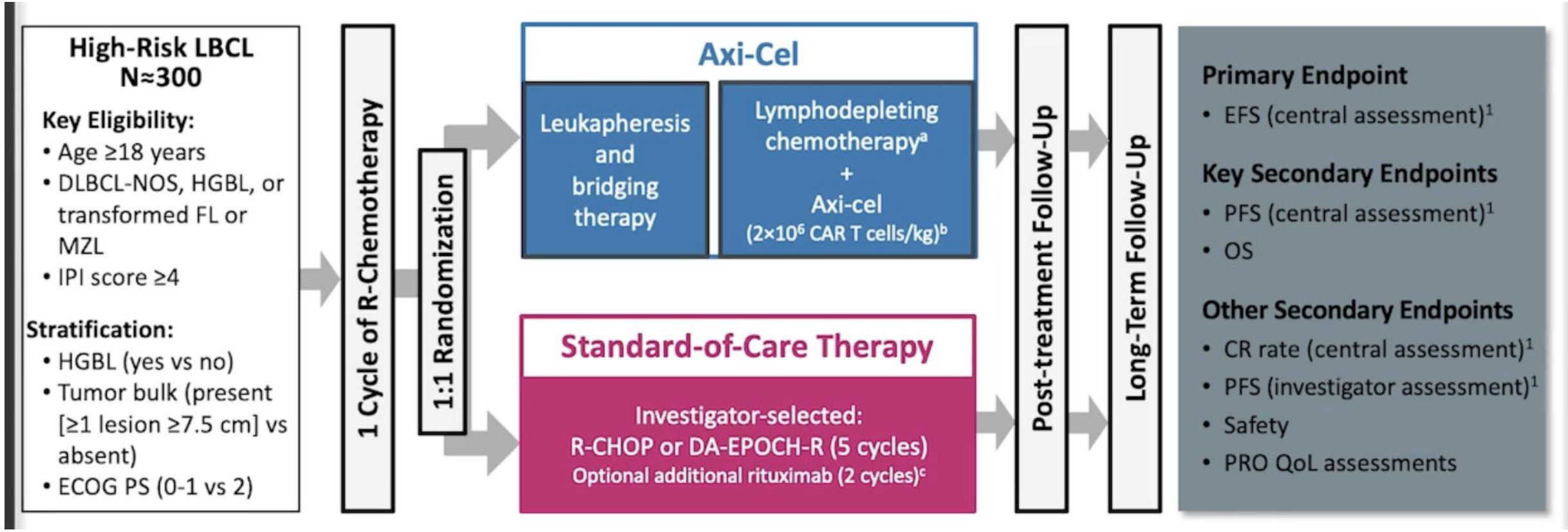


Main outcomes:

- **Median FU 47 months**
- **EFS at 3 yr: 73%**
- **OS at 3 yr: 81%**
- **No new safety signals**

Chavez J, et al. Blood 2025.

Move up! CAR T in 1st line (high risk): ZUMA-23 study



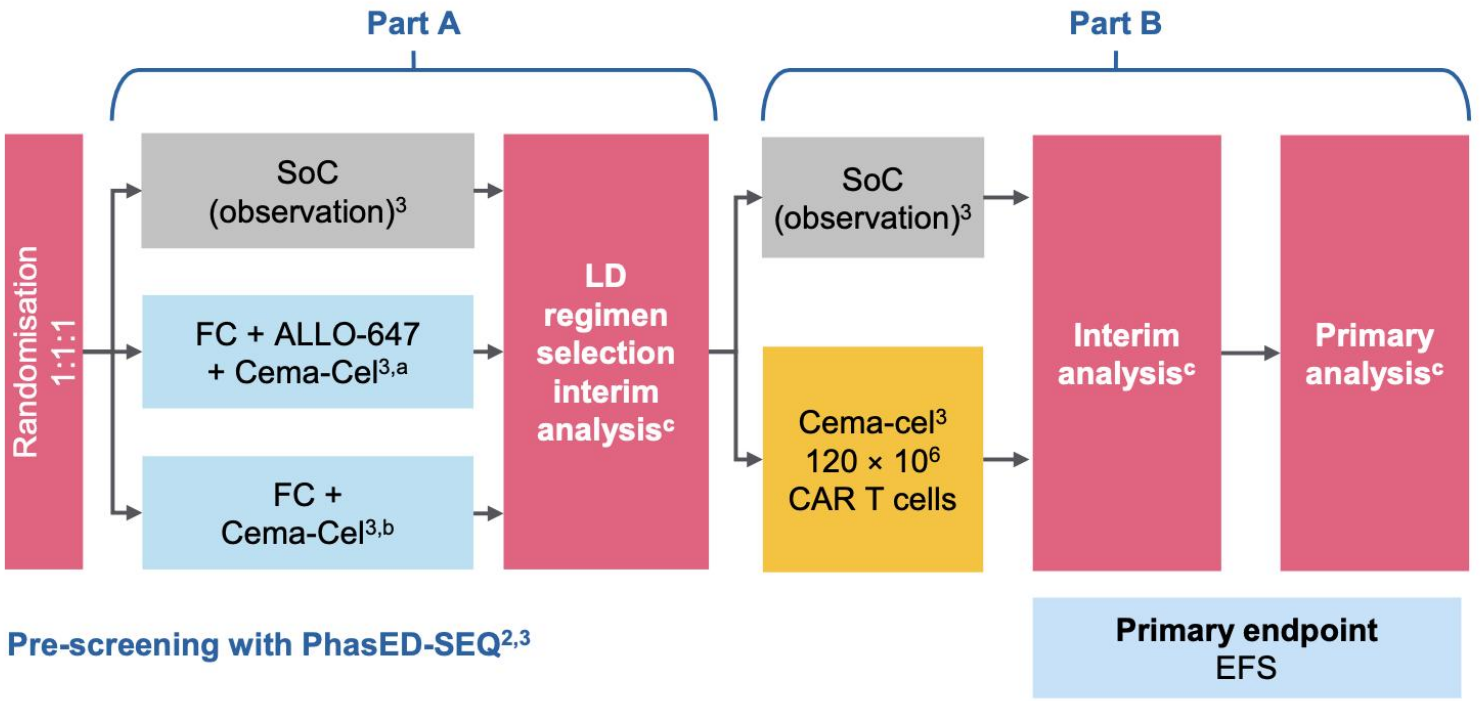
Move up! Allogeneic CAR T in 1st line DLBCL with positive MRD at EoT: ALPHA-3 trial

ALPHA-3 1L

Pivotal trial investigating cemacabtagene ansegedleucel as part of 1L treatment regimen for patients with newly diagnosed and treated DLBCL who are likely to relapse and need further therapy[1–3]

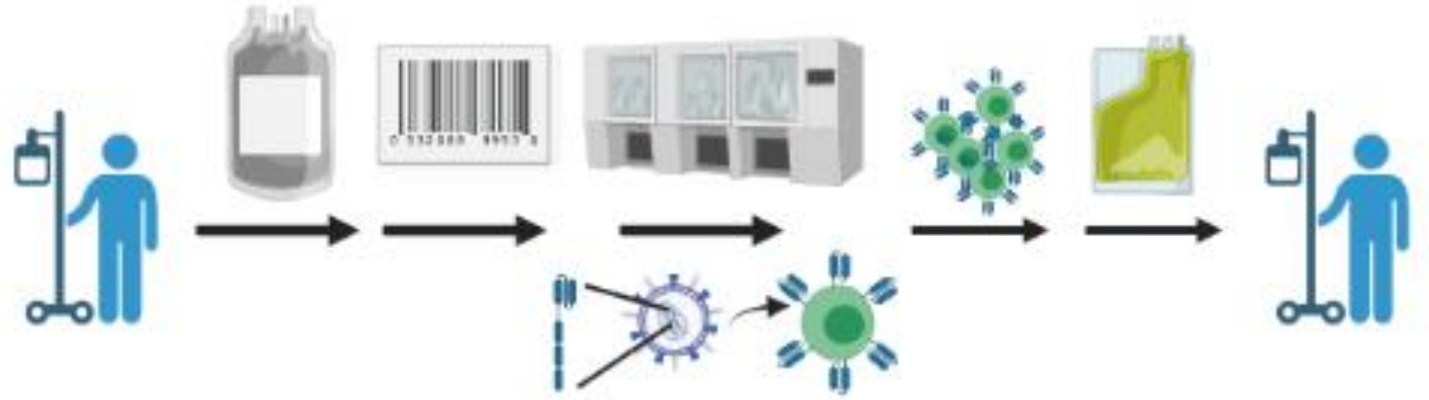
Key inclusion criteria

- Newly diagnosed or pretreated DLBCL[1]
  - ➢ No upfront risk assessment (e.g. IPI score or double hit or HGBL)[2]
- **MRD positive at the end of 1L therapy[3]**



Estimated N≈240

Current barriers in CAR T-cell therapy



1 

Long manufacturing time (3-6 weeks)

2 

Some manufacturing failures

3 

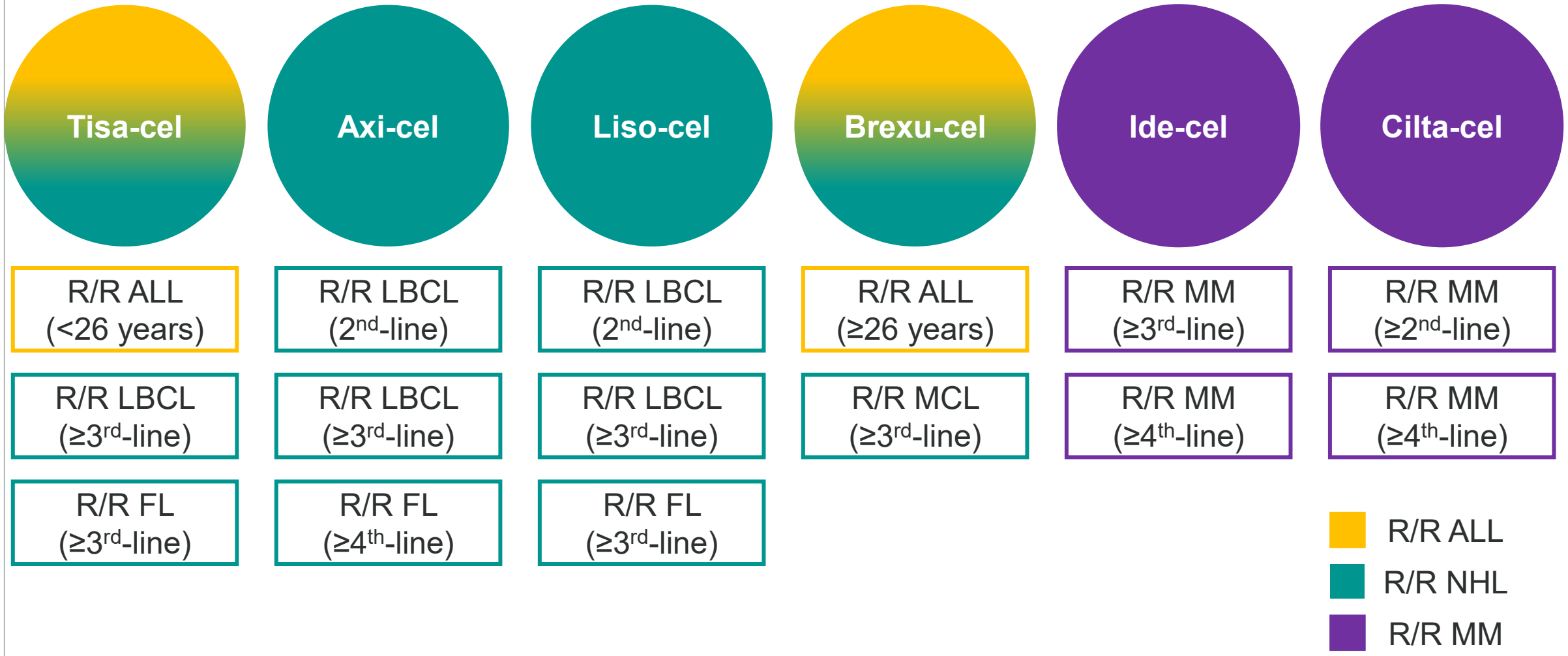
High costs

4 

Long term success rate 40%

Short and long term toxicity

CAR-T products and indications approved by the European Commission by April 2025 for R/R ALL, NHL and MM



Access to commercial CAR-T therapy across Europe as of April 2025

Country	R/R ALL		R/R LBCL		R/R MCL	R/R FL		R/R MM			Total CAR-T products and indications reimbursed
	Patients <26 years	Patients ≥26 years	2nd-line	≥3rd-line	≥3rd-line	≥3rd-line*	≥4th-line	≥2nd-line	≥3rd-line	≥4th-line	
Austria			2	3						2	14
Germany			2	3					XXXXXXXXXX	2-->1	14-->12
France			2	2						1	10
Italy			1	3						1	10
Czech Republic			1-->2	2-->3						1	8-->12
Finland			1	2							8
Spain			1	2						1-->2	7-->9
Greece			1	2							6-->7
United Kingdom			1-->2	2							6-->7
Belgium			1	2							5
Luxembourg			1	1							5
Slovakia				2							5
Sweden			1-->2	1-->2							5-->7
Norway			1	1							4-->5
Poland			1	2							4-->6
Portugal				2							4
Ireland				2							3
Netherlands			2	2-->3							3-->6
Croatia				1							2
Denmark			1-->2	2						1	2-->6
Hungary				1							2
Romania				1							2
Slovenia				1							2
Bulgaria											0
Cyprus											0
Estonia											0
Iceland											0
Latvia											0
Liechtenstein											0
Lithuania											0
Malta											0

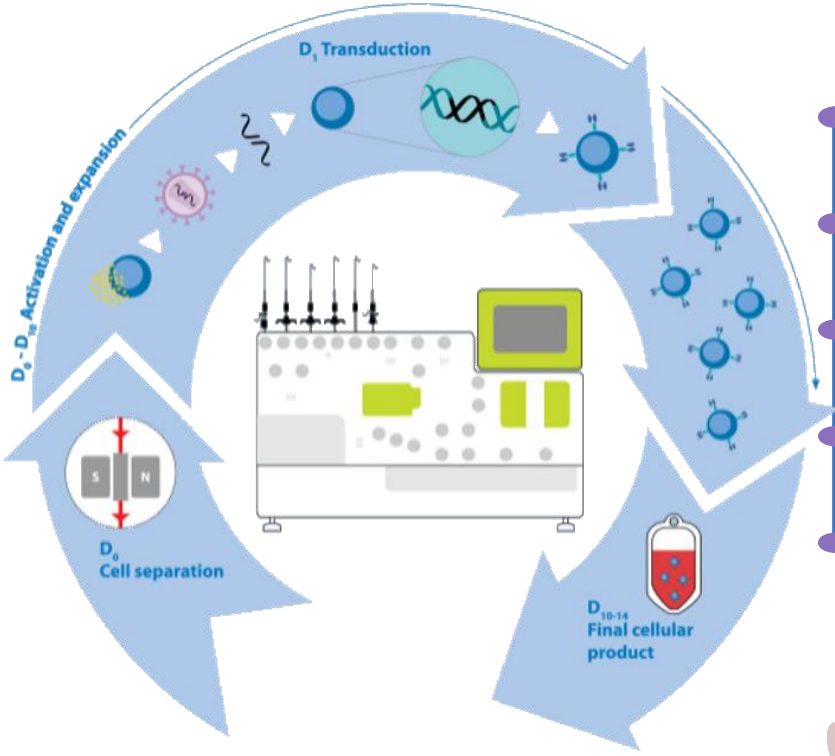
Pennings, Hemasphere 2026

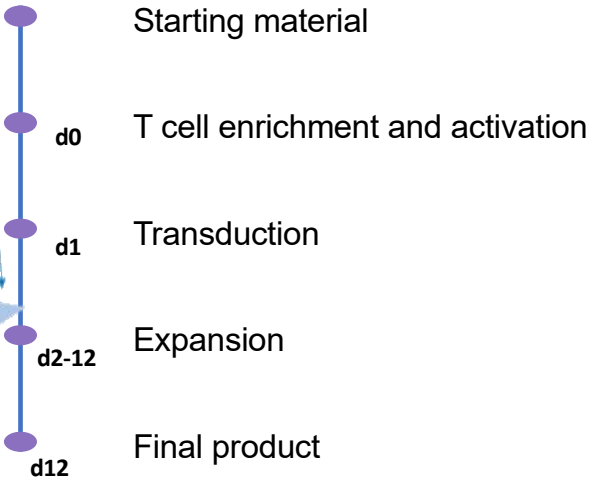
HOVON161 study: better, faster and… cheaper CARs!
Point-of-care production (PI Tom van Meerten)

R

SOC = commercial CD19 CAR T-cells

Experimental arm = PoC ARI-0001 CAR T-cells



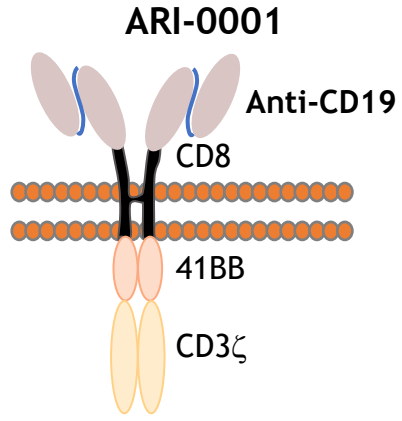


Improvement in Quality

- Fresh out – fresh in
- Optimized production process
- Transparency in ATMP specifications

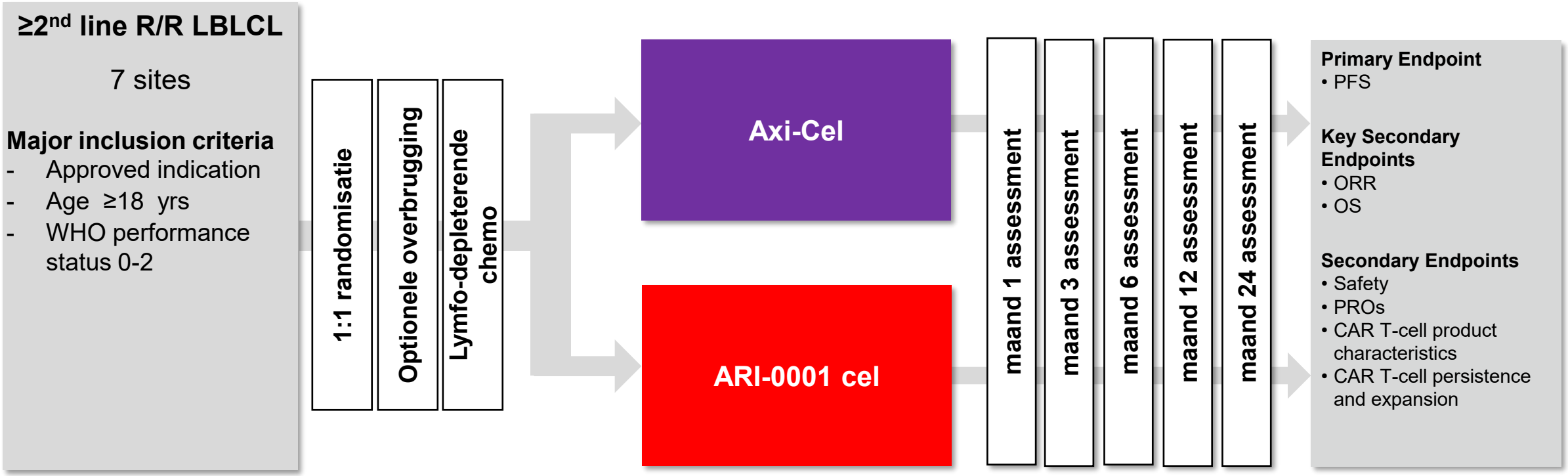
Improvement in Logisics

- Vein-to-vein time 7-12 days



ZonMw umcg

HOVON 161: trial design



- Primary endpoint: PFS
- Major secondary endpoints:
  - ORR, CR, OS
  - safety and toxicity of ARI-0001 and Axi-cel
  - quality of life (QoL)
  - costs associated with ARI-0001 vs Axi-cel
  - functional characteristics of the ARI-0001 CAR product

HOVON

CTCG Cellular Therapy Center Groningen

umcg

ATALANTA-1 Study Design and Objectives

Key eligibility criteria

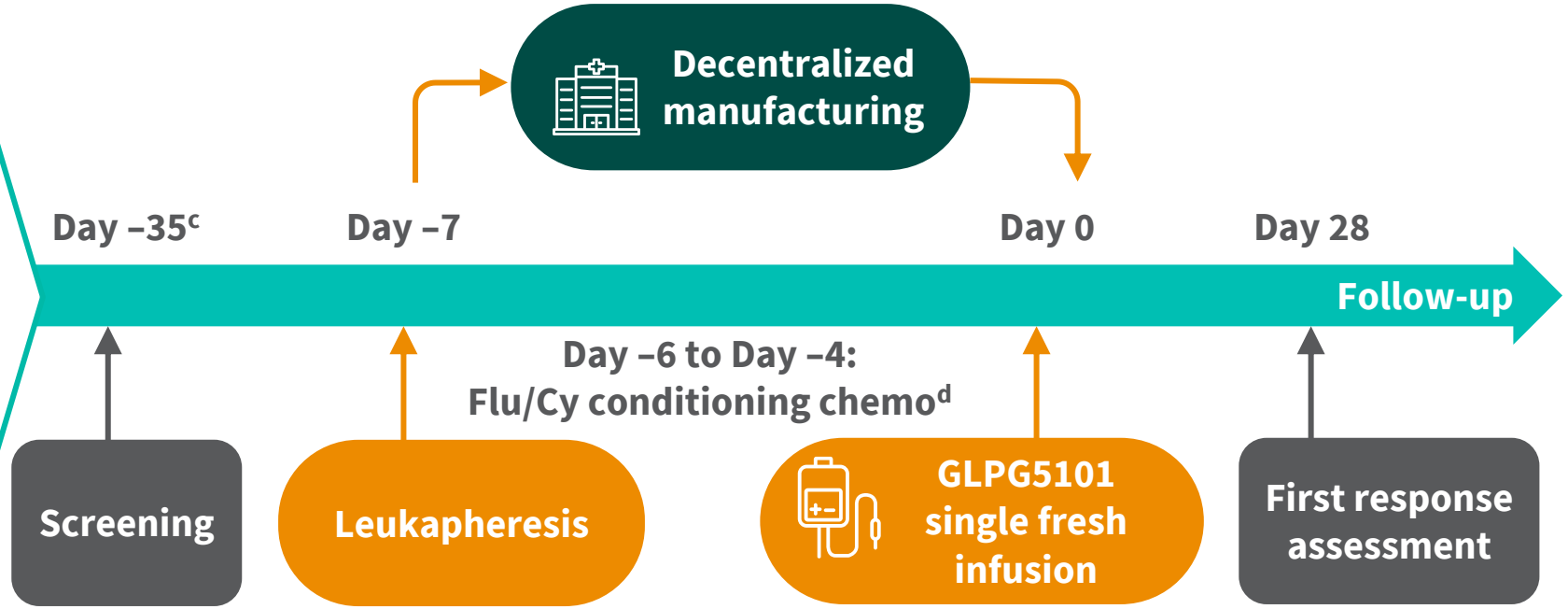
- No prior CD19-targeted therapies

Phase 1 dose escalation:

- **DLBCL**
  - Primary refractory or first relapse
- **FL, MZL, MCL**
  - Relapsed or refractory after 2 prior treatments

Phase 2 expansion cohorts:

- DLBCL, HR DLBCL,[b] FL + MZL, MCL, BL, PCNSL



Phase 1 primary objectives:
Safety and determination of an RP2D

Phase 2 primary objective:
Efficacy (ORR)

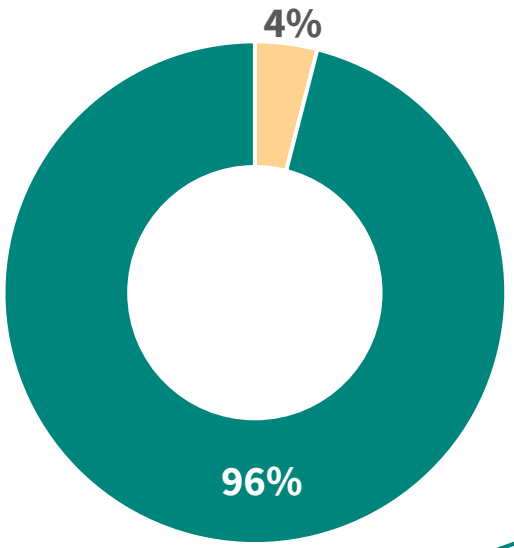
Phase 1/2 secondary objectives:
Safety
Efficacy (including duration of response and minimal residual disease)
Pharmacokinetics and pharmacodynamics
Feasibility of decentralized manufacturing

[a]CTIS: 2022-502661-23-00; NCT06561425. [b]Patients with no prior therapies and IPI 3–5, or double/triple-hit lymphoma on interim PET scan. [c]Screening could take place up to a maximum of 28 days prior to leukapheresis. [d]Conditioning chemotherapy: fludarabine IV (30 mg/m^2/day); cyclophosphamide IV (300 mg/m^2/day). BL, Burkitt lymphoma; Cy, cyclophosphamide; FL, follicular lymphoma; Flu, fludarabine; (HR) DLBCL, (high-risk) diffuse large B-cell lymphoma; IPI, international prognostic index; IV, intravenous; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; ORR, objective response rate; PCNSL, primary central nervous system lymphoma; PET, positron emission tomography; RP2D, recommended Phase 2 dose.

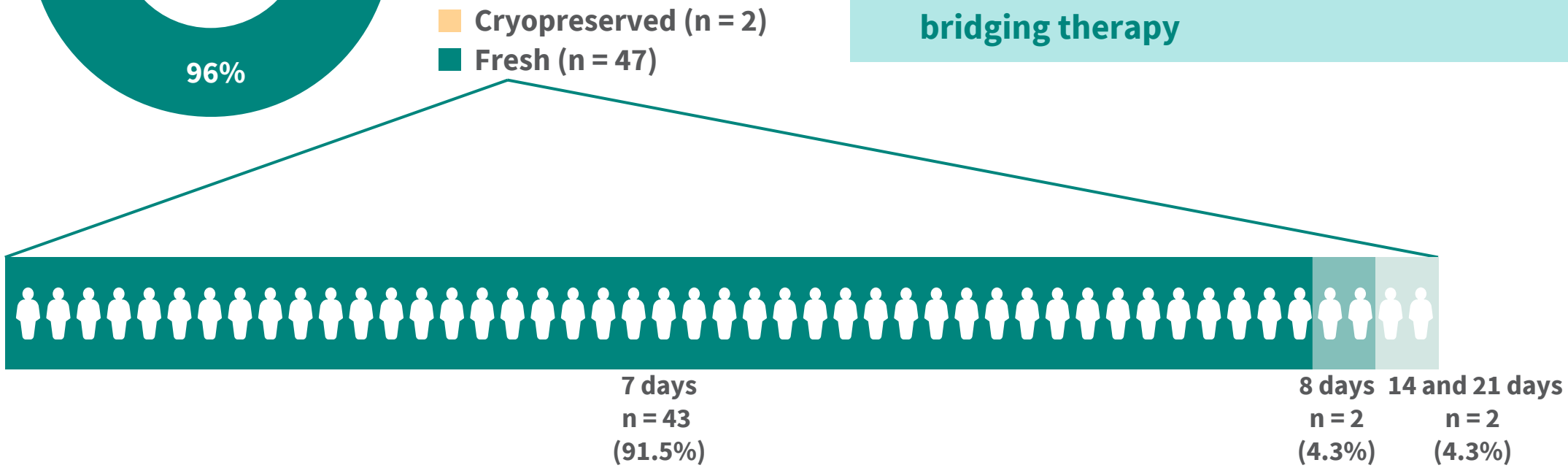
Presented at the 66th ASH Annual Congress: December 7–10, 2024; San Diego, CA, USA

Decentralized Manufacturing

Enabling fresh product infusion with a 7-day vein-to-vein time



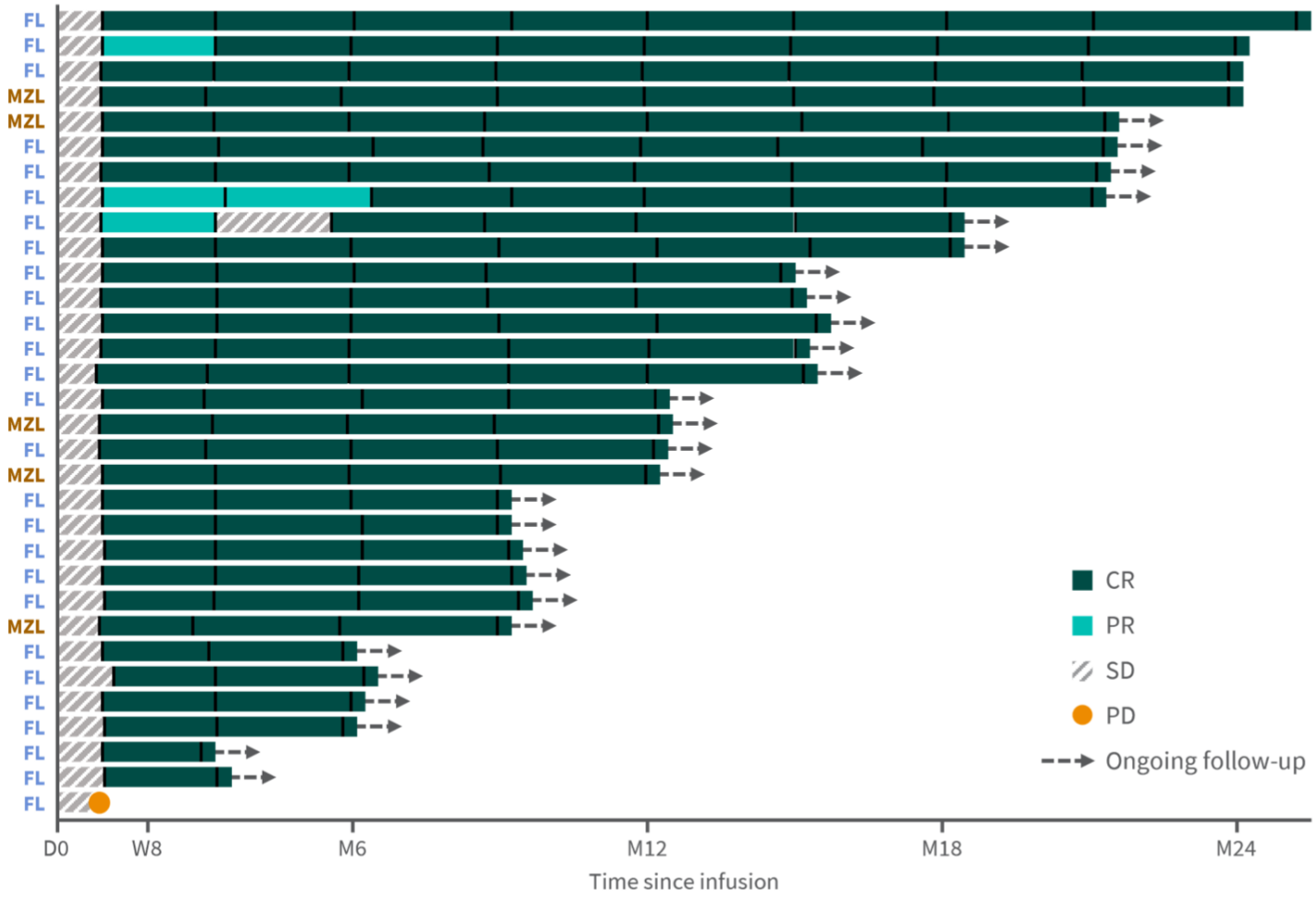
- **47/49 (96%)** of patients who received an infusion were given a fresh product[a]
- A **vein-to-vein time of 7 days** was achieved in **43/47 (91.5%)** patients who received a fresh product
- Short vein-to-vein time **eliminated the need for bridging therapy**



[a]Two patients received cryopreserved product with a vein-to-vein time of 13 days. Both patients were in CR at data cutoff. **Data cutoff: 25 April 2024.**
CR, complete response.

Efficacy: Response over time iNHL cohort

Durable responses were observed in patients who received a CAR T-cell infusion



Response over time presented for data available up to **3 March 2025**

FL (n = 27)/MZL (n = 5) (N = 32)
Median follow-up in study: **12.25 months** (range: 1.8–25.3)

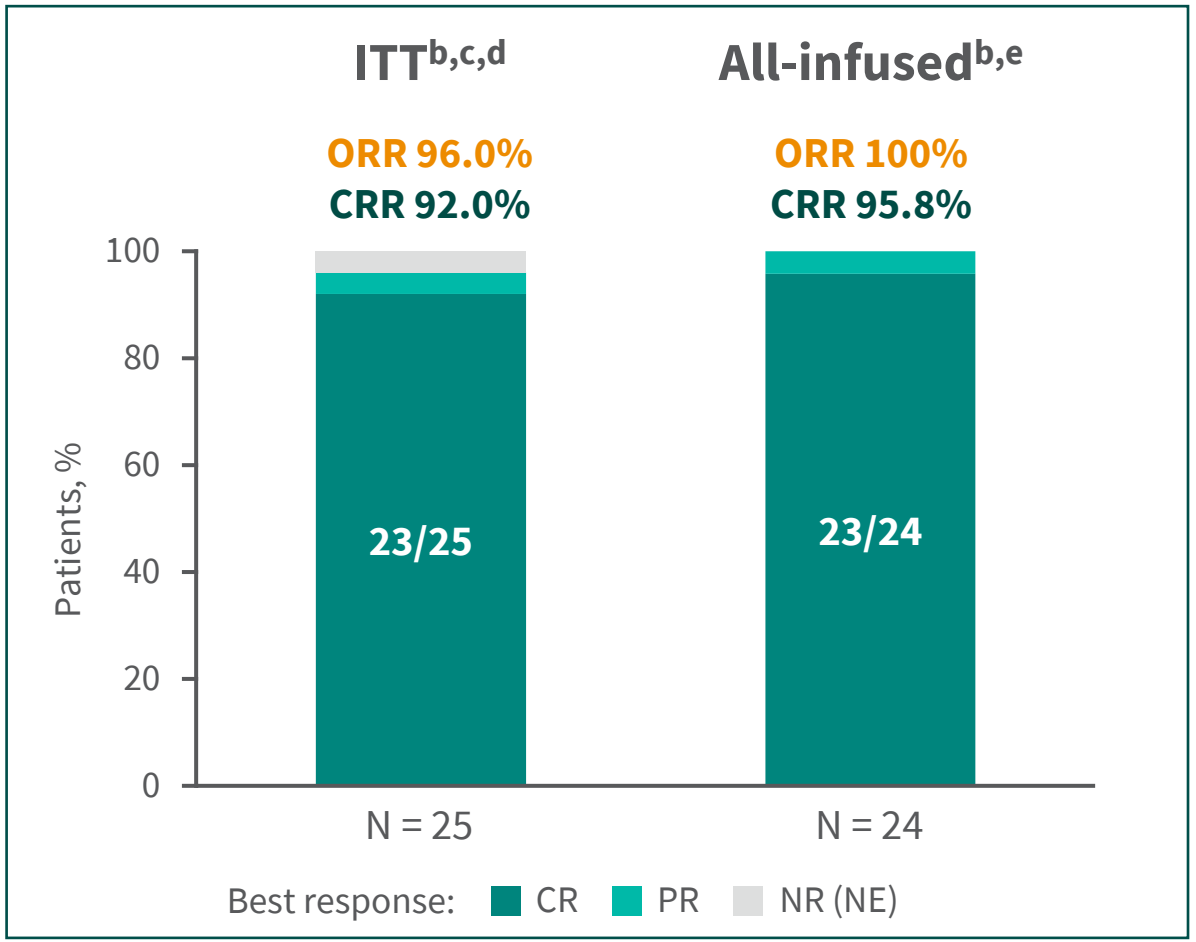
- No deaths reported
- No relapses observed in responding patients

:t response carried forward until the date of study completion (24 months), or the cutoff date for ongoing patients. **Data cutoff: 3 March 2025.**
infused set = all patients who received a CAR T-cell infusion, at any dose. Data are pooled across DLs: DL1, 35–50 × 10^6; DL2, 85–110 × 10^6. CAR, chimeric antigen receptor; CR, complete response; ay; DL, dose level; FL, follicular lymphoma; M, month; MZL, marginal zone lymphoma; PD, progressive disease; PR, partial response; SD, stable disease; W, week.

Presented at the 18th ICML: June 17–21, 2025; Lugano, Switzerland

High ORR and CRR Observed in 3L+ R/R MCL[a]

Best Response to Treatment at Any Time After a GLPG5101 Infusion



MRD[f] negativity:

- **90%** (9/10) of MRD-evaluable patients were MRD-negative at CR
  - 7/9 MRD-negative patients remained in CR at time of data cutoff
- No grade ≥3 CRS and only 1 grade 3 ICANS

[a]Only 1 patient had 1 prior line of therapy. [b]Data presented exclude patients who were alive and still in the study at data cutoff without a first confirmed response assessment. [c]One patient who did not receive a CAR T-cell infusion was not evaluable. [d]ITT set = all leukapheresed patients. [e]All infused set = all patients who received a CAR T-cell infusion at any dose. [f]MRD was evaluated using next-generation sequencing with the cloneSEQ® assay (Adaptive Biotechnologies, Seattle, WA, USA). Data are pooled across DLs: DL1, 35–50 × 10^6; DL2, 85–110 × 10^6 CAR T cells. **Data cutoff: 2 September 2025**.

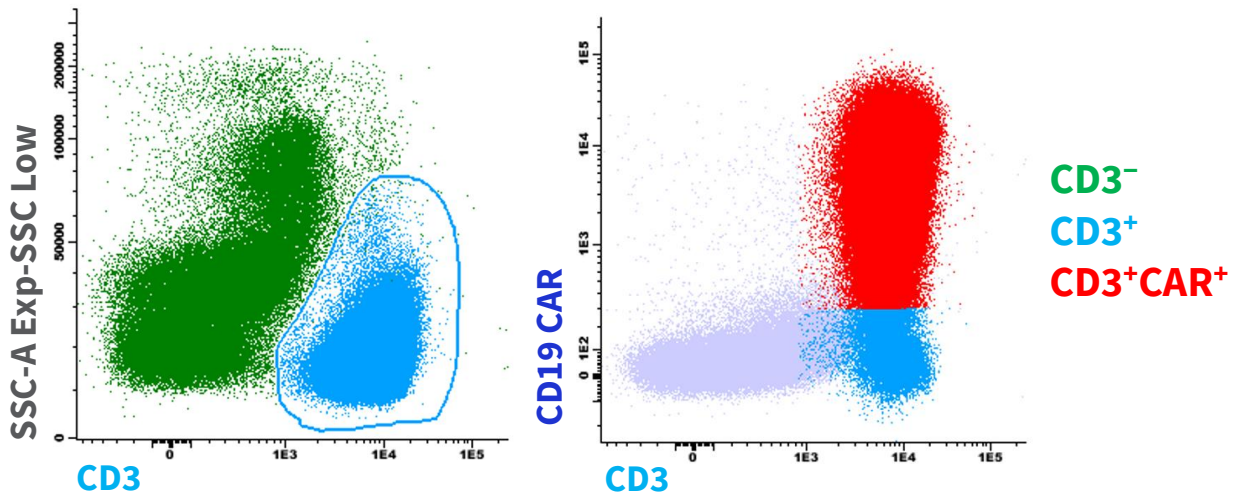
3L+, third or later lines of therapy; CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; DL, dose level; ITT, intention-to-treat; MCL, mantle cell lymphoma; MRD, minimal residual disease; NE, not evaluable; NR, no response; ORR, objective response rate; PR, partial response; R/R, relapsed/refractory.

Presented at the 66th ASH Annual Congress: December 7–10, 2024; San Diego, CA, USA

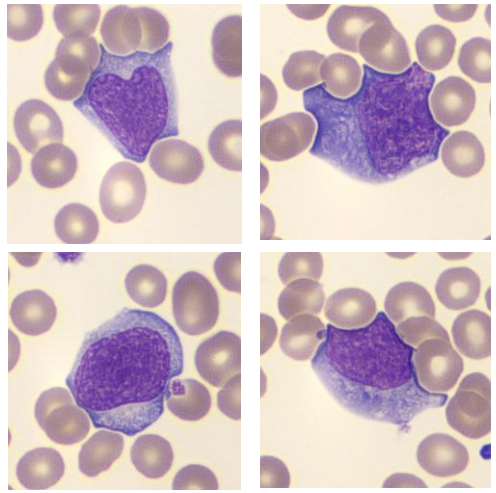
Robust *In Vivo* CAR T-Cell Expansion After GLPG5101 Infusion in a Patient With MCL

- Patient infused with GLPG5101 at 110 × 10^6 CAR^+ T cells (DL2)
- **Robust *in vivo* expansion** of GLPG5101 at Day 10 post-infusion:
  - White blood cells 12.3 × 10^9/L (ALC 11.43)
- At Day 10 post-infusion, morphologically enlarged and spreading lymphocytes observed in PB (“Dutch skirt lymphocytes’’)
- Grade 2 CRS reported Days 7–9, requiring 1 dose of tocilizumab; no ICANS reported to date
- CMR confirmed by PET-CT at Month 1

Flow cytometry in PB at Day 10 post-infusion of GLPG5101 (GLPG5101 accounts for 94% of the $CD3^+$ T cells)



Morphology of lymphocytes in PB at Day 10 post-infusion of GLPG5101



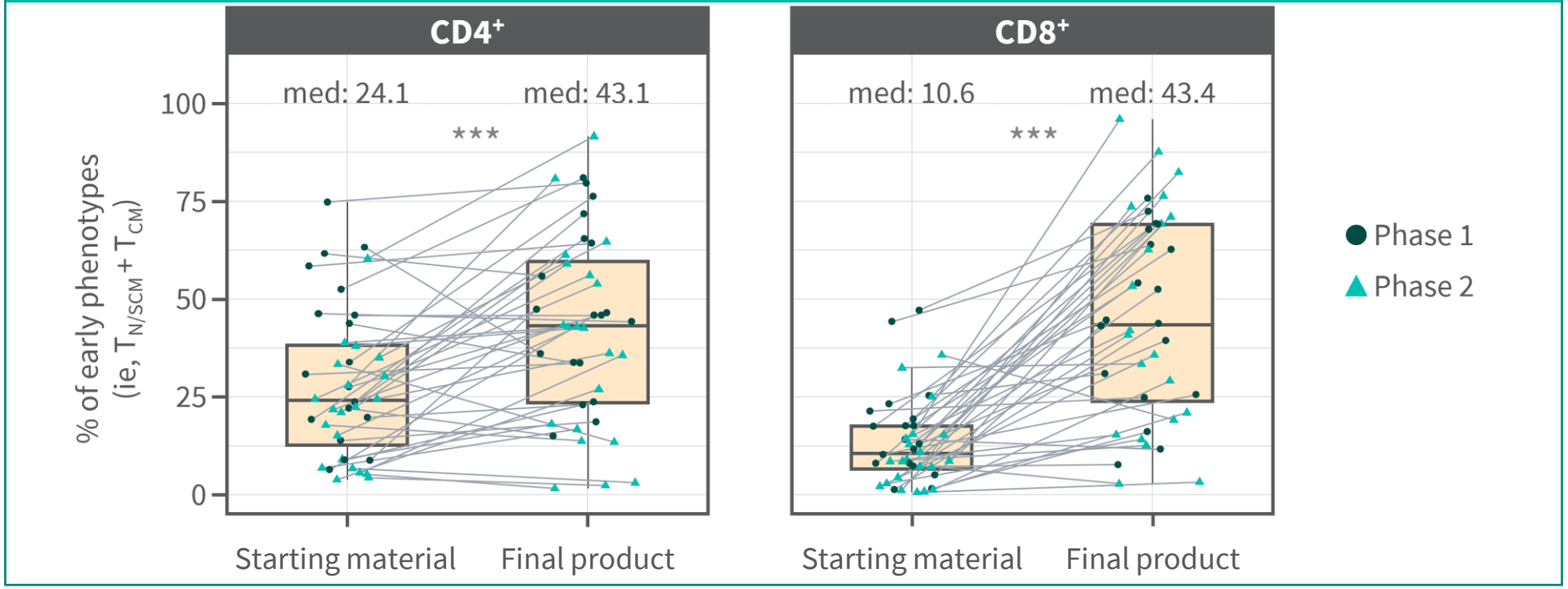
Local analysis: non-validated data. Images kindly provided by Prof. Marie José Kersten, Johan Dobber, and Sharon Hoekstra, LYMMCARE (Lymphoma and Myeloma Center Amsterdam), Amsterdam University Medical Center. ALC, absolute lymphocyte count; CAR, chimeric antigen receptor; CMR, complete metabolic response; CRS, cytokine release syndrome; DL, dose level; ICANS, immune effector cell-associated neurotoxicity syndrome; MCL, mantle cell lymphoma; PB, peripheral blood; PET-CT, positron emission tomography–computed tomography.

Presented at the 66th ASH Annual Congress: December 7–10, 2024; San Diego, CA, USA

Product Characterization

- The proportion of **early phenotype CD4⁺ and CD8⁺ CAR T-cells increased significantly** in the final product, compared with the early phenotype CD4⁺ and CD8⁺ T cells in the starting material
- The CD4:CD8 ratio of CAR⁺ T cells increased in the final product, compared with ratio of CD4:CD8 T cells in the starting material (median [Q1, Q3] increase 0.8 [0.05, 2.02])

Proportion of naïve/stem cell memory + central memory T cells (N = 40)



Exploratory flow cytometry analysis of T-cell subsets in the apheresis starting material and final product. Nonparametric paired-samples Wilcoxon tests were used to assess the statistical significance of the differences in early memory phenotype T-cell subsets ($T_{N/SCM}$ and T_{CM}) in the final product compared with the starting material. Early phenotype CD4⁺ and CD8⁺ (CAR) T cells: naïve/stem cell memory T cells (CD45RO⁻CD197⁺ $T_{N/SCM}$); central memory T cells (CD45RO⁺CD197⁺ T_{CM}). Percentage of early phenotype T cells (sum of CD45RO⁻CD197⁺ $T_{N/SCM}$ and CD45RO⁺CD197⁺ T_{CM}) of CD4⁺ or CD8⁺ (gated on CAR⁺ T cells for final product) for paired patient samples (N = 40). **Data cutoff: 25 April 2024.** ***P < 0.001

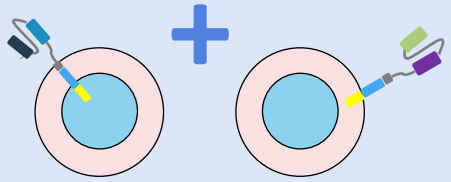
CAR, chimeric antigen receptor; med, median; Q, quartile; T_{CM}, central memory T cells; $T_{N/SCM}$, naïve/stem cell memory T cells.

Presented at the 66th ASH Annual Congress: December 7–10, 2024; San Diego, CA, USA

What novel dual CAR T strategies are being explored that could help overcome resistance by antigen escape?

Co-administration[1]

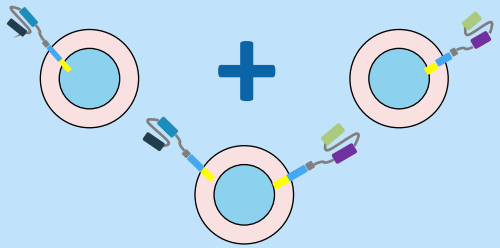
Anti-CD19 Anti-CD20/22



Examples
ChiCTR-OIB-17013670[2]

Co-transduction[1]

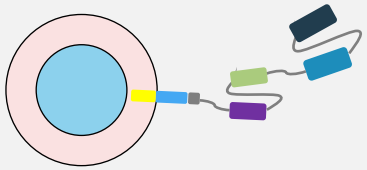
Anti-CD19 Anti-CD20/22



Examples
AUTO1[3]

Tandem CARs[1]

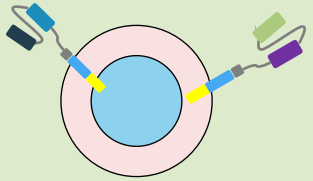
Anti-CD19-CD20/22



Examples
CD19-22.BB.z-CAR[4]
Prizlon-cel[5]
Zamto-cel[6]

Bicistronic CARs[1]

Anti-CD19 Anti-CD20/22



Examples
KITE-363[7]
KITE-753[7]
AUTO3[8]

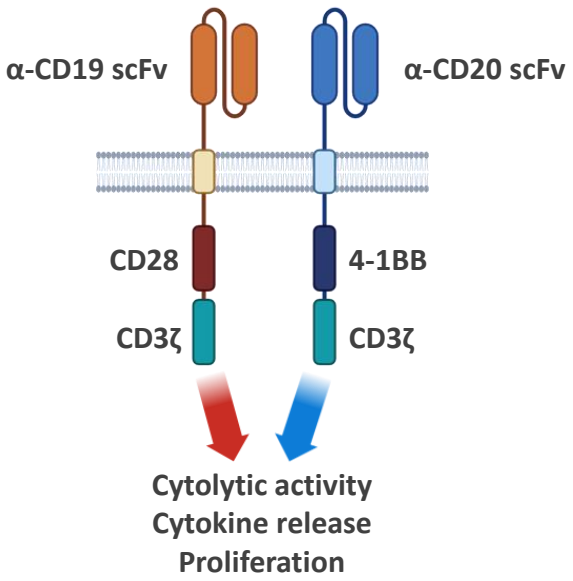
Several dual-target CAR T-cell therapies are being investigated aimed at addressing issues of antigen escape and relapse[9]

References can be requested from Gilead Switzerland.
CAR, chimeric antigen receptor; CD, cluster of differentiation.
1. Brillembourg H, *et al. Br J Haematol.* 2024;204:1649–1659; 2. Pan J, *et al. Blood.* 2020;135:387–391; 3. Ghorashian S, *et al. Blood.* 2022;140:10352–10354; 4. Spiegel JY, *et al. Nat Med.* 2021; 27:1419–1431; 5. Liang A, *et al.* EHA 2024 (Abstract P1475; poster); 6. Shah NN, *et al.* ICML 2023 (Abstract 096; oral 16); 7. https://clinicaltrials.gov/study/NCT04989803 (accessed March 2025); 8. Roddie C, *et al. Blood.* 2023;141:2470–2482; 9. Zhang C, et al. *J Immunol Res.* 2025;2025:5845167.

KITE-363 and KITE-753: 2 Independently Expressed CD19 and CD20 CARs With Synergistic 4-1BB/CD28 Signaling

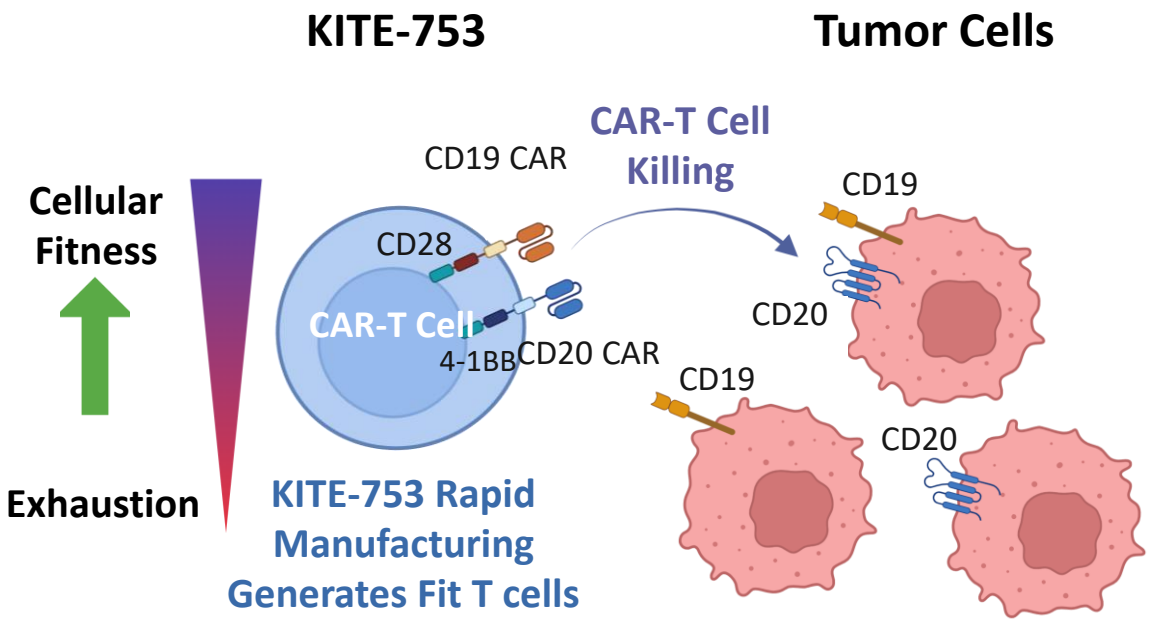
Smart Targeting With Synergistic Signaling

Independently Targets CD19 and CD20



Dual Costimulation With CD28 and 4-1BB Boosts CAR T-Cell Performance

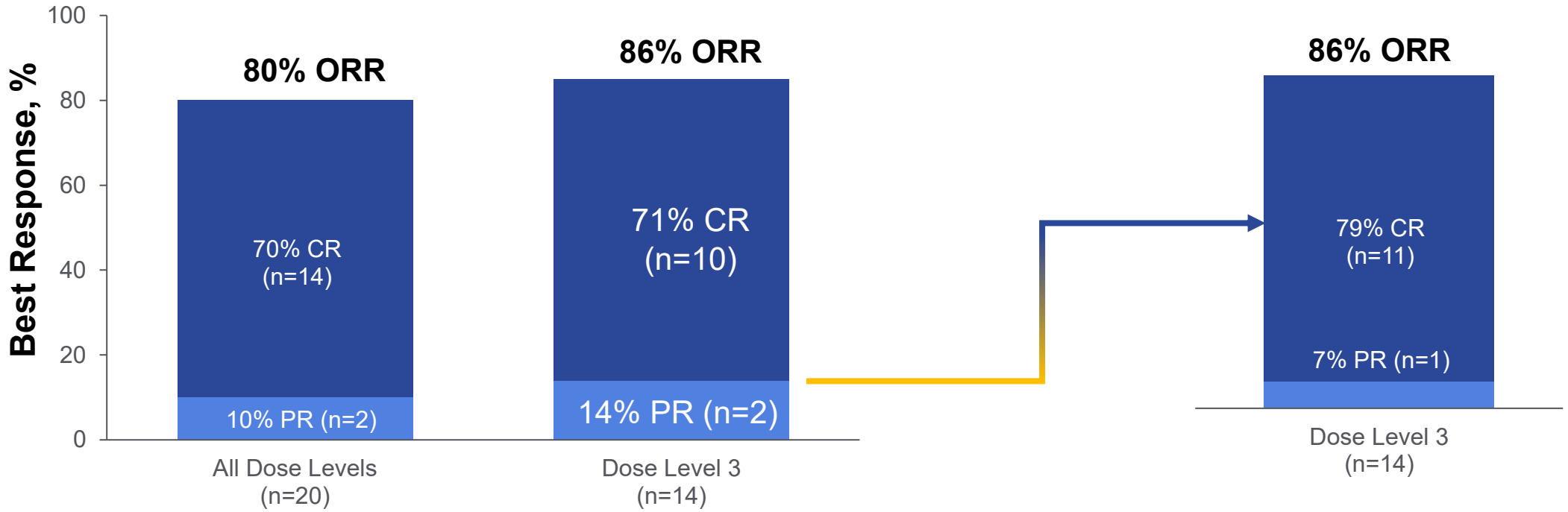
KITE-753 Mechanism of Action



- KITE-363 and KITE-753 are **bicistronic CAR T-cell therapies** designed to prevent antigen escape through dual-targeting of CD19 and CD20
- They use the same bicistronic construct, with **synergistic signaling** through CD28/4-1BB co-stimulatory domains
- KITE-753 uses a rapid **manufacturing** process that preserves **naive and stem cell memory T cells** in the product

scFv, single-chain variable fragment.

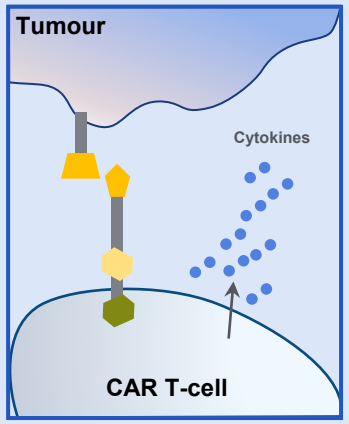
High ORR and CR Rate With KITE-753 in CAR-Naive Patients



- Median time to first response among all patients (N=30) was 29 days
- In CAR-naive patients in dose level 3, 9 of the 11 patients with CRs had a CR at their 1-month assessment; the remaining 2 had a CR by their 3-month assessment (1 after the data cutoff)
- In patients with prior CAR exposure (n=10), 3 achieved a CR and 2 had a PR

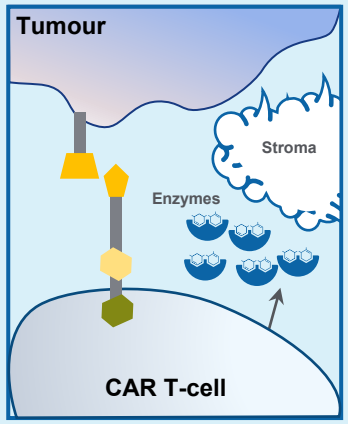
Can next-generation armoured CARs help overcome the immunosuppressive TME?

TRUCKS



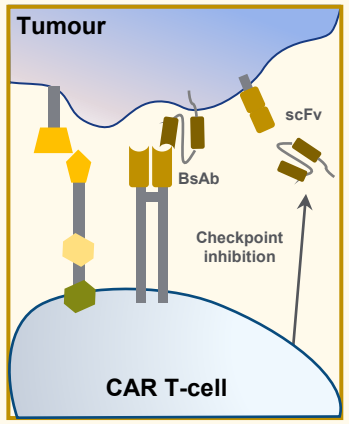
Engineered to boost the immune response within the TME by releasing cytokines upon recognising target cells

Enzyme-secreting CARs



Designed to break down dense tumour stroma, allowing CAR-T cells to better penetrate and reach target cells

BsAb- or scFv-secreting CARs



Engineered to redirect other T cells to attack target cells and can block immune checkpoints to enhance T-cell activity

Armoured CARs with engineered micropharmacies aim to improve their persistence, penetration, and overall performance within the hostile TME

References can be requested from Gilead Switzerland.
BsAb, bispecific antibody; CAR, chimeric antigen receptor; TME, tumour microenvironment; TRUCK, T cells redirected for antigen-unrestricted cytokine-initiated killing; scFv, single-chain variable fragment.
Adapted from Carcopino C, *et al. IOTECH.* 2024;24:100739.

In vivo CARs: paradigm shift or the new hype?

Science

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RESEARCH ARTICLE | IMMUNOTHERAPY

In vivo CAR T cell generation to treat cancer and autoimmune disease

THERESA L. HUNTER, YANJIE BAO, YAN ZHANG, DAIKI MATSUDA, ROMINA RIENER, ANNABEL WANG, JOHN J. LI, FERRAN SOLDEVILA, DAVID S. H. CHU, [...], AND HAIG AGHAJANIAN +30 authors Authors Info & Affiliations

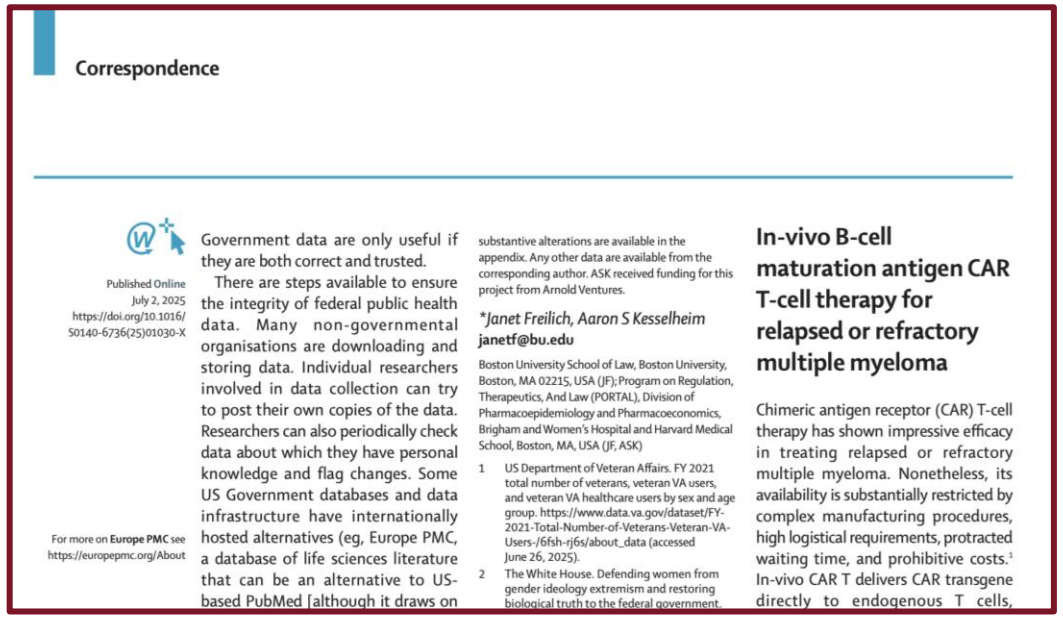
SCIENCE · 19 Jun 2025 · Vol 388, Issue 6753 · pp. 1311-1317 · DOI: 10.1126/science.ads8473

62.537 77

In vivo CAR T cells gain traction, with AbbVie's US$2.1 billion acquisition of Capstan Therapeutics

By Asher Mullard

AbbVie will pay US$2.1 billion to acquire Capstan Therapeutics and its in vivo CAR T technology, which uses mRNA-loaded lipid nanoparticles (LNPs) to reprogramme immune cells. Capstan's lead asset is designed to reset the immune system for the treatment of B-cell-driven autoimmune diseases, but the technology could also have applications in cancer and



Correspondence

Published Online July 2, 2025 https://doi.org/10.1016/S0140-6736(25)01030-X

For more on Europe PMC see https://europepmc.org/About

Government data are only useful if they are both correct and trusted.

There are steps available to ensure the integrity of federal public health data. Many non-governmental organisations are downloading and storing data. Individual researchers involved in data collection can try to post their own copies of the data. Researchers can also periodically check data about which they have personal knowledge and flag changes. Some US Government databases and data infrastructure have internationally hosted alternatives (eg, Europe PMC, a database of life sciences literature that can be an alternative to US-based PubMed [although it draws on

substantive alterations are available in the appendix. Any other data are available from the corresponding author. ASK received funding for this project from Arnold Ventures.

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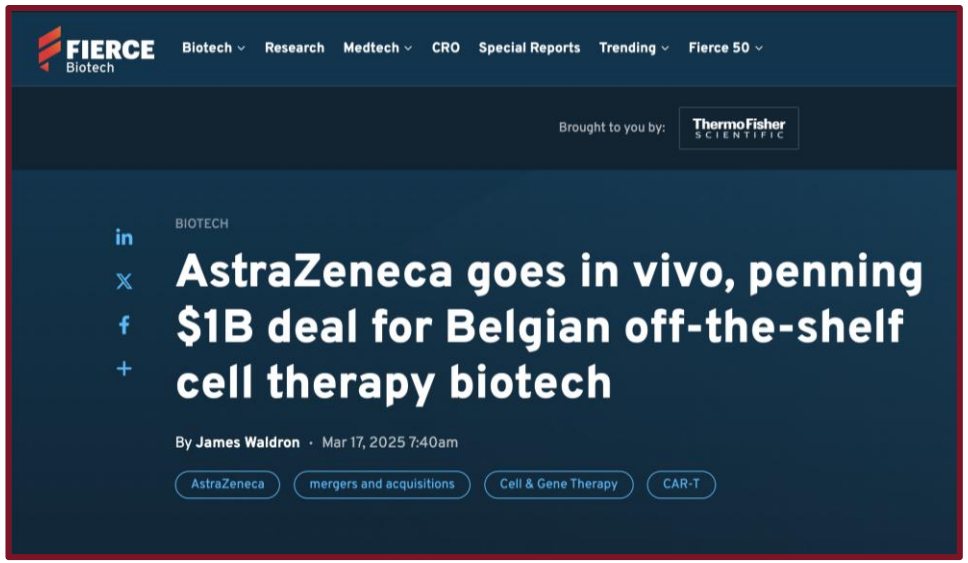
1 US Department of Veteran Affairs. FY 2021 total number of veterans, veteran VA users, and veteran VA healthcare users by sex and age group. https://www.data.va.gov/dataset/FY-2021-Total-Number-of-Veterans-Veteran-VA-Users-/6fsh-rj6s/about_data (accessed June 26, 2025).

2 The White House. Defending women from gender ideology extremism and restoring biological truth to the federal government.

In-vivo B-cell maturation antigen CAR T-cell therapy for relapsed or refractory multiple myeloma

Chimeric antigen receptor (CAR) T-cell therapy has shown impressive efficacy in treating relapsed or refractory multiple myeloma. Nonetheless, its availability is substantially restricted by complex manufacturing procedures, high logistical requirements, protracted waiting time, and prohibitive costs.[1] In-vivo CAR T delivers CAR transgene directly to endogenous T cells,



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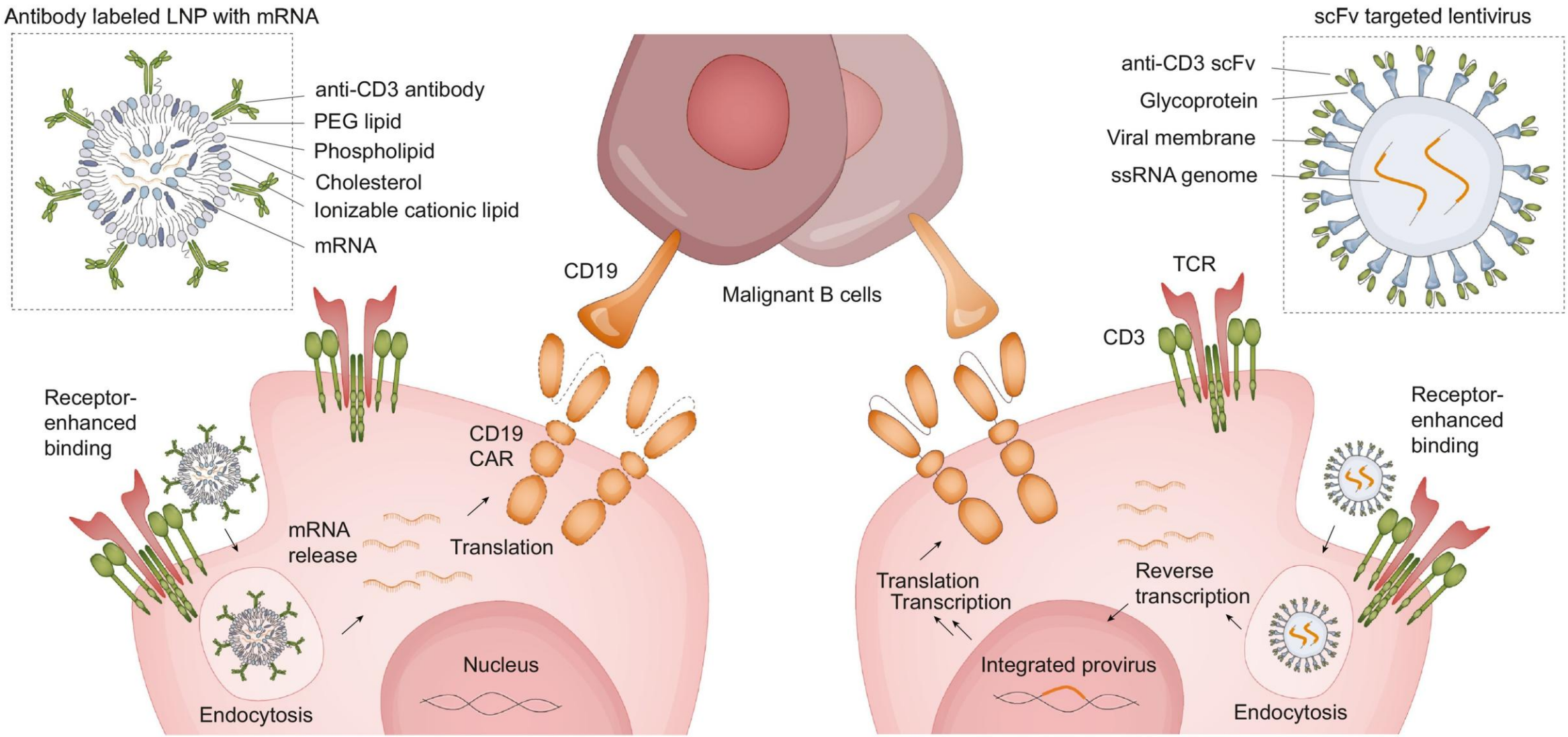
BIOTECH

AstraZeneca goes in vivo, penning $1B deal for Belgian off-the-shelf cell therapy biotech

By James Waldron · Mar 17, 2025 7:40am

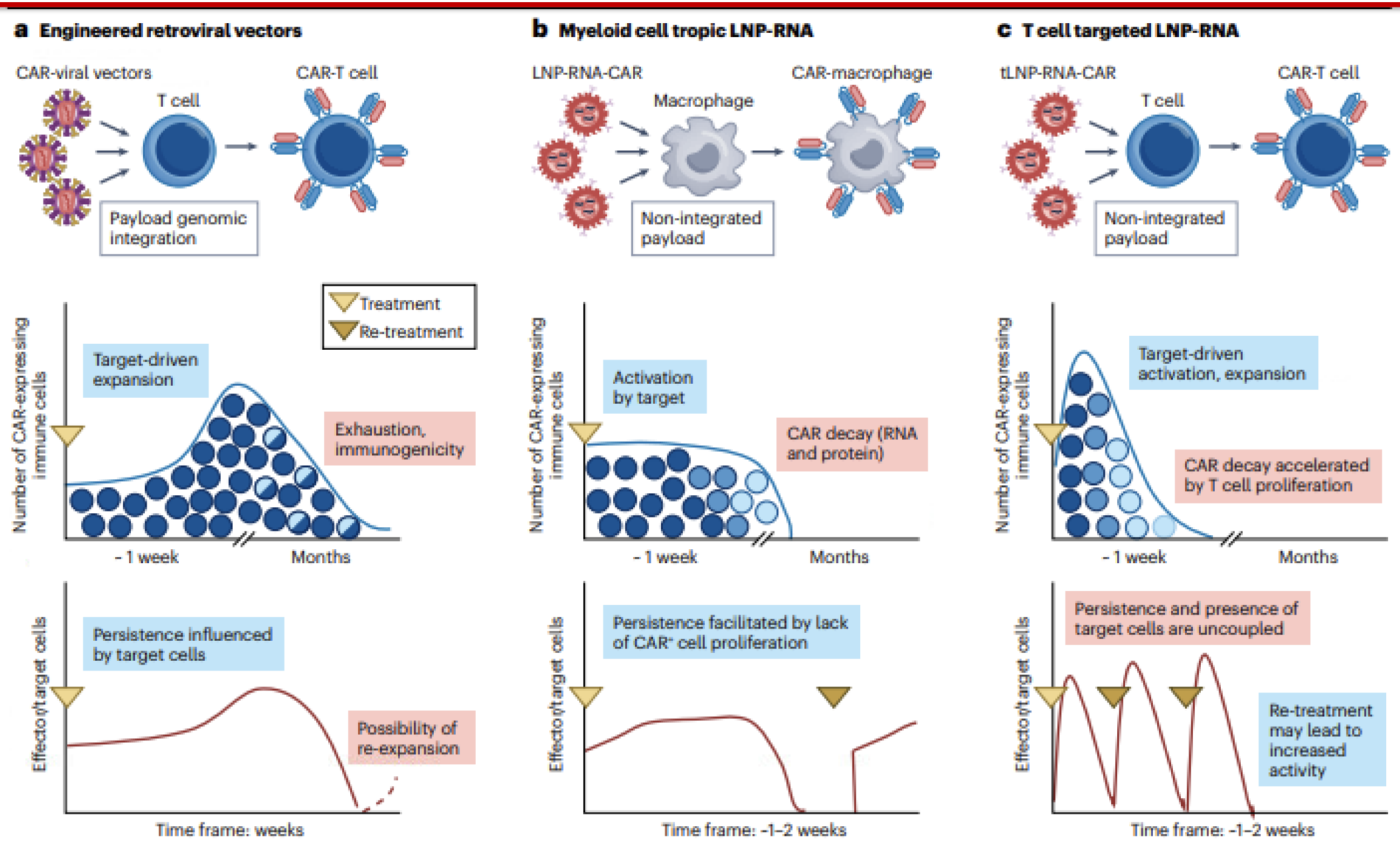
AstraZeneca mergers and acquisitions Cell & Gene Therapy CAR-T



- Transient CAR expression provides a safety advantage but may require multiple doses to provide a strong therapeutic effect.
- Serial dosing may:
  - Elicit an adaptive immune response against the CAR.
  - Enable real-time dose adjustment to minimize toxicities.
  - Prevent exhaustion in T cells.

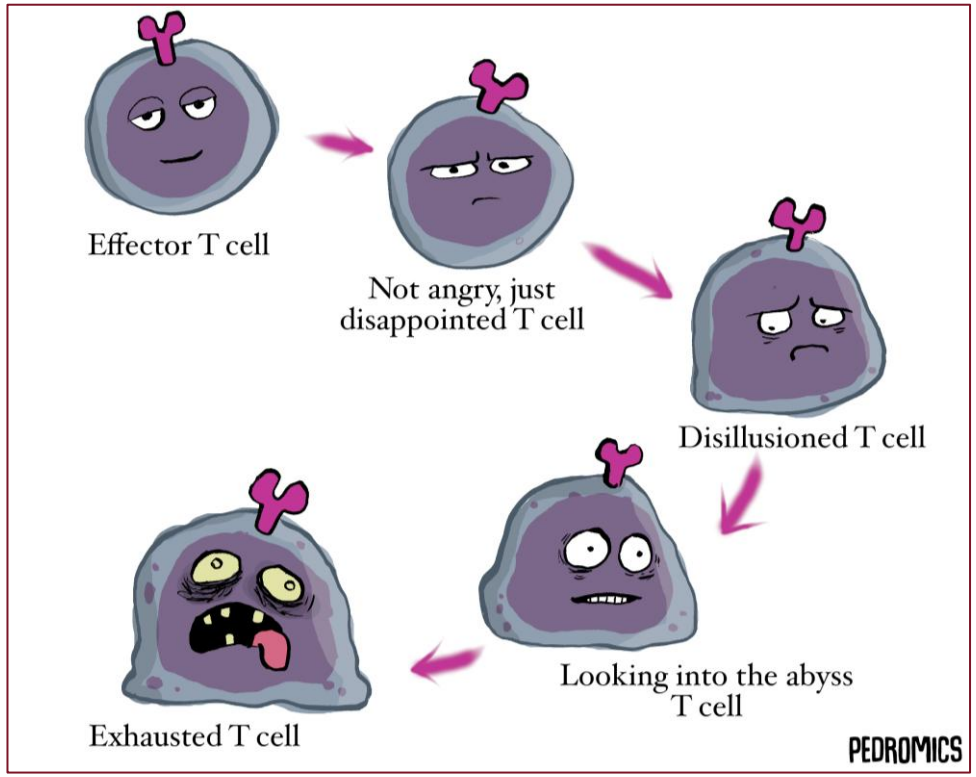
- A single dose can permanently modify T cells and provide long-term protection.
- Transduction of off-target cells (malignant cells, germ cells, or stem cells) carries the risk of epitope masking, germline modification, or novel malignancies, respectively.
- Low transduction efficiency may be overcome by proliferation.

In vivo CAR T - differences viral vs LNP targeting

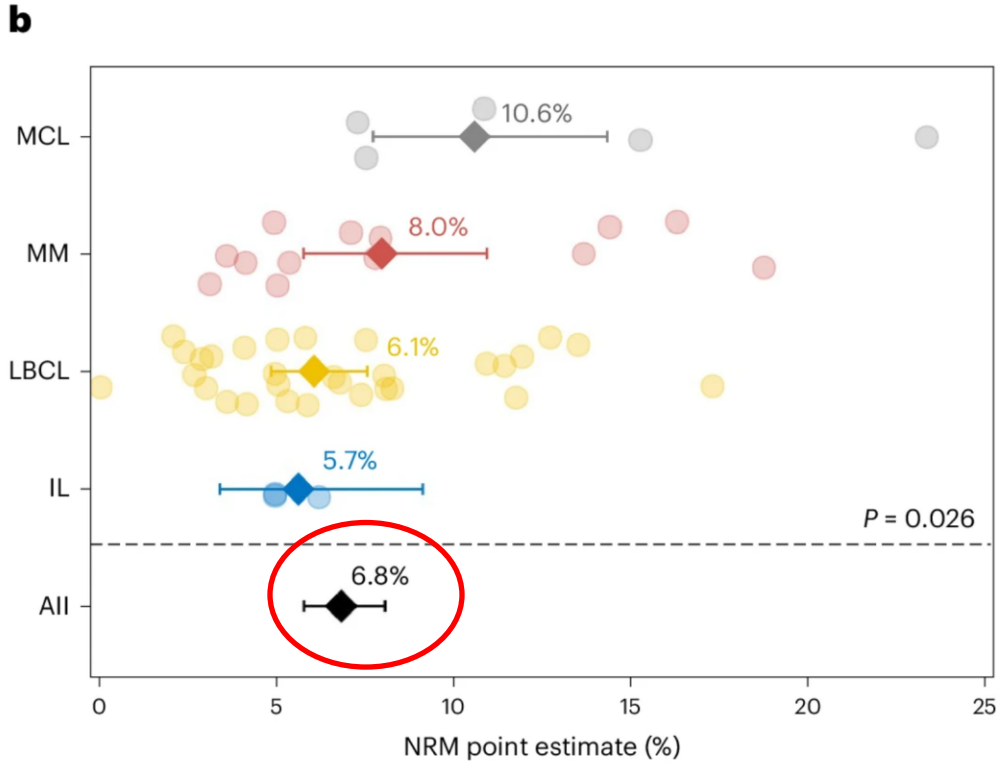


Conclusions

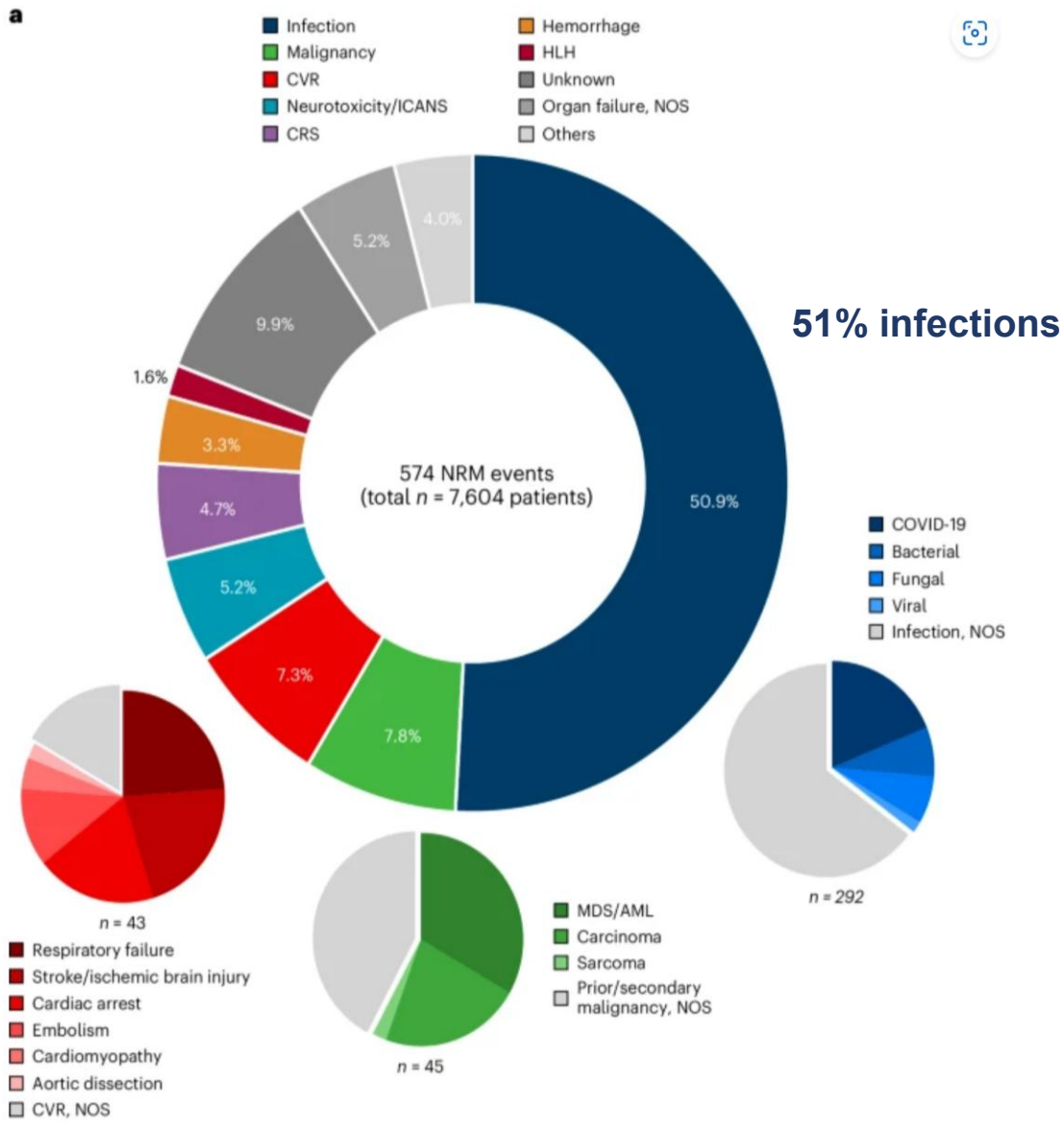
- CAR T standard of care in:
  - ≥3nd line DLBCL/tFL/PMBCL
  - DLBCL 2nd line if transplant-eligible and primary refractory or relapse ≤1 yr
  - Hopefully soon: 2nd line non-transplant-eligible
- Important areas of research
  - Predict/prevent resistance
  - Management of short and long-term toxicity (infections, second malignancies)
  - Management of financial toxicity
  - Optimal sequencing of available therapies



Non-relapse mortality after CAR T

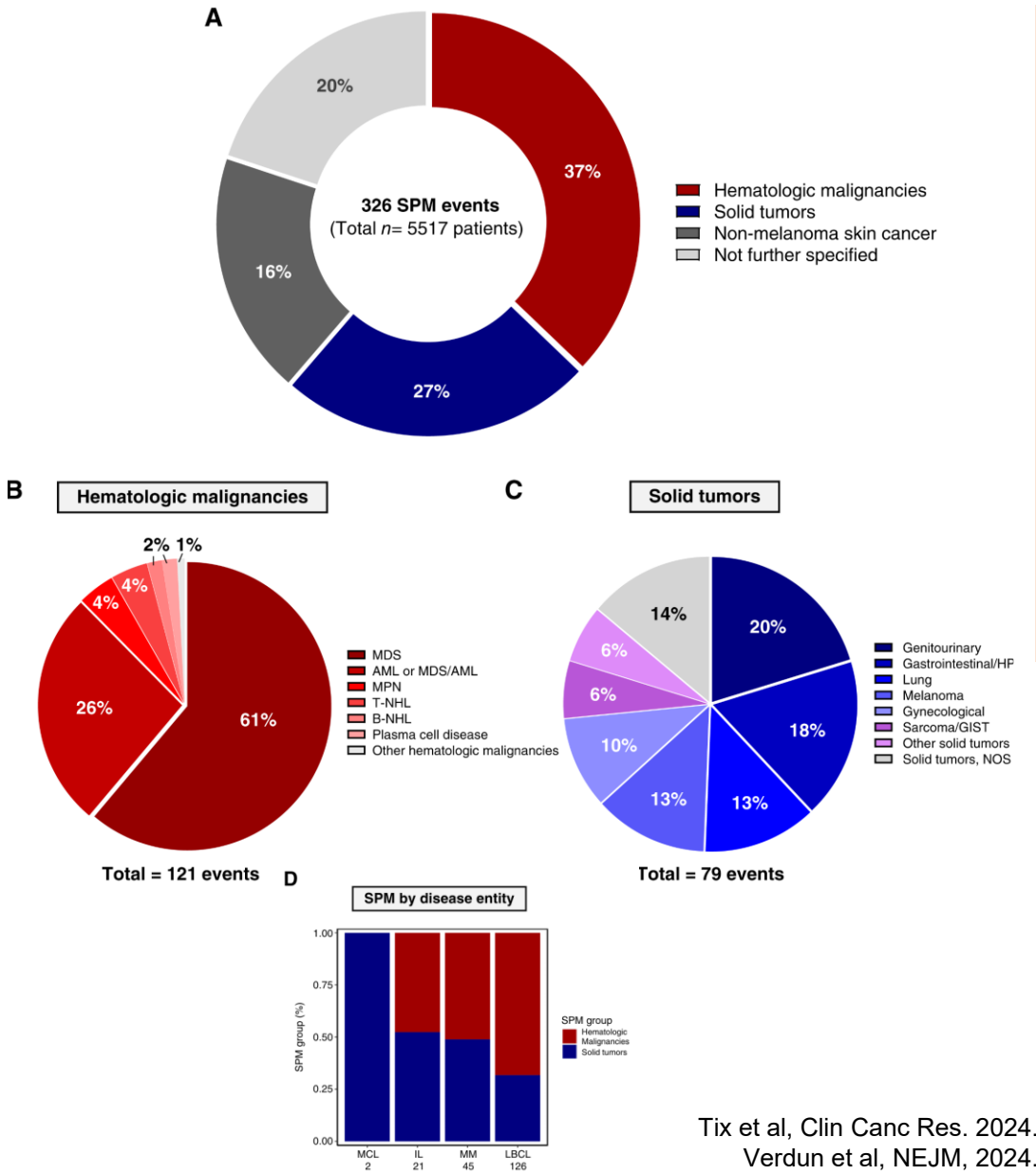


- 12-month NRM in NL R/R DLBCL cohort: 6.1%
- Infections are the major driver of NRM!



Cordas dos Santos et al, Nature Med. 2024.

Secondary malignancies after CAR T



Meta-analysis
Median follow-up 22 M
Total cohort (N=5517 NHL/MM patients): 6% sec. malignancies
LBCL 5.3%
iNHL 8.7%
MM 6%
MCL 4.3%

No difference CAR-T vs SOC in randomized studies

FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

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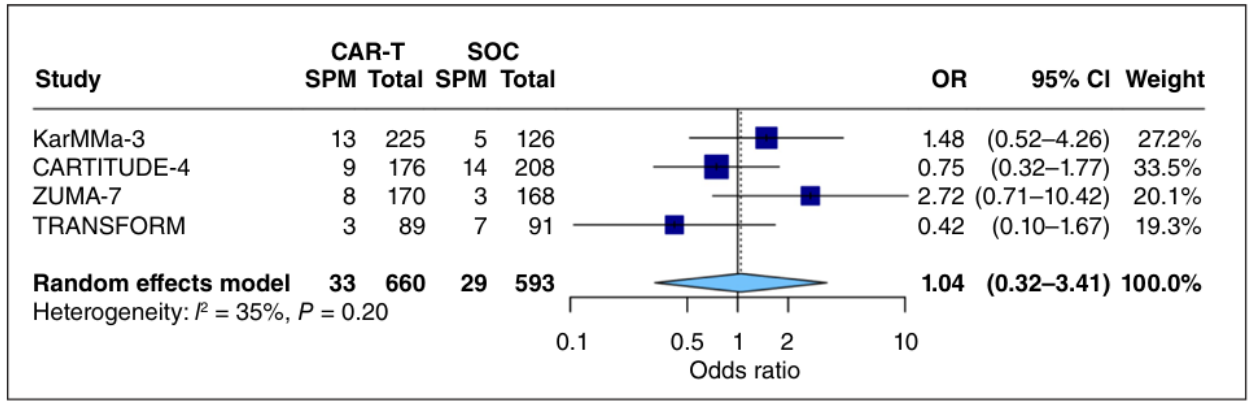
November 28, 2023

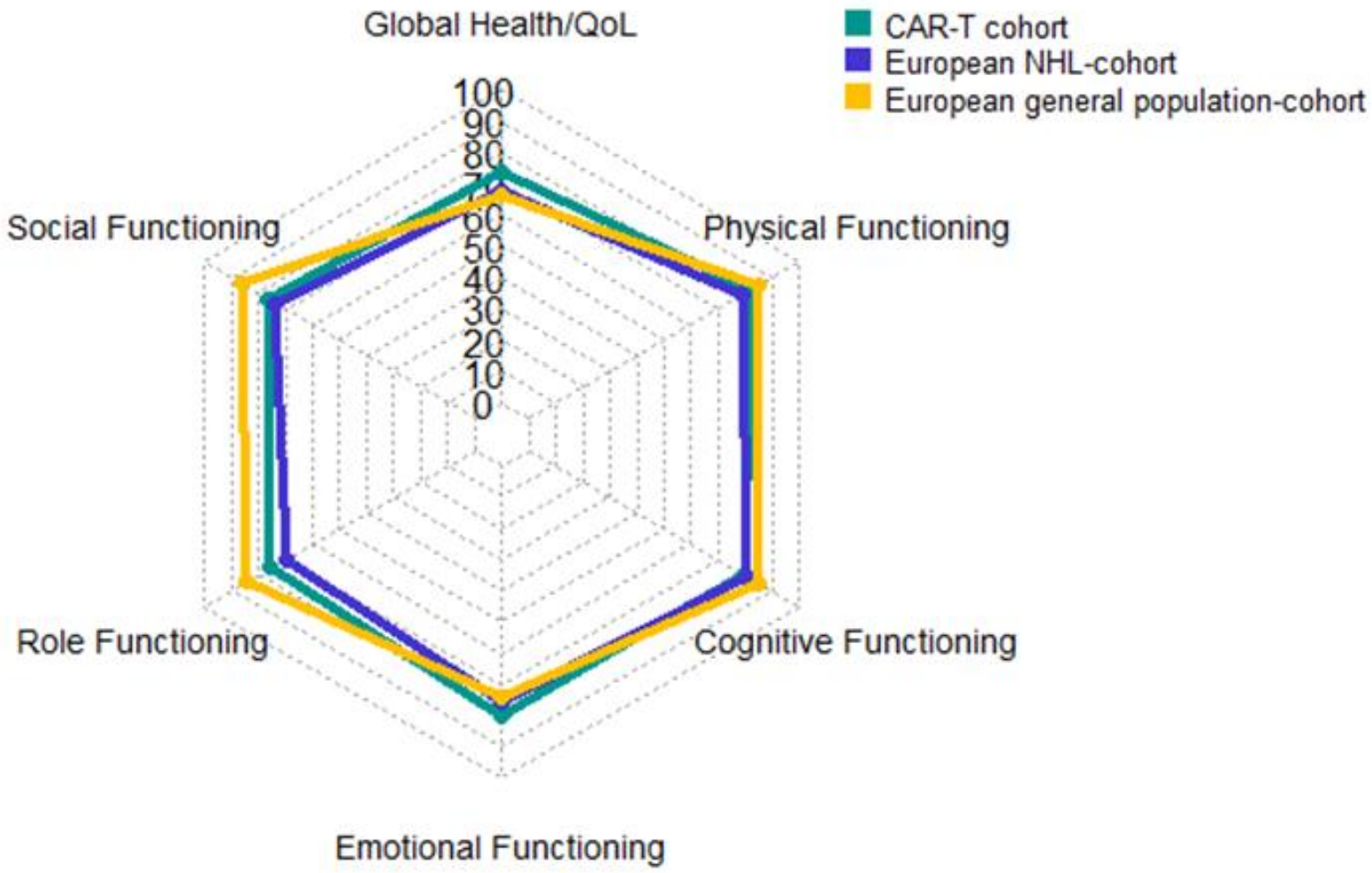
Incidence of T-cell malignancy
FDA 22/27000 infusions **= <0.1%**
So far 3 cases with insertion of CAR transgene in T-cel clone



Tix et al, Clin Canc Res. 2024.
Verdun et al, NEJM, 2024.

Long-term Quality of Life in CAR T-treated patients (n=400)

EORTC QLQ-C30 mean domain scores of the functioning-subscales per cohort



Pennings, Spanjaart, Blood Adv 2025

CAR T-cell therapy: what does it mean for patients?

CAR T-cell-care = teamwork!