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MD Anderson Cancer Center
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Cord Blood CAR NK Cell Therapy

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Disclosures

- License agreement and research agreement with Takeda to develop CB-CAR NK cells for the treatment of B-cell malignancies and other cancers.

- Educational grant:
  - Affimed; Pharmacyclics

- SAB:
  - Virogen; Adicet Bio

NK Cells

- Innate immune system
- CD56+CD3-
- Differentiate in the BM
- No antigen priming
- Primarily in blood
- No/low risk of GVHD
- Recognition takes place through complex array of receptors

T Cells

- Adaptive immune system
- CD3+CD4+ or CD3+CD8+
- Differentiate in the thymus
- Antigen priming required
- Antigen specific
- Allogeneic T cells induce GVHD
- Recognize targets through TCR rearrangement

Advantages of NK cells over T cells for CAR therapy

CAR-T

- Autologous Product
  - Production time
  - Cost
  - 1 patient, 1 product
- If allogeneic: GVHD Risk
- Toxicity: cytokine release syndrome; neurotoxicity (50% need ICU care)
- CAR-mediated killing

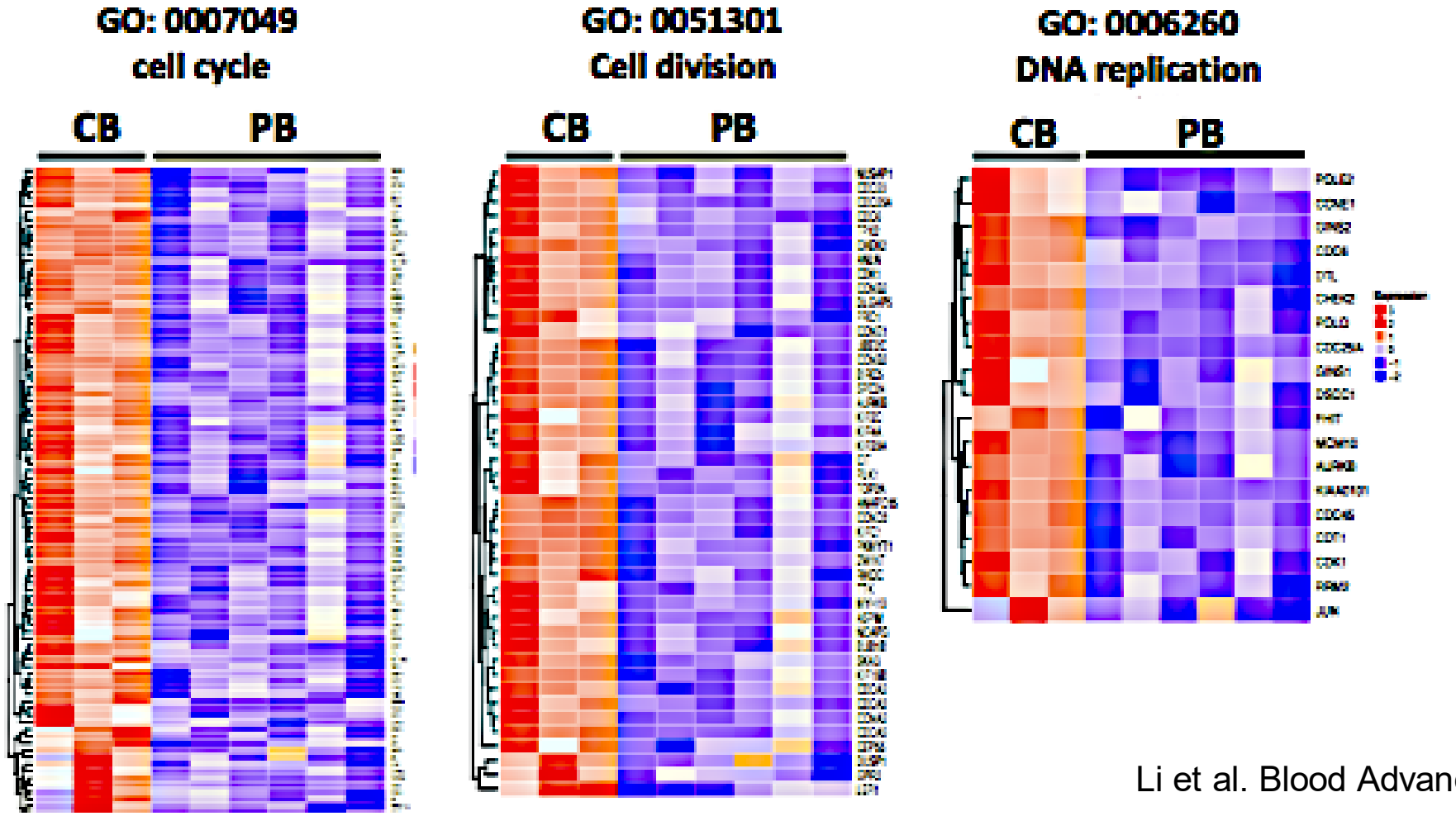
CD19 CAR-NK

- Allogeneic Product
  - “Off the shelf”
  - Potential low cost
  - 1 cord, > 100 doses
- Low/absent GVHD
- CAR + NK Receptor mediated

NK cell immunotherapy for the treatment of cancer

- Improve persistence
- Antigen-specificity
- Logistics: NK cells need to be collected on an individual case basis:
  - From a healthy donor (allogeneic source) – haploidentical donor or **cord blood** (MDACC CB Bank) **– we have treated >50 patients with doses of >10e8/kg CB-NK with no toxicity**
  - Others use NK92 cell line, HSC or iPSCs
  - From the patient (autologous- *less effective*)

Higher expression of genes involved in cell cycle, cell division and DNA replication in cord blood (CB) versus peripheral blood (PB) NK cells



Li et al. Blood Advances 2019; 3 (23)

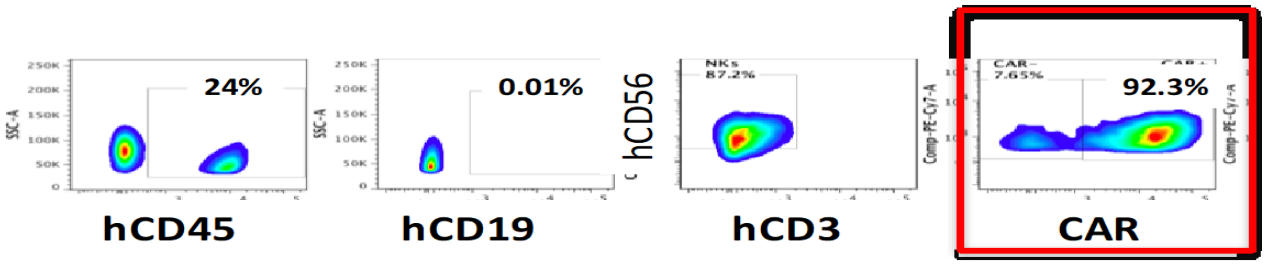
CAR NK cells persist & control Raji tumor in NSG mouse model

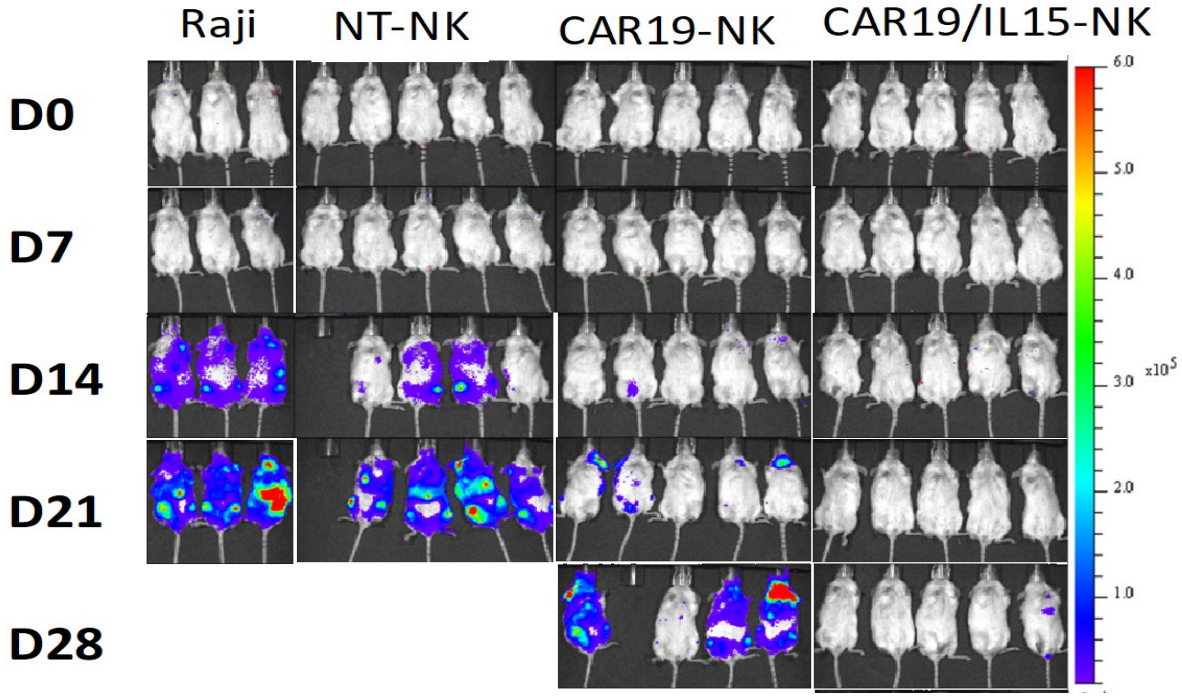
Armored CAR

Pietro Dotti- BCM

Day 70 Post Infusion

Blood

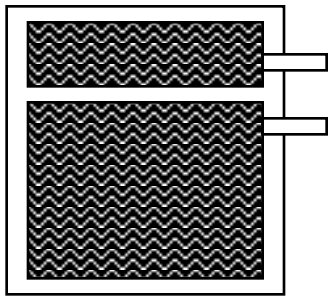




Liu et al. Leukemia 2017

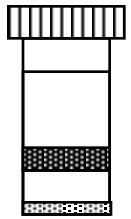
Clinical CAR-NK Transduction & Expansion

Day 0



Frozen cord
Blood unit

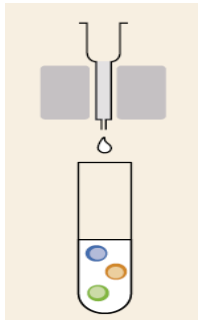
Thaw



Ficoll

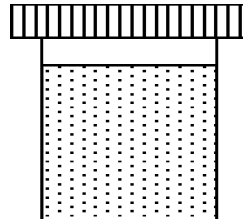
MNC

CD3/14/19 depletion
(CliniMACS)



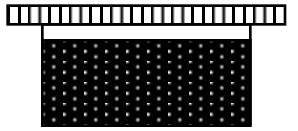
Negatively-selected
NK cells

Culture Flask



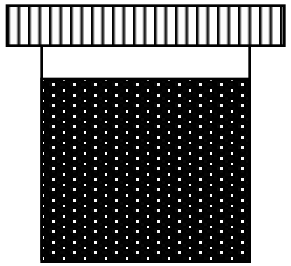
Culture condition:
γ-irradiated K562-based feeder (mbIL21, 41BBL, CD48)
+ IL-2 200u/ml

Day 6



Transduce with retroviral supernatant

Day 9



Culture condition:
γ-irradiated K562-based feeder (mbIL21, 41BBL, CD48)
+ IL-2 200u/ml

Day 15

Flow cytometry CAR
CD56
CD16
CD3

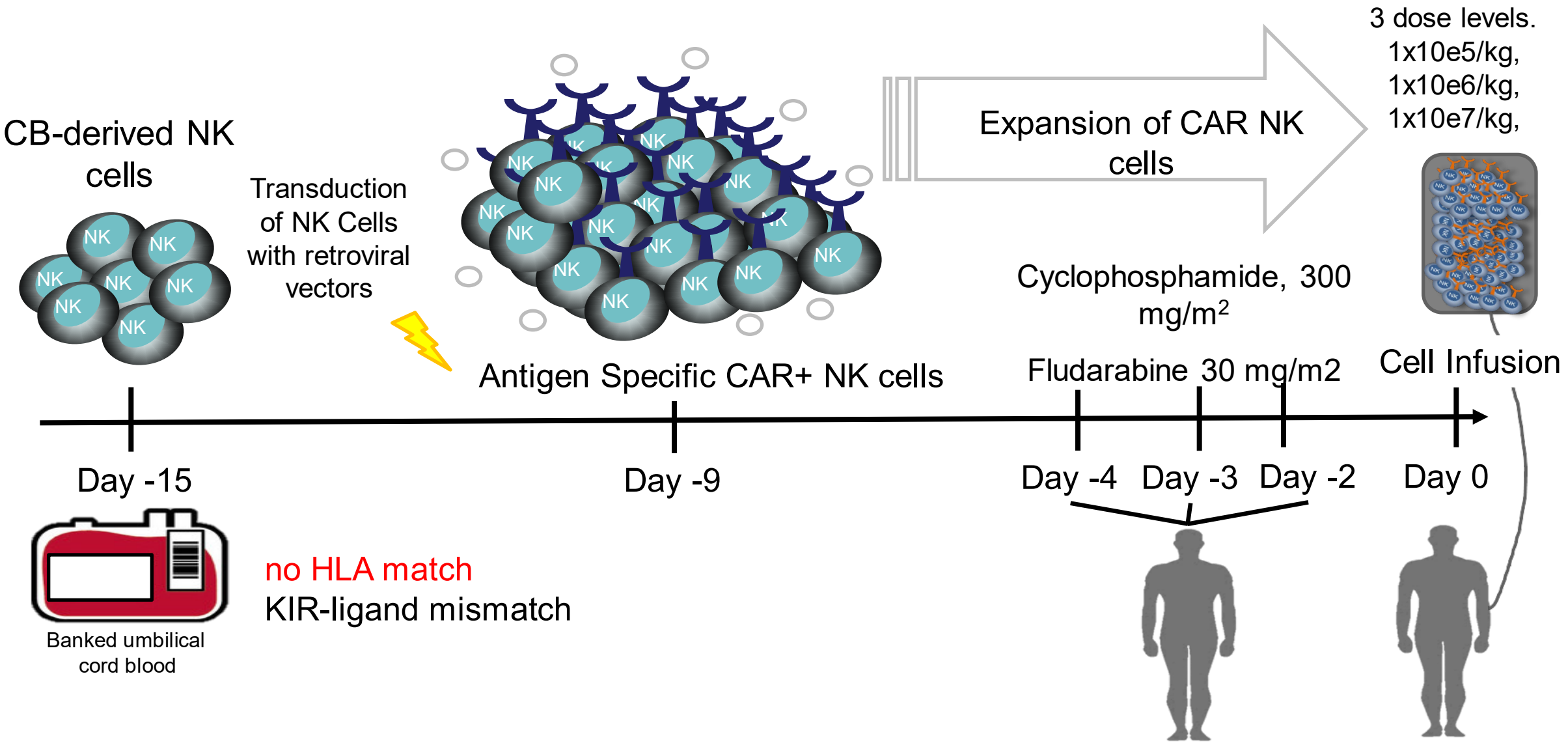
CD19
CD14
CD45

Characteristics of iC9/CAR.19/IL15-transduced CB-NK cells generated from 5 different CB units after 14 days of culture

	Starting Cell Number ($\times 10^6$)	NK Fold Expansion	NK Absolute Count at Day14 ($\times 10^8$)	CAR Transduction Efficiency (%)
>100 doses of CAR NK cells can be generated from one cord blood unit				
CAR-CBNK#3	20	7369.6	1530	64.4
CAR-CBNK#4	20	2514.3	500	47.8
CAR-CBNK#5	20	2221.8	440	67.5
Median	**20**	**2221.8**	**440**	**66.6**

CAR NK Cells in Patients With Relapsed/ Refractory B-lymphoid Malignancies (CLL, NHL, ALL)

PI: Katy Rezvani MD, PhD; MD Anderson Cancer Center



Liu et al. N Engl J Med 2020;382:545-53.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

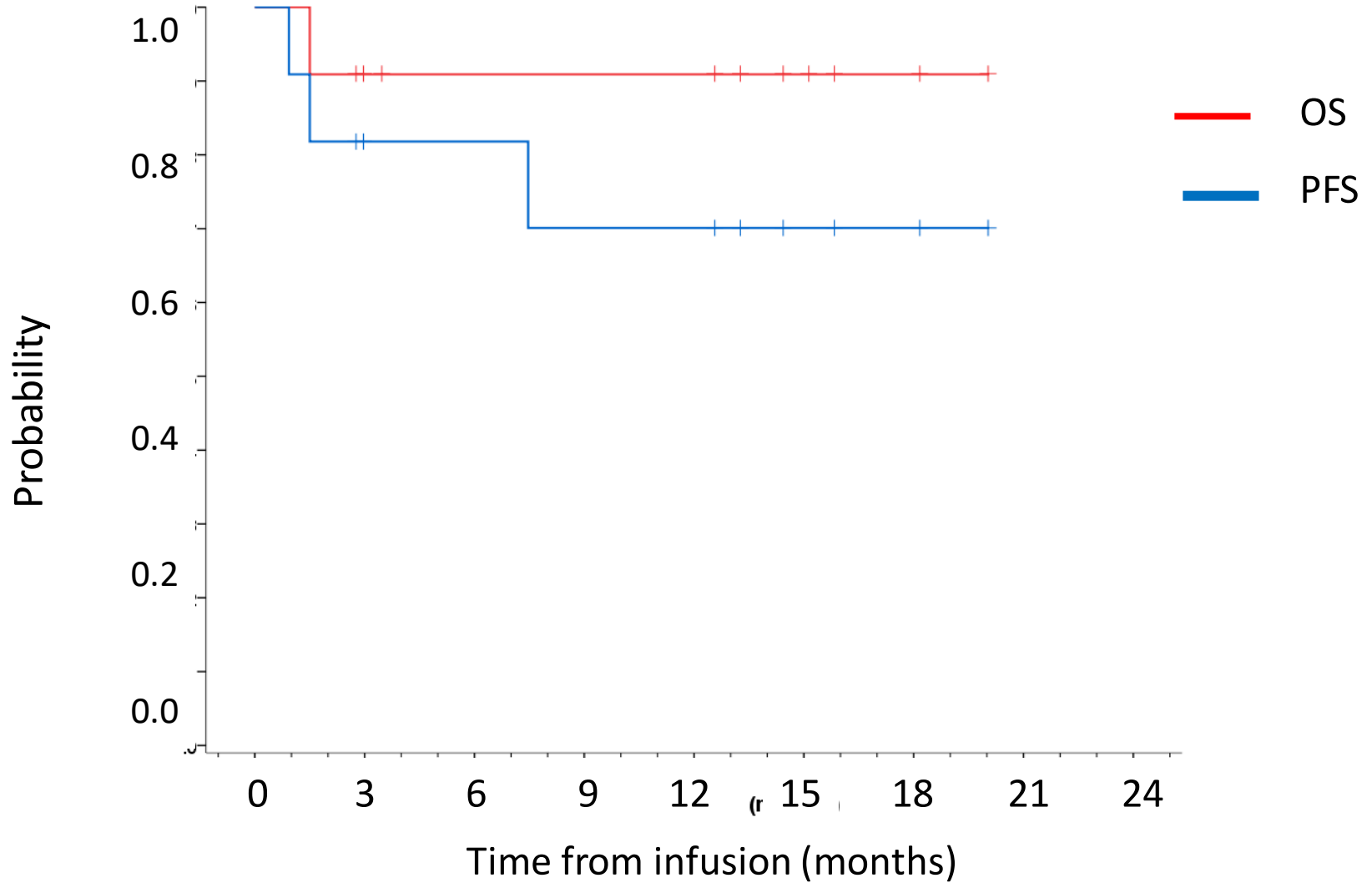
Use of CAR-Transduced Natural Killer Cells in CD19-Positive Lymphoid Tumors

Enli Liu, M.D., David Marin, M.D., Pinaki Banerjee, Ph.D., Homer A. Macapinlac, M.D., Philip Thompson, M.B., B.S., Rafet Basar, M.D., Lucila Nassif Kerbauy, M.D., Bethany Overman, B.S.N., Peter Thall, Ph.D., Mecit Kaplan, M.S., Vandana Nandivada, M.S., Indresh Kaur, Ph.D., Ana Nunez Cortes, M.D., Kai Cao, M.D., May Daher, M.D., Chitra Hosing, M.D., Evan N. Cohen, Ph.D., Partow Kebriaei, M.D., Rohtesh Mehta, M.D., Sattva Neelapu, M.D., Yago Nieto, M.D., Ph.D., Michael Wang, M.D., William Wierda, M.D., Ph.D., Michael Keating, M.D., Richard Champlin, M.D., Elizabeth J. Shpall, M.D., and Katayoun Rezvani, M.D., Ph.D.

N Engl J Med 2020;382:545-53. February 6, 2020

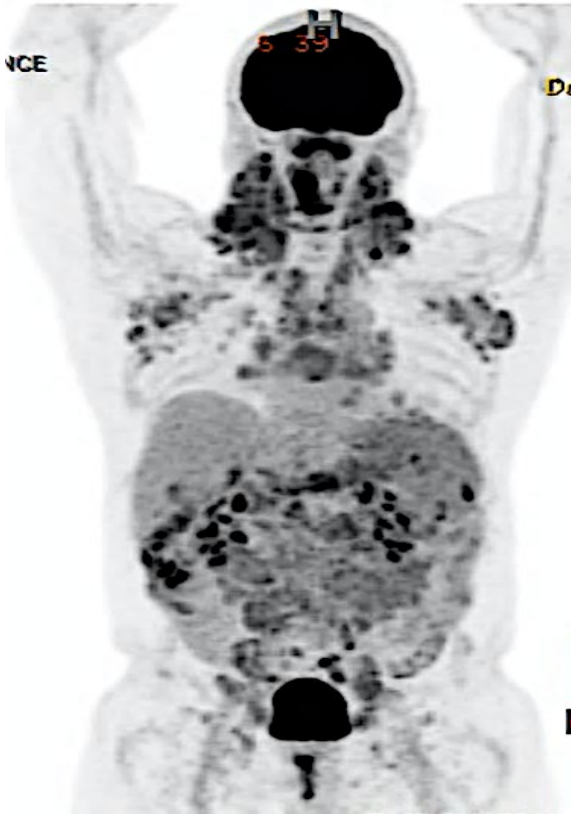
Dose level	Diagnosis	Age/Sex	Cytogenetics	Lines of treatment
Dose level 1 1 x 10e5 CAR NK/kg	Relapsed transformed double-hit DLBCL	47/M	Double hit (C-MYC and BCL-2)	3 (including ASCT)
	Refractory DLBCL	59/M	complex cytogenetics	7
	CLL	59/F	17p del	4 (including ibrutinib and venetoclax)
Dose level 2 1 x 10e6 CAR NK/kg	CLL	56/M	17p del	4 (including ibrutinib)
	CLL/Richter's transformation	61/M	Trisomy 21, unmutated	5 (including ibrutinib) Progressive disease on HyperCVAD prior to admission
	CLL/Richter's transformation	60/F	17p del	5 (including ibrutinib and venetoclax)
	CLL	66/F	del ATM +SPEN, +SF3B1,	4 (including ibrutinib)
Dose level 3 1 x 10e7 CAR NK/kg	Refractory DLBCL	64/M	complex cytogenetics	11 (including ASCT)
	Relapsed transformed double-hit DLBCL	70/M	complex cytogenetics	4 (including ASCT)
	Relapsed Follicular lymphoma	61/F	t14;18	4 (including ASCT)
	Relapsed Follicular lymphoma	60/M	14;18	4 (Progressed before ASCT).

Clinical Response to NK-CAR therapy

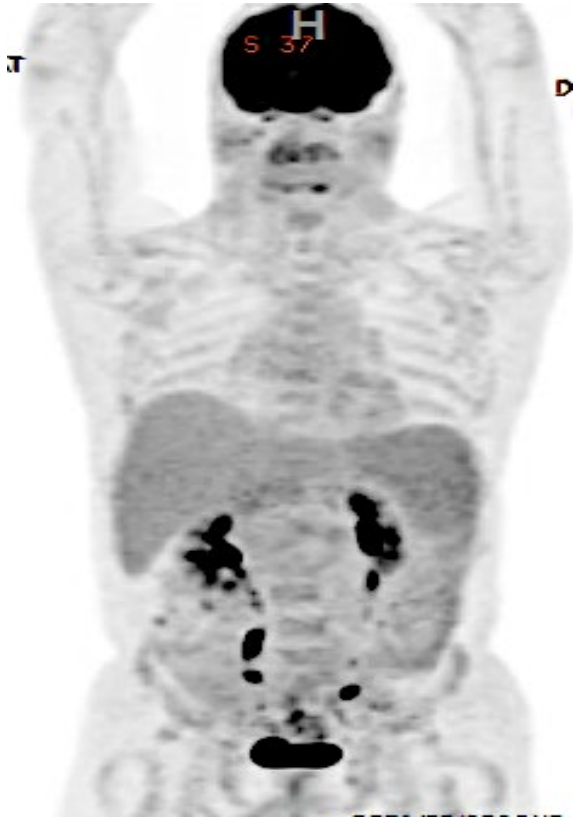


Patient 5 Achieved Complete Response in Richter's (1 x 10e6/kg)

Pre-admission



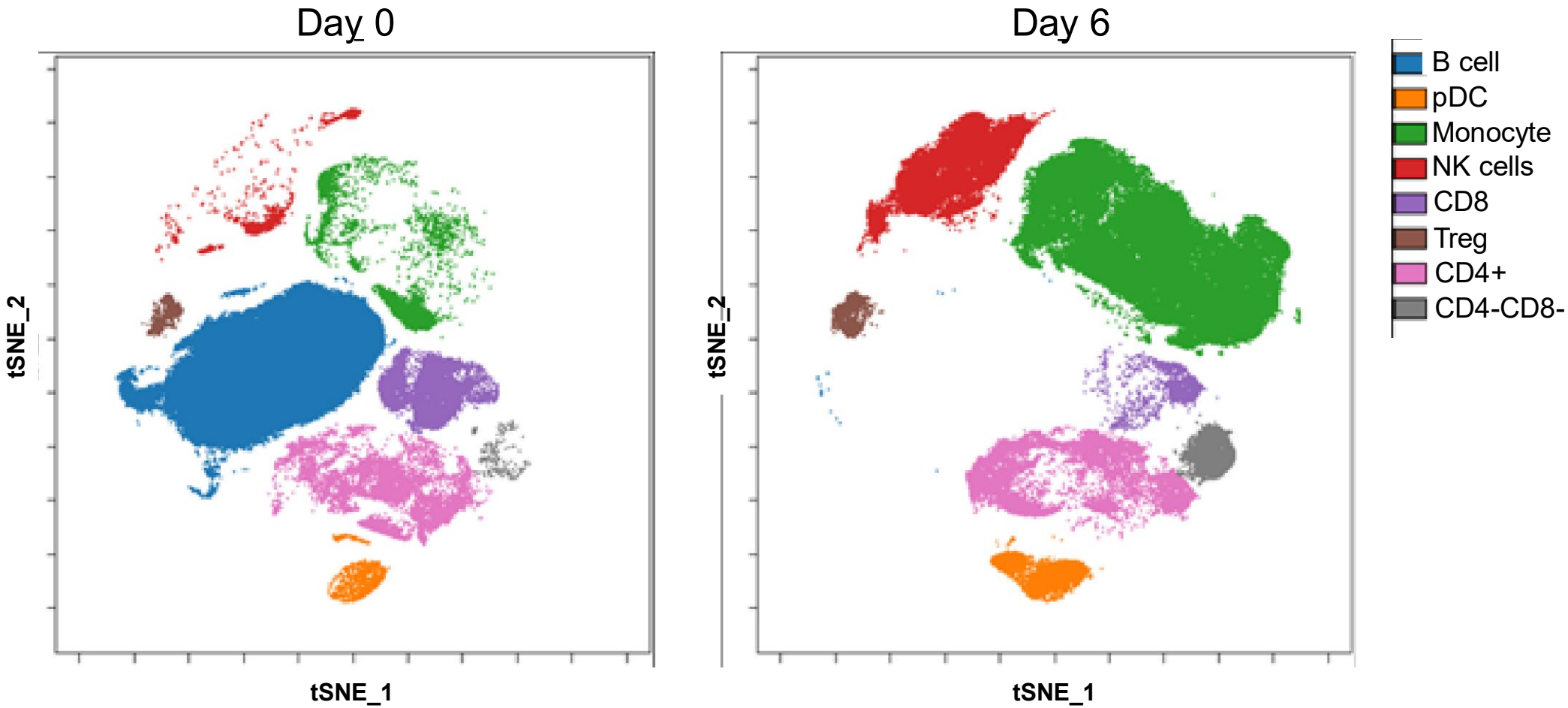
Day 30 post CAR NK



Liu et al. N Engl J Med 2020;382:545-53.

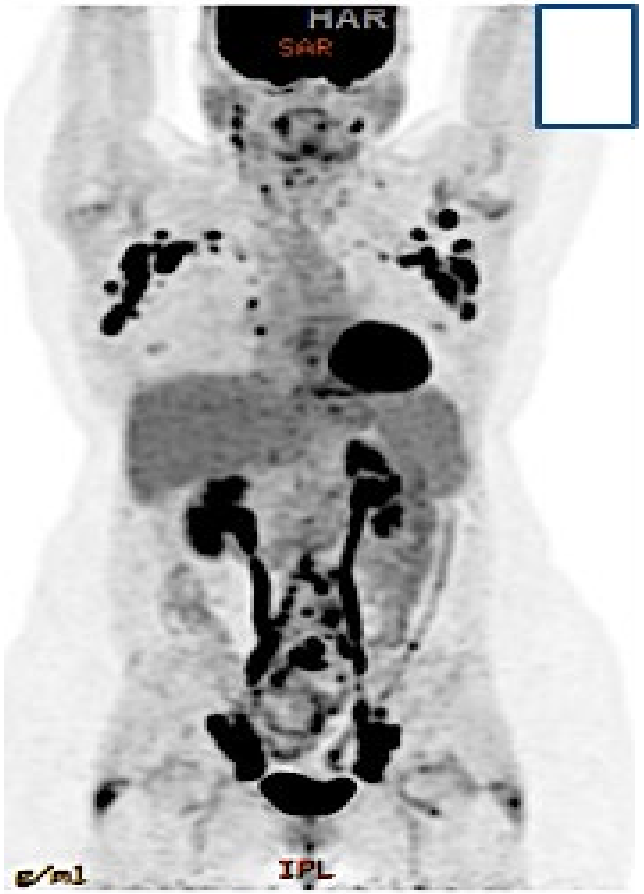
Selective depletion of B cells after CAR NK infusion

Rafet Basar

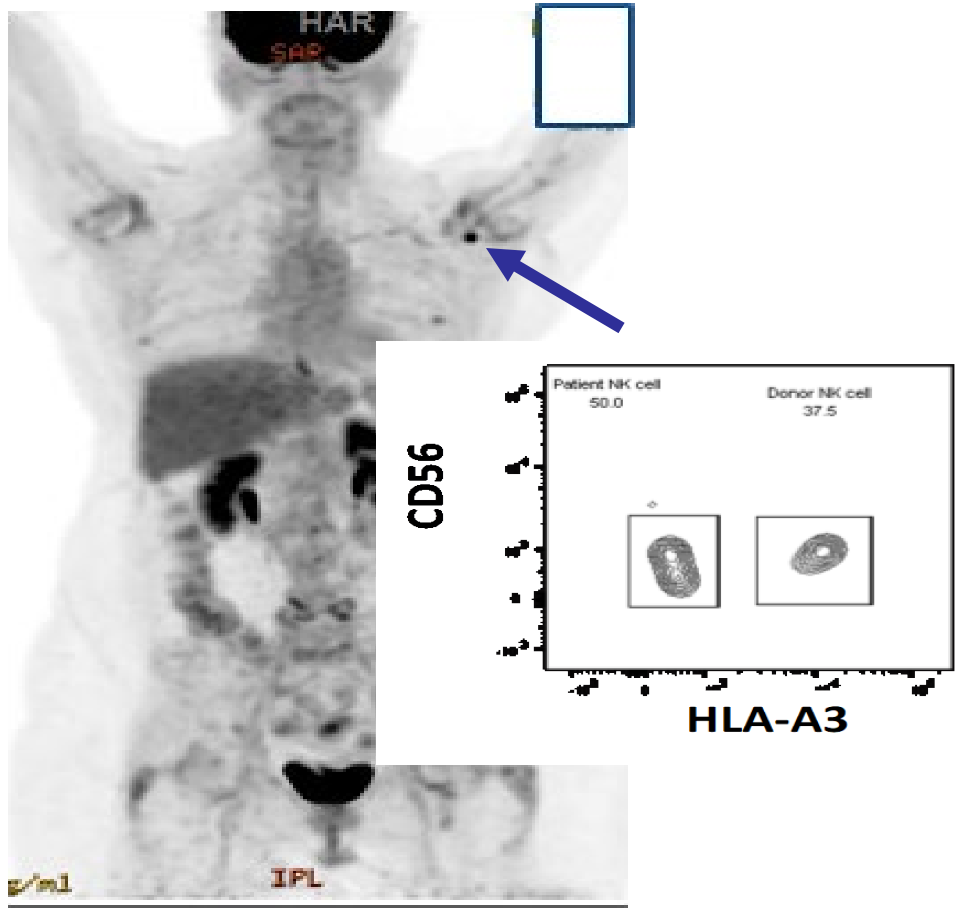


Patient #6- achieved CR. CAR NK cell traffic to sites of disease

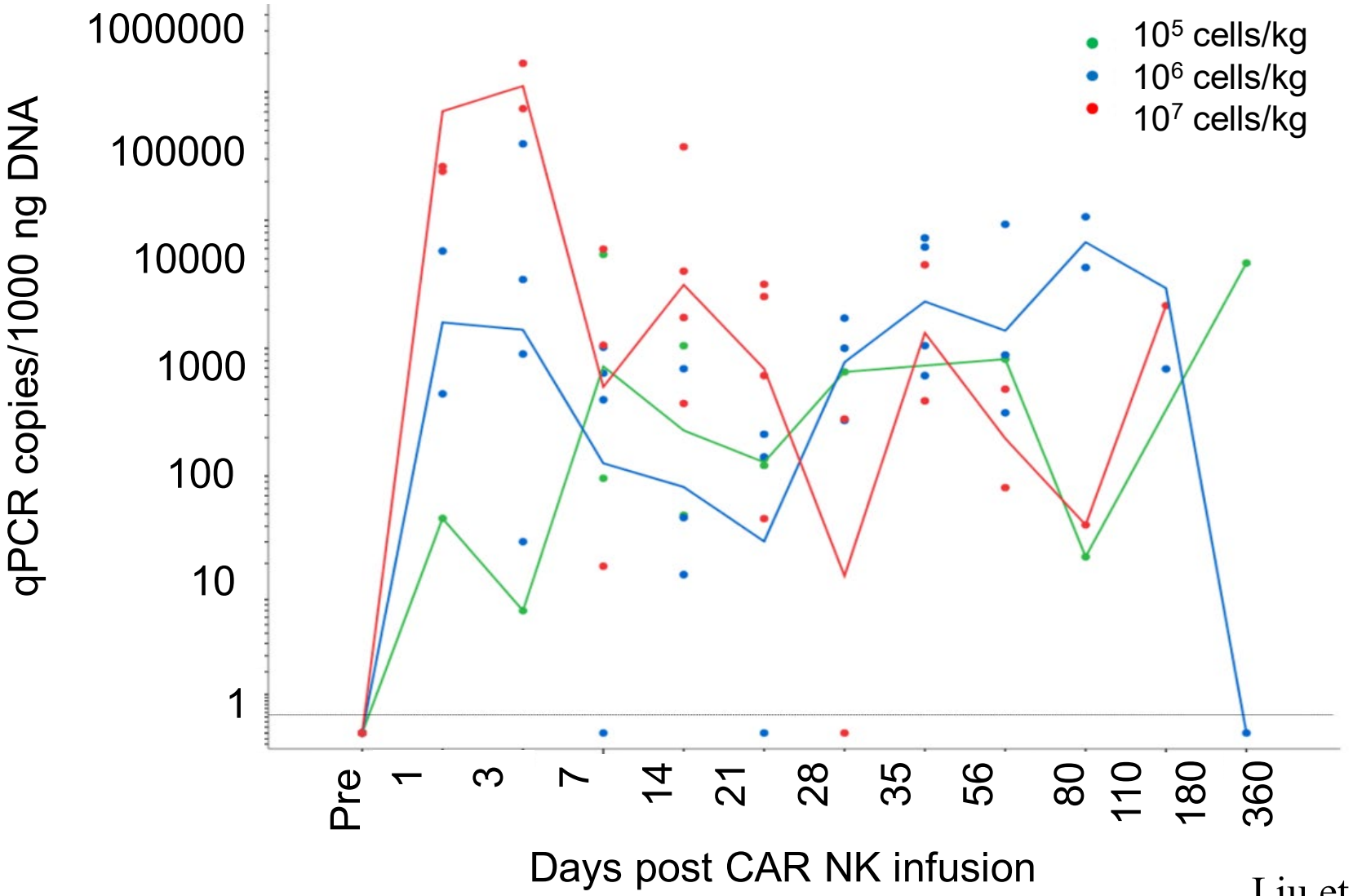
Pre-admission



Day 30 post CAR NK

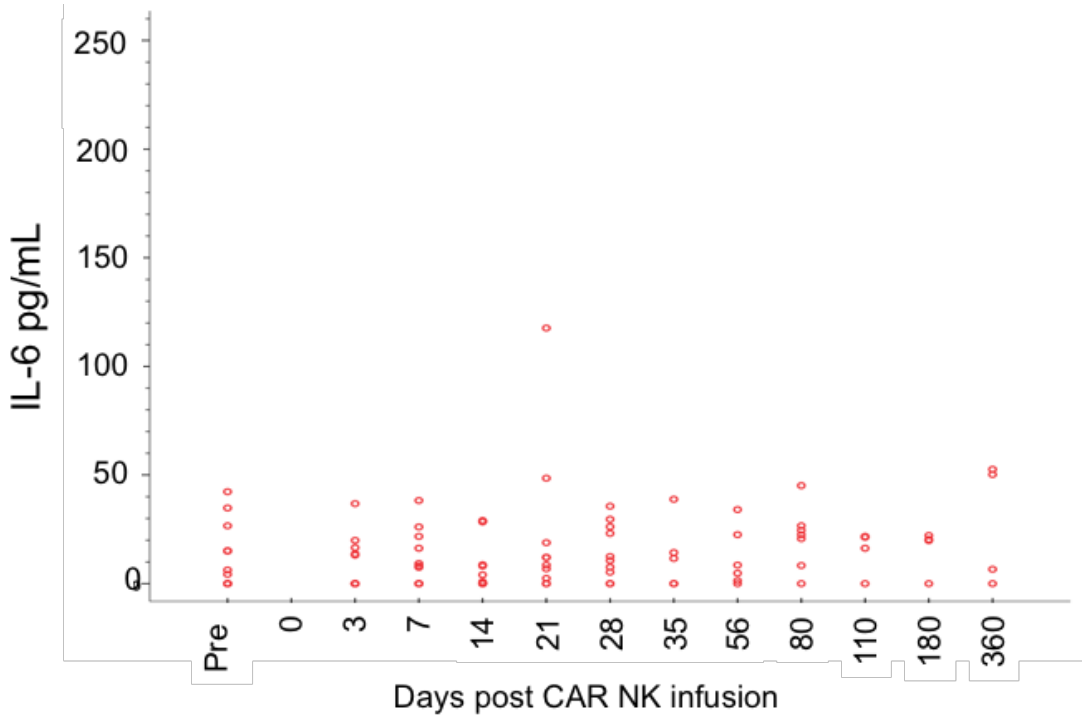


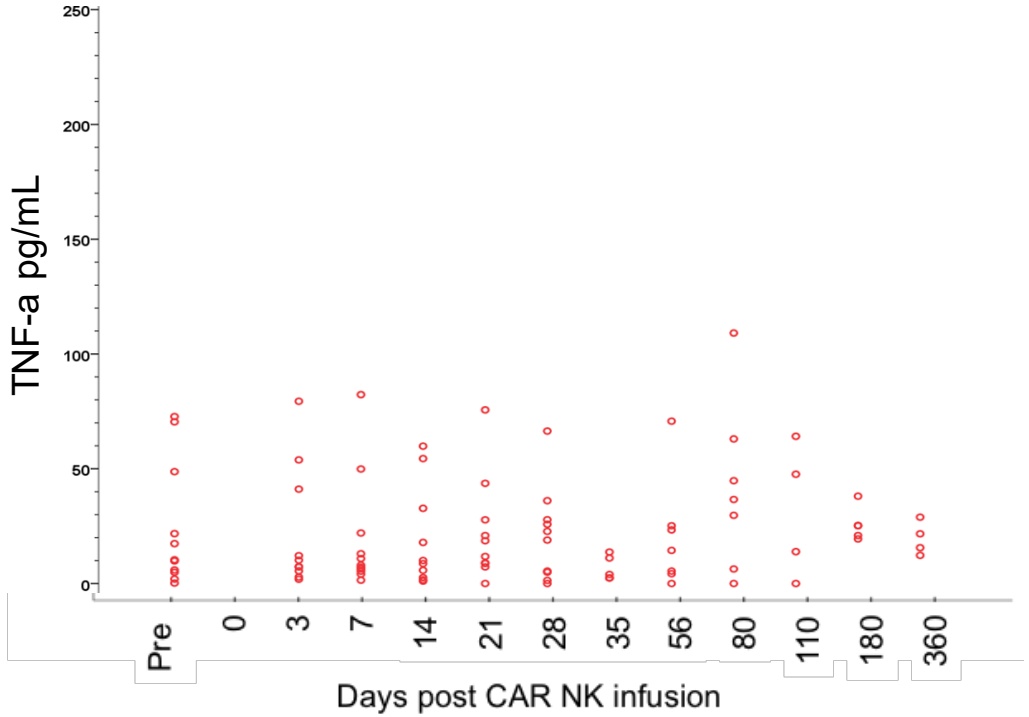
CAR NK cells are detectable up to 12 months post infusion



Liu et al. N Engl J Med 2020;382:545-53.

The cytokine profile after CAR NK cell therapy does not support CRS





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Summary

- CB-NK cells can be engineered to express a CAR to redirect their specificity and a cytokine to enhance their *in vivo* proliferation and persistence

- A first-in-human clinical trial of CAR19/IL15 transduced cord blood NK cells resulted in responses in 8/11 patients with no CRS or neurotoxicity

- CB CAR NK against other targets under development

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Nadima Uprety

Patients and their families

MD Anderson CLL Moonshot
MD Anderson Lymphoma Moc

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