

# CAR-T Cells: Progress in Haematological Malignancies

**Gerhard Ehninger**

Prof. em. Internal Medicine  
Technical University Dresden

CEO Cellex and CMO GEMoaB (Dresden+Cologne)

February 10-12, 2020  
*CDDF Conference*

# Potential Conflicts of Interest

## **1. Positions and Ownership**

CMO GEMoaB GmbH and CEO Cellex GmbH  
Ownership GEMoaB and Cellex

## **2. Consultant**

Janssen

## **3. Stock**

BMS, Fresenius, Qiagen

## **4. Speaker**

-

## **5. Financial Support**

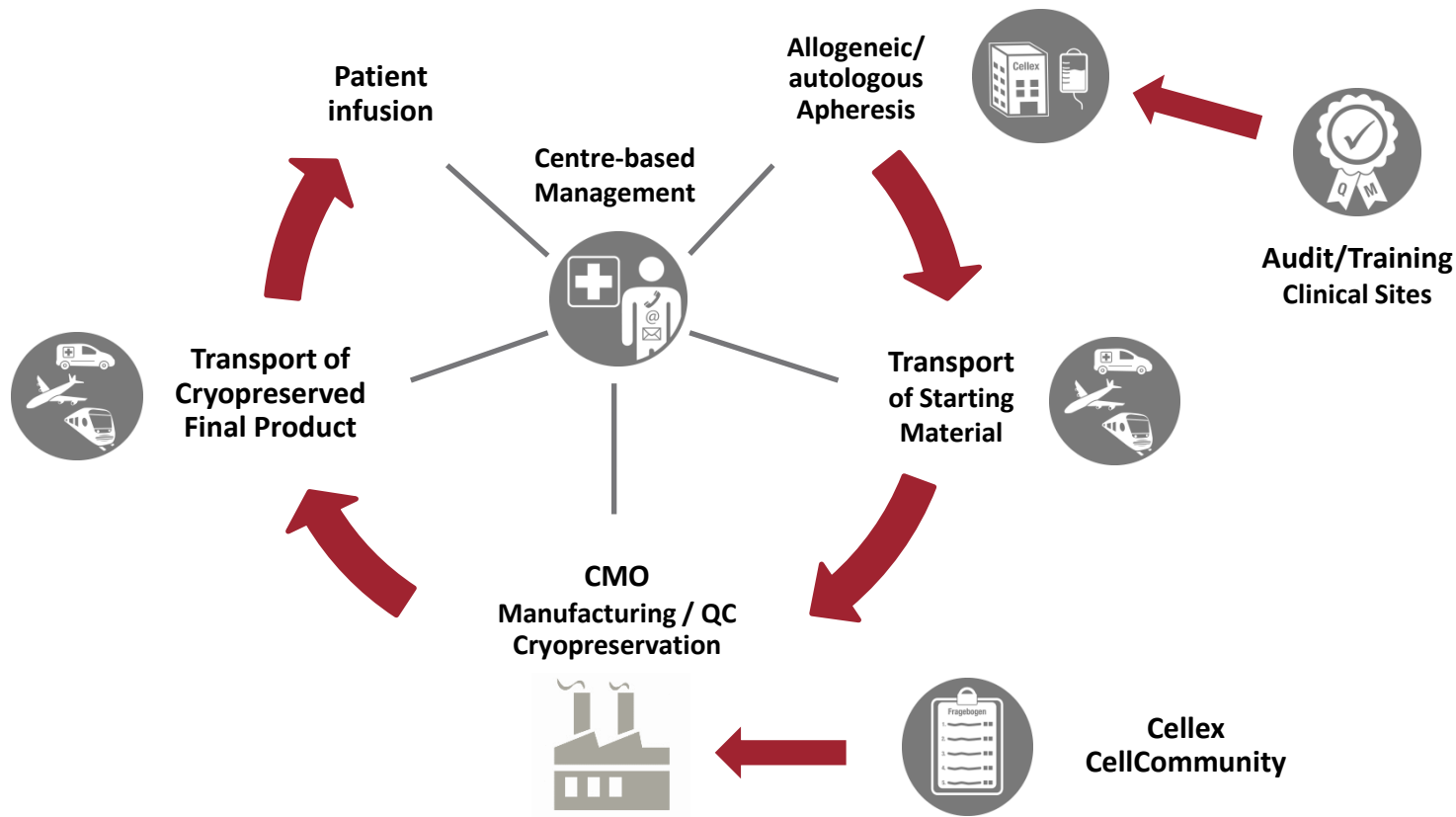
BMS (Celgene)

## **6. Any Other Relationship**

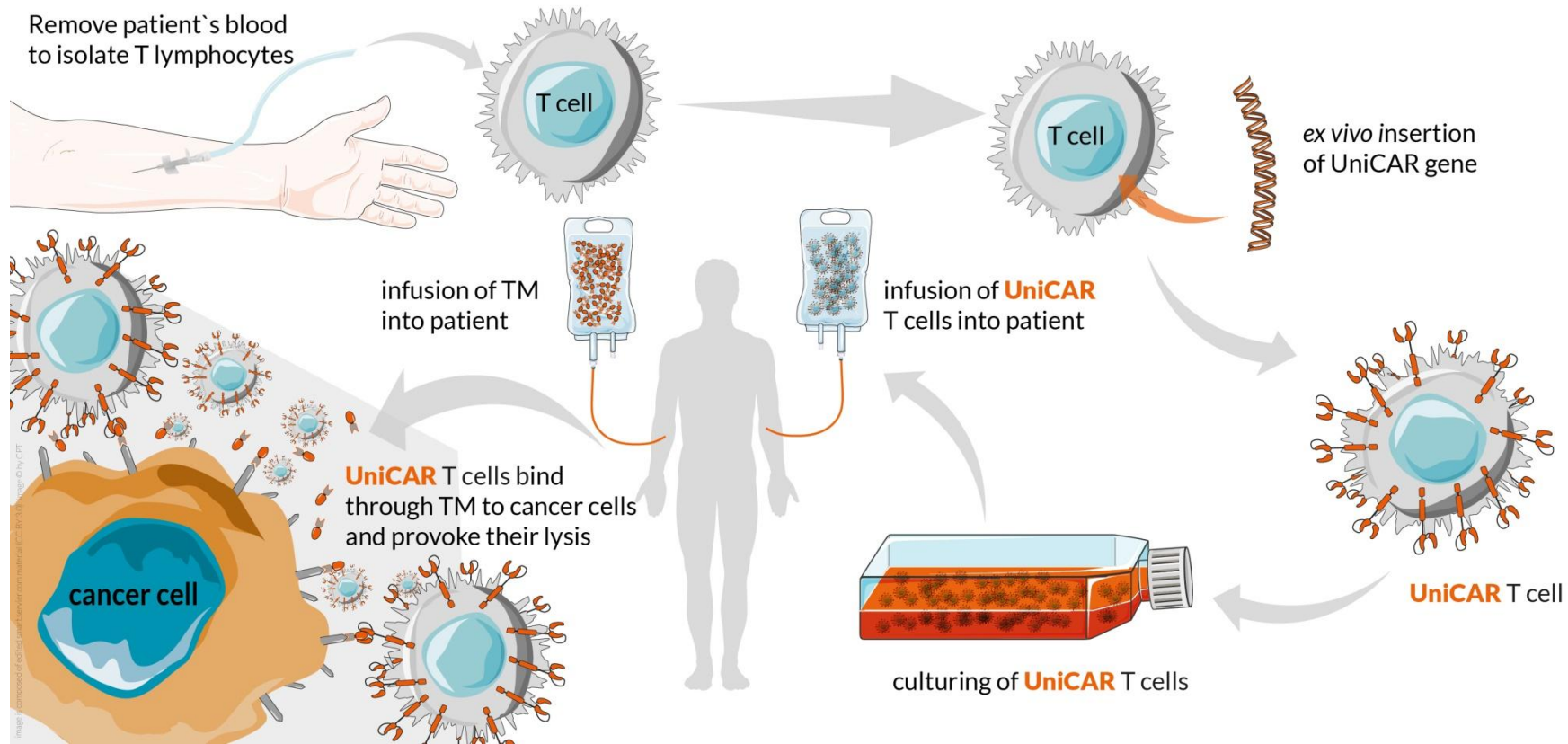
-

Source – Wells Fargo Securities Conference, November 2017

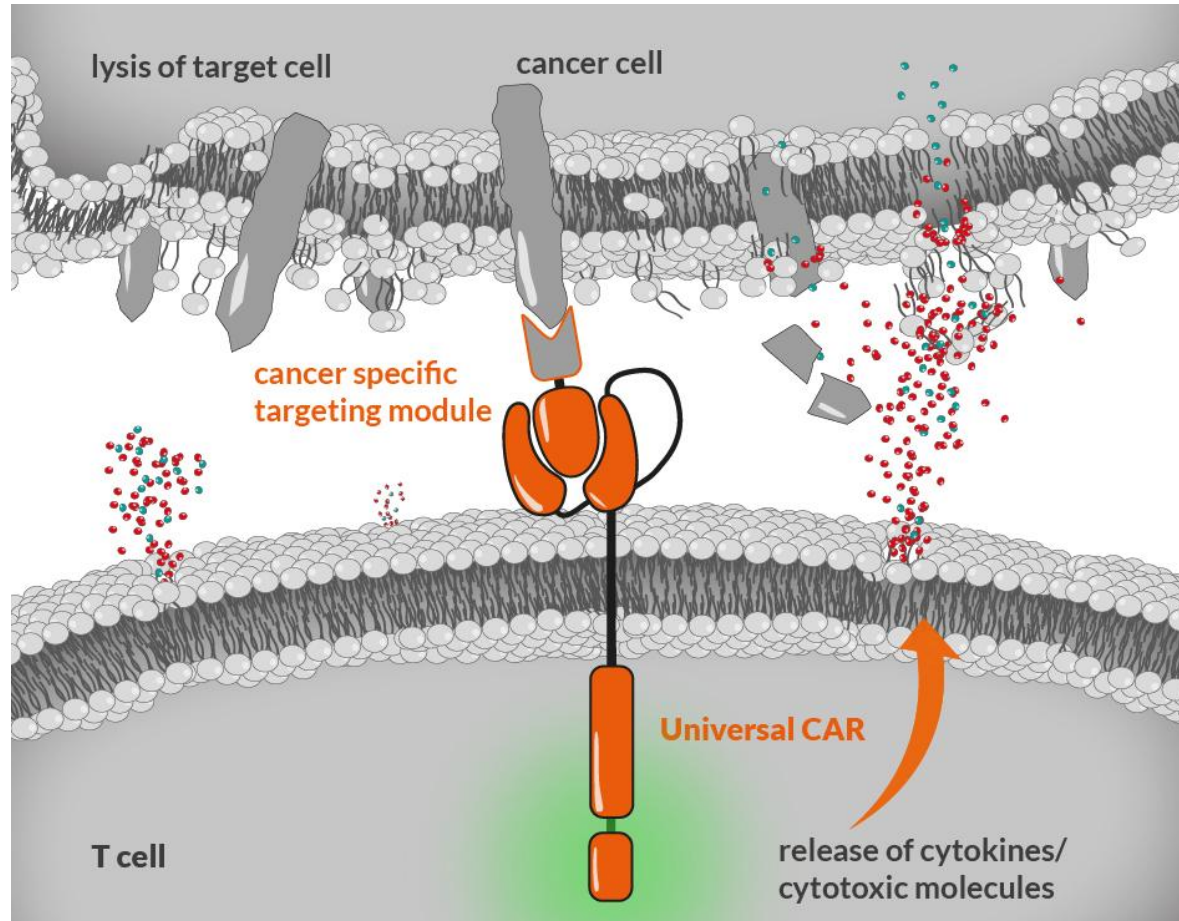
# CAR-T: Manufacturing of a Complex Cellular Product



# Autologous UniCAR02-T production cycle



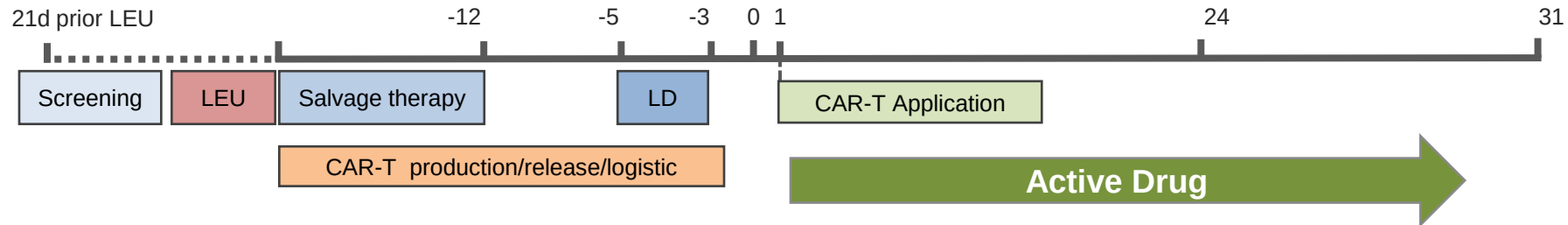
# UniCAR-T: TM-dependent activation and lysis



# General problems for all cellular therapies

- Setting up a reliable, consistent and scalable manufacturing system
- Automation needed
- Allogeneic products needed for immediate treatment
- Limited supply resources for goods
- Road blocks by multiple patents
- (Excessively) high pricing
- Regulatory hurdles

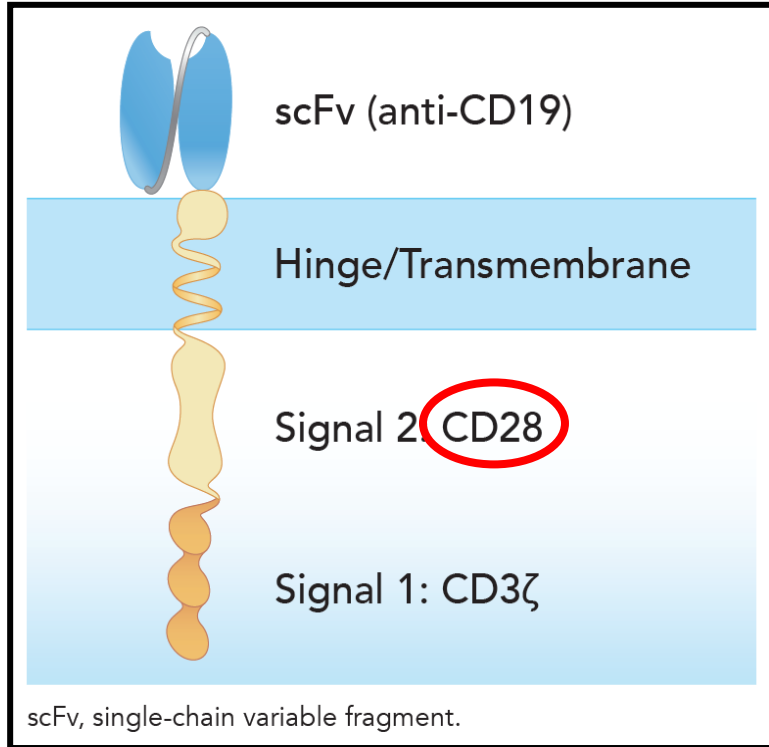
# CAR-T Dosing and Scheduling



# Diffuse Large B-Cell-Lymphoma

## CD19-CAR-T-Cells – Axicaptagen-Ciloleucel („ZUMA-1“)

(Locke et al, Lancet Oncol 20: 31, 2019)



119 patients with refractory/relapsed  
DLBCL, PMBCL oder tFL  
108 received Axi-Cel  
101 with median Follow-up of 27 months

Lymphodepletion Fludarabin-Cyclophosphamide  
Intervall apheresis – reinfusion: 17 days

|                          |      |
|--------------------------|------|
| Overall response rate    | 83 % |
| Complete remission       | 58 % |
| Remission $\geq$ 2 years | 39 % |

### Grad 3/4-adverse events

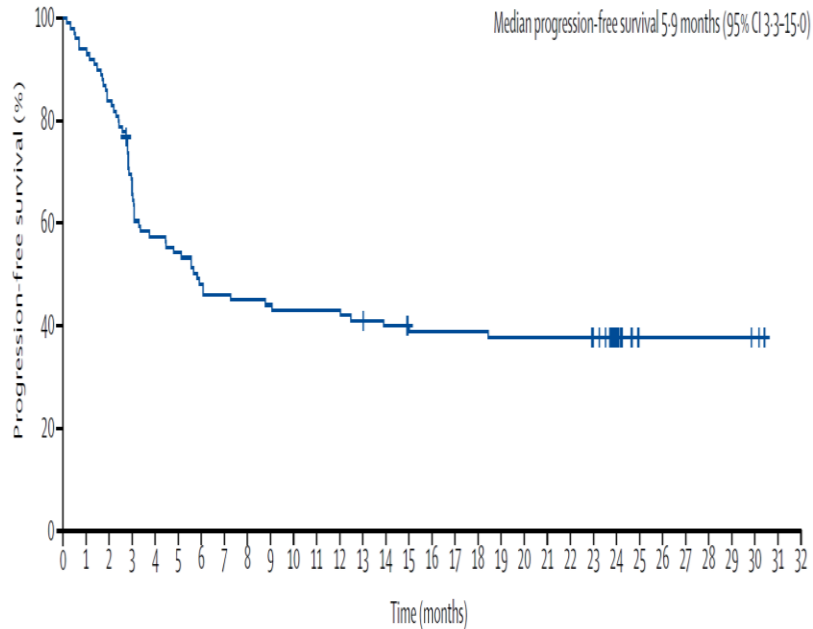
|               |                                       |
|---------------|---------------------------------------|
| ‘CRS’         | 11 % (start day 2 / Duration 8 days)  |
| Neurotoxicity | 32 % (start day 5 / Duration 17 days) |

# Diffuse Large B-Cell-Lymphoma

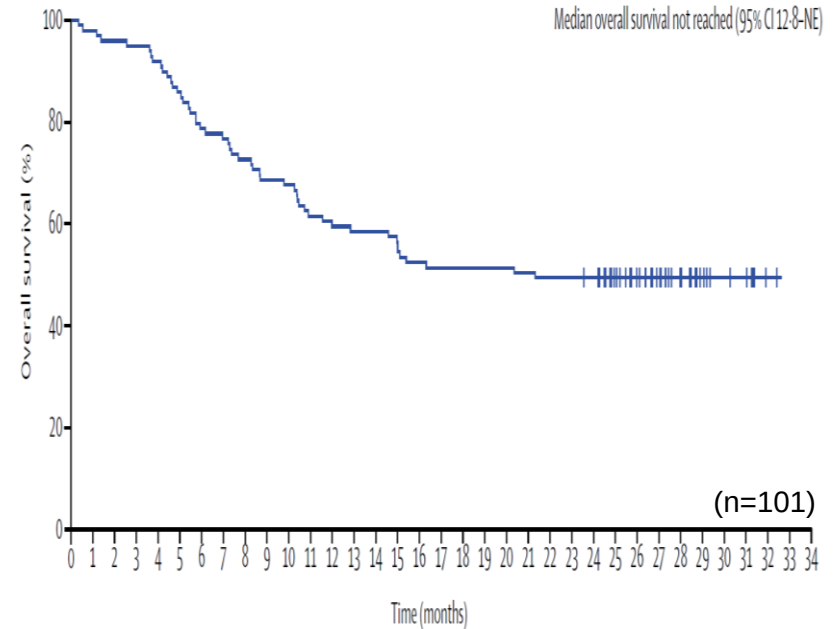
## *CD19-CAR-T-Cells – Axicaptagen-Ciloleucel (,ZUMA-1‘)*

(Locke et al, Lancet Oncol 20: 31, 2019)

### Progression-free survival

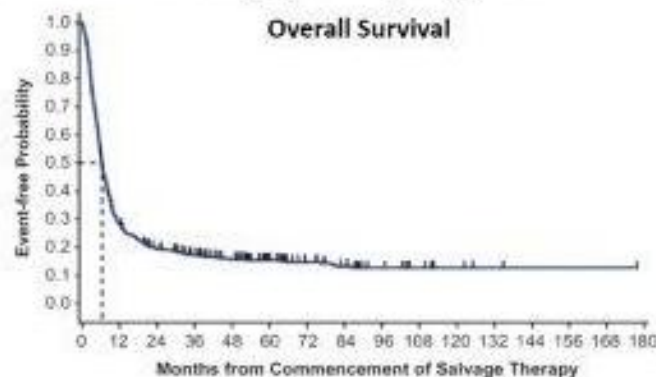


### Overall survival



## Background – SCHOLAR-1 (Retrospective Non-Hodgkin Lymphoma Research)

- SCHOLAR-1, a retrospective, international, patient-level, multi-institution study and the largest reported analysis of outcomes in patients with refractory large B cell lymphoma, demonstrated that these patients have a very poor prognosis<sup>1</sup>
  - N = 636 (post-rituximab era, 2000-2017)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 mo
  - These results provided a benchmark for evaluation of new approaches
- Previous analyses of SCHOLAR-1 standardized to ZUMA-1 with  $\geq 6$  mo follow-up suggested the benefit of axi-cel in refractory large cell lymphoma<sup>2</sup>



CR, complete response; ORR, objective response rate; OS, overall survival.

1. Crump M, et al. *Blood*. 2017;130:1800-1808. 2. Neelapu SS, et al. *Ann Oncol*. 2017;28(suppl 5): v403-v427 (abst1161P).

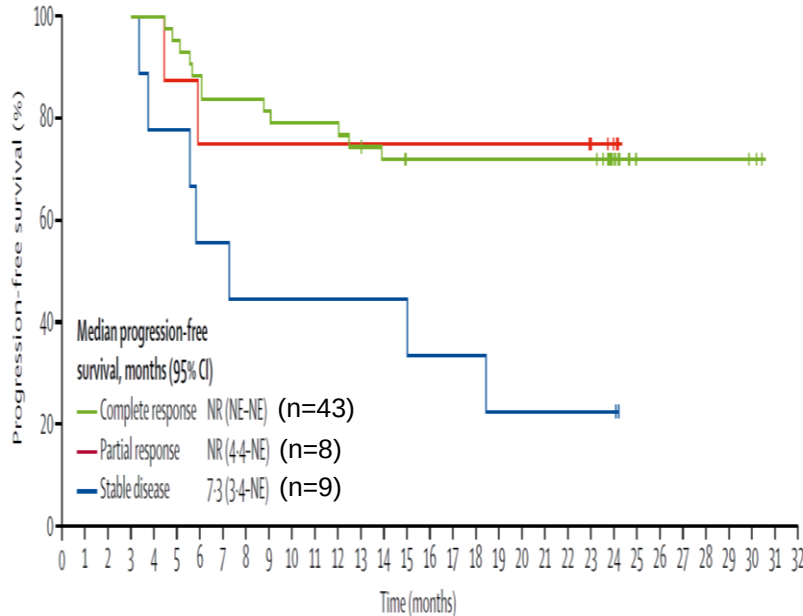


# Diffuse Large B-Cell-Lymphoma

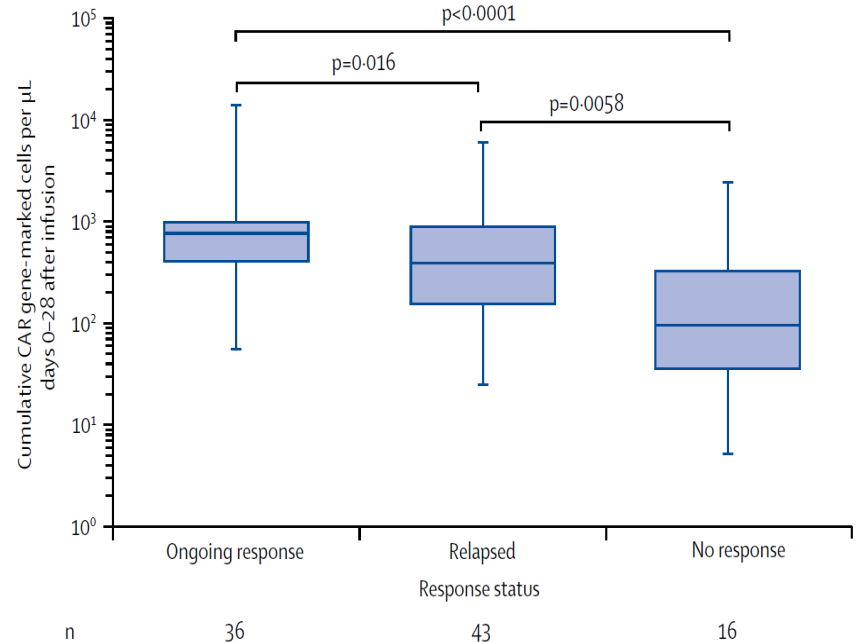
## CD19-CAR-T-Cells – Axicaptagen-Ciloleucel (,ZUMA-1')

(Locke et al, Lancet Oncol 20: 31, 2019)

### PFS and response rate



### Response rate and cell dose

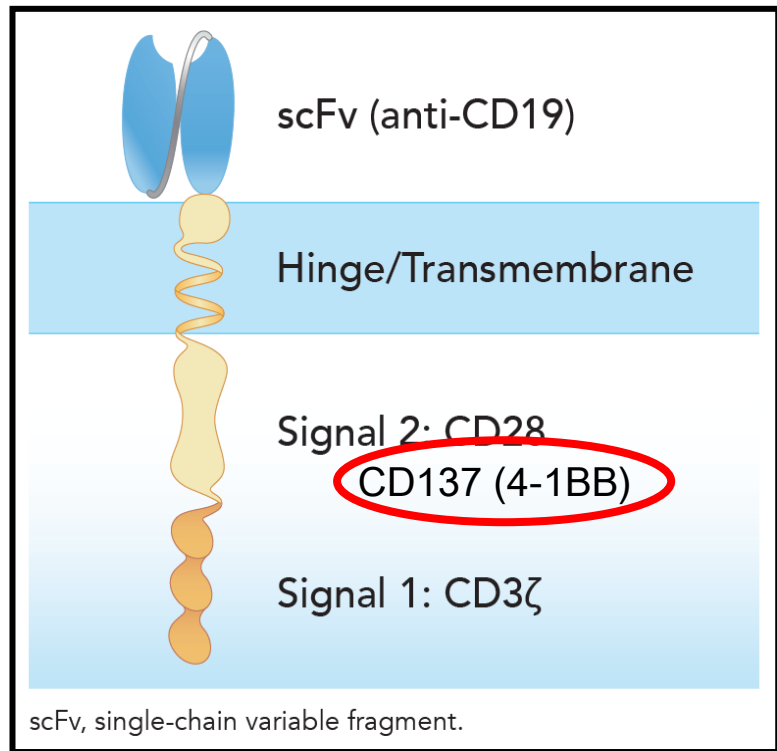


Courtesy of U. Dührsen

# Diffuse Large B-Zell-Lymphoma

## CD19-CAR-T-Cells – Tisagen-Lecleucel (,JULIET‘)

(Schuster et al, N Engl J Med 380: 45, 2019)



165 with refractory/relapsed DLBCL  
111 received Tisa-Cel (Follow-up 14 months)  
93 with Follow-up  $\geq$  3 months

92 % Bridging therapies  
93 % Lymphodepletion with Flu-Cy or Bendamustin  
Intervall apheresis – reinfusion: 54 days !

|                           |      |
|---------------------------|------|
| Response rate             | 52 % |
| Complete Remission        | 40 % |
| Remission $\geq$ 6 Months | 33 % |

### Grad 3/4-adverse events

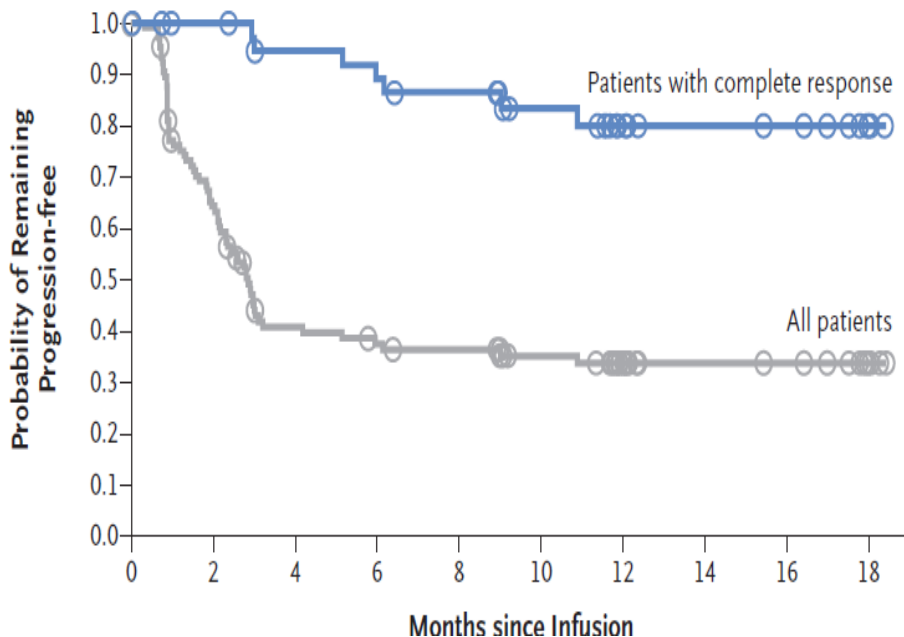
|               |                                       |
|---------------|---------------------------------------|
| ,CRS‘         | 22 % (start day 3 / duration 7 days)  |
| Neurotoxicity | 12 % (start day 6 / duration 14 days) |

# Diffuse Large B-Zell-Lymphoma

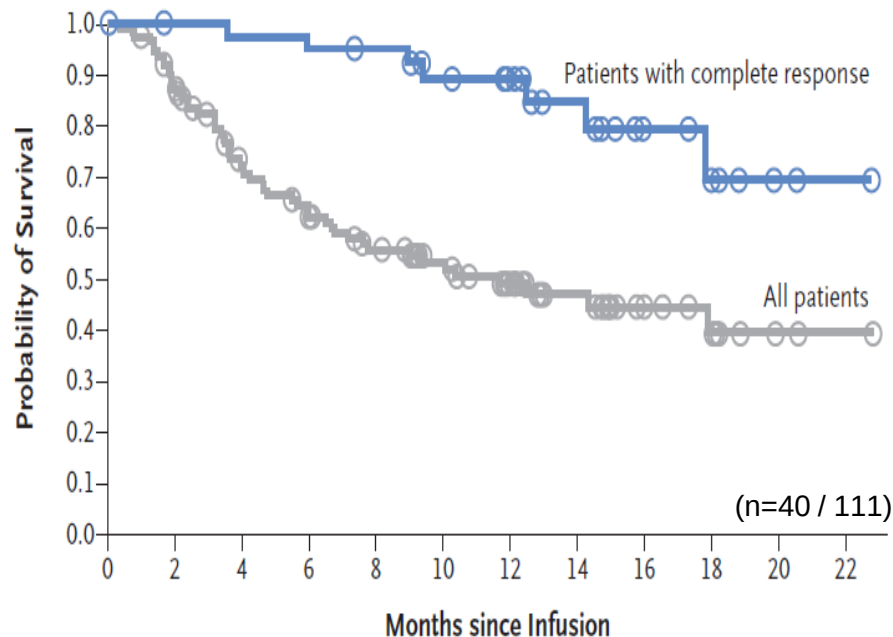
## CD19-CAR-T-Cells – Tisagen-Lecleucel (*JULIET*)

(Schuster et al, N Engl J Med 380: 45, 2019)

### Progression-free survival



### Overall survival



Courtesy of U. Dührsen

# Diffuse Large B-Zell-Lymphoma

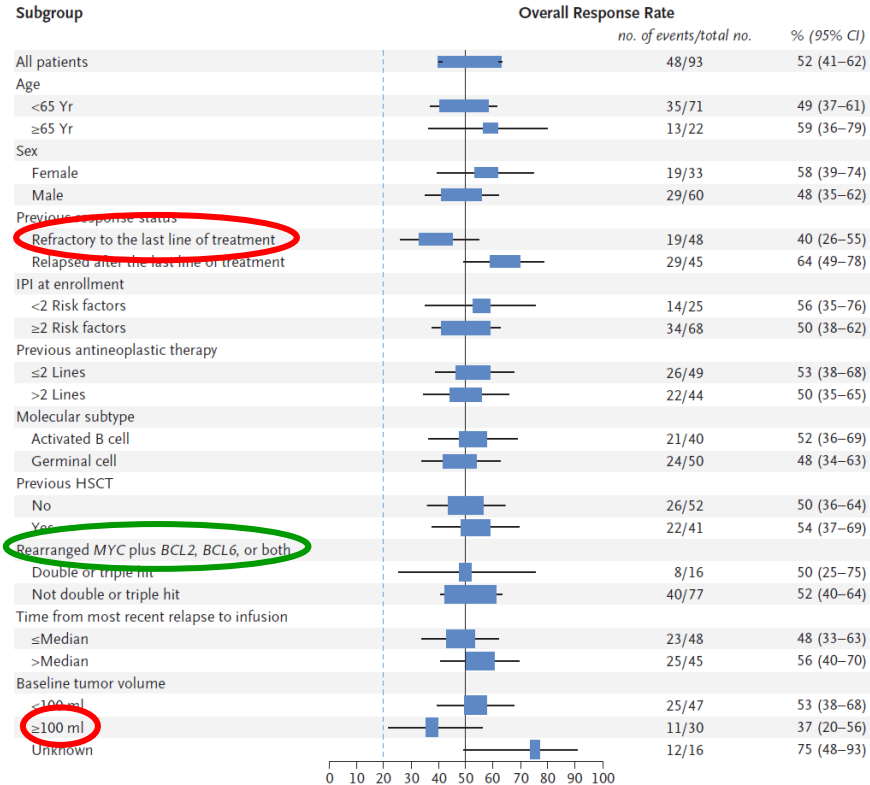
## CD19-CAR-T-Cells – Tisagen-Lecleucel (,JULIET‘)

(Schuster et al, N Engl J Med 380: 45, 2019)

Refractory disease!

Molecular  
Subtype !

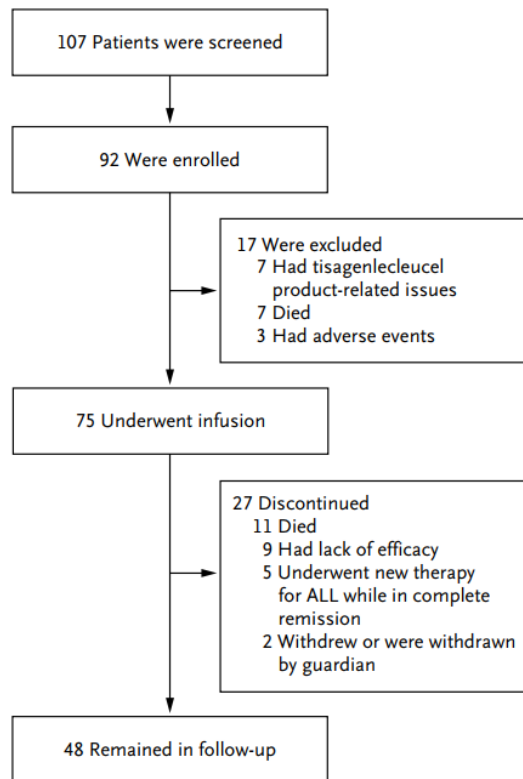
Tumor mass !



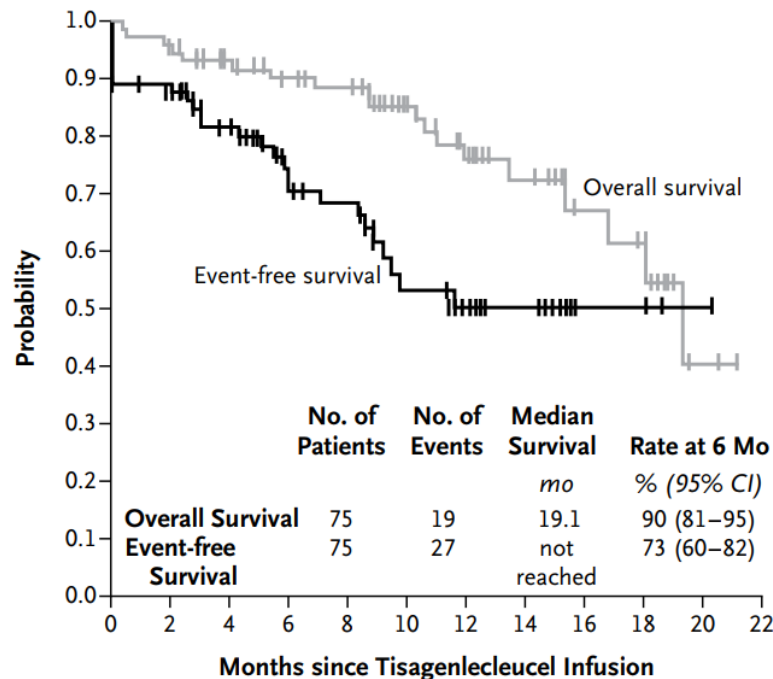
# Children and Young Adults with B-Cell Lymphoblastic Leukemia

## CD19-CAR-T-Cells – Tisagenlecleucel

(Maude et al, N Engl J Med ;378:439-48, 2018)



Event-free and Overall Survival



No. at Risk

|                     |    |    |    |    |    |    |    |    |    |   |   |   |
|---------------------|----|----|----|----|----|----|----|----|----|---|---|---|
| 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 |

## Published Data from Phase I/II Clinical Studies Show Significant Treatment-Related Toxicities With CD19 CAR-T in NHL and ALL

|                | Axicabtagene ciloleucel          | Tisagenlecleucel                 |                                      | JCAR017                                     |
|----------------|----------------------------------|----------------------------------|--------------------------------------|---------------------------------------------|
|                | ZUMA 1 (adult, NHL) <sup>1</sup> | Juliet (adult, NHL) <sup>2</sup> | ELIANA (pediatric, ALL) <sup>3</sup> | Transcend NHL 001 (adult, NHL) <sup>4</sup> |
| CRS (≥ Gr 3) % | 93 (11) %                        | 74 (24) %                        | 77 (47) %                            | 35 (1) %                                    |
| NT (≥ Gr 3), % | 67 (32) %                        | 58 (18) %                        | 40 (13) %                            | 19 (12) %                                   |
| ICU (%)        | NR                               | NR                               | 47%                                  | NR                                          |

High rate and severity of **treatment-related toxicity** (on target/on tumor and on target/off tumor) observed in clinical trials of all CD19 CAR-T products.

Eliana trial: The probability of maintenance of **B-cell aplasia** at 6 months after infusion was 83% (95% CI, 69 to 91).

<sup>1</sup>Neelapu SS et al. 2017, NEJM

<sup>2</sup>Schuster SJ et al. 2019, NEJM

<sup>3</sup>Maude SL et al. 2017, NEJM

<sup>4</sup>Abramson JS et al. 2018. J Clin Oncol. 36, Abstract 7505.

# Despite Advances in AE & Patient Management the Issue of Treatment-Related Toxicities With CAR-T Remains Unsolved – Real Life Data and Practice Guidelines

|                | Axicabtagene ciloleucel          |                                          |
|----------------|----------------------------------|------------------------------------------|
|                | ZUMA 1 (adult, NHL) <sup>1</sup> | Post-Marketing (adult, NHL) <sup>2</sup> |
| CRS (≥ Gr 3) % | 93 (11) %                        | 96 (17) %                                |
| NT (≥ Gr 3), % | 67 (32) %                        | 76 (38) %                                |
| ICU (%)        | NR                               | 30%                                      |

- Rate and severity of **treatment-related toxicity** is not improved through better treatment guidelines
- Intensive follow-up after administration of CD19 CAR-T for up to 6 weeks required
- **ICU reservation is still required for all patients treated with CAR-T cells<sup>3</sup>**

<sup>1</sup>Neelapu SS et al. 2017, NEJM    <sup>2</sup>Jacobson CA et al. 2018, Blood 132, Abstract 92

<sup>3</sup>Graham C et al. 2018, Clin Med

## The Other Side of CAR T-Cell Therapy: Cytokine Release Syndrome, Neurologic Toxicity, and Financial Burden

[Bianca Santomasso](#), MD, PhD<sup>1</sup>; [Carlos Bachier](#), MD<sup>2</sup>; [Jason Westin](#), MD<sup>3</sup>; [Katayoun Rezvani](#), MD, PhD<sup>3</sup>; and [Elizabeth J. Shpall](#), MD<sup>3</sup>

[Show Less](#)

<sup>1</sup>Memorial Sloan Kettering Cancer Center, New York, NY

<sup>2</sup>Sarah Cannon Center for Blood Cancer, Nashville, TN

<sup>3</sup>The University of Texas MD Anderson Cancer Center, Houston, TX

“With more experience and collaboration, hopefully the toxicities and the costs will come down, increasing the availability of CAR T cells to patients in need”

Santomasso et al. 2019, American Society of Clinical Oncology Educational Book

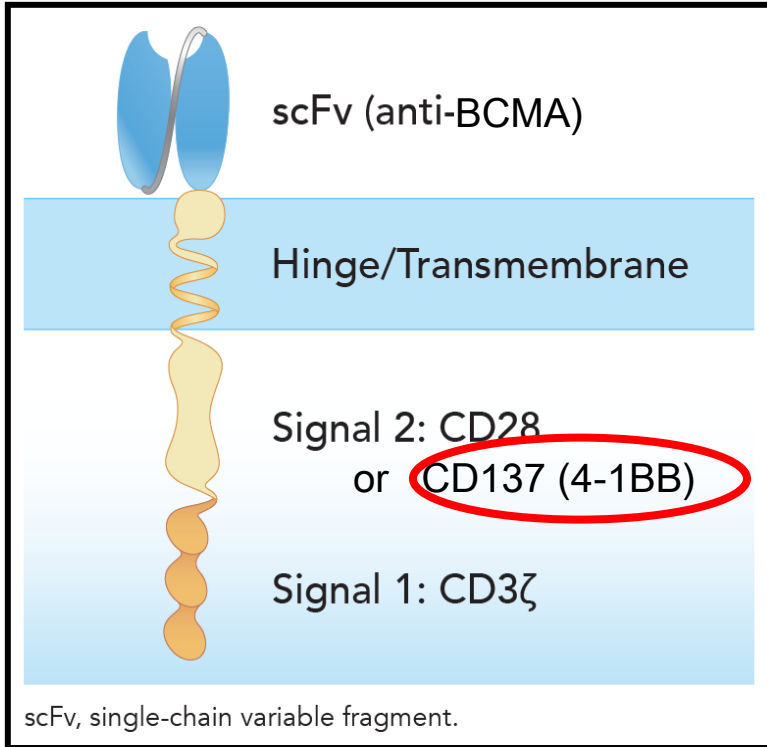
“No impact of tocilizumab or corticosteroids on the expansion rate was observed. This work ... may be clinically impactful as future studies examine prophylactic interventions in patients at risk of higher grade cytokine release syndrome”

Stein et al. 2019, Pharmacometrics & Systems Pharmacology

# Multiple Myeloma

## BCMA-CAR-T-Cells – *bb2121*

(Raje et al, N Engl J Med 380: 1726, 2019)



36 patients with refractory/relapsed MM,  
~7 line of therapies, 97% post-ASCT  
33 received bb2121 (Follow-up 11 months)

Lymphodepletion Fludarabin-Cyclophosphamid  
Phase II-cell dose: 150 - 450 x 10<sup>6</sup> CAR-T-Zellen

|                                     |       |
|-------------------------------------|-------|
| Overall response rate               | 85 %  |
| Complete Remission                  | 45 %  |
| MRD-negative at CR/PR               | 100 % |
| Remission duration $\geq$ 12 months | 42 %  |

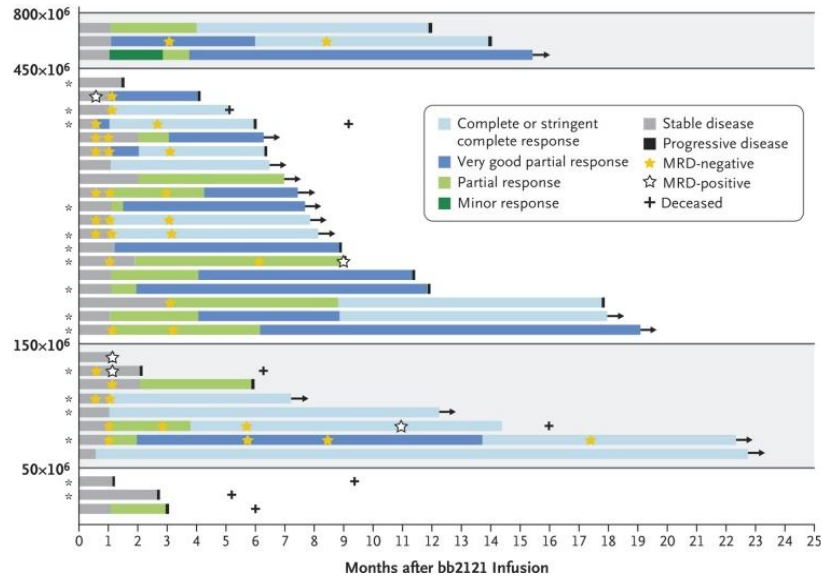
| <u>Adverse events</u> | <u>All Grades</u> | <u>Grade 3/4</u> |
|-----------------------|-------------------|------------------|
| ,CRS‘                 | 76 %              | 6 %              |
| Neurotoxicity         | 42 %              | 3 %              |

# Multiple Myeloma

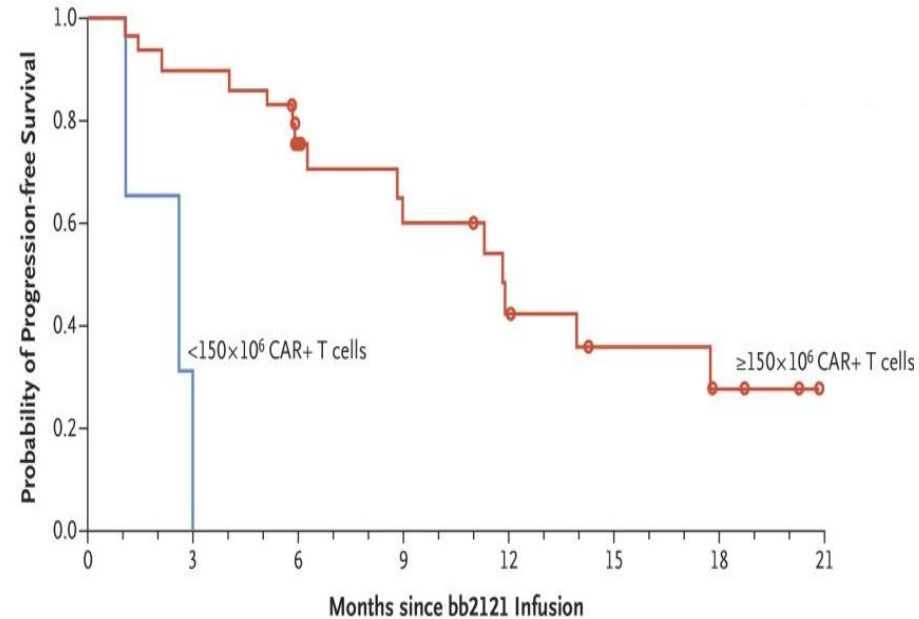
## BCMA-CAR-T-Cells – bb2121

(Raje et al, N Engl J Med 380: 1726, 2019)

### Best Response



### Progression-free Survival

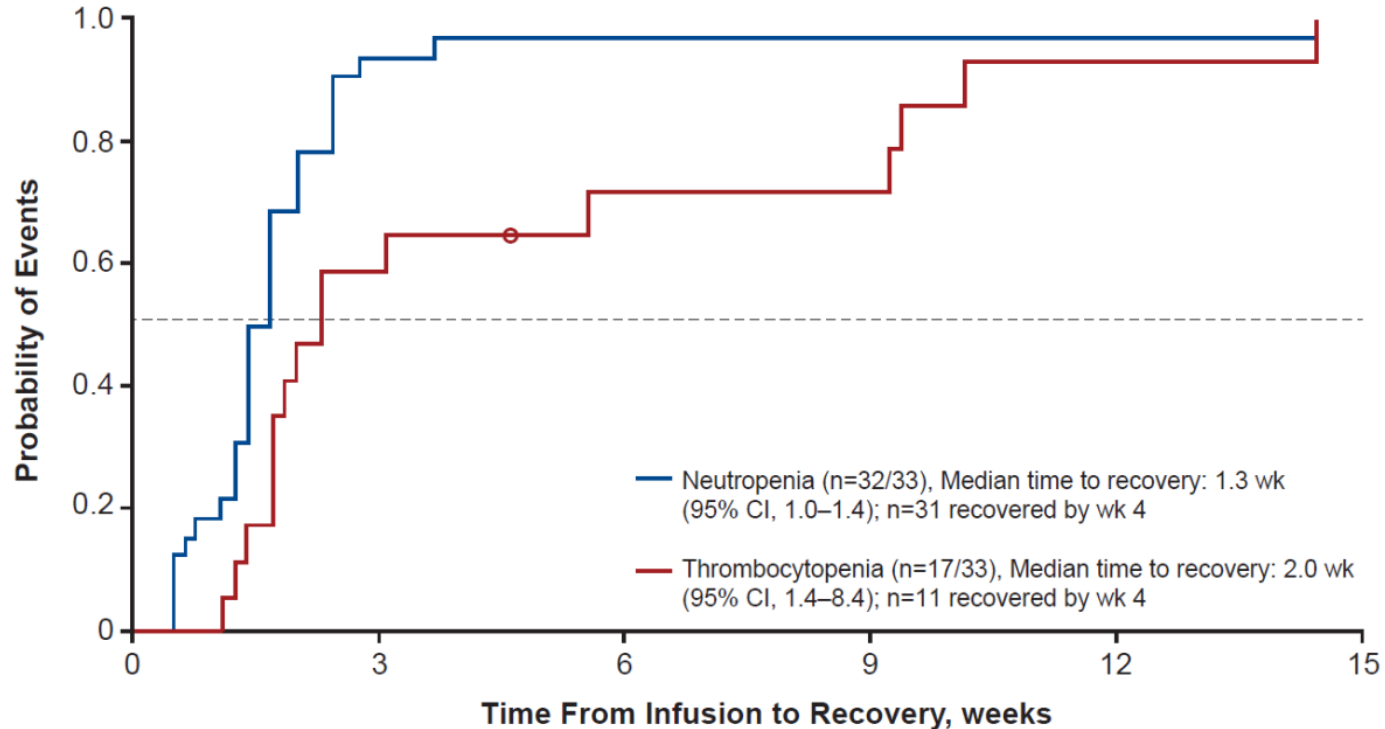


# Multiple Myeloma

## BCMA-CAR-T-Cells – bb2121

(Raje et al, N Engl J Med 380: 1726, 2019)

### Time to Recovery of Grade 3/4 Cytopenia



# Immunotherapy with CAR-T is a new therapeutic venue in MM

CAR-T cell therapy against multiple myeloma shows promising results in the eradication of the disease

| Product name                      | CART-BCMA                                                   | bb2121                                                  | LCAR-B3SM/Janssen                                       | FCARB143         | FCARB125         |
|-----------------------------------|-------------------------------------------------------------|---------------------------------------------------------|---------------------------------------------------------|------------------|------------------|
| Institution                       | Upenn/Novartis                                              | BlueBird//Celgene                                       | Nanjing Legend Biotech                                  | Juno/Fred Hutch  | Juno/MSKCC       |
| scFv derived from                 | Human library                                               | Murine hybridoma                                        | Murine hybridoma                                        | Human library    | Human library    |
| Co-stimulatory domains            | 4-1BB                                                       | 4-1BB                                                   | 4-1BB                                                   | 4-1BB            | 4-1BB            |
| Elimination gene                  | None                                                        | None                                                    | None                                                    | None             | None             |
| Gene transfer                     | Lentivirus                                                  | Lentivirus                                              | Lentivirus                                              | Lentivirus       | Retrovirus       |
| Conditioning                      | None (cohort 1)<br>> Cy                                     | Cy/Flu                                                  | Cy                                                      | ---              | Cy>Cy/Flu        |
| BCMA Ag required                  | No requirement                                              | >50%                                                    | „Clear expression“                                      | ---              | >1%              |
| clinicaltrials.gov identification | NCT02546167                                                 | NCT02658929                                             | NCT03090659                                             | NCT03338972      | NCT03070327      |
| Median prior lines                | 7                                                           | 7                                                       | 4                                                       | ---              | ---              |
| Efficacy                          | CR: 1<br>VGPR: 1<br>PR: 4<br>10 evaluable pts<br>(cohort 3) | CR: 50%<br>VGPR: 36%<br>PR: 9%<br>11 pts MRD-<br>22 pts | CR: 74%<br>VGPR: 4%<br>PR: 11%<br>39 pts MRD-<br>57 pts | Not yet reported | Not yet reported |

However, there are still problems to face:

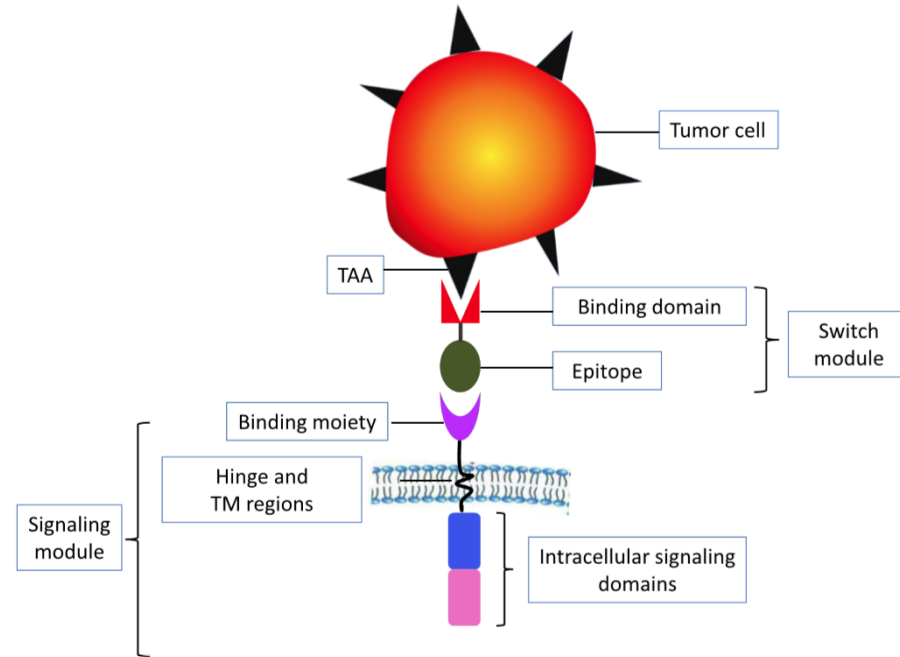
- Relapse has been observed as a common phenomenon after CAR immunotherapy treatment
- Cytokine release syndrome and suppression of hematopoiesis are well known toxicities

Data ASH 2018/19

# Reasons for Disease Relapses

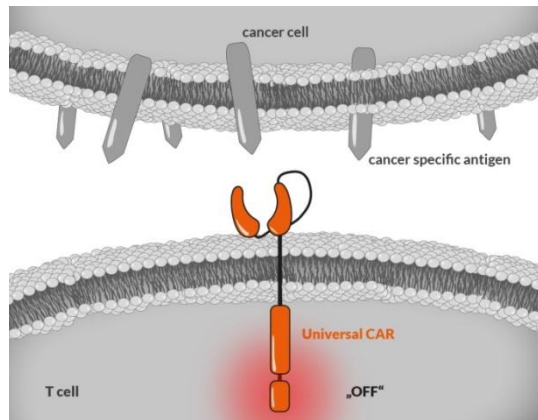
- Antigen loss
- Reduction of antigen expression
- Selection of cells being negative for target
- CAR-T exhaustion
- CAR-T loss
- PD1-L overexpression
- Other inhibitory signals
- Endogenous tumor cell factors (e.g. p53 loss)
- Inhibitory tumor milieu
- ....

# Concept of Adapter CARs

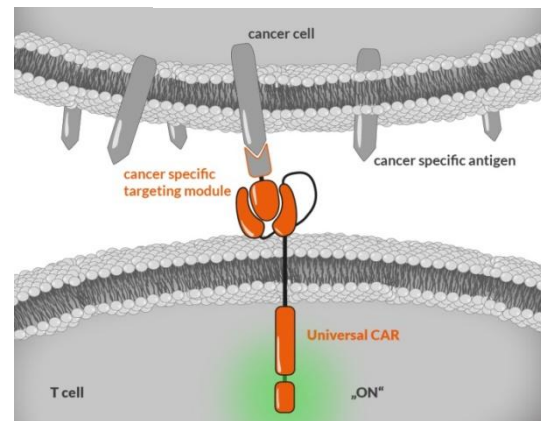
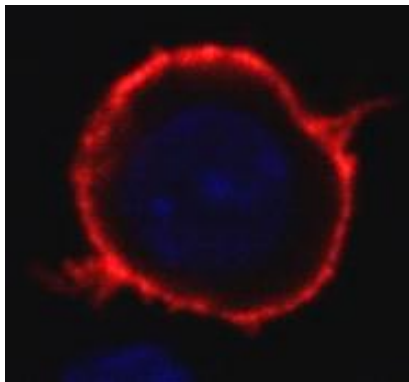


**Fig. 1** The schematic structure of a universal CAR system. The universal CAR (UniCAR) system splits the conventional CAR into two modules. The two modules are (1) the signaling module, which harbors a binding moiety to a specific epitope combined with the intracellular signaling domains via hinge and the transmembrane regions (TM) and (2) a switching module, which is a bispecific fusion molecule with one binding domain directed against a tumor-associated antigen (TAA) and an epitope specifically recognized by the signaling module

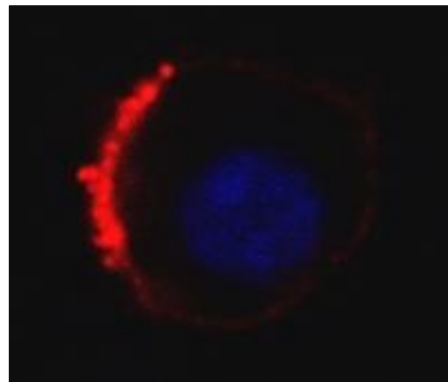
## TM-mediated cross-linkage of UniCAR-T

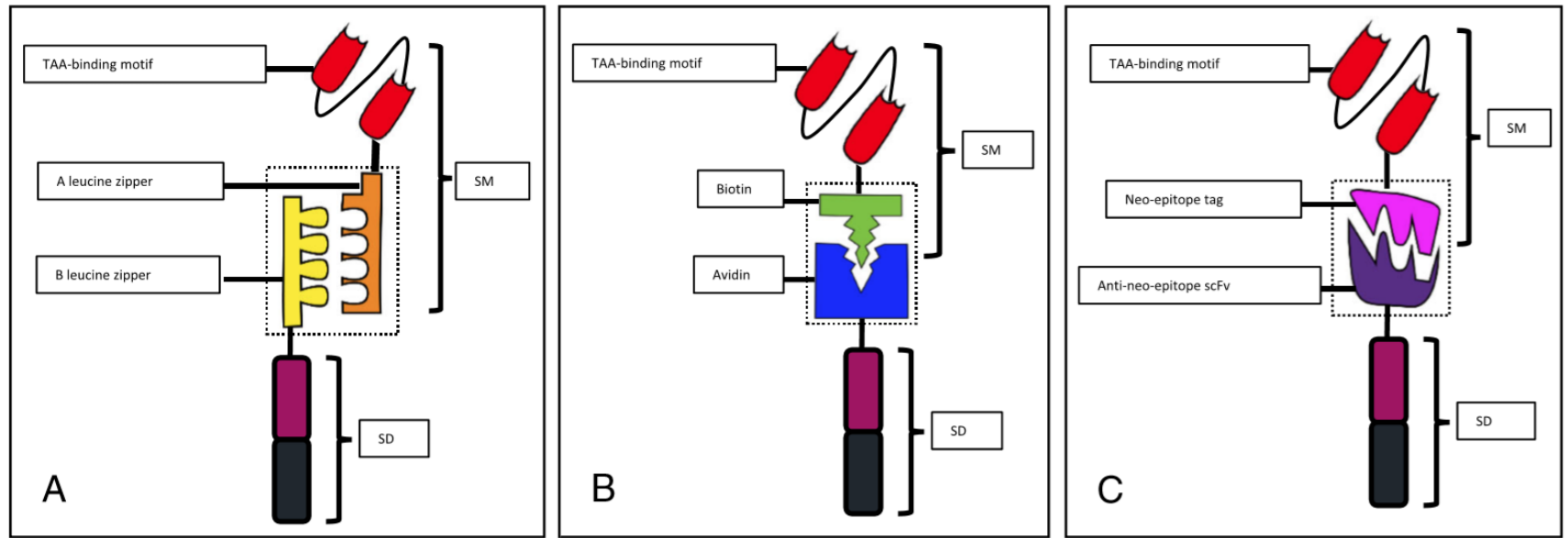


Homogenous distribution of **UniCARs** on engineered T cell in sleeping mode



Polarization of **UniCARs** upon TM-mediated cross-linkage to cancer cell





**Fig. 2** The schematic structures of switching modules. **a** SUPRA CAR. A switch molecule (SM) with a leucine zipper linked to an antigen-specific scFv (TAA-binding motif) (A leucine zipper) paired with a cognate leucine zipper-containing universal receptor (B leucine zipper) linked to the intracellular signaling domain (SD) of the engineered T cells. **b** BBIR CAR. BBIR CAR is composed of an extracellular avidin motif linked to an intracellular signaling domain. The switch molecule is a biotinylated antigen-binding motif, i.e., a monoclonal antibody, scFv, or other tumor-specific ligands that selectively bind to avidin within the BBIR. **c** Switch modules with neo-epitope tagging. In this platform, the switching modules contain a neo-epitope that is tagged to a TAA-binding motif. The CAR is composed of a neo-epitope-specific scFv linked to the intracellular SD domain. These neo-epitopes are usually exogenous amino acid epitopes that are not present in human. Three tags are currently explored, FITC, 5B9, and PNE

Fluorescein isothiocyanate (**FITC**)  
 Nuclear protein (**5B9**)=Our UniCAR adaptor  
 Transcription factor GCN4 (**PNE**)

# Landscape: Switch on/off CAR-T Assets in Development

| Company               | Technology                                                                                     | Developmental stage                                                         | Platform limitations                                                                                                                       |
|-----------------------|------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| GEMoAB                | Chimeric receptor with CD3z, CD28 and anti-La scFv<br>Switch: tagged humanized scFv or peptide | Start of phase 1 Q1/2020                                                    | No obvious limitations                                                                                                                     |
| Unum                  | Chimeric receptor with CD3z, 41BB and CD16 ECD<br>Switch: humanized/chimeric full-length mAb   | Phase I in NHL (rituximab), MM (SEA-BCMA), Her2+ solid tumors (trastuzumab) | Slow off switch due to <b>long half-life of mAb</b> , CD16 is <b>cross-reactive with endogenous Abs</b>                                    |
| Miltenyi              | Chimeric receptor with CD3z, 41BB and anti-biotin scFv<br>Switch: biotinylated full-length mAb | Pre-clinical                                                                | Slow off switch due to <b>long half-life of mAb</b> , cross-reactive, <b>biotin is hapten and 10% of naïve humans have anti-biotin Abs</b> |
| Endocyte/<br>Novartis | Chimeric receptor with CD3z, CD28 and anti-FITC scFv<br>Switch: FITC-labeled folate            | Pre-clinical, IND submission announced                                      | <b>FITC is a hapten</b><br>(high immunogenicity risk)                                                                                      |
| Calibr                | Chimeric receptor with CD3z, 41BB and anti-GCN4 scFv<br>Switch: tagged humanized Fab           | Pre-clinical, IND submission announced                                      | <b>GCN4 is yeast protein</b><br>(high immunogenicity risk)                                                                                 |
| Bellicum              | Chimeric receptor with CD3z and anti-tumor scFv<br>Inducible 41BB costimulatory signal         | Phase I in PSCA+ solid tumors                                               | <b>Only costimulatory signal can be turned off</b>                                                                                         |
| Xyphos                | Chimeric receptor with CD3z, 41BB and mut. NKG2D<br>Switch: tagged humanized full-length mAb   | Pre-clinical, start of phase I planned for 2021 (rituximab & trastuzumab)   | Slow off switch due to <b>long half-life of mAb</b> , strong binding to effector cell poses safety risk                                    |

# Recently Published PK Data on Rituximab Show an Increasing Serum Half-life per Treatment Cycle and a Very Long Elimination Half-Life of CD20-Bound Antibody

Received: 23 January 2019 | Revised: 10 April 2019 | Accepted: 2 May 2019

DOI: 10.1111/bcp.13991

## ORIGINAL ARTICLE



### Nonlinear pharmacokinetics of rituximab in non-Hodgkin lymphomas: A pilot study

David Ternant<sup>1,2</sup>  | Hélène Monjanel<sup>3</sup> | Yann Venel<sup>4</sup> | Caroline Prunier-Aesch<sup>5</sup> | Flavie Arbion<sup>6</sup> | Philippe Colombat<sup>3,7</sup> | Gilles Paintaud<sup>1,2</sup> | Emmanuel Gyan<sup>3,7</sup>

- Repeated dosing significantly extends serum half-life (median ~ 6 weeks)
- Pharmacokinetic of Rituximab is dependent on tumor mass: elimination half-life after 1st injection 2 – 100 days

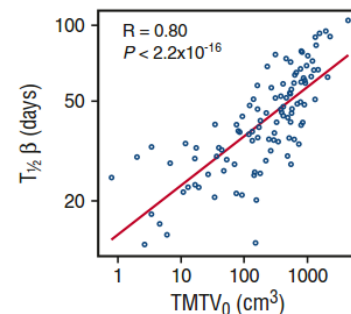
## Regular Article

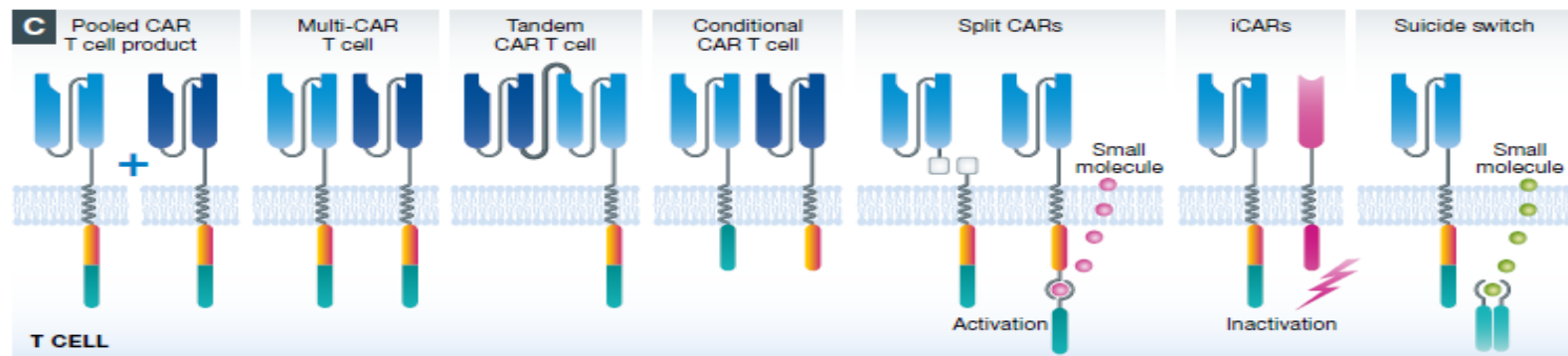
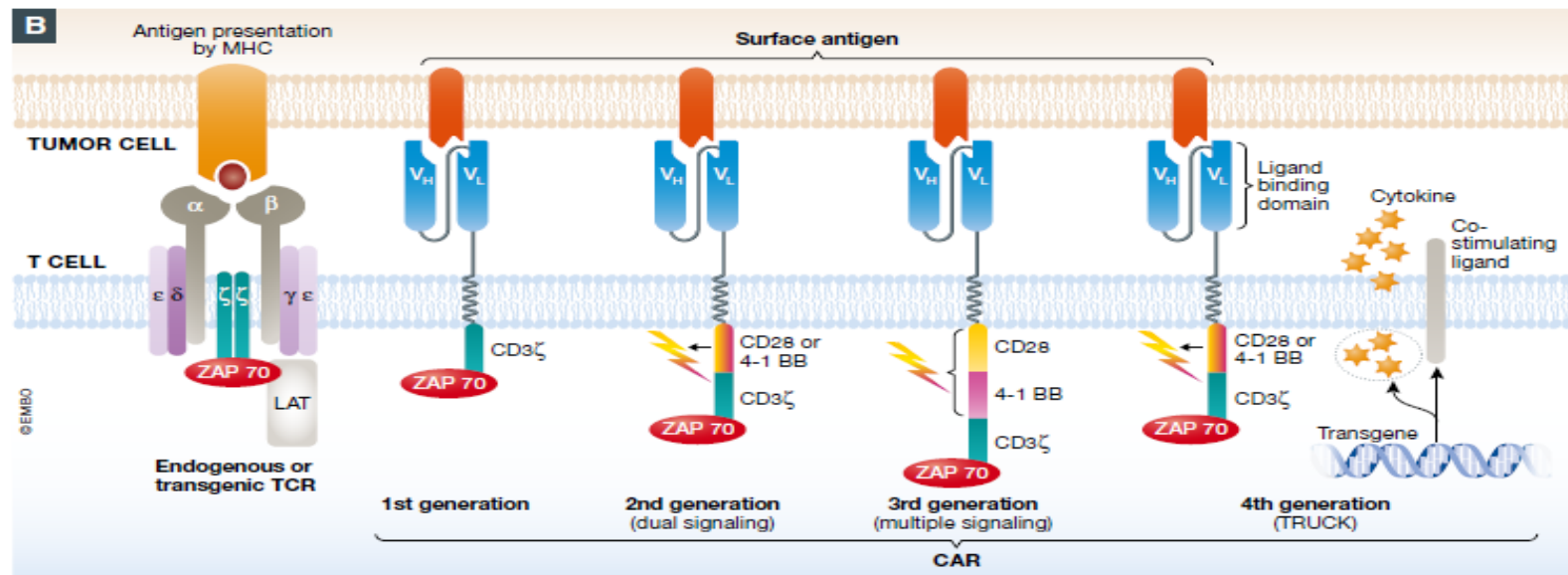


### CLINICAL TRIALS AND OBSERVATIONS

### Rituximab exposure is influenced by baseline metabolic tumor volume and predicts outcome of DLBCL patients: a Lymphoma Study Association report

Mira Tout,<sup>1</sup> Olivier Casasnovas,<sup>2</sup> Michel Meignan,<sup>3</sup> Thierry Lamy,<sup>4</sup> Franck Morschhauser,<sup>5</sup> Gilles Salles,<sup>6</sup> Emmanuel Gyan,<sup>7</sup> Corinne Haioun,<sup>8</sup> Mélanie Mercier,<sup>9</sup> Pierre Feugier,<sup>10</sup> Sami Boussetta,<sup>11</sup> Gilles Paintaud,<sup>1,12</sup> David Ternant,<sup>1,12</sup> and Guillaume Cartron<sup>13,14</sup>





# Summary

- Highly efficient anti-tumor response of anti-CD19 CAR-T cells against ALL and NHL (anti-BCMA against myeloma)
- CAR-T cells are one of the first marketed cellular products
- Heterogenous landscape: Cell type, source, process, costimulation, switch mechanism etc.
- Major limitations are: Toxicities, resistance, production time, price, health care providers, and ...
- Next steps: Allogeneic products, switchable CARs, multitargeting, automation of production process

# Acknowledgements

## Cellex Patient Treatment

**Marc Cartellieri**

Johannes Spehr

Julia Riewaldt, Jana Hase, Traugott Leopold,

Patrizia Di Benedetto, Martina Raupach,

Christiane Kahle, Susann Gerber, Glenn Gröbe, Sarah

Tröger, Rebecca Christiana, Katrin Zimmermann,

Nicole Kronstein, Josephine Dietrich, Jan-Erik Meyer,

Susann Helas



Cellex Patient Treatment

## GEMoaB Monoclonals GmbH

**Armin Ehninger**

**Michael Pehl**

Marika Geissler

Cordula Gründer

Kristin Franke

Julia Huffziger, Ulrike Böhmer, Jana Fiebiger,

Ilka Müller, Juliane Schneider, Therese Miersch,

Alexander Schiewart, Andre Herbrig,

Christin Eger, Simon Loff



Novel Immunotherapeutic concepts

## Cellex Cell Professionals

**Carla Kreissig**

Volker Knöll

Helen Springer-Frauenhoff,

Darin Alannan, Sonja Schallenberg,

Franziska Goddard, Can Korkmaz

Sabine Schöffel-Weiß, Kai Schormann



## Fraunhofer ITEM Braunschweig

Holger Ziehr

Kathrin Bohle

Stefanie Hebecker, Markus Heine

Annabel Nieter, Ute Pägelow, Nico Langer



**Fraunhofer**  
ITEM

**ABX**

*advanced biochemical compounds*

Alexander Höpping, Linda Evermann



Julie Leclercq, Benoît Pech, Benoît Pinteaur

SPONSORED BY THE



Federal Ministry  
of Education  
and Research



Europäische Union

Europa fördert Sachsen.



Europäischer Sozialfonds

SACHSEN



## University Hospital Dresden UCC

**& HZDR**

Michael Bachmann

Stefanie Koristka

Anja Feldmann

Claudia Arndt



## University Hospital Dresden

**Internal Medicine I**

**Martin Wermke**

Malte von Bonin

Martin Bornhäuser



## University Hospital Würzburg

**CCC**

**Ralf Bargou**

Maria-Elisabeth Goebeler

**Hermann Einsele**



Comprehensive Cancer Center  
Mainfranken