Introduzione

Mario Luppi
Cattedra ed UO-C di Ematologia
UNIMORE, AOU Modena

10:10 – 11:10 **I CAR-T NELLA TERAPIA DEI LINFOMI**

Introduzione	*M. Luppi (Modena)*
Quali sono i pazienti candidabili?	*B. Casadei (Bologna)*
I risultati ottenuti	*C. Pellegrini (Bologna)*
Discussione	

Advisory Boards

Abbvie, Daiichi-Sankyo, Gilead Sci., Jazz, MSD, Novartis, Sanofi

Travel grants

Gilead Sci., Sanofi

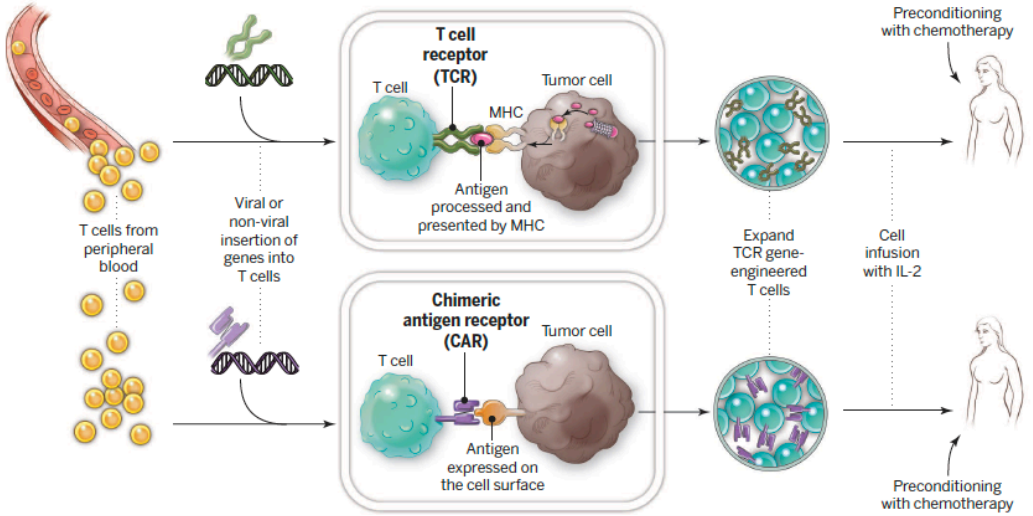
Adoptive cell therapy to cancers based on techniques of gene-modification of peripheral blood lymphocytes to introduce anti-tumor receptors into normal T cells, that could be used for therapy.

The insertion of a conventional TCR into a patient's T cell, followed by the expansion and their re-infusion

Adoptive cell transfer as personalized immunotherapy for human cancer

Steven A. Rosenberg* and Nicholas P. Restifo*

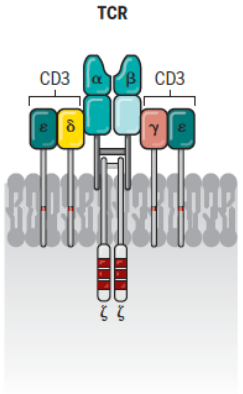
3 APRIL 2015 • VOL 348 ISSUE 6230



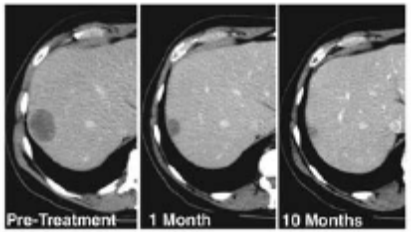
The insertion of a CAR into a patient's T cell, followed by the expansion of these cells and their re-infusion.

Table 1. Patient demographics, treatments received, and clinical outcome. Ln, lymph node; Cu, cutaneous; Sub, subcutaneous; Li, liver; Lu, lung; Ad, adrenal; Pa, pancreas; Br, brain; Hi, hilum. NR, no response; PR, partial response; MR, minor or mixed response.

Cohort	Patient	Age/sex	Total cells infused ($\times 10^{-9}$)	CD4/CD8 (%)	VB12 (%)	MART-1 cells infused ($\times 10^{-9}$)‡	Days in culture	Doubling time (days)†	IL-2 doses§	Sites of evaluable disease	Response (duration in months)‖
1	1	28/M	11.0	27/73	67	7.4	19	8.7	7	Ln, Cu	NR
	2a*	44/F	13.0	3/95	64	8.3	19	11.9	10	Ln, Cu	NR
	3	58/M	14.0	17/82	35	4.9	19	10.0	11	Cu, Sub	NR
2	4	52/M	1.0	50/50	42	0.5	6	1.4	9	Li, Sub	PR(21)
	5	50/M	12.0	18/82	17	2.2	8	1.0	7	Lu, Ln, Sub	NR
	6	55/F	7.0	37/72	51	3.6	7	1.3	8	Lu, Ln	NR
	7	56/M	9.0	75/21	40	3.6	7	1.0	5	Lu, Ln	NR
	8	37/M	6.1	68/40	32	1.9	7	1.3	12	Lu, Ln	NR
	9	53/M	4.2	72/24	41	1.7	7	2.0	9	Ln, Ad, Sub	MR
	10	45/M	8.6	53/30	34	2.9	6	0.6	5	Ln, Sub	
	11	45/M	6.3	7/92	45	2.8	6	0.8	5	Lu, Pa, Ln	NR
	12	32/F	4.7	30/60	61	2.9	6	0.7	5	Br, Sub	NR
	13	41/M	7.7	40/67	42	3.2	6	0.9	7	Lu, Sub	NR
	2b*	44/F	2.1	30/59	53	1.1	6	1.9	14	Ln, Cu	NR
3	14	30/M	86	11/60	40	34.4	18+9	0.9	5	Hi	PR(20)
	15	51/M	38	16/82	45	17.1	18+9	3.3	8	Lu	NR
	16	25/F	33	13/76	21	6.9	18+9	1.2	2	Lu, Li, Sub	NR
	17	20/F	23	17/78	30	6.9	17+8	1.1	3	Lu, Ln, Sub	NR



The first TCR T cell cancer immunotherapy used in the clinic was tested against metastatic melanoma and utilized a TCR that bound a human lymphocyte antigen A2 (HLA-A2)–restricted peptide from a melanocytic differentiation antigen



Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes

Richard A. Morgan, Mark E. Dudley, John R. Wunderlich, Marybeth S. Hughes, James C. Yang, Richard M. Sherry, Richard E. Royal, Suzanne L. Topalian, Udai S. Kammula, Nicholas P. Restifo, Zhili Zheng, Azam Nahvi, Christiaan R. de Vries, Linda J. Rogers-Freezer, Sharon A. Mavroukakis, Steven A. Rosenberg*

6 OCTOBER 2006 VOL 314 **SCIENCE**

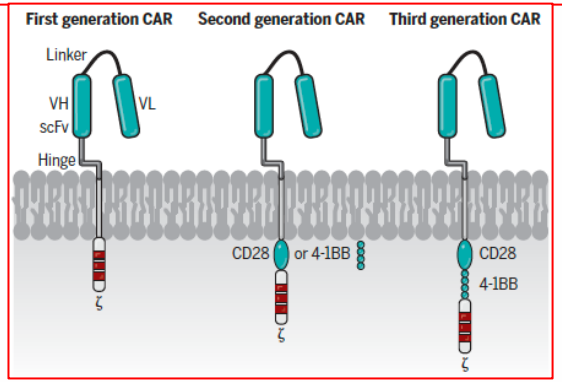
Pioneering work by Zelig Eshhar at the Weizmann Institute on redirecting the specificity of genetically engineered T cells to target antigens on tumor cells led to the development of chimeric antigen receptor (CAR) proteins cells.

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*



CAR proteins are fusion proteins composed of an extracellular portion that is usually derived from an antibody and intracellular signaling modules derived from T cell signaling proteins.
First-generation CARs contain CD3z, whereas second-generation CARs possess a costimulatory endodomain (e.g., CD28 or 4-1BB) fused to CD3z. Third-generation CARs consist of two costimulatory domains linked to CD3z.

CAR T cells allow MHC-independent recognition of tumor targets.

Work by Michel Sadelain and Dario Campana on the addition of costimulatory domains to CAR T cells led to better T-cell receptor signaling with potent and sustained activity of engineered cells.

Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor

John Maher, Renier J. Brentjens, Gertrude Gunset, Isabelle Rivière, and Michel Sadelain*

nature biotechnology • VOLUME 20 • JANUARY 2002 •

Leukemia (2004) 18, 676–684
© 2004 Nature Publishing Group All rights reserved 0887-6924/04 $25.00
www.nature.com/leu

Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia

C Imai[1], K Mihara[1], M Andreansky[1], IC Nicholson[2], C-H Pui[1,3,4], TL Geiger[3] and D Campana[1,3,4]

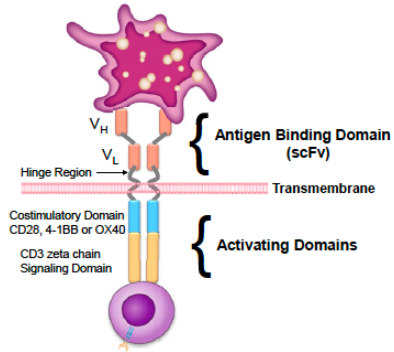
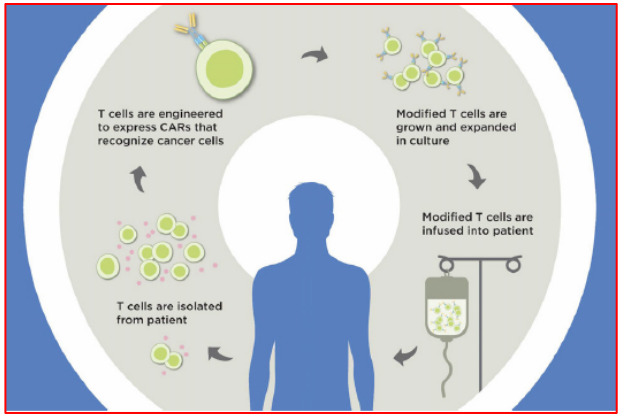


FIGURE 1. Chimeric Antigen Receptor



HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

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

Bianca Santomasso, MD, PhD[1]; Carlos Bachier, MD[2]; Jason Westin, MD[3]; Katayoun Rezvani, MD, PhD[3]; and Elizabeth J. Shpall, MD[3]

2019 ASCO EDUCATIONAL BOOK | asco.org/edbook 433

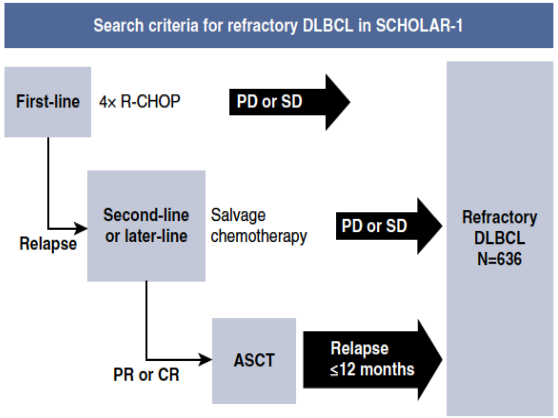
These early discoveries led to the recent clinical trials showing impressive responses in patients with refractory lymphomas, acute leukemias and other hematologic malignancies.

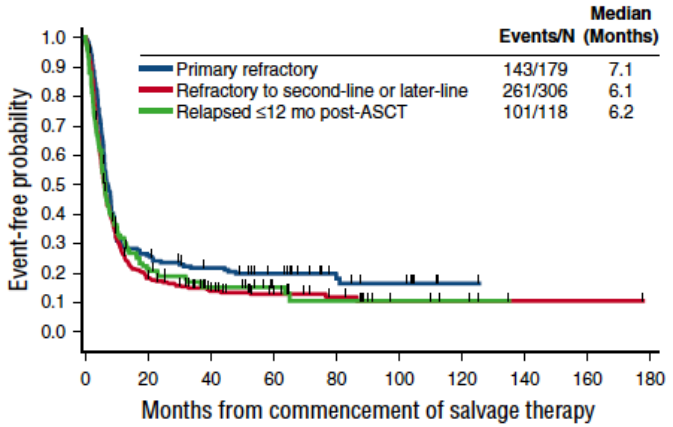
Courtesy Dr G. Perrone, Prof P. Corradini, IRCCS INT Milano

CLINICAL TRIALS AND OBSERVATIONS

Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study

DLBCL RELAPSE/REFRACTORY





Crump et al, Blood 2017

Retrospective analysis of outcomes in 636 refractory DLBCL

Response to next line of therapy: ORR 26% (CR 7%), Median OS 6.3 months.

State of the art in CAR T cell therapy for CD19+ B cell malignancies

Matthew J. Frigault and Marcela V. Maus

1586 jci.org Volume 130 Number 4 April 2020

Table 1. Summary of efficacy and toxicity from advanced CD19-directed CAR T cell therapies

	Tisagenlecleucel (95)	Axicabtagene ciloleucel (56)	Lisocabtagene maraleucel (69)
Construct	Anti-CD19–4-1BB–CD3ζ	Anti-CD19–CD28–CD3ζ	Anti-CD19–4-1BB–CD3ζ
Follow-up, months	24	27.1	12
Median prior therapies	3	3	3
Overall response	54% ORR, 40% CR	83% ORR, 58% CR	73% ORR, 53% CR
Median OS, months	10.3, not reached for patients in CR	Not reached	Not reached
PFS at 2 years, %			
All patients	Not reported	39	Not reported
In CR	78	72	Not reported
Grade 3–4 AEs	23% CRS, 11% NT	12% CRS, 31% NT	2% CRS, 10% NT
CRS grading scale used	Penn	Lee	Lee
Treatment locale	Inpatient or outpatient	Inpatient only	Inpatient or outpatient
Approval status	FDA-approved for pediatric ALL and adult R/R DLBCL	FDA-approved for adult R/R DLBCL and PMBL	Not yet approved

AEs, adverse events; CR, complete response; NT, neurotoxicity; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMBL, primary mediastinal B cell lymphoma; R/R, relapsed/refractory.

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

N ENGL J MED 382;14 NEJM.ORG APRIL 2, 2020

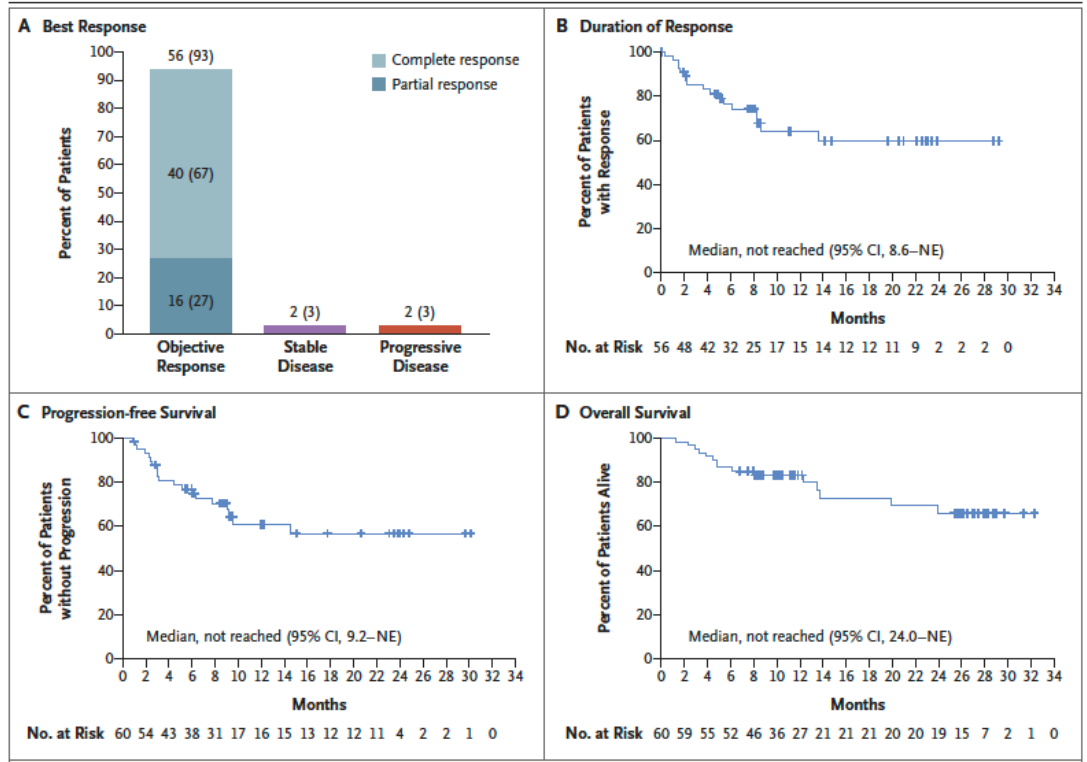


Figure 1. Objective Response, Duration of Response, Progression-free Survival, and Overall Survival.

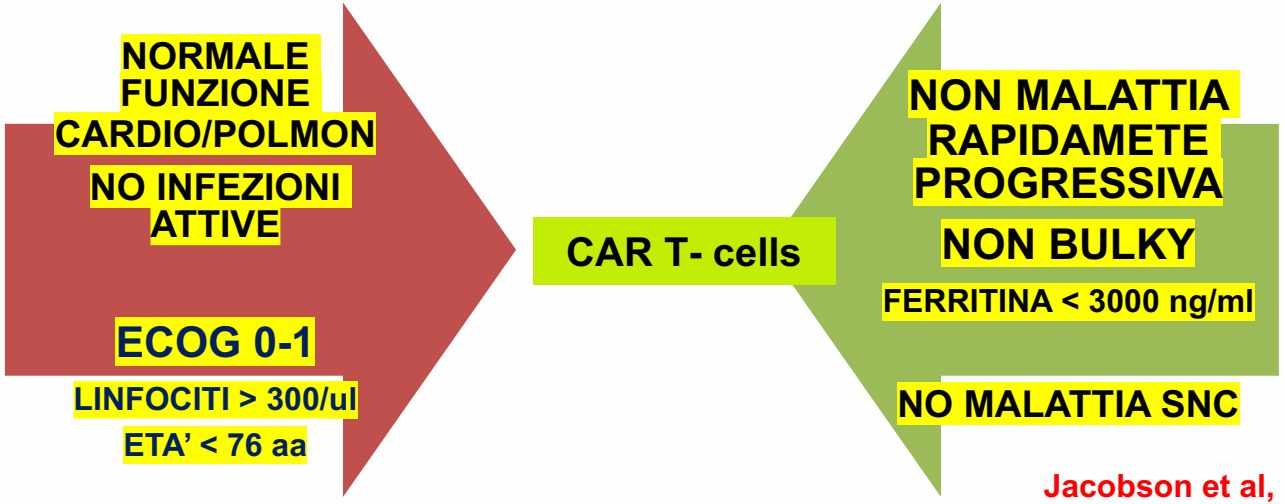
...elegibility criteria

Courtesy Dr G. Perrone, Prof P. Corradini, IRCCS INT Milano

..... in relation to anticipated ability to tolerate sequela from CRS, autoimmune disease and active infection ...

....reassessment prior to initiation of lymphodepletion...

REAL WORD DATA



Jacobson et al, Blood 2018

Table 1. R/R DLBCL. Reasons for ineligibility according to the Juliet exclusion criteria		
	N/available data	Percent
Patients ineligible	**30/82**	**37%**
ECOG 2 or higher	14/82	17%
Other histology at relapse	1/82	1%
CNS involvement	6/82	7%
Active infections	4/82	5%
EF <50%	3/82	4%
Cr >1.5	1/82	1%
AST/ALT >2 upper ULN	1/82	1%

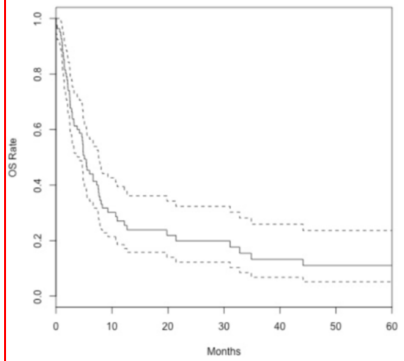


Figure 1. OS from diagnosis of 2nd relapse

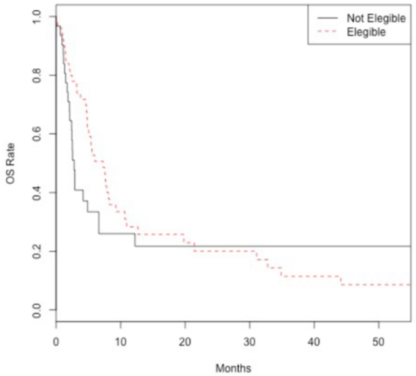


Fig 2 : OS CAR-T therapy eligible vs not eligible

Alice Di Rocco et al., Blood (2019) 134 (Supplement_1): 2888.

CAR-T related Issues

1. Ineligibility (alternative experimental option, although unsatisfactory or with uncertain benefit)

2. Inequity in the offer of such life-saving therapies, unrelated to either financial resources or clinical expertise, can only be faced by implementing the value of medical communication in the context of an Early Palliative Care interventions, allowing a more accurate goal of care discussion and prognostic awareness, as early as possible in the disease trajectory.

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A., Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H., Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N., Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H., J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

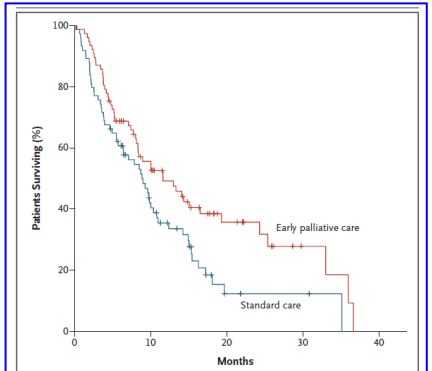
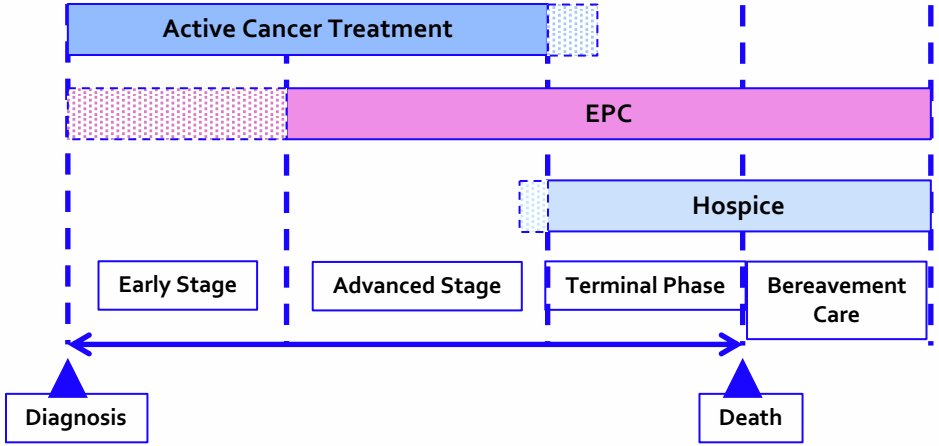


Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.
Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2009. Median estimates of survival were as follows: 9.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77 patients), and 8.9 months (95% CI, 6.3 to 11.4) in the standard care group (74 patients) (P=0.02 with the use of the log-rank test). After

Boston, Buffalo, NY, Yale

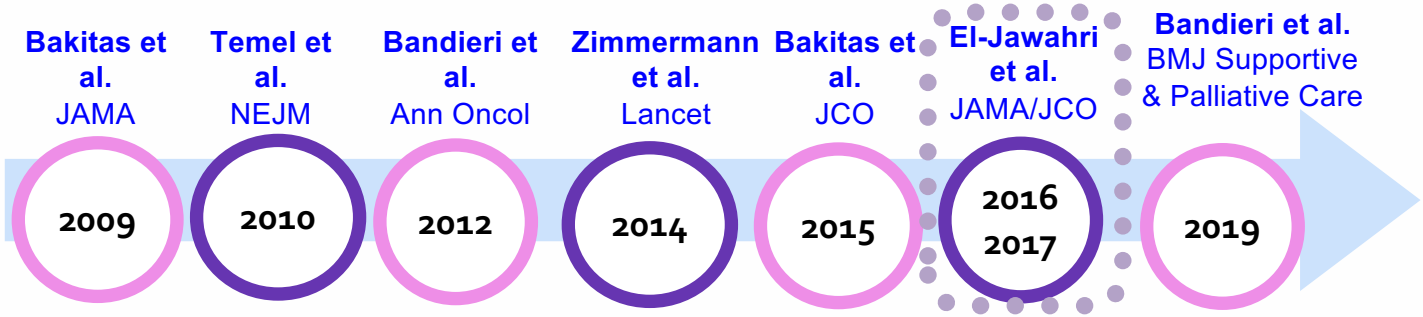
EPC in cancer patients



Ferrell et al. J Clin Oncol 2017; 35: 96-112

Benefits of EPC in cancer patients

Hematologic pts.



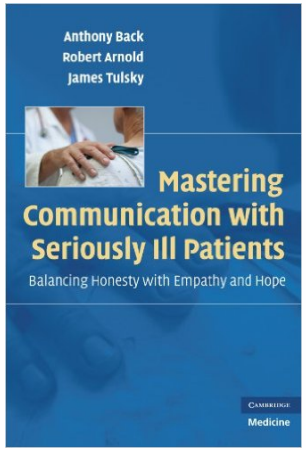
Improved **symptoms control**
Improved **quality of life**
Lower rates of **depressive symptoms**
More accurate **GOC/prognostic awareness**
Reduced **health service use at EOL**
Longer median **survival**

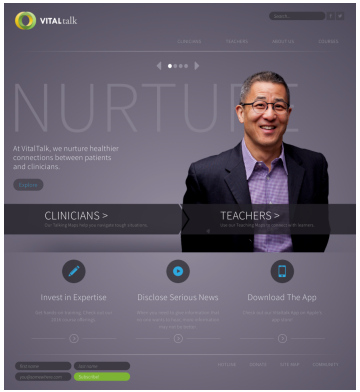
ASCO statements

Access to palliative care was defined **EARLY** when occured **within 8 weeks** from diagnosis of advanced cancer

2012
2016

Early Palliative care (EPC) and Communication





«Le **Cure Palliative/Supportive Precoci permettono di costruire in modo anticipato, una relazione di comunicazione medico-paziente e «caregiver» di lunga durata** e profonda, in cui sono **discusse e rivalutate,** durante la traiettoria di malattia, la diagnosi di malattia avanzata, **durante le fasi di cura e successiva ricaduta, la prognosi, la possibilità di ricorrere a successive linee di terapie «standard» o sperimentali oppure di astenersi dalle terapie attive** e potere, viceversa, **ricevere terapie palliative e di supporto, capaci di ridurre ed eliminare** il dolore, i sintomi fisici e **la sofferenza e di allungare una periodo di vita di qualità, con consapevolezza.»**

Washington,
Duke,
Dana Farber,
Pittsburgh.

Web site: www.vitaltalk.org

VITALtalk

FACULTY DEVELOPMENT COURSE
Aspen-Colorado, May and September 2016

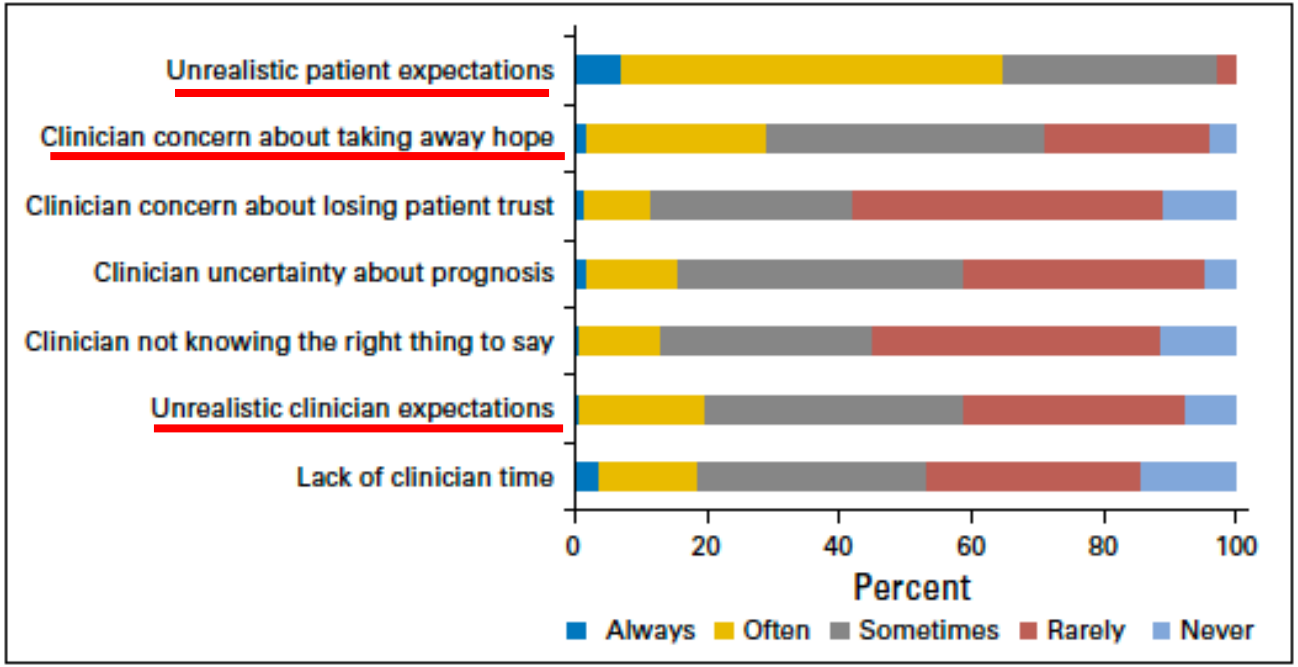
Gli aspetti Legali

Legge 219 del 22 dicembre 2017

"Norme in materia di consenso informato e di disposizioni anticipate di trattamento"

Strutture sanitarie	Ogni struttura sanitaria pubblica o privata garantisce con proprie modalità organizzative la piena e corretta attuazione dei principi di cui alla presente legge, assicurando l'informazione necessaria ai pazienti e l'adeguata formazione del personale. La formazione iniziale e continua dei medici e degli altri esercenti le professioni sanitarie comprende la formazione in materia di relazione e di comunicazione con il paziente, di terapia del dolore e di cure palliative.
«Tempo di cura»	Il tempo della comunicazione tra medico e paziente costituisce tempo di cura.

Barriers to EPC in hematologic malignancies



Perceived barriers to high-quality end-of life care as rated by 334 hematologic oncologists.

Odejide et al. JCO 2016; 34: 3126 3132

"Consider that you are seeing a patient who has developed primary refractory disease (persistent or progressive disease after receiving first-line treatment).
For which of the following would you have an end-of-life discussion with the patient now?"

Table 3. Hematologic Oncologists' Perspectives Regarding Whether Primary Refractory State Would Trigger EOL Discussions

Hematologic Cancer	Primary Refractory Disease Prompts EOL Discussion (%)	
	Yes	No
Mantle cell lymphoma	57.3*	42.7
Diffuse large B-cell lymphoma	61.9*	38.1
Follicular lymphoma	17.1	82.9
Chronic lymphocytic leukemia	19.2	80.8
Acute myeloid leukemia	91.2*	8.8
Multiple myeloma	32.9	67.1

Odejide et al. JCO 2016; 34: 3126 3132

- **Diagnosis and Monitoring by Modern Molecular and Immunologic Methods**
- **Phase I-II-III Trials**
- **CAR T Cell Therapies**

→ **HUB** and/or **SPOKES**

Personal Comment

- **Early Palliative Care Programs (EPC)** → **HUB**

ARTICLE IN PRESS

Letter to the Editor

Early Palliative Care: A Necessary Intervention for Patients Ineligibile to Approved Potentially Life-saving CAR T-cell Therapy

Leonardo Potenza,[1] Mario Luppi,[1] Fabio Efficace,[2] Eduardo Bruera,[3] Elena Bandieri[4]

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■

→ **ASH, DECEMBER 5, 2020**
2.00-2.45 P.M.
Odejide et al,
Challenging Situations for Patients with Aggressive Lymphomas - *Live Q&A*

10:30 – 12:00 **I CAR-T NELLA TERAPIA DEI LINFOMI**

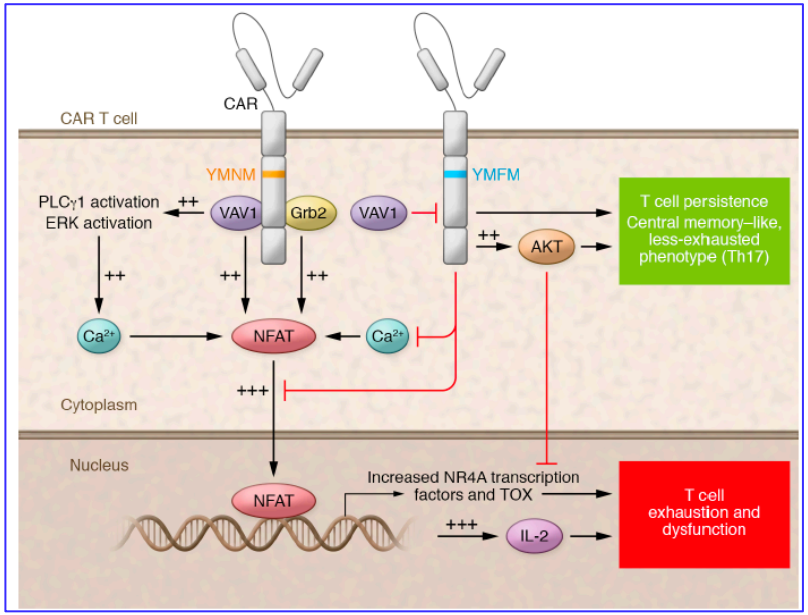
Introduzione	*M. Luppi*
Quali sono i pazienti candidabili?	*B. Casadei*
I risultati ottenuti	*C. Pellegrini*

CAR-T efficacy

Differential signaling through the CAR costimulatory domain can alter the T cell metabolism, memory differentiation, and influence long-term persistence.

A single amino acid residue in CD28 drove T cell exhaustion and hindered the persistence of CD28-based CAR-T cells and changing this asparagine to phenylalanine (CD28-YMFM) promoted durable antitumor control.

In addition, CD28-YMFM CAR-T cells exhibited reduced T cell differentiation and exhaustion as well as increased skewing toward Th17 cells.



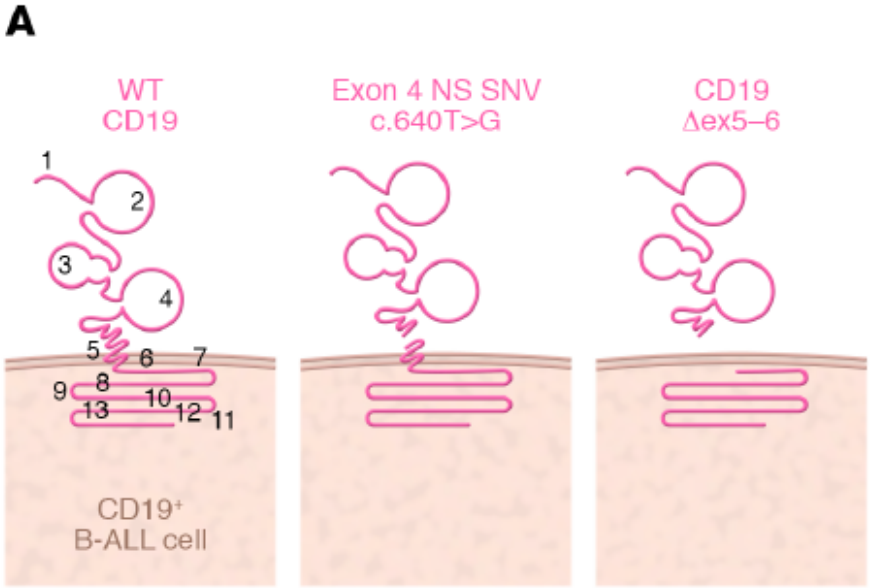
jci.org Volume 130 Number 6 June 2020

Single residue in CD28-costimulated CAR-T cells limits long-term persistence and antitumor durability

Sonia Guedan,[1,2] Aviv Madar,[3] Victoria Casado-Medrano,[4] Carolyn Shaw,[1] Anna Wing,[1] Fang Liu,[1] Regina M. Young,[1] Carl H. June,[1,5,6] and Avery D. Posey Jr.[1,5,6,7]

CAR-T efficacy

Examples of mechanisms underlying CD19– loss in B cell malignancies.



State of the art in CAR T cell therapy for CD19+ B cell malignancies

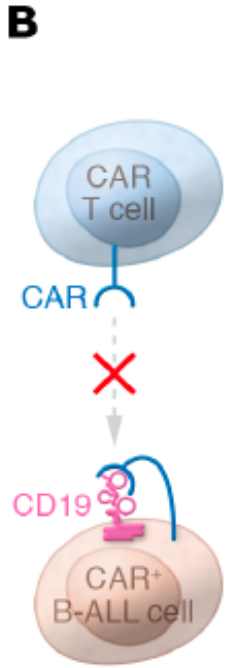
Matthew J. Frigault and Marcela V. Maus

jci.org Volume 130 Number 4 April 2020

Wild-type CD19 and observed frameshift mutations that result in lack of surface expression of the CD19 molecule in B cell leukemia. Splice variants, with loss of the exon encoding the epitope or loss of the anchoring transmembrane domain.

CAR-T efficacy

Examples of mechanisms underlying CD19– loss in B cell malignancies.



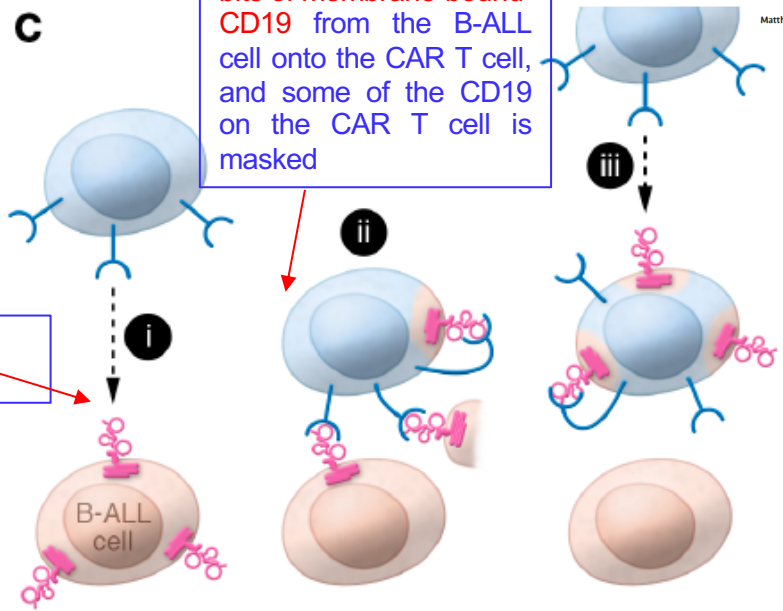
"Loss" of CD19 antigen expression has also been observed in the context of antigen masking due to CAR transduction into leukemic blasts.

CAR-transduced blasts effectively mask the target epitope from external CAR T cell killing through self-binding of CD19 on the cell surface (quite rare)

State of the art in CAR T cell therapy for CD19⁺ B cell malignancies

Matthew J. Frigault and Marcela V. Maus jci.org Volume 130 Number 4 April 2020

Examples of mechanisms underlying CD19– loss in B cell malignancies.



CAR T has trogocytosed bits of membrane-bound CD19 from the B-ALL cell onto the CAR T cell, and some of the CD19 on the CAR T cell is masked

CAR T encounters B-ALL cell

CAR T cell with membrane-bound CD19 may become susceptible to lysis by another CAR T cell.

State of the art in CAR T cell therapy for CD19⁺ B cell malignancies

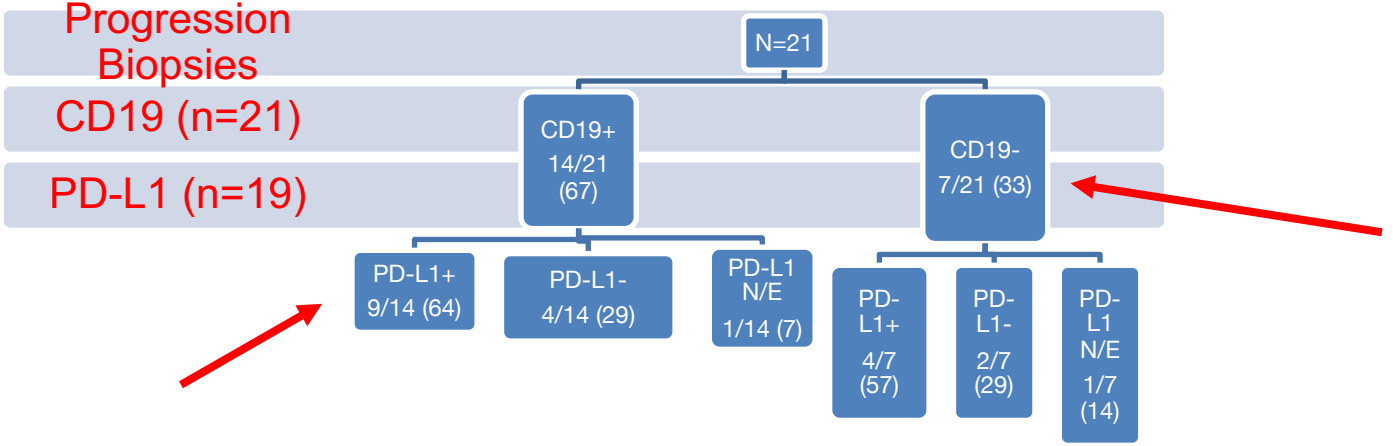
Matthew J. Frigault and Marcela V. Maus

jci.org Volume 130 Number 4 April 2020

In in vitro and animal models, CARs have been shown to induce reversible antigen loss through trogocytosis, in which the target antigen is transferred to CAR T cells during establishment of an immune synapse.

This transfer of target antigen led to a decrease in target density on tumor cells as well as an increase in fratricide and subsequent T cell exhaustion.

ZUMA-1: Preliminary analysis of B cell and immune-related molecules at progression by central review



- Post-progression tumour biopsies (21 evaluable patients)
  - 33% were CD19- by central review
  - 64% were PD-L1+ by central review

Neelapu SS, *et al.*
ASH 2017 (Abstract 578; oral).

Courtesy Dr G. Perrone, Prof P. Corradini, IRCCS INT Milano

IHC: Immunohistochemistry; N/E: not evaluable; PD-L1: programmed cell death-ligand 1

CAR-T Cell Therapy in Diffuse Large B Cell Lymphoma: Hype and Hope

HemaSphere (2019) 3:2

Georg Hopfinger[1], Ulrich Jäger[2], Nina Worel[3]

www.hemaspherejournal.com

Table 1

Study Details

Name of Trial	JULIET	ZUMA-1	TRANSCEND001 "FULL"	TRANSCEND001 "CORE"
CAR-T product	CTL019 Tisagenlecleucel	KTE-C19 Axicabtagene ciloleucel	JCAR017 Lisocabtagene maraleucel	JCAR017 Lisocabtagene maraleucel
Patient characteristics				
Disease entity	DLBCL	DLBCL, tFL, PMBCL	DLBCL, tFL, PMBCL	DLBL, tFL
Enrolled/infused, n	165/111	111/101	134/102	n.r./73
Prior lines of CHT (n), median, range	3 (1–8)	3 (1–7)	3 (1–8)	3 (2–8)
Pre-ASCT, %	49	21	37	38
Bridging therapy	Allowed	Not allowed	Allowed	Allowed
Lymphodepleting CHT, mg/m^2 per day	Flu 25/Cy 250 day 1–3	Flu 30/Cy 500 day 1–3	Flu 30/Cy 300 day 1–3	Flu 30/Cy 300 day 1–3
Toxicity				
CRS, all/grade ≥3, %	58/22	93/13	38/1	37/1
Neurotoxicity, all/grade ≥3, %	21/12	64/28	23/13	25/15
Neutropenia ± fever, all/grade ≥3, %	21/14	35/31	n.r.	n.r.
Tocilizumab, %	15	43	17	n.r.
Response				
ORR, %	52	82	75	80
CR, %	40	54	55	59
3 months ORR, %	59	82	51	59
12 months PFS, %	65	73	n.r.	n.r.
12 months OS, %	49	51–65	n.r.	n.r.

ASCT = autologous stem cell transplantation, CAR-T = chimeric antigen receptor T cell, CHT = chemotherapy, CR = complete response, CRS = cytokine release syndrome, Cy = Cyclophosphamide, DLBCL = diffuse large B cell lymphoma, Flu = Fludarabine, n.r. = not reported, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PMBCL = primary mediastinal B cell lymphoma, tFL = transformed follicular lymphoma.

CAR-T toxicity

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jci.org Volume 130 Number 4 April 2020

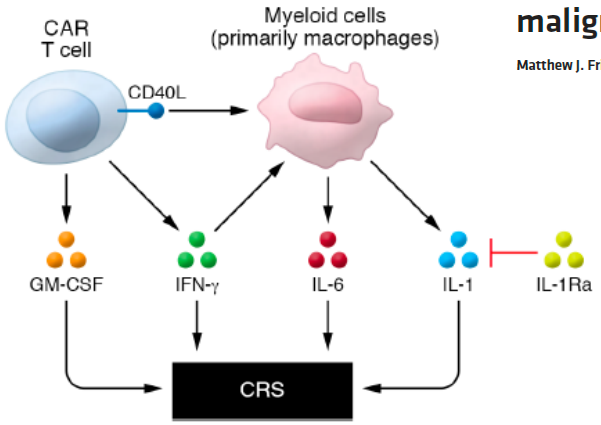


Figure 1. Summary of mechanisms discovered in two animal models designed to recapitulate cytokine release syndrome.

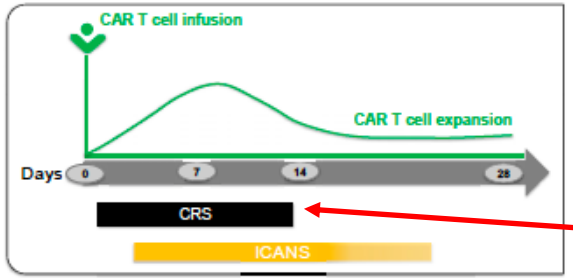


FIGURE 3. Onset and Resolution of CRS and ICANS
Abbreviations: CAR, chimeric antigen receptor; CRS, cytokine release syndrome; ICANS, immune cell–associated neurologic syndrome.

HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT

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

Bianca Santomasso, MD, PhD[1], Carlos Bachier, MD[1], Jason Westin, MD[1], Kabyonn Rezvani, MD, PhD[1], and Elizabeth J. Shpall, MD[2]

2019 ASCO EDUCATIONAL BOOK | asco.org/edbook

Use of lymphodepletion chemotherapy, higher CAR T cell dose, and disease burden,

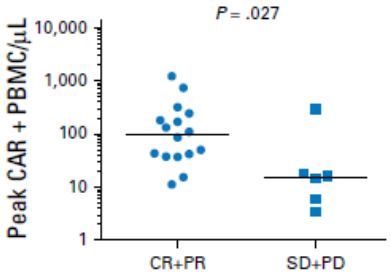
CRS is a potentially life-threatening systemic inflammatory response, triggered by release of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, TNF-α, IFN-γ, GM-CSF, MCP-1, and MIP-1β; the frequency and severity of CRS correlate with antigen-dependent T cell activation and expansion.

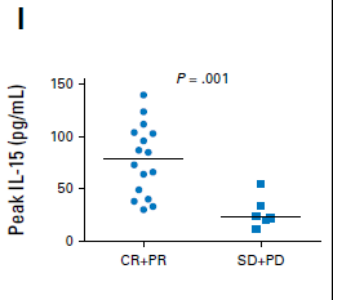
VOLUME 35 · NUMBER 16 · JUNE 1, 2017
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels

James N. Kochenderfer, Robert P.T. Somerville, Tangying Lu, Victoria Shi, Adrian Bot, John Rossi, Allen Xue, Stephanie L. Goff, James C. Yang, Richard M. Sherry, Christopher A. Klebanoff, Udai S. Kammula, Marika Sherman, Arianne Perez, Constance M. Yuan, Tatyana Feldman, Jonathan W. Friedberg, Mark J. Roschewski, Steven A. Feldman, Lori McIntyre, Mary Ann Toomey, and Steven A. Rosenberg

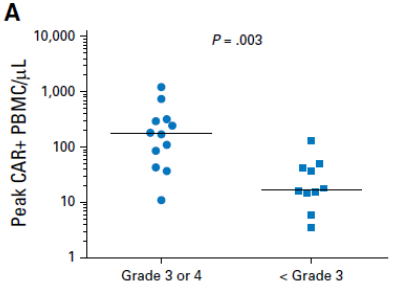
Efficacy

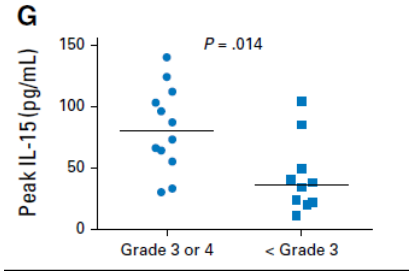




IL 15 serum levels
-5 to +14 days

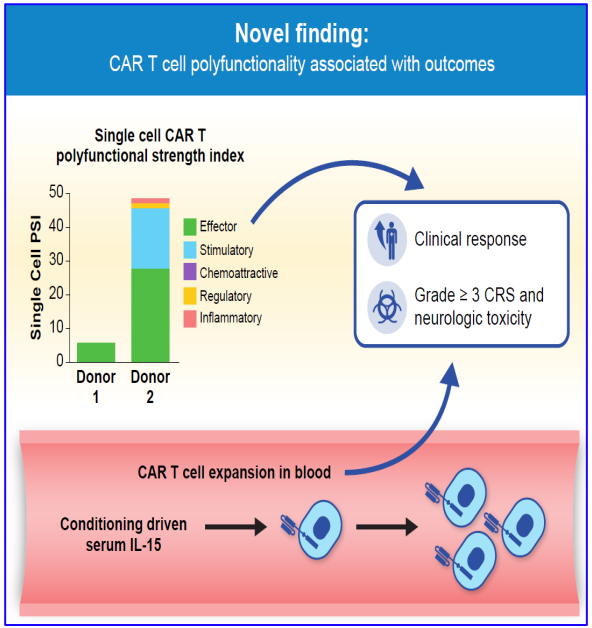
Toxicity



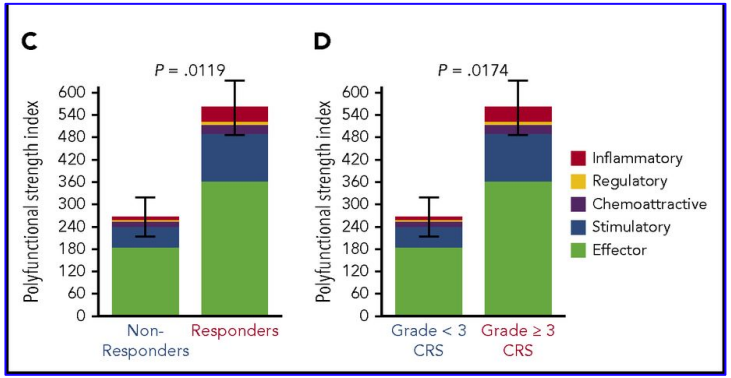


Courtesy Dr G. Perrone, Prof P. Corradini, IRCCS INT Milano

A single-cell analysis of preinfusion CD19 CAR product from pts with NHL demonstrated that CAR products contain poly-functional T-cell subsets with multiple immune programs (cytokines and chemokines, including IFN-γ, IL-17A, IL-8, and MIP-1α).



Rossi J, *et al. Blood* 2018;132: 804–814.



Measuring CAR T-cell function

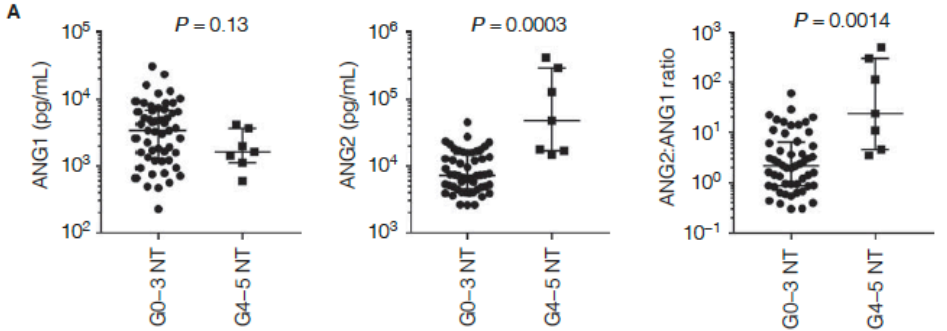
POLYFUNCTIONAL STRENGTH INDEX (PSI)
The % of poly-functional cells X the mean fluorescent intensity of the proteins secreted by the cells

PFS: polyfunctionality strength index

ANG1 is produced constitutively, primarily by vascular pericytes and platelets, and when bound to the endothelial TIE2 receptor, favors EC quiescence and stabilization.

ANG2 is stored in endothelial Weibel–Palade bodies and released upon EC activation by stimuli including inflammatory cytokines, displacing ANG1 and causing increased activation and microvascular permeability. ANG2 and ANG1 in serum from patients 1 week after CAR-T cell infusion was evaluated and the serum ANG2 concentration (P = 0.0003) and the ANG2:ANG1 ratio (P = 0.0014) were higher in patients with grade ≥4 neurotoxicity compared with those with grade ≤3 neurotoxicity

Published OnlineFirst October 12, 2017; DOI: 10.1158/2159-8290.CD-17-0698

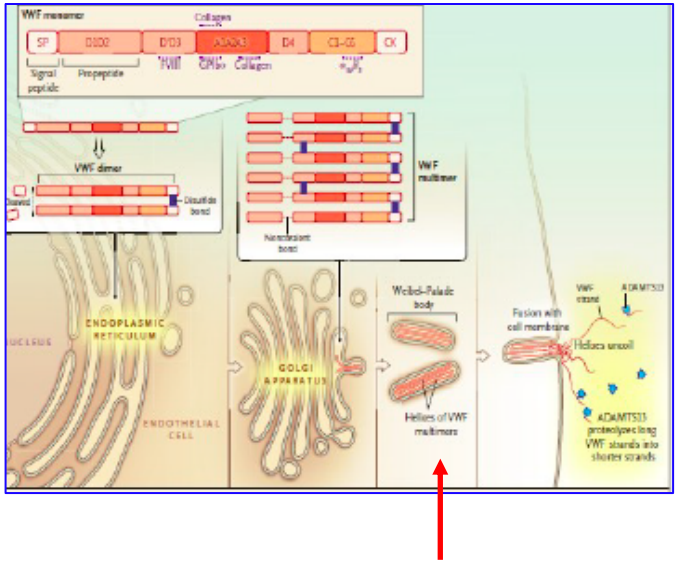


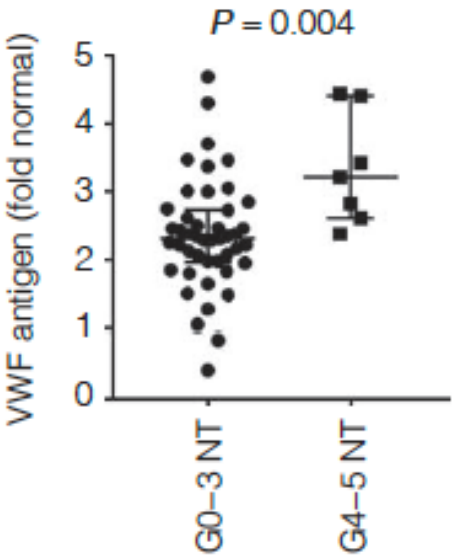
In vivo, severe neurotoxicity confirmed by evaluating the concentration of von Willebrand factor (VWF), a glycoprotein involved in hemostasis that, like ANG2, is stored in endothelial Weibel–Palade bodies and released on EC activation.

Patients with grade ≥4 neurotoxicity had higher concentrations of VWF in serum (P = 0.004), which in some patients was 4- to 5-fold higher than those observed in pooled serum from healthy donors.

IL8 is sequestered with VWF in Weibel–Palade bodies and was also elevated during severe neurotoxicity

Published OnlineFirst October 12, 2017; DOI: 10.1158/2159-8290.CD-17-0698





CAR-T toxicity

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Clinical presentation, management, and biomarkers of neurotoxicity after adoptive immunotherapy with CAR T cells

Philipp Karschnia,[1,2] Justin T. Jordan,[1] Deborah A. Forst,[1] Isabel C. Arrillaga-Romany,[1] Tracy T. Batchelor,[1] Joachim M. Baehring,[2] Nathan F. Clement,[3] L. Nicolas Gonzalez Castro,[1] Aline Herlopian,[2] Marcela V. Maus,[4] Michaela H. Schwaiblmair,[1] Jacob D. Soumerai,[5] Ronald W. Takvorian,[5] Ephraim P. Hochberg,[5] Jeffrey A. Barnes,[5] Jeremy S. Abramson,[5] Matthew J. Frigault,[4] and Jorg Dietrich[1]

[1]Division of Neuro-Oncology, Department of Neurology, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [2]Department of Neurology, Yale School of Medicine, New Haven, CT; [3]Department of Pathology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; and [4]Cellular Immunotherapy Program and [5]Hematology & Oncology Division, Department of Medicine, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA

KEY POINTS

- **Neurotoxicity after CAR T cells is associated with cytokine release syndrome; serum levels of inflammatory markers correlate with severity.**
- **Grade 3-4 neurotoxicity is a negative prognostic factor for OS, and a short course of steroids does not appear to alter outcome.**

Lower platelet counts (biomarker of blood-brain barrier disruption, which in turn has been proposed to be an important factor in the pathogenesis of neurotoxicity at time of CAR T-cell infusion) were associated with more severe neurotoxicity.

Cytokine release syndrome occurred in 24 of 25 patients (96%). Serum levels of ferritin peaked with onset of neurologic symptoms, and higher ferritin levels were associated with higher neurotoxicity grade. Grade 3-4 neurotoxicity correlated negatively with overall survival.

Comment-clinical practice relevance-

Jain et al., BBMT, 2019

Table 9
Suggested Infection Prophylaxis for Patients Undergoing Anti-CD19 CAR-T Therapy

Infection	Prophylaxis	Duration
Gram-negative bacteria with *Pseudomonas* coverage	Levofloxacin	Start when patient becomes neutropenic Stop when neutropenia resolves
Candida species	Fluconazole or micafungin	Start when patient becomes neutropenic Stop when neutropenia resolves
Mold species	Posaconazole or voriconazole	Start if neutropenia persists >2-3 weeks or Corticosteroids course > 3 days Stop when neutropenia resolves and/or steroids are stopped
Pneumocystis jiroveci	Trimethoprim-sulfamethoxazole or alternative as clinically indicated	Start days 21-28 after CAR-T administration Continue for at least 6 months
HSV and VZV	Assess HSV, VZV serologies before CAR-T therapy If seropositive for HSV11, HSV12 or VZV: acyclovir or valacyclovir	Start with initiation of lymphodepletion chemotherapy Continue for at least 1 year after CAR-Ts

- Heterogeneity among trials (possible different infectious risk related to preparations?)
- Major focus on respiratory viruses instead of CMV, EBV, HHV-6, BK and co-pathogens
- 18-34% pts. develop bacterial>viral>fungal infections within the first 2 mos, (ALL>>NHL /CLL).
- Antibacterial prophylaxis vs antibacterial empiric therapy*
- Risk factors: 73% of infections occurred after the CRS severity grade peaked

Yakoub-Agha et al., Haematologica, 2019

	Trials	EBMT recommendation	Comment
Neutropenia	G-CSF should be used according to published guidelines	G-CSF to shorten duration of neutropenia from 14 days post-infusion can be considered	Avoid if patient has CRS or ICANS There are theoretical concerns regarding macrophage activation
Antibacterial prophylaxis	Not recommended	Not recommended*	Can be considered in case of prolonged neutropenia and should be based on local guidelines e.g. with levofloxacin or ciprofloxacin
Anti-viral	Subjects should receive prophylaxis for infection with herpes virus, according to NCCN guidelines or standard institutional practice	Valaciclovir 500 mg bid or aciclovir 800mg bd	Start from LD conditioning until one year post-CAR T-cell infusion and/or until $CD4^+$ count $>0.2x10^9/L$
Anti-pneumocystis	Subjects should receive prophylaxis for infection with pneumocystis pneumonia, according to NCCN guidelines or standard institutional practice	Co-trimoxazole 480 mg once daily or 960 mg three times each week To start from LD conditioning until one year post-CAR-T cell infusion and/or until $CD4^+$count $>0.2x10^9/L$	Can be started later depending on centre guidelines. In case of co-trimoxazole allergy, pentamidine inhalation (300 mg once every month), dapsone 100 mg daily or atovaquone 1500 mg once daily are other agents to consider
Systemic anti-fungal prophylaxis	Subjects should receive prophylaxis for infection with fungal infections according to NCCN guidelines or standard institutional practice	Not recommended routinely; however, consider in patient with prolonged neutropenia and on corticosteroids	In patients with prior allo-HCT, prior invasive aspergillosis and those receiving corticosteroids, posaconazole prophylaxis should be considered
IV Immunoglobulin	Gammaglobulin will be administered for hypogammaglobulinaemia according to institutional guidelines. At a minimum, trough IgG levels should be kept above 400 mg/dL, especially in the setting of infection	Routine in children, consider in adults who have had infections with encapsulated organisms	Clinical evidence does not support routine use in adults following allo-HCT

Table 10. Anti-infective prophylaxis after CAR T cell therapy

Table 4
Summary of Late Adverse Events after CD19-Targeted CAR-T Cell Therapy.

Late Adverse Event	Entire Cohort (N = 86)	Ongoing CR (N = 21)	Non-Ongoing CR (N = 65)	*P* Value*
Cytopenias (evaluated only in patients with ongoing CR and no diagnosis of subsequent MDS), n/N (%)	–	3/19 (16)	–	–
Hypogammaglobulinemia, n/N (% of patients with available data)	28/42 (67)	14/19 (74)	14/23 (61)	.51
Infection density; mean number of infections/100 days at risk (number of patients evaluated)	.57 (53)	0.57 (20)	0.58 (33)	.58†
Subsequent malignancies, n (%)				.08
All subsequent malignancies	13 (15)	6 (29)	7 (11)	
MDS	4 (5)	2 (10)	2 (3)	.25
Non-melanoma skin cancer	6 (7)	2 (10)	4 (6)	.63
Immune-related events, n (%)	7 (8)	2 (10)	5 (8)	1.00
Neurologic events, n (%)	9 (10)	2 (10)	7 (11)	1.00
Cerebrovascular accident/transient ischemic attack, n (%)	4 (5)	0 (0)	4 (5)	.57
Psychiatric events, n (%)	8 (9)	2 (10)	6 (9)	1.00
GVHD, n/N (% of patients with previous allogeneic HCT)	3/15 (20)	3/8 (38)	0/7 (0)	.20

* Ongoing CR versus non-ongoing CR; *P* values calculated using Fisher's exact test.
† *P* value calculated using the *t* test from 100 bootstrap samples.

Biol Blood Marrow Transplant 26 (2020) 26–33
ELSEVIER
Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org
ASTCT

Cellular Therapy

Late Events after Treatment with CD19-Targeted Chimeric Antigen Receptor Modified T Cells

Ana Cordeiro[1,2], Evandro D. Bezerra[3], Alexandre V. Hirayama[1], Joshua A. Hill[1,3], Qian V. Wu[4], Jenna Voutsinas[4], Mohamed L. Sorror[1,3], Cameron J. Turtle[1,3,5], David G. Maloney[1,3,5], Merav Bar[1,3,*]

Beyond 90 days after CAR-T cell infusion—in patients who survived at least 1 year after therapy.

During the longitudinal care of CAR T cell patients, it is of great importance that clinicians increase their awareness of the long-term complications associated with CD19 CAR T cells.

Infectious and neurologic/psychiatric events that can arise months to years after CAR T therapy are a concern.

10:30 – 12:00 **I CAR-T NELLA TERAPIA DEI LINFOMI**

Introduzione	*M. Luppi*
Quali sono i pazienti candidabili?	*B. Casadei*
I risultati ottenuti	*C. Pellegrini*