
# CAR-T: la nuova frontiera dell'immunoterapia

## Stato dell'arte

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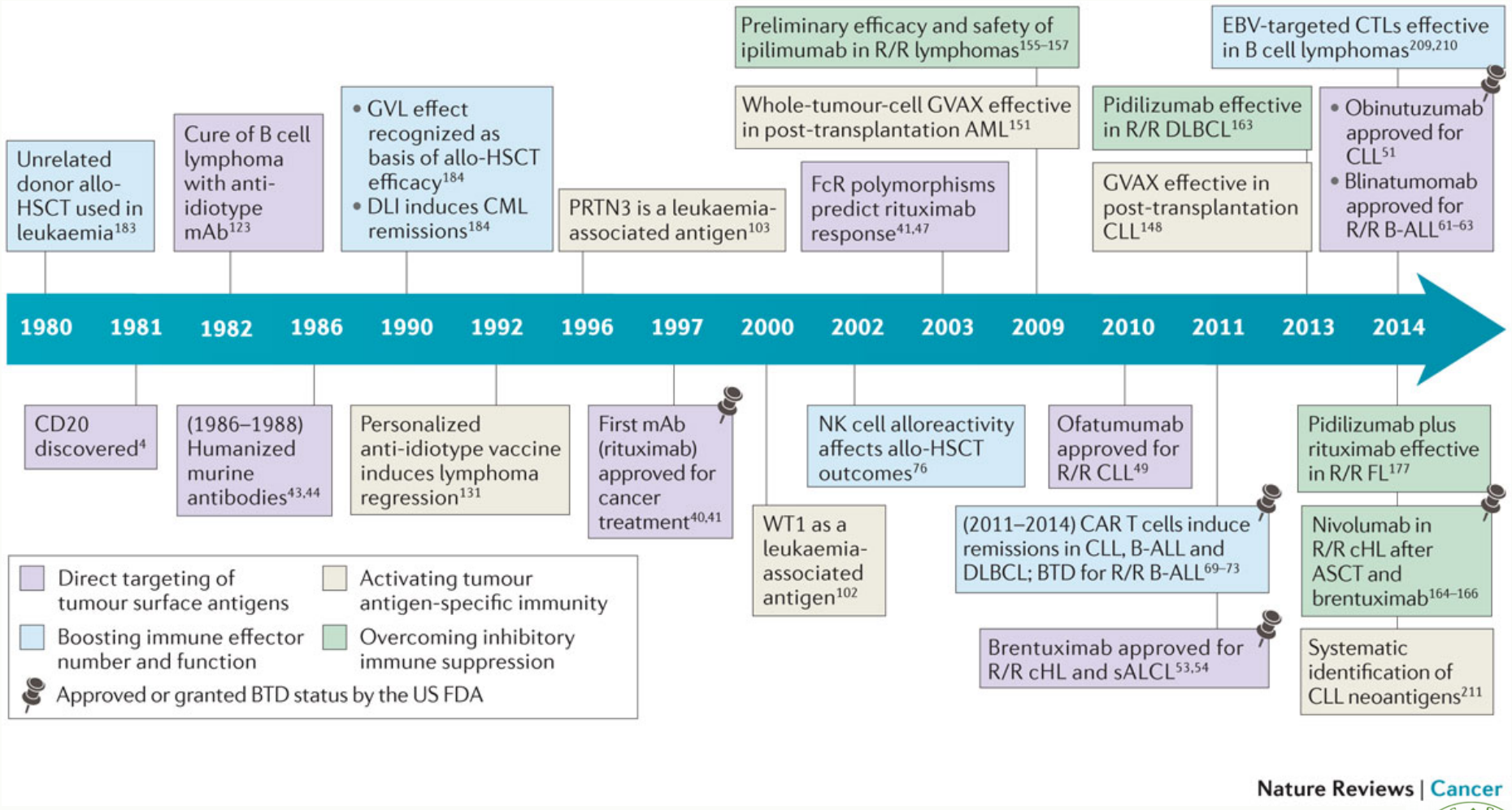
# Adoptive Immunotherapy


**When cancer and immunology meet**

An old and up-to-date history at the forefront of immunotherapy of hematological malignancies

Ebb and flow of Immunology of Cancer

# Timeline of Immunotherapeutic Advances in Haematological Malignancies



# Nodes of Cancer Immunotherapy

## 1 DIRECT TARGETING OF SURFACE ANTIGENS

**Monoclonal Antibodies**

**CD20 specific**

- Type I (Rituximab, Ofatumumab) redistribute CD20 into large lipid rafts: ADCC, CDC
- Type II (obinutuzumab): no rridistribution; high ADCC and direct killing

**CD52** (alentuzumab) expressed on T and Mo cells

**CD30** (Brentuximab)

**SLAMF7/CS1**(Elotuzumamb)

**CD38** (Daratumumab)

**Bispecific T cell engagers (BiTEs)**

**CD3/CD19** (Blinatumomab)

**CD3/CD33**

## 2 BOOSTING IMMUNE EFFECTOR NUMBER AND FUNCTION

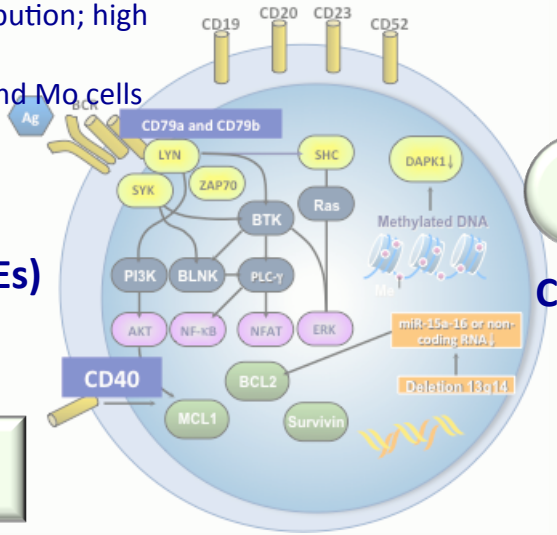
**clinical scenarios post allo-transplant:**

- DLI for leukaemic relapse
- CTLs for EBV-associated lymphoproliferative malignancies

**CAR T cells**

**NK cell alloreactivity**

**Agonistic stimulation of immune effector function**




## 3 ACTIVATING TUMOR ANTIGEN-SPECIFIC IMMUNITY

**Cancer Vaccination:**

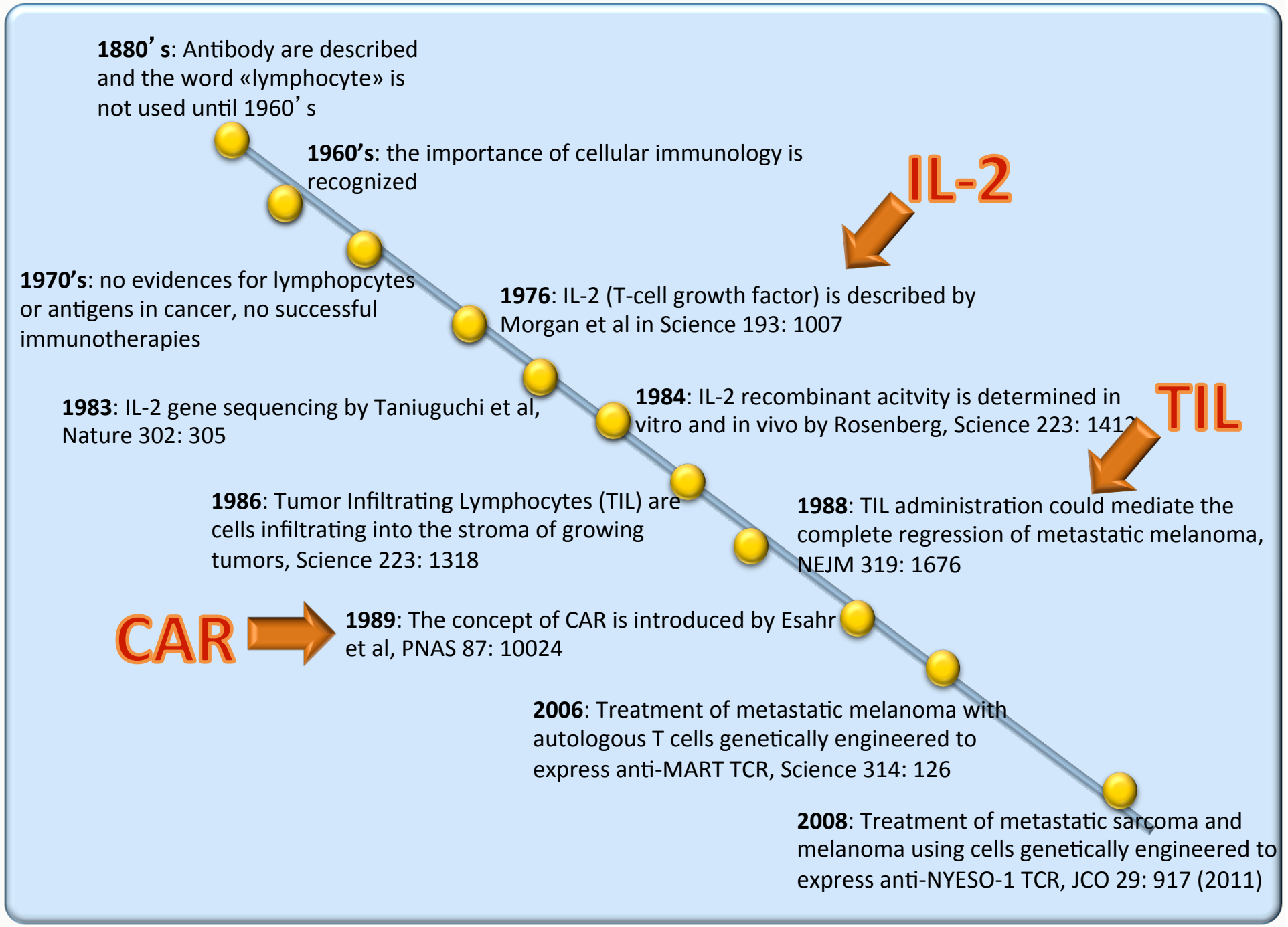
- WT1
- BCR-ABL fusion protein

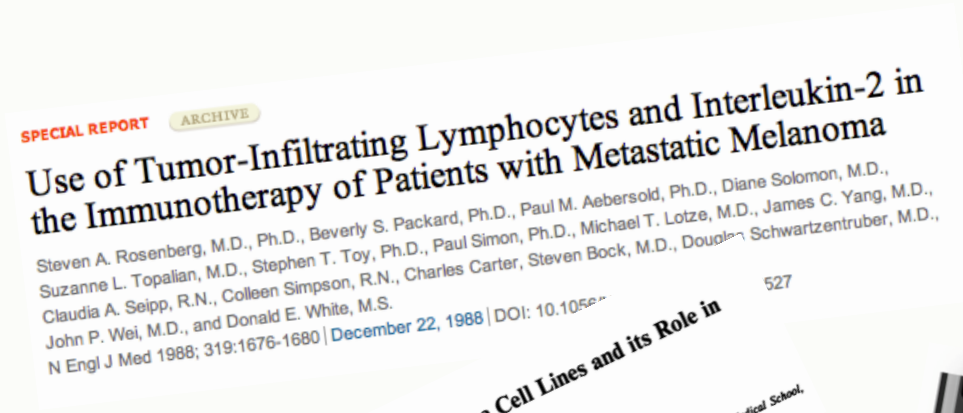
## 4 OVERCOMING INHIBITORY IMMUNE SUPPRESSION

**Co-inhibitory molecules:** **two main chechpoints:**

- **CTLA4** (ipilimumab)
- **PD1**
  - PIDILIZUMABI (IgG1, DLBCL after ASCT)
  - NIVOLUMAB (cHL), PEMBROLIZUMAB
- **TIM3:** (T cell immunoglobulin and mucin domain
- **LAG3:** (lymphocyte activation gene 3 protein)
- **KIRs:** (LIRILUMAB binds KIR)

**$T_{Reg}$ cells, $B_{Reg}$ cells and MDSCs**


**1880's**: Antibody are described and the word «lymphocyte» is not used until 1960's
**1960's**: the importance of cellular immunology is recognized
IL-2
**1970's**: no evidences for lymphopcytes or antigens in cancer, no successful immunotherapies
**1976**: IL-2 (T-cell growth factor) is described by Morgan et al in Science 193: 1007
**1983**: IL-2 gene sequencing by Taniuguchi et al, Nature 302: 305
**1984**: IL-2 recombinant acitvity is determined in vitro and in vivo by Rosenberg, Science 223: 141
TIL
**1986**: Tumor Infiltrating Lymphocytes (TIL) are cells infiltrating into the stroma of growing tumors, Science 223: 1318
**1988**: TIL administration could mediate the complete regression of metastatic melanoma, NEJM 319: 1676
CAR
**1989**: The concept of CAR is introduced by Esahr et al, PNAS 87: 10024
**2006**: Treatment of metastatic melanoma with autologous T cells genetically engineered to express anti-MART TCR, Science 314: 126
**2008**: Treatment of metastatic sarcoma and melanoma using cells genetically engineered to express anti-NYESO-1 TCR, JCO 29: 917 (2011)



SPECIAL REPORT ARCHIVE

# Use of Tumor-Infiltrating Lymphocytes and Interleukin-2 in the Immunotherapy of Patients with Metastatic Melanoma

Steven A. Rosenberg, M.D., Ph.D., Beverly S. Packard, Ph.D., Paul M. Aebersold, Ph.D., Diane Solomon, M.D., Suzanne L. Topalian, M.D., Stephen T. Toy, Ph.D., Paul Simon, Ph.D., Michael T. Lotze, M.D., James C. Yang, M.D., Claudia A. Seipp, R.N., Colleen Simpson, R.N., Charles Carter, Steven Bock, M.D., Douglas Schwartzentruber, M.D., John P. Wei, M.D., and Donald E. White, M.S.

N Engl J Med 1988; 319:1676-1680 | December 22, 1988 | DOI: 10.1056/...

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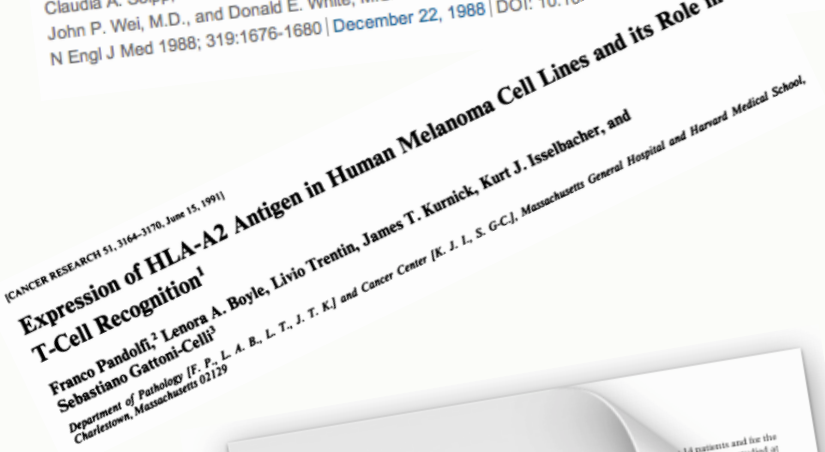

[CANCER RESEARCH 51, 3164–3170, June 15, 1991]

# Expression of HLA-A2 Antigen in Human Melanoma Cell Lines and its Role in T-Cell Recognition[1]

Franco Pandolfi,[2] Lenora A. Boyle, Livio Trentin, James T. Kurnick, Kurt J. Isselbacher, and Sebastiano Gattoni-Celli[3]

Department of Pathology [F. P., L. A. B., L. T., J. T. K.] and Cancer Center [K. J. I., S. G-C.], Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129

# B7 Costimulatory Molecules from Malign... Patients with B-Cell Chronic Lymphopro... Disorders Trigger T-Cell Proliferation

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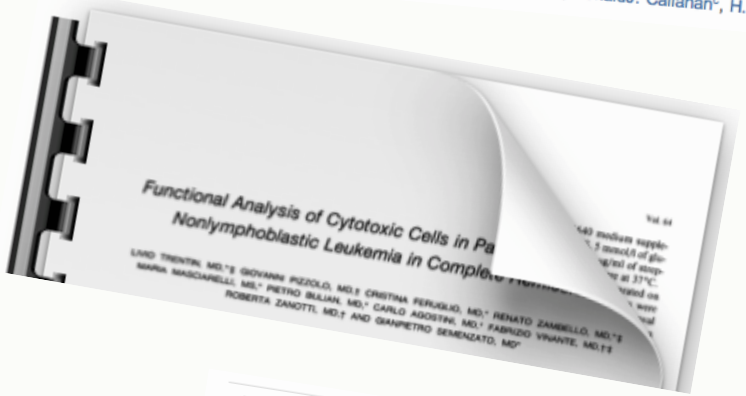
Alessandra Perin, M.D.,[1]
Marta Siviero, M.D.,[1]
Francesco Piazza, M.D.,[1]
Monica Facco, M.D.,[1]
Carmela Gurrieri, M.D.,[1]
Silvia Salvan, M.D.,[1]
Fausto Adami, M.D.,[1]
Carlo Agostini, M.D.,[1]
Giovanni Pizzolo, M.D.,[2]
Renato Zambello, M.D.,[1]
Gianpietro Semenzato, M.D.,[1]

BACKGROUND. B7 family molecules are involved in T-B cell communications after interaction with their ligands CD28 and CD152. They play a key role in costimulatory mechanisms and during antigen presentation by efficient antigen presenting cells. B7 molecules are usually absent or expressed at low intensity on B lymphocytes from healthy subjects. In this study, the authors addressed the questions of whether B7 molecules are expressed and modulated in vivo on malignant B lymphocytes from patients with chronic lymphoproliferative diseases of B-cell type and whether they are able to trigger allogeneic T cell reactions.

METHODS. Malignant B cells from the peripheral blood of 82 patients with B-cell chronic lymphocytic leukemia, mantle cell lymphoma, hairy cell leukemia, and its variant form were investigated for the expression of B7 molecules on the cell surface and for the ability to trigger allogeneic T lymphocytes in different experimental conditions.



# Functional Analysis of Cytotoxic Cells in Pa... Nonlymphoblastic Leukemia in Comple...

LIVIO TRENTIN, MD,*‡ GIOVANNI PIZZOLO, MD,‡ CRISTINA FERUGLIO, MD,* RENATO ZAMBELLO, MD,*‡ MARIA MASCHARELLI, MD,* PIETRO BULIAN, MD,* CARLO AGOSTINI, MD,* FABRIZIO VINANTE, MD,†‡ ROBERTA ZANOTTI, MD,† AND GIANPIETRO SEMENZATO, MD*

THE LANCET

Volume 333, Issue 8638, 18 March 1989, Pages 577–580

Originally published as Volume 1, Issue 8638

# TUMOUR-INFILTRATING LYMPHOCYTES AND INTERLEUKIN-2 IN TREATMENT OF ADVANCED CANCER

RichardL. Kradin, DavidS. Lazarus[b], StevenM. Dubinett[b], Julie Gifford[a], Beverly Grove[a], JamesT. Kurnick[a], FredericI. Preffer[a], ClareE. Pinto[a], Elise Davidson[a], RonaldJ. Callahan[c], H.William Strauss[c]

ELSEVIER

Cellular Immunology

Volume 141, Issue 2, May 1992, Pages 332–341

# Phenotypic and functional characterization of cytotoxic cells derived from endomyocardial biopsies in human cardiac allografts

Livio Trentin*, Renato Zambello*, Giuseppe Faggian†, Ugolino Livi†, Gaetano Thiene‡, Giuseppe Gasparotto*, Carlo Agostini*

*Br. J. Cancer* (1994), **69**, 1046–1051



# Functional role of IL-2 receptors on tumour-infiltrating lymphocytes

L. Trentin[1], R. Zambello[1], P. Bulian[1], A. Cerutti[1], A. Milani[1], E. Pirone[2], D. Nitti[2], C. Agostini[1] & G. Semenzato[1]

[1]*Padua University School of Medicine, Department of Clinical Medicine, First Medical Clinic and Clinical Immunology Section, Padova, Italy;* [2]*Department of Surgery, 35128 Padova, Italy.*

## IL-2

→ Established the potential to cure metastatic solid tumor by manipulating T-cell responses;
→ Treatment for metastatic melanoma and renal cell carcinoma.

## TIL

→ T-cells growing from resected metastatic tumor deposits;
→ High response rates and reproducible complete and durable responses in metastatic melanoma.

Now, efforts are focused on:
→ Improving TIL therapy
→ Extending TIL and other cellular therapies to different malignancies

One promising strategy is to administer T-cells that have been gentically engineered to express tumor-specific antigen receptors

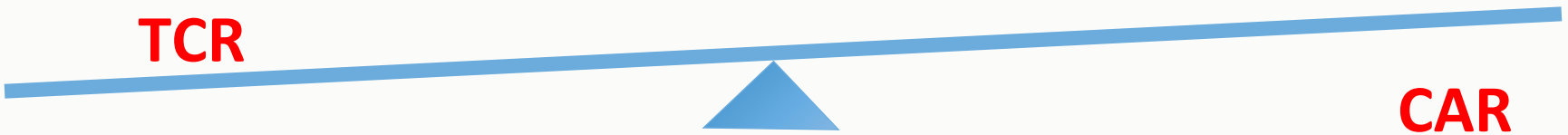
## CARs

Antigen receptor gene therapy

| Target | Receptor type | Cancers | Protocol status |
|---|---|---|---|
| NY-ESO-1 | TCR | Epithelial malignancies and sarcoma | Accruing |
| CD19 | CAR | Lymphomas | Accruing |
| VEGFR2 | CAR | All cancers | Accruing |
| EGFRvIII | CAR | Glioblastoma | Accruing |
| Mesothelin | CAR | Pancreatic, ovarian, mesothelioma | Accruing |
| 2G-1 | TCR | Kidney | Closed |
| MART-1 | TCR | Melanoma | Closed |
| gp100 | TCR | Melanoma | Closed |
| CEA | TCR | Colorectal | Closed |
| MAGE-A3 (MHC I) | TCR | Epithelial malignancies | Closed |
| SSX-2 | TCR | Epithelial malignancies | In development |
| CSP4 (HMWAg) | CAR | Melanoma, breast, pancreatic | In development |
| HPV-16 E6 | TCR | Oropharyngeal, cervical, other anogenital | In development |
| MAGE-A3 (MHC II) | TCR | Epithelial malignancies | In development |
| TIL therapy | | | |
| Cutaneous melanoma | | | |
| Ocular melanoma | | | |
| Gastrointestinal cancers | | | |
| Human papillomavirus-positive cancers (uterine cervix, oropharynx, anus, etc.) | | | |

Hinrichs & Rosenberg;
Immunological Reviews 2014, 257: 56-71

# T cells with engineered CARs and TCRs: which is better




1. Sensitive signal amplification derived from evolution
2. Low avidity
3. Targets intracellular proteome
4. Requires MHCI expressione and HLA matching on tumor
5. Life long persistence (14 years)
6. Serial Killers
7. Toxicity difficult to predict

1. Signal amplification from synthetic biology
2. Avidity controllable
3. Targets only surface structures
4. MHC independent: “off the shelf”
5. Decade long persistence
6. Serial Killers

# CARs vs TCRs / CARs vs BiTEs

## CAR vs TCR

- TCR can target intracellular antigens

- CAR are not HLA restricted
- Off-target effects are more predictable
- Artificial nature of CARs allows more engineering possibilities

## CARs vs BiTE

- Mass produced, simple therapeutic agent
- Short hal-life allows control of toxicity

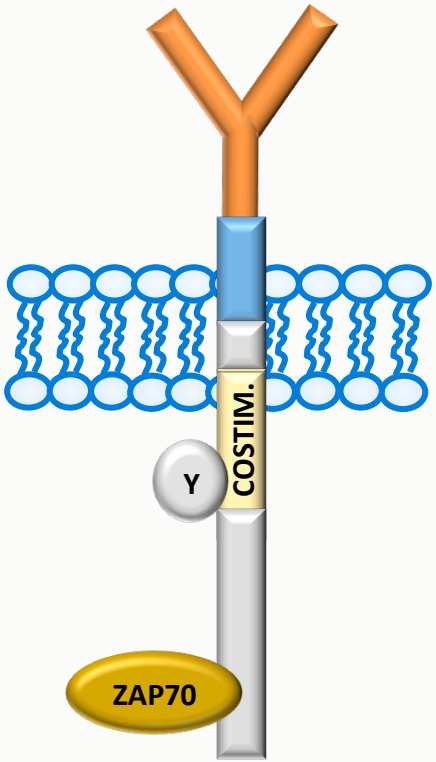
- Active migration of CAR T cells may overcome some bo-istribution problems
- Establishment of CAR immunological memory
- Engineering possibilities are much broader for CARs

# Questions facing the CAR field

- Is long term persistence of CAR cells desired?
- Which approaches give durable persistence of CARTs?
- What is the best vector to introduce the CAR: retroviral or lentiviral
- What is the optimal T cell type and composition of the infused product?

# Chimeric Antigen Receptors (CARs)

CARs are synthetic receptors that combine the extracellular single-chain variable fragment (scFv) of an antibody with a transmembrane (TM) domain and intracellular signaling domains derived from molecules involved in T-cell signaling.
They can confer to T-cells non-MHC-restricted recognition of cell surface antigens.



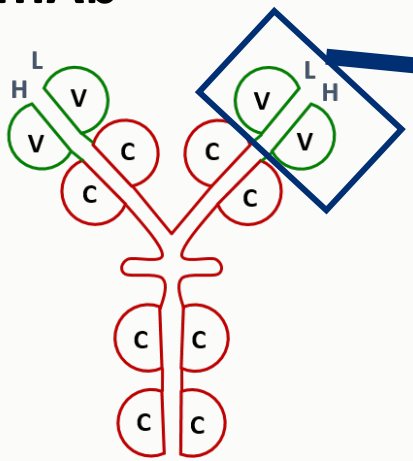

**Extracellular target-binding module** → Usually derived from scFv determinants isolated from antibodies

**Transemembrane module anchoring the CAR into the cell membrane** → Usually derived from molecules involved in T-cells function such as the CD8 and CD4 coreceptor molecules

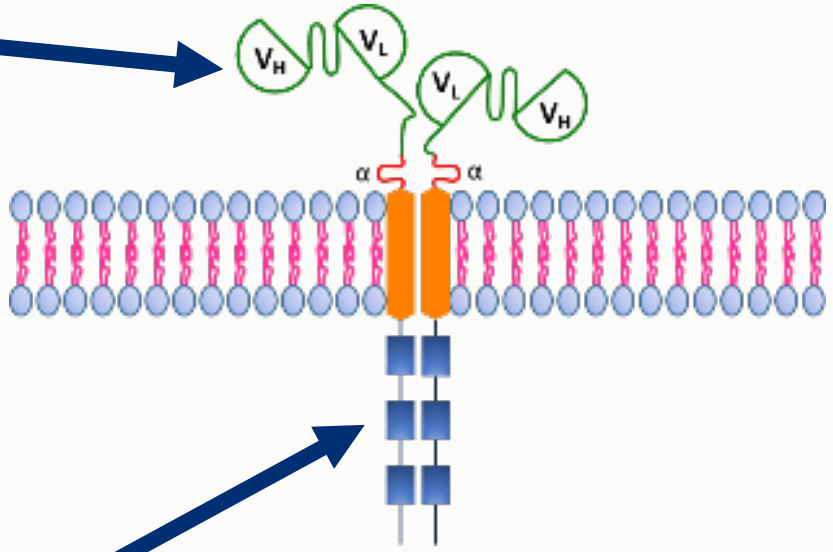
**Intracellular signaling module**

# Creation of a CAR T-cell

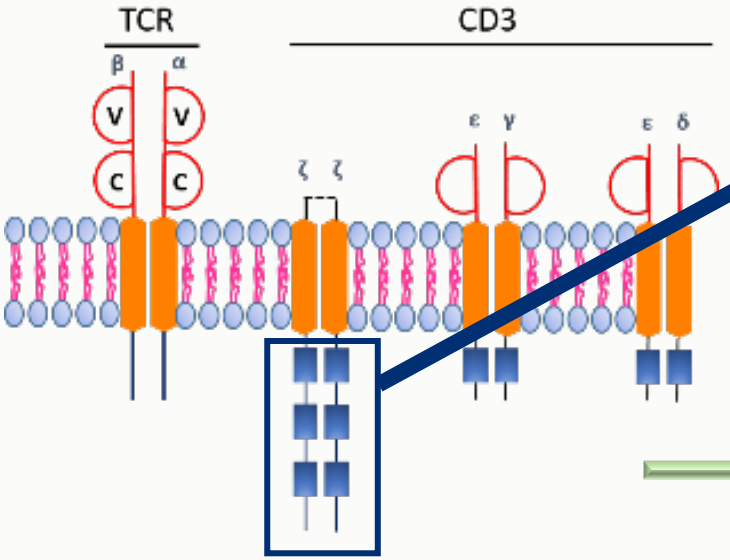
## α-TAA mAb



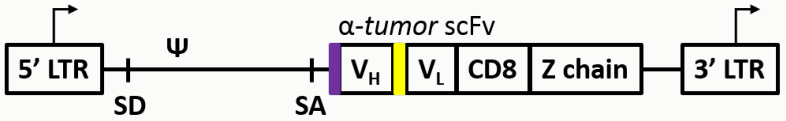

## α-TAA scFv—CD8-ζ



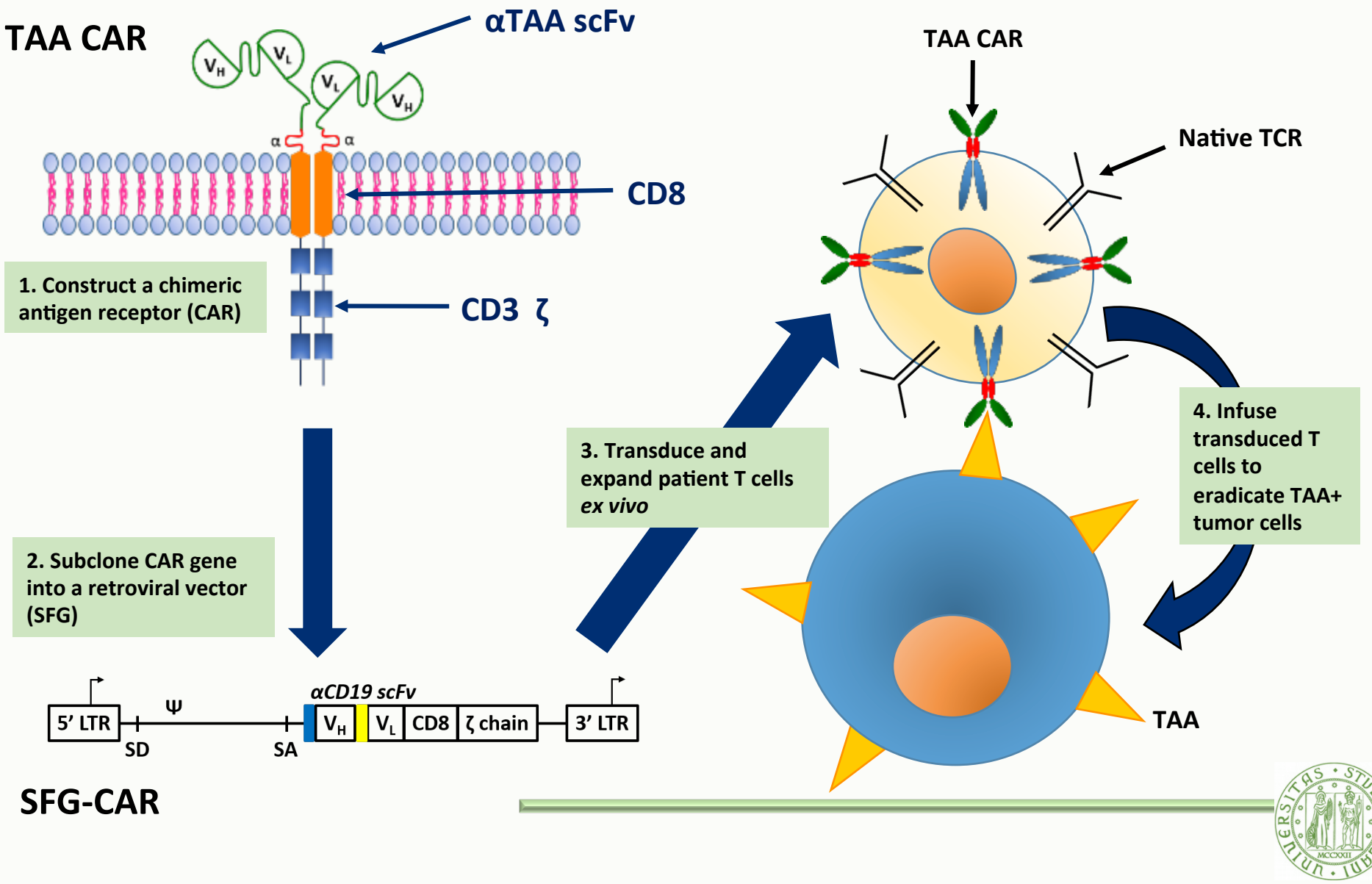

## TCR complex



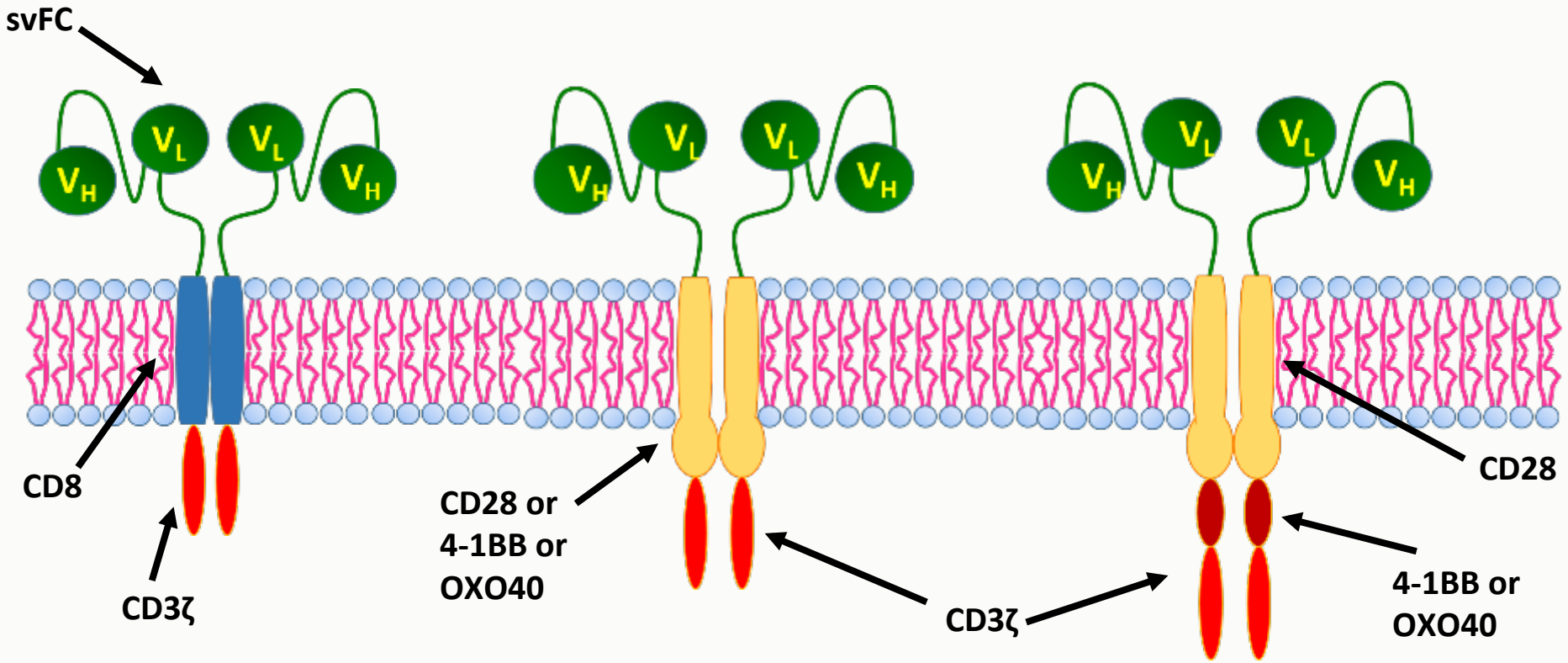

## CAR retroviral vector



# Creation of a CAR T-Cell



# CARs Immunotherapy




**First-Generation CAR**
**scFv-CD3ζ**

**Second-Generation CAR**
**scFv-CD28-CD3ζ**

**Third-Generation CAR**
**scFv-CD28-4-1BB-CD3ζ**
**scFv-CD28-OX40-CD3ζ**

# Chimeric Antigen Receptors (CARs)

**First-generation CARs**

CARs contained only the CD3ζ chain signaling domain → **Modest efficacy on lymphoma and ovarian cancer**

**Second-generation CARs**

Incorporation of additional signaling domains from costimulatory (i.e. CD28) and accessory functional T-cell molecules, → **Lasting complete responses in clinical trials in most pediatric and adult patients with R/R ALL and some adult patients with R/R CLL**

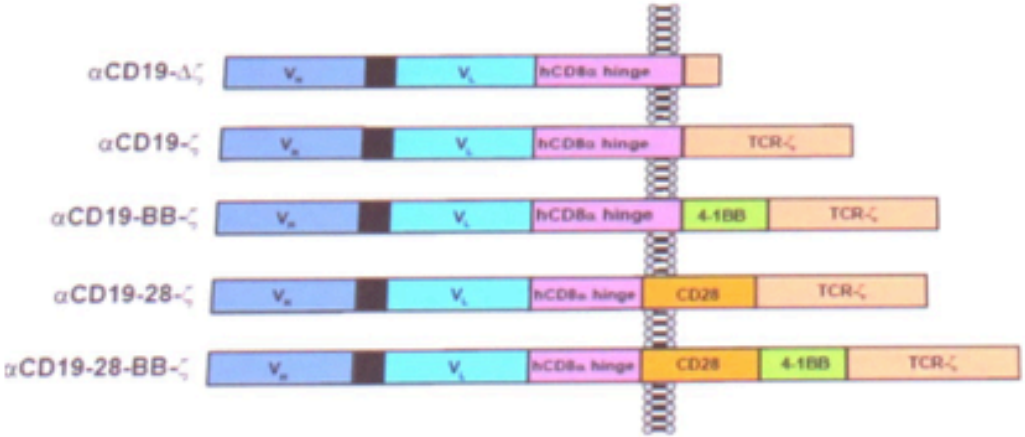
**Third-generation CARs**

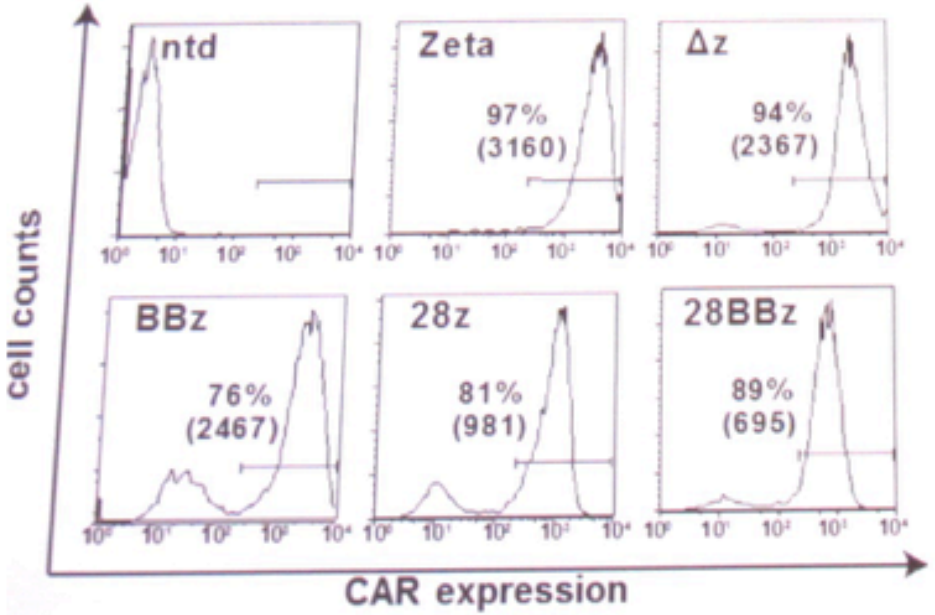
Incorporation of a second costimulatory domain to further improve T-cell expansion, cytotoxicity and *in vivo* persistance.

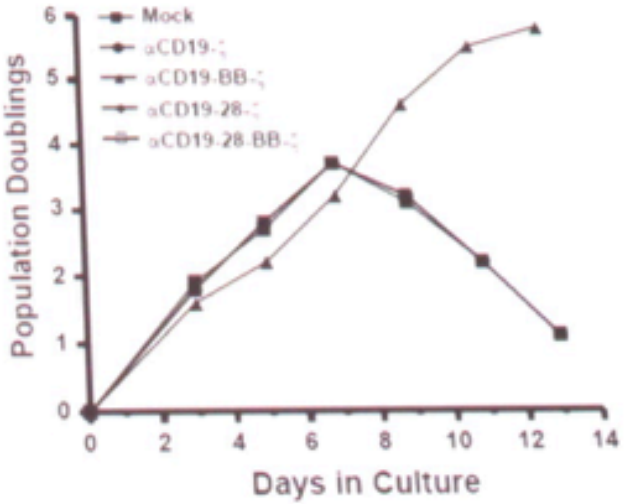

**CAR-engineered T cells have been generated against many different TAA for both solid and hematologic malignancies: CD19, CD20, CD33, B-cell maturation antigen, CD22, CD23, CD30, CD38, CD44v6, ROR1, k-light chain, Lewis Y antigen, NKp30, TAG-72, CD70, CA-IX, ErbB2/Her-2/Neu, GD2, GD3, L1CAM, VEGF-R2, EGFR, MUC-1, MUC-16, PSMA, PSCA, 5T4 oncofetal antigen, NCAM, mesothelin, fibroblast activating protein, folate receptor-α, NKG2D, IL-11 receptor α-chain, CEA, IL-13Rα2 and EphA2.**

# Design of a CTL019:

## 4-1BB domain promotes CAR T cells proliferation/survival

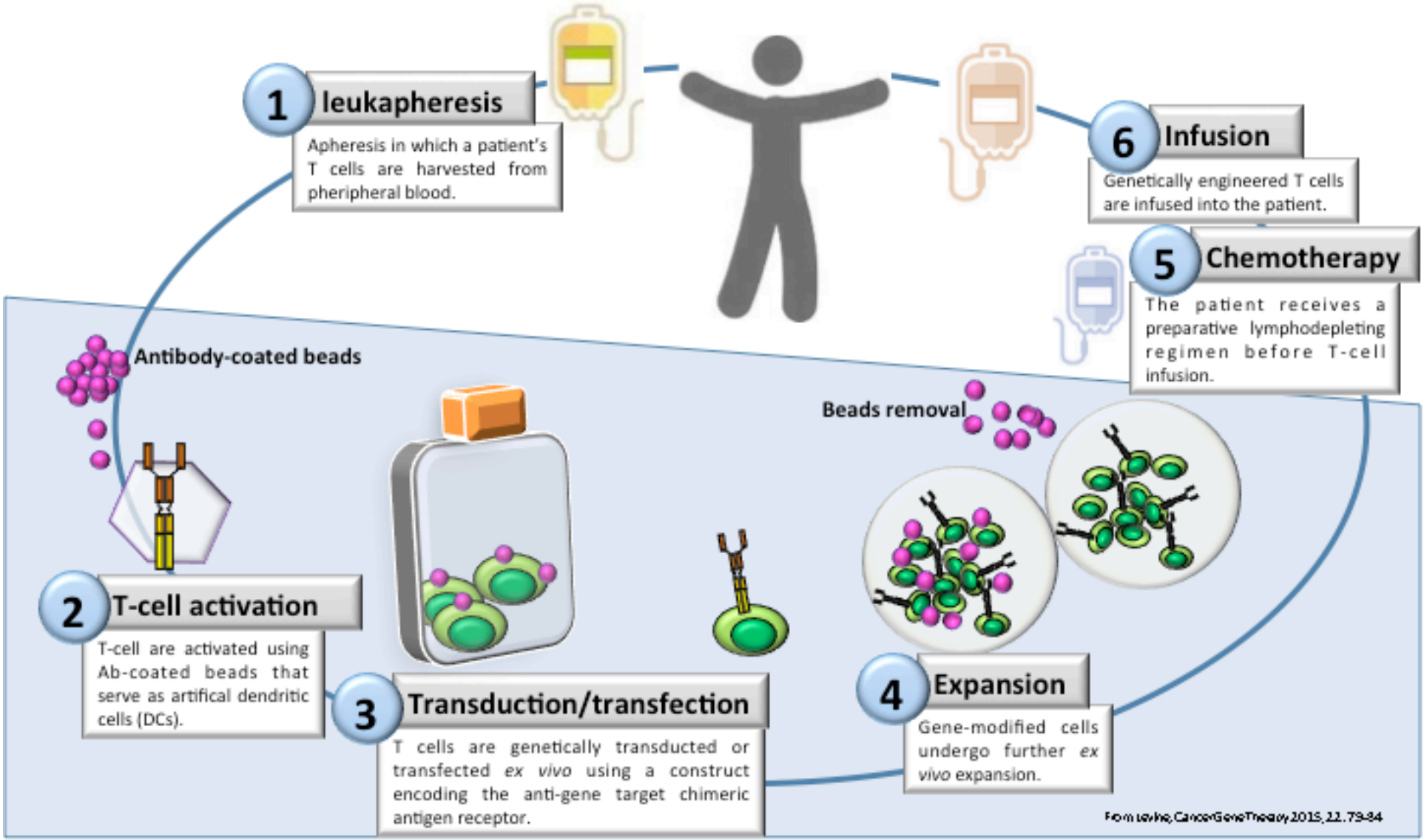



Finney et al. J Immunol 2004
Imai et al. Leukemia 2004
Milone, et al. Mol Ther 2009
Carpenito, et al. PNAS 2009

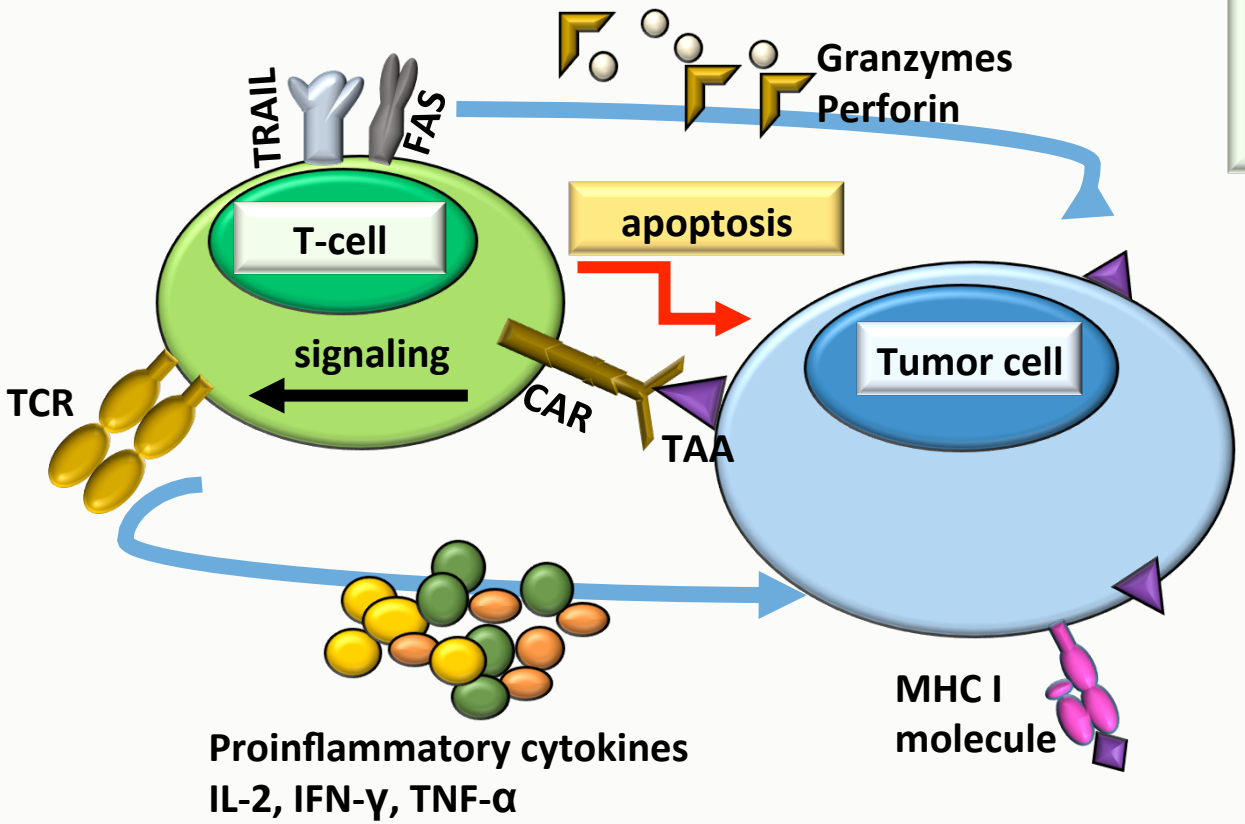
# CAR T-Cell Manufacturing



# Advantage of Chimeric Antigen Receptors (CARs)

- HLA-independent antigen recognition
- CARs active in both CD4+ and CD8+ T cells
- Target antigens include proteins, carbohydrates and glycolipids
- Significant quantities of tumor specific T cells are rapidly generated
- Minimal risk of generating undesired autoimmunity or GvHD

# T-CARs: Mechanism of Killing




CAR-modified T cells can recognize tumor cells via binding of the CAR to its TAA independent of TCR-MHC/ Peptide interactions.

T cells are activated and can efficiently eliminate tumor cells by the secretion of perforin and granzymes as well as the expression of FasL and tumor necrosis factor-related apoptosis inducing ligand (TRAIL). In addition, other tumor-infiltrating immune cells can be activated by the secretion of various cytokines.

# Comparison of antigen-specific immunotherapy approaches to B-cell malignancies

| Technology | CART | ADC | BITE |
|---|---|---|---|
| **Example** | CART19 (Penn)<br>CTL019 (Novartis)<br>(autologous ex vivo expanded T cells transduced with an anti-CD19 scFv) | Inotuzumab (anti-CD22 Mab linked to calichemycin) | Bilatumumab (anti-CD3 anti-CD19 bispefic antibody) |
| **Dosing** | One infusion | Once every 3 weeks; or weekly | Continuous inusion 28 days on, 14 days off |
| **Complete response (relapsed/refractory B-ALL** | 90% (173) | 19% (174) | 66% (1675) |
| **Survival** | 78% 6 months OS | 5-6 months median | 9 months median |
| **Major toxicity** | Cytokine release syndrome, encephalopathy | Fever, hepatotoxicity | Cytokine release syndrome, encephaloathy |
| **Antigen-loss relapses noted?** | Yes | No | Yes |
| **Major challenges** | Complex process to manufacture an invidualized product | Relatively lower response rates | Burdensome infusion regimen |

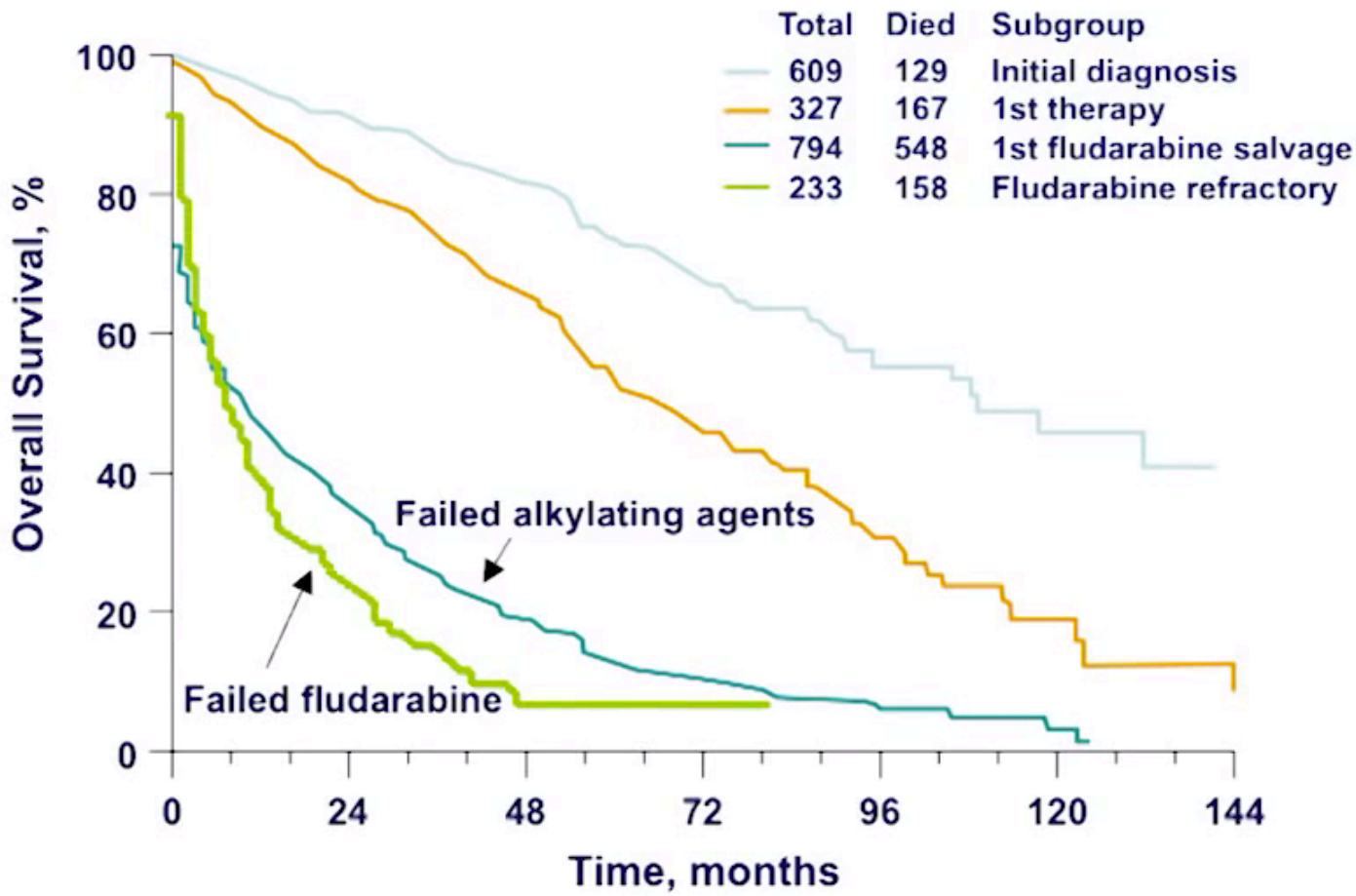
**Gill et al. Immunol Rev. 2015;263(1):68-89.**

# Refractory CLL – A Great Unmet Medical Need

## CAR-T cells

## in CLL

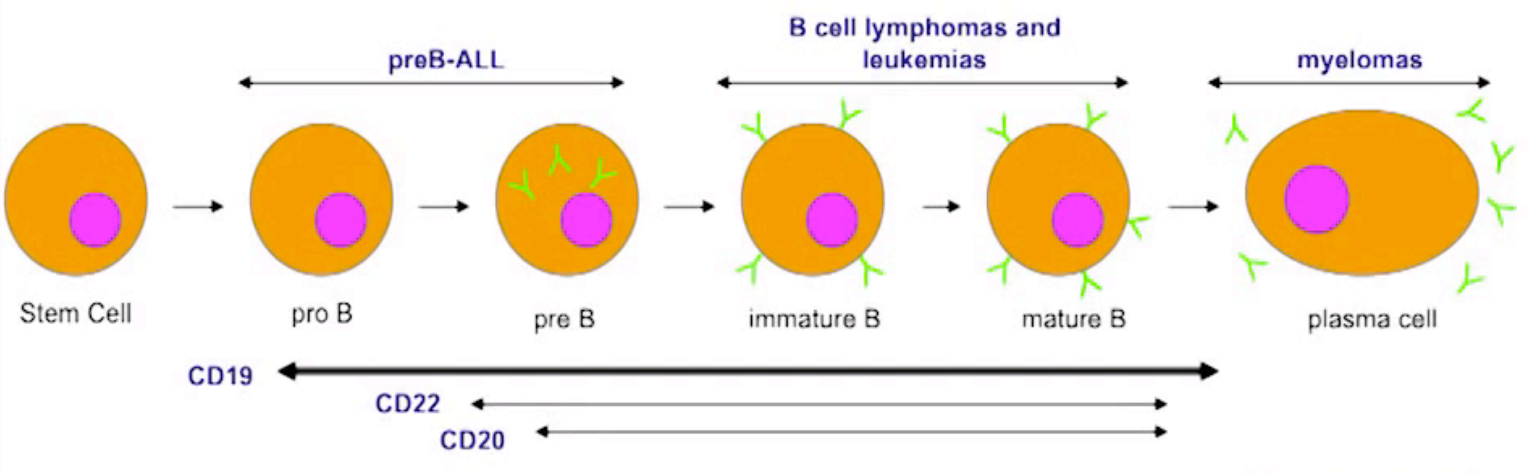
# Refractory CLL – A Great Unmet Medical Need




M Keating, Unpublished

# CD19: An ideal tumor target

- CD19 expression is restricted to B cells and possibly follicular dendritic cells
- CD19 is not expressed on pluripotent bone marrow stem cells
- CD19 is expressed on the surface of most B cell malignancies
- Antibodies agaist CD19 inhibit growth of tumor cells



# CARs Meet Leukemia

- 30 patients with advanced, heavily pre-treated CLL

  - 11 with del17p
  - 1-10 prior regimens

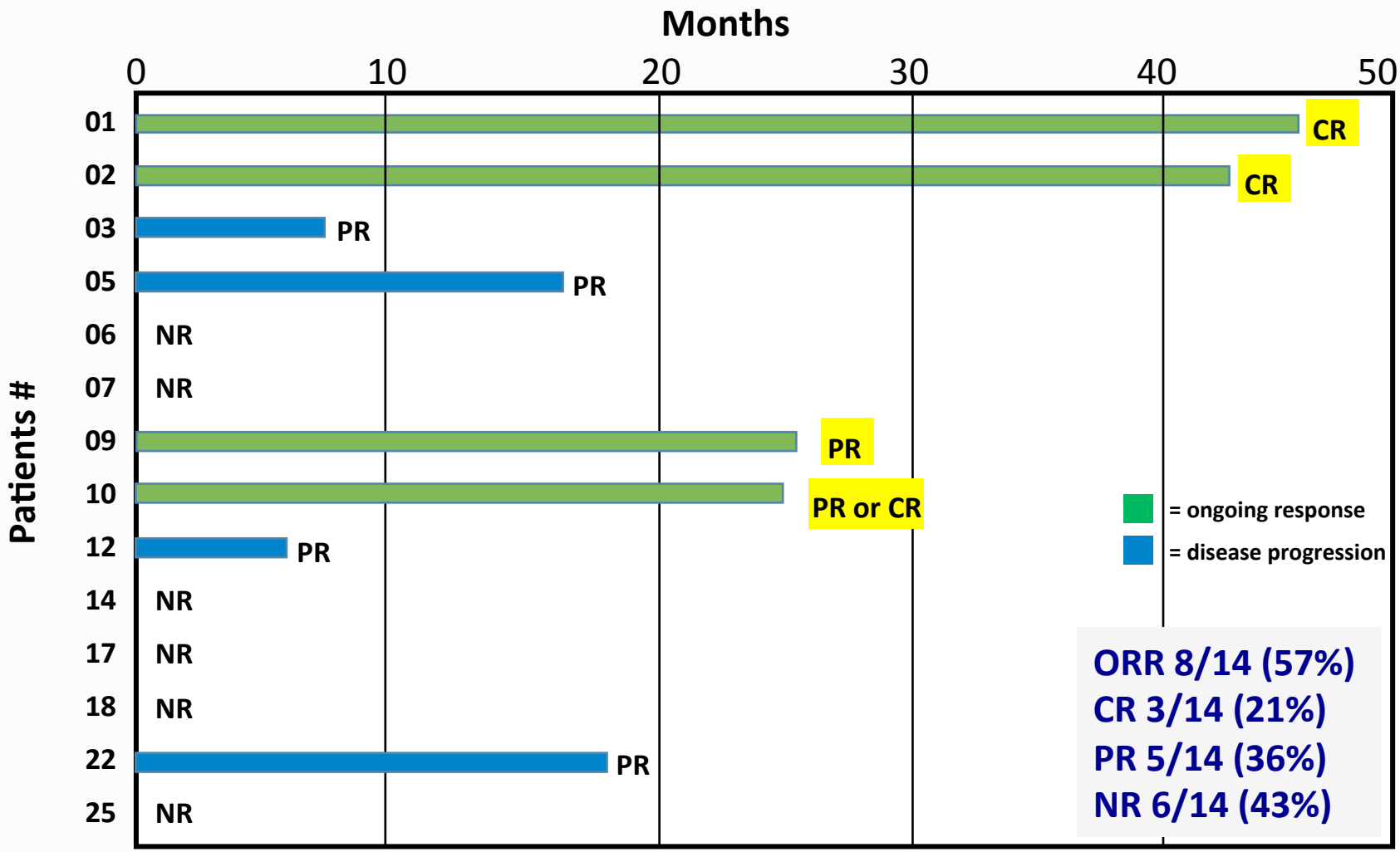
# CLL Pilot Study Design and Considerations

- Single center pilot trial of CTL019 (formally CART19) cells
- Primary objective:
  - safety, feasibility and immunogenicity of CTL019 in patients with CD19+ leukemia and lymphoma
- Detailed inclusion/exclusion at clinicaltrials.gov (NCT01029366)
  - CD19+ B cell malignancies with no available curative options (such as autologous or allogeneic SCT)
  - CLL: failed ≥2 prior therapies, progression withih 2 years of last treatment.
  - Limited prognosis (<2 years ) with avaible therapies

# CTL019 Phase I Trial for R/R CLL Pilot Study Design and Considerations

- N=14
- 12 men, 2 women
- Median age 66 (51-78)
- Prior therapies; median 4 (1-10)
- P53 deletion, 6/14
- Lymphodepleting chemotherapy
  - Bendamustine (6)
  - PC (5)
  - FC (3)

# CTL019 for R/R CLL: Durable Responses in Phase I




**Randomized Phase II Dose Optimization in R/R CLL**
**Porter et al.**

# CTL019 (CART19) Dose Optimization Trial

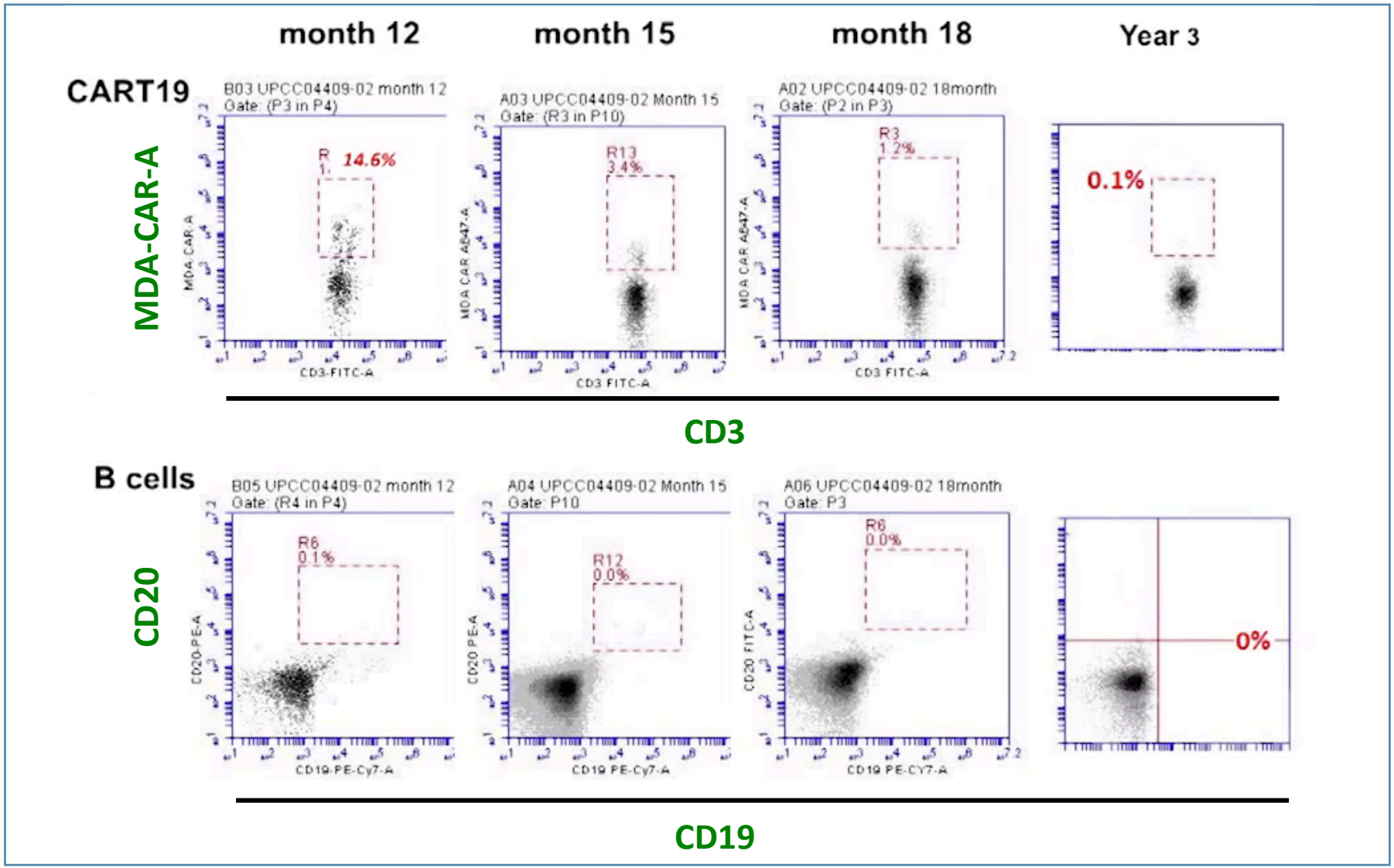
- Randomization between 5 x 10^7 and 5 x 10^8

  CTL019 cells
- 16 patients 28+ days (21 enrolled)
- Primary endpoint CR by 3 mo
- Demographics
  - 12 men, 4 women median age 62 (54-78)
  - 4 prior therapies

# Overall Response of CLL to CTL019 (04409 + 03712)

| | | |
|---|---|---|
| • CR | 7/30 | (23%) |
| • PR | 7/30 | (23%) |
| • Major responses | 14/30 | (46%) |

# CAR T-19 Persistence and B cell Aplasia



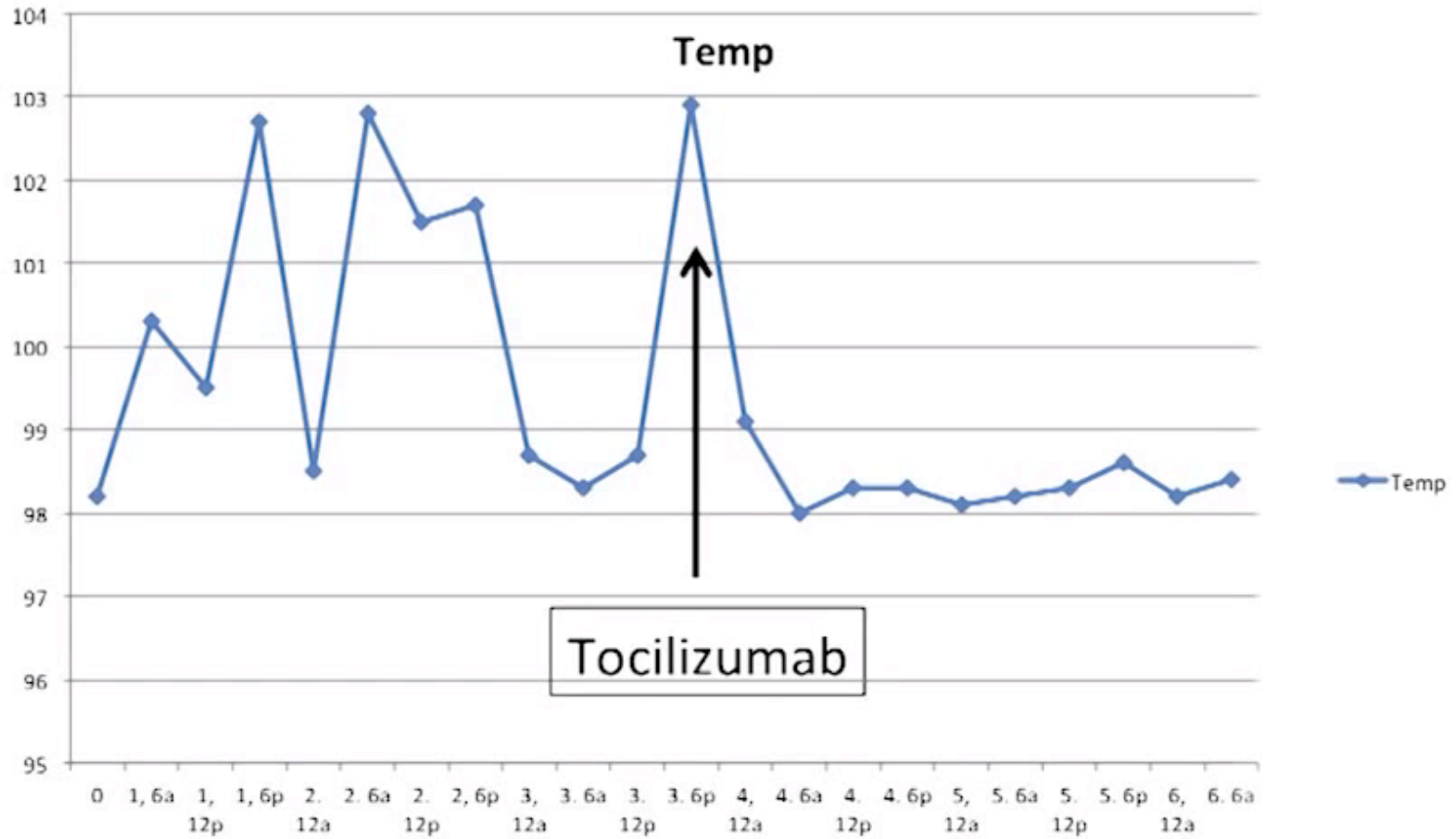
# Toxicity: CTL019 (CART19)

- No significant infusional toxicity.
- Hepatotoxicity (reversible, grade 3-4 responding patients).
- Renal toxicity (grade 3-4)
  - Related to TLS, ATN from hypotension
  - Reversible.
- B cell aplasia and hypogammaglobulinemia in patients achieving CR
  - Supported with IVIG
  - No excessive or frequent infections.
- Tumor Lysis syndrome.
- Cytokine Release Syndrome (CRS).

# CART19 Associated Cytokine Release Syndrome

- All responding patients developed a CRS
  - High fevers, myalgias, nause, hypotension, hypoxia, etc.
  - Very high levels of IL6
  - IFN-gamma, modest TNF-alfa
  - Mild increases in IL2
  - patients with NR had CRS
- Rapidly reversed with steroids, tocilizumab
  - Treatment CRS day 2-10
    - patients with CR/PR treated, 1 NR patient treated
  - *Will early treatment for CRS abrogate response?*
- CRS associated with HLH/MAS (Hemofagocytosis, hemolysis, DIC, ferritin > 500,000, altered MS

# Temperature Response to Tocilizumab 04409-10



# Determinants of response

- T cell expansion
- All responding patients develop CRS
- Unknown
  - Preinfusion T cell activity?
  - Preinfusion CD8 function
  - Post expansion CD8 function
  - Cytokine profile
  - Patient characteristics?
  - Disease characteristic?

# Refractory ALL– A Great Unmet Medical Need

## CAR-T cells

## in ALL

# Relapsed / Refractory ALL

| Reference | Year | Therapy | N Pts | CR Rate | Survival |
|---|---|---|---|---|---|
| **1st Salvage** | | | | **34-44%** | |
| Thomas et al. | 1999 | Various | 314 | 31% | 6% |
| Tavernier et al. | 2007 | Various | 421 | 44% | 8% |
| Fielding et al. | 2007 | Various | 609 | 44% | 7% |
| Vives et al. | 2008 | Various | 198 | 42% | 5% |
| Gokbuget et al. | 2012 | Various | 547 | 42% | 24% |
| **2nd Salvage** | | | | **18-33%** | |
| O'Brien et al. | 2008 | Various | 288 | 18% | 3mo |
| Gokbuget et al. | 2012 | Various | 82 | 33% | 13% |
| **Relapsed after SCT** | | | | **23%** | |
| Gokbuget et al. | 2012 | Various | 48 | 23% | 15% |

| | |
|---|---|
| **Number Pts** | **> 2000** |
| **Survival** | **< 10% at 2 yrs** |

**N. Goekbuget, German Multicenter ALL**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.

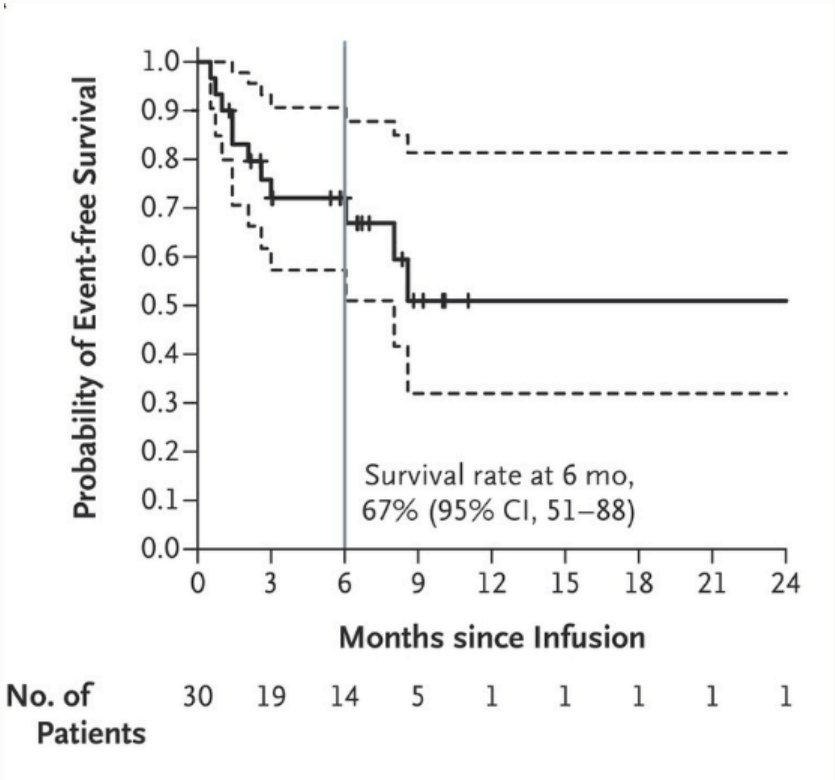
**N Engl J Med 2014.**

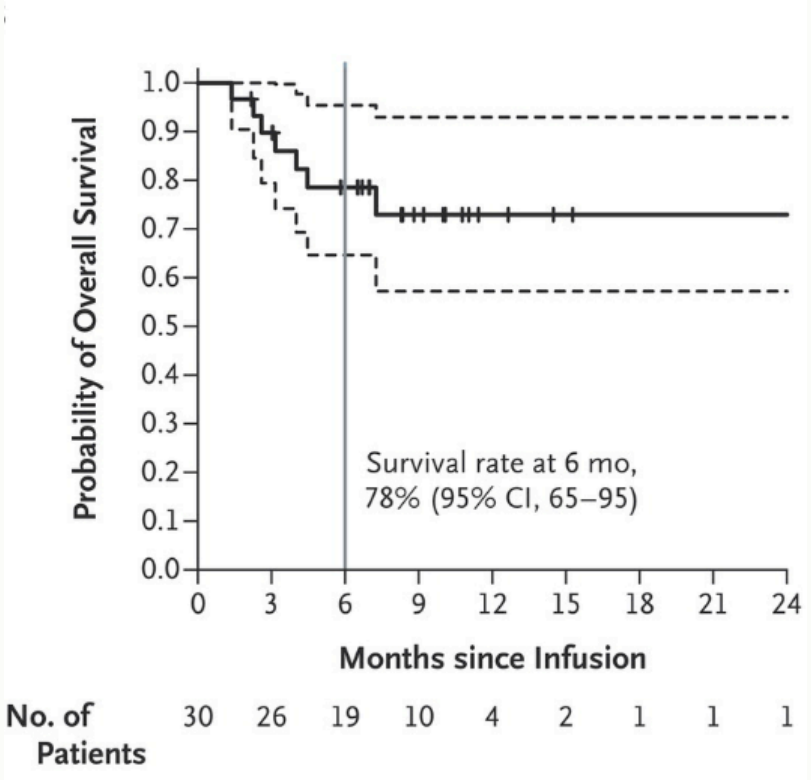
# Baseline Characteristics of the Patients

| Characteristic | Pediatric Cohort (N = 25) | Adult Cohort (N = 5) | Total (N = 30) |
|---|---|---|---|
| **Sex – no. (%)** | | | |
| Female | 11 (44) | 1 (20) | 12 (40) |
| Male | 14 (56) | 4 (80) | 18 (60) |
| **Age at infusion – yr** | | | |
| Median | 11 | 47 | 14 |
| Range | 5-22 | 26-60 | 5-60 |
| **Allogeneic transplatation – no. (%)** | 18 (72) | 0 | 18 (60) |
| **Primary refractory disease – no. (%)** | 0 | 3 (60) | 3 (10) |
| **Relapse – no. (%)** | | | |
| 1 | 3 (12) | 2 (40) | 5 (17) |
| ≥2 | 22 (88) | | 22 (73) |
| **Baseline burden of acute lymphoblastic leukemia – no. (%)** | | | |
| Presence of decteble disease† | 20 (80) | 4 (40) | 24 (80) |
| Morphologic remission‡ | | 1 (20) | 1 (3) |
| Absence of minimal residual disease | 5 (20) | | 5 (17) |
| **High-risk cytogenetic factors – no.** | | | |
| BCR-ABL1 | 2 | | |
| IKZF1 deletion | 2 | | |
| MLL translocation | 1 | | |
| Hypodiploidy | 1 | | |
| **CNS status – no. ∫** | | | |
| CNS-1 | 23 | | |
| CNS-2 | 2 | | |

Maude SL et al. N Engl J Med 2014;371:1507-1517.

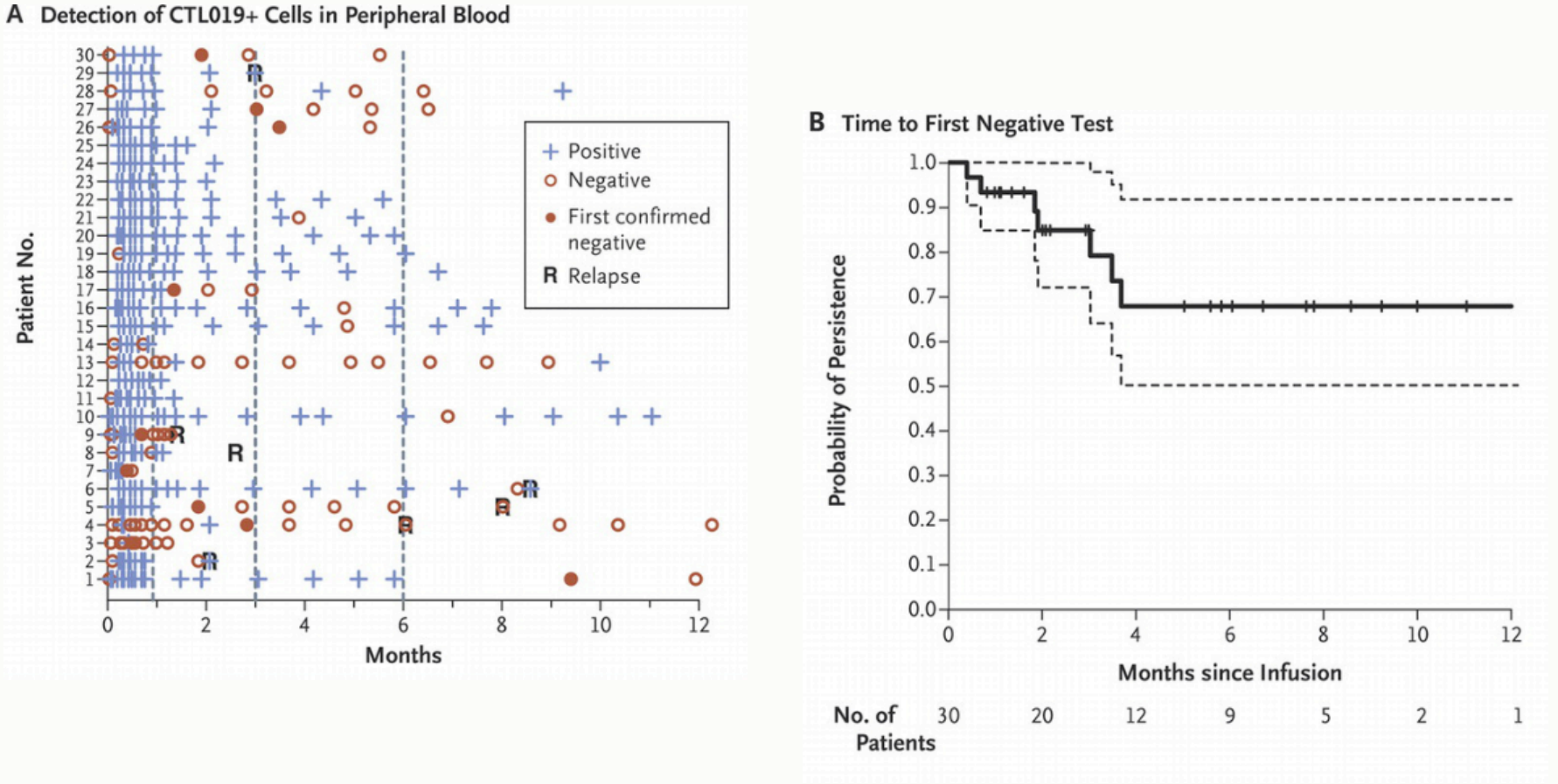
# Probability of Event Free Survival and Overall Survival at 6 Months




Maude SL et al. N Engl J Med 2014;371:1507-1517.

# Persistence of CTL019




Maude SL et al. N Engl J Med 2014;371:1507-1517.

# CTL019 Manufacture and Dose

| Subject ID | PBMC Input ($x10^8$) | PBMC Yield ($x10^{10}$) | Percent transduced | CTL019+ cells infused Total ($x10^8$) | CTL019+ cells infused $x10^6$/kg | Response | Severe CRS (Y/N) |
|---|---|---|---|---|---|---|---|
| 1 | 4.50 | 0.73 | 11.6% | 3.78 | 11.55 | CR | Y |
| 2 | 3.66 | 1.16 | 14.4% | 0.39 | 1.52 | CR | N |
| 3 | 4.00 | 1.48 | 18.3% | 0.38 | 1.86 | NR | N |
| 4 | 4.30 | 1.43 | 25.3% | 0.48 | 2.54 | CR | N |
| 5 | 0.91 | 1.06 | 35.9% | 0.86 | 3.59 | CR | N |
| 6 | 3.61 | 1.67 | 21.4% | 4.28 | 5.94 | CR | N |
| 7 | 2.00 | 1.75 | 16.2% | 0.30 | 1.62 | NR | N |
| 8 | 4.50 | 1.57 | 10.7% | 0.34 | 1.07 | CR | N |
| 9 | 0.30 | 0.18 | 42.7% | 1.45 | 4.27 | CR | Y |
| 10 | 3.60 | 2.74 | 45.3% | 9.06 | 17.36 | CR | N |
| 11 | 4.50 | 1.29 | 30.4% | 1.26 | 3.04 | CR | Y |
| 12 | 4.40 | 2.58 | 35.3% | 1.73 | 3.53 | CR | Y |
| 13 | 4.50 | 2.41 | 20.9% | 3.68 | 8.35 | CR | N |
| 14 | 4.50 | 0.93 | 21.5% | 3.58 | 8.61 | NR | N |
| 15 | 3.70 | 1.89 | 37.4% | 3.83 | 14.96 | CR | N |
| 16 | 3.50 | 0.75 | 38.8% | 7.76 | 6.63 | CR | Y |
| 17[1] | 4.50 | 2.36 | 32.6% | 1.63 | 2.74 | CR | N |
| 18 | 2.14 | 1.46 | 34.0% | 4.53 | 13.60 | CR | N |
| 19 | 3.88 | 0.30 | 22.8% | 2.06 | 9.12 | CR | N |
| 20 | 4.50 | 0.79 | 33.8% | 6.76 | 11.99 | CR | Y |
| 21 | 2.67 | 0.38 | 18.3% | 1.43 | 7.32 | CR | N |
| 22 | 4.50 | 1.20 | 19.5% | 3.43 | 7.80 | CR | N |
| 23 | 4.50 | 0.05 | 33.8% | 1.01 | 1.58 | CR | N |
| 24 | 4.50 | 1.93 | 16.4% | 0.54 | 1.64 | CR | Y |
| 25 | 4.50 | 3.18 | 10.3% | 2.06 | 2.48 | CR | N |
| 26 | 4.50 | 1.47 | 13.5% | 0.68 | 0.79 | CR | Y |
| 27 | 4.18 | 1.44 | 14.6% | 0.73 | 0.76 | CR | N |
| 28 | 3.50 | 0.41 | 31.1% | 9.58 | 12.24 | CR | N |
| 29 | 1.28 | 1.54 | 5.5% | 2.76 | 3.62 | CR | N |
| 30 | 2.20 | 1.31 | 21.4% | 1.07 | 1.80 | CR | N |

PBMC, peripheral blood mononuclear cells; CR, complete remission; NR, no response

[1]Subsequent infusions at 3 and 6 months for total dose of $2.06x10^7$ CTL019 cells/kg

**CR 27/30 pts (90%)**

**CRS 8/30 pts (27%)**

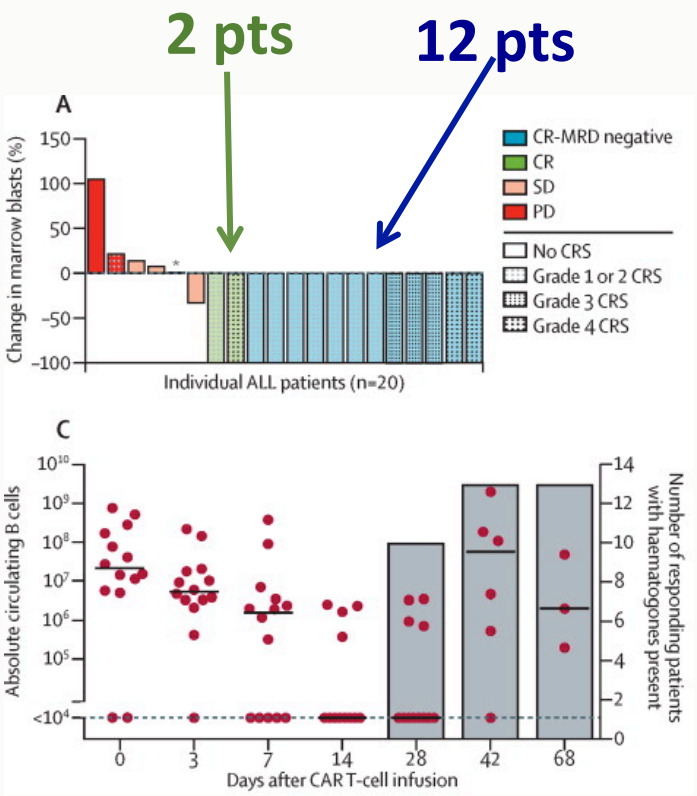
Maude SL et al. N Engl J Med 2014;371:1507-1517.

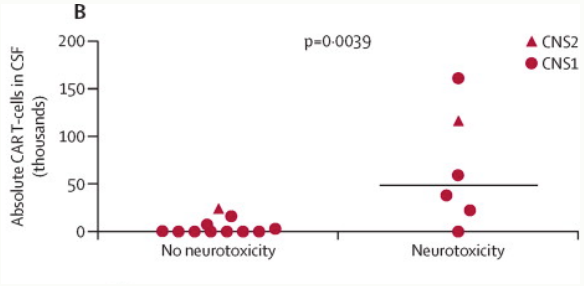
# T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial

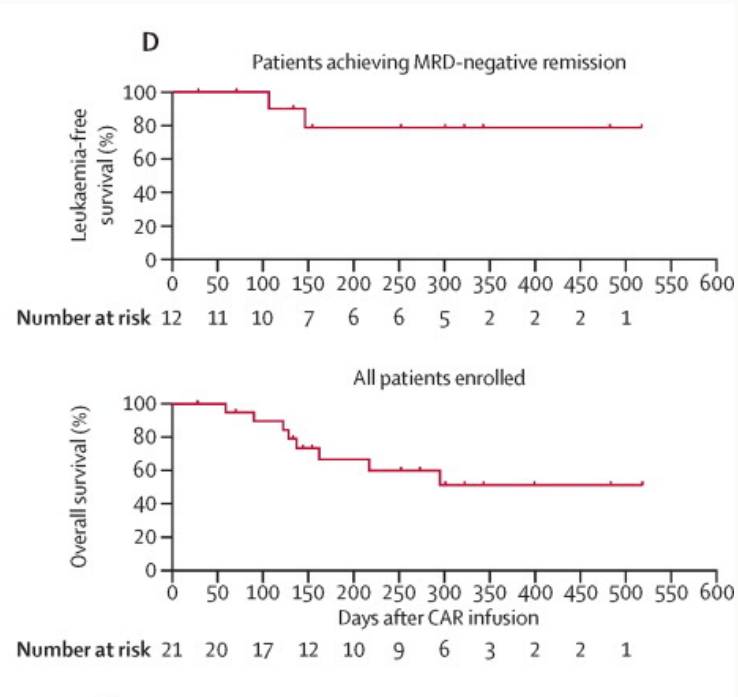
*Daniel W Lee, James N Kochenderfer, Maryalice Stetler-Stevenson, Yongzhi K Cui, Cindy Delbrook, Steven A Feldman, Terry J Fry, Rimas Orentas, Marianna Sabatino, Nirali N Shah, Seth M Steinberg, Dave Stroncek, Nick Tschernia, Constance Yuan, Hua Zhang, Ling Zhang, Steven A Rosenberg, Alan S Wayne, Crystal L Mackall*

**Lancet, 2015**

# Clinical activity of CD19-chimeric antigen receptor (CAR) T cells (I)

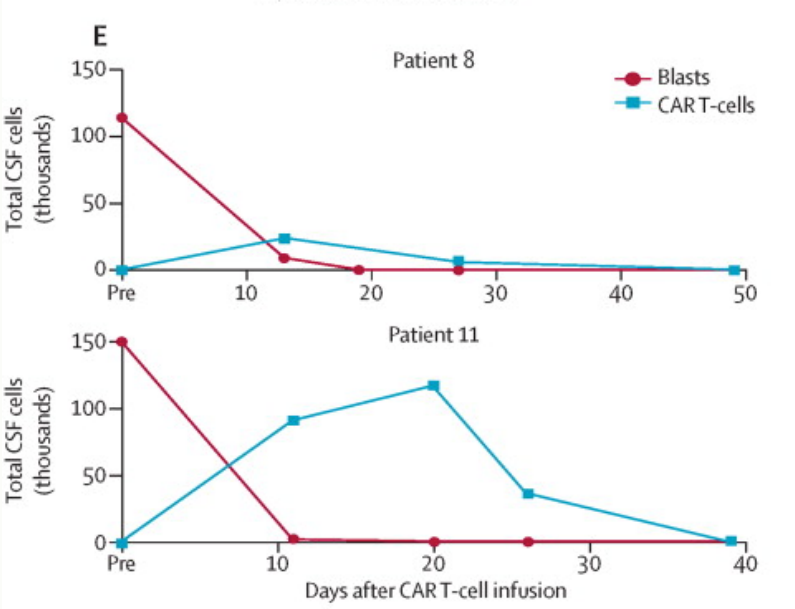


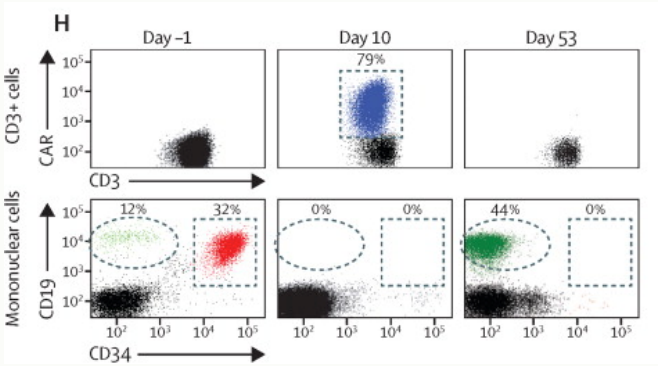



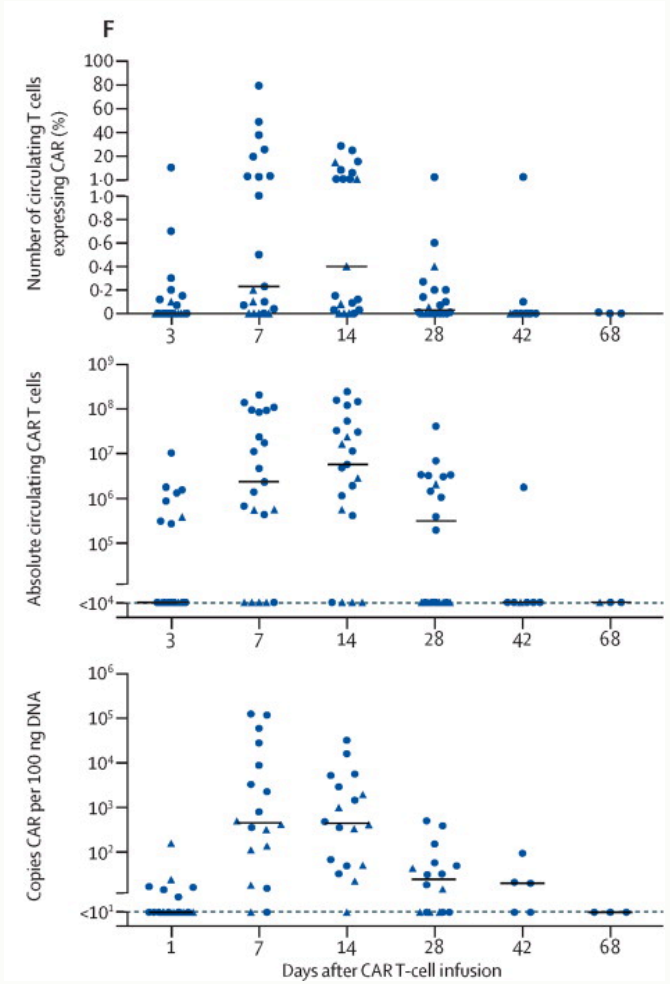




Lee et al. Lancet. 2015;385(9967):517-28.

# Clinical activity of CD19-chimeric antigen receptor (CAR) T cells (II)




Lee et al. Lancet. 2015;385(9967):517-28.

# Clinical activity of CD19-chimeric antigen receptor (CAR) T cells (III)

| | Age | Sex | Previous treatment | Number of relapses | Marrow blasts (% of mononuclear) | | CNS status | CAR dose (×10⁶/kg) | Response (day 28) | CRS grade | Absolute circulating CART cells at day 28 (×10⁶/kg) | Days until HSCT after CAR |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Pre-treatment | Post-CAR | | | | | | |
| 1 | 13 | M | C, R, I, T | 8 | 30% | 1% | 1 | 1 | CRi | 2 | 1 | .. |
| 2 | 16 | F | C, R, T | 2 | 35% | 40% | 1 | 0·03 | SD | 0 | 1·9 | .. |
| 3 | 10 | F* | C, R, I, T | Primary refractory | .. | .. | .. | 1 | PD | 1 | 0 | .. |
| 4 | 11 | F | C | Primary refractory | 58% | <0·01% | 1 | 1 | CR, MRD Neg | 1 | 2·8 | 47 |
| 5 | 10 | M | C | 1 | 10% | <0·01% | 1 | 0·48 | CR, MRD Neg | 2 | 0·4 | 82 |
| 6 | 10 | M | C | 3 | 81% | 99% | 1 | 3† | PD | 1 | 0 | .. |
| 7 | 25 | M | C, I | 1 | 50% | 0·03% | 1 | 3 | CR | 4‡ | 0 | .. |
| 8 | 18 | M | C, R, T | 1 | 0·2% | <0·01% | 2 | 1 | CR, MRD Neg | 1 | 3 | .. |
| 9 | 13 | M | C, R, I, T, CAR | 3 | 0·56% | <0·01% | 1 | 3 | CR, MRD Neg | 1 | 3·1 | 45 |
| 10 | 5 | M | C | Primary refractory | 5% | <0·01% | 1 | 3 | CR, MRD Neg | 3 | 0 | 54 |
| 11 | 23 | M | C, R | 1 | 84% | <0·01% | 2 | 1 | CR, MRD Neg | 3 | 6·5 | 54 |
| 12 | 9 | M | C | 1 | 95% | 96% | 1 | 1 | PD | 0 | 0 | .. |
| 13 | 27 | F | C | 3 | 21% | 43% | 1 | 1 | PD | 0 | 0 | .. |
| 14 | 15 | M | C, R, T | 3 | 96% | <0·01% | 1 | 1 | CR, MRD Neg | 4‡§ | 1·4 | .. |
| 15 | 5 | F | C, R, T | 1 | 15% | 10% | 1 | 1 | SD | 0 | 0 | .. |
| 16 | 25 | M | C | Primary refractory | 50% | <0·01% | 1 | 1 | CR, MRD Neg | 4‡§ | 3·1 | 63 |
| 17 | 18 | F | C | Primary refractory | 0·03% | <0·01% | 1 | 1 | CR, MRD Neg | 1 | 0·2 | 48 |
| 18 | 13 | M | C, R, T | 2 | 90% | 97% | 1 | 1 | SD | 0 | 0 | .. |
| 19 | 21 | M | C | 2 | 7·7% | <0·01% | 1 | 1 | CR, MRD Neg | 3‡ | 40·3 | 55 |
| 20 | 16 | F | C | Primary refractory | 0·7% | <0·01% | 1 | 1 | CR, MRD Neg | 1 | 0 | 46 |
| 21 | 6 | M | C | Primary refractory | 0·56% | <0·01% | 1 | 1 | CR, MRD Neg | 1 | 0 | 46 |

M=male. F=female. C=chemotherapy. R=radiation therapy. I=immunotherapy. T=allogeneic haemopoietic stem-cell transplant. CAR=CD19 chimeric antigen receptor. CRS=cytokine release syndrome. CR=complete response. MRD Neg=no minimal residual disease detected. CRi=CR with incomplete count recovery. SD=stable disease. PD=progressive disease. HSCT=haemopoietic stem-cell transplant. *Diffuse large B-cell lymphoma. †Actual dose received was 3·6×10⁶ CAR T cells per kg. ‡Tocilizumab. §Corticosteroid.

*Table 1:* **Patient demographic characteristics, response, and toxicity**

**CR 14/21 pts (66%)**

**CRS 6/24 pts (25%)**

**Lee et al. Lancet. 2015;385(9967):517-28.**

# Grade 3 and 4 toxicities, and grade 2 neurotoxicities possibly related to CD19-CAR T-cell therapy

| | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| **Adverse event** | | | |
| Acute kidney injury | .. | 1 (5%) | 0 |
| Cardiac arrest | .. | 0 | 1 (5%) |
| Cytokine release syndrome | .. | 3 (16%) | 3 (16%) |
| QTc prolongation | .. | 1 (5%) | 0 |
| Febrile neutropenia | .. | 7 (37%) | 0 |
| Fever | .. | 9 (47%) | 0 |
| Hypertension | .. | 1 (5%) | 0 |
| Hypotension | .. | 2 (11%) | 2 (11%) |
| Hypoxia | .. | 1 (5%) | 1 (5%) |
| Left ventricular systolic dysfunction | .. | 0 | 1 (5%) |
| Multi-organ failure | .. | 1 (5%) | 0 |
| Pulmonary oedema | .. | 0 | 1 (5%) |
| Respiratory failure | .. | 0 | 1 (5%) |
| **Haematological adverse event** | | | |
| Prolonged activated partial thromboplastin time | .. | 1 (5%) | 0 |
| Anaemia | .. | 13 (68%) | 0 |
| Lymphocyte count decreased | .. | 1 (5%) | 7 (37%) |
| Neutrophil count decreased | .. | 0 | 17 (89%) |
| Platelet count decreased | .. | 3 (16%) | 7 (37%) |
| White blood cell decreased | .. | 4 (21%) | 13 (68%) |

| | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|
| **Chemical laboratory abnormalities** | | | |
| ALT increased | .. | 1 (5%) | 0 |
| AST increased | .. | 2 (11%) | 0 |
| Blood bilirubin increased | .. | 1 (5%) | 0 |
| CPK increased | .. | 1 (5%) | 0 |
| Hyperglycaemia | .. | 1 (5%) | 0 |
| Hypokalaemia | .. | 9 (47%) | 0 |
| Hyponatraemia | .. | 1 (5%) | 0 |
| Hypophosphataemia | .. | 7 (37%) | 1 (5%) |
| **Nervous system event** | | | |
| Ataxia | 1 (5%) | 0 | 0 |
| Dysphasia | 0 | 1 (5%) | 0 |
| Headache | 1 (5%) | 0 | 0 |
| Tremor | 1 (5%) | 0 | 0 |

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. CPK=creatine phosphokinase.

**Lee et al. Lancet. 2015;385(9967):517-28.**

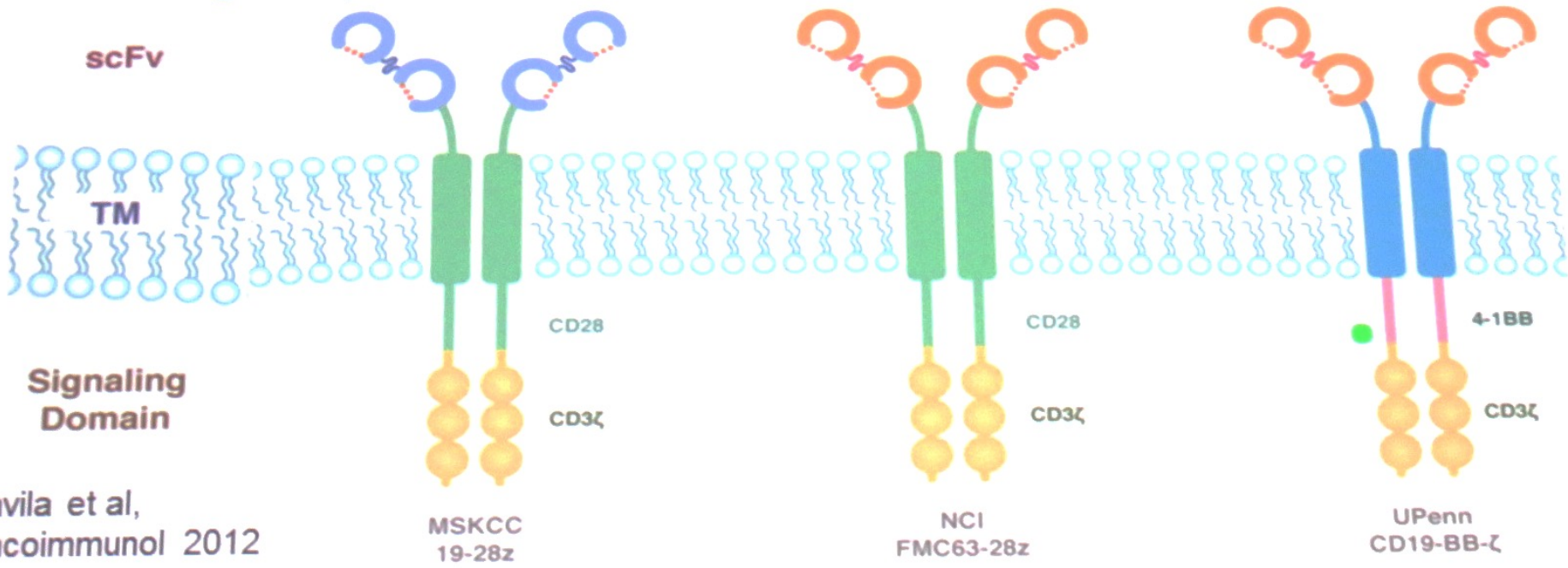
# Summay of main CAR19 data in ALL

| Reference | N: of patients | CAR vector | Response consolidation |
|---|---|---|---|
| **Brentjens et al. 2011** | 1 | SJC25C1-CD28-ζ retro | Remained in CR ➔allo |
| **Brentjens et al. 2013 Davila et al. 2014** | 10 (4 post allo) | SJC25C1-CD28-ζ retro | 10 CR + 4CRI 100 MRD- ➔7 allo-SCT |
| **Grupp et al.. 2013 Maude et al., 2014** | 30 (18 post allo-sct<) | FMC63-41BB—ζ lenti | 27 CR 22 MRD- ➔3 allo-SCT |
| **Lee et al., 2015** | 20 (7 post allo-sct) | FMC63-CD28—ζ retro | 13 CR + 1 Cri 12 MRD- ➔10 allo-SCT |

67 patients treated, complete rsponse rate 82%, 63% MRD-

# Comparing CD19 CARs for Leukemia

## CAR design important for persistence and sustained efficacy




Davila et al, Oncoimmunol 2012

| Vector | Retroviral[1] | Retroviral[2] | Lentiviral[3] |
|---|---|---|---|
| Expression | ~30 Days | ~30 Days | >4 years |
| CR in ALL | ~90% | ~80% | ~90% |
| CR in CLL | 0/8 | | 4/14 |
| PR in CLL | 0/8 | | 4/14 |
| ORR in CLL | 0% | | 57% |

# CAR 19 future challenge

- Define optimal CAR design + effector population
- Can we modulate immunotoxicity without loing efficacy?
- Defining placement of CAR therapy:
  - Frank relapse vs deepen remission
  - Bridge to allo-SCT vs alternative to SCT?
  - When to give in relation to chemo: given likely cost, which paatients benefit most?
  - How do we optimally combine with other biologics?
- Need well designed randomised studies with survival end-points
- Reduce cost and complexicity of manifacture
- Extension to other B-cell malignancies

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- Extension to other B-cell malignancies

**Extension to other B-cell malignancies**

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

*James N. Kochenderfer, Mark E. Dudley, Sadik H. Kassim, Robert P.T. Somerville, Robert O. Carpenter, Maryalice Stetler-Stevenson, James C. Yang, Giao Q. Phan, Marybeth S. Hughes, Richard M. Sherry, Mark Raffeld, Steven Feldman, Lily Lu, Yong F. Li, Lien T. Ngo, Andre Goy, Tatyana Feldman, David E. Spaner, Michael L. Wang, Clara C. Chen, Sarah M. Kranick, Avindra Nath, Debbie-Ann N. Nathan, Kathleen E. Morton, Mary Ann Toomey, and Steven A. Rosenberg*

**J Clin Oncol. 2015**

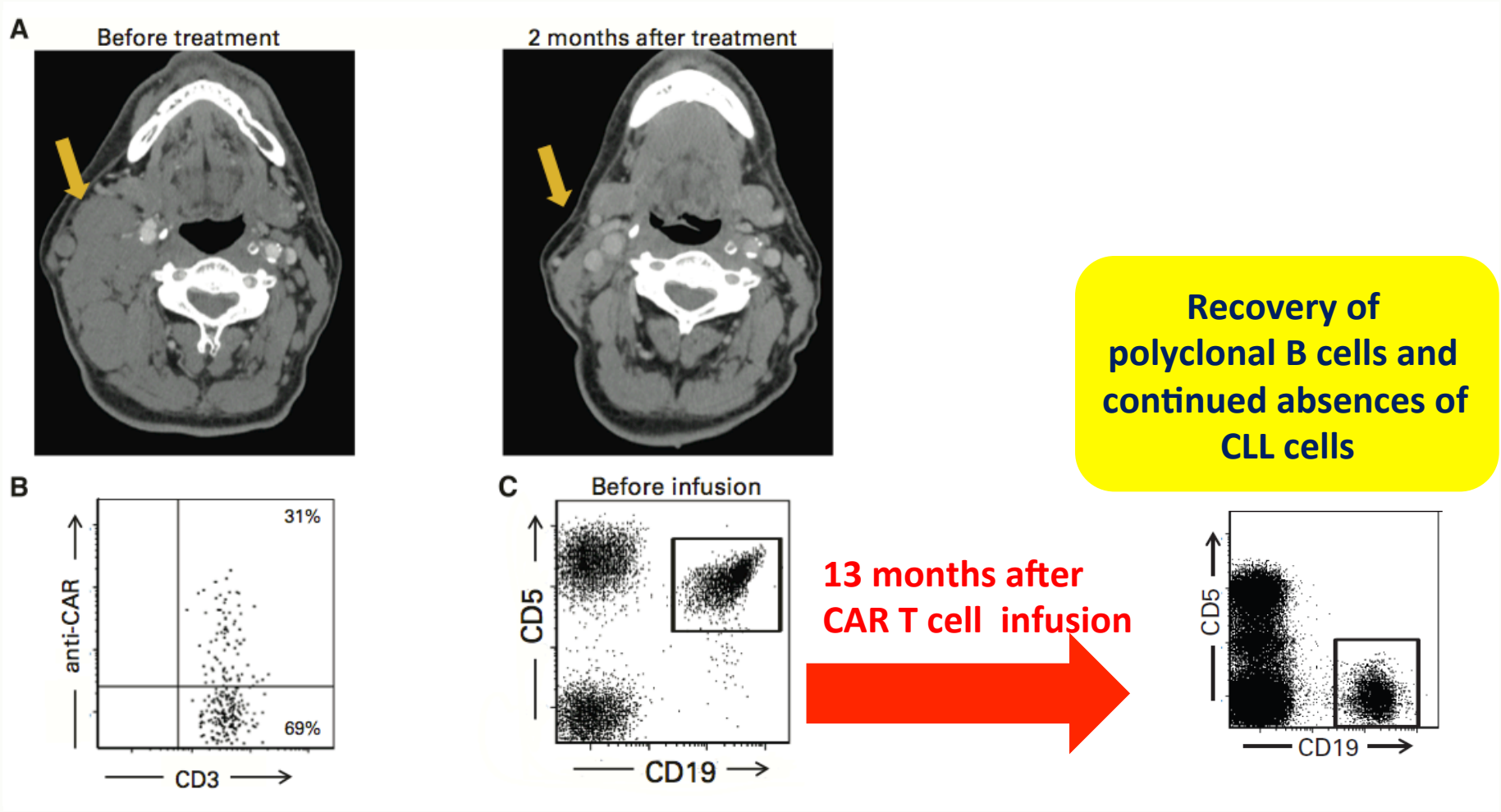
# Patient Characteristics

| Patient No. | Age (years) | Sex | Malignancy | No. of Prior Therapies[a] | sAAIPI Risk Group | Total Cyclophosphamide Dose (mg/kg)[b] | No. of CAR-Positive T Cells Infused ($\times 10^6$/kg) | Response[c] | | Grade ≥ 3 Toxicities[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Type | Duration (months) | |
| 1[e] | 56 | Male | SMZL | 4 | NA | 120 | 5 | PR | 23+[f] | Hypotension, confusion, acute renal failure, fever |
| 2 | 43 | Female | PMBCL[g] | 4 | Low | 60 | 5 | CR | 22+[f] | Fever, confusion, aphasia, facial nerve palsy, headache, urinary tract infection |
| 3 | 61 | Male | CLL (FR) | 2 | NA | 60 | 4 | CR | 23+[f] | Headache, fever, confusion, hypotension |
| 4 | 30 | Female | PMBCL[g] | 3 | High | 120 | 2.5 | NE | | Nausea, hypoxia, dyspnea, tachycardia, fever, bacteremia, malaise, vascular leak syndrome, death |
| 5[e] | 63 | Male | CLL | 4 | NA | 120 | 2.5 | CR | 15+[f] | None |
| 6 | 48 | Male | CLL (FR) | 1 | NA | 60 | 2.5 | CR | 14+[f] | None |
| 7 | 42 | Male | DLBCL NOS[g] | 5 | High | 60 | 2.5 | CR | 9+[f] | Influenza, fever, headache, bacteremia |
| 8 | 44 | Female | PMBCL[g] | 10 | High | 60 | 2.5 | CR | 12+[f] | Fever, pneumonitis, hypotension, hypoxia, bacteremia, obtundation, elevated creatinine |
| 9 | 38 | Male | PMBCL[g] | 3 | High | 120 | 2.5 | SD | 1 | Fever, aphasia, myoclonus |
| 10 | 57 | Female | Low-grade NHL[h] | 4 | NA | 60 | 1 | CR | 11+[f] | Bacteremia, fever, fatigue |
| 11 | 58 | Female | DLBCL[g] from CLL | 12 | High | 60 | 1 | PR | 1 | Bacteremia, urinary tract infection, fever |
| 12 | 60 | Female | DLBCL NOS[g] | 3 | High | 60 | 1 | NE[i] | | Fever, urinary tract infection, bacteremia, upper extremity thrombosis |
| 13 | 68 | Male | CLL | 4 | NA | 60 | 1 | PR | 4 | Dyspnea, upper extremity thrombosis, urinary tract infection, creatinine increase, hypotension |
| 14 | 43 | Male | DLBCL NOS[g] | 2 | High | 60 | 1 | CR | 6 | Fever |
| 15 | 64 | Female | DLBCL NOS[h] | 3 | Intermediate | 60 | 1 | PR | 6+[f] | Fever, aphasia, encephalopathy, neuropathy, gait disturbance |

**CR 9/15**

Kochenderfer J.N. J Clin Oncol. 2015; 20;33(6):540-9.

# CAR T cells were detected in regressing lymph node mass of CLL patients



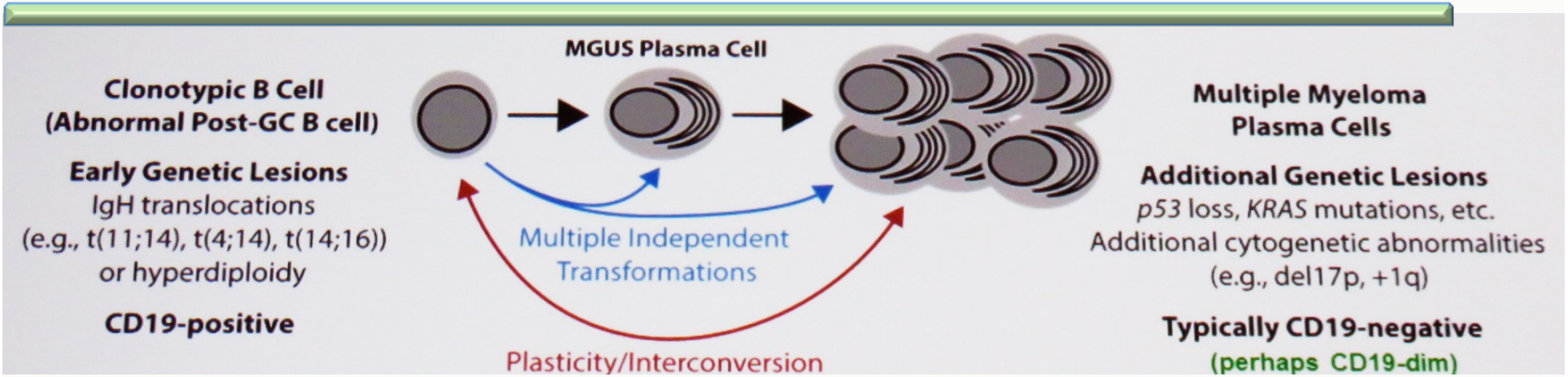

**Recovery of polyclonal B cells and continued absences of CLL cells**

Kochenderfer J.N. J Clin Oncol. 2015; 20;33(6):540-9.

# Toxicity

- Hypotension
- Neurologic toxicity
  - confusion and obtundation, aplasia and myoclonus (when CAR T cells are administered without IL-2)

# CART19 in Multiple Myeloma




- Might CTL019 be useful in multiple myeloma, even though it is "CD19-negative?"
- How can we give CTL019 so that it would work by any/all these mechanisms?
- CTL019 recognizes <100 molecules of CD19

CTL019 recognizes targets at least 40-fold below FACS detection

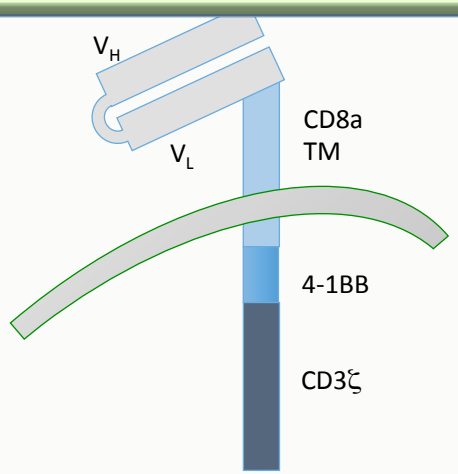
If FACS detects ~1000 copies on surface, CTL019 can recognize < 100 surface molecules of CD19

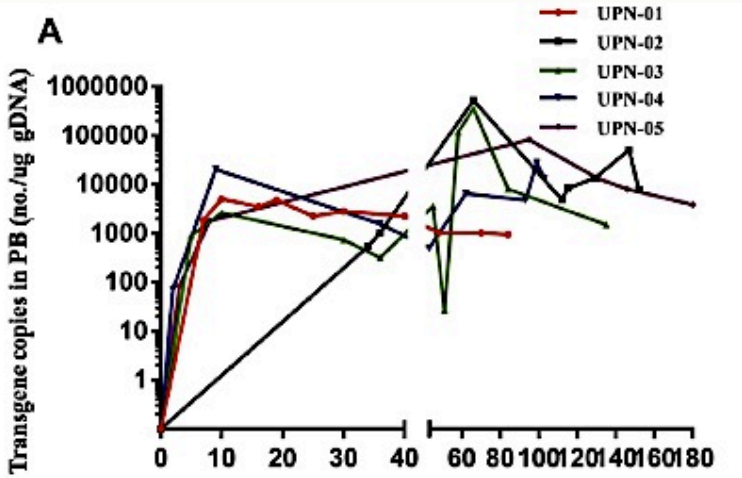
# Immunotherapy for myeloma

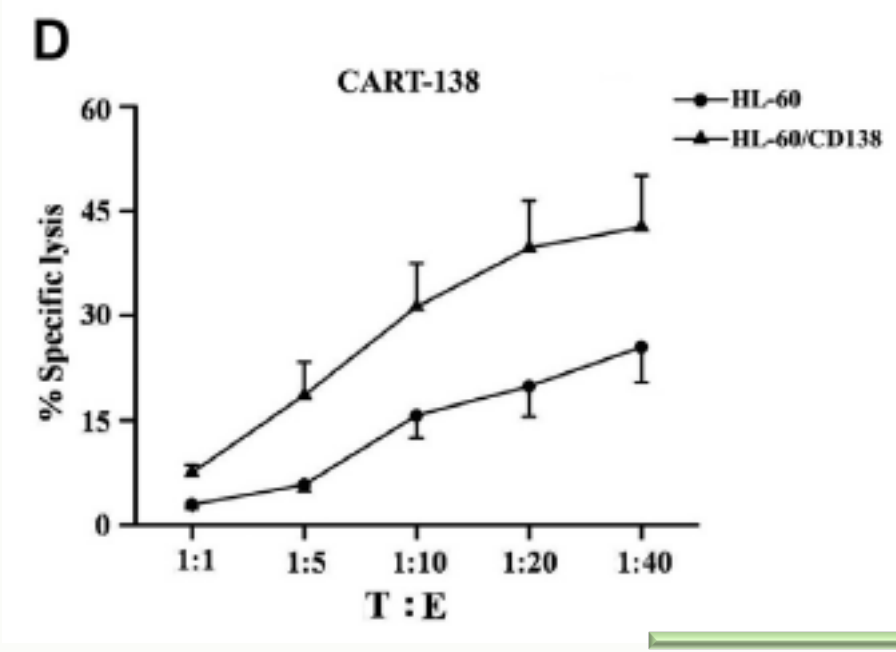
| TARGETS for CAR-T | |
|---|---|
| CD138 | Guo B et al, J Cell Immunth 2015 |
| BCMA | Ayed Ao et al, Crit Rev Onc/Hem 2015 |
| CD317 | Ayed Ao et al, Crit Rev Onc/Hem 2015 |
| CS1 | Chu J et al, Clin Cancer Res.2014 |
| CD38 | Ayed Ao et al, Crit Rev Onc/Hem 2015 |
| CD56 | Ayed Ao et al, Crit Rev Onc/Hem 2015 |
| CD74 | Ayed Ao et al, Crit Rev Onc/Hem 2015 |

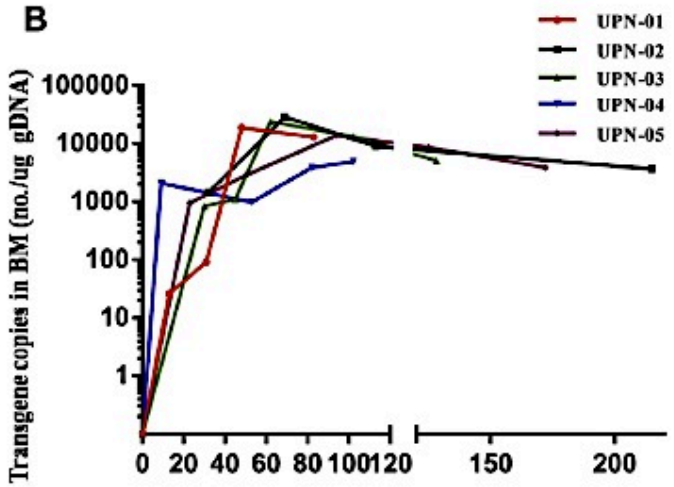
| TARGETS for CAR-NK | |
|---|---|
| CD138 | H. Jiang et al, Mol. Oncol. 2014 |
| CS1 | J. Chu et al, Clin. Cancer Res. 2014 |

# CD38-CAR-T cells immunotherapy for myeloma




Guo B et al, J Cell Immur

# Immunotherapy for myeloma

Baseline demographic and clinical patient characteristics.

| UPN | Age, y | Gender | Diagnosis/stage | The no. of prior therapies | Disease status at study entry | Conditioning regimen before T-cell infusions | Times of infusion of CIK before CART-138 | Response and time since treatment (mon) |
|---|---|---|---|---|---|---|---|---|
| 1 | 57 | Female | MM (IgG-LAM, IIIB) | 15 | PD | PCD | 2 | SD (3) |
| 2 | 62 | Male | MM (IgA-LAM, IIIA) | 8 | PD | CP | 4 | SD (3), PD |
| 3 | 55 | Female | MM (IgA-KAP, IIIA) | 18 | PD | CP | 2 | SD (7) |
| 4 | 68 | Female | MM (IgA-LAM, IIIB) | 5 | PD | CP | 3 | PD |
| 5 | 48 | Female | MM (KAP, IIIA) | 7 + auto-PBSCT | PD | VAD | 3 | SD (6) |

SD is Stable disease. PD is Progressive disease.

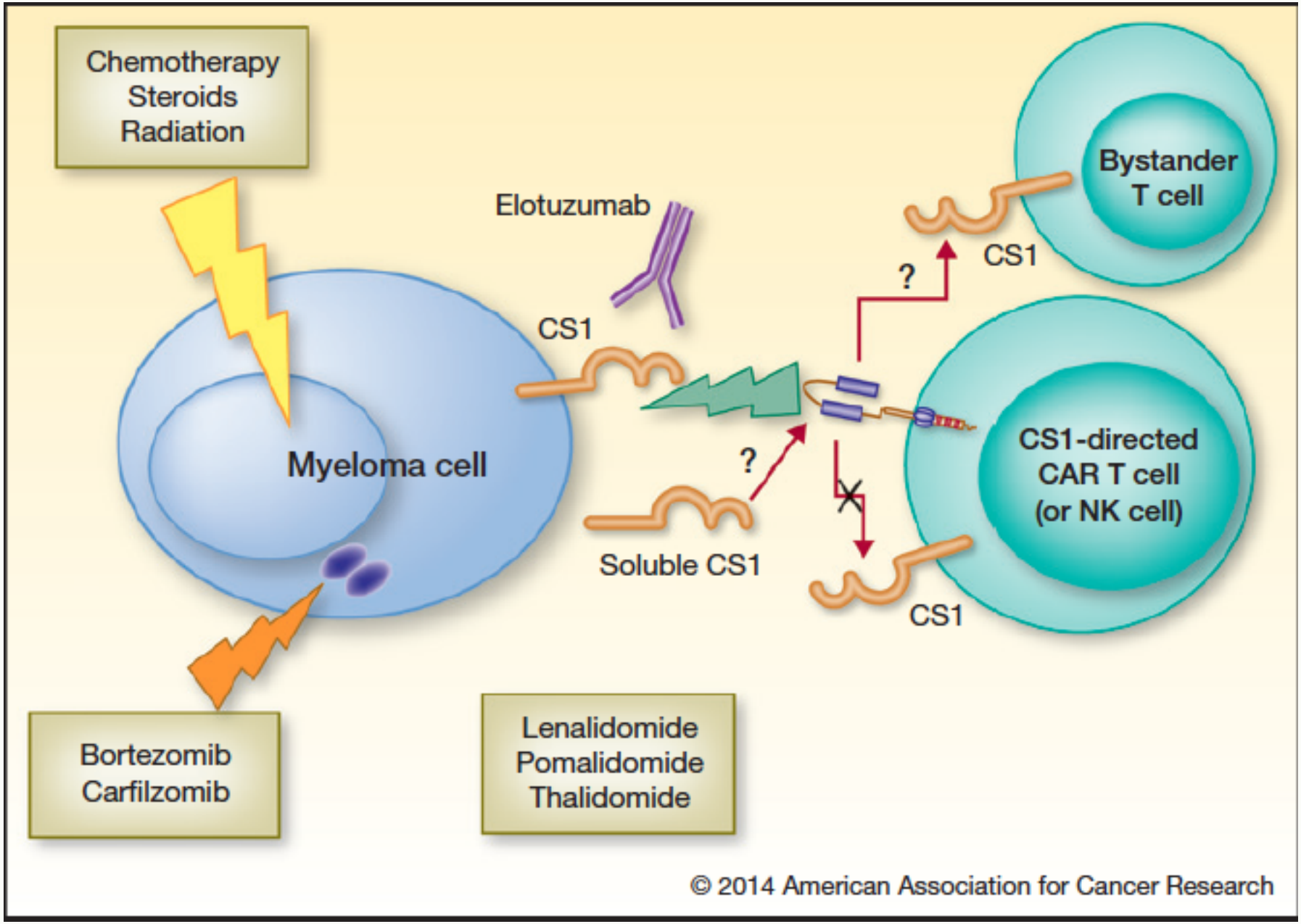
Table 2
Acute adverse events after T cell infusion.

| UPN | Adverse events | Grade | Time of occurrence | Description | Duration |
|---|---|---|---|---|---|
| 1 | Fever | 3 | 1 h after infusion | With chills, the peak temperature was 39.2 °C | 30 min |
| 2 | None | | | | |
| 3 | Fever | 3 | 4 h after infusion | With chills, nausea, the peak temperature was 39.5 °C | 90 min |
| 4 | Fever | 3 | 2 h after infusion | With chills, nausea, the peak temperature was 39.5 °C | 50 min |
| 5 | Fever | 3 | 40 min after infusion | With chills, nausea, the peak temperature was 39.6 °C | 2 h |

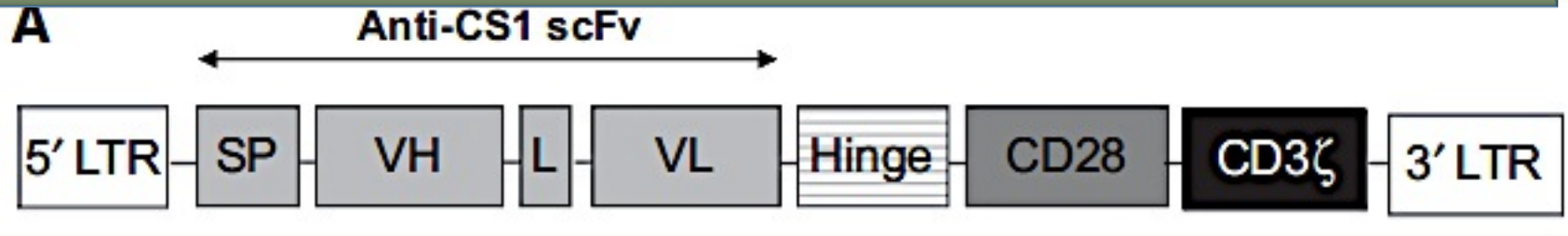
The maximum grade experienced for the corresponding toxicity for a given patient.

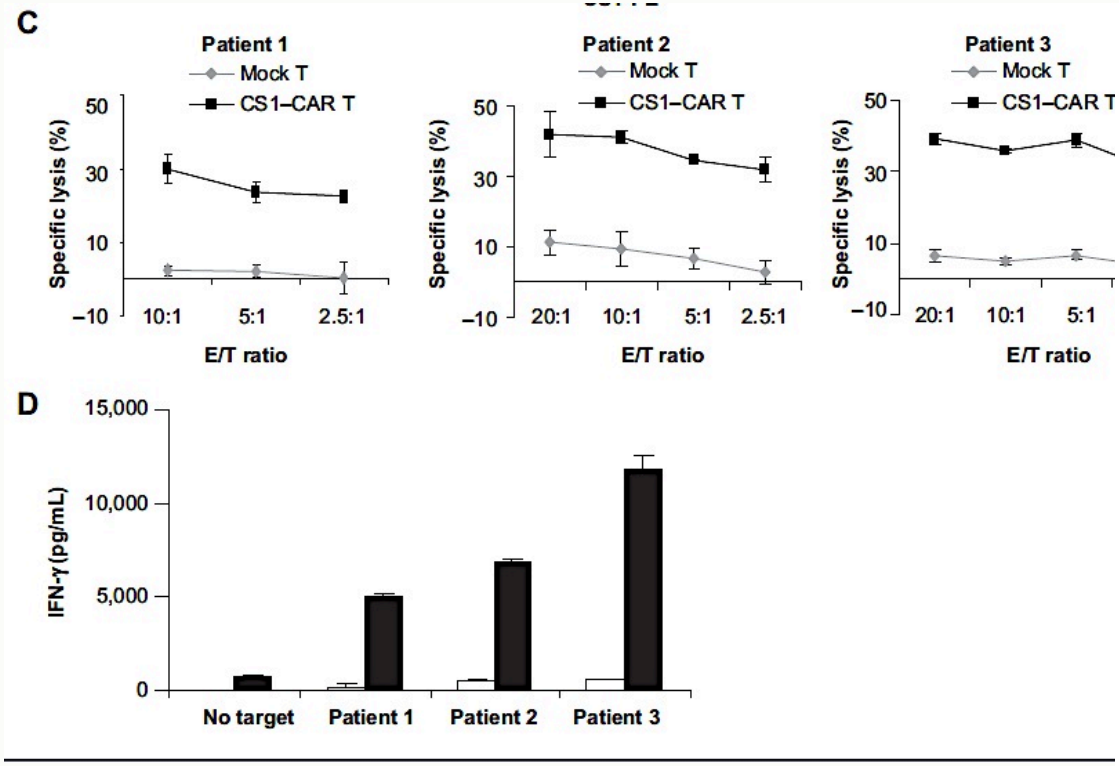
The M protein remain stable on day 14 after cell infusion. The best response was SD.
The PFS was: UNP1 3 months, UPN2 5 moths, UPN3 8 months, UPN4 1 months, UPN5 8 months.
**Median time to progression was 5 months (range 1-8m)**

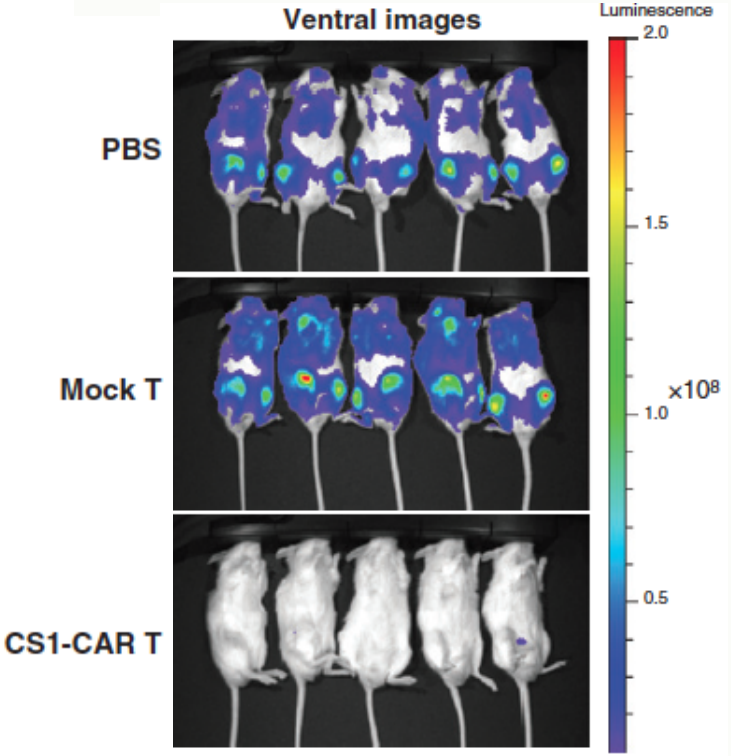
Guo B et al, J Cell Immur


Chemotherapy
Steroids
Radiation
Elotuzumab
CS1
Myeloma cell
Bystander
T cell
CS1
?
CS1-directed
CAR T cell
(or NK cell)
?
Soluble CS1
CS1
Bortezomib
Carfilzomib
Lenalidomide
Pomalidomide
Thalidomide
© 2014 American Association for Cancer Research

# CS1-CAR-T cells immunotherapy for myeloma



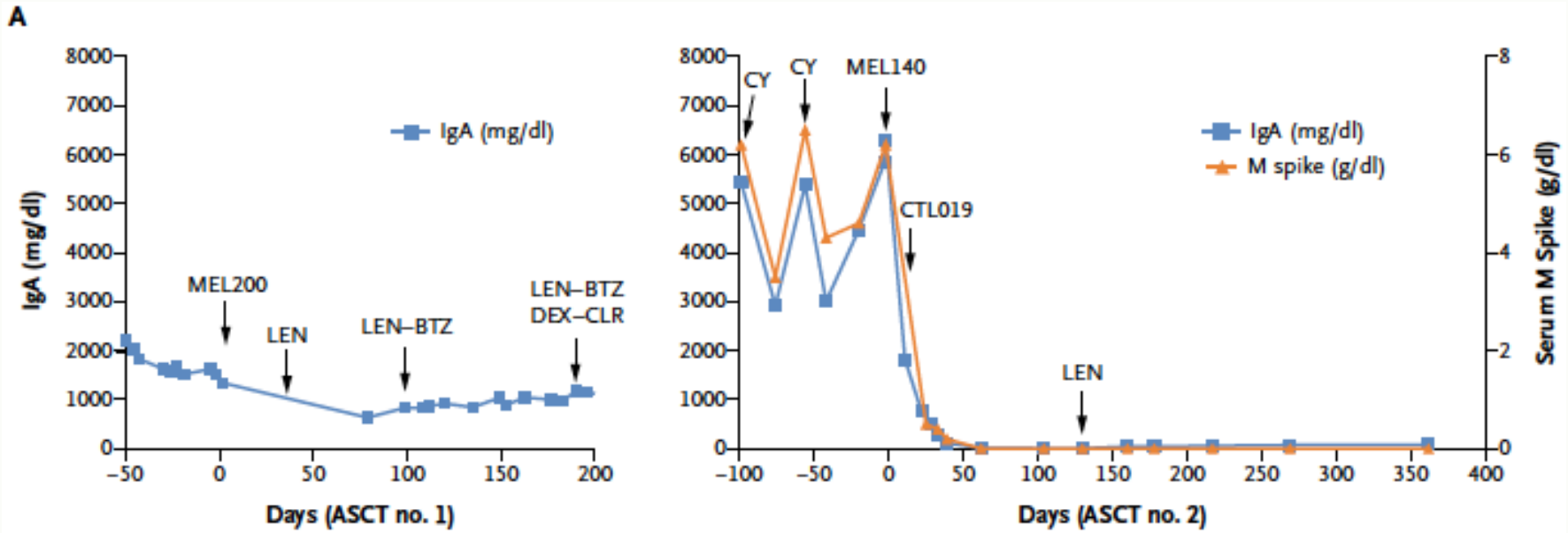



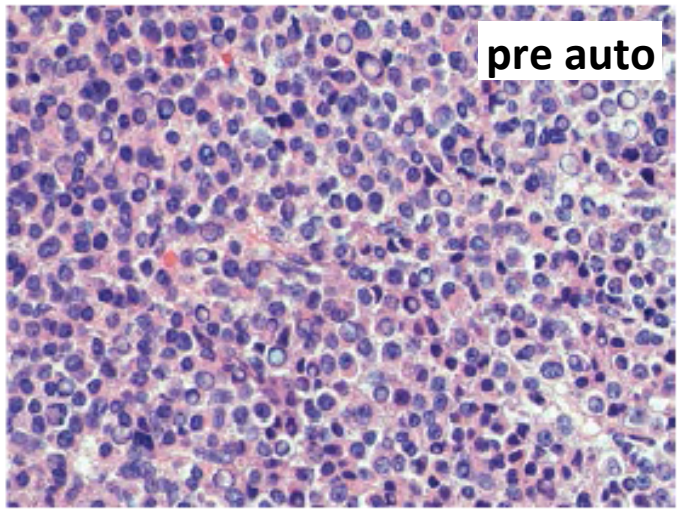



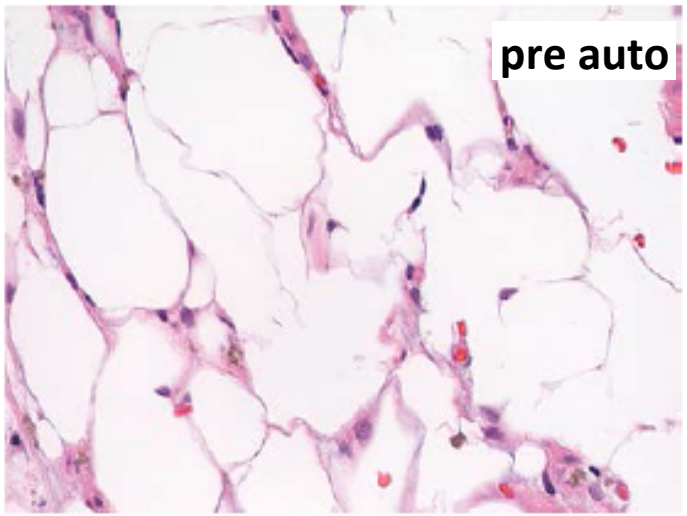

Chu J et al, Clin Cancer Resear

# CD19-CAR-T cells immunotherapy for myeloma

Patients with R/R multiple myeloma received a second auto-SCT:
Melphalan 140mg/m$^2$ → Auto-CST → CTL019 cells (autologous anti-CD19 CAR-T cells)




Garfall AL, NE.

# CAR T cells: key points

- CD19 Cars have potent anti-leukemic effects in ALL and CLL with durable responses >4 years
  - CD19 CARs induce B cell aplasia. Managed with IVIG infusion
  - CRS: related to tumor burden. Tocilizumab.
  - Multicenter trials are underway (Novartis)
- CTL019 has robust activity in DLBCL and triple refractory FL
- CTL019 in myeloma has accetable safety and promising efficacy

**CAR T cells with CD27 and ICOS signaling domains are promising**

Kawlekar et al. ASH

# CARs T-cell therapy for hematologic malignancies

| Disease | CARs T target | Adverse Events |
|---|---|---|
| **Acute Myeloid Leukemia (AML)** | CD123<br>CD33<br>CD44v6<br>CLEC12A and Lewis Y | severe hematopoietic toxicity<br>profound myeloablation<br>lethal epithelial toxicity<br>minimal toxicity |
| **Hodgking's Lymphoma (HL)** | CD30 | could theoretically induce fratricide of activated T cells |
| **T-cell Non Hodgking's Lymphoma** | CD30<br><br>possible approach would be to use natural killer cells to treat T-cell malignancies targeting non-shared antigens | most difficult application<br><br>the persistence of the NK cells would have to be closely regulated to prevent prolonged T-cell lymphopenia |
| **Myeloma** | CD137-costimulated CAR against CD138<br>CD38<br>BCMA<br>CD44v6 | |


Gill et al. Immunol Rev. 2015; 263(1):68-89

# CAR T cells: How to improve?

# Future directions

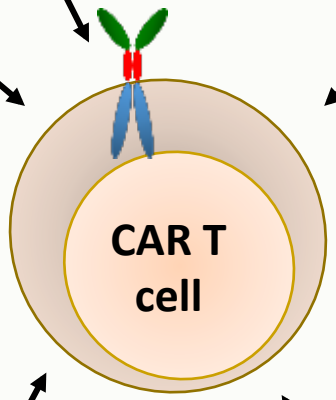
## Strategies to improve efficacy

**Increased CAR signalling:**
- Combinations of co-stimulatory domains (3rd generation CAR)
- Combinatorial specificity for tumour antigens X, Y (X AND Y)
- Optimised spacer design

**Improved effector function:**
- Selection of T cell subsets for CAR transfer
- Engineer with chemokine receptors for improved tumour trafficking
- Combination therapy with inhibitory receptor blockade (e.g. PD-1 blockade)

**Improved T cell survival:**
- Death receptor blockade (TRAIL, Fas)
- Engineer for expression of anti-apoptotic molecules
- Select virus-specific T cells for transudction

**Overcome immunosuppression:**
- Treg suppression
- Inhibitory ligand/receptor blockade
- Co-express chimeric CARs converting co-inhibitory signal to a co-stimulatory one
- Express dominant negative receptors (e.g. TGFβ)



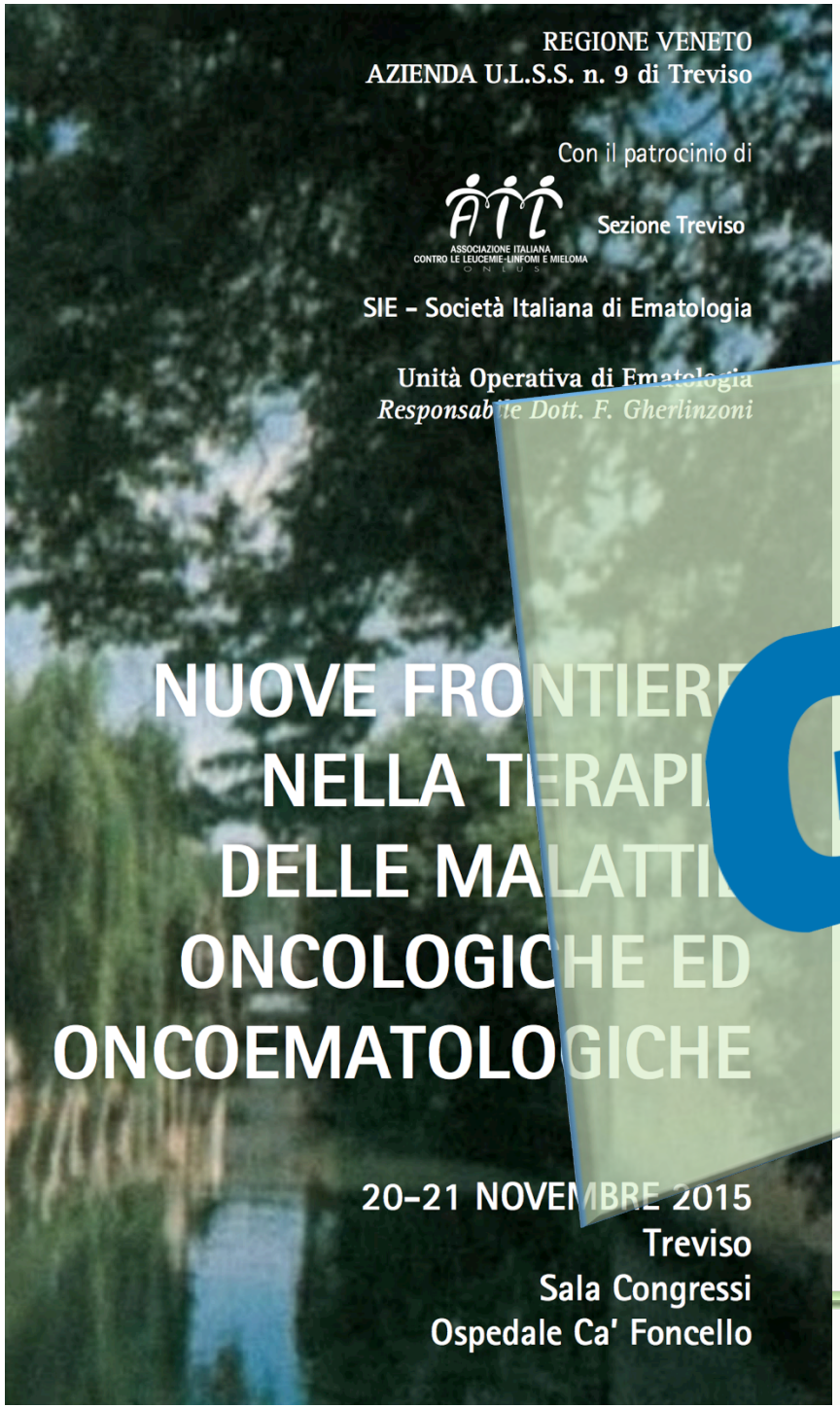

## Combined immune therapies

- With co-inhibitory receptor blockade (anti-PD-1)
- With monoclonal antibody therapy

## Strategies to improve safety

- Transient or inducible expression
- Engineer T cell with suicide gene
- Combinatorial antigen specificity for tumour antigen X and normal tissue antigen Y (X ANDNOT Y)

**Br J Haematol. 2015;169(4):463-78.**




# CAR-T: la nuova frontiera dell'immunoterapia

## Stato dell'arte

**Grazie**

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