MD Anderson Cancer Center

5 years from now: what will be the role of CAR-T in the therapeutic strategy of the “lymphoma world”?

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Disclosures

Disclosure	Company name
Research Support	Kite/Gilead, Allogene, Precision Biosciences, Adicet Bio, Sana Biotechnology, Cargo Therapeutics
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Honoraria	MJH Life Sciences, PeerView, MD Education
Speaker's Bureau	None
Employment	None
Royalties	None
Stocks / Stock Options	None
Patents	Related to cell therapy

- I will discuss investigational use of CAR T-cell therapy

Treatment options for 2nd line LBCL

Treatment options in 2020

- Second-line options for ASCT eligible
  - R-DHAP/ DHAX/ GDP/ ICE/ ESHAP/ MINE/ GemOx
- Second-line options for ASCT ineligible
  - R-GemOx/ GDP/ Benda
  - Pola-BR
  - Tafa-Len
  - R2/ Ibrutinib/ Brentuximab

Treatment options in 2026

- Second-line options for CAR-T eligible <12 mo
  - CAR-T (Axi-cel, Liso-cel)
- Second-line options for ASCT eligible >12 mo
  - R-DHAP/ DHAX/ DHAC/ GDP/ ICE/ ESHAP/ GemOx
- Second-line options for CAR-T ineligible <12 mo or transplant ineligible >12 mo
  - Epco-GemOx
  - Glofit-GemOx
  - Mosun-Pola
  - Glofit-Pola
  - Pola-R-GemOx
  - Pola-BR
  - Tafa-Len
  - R-DHAP/ DHAX/ DHAC/ GDP/ ICE/ ESHAP/ GemOx
  - R2/ Ibrutinib/ Brentuximab

Ref: NCCN Guidelines

Treatment options for ≥3rd line LBCL

Treatment options in 2020

- Second-line options not given previously
- Third-line options
  - CAR-T preferred (Axi-cel, Tisa-cel)
  - Selinexor
- Allogeneic SCT (selected cases)

Treatment options in 2026

- Second-line options not given previously
- Third-line options
  - CAR-T preferred (Axi-cel, Tisa-cel, Liso-cel)
  - Bispecific Antibodies (Epco, Glofit)
  - BV-R2
  - Lonca-T
  - Selinexor
- Allogeneic SCT (selected cases)

Ref: NCCN Guidelines

Treatment options for ≥3rd line follicular lymphoma

Treatment options in 2020

- Second-line options not previously given
  - Anti-CD20 + CHOP / CVP / Bendamustine
  - Anti-CD20 + Lenalidomide
- Tazemetostat
- *PI3Kis (Idelalisib, Copanlisib, Duvelisib)*
- *Ibritumomab tiuxetan*
- HDT + Autologous SCT
- Allogeneic SCT (selected cases)

Treatment options in 2026

- Second-line options not previously given
  - Anti-CD20 + CHOP / CVP / Bendamustine
  - Anti-CD20+Lenalidomide
  - Tafa-R2
  - Epco-R2
- Bispecific Abs (Mosunetuzumab or Epcoritamab)
- CAR T cell therapy (Axi-cel, Tisa-cel, Liso-cel)
- Obinutuzumab + Zanubrutinib
- Loncastuximab tesirine + rituximab
- *Tazemetostat*
- Allogeneic SCT (selected cases)

Ref: NCCN Guidelines

2026: Role of CAR-T in B-NHL

Subtype	Axi-cel / Brexu-cel	Tisa-cel	Liso-cel
LBCL	3rd →2nd line	3rd line	3rd →2nd line
MCL	2nd line		3rd line
FL	3rd line	3rd line	3rd line
MZL	3rd line*		3rd line
CLL			3rd line
PCNSL	2nd line		

*Compendium label

Future of CAR-T in lymphoma

- B-cell lymphomas
  - Earlier use of CAR-T
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  - CAR-T against novel targets
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- CAR-T for T-cell lymphomas

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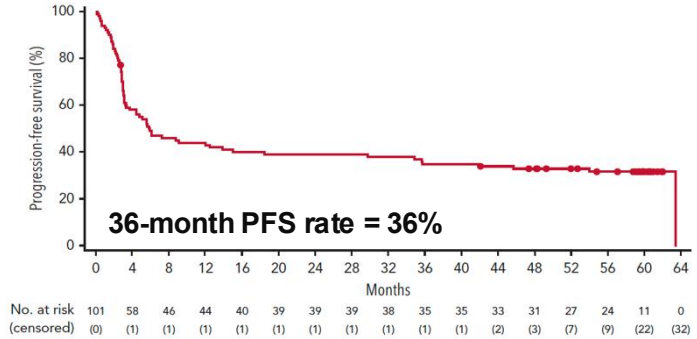
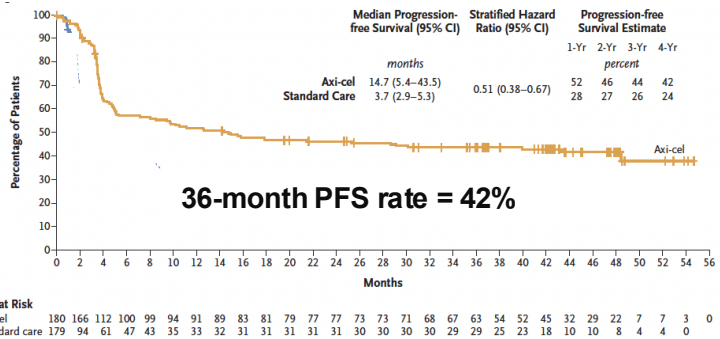
Axi-cel in LBCL: 3rd line vs. 2nd line vs. 1st line

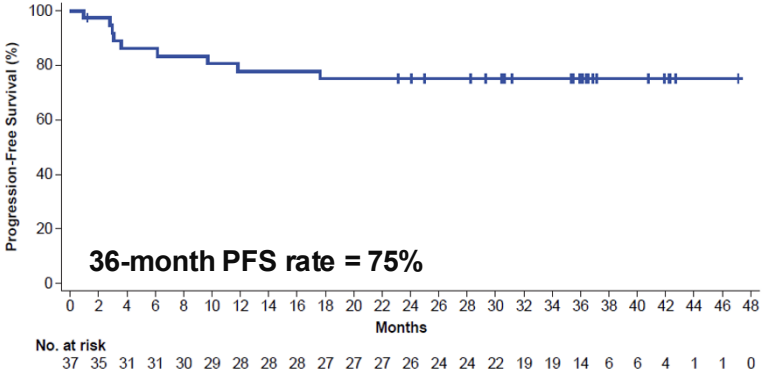
ZUMA-1: Axi-cel in ≥3rd line



ZUMA-7: Axi-cel in 2nd line

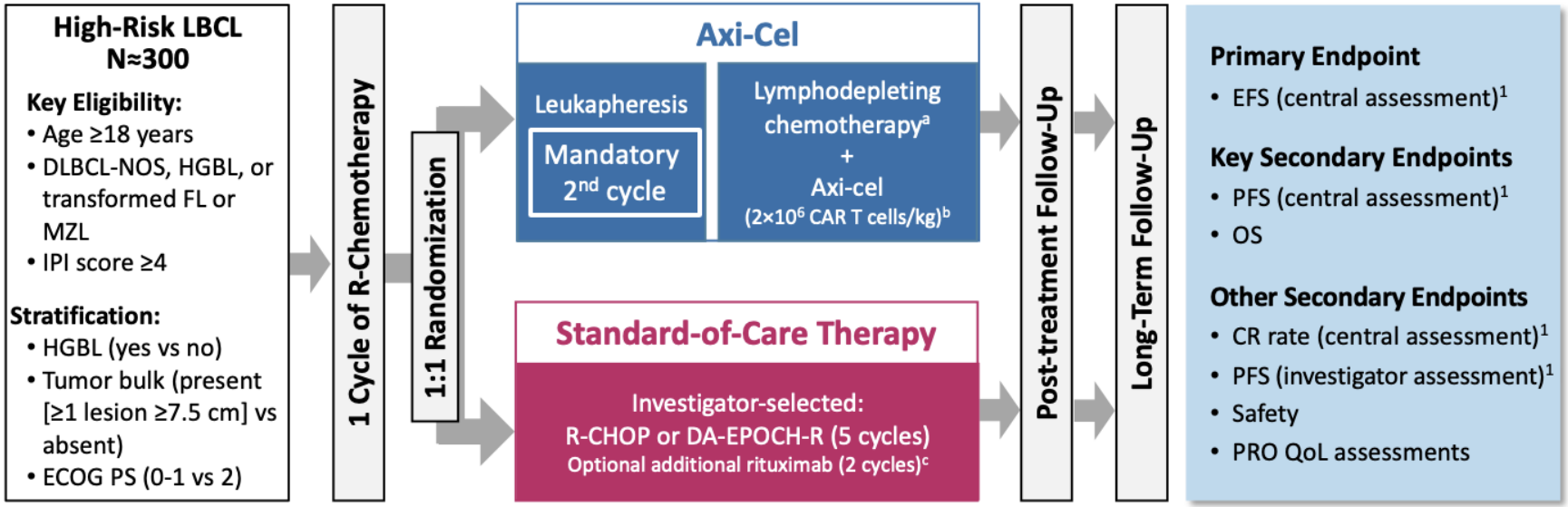


ZUMA-12: Axi-cel in 1st line



Neelapu et al, *Blood* 2023; 141(19):2307-2315
Westin JR et al. *N Eng J Med* 2023; 389(2):148-157
Chavez J…Neelapu et al, *Blood* 2025 Feb 12

ZUMA-23: Phase 3 study design



Slide courtesy: Jason Westin

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Limitations of autologous CD19 CAR T-cell therapy in LBCL

Allogeneic cell therapy

- Access
- Cost
- Manufacturing failure
- Wait time

~200 do not receive CAR-T

Relapsed/refractory LBCL (N = hypothetical 300 pts)

~100 receive SOC anti-CD19 CAR T

~40 durable response

~60 relapse after anti-CD19 CAR T

1/3

CD19 negative relapse

- Antigen escape

Dual and novel CAR-T therapies

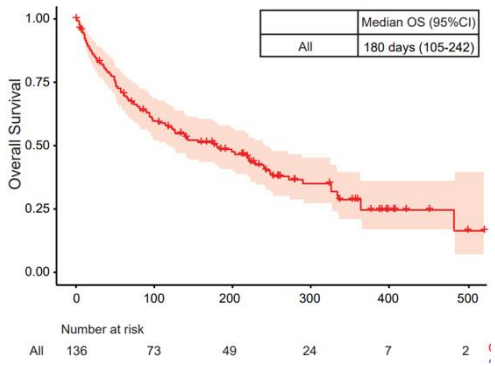
2/3

CD19 positive relapse

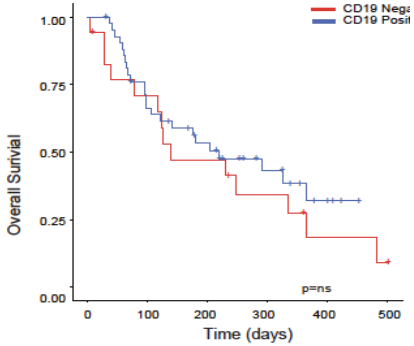
- Impaired T-cell fitness

Allogeneic cell therapy

OS after CAR-T failure in LBCL

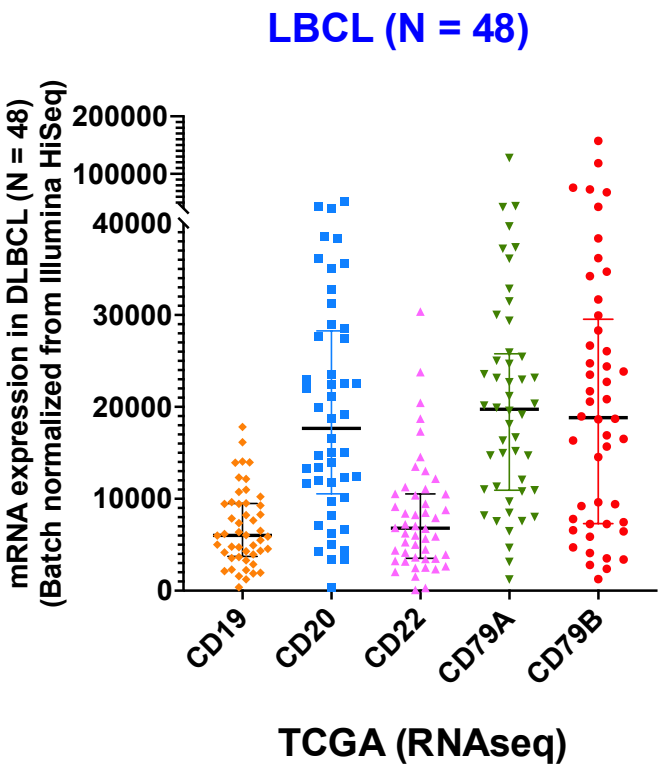


OS CD19+ vs. CD19- relapse after CAR-T failure in LBCL



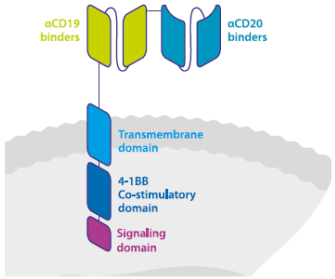
Spiegel et al. *Blood*. 2021 Apr 1;137(13):1832-1835.

Expression of pan-B-cell antigens in LBCL



CD19/CD20 dual-targeting autologous CAR-T

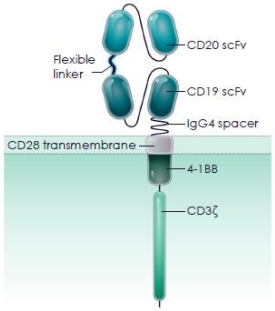
Zamto-cel



- Tandem CD19/CD20 CAR
- Administered fresh, not cryopreserved

Borchmann et al. ASH 2025, Abstract 669

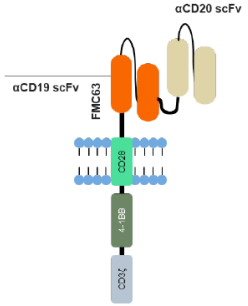
Ronde-cel



- Tandem CD19/CD20 CAR
- Selection of CD62L+ cells prior to manufacturing

Larson et al. ASH 2025, Abstract 668

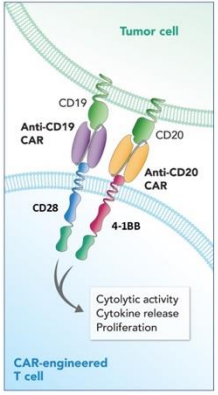
Prizlon-cel



- Tandem CD19/CD20 CAR
- Anti-CD20 scFv recognizing noncontiguous regions on CD20

Patel et al. EHA 2025

KITE-363/753



- Bicistronic CD19/CD20 CAR
- CD19 and CD20 CARs have distinct costimulatory domains

Dahiya et al. ASH 2025, Abstract 265

CAR-T against other targets in B-cell lymphomas in US

Target	Clinical Trial ID	Site(s)	Phase
CD22	NCT06340737	Stanford	1
CD20-22	NCT05607420	Multicenter	1
CD19-22	NCT05098613	Univ Colorado	1
CD19-20-22	NCT07166419	Ohio State	1
CD79b	NCT05773040	MDACC	1
CD19-79b	NCT06026319	MGH	1
BAAF-R	NCT05370430	Multicenter	1
BAFF-R	NCT06916767	Case Western	1
BAFF-R	NCT06191887	Mayo Clinic	1
CD70	NCT06492304	Multicenter	1

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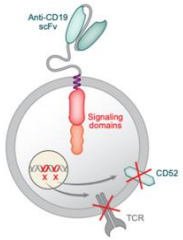
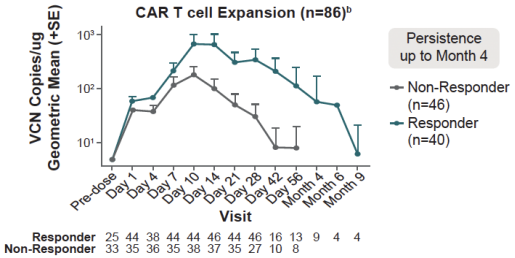
Multicenter allogeneic CAR T cell trials in B-cell malignancies

Sponsor	Year launched	CAR T product	Target disease	Current status
Allogene Therapeutics	2019	CD19 CAR-T (αβ)	B-NHL/DLBCL	Phase 3
CRISPR Therapeutics	2019	CD19 CAR-T (αβ)	B-NHL	Terminated
Precision Biosciences / Imugene	2019	CD19 CAR-T (αβ)	B-NHL, B-ALL	Phase 1
CRISPR Therapeutics	2020	CD70 CAR-T (αβ)	B-NHL, T-NHL	Terminated
Precision Biosciences	2020	CD20 CAR-T (αβ)	B-NHL, CLL	Terminated
Fate Therapeutics	2020	CD19 CAR-NK	B-NHL, CLL	Terminated
Caribou Biosciences	2021	CD19 CAR-T (αβ)	B-NHL/DLBCL	Phase 1
Takeda	2021	CD19 CAR-NK	B-NHL	Terminated
Nkarta	2021	CD19 CAR-NK	B-NHL, B-ALL, CLL	Terminated
Adicet Therapeutics	2021	CD20 CAR-T (γδ)	B-NHL	Terminated
Fate Therapeutics	2021	CD19 CAR-T (αβ)	B-NHL, B-ALL, CLL	Terminated
Athenex	2022	CD19 CAR-NKT	B-NHL, B-ALL, CLL	Terminated
CRISPR Therapeutics	2023	CD19 CAR-T (αβ)	B-NHL, CLL	Phase 1
Century Therapeutics	2023	CD19 CAR-NK	B-NHL	Terminated
Sana Biotechnology	2023	CD19 CAR-T (αβ)	B-NHL, CLL	Terminated
Fate Therapeutics	2023	CD19 CAR-NK	B-NHL	Terminated
Sana Biotechnology	2024	CD22 CAR-T (αβ)	B-NHL	Terminated
Atara Biotherapeutics	2024	CD19 CAR-T (αβ)	B-NHL	Terminated
Poseida Therapeutics	2024	CD19-20 CAR-T (αβ)	B-NHL/DLBCL	Phase 1

ALPHA 1&2 studies: Efficacy in CAR naïve R/R LBCL

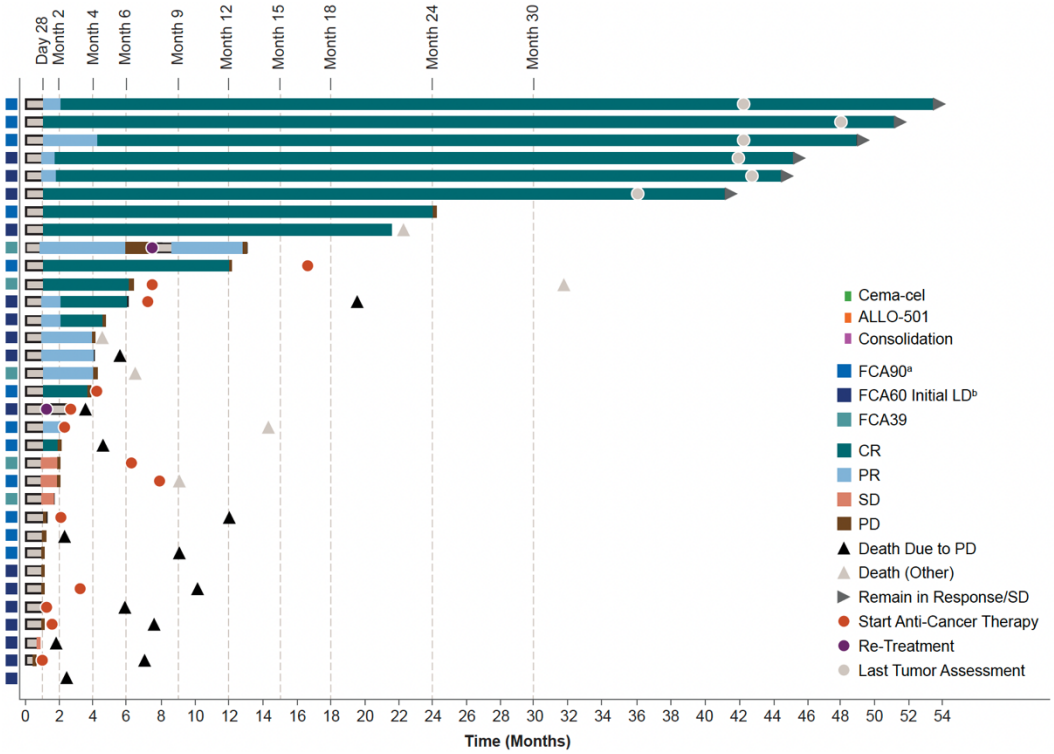
Cema-cel





Cy + Flu + Anti-CD52 Ab

	All (N=33)	Phase 2 dose (N=12)
ORR, n (%)	19 (58)	8 (67)
CRR, n (%)	14 (42)	7 (58)
6 mo CRR, n (%)	10 (30)	5 (42)
12 mo CRR, n (%)	8 (24)	4 (33)

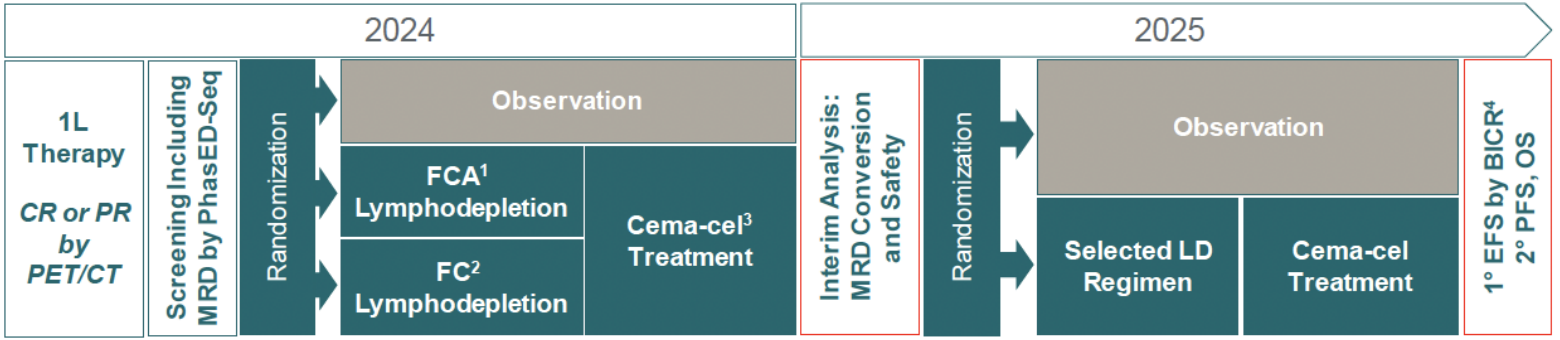


Median DOCR = 23 mo

(On ZUMA-1 median DOCR = 62 mo)

Locke et al Neelapu, *J Clin Oncol* 2025

ALPHA 3: Phase 3 study in first line LBCL



ALPHA3 Startup Underway, Enrollment Projected to Commence Mid-2024

- All LBCL potentially eligible: no upfront risk assessment (e.g., IPI score, double-hit, HGBCL)
- Approximately 110 patients in observation and treatment arms
  - All patients treated with "Selected LD Regimen" during LD selection will count toward pivotal sample
  - Continuous enrollment planned, no pause in enrollment for LD regimen selection
- Expected median time to EFS in observation arm ~8 months

- *In vivo* CARs may be tested in this setting as well

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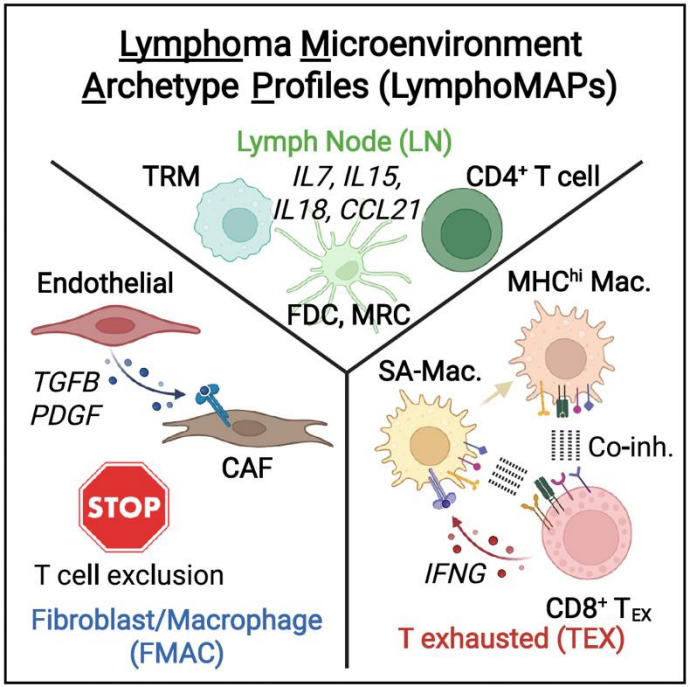
Tumor intrinsic mechanisms associated with CD19 CAR T-cell resistance in LBCL

Resistance mechanism	Comment	Reference(s)
CD19 loss	30-40% of DLBCL, tFL, and PMBCL after axi-cel	Plaks et al. *Blood* 2021 Spiegel et al. *Blood* 2021 Spiegel et al. *Nat Med* 2021
CD58 alteration	Required for CD2 co-stimulation in CAR T cells	Majzner, et al. *ASH 2020, Abstract 556* Romain et al, *J Clin Invest* 2022
***TP53* genomic alterations**	Associated with dysregulation of IFN and death receptor signaling pathways and reduced CD8 T-cell infiltration	Shouval et al. *J Clin Oncol* 2021
DNA copy number alterations	Deletion 10q23.3 leading to loss of FAS death receptor was most highly associated with poor PFS and OS	Cherng et al. *Blood* 2022
Complex genomic features	Complex structural variants, APOBEC mutational signatures, genomic damage from ROS, deletion 3p21.31 containing *RHOA* tumor suppressor	Jain et al. *Blood* 2022

Combination strategies or novel CAR designs?

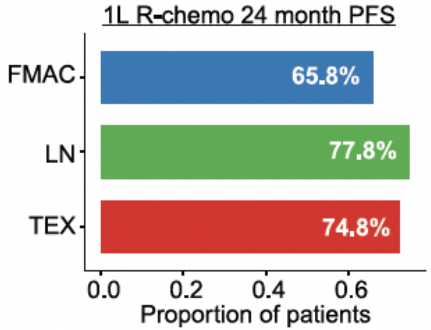
Impact of TME on CAR-T outcomes

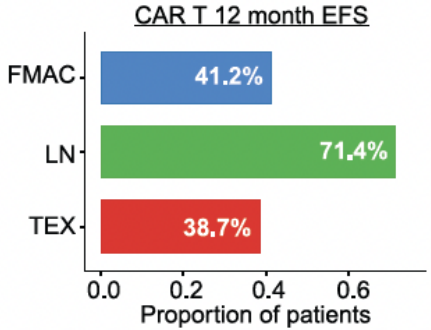


FMAC
Enriched for DZsig+ mol. subtype
Enriched for high-risk features
More frequent in later LOT
Inferior outcomes to 1L R-chemo

LN
Enriched for GCB mol. subtype
Low SUVmax
More frequent in earlier LOT
Best outcomes post CAR T

TEX
Enriched for ABC mol. subtype
No assoc. with high-risk features
Consistent across LOT
No sig. benefit from CAR T





Combination strategies?

Li X et al Green MR, *Cancer Cell*, 2025 Jul 14;43(7):1347-1364

2030: Role of CAR-T in B-NHL

Subtype	Axi-cel / Brexu-cel	Tisa-cel	Liso-cel	CD19-20 CAR	Cema-cel / *In vivo* CAR
LBCL	3rd →2nd → 1st line IPI^{Hi}	3rd line	3rd →2nd line	2nd line	1st line MRD+
MCL	2nd line		3rd line		
FL	3rd → 2nd line$^{Hi\ risk}$	3rd line	3rd → 2nd line$^{Hi\ risk}$		
MZL	3rd line*		3rd line		
CLL			3rd line		
PCNSL	2nd line		1st line		

*Compendium label

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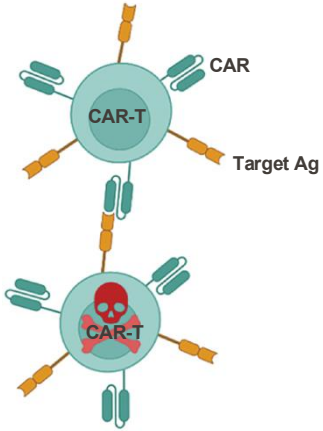
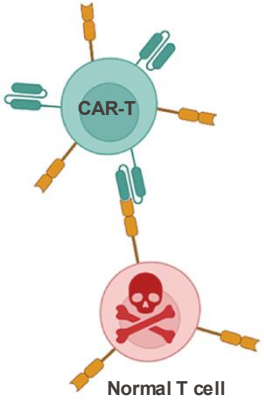
Challenges for developing CAR-T therapy for T/NK-cell malignancies

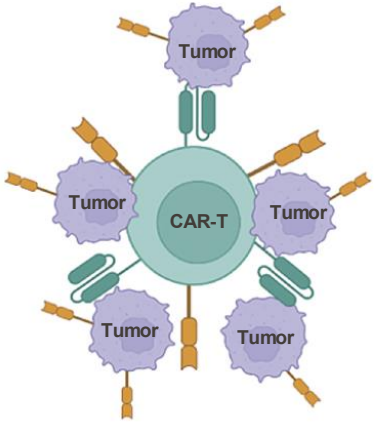
Fratricide



T-cell aplasia



Product contamination



Solutions:

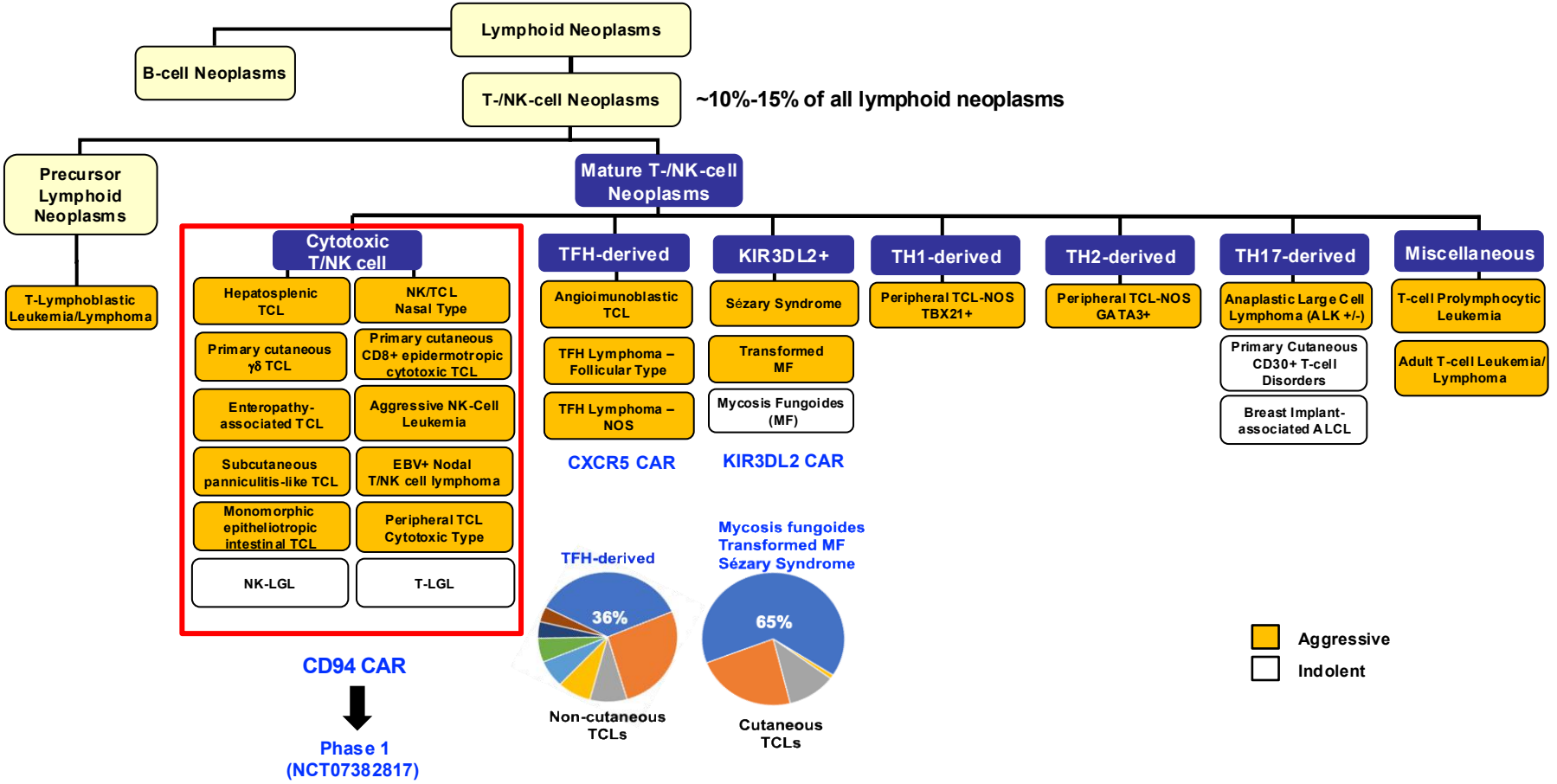
- Ag KO or KD
- Restricted expression Ag

- Restricted expression Ag
- Safety switch

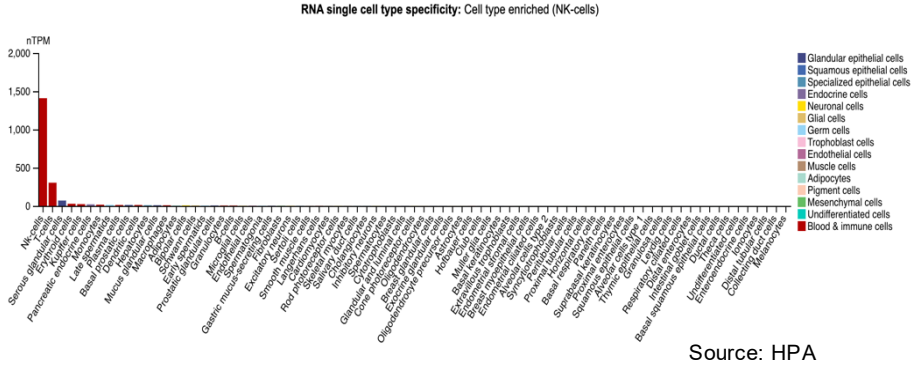
- Debulk with bridging therapy
- Allogeneic CAR T cells

Adapted from Maciocia N, et al. *Blood Adv*. 2025 Feb 25;9(4):913-923

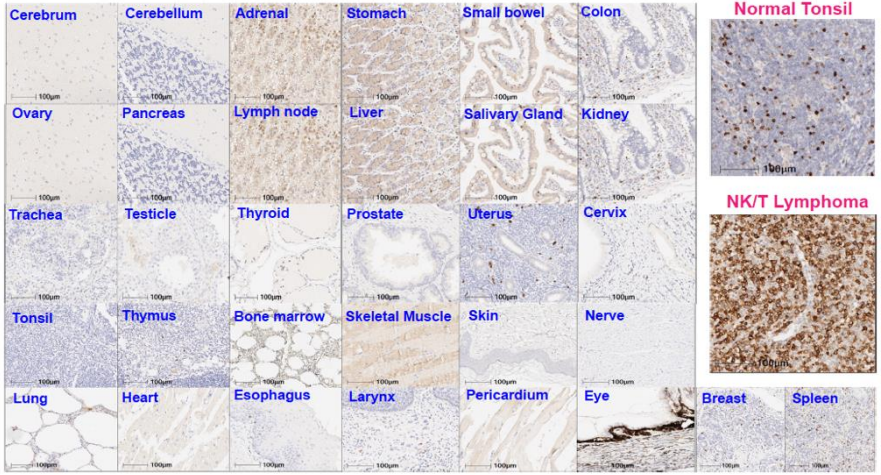
T/NK-cell leukemias and lymphomas by cell of origin

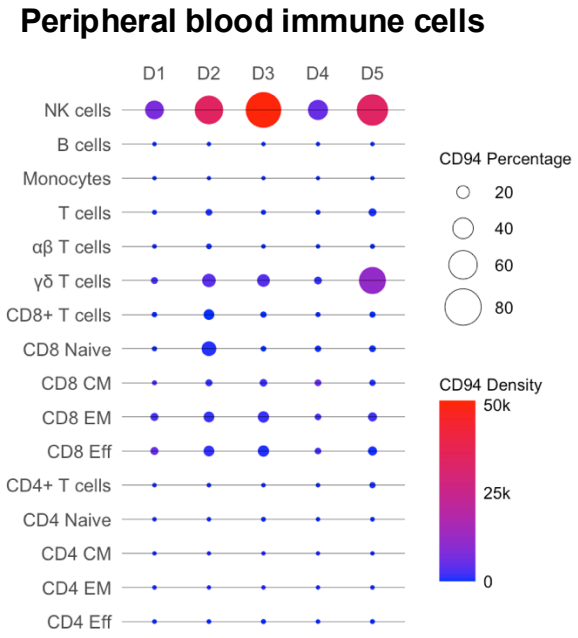


CD94 RNA and protein expression in normal tissues



Source: HPA





Cuong Le et al, *ASH 2025, Abstract 2337*

CD94 expression in T/NK malignancies

Table 1
CD94 expression on T/NK-cell proliferations.

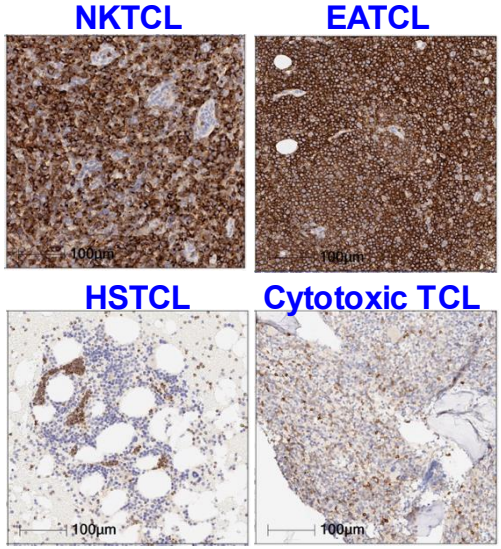
	Diagnosis	N	Positive n (%)	CD94 MFI[§] median (range)	CD94 RFI[§] median (range)
	Reactive proliferations				
	CD4 + T-cells	15	0 (0 %)	35 (4–53)	0.4 (0.1–1.0)
	CD8 + T-cells	15	4 (27 %)	191 (22–643)	2.9 (1.2–15.2)
	Neoplastic proliferations				
	T-LGLL	43	24 (56 %)	231 (32–4805)	4.6 (1.0–1601.7)
	AITL	9	1 (11 %)	28 (0.4–2164)	0.4 (0.1–32.3)
T-cell	ALCL	13	1 (8 %)	125 (34–447)	1.7 (0.5–3.7)
	PTCL-NOS	33	1 (3 %)	27 (0.9–197)	1.0 (0.1–12.0)
	PTCL-TFH	3	0 (0 %)	17 (10–65)	1.1 (0.7–2.0)
	HSTL	10	10 (100 %)	4675 (163–10012)	54.6 (3.2–577.1)
	T-PLL	4	0 (0 %)	25 (19–162)	1.0 (0.5–1.8)
	ITCL	2	0 (0 %)	60 (7–113)	0.8 (0.4–1.1)
	ATLL	1	0 (0 %)	32	1.1
	Reactive proliferations	15	15 (100 %)	3893 (632–19470)	54.1 (9.8–1947.0)
	Neoplastic proliferations				
NK-cell	CLPD-NK	3	3 (100 %)	11,214 (560–21123)	224.3 (12.8–264.0)
	ENKTL	2	2 (100 %)	11,026 (5097–16954)	77.2 (59.9–94.4)
	ANKL	1	1 (100 %)	12,718	423.9

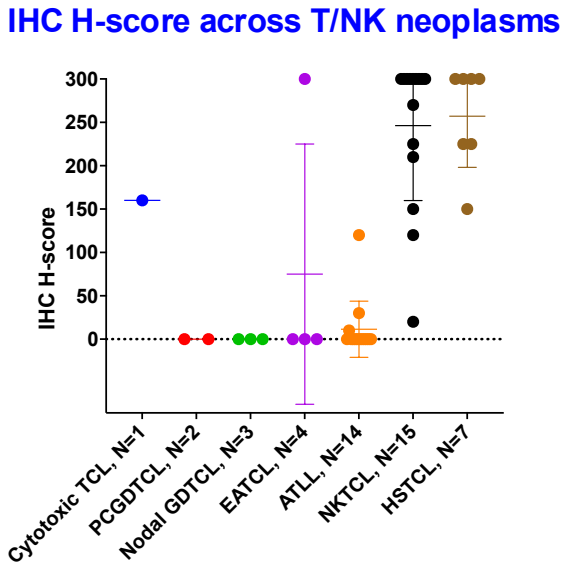
Note: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic T-cell lymphoma; ANKL, aggressive NK-cell leukemia; ATLL, adult T-cell leukemia/lymphoma; CLPD-NK, chronic lymphoproliferative disorder of NK cells; ENKTL, extranodal NK/T-cell lymphoma; HSTL, hepatosplenic T-cell lymphoma; ITCL, intestinal T-cell lymphomas; PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; PTCL-TFH, peripheral T-cell lymphoma with T follicular helper phenotype; T-LGLL, T-large granular lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia.

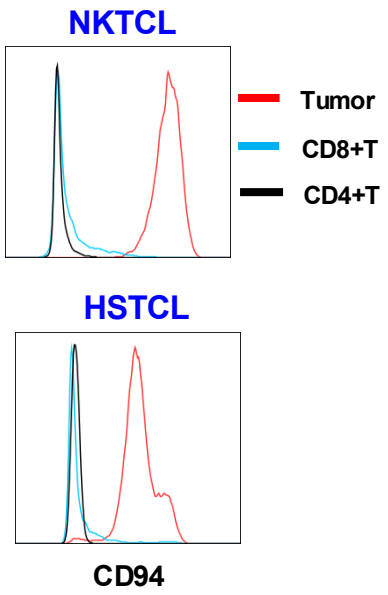
[§] On neoplastic cells within each entity of T/NK-cell neoplasm.

Fang H, et al. *Leuk Res*. 2021 May 10;108:106614

IHC: CD94 expression in T/NK malignancies (N=46)

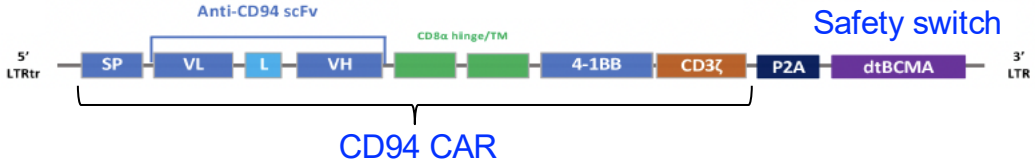


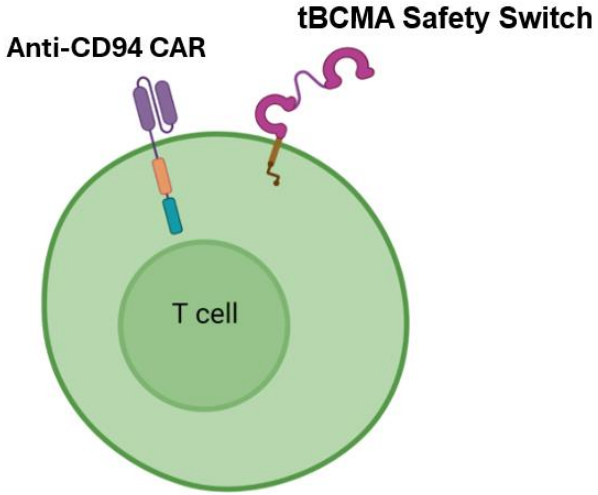




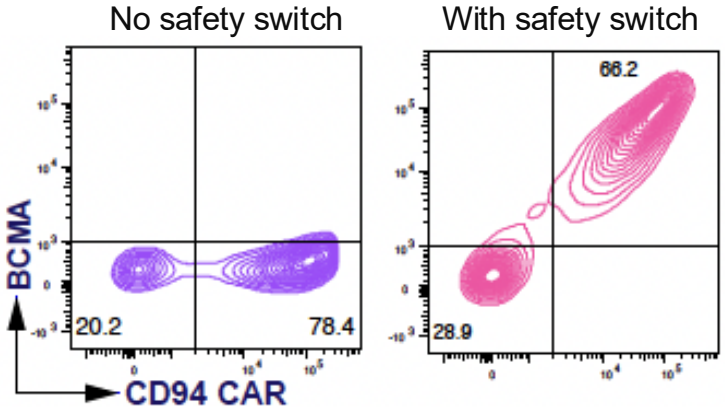
Cuong Le et al, *ASH 2025, Abstract 2337*

CD94 CAR with safety switch



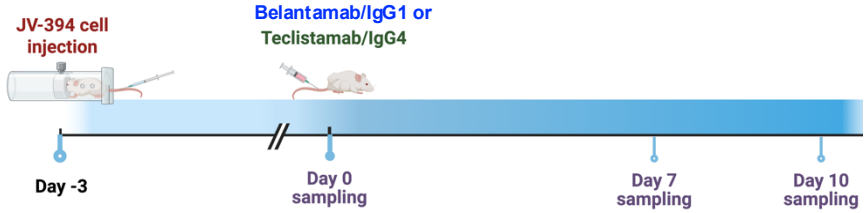


CD94 CAR expression in T cells

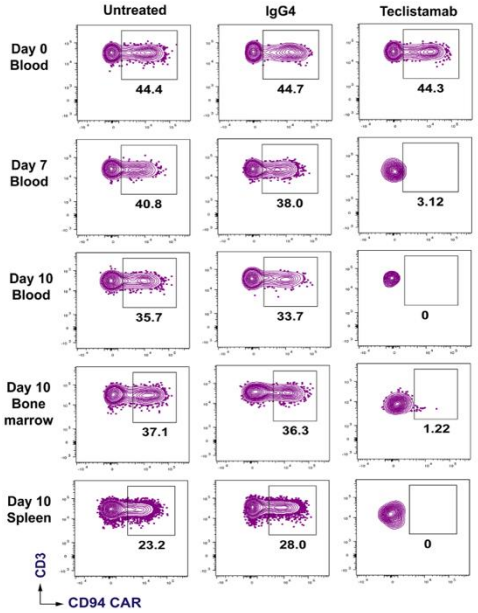


Cuong Le et al, *ASH 2025, Abstract 2337*

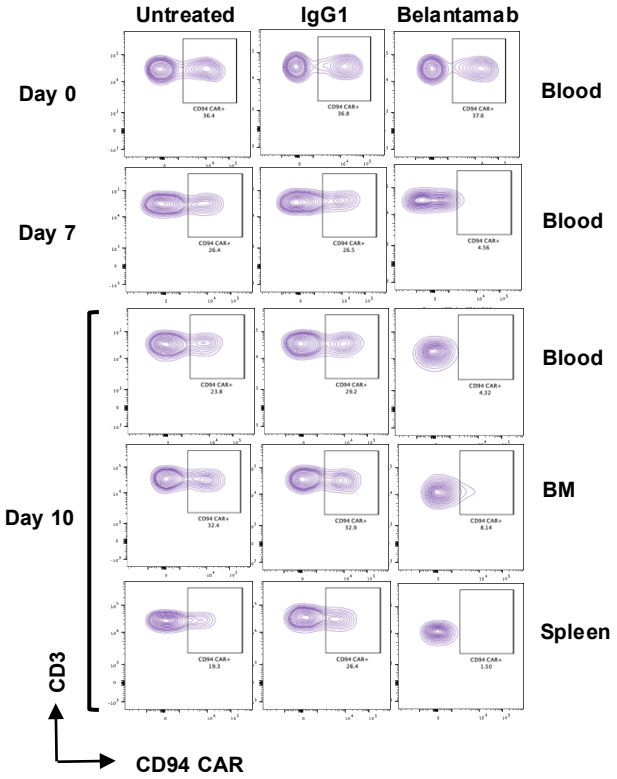
tBCMA+ CD94 CAR-T are eliminated by anti-BCMA TCE/ADC *in vivo*



Teclistamab

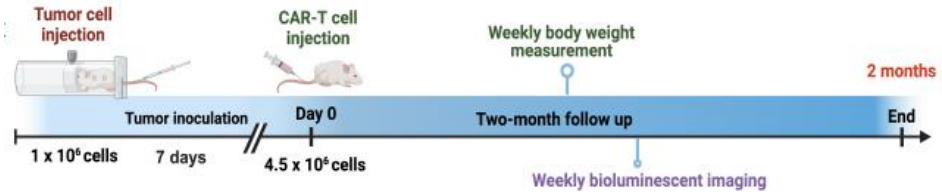


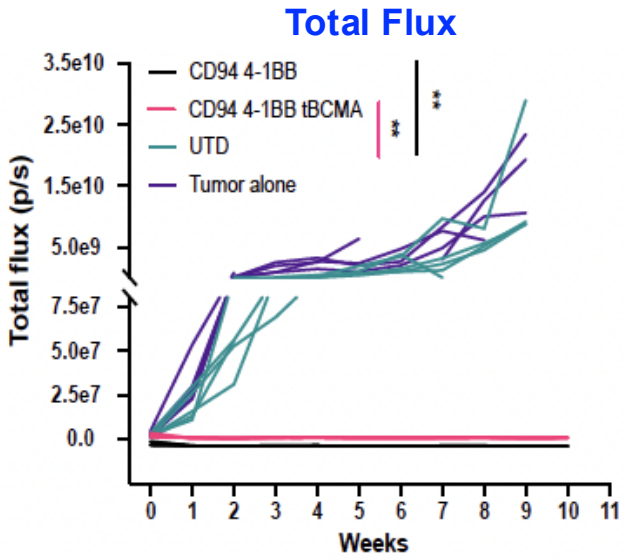
Belantamab mafodotin

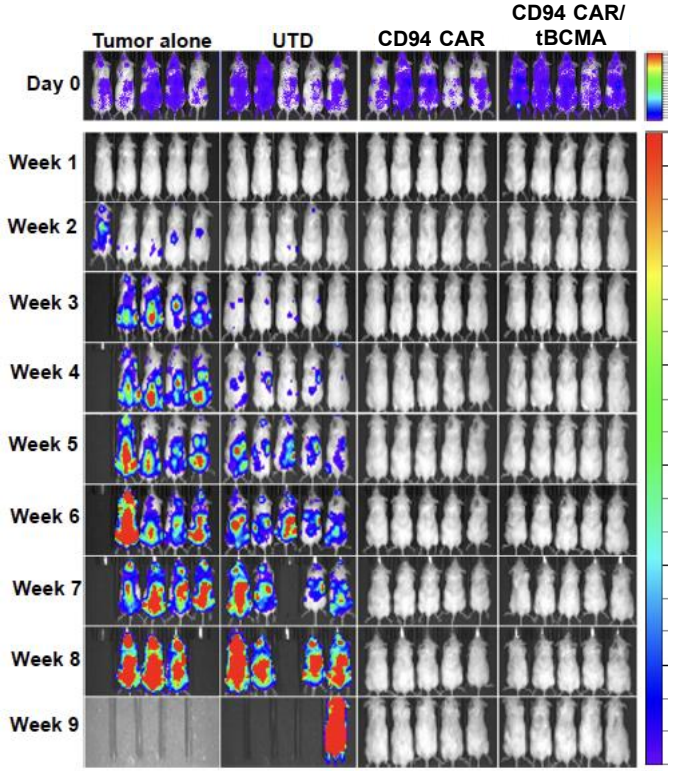


Liu et al, *ASH 2025, Abstract 7620*

Anti-tumor effects of CD94 CART in KHYG-1 cell line xenograft model



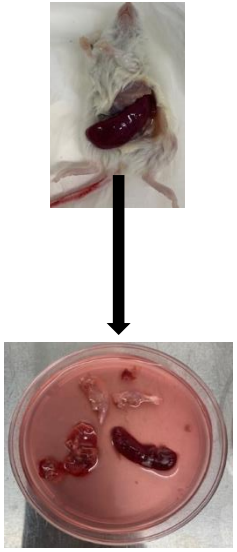




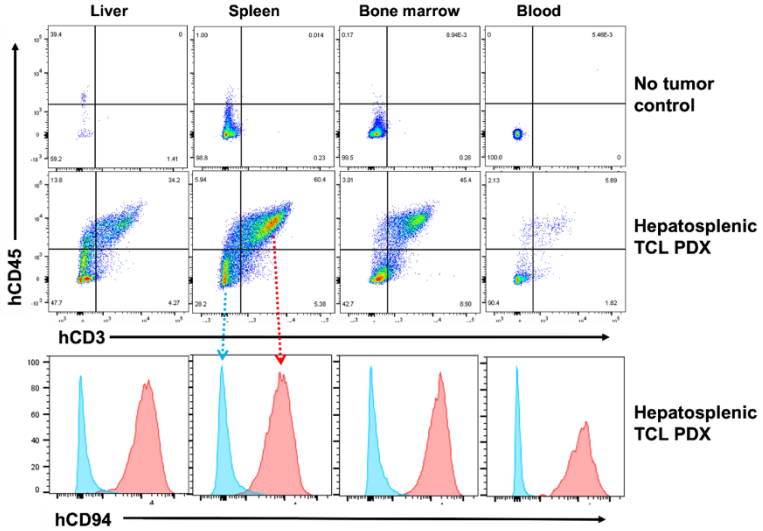
Cuong Le et al, *ASH 2025, Abstract 2337*

Anti-tumor effects of CD94 CART in hepatosplenic PDX model

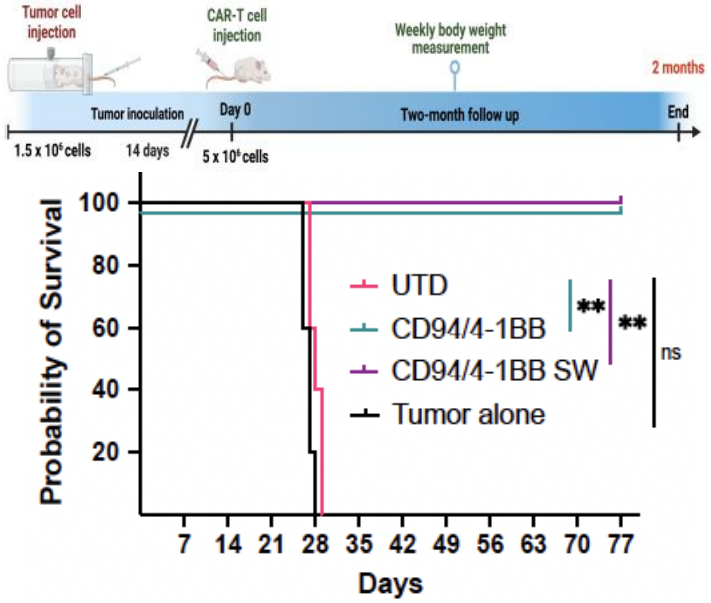
Hepatosplenic TCL PDX



Phenotype at necropsy on day 49



Hepatosplenic TCL PDX



- **Similar result observed in PDX model of extranodal NK/TCL**

Cuong Le et al, *ASH 2025, Abstract 2337*

No T cell aplasia in humanized mice

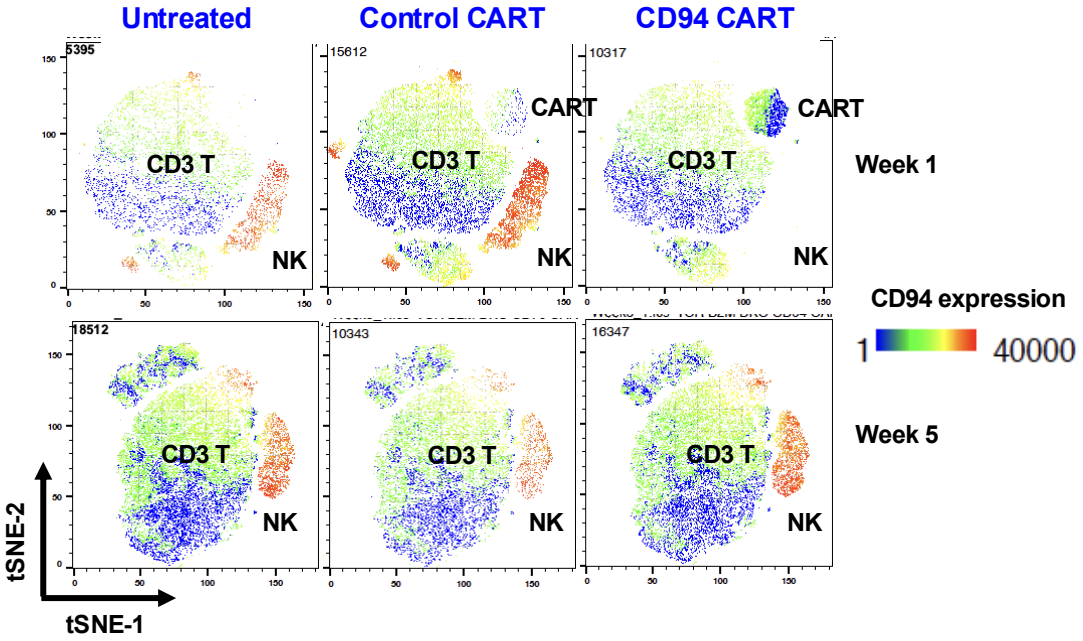
NSG-IL15 Tg mice

CD34+ cord blood stem cells

Humanized NSG-IL15 Tg mice

CD94 or control CAR T cells

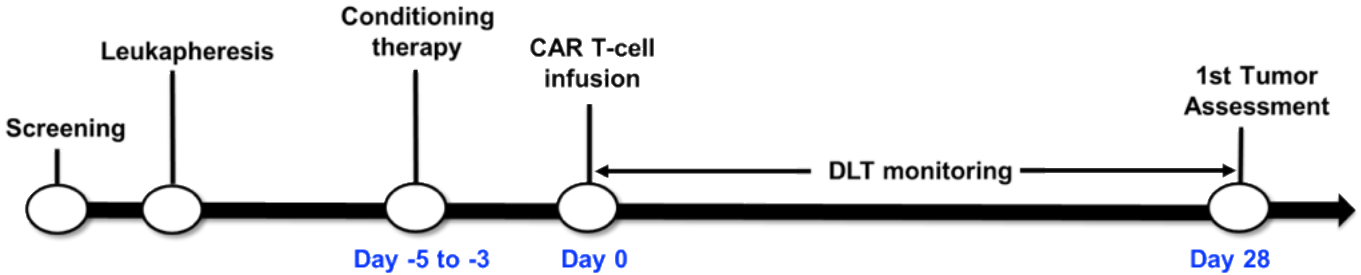
Weekly flow cytometry for T/B/NK



Elimination of CD94+ NK cells and a small subset of T cells (on-target, off-tumor effect)

Cuong Le et al, *ASH 2025, Abstract 2337*

Phase 1 trial of autologous CD94 CAR-T in r/r T/NK cell lymphomas



- Tumor assessment at baseline and months 1, 3, 6, 9, 12, 18, 24 (Lugano 2014 criteria)
- Blood samples (PBMC and plasma) at days -5, 0, 1, 3, 5, 7, 9, 11, 13, 21, 28, and months 3, 6, 9, 12
- Tumor biopsies at baseline, day 7-14, and progression

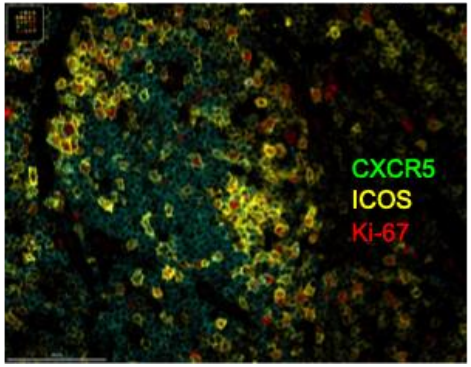
- Single center trial
- Eligibility: Cytotoxic, $\gamma\delta$, or NK neoplasms after 1 line of systemic therapy
- N = 9-18 patients for dose escalation (3 flat dose levels – $10x10^6$, $20x10^6$, and $40x10^6$)
- N = 15 patients for dose expansion
- Primary objective: Safety and identify the MTD or RP2D

Trial activated in Feb 2026

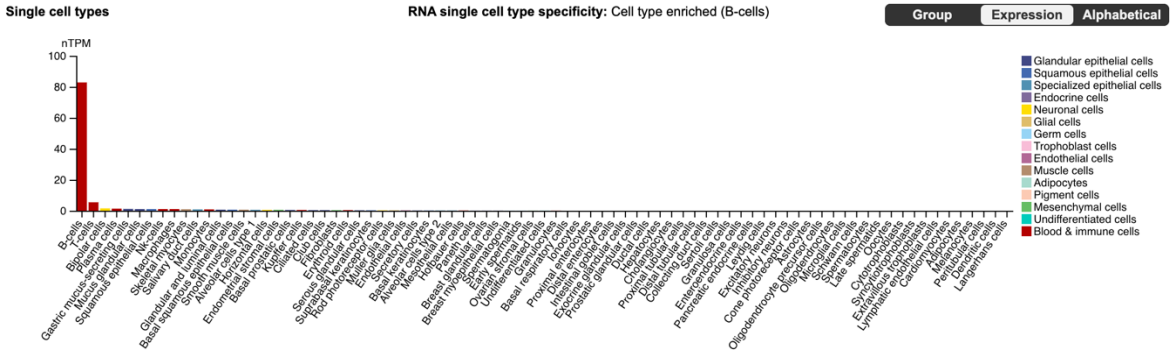
CXCR5 expression in normal and malignant cells

- CXCR5 is expressed on mature recirculating B-lymphocytes, a subpopulation of follicular helper T cells (Tfh) and skin-derived migratory dendritic cells (DCs)
- CXCL13 is the ligand for CXCR5 and controls the migration of B cells, Tfh, and DC into secondary lymphoid organs towards the chemokine gradient

COMET of AITL patient biopsy

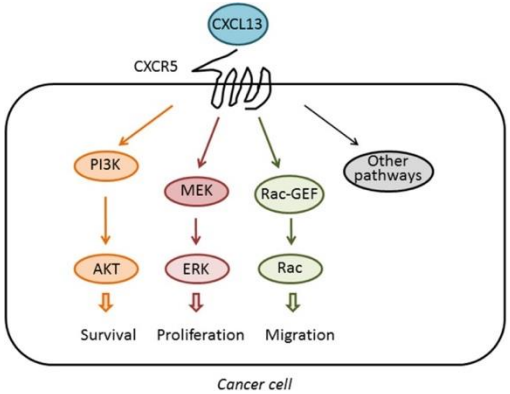


CXCR5 mRNA expression in normal human tissues (scRNAseq)



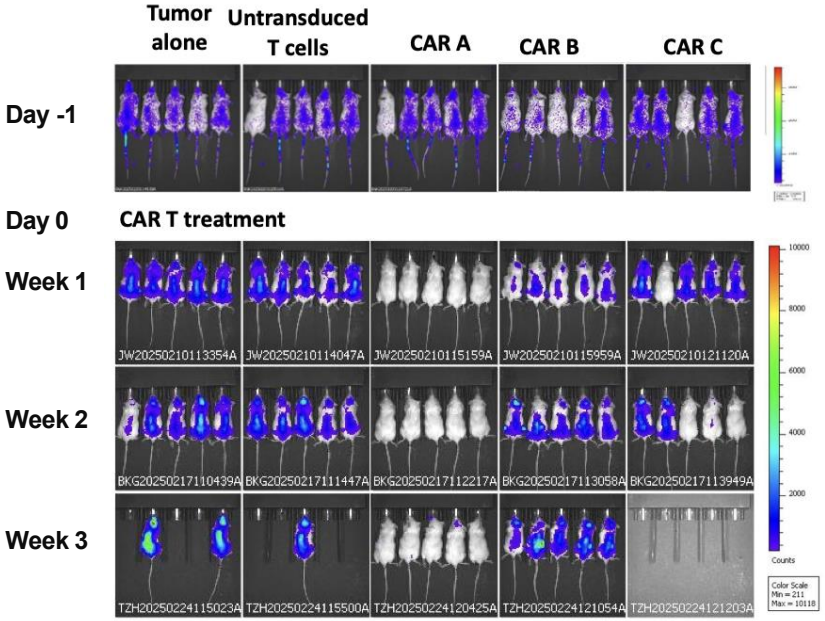
Weng et al, *ASH 2025, Abstract 3709*

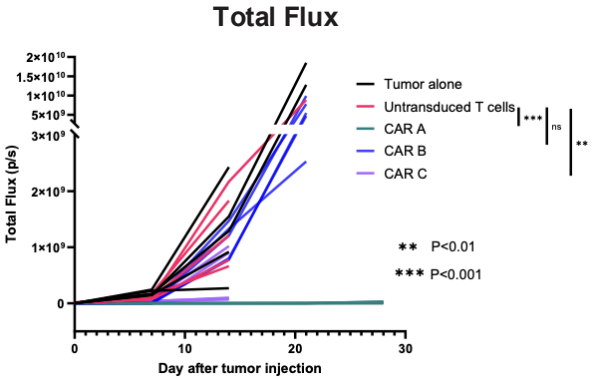
Source: HPA

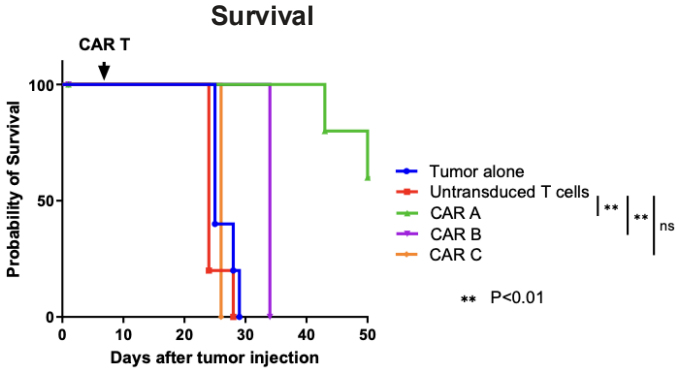


Kazanietz MG, et al. *Front Endocrinol* (Lausanne). 2019 Jul 12;10:471. doi: 10.3389/fendo.2019.00471

Efficacy of CXCR5 CAR-T in xenogtaft model



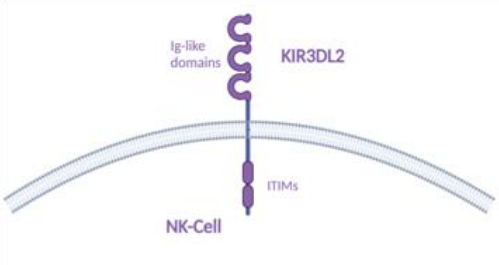




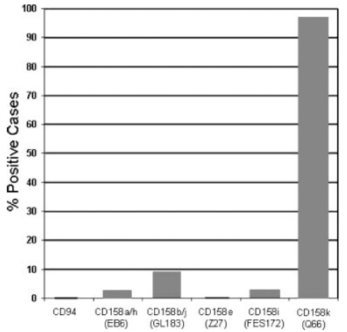
Weng et al, *ASH 2025, Abstract 3709*

KIR3DL2 expression in normal and malignant cells

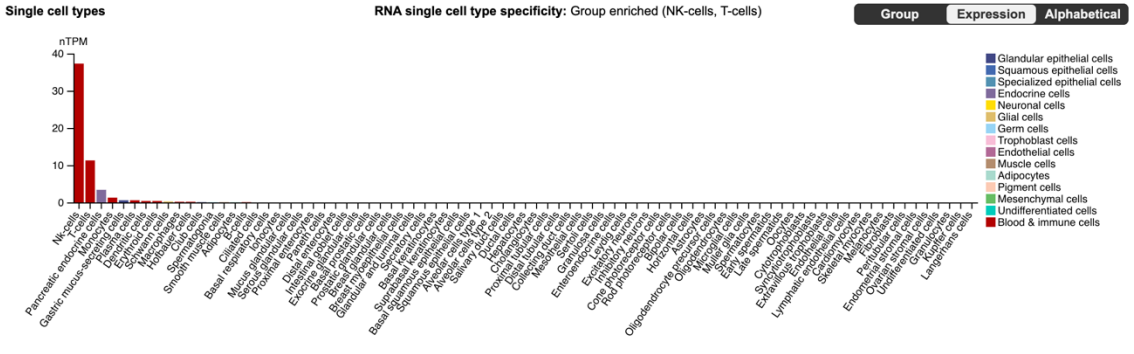
- A member of the killer cell Ig-like receptor (KIR) family
- Expressed on NK cells and a subset of T cells (mainly CD8+)



KIR protein expression in Sezary syndrome

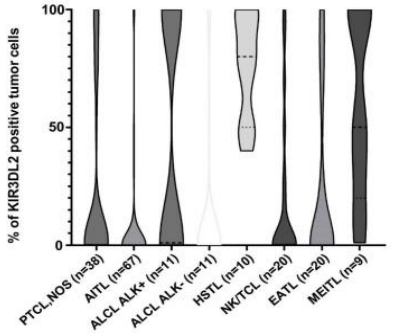


KIR3DL2 mRNA expression in normal human tissues (scRNAseq)



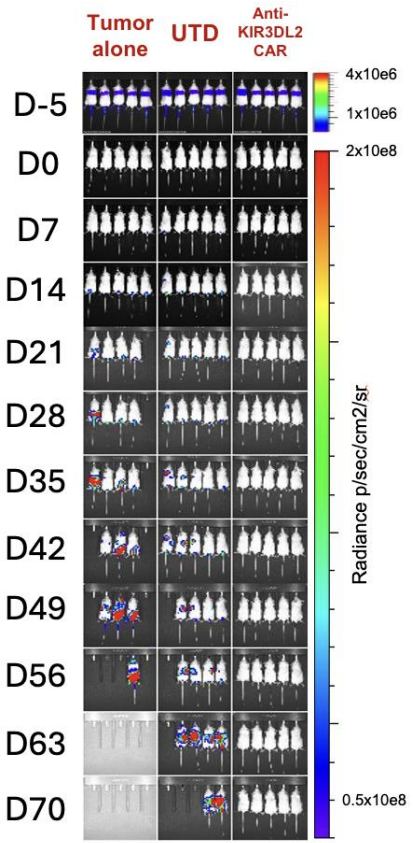
Source: HPA

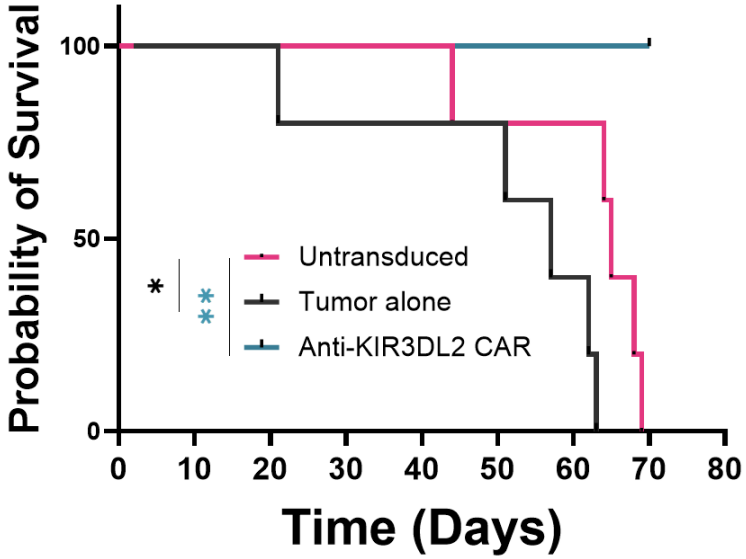
KIR3DL2 protein expression in TCLs



Bahler DW et al. *Cytometry B Clin Cytom*. 2008 May;74(3):156-62
Decroos A et al. *Haematologica*. 2023 Oct 1;108(10):2830-2836

Efficacy of KIR3DL2 CAR-T in xenograft model





Aletti et al, *ASH 2025, Abstract 7621*

Summary

- Markers associated with cell of origin such as CD94, CXCR5, and KIR3DL2 may be targeted with CAR T cell therapy in T/NK cell lymphomas
- CD94 / CXCR5 / KIR3DL2-targeting CAR T cell therapies are not expected to cause broad T cell aplasia or fratricide
- tBCMA is a novel and highly effective safety switch that can be used with various adoptive cell therapy products

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