



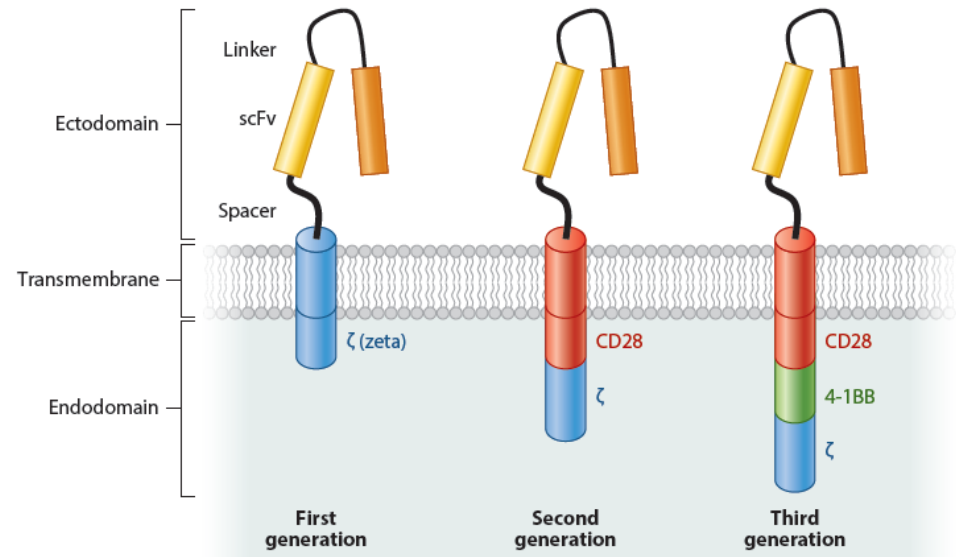
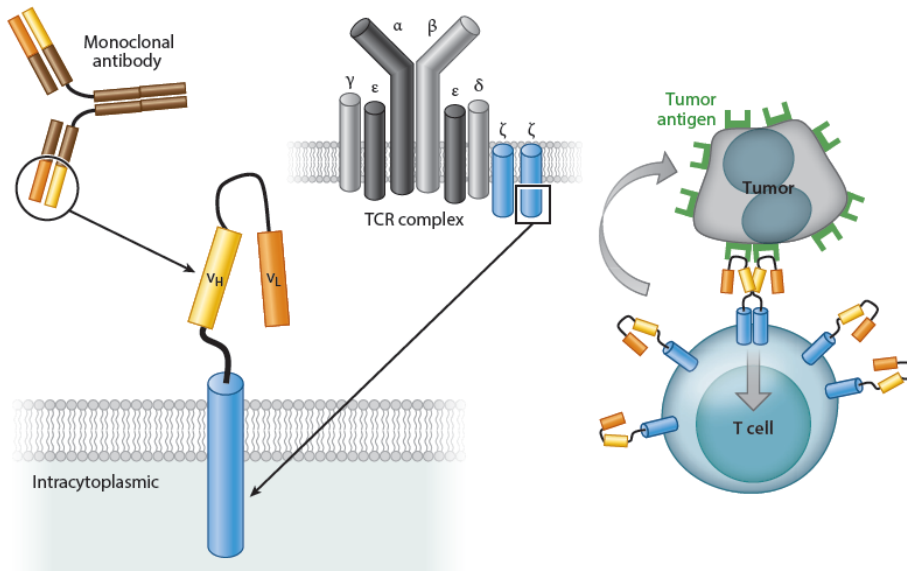
Chimeric Antigen Receptor T-cells therapy

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CHRU Montpellier, University of Montpellier

The Concept



The Concept

- Tisa-gene- Lec-leucel

- KYMRIA[®]

- ALL: R/R > 2L (< 25 y)
- DLBCL R/R > 2L



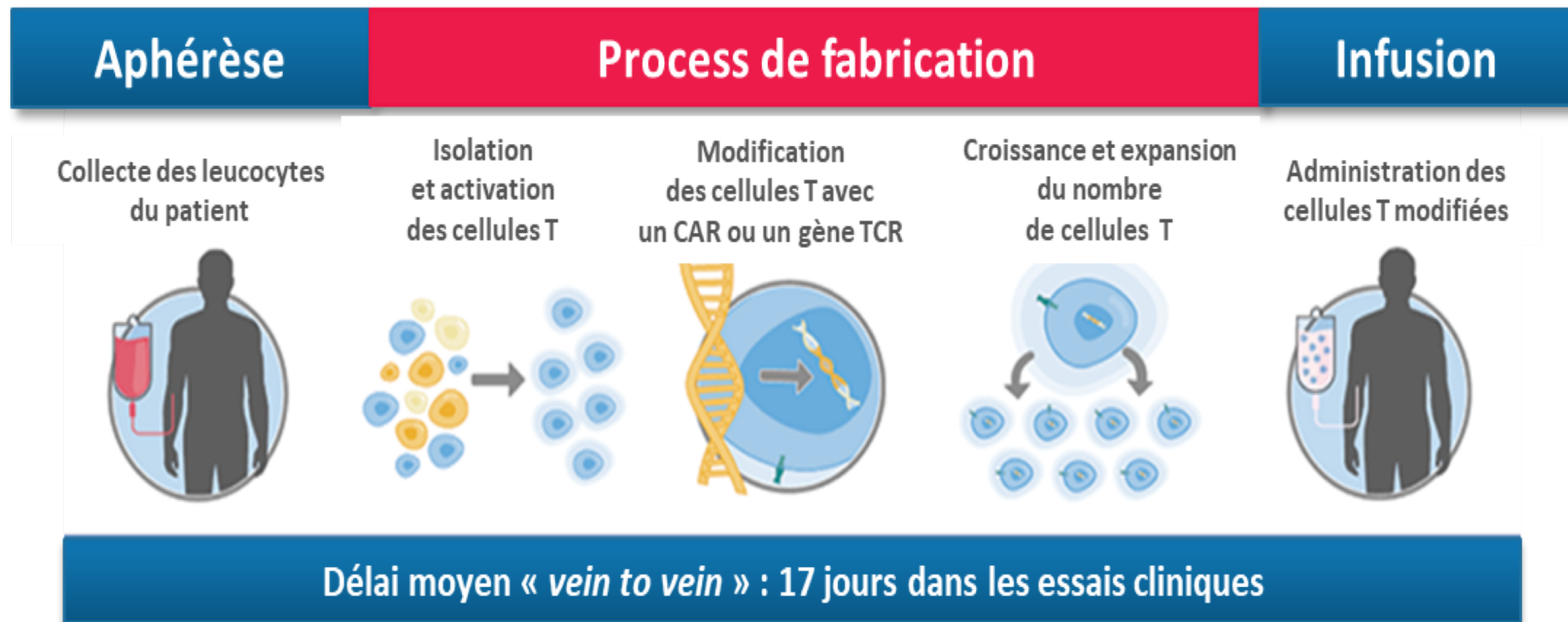
- Axi-cabtagene- Cila-Leucel

- YESCARTA[®]

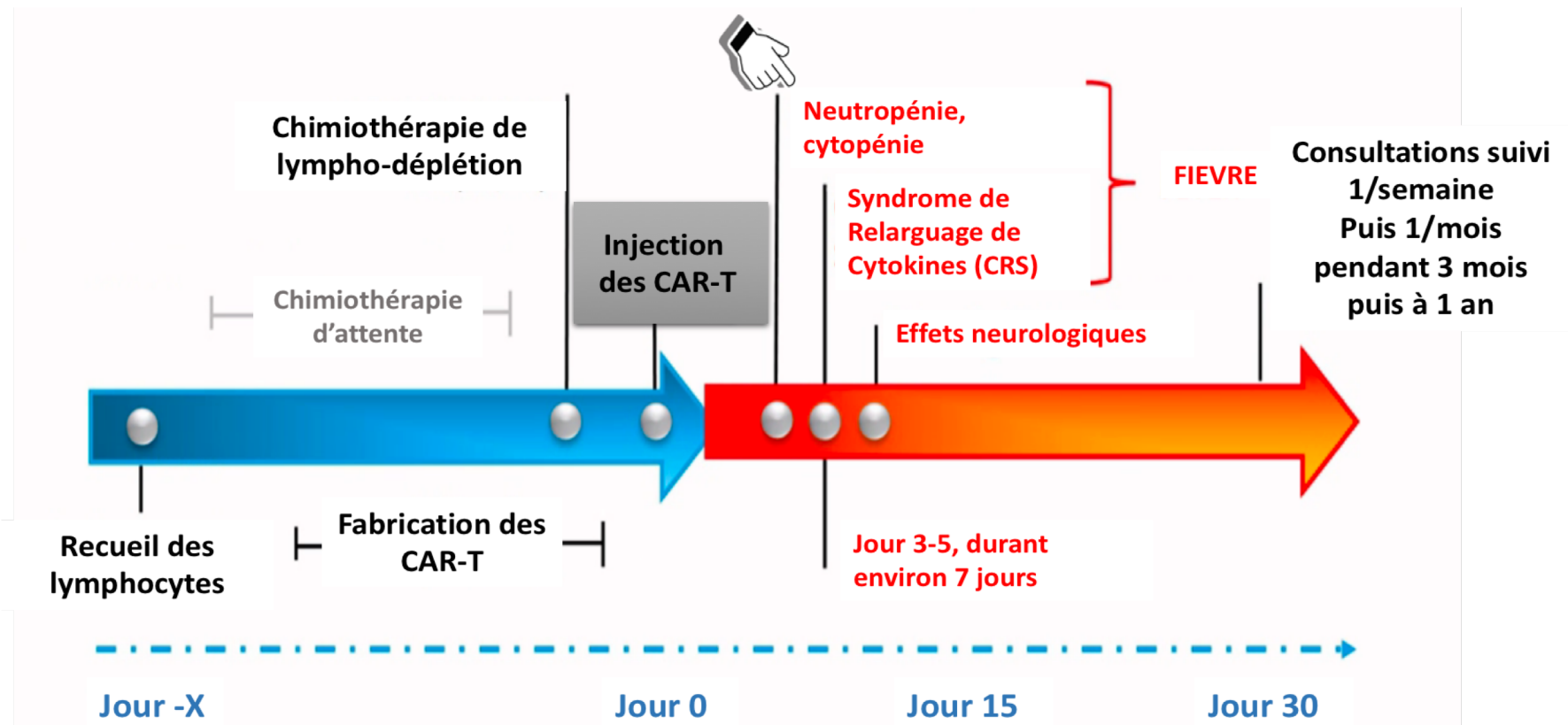
- DLBCL R/R > 2L



The Concept



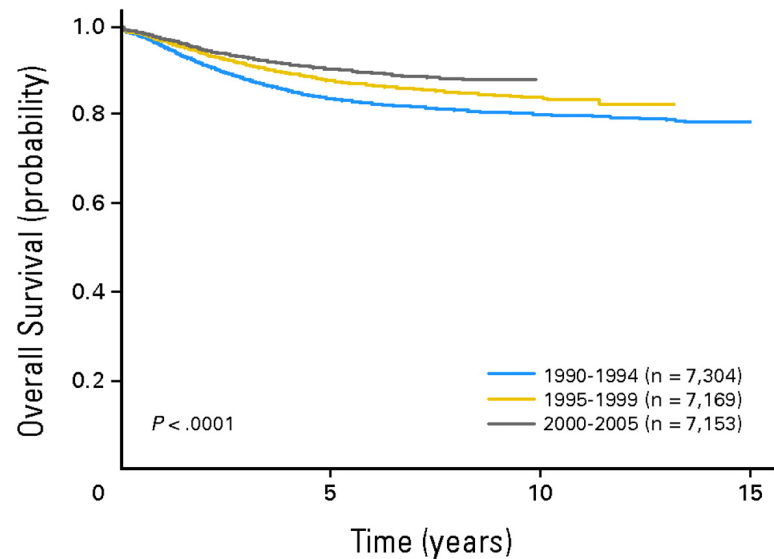
The Concept



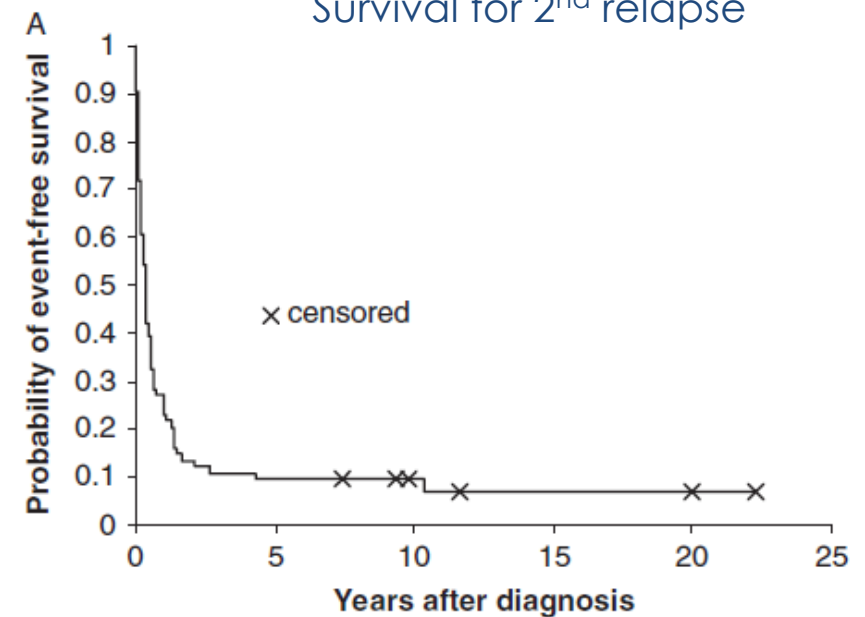
Pediatric R/R Acute Lymphoblastic Leukemia

Less than 10% of patients
alive after 2nde relapse

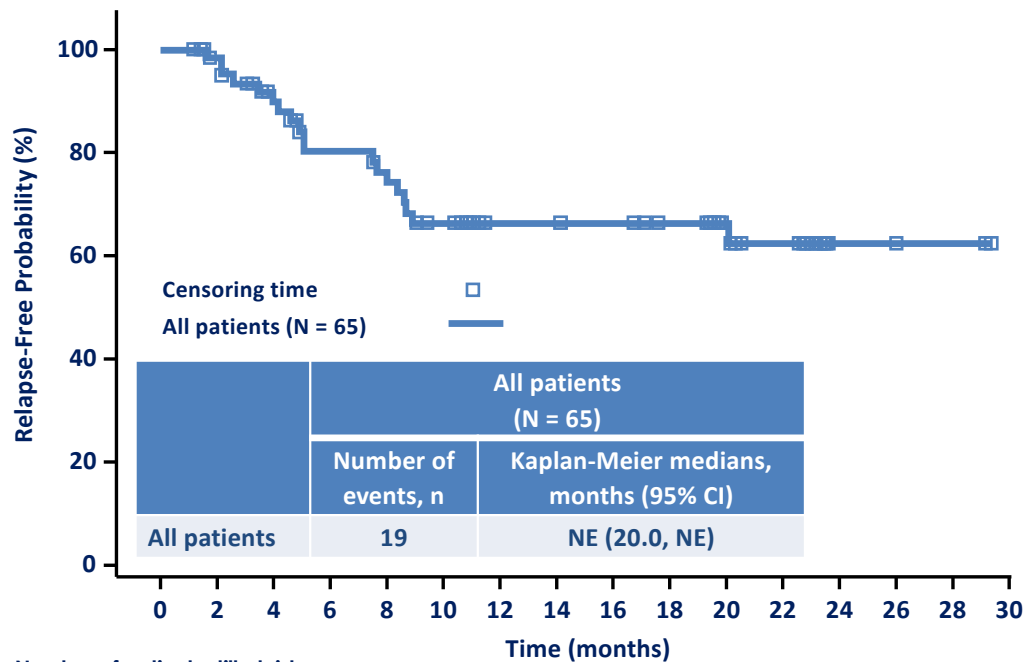
Survival for newly diagnosed ALL



Survival for 2nd relapse



CAR-T for R/R ALL: High response rate and response duration



- Overall remission rate (CR + CRi) within **3 months was 82%** (65/79; 95% CI, 72-90)^{a,b}
 - 98% (64/65) achieved MRD(-)^c bone marrow
- Relapse-free survival rate among responders
 - 12-month: 66% (95% CI, 52-77)
 - 18-month: 66% (95% CI, 52-77)
 - **24-month: 62%** (95% CI, 47-75)

Number of patients still at risk																
All patients	65	60	49	41	37	31	25	25	24	21	17	13	3	2	2	0

Note: Only patients who achieved CR or CRi were included. Time is relative to onset of remission.

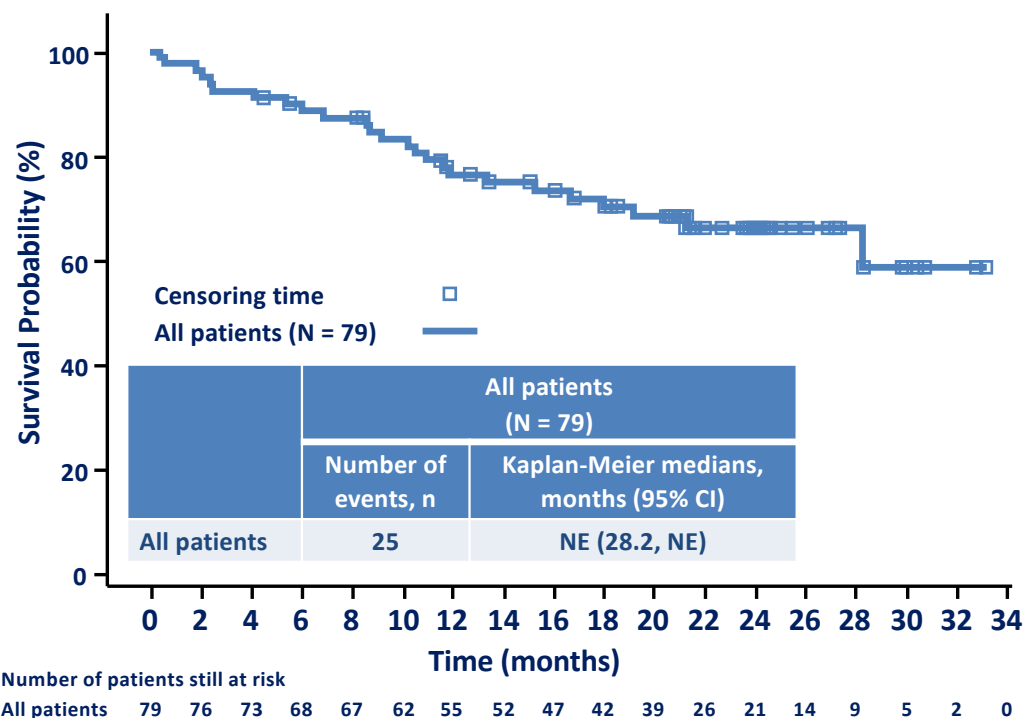
^aThe response was unknown in 6 patients.

^bWhile in remission, 8 patients went on to stem-cell transplantation.

^cMRD negative = MRD < 0.01%, as assessed by flow cytometry.

CR, complete remission; CRi, complete remission with incomplete blood count recovery; MRD, minimal residual disease, NE, not estimable.

Median overall survival not reached



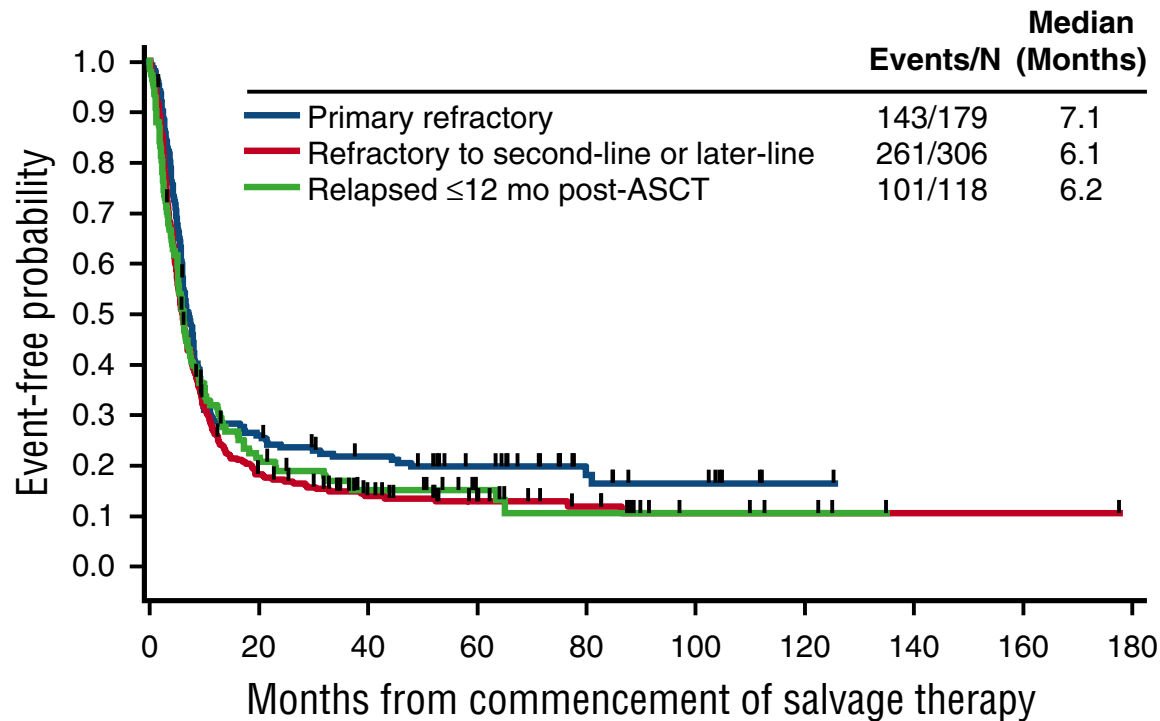
- Overall survival rates among all infused patients
 - 12-month: 76% (95% CI, 65-85)
 - 18-month: 70% (95% CI, 58-79)
 - **24-month: 66% (95% CI, 54-76)**

Note: All patients infused with tisagenlecleucel were included. Time is relative to infusion.
 CR, complete remission; CRi, complete remission with incomplete blood count recovery; NE, not estimable.

Grupp SA et al. ASH. 2018; Abs 895.

Refractory DLBCL

SCHOLAR-1

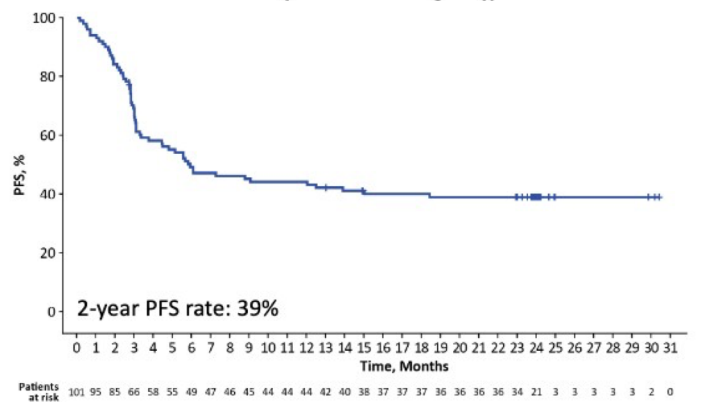


- ORR : 26%
- CR: 7%
- mOS: 6.3 mo

- Refractory disease: PD or SD as best response at anytime of treatment or relapsed < 12 mo post-ASCT
- N=636

CAR-T for Refractory DLBCL: ZUMA-1

PROGRESSION-FREE SURVIVAL



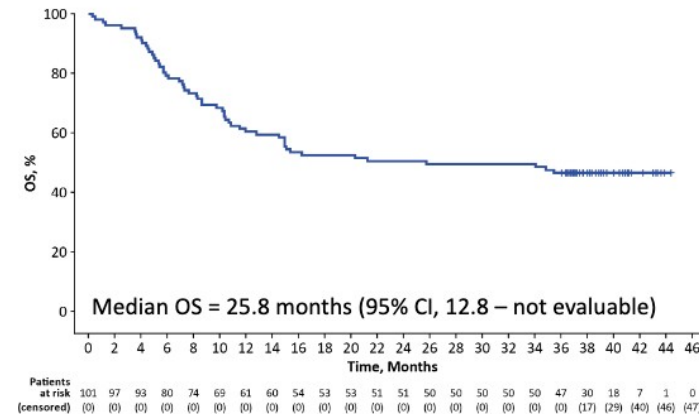
Landmark	PFS (%)
6-months	49
12-months	44
18-months	41
24-months	39

Idem SHOLAR

Median time to infusion: 17 d

Drop-out: #10% (111/101)

OVERALL SURVIVAL

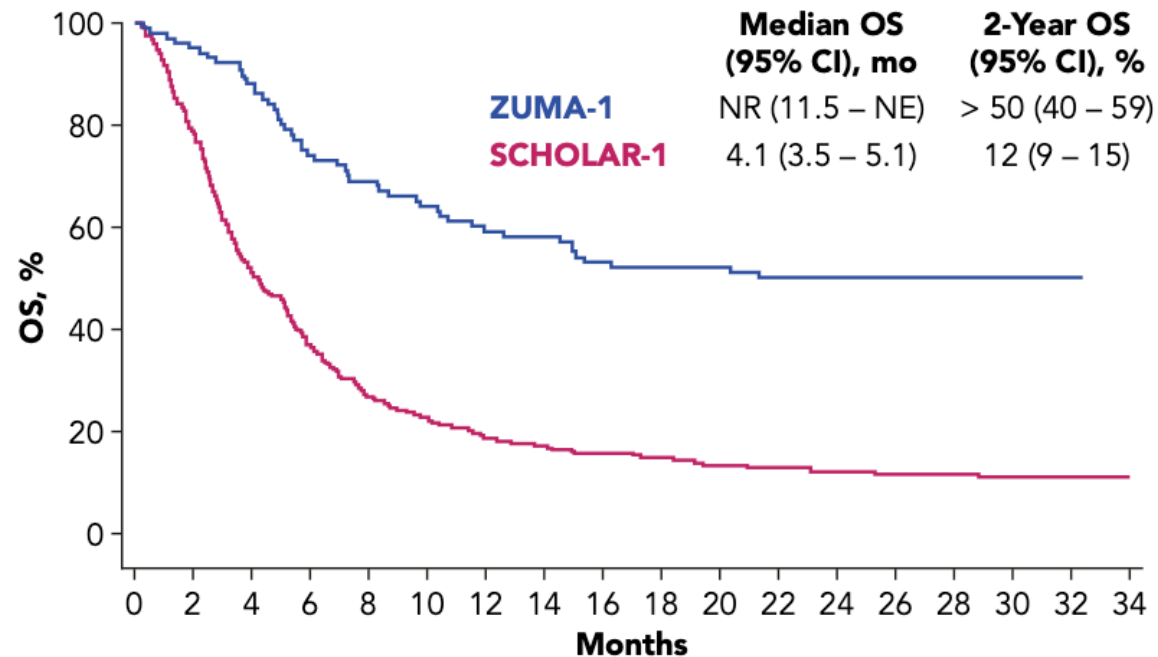


Landmark	OS (%)
6-months	78
12-months	60
18-months	53
24-months	51
36-months	47

Locke FL et al, Lancet Oncol 2019; 20: 31. Neelapu SS et al, ASH 2019: #203

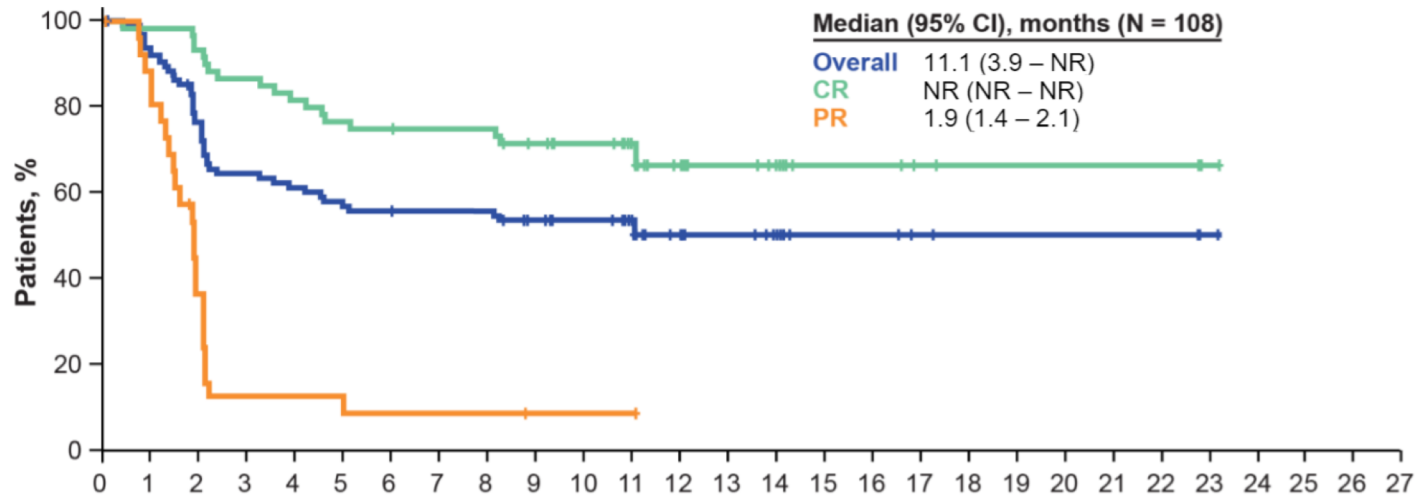
CAR-T for Refractory DLBCL: ZUMA-1

Simulation-Based Standardized OS Curves for ZUMA-1 and SCHOLAR-1



Curves were generated by standardizing ZUMA-1 and SCHOLAR-1 based on refractory category and post-refractory SCT and bootstrapping to resample 2000 times. Day 0 was the day of axi-cel infusion in ZUMA-1 and initiation of salvage therapy in SCHOLAR-1.
NE, not evaluable; NR; not reached; OS, overall survival.

Median duration not reached



	Duration of Response, months																											
Patients at Risk	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Overall	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	3	3	1	0		
CR	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	3	3	1	0		
PR	26	21	9	3	3	2	2	2	2	1	1	1	0															

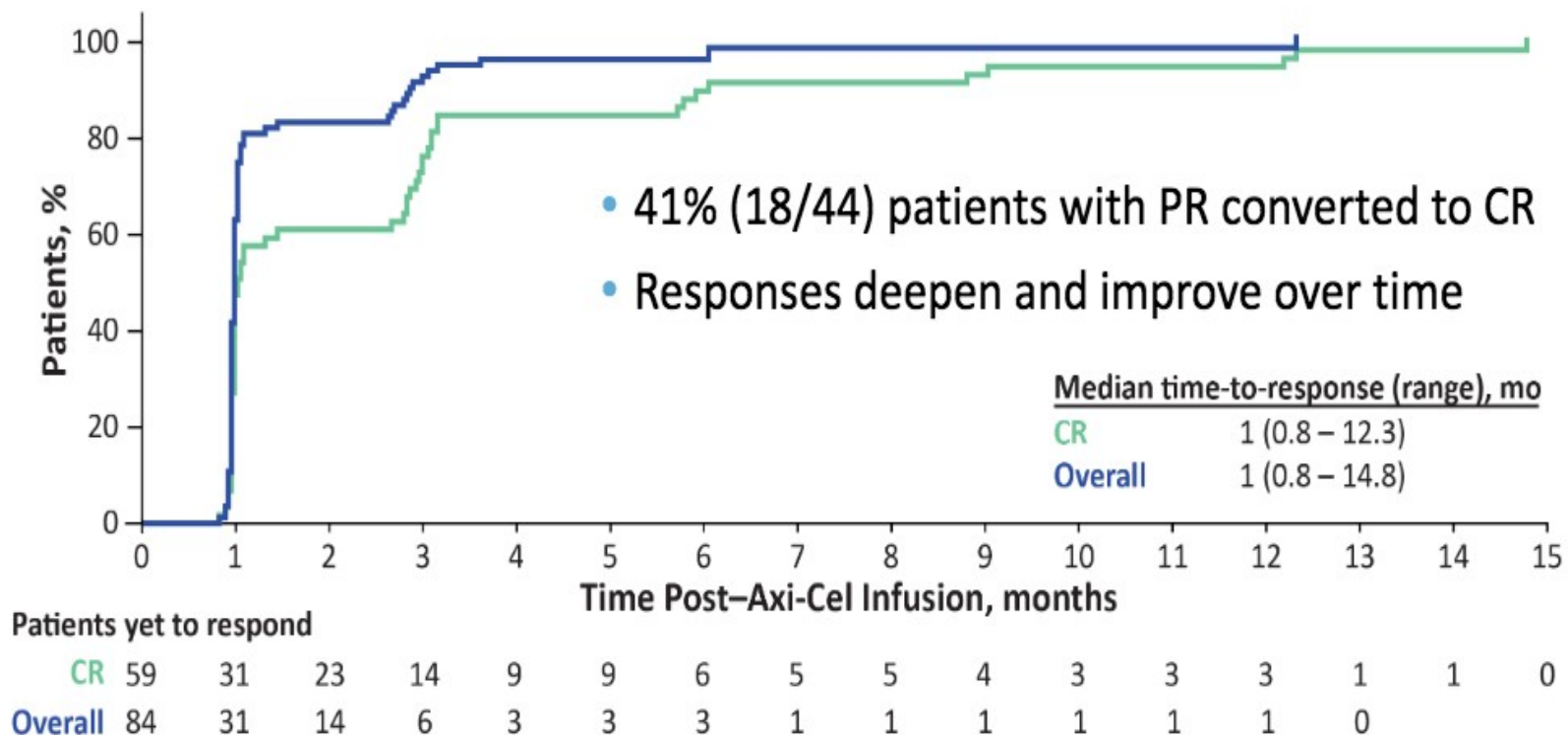
- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients have ongoing CR at 24 months

CR, complete response; NR, not reached; PR, partial response.

Neelapu et al. ASH. 2017; Abst 578.

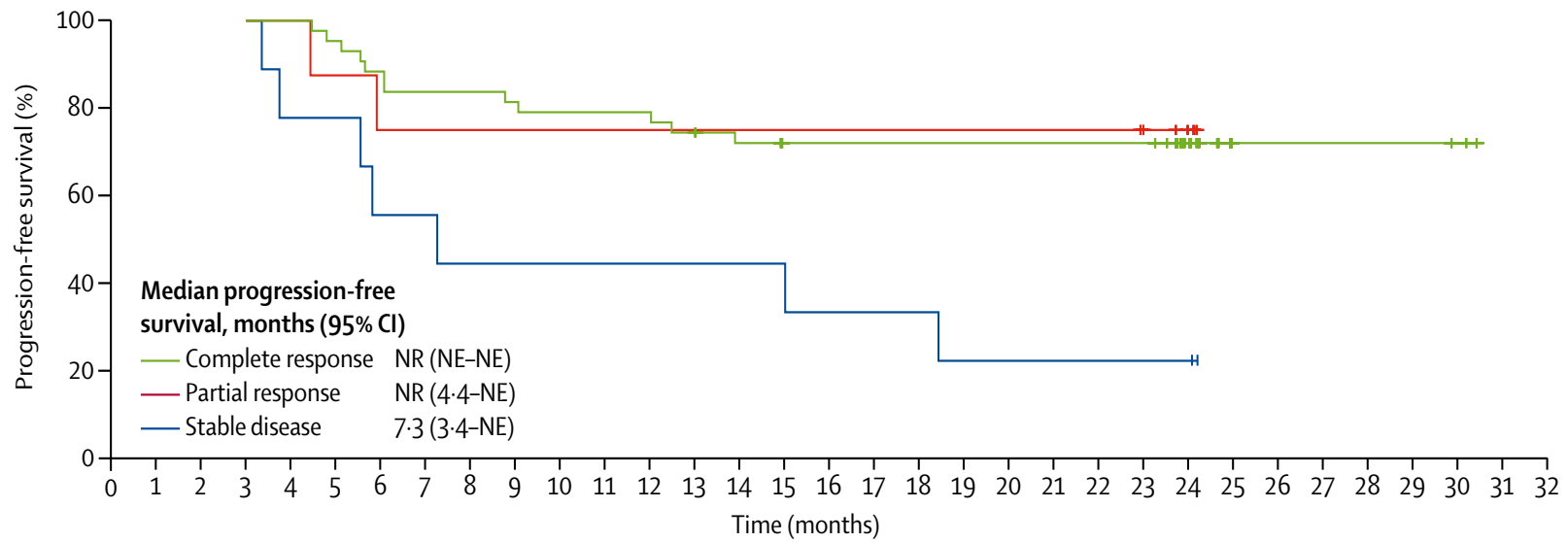


Time to objective response and complete response



Update PFS by M3 status

PFS BY RESPONSE STATUS AT M3



CAR T-cells in clinical trials

Les résultats des essais cliniques ne sont pas comparables entre-eux

- 1_ Etudes non randomisées
- 2_ Critères d'inclusion différents
- 3_ Produits cellulaires différents
- 4_ Délais de production différents
- 5_ Drop out different/population analysée différente

CAR T-cells in clinical trials

ZUMA-1¹

BOR (% , CMR, PMR)	74 (54/20)
---------------------------	------------

Landmark	OS (%)
6-months	78
12-months	60
18-months	53
24-months	51
36-months	47

JULIET²

BOR (% , CMR, PMR)	52 (40/12)
---------------------------	------------

Landmark	OS (%)
6-months	61
12-months	48
24-months	40

TRANSCEND³

BOR (% , CMR, PMR)	73 (53/20)
---------------------------	------------

Landmark	OS (%)
6-months	75
12-months	58

*Les résultats de ces études sont indépendants
et ne peuvent en aucun cas être comparés entre eux*

1- Locke FL et al, Lancet Oncol 2019; 20: 31. Neelapu SS et al, ASH 2019: #203;

2- Schuster et al, N Engl J Med 2019; 380: 45; Schuster et al ASH 2019: #

3- Abramson JS et al, ASH 2019; #241

CAR T-cells in clinical real-life

US Consortium¹

Yescarta[®]
N=274

BOR (% , CMR, PMR)	81 (57/24)
---------------------------	------------

Landmark	OS (%)
6-months	75

CIBMTR-1^{2, 3}

Kymriah[®]
N= 83

BOR (% , CMR, PMR)	58 (40/18)
---------------------------	------------

Landmark	OS (%)
6-months	67

UK Consortium⁴

Yescarta[®] ; Kymriah[®]
N=80

BOR Y (% , CMR, PMR)	37 (21/16)
-----------------------------	------------

BOR K (% , CMR, PMR)	28 (17/12)
-----------------------------	------------

Landmark	OS (%)
6-months	60

Yescarta[®]
N= 326

BOR (% , CMR, PMR)	84 (66/18)
---------------------------	------------

Landmark	OS (%)
6-months	75

**Les résultats de ces études sont indépendants
et ne peuvent en aucun cas être comparés entre eux**

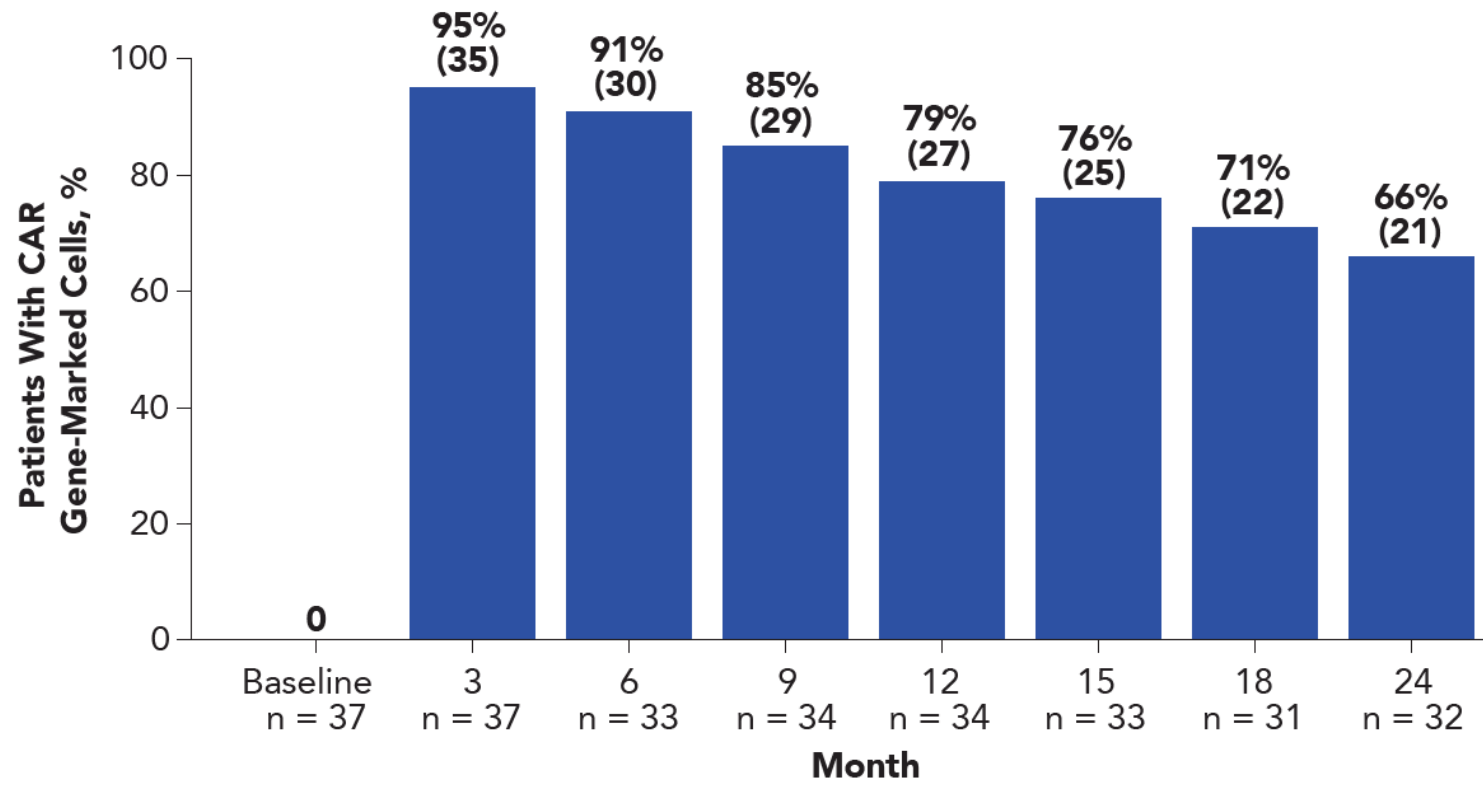
1- Jain MD et al, ASH 2019: #245

2- Jaglowski S et al, ASH 2019: #242

3- Pasquini MC et al, ASH:#764

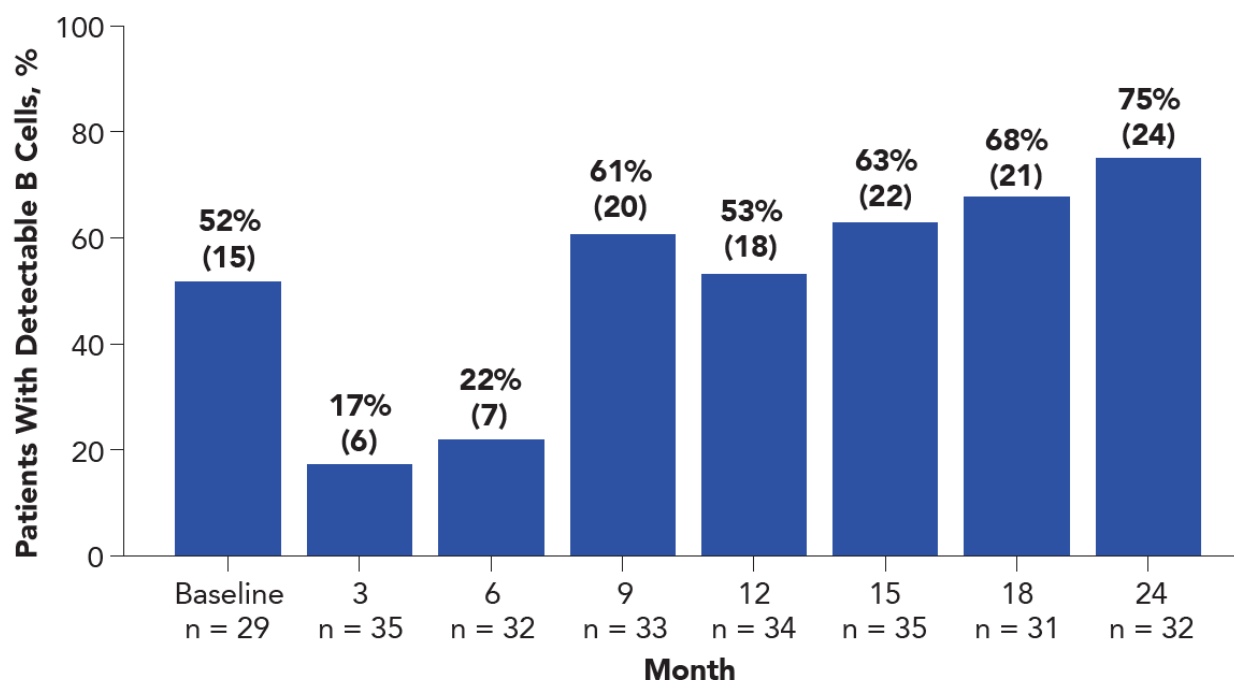
4- Kuhn A et al, ASH 2019: #767

Proportion of Patients With Detectable CAR Gene-Marked T Cells in Blood Among Patients With Ongoing Response Over Time



- The proportion of patients in ongoing response with detectable CAR T cells decreased over time

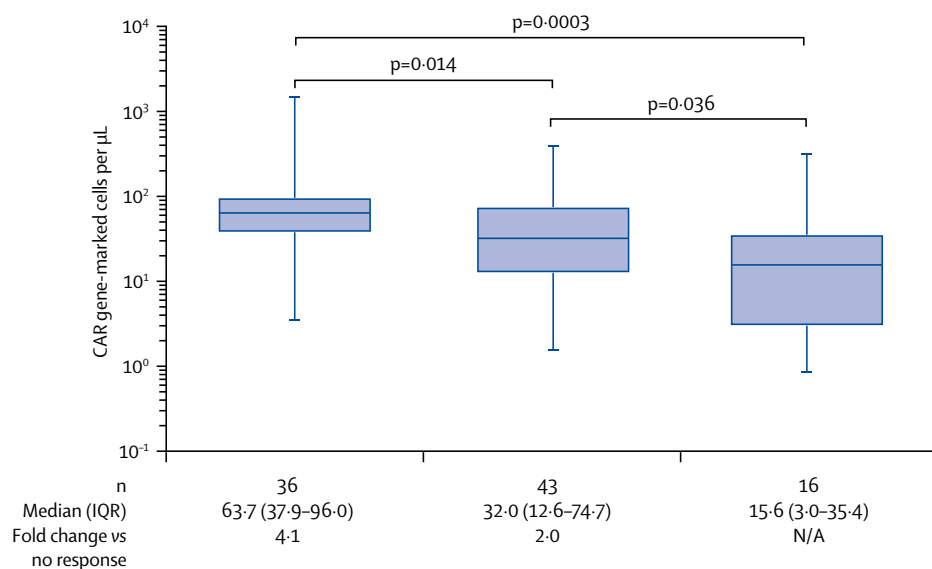
Proportion of Patients With Detectable B Cells in Blood Among Patients With Ongoing Response Over Time



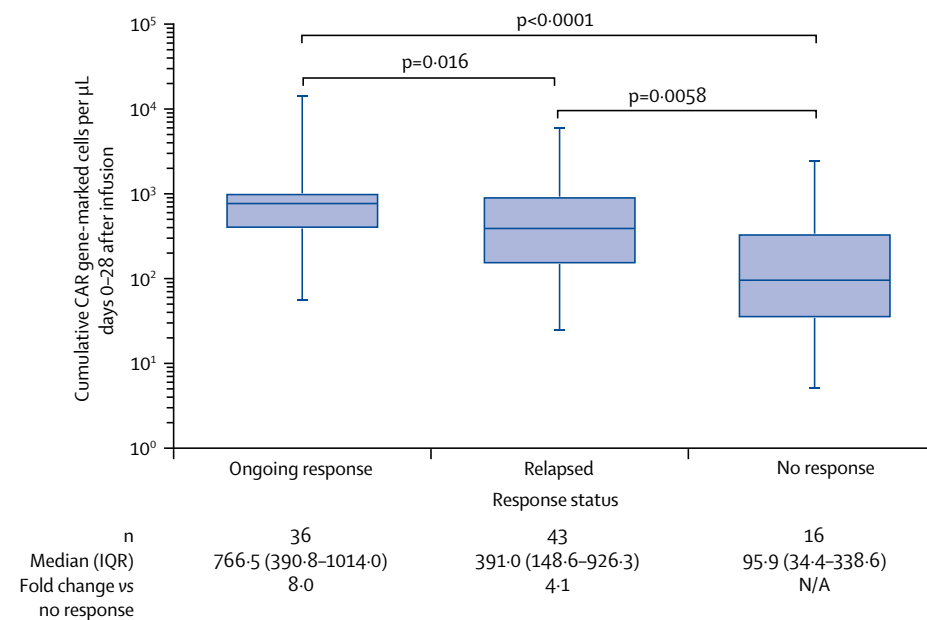
- 75% of patients (24/32) with ongoing responses had detectable B cells 2 years after axi-cel infusion
- Throughout the course of the study, 31% of patients received intravenous immunoglobulins

CAR-T cells concentrations by response

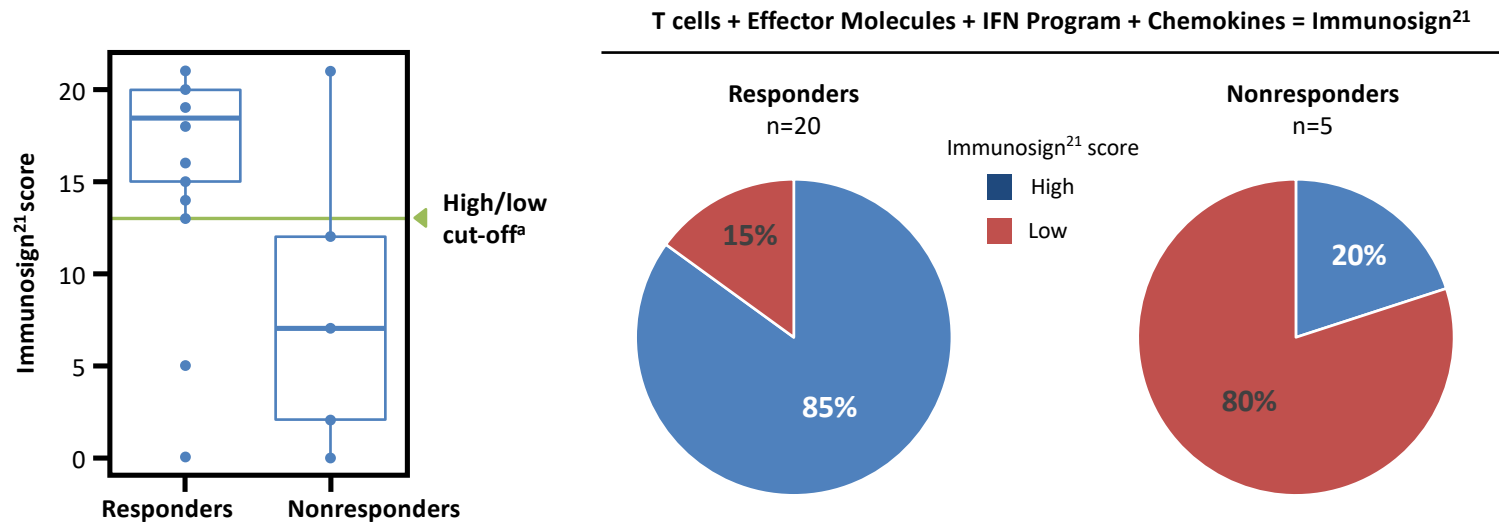
CART –cells peak of concentration



CART –cells AUC



Tumor microenvironment and response to CAR-T



- Analysis of samples from 25 ZUMA-1 patients treated with axicabtagene ciloleucel (minimum follow-up of 9 months)
- Immunosign²¹ is a pre-specified score based on the tissue expression of 21 genes with known immune function, comprising T cell activity-related genes
- A high Immunosign²¹ score was associated with objective responses at a minimum follow-up of 9 months (p=0.012)

Toxicities

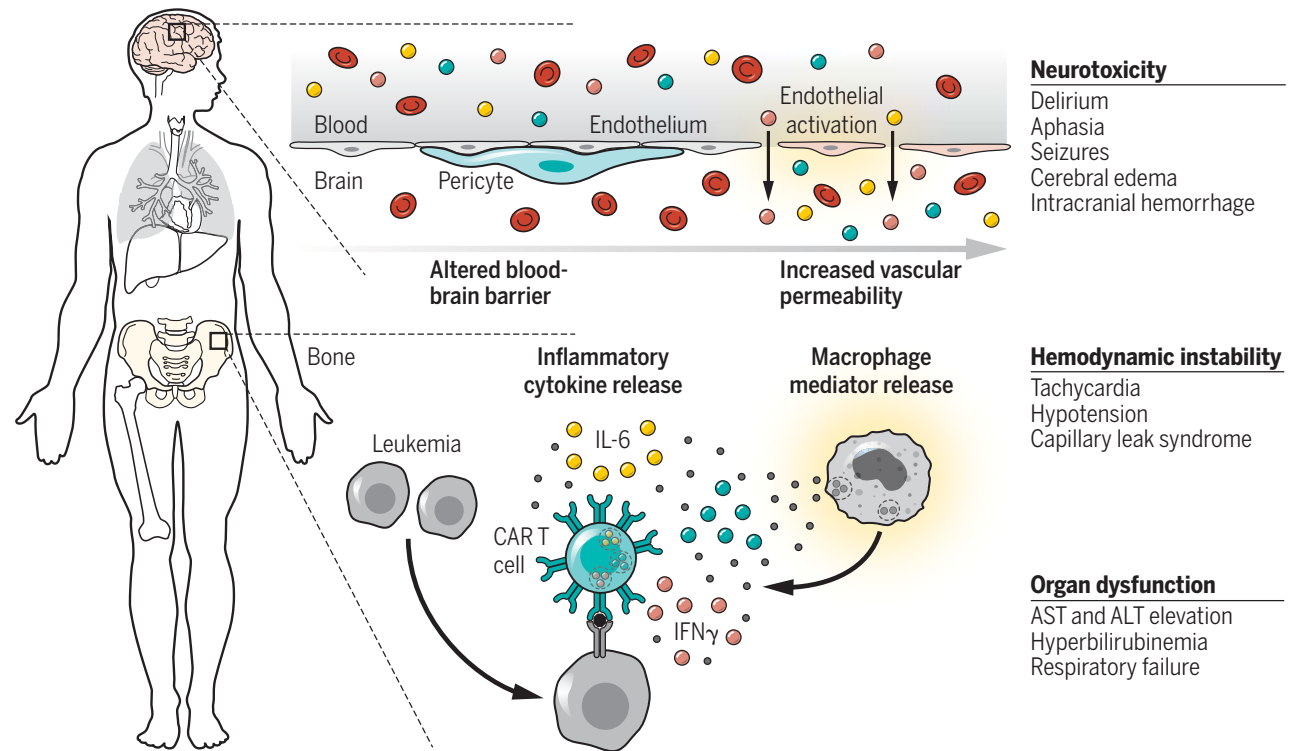


Cytokines Release Syndrome (CRS)



Neurotoxicities

Fig. 2. CAR T cell therapy is associated with cytokine release syndrome and neurotoxicity. Cytokine release syndrome has occurred with CAR T cells targeting CD19 or BCMA. When the CAR T cell engages surrogate antigens, it releases a variety of cytokines and chemokines. Macrophages and other cells of the innate immune system also become activated and contribute to the release of soluble mediators. CAR T cells are routinely observed in cerebral spinal fluid, and the cytokines may increase permeability to soluble mediators and permit increased trafficking of CAR T cells and other lymphocytes to central nervous system parenchyma. IFN, interferon; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

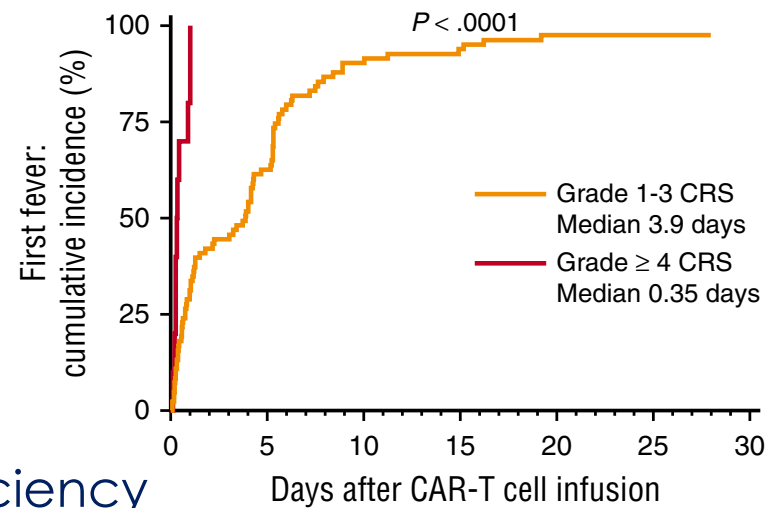


CREDITS (GRAPHIC) A. KITTERMAN/SCIENCE

Cytokines Release Syndrome

■ Symptoms

- Fever
- Hypotension
- Coagulopathy
- Capillary leak
- Respiratory and Cardiovascular insufficiency
- More frequent in ALL/NHL



CAR-T cells toxicities in real-life



	Nastoupil	Jacobson	ZUMA-1
Grade \geq 3 CRS (median)	7 % (3 j)	16 % (1 j)	13 % (2 j)
Grade \geq 3 neurotox (median)	33 % (6 j)	39 % (5 j)	28 % (5 j)
Tocilizumab	63 %	67 %	45 %
Corticoïdes	55 %	64 %	29 %
ICU	32 %	30 %	NA
Toxic deaths/ related	3 % / 1 %	7 % / ?	4 % / 2 %
Best ORR	81 %	71 %	82 %
Best RC	57 %	44 %	54 %

ASH 2018 – Nastoupil L, abstract 91 ; Jacobson C, abstract 92 ; Neelapu et al, NEJM 2017

Cytokines Release Syndrome: risk factors



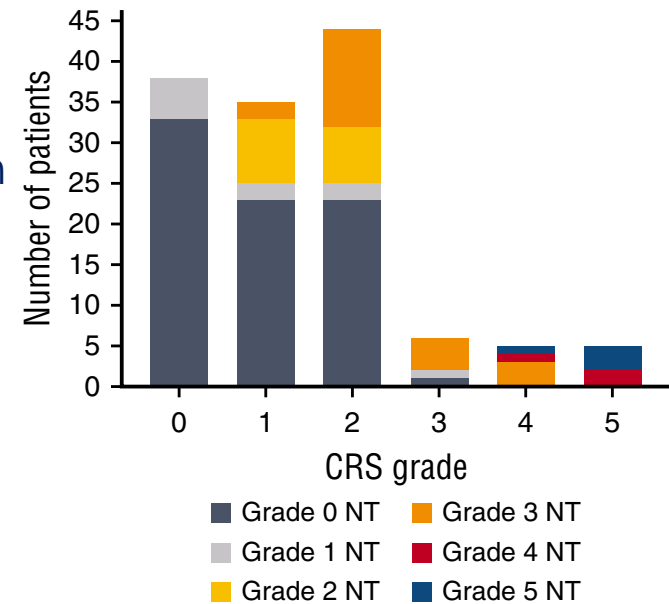
Risk factors
Marrow disease burden
Platelet count
CD8+ selection method
CPM-FDR lymphodepletion
CAR-T cells dose

Neurotoxicity: Symptoms

- Delirium
- Headache
- Decrease level of conscience or speech impairment
- Focal neurologic deficits
- Seizure
- Acute cerebral edema
- Usually after the onset of CRS or after its resolution
- More frequent in ALL/NHL

Neurotoxicity: mechanisms

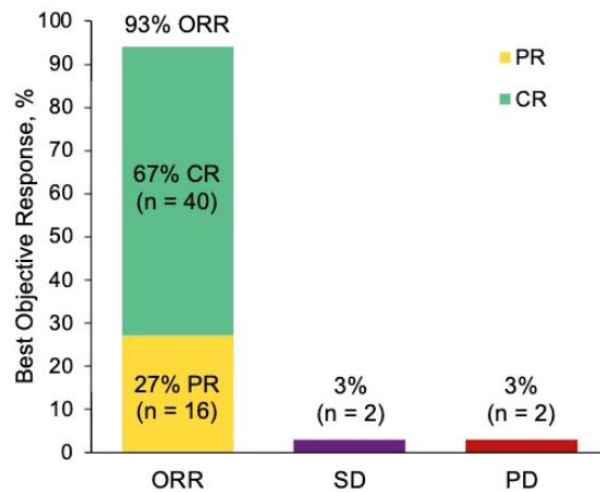
- Unknown
- Secondary to CRS:
 - Endothelial activation and vascular dysfunction
 - Hypotension, capillary leak, consumptive coagulopathy



CAR T-cells: Future Indications in Lymphoma

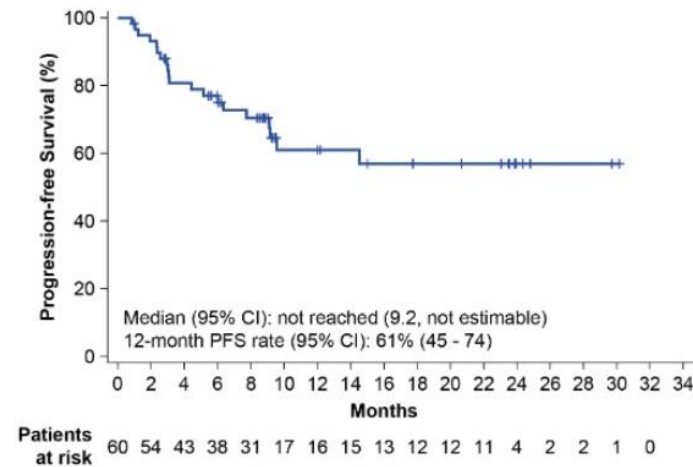
KTE-X19 in R/R Mantle Cell Lymphoma

OVERALL RESPONSE RATE

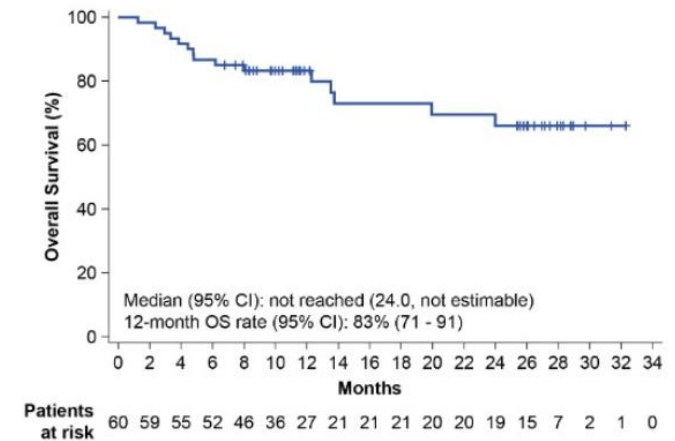


N=68, FU: 12.3 mo (7.0-32.3)

PROGRESSION-FREE SURVIVAL



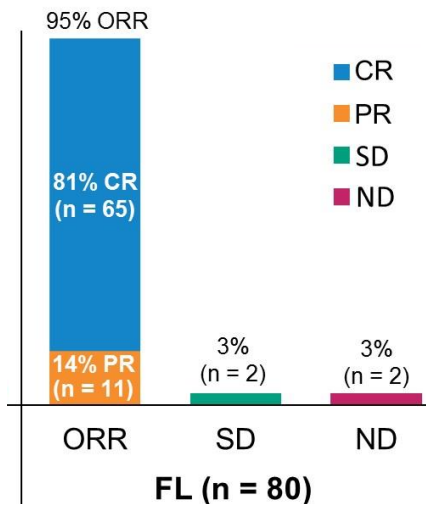
OVERALL SURVIVAL



CAR T-cells: Future Indications in Lymphoma

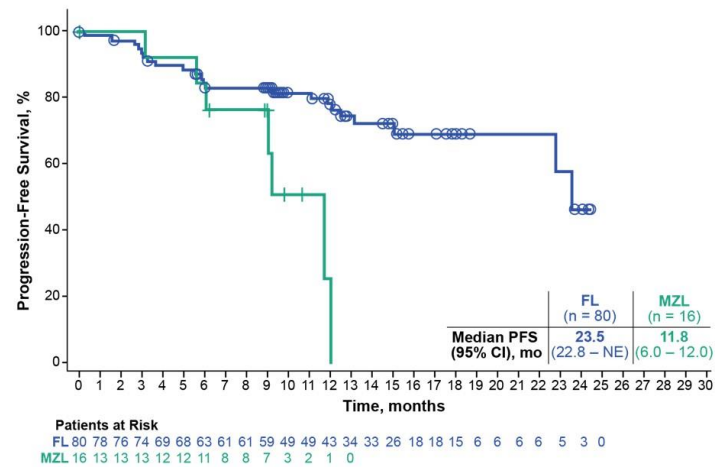
Yescarta in R/R Follicular Lymphoma

OVERALL RESPONSE RATE

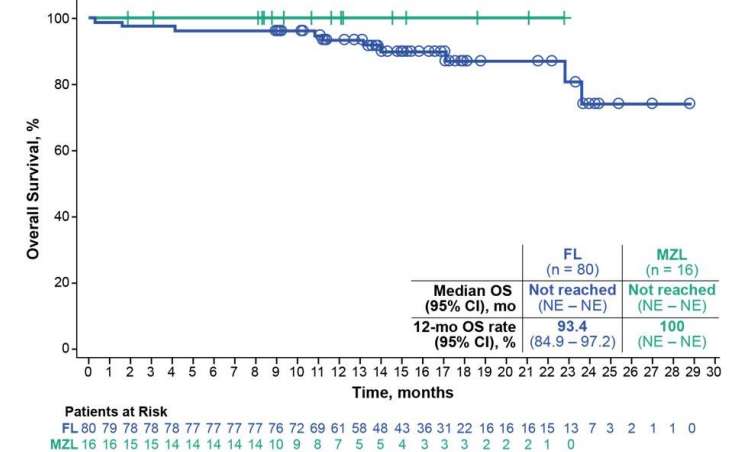


N=68, FU: 12.3 mo (7.0-32.3)

PROGRESSION-FREE SURVIVAL



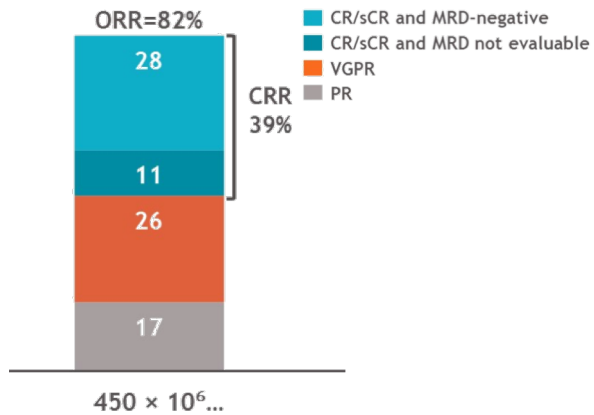
OVERALL SURVIVAL



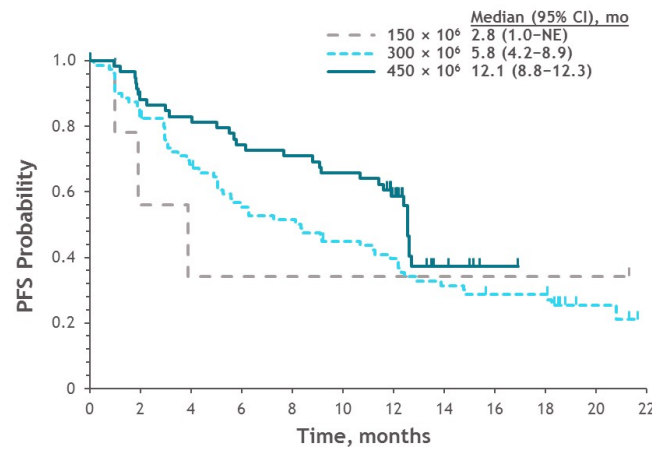
CAR T-cells: Future Indication in Myeloma

Idecaptagene vileucel in R/R Myeloma

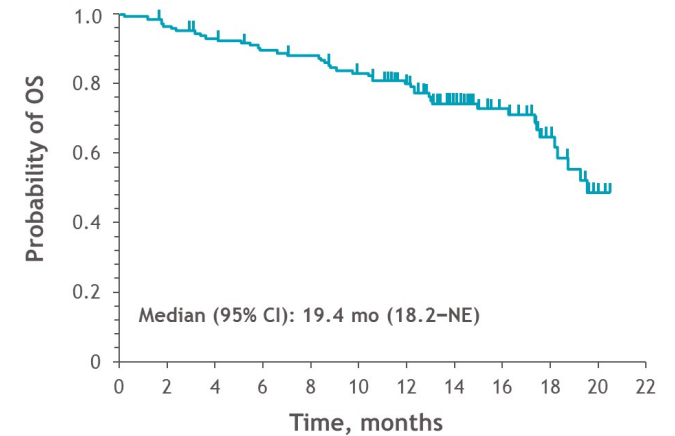
OVERALL RESPONSE RATE



PROGRESSION-FREE SURVIVAL



OVERALL SURVIVAL



CAR T-cells: CAR-T in 2021

1_ ALL R/R < 25 y

2_ ALL R/R > 25 y

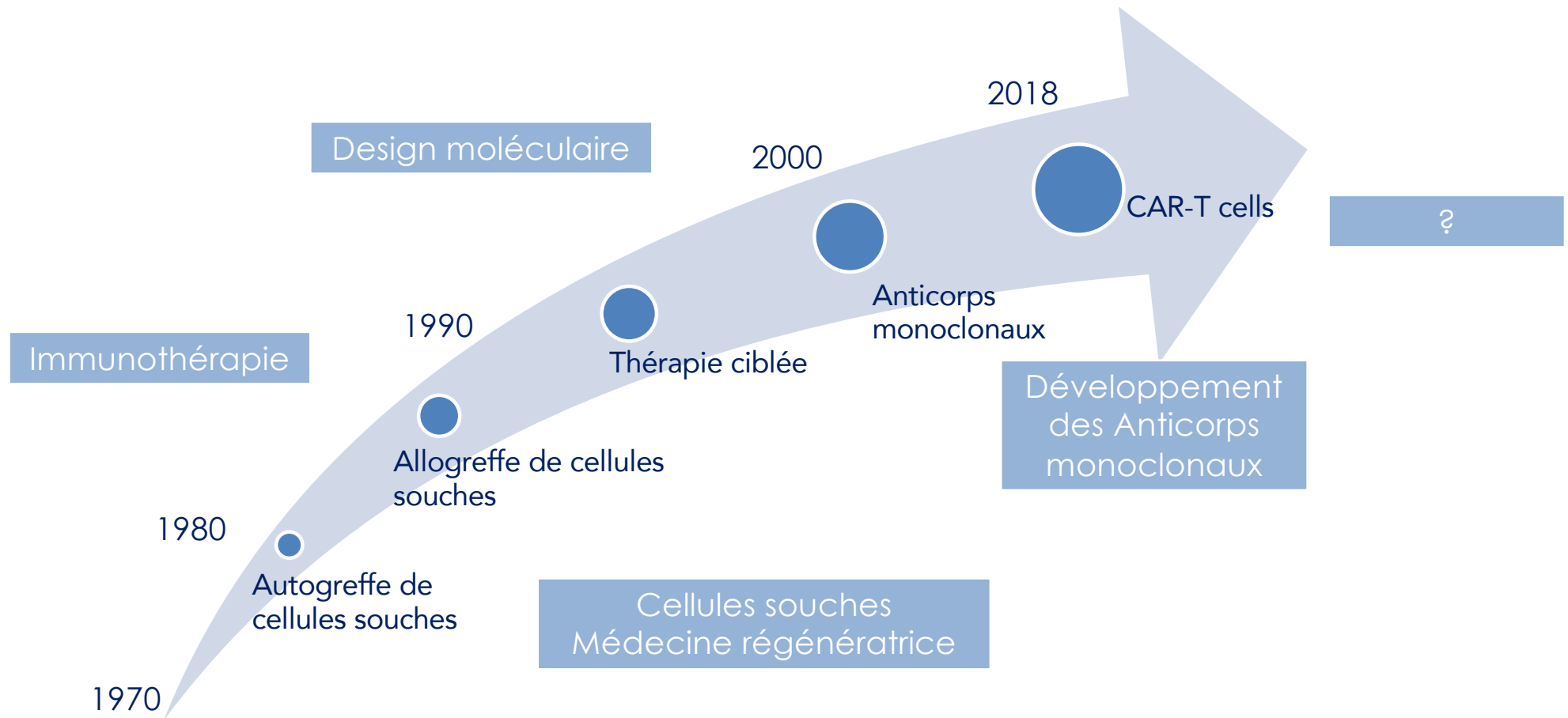
3_ DLBCL R/R > 2L

4_ MCL R/R > 3L

5_ Myeloma R/R > 3L

6_ FL R/R > 3 L

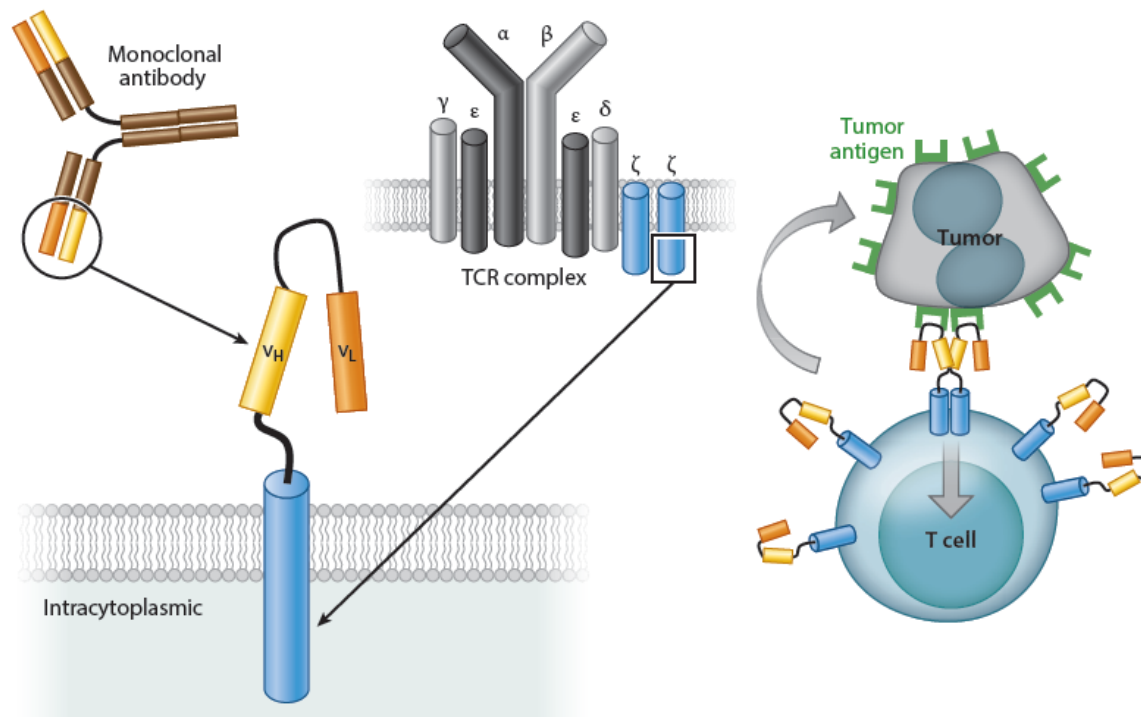
CART: Révolution médicale ?



CART: Révolution médicale?

- Une révolution thérapeutique?
- Une révolution « sociétale »?
- Une révolution médicale?

Le Concept



Nouvelles cibles

- Cancers
- Virus
- Auto-immunité

Nouvelles générations de CART

- Nouvelles cellules effectrices
 - autologue
 - allogénique
- Nouvelles constructions

CAR-T: nouvelles cibles potentielles

GASTROENTEROLOGY 2013;145:456-465

T Cells Expressing a Chimeric Antigen Receptor That Binds Hepatitis B Virus Envelope Proteins Control Virus Replication in Mice

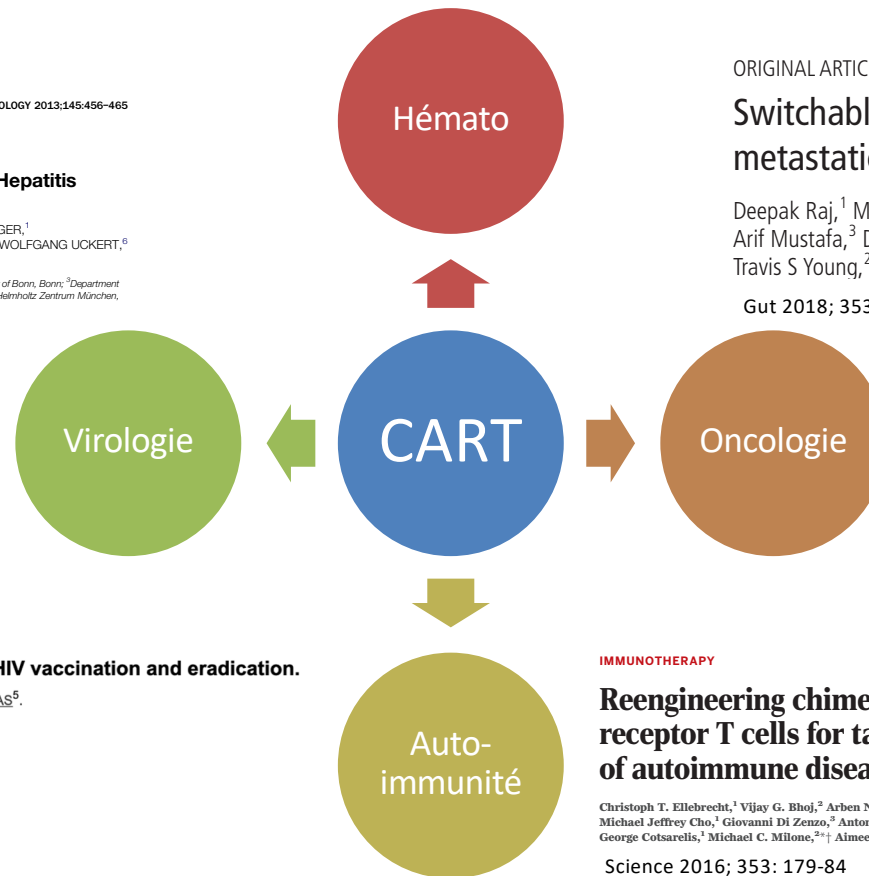
KARIN KREBS,^{1*} NINA BÖTTINGER,^{1*} LI-RUNG HUANG,² MARKUS CHMIELEWSKI,³ SILKE ARZBERGER,¹ GEORG GASTEIGER,¹ CLEMENS JÄGER,¹ EDGAR SCHMITT,⁴ FELIX BOHNE,¹ MICHAELA AICHLER,⁵ WOLFGANG UCKERT,⁶ HINRICH ABKEN,³ MATHIAS HEIKENWALDER,¹ PERCY KNOLLE,² and ULRIKE PROTZER¹

¹Institute of Virology, Technische Universität München/Heinrich-Zentrum München, München; ²Institute of Molecular Medicine, University of Bonn, Bonn; ³Department of Internal Medicine I, University Hospital Cologne, Köln; ⁴Institute for Immunology, University of Mainz, Mainz; ⁵Institute of Pathology, Heinrich-Zentrum München, München; ⁶Institute of Pathology, Heinrich-Zentrum München, München

J Cell Physiol. 2019 Feb 18. doi: 10.1002/jcp.28280. [Epub ahead of print]

Memory and CAR-NK cell-based novel approaches for HIV vaccination and eradication.

Mazarzaei A¹, Vafaei M², Ghasemian A³, Mirforoughi SA⁴, Rajabi Vardanjani H⁴, Alwan NAS⁵.



ORIGINAL ARTICLE

Switchable CAR-T cells mediate remission in metastatic pancreatic ductal adenocarcinoma

Deepak Raj,¹ Ming-Hsin Yang,¹ David Rodgers,² Eric N Hampton,² Julfa Begum,¹ Arif Mustafa,³ Daniela Lorizio,¹ Irene Garces,¹ David Propper,⁴ James G Kench,⁵ Travis S Young,² Alexandra Aicher,¹ Christopher Heeschen⁶

Gut 2018; 353: 179-84

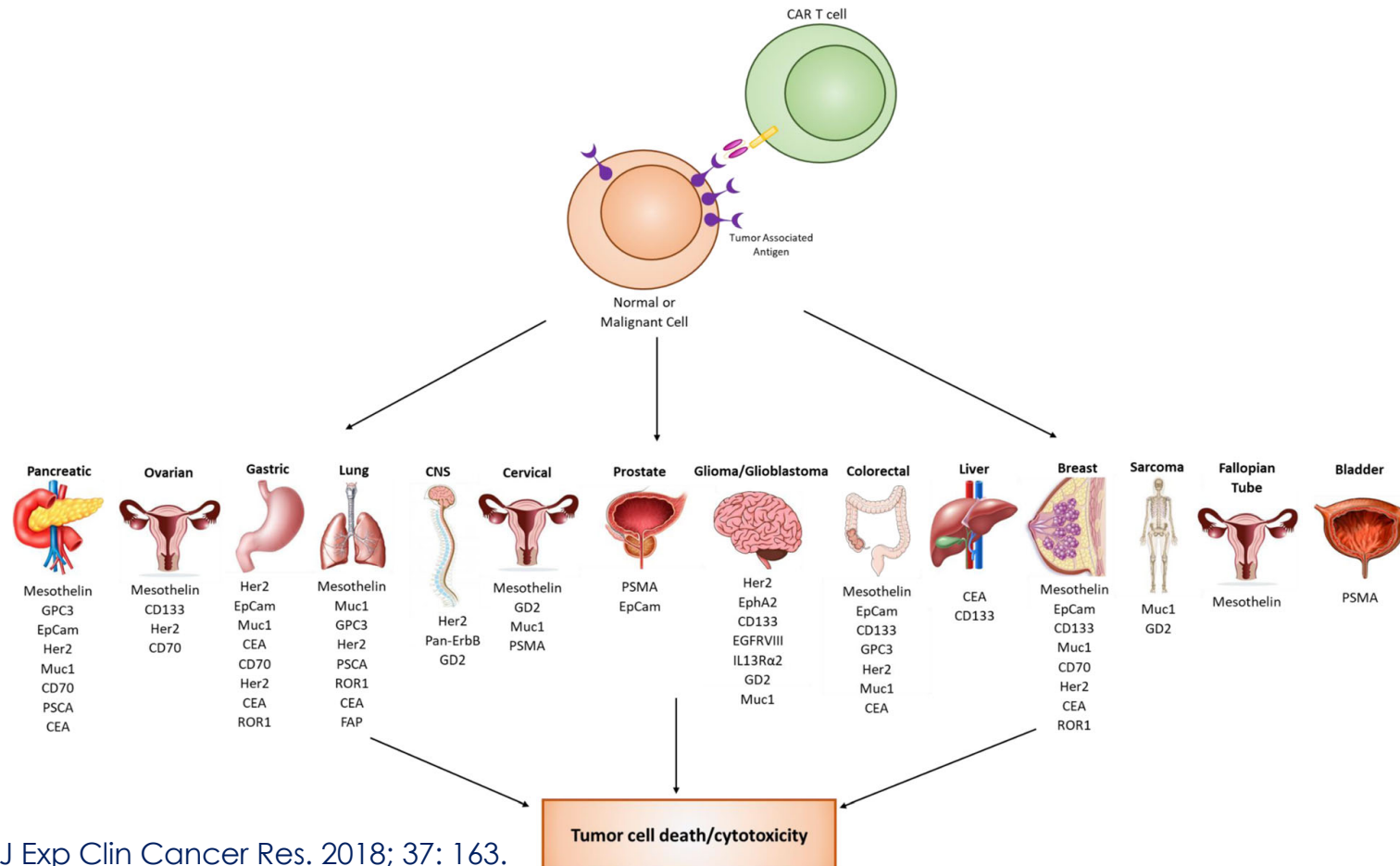
IMMUNOTHERAPY

Reengineering chimeric antigen receptor T cells for targeted therapy of autoimmune disease

Christoph T. Ellebrecht,¹ Vijay G. Bhoj,² Arben Nace,¹ Eun Jung Choi,¹ Xuming Mao,¹ Michael Jeffrey Cho,³ Giovanni Di Zenzo,² Antonio Lanzavecchia,⁴ John T. Seykora,¹ George Cotsarelis,¹ Michael C. Milone,^{2†} Aimee S. Payne^{2,†}

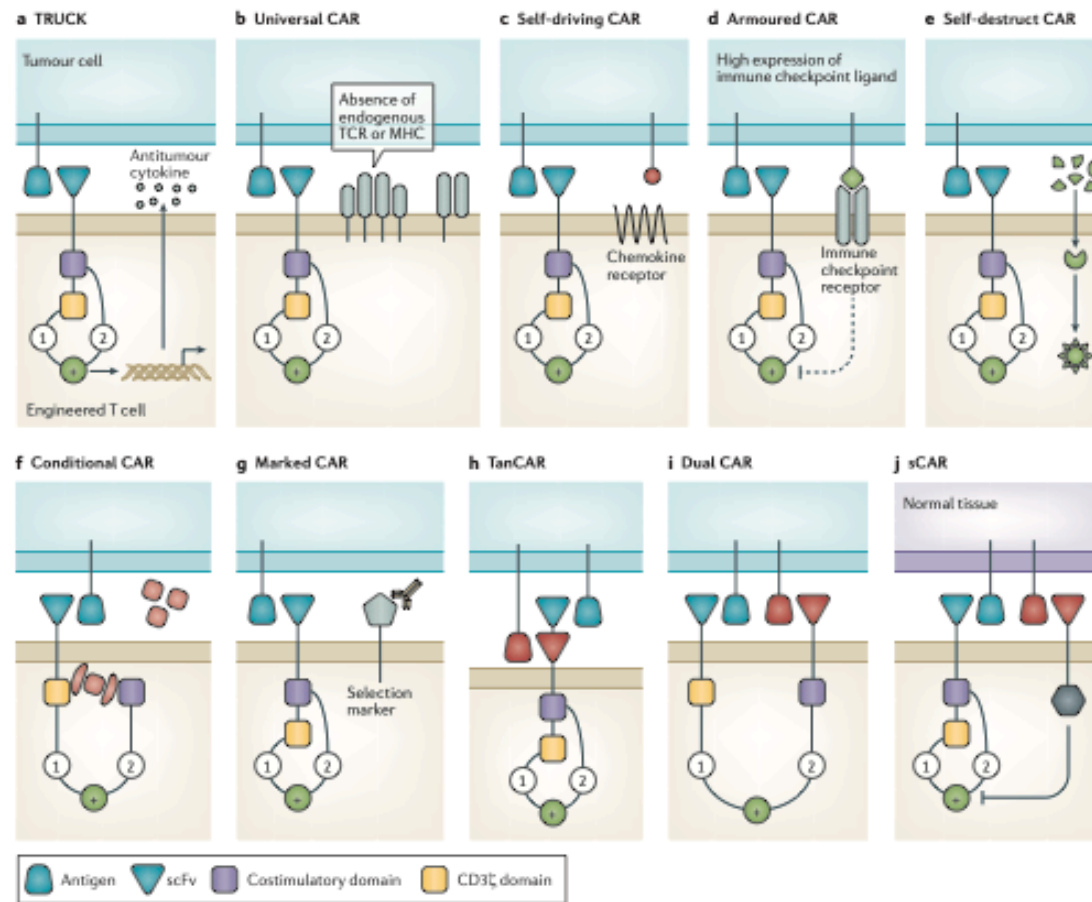
Science 2016; 353: 179-84

CAR-T et Cancer



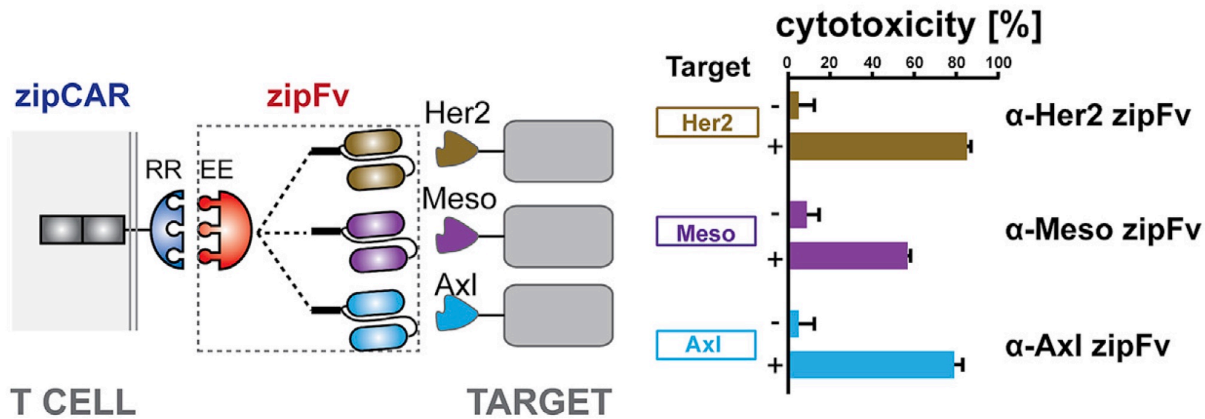
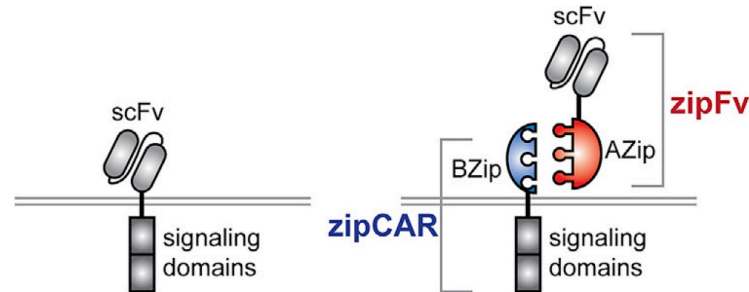
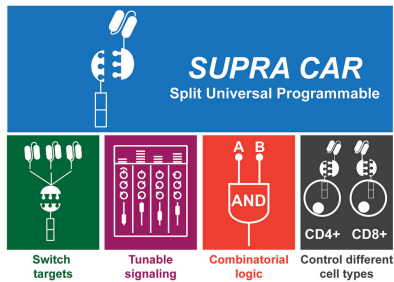
Townsend MH et al. J Exp Clin Cancer Res. 2018; 37: 163.

Future for CAR-T



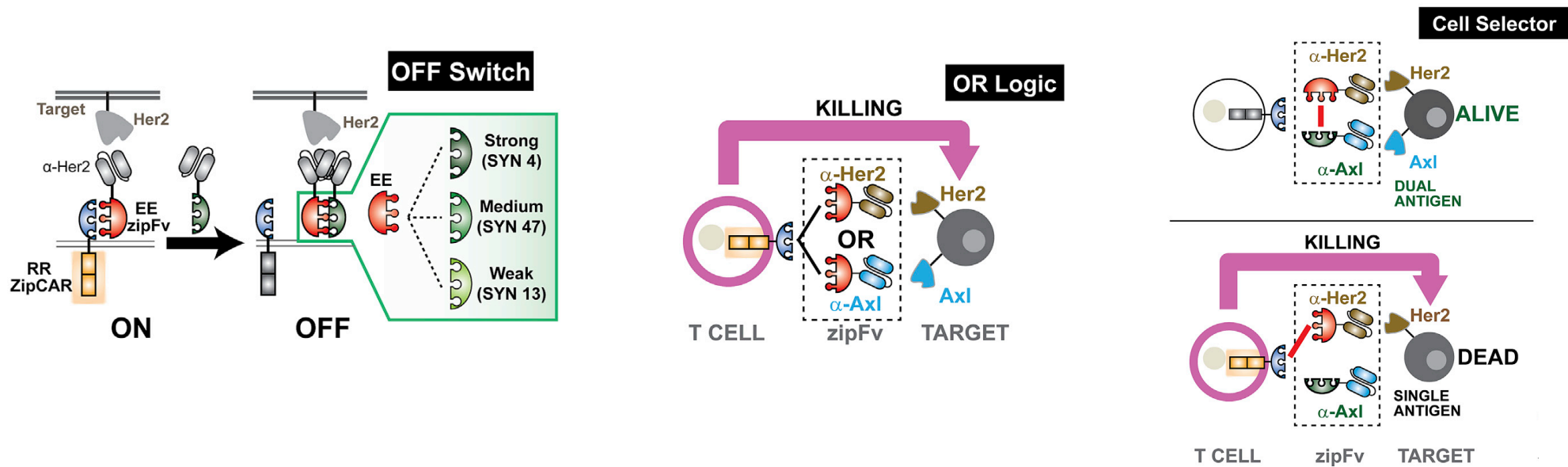
SUPRA CAR: split, universal, and programmable (SUPRA) CAR system

to switch targets without re-engineering the T cells



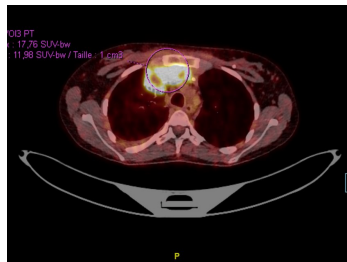
SUPRA CAR: split, universal, and programmable (SUPRA) CAR system

To finely tune T cell activation strength
To sense and logically respond to multiple antigens

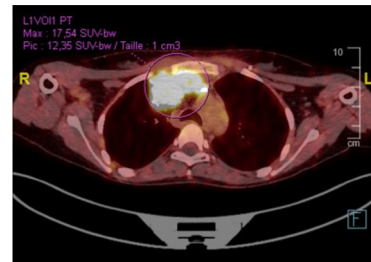


CAR-T in Montpellier

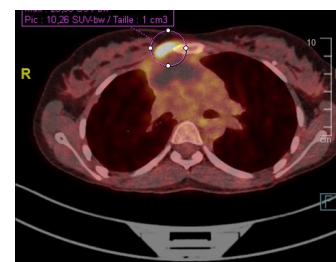
- Female, 18 years old
- DLBCL R/R disease 7L of treatments



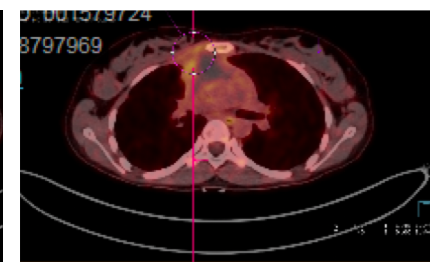
Before
infusion



M1 post-
infusion



M2 post-
infusion



M3 post-
infusion

- Au 22 sept:
 - 50 patients infused
 - 10 planned for infusion before end of nov



Département hématologie adulte Département hématologie pédiatrique

Pr Sirvent, Dr Sirvent, Dr Haouy

Pharmacie St Eloi

Dr A Quintard, Dr I Roch-Toreilles

Réanimation médicale et chirurgicale

Dr L Platon, Pr K klouche

Dr A de Jong, Pr S Jaber

Département de neurologie

Dr X Ayrignac, Pr P Labauge

Unité de thérapie cellulaire

Pr J de Vos, AM Conge

Département d'information médicale

Dr I Girault, Dr Lehman

Administration centrale

Mr Le Ludec, Mr Du Chaffault, Mme A Moulin

