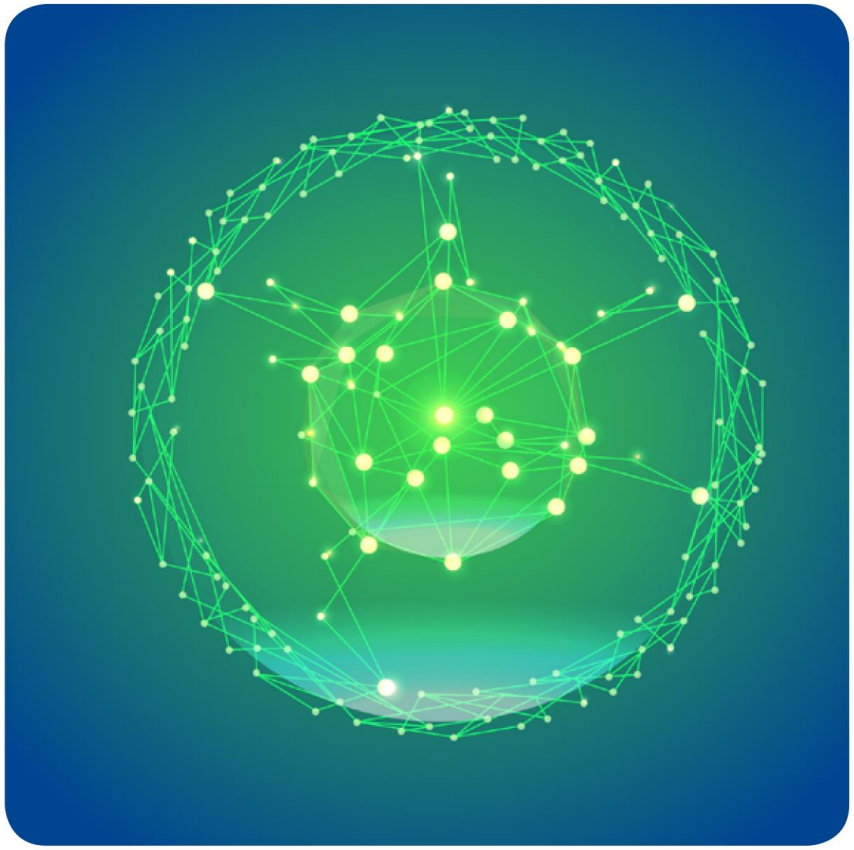


Con il patrocinio di

AReSS Agenzia Regionale per la Salute ed il Sociale Puglia

Rete Ematologica Pugliese

Rete Oncologica Pugliese

**BARI**

**REGIONE PUGLIA**

**DIPARTIMENTO PROMOZIONE DELLA SALUTE**

Via Giovanni Gentile, 52

**16 SETTEMBRE 2019**

## ROAD MAP CAR-T

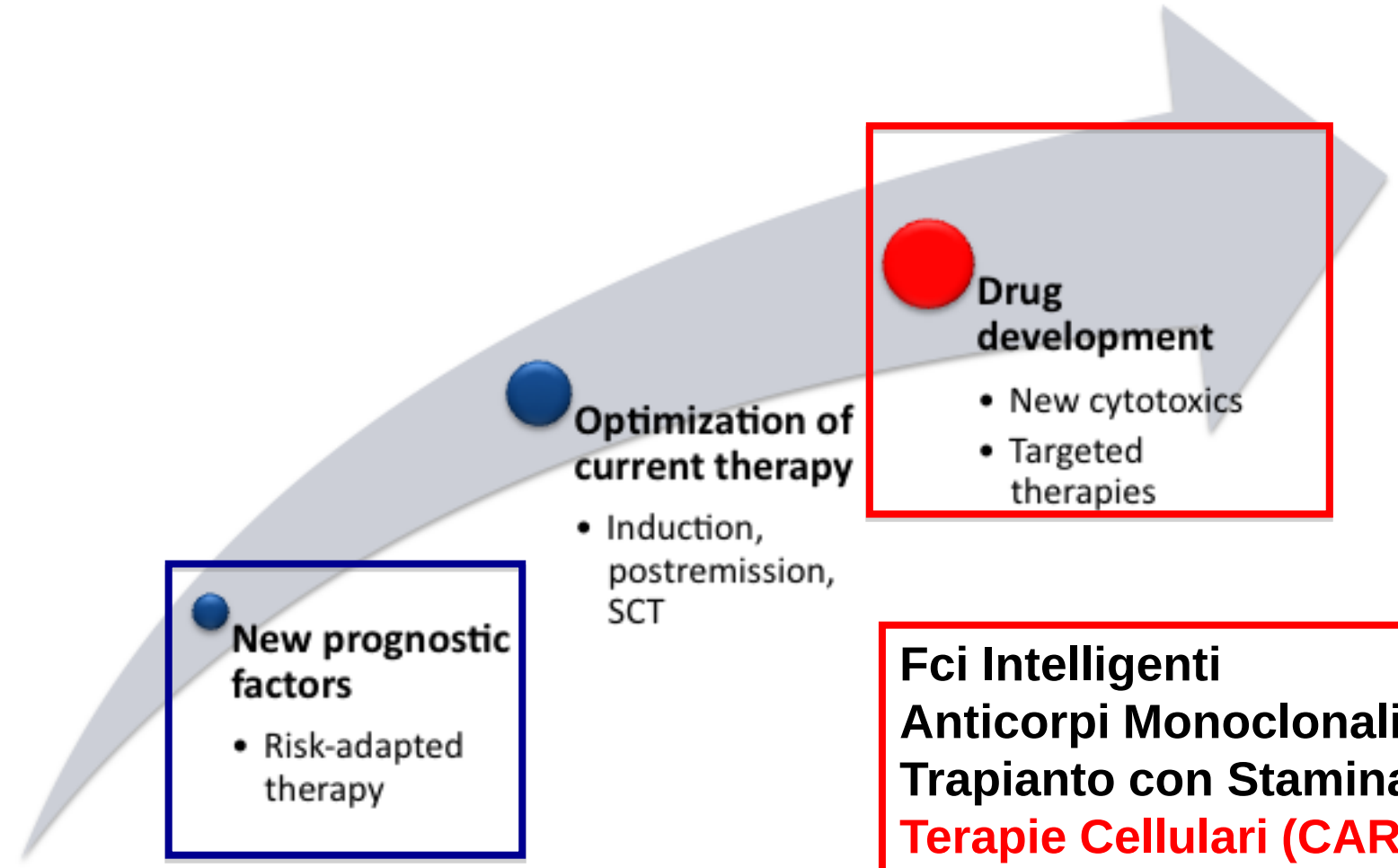
# PROSPETTIVE ATTUALI E FUTURE DELL'USO DELLE CAR-T IN ITALIA

2019 MOTORE SANITÀ Gestire il Cambiamento

## DAI DATI SCIENTIFICI ALLE PROSPETTIVE DI CURA

**PROF.SSA GIORGINA SPECCHIA**

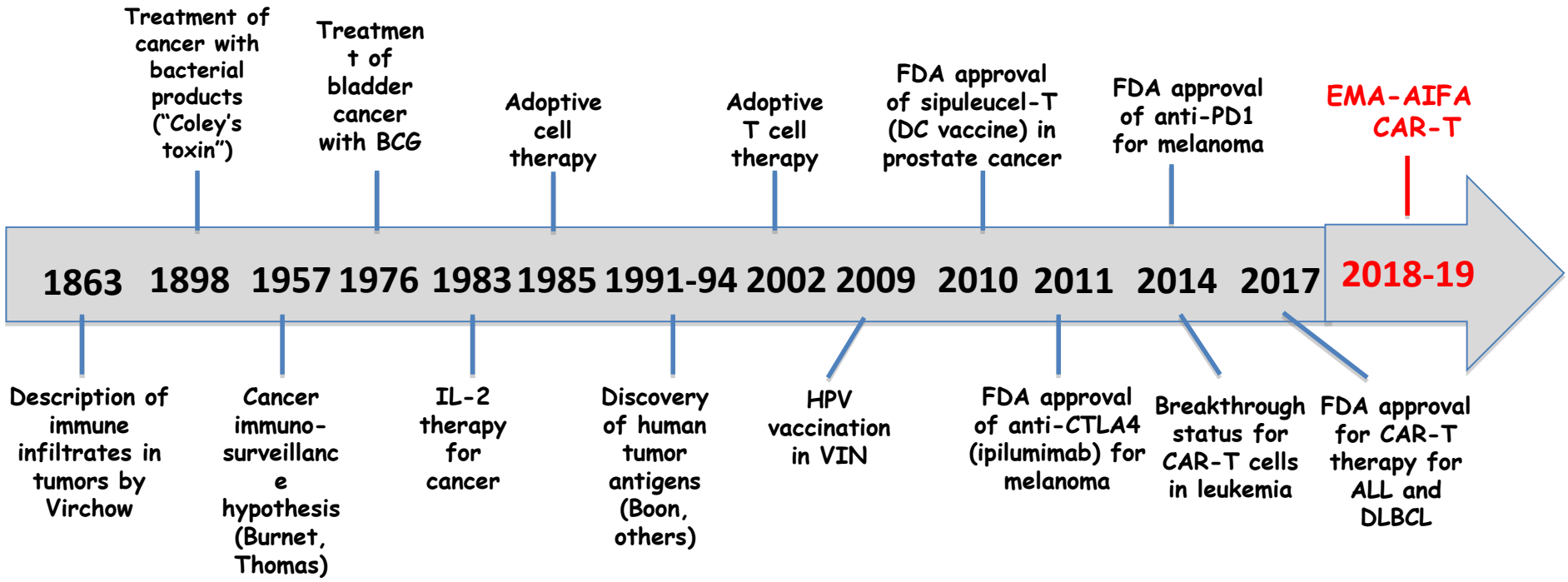
# Cosa è cambiato negli anni in Ematologia




**Biologia della cellula**

**Fci Intelligenti**
**Anticorpi Monoclonali**
**Trapianto con Staminali**
**Terapie Cellulari (CAR-T)**

# STORIA DELLA IMMUNOTERAPIA IN ONCOLOGIA-EMATOLOGIA



# Cellule CAR-T

- **CAR-T** è un acronimo che sta per **Chimeric Antigen Receptor T-cell**

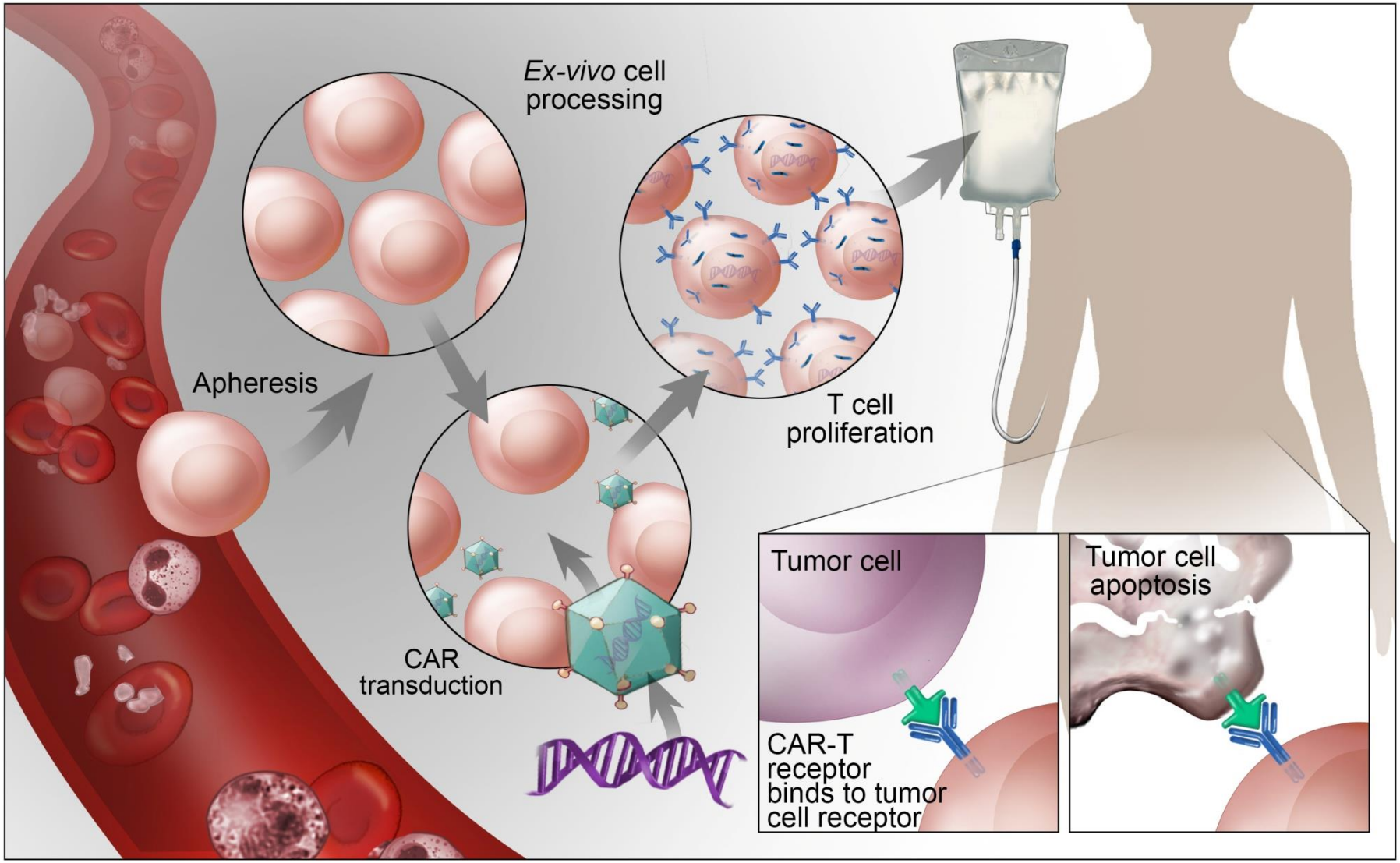
- È il nome della tecnologia, in grado di riprogrammare i linfociti T di un paziente o di un donatore sano per **"riprogrammarli» ad essere in grado di uccidere le cellule tumorali del paziente"**

- **I linfociti T del paziente o di un donatore** vengono prelevati e **geneticamente modificati in laboratorio** in modo da farli diventare capaci di esprimere sulla propria superficie, un **nuovo recettore** in grado di **individuare il tumore e attaccarlo**

- Si parla di **recettori "chimerici"** perché non esistenti in natura e sono sviluppati appositamente in laboratorio a seconda del tumore

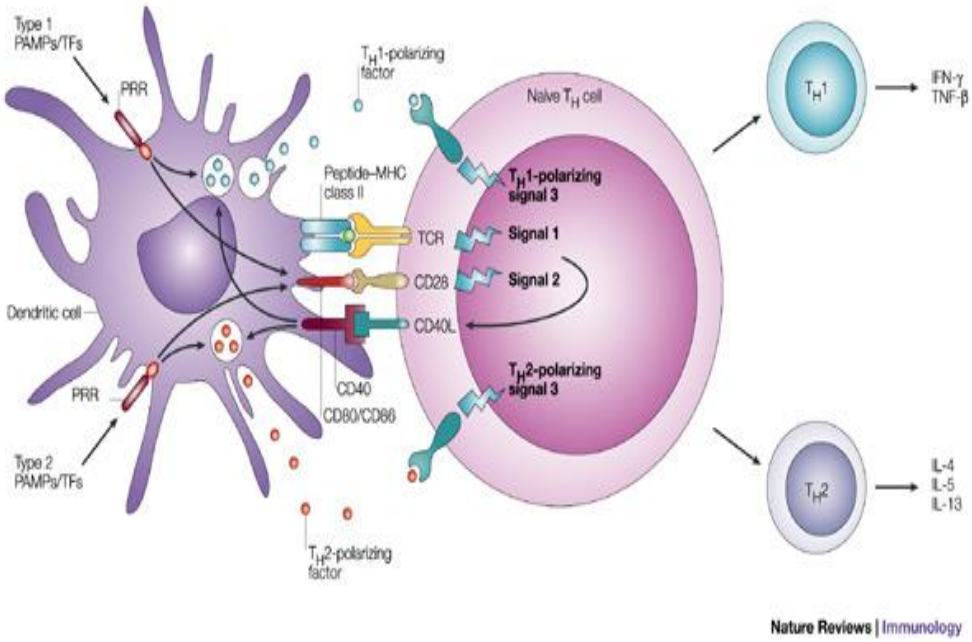
- Nel caso dei primi tumori ematologici il **bersaglio individuato** è una proteina (**chiamata CD19)** espresso da tutte le cellule tumorali di questi pazienti, ma anche dai linfociti B normali

# Le CAR-T sono linfociti del Paziente educati a riconoscere il Tumore

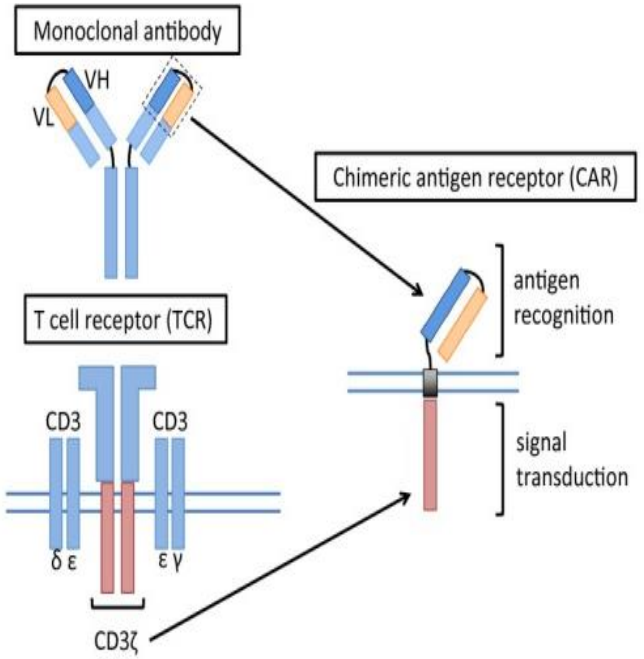


# CAR DESIGN

## Physiologic T-cell activation




## Chimeric Antigen Receptor

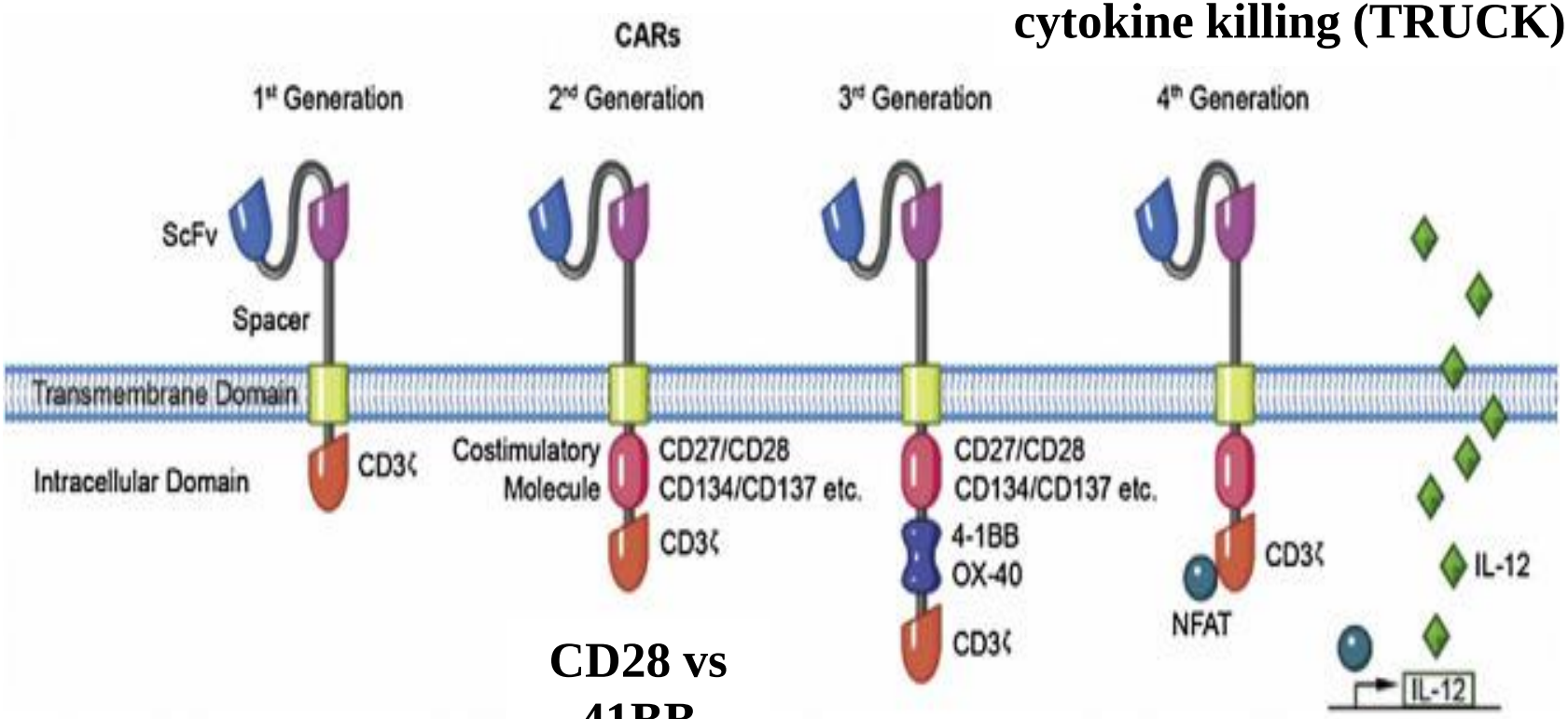



*Makita et al. Cancer Sci 2017*

# GENERATION OF CARs

**Chimeric Antigen Receptor**

**T cell redirected universal cytokine killing (TRUCK)**




**CD28 vs 41BB**

*Smith et al. J Cell Therapy 2016*

# CAR DESIGN: ANTIGEN SELECTION

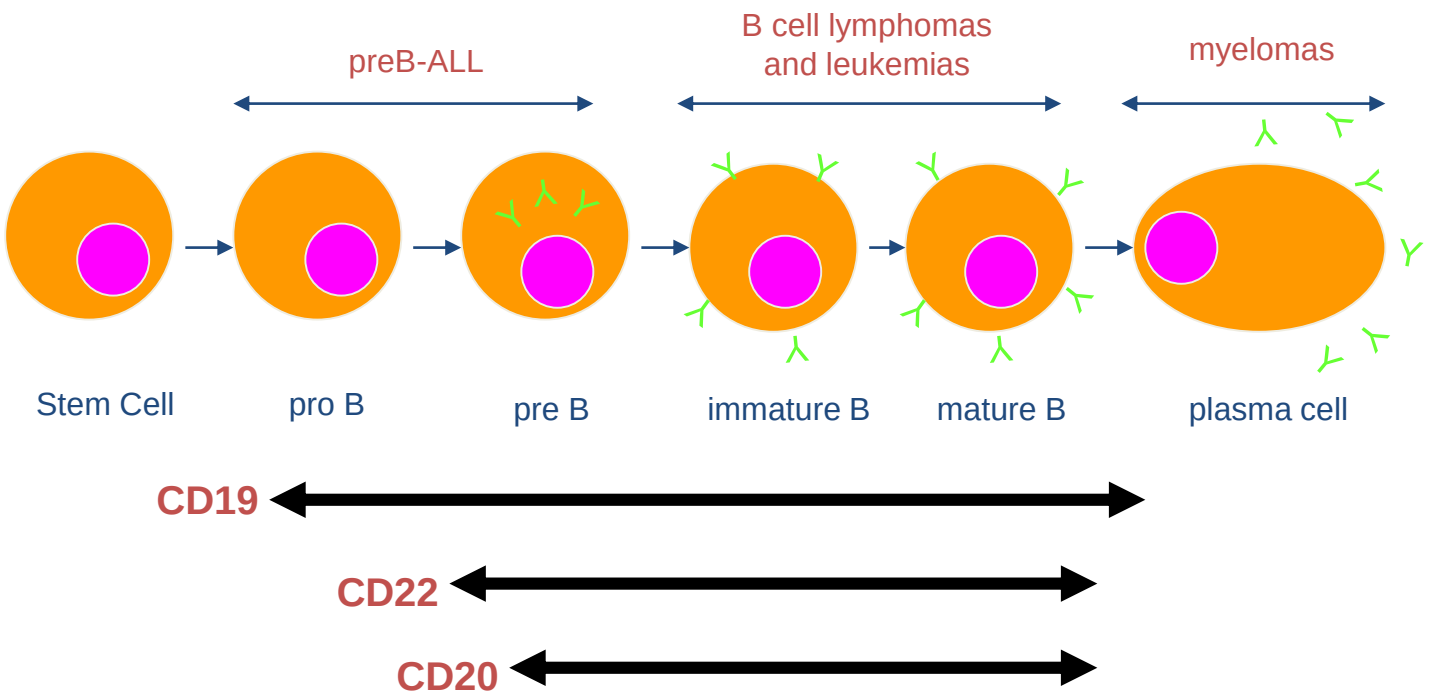
**Ideal Target:**

- **Tumor specific**
- Universally expressed on tumor cells
- Cell surface molecule
- **Expressed only on tumor cells**
  - On target, off-tumor toxicity
  - High binding affinity results in recognition of low antigen expression in normal tissue

**e.g. Pulmonary toxicity with anti-Her2 CART**

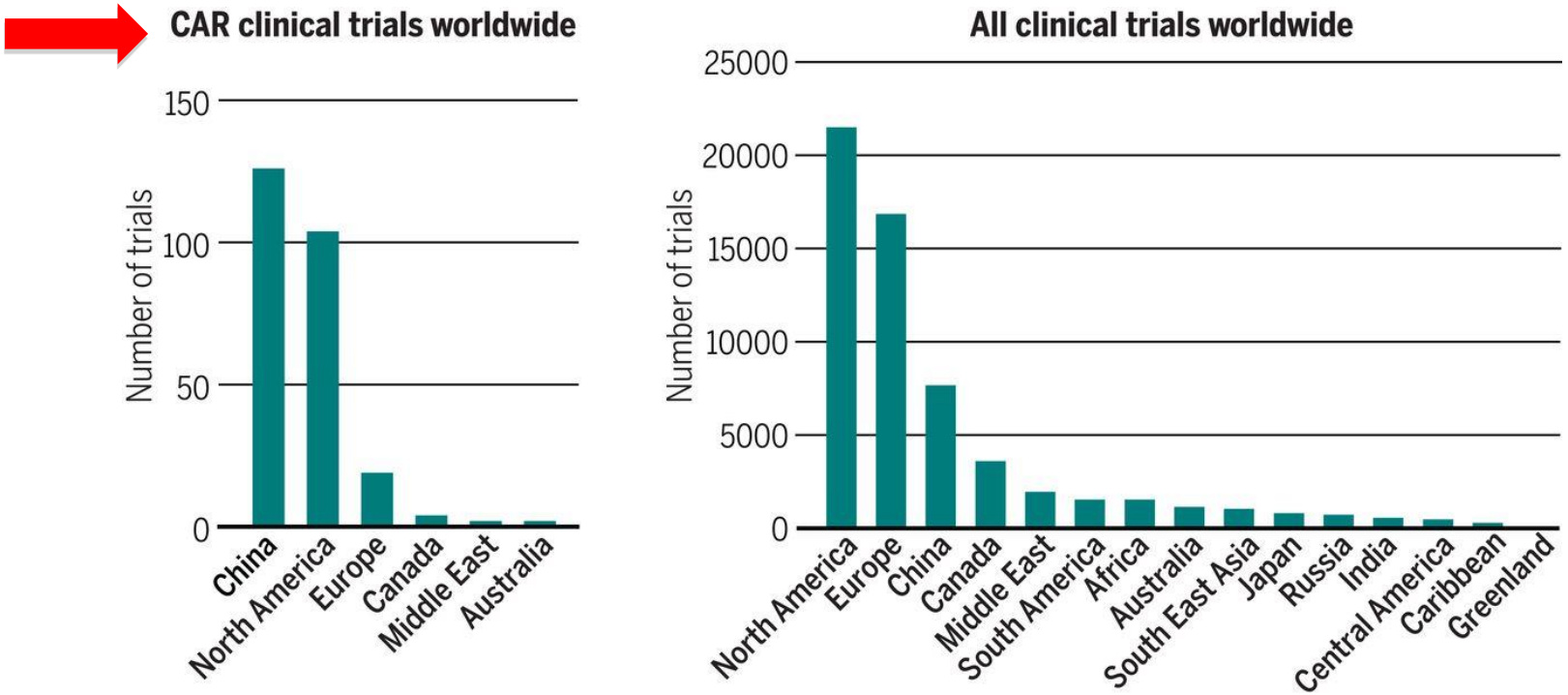
# CAR DESIGN: ANTIGEN SELECTION

## B-cell lymphoproliferative disease (LAL-NHL…..)



# CAR-T CLINICAL TRIALS

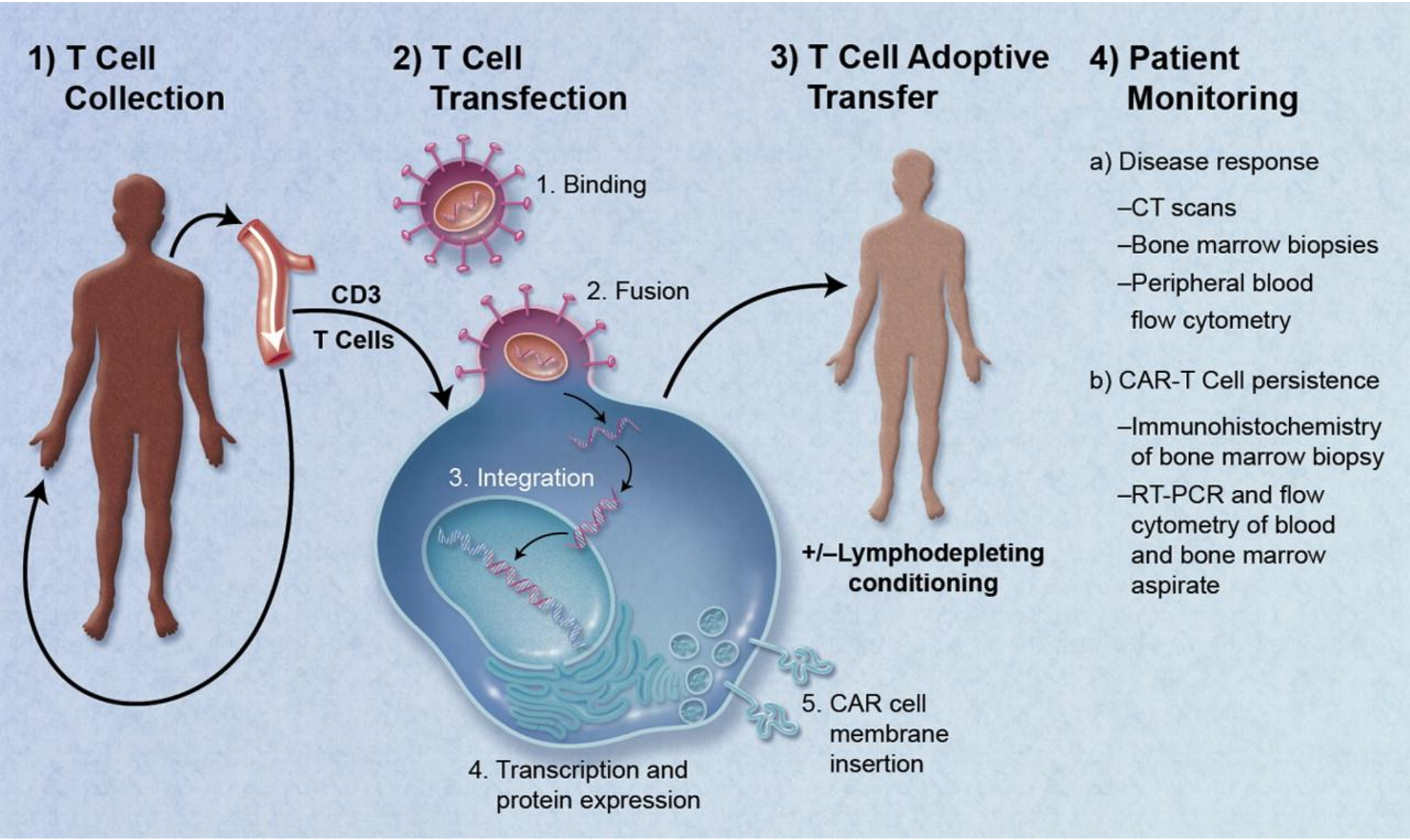
*ClinicalTrials.gov*




- 279 registered clinical trials
- **127 (46%) target CD19**
- 201 (72%) open to enrolment

*June et al. Science 2018*

# Procedure per la Terapia con CAR-T……



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

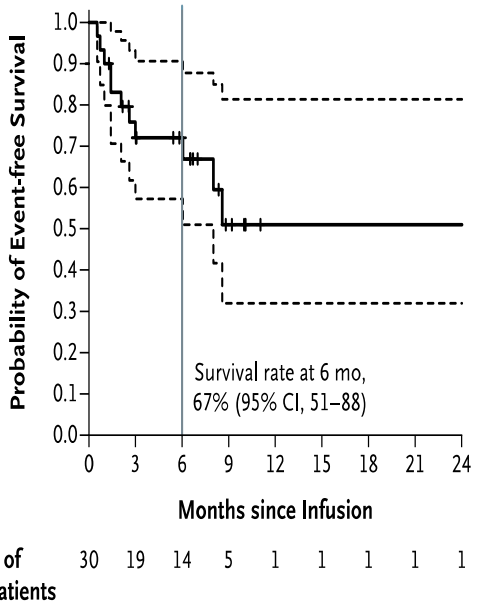
# Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

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.

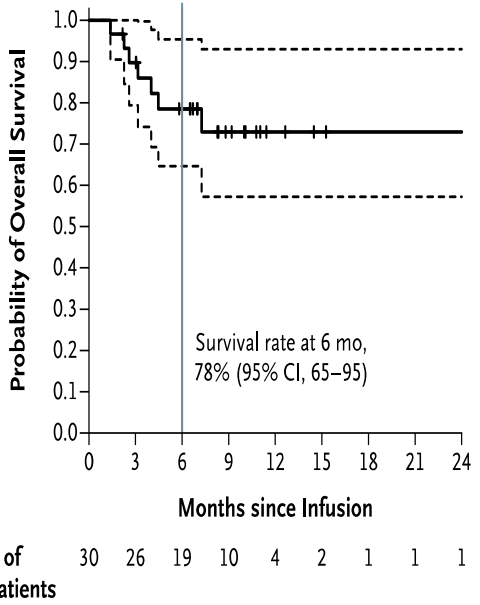
**N° Pazienti Adulti 5**
**Pediatrici 30**

N Engl J Med 2014;371:1507-17.
DOI: 10.1056/NEJMoa1407222

A




B



The NEW ENGLAND JOURNAL of MEDICINE

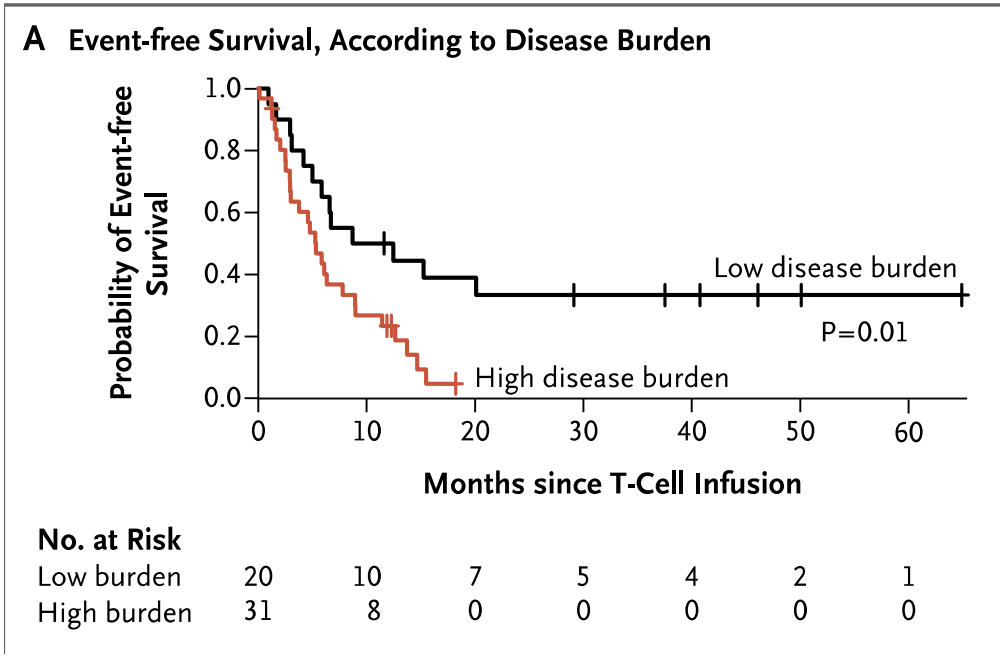
ORIGINAL ARTICLE

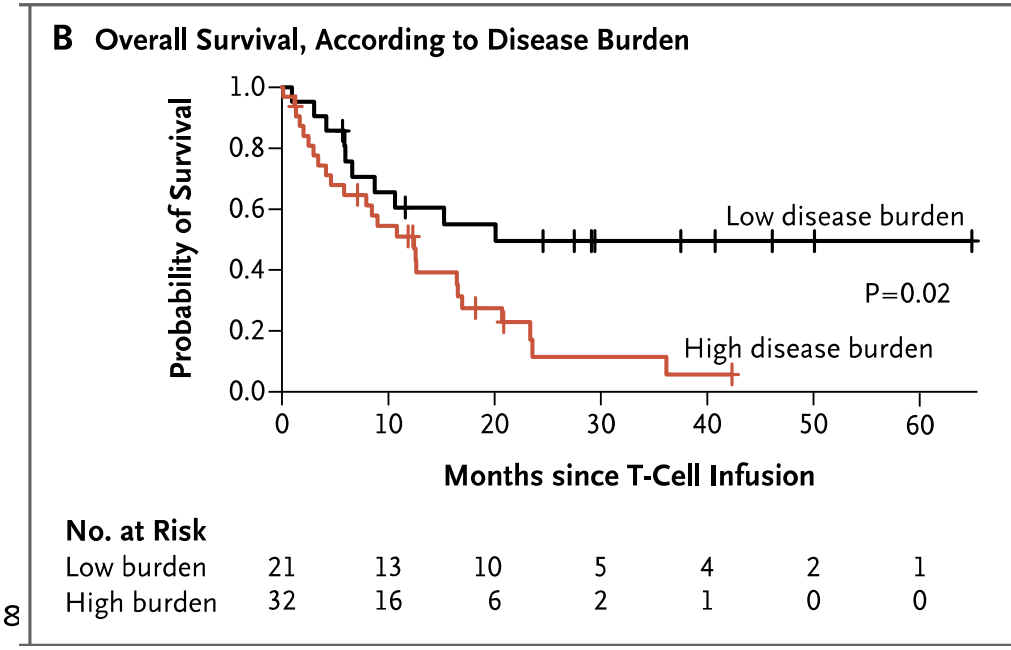
# Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia

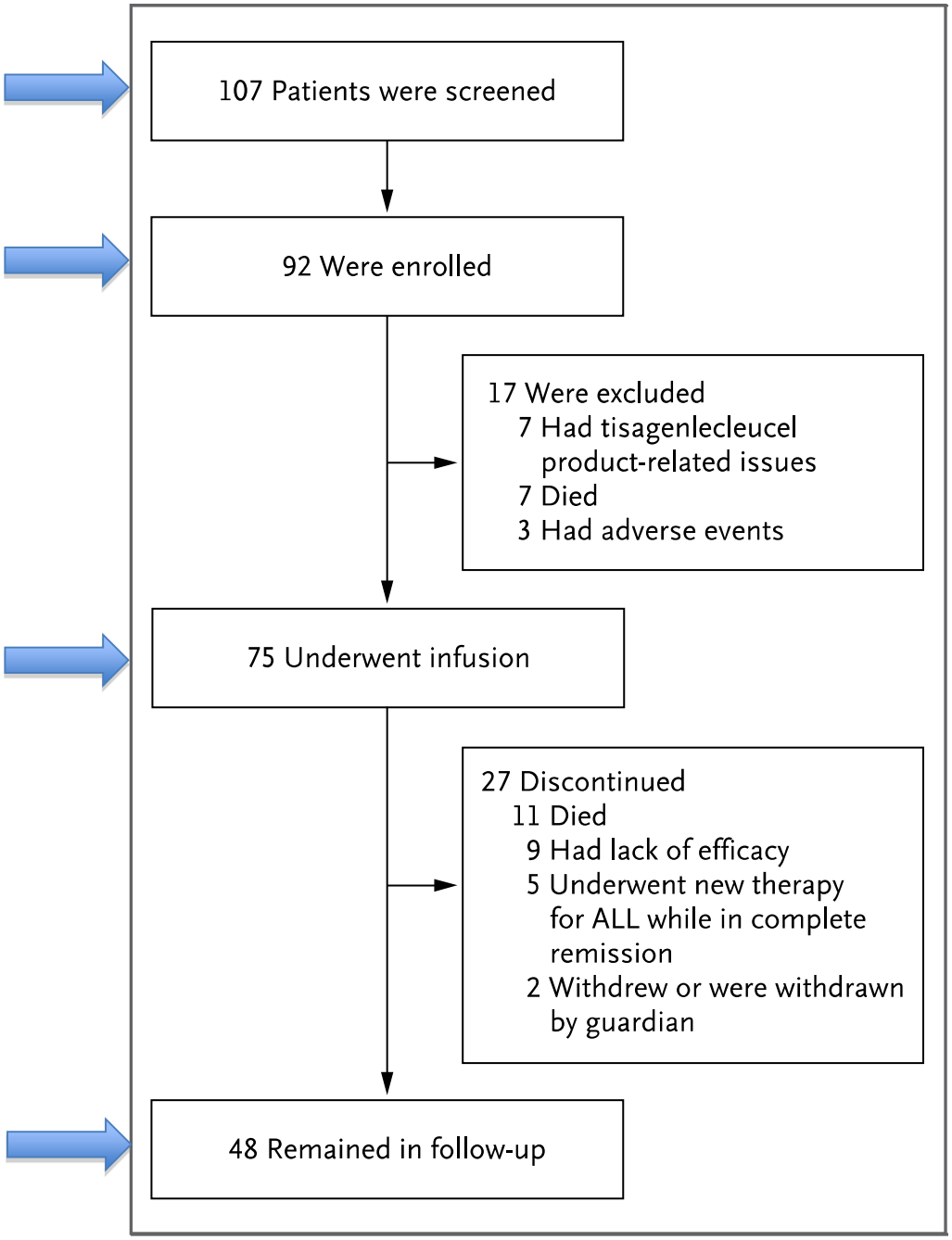
Jae H. Park, M.D., Isabelle Rivière, Ph.D., Mithat Gonen, Ph.D., Xiuyan Wang, Ph.D., Brigitte Sénéchal, Ph.D., Kevin J. Curran, M.D., Craig Sauter, M.D., Yongzeng Wang, Ph.D., Bianca Santomasso, M.D., Ph.D., Elena Mead, M.D., Mikhail Roshal, M.D., Peter Maslak, M.D., Marco Davila, M.D., Ph.D., Renier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

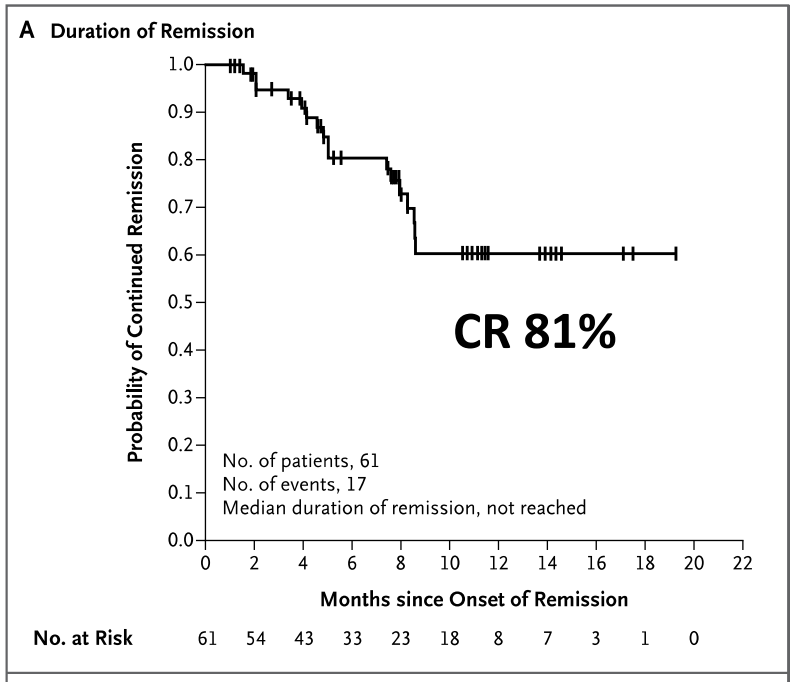
N° Pazienti
- < 30 aa **14**
- < 60 aa **31**
- > 60 aa **8**

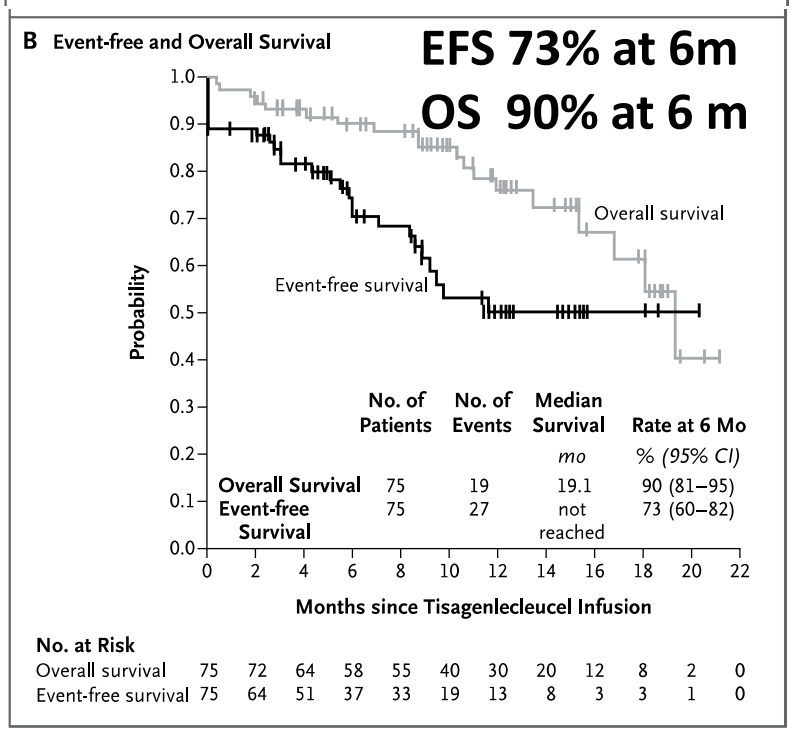
**CR 83%**
**mEFS 6 m (follow-up 29 mesi**
**mOS 12.9m**
**CRS 26%**




107 Patients were screened
92 Were enrolled
17 Were excluded
7 Had tisagenlecleucel product-related issues
7 Died
3 Had adverse events
75 Underwent infusion
27 Discontinued
11 Died
9 Had lack of efficacy
5 Underwent new therapy for ALL while in complete remission
2 Withdrew or were withdrawn by guardian
48 Remained in follow-up


A Duration of Remission
Probability of Continued Remission
CR 81%
No. of patients, 61
No. of events, 17
Median duration of remission, not reached
Months since Onset of Remission
No. at Risk
61 54 43 33 23 18 8 7 3 1 0


B Event-free and Overall Survival
EFS 73% at 6m
OS 90% at 6 m
Probability
Overall survival
Event-free survival
No. of Patients
No. of Events
Median Survival
mo
Rate at 6 Mo
% (95% CI)
Overall Survival 75 19 19.1 90 (81–95)
Event-free Survival 75 27 not reached 73 (60–82)
Months since Tisagenlecleucel Infusion
No. at Risk
Overall survival 75 72 64 58 55 40 30 20 12 8 2 0
Event-free survival 75 64 51 37 33 19 13 8 3 3 1 0

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

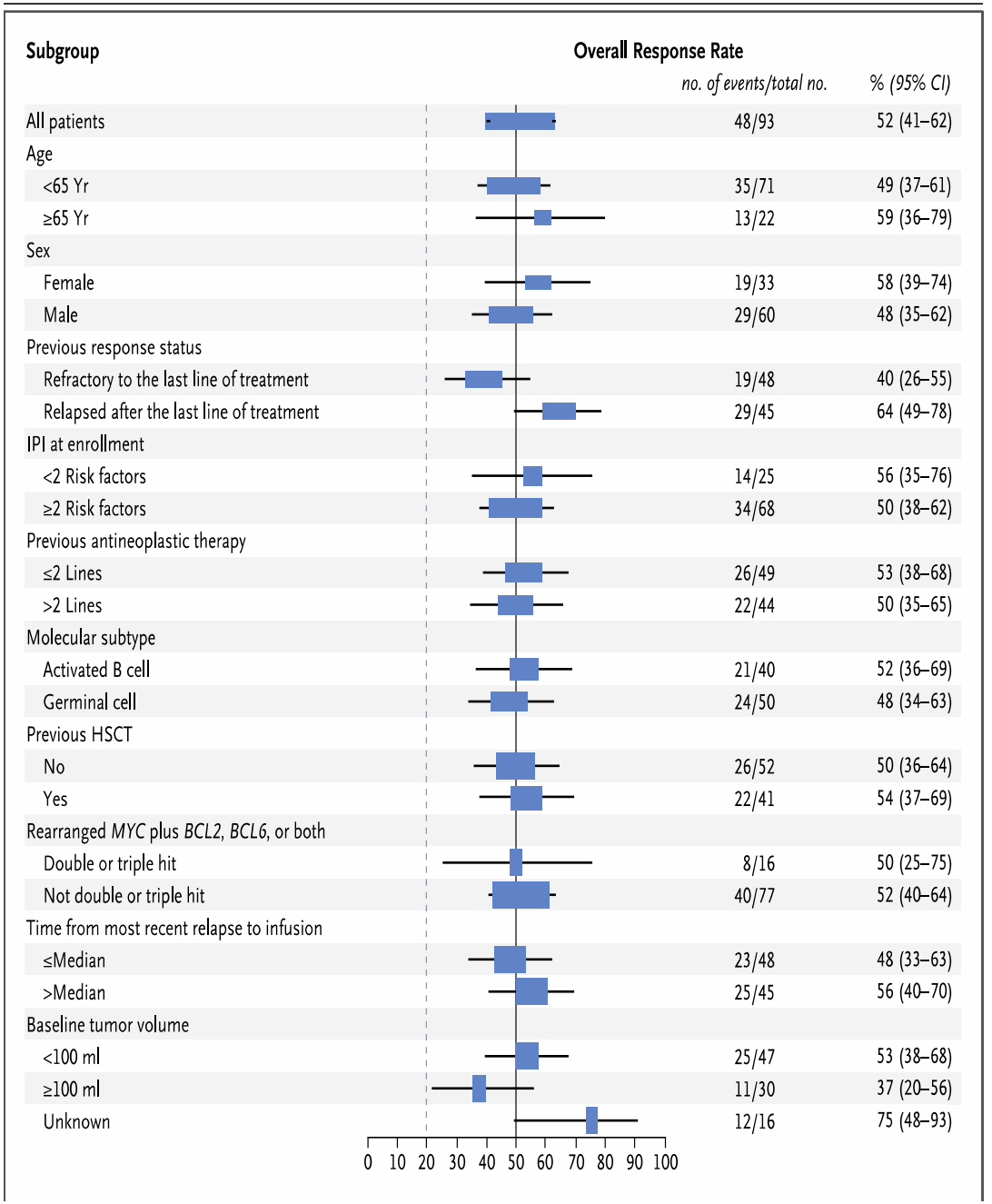
# Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma

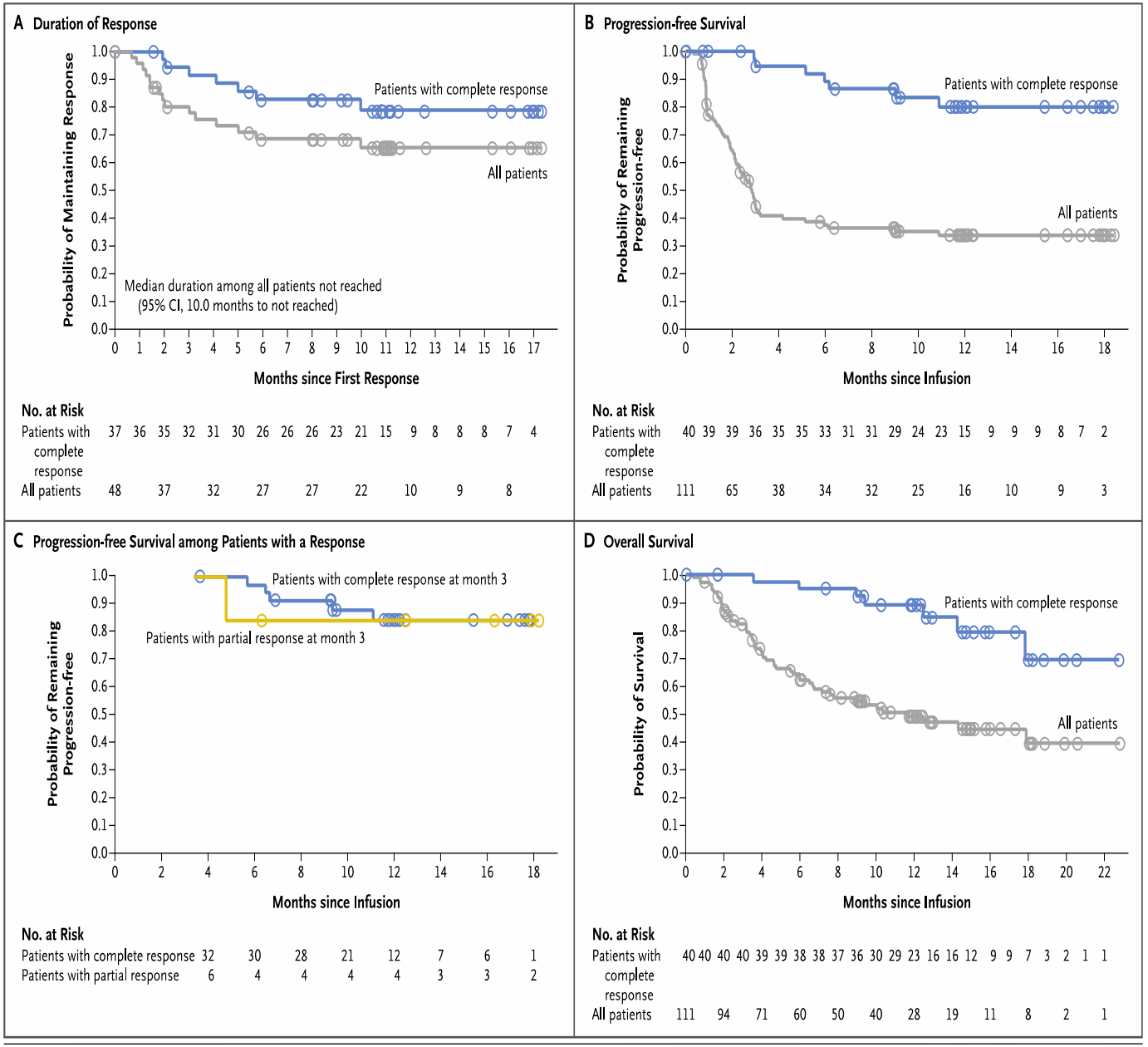
Stephen J. Schuster, M.D., Michael R. Bishop, M.D., Constantine S. Tam, M.D., Edmund K. Waller, M.D., Ph.D., Peter Borchmann, M.D., Joseph P. McGuirk, D.O., Ulrich Jäger, M.D., Samantha Jaglowski, M.D., Charalambos Andreadis, M.D., Jason R. Westin, M.D., Isabelle Fleury, M.D., Veronika Bachanova, M.D.,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

**N° Pazienti <65 aa 71**

**>65 aa 22**

N Engl J Med 2019;380:45-56.
DOI: 10.1056/NEJMoa1804980






N Engl J Med 2019;380:45-56.
DOI: 10.1056/NEJMoa1804980

# CAR-T CELL IN ADVANCED CLINICAL DEVELOPMENT FOR NHL

| Academic institute | Product | Collaborating Company |
| --- | --- | --- |
| National Cancer Institute | **Axicabtagene ciloleucel (KTE-C19, Axi-cel)**<br>– FDA/EMA Approved | Kite, A Gilead Company |
| Penn, University of Pennsylvania | **Tisagenlecleucel (CTL019)**<br>– FDA/EMA Approved | Novartis |
| Fred Hutch Cures Start Here; Seattle Children's Hospital · Research · Foundation; Memorial Sloan-Kettering Cancer Center, Established 1884 | **Lisocabtagene maraleucel (JCAR017)** | Juno Therapeutics, A Celgene Company |

# EMA CAR-T APPROVAL

- **Tisagenlecleucel (CTL019) Novartis**
  - Indicated for the treatment of paediatric and young adult patients (up to 25 years of age) with **B-cell ALL** that is **refractory or in second or later relapse**, and in adult patients with **relapsed or refractory DLBCL** after two or more lines of systemic therapy
  - FDA Approval: August 30, **2017** (ALL) May 1, **2018** (DLBCL)
    - Drug price set at $475,000 in US (+ hospitalization
  - <u>June 28, 2018: Approved by EMA</u>

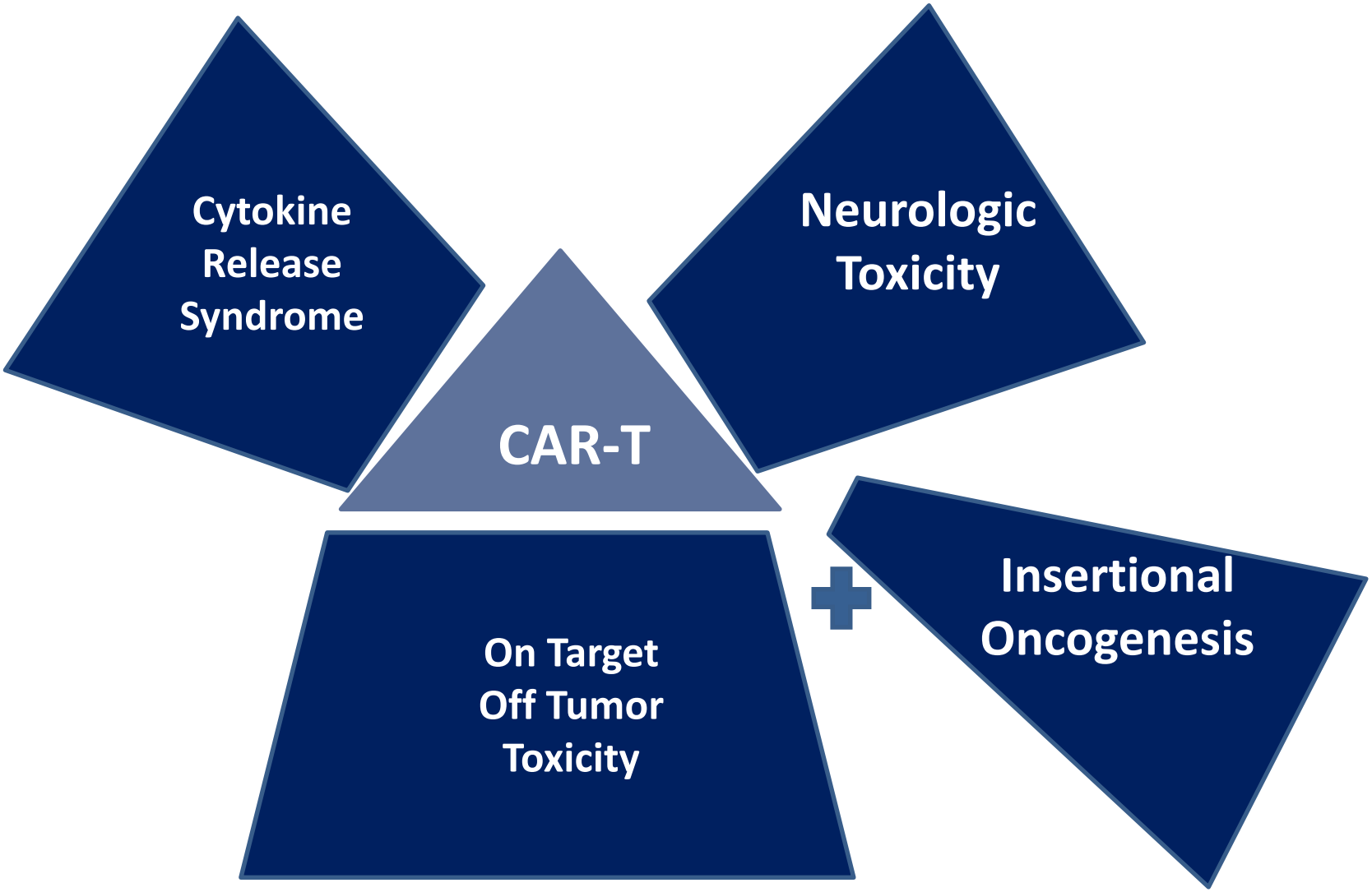

**KYMRIAH**

# EMA CAR-T APPROVAL

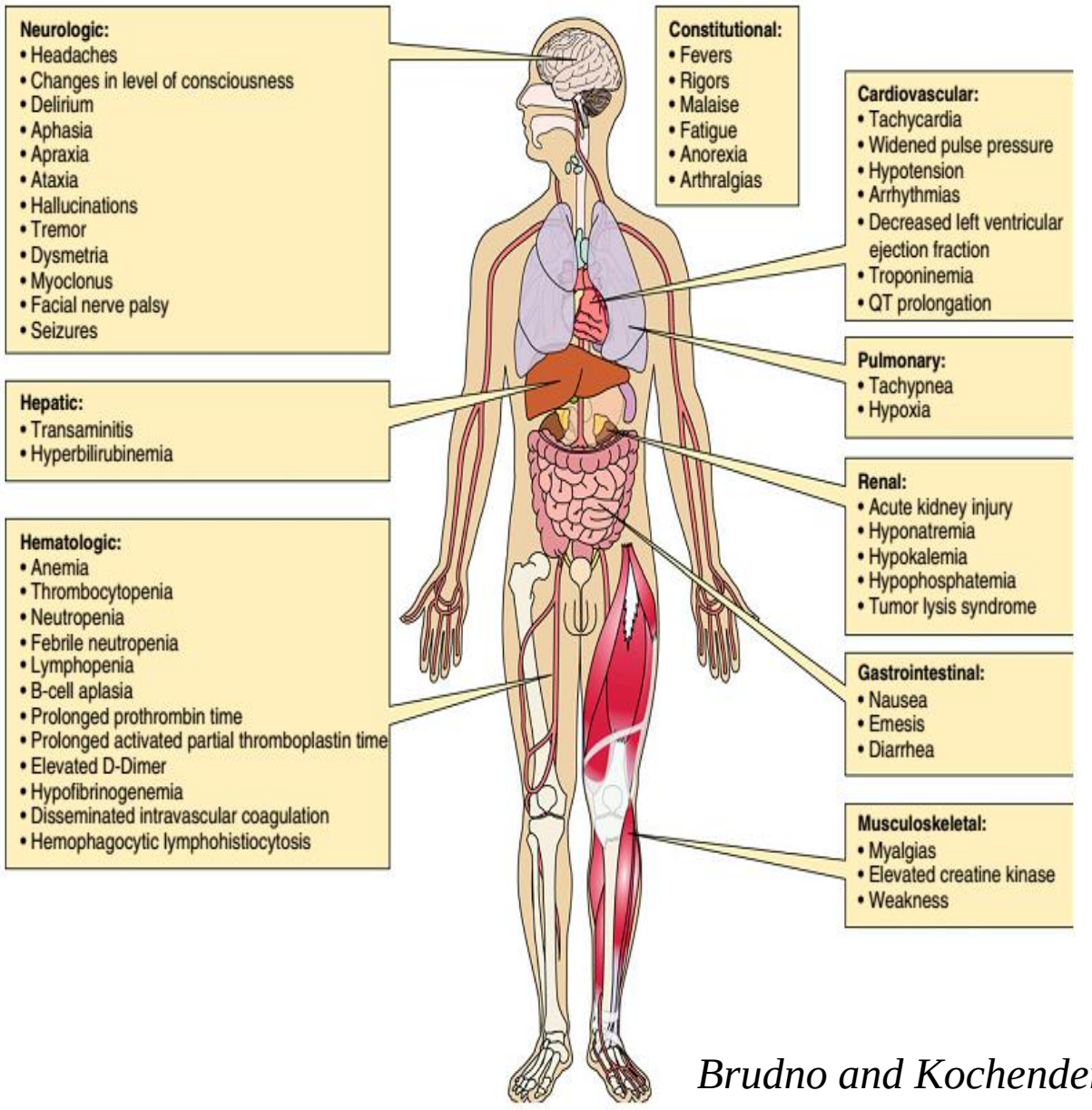
- **Axicabtagene ciloleucel (KTE-C19, Axi-cel) Kite/Gilead**
  - Indicated for the treatment of adult patients with relapsed or refractory **DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy**
  - October 18, **2017**: Approved by FDA
    - Drug price set at $373,000 in US (+ hospitalizatio costs)
  - June 28, 2018: Approved by EMA


**YESCARTA**

# CAR-T CELL TOXICITY



# CYTOKINE RELEASE SYNDROME (CRS)

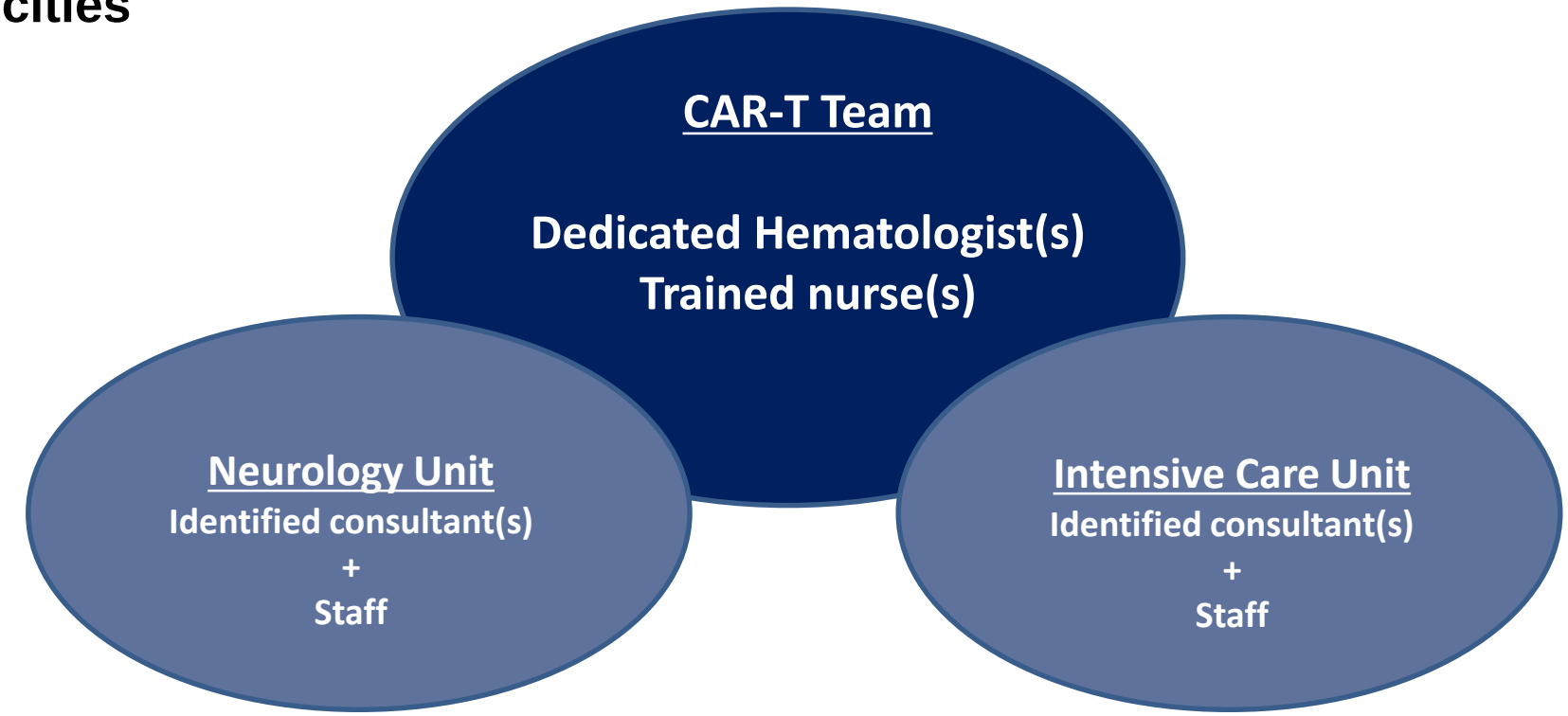



*Brudno and Kochenderfer, Blood 2016*

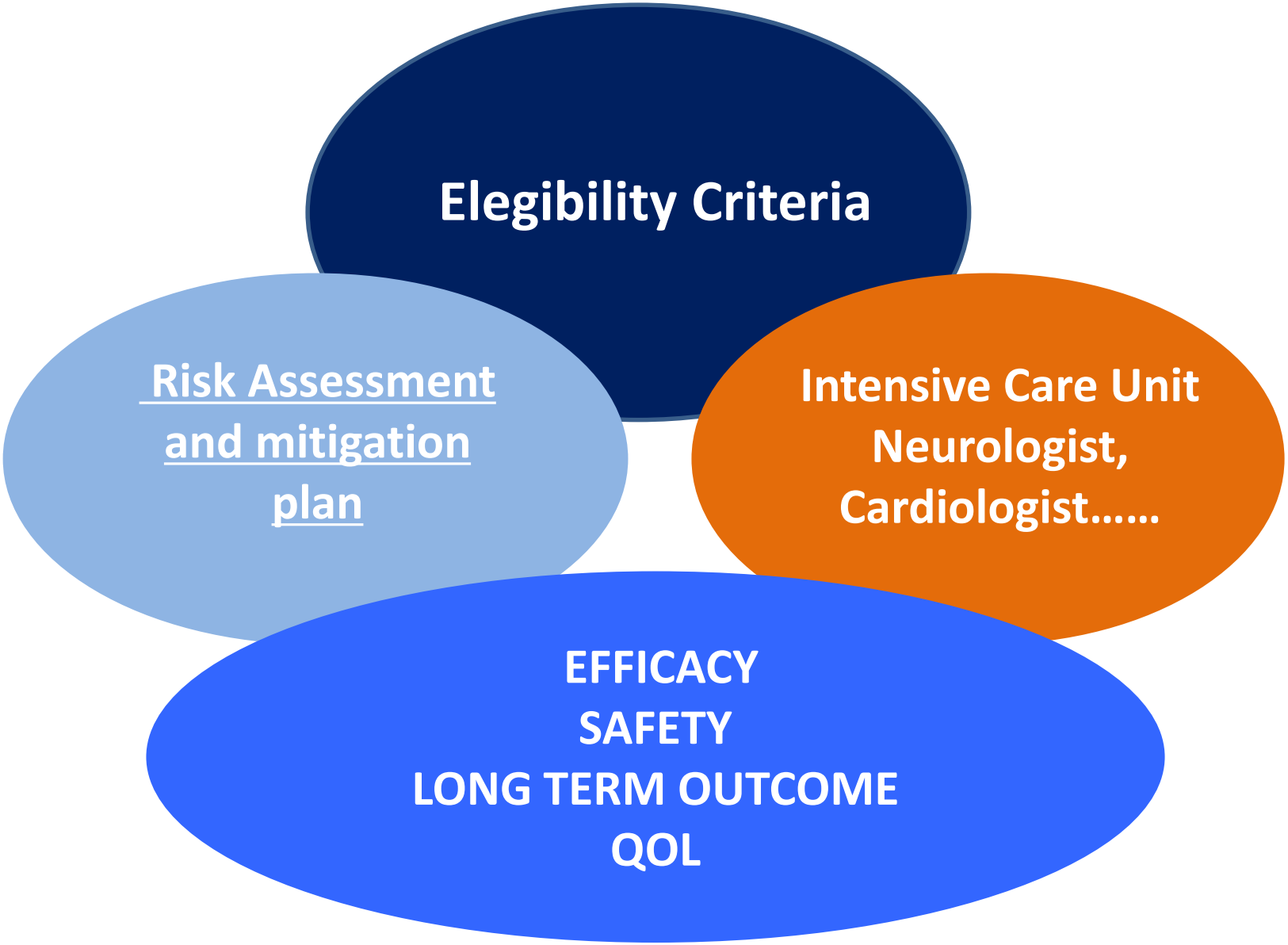
# CLINICAL RISK MANAGEMENT PLAN

**CAR-T cell therapy need strategies to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:**

- Ensuring that hospitals and their associated clinics that dispense CAR-T are **specially certified and have on-site**, immediate access to **tocilizumab**
- Ensuring those who prescribe, dispense, or administer CAR-T are aware of how to manage the **risks of cytokine release syndrome and neurological toxicities**



# Key Points of CAR-T CELL THERAPY



# La scelta della Terapia in OncoEmatologia Oggi.....

"Biologia della cellula"

"Profilo clinico"

**Efficacia**

**Tossicità**

**Costeffectiveness**

# SAFETY-RELATED ELIGIBILITY

**Table 1. Safety-related eligibility criteria for adult CAR T-cell clinical trials at the NCI**

| Clinical category | Eligibility criteria |
|---|---|
| Patient characteristics | ECOG performance status 0-1; and<br>Not pregnant or breastfeeding |
| Pulmonary | No active obstructive or restrictive pulmonary disease |
| Hematologic* | Hemoglobin ≥8.0 g/dL;<br>Platelets ≥45 000/$mm^3$ without transfusion support;<br>ANC ≥1000/$mm^3$ without growth factor support;<br>No active hemolytic anemia; and<br>No active coagulopathy |
| Other end organ function | Serum creatinine ≤1.4 mg/dL;<br>Total bilirubin ≤2.0 mg/dL;<br>Serum AST and ALT ≤3 times the institutional upper limit of normal unless liver involvement by malignancy is demonstrated;<br>No active seizure disorder; and<br>No current CNS involvement with malignancy |
| Infectious disease | No history or serologic evidence of HIV, hepatitis B, or hepatitis C; and<br>No active uncontrolled systemic infection |
| Immunologic | No active autoimmune disease; and<br>No history of primary immunodeficiency |

*Brudno and Kochenderfer, Blood 2016*

# RISK ASSESSMENT AND MITIGATION PLAN

Pre-treatment risk assessment and mitigation:

- Indication to CAR-T
- Apheresis
- Safety-related eligibility
- Seizure assessment → Neurology Consultant (need of prophylaxis?)
- Infectious assessment (viral status, prophylaxis)

# RISK ASSESSMENT AND MITIGATION PLAN

Post infusion assessment and mitigation:

- TLS prophylaxis
- Monitoring and identification of early sign and symptoms of:
  - CRS: clinical evaluation, vital signs, lab test
  - NT: clinical evaluation, tests (e.g. MMT)
  - Cardiac dysfunction (EKG, ECHO)
- Infectious assessment (Influenza test, FUO evaluation)

# NEUROTOXICITY

With Neurology Team

- Need of seizure prophylaxis or treatment
- Identification of early sign and symptomps of NT
  - Early neurologic signs: word-finding difficulties (dysphasia), attention or calculation defects (counting backward by serial 7s), and difficulty executing complex commands (handwriting)

# Trials clinici con CAR T registrati sul sito clinical trials. nih.gov

(aggiornamento 16/01/2019)

- **Italia**
- 3 trials con sponsor accademico (2 BG Roma, 1 Monza-Bergamo)
- 5 trials con sponsor industriale
- **Spagna**
- 1 trial con sponsor accademico ( Barcellona)
- 3 trials con sponsor industriale
- **Francia**
- 10 trials con sponsor industriale
- **Germania**
- 1 trial con sponsor accademico ( Heidelberg)
- 7 trials con sponsor industriale
- **Regno Unito**
- 5 trials con sponsor accademico (Londra)
- 7 trials con sponsor industriale
- **Olanda**
- 11 trials con sponsor industriale
- **TOTALE EUROPA: 53 STUDI : 10 accademici (19%)**

- **USA**
- 144 trials con sponsor accademico
- 23 trials con sponsor accademico e partecipazione industriale
- 41 trials con sponsor industriale

- **TOTALE USA: 208 STUDI : 167 accademici (80%)**

# STANDARD OPERATIVE PROCEDURES



**ALGORITMO PER IL TRATTAMENTO DELLA CYTOKINE RELEASE SYNDROME (CRS)**

| | SINTOMI PRODROMICI | PROGRESSIONE DEI SINTOMI | ULTERIORE PROGRESSIONE | NON RISPOSTA A TOCILIZUMAB | ULTERIORE ASSENZA DI MIGLIORAMENTO CLINICO |
|---|---|---|---|---|---|
| **Sintomi** | Febbricola, astenia, inappetenza (insorgenza in ore o giorni dall'infusione) | Febbre elevata (≥38 °C), ipossia (SO2<90% in aria ambiente), ipotensione lieve (PA sistolica <90 mm Hg) | Instabilità emodinamica nonostante liquidi e vasopressori a basse o alte dosi. Distress respiratorio con aumento del fabbisogno di ossigeno (FIO2 >40%) o necessità di ventilazione assistita. Rapido deterioramento clinico | assenza di miglioramento clinico in 12-18 ore | assenza di miglioramento clinico in 12-18 ore |
| **Trattamento** | Osservazione, sorveglianza colturale (emocolture ecc.)<br><br>Terapia antibiotica secondo politica istituzionale per neutropenia febbrile<br><br>Terapia sintomatologica di supporto | O2-terapia (con FIO2 ≤40%)<br><br>Idratazione +/- vasopressori a basse dosi (Dopamina < 10μg/Kg/min)<br><br>Antipiretici: Paracetamolo, FANS (es. Diclofenac)<br><br>Eseguire rx-torace | Supporto respiratorio ed emodinamico<br><br>TOCILIZUMAB (RoActemra): 8 mg/kg i.v. (dose massima: 800 mg)<br><br>Indicazione per l'inizio di Tocilizumab:<br>1. FE< 40%<br>2. Creatinina > 2.5 volte il valore precedente l'infusione<br>3. Necessità di somministrazione di Norepinefrina > 2 mcg/min per 48 ore dall'inizio della somministrazione di Norepinefrina (anche non continua)<br>4. Pressione sistolica arteriosa di 90 mmHg (negli adulti) che non è controllata con norepinefrina)<br>5. Necessità di ossigeno-terapia per > 50% o per 2 ore continuativamente.<br>6. Insufficienza respiratoria che necessita di ventilazione meccanica<br>7. PTT >2 volte il valore normale<br>8. Sanguinamento clinicamente significativo<br>9. CPK > 5 volte il valore normale | Valutare se necessario l'utilizzo di:<br>- Steroidi (con rapido tapering dopo stabilizzazione emodinamica): METILPREDNISOLONE 2 mg/kg al giorno; oppure DESAMETASONE 10-20 mg ogni 12-24h<br><br>In caso di non risposta: considerare seconda dose di TOCILIZUMAB allo stesso dosaggio della prima dose<br><br>- Supporto respiratorio ed emodinamico. | Considerare diagnosi differenziali (sepsi?)<br><br>Supporto respiratorio ed emodinamico.<br><br>Se non risposta nonostante precedente terapia considerare: CICLOFOSFAMIDE, ATG O ALEMTUZUMAB. |
| **Gestione con T.I.** | Avvertire i Rianimatori per una prima valutazione del paziente | Valutare con i Rianimatori il trasferimento, anche per l'uso di vasopressori a medie-alte dosi | Paziente in Terapia Intensiva | Paziente in Terapia Intensiva | Paziente in Terapia Intensiva |

# STANDARD OPERATIVE PROCEDURES



## ALGORITMO PER IL TRATTAMENTO DEGLI EVENTI NEUROLOGICI

| | | |
|---|---|---|
| **VALUTAZIONE BASALE** | Valutazione basale con visita specialistica Neurologica<br><br>EEG basale e dopo 1-3 giorni dall'infusione (non in regime di urgenza)<br><br>Iniziare profilassi farmacologica con LEVETIRACETAM | Profilassi farmacologica:<br>Nelle due settimane precedenti infusione iniziare la profilassi con LEVETIRACETAM 1000 (500 + 0 + 500) mg/die, introdurre il farmaco lentamente titolando 250 mg ogni 2-3 giorni sino a raggiungere la dose consigliata |
| **SINTOMI POSSIBILI** | Cefalea, confusione, alterazione del ritmo sonno/veglia, allucinazioni, disfasia, atassia, aprassia, paralisi dei nervi faciali, tremore, dismetria, convulsioni, coma | - Rivalutazione neurologica ogni 8 ore da parte dello staff<br>- Visita specialistica Neurologica urgente<br>- RMN urgente<br>- Valutare rachicentesi per escludere infezioni, malattia (in tal caso inviare campione per analisi centralizzata) |
| **ALGORITMO GESTIONE CRISI COMIZIALE** | LORAZEPAM 4 mg in 100 cc da infondere rapidamente (5-10 minuti)<br>Carico con LEVETIRACETAM 1000 mg in 15 minuti (anche in pompa o ev senza diluizione) quindi LEVETIRACETAM di mantenimento con 1000 + 0 + 1000 mg/die<br><br><u>In caso di crisi ripetute:</u><br>LORAZEPAM 4 mg in 100 cc da infondere rapidamente (5-10 minuti) ripetibile se le crisi non sono controllate<br>carico con LEVETIRACETAM 3000 mg in 15 minuti (anche in pompa o ev senza diluizione) quindi Levetiracetam di mantenimento con 1500 + 0 + 1500 mg/die | -Visita specialistica Neurologica urgente<br>-EEG urgente<br>-RMN urgente |
| **SINTOMI SEVERI** | Sintomatologia severa ma che non pone a immediato rischio di sopravvivenza, <u>presente da almeno 24 ore</u><br><br>Sintomatologia che pone a immediato rischio di sopravvivenza | Iniziare: DESAMETASONE 10-20 mg ogni 12-24h |

Cell Reports

# Engineered Tumor-Targeted T Cells Mediate Enhanced Anti-Tumor Efficacy Both Directly and through Activation of the Endogenous Immune System


## Authors

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Avanzi et al. generate CAR T cells that secrete IL-18 and show improved activity in syngeneic hematologic and solid tumor models without prior preconditioning. They further show enhanced recruitment and anti-tumor activity of endogenous T cells.