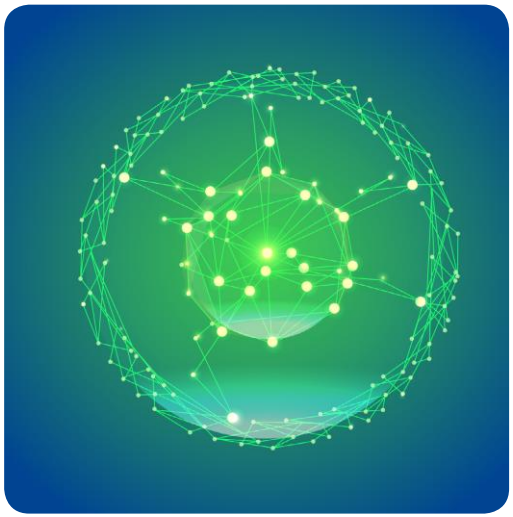


PALERMO

POLICLINICO "PAOLO GIACCONE"
AULA DELL'ACCADEMIA
DELLE SCIENZE MEDICHE
Via del Vespro, 129

3 LUGLIO 2019

ROAD MAP CAR-T

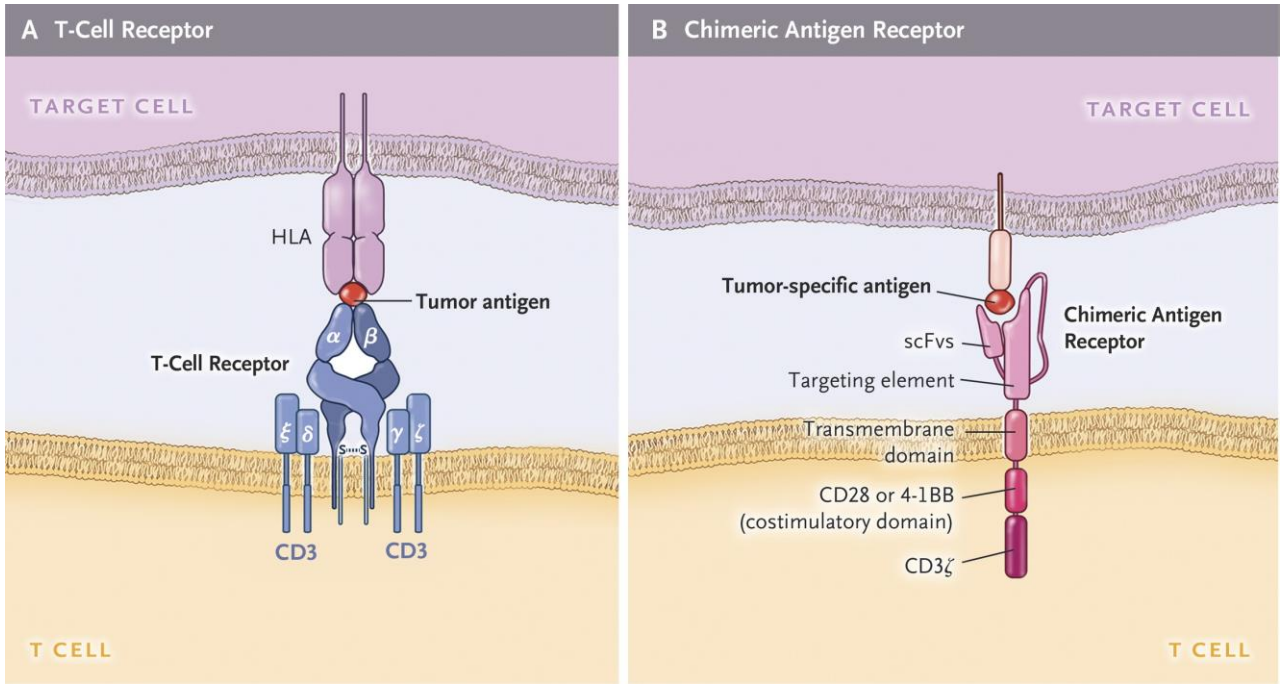
PROSPETTIVE ATTUALI E FUTURE DELL'USO DELLE CAR-T IN ITALIA

2019 MOTORE SANITÀ
Gestire il Cambiamento

Dai dati scientifici alle prospettive di cura

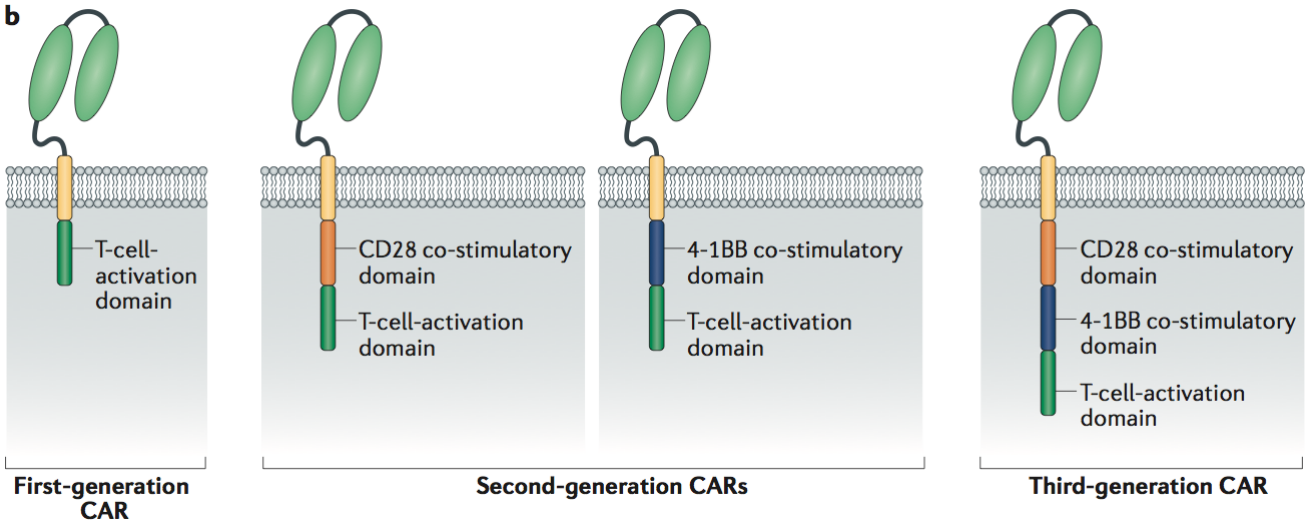
Maurizio Musso
UO Oncoematologia e TMO
Dipartimentto Oncologico La Maddalena
Palermo

Struttura di CARs e T-Cell Receptors

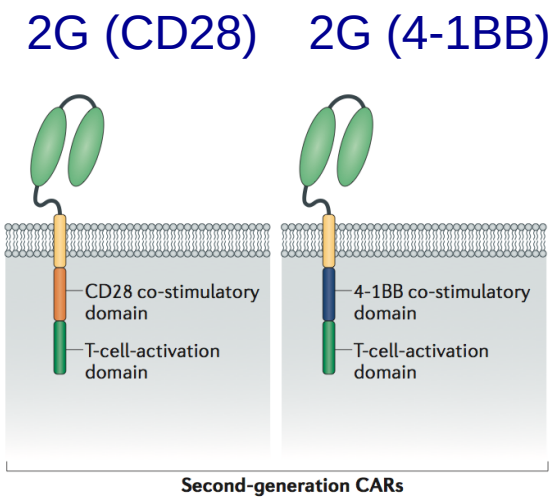


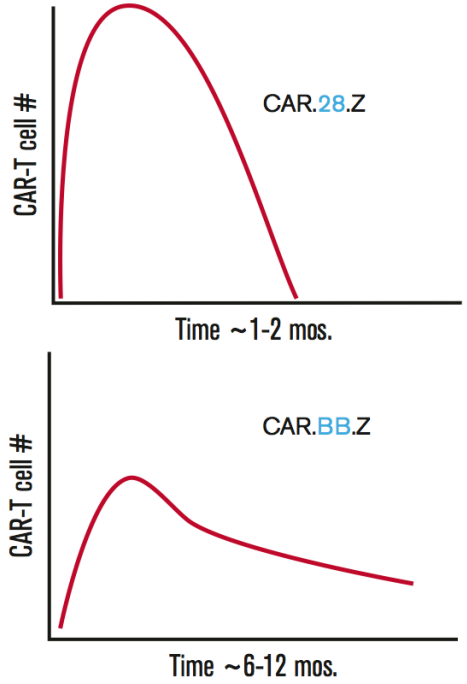
June CH, Sadelain M. N Engl J Med 2018

CAR generations



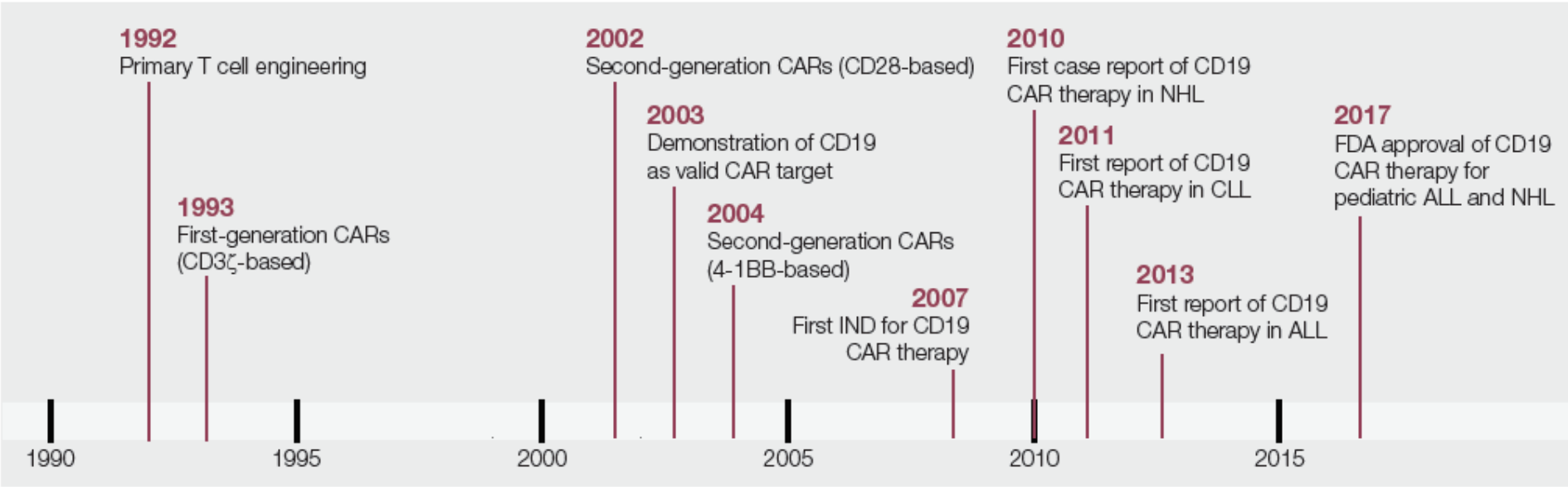
CD28 *versus* 41BB co-stimulation

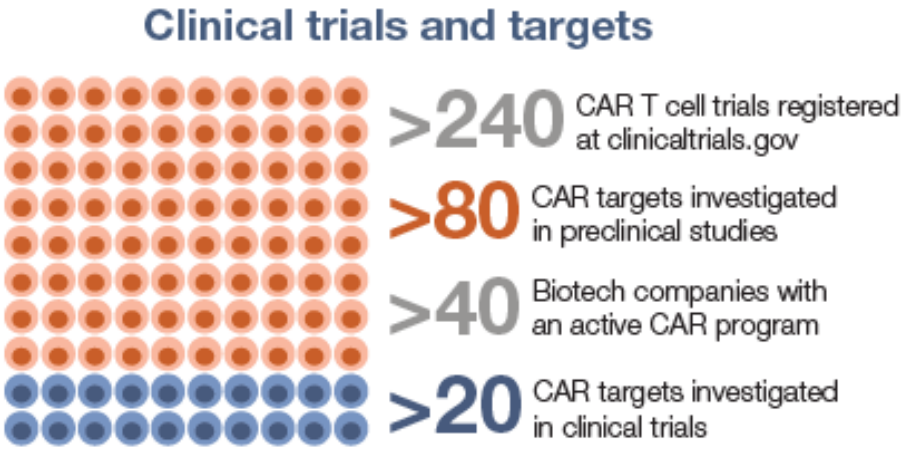




Davis, Blood Advances 2016

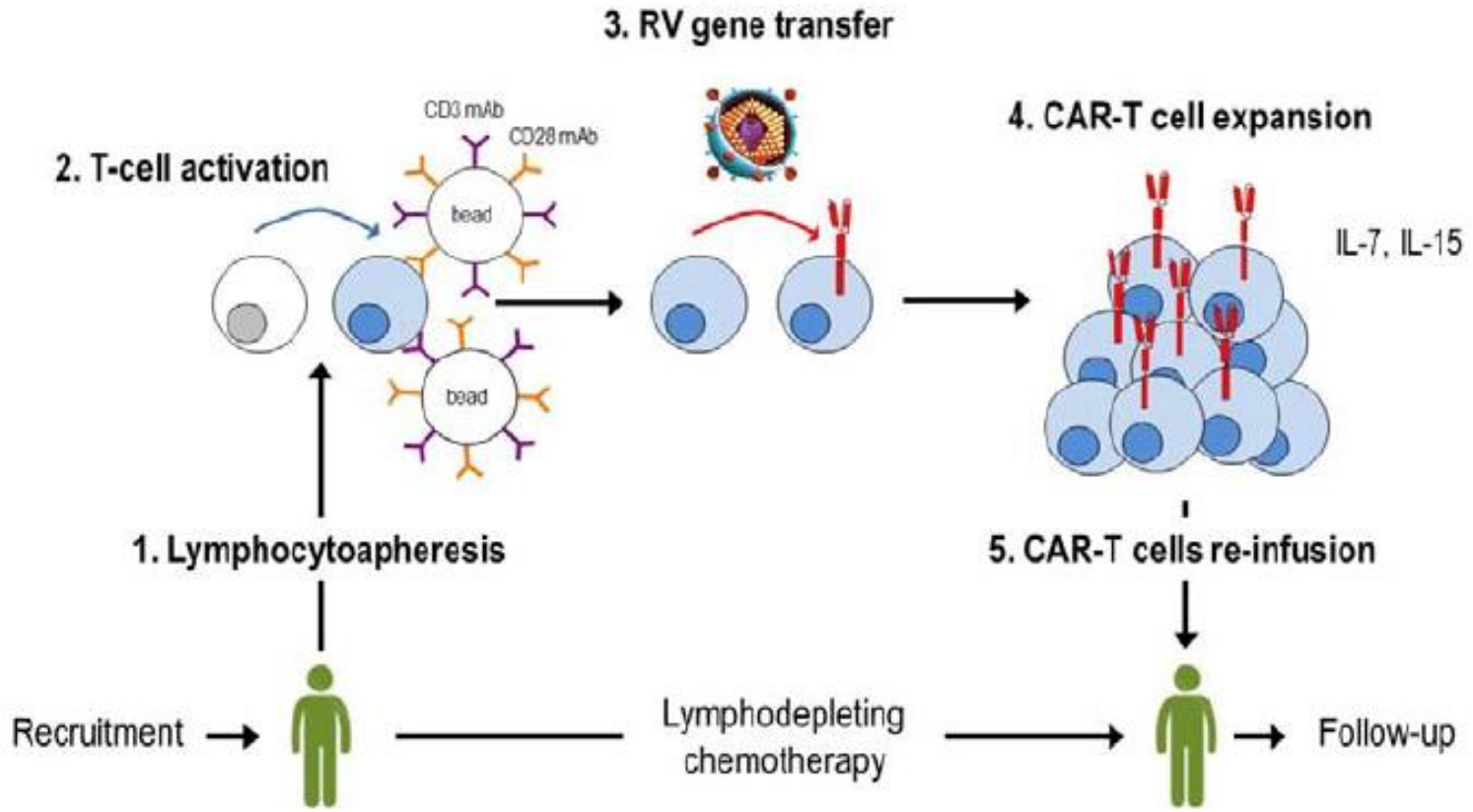
Iter di sviluppo ed approvazione CAR-CD19

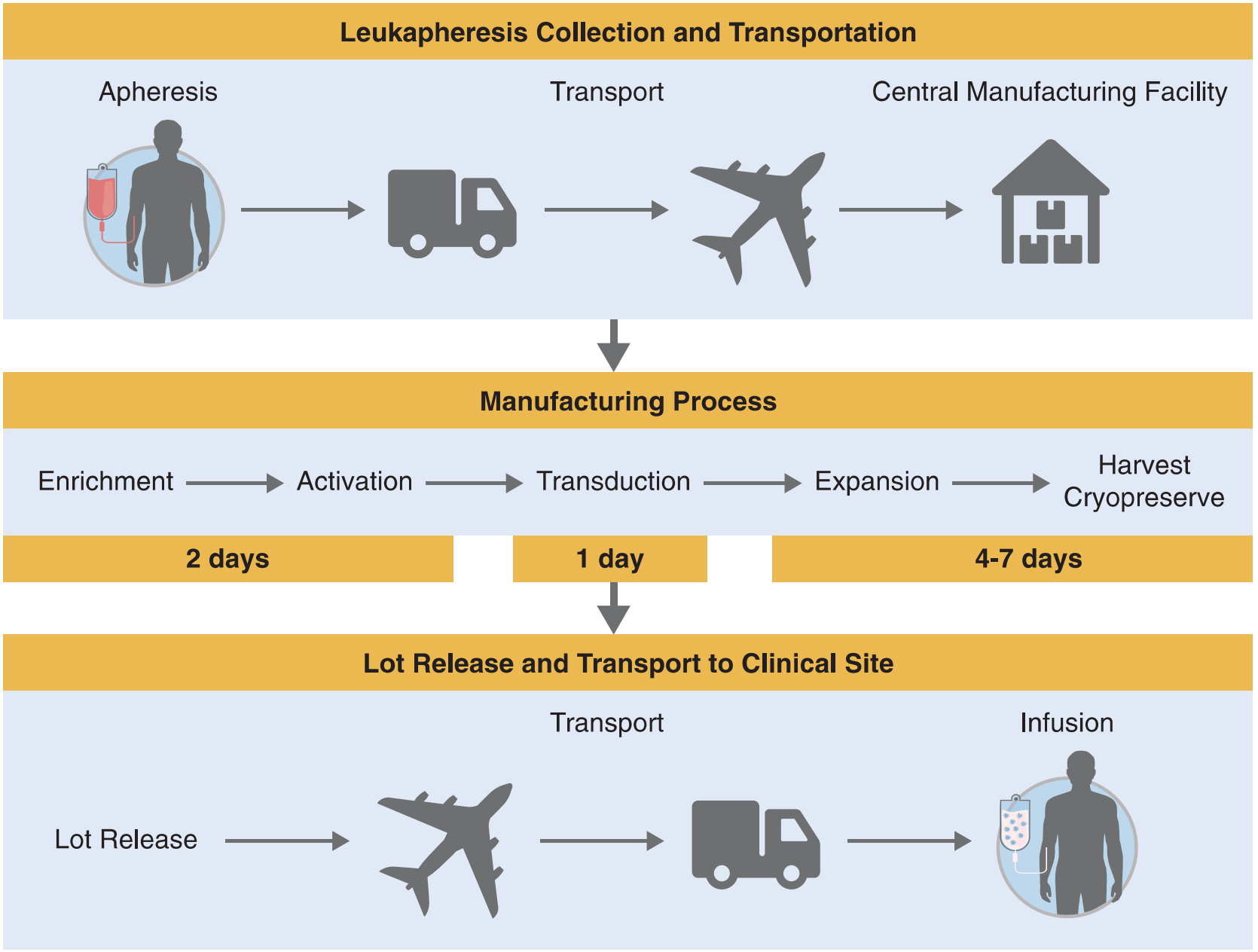




Sadelain M, Cell 2017

CAR-T: Overview del processo




Leukapheresis Collection and Transportation
Apheresis
Transport
Central Manufacturing Facility
Manufacturing Process
Enrichment
Activation
Transduction
Expansion
Harvest
Cryopreserve
2 days
1 day
4-7 days
Lot Release and Transport to Clinical Site
Transport
Infusion
Lot Release

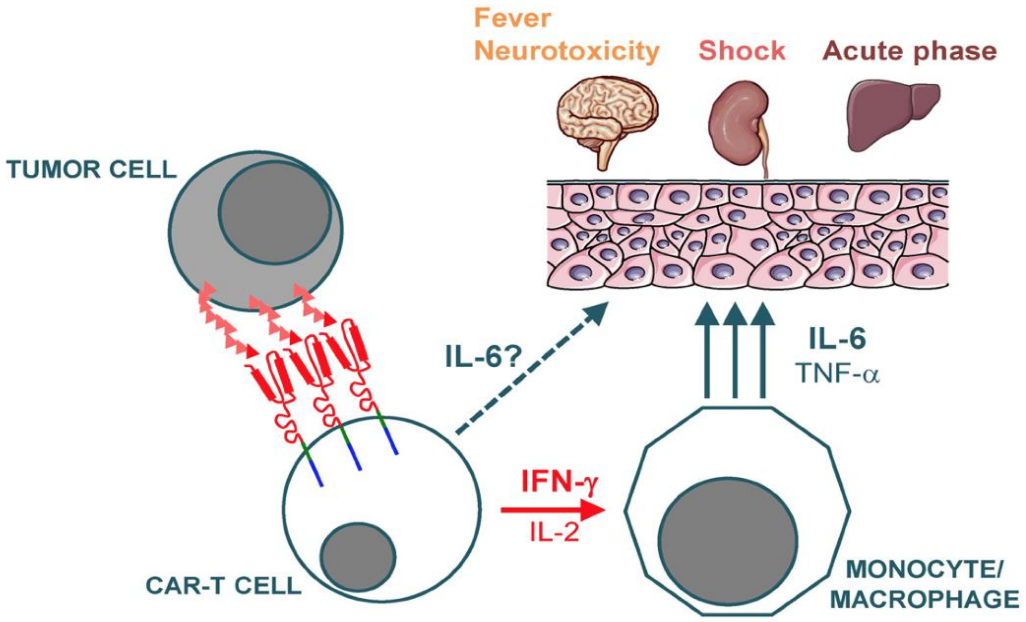
CAR-T On-Target/Off-Tumor Toxicity

- ✓ Depends on the target antigen distribution
- ✓ CAR-T might be very dangerous versus widespread antigens or selectively eliminate subpopulation with differential expression of the antigen
- ✓ Can be very severe and unpredictable
- ✓ RISKS related to step directly from mice to humans: balance clinical need vs risk

CAR-T: toxicities

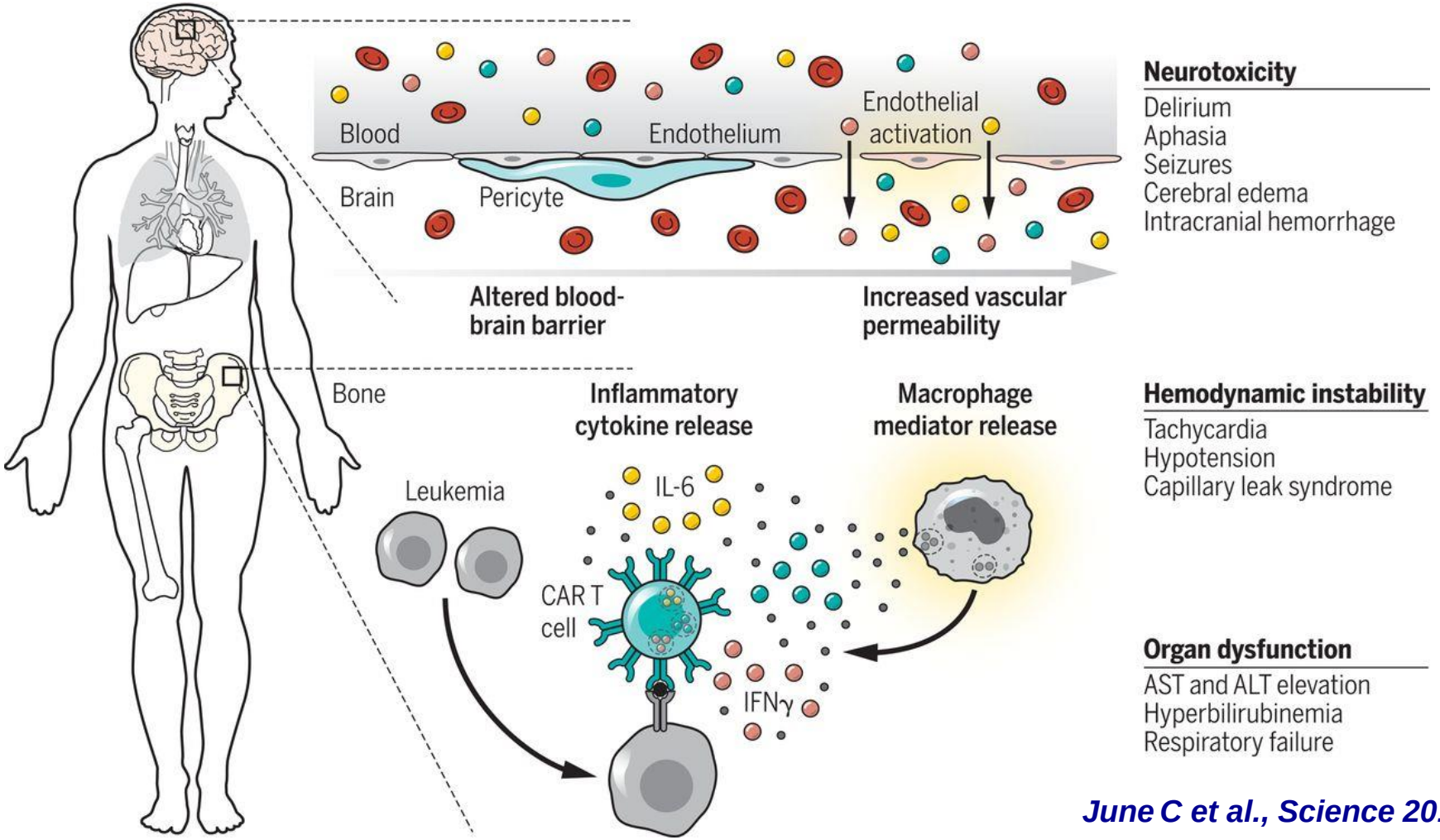
- ✓ Cytokine Releasing Syndrome (CRS)
- ✓ CAR T cell related encephalopaty syndrome (CRES)
- ✓ On target /off tumor Toxicities
- ✓ Off target Toxicities
- ✓ Allergic reactions and Tumor Lysis Syndrome (TLS)
- ✓ Infectious complications
- ✓ Insertional Oncogenesis

Cytokine Release Syndrome



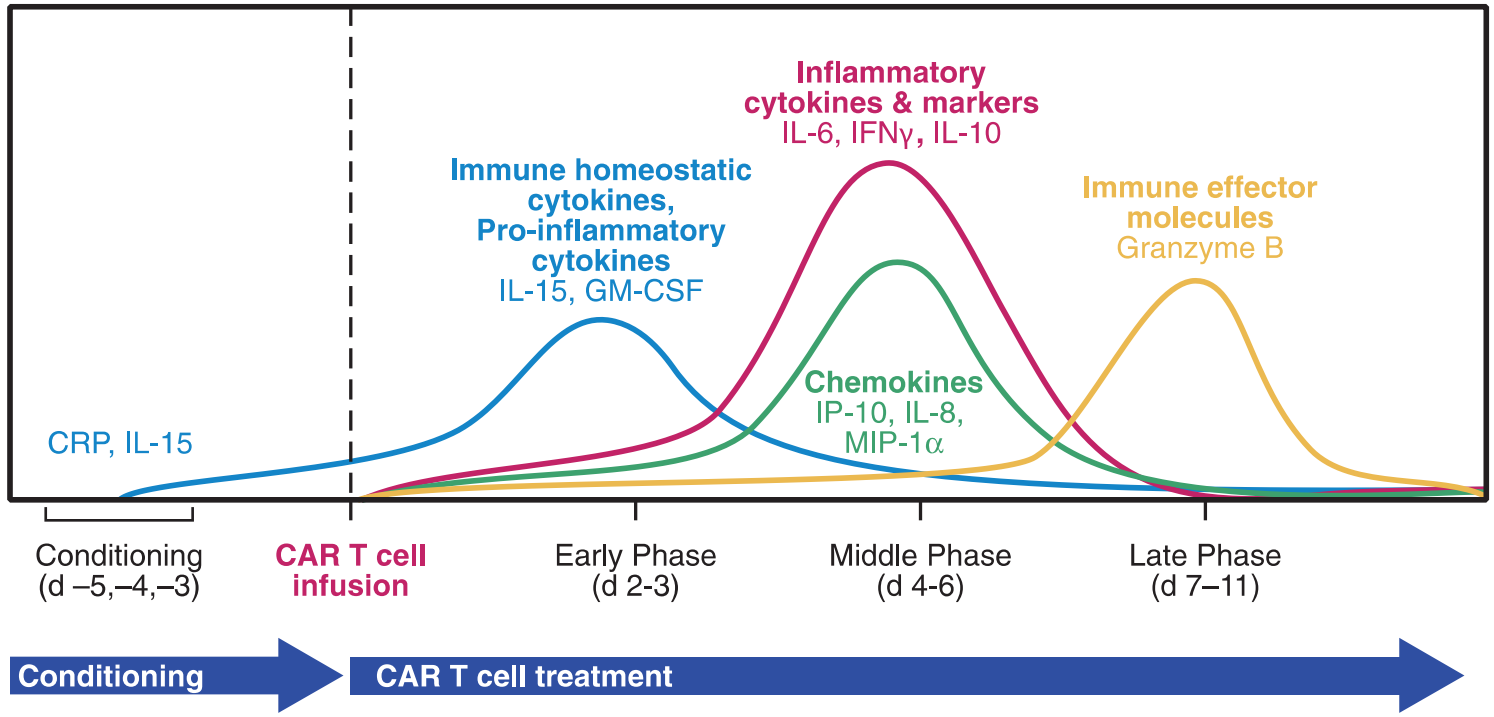
Soluble mediators in CART cells and toxicities

Macrophages and other innate immune cells become activated and contribute to the release of soluble mediators.
CAR T cells are routinely observed in cerebral spinal fluid, and the cytokines may increase permeability to soluble mediators.



June C et al., Science 2018

Kinetics of key cytokines and chemokines during CAR-T cell therapy



Roberts ZJ et Al Leukemia & Lymphoma 2017

Cytokine Release Syndrome

- ✓ Rapid inflammatory reaction (within the first 2-3 weeks)
- ✓ High fever, hypotension, hypoxia and multi-organ toxicity
- ✓ Potentially life-threatening
- ✓ C-reactive protein (CRP) and IL-6 elevations
- ✓ Ameliorated by tocilizumab (anti-IL-6R mAb)
- ✓ More frequent in patients with an high tumor burden

Therapeutics and Clinical Risk Management

Dovepress
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REVIEW

Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

Lara L Riegler[1]
Gavin P Jones[2]
Daniel W Lee[1]

[1]Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Virginia, Charlottesville, VA, USA; [2]School of Medicine, University of Virginia, Charlottesville, VA, USA

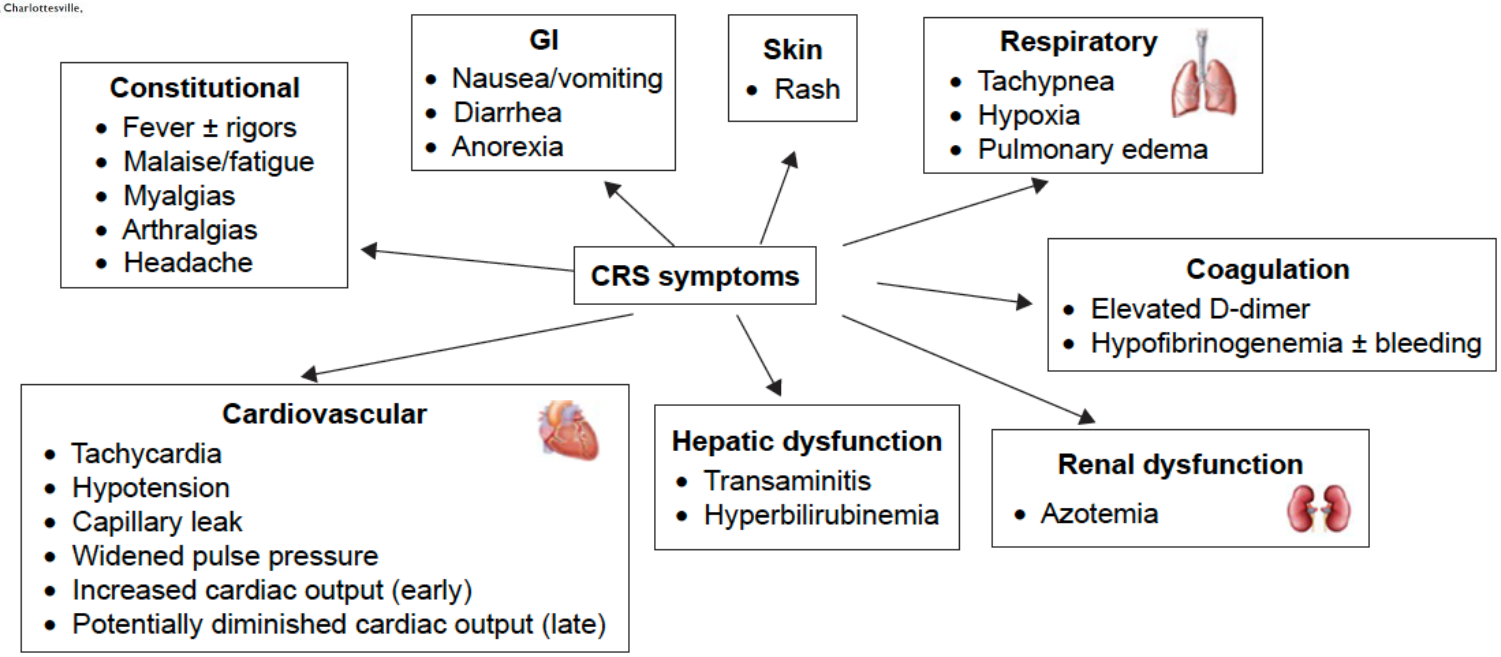


Figure 1 Symptoms of CRS.

Notes: CRS affects a number of organ systems. It requires fever at a minimum but is frequently associated with any of the symptoms shown. Additional manifestations may also rarely occur.

Abbreviations: GI, gastrointestinal; CRS, cytokine release syndrome.

Biology of Blood and Marrow Transplantation
journal homepage: www.bbmt.org

ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells

Daniel W. Lee[1,#], Bianca D. Santomasso[2,#], Frederick L. Locke[3], Armin Ghobadi[4], Cameron J. Turtle[5], Jennifer N. Brudno[6], Marcela V. Maus[7], Jae H. Park[8], Elena Mead[9], Steven Pavletic[6], William Y. Go[10], Lamis Eldjerou[11], Rebecca A. Gardner[12], Noelle Frey[13], Kevin J. Curran[14], Karl Peggs[15], Marcelo Pasquini[16], John F. DiPersio[4], Marcel R.M. van den Brink[8], Krishna V. Komanduri[17], Stephan A. Grupp[18,*], Sattva S. Neelapu[19,**]

Table 5 2018 CRS consensus grading by Lee et al[30]

Grade 1	Fever[a] ≥38°C
Grade 2	Fever[a] ≥38°C with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula or blow-by oxygen
Grade 3	Fever[a] ≥38°C with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, non-rebreather mask, or Venturi mask not attributable to any other cause
Grade 4	Fever[a] ≥38°C with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation) not attributable to any other cause
Grade 5	Death

Notes: [a]Fever is defined as temperature ≥38°C. In patients who have CRS then receive tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
Abbreviations: CRS, cytokine release syndrome; CPAP, continuous positive airway pressure; BiPAP, bilevel positive airway pressure.

Biology Blood and Marrow Transplantation 2019

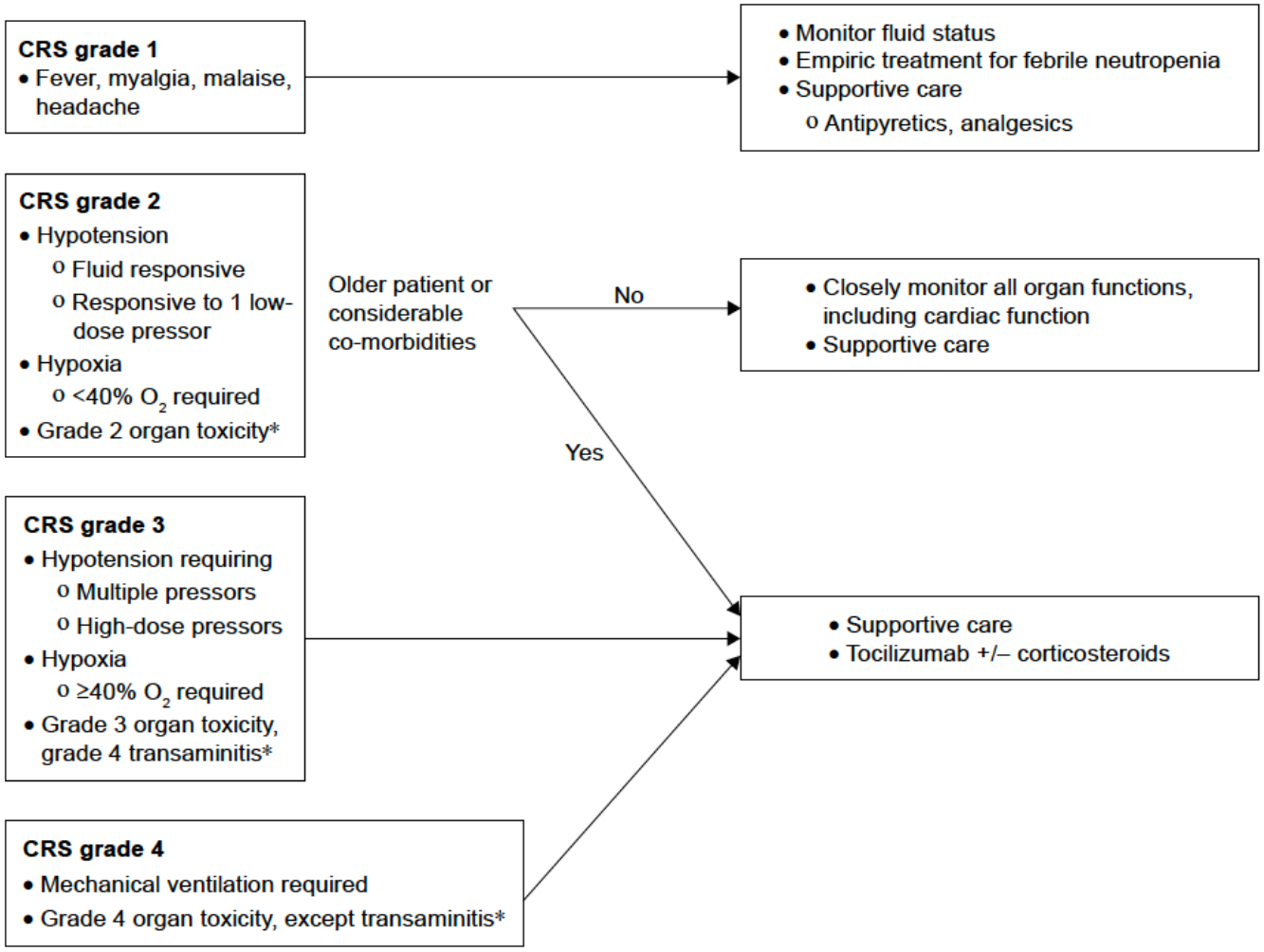
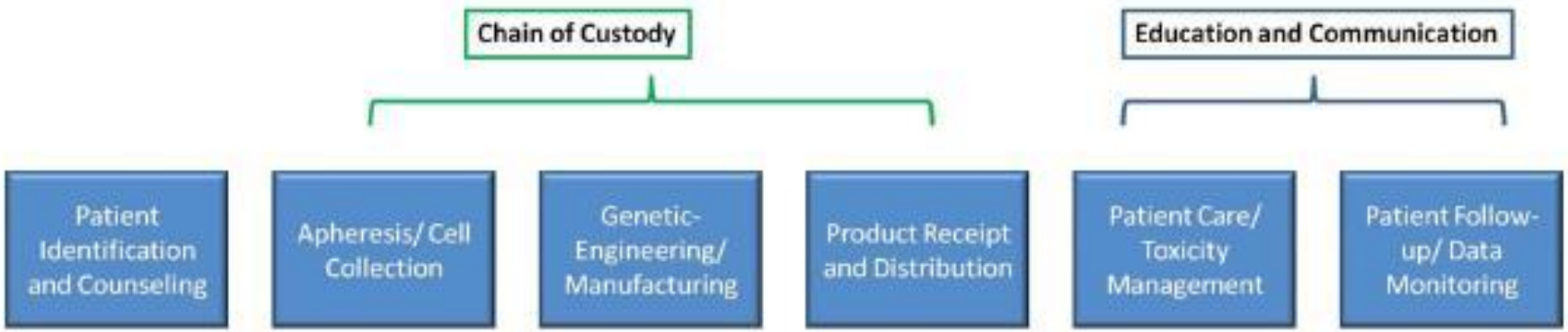


Figure 3 CRS management algorithm by Lee et al.[9]

Notes: The Lee criteria were designed in such a way so that grading can be tied to a management algorithm. Supportive care is the backbone of therapy with anti-cytokine therapy in the form of tocilizumab with or without corticosteroids implemented for grade 3 or higher CRS or for grade 2 in high-risk patients. *Grade of organ toxicities determined by CTCAE v4.03.

Abbreviations: CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.



Maus MV and Nikiforow S.
J Immunother Cancer, 2017

PATIENT SAFE

PATIENT SAFE

ARRUOLAMENTO PZ

LEUCAFERESI

CRIOPRESERVAZIONE

TRASPORTO A T° CONTROLLATA

TRATTAMENTO PZ

PRESA IN CARICO
STOCCAGGIO TEMPORANEO
SCONGELAMENTO

TRASPORTO A T° CONTROLLATA

UNITÀ CLINICA

UNITÀ RACCOLTA

UNITÀ PROCESSAZIONE

PATIENT SAFE

Immune Effector Cells: Quali Standard di riferimento?

FACT Common Standards for Cellular Therapies, First Edition

- Standards common to any type of cellular therapy
- Requirements within included in other sets of Standards
- Associated accreditation applies to programs *not* performing hematopoietic cell transplantation or immune effector cell therapy

FACT Standards for Immune Effector Cells, First Edition

- Common Standards + Immune Effector Cell-Specific Standards
- Apply to programs *only* performing immune effector cell therapy

FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration, Edition 7.0

- HCT Standards + Immune Effector Cell-Specific Standards
- Apply to transplant units that may or may not administer immune effector cells

AGENZIA ITALIANA DEL FARMACO

Ufficio Segreteria Organismi Collegiali

Roma,

Direzione Generale AIFA
SEDE

Oggetto: Criteri individuati dalla CTS ai fini dell'individuazione dei centri prescrittori delle terapie CAR-T

Come richiesto, si trasmette il parere espresso dalla Commissione Tecnico–Scientifica (CTS) relativo ai centri in oggetto, così come emendato nella seduta del 3-5 aprile 2019.

La CTS ha ritenuto utile sottolineare, innanzitutto, che la scelta dei Centri clinici che potranno essere sottoposti alla qualifica da parte delle ditte spetta necessariamente alle Regioni. A tal fine, la Commissione ritiene opportuno proporre i seguenti criteri minimi, che ovviamente dovranno affiancarsi alle autorizzazioni previste per legge:

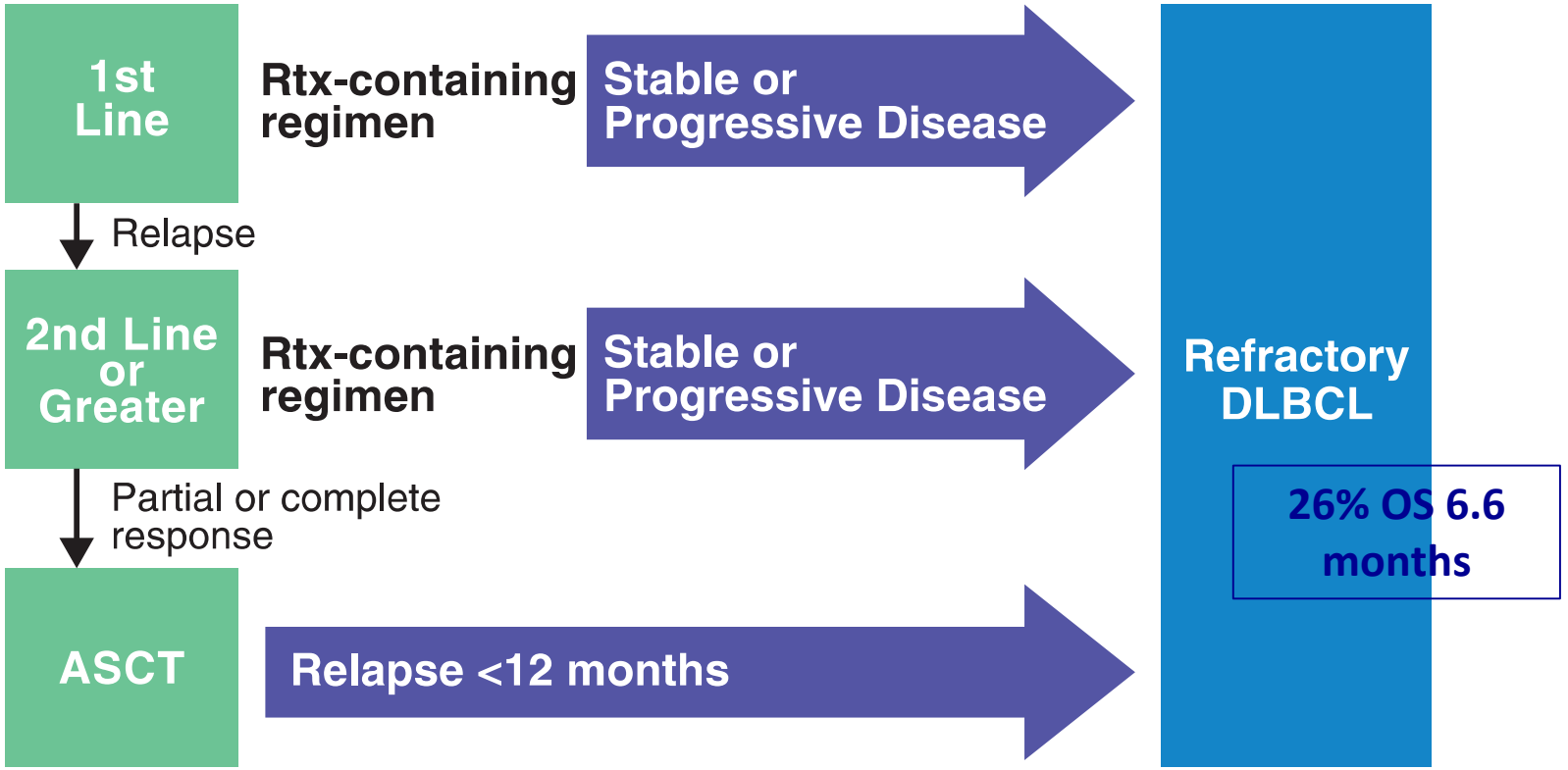
- Certificazione del Centro Nazionale Trapianti in accordo con le Direttive EU;
- Accreditamento JACIE per trapianto allogenico comprendente unità clinica, unità di raccolta ed unità di processazione;
- Disponibilità di un'unità di Terapia Intensiva e rianimazione;
- Presenza di un team multidisciplinare adeguato alla gestione clinica del paziente e delle possibili complicanze.

Si rimane a disposizione per ogni ulteriore informazione necessaria.

Il Dirigente
Alessandra Dell'Utri

CAR-T for Refractory NHL

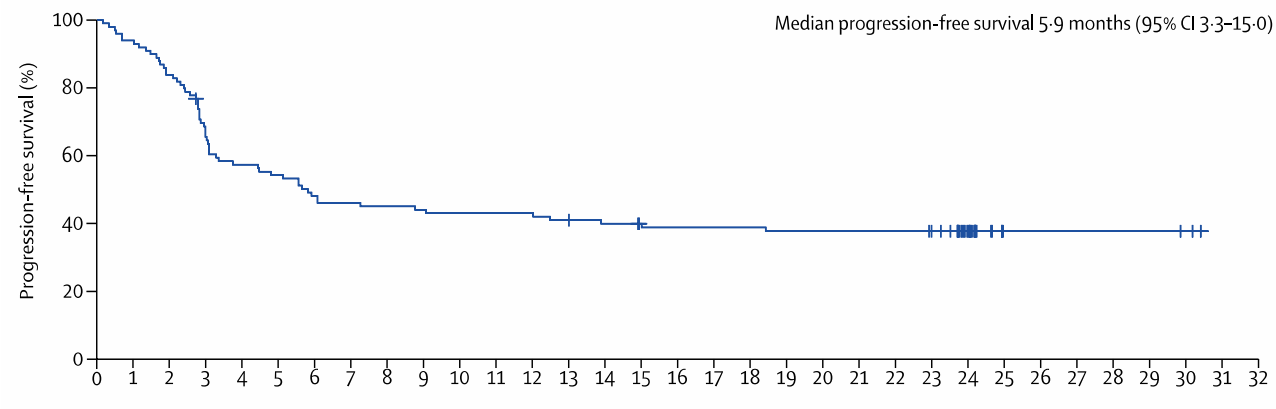
Treament schema and outcomes for refractory DLBCL

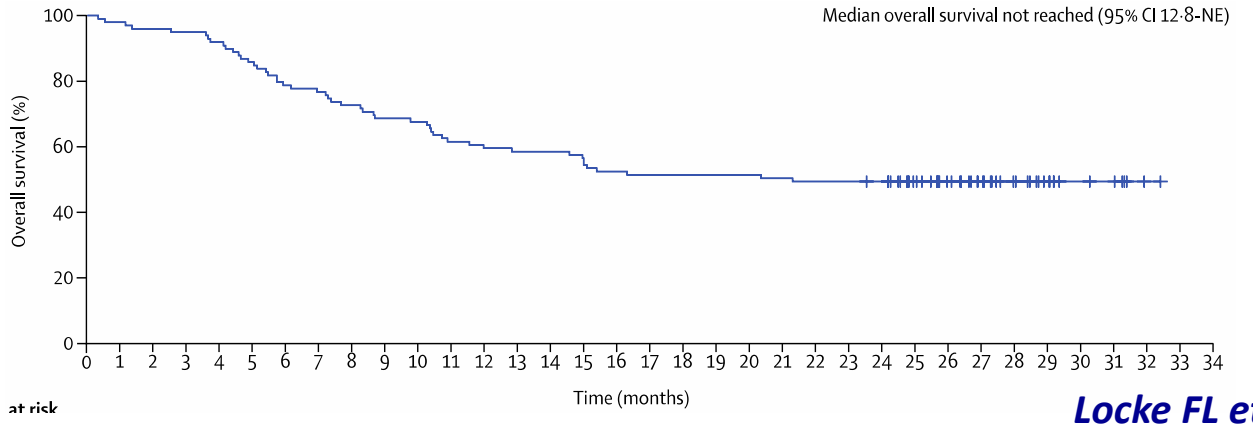


Roberts ZJ et Al Leukemia & Lymphoma 2017

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 Wiezorek, Lynn Navale, Allen Xue, Yizhou Jiang, Adrian Bot, John M Rossi, Jenny J Kim, William Y Go, Sattva S Neelapu**



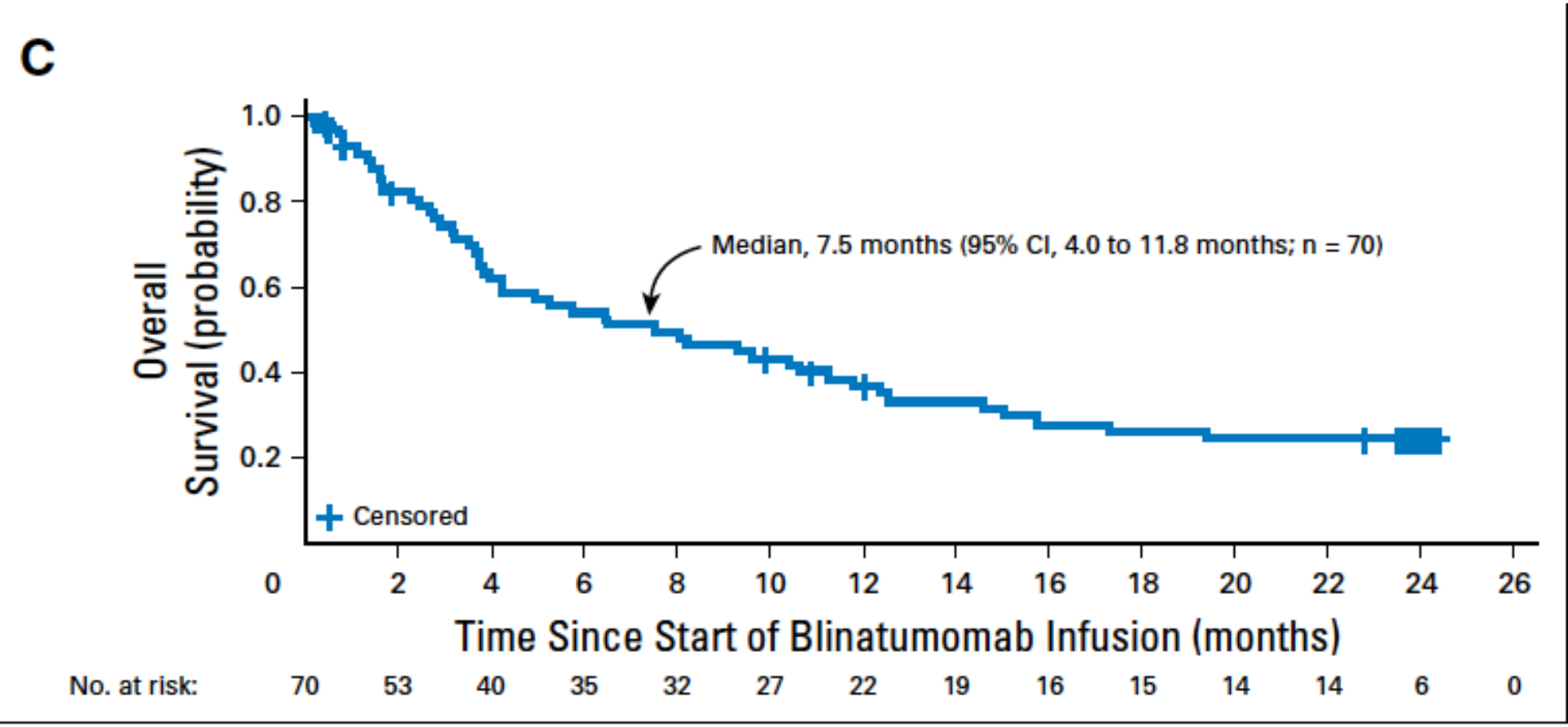


at risk

Locke FL et Al Lancet Oncol 2018

CAR-T in ALL

OS in Pediatric Relapsed/Refractory ALL

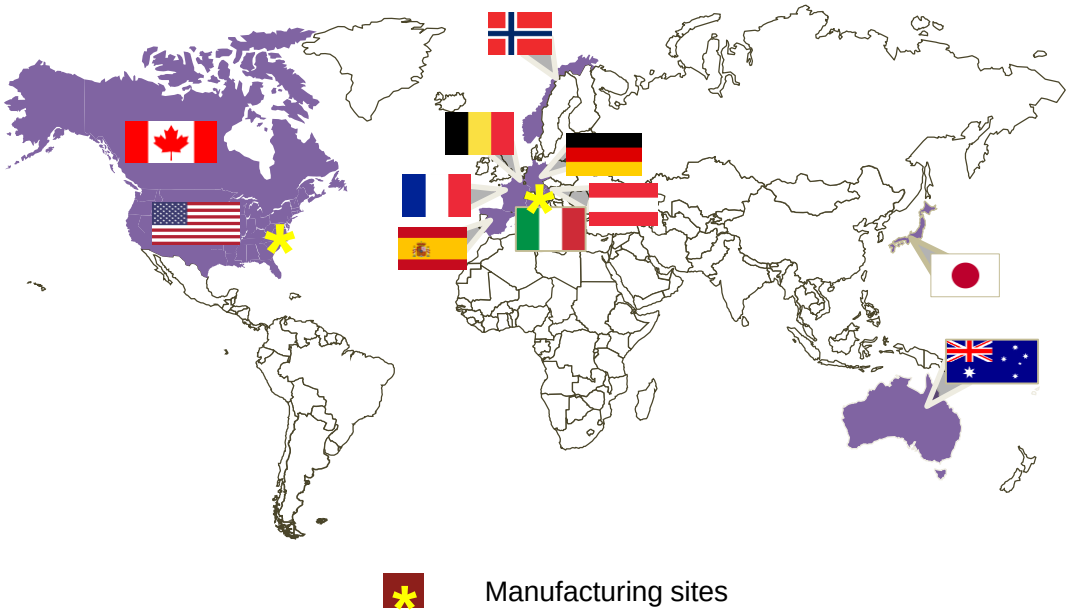


Von Stackleberg et al, JCO 2016

ELIANA: Pivotal Phase 2 Study

ELIANA is the first global, multicenter trial of CAR T-cell therapy

- ✓ Tisagenlecleucel was produced at a central manufacturing site with global distribution
- ✓ 25 sites across 11 countries in North America, Europe, and Asia-Pacific



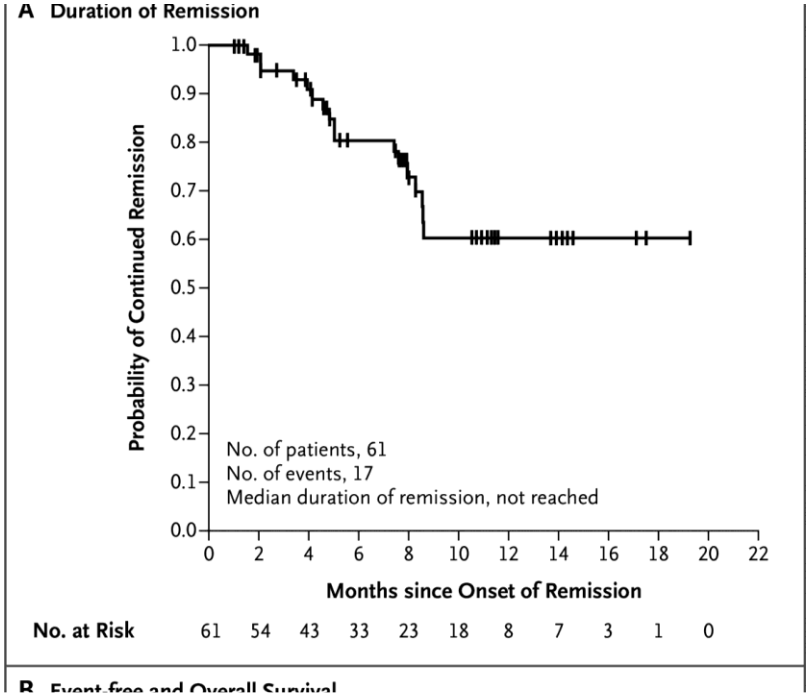
Maude SL et al. NEJM 2018

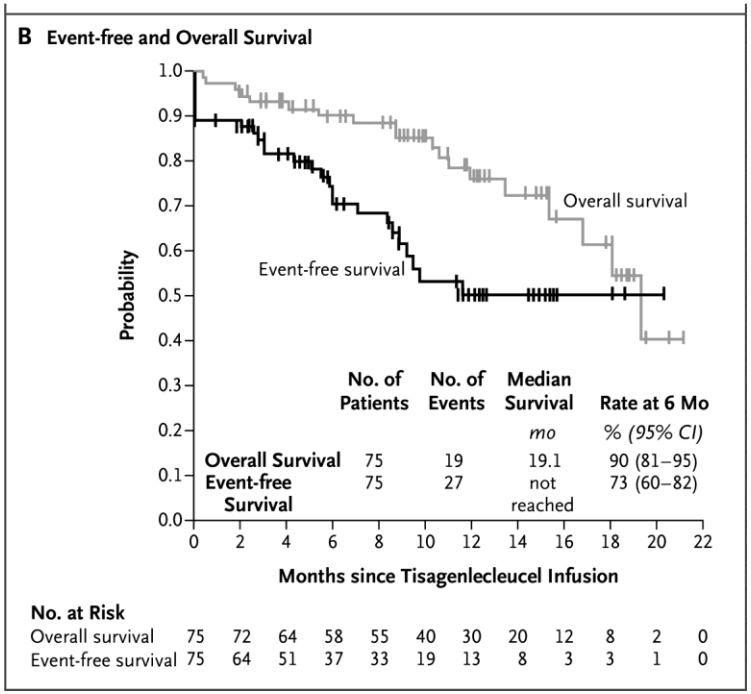
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Maude SL et al., N Engl J Med. 2018 Feb 1;378(5):439-448





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 Santomasso, 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.

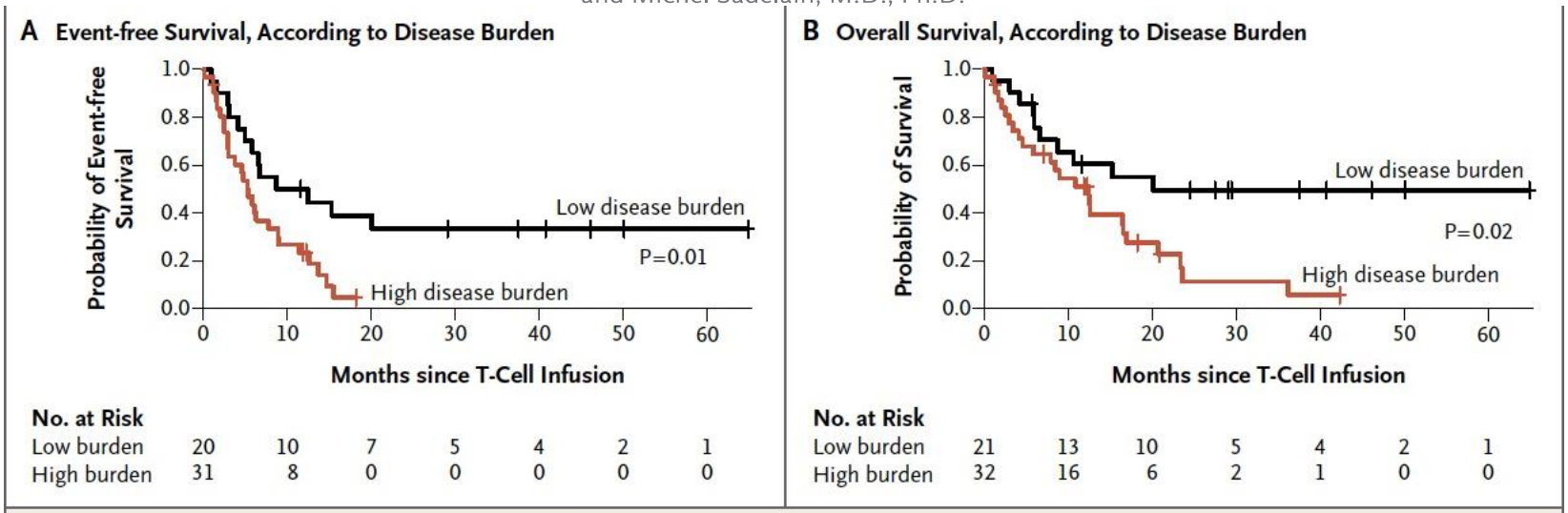


Figure 4. Event-free Survival and Overall Survival, According to Pretreatment Disease Burden.

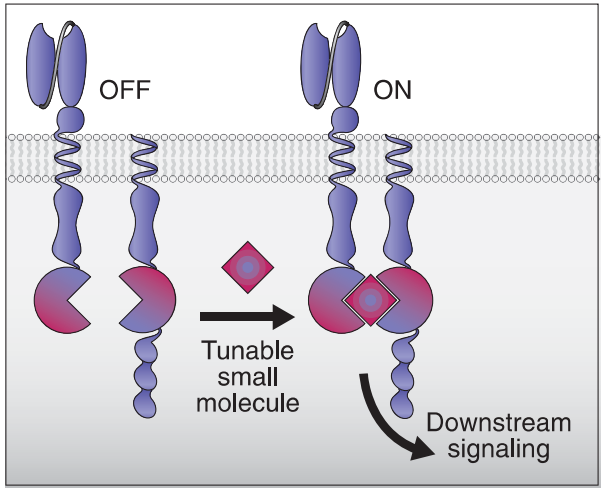
Patients with a low disease burden (<5% bone marrow blasts) at the time of T-cell infusion had significantly longer event-free survival (Panel A) and overall survival (Panel B) than did those with a high disease burden (≥5% bone marrow blasts or extramedullary disease). The median event-free survival among patients with a low disease burden was 10.6 months (95% CI, 5.9 to not reached), as compared with 5.3 months (95% CI, 3.0 to 9.0) among patients with a high disease burden (P=0.01). The median overall survival among patients with a low disease burden was 20.1 months (95% CI, 8.7 to not reached), as compared with 12.4 months (95% CI, 5.9 to 20.7) among those with a high disease burden (P=0.02).

Adapted from Park, *NEJM* 2018.

Next Generation CAR Products

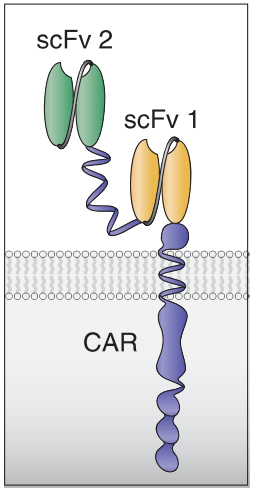
Switch CAR T Cells

CAR interaction with a small molecule switch allows for control of CAR T cell activity



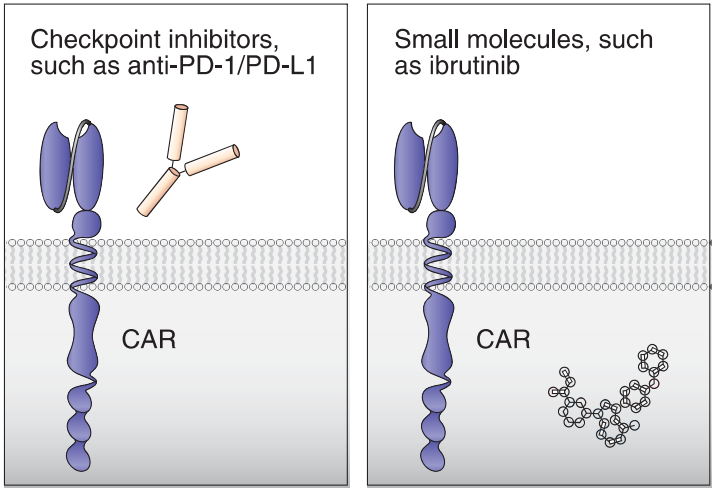
Bispecific CAR T Cells

Target multiple tumor antigens to potentially reduce tumor escape



Combination Therapies

Rational combination of CAR T cells with novel agents to target multiple cancer pathways



Roberts ZJ et Al Leukemia & Lymphoma 2017

Rapidly Evolving CAR-T Landscape