

IMMUNOTHERAPY IN HEMATOLOGICAL MALIGNANCIES, 17-19 May 2018, Cuneo



OSPEDALE SAN RAFFAELE



CAR-T

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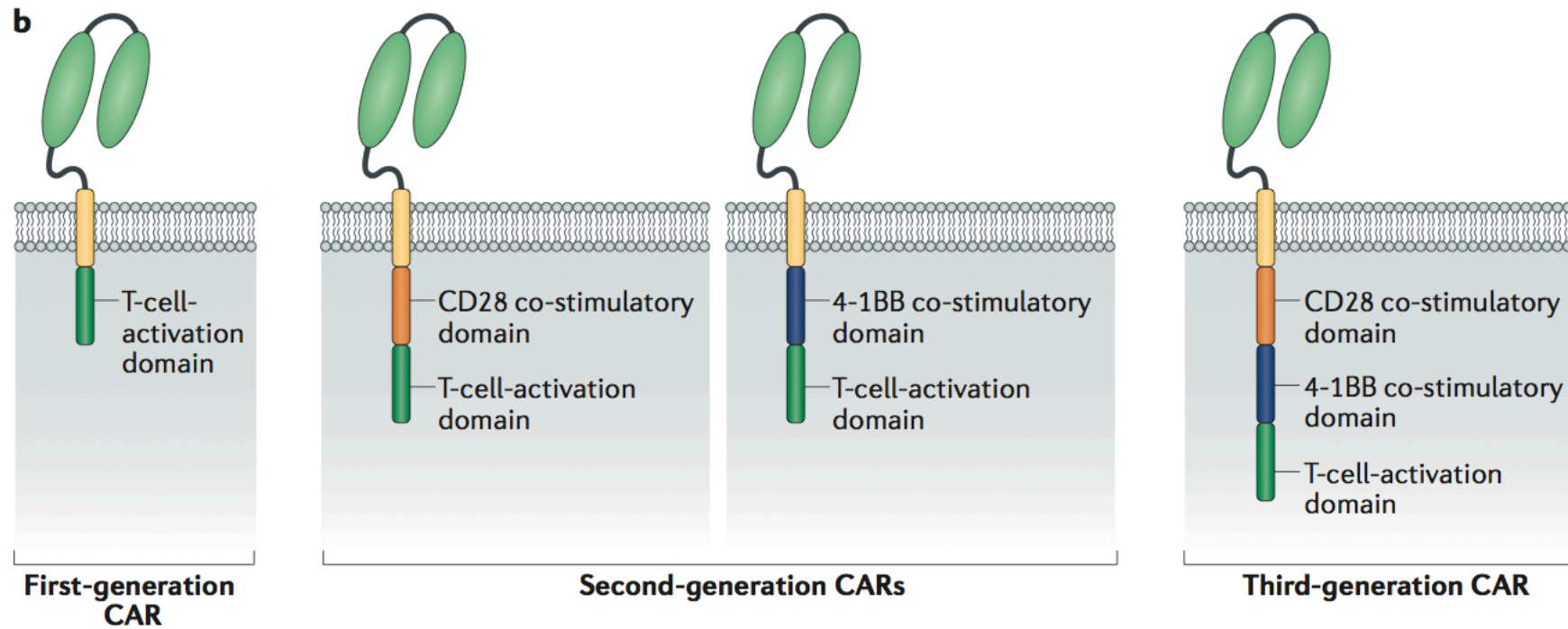
Key Points of This Talk



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- CAR-T growing interest
- CAR-T anti CD19 overview
- CAR-T Toxicities: Can Murine Models Help to Improve Their Management ?
- CAR-T 2.0
- CAR-T CD44v6

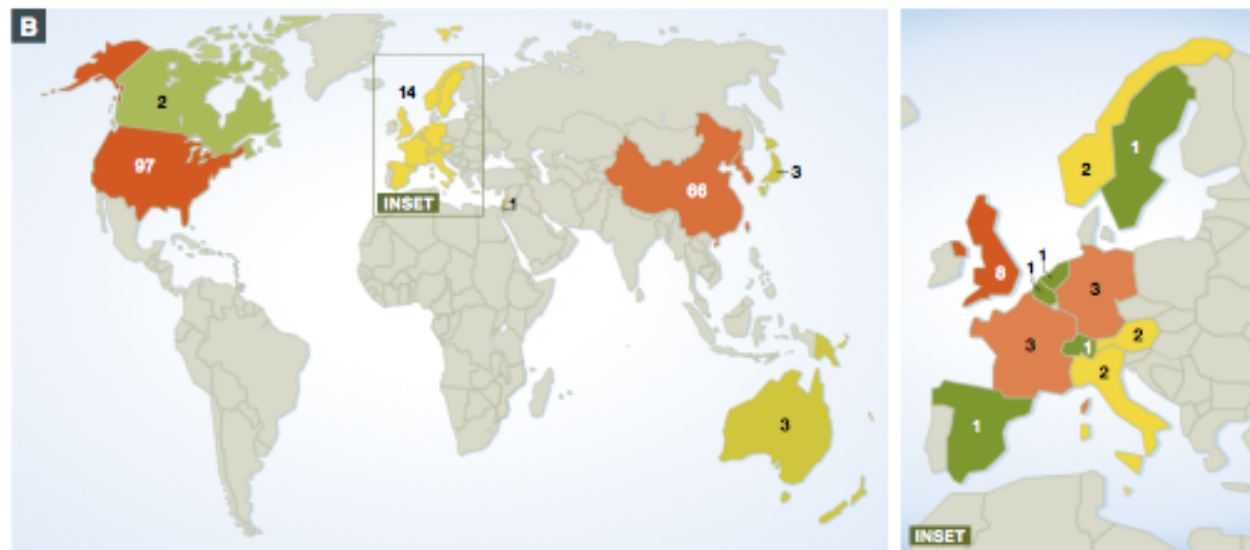
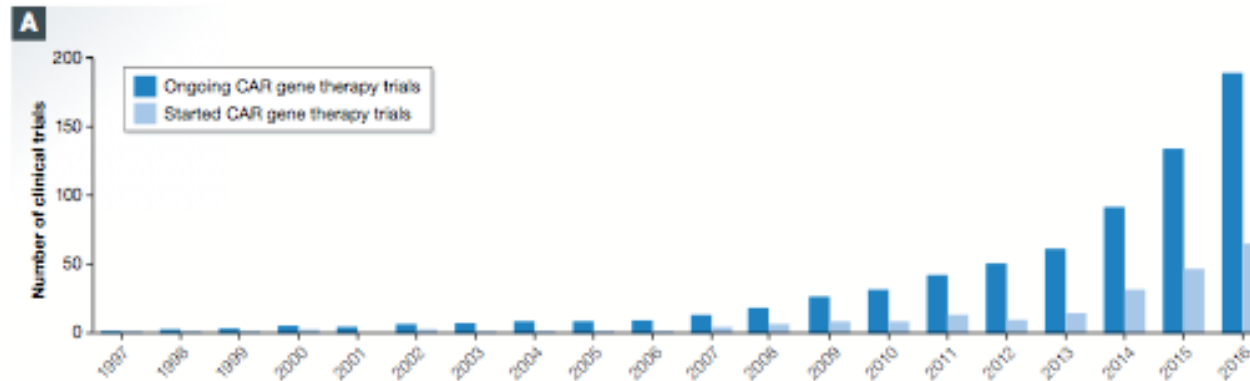
CAR generations



CAR-T GROWING NUMBERS OF TRIALS

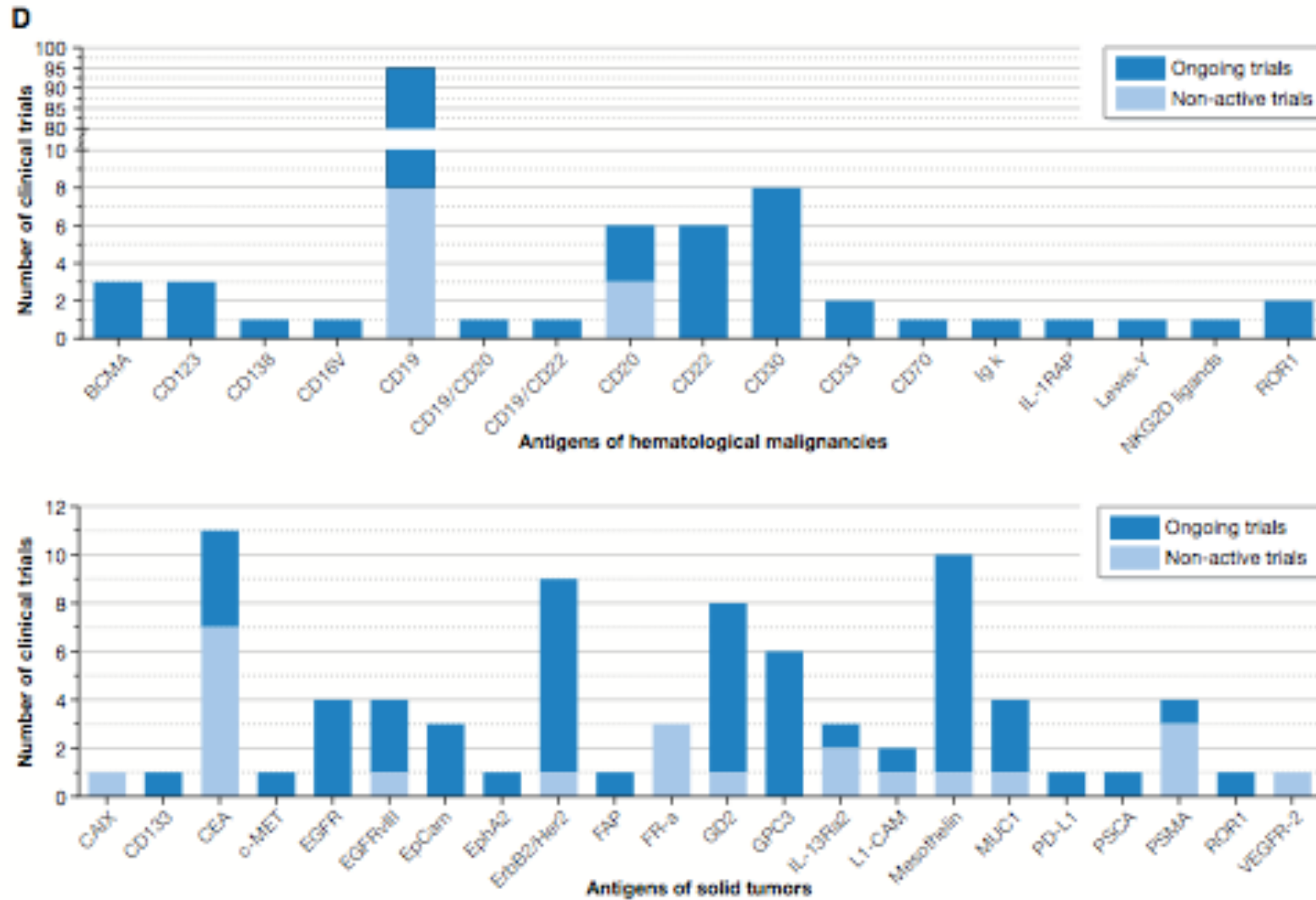


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Hartmann et al, EMBO Mol Med 2017

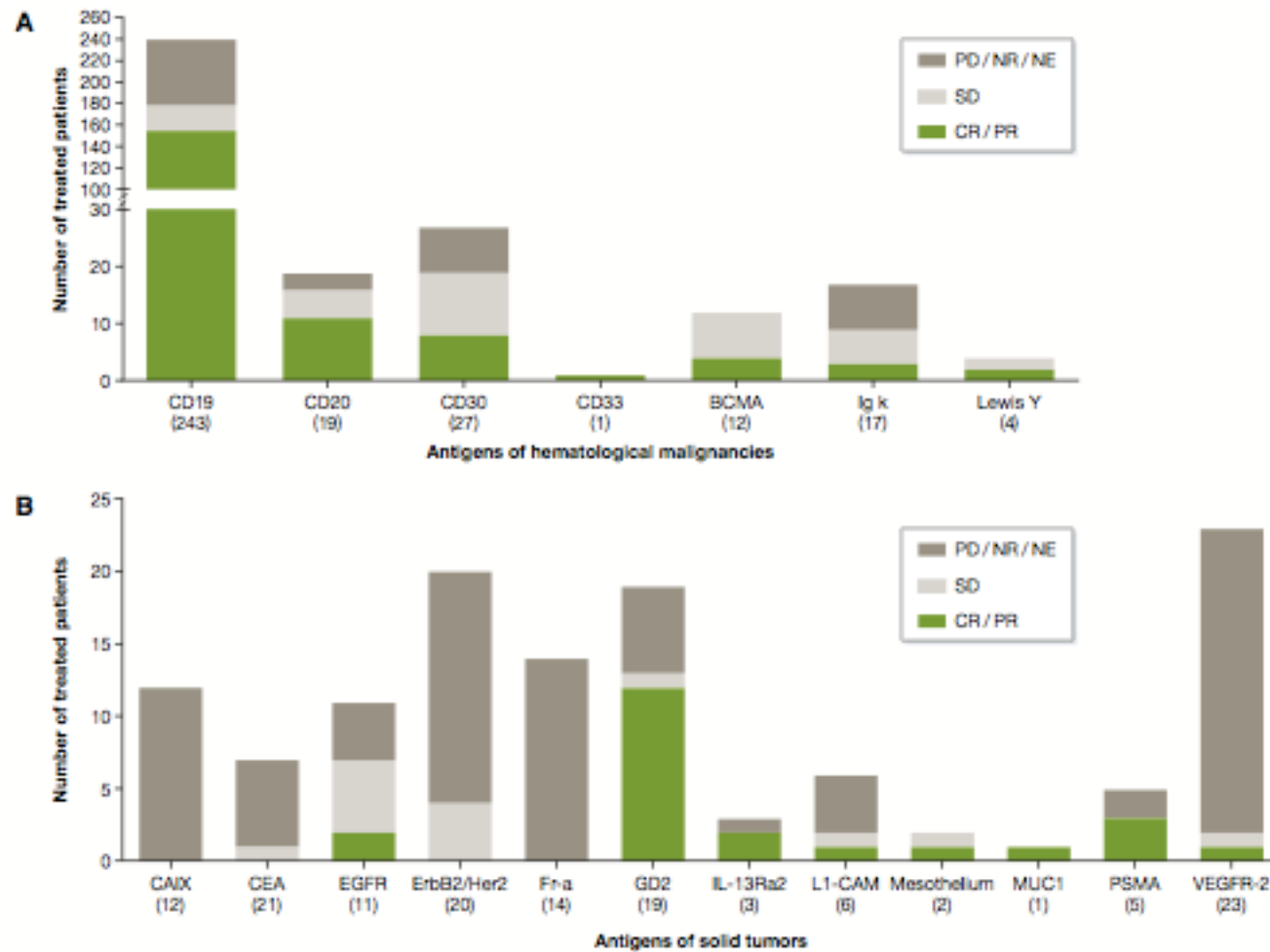
TARGETS SELECTED FOR TRIALS



TARGETS AND OUTCOME (2017)



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Hartmann et al, EMBO Mol Med 2017

Key Points of This Talk



OSPEDALE SAN RAFFAELE

- *CAR-T growing N° Trials and Targets, Interest also in solid tumors*
- **CAR-T anti CD19 overview**
- CAR-T Toxicities: Can Murine Models Help to Improve Their Management ?
- CAR-T 2.0
- CAR-T CD44v6

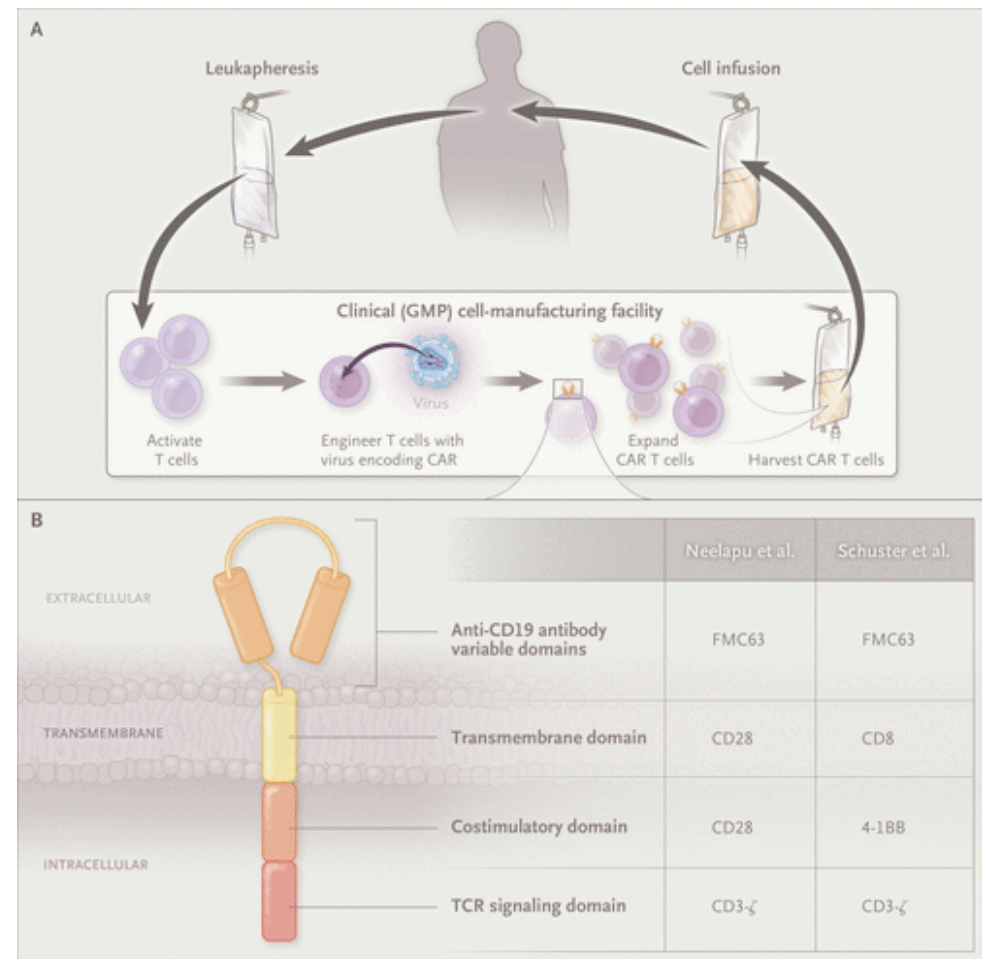
Chimeric Antigen Receptor T-Cell Therapy (CAR-T) anti CD19



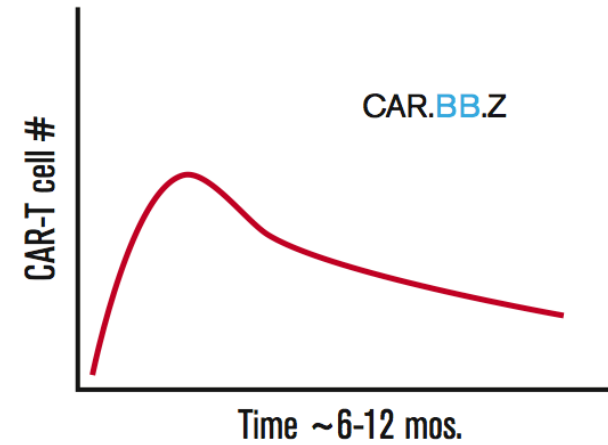
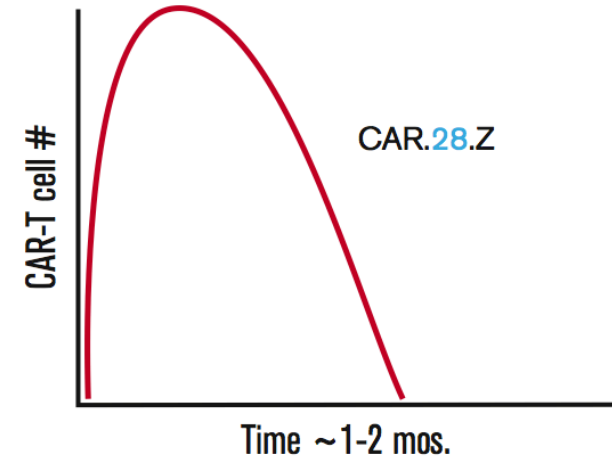
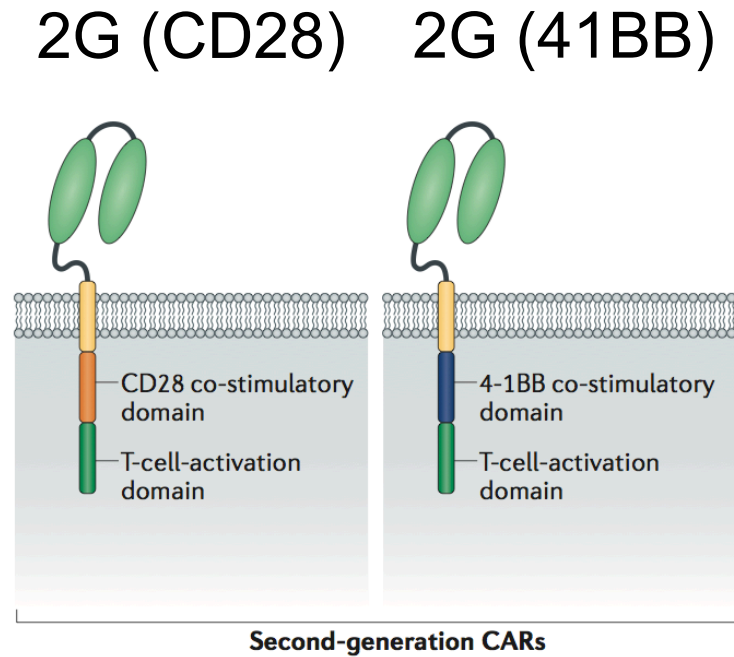
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- Feasible, highly effective in r/r ALL and DLBCL
- Toxicity (CRS and encephalopathy) severe but manageable
- High CR rates in advanced ALL and DLBCL/FL patients

(Tran E et al. NEJM Dec 2017)

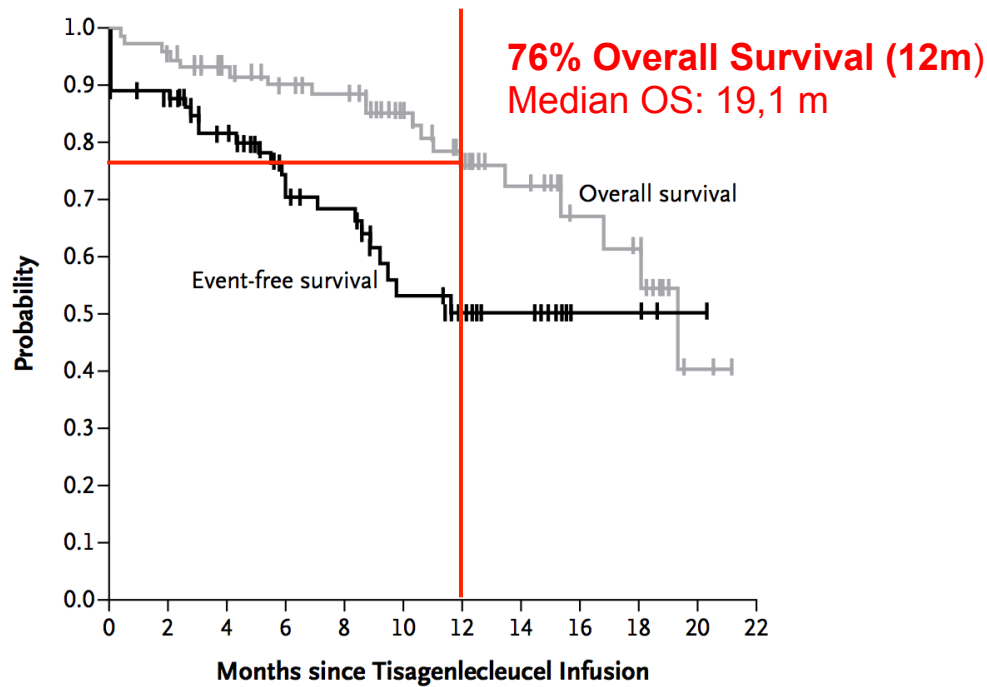


CD28 *versus* 41BB

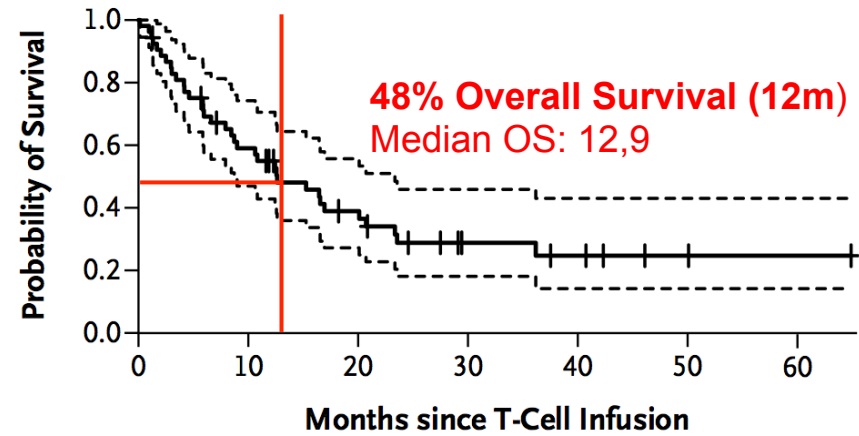


Davis, *Blood Advances* 2016

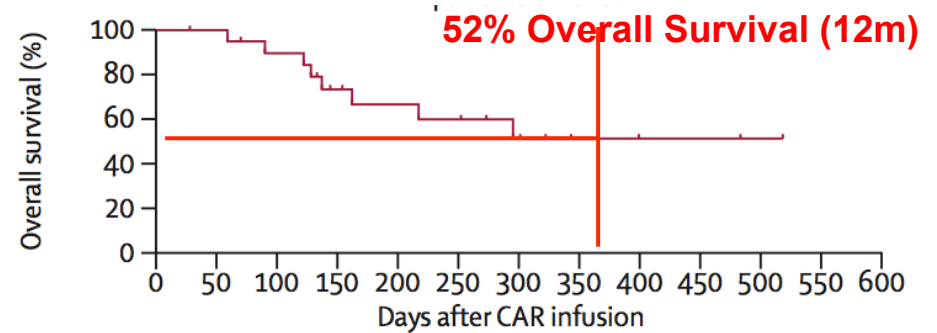
Maude, *NEJM* 2018 (Upenn, 41BB)



Park, *NEJM* 2018 (MSKCC, CD28)



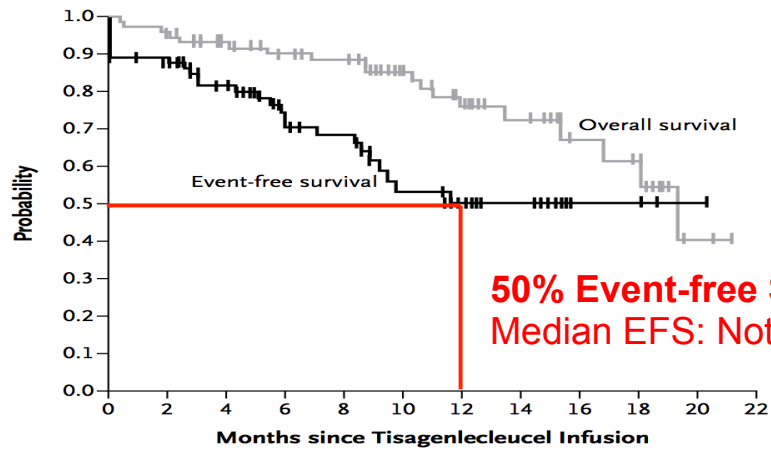
Lee, *Lancet* 2016 (NCI, CD28)



ALL

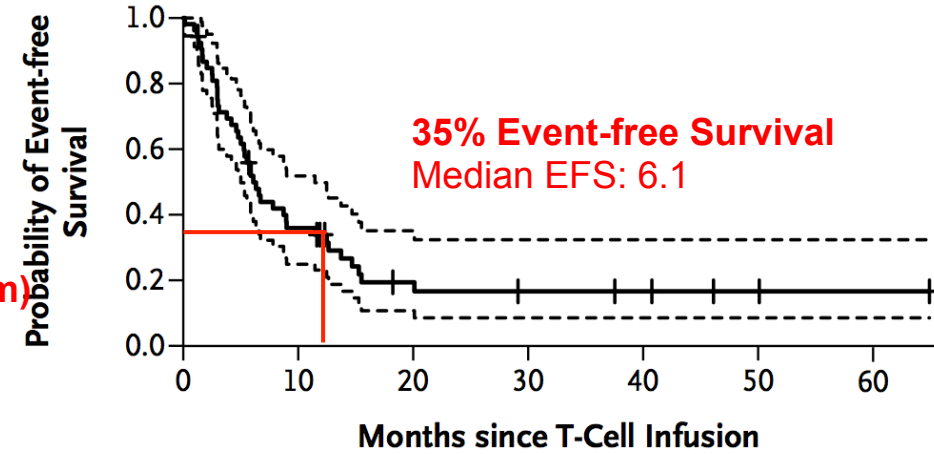


Maude, *NEJM* 2018 (Upenn)



at Risk	0	2	4	6	8	10	12	14	16	18	20	22
Overall survival	75	72	64	58	55	40	30	20	12	8	2	0
Event-free survival	75	64	51	37	33	19	13	8	3	3	1	0

Park, *NEJM* 2018 (MSKCC)



at Risk	0	10	20	30	40	50	60
Event-free survival	53	18	7	5	4	2	1

Cytokine Releasing Syndrome (CRS) G 3 or more 46%

Neurotox. G3 or more 13%

Cytokine Releasing Syndrome (CRS) G 3 or more 26%

Neurotox. G3 or more 42%

Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas

Schuster SJ et al. N Engl J Med ;377:2545-2554



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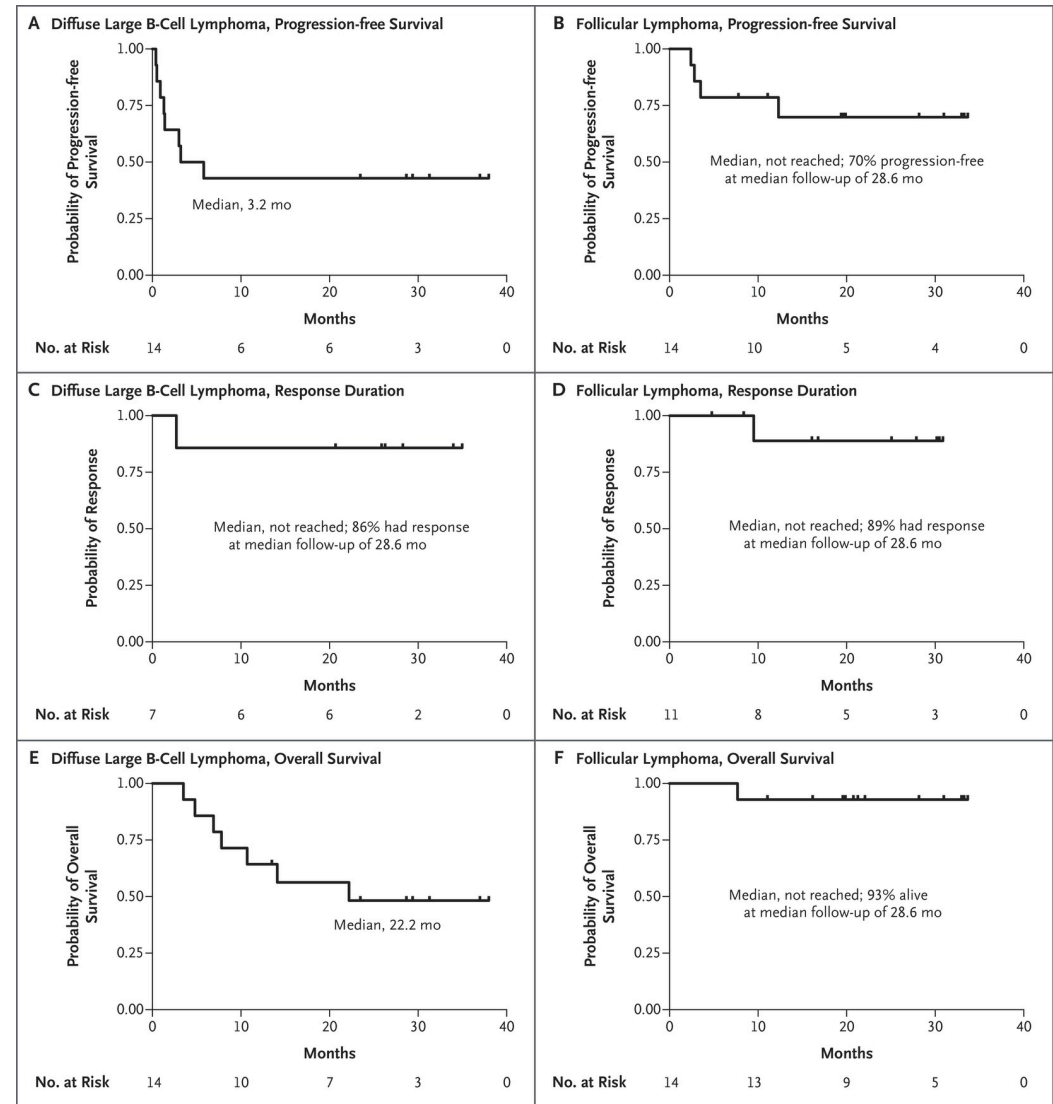
Among 38 patients with refractory diffuse large B-cell lymphoma or follicular lymphoma:

- 28 were able to receive CAR T cells;
- 16 had complete remission;
- none of those who had had a complete response at 6 months had a relapse at 28 months of follow-up;

42 % CR rate

18 % CRS G3 or more

11 % Neurotox G3 or more



Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma

Neelapu SS et al. N Engl J Med ; 2531-2544



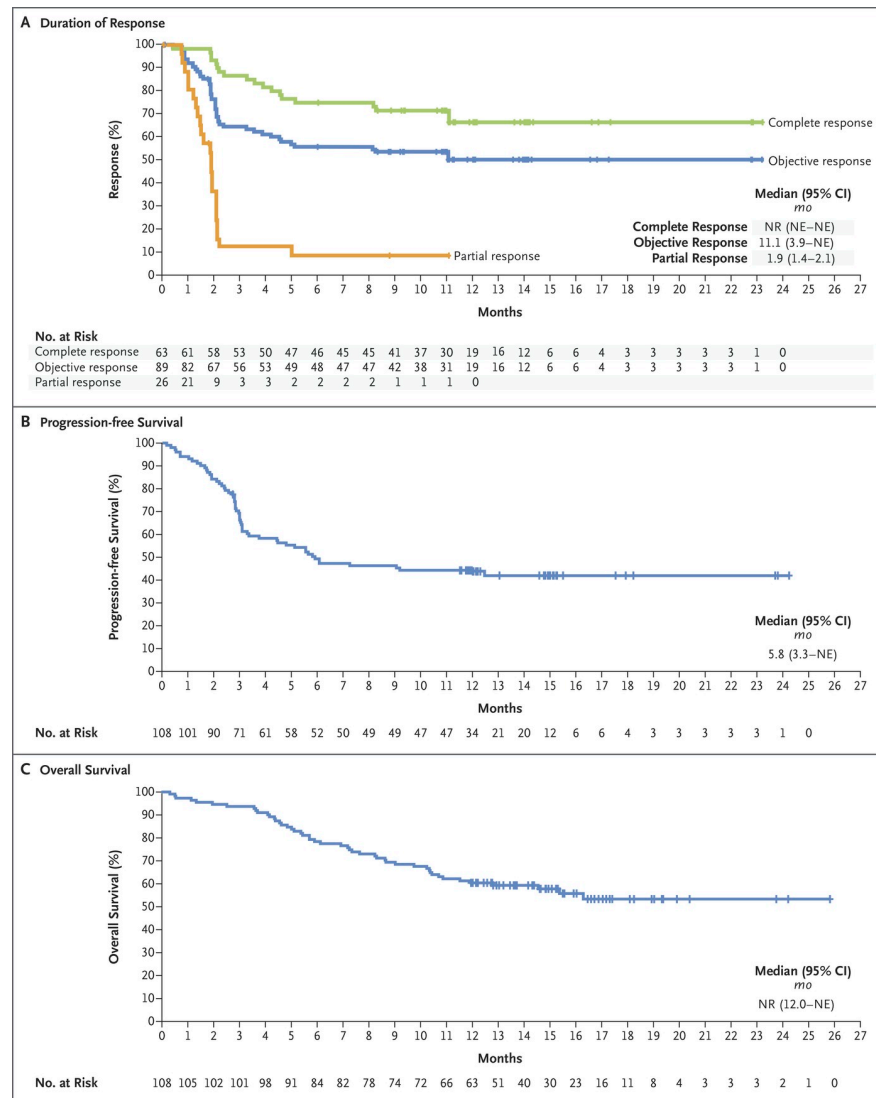
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In 101 (111 enrolled) patients with refractory large B-cell lymphoma, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (axicabtagene ciloleucel) resulted in an overall response rate of 82%, with a 52% survival at 18 months, despite serious toxic effects.

51 % CR rate

13% CRS G3 or more

28% Neurotox G3 or more



Key Points of This Talk



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- *CAR-T growing number of trials, multiple targets, interest in solid tumors*
- *CAR-T anti CD19 -> Breakthrough (R/R ALL, DLBCL FL), waiting for long term data*
- **CAR-T Toxicities: Can Murine Models Help to Improve Their Management ?**
- CAR-T 2.0
- CAR-T CD44v6

Cytokine release syndrome



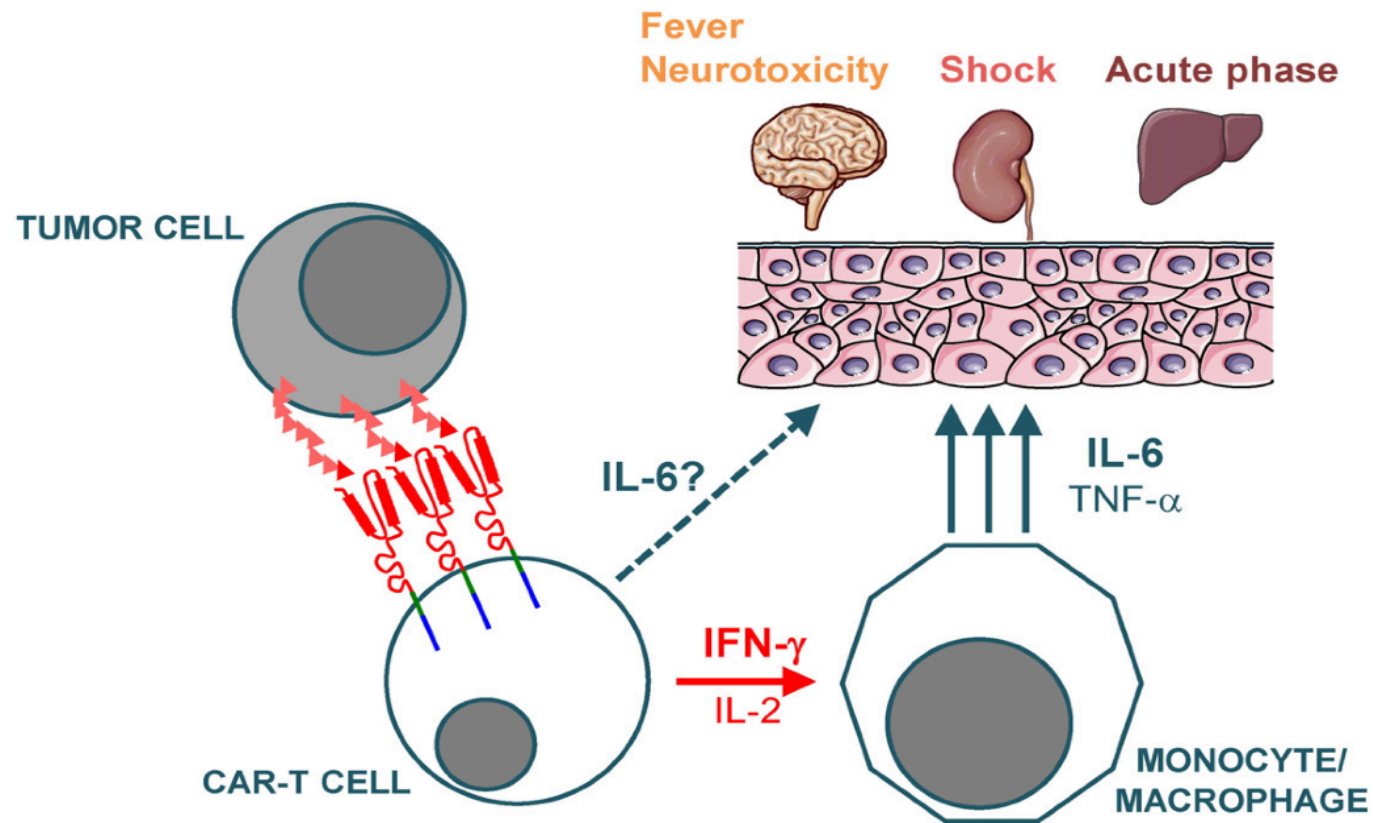
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- **Rapid** inflammatory reaction (within the first 2 weeks)
- **High fever**, hypotension, hypoxia and multi-organ toxicity
- Potentially **life-threatening**
- C-reactive protein (**CRP**) and **IL-6 elevations**
- Ameliorated by **tocilizumab** (anti-IL-6R mAb)
- More frequent in patients with an **high tumor burden**

Cytokine release syndrome



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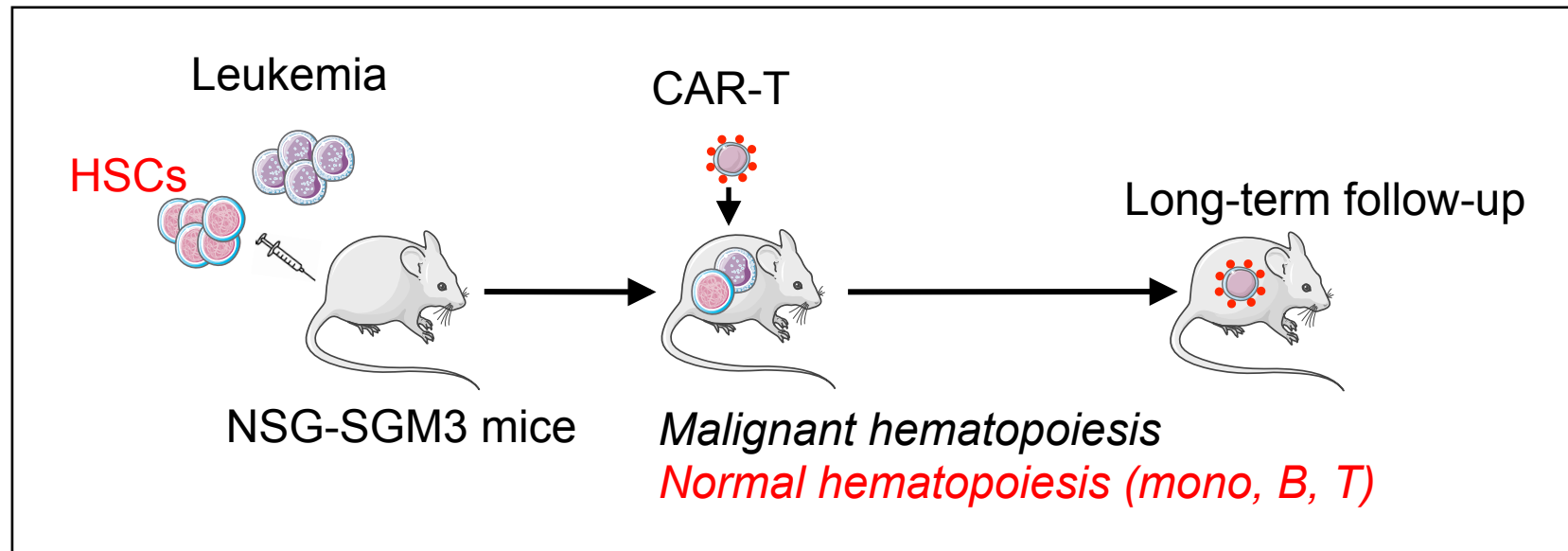


Humanized model for CAR-T



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- Long-term Efficacy
- CAR-related Toxicities: Cytokine Release Syndrome
Neurotoxicity
On-target off-tumor toxicity (hematologic)



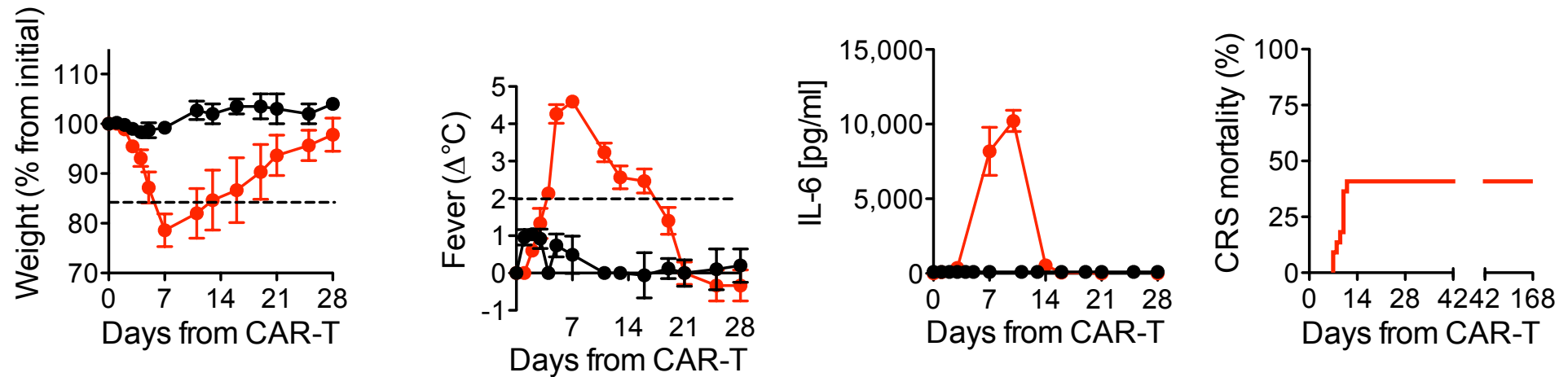
Norelli M, *Nat Med* in press

In vivo modeling of CRS



CD19 CAR-T cells

- NSG-SGM3
- humanized NSG-SGM3

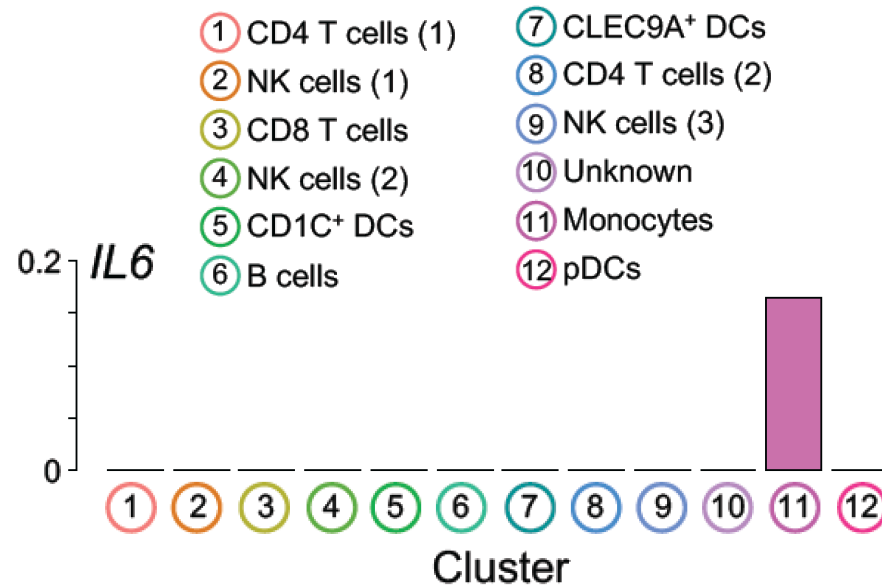


Adapted from Norelli M, *Nat Med* in press

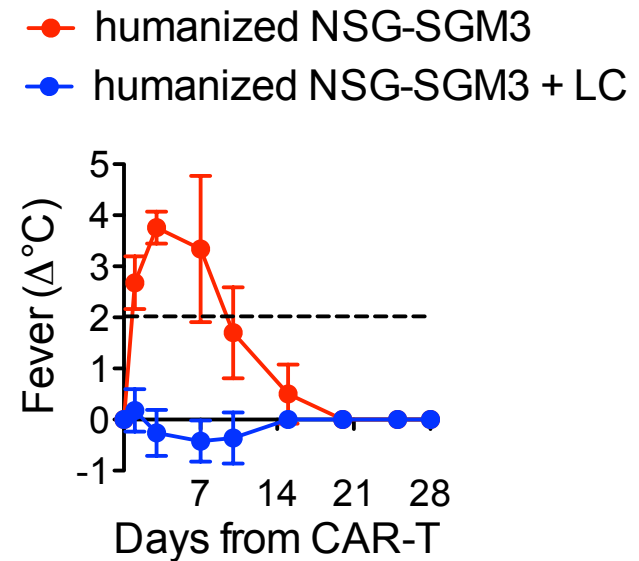
Role of monocytes in CRS



IL-6 sources



Monocyte's ablation

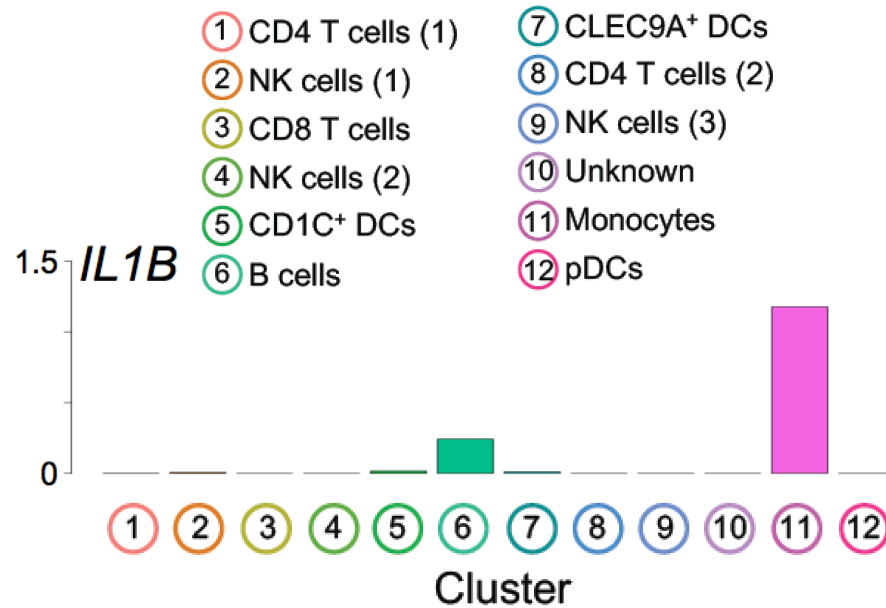


Adapted from Norelli M, *Nat Med* in press

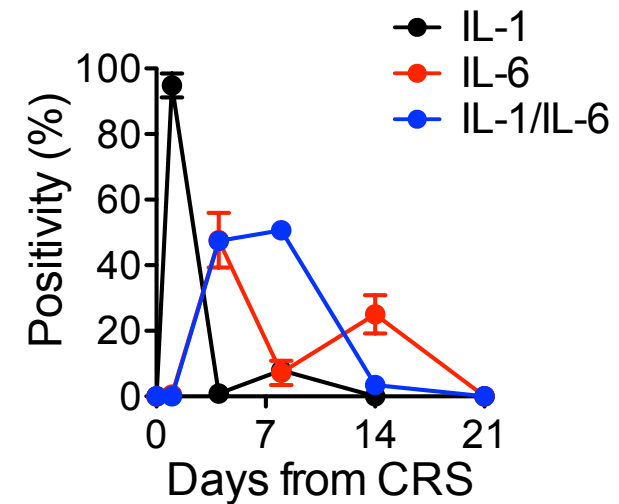
IL-1 is upstream IL-6



IL-1 sources



Monocytes (*in vivo*)



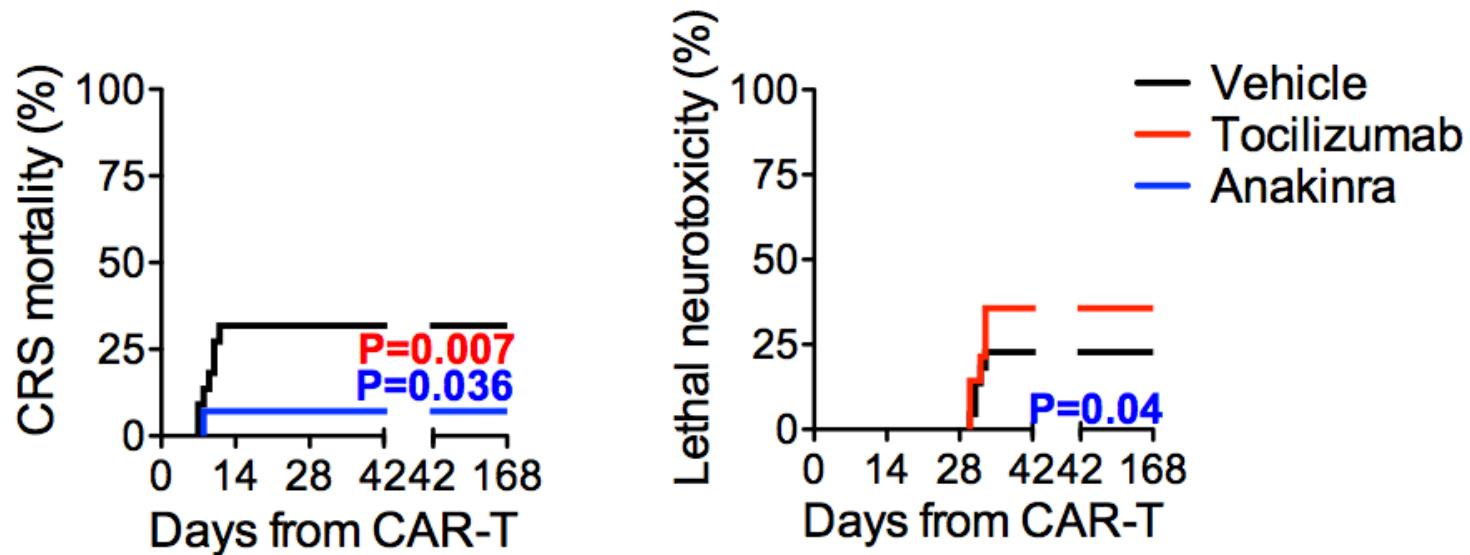
Adapted from Norelli M, *Nat Med* in press

Tocilizumab and Anakinra



Tocilizumab: inhibits IL-6 pathway (CAN'T cross the BBB)

Anakinra: Inhibits IL-1 pathway (CAN cross the BBB)



Adapted from Norelli M, *Nat Med* in press

Key Points of This Talk



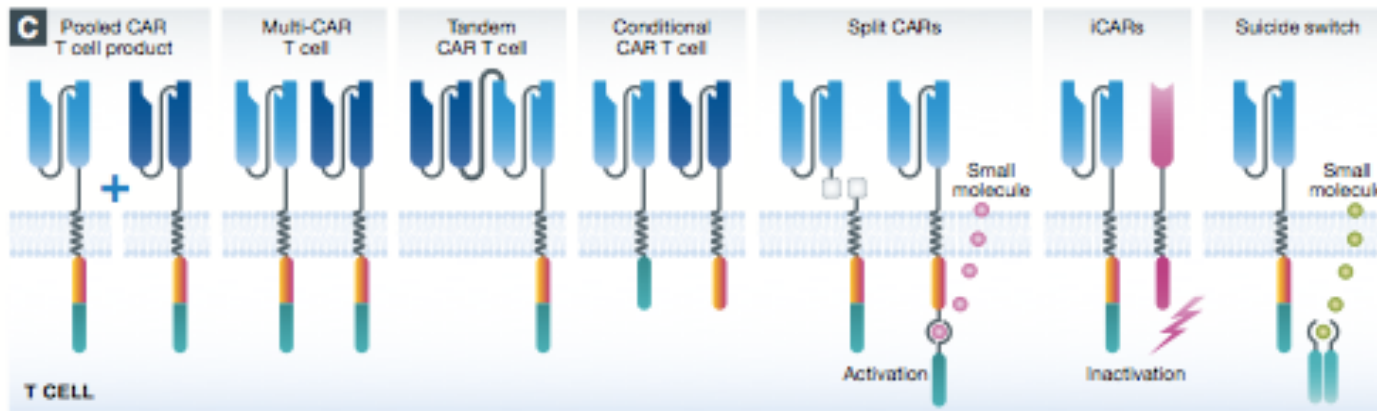
OSPEDALE SAN RAFFAELE

- *CAR-T growing number of trials, multiple targets, interest in solid tumors*
- *CAR-T anti CD19 -> Breakthrough (R/R ALL, DLBCL FL), waiting for long term data*
- *CAR-T Toxicities: Murine Models shows a role of Monocytes in CAR-T Tox and provide a rationale for IL-1 targeting*
- **CAR-T 2.0**
- CAR-T CD44v6

CART EVOLUTION ONGOING



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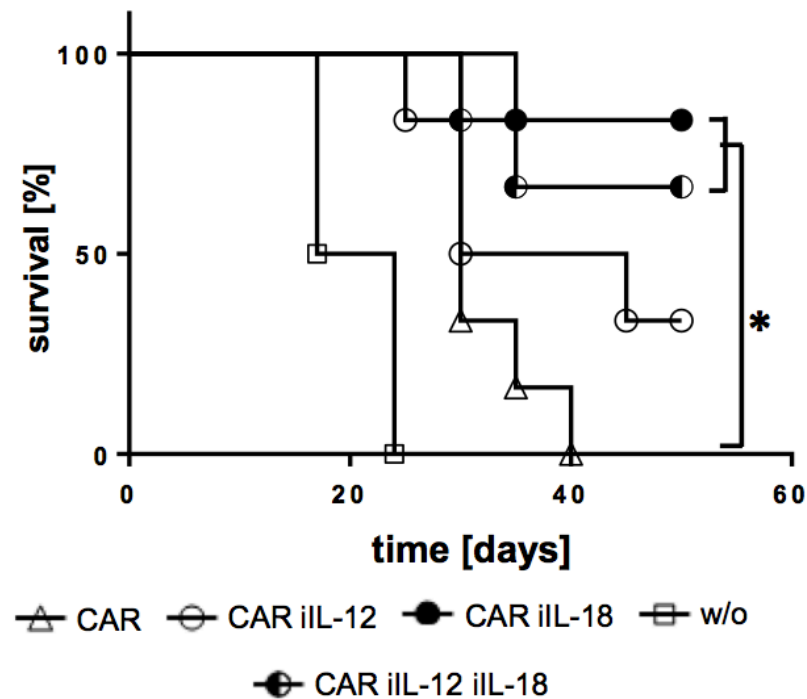
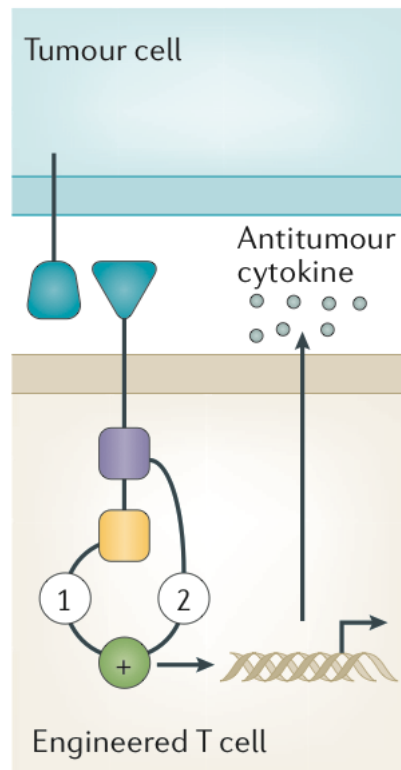


Hartmann et al, EMBO Mol Med 2017

4th generation CARs



a TRUCK

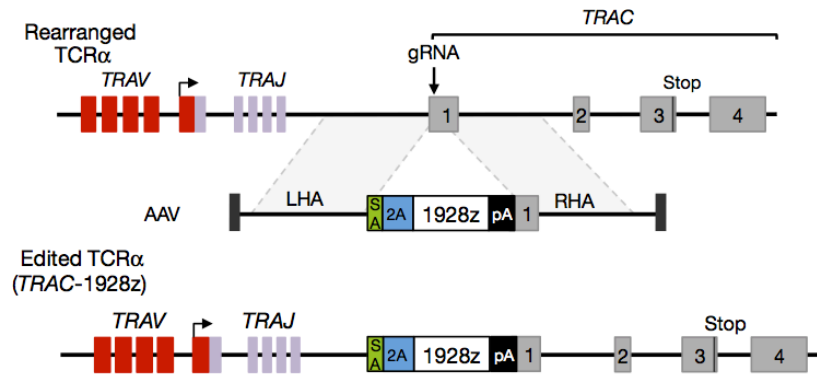


Chmielewski, *Cell reports* 2018

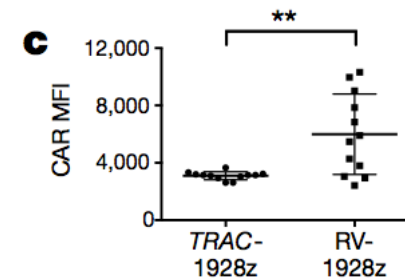
CAR targeting to the TCR locus



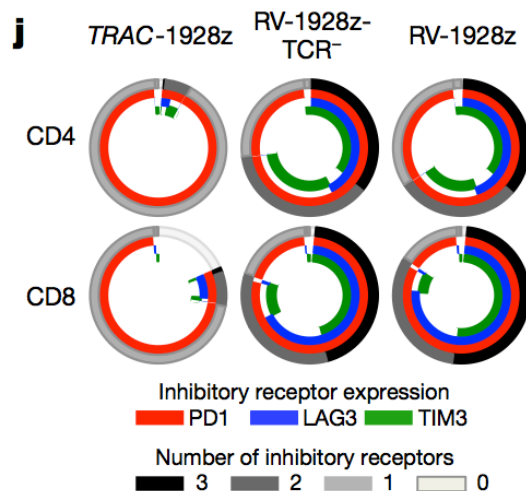
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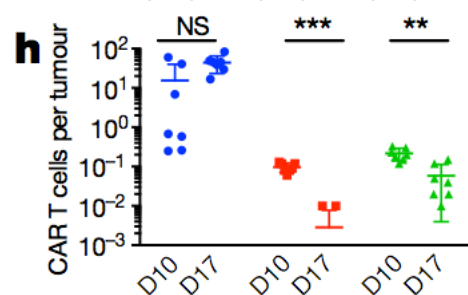
CAR expression



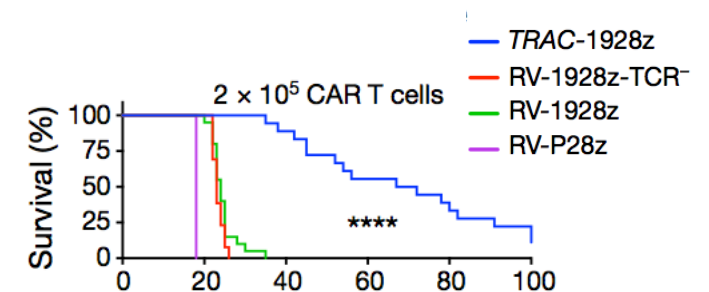
Exhaustion



Expansion



Efficacy



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- *CAR-T Toxicities: Murine Models shows a role of Monocytes in CAR-T Tox and provide a rationale for IL-1 targeting*
- *CAR-T 2.0: multiple strategies under evaluation -> opportunity but also issue for clinical research*
- **CAR-T CD44v6**

CD44v6 CAR-based strategy



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- **CD44v6**
 - oncogenic antigen
 - expressed on AML, MM and epithelial cancers
 - expressed on circulating monocytes and keratinocytes

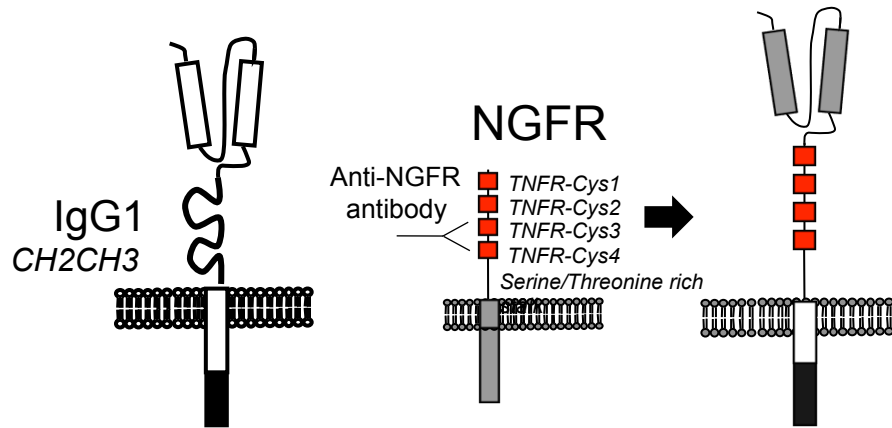
- **CD44v6 CAR-T**
 - Potent anti-leukemia/myeloma activity
 - Monocytopenia (on-target, off-tumor toxicity)
 - Co-expression with suicide genes
 - Keratinocyte resistance to killing (*in vitro*)

Casucci M, *Blood* 2013

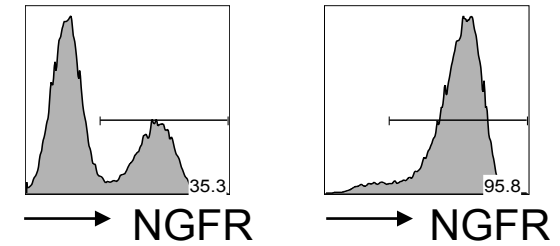
NGFR-spaced CARs



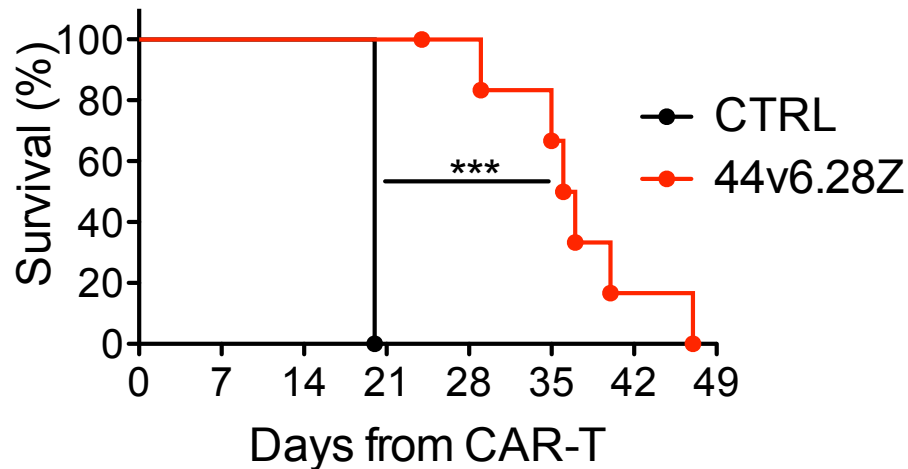
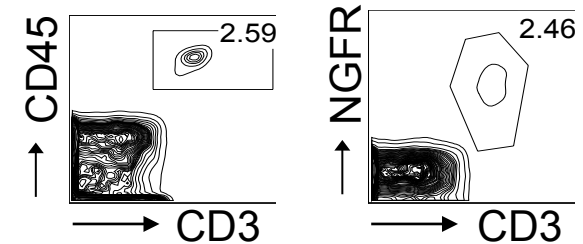
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Selection



Tracking

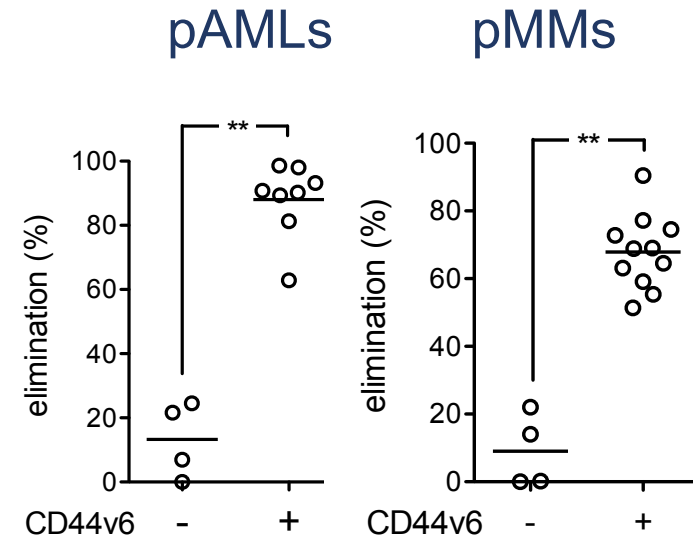


Bondanza A, Casucci M, Bonini C, WO 2016/042461
Casucci M, *Front Immunol* in press

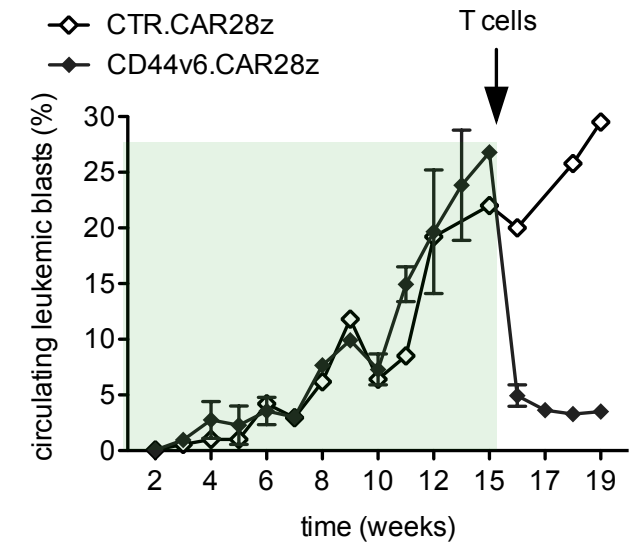
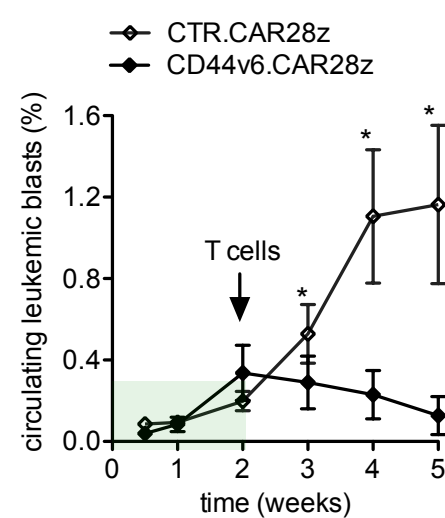
Anti-tumor efficacy



In vitro



In vivo

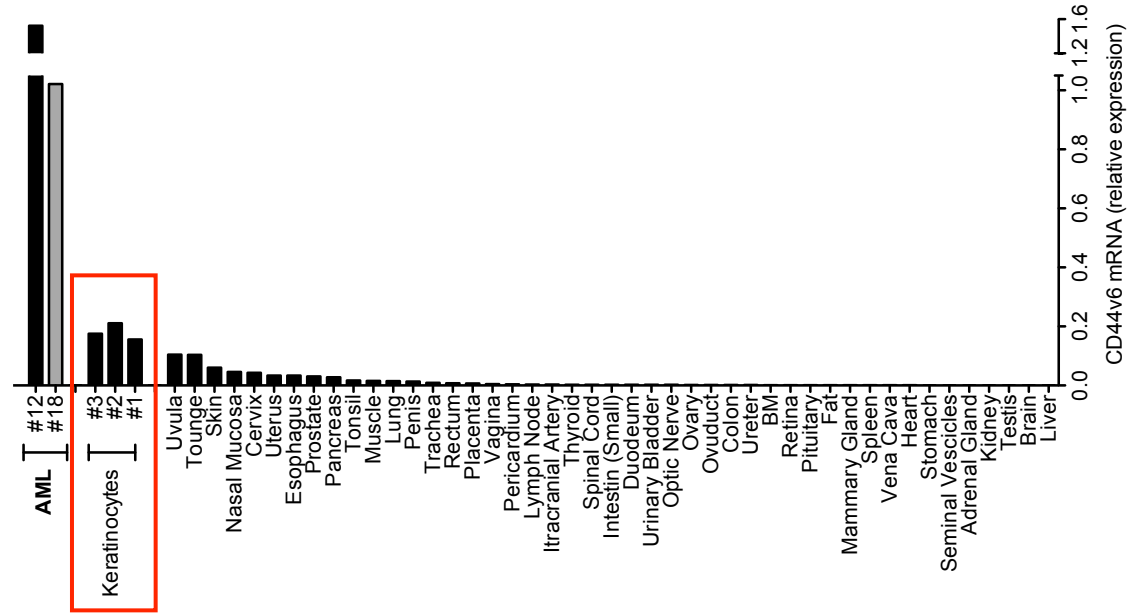


CD44v6 in healthy tissues

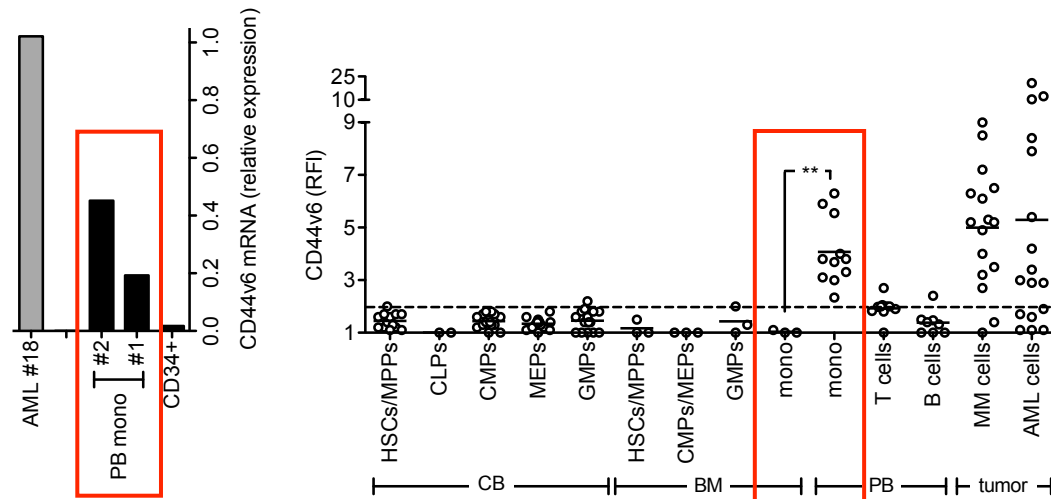


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Non-haematopoietic
Keratinocytes



Haematopoietic
Circulating monocytes



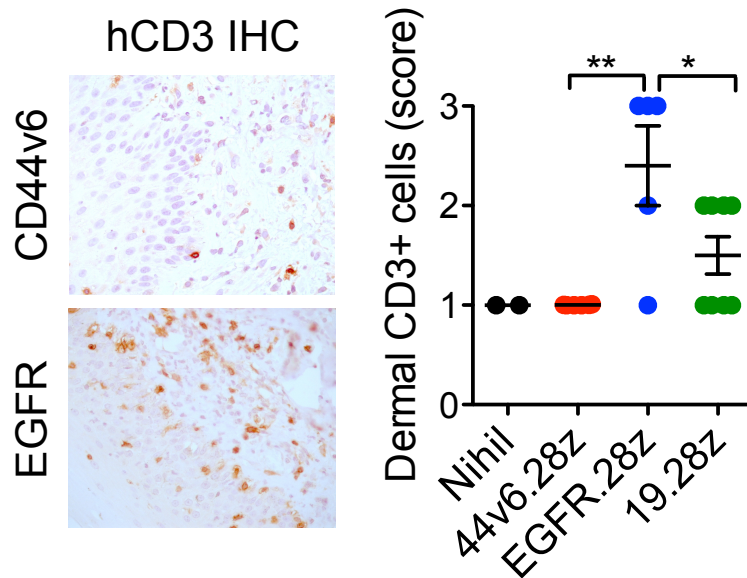
Casucci M et al, *Blood*, 2013

Keratinocyte resistance



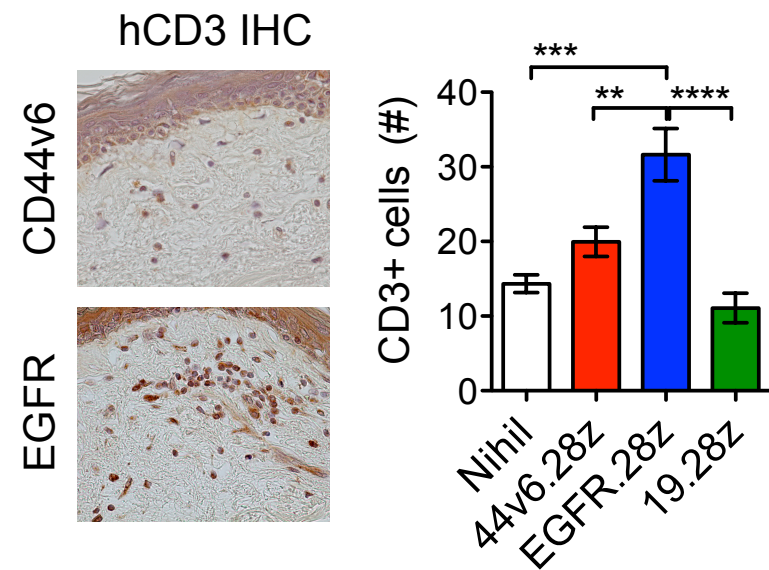
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In vivo skin xenograft



In collaboration with MolMed

Ex vivo skin explant



In collaboration with Antonella Monno

Greco B, Poster #305, room Carlo 3

CD44v6 CAR clinical trial



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Main objective:

to conduct a multicentre, first-in-man **Phase I/IIa clinical** trial to evaluate the safety and the efficacy of **CD44v6 CAR-T cells** in **refractory AML and MM**



Proof-of-principle for future applications in solid tumors

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- *CAR-T Toxicities: Murine Models shows a role of Monocytes in CAR-T Tox and provide a rationale for IL-1 targeting*
- *CAR-T 2.0: multiple strategies under evaluation -> issue for clinical research*
- *CAR-T CD44v6: phase 1 clinical trial protocol submission to HA is expected in the next months*

Aknowledgments



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EURE-CART* Group Members
(www.eure-cart.eu)

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Novartis Institutes for Biomedical Research,
Basel

Monica Casucci and Margherita Norelli

Innovative Immunotherapies Unit, San
Raffaele Scientific Institute, Milan

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