

**RETE  
EMATOLOGICA  
VENETA**

SINERGIA PER CONDIVIDERE  
ASSISTENZA  
FORMAZIONE  
RICERCA

**Gianpietro Semenzato**  
Ematologia - Dipartimento Medicina  
Azienda Ospedaliera Universitaria di Padova

**PADOVA**

**Sala Convegni VIMM**  
**Via Orus, 2**

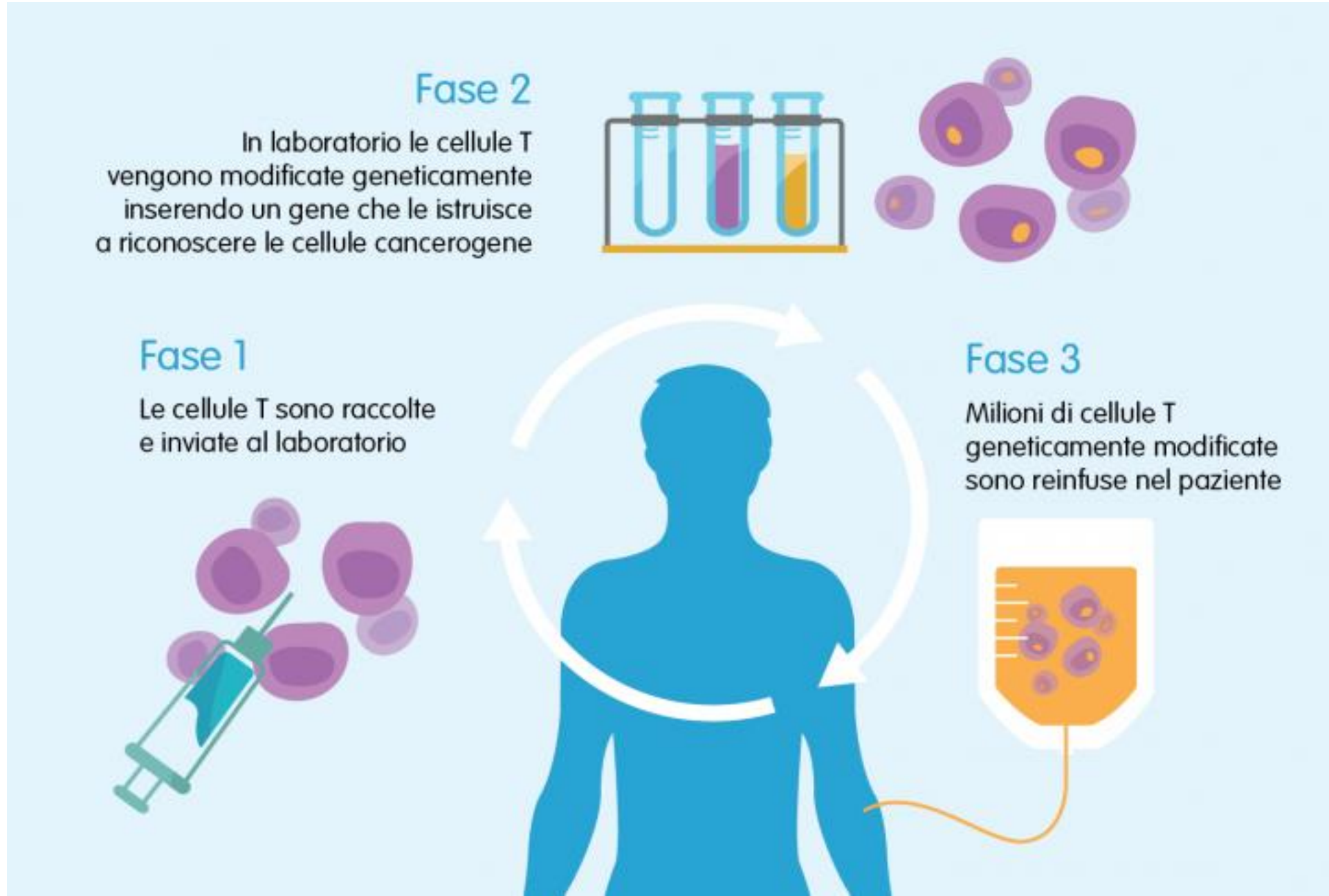
**28 MAGGIO 2019**

**ROAD MAP CAR-T**

**PROSPETTIVE ATTUALI E FUTURE  
DELL'USO DELLE CAR-T IN ITALIA**

2019 **MOTORE**   
**SANITÀ**  
Gestire il Cambiamento

# La strategia terapeutica dei Chimeric Antigen Receptors (CAR T)



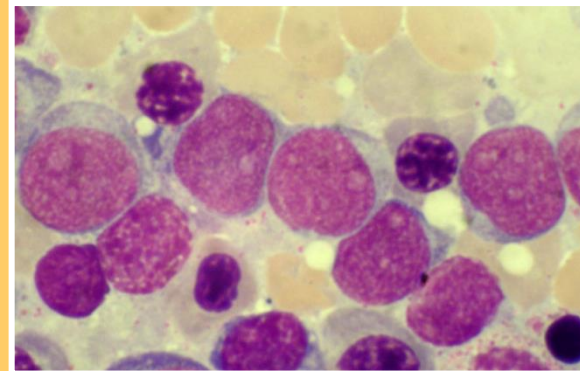
# Immunotherapy

## Passive Immunotherapy

Monoclonal antibodies



HUMORAL  
RESPONSE  
CELL MEDIATED  
RESPONSE



## Active Immunotherapy

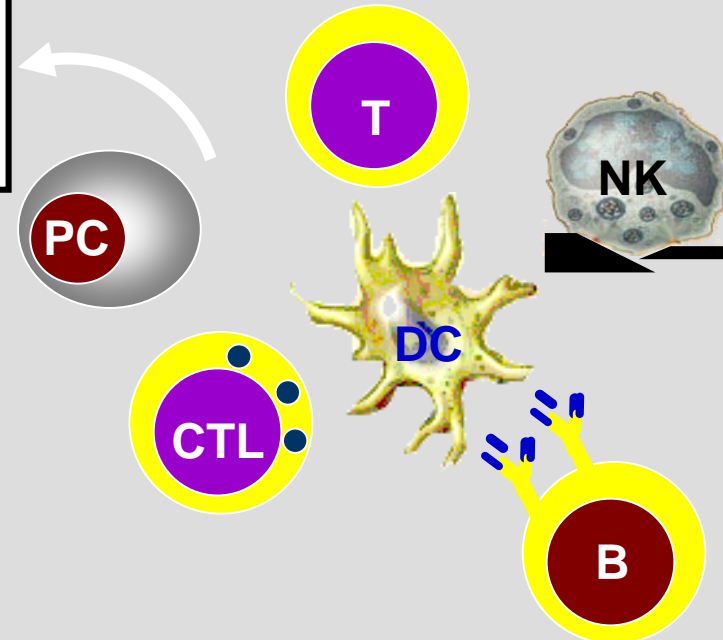
Vaccines

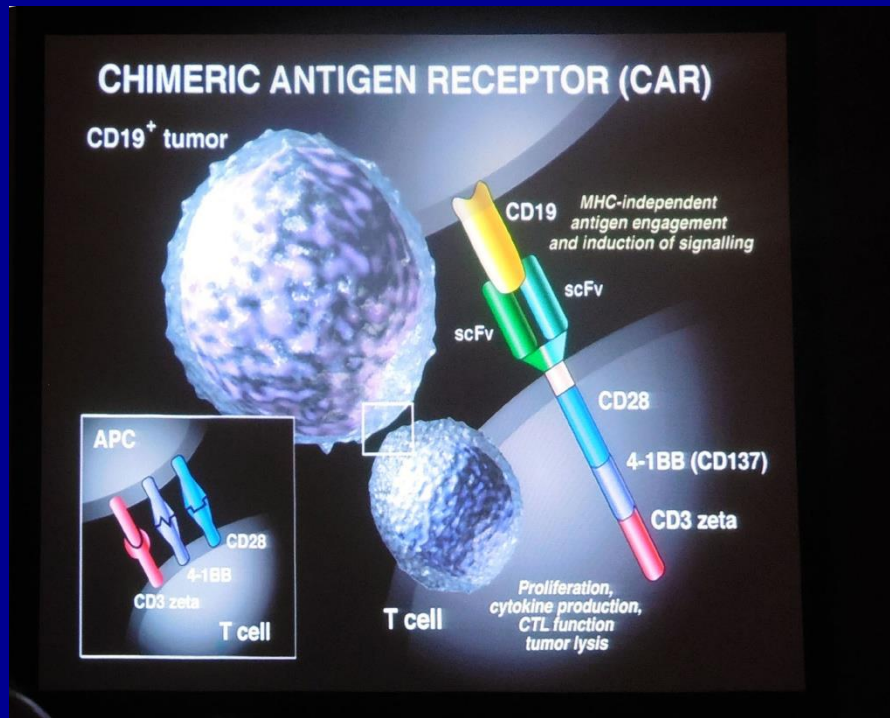
Immunostimulatory DNA sequences

Dendritic cells

Cytokines

CAR T Cells





*Featured Session on*

**Chimeric Antigen Receptors  
“CARs” Therapy:**

**Driving Immunotherapy**

**Outstanding issues**

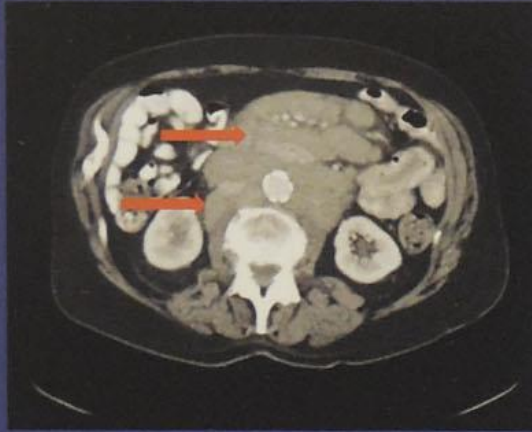
***Stephan Grupp, M.D.***  
***Childhood Cancer Research Center***  
***Perelman School of Medicine***  
***University of Pennsylvania***

***Elisabeth J. Shpall, M.D.***  
***Stem Cell Transplantation &***  
***Cellular Therapy Department***  
***MD Anderson Cancer Center***  
***University of Texas***

*New Orleans, ASH 2013 – Monday December 9, 2013*

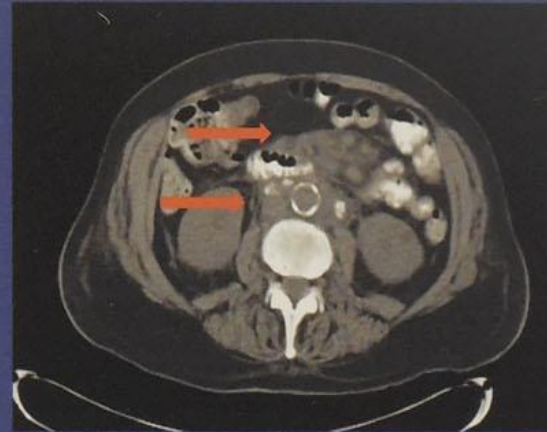
# CD19 CAR Modified T Cells Have Long Term Persistence and Induce Durable Responses in Relapsed and Refractory CLL

Patient 04409-10  
Preinfuson

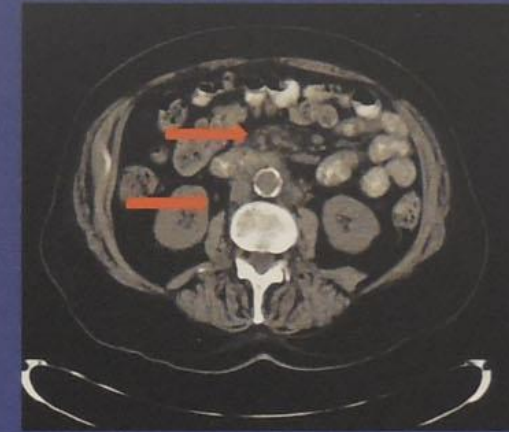


5 prior therapies,  
refractory CLL

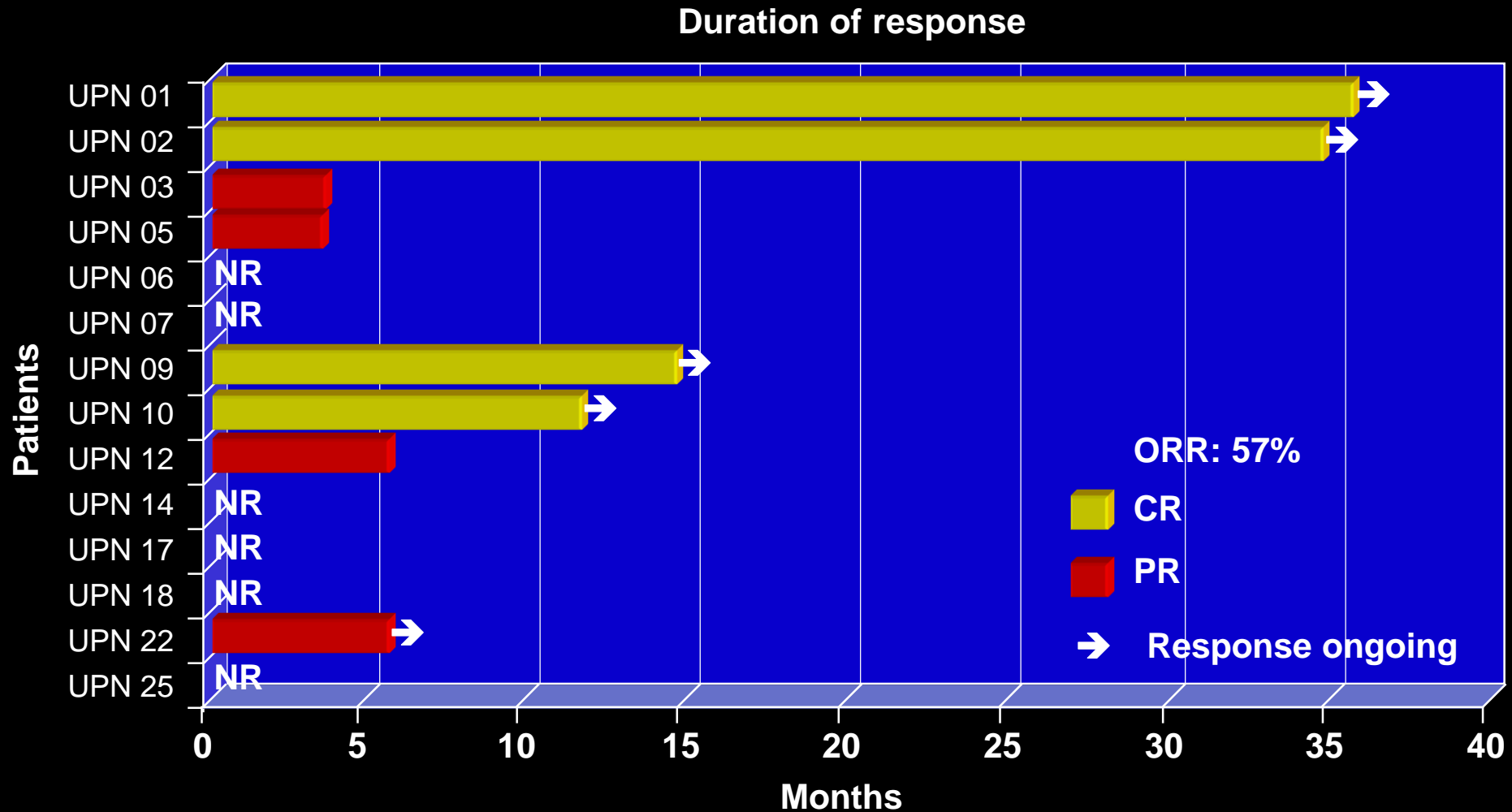
Patient 04409-10  
Day 63



Patient 04409-10  
6 months after infusion



# CD19 CAR Modified T Cells Have Long Term Persistence and Induce Durable Responses in Relapsed and Refractory CLL



Median follow-up (all patients) 12 months (range, 6-39)

Median follow-up (responding patients) 20 months (range, 6-39)

# CAR T Cells Therapy in Patients with Hematological Malignancies

The NEW ENGLAND JOURNAL of MEDICINE

## BRIEF REPORT

### Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D., Xiuyan Wang, Ph.D., Brigitte Sénéchal, Ph.D., Kevin J. Curran, M.D., Craig Sauter, M.D., Yongzeng Wang, Ph.D., Bianca Santomaso, M.D., Ph.D., Elena Mead, M.D., Mikhail Roshal, M.D., Peter Maslak, M.D., Marco Davila, M.D., Ph.D., Renier J. Brentjens, M.D., Ph.D., and Michel Sadelain, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D., Ph.D., S. Ronan Foley, M.D., P. Joy Ho, M.B., B.S., D.Phil., Stephan Mielke, M.D., John M. Magenau, M.D., Harald Holte, M.D., Ph.D., Serafino Pantano, Ph.D., Lida B. Pacaud, M.D., Rakesh Awasthi, Ph.D., Jufen Chu, Ph.D., Özlem Anak, M.D., Gilles Salles, M.D., Ph.D., and Richard T. Maziarz, M.D., for the JULIET Investigators\*

### Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial

Frederick L Locke\*, Armin Ghobadi, Caron A Jacobson, David B Miklos, Lazaros J Lekakis, Olalekan O Oluwole, Yi Lin, Ira Braunschweig, Brian T Hill, John M Timmerman, Abhinav Deol, Patrick M Reagan, Patrick Stiff, Ian W Flinn, Umar Farooq, Andre Goy, Peter A McSweeney, Javier Munoz, Tanya Siddiqi, Julio C Chavez, Alex F Herrera, Nancy L Bartlett, Jeffrey S Wieszorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu\*

The NEW ENGLAND JOURNAL of MEDICINE

## BRIEF REPORT

### Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Alfred L. Garfall, M.D., Marcela V. Maus, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., J. Joseph Melenhorst, Ph.D., Zhaohui Zheng, M.S., Dan T. Vogl, M.D., Adam D. Cohen, M.D., Brendan M. Weiss, M.D., Karen Dengel, R.N., B.S.N., Naseem D.S. Kerr, M.P.H., Adam Bagg, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., and Edward A. Stadtmauer, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

## ORIGINAL ARTICLE

### Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma

Noopur Raje, M.D., Jesus Berdeja, M.D., Yi Lin, M.D., Ph.D., David Siegel, M.D., Ph.D., Sundar Jagannath, M.D., Deepu Madduri, M.D., Michaela Liedtke, M.D., Jacalyn Rosenblatt, M.D., Marcela V. Maus, M.D., Ph.D., Ashley Turka, Lyh-Ping Lam, Pharm.D., Richard A. Morgan, Ph.D., Kevin Friedman, Ph.D., Monica Massaro, M.P.H., Julie Wang, Pharm.D., Ph.D., Greg Russotti, Ph.D., Zhihong Yang, Ph.D., Timothy Campbell, M.D., Ph.D., Kristen Hege, M.D., Fabio Petrocca, M.D., M. Travis Quigley, M.S., Nikhil Munshi, M.D., and James N. Kochenderfer, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

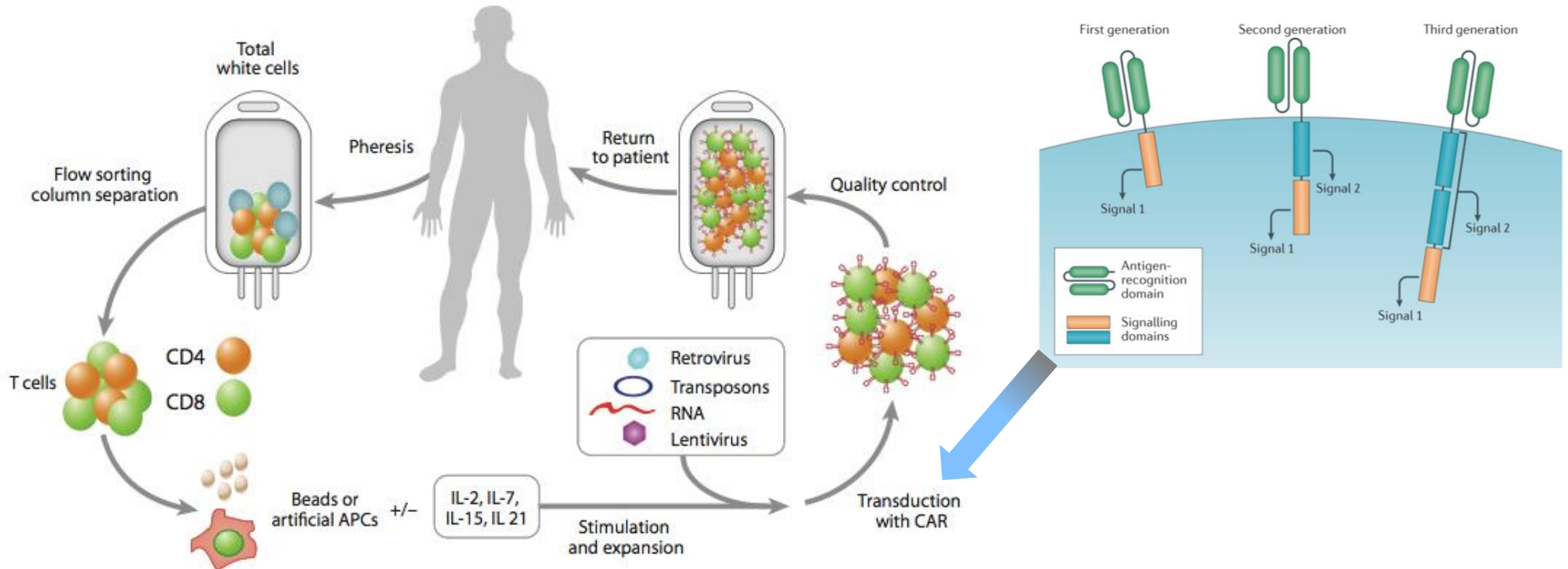
## BRIEF REPORT

### Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

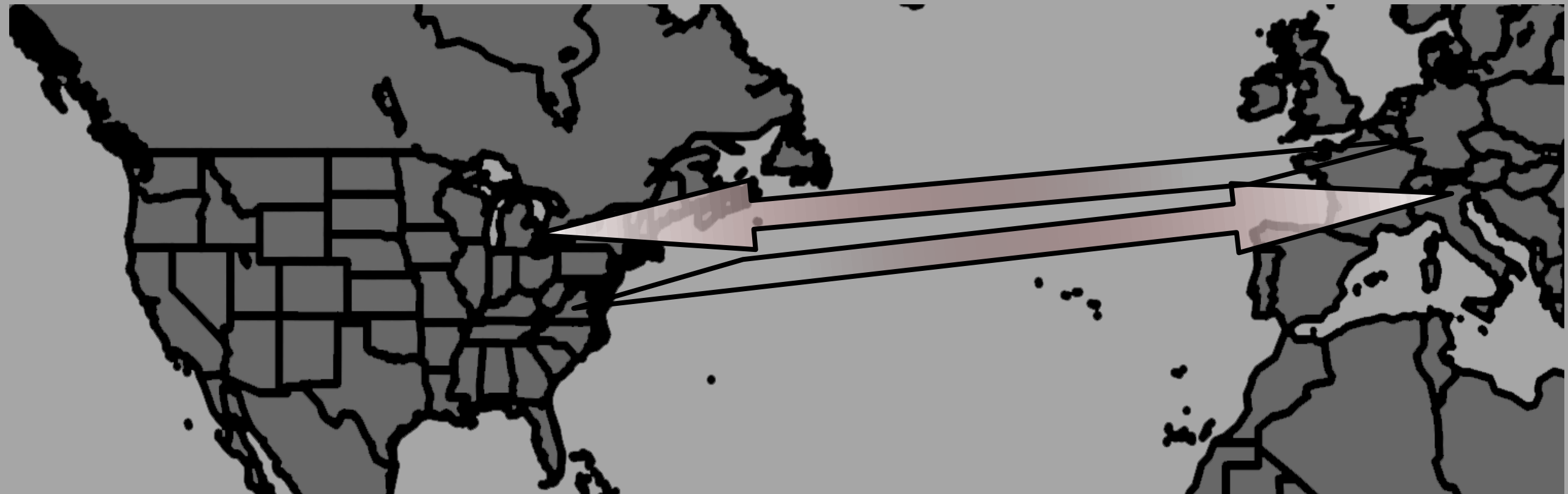
# La strategia terapeutica dei Chimeric Antigen Receptors (CAR T)

- Isolare le cellule T del paziente
- Inserire il gene che codifica per l'Ac specifico per il target
- Espandere in vitro le cellule T
- Infondere le cellule T “educate”

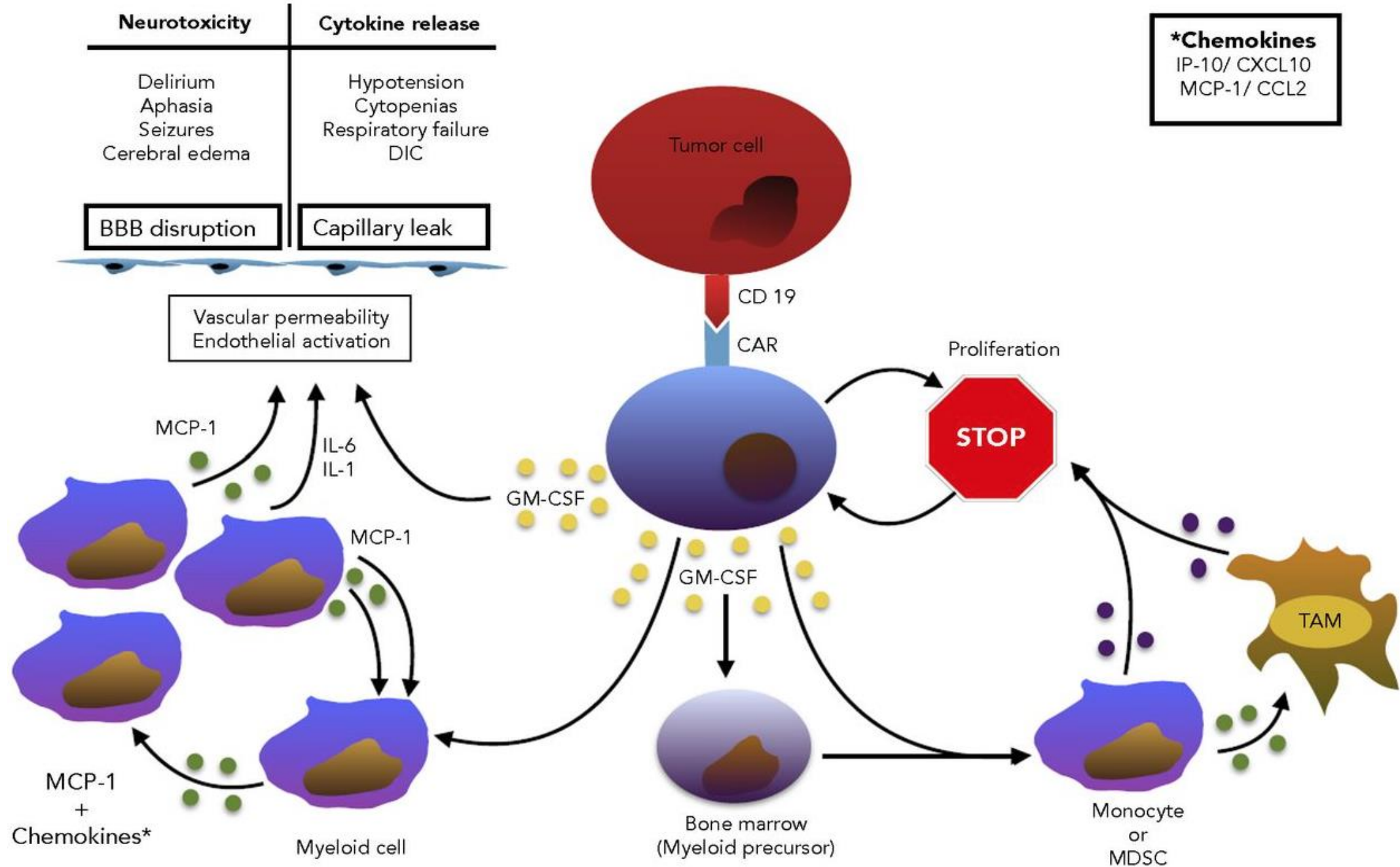




# Aspetti organizzativi



# Pathophysiological Mechanisms of Toxicity of CAR-T Cell Therapy



# EMERGENZA MEDICA

ANTIBIOTICI  
Iglob.ev

PLASMA EXP. TRASF.  
DOPAMINA



POLMONITE

SHOCK  
SETTICO

MONITORARE:  
PAO - PVC -  
SATUR. O<sub>2</sub> - DIURESIS

# Knowledge of CAR T-Cell Therapy in Hematological Malignancies

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# Knowledge of CAR T-Cell Therapy in Hematological Malignancies

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## Basic Knowledge

- ❑ 61% could not correctly identify the components of a CAR construct (antigen specific domain, the signaling domain)
- ❑ 45% did not recognize that currently approved CAR T-Cell therapies are dosed at a single infusion
- ❑ 25% demonstrated inaccurate knowledge by recommending patients wait 4 weeks after CAR T-Cell infusion before driving

# Knowledge of CAR T-Cell Therapy in Hematological Malignancies

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## Knowledge of the Clinical Data

- ❑ Very low awareness of efficacy data seen with various CAR T-Cell products used to treat R/R B-cell ALL (ELIANA Trial) or DLBCL (ZUMA1, JULIET Trials)
- ❑ Lack of competence recognizing and treating CAR T-Cell associated adverse events such as Cytokine Release Syndrome (CRS) and neurotoxicity
- ❑ 54% could not identify the appropriate role of corticosteroid therapy after CAR T-Cell administration in managing CRS and neurotoxicity
- ❑ 41% not aware that the mechanism of tocilizumab is to block IL-6 signaling

# Demographics

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## Academic

- **33% Specialist in Hematologic Malignancies**
- **8.3% Specialist in other cancers**
- **2.1% Specialist in Pediatric Hematology/Oncology**

## Community

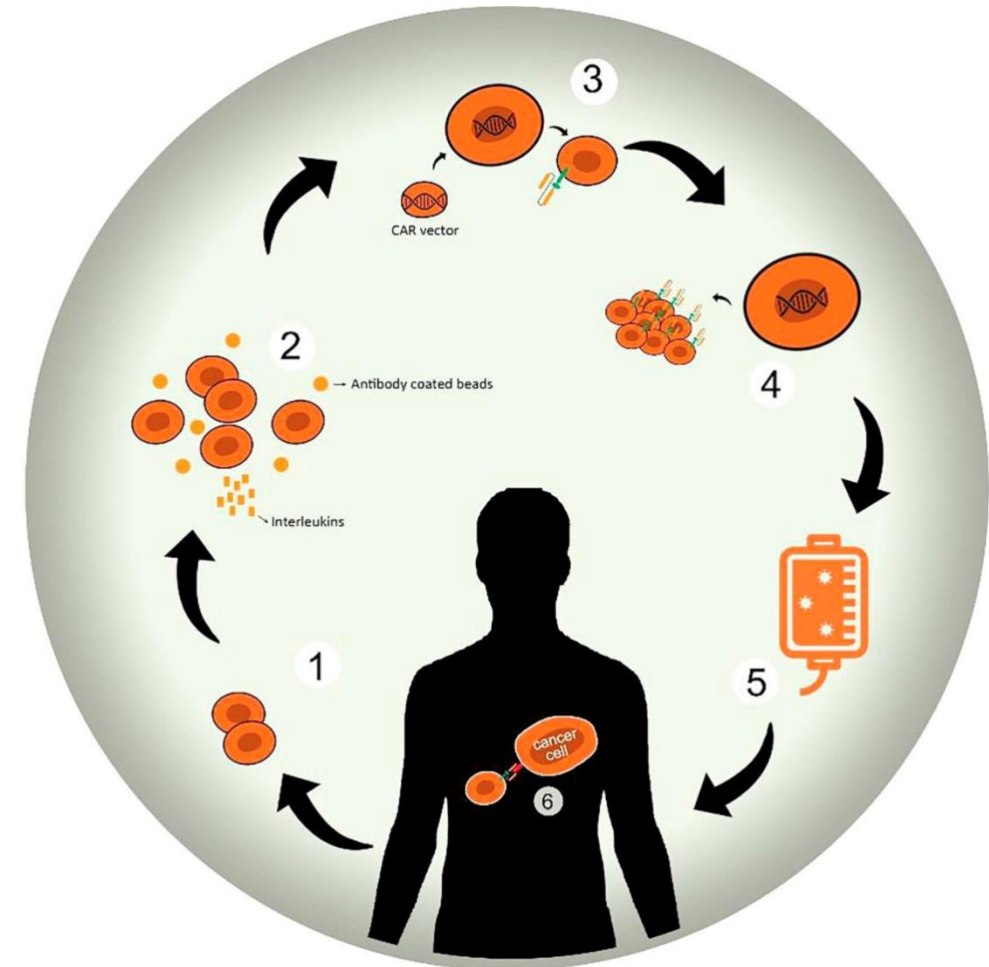
- **12.5% Specialist in Hematologic Malignancies**
- **11.5% Specialist in other cancers**
- **2.6% Specialist in Pediatric Hematology/Oncology**
- **29.7% General Hematology/Oncology**

## L' IMMUNOTERAPIA NELLE NEOPLASIE EMATOLOGICHE



**18 dicembre 2018**

**Aula Seminari del VIMM  
Via Orus, 2 - Padova**

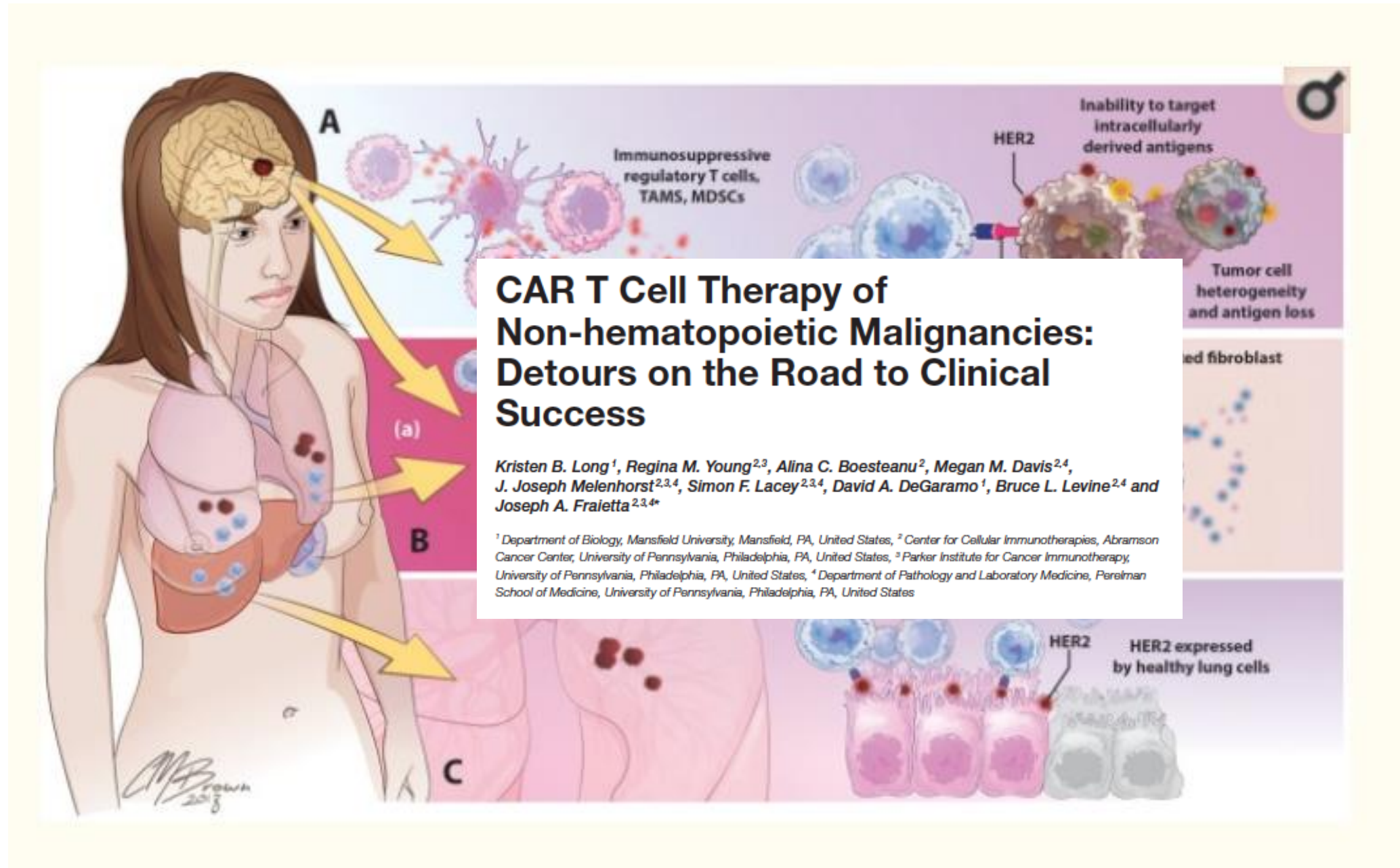




# **EVIDENCE OF CLINICAL APPLICATIONS OF CHIMERIC ANTIGEN RECEPTORS THERAPY**

- Acute Lymphoblastic Leukemia (ALL)**
- Non Hodgkin Lymphomas (NHL)**
- Chronic Lymphocytic Leukemia (CLL)**
- Multiple Myeloma (MM)**

# Barriers to successful CAR T-cell immunotherapy in solid tumors



# **EVIDENCE OF CLINICAL APPLICATIONS OF CHIMERIC ANTIGEN RECEPTORS THERAPY**

- Acute Lymphoblastic Leukemia (ALL)**
- Non Hodgkin Lymphomas (NHL)**
- Chronic Lymphocytic Leukemia (CLL)**
- Multiple Myeloma (MM)**

# Different Types of CAR-T Cells in Multiple Myeloma

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

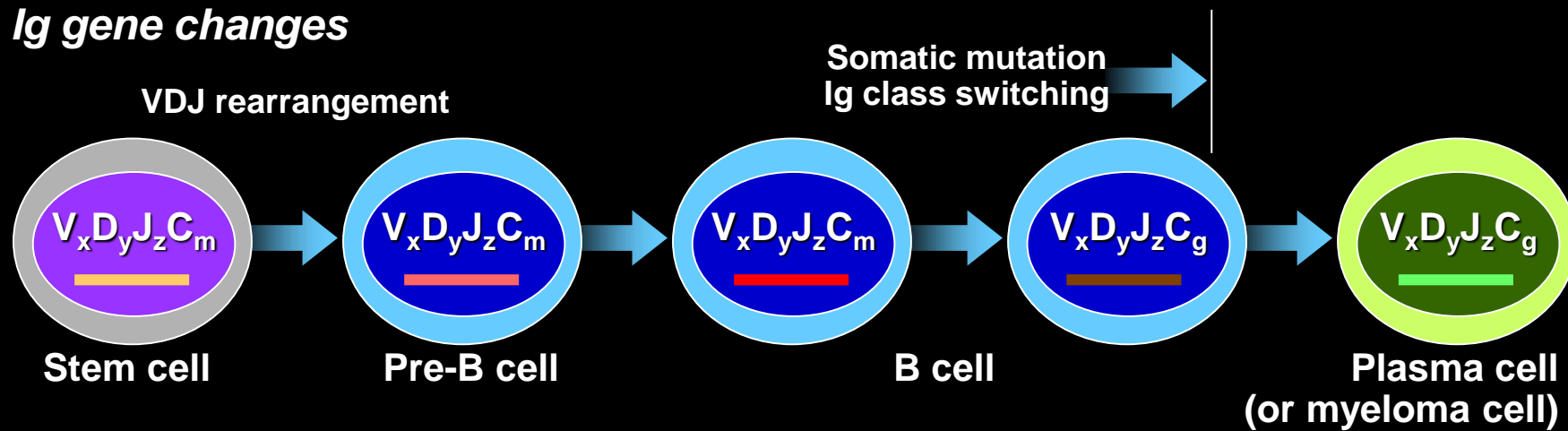
## Chimeric Antigen Receptor T Cells against CD19 for Multiple Myeloma

Alfred L. Garfall, M.D., Marcela V. Maus, M.D., Ph.D., Wei-Ting Hwang, Ph.D., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., J. Joseph Melenhorst, Ph.D., Zhaohui Zheng, M.S., Dan T. Vogl, M.D., Adam D. Cohen, M.D., Brendan M. Weiss, M.D., Karen Dengel, R.N., B.S.N., Naseem D.S. Kerr, M.P.H., Adam Bagg, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., and Edward A. Stadtmauer, M.D.

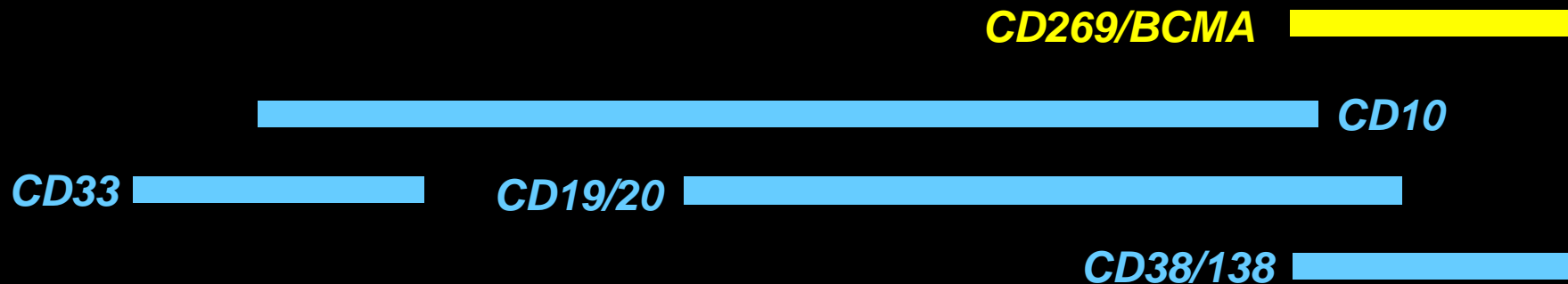
N. Engl. J. Med. 373: 1040 (2015)

- **Anti-CD19 specific CAR-T Cells**
- **Anti-CD319 specific CAR-T Cells**
- **Anti-CD138 specific CAR-T Cells**
- **Anti-BCMA specific CAR-T Cells**

# BCMA and the Development of Plasma Cells



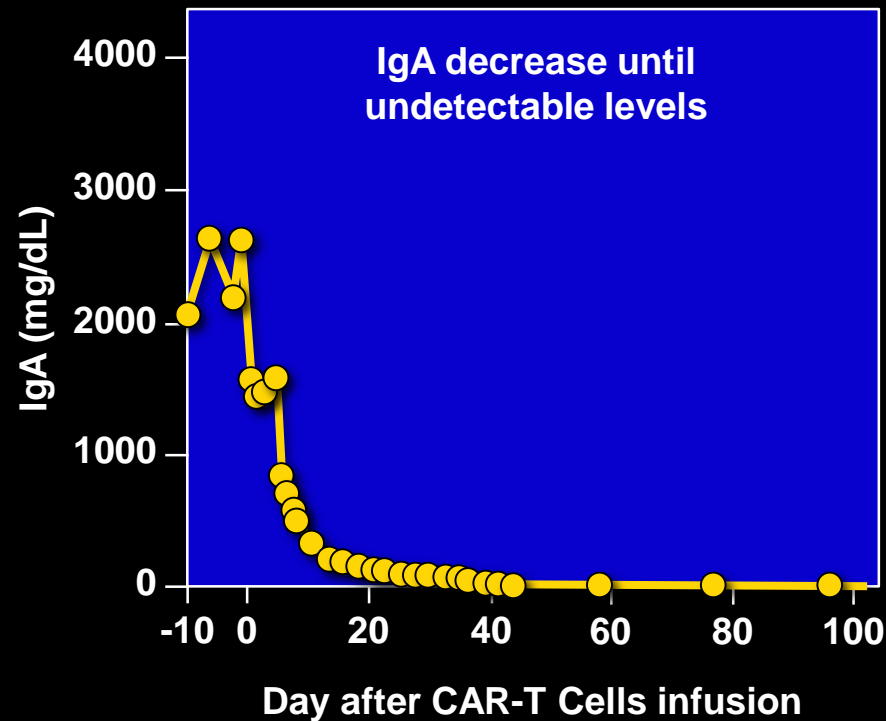
## *Cell surface markers*



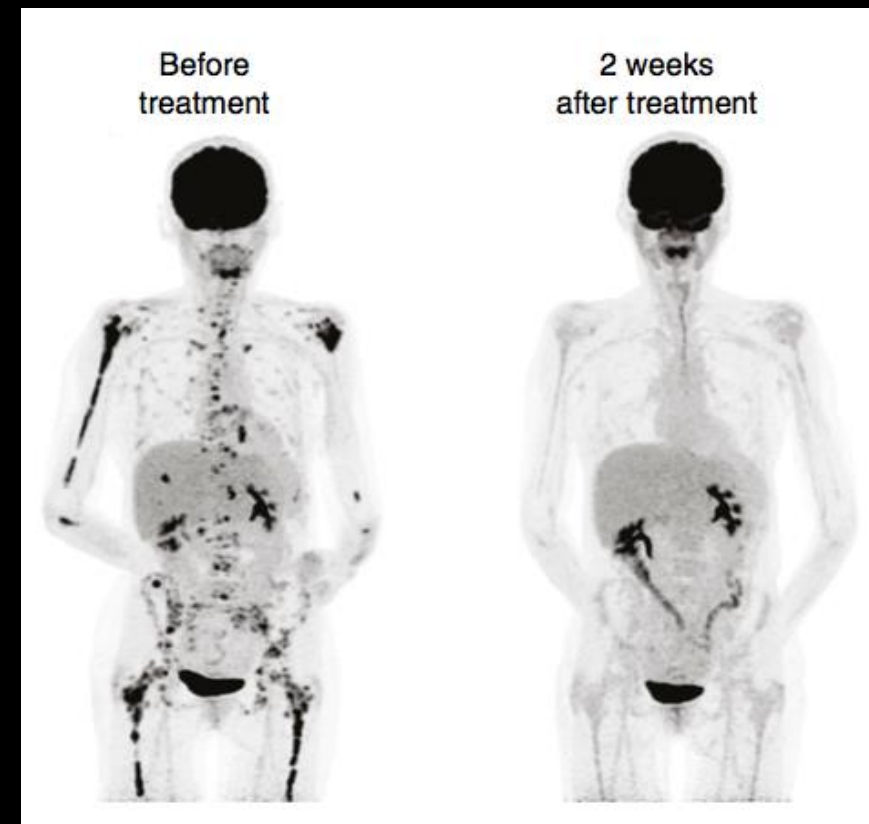
# Anti B-Cell Maturation Antigen CAR-T Cells Have Impressive Activity Against Multiple Myeloma

BCMA expression is restricted to B cells at later stages of differentiation and is requisite for PC survival

BCMA is broadly expressed at variable levels on malignant plasma cells

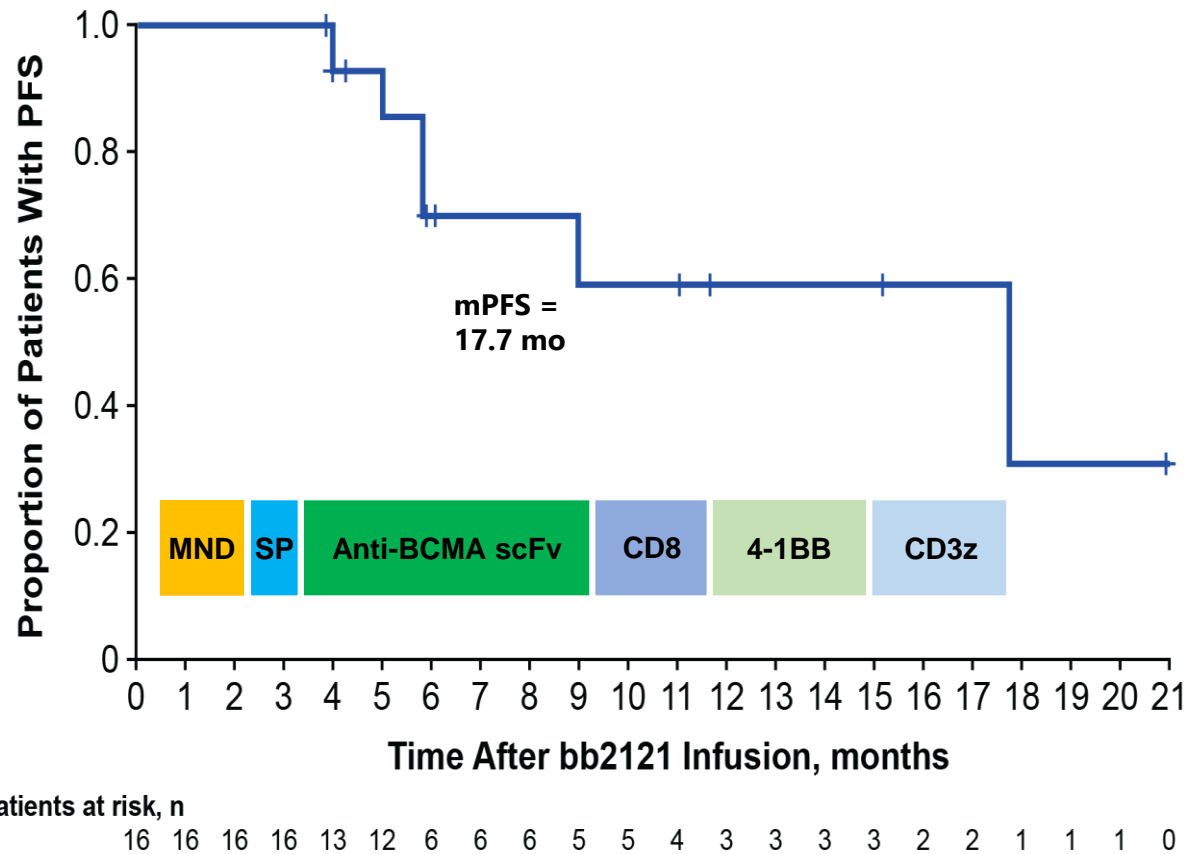


## BCMA bb2121 CAR-T Cells Infusion

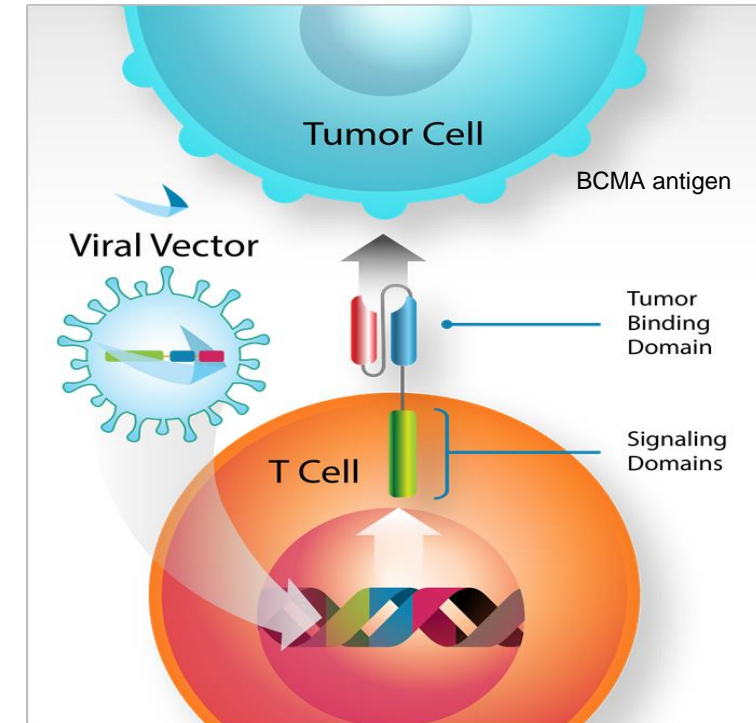


# CAR T Cells Therapy for Hematological Malignancies, Including Multiple Myeloma, Induce High ORR However Relapses Occur

Progression Free Survival in MM MRD-Negative Patients (BCMA CAR T Cell – bb2121 manufacturing)



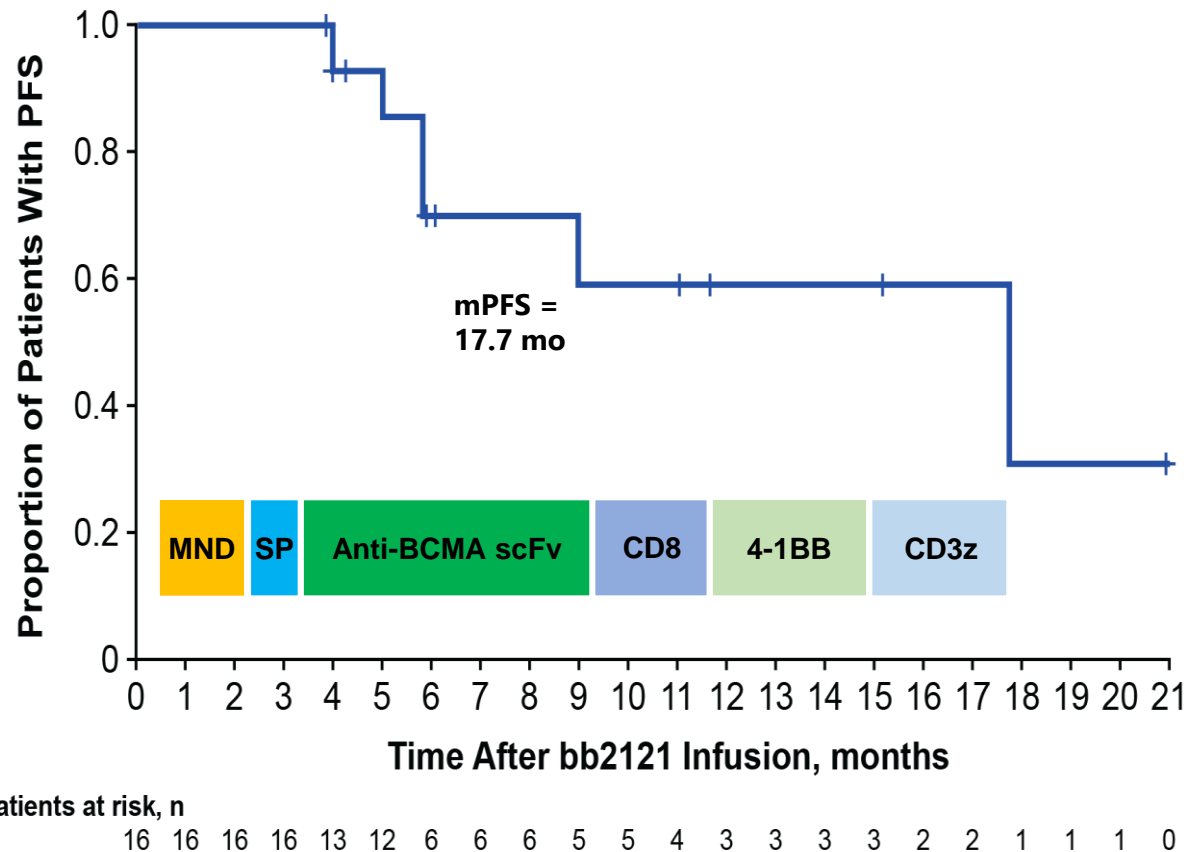
## Driving CAR T-Cells Forward



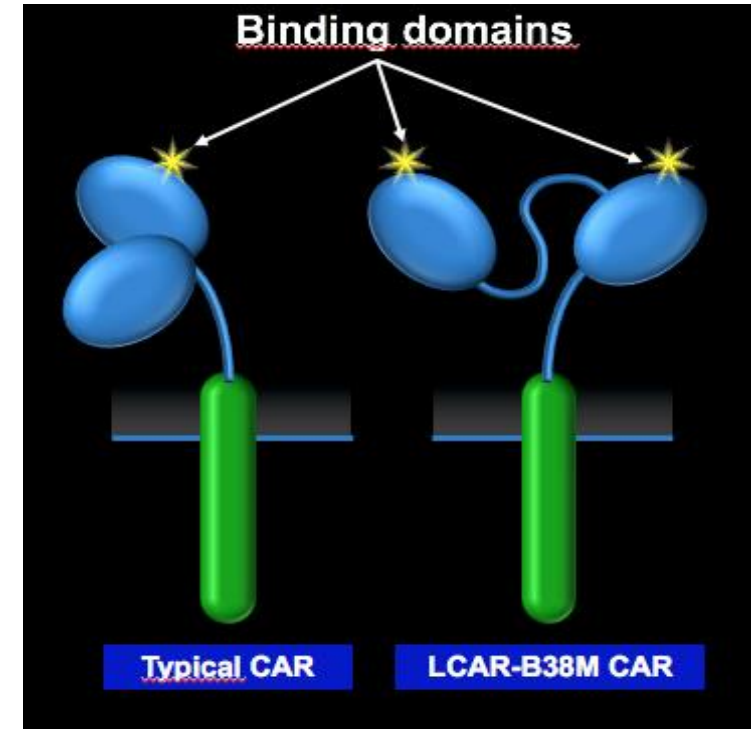
Improve the response in terms of in vivo activity and persistence of infused cells or by the identification of new determinants

# CAR T Cells Therapy for Hematological Malignancies, including Multiple Myeloma, Induce High ORR However Relapses Occur

Progression Free Survival in MM MRD-Negative Patients  
(BCMA CAR T Cell – bb2121 manufacturing)

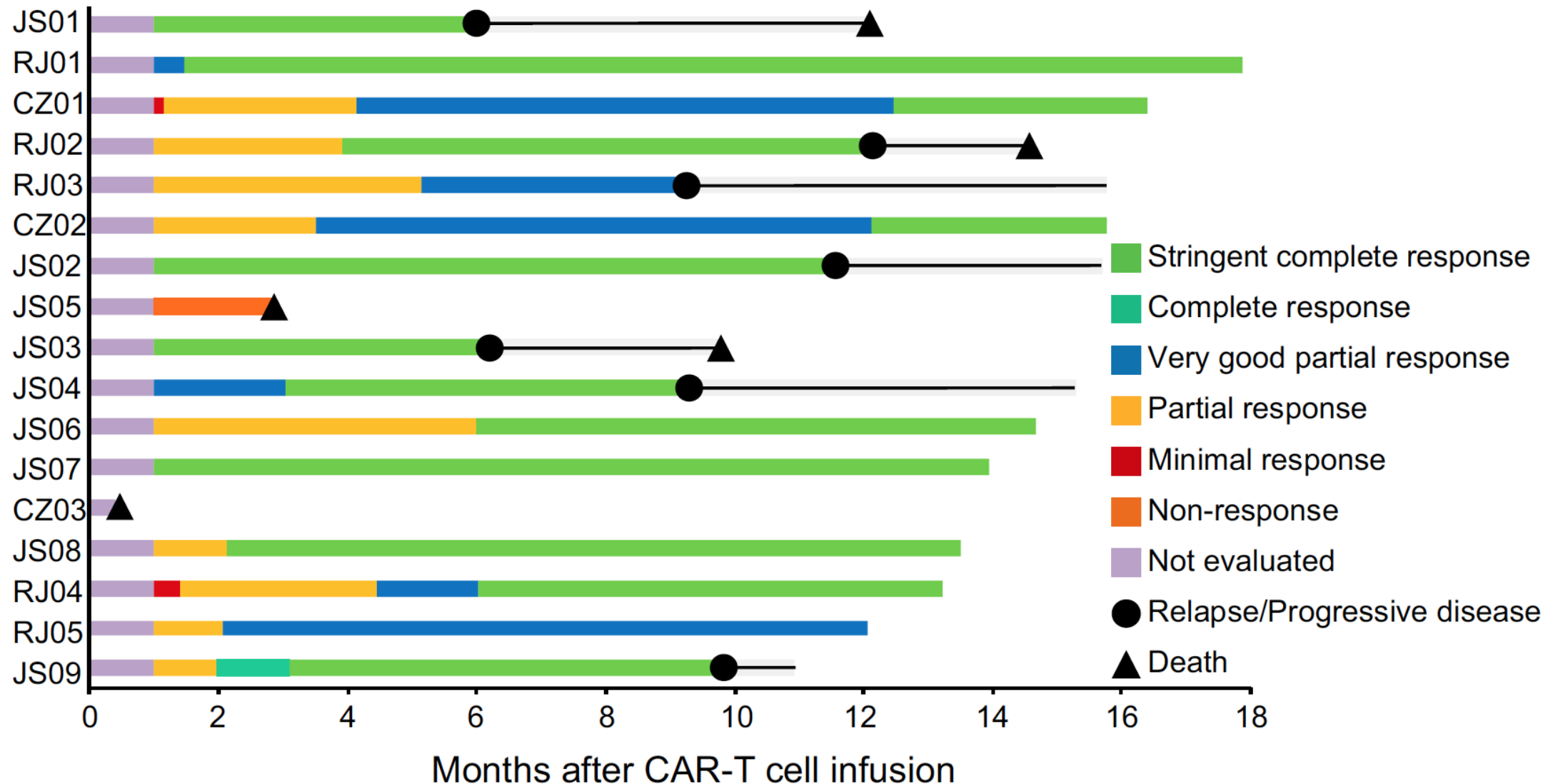


## Driving CAR T-Cells Forward



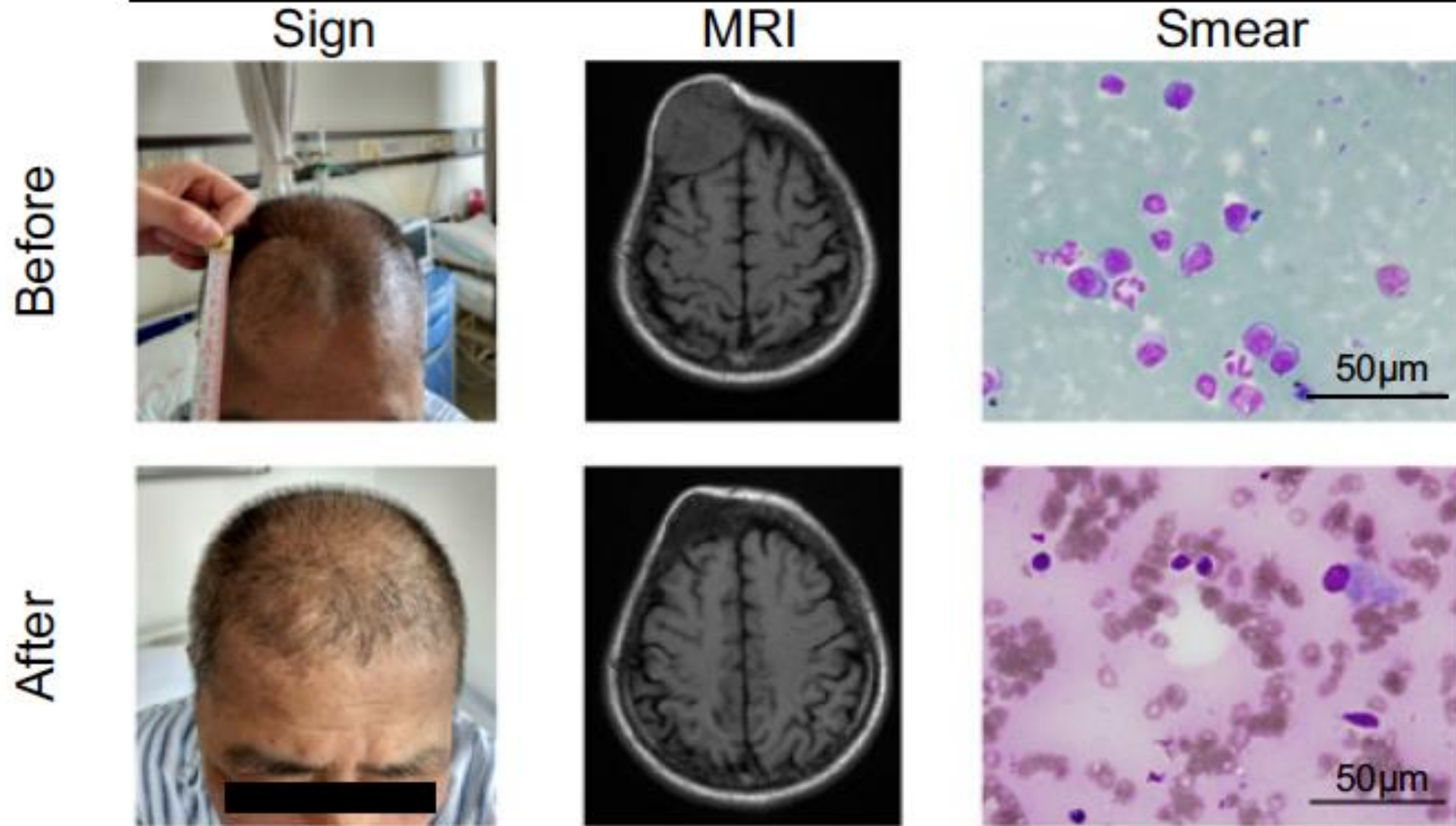


# Clinical Overall Response and Survival in Relapsed Refractory Multiple Myeloma to Biepitopic CAR T Cells against BCMA



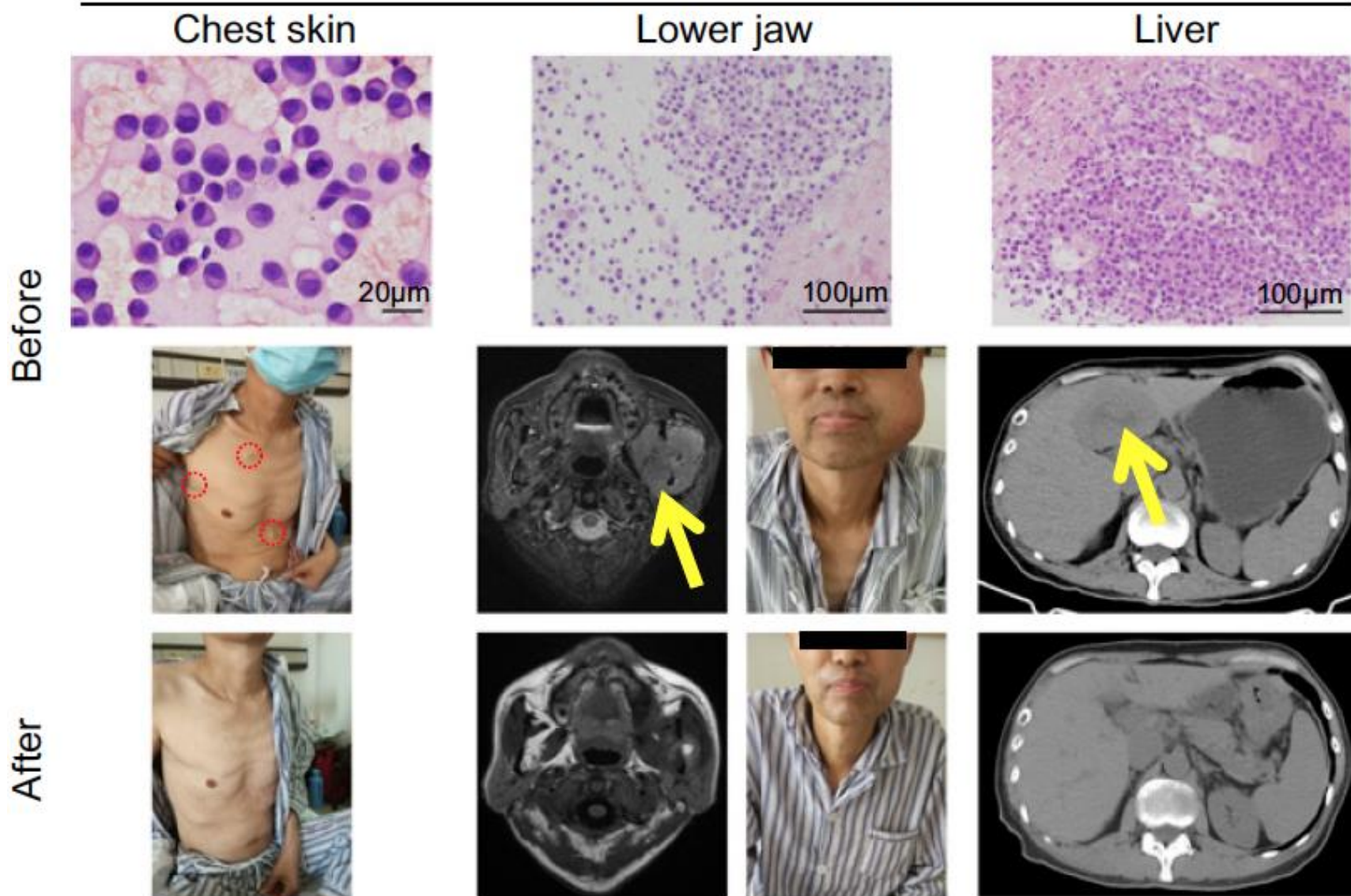
# Multiple Myeloma: Response of Extramedullary Lesions

RJ02 at initial therapy

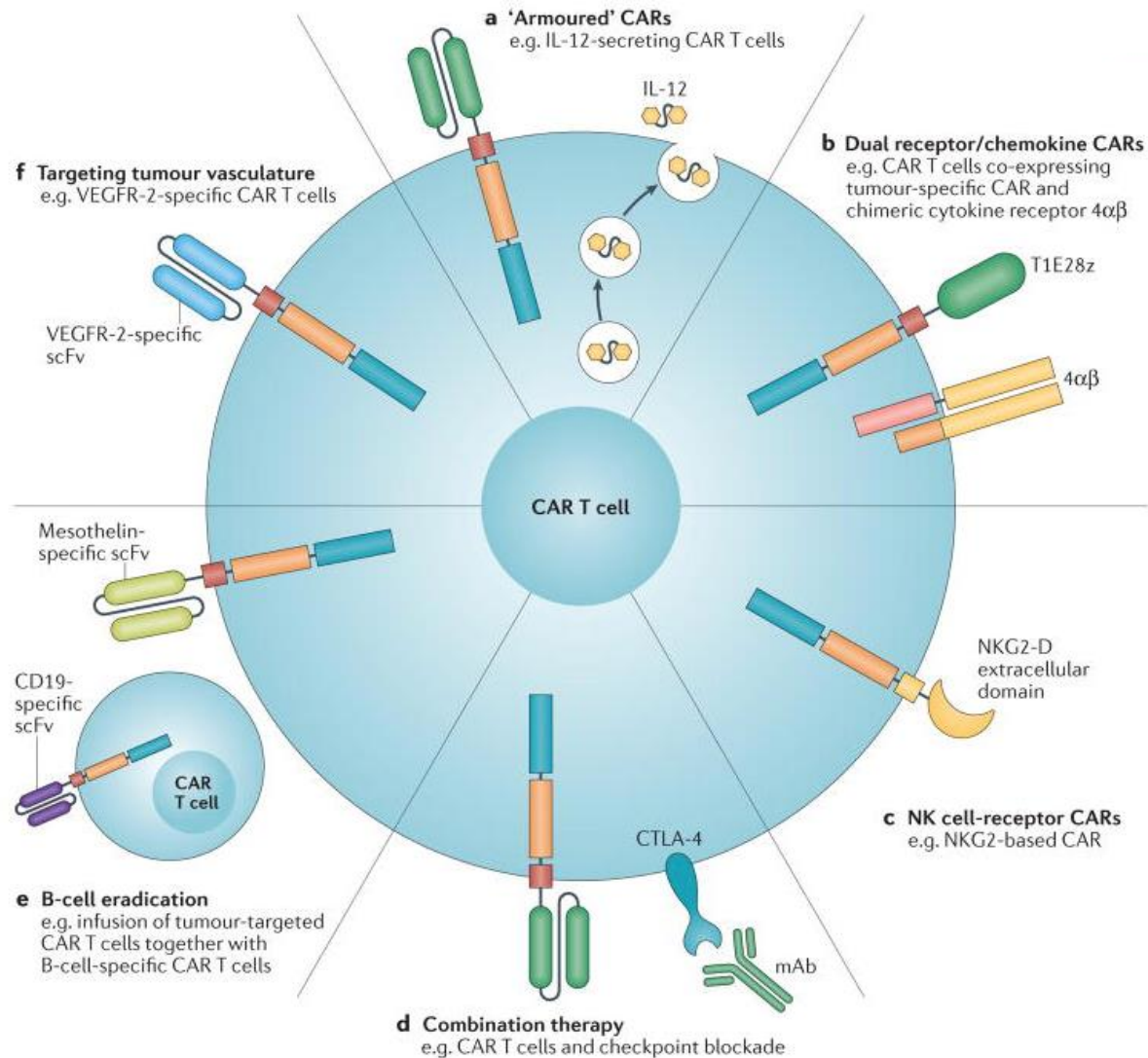


# Multiple Myeloma: Response of Extramedullary Lesions

RJ03 at initial therapy

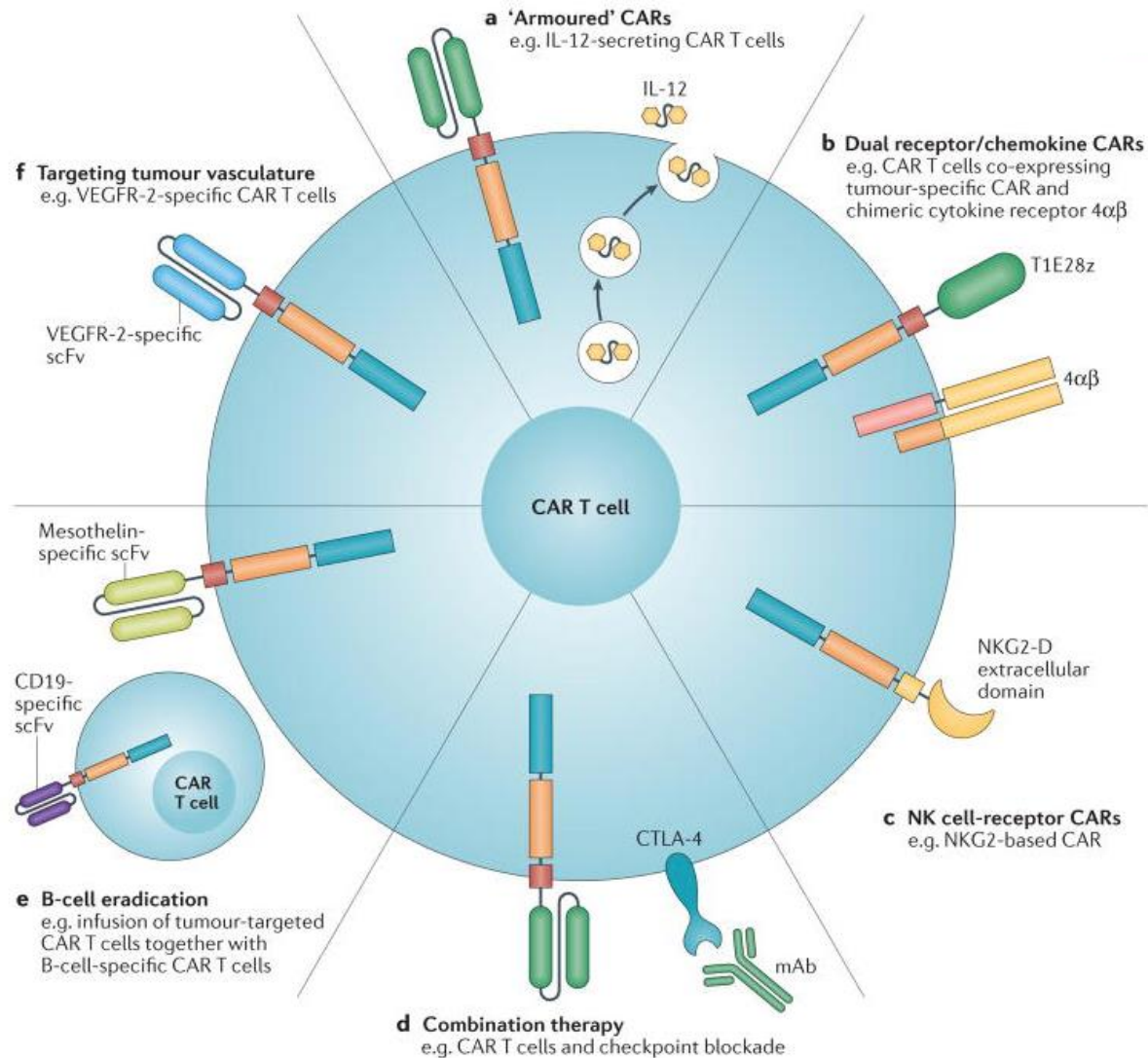


# Strategies to increase the antitumor efficacy of CAR T-cell therapy

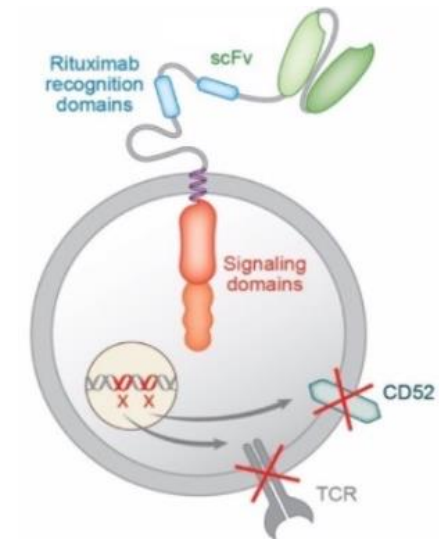


- Armoured CAR T cells to enhance efficacy and persistence
- Other surface molecules as target
- Multiple target

# Strategies to increase the antitumor efficacy of CAR T-cell therapy



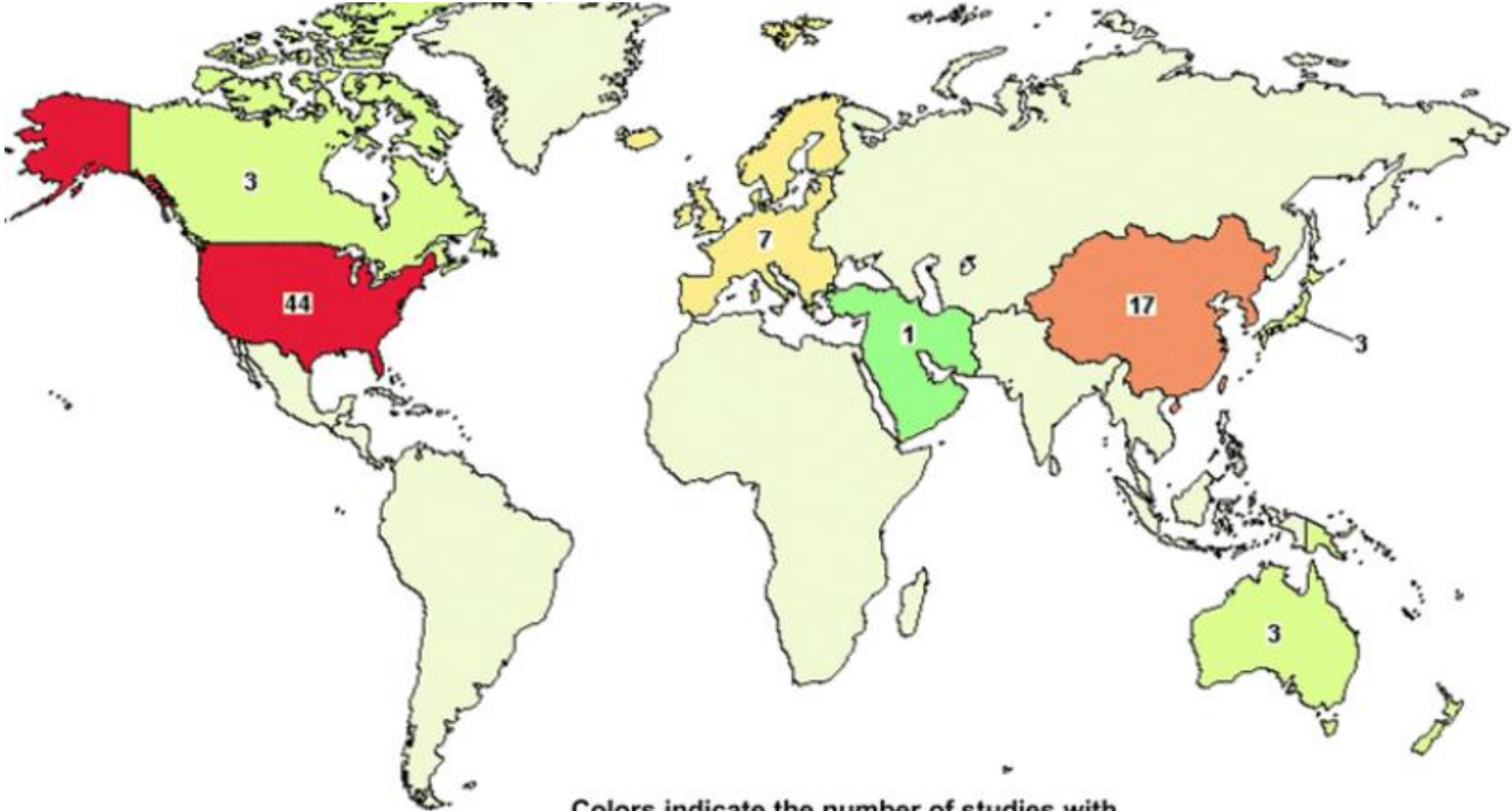
- Armoured CAR T cells to enhance efficacy and persistence
- Other surface molecules as target
- Multiple target
- CAR-T with suicide genes to control Cytokine Release Syndrome



# **Problematiche correlate alla terapia con cellule CAR-T**

- **Aspetti organizzativi**
- **Tossicità: Cytokine Release Syndrome-Neurotossicità-HLH**  
**(diagnostica, trattamento, monitoraggio)**
- **Rapporti con altre metodologie**  
**(trapianto allogenico, anticorpi bispecifici)**
- **Costi (QALY - ICER)**

# Distribution of current clinical trials with anti-CD19 in the world

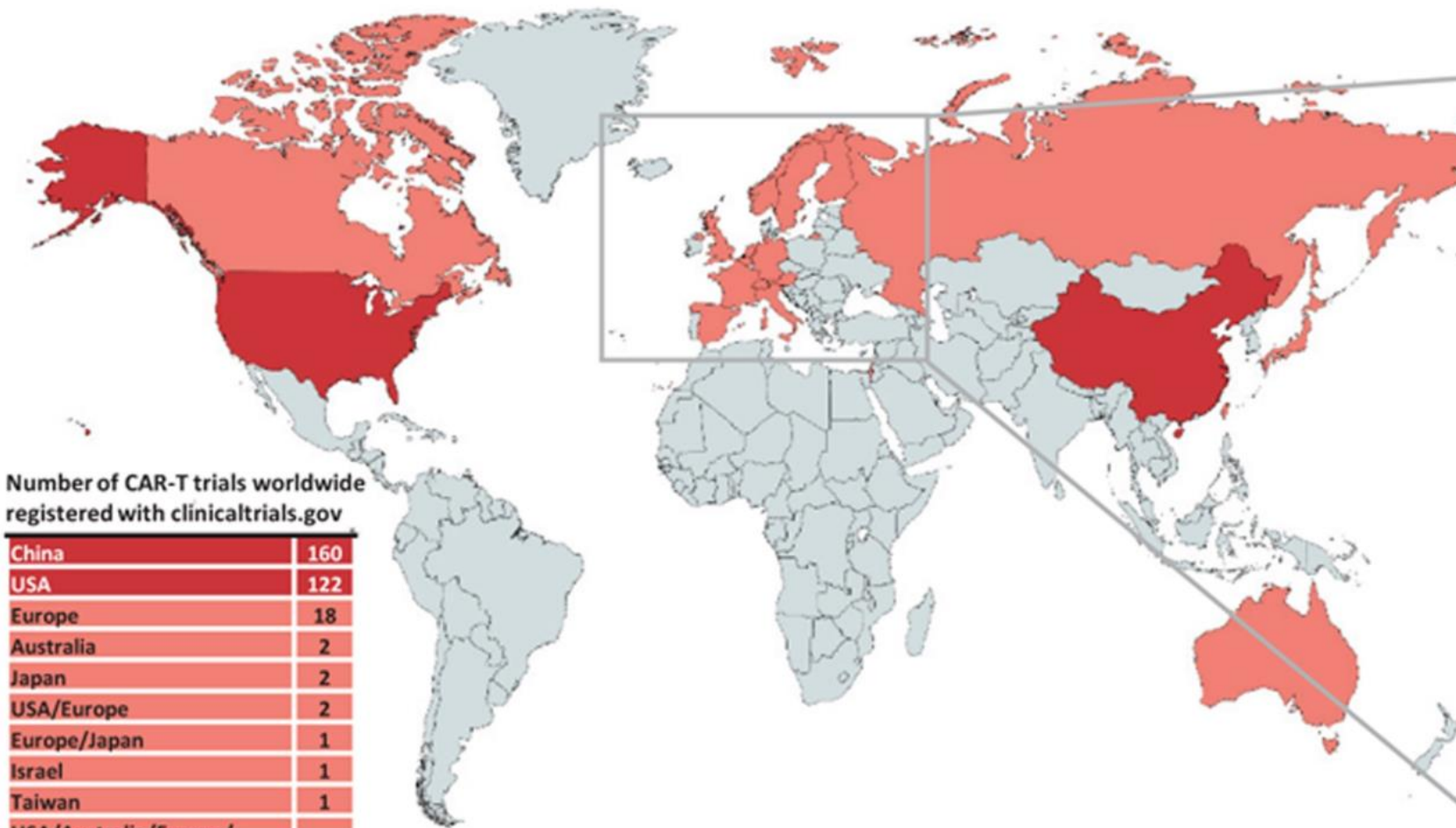


Colors indicate the number of studies with locations in the region

Least  Most

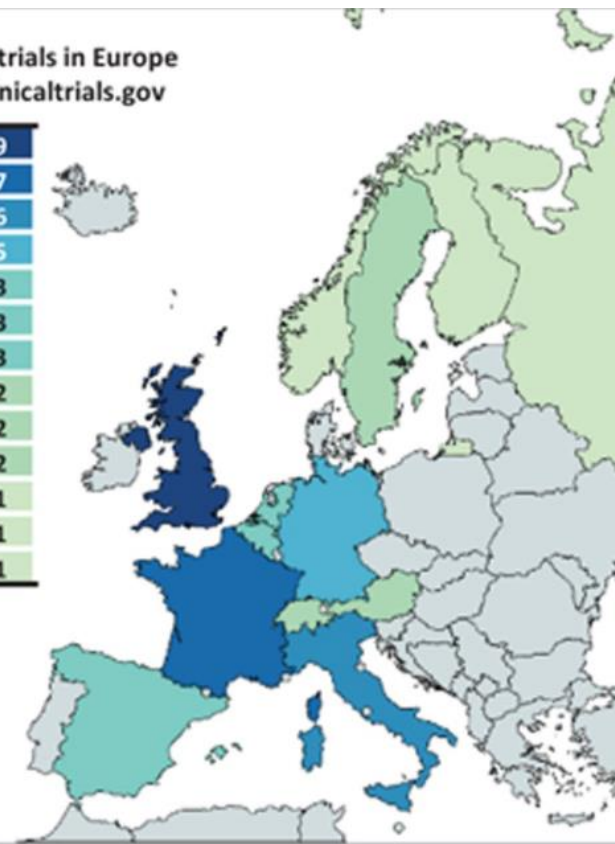
Labels give the number of studies

# Distribution of CAR-T trials worldwide registered clinicaltrials.gov



Number of CAR-T trials in Europe registered with clinicaltrials.gov

UK	9
France	7
Italy	6
Germany	5
Belgium	3
Netherlands	3
Spain	3
Austria	2
Sweden	2
Switzerland	2
Finland	1
Norway	1
Russia	1





# Limitations to Durable Remissions after CAR T Cell Therapy

