9th POSTGRADUATE
Lymphoma
Conference

AFM13 combined with cord blood-derived NK cells

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Hotel Brunelleschi

President:
P.L. Zinzani

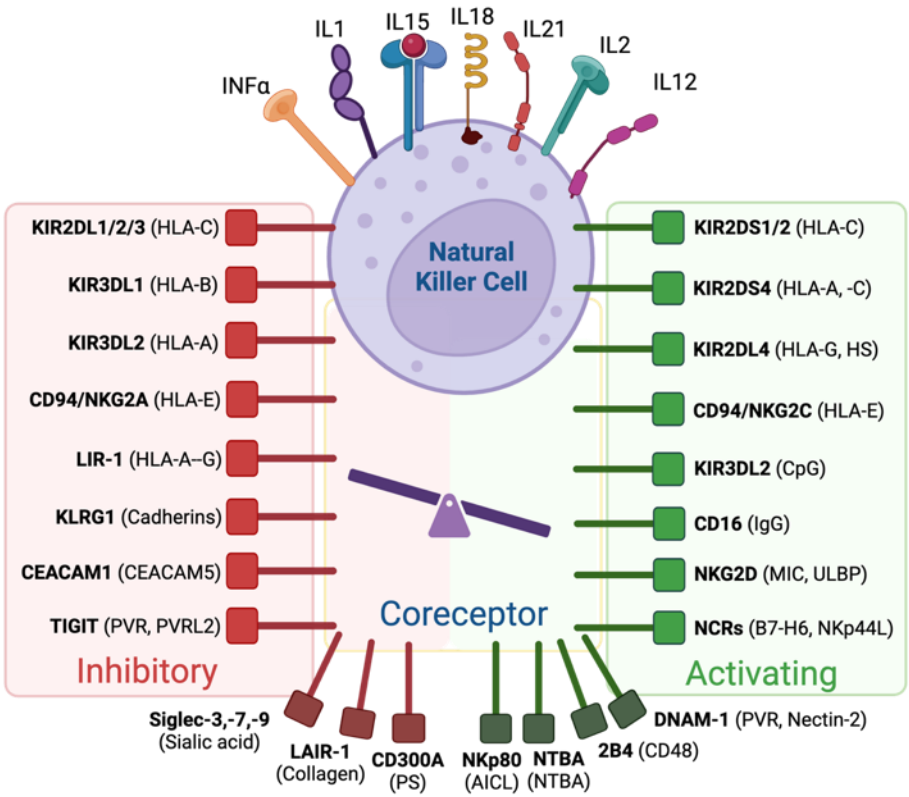
Disclosures

Disclosures of Silvia Tiberti

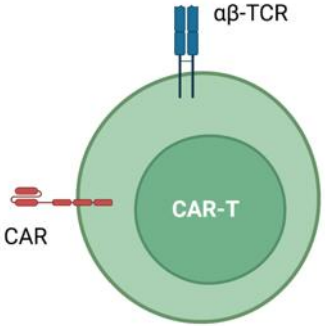
- License agreement and research agreement:
  - Takeda to develop CB-CAR NK cells for the treatment of B-cell malignancies and other cancers, which creates an institutional conflict of interest under MD Anderson policy
  - Affimed

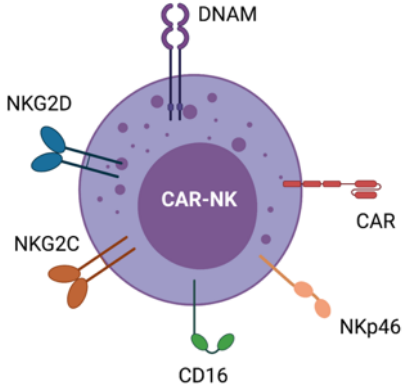
What are Natural Killer (NK) cells?

- 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



Advantages of NK cells over T cells for CAR therapy





Allogeneic: GVHD

Killing: CAR mediated

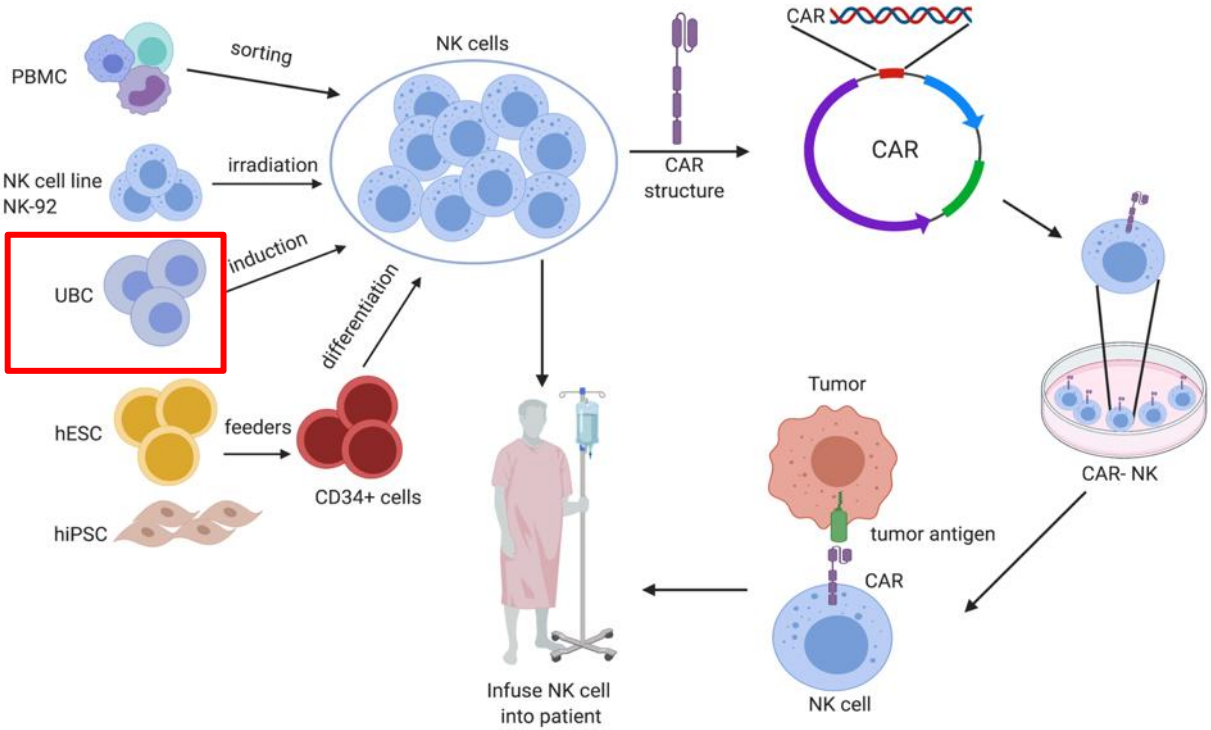
Toxicity: CRS, ICANS

Allogeneic: no GVHD-->off the shelf, lower cost

Killing: CAR mediated + innate receptors

Safety: no CRS, no ICANS

Allogeneic sources of NK cells for CAR engineering



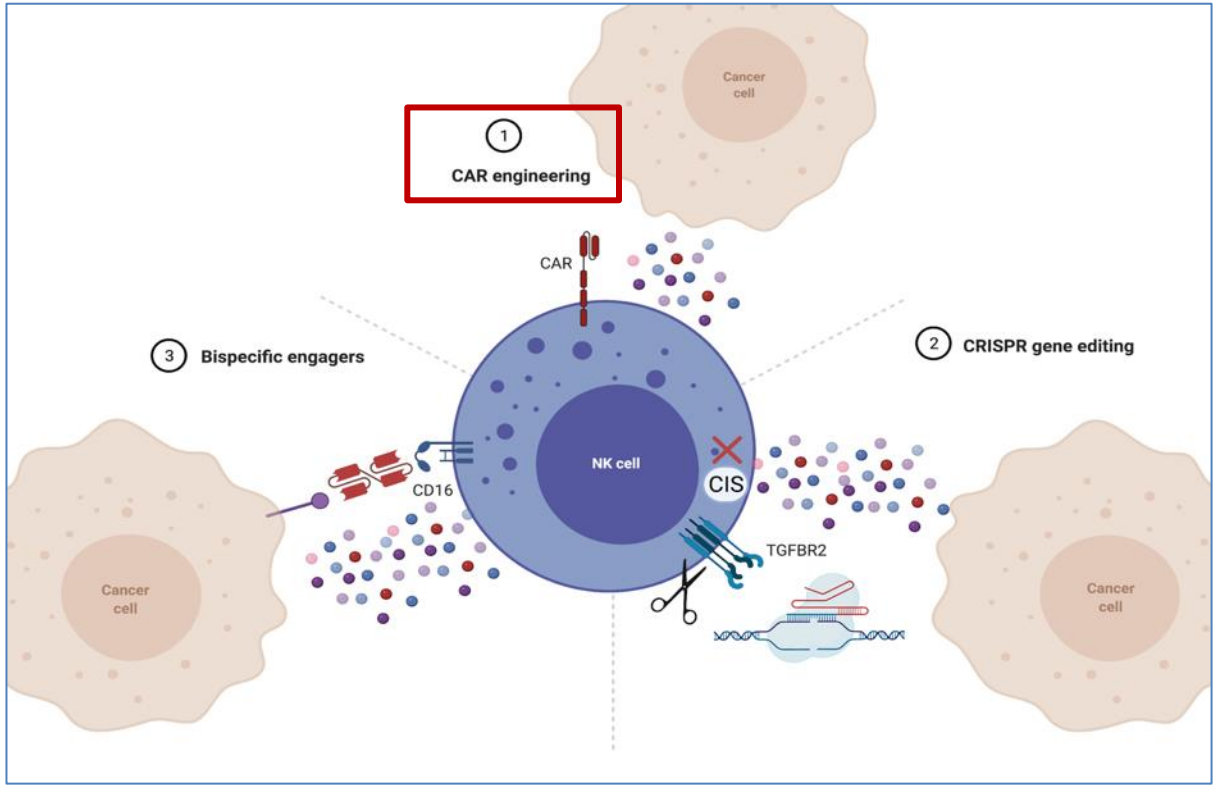
MD Anderson Cord Blood Bank

(established and lead by Dr. EJ Shpall since 2005)

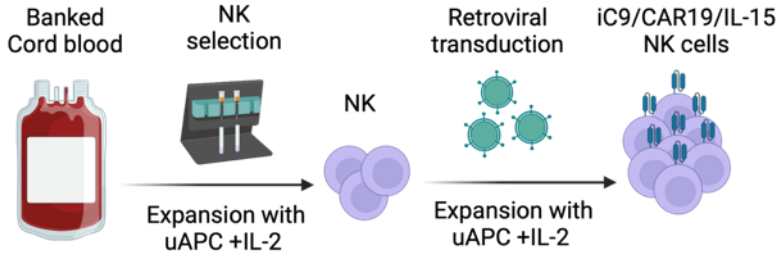
- No. Units Collected: 103,980
- No. Units Stored: 34,119
- No. Units Transplanted: 2,109
- No. Units for Research: 18,768
- Partners:
  - The Woman's Hospital of Texas
  - BCM/Harris Health Ben Taub Hospital
  - Memorial Hermann Medical Center
  - Memorial Hermann Southwest
  - Memorial Hermann Memorial City
  - Memorial Hermann Woodlands
  - St. Joseph Medical Center
  - St. John's and Providence (Detroit)

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Strategies to enhance adoptive NK cell antitumor potential



First In-human Trial of CAR19/IL15 CB-NK Cells in Lymphoid Malignancies

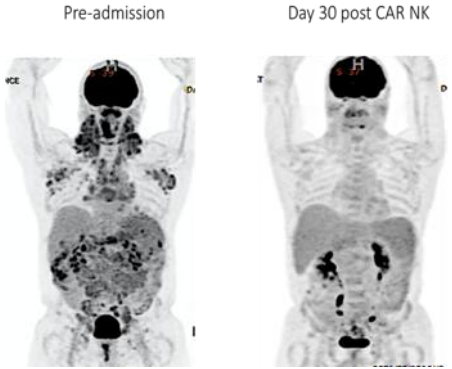


The NEW ENGLAND JOURNAL of MEDICINE

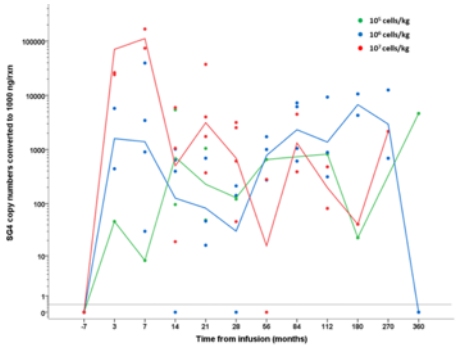
ORIGINAL ARTICLE

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.

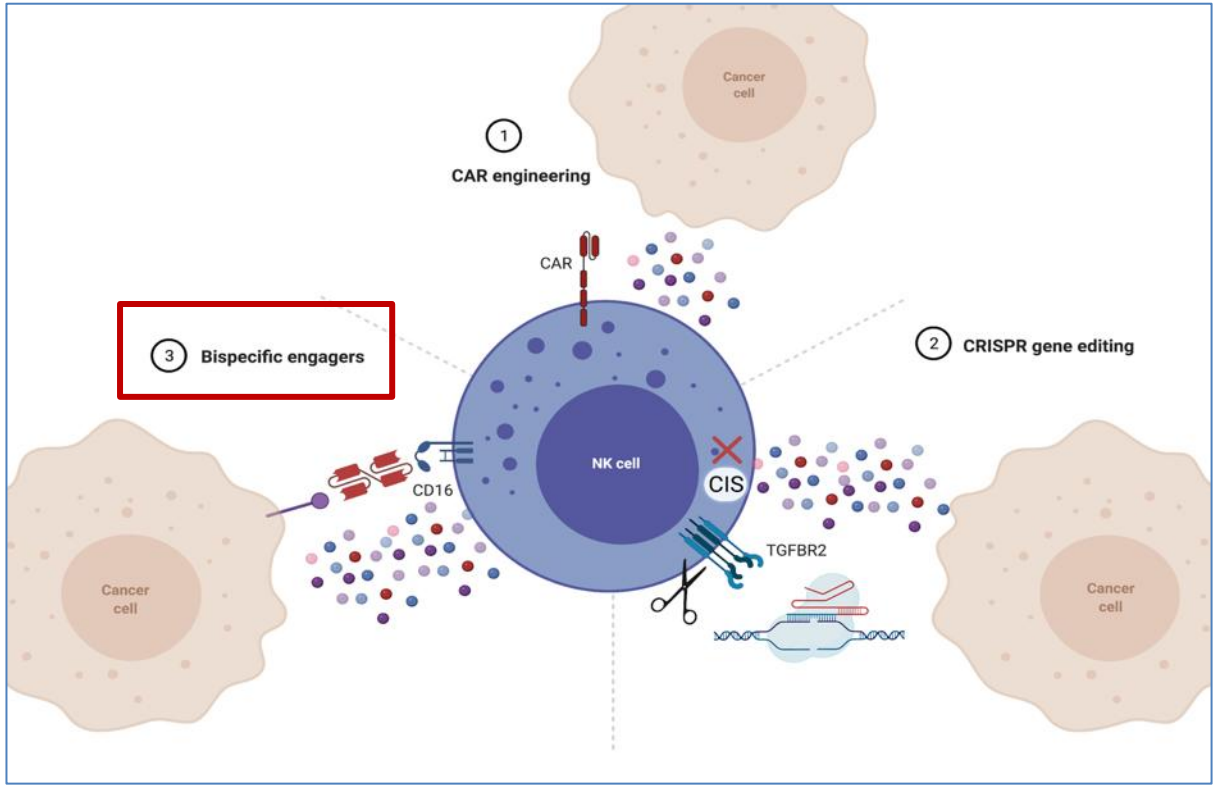


7/11 CR, No CRS, No neurotoxicity, and No GvHD



CAR NK cells are detectable > 12 months post infusion

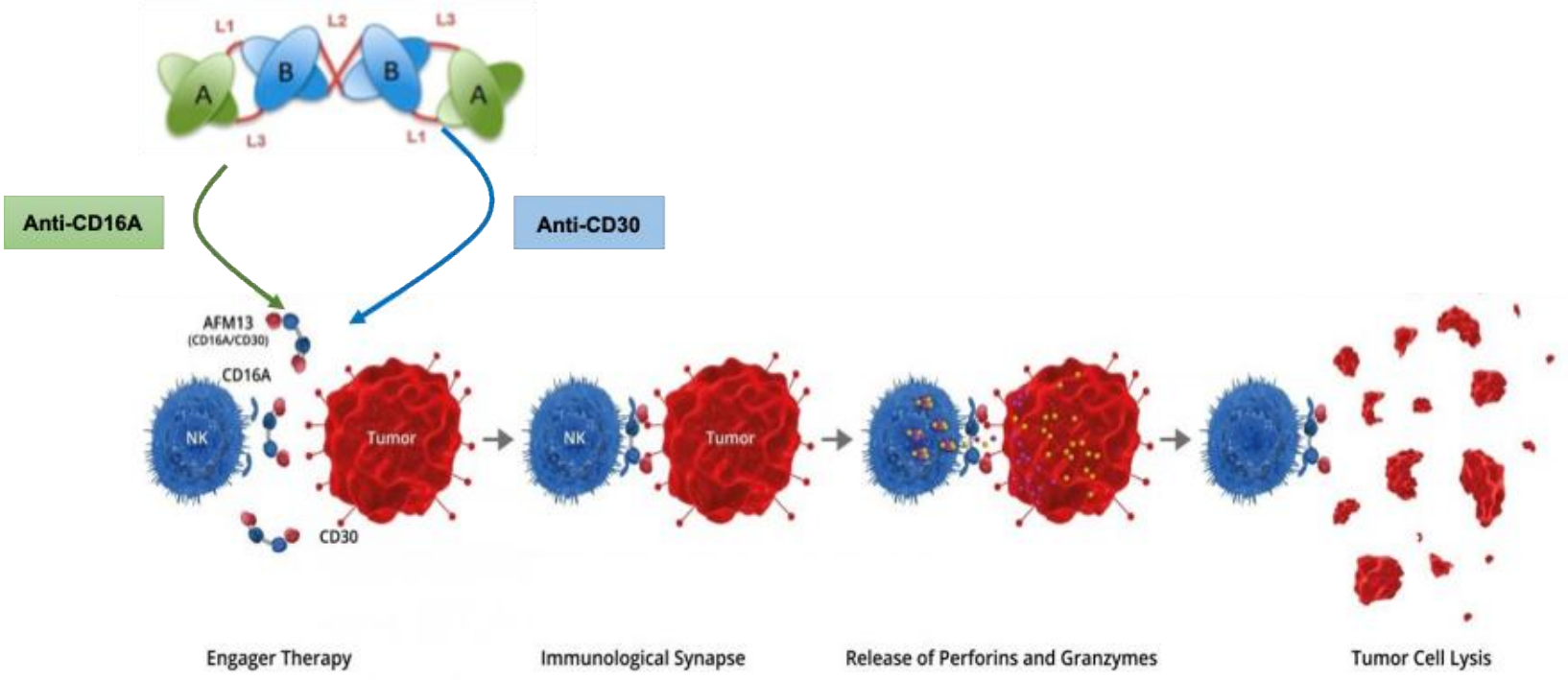
Strategies to enhance adoptive NK cell antitumor potential



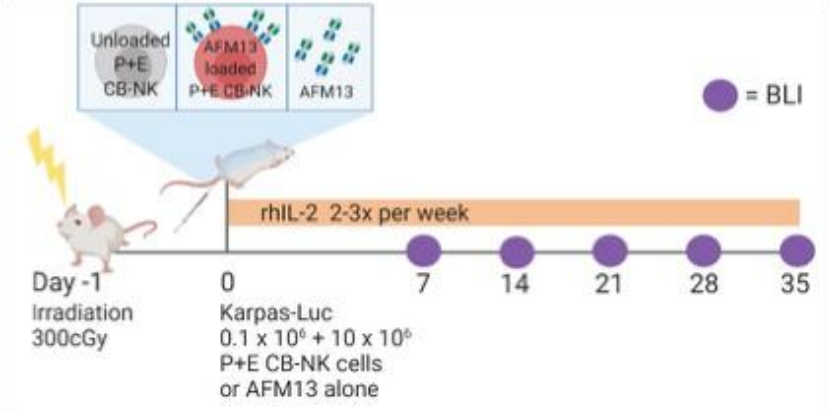
Potential of NK Cell Therapy in Hodgkin Lymphoma

- CD30 is universally expressed in classical Hodgkin and in some NHL
- AFM13 is a tetravalent bispecific antibody construct with affinity for CD30 (lymphoma cells) and CD16A (NK cells)
  - Modest activity against Hodgkin in monotherapy
- Autologous NK cells of lymphoma patients are dysfunctional
- Adoptive allogeneic NK cell immunotherapy is an active area of research
  - *Nontargeted* NK cells have shown limited clinical benefit
  - In contrast, *targeted* CD19.CAR NK are markedly active and persistent in patients with B-NHL

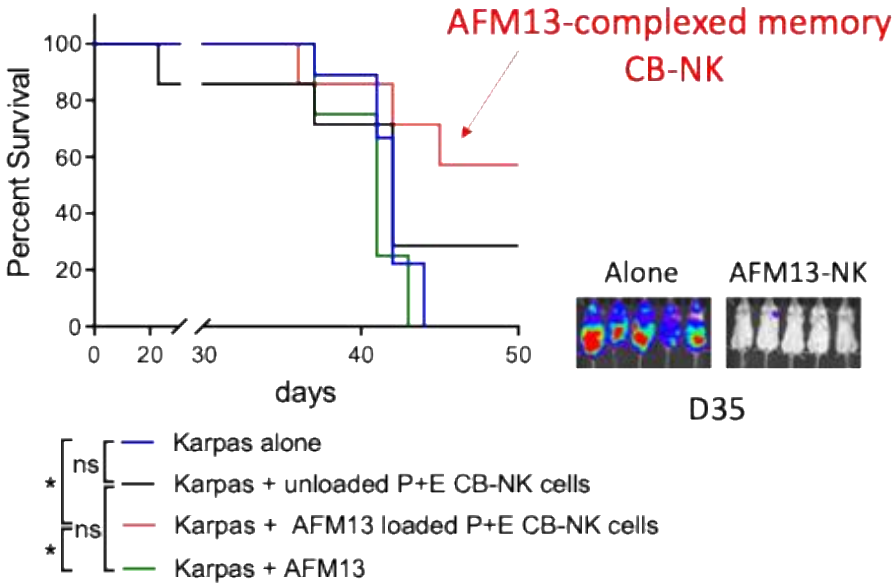
Pre-complexing allogeneic NK cells with bispecific innate cell engager AFM13 increases their cytotoxic capacity



Pre-complexing cord blood-derived NK cells with AFM13 prior to infusion facilitates CAR-like responses in a CD30+ T-NHL mouse xenograft

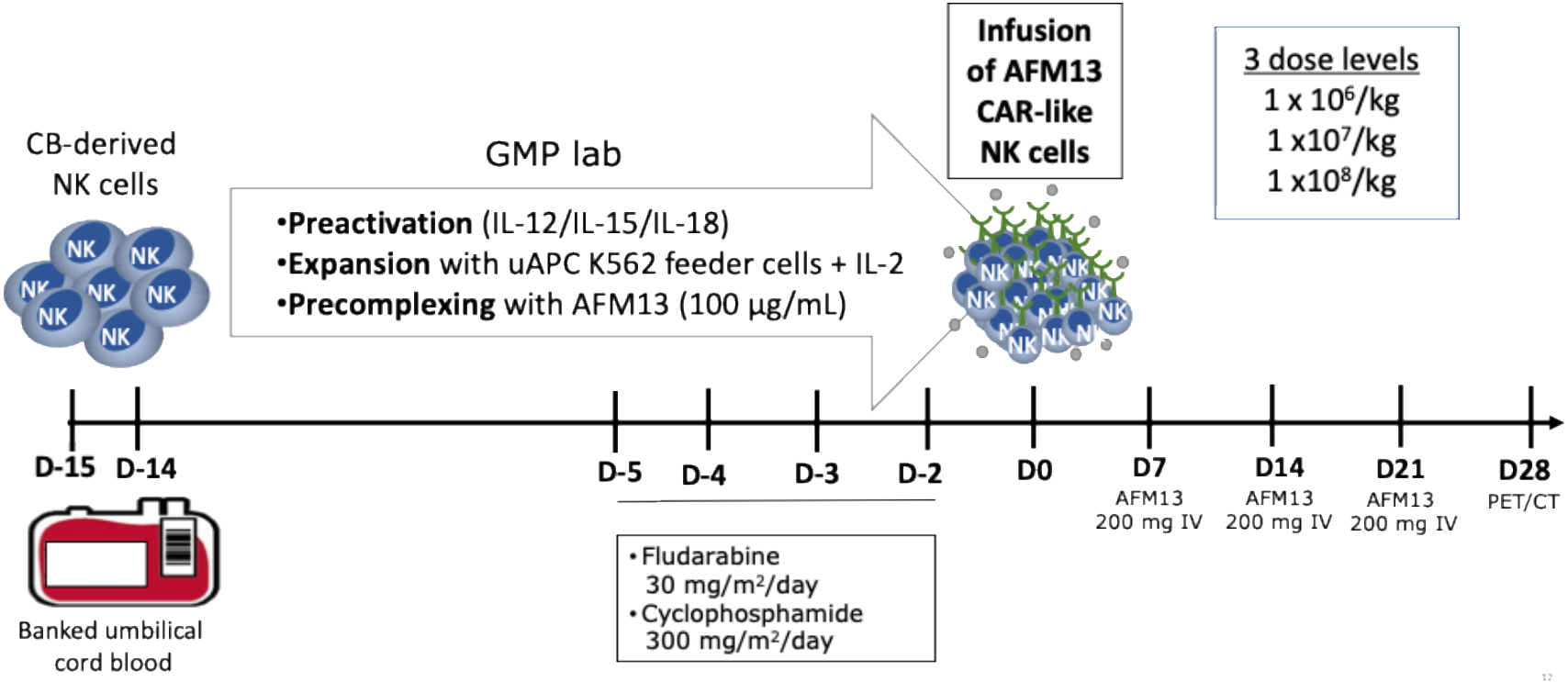


- Persistence of NK cells enhanced by pre-activation with IL-12/IL-15/IL-18 cytokines to induce a **memory phenotype**
- NK cells expanded by >1,000 fold in the presence of uAPC (K562 feeder cells)



Kerbauy et al, Clin Cancer Res 2021

AFM13-complexed CB-Derived NK cells for Refractory/Relapsed CD30^{+}Lymphoma (NCT04074746)



Study Endpoints

Primary Endpoint

- To establish the safety and recommended phase 2 dose (RP2D) of CB NK cells

- Secondary Endpoints:
- To assess the overall response, CR and PR rates
- To evaluate EFS and OS
- To quantify persistence of infused donor AFM13-NK cells in the recipient
- To study the activation phenotype of donor NK cells

Patient Population

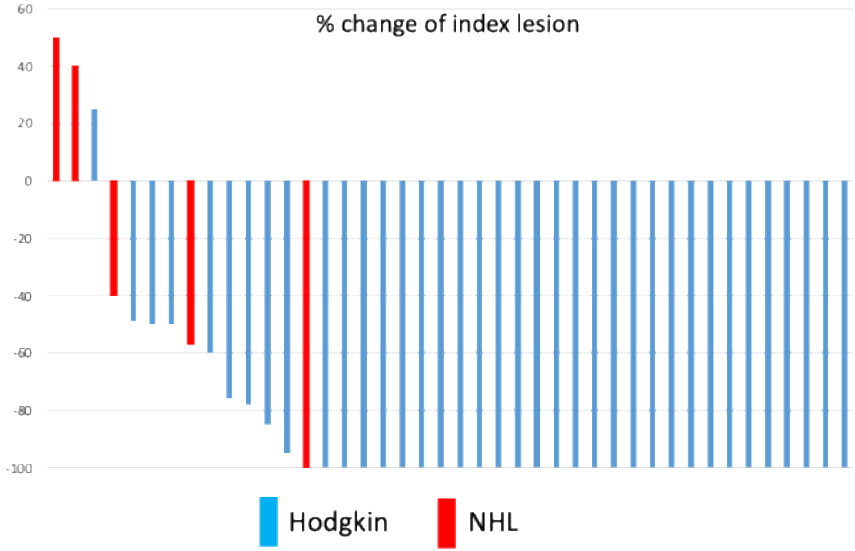
Baseline characteristics	N=42
Age, median (range)	43 (20–75)
Gender (male/female)	27 / 15
Diagnosis (Hodgkin / NHL)	37 / 5
No. prior lines therapy, median (range)	7 (1–14)
Prior brentuximab vedotin	42
Prior anti-PD-1	39
Prior SCT (autologous / allogeneic / both)	25 (15 / 4 / 6)
Prior CD30.CAR-T	4

Safety

1. No cases of cytokine release syndrome (CRS), neurotoxicity (ICANS) or GVHD
2. Infusion-related reactions were infrequent:
   - 27 (1 G3, 21 G2) in 349 infusions of AFM13 alone (7.7%)
   - 1 G2 in 117 infusions of AFM13-NK cells (0.8%)
3. Moderate myelotoxicity of lymphodepleting FluCy:
   - Neutropenia:
     - 42% pts G4, 31% G3 after cycles 1 & 2
     - 58% pts G4, 16% G3 after cycles 3 & 4
     - 1 case of neutropenic fever (1%)
   - Thrombocytopenia:
     - 16% pts G4, 8% G3 after cycles 1 & 2
     - 41% pts G4, 12% G3 after cycles 3 & 4
     - No cases of bleeding
4. No difference in toxicities between dose levels
   - No DLT was encountered
   - Dose level 3 (10^8 NK/Kg) was established as the RP2D

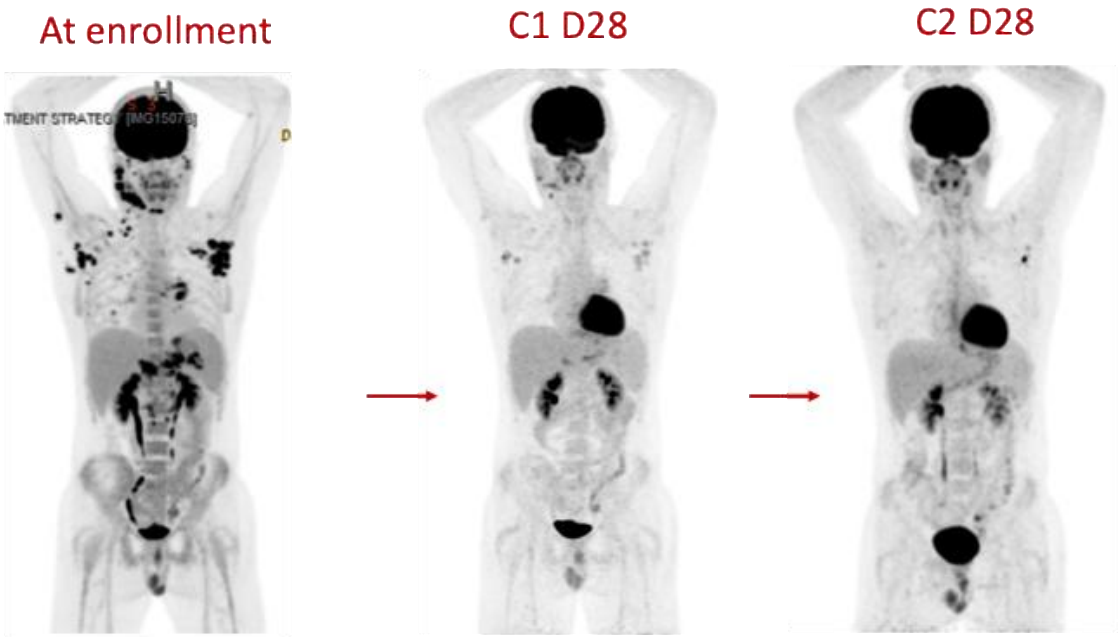
Antitumor Activity

- 39/42 responses (ORR 93%, 67% CR)
- Among 36 patients treated at the RP2D:
  - **94% ORR**
  - **72% CR**
- Among 32 cHL patients treated at the RP2D:
  - **97% ORR**
  - **78% CR**
- 10 patients in PR after C1 converted to a CR after C2
- All 4 patients who had previously experienced PD with CAR-T had a CR
- 7 patients had a CR consolidated with a SCT
  - 6 of them remain in CR at >1 year

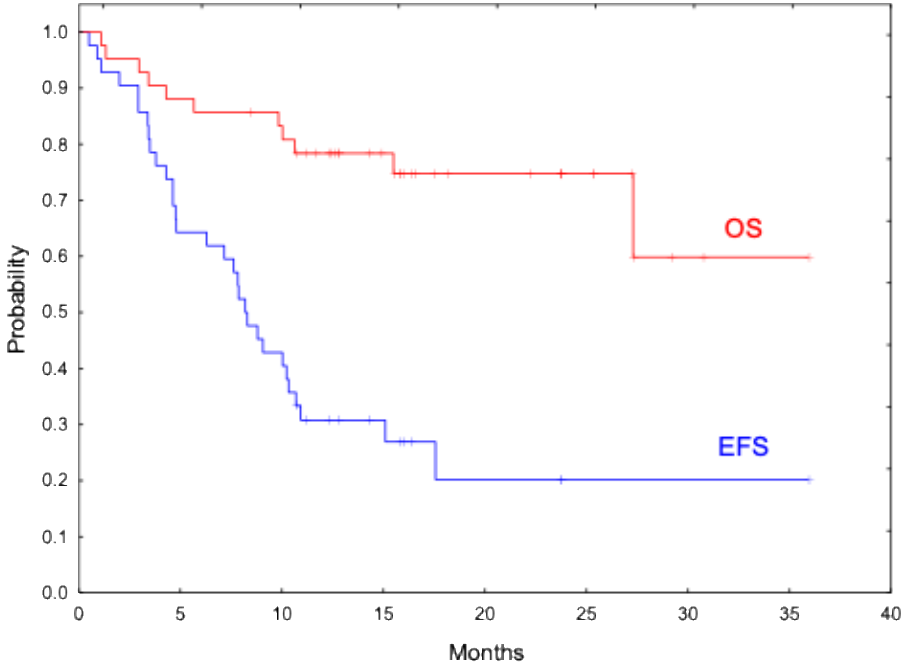


Case in point

- 37 year/old male, highly refractory Hodgkin
- 10 prior lines of therapy, including ABVD, GDP, ICE, HDC/ASCT, pembrolizumab, bendamustine-BV, BV/nivolumab, BV/everolimus and CD30.CAR-T
- B symptoms at enrollment
- Treated at dose level 3 x 2 cycles



Outcomes at median f/u of 16 (8-36) months

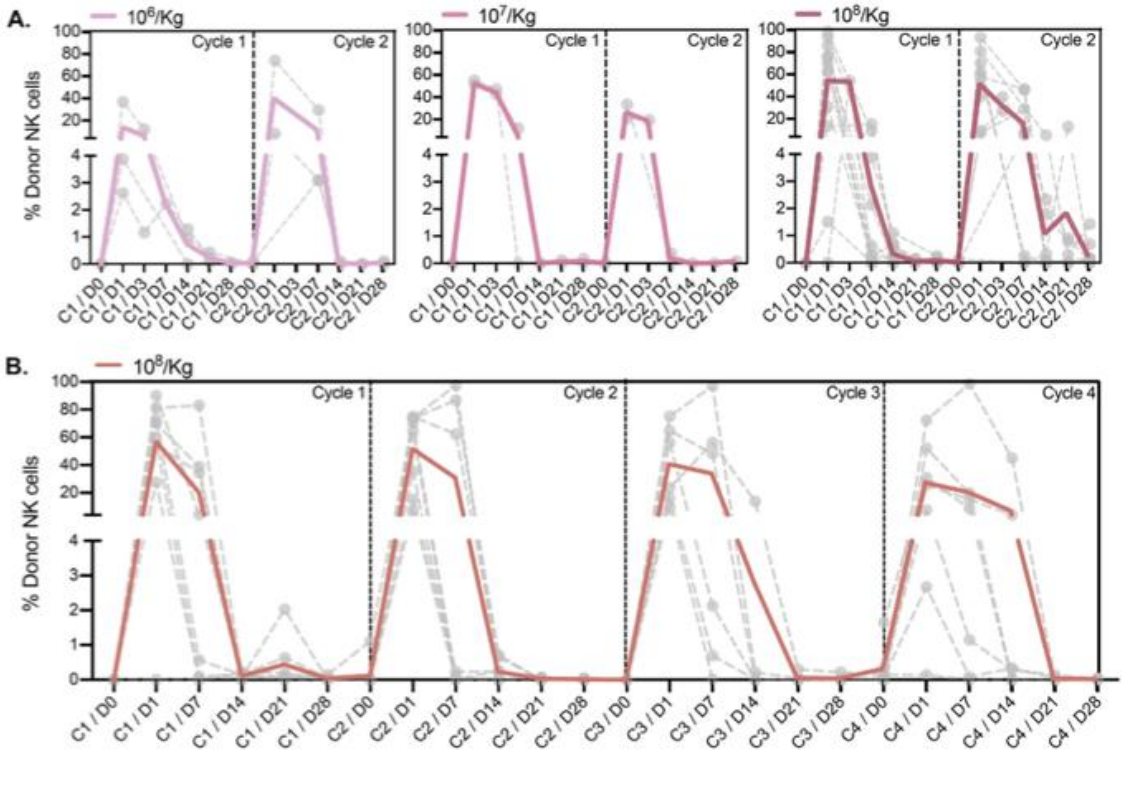


	Patients treated at RP2D			
	Overall (N=36)		Hodgkin (N=32)	
	2 cycles (N=13)	4 cycles (N=23)	2 cycles (N=12)	4 cycles (N=20)
Median EFS	8 months	10 months	8 months	10 months
At 6 months	62%	70%	67%	68%
At 12 months	31%	29%	33%	27%
Median OS	NR	NR	NR	NR
At 6 months	85%	87%	92%	85%
At 12 months	85%	85%	92%	82%

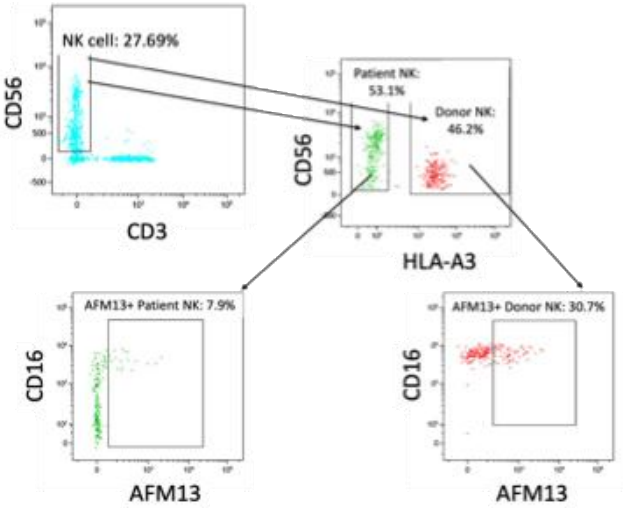
Blood levels of donor NK cells

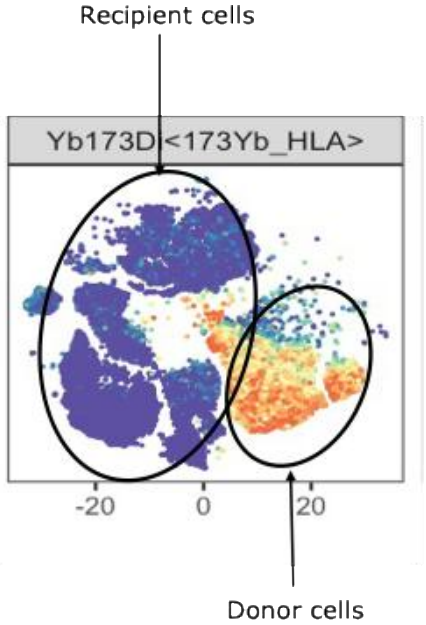
2 cycles

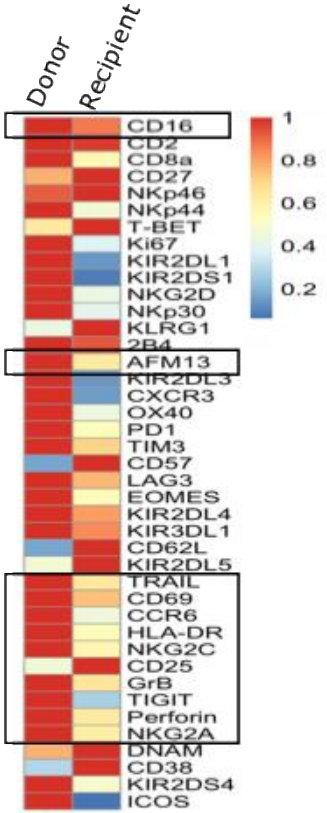
4 cycles



Donor AFM13-NK cells present an activated phenotype







Conclusions

- This is the first clinical trial using CB-derived cytokine-induced memory-like *ex vivo* expanded NK cells precomplexed with the bispecific AFM13 construct to treat patients with $CD30^+$ relapsed lymphoma, double refractory to brentuximab vedotin and checkpoint inhibitors.
- Excellent tolerability with no cases of CRS, neurotoxicity or graft-vs-host disease.
- Donor NK cells detectable in the recipient for 3 weeks with an activated phenotype.
- Donor NK cells traffic to tumor nodal sites.
- High activity in heavily pretreated patients, with 94% responses and 72% CR among patients treated at the RP2D.
- The median EFS of patients treated at the RP2D is 10 months, with 30% of them disease free at 1 year, half of them without any further treatment.

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